Universidade de Lisboa
Faculdade de Ciências
Departamento de Química e Bioquímica

Oxetane δ-Amino Acids Synthesis and Derivatisation

Susana Dias Lucas

Supervised by:

Amélia Pilar Rauter
(Professora Associada com Agregação do Departamento de Química e Bioquímica da Faculdade de Ciências da Universidade de Lisboa)

Hans Peter Wessel
(Dr. rer. nat., Vice Director,
F. Hoffmann-La Roche Ltd., Basel, Switzerland)

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“The most fundamental and lasting objective of synthesis is not production of new compounds, but production of properties.”

George S. Hammond, Norris Award Lecture, 1968

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Abstract

In the present work the potential of oxetane δ-amino acids as scaffolds was evaluated. While there is an ample precedence for the use of 6- and 5-membered carbohydrate-derived amino acids as scaffolds, there are no reports on oxetane-based libraries. The oxetane ring is an interesting source of rigidity and well-defined exit vectors, and this unit is present in some important naturally occurring bioactive molecules, such as taxol, oxetanocin or oxetin. Nevertheless, the intrinsic chemical and pharmacological properties or inherent advantages of the oxetanes are far from clear.

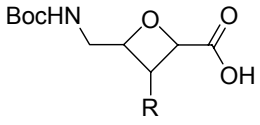
Oxetane δ-amino acids with the general structure **i** were synthesised using carbohydrates as starting materials in order to obtain different and well-defined stereochemistry. On a scaffold synthesis level, the oxetane moiety was decorated with different R groups such as hydroxyl, methoxyl or fluorine, and the resulting final scaffolds **i** exhibited D-*lyxo*, D-*ribo*, D-*arabino* and D-*xylo* configurations.

Scaffold derivatisation was performed introducing valuable pharmacophores such as 1,2,4-oxadiazoles or 1,2,3-triazoles to generate small libraries of compounds with general structures **ii** and **iii**, respectively. 1,2,4-Oxadiazoles were obtained by reaction of oxetane δ-amino acids **i**, with different hydroxyamidines *via* a basic activation followed by cyclodehydration. The scaffold was further derivatised so that the resulting compounds **ii** exhibited *tert*-butoxycarboxyl, hydrogen, acetyl or mesyl as group R_1. 1,2,3-Triazoles were obtained by the so called “click reaction” of an oxetane δ-azido ester with different acetylenes catalysed by Cu(I). Oxetanes proved to be stable under the chosen derivatisation conditions with exception of the 3-hydroxy derivatives which decomposed under basic conditions.

Moreover, corresponding 1,2,4-oxadiazole libraries were synthesised on two diastreomeric bicyclic δ-amino acids leading to a new family of compounds with general structure **iv**.

The synthesised compounds were characterised by techniques such as NMR, MS, HRMS, optical rotation, elemental analysis and, for crystalline compounds, by X-Ray crystallography.

Physicochemical and metabolic properties of the synthesised molecules were evaluated. Prediction of properties such as octanol/water partition coefficient, polar surface area, effective intestinal permeability, pKa, blood-brain barrier penetration and Andrew binding score was possible by the use of *in silico* tools. Moreover, some of the compounds experimental data on octanol/water partition coefficients, thermodynamic solubility, permeability and susceptibility towards metabolic degradation in human and mouse microsomes were obtained. All target compounds exhibited the physicochemical and metabolic properties desired in medicinal chemistry.



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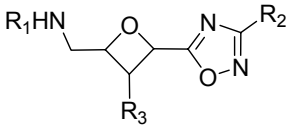

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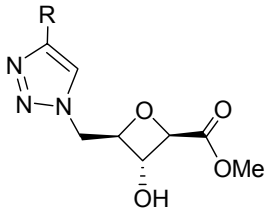

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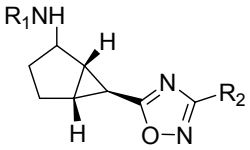


iv

Resumo

No presente trabalho foi investigado o potencial de δ-aminoácidos derivados de anéis oxetano para a construção de bibliotecas de compostos. Enquanto que para aminoácidos derivados de carbo-hidratos com anéis de seis e cinco membros o estado da arte é bastante vasto, não existem na literatura referências a bibliotecas baseadas em anéis de quatro membros. Os oxetanos exibem grande estabilidade conformacional devido à sua rigidez, o que faz com que anéis oxetano sejam moléculas-base para derivatização com vectores de orientação bem definidos.

Anéis oxetano estão presentes em alguns produtos naturais que exibem uma actividade biológica importante como é o caso do taxol, que é um dos medicamentos mais utilizados no tratamento do cancro da mama e do ovário, da oxetanocina, um nucleósido de adenina que é um antiviral de largo espectro ou da oxetina, que possui actividade antimicrobiana contra *Bacillus subtilis* e *Pyricularia orysae*. No entanto, as propriedades químicas e farmacológicas bem como as vantagens inerentes aos oxetanos estão longe de ser bem conhecidas.

δ-Aminoácidos derivados de oxetano com a estrutura geral **i** foram sintetizados no trabalho apresentado, usando carbo-hidratos como compostos de partida, de forma a obter uma estereoquímica bem definida. A metodologia ulilizada envolve a síntese de triflatos de 1,4-lactonas de 5 membros, que são submetidas a tratamento com carbonato de potássio em metanol, dando origem à contracção do anel e à formação de oxetanos com configurações D-*lyxo*, D-*ribo*, D-*arabino* e D-*xylo*, dependendo da configuração da lactona inicial. Foram desenvolvidas estratégias de síntese de δ-aminoácidos de tipo **i** derivados de oxetano, de forma a preparar análogos com grupos R distintos nomeadamente hidroxilo, metoxilo e fluor. Estes compostos foram obtidos com rendimentos globais entre 12 a 28% a partir de vias de síntese que envolvem de 9 a 14 passos reaccionais.

Numa das vias de síntese levadas a cabo para a obtenção de δ-aminoácidos derivados de oxetano, procedeu-se à oxidação da D-xilose com bromo seguida do tratamento com benzaldeído de forma a obter a já conhecida 3,5-*O*-benzilideno-D-xilono-1,4-lactona. No entanto, o ácido 2,4;3,5-di-*O*-benzilideno-D-xilónico foi identificado como produto secundário com rendimento de 37%, apesar de nunca ter sido descrito na literatura que descreve esta reacção. Para além disso, a completa caracterização completa deste composto foi levada a cabo pela primeira vez e estudos de RMN permitiram inferir a sua conformação.

A derivatização dos δ-aminoácidos derivados de oxetano foi feita com base na introdução de farmacóforos de elevado interesse biológico tais como 1,2,4-oxadiazoles ou 1,2,3-triazoles, gerando bibliotecas de compostos com estruturas de tipo **ii** e **iii**, respectivamente.

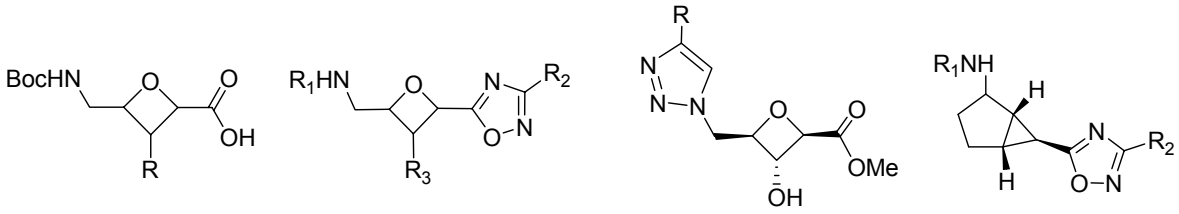
1,2,4-Oxadiazoles foram sintetizados por meio da reacção dos δ-aminoácidos com diferentes hidroxiamidinas por activação em meio básico seguida de ciclodesidratação, levando este procedimento a compostos de tipo **ii** com diferentes grupos R_2. Após a formação de 1,2,4-oxadiazoles, fazem-se modificações no grupo NHR_1 de forma a obter compostos com R_1 igual a *terc*-butoxicarbonilo, hidrogénio, acetilo ou mesilo. Aplicando esta metodologia aos diferentes δ-aminoácidos derivados de oxetano que foram sintetizados, obtiveram-se pequenas bibliotecas, geralmente de vinte compostos cada.

1,2,3-Triazoles foram obtidos através de uma reacção designada "*click reaction*" devido à sua alta eficiência e simplicidade que consistiu, neste caso, na reacção de um δ-azidoéster derivado de oxetano com diferentes acetilenos catalisada por Cu(I). Esta biblioteca de compostos foi feita recorrendo a técnicas automatizadas de química e purificação em paralelo, dando origem a quinze novos 1,2,3-triazoles derivados de oxetano num período de tempo muito reduzido.

Os δ-aminoácidos derivados de oxetano sintetizados ao longo deste trabalho provaram ser estáveis nas condições reaccionais levadas a cabo para a sua

derivatização, com excepção dos oxetanos que apresentam um hidroxilo livre no C-3 do oxetano, que sofreram uma decomposição parcial ou total quando submetidos a condições básicas.

Contidos na vasta colecção de compostos armazenados na F. Hoffmann – La Roche encontravam-se dois δ-aminoácidos estereoisómeros cuja base estrutural é um anel bicíclico. Estes compostos possuem também uma estrutura rígida e são, em princípio mais lipofílicos, o que suscitou o interesse pela comparação das suas propriedades com as dos derivados de anéis oxetano. Procedeu-se pois à síntese de compostos com estrutura geral **iv** seguindo a mesma metodologia usada para os derivados de oxetano, de forma a obter duas bibliotecas análogas de vinte compostos cada.



i **ii** **iii** **iv**

Todos os compostos sintetizados foram totalmente caracterizados recorrendo a técnicas como ressonância magnética nuclear mono- e bi-dimensional, espectrometria de massa, espectrometria de massa de alta resolução, rotação específica, análise elementar e, para compostos cristalinos, recorreu-se também à cristalografia por raio-X.

Para além da confirmação conformacional dada pela cristalografia de raio-X, esta técnica permitiu a comparação de ângulos e distâncias efectivas entre farmacóforos. As distâncias obtidas entre o grupo amida e o 1,2,4-oxadiazole dos compostos submetidos a raio-X são da mesma ordem de grandeza quer para derivados de anéis oxetano ou de anéis bicíclicos. Estes dados são bastante relevantes para futuras avaliações no âmbito da actividade biológica, uma vez que estes compostos são bastante diversificados no que diz respeito à sua estrutura e propriedades

físico-químicas e metabólicas, mas exibem relações espaciais muito próximas entre os farmacóforos.

Foram também investigadas as propriedades físico-químicas, bem como as metabólicas dos compostos sintetizados. Com recurso a técnicas computacionais foi possível calcular/prever propriedades como o coeficiente de partição octanol/água, a área polar superficial, a permeabilidade intestinal efectiva, a permeabilidade através da barreira sangue/cérebro, o factor de ligação de Andrew e a constante de dissociação. Estas técnicas constituem uma ajuda preciosa na previsão da lipofilia, permeabilidade e estado de carga das moléculas sintetizadas. Para os compostos estudados neste trabalho não foram gerados quaisquer alertas para infracção da intitulada regra dos cinco, indicando que todos eles possuem as propriedades desejadas para biodisponibilidade oral. No caso da permeabilidade intestinal efectiva, esta foi prevista a um nível médio a alto, no entanto o mesmo não se verificou para a permeabilidade da barreira sangue/cérebro, que foi prevista como sendo baixa, o que indica que estes compostos não poderão ser considerados para doenças ao nível do sistema nervoso central.

No que diz respeito às propriedades físico-químicas ou metabólicas medidas experimentalmente, o coeficiente de partição octanol/água indicou que os vários compostos derivados de oxetano apresentam diferentes lipofilias dependendo da substituição em C-3. No entanto a estereoquímica não parece ser um factor determinante para esta propriedade.

As constantes de dissociação foram medidas para algumas das aminas sintetizadas, tendo-se verificado que a estereoquímica provoca diferenças significativas nesta propriedade. As aminas derivadas de anéis bicíclicos são mais básicas que as suas correspondentes derivadas de anéis oxetano. A substituição em C-3 do anel 1,2,4-oxadiazole demonstrou não influenciar a basicidade das aminas.

Ensaios de permeabilidade estão a ser realizados na F. Hoffmann – La Roche, Ltd. com recurso a uma técnica designada “ensaio de permeabilidade em membrana

artificial paralela" (PAMPA). Esta técnica é relativamente recente e de momento estão a ser desenvolvidas técnicas computacionais para a previsão dos resultados neste tipo de ensaios. Muitos dos compostos sintetizados foram previstos como exibindo baixa permeabilidade no PAMPA. No entanto, os resultados dos ensaios demonstram que todos os compostos apresentam uma permeabilidade média a elevada. Estes resultados são bastante importantes, uma vez que dizem respeito a derivados de anéis oxetano sobre os quais havia muito pouca informação disponível, de forma que serão muito úteis para a optimização dos programas de previsão do PAMPA desta empresa.

A susceptibilidade dos compostos sintetizados à degradação via microssomas humanos e de ratos foi também testada e verificou-se que 1,2,4-oxadiazoles derivados de oxetano devem exibir biodisponibilidade média a alta, se considerarmos que o metabolismo hepático é o mais relevante. Por outro lado, os compostos bicíclicos são mais susceptíveis ao ataque microssomal.

O trabalho aqui apresentado descreve pois a síntese de δ-aminoácidos derivados de oxetano, uma família de compostos muito pouco explorada, tendo sido confirmado o seu potencial como unidades básicas derivatizáveis. A introdução de diferentes farmacóforos nas três posições disponíveis do anel oxetano permitiu obter uma biblioteca que totaliza 101 compostos. Foram também derivatizados dois δ-aminoácidos de estrutura bicíclica, originando uma biblioteca de 40 compostos. As propriedades físico-químicas e metabólicas dos compostos sintetizados foram investigadas, tendo-se verificado que estes exibem as características desejadas em química medicinal. Pelo ponto de vista da química computacional, este trabalho contribuiu para o refinamento destas técnicas, uma vez que não existem na literatura referências a propriedades moleculares de oxetanos. Os compostos sintetizados foram depositados na colecção da F. Hoffmann – La Roche, Ltd. onde serão submetidos a testes de actividade biológica.

Key Words / Palavras Chave

Oxetane δ-Amino Acids	δ-Aminoácidos derivados de oxetano
Carbohydrate Amino Acids	Aminoácidos derivados de carbo-hidratos
Ring contraction	Contracção do anel
Cyclodehydration	Ciclodesidratação
1,2,4-Oxadiazoles	1,2,4-Oxadiazoles
Click Chemistry	"*Click Chemistry*"
1,2,3-Triazoles	1,2,3-Triazoles
Compound libraries	Bibliotecas de compostos
Molecular Dynamic Optimisation	Optimização de dinâmica molecular

List of Abbreviations

A(ABX)	part A of an ABX system
ADME(T)	absorption, distribution, metabolism, elimination, (toxicity)
ASTA	solubility assay
B(ABX)	part B of an ABX system
BB(B)	blood-brain (barrier)
Boc	*tert*-butoxycarbonyl
ca.	*circa*, approximately
CAA	carbohydrate amino acid
CD	circular dichroism
CDMT	2-chloro-4,6-dimethoxy-1,3,5-triazine
CE	capillary electrophoresis
CL_{int}	intrinsic clearance
ClogP	calculated logarithm of octanol/water partition coefficient
CMC	critical micelar concentration
CNS	central nervous system
COSY	correlation spectroscopy
CSA	camphorsulfonic acid
Cy-Hex	cyclohexane
d	doublet
DAST	diethylaminosulfurtrifluoride
DCM	dichloromethane
dd	double doublet
ddd	double double doublet
DIPEA	di-propylethyl amine
DMF	dimethylformamide
DMSO	dimethylsulfoxide
DOF	degree of conformational freedom
EDC	1-[3-(dimethylamino)propyl]-3-ethyl carbodiimide
ELSD	evaporative light-scattering detector
Eq	equation
eq	equivalent(s)
Gum	glucosyl-uronic acid-methyl amine
h	hour(s)
HATU	*O*-(7-Azabenzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HBA	hydrogen bond acceptor
HBD	hydrogen bond donor
HCMV	Human cytomegalovirus
HIV	human immunodeficiency virus
HMBC	heteronuclear multiple-bond correlation
HMQC	heteronuclear multiple-quantum correlation
HPLC	high performance liquid chromatography
HSQC	heteronuclear single-quantum correlation
HSV	herpes simplex virus

HT	high throughput
HV	high vacuum
IC_{50}	inhibitory concentration (50%)
IR	infra red
LC	liquid chromatography
LYSA	lyophilised solubility assay
MadCAM-1	mucosal addressin cell adhesion molecule-1
MDO	multidimensional optimisation
min	minute(s)
MS	mass spectrometry
NADPH	nicotinamide adenine dinucleotide phosphate
NMR	nuclear magnetic ressonance
NOESY	nuclear overhauser effect spectroscopy
PAMPA	parallel artificial membrane permeability assay
PDC	pyridinium dichromate
Pd/C	palladium on charcoal
P_{eff}	effective intestinal permeability
pka	dissociation constant
PLE	pig liver esterase
PMB	*p*-methoxy benzyl
ppm	parts per million
PPTS	pyridinium *p*-toluenesulfonate
prep-HPLC	preparative high performance liquid chromatography
PSA	polar surface area
PVDF	polyvinylidene
q	quartet
QSAR	quantitative structure activity relationship
rt.	room temperature
sat soln	saturated solution
SLe^X	sialyl lewis^x
T	triplet
$T_{1/2}$	half-life time
TATU	*O*-(7-azabenzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate
TBME	*tert*-butylmethylether
TBTU	*O*-(1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluoroborate
TEMPO	2,2,6,6-tetramethylpiperidioxyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
UV	ultraviolet
VCAM-1	vascular cell adhesion molecule-1
VZV	varicella zoster virus

Contents

Introduction

The search for new drugs is a very demanding field, and a pharmaceutical company may screen millions of molecules for biological activity per year in order to find a new product. Thousands of hits are found, and most of these molecules might not have the right physical, metabolic, and safety properties. Large pharmaceutical companies can cope with about 30 molecules taken into development each year. A good year sees three molecules reaching the product stage and some years see none! When considering all the efforts to bring out a drug- product, it may cost around a billion dollar.[1]

Drugs and their targets are sparsely distributed through chemistry space. The combinatorial chemistry focuses on chemical libraries with a large number of compounds, and this tends to hide the fact that the majority of information on drug-like properties is contained in a very small number of compounds. The chemistry space for reasonably sized molecules (up to molecular weight of 600), which contain the common atoms found in drugs, is estimated to be in the range of 10^{40} to 10^{100}.[2]

During the 1990s, the development of many compounds was terminated in the clinic due to unsatisfactory pharmacokinetics (PK). It became clear that medicinal chemists needed to address this parameter for lead optimization, and therefore tools were needed to assess the relationship between structure and PK properties.[3,4]

Hit[4]
Compounds that are good starting points to drug discovery. Medicinal chemists study the chemical structure of compounds that have been found to interact with the target protein and build up hypotheses to design related structures with improved properties. The testing on various biological assays takes to a hit-to-lead process where the potential value of the hit is evaluated.

Lead[4]
A compound is designated "lead" when series of criteria, including potency, selectivity, synthetic access, ADME properties and potential for optimisation, are met. Structural changes associated with improved properties in the lead are then pursued vigorously until a compound is found that meets the stringent criteria required for a preclinical drug candidate.

[1] Avdeef, A; *Absorption and Drug Development - Solubility, Permeability and Charge State*. 1st Ed. **2003**, John Wiley & Sons, Inc. New Jersey, USA.
[2] Lipinski, CA; *J Pharm Tox Methods* **2000**, 44:235.
[3] Keller, TH; Pichota, A; Yin, Z; *Curr Op Chem Bio* **2006**, 10:357.
[4] Aherne, GW; McDonald, E; Workman, P; *Breast Cancer Res* **2002**, 4:148.

The introduction of Lipinski's 'Rule of Five' has initiated a profound change in the thinking paradigm of medicinal chemists. It states that poor absorption or permeability are related to clogP, molecular mass, and the number of hydrogen bond donors and acceptors (see chapter 1.5). Understanding the difference between biologically active small molecules and drugs became a priority in the drug discovery process.

In order to rationalise what is responsible for compound attrition, some criteria were defined for compounds that successfully pass through the development process. Diversity analysis can be applied in programs such as compound acquisition, design of combinatorial libraries, and selection of compounds for screening. These techniques are mainly used in the early stage of the drug discovery process when little is known about the biological target or how to build a large compound library to be screened against different targets. The library to be screened should produce compounds with desirable absorption, distribution, metabolism, elimination and toxicity (ADMET) properties, the so called drug-like compounds.[5]

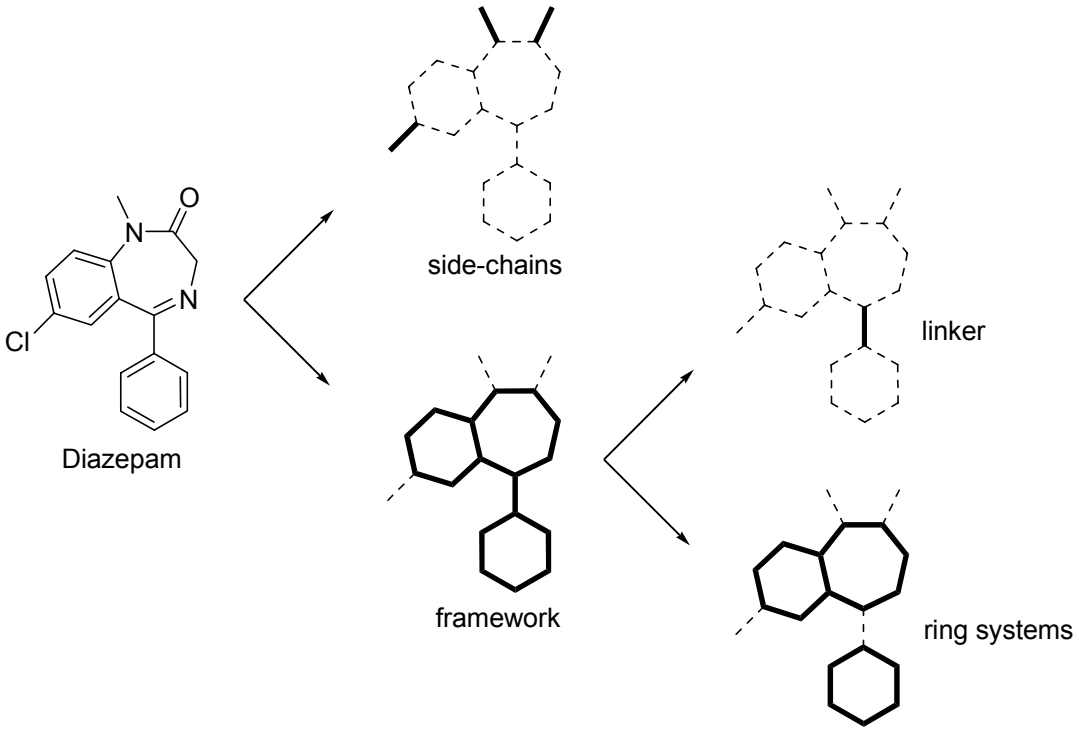
It is of great value to explore chemical series outside those that have been considered previously for the development of novel chemical entities. This is particularly important for investigating unprotected regions of chemistry space in terms of intellectual property.[6]

In recent years, the term scaffold has been used extensively to describe the core structure of a molecule. Taken literally, the core structure is the central component of a molecule: the substructure that contains the molecular material necessary to ensure that the functional groups are in a desired geometric arrangement.[5]

A decade ago, Bemis and Murcko[7] introduced a systematic approach grounded on the dissection of a molecule yielding molecular "frameworks". According to this concept, a molecule can be segmented into four fundamental units: ring systems,

[5] Gorse, A-D; *Curr Opin Med Chem* **2006**, 6:3.
[6] Brown, N; Jacoby, E; *Mini-Rev. Med Chem* **2006**, 6:1217.
[7] Bemis, YGW; Murcko, MA; J Med Chem **1996**, 39:2887.

linkers, side chains and frameworks. In Scheme 1, the different structural units are shown for the anti-anxiety agent diazepam as an example. The framework can be defined as the molecular scaffold.[8]



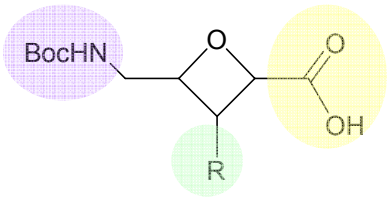
Dissection of a molecule according to Bemis and Murcko. Diazepam contains three sidechains and one framework with two ring systems and a zero-atom linker.

Scheme 1

Due to the huge number of possible drugs, methods to rationalise selection of compounds to be synthesised, with respect to scaffolds and side chains, or to choose the compounds to be screened, are required. Various computational disciplines, such as cheminformatics, ADME modelling, virtual screening or chemogenomics emerged in the past years as techniques for the efficient identification and optimization of novel molecules with a desired biological activity. For instance at Roche, computer-assisted molecular modelling resources are integrated in the medicinal chemistry organization, and there is a focus on lead generation support.[9]

[8] Schneider, G; Schneider, P; Renner, S; *QSAR Comb Sci* **2006**, 25(*12*):1162.
[9] Stahl, M; Guba, W; Kansy, M; *Drug Discov Today* **2006**, 11(*7/8*):326.

In the work presented here a new class of scaffolds, oxetane δ-amino acids (Scheme 2), was explored. The synthesis of the scaffolds was performed using carbohydrates as starting materials with different and well defined absolute configurations. Derivatisation of the amino group and acid function, and the introduction of several R groups provided different pharmacophores, furnishing small libraries on the respective oxetane δ-amino acid scaffold.



Oxetane δ-Amino Acid Scaffold.

Scheme 2

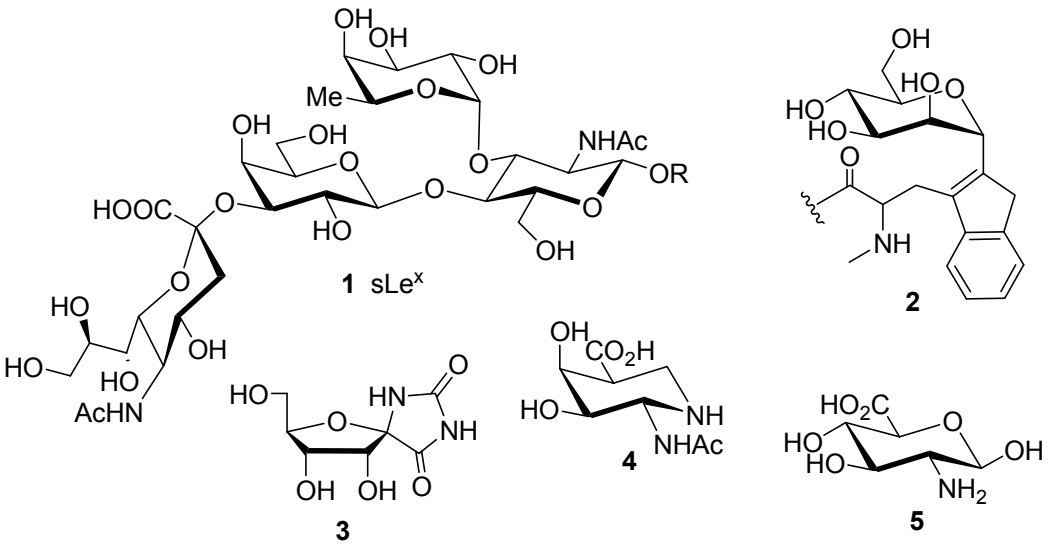
1.1 Carbohydrate Amino Acids

Amino acids and carbohydrates are two major building blocks used to generate diversity in Nature. Amino acids present the ability to form secondary structures in proteins and polypeptides as the basis of three-dimensional architecture. Carbohydrates are found in nucleotides, glycopeptides and glycolipids and communicate with their inter- and intra-cellular environment through a multitude of molecular interactions. Many of these recognition phenomena are involved in events such as metastasis, infection, and inflammation and have become a subject of intensive medical research.

Carbohydrate amino acids (CAAs) are molecules that combine the structural features of amino acids with those of carbohydrates resulting in highly substituted polyfunctionalised building blocks.

CAA cores are commonly found in Nature, and the most abundant example is sialic acid, often located peripherically on glycoproteins. So far, over 40 different naturally

occurring sialic acids have been identified.[10] An example of an important sialic acid containing oligosaccharide is sialyl Lewis^x (sLe^x) **1** (Scheme 3) which is found on the outer surface of glycolipids and glycoproteins and which is a key recognition element of the selectins, a group of cell surface proteins with carbohydrate recognition domains classified as E-, P-, and L-selectins, according to their occurrence on endothelial cells, platelets, and lymphocytes[11]. Selectin-carbohydrate interactions occur at an early stage of inflammatory reactions or metastasis, and the hope is that with sLe^x mimetics it will be possible to intervene in acute and chronic inflammatory diseases (asthma, arthritis, myocardial infarction, lung injury) and to find new anticancer agents.[12,13]



Scheme 3

Some carbohydrates are linked to proteins to form cysteine-linked glycoproteins or *C*-linked mannopyranosyl-L-tryptophan such as **2** in which a carbohydrate moiety is linked to an amino acid residue, but those will not be focused here. There are a few CAA-based peptidyl nucleosides with antibiotic activity such as polyoxim, sinefungin, and the nikkomycins and albamycins. Hydantoin derivative **3** also contains a CAA substructure and shows potent and selective antiherbal activity with no toxicity to

[10] Schweizer, F; *Angew Chem Int Ed* **2002**, 41:230.
[11] Unger, FM; *Adv Carbohydr Chem Biochem* **2001**, 57:207.
[12] Sears, P; Wong, C-H; *J Chem Soc Chem Commun* **1998**, 1161.
[13] Magnani, JL; *Archives Biochem Biophys* **2004**, 426:122.

microorganisms and animals. Other antibiotics with a CAA moiety include chryscandin, amipurimycin, miharamycin, gougerotin, blatidin, bagougeramine and aezomycin. Siastatin B **4** is among the class of CAAs in which the nitrogen is located within the carbohydrate ring structure, and this inhibitor of both β-glucuronidase and *N*-acetylneuraminidase was isolated from *Streptomyces* cultures.[14]

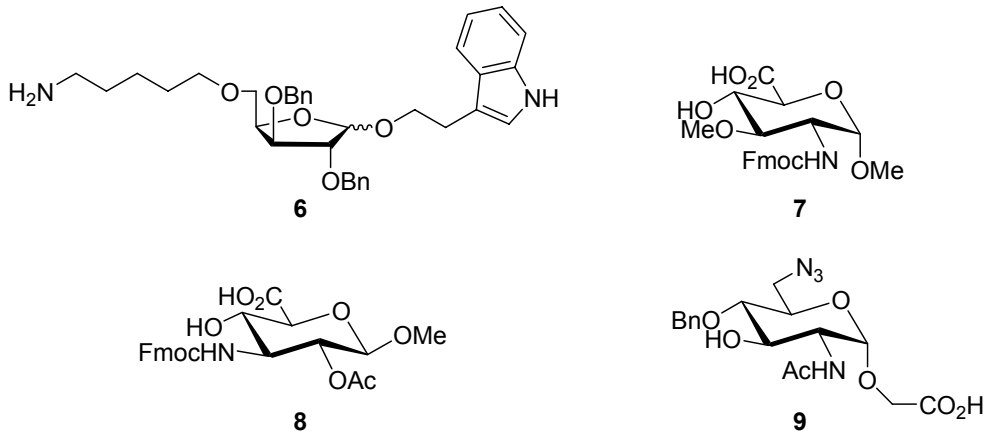
Also synthetic chemists explored CAAs as multivalent scaffolds or platforms leading to libraries of compounds with pharmacological interest, as well for the production of biomaterials for tissue engineering, and as molecular tools for the generation of nanostructures. Due to its rich stereochemistry and high degree of functionalisation, extensive work has been done and reviewed[15,16,17,18] in the field of CAAs.

Heyns and Paulsen,[19] back in the 50s, were the firsts to synthesise a CAA, glucosaminuronic acid **5**, in an effort to elucidate the structure of bacterial cell wall components and to synthesise analogues. The synthesis of CAAs usually starts from commercially available monosaccharides such as glucose, glucosamine, 1,2;5,6-di-isopropylidene glucose or galactose. The amino group of the CAA can be introduced by reduction of an azide, cyanide or nitromethane equivalent. The carboxylic function is introduced by reaction with CO_2, by a hydrolysable cyanide, via Wittig reaction and subsequent oxidation or by selective oxidation of a primary alcohol.

CAAs are an attractive source of readily available, stereochemically defined scaffolds which may contain easily convertible substituents in the rigid oxetane (this class is further discussed on chapter 1.2) and pyran rings or the more flexible furan ring. Functional groups can thus be presented in a distinct arrangement.

[14] Umezawa, H; Takeuchi, T; Komiyama, T; Morishima, H; Hamada, M; Takeuchi, T; *J Antibiot* **1974**, 27:963.
[15] Wessel, HP; Lucas, SD; *Oligossacharide mimetics. In Glycoscience: Chemistry and Chemical Biology*; Fraser-Reid, B; Tatsuda, K; Thiem, J; Eds.; Springer Verlag: Heidelberg **2008**, Part 9, 2079.
[16] Velter, I; La Ferla, B; Nicotra, F; *J Carbohydr Chem* **2006**, 25:97.
[17] Chakraborty, TK; Ghosh, S; Jayaprakash, S; *Curr Med Chem* **2002**,9:421.
[18] Gruner, SAW; Locardi, E; Lohof, E; Kessler, H; *Chem Rev* **2002**, 102:491.
[19] Heyns, K; Paulsen, H; *Chem Ber* **1955**, 88:188.

Papageorgiou[20] and Hirschmann[21] were pioneers in the use of CAA skeletons preparing peptidomimetics of somastostatin. Based on molecular dynamics, a tetrasubstituted xylose derivative **6** (Scheme 4) was used as scaffold resulting in a promising IC_{50} of 16 μM.



Scheme 4

Sofia *et al.*[22] reported the synthesis of encoded trifunctionalised saccharide scaffolds termed 'universal pharmacophore-mapping libraries'. Building blocks such as **7** and **8** which have a three-point attachment motif that consists of a carboxylic acid moiety, a free hydroxy group, and a protected amino group were used for the library construction. More recently, a 12000-compound library was achieved by using **9** as building block.

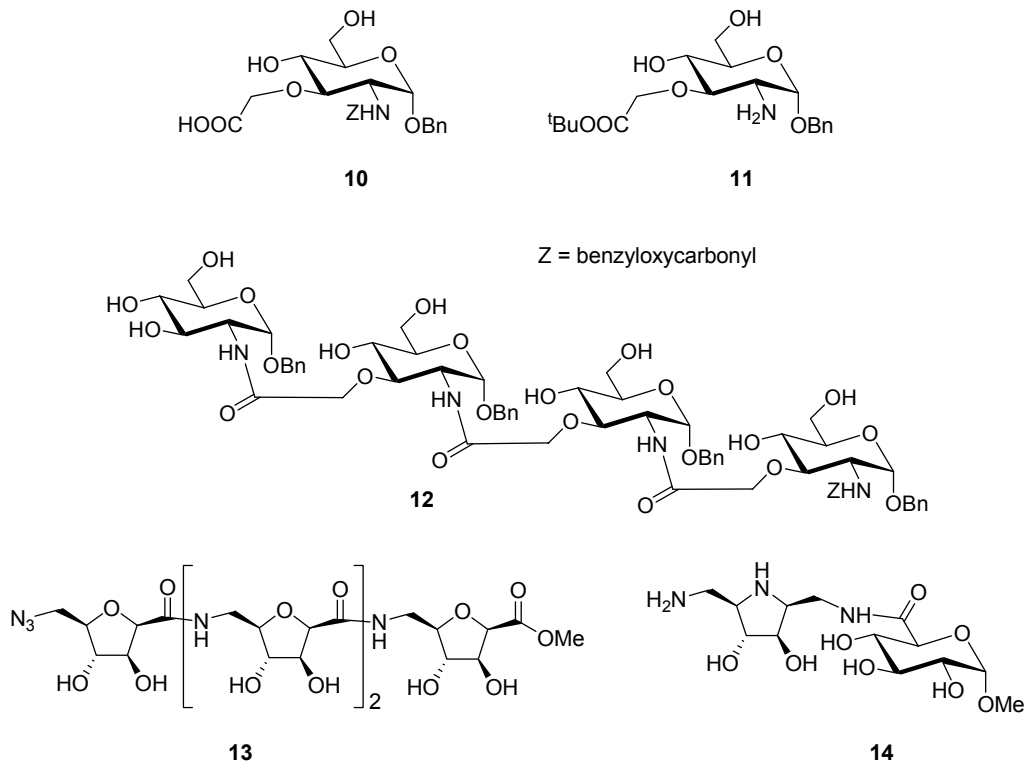
Kessler's group[23] published the design, synthesis and biological evaluation of β-D-mannose based non-peptidic mimetics of the vascular cell adhesion molecule-1 (VCAM-1) and of the mucosal addressin cell adhesion molecule-1 (MadCAM-1), which are the natural ligands of $\alpha_4\beta_1$ and $\alpha_4\beta_7$ integrin receptors. One of these derivatives showed inhibitory activity toward integrin $\alpha_4\beta_1$-mediated binding of Jurkat cell to VCAM-1.

[20] Papageorgiou, C; Haltiner, R; Bruns, C; Petcher, TJ; *Biorg Med Chem Lett* **1992**, 2:135.
[21] Hirschmann, R; Nicolaou, KC; Pietranico, S; Leahy, EM; Salvino, J; Arison, B; Cichy, MA; Spoors, PG; Shakespeare, WC; Sprengler, PA; Hamley, P; Smith III, AB; Reisine, T; Raynor, K; Maechler, L; Donaldson, C; Vale, W; Freidinger, RM; Cascieri, MR; Strader, CD; *J Am Chem Soc* **1993**, 115:12550.
[22] Sofia, MJ; Hunter, R; Chan, TY; Vaughan, A; Dulina, R; Wang, H; Gange, D; *J Org Chem* **1998**, 63:8387.
[23] Boer, J; Gottschling, D; Schuster, A; Holzmann, B; Kessler, H; *Angew Chem* **2001**,40(*20*):3870.

6-Guanidinohexoses, which can be viewed as conformationally restricted arginine mimetics, were predicted to fit in the recognition pocket of thrombin and proved to display thrombin inhibitory activity.[24]

CAA analogues have been successfully used as biopolymer building blocks to mimic oligo- and polysaccharide structures via amide bond linkages. First synthetic reports on amide-linked sugars stem from the mid-1970s. Fuchs and Lehmann[25] prepared the amino-D-*glycero*-1-D-*manno*- and amino-D-*glycero*-D-*gulo*- heptonic acids and pointed out their potential for polymerisation. With an interest in oligosaccharide mimetics for pharmaceutical applications, Wessel and co-workers[26] at Roche prepared the first amide-linked oligomers in a controlled fashion from suitably protected sugar amino acids to construct a tetramer in a [2+2] block synthesis. A standard peptide synthesis strategy in solution was applied in which **10** and **11** (Scheme 5), both equipped with an acetic acid linker and prepared in five steps from readily available glucosamine, were coupled using a mixed anhydride. The tetramer **12,** with four-atom linkers, was obtained after activation of a dimer with CDMT. Notably, no protection of hydroxyl groups was required employing this approach.

[24] Wessel, HP; Banner, D; Gubernator, K; Hilpert, K; Müller, K; Tschopp, T; *Angew Chem Int Ed Eng* **1997**, 36(*7*):751.
[25] Fuchs, E-F; Lehmann, J; *Chem Ber* **1975**, 108:2254.
[26] Wessel, HP; Mitchel, C; Lobato, CM; Schmid, G; *Angew Chem Int Ed Engl* **1995**, 34:2712.

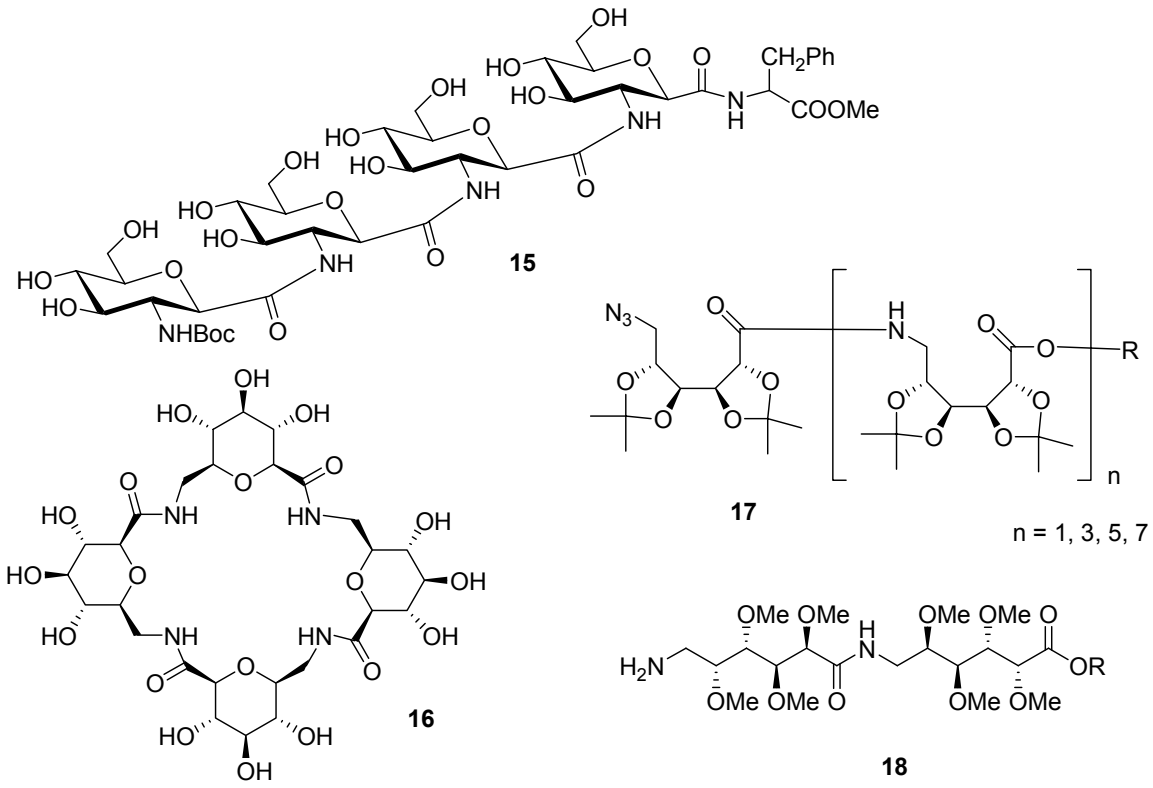


Scheme 5

The Fleet group has investigated various saccharide-peptide hybrids based on furanoid sugars; their tetramer **13**[27] can be seen as an analogue of (1→6)-linked hexofuranosides. An analogue of glycosidase inhibitors of the imino sugar family, the (1→6)-amide-linked pyrrolidine disaccharide mimetic **14**, was also reported.[28]

A mimetic of a (1→2)-linked glycoside was devised by Ichikawa's group[29] using a 3-amino-2,6-anhydro-3-deoxy-heptonic acid building block to afford tetramer **15** (Scheme 6). A two-atom linker replacing the interglycosidic oxygen also characterises this saccharide-peptide hybrid. A sulfated derivative of **15** blocked syncytium formation caused by HIV infection to CD4 cells at 50 μM concentration.

[27] Smith, MD; Long, DD, Marquess, DG, Claridge, TDW; Fleet, GWJ; *J Chem Soc Chem Commun* **1998**, 2039.
[28] McCort, I; Duréault, A; Depezay, J-C; *Tetrahedron Lett* **1998**, 39:4463.
[29] Suhara, Y; Hildreth, JEK; Ichikawa, Y; *Tetrahedron Lett* **1996**, 37:1575.



Scheme 6

Pioneered by the group of Kessler,[30] pyranoid sugar amino acid templates were described to represent turn mimetics and model peptides[31,17] including cyclic peptides.[32,33] Cyclic homooligomers of CAAs were also devised, first using glucosyl-uronic acid-methyl amine (Gum) as a monomeric unit thus creating three-atom linkers as in cyclic tetramer **16** (Scheme 6)[34]. Further examples of cyclodextrin analogues based on furanoid sugar amino acids with three-atom[35] or four-atom

[30] Graf von Roedern, E; Lohof, E; Hessler, G; Hoffmann, M; Kessler, H; *J Am Chem Soc* **1996**, 118:10156.
[31] Kessler, H; Gratias, R; Hessler, G; Gurrath, M; Müller, G; *Pure Appl Chem* **1996**, 68:1201.
[17] Chakraborty *et al. Curr Med Chem* **2006**, 25:97.
[32] van Well, RM; Overkleeft, HS; Overhand, M; Carstenen, EV; van der Marel, GA; van Boom, JH; *Tetrahedron Lett* **2000**, 41:9331
[33] Chakraborty, TK; Roy, S; Koley, D; Dutta, SK; Kunwar, AC; *J Org Chem* **2006**, 71:6240, and references cited therein.
[34] Locardi, E; Stöckle, M; Gruner, S; Kessler, H; *J Am Chem Soc* **2001**, 123:8189
[35] Chakraborty, TK; Srinivasu, P; Bikshapathy, E; Nagaray, R; Vairamani, M; Kumar, SK; Kunwar, AC; *J Org Chem* **2003**, 68:6257

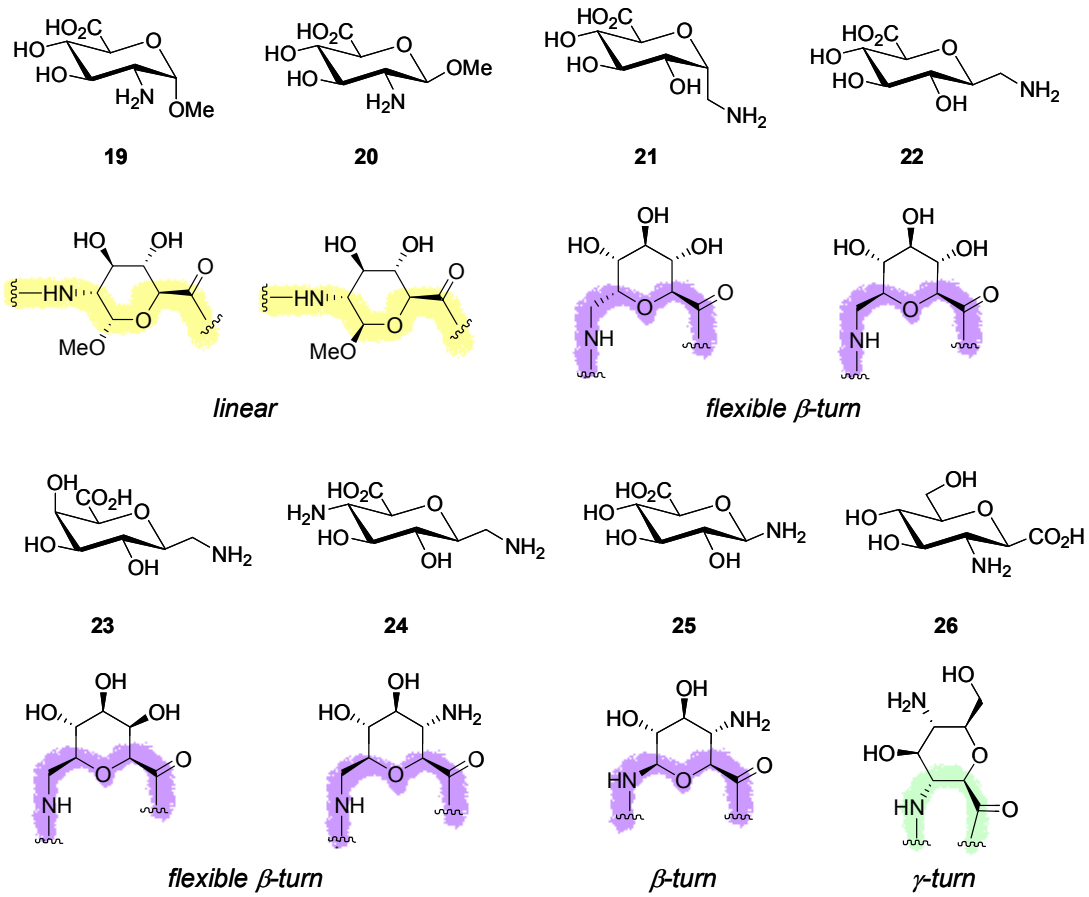
linkers[36] as well as oxetane-based cyclic homooligomers with three-atom linker[37] were described.

More recently, oligomers of open chain sugar amino acids were described such as galactonates **17** (Scheme 6) of which also cyclic analogues were prepared.[38,39] This is an extension of the work directed to polymers of amide-linked open chain sugars as hydroxylated analogues of polyamides (nylon) aiming at increased biodegradability.[40,41] Instead of starting from monomers, also amide-linked dimers such as **18** have been employed to arrive at well-defined, enantiomerically pure and stereoregular polyhydroxylated polymers.[42]

Saccharide-peptide hybrids have attracted particular attention because of their conformational properties. Oligomers of CAAs have a tendency to adopt a compact conformation, a type of oligomer termed "foldamer" by Gellman.[43] Kessler's group[30] had already demonstrated that sugar amino acids may induce specific peptide conformations and thus may allow mimicking helices or sheets.

Scheme 7 shows a CAA construction kit for pre-determined constrained local conformations in synthetic peptides containing series of CAAs. These units offer possibilities as mimetic structures for both amino acids and dipeptide isosters. CAAs **21**-**25** induce β-turns independent of the substitution pattern of the sugar ring while CAA **26** mimics a γ-turn.

[36] van Well, RM; Marinelli, L; Erkelens, K; van der Marel, GA; Lavecchia, A; Overkleeft, HS; van Boom, JH; Kessler, H; Overhand, M; *Eur J Org Chem* **2003**, 2303.
[37] Fleet, GWJ; Johnson, SW; Jones, JH; *J Peptide Sci* **2006**, 12:599.
[38] Hunter, DFA; Fleet, GWJ; *Tetrahedron Asymm* **2003**, 14:3831.
[39] Mayes, BA; Stetz, RJE; Watterson, MP; Edwards, AA; Ansell, CWG; Tranter, GE; Fleet, GWJ; *Tetrahedron Asymm* **2004**, 15:627.
[40] Mancera, M; Roffé, I; Rivas, M; Galbis, JA; *Carbohydr Res* **2003**, 338:1115.
[41] de Gracia Garcia-Martin, M; Hernandez, EB; Pérez, RR; Alla, A; Munoz-Guerra, S; Galbis, JA; *Macromolecules* **2004**, 37:5550.
[42] Romero Zaliz, CL; Varela, O; *Tetrahedron Asymm* **2005**, 16:97.
[43] Gellman, SH; *Acc Chem Res* **1998**, 31:173.
[30] Graf von Roedern *et al J Am Chem Soc* **1996**, 118:10156.



Scheme 7

Combined ^{1}H-NMR and circular dichroism (CD) spectroscopic evidence suggested that (1→5)-amide linked sialic acid oligomers in water adopt a defined secondary structure from the size of a tetramer on.[44] Similarly, a β(1→2)-amide-linked pyranoid sugar, a decamer of compound **15** (Scheme 4), formed a right-handed helix.[45] The acyl-protected furanoid oligomer **13** (Scheme 3) prepared by Fleet's group[46] was shown by calculation and ^{1}H-NMR spectroscopy in organic solvents to exhibit a β-turn secondary structure. The investigation of further analogues showed that most higher oligomers with a 2,5-*cis* stereochemistry across the tetrahydrofuran ring adopt

[44] Szabo, L; Smith, BL; McReynolds, KD; Parrill, AL; Morris, ER; Gervay, J; *J Org Chem* **1998**, 63:1074.
[45] Suhara, Y; Kurihara, M; Kittaka, A; Ichikawa, Y; *Tetrahedron* **2006**, 62:8207.
[46] Smith, MD; Claridge, TDW; Tranter, GE; Sansom, MSP; Fleet, GWJ; *J Chem Soc Chem Commun* **1998**, 2041.

a right-handed helix conformation composed of repeating β-turns and with NH_i-O_{i-2} hydrogen bonds.[47,48] A secondary structure was however not found in the D-galacto configured analogues.[49]

In the D-*manno* series, an unprotected octamer showed an ordered structure in solution based on circular dichroism,[50] but not the lower unprotected or protected homooligomers.[51] Initial X-ray and NMR evidence for a secondary structure was found in a new series of tetrafuran-based L-*ribo* configured γ-amino acids.[52] The conformational investigation of oxetane-based oligomers revealed that a β-amino acid hexamer formed a left-handed helix,[53] but δ-amino acid hexamers did not exhibit hydrogen bonded interactions but some regularity on steric grounds.[54]

CAA's are then a powerful class of compounds with promising biological importance at many levels. In particular, carbohydrate δ-amino acids have been investigated as valuable scaffolds and promising peptidomimetics (for example **5** and **7**, page 7 and 9). δ-CAA's became also important building blocks for oligomerisation and conformational properties were studied as reported for compounds such as **10**, **13** and **16** (page 11). For the introduction of δ-CAA's amine and acid functions various methodologies have been employed. For the synthesis of Gum, Kessler[55] introduced the CH_2NH_2 equivalent at the anomeric position as CH_2NO_2 via nucleophilic aldol reaction and further hydrogenation led to the desired amine. The 6-hydroxymethyl group was selectively oxidised by TEMPO to yield the desired δ-amino acid. van Boom and co-

[47] Smith, MD; Claridge, TDW; Sansom, MSP; Fleet, GWJ; *Org Biomol Chem* **2003**, 1:3647.
[48] Chakraborthy, TK; Srinivasu, P; Madhavendra, SS; Kumar, SK; Kunwar, AC; *Tetrahedron Lett* **2004**, 45:3573.
[49] Brittain, DEA; Waterson, MP; Claridge, TDW; Smith, MD; Fleet, GWJ; *J Chem Soc Perkin Trans* **2000**, 1:3655.
[50] Chakraborthy, TK; Jayaprakash, S; Srinivasu, P; Govardhana Chary, M; Diwan, PV; Nagaraj, R; Ravi Sankar, A; Kunwar, AC; *Tetrahedron Lett* **2000**, 41:8167.
[51] Smith, MD; Long, DD; Marquess, DG; Claridge, TDW; Fleet, GWJ; *Tetrahedron Lett* **1999**, 40:2191.
[52] Edwards, AA; Sanjayan, GJ; Hachisu, S; Tranter, GE; Fleet, GWJ; *Tetrahedron* **2006**, 62:7718.
[53] Claridge, TDW; Goodman, JM; Moreno, A; Angus, D; Barker, SF; Taillefumier, C; Watterson, MP; Fleet, GWJ; *Tetrahedron Lett* **2001**, 42:4251.
[54] Johnson, SW; Jenkinson, SF; Pérez-Victoria, I; Edwards, AA; Claridge, TDW; Tranter, GE; Fleet, GWJ; Jones, JH; *J Peptide Sci* **2005**, 11:517.
[55] Graf von Roedern, E; Kessler, H; *Angew Chem Int Ed Engl* **1994**, 33:667.

workers[56] reported the synthesis of partially deoxygenated δ-CAA's from fully acetylated D-glucal, in which the amine group was introduced via regioselective substitution of the primary alcohol with phthalimide under Mitsunobu conditions and the carboxylic group via hydrolysis of a cyanide. Moreover this type of compounds, when incorporated into polypeptide sequences, showed activity against the protein farnesyl tranferase and estabilised β-hairpin struture present in the native form.

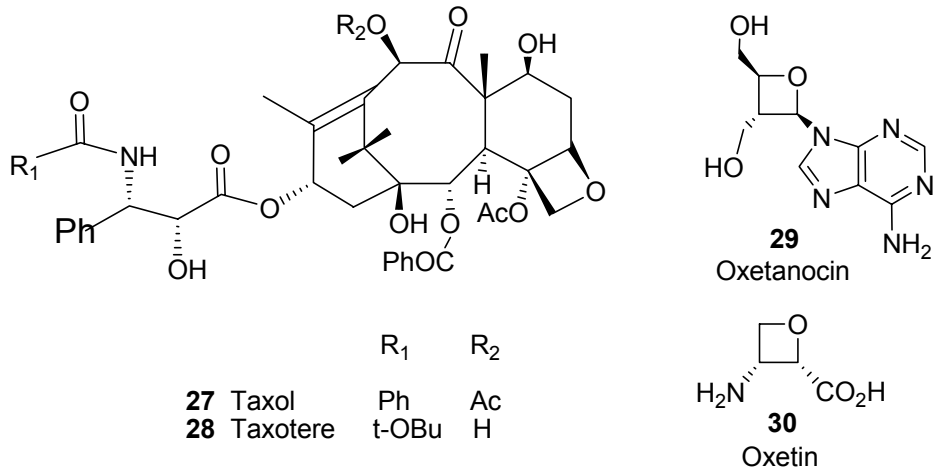
While there is ample precedence for pyranose and furanose CAAs, fewer reports were published on the synthesis and derivatisation of related oxetane amino acids and in particular of oxetane δ-amino acids,[57,58,59] which are the subject of the present work.

1.2 Oxetanes

– Source of Rigidity and Directed Exit Vectors

An oxetane is a rigid four-membered ring containing a polar oxygen atom. This unit was recently investigated at Roche[60] in order to study the lipophilicity and metabolic liability of this scaffold. There are few synthetic methodologies of relevance to their incorporation and subsequent elaboration in compounds of pharmacological interest. Taxol **27**, oxetanocin **29** and oxetin **30** (Scheme 8) are oxetane containing bioactive molecules, however, the intrinsic chemical and pharmacological properties of the oxetanes are far from clear. Meanwhile the world drug index registered 217 structures containing an oxetane ring, among these, ca. 80% are taxol related and only two reached the marketing stage.

[56] Aguilera, B; Siegal, G; Overkleeft, HS; Meeuwenoord, NJ; Rutjes, FP; van Hest, JC; Schoemaker, HE; van der Marel,GA; van Boom, JH; Overhand, M; *Eur J Org Chem* **2001**, 1541.
[57] Johnson, SW; Jenkinson (née Barker), SF; Angus, D; Jones, JH; Watkin, DJ; Fleet, GWJ; *Tetrahedron Asymm* **2004**, 15:3263.
[58] Lucas, SD; Iding, H; Alker, A; Wessel, HP; Rauter, AP; *J Carbohydr Chem* **2006**, *25*:187.
[59] Lucas, SD ; Rauter, AP; Wessel, HP; *J Carbohydr Chem* **2008**, 27(*3*):172.
[60] Wuitschik, G; Rogers-Evans, M; Müller, K; Fisher, H; Wagner, B; Schuler, F; Polonchuk, L; Carreira, E *Angew Chem Int Ed* **2006**, 45:7736.



Scheme 8

Taxol **27** was isolated from the bark of *Taxus brevifolia* in the late 1960s,[61] and its semisynthetic congener, Taxotere[62] **28** has become the drug of choice for the treatment of ovarian and breast cancer. Numerous structure-activity studies combining synthesis and bioassays have been performed for Taxol and its microtubule target, and it was shown that the oxetane ring is essential for biological activity. The four-membered ring may operate to rigidify the Taxol core and thereby enforce a favourable conformation of the side chains. On the other hand, the oxygen may exert an advantageous electrostatic force by participating in a hydrogen bond or an energy-lowering dipole-dipole interaction with the tubulin protein.[63]

Oxetanocin-A **29** is a naturally occurring oxetane adenine nucleoside, which was isolated from the fermentation broth of *Bacillus megaterium* in 1986.[64,65] This compound was found to exhibit a broad spectrum of antiviral activity, including herpes simplex virus 1 and 2 (HSV-1, HSV-2), varicella zoster virus (VZV), human cytomegalovirus (HCMV), and human immunodeficiency virus (HIV).[66] Meanwhile, replacement of adenine for guanine (oxetanocin-G) or thymine (oxetanocin-T) also led to potent antiviral agents.[67,68] These promising results prompted organic chemists

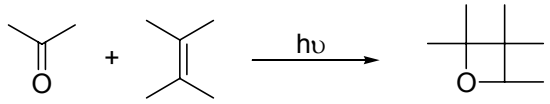
[61] Wani, MC; Taylor, HL; Wall, ME; Coggon, P; McPhail, AT; *J Am Chem Soc* **1971**, 93:2325.
[62] Bissery, M-C; Guénard, D; Guéritte-Voegelein, F; Lavelle, F; *Cancer Res* **1991**, 51:4845.
[63] Minmin, W; Cornett, B; Nettles, J; Liotta, DC; Snyder, JP; *J Org Chem* **2000**, 65:1059.
[64] Shimada, N; Hasegawa, S; Harada, T; Tomisawa, T; Fujii, A; Takita, T; *J Antibiot* **1986**, 39:1623.
[65] Nakamura, H; Hasegawa, S; Shimada, N; Fujii, A; Takita, T; Iitaka, Y; *J Antibiot* **1986**, 39:1636.
[66] Hoshino, H; Shimizu, N; Shimada, N; Takita, T; Takeuchi, T; *J Antibiot* **1987**, 40:1077.
[67] Nagahata, T; Kitagawa, M; Matsubara, K; *Antimicrob Agents Chemother* **1994**, 38:707.

to explore synthetic approaches to analogues of oxetanocin. Recently Rustullet *et al.*[69] synthesised a cyclobutane analog of oxetanocin-A using a stereoselective route based on a [2+2] photocycloaddition to a chiral furanone. However, in preliminary tests this compound was inactive against HIV.

Oxetin **30** is an oxetane derived β-amino acid and was isolated in 1984 from a fermentation broth of *Streptomyces sp*.[70] This was the first report of a natural product containing an oxetane ring, which inhibited *Bacillus subtilis* and *Pyricularia oryzae* in minimal media, and exhibited herbicidal effect.

Because enantiomers can display different pharmacological and toxicological properties, the synthesis of enantiomerically pure compounds is required to afford bioactive oxetane derivatives. For instance, only a few approaches were devised to provide optically active oxetanocins, including optical resolution and stereoselective synthesis, and the latter usually involves a large number of steps or presents moderate enantioselectivity, resulting in low overall yields. [71]

One century ago, back to 1909, Paternò and Chieffi[72] obtained oxetanes from the photocycloaddition of ketones to olefins (Scheme 9), but the potential of this reaction was only recognized after the work of Büchi, already in the 1950s, and the reaction was then coined Paternò-Büchi reaction.[73]



Scheme 9

Due to the vast amount of work in this field, several reviews were published since then. This methodology was applied in the synthesis of oxetanocin-A (Scheme 9),[74]

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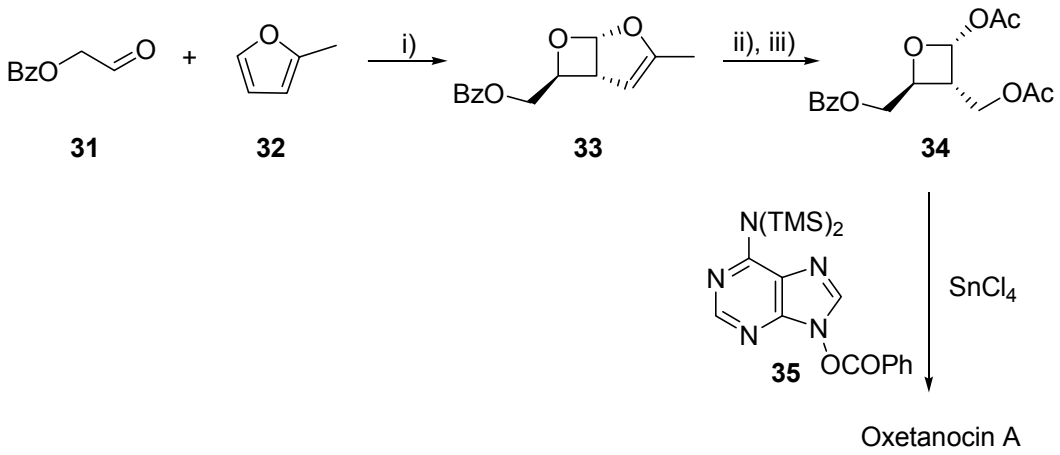
[68] Alder, J; Mitten, M; Norbeck, D; March, K; Kern, ER; Clement, J; *Antiviral Res* **1994**, 23:93.
[69] Rustullet, A; Alibés, R; March, P; Figueredo, M; Font, J; *Org Lett* **2007**, 9(*15*):2877.
[70] Ömura, S; Murata, M; Imamura, N; Iwai, Y; Tanaka, H; *J Antibiot* **1984**, 37:1324.
[71] Auria, MD; Emanuele, L; Racioppi, R; Romaniello, G; *Curr Org Chem* **2003**, 7:1443 and references therein.
[72] Paternò, E; Chieffi, G; *Gazz Chim Ital* **1909**, 39:431.
[73] Büchi, G; Inman, CG; Lipinsky, ES; *J Am Chem Soc* **1954**, 76:4327.
[74] Hambalek, R; Just, G; *Tetrahedron Lett* **1990**, 31(*38*):5445.

the photoaddition of 2-methylfuran to benzoyloxyacetaldehyde in benzene gave **33** in 25-30% yield (45-50% yield based on recovered starting material).



i) *hν*, benzene, ii) a. O_3, DCM, b. Me_2S, c. $NaBH_4$/alumina, iii) Ac_2O, py, DMAP.

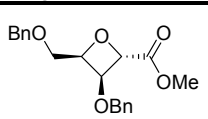
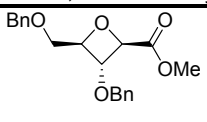
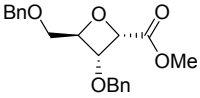
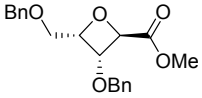
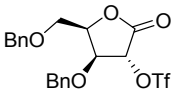
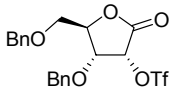
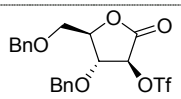
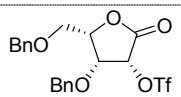
Scheme 10

Pioneered by Fleet group,[75] the ring contraction of trifluoromethanesulfonates of α-hydroxy-1,4-lactones to oxetane carboxylic esters could be accomplished by treatment with K_2CO_3 in methanol. Using 2-*O*-triflates of 3,5-di-*O*-benzyl-D-xylono-, D-ribono-, D-arabinono- and D-lyxono-1,4-lactones, ring contraction was afforded in good yields, although, in some cases a mixture of oxetane "anomers" was obtained.

D-Xylono-lactone derivative **36** (Table 1) gave the D-*lyxo*-oxetane **40**, and the contraction of the lactone **36** occurred with complete inversion of configuration at C-2. By contrast, the triflate of L-lyxono-lactone **39** gave exclusively the L-*lyxo*-oxetane **43**. Thus ring contraction occurred with retention of configuration at C-2 of the lactone. Retention of configuration was also found in the major product **39** resulting from D-ribono-lactone triflate **37**, although the arabino isomer **42** was also isolated in low yield. Ring contraction of the D-arabinono-lactone **38** gave the *ribo*-isomer **41** as major product indicating predominant inversion of configuration at C-2, and only a trace of the minor epimer **42** was formed.

[75] Witty, DR; Fleet, GWJ; Vogt, K; Wilson, FX; Wang, Y; Storer, R; Myers, PL; Wallish, CJ; *Tetrahedron Lett* **1990**, 31(33):4787.

Table 1. Ring contraction of pento-1,4-lactones by treatment with K_2CO_3/MeOH.

Starting \ Product	 **40** D-lyxo	 **41** D-ribo	 **42** D-arabino	 **43** L-lyxo
 **36** D-xylono	79%			
 **37** D-ribono		73%	~9%	
 **38** D-arabinono		70%	trace	
 **39** L-lyxono				~80%

The major product of each ring contraction had a *trans*-relationship between the C-2 and C-3 substituents of the oxetane. No incorporation of deuterium at C-2 of the methyl oxetane-2-carboxylates was observed when the oxetane methyl esters were stirred with potassium carbonate in d_4-methanol. This result indicated that the stereochemical course of the reaction is not a consequence of equilibration of the product oxetane esters.

As reported by the authors, it is apparent that open chain 4-hydroxy-2-*O*-trifluoromethanesulphonate esters are intermediates; a plausible rationalisation of the stereochemistry of the ring contraction is that the ring closure is an S_N2 displacement of triflate during which considerably greater unfavourable interactions develop when the substituents at C-2 and C-3 of the incipient oxetane are *cis* rather than *trans* to each other.

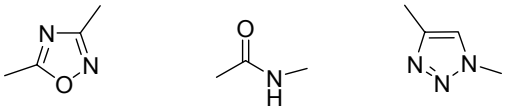
Based on this ring contraction reaction, the Fleet group investigated the synthesis of several oxetane β- and δ-amino acids aiming at oxetin analogs or at their use as scaffolds for conformational studies as potential peptidomimetics.[76,77,78,57]

From our point of view, this methodology is the most efficient for the synthesis of oxetane δ-amino acid scaffolds, with the advantage of generating the carboxylic function on the ring contraction step in reasonable to good yields.

1.3 1,2,4-Oxadiazoles and 1,2,3-Triazoles – Promising Units in Medicinal Chemistry Approaches

The peptide linkage is abundant in Nature and as such, the incorporation of groups which occupy the same physical space as a peptide bond in potential drug candidates is the aim of many laboratories. The successful replacement of the peptide linkage should improve drug candidates by giving them better stability, and absorption.[79]

1,2,4-Oxadiazoles (Scheme 11) and 1,2,3-triazoles are five-membered heterocyclic compounds which contain 1 oxygen atom and 2 nitrogens, or 3 nitrogen atoms, respectively. Peptide linkages are planar due to the conjugation of the nitrogen electron lone pair, resulting in limited rotation around the peptide bond. 1,2,4-Oxadiazoles and 1,2,3-triazoles, being planar cyclic rings, occupy the same space as a peptide linkage, leading to peptide isosteres.



1,2,4-Oxadiazole Peptide bond 1,2,3-Triazole

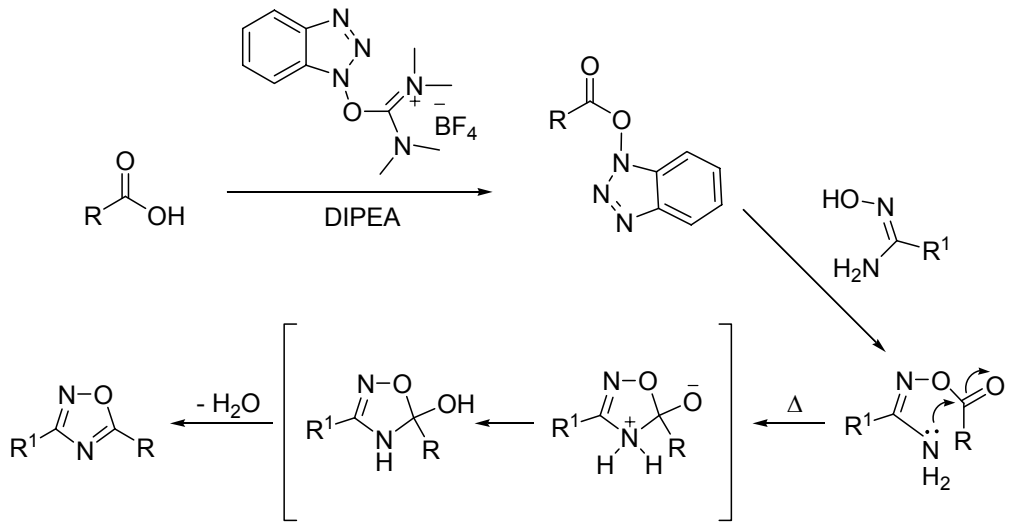
Scheme 11

[76] Barker, SF; Angus, D; Taillefumier, C; Probert, MR; Watkin, DJ; Watterson, MP; Claridge, TDW; Hungerford, NL; Fleet, GWJ. Tetrahedron Lett. **2001**, *42*, 4247.
[77] Jenkinson (née Barker), SF; Harris, T; Fleet, GWJ. Tetrahedron Asymm. **2004**, *15*, 2667.
[78] Johnson, SW; Jenkinson (née Barker), SF; Angus, D; Jones, JH; Fleet, GWJ; Taillefumier, C. Tetrahedron Asymm. **2004**, *15*, 2681.
[57] Johnson, SW *et al. Tetrahedron Asymm* **2004**, 15:3263.
[79] Ashraf, B; Alexandratos, J; Lin, Y; Elder, J H; Olson, AJ; Wlodawer, A; Goodsell, D.S; Wong, C; *ChemBioChem* **2005**, 6*:*1167.

It has been shown that 1,2,4-oxadiazoles possess a variety ofcentral nervous system (CNS) related activities. This class of heterocycles is present in muscarinic agonists,[80] serotoninergic (5-HT3) antagonists[81] and in dopamine (D4) ligands.[82] Some compounds have also shown affinities for dopamine, serotonin and norepinephrine transporters.[83] The 1,2,4-oxadiazole ring system has also been used as an urea bioisoster in β3 adrenergic receptor agonists.[84] Some articles have also reported the use of small heterocycles, among which 1,2,4-oxadiazoles, in the design of dipeptidomimetics.[85]

In a preferred approach, the synthesis of 1,2,4-oxadiazoles involves first the *O*-acylation step of an activated carboxylic acid derivative by an amidoxime, followed by cyclodehydration. Classically, the activated acid derivatives are esters, acid chlorides, symmetrical or unsymmetrical anhydrides and orthoesters. A synthesis on solid support using esters has also been published. More recently, the use of carbodiimides such as EDC, DCC and DIC for the in situ activation of carboxylic acids has been reported; however, carbodiimides are not so easy to handle and are susceptible to deactivation.[86] Poulain *et al.*[83] developed the use of 2-(1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU) for the synthesis of 1,2,4-oxadiazoles. Uronium salts are known to be easy to handle, to have quite fast coupling kinetics and to display hardly any losses of configuration during coupling. They are also known to enable efficient coupling of sterically hindered acids and to be soluble in DMF. Thus, TBTU advantageously activates the carboxylic acid for the *O*-acylation step (Scheme 12).

[80] Orlek, BS; Blaney, FE; Brown, F; Clark, MSG; Hadley, MS; Hatcher, J; Riley, GJ; Rosenberg, HE; Wadsorth, HJ; Wyman, P; *J Med Chem* **1991**, 34:2726.
[81] Swain, CJ; Baker, R; Kneen, C; Moseley, J; Saunders, J; Seward, EM; Stevenson, G; Beer, M; Stanton, J; Watling, K; *J Med Chem* **1991**, 34:140.
[82] Williams, JP; Lavrador, K; *Comb Chem High Throughput Screen* **2000**, 3:43.
[83] Carroll, FI; Gray, JL; Abraham, P; Kuzemko, MA; Lewin, AH; Boja, JW; Kuhar, MJ; *J Med Chem* **1993**, 36:2886.
[84] Mathvink, RJ; Barritta, AM; Candelore, MR; Cascieri, MA; Deng, L; Tota, L; Strader, CD; Wyvratt, MJ; Fisher, MH; Weber, AE; *Bioorg Med Chem Lett* **1999**, 9:1869.
[85] Borg, S; Vollinga, RC; Labarre, M; Payza, K; Terenius, L; Luthman, K; *J Med Chem* **1999**, 42:4331.
[86] Poulain, RF; Tartar, AL; Déprez, BP; *Tetrahedron Letters* **2001**, 42:1495 and references cited therein.



General mechanism for oxadiazole formation starting from an activated carboxylic acid and an amidoxime.

Scheme12

1,2,3-Triazoles are particularly promising as amide bond isosteres, given their favourable pharmacophoric properties and facile synthesis from readily available azide- and alkyne-functionalised derivatives of chiral amino acids. Recently, reports have surfaced describing the incorporation of 1,2,3-triazoles into peptide nanotubes, β-turn mimics, protease inhibitors, cyclopeptide analogues and peptide chain analogues.[87]

1,2,3-Triazoles act as rigid linking units that place the carbon atoms, attached to the 1,4-positions of the 1,2,3-triazole ring, at a distance of 5.0 Å (C-α distance in amides: 3.8 Å). In contrast to amides, triazoles cannot be cleaved hydrolytically or otherwise, and unlike benzene derivatives and related aromatic heterocycles, they are almost impossible to oxidize or reduce. They possess a large dipole moment of ~5 Debye (by *ab initio* calculation, RHF/6–311G**; cf. *N*-methyl acetamide: 3.7 – 4.0 Debye), and nitrogen atoms two and three function as weak hydrogen bond acceptors.[88]

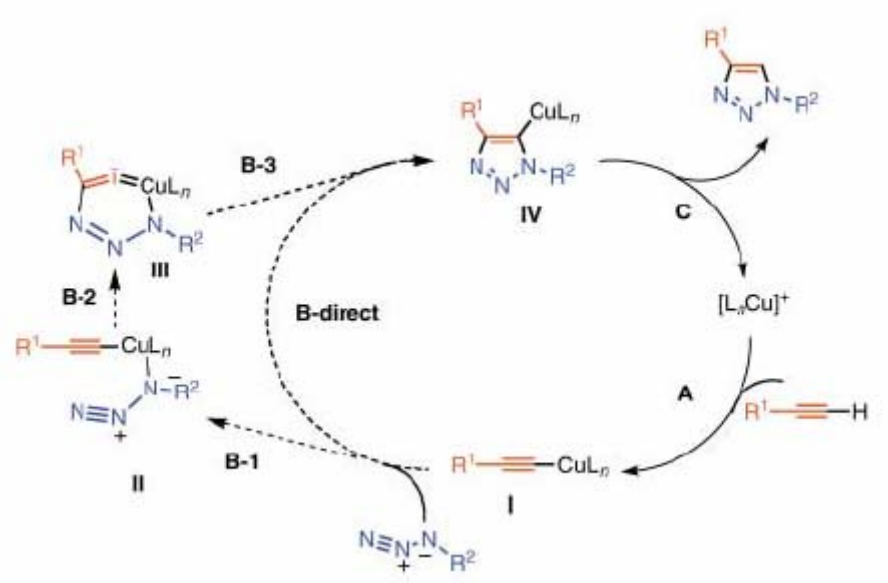
[87] Bock, VD; Speijer, D; Hiemstra, H; van Maarseveen, JH; *Org Biomol Chem* **2007**, 5:971 and references therein.
[88] Kolb, HC, Sharpless, KB; DDT **2003**, 8(24): 1128.

The research on 1,2,3-triazoles has intensified after the optimisation of Huisgen's regioselective Cu(I) catalysed 1,3-dipolar cycloaddition of alkynes and azides in 2002.[89] The Sharpless group discovered the dramatic rate acceleration of azide-alkyne coupling event under Cu(I) catalysis, and the beneficial effects of water. This connection process led to an almost 'perfect' reaction, giving birth to the first example of a click reaction.

Click Reaction[85]
Wide scope reaction, giving consistently high yields with a variety of starting materials. It must be easy to perform, be insensitive to oxygen or water, and use only readly available reagents.
Reaction work-up and product isolation must be simple, without requiring chromatographic purification.

The authors report that a number of copper (I) sources can be used, however, the catalyst is better prepared *in situ* by reduction of Cu(II) salts (such as $CuSO_4 \cdot 5H_2O$), which are less costly and often purer than Cu(I) salts. As reducing agent, ascorbic acid and/or sodium ascorbate proved to be excellent.

The mechanistic proposal for the catalytic cycle is described in Scheme 13. It begins with formation of the copper (I) acetylide **I** followed by a stepwise, annealing sequence (B-1→B-2→B-3), which proceeds via the six-membered copper containing intermediate **III**.



Mecanistic proposal for Cu(I) catalysed Huisgen's 1,3-dipolar cycloaddition of alkynes and azides.[86]

Scheme 13

[89] Rostovtsev, VV; Green, LG; Fokin, VV; Sharpless, KB; Angew Chem Int Ed **2002**, 41(*14*):2596.

In the work described here, the first example of oxetane amino acid libraries is presented, based on the introduction of 1,2,4-oxadiazoles via activation of carboxyclic acid with an uronium salt and coupling with different amidoximes, followed by cyclodehydration. A small library of 1,2,3-triazoles was also performed by reaction of different alkynes with an oxetane δ-azido ester.

1.4 Biocatalysis

The tremendous potential of enzymes as catalysts in organic transformations is nowadays widely recognised. They became practical alternatives to "traditional" organic synthesis and convenient solutions to certain intractable synthetic problems. More than 3000 enzymes have been identified so far, and this number is expected to increase with the ongoing genomic and proteomic research, being estimated that there are about 25000 enzymes in Nature.[90,91]

Enzymes have been classified into six categories according to the type of reaction they can catalyse (Table 1).The presented utility indicates the percentage of research performed with enzymes for a given class for the 1987-1996 period, the hydrolases being the most commonly used class of enzymes.[88]

Table 2. Classification of enzymes.

Enzyme class	Reaction type	Utility
Oxidoreductases	Oxidation-reduction: oxygenation of C-H, C-C, C=C bonds, or overall removal or addition of hydrogen atom equivalents	25 %
Transferases	Transfer of groups: ketonic, formyl, acyl, sugar, phosphoryl or methyl	< 5 %
Hydrolases	Hydrolysis of esters, amides, lactones, lactams, epoxides, nitriles, anhydrides, glycosides	65 %
Lyases	Addition-elimination of small molecules on C=C, C=N, C=O bonds	< 5 %
Isomerases	Isomerization such as racemization, epimerization	< 1 %
Ligases	Formation-cleavage of C-O, C-S, C-N, C-C bonds with concomitant triphosphate cleavage	< 1 %

[90] Koeller, KM; Wong, C-H; Nature **2001**, 409:232.
[91] Faber, K; Biotransformations in Organic Chemistry **1997**, 3rd Ed., Springer-Verlag, Berlin, Germany.

Typically, the rates of enzyme-mediated processes are accelerated compared to those of non-enzymatic reactions by a factor of 10^8 -10^{10}. Moreover, enzymes are environmentally acceptable and act under mild conditions - typically in a range of pH = 5-8 and within temperatures of 20-40 °C. They are compatible with each other allowing multi-enzyme systems and some of them exhibit an unexpectedly high substrate tolerance accepting a large variety of unnatural substances, and display chemo-, regio- and enantioselectivity.

Enzymes are provided by Nature in only one enantiomeric form, and it is impossible to invert the chiral induction of a given enzymatic reaction. This limitation has encouraged genomic research focusing on non-natural chiral enzymes. The control of an enzymatic reaction requires the use of narrow operation conditions, so that if the reaction proceeds slowly under certain pH and temperature ranges. The scope for changes is very small.

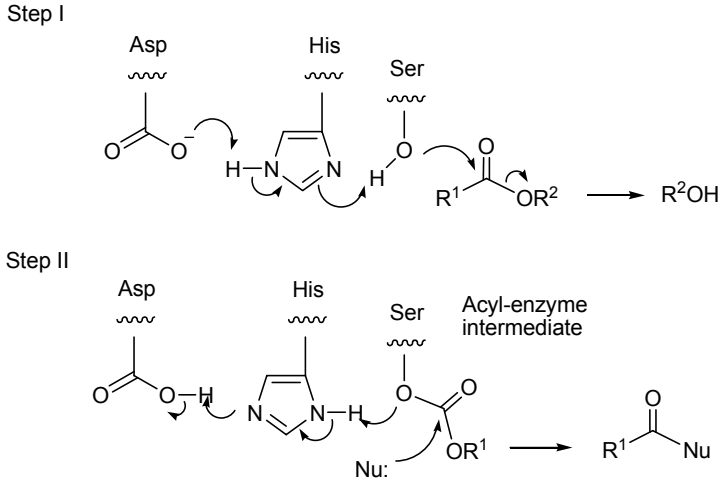
Enzymes show the highest catalytic power in their natural aqueous environment, which becomes problematic for reactions with substrates not soluble in water. In addition, water frequently gives rise to side reactions and degrades common organic reagents. The thermodynamic equilibria of many processes are also unfavourable in water, and product recovery is sometimes difficult from this medium.[92]

The technological utility of enzymes can be greatly enhanced by using them in organic solvents rather than in water. Studies over the past years revealed that this change in solvent is feasible. In general, the catalytic activity displayed by enzymes in neat organic solvents is much lower than in aqueous media. The addition of small quantities of water to enzyme suspensions in anhydrous solvents may increase the enzymatic activity by several orders of magnitude. This activating effect of water can be mimicked to a certain extent by other solvents capable of forming multiple hydrogen bonds, such as glycerol and ethylene glycol.[89]

[92] Klibanov, AM; *Nature* **2001**, 409:241.

The most used hydrolases in synthetic organic chemistry are the lipases,[93] and in Nature they are responsible for the hydrolysis of triglycerides into fatty acids and glycerol. A characteristic feature of triacylglycerol lipases is their activation over the critical micelle concentration (CMC) of the substrate in contrast to the Michaelis-Menten behaviour of esterases. This is due to a mobile lid covering the catalytic site in the absence of an aqueous/lipid interface. When the enzyme contacts the interface of a biphasic system, a conformational change seems to occur in which the lid moves to uncover the active site, and the activity is maximised when the CMC of the substrate is reached. However, when the influence of substrate concentration on hydrolytic activity of lipase L2 from *Candida Antarctica* was studied, this enzyme did not display any interfacial activation and behaved more like an esterase. Although its residues follow the sequential order characteristic of lipases, the structure of *Candida Antarctica* lipase L2 seems to be in an "open" conformation. [94,95,96]

The X-ray structure of this enzyme shows the existence of a Ser-His-Asp catalytic triad suggesting the same reaction mechanism as other lipases, involving the formation of an acyl-enzyme intermediate, which reacts then with nucleophiles such as water, alcohols or amines (Scheme 14).



General reaction mechanism of lipases.

Scheme 14

[93] Reetz, MT; *Curr Opin Chem Biol* **2002**, 6:145.
[94] Uppenberg, J; Hansen, MT; Patkar, S; Jones, TA; *Structure* **1994**, 2:293.
[95] Martinelle, M; Holmquist, M; Hult, K;. *Biochim Biophys Acta* **1995**, 1258:272.
[96] Martinelle, M; Hult, K; *Biochim Biophys Acta* **1995**, 1251:191.

In the present work, different chemical treatments of an oxetane derived methyl ester attempting its hydrolysis were found too harsh leading to decomposition. The ester was hydrolyzed by means of pig liver esterase (PLE) in aqueous media, although isolation of the desired product was difficult leading to poor yields. In contrast, the use of Lipase L2 from *Candida antarctica* in micro-aqueous systems – organic solvents containing small water contents– allowed the efficient hydrolysis and isolation of the desired carboxylic acid.

1.5 Physicochemical and Metabolic Properties

Modern drug-discovery chemistry is based on a multidimensional optimisation (MDO) approach, in which the optimisation of physicochemical properties, aspects of ADME, and safety of a lead compound have to be considered. This process benefits from the empirical knowledge of individual companies together with their databases available. With the establishment of high-throughput analytical methodologies, the amount of physicochemical data is growing rapidly, as hundreds of compounds can be measured each day. The availability of large datasets covering a sufficiently broad structural diversity increases the chances for the development of reasonably successful prediction tools. Both databases and chemoinformatics aim at enhancing the capacity of medicinal chemists to design compounds with desired physicochemical and pharmacological properties.[97]

The current work is the first report on libraries that use oxetane δ-amino acids as scaffolds. Hence it seemed crucial to investigate some of the physicochemical and phamacological properties of these molecules. It follows an overview of the studied properties that allow setting a profile for this new class of compounds.

[97] Morgenthaler, M; Schweizer, E; Hoffmann-Röder, A; Benini, F; Martin, RE; Jaeschke, G; Wagner, B; Fischer, H; Bendels, S; Zimmerli, D; Scheider, J; Diederich, F; Kansy, M; Müller, K; *Chem Med Chem* **2007**, 2:1100.

1.5.1 "The Rule of Five"

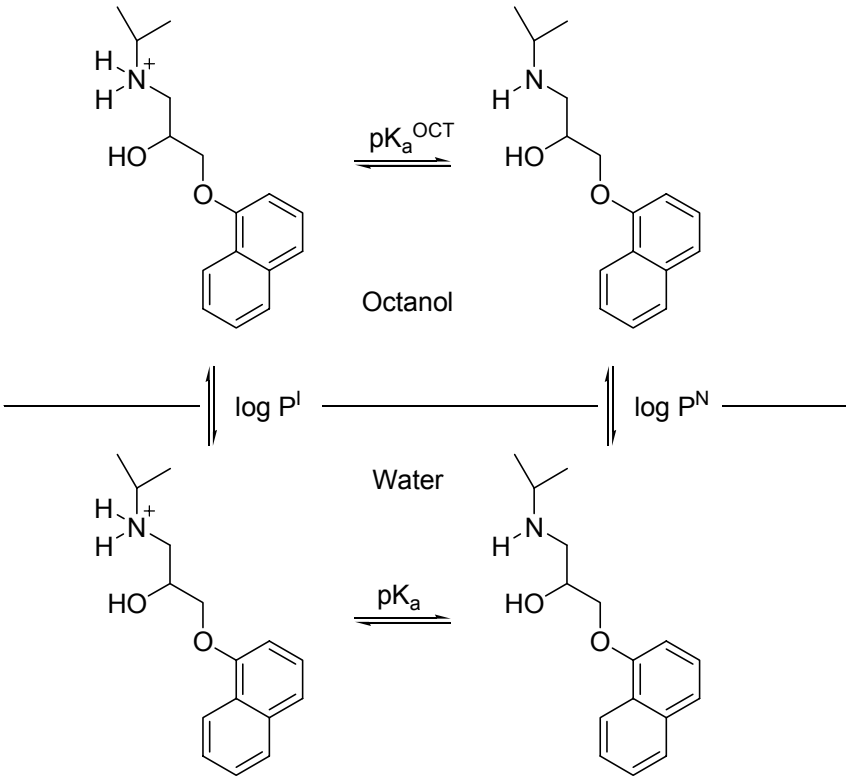
Christopher A. Lipinski and his colleagues[98,99] at Pfizer were the firsts to point out that drugs typically have physicochemical and structural parameters within certain ranges. The revolutionary rule-of-five predicts that poor absorption or permeation is more likely when there are more than 5 hydrogen-bond donors, 10 hydrogen-bond acceptors, the molecular weight is greater than 500 and the calculated log P (clogP) is greater than 5.

The original rule-of-five deals with orally active compounds and defines four simple physicochemical parameter ranges associated with 90% of orally active drugs that have achieved phase II clinical status. Many clinical candidates failed during development, and the reasons are now much better understood. The rule-of-five is now a widely used filter for drug-like properties, and references to its original publication in 1997 have exceeded 1000 citations.

1.5.2 Octanol/Water Partition Coefficient

The octanol/water partition coefficient (P) is the ratio of a compound's concentration in octanol to its concentration in water when the phases are at equilibrium (Scheme 15). Since partition coefficient values can range over many orders of magnitude, they are normally expressed in logarithmic form (log P).[100]

[98] Lipinski, CA; Lombardo, F; Dominy, BW; Feeney, P; *J Adv Drug Deliv Rev* **1997**, 23:3.
[99] Lipinski, CA; *Drug Discov Today Technol* **2004**, 1:337.
[100] Machatha, SG; Yalkowsky, SH; *Int J Pharm* **2005**, 294:185.



Scheme 15. Octanol/ water tetrad equilibria; log P^I and log P^N are used to distinguish partition coefficients of neutral species from ionized species.[101]

In the presence of ionizable molecules the parameter used is the distribution coefficient D (Eq. 1) that refers to all the present species depending on the pH, otherwise, D and P are the same.

$$\log P = \log D^{pH} + \log(1+10^{(pKa-pH)}) \qquad \textbf{Eq. 1}$$

LogP values or logD at a given pH (usually pH 7.4) usually express lipophilicity of drug molecules and have been widely used as parameters to estimate numerous properties such as membrane transport and water solubility. Large logP databases are available emerging from the importance of this parameter.[1] For instance non lipophilic drugs are not easily absorbed by passive transport. On the other hand drugs with high lipophilicity may be easily absorbed, but also get trapped inside

[101] Avdeef, A; *Curr Top Med Chem* **2001**, 1:277.
[1] Avdeef, A; *Absorption and Drug Development - Solubility, Permeability and Carge State* **2003**.

membranes or exhibit poor aqueous solubility requiring a complex formulation. Later on, drug metabolites need to be quite hydrophilic to be excreted effectively. LogP/D values therefore provide important clues about a molecule's likely interaction with body membranes.

For experimental measurements of logD, the compound of interest is distributed between water and octanol. The distribution coefficient is then calculated from the difference in concentration in the aqueous phase before and after partitioning and the ratio of the two phases. In the present work logD values were measured using a HT assay, which is derived from the conventional 'shake flask' method, in order to increase speed and throughput of the logD measurement using a commercial automated HPLC system from Sirius Analytical Instruments Ltd (GLpKa). With this technology 100 to 200 compounds were measured in one run.

Computational tools to predict logP were created and programs such as clogP® (bioByte Corp.), ACD/logPdb® (Advanced Chemistry Development Inc.) and KowWin® (Syracuse Research Corporation) have been widely used.

These programs are described as substructure approaches where the final log P is determined by summing the single-atom or fragment contributions and were designed to determine the partition coefficient of the non-ionized form of a compound. Machatha *et al.*[97] concluded that ClogP® is a more accurate predictor of the octanol/water partition coefficient than ACD/logPdb® and KowWin® when they compared these tools using an independent experimental data set. Nevertheless, all three programs are similar in many respects, and they all have user friendly interfaces.

1.5.3 pKa

The acid dissociation constant (pKa) describes the extent of ionisation in dependence of the hydroxonium ion concentration:

$BH^+ \leftrightarrows B + H^+ \quad K_a = \frac{[B][H^+]}{[BH^+]}$ (B: base) **Eq. 2**

$HA \leftrightarrows A^- + H^+ \quad K_a = \frac{[A^-][H^+]}{[HA]}$ (A: acid) **Eq. 3**

Some parameters such as lipophilicity, permeability and aqueous solubility, are pKa-dependent and are important in the understanding of drug absorption and transport processes. For example, the neutral form of an ionisable compound is less water soluble, more lipophilic, and possesses higher membrane permeability than the ionized form. Experimental knowledge of pKa values provides the precise information about the compound charge across the pH range of pharmaceutical relevance. This knowledge is highly beneficial for predicting compound ADME properties.

1.5.4 Polar Surface Area

The polar surface area (PSA) is defined as the sum of surface contributions of all polar atoms in a molecule, including attached hydrogens. The PSA has been shown to be useful in modeling intestinal absorption, and as a direct estimate of lipophilicity, is widely acknowledged as an important factor in transport across membranes. It also affords a predictive model for blood-brain barrier penetration. When compared to PSA, parameters such as molecular weight, molecular volume, or non-polar surface area do not seem to correlate strongly enough with lipophilicity to be useful for modeling absorption properties.[102,103]

1.5.5 Effective Intestinal Permeability

Effective intestinal permeability (P_{eff})**[104]** is a fundamental parameter describing both rate and extent of intestinal drug absorption. Due to experimental difficulties, very few correlation studies have been performed using direct measurements of *in vivo*

[102] Clark, DE; *J Pharm Sci* **1999**, 88:807.
[103] Clark, DE; *J Pharm Sci* **1999**, 88:815.
[104] Winiwarter, S; Bonham, NM; Ax, F; Hallberg, A; Lennernäs, H; Karlén, A; *J Med Chem* **1998**, 41:4939.

permeability of drugs and nutrients in the human intestine. Nevertheless, determination of P_{eff} in humans has become more readily accessible experimentally through the development of a jejunal perfusion system. This experimentally validated approach gives a direct *in vivo* estimation of the local absorption rate P_{eff} (in cm/s) across the intestinal barrier. Winiwarter *et al*. have determined an equation (Eq. 4) based on relevant physicochemical descriptors (PSA and H-bond donors, HBD) that allows the prediction of absorption of drugs in the human intestine.

$$\log Peff = -2.546 - 0.011\ PSA - 0.278\ HBD \qquad \textbf{Eq. 4}$$

Based on this equation the compounds are classified as low ($\log P_{eff} < -5$), medium ($-5 < \log Peff < -4$) or high ($\log Peff > -4$) absorption drugs.

1.5.6 Parallel Artificial Membrane Permeability Assay

The human absorption of an orally administrated drug depends on different physicochemical parameters (e.g. solubility, dissolution rate, permeability). A high solubility combined with a high permeability normally leads to a high human absorption. Drugs with low solubility and low permeability usually show a low human absorption. Therefore permeability measurements can help to predict the human absorption of drugs.

The idea behind the Parallel Artificial Membrane Permeability Assay (PAMPA)[105,106,107,108] developed at Roche is to predict the human intestinal permeability. pION Inc. commercialized the PSR4p assay that allows to determine

[105] Kansy, M; Senner, F; Gubernator, K; *J Med Chem* **1998**, 41:1007.
[106] Kansy, M; Fischer, H; Kratzat, K; Senner, F; Wagner, B; Parrilla, I; *Helv Chimica Acta* 2**000**, 447.
[107] Fischer,H; Kansy, M; Avdeef, A; Senner, F; *Eur J Pharm Sci* **2007**, 31:32.
[108] Avdeef, A; Bendels, S; Di, L; Faller, B; Kansy, M; Sugano, K; Yamauchi, Y; *J Pharm Sci* **2007**, 96(*11*):2893.

permeation constants by a one-point kinetic measurement. Permeation constants are used for in silico prediction of human absorption.

Among the three possible pathways through a membrane (paracellular, transcellular and active transport), 80%-90% of all drugs display transcellular permeation. In the PAMPA assay, it is based on passive diffusion, driven by a concentration gradient between donor and acceptor.

The small intestine (duodenum, jejunum and ileum) is the major absorption site with the largest absorption area. Therefore the PAMPA PSR4p assay mimics these absorption conditions using an artificial phospholipid membrane (59% phosphatidylcholine, 6% phosphatidylethanolamine, 3% lyso-phosphatidyl-choline, 4% other phospholipids, 18% triglycerides, 8% cholesterol and 2% water). The assay conditions are usually set to pH = 6.5, which is the mean pH value of the small intestine. Furthermore, 0.5% w/v glycocholic acid is added to the donor side in order to improve the solubility of lipophilic drugs. Glycocholic acid is a member of the bile acid family. It is synthesised in the liver and stored in the gallbladder. Bile acids are secreted into the duodenum during food digestion and are almost fully reabsorbed in the ileum.

In the PAMPA, a “sandwich” is formed from a 96-well fillter plate and a 96-well Roche in-house made teflon plate (Fig 1), such that each well is divided into two chambers: donor at the bottom and acceptor at the top, separated by microfilter with a pore size of 0.45 μm polyvinylidene fluoride (PVDF) from Millipore (Billerica, MA), coated with a 10% (w/v) egg-phosphatidylcholine and 0.5% (w/v) cholesterol dissolved in dodecane.

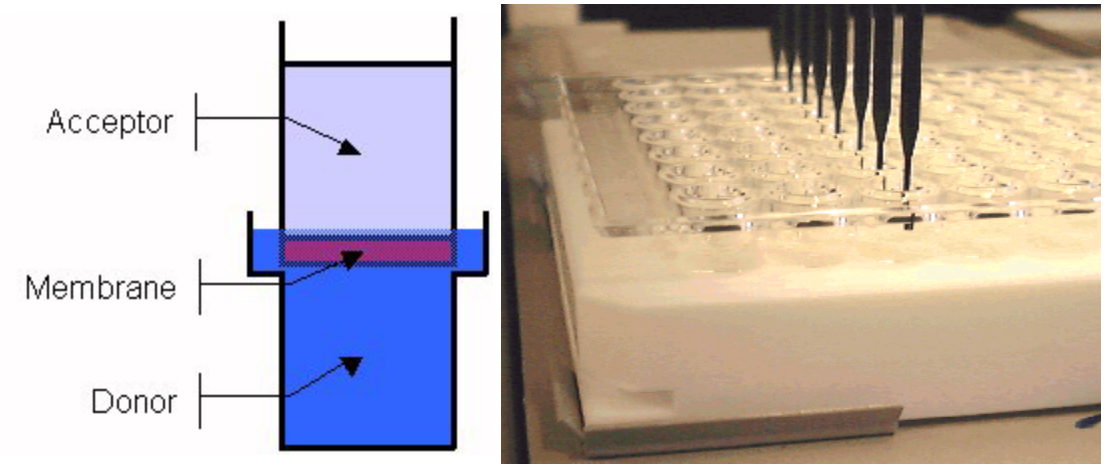


Fig 1. PAMPA PSR4p sandwich. Donor: Roche made teflon plate filled with drug/buffer solution; Membrane: filter of filterplate (hydrophobic PVDF) coated with phospholipids;
Acceptor: top of filterplate filled with buffer solution.

1.5.7 Blood-Brain Barrier Penetration

The blood-brain barrier (BBB)[103] is a complex cellular system the role of which is to maintain the homeostasis of the CNS by separating the brain from the systemic blood circulation. In drug discovery, it is important to determine whether a drug candidate molecule is capable of penetrating the BBB. For drugs targeted at the CNS, BBB penetration is demanding (unless invasive or intranasal delivery routes are being considered), whereas for drugs aimed at other sites, passage through the BBB may lead to side effects.

A common measure of the degree of BBB penetration is the ratio of the steady-state concentrations of the drug molecule in the brain and in the blood, usually expressed as log (c_{brain}/c_{blood}), or abbreviated, log BB. Experimental values of log BB cover the range about -2 to +1. Within this range, compounds with log BB >0.3 cross the membrane readily, while compounds with log BB < -1 are only poorly distributed to the brain.

[103] Clark, DE; *J Pharm Sci* **1999**, 88:815.

David E. Clark investigated the possibility of using PSA values to derive a generally applicable QSAR for log BB and concluded that using both PSA and ClogP descriptors, a successful model could be generated, based on Eq. 5.

$$\log BB = -0.0148\ PSA + 0.152\ ClogP + 0.139 \qquad \textbf{Eq. 5}$$

1.5.8 Andrew Binding Score

P. R. Andrews and co-workers[109] have calculated the average binding energies of 10 common functional groups based on the binding constants and structural components of 200 drugs and enzyme inhibitors. It was shown that, as expected, charged groups bind more strongly than polar groups, which in turn bind more tightly than non-polar groups.

The derived intrinsinc binding energies obtained in kcal/mol are given in Table 3:

Table 3. Binding energies [kcal/mol).

charged groups	CO_2^-	8.2
	PO_4^{2-}	10.0
	N^+	11.5
polar groups	N	1.2
	OH	2.5
	C=O	3.4
	O/S ethers	1.1
	halogens	1.3
non polar groups	$C(sp^2)$	0.7
	$C(sp^3)$	0.8

These values may be used to determine the fit of a drug to its receptor. The average binding energy can then be calculated by summing the intrinsic binding energies of the component groups and then subtracting two entropy related terms (14 kcal/mol for the loss of overall rotational and translational entropy and 0.7 kcal/mol for each degree of conformational freedom, DOF) (Eq. 6):

$$\Delta G = -14 - 0.7\ n_{DOF} + 0.7\ n_{C(sp2)} + 0.8\ n_{C(sp3)} + 11.5\ n_{N+} + 1.2\ n_N + 8.2\ n_{CO2-} + \\ + 10.0\ n_{PO4\ 2-} + 2.5\ n_{OH} + 3.4\ n_{C=O} + 1.1\ n_{O,S} + 1.3\ n_{hal} \qquad \textbf{Eq. 6}$$

[109] Andrews, PR; Craik, DJ; Martin, JL; *J Med Chem* **1984**, 27:1648.

However, the magnitude of the deviations to the observed values in 200 compounds studied did not allow the use of this equation in a predictive sense. They reflect the expected binding energy of an average drug, based on its pharmacophore units assuming that they will all take part in binding.

If the observed binding of a molecule is significantly stronger than the calculated average binding energy, we may deduce that most functional groups in the drug molecule are interacting favorably with the receptor and that the drug probably acts in a low energy conformation. Such a molecule should therefore provide a useful starting point in drug design. If, on the other hand, the observed binding of a drug is weaker than the calculated average binding energy, we may conclude either that the functional groups in the drug are not all interacting with the receptor or that the drug is acting in a relatively high-energy conformation. This situation would therefore demand the synthesis of rigid analogues and/or the progressive deletion of functional groups to determine which are actually involved in binding.

1.5.9 Solubility

Experimental determination of drug solubility[110] is not a single event but is performed multiple times along the drug discovery and development process, the assays and their focus can differ with the phase. Among the five key physicochemical screens in early compound screening, pKa, solubility, permeability, stability and lipophilicity, poor solubility tops the list of undesirable compound properties. Compounds with insufficient solubility carry a higher risk of failure during discovery and development since insufficient solubility may compromise other property assays, mask additional undesirable properties, influence both pharmacokinetic and pharmacodynamic properties of the compound, and finally may affect the developability of the compound. Ideally solubility liabilities should be known prior to any functional evaluations.

[110] Alsenz, J; Kansy, M; *Adv Drug Delivery Rev* **2007**, 59:546 and references cited therein.

In a broad sense, solubility may be defined as the amount of a substance that dissolves in a given volume of solvent at a specified temperature. More specifically, compound solubility can be defined as unbuffered, buffered, and intrinsic solubility. Unbuffered solubility, usually in water, means solubility at saturation of the compound at the final pH of the solution. Buffered solubility, also termed apparent solubility, refers to solubility at a given pH, measured in a defined pH-buffered system and usually neglects the influence of salt formation with counter ions of the buffering system on the measured solubility value. Intrinsic solubility means the solubility of the neutral form of an ionizable compound. For neutral (non-ionizable) compounds all three definitions coincide.

Depending on the experimental set-up, solubility measurements determine either the kinetic or the thermodynamic solubility of compounds. In most cases, kinetic solubility measurements start from dissolved compound and represent the maximum (kinetic) solubility of the fastest precipitating species of a compound. Kinetic solubility values are strongly time dependent and due to the degree of supersaturation that may occur, values are likely to overpredict the thermodynamic solubility and are not expected to be reproducible between different kinetic methods.

Solubility assays in the majority of discovery set-ups determine kinetic solubility; however, equilibrium measurement principles are being introduced more and more into early discovery compound profiling. In contrast to kinetic solubility measurements, thermodynamic solubility assays are performed by dispensing a solid compound in a liquid. Thermodynamic (equilibrium) solubility represents the saturation solubility of a compound in equilibrium with an excess of undissolved substance at the end of the dissolution process. Thermodynamic solubility is often regarded as being the ‘true’ solubility of a compound and as the ‘gold standard’ for development needs.

Alsenz and Kansy[110] have developed the LYophilized Solubility Assay (LYSA) which is the HT-solubility measurement included in Roche MDO system. They report that solubility determinations based on direct UV measurements usually deliver acceptable results, with some restrictions regarding solid state properties and impurities. The sample throughput is 360-500 samples per week in duplicate.

1.5.10 Rat and Human Liver Microsomal Metabolism Intrinsic Clearance CL_{int}

The first demonstration of the correlation between in vivo clearance values and clearance values calculated from rat liver microsomal metabolism intrinsic clearance data was made by Rane *et al*.[111]

One of the simplest methods described to predict human clearance is the use of human hepatic microsomal lability data, termed the in vitro half-life, $T_{1/2}$, approach. It measures the first-order rate constant for consumption of substrate at one concentration in the presence of human/rat liver microsomes. The intrinsic clearance is calculated by Eq. 6 and overall accuracy reported as average fold error is for basic compounds 1.37, for neutral compounds 1.99, for acidic compounds 5.05, and for all compounds 2.28:[112]

$$CL_{\text{int}} = \frac{0.693}{invitroT_{½}} \cdot \frac{mLincubation}{mgmicrosomes} \qquad \textbf{Eq. 6}$$

The use of hepatic microsomes in the prediction of clearance requires acceptance of several assumptions and caveats: 1) metabolic clearance is the major mechanism of clearance (i.e., $CL_{metabolism} >> CL_{renal} + CL_{biliary} + CL_{other}$); 2) the liver is the major organ of clearance (i.e., $Cl_{hepatic} >> \Sigma CL_{all\ other\ organs}$); 3) oxidative metabolism predominates over other metabolic routes such as direct conjugative metabolism,

[110] Alsenz, J; Kansy, M; *Adv Drug Delivery Rev* **2007**, 59:546.
[111] Rane, A; Wilkinson, GR; Shand, DG; *J Pharmacol Exp Ther* **1977**, 200:420.
[112] Obach, RS; *Drug Metab Disp* **1999**, 27:1350.

reduction, hydrolysis, etc.; 4) rates of metabolism and enzyme activities *in vitro* are truly reflective of those that exist *in vivo*.

At Roche the reference values are in agreement with Table 4. For drugs that are foreseen for oral chronic treatment CL'_{int} (microsomes) should be low. For other treatments, we have to consider that lower CL_{int} (microsomes) is reflected in lower doses.

Table 4. Reference values for CL_{int} (microsomes)

	CL_{int} µL/min/mg prot	clearance	Expected metabolic stability	Expected bioavailability (%)*
Rat	< 15	Low	High	>70
	>15 to <90	Medium	Medium	
	>90	high	low	<30
Human	<6.5	Low	High	>70
	>6.5 to <35	Medium	Medium	
	>35	high	low	<30

*only true if Phase I hepatic metabolic clearance is the major mechanism of clearance.

2. Results and discussion

The synthesis of oxetane δ-amino acids, which is the class of targeted scaffolds, will be discussed herein. These compounds were derivatised to afford small libraries of 1,2,4-oxadiazoles and 1,2,3-triazoles. Moreover, two bicyclic scaffolds with a δ-amino acid function, available at Roche in-house collection, were derivatised with the same methodology to give the corresponding 1,2,4-oxadiazole libraries for comparison with the previous class of compounds. Furthermore, discussion on the structure elucidation of the studied compounds, in particular when their stereochemical assignment needed to be clarified, is presented. Finally the results obtained for the physicochemical and metabolic properties of the individual compounds of the achieved libraries will be discussed.

2.1 Scaffold Synthesis

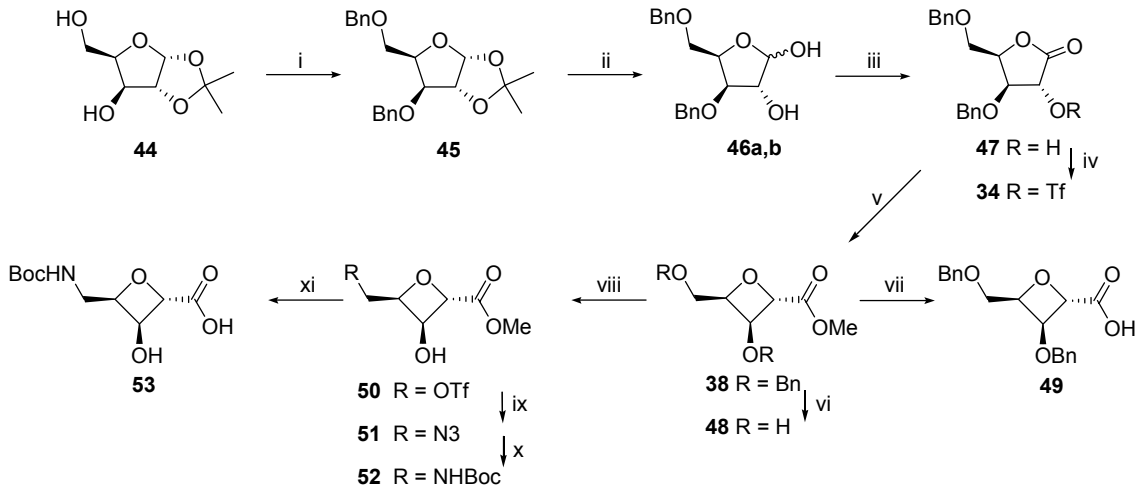
The syntheses of oxetane δ-amino acids which contain hydroxy, methoxy or fluoride as substituents at C-3 were successfully accomplished. Readily available carbohydrates such as D-xylose or 1,2-isopropylidene-D-xylose were used as starting materials. Regio- and stereoselective reactions were explored for the preparation of new oxetane δ-amino acids.

2.1.1 Chemoenzymatic Synthesis of 2,4-Anhydro-5-*N*-(tert-butoxycarbonyl)amino-5-deoxy-D-*lyxonic* Acid

Starting from commercial 1,2-isopropylidene-D-xylose **44**, the first oxetane δ-amino acid synthesised was 2,4-anhydro-5-*N*-(*tert*-butoxycarbonyl)amino-5-deoxy-D-lyxonic acid **53** (Scheme 16).[58]

By means of the well-established benzylation/de-isopropylidenation sequence, a mixture of α/β isomers **46a,b** was obtained (α/β ratio1:4 by ^{1}H-NMR integration). For the acetal cleavage the use of 30 % acetic acid gave the best results, conditions that had been employed in the *arabino* series.[113]

[58] Lucas *et al. J Carbohydr Chem* **2006**, *25*:187.
[113] Ning, J; Kong, F; *Carbohydr Res* **1997**, 300(*4*):355.



i) a. NaH, DMF, rt, 2.5 h, b. BnBr, rt, 2.5 h, 100%; *ii*) AcOH 30%, reflux, 3 h, 88%; *iii*) Br_2, $BaCO_3$, H_2O/dioxane 2:1, rt, 4 h, 73%; *iv*) Tf_2O, DCM, pyridine, -17 °C, 40 min; *v*) K_2CO_3, MeOH, -12 °C, 30 min, 90% (2 steps); *vi*) H_2, Pd/C, MeOH/dioxane 1:1, rt, 40 min, 85%; *vii*) 1N LiOH, THF, 0-5 °C, 30 min, quantitative; *viii*) Tf_2O, Et_2O/DCM 5:1, 4 Å molecular sieves, -15 °C, 50 min; *ix*) LiN_3, acetone, rt, 30 min, 65% (2 steps); *x*) H_2, Pd/C, EtOAc, Boc_2O, rt, 2 h, 88%; *xi*) L2- *Candida antarctica*, TBME/H_2O, 45°C, 3 d, quantitative.

Scheme 16

Oxidation of **46a,b** with bromine furnished the known 3,5-di-*O*-benzyl-D-xylono-γ-lactone **47**.[75] It was important to carry out this reaction in the dark to avoid radical-mediated debenzylation. By optimising the water/dioxane ratio the yield could be improved to reach 73%.

Triflation of **47** furnished lactone **34,** which was subjected to treatment with potassium carbonate in methanol leading to ring contraction and formation of the oxetane carboxylic acid ester **38** as described by the Fleet group.[75] At this stage we tested the feasibility of the ester cleavage. Indeed, treatment of **38** with lithium hydroxide gave the free carboxylic acid **49**[114] in a clean reaction and in excellent yield.

Palladium catalysed hydrogenation of **38** yielded the debenzylated oxetane derivative **48**. For this central intermediate an alternative approach via 3,5-di-*O*-

[75] Witty *et al. Tetrahedron Lett* **1990**, 31(33):4787.
[114] Saksena, AK; Ganguly, AK; Girijavallabhan, VM; Pike, RE; Chen, Y-T; Puar, MS; *Tetrahedron Lett* **1992**, 33(*50*):7721.

benzylidene-D-xylono-γ-lactone was already described.[75] For the activation of the primary hydroxyl group, **48** was reacted with triflic anhydride in diethyl ether/ dichloromethane in the presence of dry molecular sieves. This methodology[115] allows facile triflation under non-basic reaction conditions and mild work-up. The best results were obtained when the reaction mixture was concentrated in the presence of molecular sieves. The triflate **50** was the single product formed as judged by TLC, and the residue was reacted without further purification, with lithium azide in acetone, to furnish azide **51** in 65% yield over the two steps.

The azide **51** was reduced by hydrogenolysis in the presence of *tert*-butoxycarbonyl anhydride to afford the protected amine **52** in a very good yield (88%). Surprisingly, and in contrast to our experience with the conversion of the ester **38** to the acid **49**, the transesterification of **52** under basic conditions was not successful in our hands. As interference of the amino group might be expected, the transesterification of azide **51** under basic conditions was investigated, but led to complex mixtures which could not be characterized by NMR.

Readily available pig liver esterase (PLE) is a standard esterase and was used as the first enzymatic approach to hydrolyse methyl 2,4-anhydro-5-*N*-(*tert*-butoxycarbonyl)amino-D-lyxonate **52**. The reaction was performed in aqueous media under pH control (phosphate buffer, pH 7-7.2). After 1 day complete conversion was observed (HPLC). However, acidification to pH 3 with diluted H_2SO_4 led to decomposition of the target compound. Moreover, when isolation was tried without acidification, either by lyophilisation followed by organic solvent wash or by reversed phase chromatography with RP-18 of the aqueous solution, the results were not satisfactory. The isolation of the product from the buffer salts was not efficient, leading to low yields.

The hydrophilic character of the product was then an effective problem for its isolation from aqueous solutions. The use of an organic solvent for the enzymatic reaction seemed to be a reasonable alternative, since product isolation from micro

[75] Witty *et al. Tetrahedron Lett* **1990**, 31(33):4787.
[115] Wessel, HP; Ruiz, N; *J Carbohydr Chem* **1991**, 10:901.

aqueous reaction systems can be achieved by simply filtering off the enzyme and evaporation of the organic solvent. Therefore, an enzyme screening for the ester hydrolysis of **52** in micro aqueous systems was carried out. Several lipases from different microorganisms such as *Candida antarctica, Candida rugosa, Arthobacter ureafaciens, Rhizomucor miehei, Burkholderia cepacia, Thermomyces lanuginose or Aspergillus oryzae* and the polyethylene glycol co-lyophilized esterases from pig liver and *Mucor miehei* displayed hydrolytic activity on this substrate. The highest activity was shown by lipase L2 from *Candida antarctica*. The enzymatic activity depends upon the organic solvent and water contents, and the screening of solvents and water amount for the activity of lipase L2 from *Candida antarctica* is presented in Table 4. TBME saturated with water gave the highest activity, while acetonitrile and the commonly used diisopropyl ether and diethyl ether also led to a good activity.

Table 4. Screening of organic solvents with different water content for lipase L2 from *Candida antarctica* activity on the hydrolysis of **52** at rt.

Medium		Conversion after 2 h		Conversion after 1 d	
Solvent	[H_2O]	Substrate %	Product %	Substrate %	Product %
Nonane	0.008	-	-	55.3	44.7
Heptane	0.01	-	-	73.3	26.7
Cy-Hex	0.01	-	-	65.2	34.8
Pentane	0.012	-	-	79.1	20.9
Toluene	0.033	100	0	66.1	33.9
Chloroform	0.008	100	0	66.6	33.4
DCM	0.072	100	0	26.5	73.5
Dichloroethane	0.15	100	0	63.4	36.6
DCM	0.2	100	0	47.0	53.0
Diisopropyl ether	0.2	79.8	20.2	24.3	75.7
Diethyl ether	0.2	100	0	51.3	48.7
TBME	0.2	66.3	33.7	28.5	71.5
Diisopropyl ether	0.62	41.9	58.1	17.1	82.9
Diethyl ether	1.3	65.6	34.4	8.2	91.8
TBME	**1.4**	**14.5**	**85.5**	**5.7**	**94.3**
Dioxane	1.4	87.5	12.5	43.1	56.9
THF	1.4	100	0	60.9	39.1
MeCN	1.4	86.3	13.7	14.8	85.2
Dioxane	5	80.1	19.9	31.0	69.0
THF	5	91.8	8.2	45.2	54.8
MeCN	5	83.5	16.5	17.2	82.8
Heptane*	0.01	100	0	100	0

* blank

Mild cleavage of the methyl ester **52** was then achieved with immobilised lipase L2 from *Candida antarctica* in TBME saturated with water, and on a gram scale the free acid **53** was isolated in quantitative yield as a hygroscopic white foam, containing ca.

3-4% of the ester **52** and ca. 5% TBME. Moreover, the increase of temperature to 45 °C and reaction time to 3 days did not allow the complete conversion of the ester to the corresponding acid as monitored by HPLC, suggesting the existence of an equilibrium when ca. 95% of conversion is reached. Thus, this chemoenzymatic approach allowed the successful synthesis of 2,4-anhydro-5-*N*-(*tert*-butoxycarbonyl)amino-5-deoxy-D-lyxonic acid **53**.

For the synthesis of the 3-methoxyoxetane δ-amino acid scaffolds (2.1.2 and 2.1.3) the chosen synthetic route took advantage of the stability of a primary azide function early introduced in order to avoid protection/deprotection steps over the synthetic pathway.[59]

2.1.2 Synthesis of 2,4-Anhydro-5-*N*-(tert-butoxycarbonyl)amino-5-deoxy-3-O-methyl-D-*lyxonic* Acid

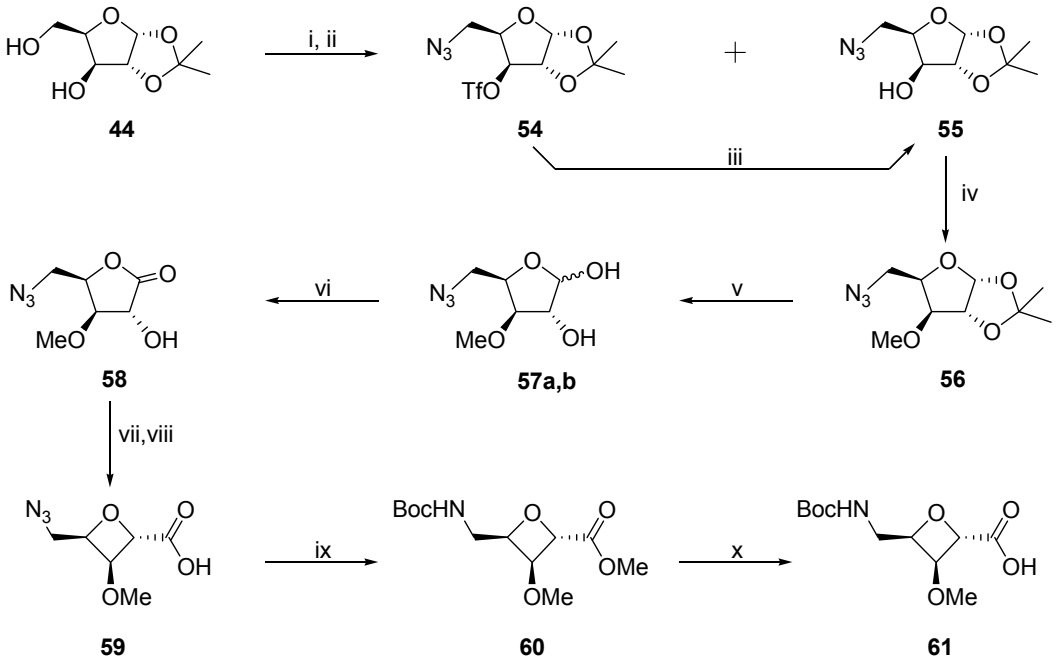
Treatment of 1,2-*O*-isopropylidene-α-D-xylofuranose **44** with triflic anhydride followed by displacement with sodium azide furnished the over-triflated by-product **54,** isolated in 23% yield, together with the desired primary azide **55** in 63% yield (Scheme 17). These results compete favourably with syntheses via a tosylate[116,117,118] or introduction of the azide from **1** via a zinc salt mediated Mitsunobu reaction.[119]

Treatment of the triflate **54** with MeONa/MeOH at rt for 24 h aiming at nucleophilic substitution by the methoxide failed and quantitatively yielded the D-*xylo*-azide **55** instead. Methylation of **55** by a standard procedure using iodomethane and sodium hydride in THF gave **56**[116] in quantitative yield.

Hydrolysis of the isopropylidene group was achieved with 30% aqueous acetic acid to give a 2:1 α/β-anomeric mixture of 5-azido-3-*O*-methyl-α,β-D-xylofuranose in 88%

[59] Lucas *et al. J Carbohydr Chem* **2008**, 27(*3*):172.
[116] Tulshian, DB; Fundes, AF; Czarniecki, M; *Bioorg Med Chem Lett* **1992**, 2*(6)*:515.
[117] Yamashita, M; Takahashi, C; Seo, K; *Heterocycles* **1993**, 36*(4)*:651.
[118] Kefurt, K; Kefurtova, Z; Markova, V; Slivova, K; *Collect Czech Chem Commun* **1996**, 61:1027.
[119] Moravcová, J; Spilová, L; Capková, J; Chéry, F; Rollin, P. *Collect Czech Chem Commun* **2000**, 65:1745.

yield. Selective anomeric oxidation with bromine was performed employing the conditions previously optimised to give the lactone **58** in 76% yield. Using the already mentioned methodology for the ring contraction of pentano-1,4-lactones to oxetane carboxylic esters we obtained the oxetane **59** in 67% yield. Hydrogenolysis of the azide in the presence of *tert*-butoxycarbonyl anhydride gave the protected amine **60** in 83% yield.

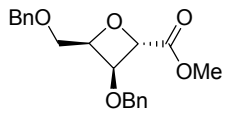
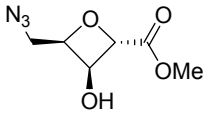
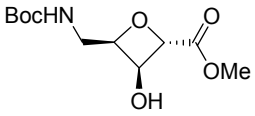
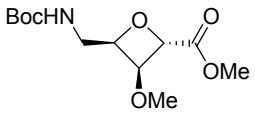


i) Tf_2O, DCM, Py, -12 ºC, 30 min; *ii*) NaN_3, acetone, rt, overnight, 23%(**54**), 62%(**55**); *iii*) MeONa/MeOH, rt, 24 h, quantitative; *iv*) MeI, NaH, DMF, 1 h, quantitative; *v*) AcOH 30%, reflux, 2 h, 88%; *vi*) Br_2, $BaCO_3$, H_2O/dioxane 2:1, rt, 4 h, 76%; *vii*) Tf_2O, DCM, Py, -12 ºC, 15 min; *viii*) K_2CO_3, MeOH, -12 ºC to 0ºC, 1h, 67%; *ix*) H_2, Pd/C, EtOAc, Boc_2O, rt, 2 h, 83%; *x*) LiOH 1N, 0-5 ºC, 30 min, 89%.

Scheme 17

Saponification with lithium hydroxide allowed the synthesis of the oxetane δ-amino acid **61** in a very good yield (89%). When compared to the previous work on the synthesis of 2,4-anhydro-5-*N*-(*tert*-butoxycarbonyl)amino-D-lyxonic acid (2.1.1), where basic saponification led to complete degradation (Table 5), these results suggest that the free hydroxyl group was indeed responsible for the previous failure of this reaction, rather than the presence of the amino function, probably due to deprotonation and further intra- or intermolecular reactions resulting in the decomposition of the material.

Table 5. Oxetane δ-amino ester substrates and corresponding saponification yield.

	 **38**	 **51**	 **52**	 **60**
yield	Quantitative	Decomposition	Decomposition	89%

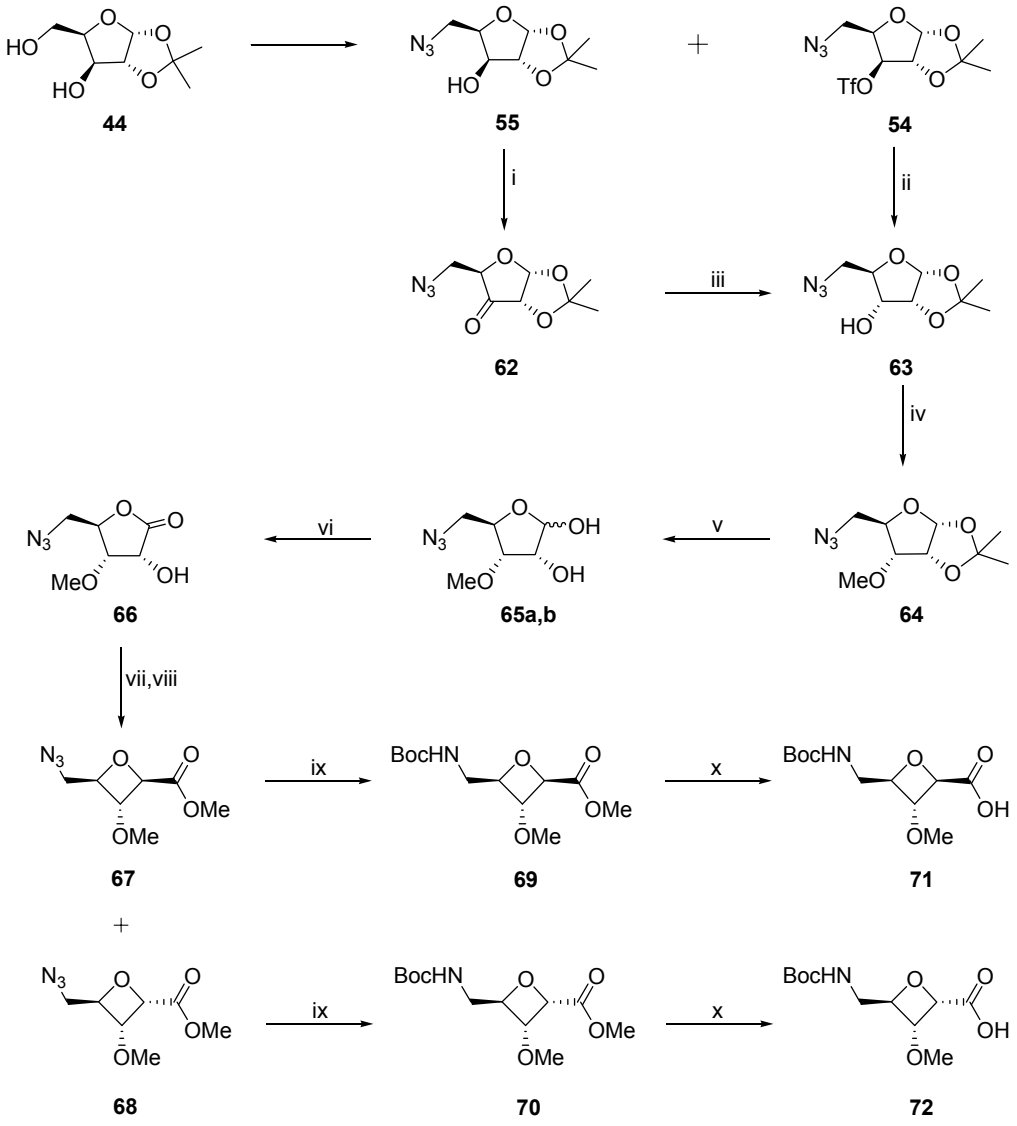
2.1.3 Synthesis of 2,4-Anhydro-5-*N*-(tert-butoxycarbonyl)amino-5-deoxy-3-*O*-methyl-D-*ribonic* and D-*arabinonic* acids

For the synthesis of 2,4-anhydro-5-*N*-(*tert*-butoxycarbonyl)amino-5-deoxy-3-*O*-methyl-D-ribonic acid (**71**) starting from the azide **55** (Scheme 18), we made use of a well established oxidation/reduction sequence.[120] Oxidation with pyridinium dichromate (PDC) of **55** under reflux conditions led to the keto sugar **62** in 89% yield. The use of PDC at room temperature was previously reported to give **62** in 80% yield,[121] while ruthenium dioxide–sodium periodate oxidizing conditions gave 71% of **62.** This keto sugar was reduced to the D-*ribo*-derivative **63** with sodium borohydride in 92% yield. Attempted inversion of configuration via triflate **54** using sodium trifluoroacetate led to a poor 10% yield of **63**.

Methylation of 5-azido-5-deoxy-1,2-*O*-isopropylidene-α-D-ribofuranose **63** gave the fully protected derivative **64**[116] in quantitative yield. Isopropylidene hydrolysis with 30% aqueous acetic acid afforded the free furanose in 85% yield as a 1:1 mixture of α/β-anomers, **65a,b**. Selective anomeric oxidation by bromine gave the ribonolactone **66** in 67% yield. The ring contraction reaction led to a mixture of isomeric D-*ribo*- and D-*arabino*-oxetanes **67** and **68** isolated in 53 and 7% yield,

[120] Baker, DC; Horton, D; Tindall, CG; Carbohydr Res **1972**, 24*(1)*: 192.
[121] Ewing, DF; Goethals, G; Mackenzie, G; Martin, P; Ronco, G; Vanbaelinghem, L; Villa, P; Carbohydr Res **1999**, 321:190–196.
[116] Tulshian *et al. Bioorg Med Chem Lett* **1992**, 2*(6):*515.
[75] Witty *et al. Tetrahedron Lett* **1990**, 31(33):4787.

respectively. These results are in agreement with those obtained by Witty et al.[75] for the ring contraction of a different ribono-1,4-lactone.



Scheme 18: *i*) PDC, Ac_2O, DCM, reflux, 3 h, 89%; *ii*) CF_3COONa, butanone, rt, overnight, 10%; *iii*) $NaBH_4$, EtOH/H_2O 6:1, rt, overnight, 94%; *iv*)MeI, NaH, DMF, 30 min, quantitative; *v*) AcOH 30%, reflux, 1 h, 86%; *vi*) Br_2, $BaCO_3$, H_2O/dioxane 2:1, rt, 1.5 h, 67%; *vii*) Tf_2O, DCM, Py, -12 ºC, 15 min; *viii*) K_2CO_3, MeOH, -12 ºC to 0 ºC, 1 h, 53%(**67**), 7%(**68**); *ix*) H_2, Pd/C, EtOAc, Boc_2O, rt, 2h, 81%(**69**), 85%(**70**); *x*) LiOH 1N, HCl 1N, 0-5 ºC, 30 min, 89%(**71**), 92%(**72**).

Hydrogenolysis of the azide **67** in the presence of Boc_2O gave the protected amine **69** in 81% yield. The same procedure was used to transform **68** to **70** in 85% yield. Lithium hydroxide was again very efficient for the saponification of **69** and **70,** which

occurred in 89% and 92% yield, to give the final oxetane δ-amino acids **71** and **72**, respectively.

The stability of the 5-azide function along the chosen approach to 3-methoxyoxetane δ-amino acids (2.1.2 and 2.1.3) allowed a straightforward synthesis of the three new methoxyoxetane δ-amino acids **61**, **71** and **72** differing in stereochemistry and with well defined exit vectors particularly interesting for further derivatisation.

2.1.4 Synthesis of 2,4-Anhydro-5-*N*-(tert-butoxycarbonyl)amino-5-deoxy-3-fluoro-D-*arabinonic* acid

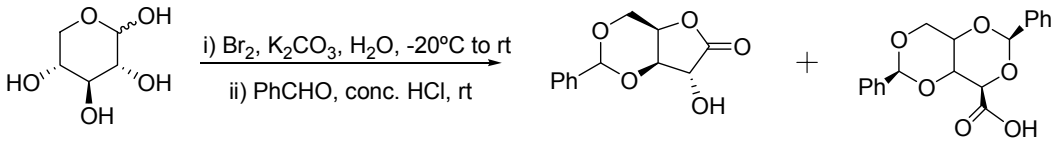
It has been well recognised that the presence of fluorine can induce favourable properties in bioactive compounds, becoming highly important in medicinal chemistry approaches. Quite often, fluorine is introduced to improve the metabolic stability by blocking metabolically labile sites. Fluorine can also be used to modulate physicochemical properties, such as lipophilicity or basicity. It may exert a substantial effect on the conformation of a molecule, and is being used to enhance the binding affinity to target proteins.[122,123]

For the introduction of a C-F bond in an oxetane δ-amino acid scaffold the chosen approach was based on the use of DAST as fluorination agent on the azide **51** (Scheme 20). Moreover an alternative synthesis of **51** was also employed.

Starting from readily available D-xylose we made use of a straightforward anomeric oxidation and benzylidene protection previously reported by Fleet's group[77] to achieve the 1,4-xylonolactone **74** (Scheme 19). Although the yields were reported to be in the range of 50%, we could only reach 39%. However, we were able to identify a previously not reported by-product formed in considerable amount (37%). MS, ^{1}H-NMR and IR spectroscopy allowed the structural assignment of this compound as

[122] Böhm, H-J; Banner, D; Bendels, S; Kansy, M; Kuhn, B; Müller, K; Obst-Sander, U; Stahl, M; *Chem Bio Chem* **2004**, 5:637.
[123] Müller, K; Faeh, C; Diederich, F; *Science* **2007**, 317:1881.
[77] Jenkinson (née Barker) *et al.* Tetrahedron Asymm. **2004**, *15*, 2667.

the known 2,4;3,5-dibenzylidene xylonic acid **75** (for the structural elucidation see chapter 2.5.5). Its melting point and specific rotation were in agreement with those reported in the literature[124] and confirmed the proposed structure.

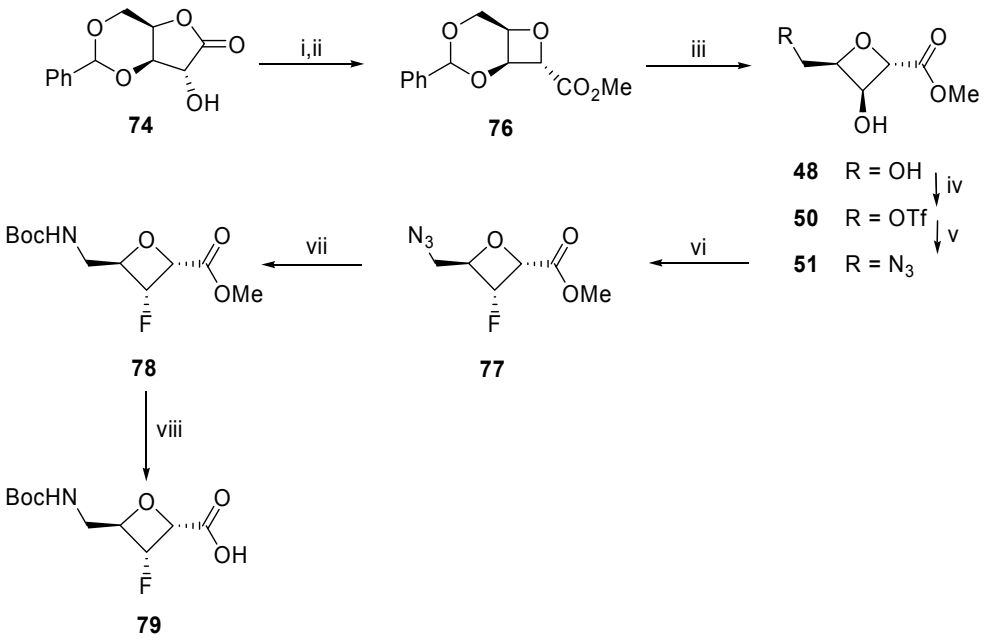


Scheme 19. One-pot anomeric oxidation and benzylidene protection of D-xylose.

Ring contraction of the 1,4-lactone **74** using the previously mentioned triflation followed by treatment with potassium carbonate led to the benzylidene protected oxetane **76** in 65% yield (Scheme 20). Deprotection was accomplished by catalytic hydrogenation affording the known diol **48**[59,78] in 87% yield. This compound was reacted further as explained in section 2.1.1 using a non-basic triflation, followed by selective introduction of a primary azide by means of sodium azide to furnish the intermediate **51**.

The oxetane derivative **51** containing a free hydroxyl group was then the key intermediate for the fluoride introduction at C-3. The first attempt to direct substitution of the hydroxyl by fluoride made use of the standard reaction with diethylaminosulfur trifluoride (DAST) in DCM. However, reaction either at rt or under reflux conditions gave the desired fluoroderivative **77** in poor yield. Theoretical studies on fluorination reaction by DAST[125] indicate that the formation of fluoride ions is very endoenergetic when the reaction takes place in solvents with low dielectric constant as DCM. In addition, fluoride ion formation may be induced by the presence of pyridine. Since adding pyridine did not lead to any improvement in the yield of **77**, the reaction was then tried using MeCN as solvent, and the reaction conditions were optimised as follows: DAST was added at –20 ºC, and the mixture was warmed up to reach reflux conditions to afford the fluoroderivative **77** with the yield of 75%.

[124] Zinner, H; Voigt H; Voigt, J; *Carbohyd Res* **1968**, 7:38.
[59] Lucas *et al. J Carbohydr Chem* **2008**, 27(*3*):172.
[78] Johnson, *et al.* Tetrahedron Asymm. **2004**, *15*, 2681.
[125] Baptista, L; Bauerfeldt, GF; Arbilla, G; Silva, EC; *J Mol Struct:THEOCHEM* **2006**, 761:73-81.



i) Tf_2O, DCM, Py, -30 ºC, 1 h; ii) K_2CO_3, MeOH, -12 ºC, 4 h, 65% (2 steps); iii) H_2, Pd/C, MeOH/dioxane 1:1, rt, 2 h, 87%; iv) Tf_2O, Et_2O/DCM 5:1, 4 Å molecular sieves, -15 ºC, 50 min.; v) NaN_3, acetone, rt, 2h, 72% (2 steps); vi) DAST, MeCN, -20 ºC to reflux, 1h, 75%; vii) H_2, Pd/C, EtOAc, Boc_2O, rt, 2h, 85%; viii) LiOH 1N, HCl 1N, 0-5 ºC, 1h, 97%.

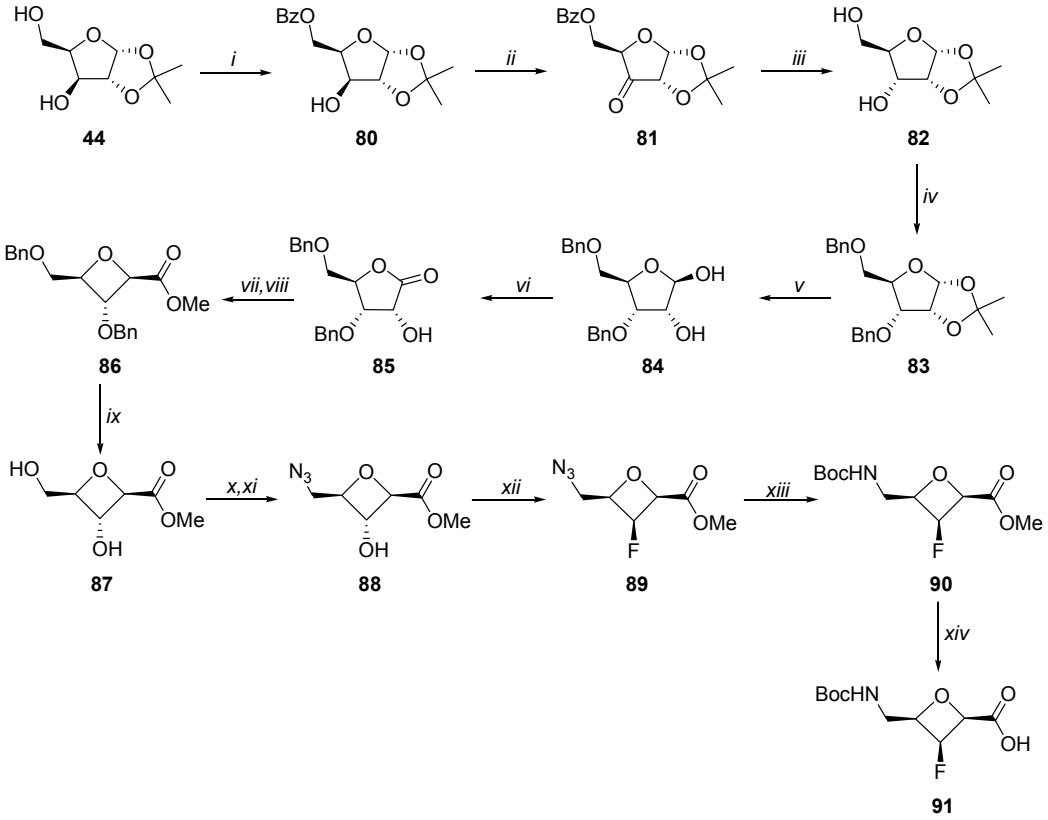
Scheme 20

One-pot reduction of azide **77** in the presence of *tert*-butoxycarbonyl anhydride furnished the protected amine **78** in a good yield. Once again, in the absence of a hydroxyl substituent at C-3, the saponification by means of LiOH was a very clean reaction giving the desired oxetane δ-amino acid **79** in 97% yield.

2.1.5 Synthesis of 2,4-Anhydro-5-*N*-(tert-butoxycarbonyl)amino-5-deoxy-3-fluoro-D-*xylonic* acid

With a view to the synthesis of benzyl protected D-ribono-1,4-lactone **85** (Scheme 21), we made use of a selective benzoyl protection of 1,2-*O*-isopropylidene-α-D-xylofuranose **44** at the primary alcohol, so that the well established PDC oxidation followed by $NaBH_4$ procedure led to the necessary inversion of configuration at C-3 together with benzoyl cleavage to afford 1,2-*O*-isopropylidene-α-D-ribofuranose **82** in good yield. Benzylation of the diol **82** and further isopropylidene hydrolysis led, in

this case, to the β-anomer **84**, that was further oxidised with bromine to give the desired α-hydroxy lactone **85** in 79% yield.



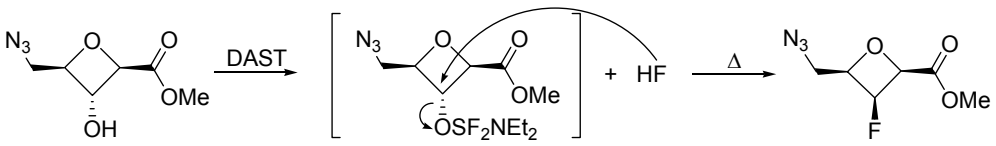
i) BzCl, Et_3N, DCM, 0-5 ºC, 1.5 h, 90%; *ii*) PDC, Ac_2O, DCM, reflux, 2.5 h, 83%; *iii*) $NaBH_4$, EtOH/H_2O 7:1, rt, overnight, 89%; *iv*) a.NaH, DMF, rt, 2 h, b. BnBr, DMF, rt, 2h, 90%; *v*) AcOH (30%, aq.), reflux, 2 h, 91%; *vi*) Br_2, $BaCO_3$, dioxane/H_2O 1:2, rt, 3 h, 79 %; *vii*) Tf_2O, DCM, py, -30 to -10 ºC, 15 min; *viii*) K_2CO_3, MeOH, -12 ºC, 1 h; *ix*) H_2, Pd/C 10%, MeOH/dioxane 1:1, rt, 2 h; *x*) Tf_2O, DCM, py, -30 ºC; *xi*)NaN_3, acetone, rt, overnight, 53% from **85**; *xii*) DAST, Py, MeCN, -20 ºC (1.5 h), 50 ºC (3 h); *xiii*) H_2, Pd/C, EtOAc, Boc_2O, rt, 1.5 h, 52% over 2 steps; *xiv*) LiOH 1N, HCl 1N, 0-5 ºC, 30 min, 97%.

Scheme 21

For the synthesis of the oxetane δ-azido ester **88**, the best yields were obtained when no intermediary purification was made after the synthesis of lactone **85**. Ring contraction was achieved by triflation and treatment with K_2CO_3 in methanol. The resulting crude **86** was hydrogenated but triflation of the diol **87** was not possible using the non-basic procedure due to the low solubility of the diol **87** in DCM. Hence triflation was performed with triflic anhydride in DCM and in the presence of pyridine. After reaction with sodium azide in acetone the desired compound **88** was obtained in a 53% overall yield from the lactone **85**. An alternative synthesis of **87** using a

longer synthetic scheme starting from diacetone glucose was previously reported.[126] Azide **88** also proved to be very interesting as starting material for the first approach towards click chemistry in oxetane scaffolds (see chapter 2.4).

The attempt to synthesise the fluoro derivative **89**, that exhibits all the subtituents pointing to the same side of the oxetane ring, was made reacting the azide **88** with DAST in MeCN. Although 2 h after the addition of DAST and stirring at -20 ºC we could identify a single new spot by TLC, after work up and flash chromatography the MS of the fractions suggested the presence of the intermediate **92** (Scheme 22) in agreement with Tewson and Welch's[127] proposal for other DAST reactions. However, after solvent evaporation decomposition was observed and no more analytical data were obtained.



88 **92** **89**

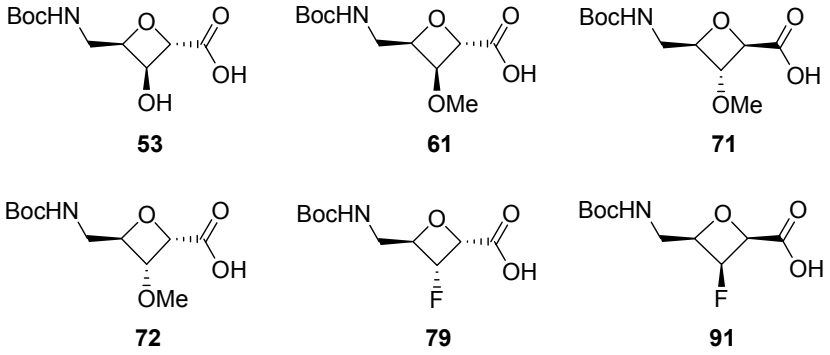
Fluorination of **88** by DAST reagent.

Scheme 22

Azide **88** was then submitted to treatment with DAST, and after the formation of the intermediate **92** the mixture was heated at 50 ºC to afford the desired product **89**. In this case it was shown that addition of 1 eq of pyridine improved the reaction rate. Compound **89** is volatile, and the best results were obtained when no purification was performed, so that after DAST reaction and work-up the crude **89** was further hydrogenated in the presence of *tert*-butoxycarbonyl anhydride to achieve the protected amine **90** (Scheme 21) in 52% yield over the two steps. In agreement with the results for the saponification of the fluoro derivative **78**, treatment of **90** with 1 N LiOH led to the δ-amino acid **91** in the excellent yield of 97%.

[126] Wang, Y; Fleet, GWJ; Wilson, FX; Storer, R; Myers, PL; Wallis, CJ; Doherty, O; Watkin, DJ; Vogt, K.; Witty, DR; Peach, JM; *Tetrahedron Lett* **1991**, 23(*13*):1675.
[127] Tewman, TJ; Welch, MJ; *J Org Chem* **1978**, 43(*6*):1090.

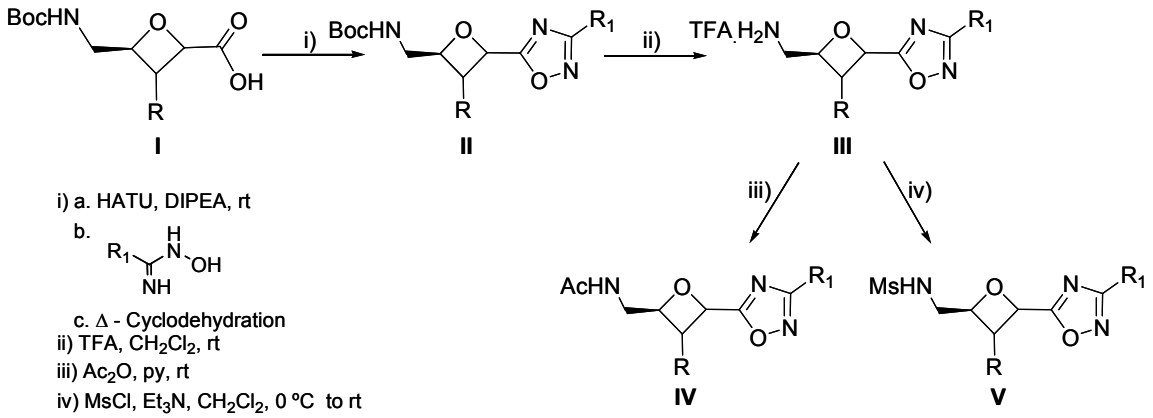
The synthesis of oxetane δ-amino acid scaffolds **53**, **61**, **71**, **72**, **79** and **92** (Scheme 23) was thus successfully accomplished in the present work. Strategically, we targeted the free carboxylic acid to allow the coupling of these units with hydroxyamidines in order to afford different oxadiazoles on oxetane scaffolds by the already mentioned cyclodehydration mechanism (see chapter 1.3).



Scheme 23

2.2 Library Construction on Oxetane δ- Amino Acid Scaffolds

Being 1,2,4-oxadiazoles valuable pharmacophores (see chapter 1.3) we made use of the reaction of the carboxylic acid on the oxetane scaffold with different hydroxyamidines (Scheme 24) to generate libraries of compounds. This procedure takes us to the targeted 1,2,4-oxadiazoles with a lipophilic Boc protected amine unit on the opposite side of the oxadiazole. Hence, the Boc cleavage by means of TFA leads to the hydrophilic free amine **III**. In a midway of lipophilicity will then be the corresponding *N*-acetyl amines with general structure **IV**, and the *N*-mesyl amines with general structure **V**.

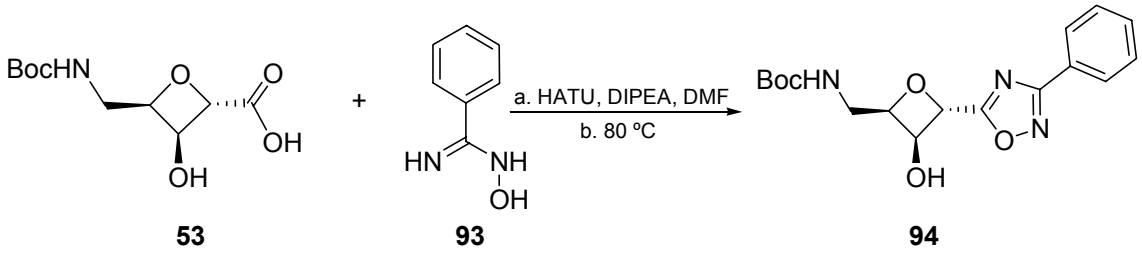


General approach to library construction on oxetane δ-amino acid scaffolds.

Scheme 24

2.2.1 Library using 2,4-Anhydro-5-*N*-(tert-butoxycarbonyl)amino-5-deoxy-D-*lyxonic* Acid (53) as Scaffold

The first attempt to prepare oxadiazoles starting from an oxetane δ-amino acid was made using 2,4-anhydro-5-*N*-*(tert*-butoxycarbonyl)amino-5-deoxy-D-lyxonic acid (**53)** (Scheme 25) as scaffold. Its coupling to benzamidoxime **93** was performed in the presence of HATU and DIPEA in DMF, and further heating at 80 ºC led to complete cyclisation as indicated by TLC. Nevertheless, isolation of the desired product **94** was only possible up to a maximum yield of 30%. The use of other coupling agents, such as 2-chloro-4,6-dimethoxy-1,3,5-triazine (CDMT) or 2-(7-aza-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (TATU) did not improve the reaction yield.

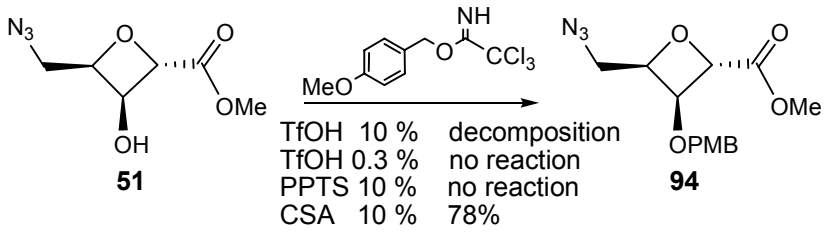


Test reaction for oxadiazole formation using **53** as scaffold.

Scheme 25

Rationalising in terms of scaffold stability under basic conditions, we had the finding from previous reactions (see chapter 2.1.2) that the free -OH group at C-3 of the oxetane ring can confer some instability to these molecules. Thus the protection of the hydroxyl group seemed the logical way to proceed. The protective group chosen was the *p*-methoxybenzyl (PMB) group so that it could be introduced under mild acidic conditions, be stable under basic conditions and be easily removed by TFA, if possible together with the cleavage of the Boc group.

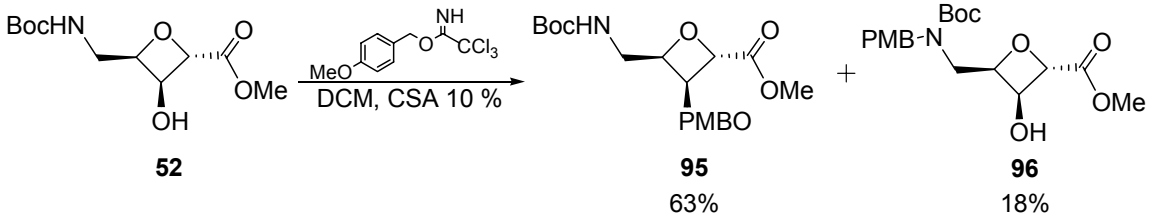
To avoid the conventional alkylations under strongly basic conditions, Wessel et al.,[128] back in the 1980's, reported the use of trichloroacetimidates to accomplish alkylations under mild acidic conditions using catalytic triflic acid (TfOH). As a test reaction, the protection of the azide **51** (Scheme 26) with PMB trichloroacetimidate was attempted. It was found that the use of 10% TfOH as catalyst led to decomposition. When the concentration of the same catalyst was reduced to 0.3%, no reaction occurred. Using 10% pyridinium *p*-toluenesulfonate (PPTS) as catalyst no reaction was observed. Finally, when the catalyst was camphorsulfonic acid (CSA) (10%), the desired protected compound **94** was obtained in a 78% yield.



Scheme 26

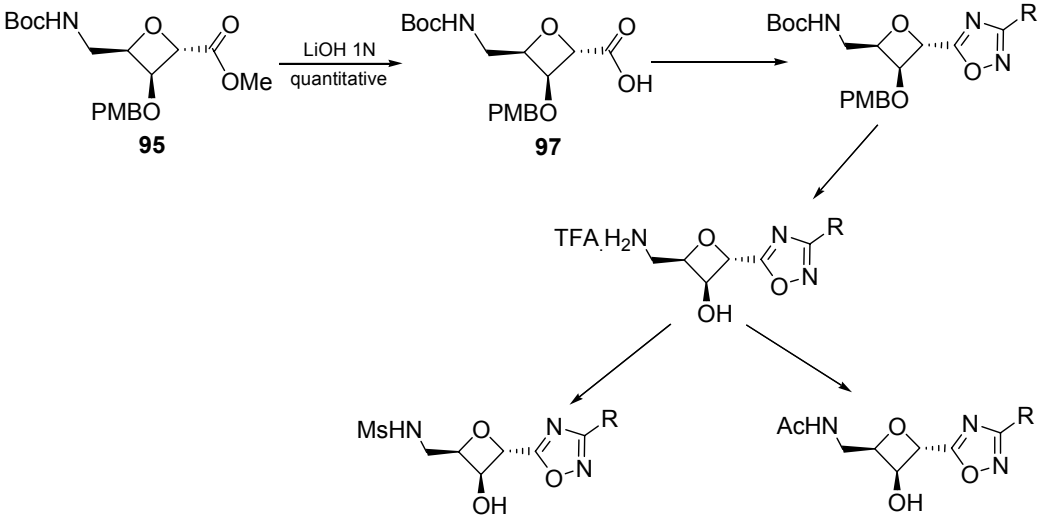
CSA was then used as catalyst for the protection of the ester **52** (Scheme 27), and *p*-methoxybenzyl trichloroacetimidate as protecting agent. However, a mixture of the desired product **95** and compound **96**, resulting from the p-methoxybenzylation on the secondary amine, was obtained. The separation of these two compounds was possible but tedious due to the similar chromatographic behaviour of both **95** and **96**.

[128] Wessel, HP; Iversen, T; Bundle, DR; *J Chem Soc Perkin Trans I* **1985**, 2247.



Scheme 27

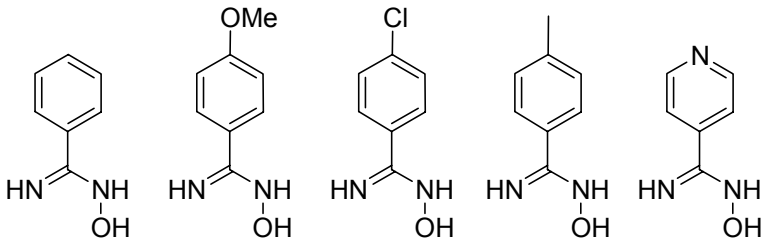
Subsequent to the protection of **52**, ester hydrolysis of **95** was accomplished in quantitative yield by treatment with aqueous LiOH, and the result encouraged us to move towards the library construction on this scaffold according to Scheme 28.



General approach to library construction on scaffold **97**.

Scheme 28

The hydroxyamidines chosen for library formation were aromatic compounds leading to different R groups (Scheme 29) such as a phenyl group as in **93**, also a *p*-methoxyphenyl and a *p*-chlorophenyl group were chosen presenting electron-withdrawing substituents on the phenyl ring. Hydroxyamidine **100** has *p*-methylphenyl as R group and displays an electron-donating effect of the CH_3 substituent on the ring. A *p*-pyridinyl was selected as R group in order to afford a heteroaromatic substituent.

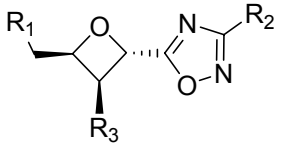


93 **98** **99** **100** **101**

Scheme 29

The results obtained for the synthesis of each individual compound of this first oxetane-based library are presented in Table 6. Reaction of carboxylic acid **97** with different hydroxyamidines (**93**, **98**-**101**) led to oxadiazoles in reasonable yields. The use of TFA for Boc cleavage furnished the desired free hydroxyl group at C-3 in 53 to 98% yield.

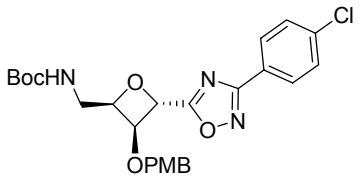
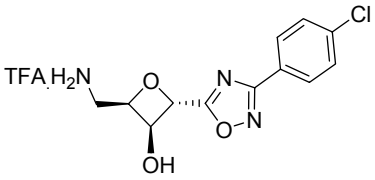
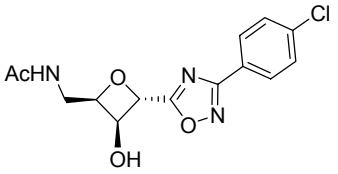
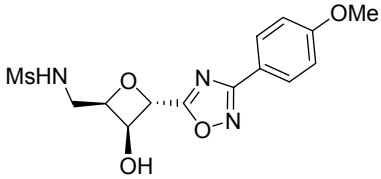
Table 6. Results obtained for the library based on scaffold **97**.



R_1	R_2	R_3	Starting Material	Product	Yield (%)
NHBoc	Ph	OPMB	**97**	**102**	43
NHBoc	*p*-OMePh	OPMB	**97**	**103**	65
NHBoc	*p*-ClPh	OPMB	**97**	**104**	59
NHBoc	*p*-MePh	OPMB	**97**	**105**	79
NHBoc	*p*-Py	OPMB	**97**	**106**	50
NH_2	Ph	OH	**102**	**107**	74
NH_2	*p*-OMePh	OH	**103**	**108**	98
NH_2	*p*-ClPh	OH	**104**	**109**	97
NH_2	*p*-MePh	OH	**105**	**110**	53
NH_2	*p*-Py	OH	**106**	**111**	89
NHAc	Ph	OH	**107**	**112**	50
NHAc	*p*-OMePh	OH	**108**	**113**	53
NHAc	*p*-ClPh	OH	**109**	**114**	47
NHAc	*p*-MePh	OH	**110**	**115**	48
NHAc	*p*-Py	OH	**111**	**116**	39
NHMs	Ph	OH	**107**	**117**	29
NHMs	*p*-OMePh	OH	**108**	**118**	23
NHMs	*p*-ClPh	OH	**109**	**119**	32
NHMs	*p*-MePh	OH	**110**	**120**	31
NHMs	Py	OH	**111**	**121**	24

However, the yields obtained for acetylation and mesylation of the free amines **107**-**111** were very poor for this type of reaction. As these reactions were performed under basic conditions, this indicates again the instability conferred by the free hydroxyl group in C-3. In fact, the chemical stability of compounds **104**, **109**, **114** and **118** was tested using the ASTA stability assay (Table 7), in which the compounds were stirred at five different pH values at 37 ºC for two hours. After that time the stability was determined by UV peak integration.

Table 7. ASTA results for compounds **104**, **109**, **114** and **118**.

	pH	t_0 area	t_{2h} area	Recovery (%)	Result
 **104**	1	587	530	90.3	Probable instability: growing peak (UV)
	4	595	569	95.6	Stable
	6	581	574	98.8	Stable
	8	580	571	98.4	Stable
	10	570	559	98.1	Stable
 **109**	1	278	262	94.2	Stable
	4	261	249	95.4	Stable
	6	237	207	87.3	Instable
	8	18	9	50.0	Instable
	10	0	0	0	Instable
 **114**	1	315	304	96.5	Stable
	4	315	311	98.7	Stable
	6	166	150	90.4	Instable
	8	0	0	0	Instable
	10	0	0	0	Instable
 **118**	1	374	373	99.7	Stable
	4	374	371	99.2	Stable
	6	361	383	106.1	Probable instability: growing shoulder
	8	43	36	83.7	Instable
	10	0	0	0	Instable

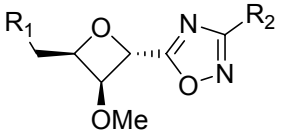
The ASTA results confirm that the free hydroxyl group at C-3 leads to instability of these oxetane derived compounds, while the corresponding PMB ether **104** was stable at least until pH 10. The stability issues explain the poor yields of the

acetylation and mesylation reactions, in which the free hydroxyl derivatives **107**-**111** are reacted in the presence of pyridine or triethylamine, respectively. Compound **53** would then only be appealing as scaffold to afford libraries in which the synthesis involves non-basic approaches.

2.2.2 Library using 2,4-Anhydro-5-*N*-(tert-butoxycarbonyl) amino-5-deoxy-3-*O*-methyl-D-*lyxonic* Acid (61) as Scaffold

The use of 2,4-anhydro-5-*N*-(*tert*-butoxycarbonyl)amino-5-deoxy-3-*O*-methyl-D-lyxonic acid **61** was foreseen to be less problematic due to the absence of the free hydroxyl at C-3. Hence, the proposed approach to 3-methoxyoxetane followed the steps previously mentioned in Scheme 24. When the acid **61** was reacted with hydroxyamidines **93**, **98**, **99**, **100**, **101**, the corresponding oxadiazoles were obtained in 55 to 72% yield (Table 8).

Table 8. Results obtained for the library based on scaffold **61**.



R_1	R_2	Starting Material	Product	Yield (%)
NHBoc	Ph	**61**	**122**	69
NHBoc	*p*-OmePh	**61**	**123**	68
NHBoc	*p*-ClPh	**61**	**124**	72
NHBoc	*p*-MePh	**61**	**125**	55
NHBoc	*p*-Py	**61**	**126**	59
NH_2	Ph	**122**	**127**	86
NH_2	*p*-OmePh	**123**	**128**	82
NH_2	*p*-ClPh	**124**	**129**	87
NH_2	*p*-MePh	**125**	**130**	87
NH_2	*p*-Py	**126**	**131**	59
NHAc	Ph	**127**	**132**	90
NHAc	*p*-OmePh	**128**	**133**	95
NHAc	*p*-ClPh	**129**	**134**	99
NHAc	*p*-MePh	**130**	**135**	88
NHAc	*p*-Py	**131**	**136**	90
NHMs	Ph	**127**	**137**	93
NHMs	*p*-OMePh	**128**	**138**	72
NHMs	*p*-ClPh	**129**	**139**	95
NHMs	*p*-MePh	**130**	**140**	74
NHMs	Py	**131**	**141**	59

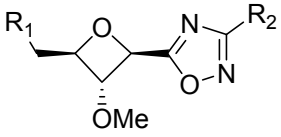
Boc cleavage was accomplished by treatment with TFA in good yields, except for the pyridinyl substituted oxadiazole, with which the corresponding free amine was only isolated in 59% yield.

As expected, the acetylation and mesylation of the amines **127** to **131** under basic conditions led to the desired products in good to excellent yields. These results confirmed the stability of a 3-methoxyoxetane derivative, in contrast to the previous results in which the scaffold exhibited the same stereochemistry but a free hydroxyl group rather than a methoxyl in C-3.

2.2.3 Library using 2,4-Anhydro-5-*N*-(tert-butoxycarbonyl) amino-5-deoxy-3-*O*-methyl-D-*ribonic* Acid (71) as Scaffold

The previously described methodology was applied to generate the corresponding 20-compound library on the 3-methoxyoxetane **71** that presents a D-*ribo* configuration. Once again the results were good (Table 9) when compared to those obtained with the free hydroxyl oxetane derivative and, with some exceptions, quite comparable to the previous library on a D-*lyxo* 3-methoxyoxetane. Therefore it can be deduced that stereochemical effects are not significant for the reactions presented herein.

Table 9. Results obtained for the library based on scaffold **71**.

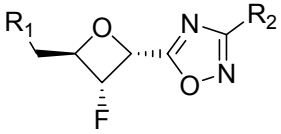


R_1	R_2	Starting Material	Product	Yield (%)
NHBoc	Ph	**71**	**142**	60
NHBoc	*p*-OMePh	**71**	**143**	46
NHBoc	*p*-ClPh	**71**	**144**	75
NHBoc	*p*-MePh	**71**	**145**	84
NHBoc	*p*-Py	**71**	**146**	83
NH_2	Ph	**142**	**147**	80
NH_2	*p*-OMePh	**143**	**148**	98
NH_2	*p*-ClPh	**144**	**149**	85
NH_2	*p*-MePh	**145**	**150**	90
NH_2	*p*-Py	**146**	**151**	94
NHAc	Ph	**147**	**152**	91
NHAc	*p*-OMePh	**148**	**153**	82
NHAc	*p*-ClPh	**149**	**154**	92
NHAc	*p*-MePh	**150**	**155**	83
NHAc	*p*-Py	**151**	**156**	92
NHMs	Ph	**147**	**157**	83
NHMs	*p*-OMePh	**148**	**158**	76
NHMs	*p*-ClPh	**149**	**159**	99
NHMs	*p*-MePh	**150**	**160**	79
NHMs	Py	**151**	**161**	85

2.2.4 Library using 2,4-Anhydro-5-*N*-(tert-butoxycarbonyl) amino-5-deoxy-3-fluoro-D-*arabinonic* Acid (79) as Scaffold

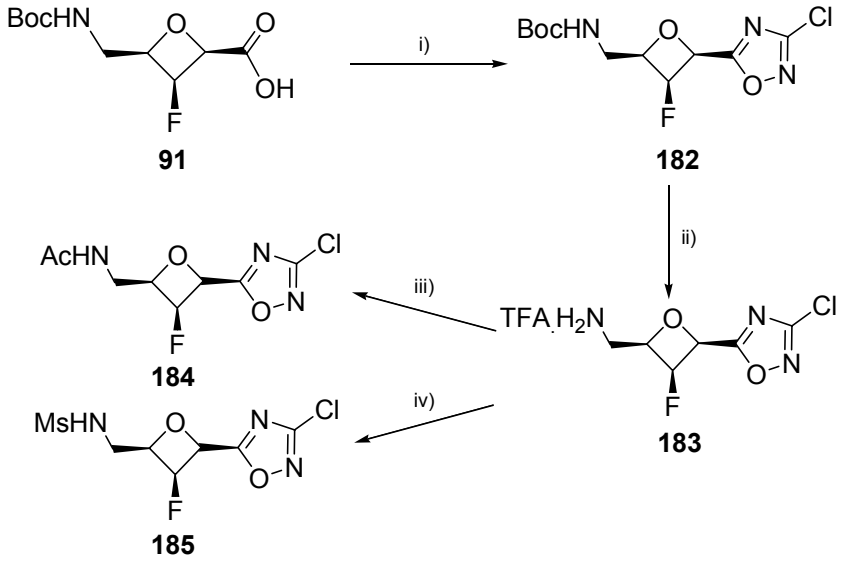
With a fluoride substituent at C-3 and a stereochemistry different from the previously reported scaffolds, **79** was reacted with the hydroxyamidines **93**, **98**, **99**, **100** and **101** (Table 10). After cyclodehydration, the corresponding oxadiazoles **162** to **166** were obtained in yields between 55 and 84%. Boc cleavage was accomplished by treatment with TFA to give the free amines **167**-**171,** which were further reacted with acetic anhydride or mesyl chloride in basic media to afford the corresponding acetylated and mesylated derivatives in good yields. Hence, the synthesised scaffold **79** and subsequent derivatives were stable under acidic (TFA) and basic (Py, ET_3N) conditions.

Table 10. Results obtained for the library based on scaffold **79**.

		Starting Material	Product	Yield (%)
R_1	R_2			
NHBoc	Ph	**79**	**162**	81
NHBoc	*p*-OMePh	**79**	**163**	83
NHBoc	*p*-ClPh	**79**	**164**	84
NHBoc	*p*-MePh	**79**	**165**	71
NHBoc	*p*-Py	**79**	**166**	55
NH_2	Ph	**162**	**167**	94
NH_2	*p*-OMePh	**163**	**168**	63
NH_2	*p*-ClPh	**164**	**169**	75
NH_2	*p*-MePh	**165**	**170**	76
NH_2	*p*-Py	**166**	**171**	88
NHAc	Ph	**167**	**172**	71
NHAc	*p*-OMePh	**168**	**173**	98
NHAc	*p*-ClPh	**169**	**174**	88
NHAc	*p*-MePh	**170**	**175**	90
NHAc	*p*-Py	**171**	**176**	98
NHMs	Ph	**167**	**177**	74
NHMs	*p*-OMePh	**168**	**178**	96
NHMs	*p*-ClPh	**169**	**179**	83
NHMs	*p*-MePh	**170**	**180**	55
NHMs	Py	**171**	**181**	72

2.2.5 Derivatisation of 2,4-Anhydro-5-*N*-(tert-butoxycarbonyl) amino-5-deoxy-3-fluoro-D-*xylonic* Acid (91)

To furnish some comparative examples of related oxadiazoles on a 3-fluorooxetane with a different stereochemistry than those reported above, 2,4-anhydro-5-*N*-(*tert*-butoxycarbonyl)-amino-5-deoxy-3-fluoro-D-xylonic acid **91** was reacted with *p*-chlorophenyl hydroxyamidine **99** to afford the oxadiazole **182** in 79% yield (Scheme 30). Boc cleavage was accomplished by treatment with TFA in 90% yield. Acetylation and mesylation of **183** were achieved in 82% and 84% yield, respectively.



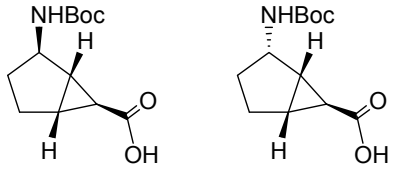
i) a. HATU, DIPEA, rt; b.hydroxyamidine; c.80 ºC, 79%; ii) TFA, DCM, rt, 90%; iii) Ac_2O, Py, rt, 82%; iv) MsCl, Et_3N, DCM, 0 ºC to rt, 84%.

Scheme 30

In conclusion, the syntheses of small libraries based on oxetane δ-amino acid scaffolds were successfully accomplished. While 2,4-anhydro-5-*N*-(*tert*-butoxycarbonyl)amino-5-deoxy-D-lyxonic acid (**53**) proved to be unstable under the basic conditions for derivatisation, the methodology chosen proved to be efficient and not dependent on stereochemistry with 3-methoxy or 3-fluoro-oxetane δ-amino acids.

2.3 Library Construction on Bicyclic δ- Amino Acid Scaffolds

Amongst the vast Roche in-house collection of compounds, the racemic bicyclic δ-amino acids **186** and **187** seemed interesting for comparison with the oxetane based analogs. The bicyclic system confers rigidity to the scaffold, which is more lipophilic than the oxetane. Hence, the corresponding 20-compound libraries were efficiently prepared using the already described methodology.

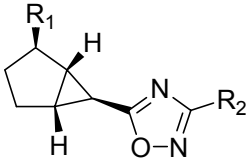


186 **187**

Scheme 31

To afford the oxadiazoles **188**-**192** (Table 11), **186** was submitted to coupling with the hydroxyamidines **93**, **98**, **99**, **100** and **101** in the presence of DIPEA and using HATU as coupling agent. Heating the reaction mixture allowed the already mentioned cyclodehydration, and the target products were obtained in 38% to 57% yield. It was observed that for complete cyclodehydration these reactions needed higher temperature when compared to the corresponding reactions on oxetane δ-amino acid scaffolds (100 ºC instead of 80 ºC). Even after the increase in temperature, the time for completion was also longer (usually overnight), the yields were lower than for the corresponding reactions with oxetane δ-amino acid scaffolds, when the scaffold **186** was reacted.

Table 11. Results obtained for the library based on scaffold **186**.

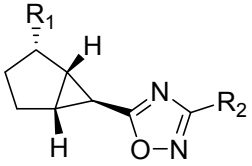


R_1	R_2	Starting Material	Product	Yield (%)
NHBoc	Ph	**186**	**188**	53
NHBoc	*p*-OMePh	**186**	**189**	66
NHBoc	*p*-ClPh	**186**	**190**	38
NHBoc	*p*-MePh	**186**	**191**	57
NHBoc	*p*-Py	**186**	**192**	57
NH_2	Ph	**188**	**193**	62
NH_2	*p*-OMePh	**189**	**194**	89
NH_2	*p*-ClPh	**190**	**195**	98
NH_2	*p*-MePh	**191**	**196**	77
NH_2	*p*-Py	**192**	**197**	90
NHAc	Ph	**193**	**198**	99
NHAc	*p*-OMePh	**194**	**199**	99
NHAc	*p*-ClPh	**195**	**200**	96
NHAc	*p*-MePh	**196**	**201**	99
NHAc	*p*-Py	**197**	**202**	98
NHMs	Ph	**193**	**203**	96
NHMs	*p*-OMePh	**194**	**204**	97
NHMs	*p*-ClPh	**195**	**205**	89
NHMs	*p*-MePh	**196**	**206**	99
NHMs	Py	**197**	**207**	79

Boc cleavage was accomplished by treatment with TFA to give the free amines **193**-**197** in yields between 62% and 98%. These compounds were further reacted with acetic anhydride or mesyl chloride in basic medium to afford the corresponding acetylated and mesylated derivatives in very good yield. Thus, compound **186** showed to be a feasible scaffold for the targeted libraries.

Once again, the use of the bicyclic δ-amino acid **187** for oxadiazole synthesis showed the requirement of higher temperature for cyclodehydration. After heating at 100 ºC, the desired oxadiazoles **208**-**212** (Table 12) were obtained in reasonable yields. Reaction of **208**-**212** with TFA led to the free amines **213**-**217** with yields in the range of 71 to 97%. Treatment of **213**-**217** with acetic anhydride or mesyl chloride gave the corresponding *N*-acetyl and *N*-mesyl derivatives in good yields.

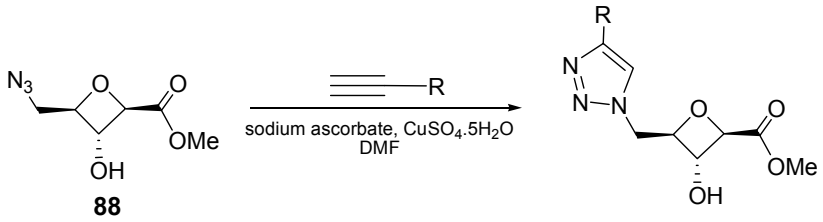
Table 12. Results obtained for the library based on scaffold **187**.



R_1	R_2	Starting Material	Product	Yield (%)
NHBoc	Ph	**187**	**208**	48
NHBoc	*p*-OMePh	**187**	**209**	67
NHBoc	*p*-ClPh	**187**	**210**	64
NHBoc	*p*-MePh	**187**	**211**	52
NHBoc	*p*-Py	**187**	**212**	41
NH_2	Ph	**208**	**213**	97
NH_2	*p*-OMePh	**209**	**214**	81
NH_2	*p*-ClPh	**210**	**215**	84
NH_2	*p*-MePh	**211**	**216**	71
NH_2	*p*-Py	**212**	**217**	84
NHAc	Ph	**213**	**218**	63
NHAc	*p*-OMePh	**214**	**219**	97
NHAc	*p*-ClPh	**215**	**220**	98
NHAc	*p*-MePh	**216**	**221**	68
NHAc	*p*-Py	**217**	**222**	99
NHMs	Ph	**213**	**223**	71
NHMs	*p*-OMePh	**214**	**224**	64
NHMs	*p*-ClPh	**215**	**225**	93
NHMs	*p*-MePh	**216**	**226**	80
NHMs	Py	**217**	**227**	63

2.4 Triazole library starting from an Oxetane δ-Azido Ester Scaffold

Click reactions (see chapter 1.3) are very attractive for medicinal chemistry purposes. Efficiency and practical simplicity are crucial qualities for synthesis in an industrial environment. As 1,2,3-triazoles are promising pharmacophores (see chapter 1.3), an approach towards their synthesis on an oxetane scaffold was tried using the click Huisgen's 1,3-dipolar cycloaddition of alkynes to the oxetane δ-azido ester **88** (Scheme 32), catalysed by copper (I).



Scheme 32

Libraries can be built up manually and sequentially as demonstrated above, and this methodology was particularly taken in account in the current work. Nevertheless, the efficiency can be increased using automated parallel chemistry.

The use of a click reaction to form a library in one single scaffold opened the way to the synthesis in a parallel fashion. In fact, the workflow for compound production in a pharmaceutical company has to be based on simple procedures, so that automated production can be feasible. This process is exemplified in Fig. 3 and usually starts with the selection of a core/scaffold. Then the appropriate chemistry will be established and a new library designed based on the available building blocks (either commercial or synthesised in-house).

Following the building block retrieval, the scaffold is reacted in parallel with different building blocks. The reaction mixtures are analysed by LC-MS and the collected crude products go to a HT purification laboratory. After preparative HPLC (prep-HPLC) purification, the fractions are analysed again, the solvents used during purification process are then removed and the products usually obtained as lyophilised powders. Once the fractions are collected in pre-tared propylene vials, the yield is then obtained by automated weight measurement of the fractions that contain the pure products. The new compounds are then transfered to standard pre-tared glass vials with bar code identification and registered in the company database. The compounds are then delivered to the logistic department, where screening plates are prepared and compounds are stored.

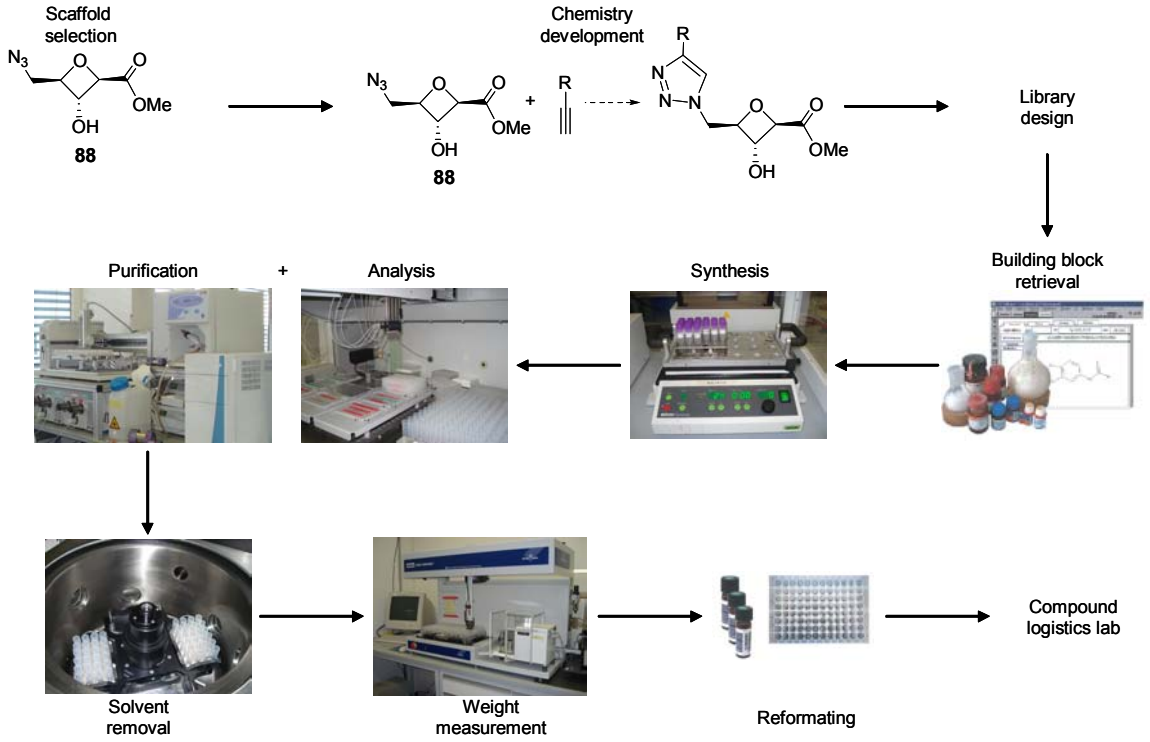


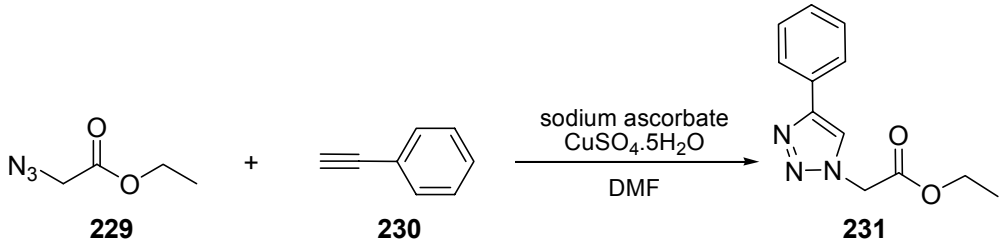
Fig. 3. Typical workflow for library production using automated medicinal chemistry techniques.

In our approach to automated synthesis of 1,2,3-triazoles with an oxetane scaffold we decided to use DMF as reaction solvent so that the reaction mixture could be directly injected on the prep-HPLC with no further work-up. After the injection onto a

reverse phase column and using acidic (10% TfOH) or basic (10% Et_3N) water/acetonitrile gradient, the residual salts from the catalyst could be removed with the water flow, allowing the easy recovery of the desired products after the increase of acetonitrile.

As a test reactions solid copper sulphate and sodium ascorbate were added to a DMF solution of **88** and phenylacetylene. After stirring at rt for 3h, the corresponding phenyl substituted triazole **228** (Table 12) was obtained in 77% yield. Some reports have been made on the use of microwave to accelerate this type of reaction.[129] Thus, after adding the same reaction components in a sealed flask, the mixture was sunmitted to microwave irradiation at 80 ºC for 2 min leading to the desired product **228** in 73% yield.

To further improve the yields phenylacetylene was reacted with ethyl azidoacetate (**229**) as a test azide. In DMF (Scheme 33) and after addition of solid sodium ascorbate and copper sulphate, the corresponding 1,2,3-triazole **231** was obtained in 76% yield after stirring at rt for 2h. When the same catalytic system was added as an 1M aqueous solution of both sodium ascorbate and copper sulphate, the yield was reduced to 72%. Nevertheless the reaction was completed after 1.5 h. When the reaction was performed adding two separated 1M aqueous solutions of sodium acetate and copper sulphate, it was complete after 45 min and the yield was increased to 99%. Hence, this was the procedure selected for the addition of acetylenes to the oxetane δ-azido ester **88**. Moreover, it was decided not to use the microwave conditions because the microwave apparatus does not allow parallel reactions and between each sample, time for heating and cooling is required.



229 **230** **231**

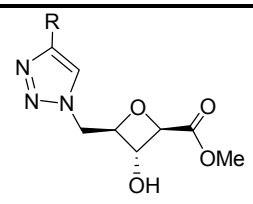
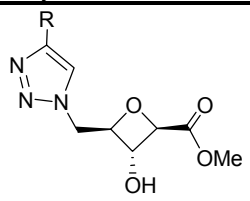
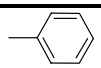
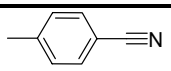
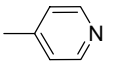
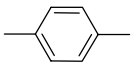
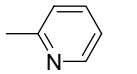
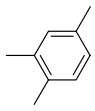
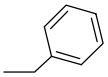
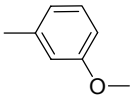
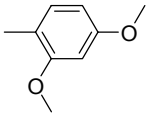
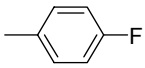
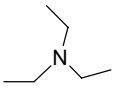
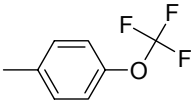
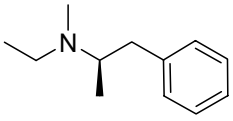
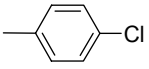
Testing reaction with the azide **229**

Scheme 33

[129] Khanetskyy, B; Dallinger, D; Kappe, CO; *J Comb Chem* **2004,** 6:884.

A final test to all the process was made by reacting scaffold **88** with cyclohexyl acetylene in DMF, with addition of two separate 1 M aqueous solutions of sodium ascorbate and copper sulphate. After stirring for 1 h the reaction was complete (LC-MS), and the reaction mixture was injected directly onto the preparative HPLC column. As the UV response for detection was not ideal, the ELSD (Evaporative Light Scattering Detection) was chosen as detection method. However, the product retrieved after purification led only to a reasonable yield of 62 % yield for **232** (Table 13). In fact, prep-HPLC often leads to a non-quantitative recovery in parallel synthesis. The purification process is not optimised for each individual compound because the goal is to purify the largest number of compounds that may display different responses to the chosen purification method.

Table 13. Results obtained for the library based on scaffold **88**.

 -R	Product	Yield (%)	 -R	Product	Yield (%)
	**228**	77		**240**	98
	**232**	62		**241**	71
	**233**	77		**242**	59
	**234**	40		**243**	72
	**235**	95		**244**	78
	**236**	86		**245**	66
	**237**	70		**246**	66
	**238**	34		**247**	58
	**239**	41			

The aim in the synthesis and purification of a library in a pharmaceutical company is usually to obtain enough material for biological testing. The reactions must be clean and straightforward, but the recovery yield will be only an issue when a compound becomes a potential product. Therefore we continued with the parallel synthesis of a 15-compound library to give compounds **233**-**247** (Table 13) using the reaction conditions worked out thus far.

The parallel Huisgen's 1,3-dipolar cycloaddition of alkynes to the oxetane δ-azido ester **88** catalysed by copper(I) was complete after 1 h as seen by LC-MS. All reactions were clean and led to complete conversion of the starting materials to the desired products, as exemplified by the chromatogram shown in Fig. 4 for the reaction of **88** with *p*-methylphenyl acetylene.

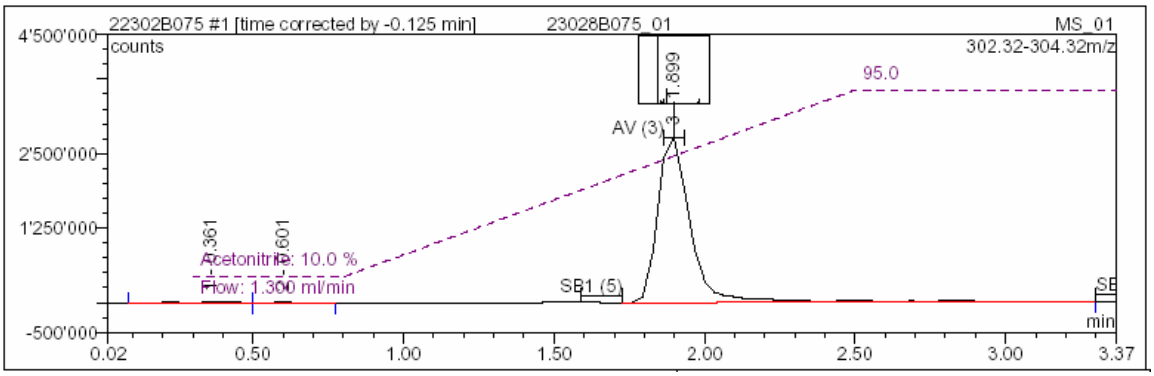


Fig. 4. LC-MS chromatogram of the crude reaction of **88** with p-methylphenyl acetylene.

Once a low response to UV or scatter detection was obtained for some of the products, the MS detection seemed the more efficient detection method for the prep-HPLC purification.

In order to evaluate the efficiency of this click reaction, the crude **235** was flash chromatographed and an excellent yield was obtained (95%). Moreover the LC-MS chromatogram of the crude **240**, showed a low intensity peak with the available detection methods, and it was also flash chromatographed to give an excellent 98% yield of pure **240**.

Compounds **241**, **246** and **247** proved to be very basic for standard acidic purification (10% of TfOH) according to their evaluation by LC-MS, and the separation from the copper salts would not be efficient. Thus, **241** and **246** were purified on the basic mode of prep-HPLC (10% of Et_3N), and **247** was flash chromatographed on a basic amine column since it showed very low response to the available detection methods by LC-MS. However, it seemed that some **247** was retained in the column leading only to a 58% yield of the pure product.

In conclusion, the 1,2,3-triazole synthesis showed to be a quantitative transformation, and any lowered yields are related to the purification process. The lower yields presented in Table 12 were obtained for the compounds that displayed a lower response for MS detection. In any case, the amounts obtained for each compound were sufficient for testing and for storage in the Roche compound depository.

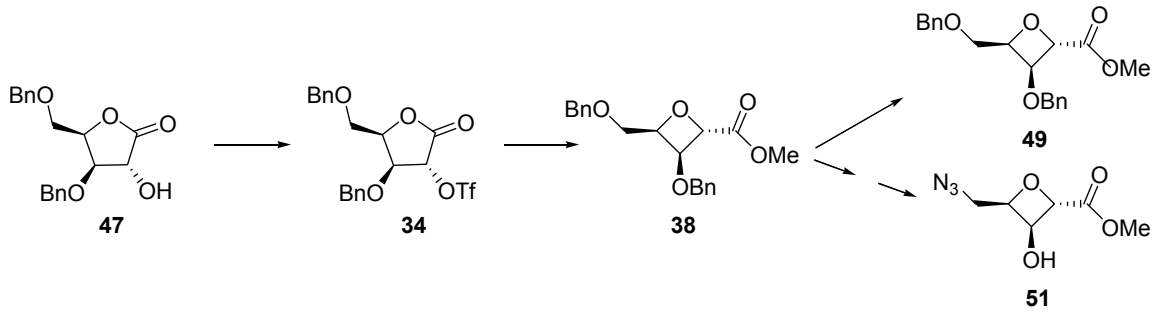
2.5 Structural Assignments

The following chapter will focus on the structural assignment of the compounds synthesised. Based on analytical data (MS, IR, 1D NMR and 2D NMR) it was possible to clarify stereochemical questions and assign the structure of the by-product 2,4,3,5-di-*O*-benzylidene-D-xylonic acid.

2.5.1 D-*lyxo* Configured Oxetanes

The ring contraction reaction of 1,4-lactones was reported by Fleet's group to give oxetanes with well-defined stereochemistry. In this work (chapter 2.1.1), the synthesis of D-*lyxo* configured oxetanes such as **38**, **49** and **51** (Scheme 34) was described. The ^{1}H NMR data obtained for the known **38** were in agreement with

those reported in the literature.[75] However, no coupling constants were available for comparison.



Scheme 34

The observation of long range coupling constants in the resulting derivatives **38** ($J_{2,4}$ = 0.4 Hz) and **49** ($J_{2,4}$ = 0.8 Hz) did not seem to be in keeping with the D-*lyxo* configuration postulated[75] as ^4J coupling constants in sterically fixed systems are usually indicative of a W-configuration.[130] Thus, with the observation of a $^4J_{2,4}$ long range coupling, both protons H-2 and H-4 might be expected to be on the same side of the oxetane ring. Therefore, the crystalline azide **51** was subjected to X-ray crystallographic investigation which clearly showed the D-*lyxo* configuration with the protons H-2 and H-4 on opposite faces of the oxetane ring (Fig. 5). The oxetane ring has a relative high pucker angle of 13.2° but it can not account for a W-configuration. Thus, in this case the "W-rule" for ^1H NMR long range couplings does not apply.

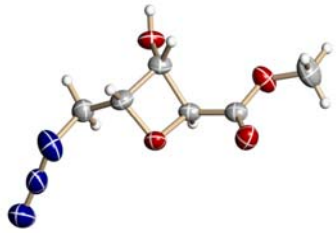


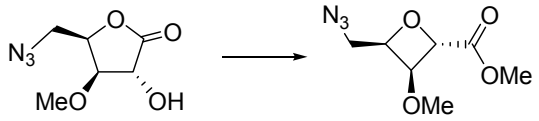
Fig. 5. Ortep plot of azide **51**.

[75] Witty *et al. Tetrahedron Lett* **1990**, 31(33):4787.
[130] a) Günther, H. *NMR-Spektroskopie*, Georg Thieme Verlag: Stuttgart **1973**; 122. b) Atta-ur-Rahman. *Nuclear Magnetic Resonance-Basic Principles*, Springer-Verlag: New York **1986**; 85.

X-ray structures of related non-annelated oxetane derivatives prepared by Paternò-Büchi[131] or ring contraction reactions[132,77] have also been reported.

The D-*lyxo* configuration was then unequivocally assigned. The construction of libraries on D-*lyxo* oxetanes gave access to a great number of NMR data. It was observed that H-2 and H-3, which are *trans*-oriented vicinal protons, exhibit a coupling constant in the range of 3.7 to 5.7 Hz (average 4.7 Hz) and for the *cis*-oriented H-3 and H-4, the obtained coupling constant was in the range of 5.7 to 7.1 Hz (average 6.8 Hz).

The synthesis of 3-methoxy oxetanes with D-*lyxo* configuration was achieved in the present work by means of ring contraction of the 3-methoxyxylono-1,4-lactone **58** (Scheme 35). For this 3-methoxy oxetane and its derivatives, the coupling constants for both *cis*- and *trans*-related vicinal protons were in the above mentioned range.



58 **59**

Scheme 35

The ^{1}H NMR and COSY spectra for the D-*lyxo* oxetane **59** is depicted in Fig. 6 to exemplify the ^{1}H NMR pattern for this configuration. The corresponding signal for H-2 is a doublet (d) at δ 5.05 ppm with a $J_{2,3}$ of 4.8 Hz followed by a quartet (q) at δ 4.92 ppm assigned to H-4, indicating that $J_{3,4} \approx J_{4,5a} \approx J_{4,5b} \approx 6.3$ Hz. At δ 4.44 ppm a double doublet (dd) is obtained for H-3, which exhibits the expected $J_{2,3}$ and $J_{3,4}$ of 4.8 and 6.6 Hz, respectively. The singlet at δ 3.86 ppm integrates 3H and appears in the typical region of the methyl esters. At δ 3.69 ppm the signal of H-5a is observed presenting the typical part A pattern of the ABX system to which it belongs, while part B corresponds to H-5b at δ 3.64 ppm. The observed $J_{5a,5b}$ = 13.2 Hz is in agreement with the expected geminal coupling constant. The assignments were

[131] a) Bach, T; Jödicke, K; Kather, K; Hecht, J; *Angew Chem Int Ed* **1995**, 34:2271. b) Kotila, S; Jäntti, A; Penttinen, S; Bach, T; *Acta Cryst* **1996**, C52:1722. c) Bach, T; Jödicke, K; Kather, K; Fröhlich, R; *J Am Chem Soc* **1997**, 119:2437.
[132] a) Suzuki, M; Tomooka, K; *Synlett* **2004**, 4:651.
[77] Jenkinson (née Barker) *et al. Tetrahedron Asymm* **2004**, *15*, 2667.

confirmed by a 2D COSY experiment (Fig. 7) where H-2 exhibits only one cross peak with H-3, and H-3 shows a second coupling with H-4. In addition H-4 shows cross peaks with H-3 and with H-5a and H-5b.

Moreover, the stereochemistry was confirmed by X-ray crystallography after derivatisation of the corresponding 3-methoxy oxetane δ-amino acid. X-ray of compounds **125** and **130** (Fig. 8) clearly showed the D-*lyxo* configuration with the oxadiazole ring oriented below the oxetane moiety, while the methoxy and the amino groups were on the upper side of the oxetane ring, well establishing that no configurational changes had resulted from the oxadiazole formation.

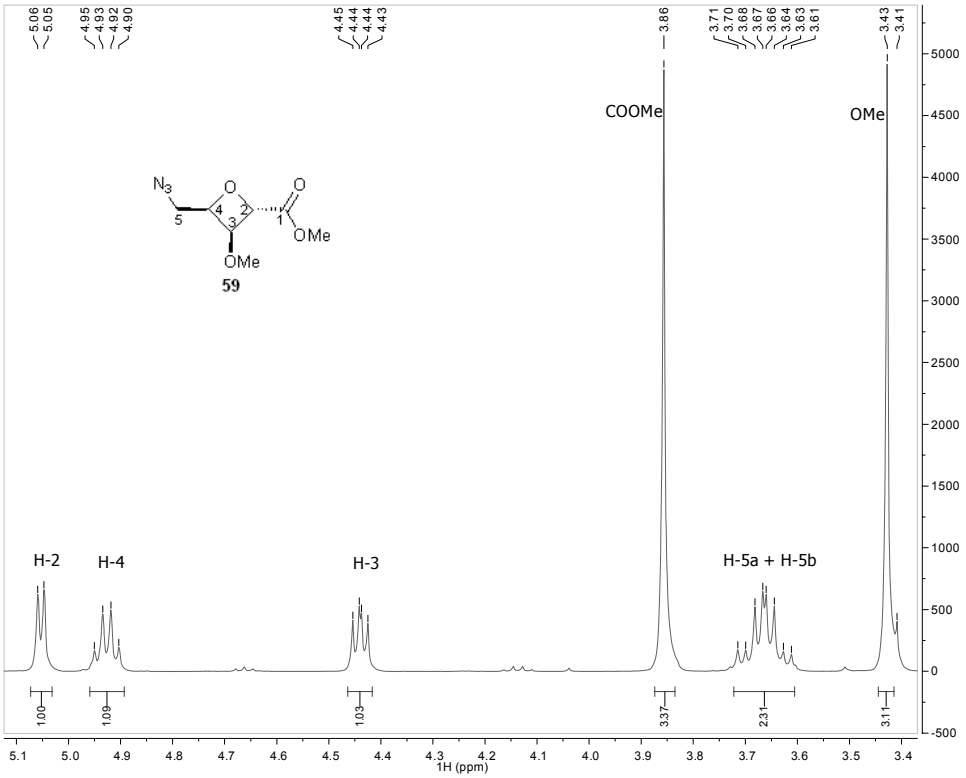


Fig. 6. 1H NMR spectrum of **59** in $CDCl_3$ at 400 MHz.

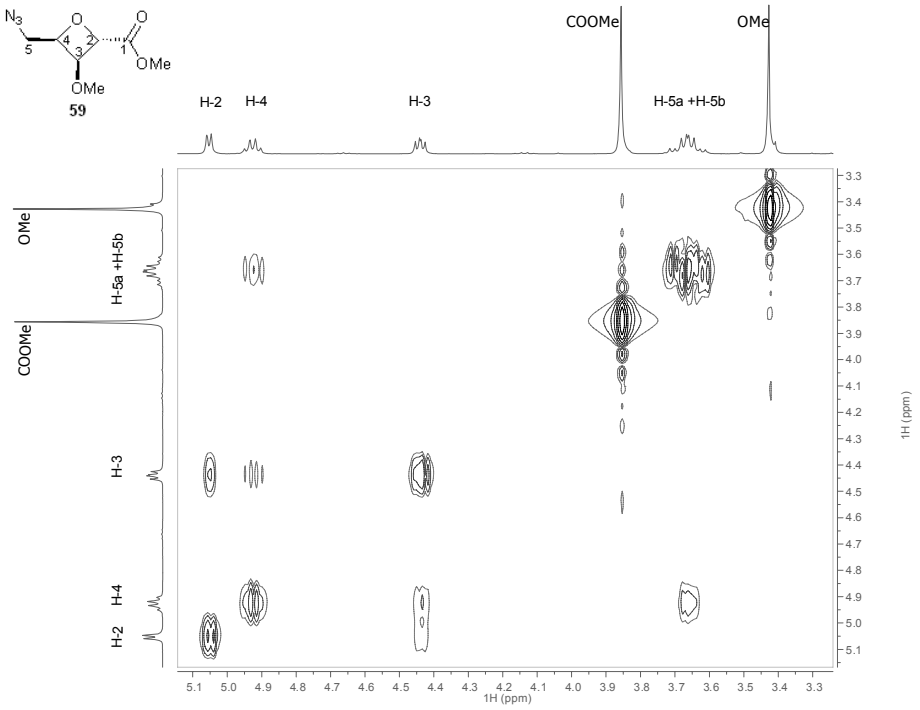


Fig. 7. 2D-COSY spectrum of **59** in $CDCl_3$ at 400 MHz.

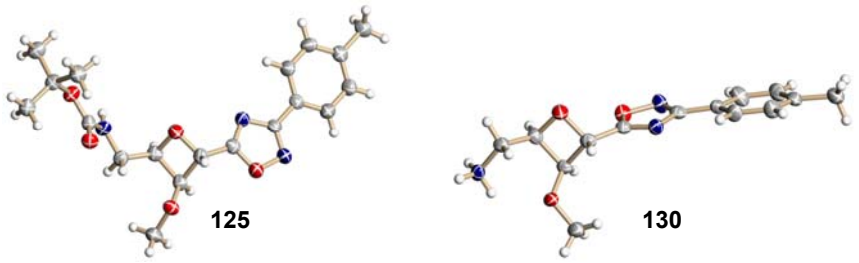
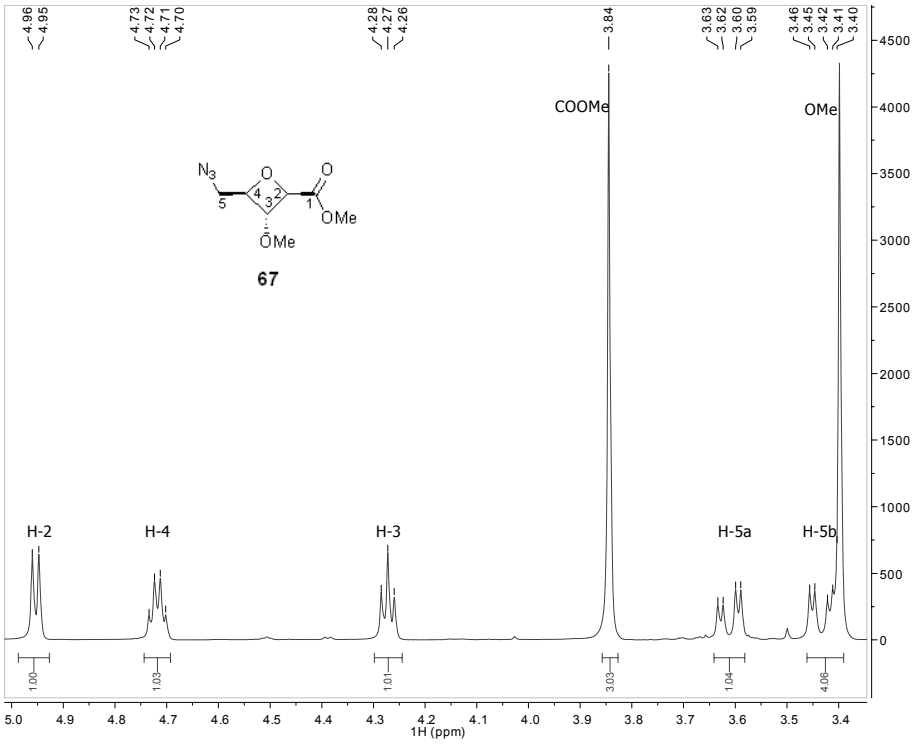


Fig. 8. Ortep plot for compounds **125** and **130**.

2.5.2 D-*ribo* Configured Oxetanes

Ring contraction of D-ribono-1,4-lactones was reported to yield D-*ribo* configured oxetanes as major products.[59,75] This was confirmed by the expected triplet for H-3 at δ 4.27 ppm in the ^{1}H NMR spectrum of **67** (Fig. 9). Once H-3 has a *trans*-relationship with both H-2 and H-4, $J_{2,3}$ is the same as $J_{3,4}$ with a value of 5.0 Hz, characteristic for *trans*-related vicinal protons in similar oxetane systems as mentioned above.

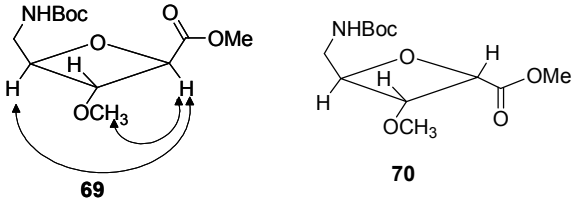
[59] Lucas *et al. J Carbohydr Chem* **2008**, 27(*3*):172.
[75] Witty *et al Tetrahedron Lett* **1990**, *31*(33):4787.



67

Fig. 9. ^{1}H NMR spectrum of **67** in $CDCl_3$ at 400 MHz.

A 2D NOESY experiment for the NHBoc derivative **69** (Fig. 10) showed a cross peak between H-2 and H-4 and between the H-2 and the 3-methoxy protons reinforcing the assigned stereochemistry. Moreover, the corresponding cross peaks were not detected for the D-*arabino* derivative **70**.



69 **70**

Fig. 10. Long-range correlations observed by 2D-NOESY in $CDCl_3$ at 400 MHz that differentiate compounds **69** and **70**.

2.5.3 D-*arabino* Configured Oxetanes

As an example in the D-*arabino* series, the ^{1}H NMR spectrum of the fluoro derivative **77** is presented in Fig. 11. Here the characteristic couplings of the fluorine atom with the geminal and vicinal protons are also observed. The H-3 signal is a ddd at δ 5.53 ppm with a characteristic $J_{3,F}$ of 56.1 Hz. Moreover, the signals for H-2 and H-4 exhibit coupling constants with the fluorine of 15.2 Hz and 19.1 Hz, respectively.

Coupling constants of D-*arabino* configured oxetanes are no exception to the previous mentioned characteristic values for *trans*- and *cis*-oriented vicinal protons on the oxetane ring, and the average of $J_{2,3}$ and $J_{3,4}$ for the D-*arabino* 3-fluoro oxetane library is 6.5 ± 0.4 Hz and 5.0 ± 0.3 Hz, respectively.

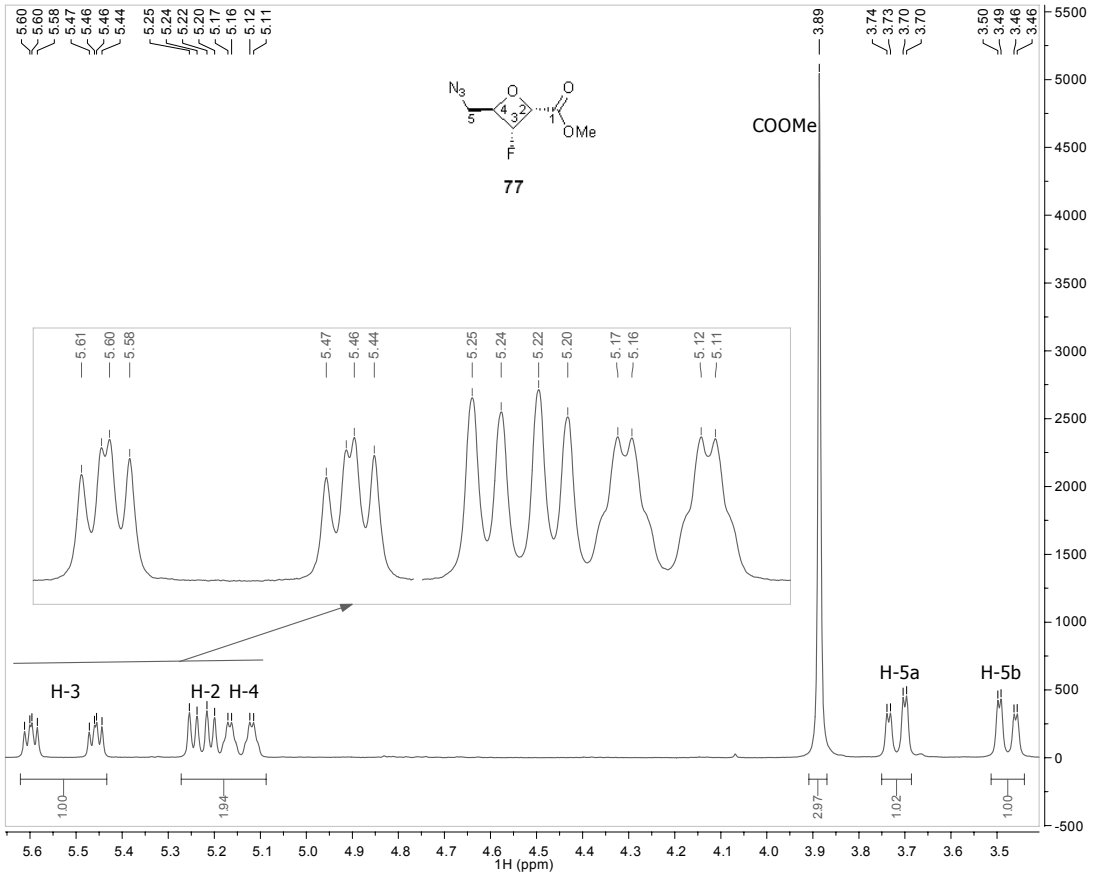


Fig. 11. ^{1}H NMR spectrum of **77** in $CDCl_3$ at 400 MHz.

2.5.4 D-*xylo* Configured Oxetanes

D-*Xylo* configured oxetane derivatives were obtained by fluorination with DAST of the corresponding the D-*ribo* 3-hydroxy oxetane **88** (see chapter 2.1.5) with inversion of configuration at C-3. The seven D-*xylo* fluorinated oxetanes synthesised show the expected dt for the H-3 signal as shown on the ^{1}H NMR spectrum of compound **90** depicted in Fig. 12. Nevertheless, the exhibited $J_{2,3}$ and $J_{3,4}$ ($J_{2,3}\approx J_{3,4}$) values are between 6.0 and 5.6 Hz with an average of 5.8 Hz, falling into the border line between the values characteristic for *cis*- or *trans*-oriented vicinal protons on the studied oxetane systems. Fortunately, it was possible to have X-ray crystallographic data for the oxadiazole derivative **183**, confirming unequivocally the D-*xylo* configuration, with all the substituents on the same side of the oxetane ring (Fig. 13).

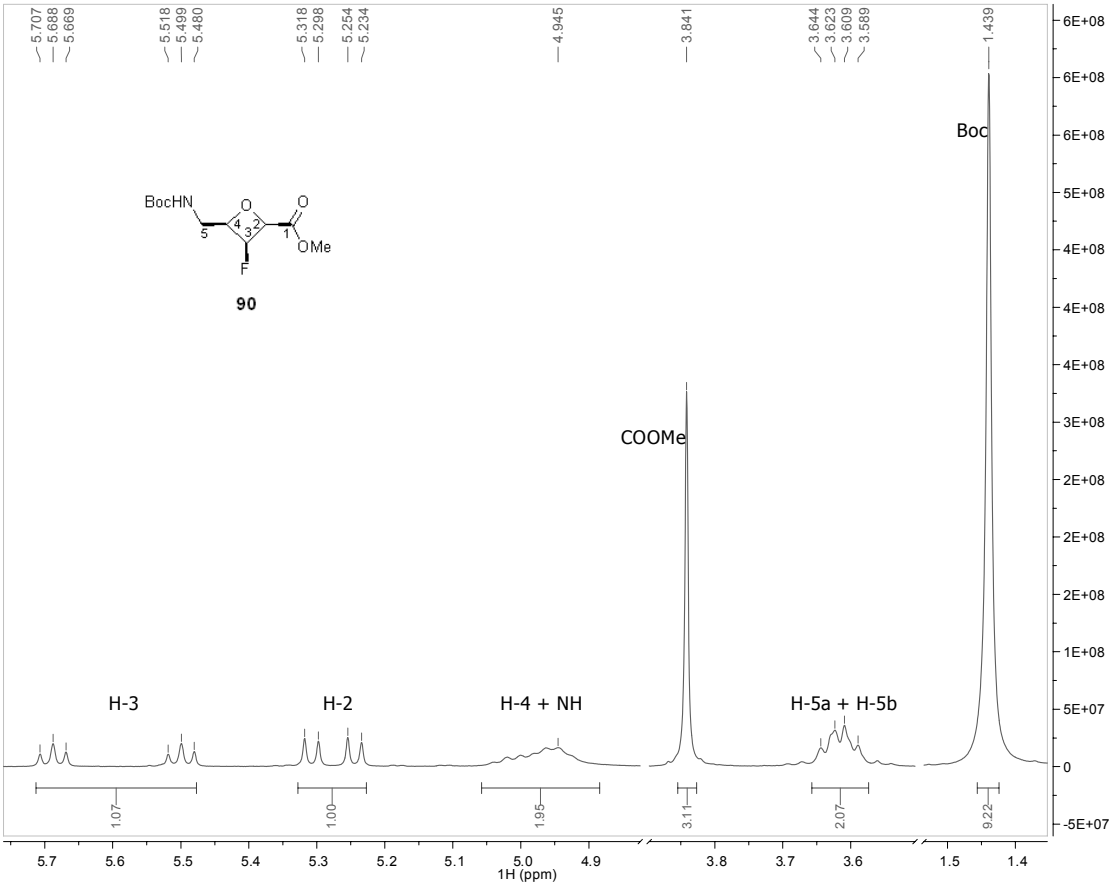


Fig. 12. 1H NMR spectrum of **90** in $CDCl_3$ at 400 MHz.

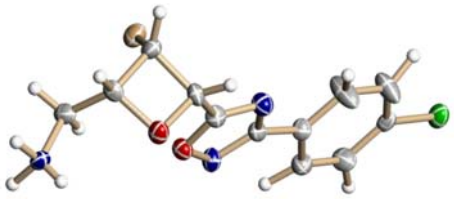
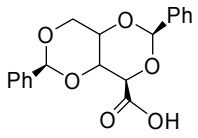


Fig. 13. Ortep plot of compound **183**.

2.5.5 Structural Assignment of 2,4;3,5-Di-*O*-benzylidene-D-*xylonic* Acid

For the known 2,4;3,5-di-*O*-benzylidene-D-xylonic acid **75** (see chapter 2.1.4) NMR data were not available in the literature, and the ^{1}H NMR spectrum (Fig. 14) did not allow by itself the clear identification of the by-product **75**. Nevertheless, melting point and specific rotation were in agreement with those reported in the literature.[124] An IR spectrum showed the carbonyl band at 1738 cm^{-1} and a band at 2580-2620 cm^{-1} for the hydroxyl group indicative of the carboxylic acid function.



75

With this evidence on the identity of the by-product, the ^{1}H NMR signals were easily assigned from 1D ^{1}H NMR and 2D COSY experiments, with the exception of protons H-6 and H-7, which could not be distinguished from each other. The assignment of H-6 and H-7 was possible by 2D HMBC (Fig. 15), in which a long- range coupling between C-7 and H-5a/H-5b was observed, which was not detected for C-6. Then, by 2D HSQC (Fig. 16) correlations C-6/H-6 and C-7/H-7 were observed, respectively. From a 2D NOESY experiment (Fig. 17), a cross peak between H-4 and H-6 was observed, which suggested the correct conformation of **75** as the double chair depicted in Fig. 17**.** All ^{3}J proton-proton couplings were small and thus in keeping with this conformational assignment.

[124] Zinner *et al Carbohydr Res* **1968**, 7:38.

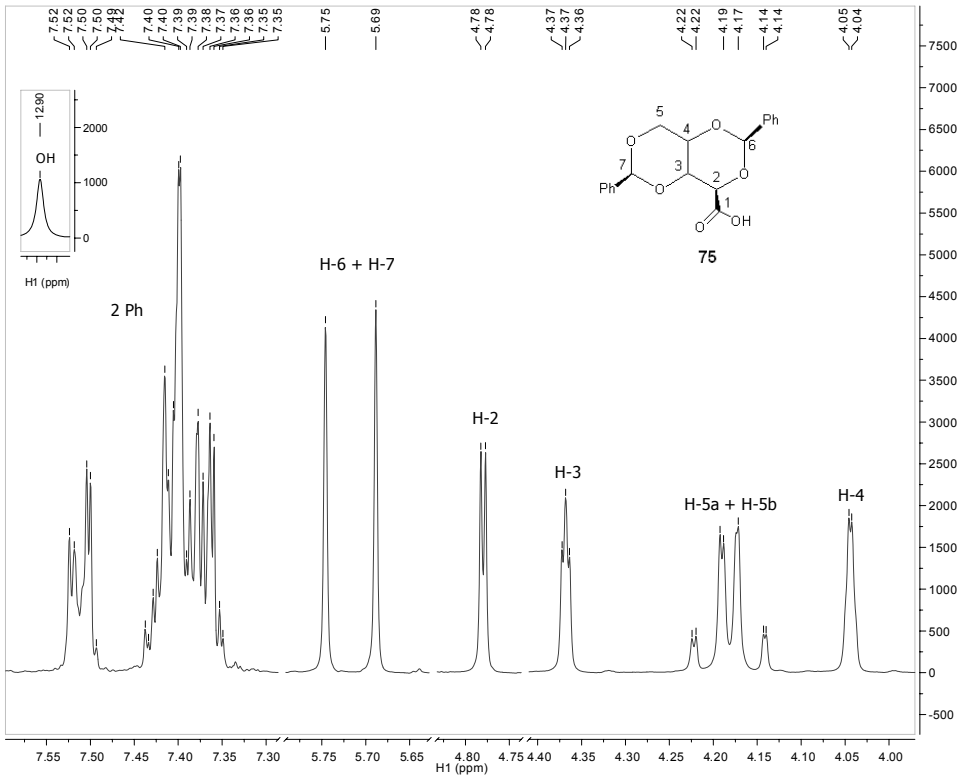


Fig. 14. ^{1}H NMR spectrum of compound **75** in DMSO at 400 MHz.

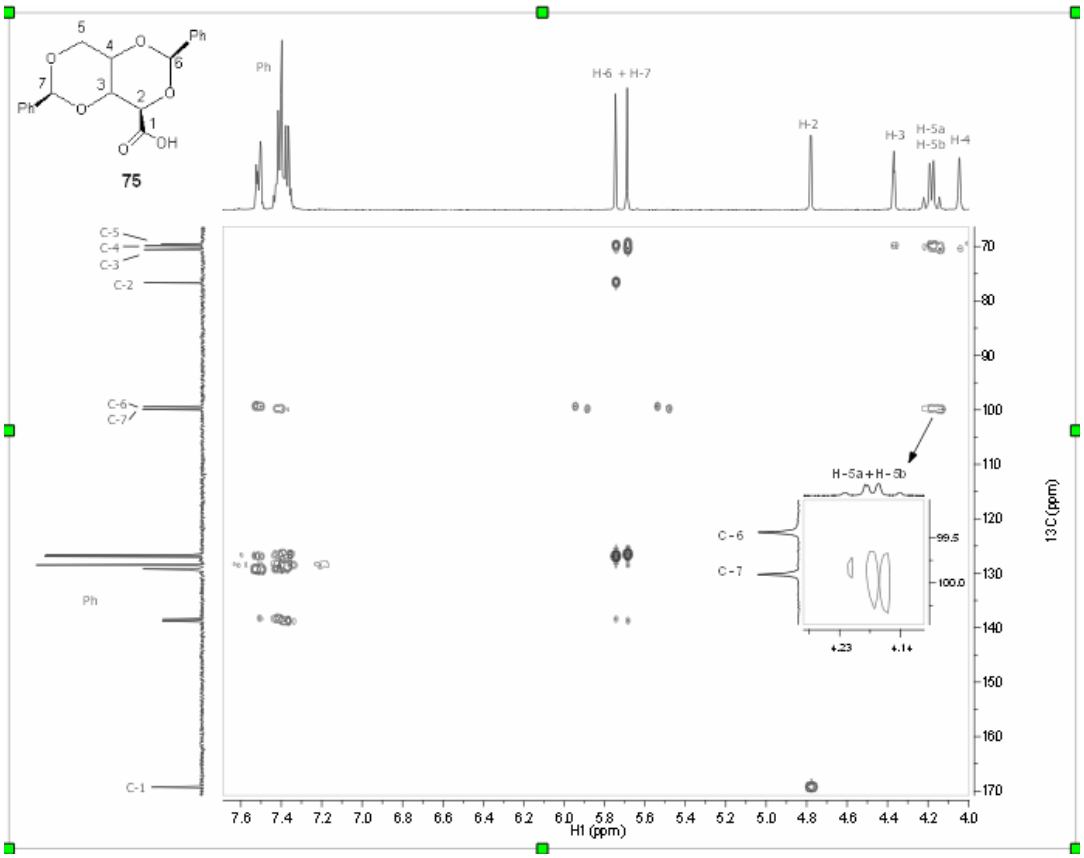


Fig. 15. 2D HMBC spectrum of compound **75** in DMSO at 100 MHz.

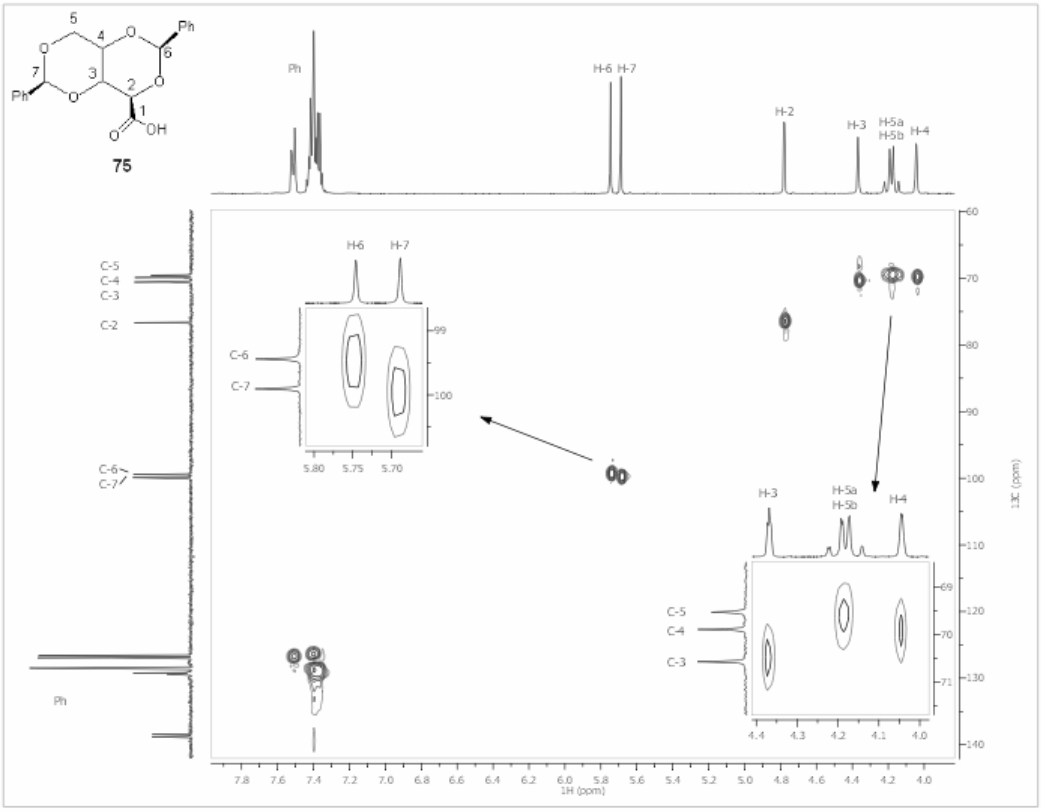


Fig. 16. 2D HSQC spectrum of compound **75** in DMSO at 100 MHz.

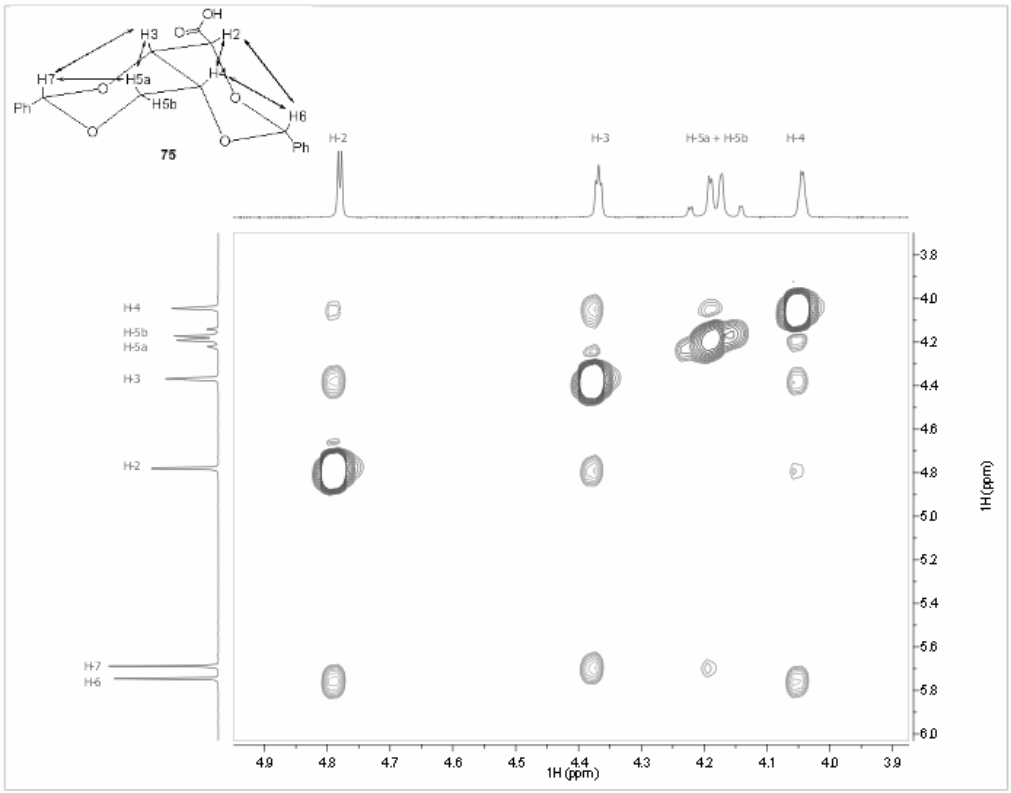
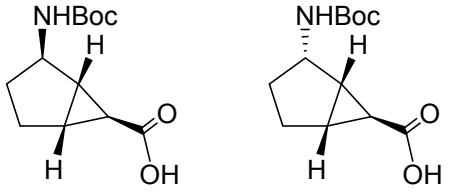


Fig. 17. 2D NOESY spectrum of compound **75** in DMSO at 100 MHz.

2.5.6 Structural Assignment of the Bicyclic Compounds Studied

The racemic bicyclic δ-amino acids **186** and **187**, available in the Roche collection of compounds, were used to generate 20-compound libraries with the same methodology for oxadiazole formation as applied to the oxetane scaffolds (see section 2.3). The spectra pattern for the resulting compounds is quite different from that of the corresponding oxetane derivatives, as expected.



186 **187**

NMR assignments were made based on ^{1}H NMR, 2D COSY and 2D HMQC experiments. As an example, the 1H NMR 2D COSY and 2D HSQC spectra of compound **204** are depicted in Figs. 18-20. Coupling between H-2 and H-3b and between H-3a,b and H-4a,b were detected in 2D COSY. Both H-3a and H-3b showed a 2D HSQC cross peak with a single carbon allowing the confirmation of these two protons as geminal protons. Assignment of H-6 and H-4a,b was based on the observed 2D HSQC cross peaks between the multiplet at δ 2.04-1.97 ppm and the carbon signal at δ 16.3 ppm for C-6, characteristic of isocyclopropyl carbons, and that of C-4 at δ 24.8 ppm.

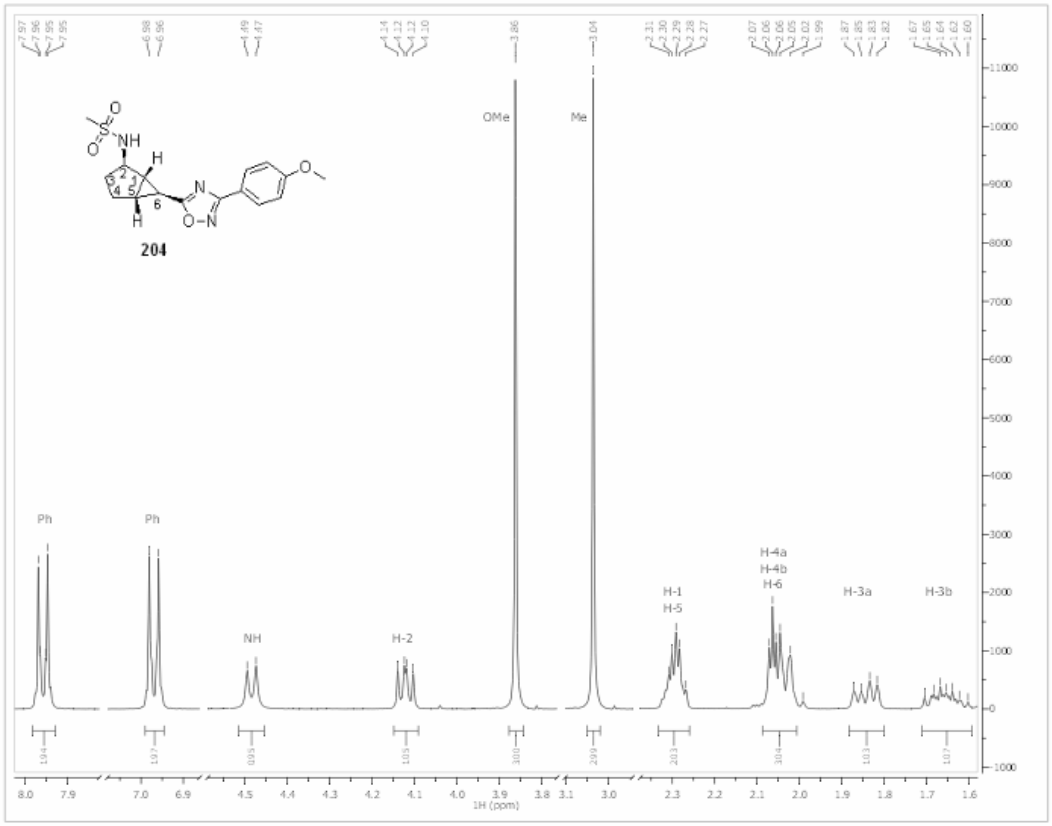


Fig. 18. ^{1}H NMR spectrum of compound **204** in $CDCl_3$ at 400 MHz.

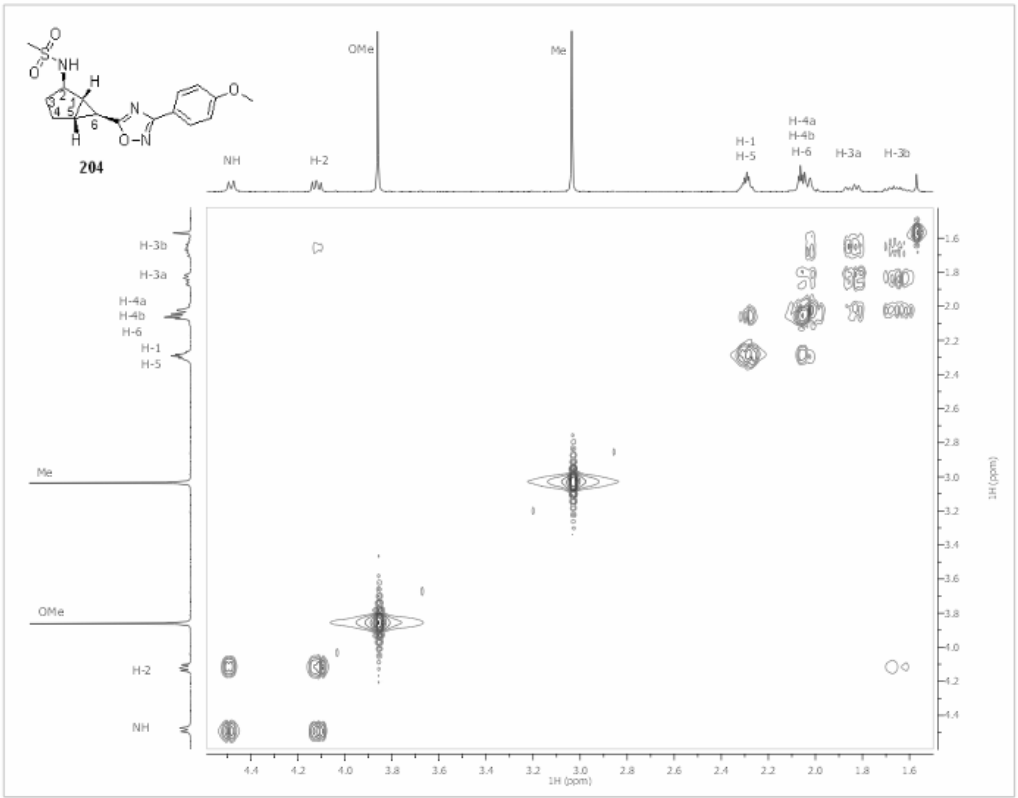


Fig. 19. 2D COSY spectrum of compound **204** in $CDCl_3$ at 400 MHz.

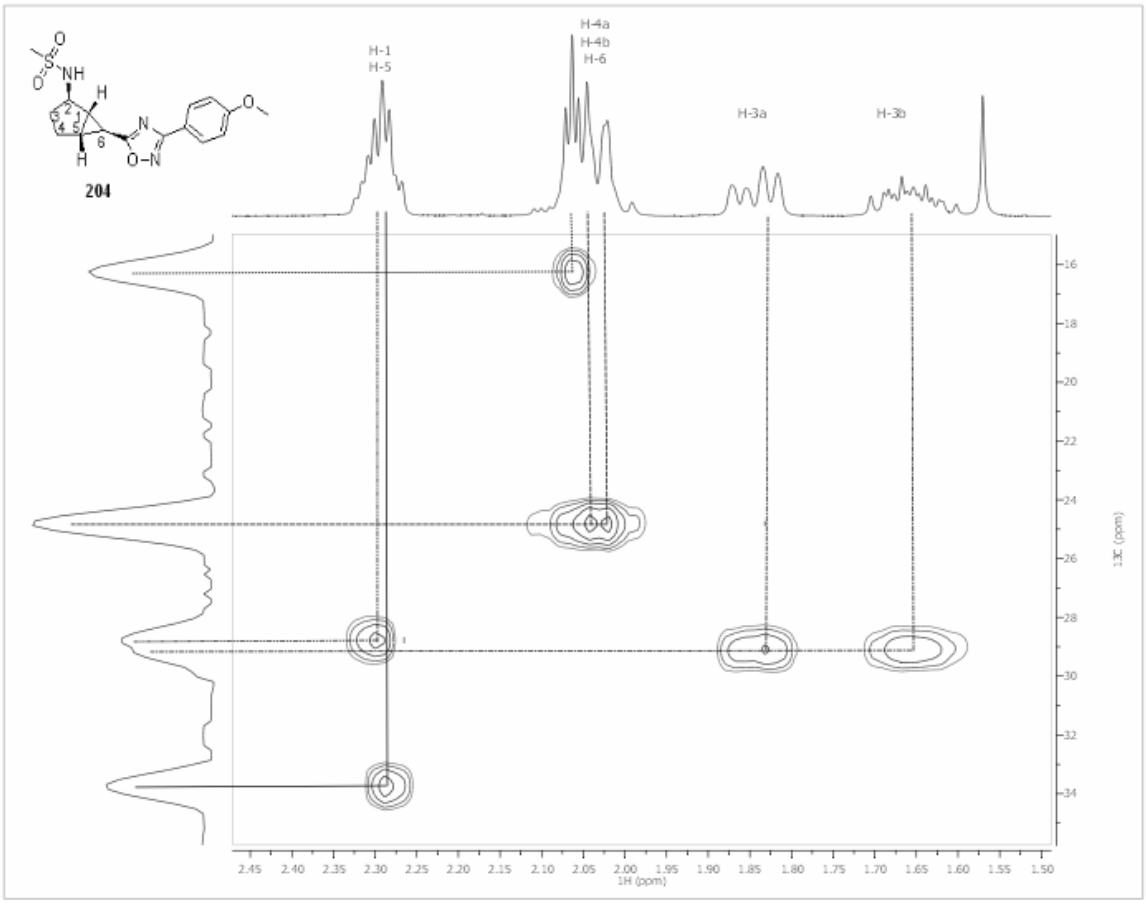


Fig. 20. 2D HSQC spectrum of compound **204** in $CDCl_3$ at 400 MHz/ 100 MHz.

The ^{1}H NMR of compound **226** is given as an example of the characteristic pattern for the 20-compound library on scaffold **187** (Fig. 21). Peak assignments were also based on 2D COSY and 2D HSQC experiments.

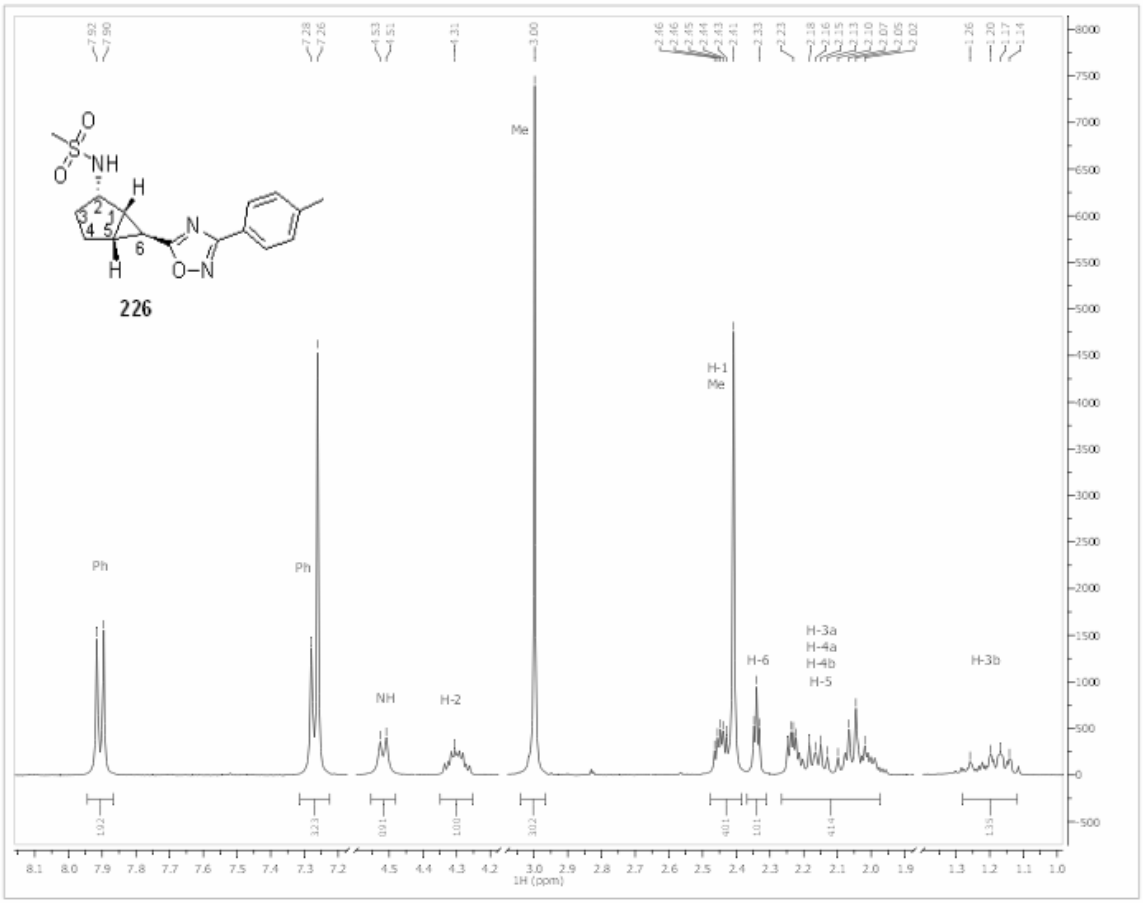
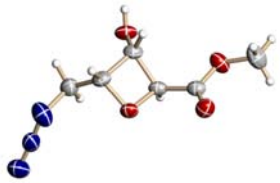
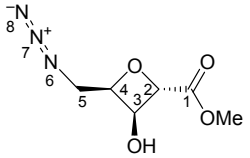
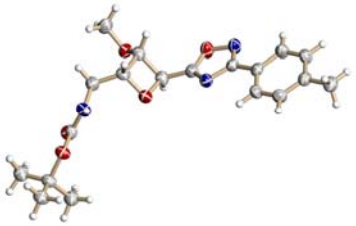
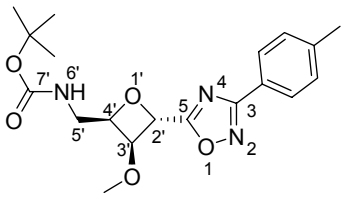
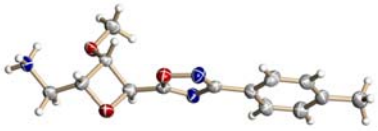
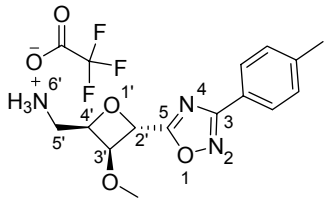
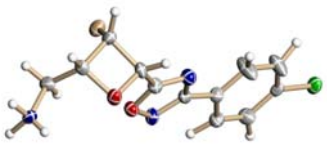
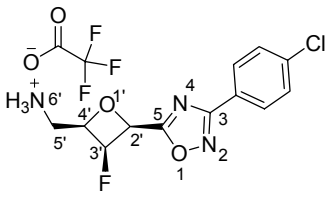
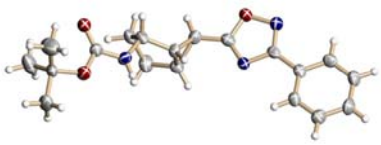
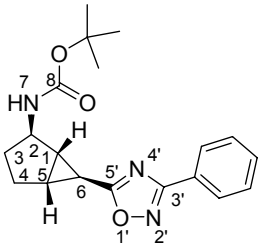
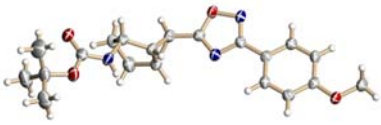
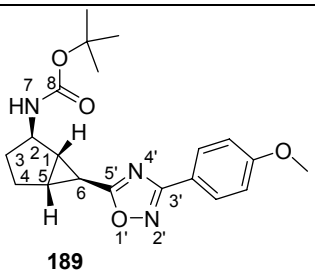


Fig. 21. ^{1}H NMR spectrum of compound **226** in $CDCl_3$ at 400 MHz.

2.5.7 X-Ray Crystallography

As previously mentioned, crystalline compounds were submitted to X-ray crystallography. Besides the great importance of this technique to confirm the stereochemistry of the synthesised compounds, data as distances and angles between the main functionalities as well the torsion and puckering angles for the so far little studied oxetane scaffolds are of great value and may give some clues related to the biological activity, which should be studied on the extension of the work here presented. Table 14 shows some crystallographic data obtained for compounds **51**,**125**,**130**,**183**,**188** and **189**.

Table 14. Crystallographic data for compounds **51**, **125**, **130**, **183**, **188** and **189**.

	 **51**	Distance N6 to C1=O	5.8 Å
		Angle C5N6N7 vs C2C1=O	64.7º
		Ring puckering	13.2º
		Ring torsion	9.3º
	 **125**	Distance N6' to O1	6.4 Å
		Angle C5'N6'C7' vs O1C5N4	45.5º
		Ring puckering	6.3º
		Ring torsion	4.5º
	 **130**	Distance N6' to O1	5.8 Å
		Angle C4'C5'N6' vs O1C5N4	46.1º
		Ring puckering	6.9º
		Ring torsion	5.0º
	 **183**	Distance N6' to O1	4.3 Å
		Angle C4'C5'N6' vs O1C5N4	53.7º
		Ring puckering	1.7º
		Ring torsion	1.2º
	 **188**	Distance N7 to O1'	6.0 Å
		Angle C2N7N8 vs O1'N4'C5'	31.4º
		Angle C1C5C6 vs C1C4C5	77.5º
	 **189**	Distance N7 to O1'	6.0 Å
		Angle C2N7N8 vs O1'N4'C5'	28.2º
		Angle C1C5C6 vs C1C4C5	77.7º

Compounds **51**, **125** and **130**, have all D-*lyxo* configuration, **51** exhibits the higher angle between the azide and the ester when compared to the angles between the amide group and oxadiazole ring on **125** and **130**. It is also interesting to notice that for **51,** in which the substituents in the oxetane ring are smaller, the puckering and torsion angles are almost the double of those for the oxadiazole substituted D-*lyxo* oxetanes.

All substituents of **183** are on the same side of the oxetane ring and this leads to a lower distance between the amino function and the oxadiazole and to an almost flat oxetane ring with puckering and torsion angles of 1.7º and 1.2º, respectively.

The bicyclic compounds **188** and **189** exhibit lower angles between the planes that contain the amide group and the oxadiazole ring, probably resulting from the angle between the two rings of the bicyclic scaffold of 77.5º and 77.7º for **188** and **189**, respectively. Moreover, the effective distance between the amide group and the oxadiazole is in the same order of magnitude as that observed for the D-*lyxo* configured oxetanes.

2.6 Evaluation of Physicochemical and Metabolic Properties

Multidimensional optimisation (MDO) is nowadays a key step for drug-discovery. A new drug is much more than its biological activity; the more potent molecule for any given biological target will not be a drug if it does not display the right ADME properties.

Chemical and pharmacological properties of oxetanes are far from clear and besides the work published by Roche researchers[60] there is no report of oxetane-containing ADME databases. The oxetane scaffolds synthesised in the present work proved to be stable and are particularly interesting as they can accommodate three different

[60] Wuitschik *et al. Angew Chem Int Ed* **2006**, 45:7736.

functions well-oriented in space. The oxetane scaffolds have been synthesised in various diastereomeric forms using carbohydrates as starting materials. The value of the oxetane scaffolds was, in our point of view, enlarged by the introduction of 1,2,4-oxadiazole or 1,2,3-triazole units, well-known in medicinal chemistry for their function as peptide isosteres and for a wide range of biological activities.

The derivatisation at the three possible sites of the oxetanes led to a set of small libraries with 101 compounds overall. Moreover, the synthesis of related 20-compound libraries on two bicyclic scaffolds with different stereochemistries was found interesting for the comparison of physicochemical and metabolic properties.

2.6.1 *In Silico* Tools

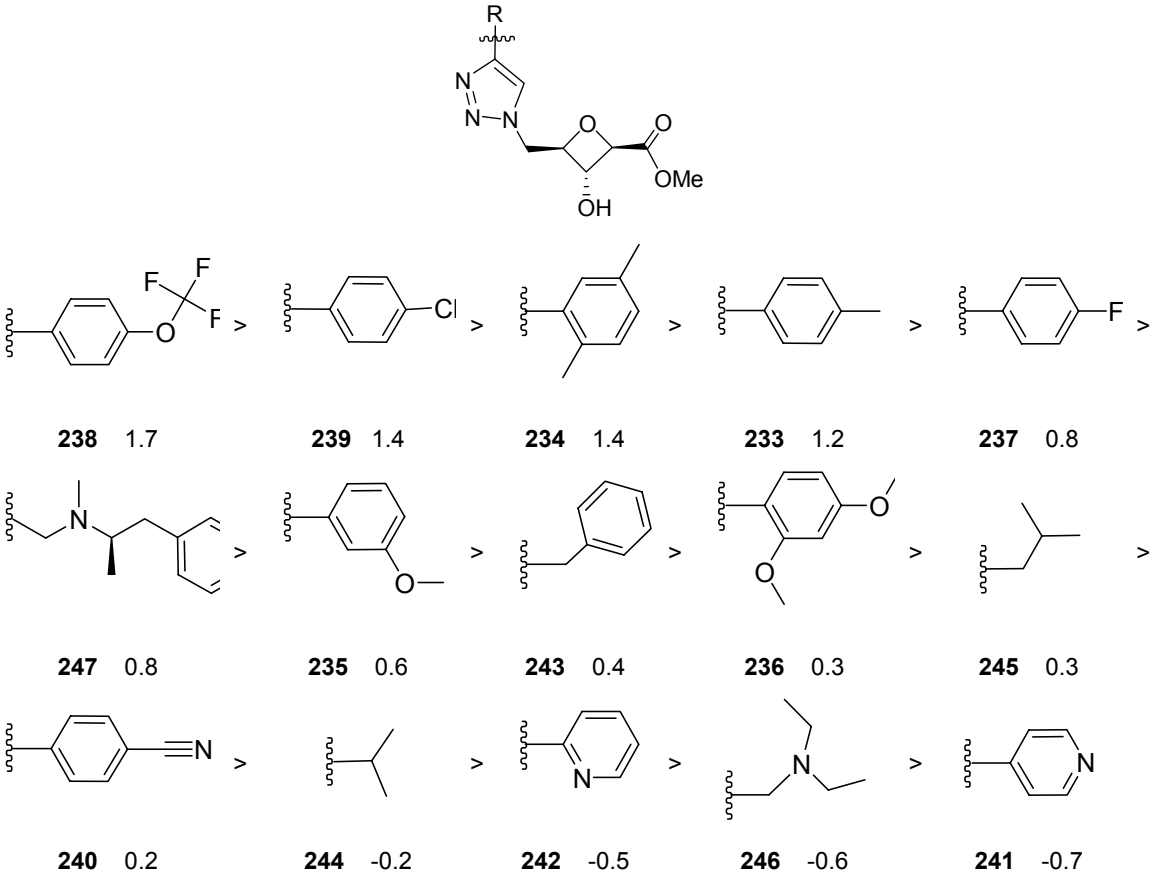
To evaluate the physicochemical and metabolic properties of the synthesised compounds, the first step was the use some of the *in silico* predictive tools available at F. Hoffmann- La Roche Ltd. These techniques allow the creation of flags based for instance on the Rule Of Five (ROF) and a fast access to properties such as polar surface area (PSA), pKa, intestinal permeability (P_{eff}), blood-brain barrier (BBB) penetration and an estimation for binding based on Andrew binding score. Equations given in the introduction of this work for the calculations of above mentioned parameters, more specifically the correlation factors between them, were optimised at Roche taking in account the in-house collection of compounds and their properties.

The all set of synthesised compounds, with oxetane and bicyclic scaffolds generate no ROF alerts (see Tables A-7 to A-15 in the Appendix) indicating that all the compounds exhibit properties in the range of desired absorption and permeation.

For the prediction of the lipophylic character the clogP values were calculated, the decadic logarithm of the octanol/water partition coefficients. The results for the oxadiazole libraries either in oxetane or bicyclic scaffolds were as expected: the

NHBoc derivatives were predicted to be the more lipophilic compounds, while the free amine, acetyl and mesyl derivatives exhibited very similar clogP ranges, and for the most part of the individual libraries the compounds that contained the acetyl moiety were the more lipophobic followed by the free amine and the mesylates. For the oxadiazole substituents the order of lipophilicity was *p*-ClPh>*p*-MePh>*p*-OMePh>Ph>*p*-Py with *p*-OMe and Ph being almost equivalent.

For the triazole library on an oxetane scaffold the order of lipophilicity is given below (Scheme 36), depending on the triazole substituent. The *p*-CF_3OPh substituent conferred the highest lipophilicity, the *p*-Py substituent the lowest. The substitution pattern on the aromatic ring is also an important factor. The introduction of a basic center as triazole substituent decreased, as expected, the lipophilicity, and also the position of the nitrogen atom on the pyridinyl substituents had an influence .



clogP values for 1,2,3-triazole library

Scheme 36

The bicyclic scaffolds were, as expected, more lipophilic than the oxetanes, with the exception of those cases in which the position 3 of the oxetane was protected with the PMB group. The different oxetane scaffolds showed different lipophylicities depending on the substitution at C-3, the fluoride derivatives were more lipophilic than the 3-methoxy and 3-hydroxy oxetanes.

The PSA is the sum of surface contributions of all polar atoms in a molecule, and these calculated values showed that libraries based on the bicyclic scaffolds exhibited the lowest PSA values. Compared to oxetane scaffolds, the free hydroxyl derivatives showed higher PSA values than the 3-methoxy ones, and those were higher than the obtained PSA values for libraries in which the oxetane had a fluorine atom as substituent at C-3. The stereochemistry had a small influence on the PSA values. Comparing the 3-methoxy derivatives, the D-*ribo* configured showed slightly higher values than the corresponding D-*lyxo* configured derivatives. In the same way the fluoride containing with D-*xylo* configuration showed slightly higher values than the corresponding compounds with D-*arabino* configuration. Both bicyclic derived libraries had very similar PSA values, and in this case the stereochemistry did not lead to changes in these calculated values.

Predicted log Peff lower than -5 indicate a low intestinal permeability with high probability. For all compounds synthesised this predicted value was higher than -5 with the only two exceptions compounds **111** and **121** which belong to the 3-hydroxyl oxetane family. In fact, the oxetane scaffold containing a free hydroxyl group at C-3 led to compounds with logPeff values more close to -5 than any other scaffold, either oxetane or bicyclic.

In terms of blood-brain barrier penetration expressed as log (C_{brain}/C_{blood}) - log BB - the values obtained are usually in the range of -2 to +1, and when log BB>0.3 the compounds cross the membrane readily, on the other hand if log BB<-1 compounds are only poorly distributed to the brain. In general, the predicted values of log BB obtained for all the libraries synthesised in the present work indicate that these compounds will be badly or poorly distributed to the brain with the log BB in the

range of -2.20 to -0.11. This may be favourable taking in account the undesired BBB penetration for drugs that are not targeted to the CNS.

As explained in the introduction of the present work, Andrew binding scores are not used in a predictive sence of binding. It is calculated by summing the intrinsic binding energies of the component groups, and consequently in our set of compounds, the mesyl derivatives exhibited higher Andrew binding scores, followed by the Boc and acetyl devivatives, and in the end of the table we find the free amines. The values obtained are important for future comparison with experimental bindings to a given target, when it will give to medicinal chemists clues about the participation of all pharmacophores in binding.

pKa prediction was also performed, for the D-*lyxo* oxetane derivatives containing a free hydroxyl at C-3 the results obtained reflected the free amine basicities but very importantly refleted also the acidic character of the free hydroxyl compounds.

The pKa of the synthesised free amines origin was predicted to be in the range in the range of 8.7-9.0 for the oxetane family, and the calculated pKa for the bicyclic derivatives was 10.7. The stereochemistry of the scaffold or the substituents on the oxadiazole (far away from the basic center) did not affect the pKa values of the corresponding amines. On the other hand, a slight difference was observed for similar compounds exhibiting different substituents at C-3 of the oxetane; the amines on the free 3-hydroxyl derivatives were predicted to be more basic than the 3-methoxy ones, and those were more basic that the 3-fluoro derivatives, even though the difference was very small.

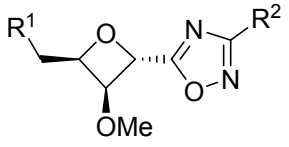
Triazoles acidity leads to predicted pKa's in the range of 12.5 to 12.7, and the different substituents in the triazole ring seem not to be an important feature for this acidity. Oxetane-derived triazoles that contained basic centers such as **246** and **247** exhibited predicted pKa values (BASE) of 10.3 and 9.3, respectively.

2.6.2 Experimental Physicochemical and Metabolic Properties

After the *in silico* predictions, experimental measurements of key properties take place in the MDO process. In the current work, some of the compounds synthesised were submitted to measure octanol/water partition coefficients and solubility, as well as the artificial membrane permeability to evaluate human intestinal permeability. The susceptibility of the synthesised compounds towards degradation in human and mouse microsomes was also evaluated. These results are summarised in Tables A-16 to A-18 in the Appendix.

In agreement with the results predicted for clogP, the measured high-throughput logD (HTlogD) indicated, as expected, that Boc containing compounds were the more lipophilic compounds of each individual library. On the other hand, a change in the order of lipophylicity of the free amines, acetates and mesylates was observed. In fact, the measurement of this property under physiological conditions (usually at pH 7.4) was enough to cause small changes, especially when the predicted values of clogP for these three different functions were quite close to each other. Table 15 presents a comparison of clogP and HTlogD values for some of the measured compounds. Experimental values indicate that after the *N*-Boc containing compounds the more lipophilic are the *N*-acetyl derivatives and the mesylates, being the more hydrophilic the free amines. Bicyclic libraries showed slightly higher lipophilicities than the oxetane-based ones.

Table15. Comparison of ClogP and HTlogD values



R^1 \ R^2	Ph		*p*-ClPh	
	ClogP	HTlogD	ClogP	HTlogD
NHBoc	2.2	3.3	2.9	4.0
NH_2	0.4	0.4	1.1	1.1
NHAc	0.2	1.6	0.9	2.3
NHMs	0.4	1.8	1.1	2.2

The LYSA assay results are closely related to lipophylicity. Thermodynamic solubility is higher for more hydrophilic compounds. As expected, the less lipophilic Boc containing compounds are less soluble, and the more hydrophilic free amines present higher solubilities, the acetylates and mesylates present intermediate values of solubility. For the 3-fluoro oxetanes with D-*lyxo* configuration the mesylate and the acetate tested exhibited much lower solubility than the corresponding amine, and for the bicyclic compounds the mesylates exhibit much lower solubility when compared to the corresponding free amines and *N*-acetyl amines.

The pKa values of several amines were mesured by Capillary Electrophoresis. While the predicted pKa's did not distinguish between diferent stereochemistries, the CE mesurements indicate that for 3-methoxy oxetanes, the amines with D-*lyxo* configuration were more basic than the ones with D-*ribo* configuration (Fig 22). Bicyclic-derived amines exhibited, as predicted by insilico tools, higher basicity. For the measured compounds, ubstituents at C-3 of 1,2,4-oxadiazole unit did not interfere, as expected, with amine basicity since they are too far away from this function.

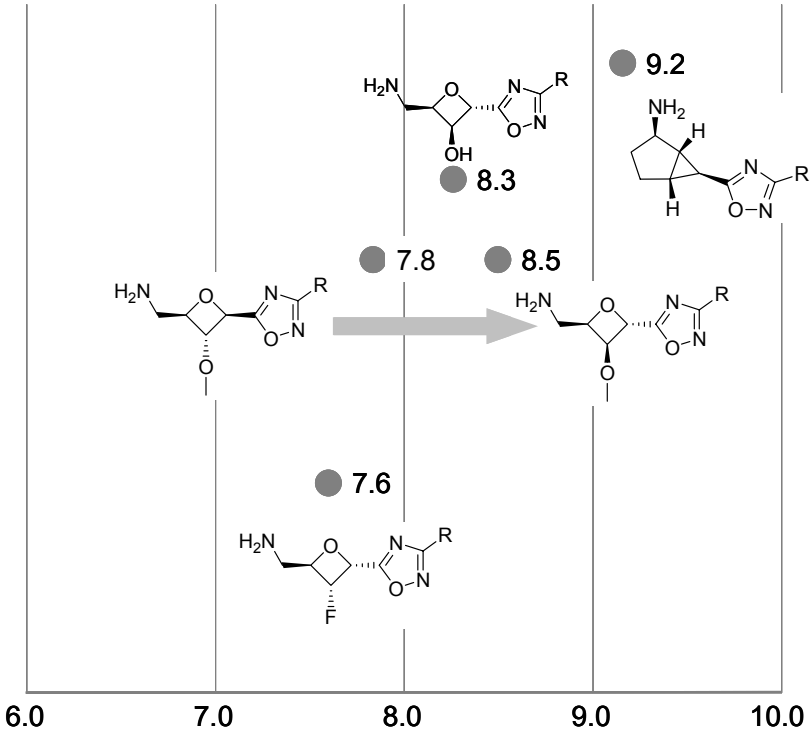


Fig. 22. CEpKa values for oxetane- and bicyclic-based amines.

At F. Hoffmann-La Roche Ltd. the value of PAMPA is being fully explored for the prediction of human intestinal permeability since several years. Meanwhile a predictive *in silico* tool to predict PAMPA results is also being optimised. As a consequence, all compounds predicted to exhibit medium to high (M2H) permeability are no longer tested with the PAMPA assay. On the other hand, all compounds that are predicted to be borderline or of low permeability are being tested.

In the set of compounds synthesised in this work and that were submitted for PAMPA, some of the compounds predicted with M2H permeability were tested confirming the *in silico* results, but all compounds predicted to be borderline or of low permeability lead to M2H permeability in the PAMPA assay. These results led to a high percentage of error for the predictive tool which might be explained by the lack of knowledge concerning oxetane scaffolds. The error on bicyclic compounds was lower, reinforcing the importance of the present work. Moreover, the experimental PAMPA was in agreement with the predicted in silico Peff values (chapter 2.6.1).

As mentioned above the susceptibility of the synthesised compounds towards degradation in human and mouse microsomes was evaluated. The intrinsic clearance (CL_{int}) is the rate constant of the first-order decay of a given compound, normalised for the protein concentration in the incubation. A medium (M) clearance leads to an expected bioavailability to be higher than 30% and a low (L) clearance lower than 30%, if the hepatic clearance is the major mechanism of clearance. The resulsts for intrinsic clearance rates mesured in human (hCL_{int}) and mouse (mCL_{int}) liver microsomes are also presented in Tables A-16 to A-18 in the Appendix. All oxadiazole libraries on oxetane scaffolds displayed medium to low clearance either in human or mouse microsomes. The only triazole containing compound tested showed as expected a high susceptibility to microsomal atack, due to the presence of an ester group. This library was clearly not targeted as drug-like library but as interesting intermediates to be further derivatised.

The oxadiazole libraries based on the bicyclic scaffolds showed to be more susceptible to microsomal attack than the corresponding oxetane based libraries, especially true for mouse microsomes, in which some of the compounds showed high (H) clearance rates.

3. Conclusions

The synthesis of new oxetane δ-amino acid scaffolds with D-*lyxo* (**53**), D-*ribo* (**61**), D-*arabino* (**72**, **79**) and D-*xylo* (**92**) configuration was accomplished in the present work starting from D-xylose or 1,2-*O*-isopropylidene-α-D-xylofuranose in overall yields in the range of 12% to 28%, over 9 to 14 steps. Compound **53** contains a free hydroxyl group at C-3, and the synthesis was achieved *via* a chemoenzymatic approach. A straightforward synthesis of **61** and **72** was worked out relying on the stability of a primary azide function along the chosen strategy. The 3-fluoro derivatives **79** and **92** were obtained by reaction of a free hydroxyl group at C-3 of an oxetane with DAST leading to inversion of configuration.

Selective bromine oxidation of D-xylose followed by treatment with benzaldehyde was previously reported to afford the 3,5-*O*-benzylidene protected xylono-1,4-lactone **74** without any reference to the formation of by-products. We were able to isolate the by-product 2,4;3,5-di-*O*-benzylidene-D-xylonic acid (**75**) in 37% yield. For the first time an NMR characterisation of **75** was performed, and its conformation was derived.

Synthesis of the 3-hydroxy oxetane δ-amino acid **53** was only possible by means of an enzymatic reaction to achieve methyl ester hydrolysis in the very last step of the synthetic scheme. In contrast, the hydrolysis of the 3-methoxy and 3-deoxy-3-fluoro carboxylic ester precursors of the acids **61**, **71**, **72**, **79** and **92** was easily performed by standard LiOH treatment in very good to quantitative yields. The full characterisation of this type of compound with a free carboxylic acid was accomplished.

The free carboxylic acid function was strategically targeted to allow the coupling of the scaffolds with hydroxyamidines to form 1,2,4-oxadiazoles while the *N-tert*-butoxycarbonylamino group was envisaged for cleavage after oxadiazole formation to give the corresponding free amines. Further acetylation and mesylation led to small libraries (usually 20-compound libraries) of new oxetane-based compounds in good yields. The same methodology was applied using the bicyclic δ-amino acid scaffolds **186** and **187** to give corresponding 20-compound libraries. Bicyclic derived

1,2,4-oxadiazoles were obtained in lower yields than those synthesised from the oxetane scaffolds suggesting that structural restraints may be an issue in the cyclodehydration.

The oxetane δ-azido ester **88** was submitted to click chemistry by treatment of the azide with 15 different acetylenes under Cu(I) catalysis to give the corresponding 1,2,3-triazoles in an automated fashion. Other than in the single synthesis approach, the automated purification did not allow the quantitative recovery of products.

All scaffolds synthesised proved to be stable under the reaction conditions chosen to afford the desired libraries with the exception of the 3-hydroxy scaffold **53** that led to poor results. The chemical stability of derivatives based on scaffold **53** was evaluated, and it was shown that the oxetane-derived compounds with a free hydroxy at C-3 decomposed under basic conditions.

X-Ray crystallography confirmed the structural assigments of oxetane- and bicyclic-based compounds. It was shown that bicyclic compounds exhibit lower angles between the plane that contains the amide group and the one that contains the 1,2,4-oxadiazole ring. Moreover, the effective distance between the amide group and the 1,2,4-oxadiazole in the bicyclic compounds was of the same order of magnitude as that observed for the D-*lyxo* configured oxetanes. These results are interesting in terms of future evaluation of biological activities, since the oxetane- and the bicyclic-derived compounds are structurally diverse and exhibit different physicochemical and metabolic properties, but they display close spatial relations between the pharmacophores.

The evaluation of the physicochemical and metabolic properties of the compounds synthesised made use of *in silico* tools for the prediction of several properties such as clogP, PSA, Peff, log BB, Andrew binding scores and pKa. These tools give a valuable help in predicting lipophilicity, intestinal permeability and state of charge. No alerting flags were created for ROF indicating that the properties of these molecules are in the desired range for oral bioavailability. Intestinal effective permeability was predicted to be medium to high. The blood-brain barrier penetration was predicted to be low indicating that those compounds will be safe with respect to CNS side effects.

The various oxetane derivatives displayed different lipophylicities depending on the substitution at C-3. The 3-deoxy-3-fluoro derivatives were the most lipophilic compounds followed by the 3-methoxy oxetanes and then by the 3-hydroxy derivatives. 1,2,4-Oxadiazoles with the bicyclic core showed to be more lypophilic than the oxetane-based compounds.

From CEpKa measurements it could be concluded that the amines with D-*lyxo* configured scaffold were more basic than the ones on a D-*ribo* oxetane. Amines linked to bicyclic cores exhibited, as predicted by *in silico* tools, higher basicity. For the measured compounds, substituents at position 3 of the 1,2,4-oxadiazole ring did not interfere with amine basicity.

PAMPA results showed that the libraries synthesised would exhibit medium to high intestinal permeation. Evaluation of the microsomal susceptibility towards degradation in human and mouse microsomes showed that all oxetane-derived 1,2,4-oxadiazole compounds, were expected to exhibit medium to high biovailability when assuming that hepatic clearance were the major path of clearance,. On the other hand, the bicyclic compounds were more susceptible to microsomal attack.

In summary, the present work describes the synthesis of the unexplored oxetane δ-amino acids family and their feasability as scaffolds was investigated. Six oxetane scaffolds were then derivatised, so that different pharmacophores were introduced on the three available positions of the oxetane rings affording a 101-compound oxetane-based library. Moreover, two bicyclic δ-amino acids were also derivatised using similar methodology to afford a 40-compound library. The physicochemical and metabolic properties were evaluated, and the compounds synthesised exhibited the desired properties for medicinal chemistry purposes. From the *in silico* point of view, this work brings valuable information for prediction tools refinement as there are no previous reports on comparable molecular properties of oxetanes. The compounds obtained will remain in the Roche collection where they are submitted to HT screening for biological activity.

4. Experimental

4.1 General Methods

Solvents and reagents were bought from Fluka, Merck, Aldrich or Acros Organics (Acros Organics showed to have the most pure DAST reagent). Lipase L2 from *Candida antarctica* was purchased from Boehringer Mannheim as lyophilisate (Chirazyme L-2, lyo., BM; 1836021) and in an immobilized form (Chirazyme L2, c.-f. C2, lyo.; 1816969).

Solutions were concentrated below 50 °C *in vacuo* on Büchi rotary evaporators.

Qualitative TLC was performed on precoated Silica Gel 60F-254 plates (Merck); compounds were detected by UV light (254 nm) and spraying with a 10% solution of conc. sulfuric acid in methanol or with a cerium sulfate aqueous solution, followed by heating. Column chromatography was carried out on Silica Gel (63-200, 60 Å) from Chemie Brunschwig or 60G (0.040-0.063 mm) from Merck. Flash chromatography was made using a Combi Flash Companion device from Isco with RediSep® normal-phase silica flash columns or when necessary RediSep® Rf amine columns.

Melting points were determined with Electrothermal 9100, Büchi C-540 or Büchi 510 capillary apparatus and are uncorrected.

Optical rotations were measured on Perkin Elmer 241 spectrometer in a 1 dm cell at given temperatures, either at Faculdade de Ciências da Faculdade de Ciências da Universidade de Lisboa (FCUL) or at F. Hoffmann- La Roche Ltd.

NMR spectra were recorded on Bruker spectrometers: Avance 300 (300 MHz for ^{1}H-NMR) or AM 400 (400 MHz for ^{1}H-NMR and 100 MHz for ^{13}C-NMR) at F. Hoffmann-La Roche Ltd., and Avance 400 (400 MHz for ^{1}H-NMR and 100 MHz for ^{13}C-NMR) at FCUL. Chemical shifts are given in ppm relative to tetramethylsilane.

Mass spectra were recorded on API III Sciex, Perkin Elmer for negative (ISN) and positive (ISP) electrospray ionization. High resolution mass spectra were recorded

on a Finnigan LTQ FT from Thermo for positive (ESI) and negative (NSI) electrospray ionization at F. Hoffmann- La Roche Ltd.

Elemental analyses were performed by Solvias AG, Basel, Switzerland.

For crystal structure analysis of compounds **51**, **125**, **130**, **188** and **189**, a single crystal was mounted in a loop and cooled to 150 K in a nitrogen stream; data were collected on a STOE Imaging Plate Diffraction System (STOE, Darmstadt) with Mo-radiation (0.71 Å) and data processed with STOE IPDS-software; the crystal structure was solved and refined with ShelXTL (Bruker AXS, Karlsruhe), at F. Hoffmann- La Roche Ltd. For crystal structure analysis of compound **183**, data were collected on a Gemini R Ultra diffractometer (Oxford Diffraction, Abingdon, UK) by 100K using Cu-K-alpha-radiation (1.54184Å) and processed with the Crysalis-package. Structure solution and refinement was performed using the ShelX[133] software.

HPLC-MS was composed of the pump, the vacuum degasser and the UV detector all from Agilent 1100, the ELSD detector was from Sedere, the MS detector a single mass detector from Thermo, the liquid handler was a 215 from Gilson, and the column used was from Phenomenex :Gemini:3u C18 110A 30x3.00 mm.

The prep-HPLC pump was an SD-1 from Varian, the UV detector a UVD340U from Dionex, the ELSD detector was from Sedere, the liquid handler was a 215 from Gilson, and the column used is from Penomenex: Gemini 5u C18 110A 50x21.2 mm.

For ASTA measurements the buffers used were pH 1 (Merck Titrisol buffer - 2 mM Glycin/120 mM HCl/3 mM NaCl), pH 4 (Merck Titrisol buffer - 56 mM Citrate/44 mM HCl/110 mM NaOH), pH 6 (Merck Titrisol buffer - 60 mM Citrate/160 mM NaOH), pH 8 (Merck Titrisol buffer - 110 mM Borate/56 mM NaOH/44 mMHCl) and pH 10 (Merck Titrisol buffer - 50 mM Boric acid/44 mM NaOH/50 mM HCl).

[133] Sheldrick, GM; *Acta Cryst* **2008**, A64:112.

For CEpKa measurements only small amounts of sample were required. A medium-throughput pKa screening assay using CE (pKa Analyzer ProTM) was developed by Advanced Analytical and installed at Roche in Basel providing a rapid, parallel, automated approach for the measurement of compound pKa values by capillary electrophoresis. 96 Fused-silica capillaries in parallel allowed analyzing simultaneously 96 different sample solutions within 14 minutes (Fig. 23). The capillaries, with an inner diameter of 75 μm and 55 cm in total length were filled with dilute aqueous buffer solutions (ionic strength 0.05 M). About 10 nL of each sample solution (0.2 mM) was gathered at one end of the capillary by vacuum-assisted injection, and a 3.5 kV potential was applied between the ends of the capillaries. 96 capillaries were arranged in parallel for direct injection from 96-well sample plates; capillary outlets were bundled to a common reservoir enabling vacuum-assisted separation. Samples were separated by the application of a high voltage with vacuum flow and detected by UV light at 214 nm passing through the detection window.

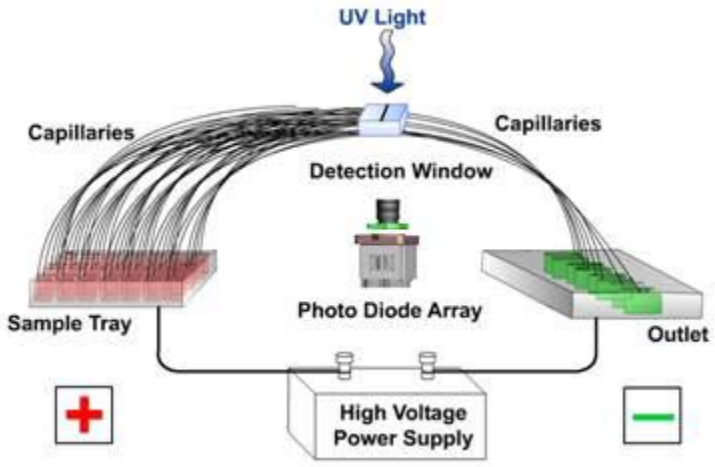


Fig. 23. Ilustration of CEpKa device

The effective mobility of ionizable compounds was dependent on the fraction of the compound in the charged form. The plot of the effective mobility versus pH had a sigmoidal shape the inflection point of which defined the pKa value.

For PAMPA, compounds were introduced as 10mM DMSO stock solutions in a 96-well microtitre plate. An automated liquid handling system drew an aliquot of the DMSO stock solution and mixed it into a buffer solution (0.05M MOPSO with 0.5% (w/v) glycocholic acid at pH 6.5), so that the final sample concentration was 150 μM and the DMSO concentration was 1.5% (v/v). A part of the sample solution was filtered, using a 96-well PVDF filter plate from Corning (Corning, NY) and added to the donor compartments. In the acceptor compartment the same buffer system at the same pH as in the donor compartment was used but devoid of glycocholic acid. After 18 hours the sandwich plates were separated, and both the donor and acceptor compartments were measured for the amount of material present by comparison with the UV spectra (250–500 nm) obtained from reference standards. Mass balance was used to determine the amount of material remaining in the membrane barrier. All measurements were run in triplicate, and the reproducibility was ±4%. Effective permeability values (*P*eff) were calculated as described by Avdeef *et al*..[134] The PAMPA Evolution Software v2.2 from *p*ION Inc. was then used for *P*eff calculations.

Solubilities presented in the current work were determined by LYSA, and for this assay, 0.02 mL of a 10 mM compound stock solution in DMSO was evaporated under low pressure (Genevac), and the obtained solid material (usually a film) was handled as in standard equilibrium measurements (Fig. 2). Rigorous stirring of the sample was maintained for 12 h at room temperature. The use of vertical stirring equipment is highly recommended in order to get good results. For calibration measurements, aliquots of DMSO stock solutions were transferred to microtitre plates and diluted with buffer to a final concentration of 25% to keep the compound in solution. Caution had to be taken for low molecular weight compounds (<250), which may be lost during DMSO evaporation.

[134] Avdeef, A; Strafford, M; Block, E; Balogh, MP; Chambliss, W; Khan, I; *Eur J Pharm Sci* **2001** 14:271.

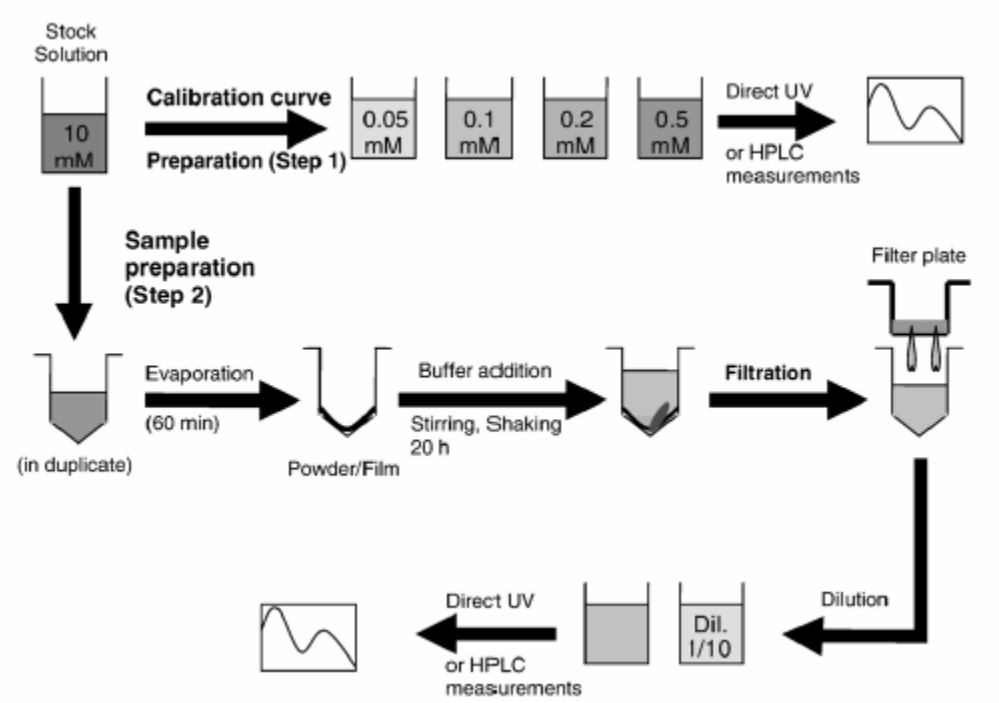


Fig. 24. Standard setup for the Roche in house LYophilisation Solubility Assay (LYSA). A DMSO stock solution (10 mM) is used for the preparation of the samples. Solid samples were prepared by evaporation using a Genevac HT-4 series II (full vacuum for 60 min at 35 °C and 500 G). Similar to standard equilibrium experiments, samples are stirred for 1 h, shaken for 2 h, and left in contact with undissolved sample for an additional 16 h. After filtration the concentration is determined by direct UV or HPLC. Calibration solutions were prepared in parallel from the DMSO stock solutions.

For hCL_{int} and mCL_{int} determination the first-order rate constant for consumption of substrate at one concentration (1-10mM) in the presence of human/mouse liver microsomes (0.5-1.0 mg prot/mL; normally pooled from 10 subjects and kept frozen at – 80 ºC; commercial source: GENTEST) was measured in the presence of the cofactor NADPH. The reaction was carried out at 37 °C in 0.1 M phosphate buffer pH 7.4 for 30 min while aliquots were taken for at least 5 time points. The samples were analysed by LC-MS.

4.2 Synthesis of Oxetane δ-Amino Acid Scaffolds

4.2.1 General Procedures (GP's)

4.2.1.1 Benzylation

A 1 M solution of the starting diol in absolute DMF was added dropwise at rt to a 1.3 M suspension of sodium hydride (60% in mineral oil, 2.3 eq,) in absolute DMF. After stirring the mixture until release of H_2 stopped it was cooled to 10 ºC, and benzyl bromide (2.5 eq) was added dropwise. The reaction mixture was allowed to reach rt and was stirred until protection was complete, then the reaction was quenched by careful addition of isopropanol (3% v/v). DMF was evaporated under HV. After addition of water and brine (1:1) the product was extracted twice with EtOAc, and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated.

4.2.1.2 Isopropylidene Cleavage

A 0.08 M solution of the starting isopropylidene derivative in aqueous acetic acid (30%) was stirred under reflux conditions (≈ 112 °C) until deprotection was complete according to TLC. The solvents were evaporated under HV.

4.2.1.3 Selective Anomeric Oxidation

To a 0.03 M solution of the free diol in dioxane/water (1:2) was added barium carbonate (1.4 eq). After cooling the solution to 0 ºC, bromine (8 eq) was added dropwise. The reaction mixture was stirred in the dark until oxidation was complete. The reaction mixture was then cooled to +10 °C, and sodium carbonate was added until neutralization. In order to destroy the bromine residues, sodium thiosulfate was added until a white precipitate appeared, and the reaction mixture was filtered over Celite. The solvents were evaporated under HV, and after the addition of water the

product was extracted with EtOAc. The organic phases were washed with brine, dried with $MgSO_4$, filtered and concentrated.

4.2.1.4 Triflation under basic conditions

To a 0.2 M solution of the starting free alcohol in DCM was added pyridine (1.8 eq). To the solution cooled to -12 ºC trifluoromethanesulfonic anhydride (1.2 eq) was added dropwise. When the triflation was complete the reaction mixture was diluted with DCM and washed with sat soln of $NaHCO_3$ and then with 1N HCl solution. After drying with $MgSO_4$, filtration and evaporation of the solvent, the product was immediately used for the next reaction step without further purification.

4.2.1.5 Ring Contraction

To a 0.12 M solution of triflated lactone in absolute MeOH at -12 °C was added potassium carbonate (1eq). The resulting suspension was stirred until ring contraction was complete, and the reaction mixture was filtered over Celite. The filtrate was concentrated.

4.2.1.6 Catalytic Hydrogenation

To a 0.07 M solution of starting material in MeOH/dioxane 1:1 was added Pd/C (10% m/m). The reaction mixture was stirred at rt under hydrogen atmosphere until deprotection was complete. The catalyst was then removed by filtration, and the filtrate was concentrated to dryness.

4.2.1.7 Ester Hydrolysis by LiOH

To a 0.06 M solution of ester derivative in THF was added 1N aqueous LiOH (3 eq) at 0-5 ºC, and the mixture was stirred until complete consumption of starting material. Then, maintaining the temperature range, 1N HCl (3 eq) was added, and the mixture was stirred for 30 min. Brine was added, and the product was extracted

3 times with TBME. The organic layers were combined, dried over $MgSO_4$, filtered, and the solvent was evaporated.

4.2.1.8 Triflate displacement by sodium azide

To a 0.1 M acetone solution of a crude triflate (considering quantitative triflation) was added sodium azide (6eq). After stirring overnight at rt the reaction mixture was concentrated. Iced water was added, and the product was extracted with TBME. The combined organic layers were washed with brine, dried with $MgSO_4$, filtered, and concentrated.

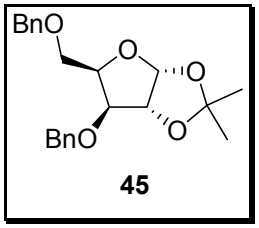
4.2.1.9 One-Pot Azide Reduction and Boc Protection

To a 0.12 M solution of the starting azide in EtOAc was added Pd/C (10% m/m), and the suspension was stirred vigorously for 30 min. under hydrogen atmosphere. A 0.12 M solution of Boc_2O in EtOAc (1.05 eq) was then added, and the reaction mixture was stirred at rt under H_2 atmosphere until the reaction was complete. The catalyst was removed by filtration, and the solvent was evaporated.

4.2.1.10 Methylation

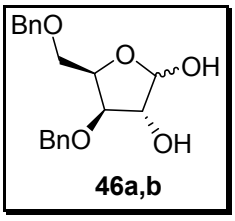
To a 0.15 M THF solution of a free alcohol was added sodium hydride (60% dispersion in mineral oil, 2.2 eq), and the suspension was stirred at rt until release of H_2 stopped. Methyl iodide (2 eq) was then added, and the mixture was further stirred at rt until methylation was complete. After quenching excess of NaH with MeOH, the reaction mixture was diluted with EtOAc, washed with water and brine, dried over $MgSO_4$, filtered, and concentrated.

4.2.2 Chemoenzymatic Synthesis of 2,4-Anhydro-5-*N*-(t-butoxycarbonyl)amino-D-*lyxonic* Acid (83)



45

3,5-Di-*O*-benzyl-1,2-*O*-isopropylidene-α-D-xylofuranose (45)[135,113]. Starting with 1,2-*O*-isopropylidene-α-D-xylofuranose (104 g, 0.55 mol) and using GP 4.2.1.1 (reaction time 2.5 h) the obtained residue was chromatographed (EtOAc/Cy-Hex 1:2) to give the pure desired product as colourless oil (126 g, 0.34 mol, 62 %). Impure fractions were rechromatographed using the same solvent system to yield more pure compound (76g, 0.21 mol, 38 %; total yield 100%). MS: *m/z* 371.3 $[M+H]^+$; 388.2 $[M+NH_4]^+$, 393.2 $[M+Na]^+$. ^{1}H NMR ($CDCl_3$): δ 7.26-7.36 (m, 10H, 2Ph), 5.93 (d, 1H, $J_{1,2}$ = 3.8 Hz, H-1), 4.62 (dd, 1H, $J_{2,3}$ = 3.0 Hz, H-2), 4.52,4.61 (AB, 2H, 1H, $J_{a,b}$ = 11.8 Hz, OCH_2Ph), 4.51,4.68 (AB, 2H, 1H, $J_{a',b'}$ = 12.2 Hz, $OCH_2'Ph$), 4.40 (ddd, 1H, $J_{4,5b}$ = 3.0 Hz, H-4), 3.97 (dd≈d, 1H, $J_{3,4}$ = 6.1 Hz, H-3), 3.78 (A(ABX), 1H, $J_{4,5a}$ = 3.0 Hz, H-5a), 3.73 (B(ABX), 1H, $J_{5b,5a}$ 6.1 Hz, H-5b), 1.31,1.48 (2s, 3H, 3H, 2Me (*i*-prop)).

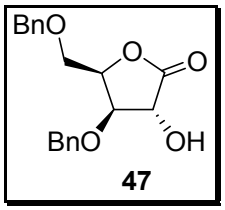


46a,b

3,5-Di-*O*-benzyl-α,β-D-xylofuranose (46a,b). Starting with 3,5-di-*O*-benzyl-1,2-*O*-isopropylidene-α-D-xylofuranose (43.9 g, 0.12 mol) and using GP 4.2.1.2 (reaction time 3 h), **46a,b** was obtained after chromatography with EtOAc/Cy-Hex (1:2, 1:1, 3:2) as a mixture of isomers (34.63 g, 0.10 mol, 88 %, α/β ca. 4:1 by NMR

[135] Matsuda, F; Terashima, S; *Tetrahedron* **1988**, 44(*15*):4721.
[113] Ning, J; Kong, F; *Carbohydr Res* **1997**, 300(*4*):355.

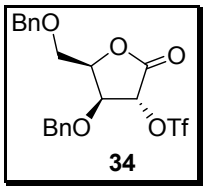
integration). ^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ: 7.38-7.26 (m, 12.5H, 2Ph (α+β)), 5.50 (t, 1H, $J_{1\alpha,2\alpha} \approx J_{1\alpha,OH} \approx$ 4.8 Hz, H-1α), 5.10 (d, 0.25H, $J_{1\beta,OH1\beta}$ =11.5 Hz, $J_{1\beta,2\beta} \approx$ 0 Hz, H-1β), 4.71-4.47 (m, 5.25H, 2OC*H*$_2$Ph (α+β), H-4β), 4.42 (q, 1H, H-4α), 4.26 (dd , 0.25H, $J_{2\beta,3\beta}$ = 2.4 Hz, $J_{3\beta,4\beta}$ = 5.0 Hz, H-2β), 4.22 (br ddd, 1H, $J_{2\alpha,3\alpha}$ = 2.4 Hz, H-2α), 4.02 (dd, 0.25H, $J_{3\beta,4\beta}$ = 5.0 Hz, H-3β), 4.00 (dd ≈ t, 1H, $J_{3\alpha,4\alpha}$ = 5.0 Hz, H-3α), 3.86 (d, 0.25H, OH-1β), 3.78 (A(ABX), 1H, $J_{4\alpha,5a\alpha}$ = 5.0 Hz, $J_{5a\alpha,5b\alpha}$ = 9.8 Hz, H-5aα), 3.73 (B(ABX), 1H, $J_{4\alpha,5b\alpha}$ = 4.8 Hz, H-5bα), 3.68 (A(ABX), 0.25H, $J_{4\beta,5a\beta}$ = 5.5 Hz, $J_{5a\beta,5b\beta}$ = 7.0 Hz, H-5aβ), 3.67 (B(ABX), 0.25H, $J_{4\beta,5b\beta}$ = 3.8 Hz, H-5bβ), 3.63 (d, 1H, OH-1α), 2.80 (d, 1H, $J_{2\alpha,\ 2\alpha\text{-OH}}$ = 6.0 Hz, OH-2α), 2.13 (d, 0.25H, $J_{2\beta,\ OH\text{-}2\beta}$ = 6.0 Hz, OH-2β).



47

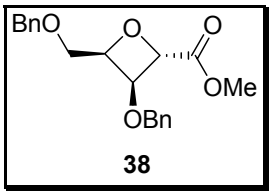
3,5-Di-*O*-benzyl-D-xylono-1,4-lactone (47). Starting from **46a,b** (57.3 g, 0.17 mol) and after using GP 4.2.1.3 (reaction time 4h) the product was crystallised from a mixture of ether and n-hexane to give colourless crystals of **47** (41.5 g, 0.13, 73 %). m.p. 64 - 65 °C, lit.[75] m.p. 70 °C. $[\alpha]_D^{20}$ +54° (*c* 0.5, $CHCl_3$), lit.[75]: $[\alpha]_D^{20}$ +40.0° (*c* 1.00, $CHCl_3$). MS (ionspray): *m/z* 346.1 $[M+ NH_4]^+$, 351.3 $[M+Na]^+$. ^{1}H NMR, COSY (400 MHz, $CDCl_3$): δ: 7.39-7.29 (m, 10H, 2Ph), 4.83;4.66 (AB, 2H, $J_{a,b}$ = 12.0 Hz, OCH_2Ph), 4.81 (dd, 1H, $J_{2,3}$ = 8.0 Hz, H-2), 4.58 (ddd≈dt, 1H, $J_{4,5a}$ = 2.2 Hz, H-4), 4.58;4.52 (2d, 2H, $J_{a',b'}$ = 12.0 Hz, OCH_2'Ph), 4.37 (t, 1H, $J_{3,4}$ = 8.0 Hz, H-3), 3.79 (A(ABX), 1H, $J_{5a,5b}$ = 11.0 Hz, H-5a), 3.71 (B(ABX), 1H, $J_{4,5b}$ = 2.8 Hz, H-5b).

[75] Witty *et al* *Tetrahedron Lett* **1990**, *31*(33):4787.



34

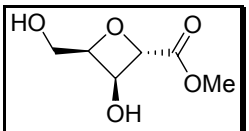
3,5-Di-*O*-benzyl-2-*O*-trifluoromethansulfonyl-D-xylono-1,4-lactone (34). Starting with **47** (27 g, 82.2 mmol) and using GP 4.2.1.4 (reaction time 40 min) crude compound **34** was obtained. MS (ionspray): *m/z* 478.1 $[M+ NH_4]^+$, 483.3 $[M+Na]^+$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.43 - 7.26 (m, 10H, Ph), 5.89 (d, 1H, $J_{2,3}$ = 7.9 Hz, H-2), 4.79, 4.59 (2d, 2H, $J_{a,b}$ = 11.8 Hz, OCH_2Ph), 4.59, 4.52 (2d, 2H, $J_{a',b'}$ = 11.8 Hz, CH_2'Ph), 4.56 (t, 1H, $J_{3,4}$ = 7.9 Hz, H-3), 4.51 (ddd, 1H, $J_{4,5a}$ = 1.2 Hz, H-4), 3.74 (A(ABX), 1H, $J_{5a,5b}$ = 11.0 Hz, H-5a), 3.66 (B(ABX), 1H, $J_{4,5b}$ =2.4 Hz, H-5b).



38

Methyl 2,4-Anhydro-3,5-di-*O*-benzyl-D-lyxonate (38). Starting from triflate **34** (considered 82.2 mmol) and after GP 4.2.1.5 (reaction time 30 min) a residue was obtained which was chromatographed (EtOAc/Cy-Hex 1:2) to give the title compound as colourless oil (25.4 g, 74.2 mmol, 90 % from **47**). $[\alpha]_D^{20}$ -18° (*c* 0.5, $CHCl_3$) [lit.[75]: $[\alpha]_D^{20}$ -17.9 º (*c* 1.0, $CHCl_3$)]. MS (ionspray): *m/z* 360.1 $[M+ NH_4]^+$, 365.3 $[M+Na]^+$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32-7.27 (m, 10H, Ph), 5.06 (dd, 1H, $J_{2,3}$ = 5.1 Hz, $J_{2,4}$ = 0.4 Hz, H-2), 5.00 (dddd≈dq, 1H, $J_{4,5a}$ = 5.6 Hz, H-4), 4.62 (dd, 1H, $J_{3,4}$ = 6.6 Hz, H-3), 4.61,4.60 (AB, 2H, $J_{a,b}$ = 12.0 Hz, OCH_2Ph), 4.60, 4.53 (AB, 2H, $J_{a',b'}$ = 11.7 Hz, OCH_2'Ph), 4.42 (A(ABX), 1H, $J_{5a,5b}$ = 10.9 Hz, H-5a), 3.94 (B(ABX), 1H, $J_{4,5b}$ = 6.0 Hz, H-5b), 3.81 (s, 3H, OMe).

[75] Witty *et al* *Tetrahedron Lett* **1990**, *31*(33):4787.

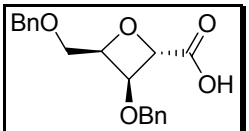


48

Methyl 2,4-Anhydro-D-lyxonate (48). Procedure A: From benzyl derivative **38** (13.0 g, 38.0 mmol) using GP 4.2.1.6 (reaction time 40 min) and after chromatography over silica gel (EtOAc) the desired product was obtained as a colourless oil (5.24 g, 32.3 mmol, 85 %);

Procedure B: Starting from the benzylidene derivative **76** (9.4 g, 37.6 mmol) applying GP 4.2.1.6 (reaction time 2 h) and after chromatography over silica gel (EtOAc), the desired product was obtained as colourless solid (5.54 g, 34.2 mmol, 91%).

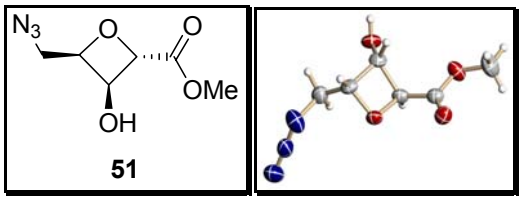
Data: $[\alpha]_D^{20}$ -18 ° (*c* 0.5 , $CHCl_3$) [lit.[139]: crystalline solid, $[\alpha]_D^{24}$ -27.1 º (*c* 0.92, $CHCl_3$)]. MS: (ionspray) *m/z* 180.1 $[M+ NH_4]^+$, 185.3 $[M+Na]^+$.The ^1H NMR data were in full agreement with reported values.[114]



49

2,4-Anhydro-3,5-di-*O*-benzyl-D-lyxonic acid (49). From methyl ester **38** (100 mg, 0.292 mmol) and using GP 4.2.1.7 (reaction time 30 min) the desired compound was obtained as a colourless foam (95 mg, quantitative), $[\alpha]_D^{20}$ -10.6° (*c* 1.0, $CHCl_3$). MS: (ionspray) *m/z* 346.4 $[M+NH_4]^+$, 351.3 $[M+Na]^+$, 674.4 $[2M+ NH_4]^+$. ^1H NMR (300 MHz, $CDCl_3$): δ 7.28-7.38 (m, 10H, Ph), 5.10 (dd, 1H, $J_{2,3}$ = 5.1 Hz, $J_{2,4}$ = 0.8 Hz, H-2), 5.03 (dddd≈dq, 1H, H-4), 4.64 (dd, 1H, $J_{3,4}$ = 6.5 Hz, H-3), 4.62;4.56 (AB, 2H, $J_{a,b}$ = 11.6 Hz, CH_2Ph), 4.65;4.50 (AB, 2H, $J_{a',b'}$ = 12.0 Hz, $CH_2'Ph$), 3.96 (A(ABX), 1H, $J_{4,5a}$ = 5.7 Hz, $J_{5a,5b}$ = 11.0 Hz, H-5a), 3.92 (B(ABX), 1H, $J_{4,5b}$ = 6.1 Hz, H-5b). Anal. Calcd. for $C_{19}H_{20}O_5$ (328.37): C, 69.50; H, 6.14. Found: C, 69.39; H, 6.16.

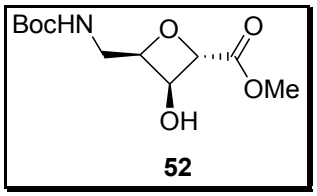
[114] Saksena *et al. Tetrahedron Lett.* **1992**, 33(*50*):7724.



51

Methyl 2,4-Anhydro-5-azido-5-deoxy-D-lyxonate (51). To a suspension of diol **48** (1.014 g, 6.24 mmol) and molecular sieves (4Å, ca. 1g) in dry DCM and dry ether (175 mL, 1:5) at -15 °C was added dropwise a solution of trifluoromethanesulphonic anhydride (1.03 mL, 6.55 mmol) in dry ether (175 mL). After stirring for 50 min the mixture was concentrated at rt, and the resulting triflate **50** was reacted immediately without further purification. MS: *m/z* 312.0 $[M+ NH_4]^+$, 606.4 $[2M+ NH_4]^+$.

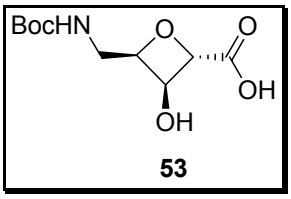
To the crude triflate **50** (1.836 g) in acetone (300 mL), still in the presence of 4Å molecular sieves, was added lithium azide (3.06 g; 62.4 mmol). After stirring for 30 min the reaction mixture was concentrated and then washed with 100 mL of iced water. The organic layer was then extracted five times with TBME, washed with brine, dried over $MgSO_4$, filtered, and the filtrate was concentrated. Chromatography of the residue over silica gel (EtOAc/Cy-Hex 1:1) furnished the pure product **51** (766 mg, 65 %) as colourless crystals, m.p. 67-70 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.08 (d, 1H, $J_{2,3}$ = 5.3 Hz, H-2), 4.95 (ddd, 1H, $J_{4,5a}$ = 4.3 Hz, H-4), 4.87 (dd, 1H, $J_{3,4}$ = 7.0 Hz, H-3), 3.85 (A(ABX), 1H, $J_{5a,5b}$ = 13.6 Hz, H-5a), 3.83 (s, 3H, OMe), 3.62 (B(ABX), 1H, $J_{4,5b}$ = 3.3 Hz, H-5b).



52

Methyl 2,4-Anhydro-5-*N*-(*t*-butoxycarbonyl)amino-5-deoxy-D-lyxonate (52). Starting from azide **51** (510.2 mg, 2.73 mmol), using GP 4.2.1.9 (reaction time 2 h) and after chromatography of the residue over silica gel (EtOAc/Cy-Hex 1:2) the pure product **52** (624.8 mg, 2.39 mmol, 88 %) was obtained as a colourless solid. m.p.

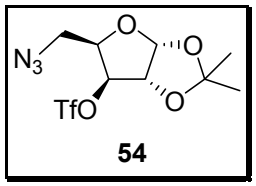
93-96 ºC. MS: (ionspray) *m/z* 262.0 $[M+H]^+$; 279.1 $[M+ NH_4]^+$, 280.3 $[M+Na]^+$. ^1H NMR (300 MHz, $CDCl_3$): δ 5.01 (br t, 1H, NH), 4.81 (d, 1H, $J_{2,3}$ = 3.8 Hz, H-2), 4.79 (ddd, 1H, $J_{4,5b}$ = 6.2 Hz, H-4), 4.76 (ddd≈dd, 1H, $J_{3,4}$ = 3.2 Hz, H-3), 3.81 (s, 3H, OMe), 3.78 (ddd≈dd, 1H, $J_{4,5a}$ = 7.1 Hz, H-5a), 3.30 (ddd≈dd, 1H, $J_{5a,5b}$ = 13.4 Hz, H-5b), 1.44 (s, 9H, Boc). Anal. Calcd. for $C_{11}H_{19}NO_6$ (261.28): C, 50.57; H, 7.33; N, 5.36. Found: C, 50.48; H, 7.36; N, 5.33.



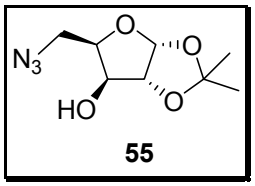
53

2,4-Anhydro-5-*N*-(*t*-butoxycarbonyl)amino-5-deoxy-D-lyxonic Acid (**53**)**.** To a solution of carboxylic ester **52** (1.0 g; 3.65 mmol) in TBME saturated with water (330 mL) was added commercial lipase L2-*Candida antarctica* (500 mg) at 45 °C. The reaction mixture was stirred for 3 days. After filtration of the immobilized enzyme the concentration of filtrate gave the crude product **53** as a colourless foam (941 mg, 3.81 mmol, 105 %) containing 4.3% ester **52** and 5% TBME. $[\alpha]_D^{20}$ -4.7° (*c* 1.1, MeOH) MS (ionspray neg.): *m/z* 246.3 $[M-H]^-$, 493.3 $[2M-H]^-$, 515.3 $[2M-H+Na]^-$. ^1H NMR (300 MHz, MeOD): δ 4.78 (d, 1H, H-2), 4.64 (br dd, 1H, $J_{2,3}$ = 5.7 Hz, $J_{3,4}$ = 6.9 Hz, H-3), 4.61 (ddd, 1H, H-4), 3.44 (A(ABX), 1H, $J_{4,5a}$ = 4.9 Hz, $J_{5a,5b}$ = 14.5 Hz, H-5a), 3.36 (B(ABX), 1H, $J_{4,5b}$ = 6.2 Hz, H-5b), 1.34 (s, 9H, Boc). Anal. Calcd. for $C_{10}H_{17}NO_6$ (247.25): C, 48.58; H, 6.93; N, 5.67. Found: C, 49.12; H, 6.92; N, 5.32 (an analytical sample was chromatographed with EtOAc/MeOH/H_2O 85:10:5).

4.2.3 Synthesis of 2,4-Anhydro-5-*N*-(tert-butoxycarbonyl)amino-5-deoxy-3-*O*-methyl-D-*lyxonic* acid (61)



54



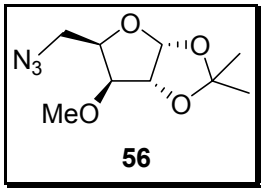
55

5-Azido-5-deoxy-1,2-*O*-isopropylidene-3-*O*-trifluoromethanesulfonyl–α-D-xylofuranose (54) and 5-azido-5-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranose (55). 1,2-*O*-isopropylidene-D-xylofuranose (5.0 g, 26.3 mmol) was reacted according to GP 4.2.1.4 (reaction time 30 min), and the obtained crude triflate was reacted using GP 4.2.1.8 (overnight). Chromatography (EtOAc/Cy-Hex 1:2) of the residue obtained furnished compound **54** as a colourless oil (2.09 g, 6.0 mmol, 23%) followed by the pure desired product **55** as a colourless solid (3.51 g, 16.3 mmol, 62 %).

To a solution of triflate **54** in MeOH (100 mL) at ca. 0 ºC was added metallic sodium until pH≈ 9, then the mixture was stirred at rt overnight and neutralised with Amberlite IR-120. After filtration of the resin and solvent evaporation the obtained residue was chromatographed (EtOAc/Cy-Hex 1:1) to give **55** in quantitative yield.

Physical data of **54**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.02 (d, 1H, $J_{1,2}$ = 3.6 Hz, H-1), 5.18 (d, 1H, $J_{3,4}$ = 1.8 Hz, H-3), 4.76 (d, 1H, $J_{2,3}$ ≈ 0 Hz, H-2), 4.43 (ddd≈td, 1H, H-4), 3.72 (A(ABX), 1H, $J_{4,5a}$ = 7.0 Hz, $J_{5a,5b}$ = 12.6 Hz, H-5a), 3.50 (B(ABX), 1H, $J_{4,5b}$ = 6.1 Hz, H-5b), 1.53 (s, 3H, *i*-prop), 1.35 (s, 3H, *i*-prop); ^{13}C NMR (100MHz, $CDCl_3$): δ 120.1 (CF_3), 113.4 (Cq *i*-prop), 104.7 (C-1), 87.9 (C-3), 83.2 (C-2), 77.3 (C-4), 48.6 (C-5), 26.6 (Me *i*-prop), 26.4 (Me *i*-prop).

Physical data of **55**: m.p. 59.8-60.2 ºC (lit.[118] m.p. 60 ºC, lit.[136] m.p. 64 ºC). $[\alpha]_D^{20}$ -36º (*c* 1.0, $CHCl_3$) [lit.[136]: $[\alpha]_D^{25}$ -36.3º (c 1.0, $CHCl_3$)]. ^1H and ^{13}C NMR were in agreement with literature data. [118,136] Anal. Calcd. for $C_8H_{13}N_3O_4$ (215.21): C, 44.65; H, 6.09; N, 19.53. Found: C, 44.48; H, 5.92; N, 19.33.

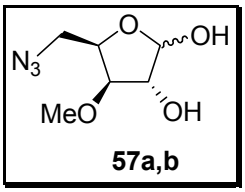


56

5-Azido-5-deoxy-1,2-*O*-isopropylidene-3-*O*-methyl-α-D-xylofuranose (56). Starting from 5-azido-5-deoxy-1,2-*O*-isopropylidene-D-xylofuranose **55** (3 g, 13.8 mmol) and proceeding as described in GP 4.2.1.10 (reaction time 1 h) was obtained

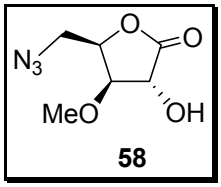
the crude product which after column chromatography (EtOAc/Cy-Hex 1:3) gave compound **56**[116] as colourless oil in quantitative yield (3.16 g, 13.8 mmol). $[\alpha]_D^{20}$ -37º (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 5.90 (d, 1H, $J_{1,2}$ = 3.8 Hz, H-1), 4.60 (d, 1H, $J_{2,3} \approx 0$ Hz, H-2), 4.30 (ddd≈dt, 1H, H-4), 3.73 (d, 1H, $J_{3,4}$ = 3.1 Hz, H-3), 3.53 (A(ABX), 1H, $J_{4,5a}$ = 6.8 Hz, $J_{5a,5b}$ = 12.4, H-5a), 3.49 (B(ABX), 1H, $J_{4,5b}$ = 6.3 Hz, H-5b), 3.43 (s, 3H, OMe), 1.51 (s, 3H, *i*-prop), 1.33 (s, 3H, *i*-prop); ^{13}C NMR (100 MHz, $CDCl_3$): δ 112.0 (Cq *i*-prop), 105.2 (C-1), 83.9 (C-3), 81.5 (C-2), 78.8 (C-4), 57.8 (OMe), 49.0 (C-5), 26.9 (Me *i*-prop), 26.4 (Me *i*-prop). Anal. Calcd. for $C_9H_{15}N_3O_4$ (229.24): C, 47.16; H, 6.60; N, 18.33. Found: C, 47.27; H, 6.51; N, 18.31.

[118] Kefurt, K; Kefurtova, Z; Markova, V; Slivova, K; *Collect Czech Chem Commun* **1996**, 61:1027.
[136] Ewing, DF; Goethals, G; Mackenzie, G; Martin, P; Ronco, G; Vanbaelinghem, L.; Villa, P J; *Carbohydr Chem* **1999**, 18:441.
[116] Tulshian *et al. Bioorg Med Chem Lett* **1992**, 2:515.



57a,b

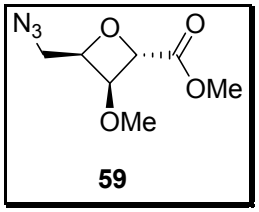
5-Azido-5-deoxy-3-*O*-methyl-α,β-D-xylofuranose (57a,b). From xylofuranose **56** (3.0 g, 13.1 mmol) and proceeding as described in GP 4.2.1.2 (reaction time 2 h) and chromatographing with EtOAc/Cy-Hex 1:1 the desired product **57a,b** was obtained as a mixture of anomers (2.18 g, 88 %, α/β ca. 1:0.4 by NMR integration) as a colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.50 (d, 1H, $J_{1\alpha,2\alpha}$ = 4.0 Hz, H-1α), 5.10 (d, 0.4H, $J_{1\beta,2\beta}$= 9.6 Hz, H-1β), 4.46-4.38 (m, 1.4H, H-4α, H-4β), 4.31 (br s, 0.4H, H-2β), 4.22 (br t, 1H, H-2α), 3.83 (dd, 1H, $J_{2\alpha,3\alpha}$ = 3.1 Hz, $J_{3\alpha,4\alpha}$ = 5.1 Hz, H-31α), 3.79 (d, 0.4H, $J_{3\beta,4\beta}$ = 4.4 Hz, H-3β), 3.57-3.38 (m, 3.2H, H-5aα, H-5bα, H-5aβ, H-5bβ, OH-1β), 3.50 (s, 1.2H, OMeβ), 3.46 (s, 3H, OMeα); ^{13}C NMR (100 MHz, $CDCl_3$): δ 103.4 (C-1β), 96.1 (C-1α), 85.4, 84.6 (C-3α, C-3β), 80.8, 77.4 (C-4α, C-4β, C-2β), 75.4 (C-2α), 58.6, 58.0, 50.7, 50.4 (C-5aα, C-5bα, C-5aβ, C-5bβ, OMeα, OMeβ). Anal. Calcd. for $C_6H_{11}N_3O_4$ (189.17): C, 38.10; H, 5.86; N, 22.21. Found: C, 38.07; H, 5.58; N, 22.32.



58

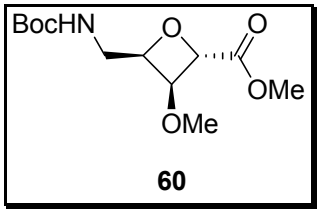
5-Azido-5-deoxy-3-*O*-methyl-D-xylono-1,4-lactone (58). Starting with **57a,b** (2.0 g, 10.56 mmol) and using GP 4.2.1.3 (reaction time 4 h) a residue was obtained that after chromatography with EtOAc/Cy-Hex 1:1 gave the desired product **58** (1.50 g, 8.0 mmol, 76%) as a colourless oil. $[\alpha]_D^{20}$ + 47° (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$; COSY): δ 4.73 (ddd≈td, 1H, $J_{4,3}$ = 7.6 Hz, $J_{4,5a} \approx J_{4,5b} \approx$ 3.7 Hz, H-4), 4.66 (d, 1H, $J_{2,3}$ = 7.6 Hz, H-2), 4.20 (t, 1H, $J_{3,4} \approx J_{2,3}$, H-3), 3.66-3.64 (m, 2H, H-5a, H-5b), 3.56 (s, 3H, OMe), 2.97 (br s, 1H, OH-2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.9

(C=O), 81.6 (C-3), 76.8 (C-4), 71.9 (C-2), 58.6 (OMe), 50.0 (C-5). Anal. Calcd. for $C_6H_9N_3O_4$ (187.16): C, 38.51; H, 4.85; N, 22.45. Found: C, 38.53; H, 4.77; N, 22.49.



59

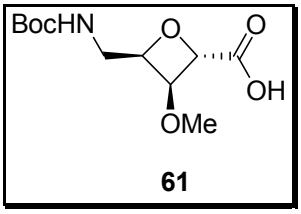
Methyl 2,4-anhydro-5-azido-5-deoxy-3-*O*-methyl-D-lyxonate (59). From the γ-lactone **58** (1.0 g, 5.34 mmol) and proceeding as described in GP 4.2.1.4 (reaction time 1h) was obtained the crude 5-azido-3-*O*-methyl-2-*O*-trifluoromethanesulfonyl-D-xylono-1,4-lactone which was submitted to GP 4.2.1.5 (reaction time 4h) to give the crude **59** that was chromatographed (EtOAc/Cy-Hex 1:2) furnishing the desired oxetane as a colourless oil (720 mg, 3.58 mmol, 67% yield). $[\alpha]_D^{20}$ -51º (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.05 (d, 1H, $J_{2,3}$ = 4.8 Hz, H-2), 4.44 (dd, 1H, $J_{3,4}$ = 6.6 Hz, H-3), 4.92 (q, 1H, H-4, $J_{3,4} \approx J_{4,5a} \approx J_{4,5a} \approx 6.3$), 3.86 (s, 3H, OMe), 3.69 (A(ABX), 1H, $J_{4,5a}$ = 6.1 Hz, $J_{5a,5b}$ = 13.2 Hz, H-5a), 3.64 (B(ABX), 1H, $J_{4,5b}$ = 6.3 Hz, H-5b), 3.43 (s, 3H, OMe); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.7 (C-1), 84.0 (C-2), 82.5 (C-4), 77.1 (C-3), 57.5 (OMe), 52.6 (COO*Me*), 50.4 (C-5). Anal. Calcd. for $C_7H_{11}N_3O_4$ (201.18): C, 41.79; H, 5.51; N, 20.89. Found: C, 42.05; H, 5.32; N, 20.58.



60

Methyl 2,4-Anhydro-5-*N*-(*tert*-butoxycarbonyl)amino-5-deoxy-3-*O*-methyl-D-lyxonate (60). Using GP 4.2.1.9 (reaction time 2h) and azide **59** as starting material (766 mg, 3.8 mmol) the product **30** was obtained after chromatography over silica gel eluting with EtOAc/ Cy-Hex 1:2, as a colourless oil (871 mg, 3.16 mmol, 83 %). $[\alpha]_D^{20}$ -35º (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.99 (d, 1H, $J_{2,3}$ = 4.9 Hz, H-

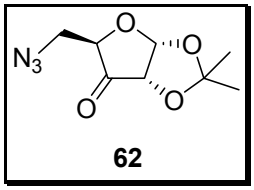
2), 4.96-4.76 (m, 2H, H-4, NH), 4.39 (dd, 1H, $J_{3,4}$ = 6.5 Hz, H-3), 3.83 (s, 3H, OMe), 3.61 (ddd, 1H, $J_{5a,5b}$ = 12.8 Hz, $J_{5a,NH} \approx J_{4,5a} \approx$ 6.8 Hz, H-5a), 3.56-3.49 (m, 4H, H-5b, OMe), 1.44 (s, 9H, Boc); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.8 (C=O COOMe), 155.9 (C=O Boc), 83.7 (C-2), 82.4 (C-4), 77.4 (C-3), 57.6 (COO*Me*), 52.5 (OMe), 40.5 (C-5), 28.4 (3Me *t*-Bu). Anal. Calcd. for $C_{12}H_{21}NO_6$ (275.30): C, 52.35; H, 7.69; N, 5.09. Found: C, 51.86; H, 7.31; N, 5.31.



61

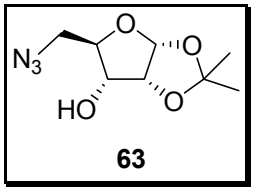
2,4-Anhydro-5-*N*-(*tert*-butoxycarbonyl)amino-5-deoxy-3-*O*-methyl-D-lyxonic acid (61). Hydrolysis of the methyl ester **60** (501.7 mg, 1.82 mmol) was achieved employing GP 4.2.1.7 (reaction time 30 min) to give the product **61** as a colourless hygroscopic foam (424 mg, 1.62 mmol, 89%). ^{1}H NMR (400 MHz, acetone-d_6): δ 5.82 (br s, 1H, NH), 4.93 (d, 1H, $J_{2,3}$ = 4.7 Hz, H-2), 4.79 (q, 1H, $J_{3,4} \approx J_{4,5a} \approx J_{4,5b} \approx$ 6.5 Hz, H-4), 4.46 (dd, 1H, $J_{3,4}$ = 6.3 Hz, H-3), 3.56-3.40 (m, 2H, H-5a, H-5b), 3.39 (OMe), 1.40 (s, 9H, Boc); ^{13}C NMR (100 MHz, acetone-d_6): δ 170.2 (COOH), 156.7 (C=O Boc), 83.7 (C-2), 82.2 (C-4), 77.9 (C-3), 78.8 (Cq Boc), 57.3 (OMe), 40.9 (C-5), 28.3 (3Me *t*-Bu). HRMS (NSI) *m/z* 260.11397 $[M-H]^-$, calcd. 260.11396 for $C_{11}H_{18}NO_6$.

4.2.4 Synthesis of 2,4-Anhydro-5-*N*-(tert-butoxycarbonyl)amino-5-deoxy-3-*O*-methyl-D-*ribonic* and D-*arabinonic* Acids



62

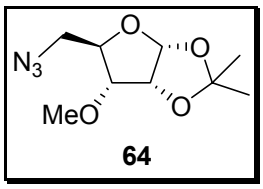
5-Azido-5-deoxy-1,2-*O*-isopropylidene-α-D-*erythro*-pentofuranos-3-ulose (62). Starting from 5-azido-5-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranose **55** (2.71 g, 12.6 mmol) in anhydrous DCM (45 mL) was added PDC (3.32 g, 8.8 mmol) and Ac_2O (3.6 mL, 38.1 mmol), and the mixture was stirred for 3h under reflux. Diethyl ether was added (100 mL), and the brown suspension was filtered over a Florisil® column (Supelco/Sigma-Aldrich, 100-200 mesh) eluting with diethyl ether. The product was crystallised from DCM/Cy-Hex to give a colourless solid (2.392 g, 11.2 mmol, 89% yield). m.p. 54.2-55.0 ºC. $[\alpha]_D^{25}$ +187º (*c* 1.0, $CHCl_3$), (lit.[121] $[\alpha]_D^{25}$ +185.2º (*c* 1.1,$CHCl_3$)). NMR data were in full agreement with the literature.[121]



63

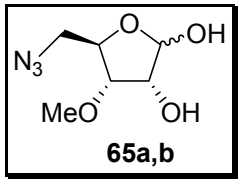
5-Azido-5-deoxy-1,2-*O*-isopropylidene-α-D-ribofuranose (63). Treatment of the ulose **62** with $NaBH_4$ in $EtOH/H_2O$[118] gave the desired product **63** as colourless oil in 94% yield. $[\alpha]_D^{25}$ +63º (*c* 1.0, $CHCl_3$), (lit.[118] $[\alpha]_D^{20}$ +65.5º (*c* 0.5, $CHCl_3$)). NMR data were in full agreement with the literature.[118]

[121] Ewing *et al. Carbohydr Res* **1999**, 321:190.
[118] Kefurt *et al*. *Collect Czech Chem Commun* **1996**, 61:1027.



64

5-Azido-5-deoxy-1,2-*O*-isopropylidene-3-O-methyl-α-D-ribofuranose (64). Starting from 5-azido-5-deoxy-1,2-*O*-isopropylidene-α-D-ribofuranose **63** (1.98 g, 9.2 mmol) and proceeding as described in GP 4.2.1.10 (reaction time 30 min) the known product **64**[117] was obtained as colourless oil (2.13 g, 9.3 mmol, quantitative) after chromatography (EtOAc/Cy-Hex 1:4 to 1:2). $[\alpha]_D^{25}$ +161° (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.80 (d, 1H, $J_{1,2}$ = 3.6 Hz, H-1), 4.71 (t, 1H, H-2), 4.14 (ddd≈dt, 1H, H-4), 3.72 (A(ABX), 1H, $J_{4,5a}$ = 2.5 Hz, $J_{5a,5b}$ = 13.5 Hz, H-5a), 3.65 (dd, 1H, $J_{2,3}$ 4.1 Hz, $J_{3,4}$ = 8.0 Hz, H-3), 3.50 (s, 3H, OMe), 3.32 (B(ABX), 1H, $J_{4,5b}$ = 3.8 Hz, H-5b), 1.59 (s, 3H, *i*-prop), 1.38 (s, 3H, *i*-prop). ^{13}C NMR (100 MHz, $CDCl_3$): δ 113.4 (Cq *i*-prop), 104.1 (C-1), 80.6 (C-3), 77.4 (C-4), 77.0 (C-2), 58.6 (OMe), 50.7 (C-5), 26.9 (Me *i*-prop), 26.5 (Me *i*-prop). Anal. Calcd. for $C_9H_{15}N_3O_4$ (229.24): C, 47.16; H, 6.60; N, 18.33. Found: C, 47.17; H, 6.52; N, 18.46.

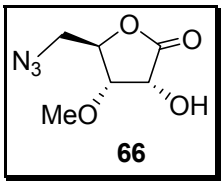


65a,b

5-Azido-5-deoxy-3-*O*-methyl-α,β-D-ribofuranose (65a,b). Submitting 5-azido-5-deoxy-1,2-*O*-isopropylidene-3-O-methyl-α-D-ribofuranose **64**, (2.0 g, 8.7 mmol) to GP 4.2.1.2 (reaction time 1 h) and after chromatography (EtOAc/Cy-Hex 1:1) the desired product **65a,b** was obtained as a colourless oil (1.42 g, 7.5 mmol, 86% yield, α/β 1:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.37-5.32 (m, 2H, H-1α, H-1β), 4.21 (ddd≈q, 1H, H-4α), 4.18 (br t, 1H, $J_{1\alpha,2\alpha} \approx J_{2\alpha,3\alpha} \approx$ 4.5 Hz, H-2α), 4.15-4.11 (m, 2H, H-2β, H-4β), 4.00 (dd, 1H, $J_{2\beta,3\beta}$ = 4.6 Hz, $J_{3\beta,4\beta}$ = 6.9 Hz, H-3β), 3.70 (dd≈t, 1H, $J_{2\alpha,3\alpha}$ = 5.0

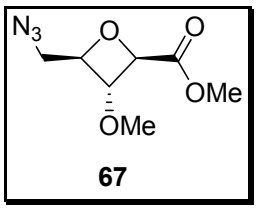
[117] Yamashita, M.; Takahashi, C.; Seo, K. Heterocycles **1993**, *36(4)*, 651-654.

Hz, $J_{3\alpha,4\alpha}$ = 5.5 Hz, H-3α), 3.61 (A(ABX), 1H, $J_{4\beta,5a\beta}$ = 3.7 Hz, H-5aβ), 3.56 (A(ABX), 1H, $J_{4\alpha,5a\alpha}$ = 4.0 Hz, H-5aα), 3.49 (s, 3H, OMeα), 3.46 (s, 3H, OMeβ), 3.39 (B(ABX), 1H, $J_{4\beta,5b\beta}$ = 5.2 Hz, $J_{5a\beta,5b\beta}$ = 13.1 Hz, H-5bβ), 3.32 (B(ABX), 1H, $J_{4\alpha,5b\alpha}$ = 3.9 Hz, $J_{5a\alpha,5b\alpha}$ = 13.2 Hz, H-5bα); ^{13}C NMR (100 MHz, $CDCl_3$): δ 102.3 (C-1β), 97.1 (C-1α), 81.1 (C-3β), 80.4 (C-3α), 80.0 (C-4β), 79.1 (C-4α), 73.2 (C-2β), 70.1 (C-2α), 58.9 (OMeα), 58.6 (OMeβ), 53.3 (C-5β), 52.2 (C-5α). HRMS (ESI) *m/z* 248.08925 $[M+OAc]^+$, calcd. 248.08881 for $C_8H_{14}N_3O_6$. Anal. Calcd. for $C_6H_{11}N_3O_4$ (189.17): C, 38.10; H, 5.86; N, 22.21. Found: C, 38.10; H, 5.78; N, 21.99.

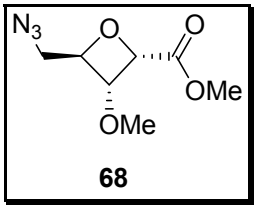


66

5-Azido-5-deoxy-3-*O*-methyl-D-ribono-1,4-lactone (66). Starting from **65a,b** (1.33 g, 7.0 mmol) and applying GP 4.2.1.3 (reaction time 1.5 h), the desired product **66** was obtained as a colourless oil (880 mg, 4.70 mmol, 67%) after chromatography (EtOAc/Cy-Hex 1:1). $[\alpha]_D^{25}$ +60° (*c* 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 4.63 (d, 1H, $J_{2,3}$ = 5.9 Hz, H-2) 4.55 (dd≈t, 1H, H-4), 3.90 (d, 1H, $J_{3,4} \approx 0$ Hz, H-3), 3.74 (A(ABX), 1H, $J_{4,5a}$ = 4.3 Hz, $J_{5a,5b}$ = 13.4 Hz, H-5a), 3.65 (B(ABX), 1H, $J_{4,5b}$ = 3.7 Hz, H-5b), 3.52 (s, 3H, OMe); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.50 (C=O), 79.35 (C-4), 77.96 (C-3), 68.14 (C-2), 58.45 (OMe), 51.91 (C-5). HRMS (ESI) *m/z* 246.07358 $[M+OAc]^+$, calcd. 246.07316 for $C_8H_{12}N_3O_6$. Anal. Calcd. for $C_6H_9N_3O_4$ (187.16): C, 38.51; H, 4.85; N, 22.45. Found: C, 38.46; H, 4.89; N, 22.07.



67



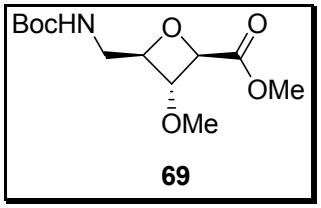
68

Methyl 2,4-anhydro-5-azido-5-deoxy-3-*O*-methyl-D-ribonate (67) and Methyl 2,4-anhydro-5-azido-5-deoxy-3-*O*-methyl-D-arabinonate (68). Applying GP 4.2.1.4 to

lactone **66** (812 mg, 4.34 mmol, reaction time 15 min) furnished the crude 5-azido-3-*O*-methyl-2-*O*-trifluoromethanesulfonyl-D-xylono-1,4-lactone (assumed 4.34 mmol) that was then submitted to GP 4.2.1.5 and chromatographed (EtOAc/Cy-Hex 1:3) to give compound **67** (465.5 mg, 2.31 mmol, 53%) followed by compound **68** (61.0 mg, 0.3 mmol, 7%).

Data for compound **67**: Colourless oil, $[\alpha]_D^{25}$ +140º (*c* 1.0, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.95 (d, 1H, $J_{2,3}$ = 5.1 Hz, H-2) 4.72 (bq, 1H, H-4), 4.27 (t, 1H, $J_{2,3} \approx J_{3,4} \approx$ 5.0 Hz, H-3), 3.84 (s, 3H, COOMe), 3.61 (A(ABX), 1H, $J_{4,5a}$ = 4.0 Hz, $J_{5a,5b}$ = 13.8 Hz, H-5a), 3.44 (B(ABX), 1H, $J_{4,5b}$ = 4.0 Hz, H-5b), 3.40 (s, 3H, OMe); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.2 (C=O), 84.2 (C-4), 81.7 (C-2), 78.4 (C-3), 57.1 (OMe), 52.7 (C-5), 52.5 (COO*Me*). HRMS (ESI) *m/z* 219.10882 $[M+NH_4]^+$, calcd. 219.10878 for $C_7H_{15}N_4O_4$. Anal. Calcd. for $C_7H_{11}N_3O_4$ (201.18): C, 41.79; H, 5.51; N, 20.89. Found: C, 41.44; H, 5.42; N, 20.87.

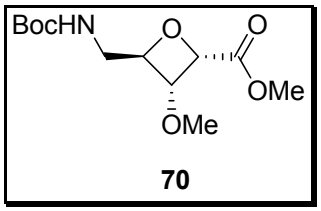
Data for compound **68**: Colourless oil, $[\alpha]_D^{25}$ +68º (*c* 1.0, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.17 (d, 1H, $J_{2,3}$ = 6.9 Hz, H-2) 4.95 (br ddd, 1H, H-4), 4.51(dd, 1H, $J_{3,4}$ = 5.5 Hz, H-3), 3.86 (s, 3H, COOMe), 3.65 (A(ABX), 1H, $J_{4,5a}$ = 3.7 Hz, $J_{5a,5b}$ = 13.9 Hz, H-5a), 3.39 (B(ABX), 1H, $J_{4,5b}$ = 3.4 Hz, H-5b), 3.35 (s, 3H, OMe); ^{13}C NMR (100 Hz, $CDCl_3$): δ 169.8 (C=O), 87.5 (C-4), 81.4 (C-2), 75.9 (C-3), 58.4 (OMe), 52.8 (C-5), 52.4 (COO*Me*). HRMS (ESI) *m/z* 219.10884 $[M+NH_4]^+$, calc. 219.10878 for $C_7H_{15}N_4O_4$. Anal. Calcd. for $C_7H_{11}N_3O_4$ (201.18): C, 41.79; H, 5.51; N, 20.89. Found: C, 41.65; H, 5.72; N, 20.74.



69

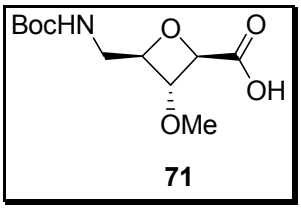
Methyl 2,4-anhydro-5-*N*-(*tert*-butoxycarbonyl)amino-5-deoxy-3-*O*-methyl-D-ribonate (69). Starting from the azide **67** (330 mg, 1.64 mmol) and using GP 4.2.1.9 (reaction time 2 h), gave a crude product that was chromatographed (EtOAc/Cy-Hex 1:2) to yield the pure product **69** (390 mg; 1.41 mmol, 81 %) as a colourless oil. $[\alpha]_D^{25}$

+3º (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 5.31(br s, 1H, NH), 4.93 (d, 1H, $J_{2,3}$ 5.0 Hz, H-2), 4.70 (br q, 1H, J ≈ 4.9 Hz, H-4), 4.13 (t, 1H, $J_{2,3} \approx J_{3,4} \approx$ 4.8 Hz, H-3), 3.84 (s, 3H, COOMe), 3.52 (br ddd, 1H, H-5a), 3.37 (s, 3H, OMe), 3.33 (dt, 1H, $J_{4,5b} \approx J_{5b,NH} \approx$ 3.9 Hz, $J_{5a,5b}$ = 15.1, H-5b), 1.45 (s, 9H, Boc); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.1 (C=O), 155.8 (C=O Boc), 85.7 (C-4), 81.6 (C-2), 79.1 (Cq Boc), 78.7 (C-3), 57.3 (OMe), 52.6 (COO*Me*), 42.8 (C-5), 27.9 (3Me-Boc). HRMS (ESI) *m/z* 293.17071 $[M+NH_4]^+$, calcd. 293.17071 for $C_{12}H_{25}N_2O_6$. Anal. Calcd. for $C_{12}H_{21}NO_6$ (275.30): C, 52.35; H, 7.69; N, 5.09. Found: C, 52.09; H, 7.41; N, 5.30.



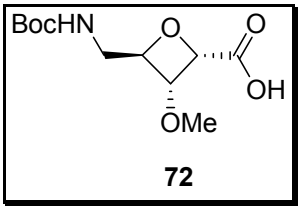
70

Methyl 2,4-anhydro-5-*N*-(*tert*-butoxycarbonyl)amino-5-deoxy-3-*O*-methyl-D-arabinonate (70). Starting from the azide **68** (125 mg, 0.62 mmol) and using GP 4.2.1.9 (reaction time 2 h), gave a crude product that was chromatographed (EtOAc/Cy-Hex 1:2) to yield the pure product **70** (147 mg, 0.53, 85 %) as a colourless oil. $[\alpha]_D^{25}$ +112º (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 5.09 (d, 1H, $J_{2,3}$ = 7.2 Hz, H-2), 4.93 (br s, 1H, NH), 4.85 (br q, J = 4.7 Hz, H-4), 4.36 (dd, 1H, $J_{3,4}$ = 5.9 Hz, H-3), 3.85 (s, 3H, COOMe), 3.50 (ddd, 1H, $J_{5a,5b}$ = 15.0 Hz, $J_{5a,NH}$ = 7.0 Hz, $J_{4,5a}$ = 4.5 Hz, H-5a), 3.39 (dt, 1H, $J_{4,5b} \approx J_{5b,NH} \approx$ 4.5 Hz, H-5b), 3.33 (s, 3H, OMe), 1.46 (s, 9H, Boc); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.9 (C=O COOMe), 156.1 (C=O Boc), 88.2 (C-4), 81.0 (C-2), 79.8 (Cq Boc), 75.8 (C-3), 58.0 (OMe), 52.2 (COO*Me*), 42.8 (C-5), 28.3 (3Me-Boc). HRMS (ESI) *m/z* 293.17060 $[M+NH_4]^+$, calcd. 293.17071 for $C_{12}H_{25}N_2O_6$. Anal. Calcd. for $C_{12}H_{21}NO_6$ (275.30): C, 52.35; H, 7.69; N, 5.09. Found: C, 51.86; H, 7.31; N, 5.31.



71

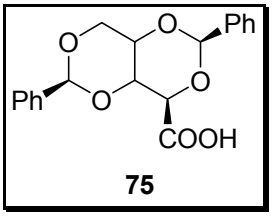
2,4-Anhydro-5-*N*-(*tert*-butoxycarbonyl)amino-5-deoxy-3-*O*-methyl-D-ribonic acid (71). Hydrolysis of the methyl ester **69** (60 mg; 0.22 mmol) was achieved using GP 4.2.1.7 (reaction time 30 min) to give product **71** as a colourless waxy solid (50.6 mg, 89%). ^{1}H NMR (400 MHz, acetone-d_6): δ 6.96 (br s, 1H, NH), 5.59 (d, 1H, $J_{2,3}$ = 4.7 Hz, H-2), 5.31 (q, 1H, $J_{3,4} \approx J_{4,5a} \approx J_{4,5b} \approx$ 4.9 Hz, H-4), 4.92 (t, 1H, H-3), 3.21-4.04 (m, 5H, H-5a, H-5b, OMe), 1.42 (s, 9H, Boc); ^{13}C NMR (100 Hz, acetone-d_6): δ 171.5 (COOH), 157.1 (C=O Boc), 85.6 (C-4), 81.6 (C-2), 80.2 (C-3), 79.1 (Cq Boc), 56.6 (OMe), 43.3 (C-5), 28.4 (3Me *t*-Bu). HRMS (NSI) *m/z* 260.11406 $[M-H]^-$, calcd. 260.11396 for $C_{11}H_{18}NO_6$.



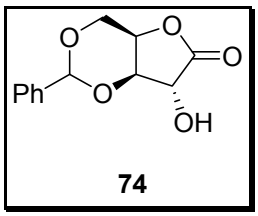
72

2,4-Anhydro-5-*N*-(*tert*-butoxycarbonyl)amino-5-deoxy-3-*O*-methyl-D-arabinonic Acid (72). Hydrolysis of the methyl ester **70** (60 mg; 0.22 mmol) was achieved employing GP 4.2.1.7 (reaction time 30 min) to give the product **72** as a colourless hygroscopic foam (52.3 mg, 92%). ^{1}H NMR (400 MHz, acetone-d_6): δ 5.18 (d, 1H, $J_{2,3}$ = 7.3 Hz, H-2), 4.81 (q, 1H, $J_{3,4} \approx J_{4,5a} \approx J_{4,5b} \approx$ 5.3 Hz, H-4), 4.54 (dd, 1H, H-3), 3.47 (d, 2H, H-5b, $J_{4,5a} = J_{4,5b}$ = 5.0 Hz, H-5a), 3.41 (s, 3H, OMe), 1.39 (s, 9H, Boc); ^{13}C NMR (acetone-d_6): δ 171.5 (COOH), 157.1 (C=O Boc), 85.6 (C-4), 81.6 (C-2), 80.2 (C-3), 79.1 (Cq Boc), 56.8 (OMe), 43.3 (C-5), 28.4 (3Me *t*-Bu). HRMS (NSI) *m/z* 260.11403 $[M-H]^-$, calcd. 260.11396 for $C_{11}H_{18}NO_6$.

4.2.5 Synthesis of 2,4-Anhydro-5-*N*-(tert-butoxycarbonyl)amino-5-deoxy-3-fluor-D-*arabinonic* Acid



75



74

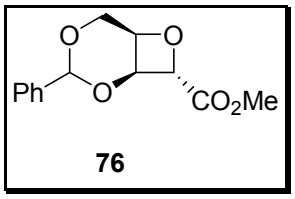
2,4;3,5-Di-*O*-benzylidene-D-xylonic Acid (75) and 3,5-*O*-Benzylidene-D-xylono-1,4-lactone (74). A solution of D-xylose (20.0 g, 0.13 mol) in water (54 mL) was cooled in an ice water bath. Potassium carbonate (22.6 g, 0.16 mol) was then added in portions while keeping the temperature below 20 ºC. The mixture was cooled to 5 ºC, and bromine (8 mL, 0.15 mol) added dropwise over 45 min while keeping the temperature below 10 ºC. The resulting orange solution was stirred at 10 ºC for 30 min and then at rt overnight, when one major product was observed. The reaction was quenched by careful addition of 88% formic acid (1.66 mL) until the solution become colourless. The solution was concentrated at 50 ºC *in vacuo*, and acetic acid (13.4 mL) was added. The reaction mixture was concentrated at 50 ºC to remove any residual water. The crude xylono-1,4-lactone was used without purification.

To a solution of the crude lactone (assumed 19.7 g, 0.13 mol) in benzaldehyde (200 mL) was added HCL conc. (15 mL). The reaction was stirred at room temperature overnight to give two different products identified by TLC (EtOAc/Cy-Hexane 1:1). The mixture was concentrated under HV to a quarter volume. Diethylether (80 mL) was added, and a precipitate formed. The mixture was filtered, and the residue was washed with ether. The filtrate was concentrated *in vacuo*, and chromatographed (1:3 EtOAc/Cy-Hex) to give the desired benzylidene protected lactone **74** as a colourless solid (12.0 g, 51 mmol, 39%). The solid residue of the filtration was then washed with acetone to separate the by-product from the residual salts. The filtrate was concentrated *in vacuo*, and the by-product recrystallised from acetone/*n*-hexane to give compound **75** as a colourless solid (16.5 g, 48 mmol, 37%).

Data for **74**: $[\alpha]_D^{20}$ +11.2 (*c*, 1.0, CH_2Cl_2). ^{1}H NMR, COSY (400 MHz, $CDCl_3$): δ 7.46-7.44 (m, 2H, Ph),7.38-7.36 (m, 3H, Ph) 5.54 (s, 1H, CHPh), 4.59-4.53 (m, 3H, H-2,

H-4, H-5a), 4.32 (br s, 1H, H-3), 4.19 (B(ABX), 1H, $J_{4,5b}$ = 1.8 Hz, $J_{5a,5b}$ = 13.5 Hz, H-5b), 3.41 (br s, 1H, OH).

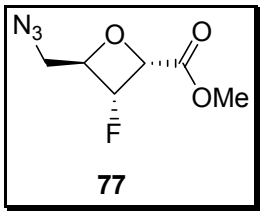
Data for **75**: $[\alpha]_D^{20}$ -18.6 (*c*, 1.00, DMF), Lit.[124] $[\alpha]_D^{20}$ -21.13 (*c*, 1.05, DMF). m.p. 202.2-203.0 ºC, Lit.[124] 198.5-200.0 ºC. MS(ionspray): 343.1 $[M+H]^+$, 360.4 $[M+NH_4]^+$, 365.1 $[M+Na]^+$. ^{1}H NMR, COSY, NOESY (400 MHz, DMSO): δ 12.90 (s, 1H, COOH), 7.52-7.50 (m, 2H, Ph), 7.44-7.35 (m, 8H, Ph), 5.75 (s, 1H, C*Ha*HbPh), 5.69 (s, 1H, CHa*Hb*Ph), 4.78 (d, 1H, $J_{2,3}$ = 2.1 Hz, H-2), 4.37 (br t, 1H, $J_{2,3} \approx J_{3,4} \approx$ 1.8 Hz, H-3), 4.21 (A(ABX), 1H, $J_{4,5a}$ = 1.8 Hz, $J_{5a,5b}$ = 12.8 Hz, H-5a), 4.16 (B(ABX), 1H, $J_{4,5b}$ = 1.3 Hz, H-5b), 4.04 (br q, 1H, H-4). ^{13}C NMR, HSQC, HMBC (100 MHz, DMSO): δ 169.28 (COOH), 138.78 (Ph), 138.43 (Ph), 129.37 (Ph), 129.21 (Ph), 128.50 (Ph), 128.47 (Ph), 126.92 (Ph), 126.58 (Ph), 99.5 (*C*HaPh), 99.9 (*C*HbPh), 76.63 (C-2), 70.55 (C-3), 69.87 (C-4), 69.51 (C-5). IR (cm^{-1}): 2580-2620 (COOH), 1738 (C=O(COOH)), 1608+1498 (aromatic), 1097 (COC), 763+700 (Ph, monosubstituted).



76

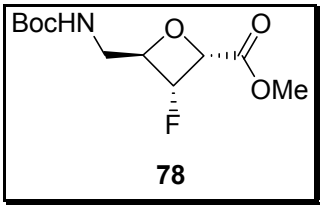
Methyl 2,4-anhydro-3,5-*O*-benzylidene-D-lyxonate (76). From 3,5-*O*-benzylidene-D-xylono-1,4-lactone **75** (11.9 g, 50.4 mmol) and proceeding as described in GP 4.2.1.4 (temperature ≈ -30 ºC, reaction time 1h) was obtained crude 3,5-*O*-benzylidene-2-*O*-trifluoromethanesulfonyl-D-xylono-1,4-lactone which was submitted to GP 4.2.1.5 (reaction time 4 h) to give the crude oxetane that was chromatographed (EtOAc/Cy-Hex 1:3) to furnish pure oxetane **76** (8.17 g, 32.7 mmol, 65% yield) as a colourless solid. $[\alpha]_D^{20}$ = -3.2 (*c*, 1.0 in DCM). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48-7.29 (m, 5H, Ph), 5.42 (s, 1H, C*H*Ph), 4.99 (d, 1H, $J_{2,3}$ 2.2 Hz, H-2), 4.92 (dd, 1H, $J_{3,4}$ 5.1 Hz, H-3), 4.89 (dd, 1H, $J_{4,5a}$ 0 Hz, $J_{4,5b}$ 2.5 Hz, H-4), 4.30 (d, 1H, $J_{5a,5b}$ 14.0 Hz, H-5a), 3.99 (dd, 1H, H-5b), 3.94 (s, 3H, OMe).

[124] Zinner *et al* *Carbohydr Res* **1968**, 7:38.



77

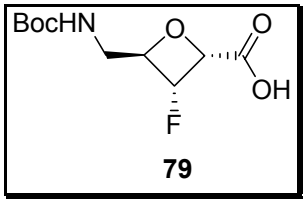
Methyl 2,4-Anhydro-5-azido-5-deoxy-3-fluoro-D-arabinonate (77). To a solution of **51** (500 mg, 2.7 mmol) in acetonitrile (40 mL) at –20 ºC was added DAST (8.1 mmol, 1.0 mL), and the mixture was stirred for 20 min. The temperature was then raised to reflux temperature over 1 h. After concentration, the mixture was dissolved in DCM (50 mL) and washed with a sat. soln. of $NaHCO_3$ (30 mL). After drying over $MgSO_4$, filtration and concentration the residue obtained was chromatographed (EtOAc/Cy-Hex 1:4) to yield the desired fluoro derivative as colourless oil (383 mg, 2.02 mmol, 75%). MS: *m/z* 190.3 $[M+H]^+$, 212.1 $[M+Na]^+$. ^1H NMR (300 MHz, $CDCl_3$): δ 5.53 (ddd, 1H, $J_{2,3}$ 6.7 Hz, $J_{3,4}$ 4.5 Hz, $J_{3,F}$ 56.1 Hz, H-3), 5.23 (ddd, 1H, $J_{2,4}$ 1.1 Hz, $J_{2,F}$ 15.2 Hz, H-2), 5.14 (dddd, 1H, $J_{4,5a}$ 3.4 Hz, $J_{4,5b}$ 3.0 Hz, $J_{4,F}$ 19.1 Hz, H-4), 3.89 (s, 3H, OMe), 3.72 (A(ABX), 1H, $J_{5a,5b}$ 14.2 Hz, H-5a) 3.48 (B(ABX), 1H, H-5b). Anal. Calcd. for $C_6H_8FN_3O_3$ (189.15): C, 38.10; H, 4.26; N, 22.22. Found: C, 38.38; H, 4.32; N, 21.98.



78

Methyl 2,4-Anhydro-5-*N*-(*t*-butoxycarbonyl)amino-5-deoxy-3-fluoro-D-arabinonate (78). Submitting azide **77** (1.14 g, 6.0 mmol) to GP 4.2.1.9 (reaction time 2h) followed by chromatography (EtOAc/ Cy-Hex 1:2) of the obtained residue gave the pure product **78** (1.35 g, 5.1 mmol, 85 %) as a colourless oil. ^1H NMR (400 MHz, $CDCl_3$): δ 5.37 (ddd, 1H, $J_{2,3}$ 6.8 Hz, $J_{3,4}$ 4.8 Hz, $J_{3,F}$ 56.0 Hz, H-3), 5.13 (ddd, 1H, $J_{2,F}$ 14.8 Hz, H-2), 5.03 (dddd, 2H, $J_{4,5a}$ 3.4 Hz, $J_{4,5b}$ 3.0 Hz, $J_{4,F}$ 19.1 Hz, H-4), 4.93 (br s, 1H, NH), 3.86 (s, 3H, OMe), 3.58 (dd, 1H, $J_{4,5a}$ 4.4 Hz, $J_{5a,5b}$ 14.8 Hz, $J_{5a,NH}$ 7.2 Hz, H-5a), 3.41 (ddd, 1H, $J_{5b,NH}$ 4.7 Hz, $J_{5a,5b}$ 14.8 Hz, H-5b), 1.46 (s, 9H,

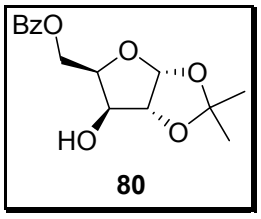
Boc). Anal. Calcd. for $C_{11}H_{18}FNO_5$ (263.27): C, 50.19; H, 6.89; N, 5.32. Found: C, 49.96; H, 6.74; N, 5.35.



79

2,4-Anhydro-5-*N*-(*t*-butoxycarbonyl)amino-5-deoxy-3-fluoro-D-arabinonic Acid (79). Hydrolysis of the methyl ester **78** (1.5 g, 5.7 mmol) was achieved using GP 4.2.1.7 (reaction time 1 h) to give the product **79** as a colourless hygroscopic foam (1.38 g, 5.54 mmol, 97%). MS (ionspray neg.): *m/z* 248.3 $[M-H]^-$. ^1H NMR (300 MHz, acetone-d_6):): δ 5.41 (ddd, 1H, $J_{2,3}$ 6.7 Hz, $J_{3,4}$ 4.7 Hz, $J_{3,F}$ 55.7 Hz, H-3), 5.18 (dd, 1H, $J_{2,F}$ 15.3 Hz, H-2), 5.03 (br dq, 1H, $J_{4,5a} \approx J_{4,5b} \approx 4.3$ Hz, $J_{4,F}$ 19.5 Hz, H-4), 3.54-3.39 (m, 2H, H-5a, H-5b), 1.47 (s, 9H, Boc). HRMS (pNSI) *m/z* 272.09052 $[M+Na]^+$, calcd. 272.09047 for $C_{10}H_{16}FNO_5Na$.

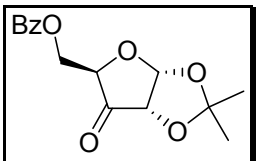
4.2.6 Synthesis of 2,4-Anhydro-5-*N*-(tert-butoxycarbonyl)amino-5-deoxy3-fluoro-D-*xylonic* Acid



80

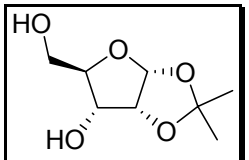
5-*O*-Benzoyl-1,2-*O*-isopropylidene-α-D-xylofuranose (80). To a solution of 1,2-*O*-isopropylidene-α-D-xylofuranose (50.02 g; 0.26 mol) in DCM (1 L) in an ice bath was added Et_3N (108 mL, 0.78 mol). Benzoyl chloride (33.2 mL, 0.29 mol) was added dropwise during 30 min. The mixture was stirred for 1.5 h at 0-5 °C, and the reaction was quenched by the addition of water (50 mL). The organic phase was washed twice with a sat. soln. of $NaHCO_3$ (250 mL), dried with $MgSO_4$, filtered, and the

solvents were evaporated. Column chromatography (EtOAc/Cy-Hex 1:3, 2:3, 1:1) of the residue gave the desired product as a colourless solid (68.9g, 0.23 mol, 90%). MS (ionspray): *m/z* 295.2 $[M+H]^+$, 312.2 $[M+NH_4]^+$. ^1H NMR (300 MHz, $CDCl_3$): δ 7.46-8.04 (m, 5H, Ph), 5.96 (d, 1H, $J_{1,2}$ = 3.6 Hz, H-1), 4.81 (A(ABX), 1H, $J_{4,5a}$ = 9.4 Hz, $J_{5a,5b}$ = 12.7 Hz, H-5a), 4.60 (d, 1H, $J_{2,3} \approx 0$ Hz, H-2), 4.38 (B(ABX), 1H, H-5b), 4.37 (ddd, H, $J_{4,5b}$ = 4.5 Hz, H-4), 4.17 (br dd, 1H, $J_{3,4}$ = 2.2 Hz, H-3), 3.23 (d, 1H, $J_{3,OH}$ = 4.0 Hz, OH), 1.51 (s, 3H, Me(*i*-prop)), 1.33 (s, 3H, Me(*i*-prop)).



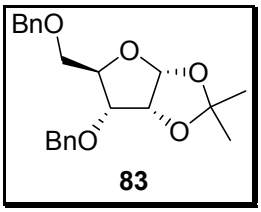
81

5-*O*-Benzoyl-1,2-*O*-isopropylidene-α-D-erythro-pent-3-ulofuranose (81). A solution of 5-*O*-benzoyl-1,2-*O*-isopropylidene-α-D-xylofuranose (20.03 g, 0.068 mol) in DCM (200 mL) was treated with pyridinium dichromate (13.08 g, 0,035 mol) and acetic anhydride (19.3 mL, 0.204 mol) over 2.5 h at reflux. The reaction mixture was diluted with ether (50 mL) and filtered through a silica gel column (300g, ether/DCM 1:4, then 2:3). After evaporation of solvents, the residue was chromatographed over silica gel (EtOAc/Cy-Hex, 1:3, 2:3, 1:1) to afford a colourless solid (16.44 g, 83%). MS (ionspray): *m/z* 310,1 $[M+NH_4]^+$, 315,3 $[M+Na]^+$. ^1H NMR (300 MHz, $CDCl_3$): δ 7.44-7.95 (m, 5H, Ph), 6.14 (d, 1H, $J_{1,2}$ = 4.4 Hz, H-1), 4.71 (A(ABX), 1H, $J_{4,5a}$ = 2.8 Hz, H-5a), 4.69 (dd≈br s, 1H, H-4), 4.47 (B(ABX), 1H, $J_{4,5b}$ = 4.7 Hz, $J_{5a,5b}$ = 13.4 Hz, H-5b), 4.44 (d, 1H, H-2), 1.52 (s, 3H, Me(*i*-prop)), 1.44 (s, 3H, Me(*i*-prop)).



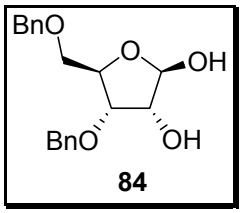
82

1,2-O-Isopropylidene-α-D-ribofuranose (82). To a solution of the keto sugar **81** (15.34 g, 52 mmol) in EtOH/H_2O 7:1 cooled in an ice-bath was added sodium borohydride (2.38 g, 63 mmol) under stirring. The reaction mixture was allowed to reach rt, and stirring was continued overnight (16.5 h). The reaction mixture was passed through Amberlite columns (IRC-50, 120g followed by IRA-400, 120 g, washing with EtOH). After concentration, the residue was chromatographed over silica gel (450 g) with EtOAc/MeOH/H_2O (93:5:2) to give the desired product **82** (8.9 g, 46.8 mmol, 89%). MS (ionspray): *m/z* 208.1 $[M+NH_4]^+$, 213.3 $[M+Na]^+$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.83 (d, 1H, $J_{1,2}$ = 3.9 Hz, H-1), 4.59 (dd≈t, 1H, $J_{2,3}$ = 5.1 Hz, H-2), 4.01 (ddd≈dt, 1H, H-3), 3.97 (ddd, 1H, $J_{4,5a}$ = 2.4 Hz, H-5a), 3.84 (br ddd, 1H, $J_{3,4}$ = 9.0 Hz, $J_{4,5b}$ = 3.6 Hz, H-4), 3.76 (ddd, 1H, $J_{5a,5b}$ = 12.0 Hz, H-5b), 2.38 (d, 1H, $J_{3,OH-3}$ = 10.5 Hz, OH-3), 2.05 (br s, 1H, OH-5), 1.58 (s, 3H, Me(*i*-prop)), 1.38 (s, 3H, Me(*i*-prop)).



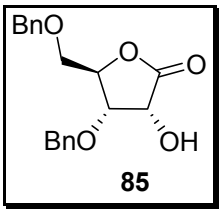
83

3,5-Di-*O*-benzyl-1,2-O-isopropylidene-α-D-ribofuranose (83). Starting from 1,2-isopropylidene-α-D-ribofuranose **82** (8.9g, 46.8 mmol) and using GP 4.2.1.1 (reaction time 2 h) the residue obtained was chromatographed (EtOAc/Cy-Hex 1:9, 3:7) to give the desired product as colourless oil (15.6 g, 90%). MS (ionspray): *m/z* 371.4 $[M+H]^+$, 388.3 $[M+ NH_4]^+$, 393.3 $[M+Na]^+$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36-7.26 (m, 10H, 2Ph), 5.76 (d, 1H, $J_{1,2}$ = 3.8 Hz, H-1), 5.54 (A(AB), 1H, $J_{a,b}$ = 11.9 Hz, OC*Ha*HbPh), 4.73 (B(AB), 1H, OCHa*Hb*Ph), 4.57 (A(AB), 1H, $J_{a',b'}$ = 12.2 Hz, OC*Ha*'Hb'Ph), 4.56 (dd≈t, 1H, H-2), 4.49 (B(AB), 1H, OCHa'*Hb*'Ph), 4.18 (ddd, 1H, $J_{4,5a}$ = 2.2 Hz, $J_{4,5b}$ = 3.8 Hz, H-4), 3.86 (dd, 1H, $J_{2,3}$ = 4.3 Hz, $J_{3,4}$ = 8.9 Hz, H-3), 3.76 (A(ABX), 1H, $J_{5a,5b}$ = 11.3 Hz, H-5a), 3.57 (B(ABX), 1H, H-5b), 1.59 (s, 3H, *i*-prop), 1.36 (s, 3H, *i*-prop).



84

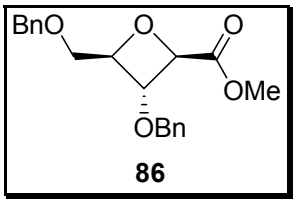
3,5-Di-*O*-benzyl-β-D-ribofuranose (84). Starting with 3,5-di-*O*-benzyl-1,2-*O*-isopropylidene-α-D-ribofuranose (89.3 g; 0.24 mol) and using GP 4.2.1.2 (reaction time 2 h), the reaction mixture was cooled in an ice-bath over 1 h, and precipitation of the product was observed. Then the colourless solid was filtered and dried to yield the title compound **84** (60.6 g, 0.18 mol, 76%). The filtrates were concentrated, and the residue was chromatographed (EtOAc/Cy-Hex 1:1) to obtain more of the desired substance (11.54 g, 0.035 mol, 15%, total yield 72.14 g, 0.22 mol, 91%). MS: *m/z* 348.3 $[M+ NH_4]^+$, 353.4 $[M+Na]^+$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39-7.26 (m, 10H, Ph), 5.23 (d, 1H, $J_{1,2}$ = 7.4 Hz, H-1), 4.61 (A(AB), 1H, $J_{a,b}$ = 8.3 Hz, OC*Ha*HbPh), 4.56 (B(AB), 1H, OCHa*Hb*Ph), 4.51 (A(AB), 1H, $J_{a',b'}$ 5.6 Hz OC*Ha'*Hb'Ph,), 4.48 (B(AB), 1H, OCHa'*Hb'*Ph), 4.28 (dd, 1H, $J_{3,4}$ = 5.9 Hz, H-3), 4.21 (ddd, 1H, $J_{4,5a}$ = 3.0 Hz, $J_{4,5b}$ = 2.9 Hz, H-4), 4.03 (dd, 1H, $J_{2,3}$ = 4.7 Hz, H-2), 3.64 (A(ABX), 1H, $J_{5a,5b}$ = 10.3 Hz, H-5a), 3.55 (B(ABX), 1H, H-5b), 3.36 (br s, 1H, OH-1), 2.69 (d, 1H, OH-2). Obs: The ^{1}H NMR shows a small amount of the α isomer (≈5%)



85

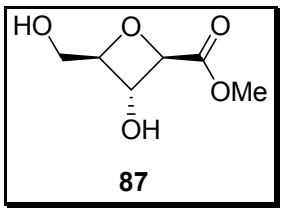
3,5-Di-*O*-benzyl-D-ribono-1,4-lactone (85). From 3,5-di-*O*-benzyl-β-D-ribofuranose (17.8 g, 53.8 mmol) and using GP 4.2.1.3 (reaction time 3 h) a crude product was obtained which was chromatographed over silica gel (EtOAc/Cy-Hex 1:2) to give the desired lactone (14.02 g, 42.7 mmol, 79%) as a colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38-7.22 (m, 10H, Ph), 4.72-4.64 (AB, 2H, $J_{a,b}$ = 12.0 Hz, OCH_2Ph), 4.67 (dd, 1H, $J_{2,3}$ = 5.9 Hz, H-2), 4.55-4.23 (AB, 2H, $J_{a',b'}$ = 11.9 Hz, OCH_2'Ph), 4.50 (dd≈t,

1H, H-4), 4.19 (d, 1H, $J_{3,4} \approx 0$ Hz, H-3), 3.67 (A(ABX), 1H, $J_{4,5a} = 3.0$ Hz, $J_{5a,5b} = 10.9$ Hz, H-5a), 3.56 (B(ABX), 1H, $J_{4,5b} = 2.5$ Hz, H-5b), 2.82 (d, 1H, $J_{2,OH-2} = 9.5$ Hz, OH-2).



86

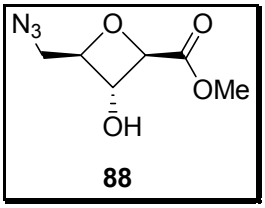
Methyl 2,4-Anhydro-3,5-di-*O*-benzyl-D-ribonate (86). Starting from 3,5-di-*O*-benzyl-D-ribono-1,4-lactone **20** (4.3 g, 13.1 mmol) and proceeding as in GP 4.2.1.4 was obtained the crude 3,5-*O*-benzyl-2-*O*-trifluoromethanesulfonyl-D-xylono-1,4-lactone which was submitted to GP 2.1.5 to give a crude **21.** This was filtrated over a silica gel column (aplied with DCM and eluted with EtOAc) in order to remove the triflate salts and the obtained residue (3.93 g) was used for the following reaction with no further purification. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36-7.28 (m, 10H, 2Ph), 5.01 (d, 1H, $J_{2,3} = 5.2$ Hz, H-2), 4.76 (ddd, 1H, $J_{3,4} \approx 4.9$ Hz, H-4), 4.67-4.60 (AB, 2H, $J_{a,b} = 8.7$ Hz, OCH_2Ph), 4.54-4.48 (AB, 2H, $J_{a',b'} = 5.4$ Hz, $OCH_2'Ph$), 4.52 (dd≈t, 1H, H-3), 3.61 (A(ABX), 1H, $J_{4,5a} = 3.7$ Hz, $J_{5a,5b} = 11.5$ Hz, H-5a), 3.55 (B(ABX), 1H, $J_{4,5b} = 4.0$ Hz, H-5b), 3.25 (s, 3H, OMe).



87

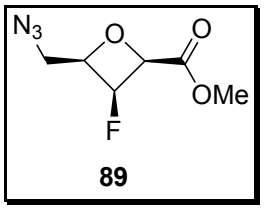
Methyl 2,4-Anhydro-D-ribonate (22). The obtained residue of methyl 2,4-anhydro-3,5-di-*O*-benzyl-D-ribonate **21** (3.93 g, assumed 11.5 mmol) was submitted to GP 2.1.6 (reaction time 3 h) and after filtration of the catalyst, the obtained crude product (colourless oil) was reacted without further purification (1.62 g). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.95 (d, 1H, $J_{2,3} = 4.9$ Hz, H-2), 4.74 (t, 1H, H-3), 4.71 (ddd, 1H, $J_{3,4} = 5.1$

Hz, H-4), 3.84 (A(ABX), 1H, $J_{4,5a}$ = 2.5 Hz, $J_{5a,5b}$ = 13.4 Hz, H-5a), 3.80 (s, 3H, OMe), 3.65 (B(ABX), 1H, $J_{4,5b}$ = 2.0 Hz, H-5b).



88

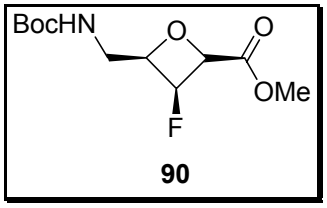
Methyl 2,4-Anhydro-5-azido-5-deoxy-D-ribonate (23). Methyl 2,4-anhydro-D-ribonate (1.62 g, assumed 10.0 mmol) was reacted according to GP 2.1.4 (but using only 1 eq of Py and keeping the temperature bellow -30 ºC), and the obtained crude triflate was reacted using GP 2.1.8, and the residue obtained was chromatographed (EtOAc/Cy-Hex 1:4) to furnish compound **23** as a colourless oil (1.29 g, 6.9 mmol, 53% from lactone **20**). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.95 (d, 1H, $J_{2,3}$ = 4.8 Hz, H-2), 4.76-4.69 (m, 2H, H-3, H-4), 3.84 (s, 3H, OMe), 3.63 (A(ABX), 1H, $J_{4,5a}$ = 3.0 Hz, $J_{5a,5b}$ = 13.7 Hz, H-5a), 3.44 (B(ABX), 1H, $J_{4,5b}$ = 3.3 Hz, H-5b), 3.26 (br d, 1H, OH).



89

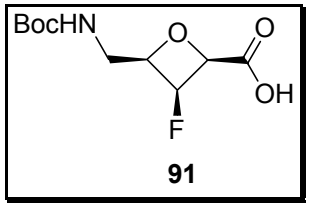
Methyl 2,4-Anhydro-5-azido-5-deoxy-3-fluoro-D-xylonate (50). To a solution of azide **23** (263.4 mg, 1.41 mmol) in acetonitrile (10 mL) at –20 ºC was added DAST (0.36 mL, 2.75 mmol), and the mixture was stirred until conversion into the intermediate (1.5 h, see scheme 22). The solution was then allowed to reach rt, and pyridine (0.11 mL, 1.4 mmol) was added while the temperature was increased to 50 ºC. After 3 h complete consumption of the intermediate was observed, and the brown solution was cooled, diluted with diethylether and washed with sat. soln. of $NaHCO_3$. The aqueous layer was washed with diethylether and the organic phases were combined, dried and concentrated. The evaporation of diethyl ether was monitored so that evaporation of the product could be avoided. The crude compound

89 was reacted without further purification. H^1 NMR (300 MHz, $CDCl_3$): δ 5.65 (dt, 1H, $J_{2,3} \approx J_{3,4} \approx 5.8$ Hz, $J_{3,F} = 56.2$ Hz, H-3), 5.30 (dd, 1H, $J_{2,F} = 18.4$ Hz, H-2), 5.02-4.91 (m, 1H, $J_{4,F} = 15.5$ Hz, H-4), 3.86 (s, 3H, OMe), 3.80 (A(ABX), 1H, $J_{4,5a} = 1.7$ Hz, H-5a), 3.67 (B(ABX), 1H, $J_{5a,5b} = 13.0$ Hz, H-5b).



90

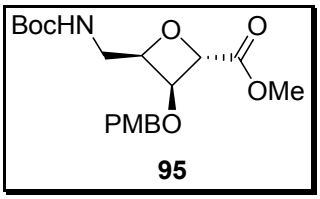
Methyl 2,4-Anhydro5-*N*-(*t*-butoxycarbonyl)amino-5-deoxy-3-fluoro-D-xylonate (90). Submitting the crude azide **89** (considered 1.41 mmol) to GP 4.2.1.9 (reaction time 1.5 h) followed by chromatography of the residue obtained (EtOAc/heptane 1:4 to 1:1) yielded the pure product **90** as a colourless oil (193 mg, 0.73 mmol, 52 %). $[\alpha]_D^{20}$ 40.98 (*c*, 0.891, $CHCl_3$). H^1 NMR (300 MHz, $CDCl_3$): δ 5.60 (dt, 1H, $J_{2,3} \approx J_{3,4} \approx$ 5.6 Hz, $J_{3,F} = 56.6$ Hz, H-3), 5.28 (dd, 1H, $J_{2,F} = 18.9$ Hz, H-2), 5.04-4.91 (m, 2H, H-4, NH), 3.84 (s, 3H, OMe), 3.69-3.54 (m, 2H, H-5a, H-5b), 1.44 (s, 9H, Boc). HRMS (pNSI) *m/z* 264.12418 $[M+H]^+$, calcd. 264.12418 for $C_{11}H_{18}FNO_5$.



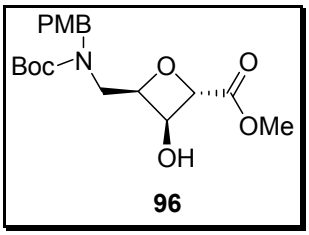
91

2,4-Anhydro-5-*N*-(*t*-butoxycarbonyl)amino-5-deoxy-3-fluoro-D-arabinonic Acid (91). Hydrolysis of the methyl ester **90** (97.8 mg, 0.38 mmol) was achieved using GP 4.2.1.7 (reaction time 30 min) to give the product **91** as a colourless hygroscopic foam (91.7 mg, 0.37 mmol, 97%). MS (ionspray neg.): *m/z* 248.3 $[M-H]^-$. H^1 NMR (300 MHz, $CDCl_3$): δ 5.64 (dt, 1H, $J_{2,3} \approx J_{3,4} \approx 6.0$ Hz, $J_{3,F} = 56.1$ Hz, H-3), 5.29 (dd, 1H, $J_{2,F} = 17.8$ Hz, H-2), 5.01-4.86 (m, 2H, H-4, NH), 4.08-3.95 (m, 1H, H-5a), 3.29-3.19 (m, 1H, H-5b), 1.46 (s, 9H, Boc). HRMS (pNSI) *m/z* 272.09057 $[M+Na]^+$, calcd. 272.09047 for $C_{10}H_{16}FNO_5Na$.

4.2.7 Protection of 52 and Chemical Hydrolysis



95



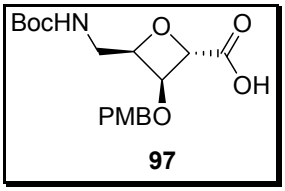
96

Methyl 2,4-Anhydro-5-*N*-(*tert*-butoxycarbonyl)amino-5-deoxy-3-*O*-*p*-methoxybenzyl-D-lyxonate (95) and Methyl 2,4-Anhydro-5-*N*-(*tert*-butoxycarbonyl)amino-5-*O*-*p*-methoxybenzyl-5-deoxy-D-lyxonate (96). To a solution of methyl 2,4-anhydro-5-*N*-(*t*-butoxycarbonyl)amino-D-lyxonate **52** (0.8 g, 3 mmol) in DCM (30 mL) was added *p*-metoxybenzyl trichloroacetimidate (2.57 mL, 12 mmol) and (+)-camphorsulfonic acid (0.08 g, 0.3 mmol). The mixture was stirred overnight at rt, and pyridine was added (0.2 mL). The mixture was then diluted in DCM and washed with water. After drying, filtration and concentration, DCM/n-hexane was added in order to eliminate by filtration solid undesired residues of the reaction. Flash chromatography of the filtrate using heptane/EtOAc gradient gave the title compound **95** as a colourless oil (0.74 g, 1.9 mmol, 63%) and the by-product methyl 2,4-anhydro-5-*N*-(*tert*-butoxycarbonyl,*p*-methoxybenzyl)amino-D-lyxonate **96** as a colourless oil (0.22, 0.6 mmol, 19%).

Data for **95**: $[\alpha]_D^{20}$ = -23.79° (*c* 0.8, $CHCl_3$). ^{1}H NMR, COSY (400 MHz, $CDCl_3$): δ 7.24 (br d, 2H, Ph), 6.99 (br d, 2H, Ph), 5.04 (d, 1H, $J_{2,3}$ = 4.9 Hz, H-2), 4.89-4.78 (m, 2H, H-4, NH), 4.58 (A(AB), 1H, $J_{a,b}$ = 11.5 Hz, OC$H_a$$H_b$Ph), 4.57 (dd, 1H, $J_{3,4}$ = 6.7 Hz, H-3), 4.42 (B(AB), 1H, OC$H_a$$H_b$Ph), 3.81 (s, 6H, OMe, OMe(Ph)), 3.73-3.62 (m, 1H, H-5a), 3.57-3.49 (m, 1H, H-5b), 1.43 (s, 9H, Boc). HRMS (ESI) *m/z* 404.16776 $[M+Na]^+$, calcd. 404.16797 for $C_{19}H_{27}NO_7Na$.

Data for **96**: $[\alpha]_D^{20}$ = -28.62° (*c* 0.8, $CHCl_3$). MS: (ionspray) *m/z* 382.3 $[M+H]^+$, 404.3 $[M+Na]^+$. ^{1}H-NMR, COSY (400 MHz, $CDCl_3$): δ 7.14 (br d, 2H, Ph), 6.87(br d, 2H, Ph), 5.82 (br s, 1H, OH), 4.85-4.80 (m, 2H, H-2, H-4), 4.70 (br td, 1H, $J_{2,3}$ = 4.5 Hz, $J_{3,4} \approx J_{3,OH} \approx$ 5.7 Hz, H-3), 4.50 (A(AB), 1H, $J_{a,b}$ = 15.4 Hz, OC$H_a$$H_b$Ph), 4.30 (B(AB),

1H, OCH_aH_bPh), 4.00 (br dd, 1H, H-5a), 3.80 (s, 6H, OMe, OMe(Ph)), 3.10 (d, 1H, $J_{5a,5b}$ = 14.9 Hz, H-5b), 1.48 (s 9H, Boc).



97

2,4-Anhydro-5-*N*-(*tert*-butoxycarbonyl)amino-5-deoxy-3-*O*-*p*-methoxybenzyl-D-lyxonic Acid (97). Starting with methyl ester **95** (0.66 g, 1.7 mmol) and using GP 4.2.1.7 (reaction time 25 min) the product **97** was obtained as colourless foam (0.59 g, 1.6 mmol, 93 %). MS: (ionspray, neg) *m/z* 366.3 $[M-H]^-$. ^{1}H-NMR (300 MHz, MeOD) δ 7.31 (br d, 2H, Ph), 6.93 (br d, 2H, Ph), 5.03 (d, 1H, $J_{2,3}$ = 5.0 Hz, H-2), 4.78 (q, 1H, $J_{3,4} \approx J_{4,5a} \approx J_{4,5b} \approx$ 6.4 Hz, H-4), 4.64-4.69 (m, 2H, H-3, OCH_aH_bPh), 4.46 (B(AB), 1H, $J_{a,b}$ = 11.5 Hz, OCH_aH_bPh), 3.81 (s, 3H, OMe(Ph)), 3.50 (d, 2H, H-5a, H-5b), 1.45 (s 9H, Boc). HRMS (ESI) *m/z* 390.15219 $[M+Na]^+$, calcd. 390.15232 for $C_{18}H_{25}NO_7Na$.

4.3 *Library Construction*

4.3.1 General Procedures

4.3.1.1 Oxadiazole formation from carboxylic acids

To a 0.1 M solution of the starting carboxylic acid in DMF at rt was added of DIPEA (1.2 eq) and of HATU (1.2 eq). The mixture was stirred for 15 min in order to activate the acid and after this the hydroxyamidine (1.2 eq) was added and the mixture was stirred for 15 min more in order to provide the coupling. The solution was heated at 80 °C (for libraries on oxetane scaffolds) or at 100 ºC (for libraries on bicyclic scaffolds) until cyclisation was complete. After cooling to rt, diethyl ether was added and the mixture was washed with H_2O, the aqueous layer was extracted twice with

diethyl ether, the organic layers were combined, dried over $MgSO_4$, filtered and the solvent evaporated.

4.3.1.2 *N-tert*-Butoxycarbonyl cleavage

To a 0.03 M solution of the starting Boc protected amine in DCM cooled in an ice bath was added TFA (10 eq or 15 eq in cases that removal of PMB group is made on the same reaction step). The temperature was allowed to warm up to rt and the mixture was stirred until deprotection was complete. The reaction mixture was concentrated in vacuum and DCM was added twice in order to co-evaporate the TFA excess.

4.3.1.3 Acetylation

To a 0.05 M solution of the starting free amine in pyridine at rt was added acetic anhydride (1.3 eq) and the mixture was stirred until acetylation was complete. Pyridine was co-evaporated with toluene.

4.3.1.4 Mesylation

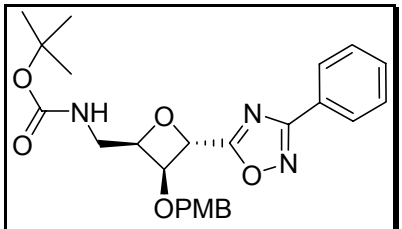
To a 0.02 M solution of the starting amine in DCM was added triethylamine (1.25 eq) and the solution was cooled with an ice bath. Methanesulfonyl chloride was then added (1.5 eq) and the mixture was allowed to reach rt and stirred until the reaction was finished. The mixture was then diluted in DCM and washed once with 1M HCl and once with sat soln of $NaHCO_3$ (in cases in which the oxadiazole substituent is a pyridinyl the reaction mixture was washed twice with H_2O). The aqueous layers were extracted once with DCM, the organic layers were combined, dried over $MgSO_4$, filtered and the solvent evaporated.

4.3.1.5 Triazole Synthesis

To a solution of azide **23** (0.14 mmol, 27 mg) and acetylene (0.16 mmol, 1.1 eq) in DMF (0.6ml) was added an aqueous 0.1M solution of $CuSO_4$ (0.1 ml) and an aqueous 0.1M solution of sodium ascorbate (0.1 ml) and the mixture shaken for 1h at rt. The reaction mixture was injected directly on preparative HPLC. The obtained fractions were centrifuged under HV to give the corresponding products as lyophilised powders.

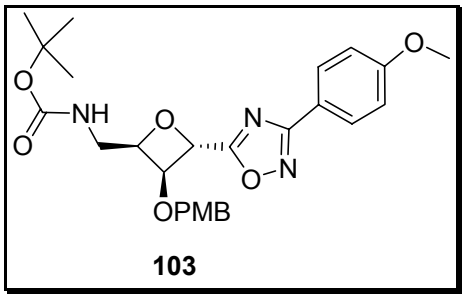
4.3.2 Library Construction on Oxetane δ-Amino Acid Scaffolds

4.3.2.1 Library on 2,4-Anhydro-5-*N*-(tert-butoxycarbonyl)amino-3-*O*-*p*-methoxybenzyl-D-*lyxonic* Acid (97).



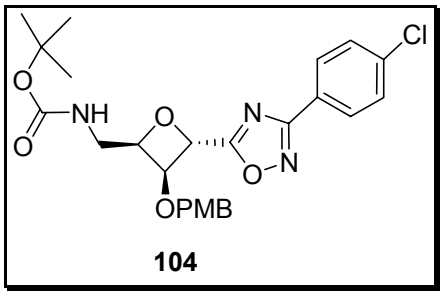
102

5-[(2*S*,3*S*,4*R*)-5-*N*-(*tert*-Butoxycarbonyl)amino-3-*O*-*p*-methoxybenzyl-oxetan-2-yl]-3-phenyl-1,2,4-oxadiazole (102). Starting with **97** (204.2 mg, 0.556 mmol) using general procedure 4.3.1.1 (cyclisation time 3 h), and after flash chromatography using heptane/EtOAc gradient, the title compound was obtained as a colourless oil (112.1 mg, 0.240 mmol, 43%). $[\alpha]_D^{20.0}$ -10.16 (*c* 0.729, $CHCl_3$). MS: (ionspray) m/z 412.2 $[M\text{-}t\text{Bu}+H]^+$, 468.2 $[M+H]^+$, 490.2 $[M+Na]^+$. H^1 NMR (300 MHz, $CDCl_3$): δ 8.11-8.08 (m, 2H, Ph), 7.54-7.46 (m, 3H, Ph), 7.19 (d, 2H, J = 8.6 Hz, PMB), 6.80 (d, 2H, PMB), 5.63 (d, 1H, $J_{2,3}$ = 5.2 Hz, H-2), 5.06-4.89 (m, 2H, H-4, NH), 4.88 (dd, 1H, $J_{3,4}$ = 7.0 Hz, H-3), 4.57;4.49 (AB, 2H, $J_{a,b}$ = 11.7 Hz, CH_2(PMB)), 3.81-3.59 (m, 5H, H-5a, H-5b, OMe), 1.46 (s, 9H, Boc).



103

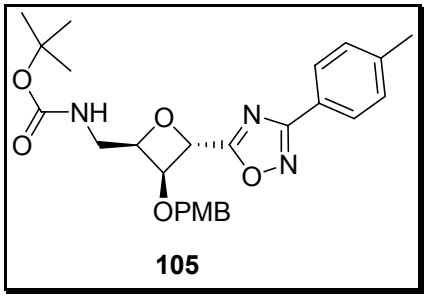
5-[(2*S*,3*S*,4*R*)-5-*N*-(*tert*-Butoxycarbonyl)amino-3-*O*-*p*-methoxybenzyl-oxetan-2-yl]-3-*p*-methoxyphenyl-1,2,4-oxadiazole (103). Starting with **97** (362.3 mg, 0.986 mmol) using general procedure 4.3.1.1 (cyclisation time 3.5 h), and after flash chromatography using heptane/EtOAc gradient, the title compound was obtained as a light brown oil (316.6 mg, 0.636 mmol, 65%). $[\alpha]_D^{20.0}$ -8.423 (*c* 0.772, $CHCl_3$). MS: (ionspray) m/z 442.2 $[M\text{-}t\text{Bu}+H]^+$, 498.2 $[M+H]^+$, 520.2 $[M+Na]^+$. H^1 NMR (300 MHz, $CDCl_3$): δ 8.03 (br d, 2H, J = 8.9 Hz, Ph), 7.19 (br d, 2H, J = 8.7 Hz, PMB), 7.00 (br d, 2H, Ph), 6.81 (br d, 2H, PMB), 5.62 (d, 1H, $J_{2,3}$ = 5.1 Hz, H-2), 5.05-4.89 (m, 2H, H-4, NH), 4.86 (dd, 1H, $J_{3,4}$ = 7.0 Hz, H-3), 4.55;4.49 (AB, 2H, $J_{a,b}$ = 11.6 Hz, CH_2(PMB)), 3.88 (s, 3H, OMe(Ph)), 3.80-3.58 (m, 5H, H-5a, H-5b, OMe(PMB)), 1.46 (s, 9H, Boc).



104

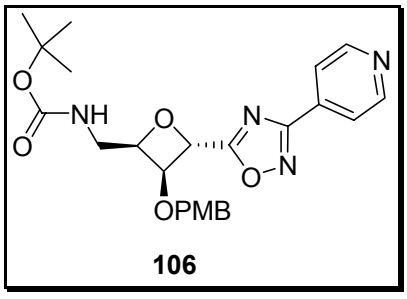
5-[(2*S*,3*S*,4*R*)-5-*N*-(*tert*-Butoxycarbonyl)amino-3-*O*-*p*-methoxybenzyl-oxetan-2-yl]-3-*p*-chlorophenyl-1,2,4-oxadiazole (104). Starting with **97** (210.3 mg, 0.512 mmol) using general procedure 4.3.1.1 (cyclisation time 3 h), and after flash chromatography using heptane/EtOAc gradient, the title compound was obtained as a light yellow oil (169.4 mg, 0.337 mmol, 59%). $[\alpha]_D^{20.0}$ -4.984 (*c* 0.682, $CHCl_3$). MS: (ionspray) m/z 446.1 $[M\text{-}t\text{Bu}+H]^+$, 502.2 $[M+H]^+$, 524.3 $[M+Na]^+$. H^1 NMR (300 MHz,

$CDCl_3$): δ 8.04 (br d, 2H, J = 8.6 Hz, Ph), 7.48 (br d, 2H, Ph), 7.19 (br d, 2H, J = 8.7 Hz, PMB), 6.80 (br d, 2H, PMB), 5.62 (d, 1H, $J_{2,3}$ = 5.1 Hz, H-2), 5.02 (br q, 1H, H-4), 4.92 (br s, 1H, NH), 4.86 (dd, 1H, $J_{3,4}$ = 7.0 Hz, H-3), 4.56;4.49 (AB, 2H, $J_{a,b}$ = 11.6 Hz, CH_2(PMB)), 3.81-3.58 (m, 5H, H-5a, H-5b, OMe(PMB)), 1.46 (s, 9H, Boc). HRMS (ESI) *m/z* 502.17395 $[M+H]^+$, calcd. 502.17394 for $C_{25}H_{29}ClN_3O_6$.



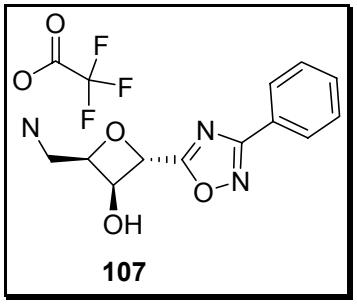
105

5-[(2*S*,3*S*,4*R*)-5-*N*-(*tert*-Butoxycarbonyl)amino-3-*O*-*p*-methoxybenzyl-oxetan-2-yl]-3-*p*-methylphenyl-1,2,4-oxadiazole (105). Starting with **97** (230.0 mg, 0.626 mmol) using general procedure 4.3.1.1 (cyclisation time 3 h), and after flash chromatography using heptane/EtOAc gradient, the title compound was obtained as a colourless oil (239.0 mg, 0.496 mmol, 79%). $[\alpha]_D^{20.0}$-6.748 (*c* 0.762, $CHCl_3$). MS: (ionspray) m/z 426.0 $[M-t\text{Bu}+H]^+$, 482.4 $[M+H]^+$, 504.3 $[M+Na]^+$. H^1 NMR (300 MHz, $CDCl_3$): δ 7.98 (br d, 2H, J = 8.1 Hz, Ph), 7.30 (br d, 2H, Ph), 7.19 (br d, 2H, J = 8.7 Hz, PMB), 6.80 (br d, 2H, PMB), 5.63 (d, 1H, $J_{2,3}$ = 5.1 Hz, H-2), 5.05-4.91 (m, 2H, H-4, NH), 4.87 (dd, 1H, $J_{3,4}$ = 7.0 Hz, H-3), 4.55;4.50 (AB, 2H, $J_{a,b}$ = 11.6 Hz, CH_2(PMB)), 3.81-3.58 (m, 5H, H-5a, H-5b, OMe(PMB)), 2.43 (s, 3H, Me(Ph)), 1.46 (s, 9H, Boc).



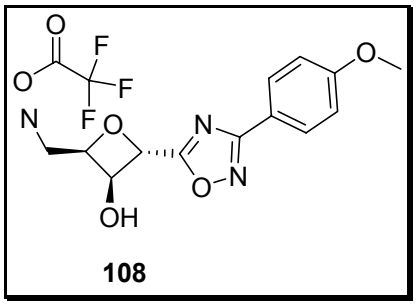
106

5-[(2*S*,3*S*,4*R*)-5-*N*-(*tert*-Butoxycarbonyl)amino-3-*O*-*p*-methoxybenzyl-oxetan-2-yl]-3-*p*-methylphenyl-1,2,4-oxadiazole (106). Starting with **97** (217.0 mg, 0.591 mmol) using general procedure 4.3.1.1 (cyclisation time 5 h), and after flash chromatography using heptane/EtOAc gradient, the title compound was obtained as a light yellow oil (137.8 mg, 0.294 mmol, 50%). $[\alpha]_D^{20.0}$ -3.297 (*c* 0.579, $CHCl_3$). MS: (ionspray) m/z 469.3 $[M+H]^+$, 490.9 $[M+Na]^+$. H^1 NMR (300 MHz, $CDCl_3$): δ 8.82-8.78 (m, 2H, Py), 8.01-7.99 (m, 2H, Py), 7.23 (br d, 2H, J = 8.6 Hz, PMB), 6.82 (br d, 2H, PMB), 5.64 (d, 1H, $J_{2,3}$ = 5.0 Hz, H-2), 5.04-4.90 (m, 2H, H-4, NH), 4.90 (dd, 1H, $J_{3,4}$ = 6.9 Hz, H-3), 4.54;4.50 (AB, 2H, $J_{a,b}$ = 11.6 Hz, CH_2(PMB)), 3.81-3.57 (m, 5H, H-5a, H-5b, OMe(PMB)), 1.44 (s, 9H, Boc).



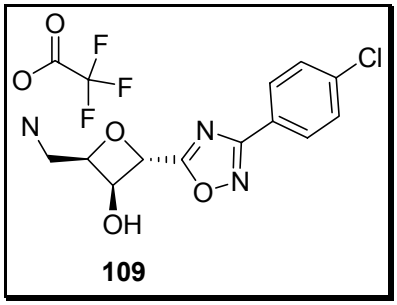
107

5-[(2*S*,3*S*,4*R*)-5-Amonium-3-hydroxy-oxetan-2-yl]-3-phenyl-1,2,4-oxadiazole Trifluoroacetate (107). Starting with **102** (98.3 mg, 0.210 mmol) using general procedure 4.3.1.2 (reaction time 8 h), flash chromatography using EtOAc/MeOH gradient, the title compound was obtained as a light red waxy solid (56.3 mg, 0.156 mmol, 74%). $[\alpha]_D^{20.0}$ -7.654 (*c* 0.927, MeOH). MS: (ionspray) m/z 248.1 $[M\text{-}TFA+H]^+$. ^{1}H NMR (300 MHz, MeOD): δ 8.14-8.10 (m, 2H, Ph), 7.62-7.53 (m, 3H, Ph), 5.82 (d, 1H, $J_{2,3}$ = 4.1 Hz, H-2), 5.26-5.18 (m, 2H, H-3, H-4), 3.56 (A(ABX), 1H, $J_{4,5a}$ = 6.0 Hz, $J_{5a,5b}$ = 13.9 Hz, H-5a), 3.38 (B(ABX), 1H, $J_{4,5b}$ = 3.8 Hz, H-5b).



108

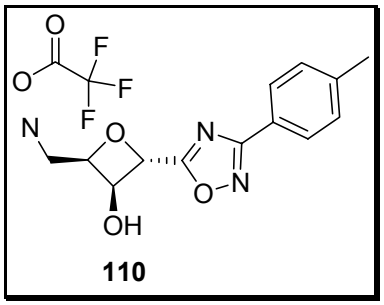
5-[(2*S*,3*S*,4*R*)-5-Amonium-3-hydroxy-oxetan-2-yl]-3-*p*-methoxyphenyl-1,2,4-oxadiazole Trifluoroacetate (108). Starting with **103** (203.6 mg, 0.409 mmol) using general procedure 4.3.1.2 (reaction time 7 h), flash chromatography using EtOAc/MeOH gradient, the title compound was obtained as a light yellow waxy solid (158.3 mg, 0.405 mmol, 99%). $[\alpha]_D^{20.0}$ -5.885 (*c* 1.020, MeOH). MS: (ionspray) m/z 278.2 $[M\text{-}TFA+H]^+$. ^{1}H NMR (300 MHz, MeOD): δ 8.04 (br d, 2H, J = 9.0 Hz, Ph), 7.10 (br d, 2H, Ph), 5.80 (d, 1H, $J_{2,3}$ = 4.6 Hz, H-2), 5.24 (ddd, 1H, H-4), 5.19 (dd, 1H, $J_{3,4}$ = 6.7 Hz, H-3), 3.90 (s, 3H, OMe), 3.60 (A(ABX), 1H, $J_{4,5a}$ = 6.1 Hz, $J_{5a,5b}$ = 13.9 Hz, H-5a), 3.39 (B(ABX), 1H, $J_{4,5b}$ = 3.9 Hz, H-5b).



109

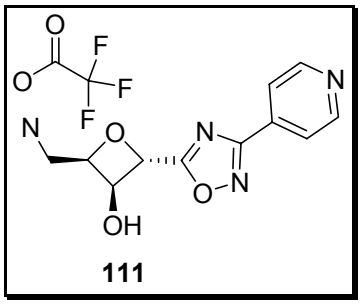
5-[(2*S*,3*S*,4*R*)-5-Amonium-3-hydroxy-oxetan-2-yl]-3-*p*-chlorophenyl-1,2,4-oxadiazole Trifluoroacetate (109). Starting with **104** (108.6 mg, 0.216 mmol) using general procedure 4.3.1.2 (reaction time 6 h), flash chromatography using EtOAc/MeOH gradient, the title compound was obtained as a viscous colourless oil (83.2 mg, 0.210 mmol, 97%). $[\alpha]_D^{20.0}$ -7.191 (*c* 1.015, MeOH). ^{1}H NMR (300 MHz, MeOD): δ 7.98 (d, 2H, J = 8.5 Hz, Ph), 7.46 (d, 2H, Ph), 5.67 (d, 1H, $J_{2,3}$ = 4.0 Hz, H-2), 5.06-4.99 (m, 2H, H-3, H-4), 3.31 (A(ABX), 1H, $J_{4,5a}$ = 5.6 Hz, $J_{5a,5b}$ = 14.0 Hz, H-

5a), 3.22-3.16 (m, B(ABX), 1H, H-5b+MeOH). HRMS (ESI) *m/z* 282.06387 $[M+H]^+$, calcd. 282.06400 for $C_{12}H_{13}ClN_3O_3$.



110

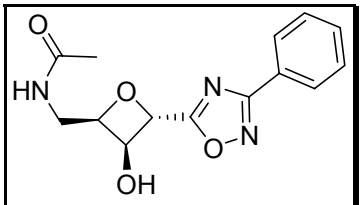
5-[(2*S*,3*S*,4*R*)-5-Amonium-3-hydroxy-oxetan-2-yl]-3-*p*-methylphenyl-1,2,4-oxadiazole Trifluoroacetate (110). Starting with **105** (189.0 mg, 0.392 mmol) using general procedure 4.3.1.2 (reaction time 5 h), flash chromatography using EtOAc/MeOH gradient, the title compound was obtained as a brown waxy solid (71.3 mg, 0.190 mmol, 48%). $[\alpha]_D^{20.0}$ -7.235 (*c* 0.897, MeOH). MS: (ionspray) m/z 262.3 [M-TFA+H]$^+$. ^{1}H NMR (300 MHz, MeOD): δ 7.99 (br d, 2H, J = 8.2 Hz, Ph), 7.38 (br d, 2H, Ph), 5.81 (d, 1H, $J_{2,3}$ = 4.4 Hz, H-2), 5.24 (ddd, 1H, H-4), 5.20 (dd, 1H, $J_{3,4}$ = 6.7 Hz, H-3), 3.60 (A(ABX), 1H, $J_{4,5a}$ = 6.0 Hz, $J_{5a,5b}$ = 13.8 Hz, H-5a), 3.39 (B(ABX), 1H, $J_{4.5b}$ = 3.6 Hz, H-5b), 2.45 (s, 3H, Me(Ph).



111

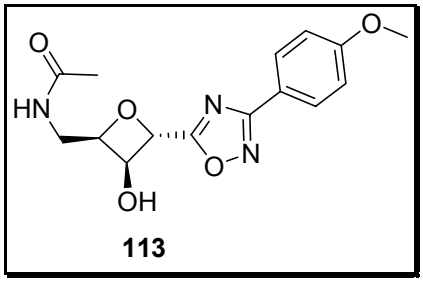
5-[(2*S*,3*S*,4*R*)-5-Amonium-3-hydroxy-oxetan-2-yl]-3-*p*-pyridinylphenyl-1,2,4-oxadiazole Trifluoroacetate (111). Starting with **106** (118.2 mg, 0.252 mmol) using general procedure 4.3.1.2 (reaction time 5 h), flash chromatography using EtOAc/MeOH gradient, the title compound was obtained as a brown waxy solid (81.4 mg, 0.225 mmol, 89%). $[\alpha]_D^{20.0}$ -6.383 (*c* 0.875, MeOH). MS: (ionspray) m/z 249.1 [M-

TFA+H]$^+$. ^{1}H NMR (300 MHz, MeOD): δ 8.72-8.59 (m, 2H, Py), 8.06-8.03 (m, 2H, Ph), 5.79 (d, 1H, $J_{2,3}$ = 4.6 Hz, H-2), 5.26 (ddd, 1H, H-4), 5.20 (dd, 1H, $J_{3,4}$ = 6.6 Hz, H-3), 3.61 (A(ABX), 1H, $J_{4,5a}$ = 6.1 Hz, $J_{5a,5b}$ = 13.8 Hz, H-5a), 3.37 (B(ABX), 1H, $J_{4.5b}$ = 3.8 Hz, H-5b).



112

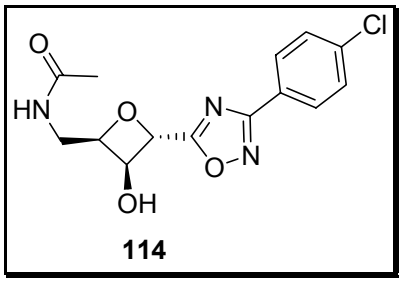
5-[(2*S*,3*S*,4*R*)-5-*N*-Acetyl-amino-3-hydroxy-oxetan-2-yl]-3-phenyl-1,2,4-oxadiazole (112) Starting with **107** (23.6 mg, 0.065 mmol) using general procedure 4.3.1.3 (reaction time 3h), and after flash chromatography using heptane/EtOAc gradient, the title compound was obtained as colourless waxy solid (9.4 mg, 0.032 mmol, 50%). $[\alpha]_D^{20.0}$ -2.231 (*c* 1.022, $CHCl_3$). MS: (ionspray) m/z 290.0 [M+H]$^+$, 312.1 [M+Na]$^+$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.10-8.07 (m, 2H, Ph), 7.52-7.45 (m, 3H, Ph), 6.60 (br t, 1H, NH), 5.65 (d, 1H, $J_{2,3}$ = 4.1 Hz, H-2), 5.10-5.01 (m, 2H, H-3, H-4), 4.01 (quintet, 1H, $J_{4,5a} \approx J_{5a,NH} \approx$ 7.1 Hz, H-5a), 3.53 (ddd, 1H, $J_{4,5b}$ = 3.5 Hz, $J_{5b,NH}$ = 6.3 Hz, $J_{5a,5b}$ = 14.6 Hz, H-5b), 2.08 (s, 3H, Me(Ac)).



113

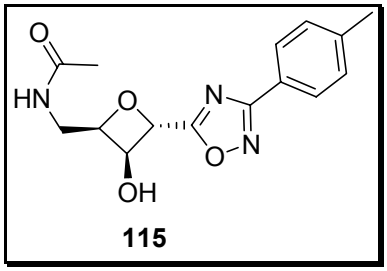
5-[(2*S*,3*S*,4*R*)-5-*N*-Acetyl-amino-3-hydroxy-oxetan-2-yl]-3-*p*-methoxyphenyl-1,2,4-oxadiazole (113) Starting with **108** (40.5 mg, 0.103 mmol) using general procedure 4.3.1.3 (reaction time 2h), and after flash chromatography using heptane/EtOAc gradient, the title compound was obtained as colourless viscous oil

(17.6 mg, 0.055 mmol, 53%). $[\alpha]_D^{20.0}$ -3.028 (*c* 0.985, $CHCl_3$). MS: (ionspray) m/z 320.1 $[M+H]^+$, 342.1 $[M+Na]^+$. ^1H NMR (300 MHz, $CDCl_3$): δ 8.04 (br d, 2H, J = 8.6 Hz, Ph), 6.99 (br d, 2H, Ph), 6.15 (br t, 1H, NH), 5.61 (d, 1H, $J_{2,3}$ = 3.8 Hz, H-2), 5.07-4.99 (m, 2H, H-3, H-4), 4.03 (quintet, 1H, $J_{4,5a} \approx J_{5a,NH} \approx 7.3$ Hz, H-5a), 3.87 (s, 3H, OMe(Ph)), 3.46 (ddd, 1H, $J_{4,5b}$ = 3.0 Hz, $J_{5b,NH}$ = 6.4 Hz, $J_{5a,5b}$ = 14.7 Hz, H-5b), 2.08 (s, 3H, Me(Ac)). HRMS (ESI) *m/z* 342.10590 $[M+Na]^+$, calcd. 342.10604 for $C_{15}H_{15}N_3O_5Na$.



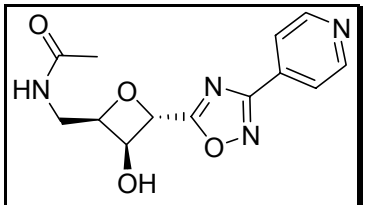
114

5-[(2*S*,3*S*,4*R*)-5-*N*-Acetyl-amino-3-hydroxy-oxetan-2-yl]-3-*p*-chlorophenyl-1,2,4-oxadiazole (114) Starting with **109** (25.3 mg, 0.049 mmol) using general procedure 4.3.1.3 (reaction time 2h), and after flash chromatography using heptane/EtOAc gradient, the title compound was obtained as colourless viscous oil (10.6 mg, 0.033 mmol, 67%). $[\alpha]_D^{20.0}$ -1.531 (*c* 0.457, MeOH). ^1H NMR (300 MHz, $CDCl_3$): δ 8.05 (br d, 2H, J = 8.6 Hz, Ph), 7.47 (br d, 2H, Ph), 6.04 (br t, 1H, NH), 5.60 (d, 1H, $J_{2,3}$ = 3.7 Hz, H-2), 5.05-5.00 (m, 2H, H-3, H-4), 4.05 (quintet, 1H, $J_{4,5a} \approx J_{5a,NH} \approx 7.2$ Hz, H-5a), 3.42 (ddd, 1H, $J_{4,5b}$ = 2.5 Hz, $J_{5b,NH}$ = 6.6 Hz, $J_{5a,5b}$ = 15.0 Hz, H-5b), 2.08 (s, 3H, Me(Ac)). HRMS (ESI) *m/z* 324.07446 $[M+H]^+$, calcd. 324.07446 for $C_{14}H_{15}ClN_3O_4$.



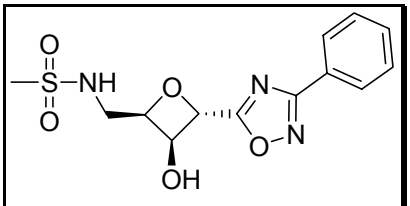
115

5-[(2*S*,3*S*,4*R*)-5-*N*-Acetyl-amino-3-hydroxy-oxetan-2-yl]-3-*p*-methylphenyl-1,2,4-oxadiazole (115) Starting with **110** (28.8 mg, 0.077 mmol) using general procedure 4.3.1.3 (reaction time 3h), and after flash chromatography using heptane/EtOAc gradient, the title compound was obtained as colourless viscous oil (11.2 mg, 0.037 mmol, 48%). $[\alpha]_D^{20.0}$ -2.385 (*c* 0.838, MeOH). MS: (ionspray) m/z 304.0 $[M+H]^+$, 326.1 $[M+Na]^+$.^{1}H NMR (300 MHz, MeOD): δ 7.98 (br d, 2H, J = 8.2 Hz, Ph), 7.36 (br d, 2H, Ph), 5.71 (d, 1H, $J_{2,3}$ = 4.8 Hz, H-2), 5.08 (dd, 1H, $J_{3,4}$ =6.8 Hz, H-3), 5.01 (m, 1H, H-4), 3.83-3.66 (m, 2H, H-5a, H-5b), 2.44 (s, 3H, Me(Ph)), 2.01 (s, 3H, Me(Ac)).



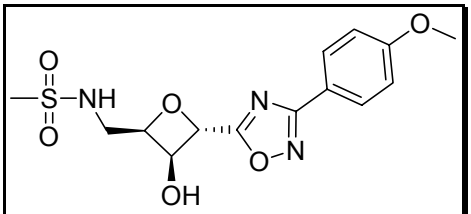
116

5-[(2*S*,3*S*,4*R*)-5-*N*-Acetyl-amino-3-hydroxy-oxetan-2-yl]-3-*p*-pyridinyl-1,2,4-oxadiazole (116) Starting with **111** (28.7 mg, 0.079 mmol) using general procedure 4.3.1.3 (reaction time 3h), and after flash chromatography using heptane/EtOAc gradient, the title compound was obtained as colourless waxy solid (9.0 mg, 0.031 mmol, 39%). $[\alpha]_D^{20.0}$ -2.639 (*c* 0.906, MeOH). ^{1}H NMR (300 MHz, MeOD): δ 8.81-8.79 (m, 2H, Py), 8.13-8.10 (m, 2H, Ph), 5.69 (d, 1H, $J_{2,3}$ = 5.0 Hz, H-2), 4.97 (dd, 1H, $J_{3,4}$ =6.8 Hz, H-3), 4.95.4.93 (m, 1H, H-4), 3.82-3.67 (m, 2H, H-5a, H-5b), 2.03 (s, 3H, Me(Ac)).



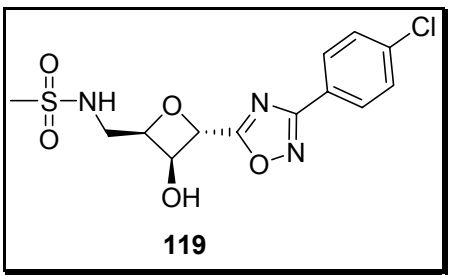
117

5-[(2*S*,3*S*,4*R*)-5-*N*-Mesyl-amino-3-hydroxy-oxetan-2-yl]-3-phenyl-1,2,4-oxadiazole (117). Starting with **107** (22.3 mg, 0.062 mmol) using general procedure 4.4.3.1.4 (reaction time 3 h), and after flash chromatography using heptane/EtOAc gradient, the title compound was obtained as a colourless viscous oil (5.8 mg, 0.018 mmol, 29%). $[\alpha]_D^{20.0}$ -1.342 (*c* 0.527, MeOH). MS: (ionspray) m/z 326.1 $[M+H]^+$, 348.1 $[M+Na]^+$. ^{1}H NMR (300 MHz, MeOD): δ 8.14-8.10 (m, 2H, Ph), 7.60-7.52 (m, 3H, Ph), 5.57 (d, 1H, $J_{2,3}$ = 4.9 Hz, H-2), 5.13 (dd, 1H, $J_{3,4}$ = 6.8 Hz, H-3), 5.09-5.02 (m, 1H, H-4), 3.70 (A(ABX), 1H, $J_{4,5a}$ = 6.8 Hz, $J_{5a,5b}$ = 14.3 Hz, H-5a), 3.63 (B(ABX), 1H, $J_{4,5b}$ = 5.0 Hz, H-5b), 3.05 (s, 3H, Me(Ms)).



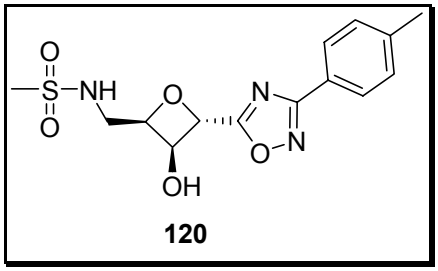
118

5-[(2*S*,3*S*,4*R*)-5-*N*-Mesyl-amino-3-hydroxy-oxetan-2-yl]-3-*p*-methoxyphenyl-1,2,4-oxadiazole (118). Starting with **108** (43.2 mg, 0.110 mmol) using general procedure 4.4.3.1.4 (reaction time 2 h), and after flash chromatography using heptane/EtOAc gradient, the title compound was obtained as a colourless waxy solid (9.2 mg, 0.026 mmol, 23%). $[\alpha]_D^{20.0}$ -1.289 (*c* 0.698, MeOH). MS: (ionspray) m/z 356.0 $[M+H]^+$, 378.1 $[M+Na]^+$. ^{1}H NMR (300 MHz, MeOD): δ 8.07-8.02 (m, 2H, Ph), 7.12-7.07 (m, 2H, Ph), 5.74 (d, 1H, $J_{2,3}$ = 4.8 Hz, H-2), 5.11 (dd, 1H, $J_{3,4}$ = 6.8 Hz, H-3), 5.07-5.01 (m, 1H, H-4), 3.90 (s, 3H, OMe(Ph)), 3.70 (A(ABX), 1H, $J_{4,5a}$ = 6.7 Hz, $J_{5a,5b}$ = 14.4 Hz, H-5a), 3.62 (B(ABX), 1H, $J_{4,5b}$ = 4.9 Hz, H-5b), 3.04 (s, 3H, Me(Ms)).



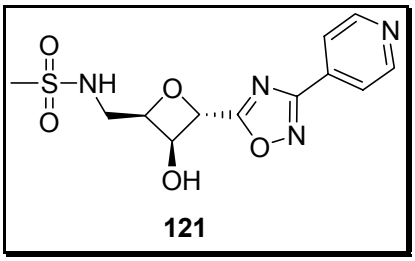
119

5-[(2*S*,3*S*,4*R*)-5-*N*-Mesyl-amino-3-hydroxy-oxetan-2-yl]-3-*p*-chlorophenyl-1,2,4-oxadiazole (119). Starting with **109** (25.2 mg, 0.064 mmol) using general procedure 4.4.3.1.4 (reaction time 2 h), and after flash chromatography using EtOAc, the title compound was obtained as a colourless solid (7.4 mg, 0.021 mmol, 32%). $[\alpha]_D^{20.0}$ -1.764 (*c* 0.893, MeOH). MS: (ionspray) m/z 360.1 $[M+H]^+$, 382.1 $[M+Na]^+$. ^{1}H NMR (300 MHz, MeOD): δ 8.13-8.08 (m, 2H, Ph), 7.61-7.56 (m, 2H, Ph), 5.77 (d, 1H, $J_{2,3}$ = 4.9 Hz, H-2), 5.12 (dd, 1H, $J_{3,4}$ = 6.7 Hz, H-3), 5.08-5.02 (m, 1H, H-4), 3.70 (A(ABX), 1H, $J_{4,5a}$ = 6.8 Hz, $J_{5a,5b}$ = 14.4 Hz, H-5a), 3.62 (B(ABX), 1H, $J_{4,5b}$ = 4.9 Hz, H-5b), 3.04 (s, 3H, Me(Ms)).



120

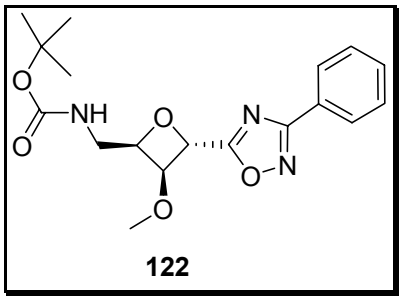
5-[(2*S*,3*S*,4*R*)-5-*N*-Mesyl-amino-3-hydroxy-oxetan-2-yl]-3-*p*-methylphenyl-1,2,4-oxadiazole (120). Starting with **110** (29.0 mg, 0.077 mmol) using general procedure 4.3.1.4 (reaction time 2.5 h), and after flash chromatography using EtOAc, the title compound was obtained as a colourless waxy solid (8.1 mg, 0.024 mmol, 31%). $[\alpha]_D^{20.0}$ -2.074 (*c* 0.997, MeOH). MS: (ionspray) m/z 340.1 $[M+H]^+$, 362.1 $[M+Na]^+$. ^{1}H NMR (300 MHz, MeOD): δ 7.99 (br d, 2H, J = 8.2 Hz, Ph), 7.37 (br d, 2H, Ph), 5.75 (d, 1H, $J_{2,3}$ = 4.9 Hz, H-2), 5.12 (dd, 1H, $J_{3,4}$ = 6.8 Hz, H-3), 5.08-5.02 (m, 1H, H-4), 3.70 (A(ABX), 1H, $J_{4,5a}$ = 6.8 Hz, $J_{5a,5b}$ = 14.5 Hz, H-5a), 3.62 (B(ABX), 1H, $J_{4,5b}$ = 4.9 Hz, H-5b), 3.05 (s, 3H, Me(Ms)), 2.44 (s, 3H, Me(Ph)).



121

5-[(2*S*,3*S*,4*R*)-5-*N*-Mesyl-amino-3-hydroxy-oxetan-2-yl]-3-*p*-pyridinyl-1,2,4-oxadiazole (121). Starting with **111** (32.4 mg, 0.089 mmol) using general procedure 4.3.1.4 (reaction time 3.5 h), and after flash chromatography using EtOAc/MeOH gradient, the title compound was obtained as a colourless viscous oil (6.9 mg, 0.021 mmol, 24%). $[\alpha]_D^{20.0}$ -1.586 (*c* 0.828, MeOH). MS: (ionspray) m/z 327.1 $[M+H]^+$, 349.1 $[M+Na]^+$. ^{1}H NMR (300 MHz, MeOD): δ 8.81-8.79(m, 2H, Py), 8.12-8.09 (m, 2H, Ph), 5.73 (d, 1H, $J_{2,3}$ = 5.0 Hz, H-2), 5.10 (dd, 1H, $J_{3,4}$ = 6.8 Hz, H-3), 5.07-5.02 (m, 1H, H-4), 3.69 (A(ABX), 1H, $J_{4,5a}$ = 6.7 Hz, $J_{5a,5b}$ = 14.6 Hz, H-5a), 3.62 (B(ABX), 1H, $J_{4,5b}$ = 4.9 Hz, H-5b), 3.06 (s, 3H, Me(Ms)).

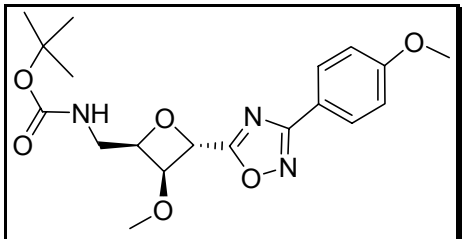
4.3.2.2 Library on 2,4-Anhydro-5-*N*-(*tert*-butoxycarbonyl)amino-3-*O*-methyl-D-lyxonic acid (61)



122

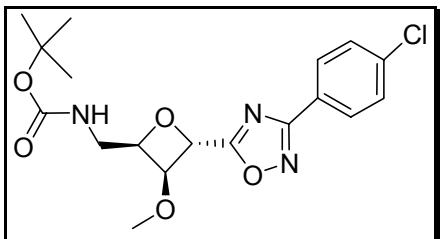
5-[(2*S*,3*S*,4*R*)-5-*N*-(*tert*-Butoxycarbonyl)amino-3-methoxy-oxetan-2-yl]-3-phenyl-1,2,4-oxadiazole (122). Starting with **61** (45.0 mg, 0.17 mmol) using general procedure 4.3.1.1 (cyclisation time 1.5 h), and after flash chromatography using heptane/EtOAc gradient, the title compound was obtained as a light yellow oil (43.0 mg, 0.12 mmol, 69%). $[\alpha]_D^{20.0}$ -32.84 (*c* 0.776, $CHCl_3$). MS: (ionspray) m/z 262.0 [M-

Boc+H]$^+$, 306.3 [M-*t*-Bu+H]$^+$, 362.4 [M+H]$^+$, 379.4 [M+NH_4]$^+$, 384.1 [M+Na]$^+$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.14-8.10 (m, 2H, Ph), 7.55-7.46 (m, 3H, Ph), 5.75 (d, 1H, $J_{2,3}$ = 4.9 Hz, H-2), 5.06 (ddd≈q, 1H, H-4), 4.68 (dd, 1H, $J_{3,4}$ = 6.6 Hz, H-3), 3.75 (br dd, 1H, $J_{4,5a}$ = 5.3 Hz, $J_{5a,5b}$ = 14.4 Hz, H-5a), 3.63 (br dd, 1H, $J_{4,5b}$ = 5.9 Hz, H-5b), 3.42 (s, 3H, OMe), 1.46 (s, 9H, Boc).



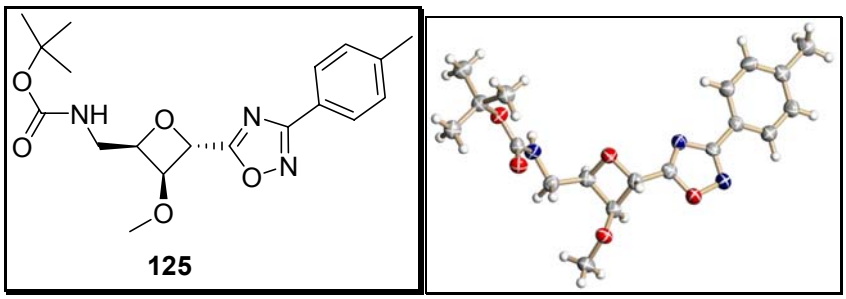
123

5-[(2*S*,3*S*,4*R*)-5-*N*-(*tert*-Butoxycarbonyl)amino-3-methoxy-oxetan-2-yl]-3-*p*-methoxyphenyl-1,2,4-oxadiazole (123). Starting with **61** (50.0 mg, 0.19 mmol) using general procedure 4.3.1.1 (cyclisation time 2 h), and after flash chromatography using heptane/EtOAc gradient, the title compound was obtained as colourless viscous oil that after recrystallisation with EtOAc/n-Hex gave the title compound as colourless crystals (51.0 mg, 0.13 mmol, 68%). m.p. 172.1-172.6 ºC. $[\alpha]_D^{19.8}$-40.72 (*c* 0.818, $CHCl_3$). MS: (ionspray) m/z 292.1 [M-Boc+H]$^+$, 336.3 [M-*t*-Bu+H]$^+$, 392.4 [M+H]$^+$, 409.4 [M+NH_4]$^+$, 414.1[M+Na]$^+$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.05 (br d, J = 8.7 Hz, 2H, Ph), 6.99 (br d, 2H, Ph), 5.73 (d, 1H, $J_{2,3}$ = 4.9 Hz, H-2), 5.06 (ddd≈q, 1H, H-4), 4.94 (br t, 1H, NH), 4.67 (dd, 1H, $J_{3,4}$ = 6.7 Hz, H-3), 3.87 (s, 3H, Ph-OMe), 3.79-3.71 (m, 1H, H-5a), 3.67-3.58 (m, 1H, H-5b), 3.42 (s, 3H, OMe), 1.46 (s, 9H, Boc).



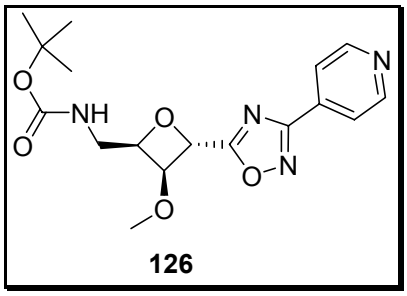
124

5-[(2*S*,3*S*,4*R*)-5-*N*-(*tert*-Butoxycarbonyl)amino-3-methoxy-oxetan-2-yl]-3-*p*-chlorophenyl-1,2,4-oxadiazole (124). Starting with **61** (50.0 mg, 0.19 mmol) using general procedure 4.3.1.1 (cyclisation time 3 h), and after flash chromatography using heptane/EtOAc gradient, the title compound was obtained as a light yellow viscous oil (54.4 mg, 0.14 mmol, 72%). $[\alpha]_D^{19.8}$ -42.38 (*c* 0.748, $CHCl_3$). MS: (ionspray) m/z 296.3 $[M\text{-Boc+H}]^+$, 340.0 $[M\text{-}t\text{-Bu+H}]^+$, 396.3 $[M+H]^+$, 418.3$[M+Na]^+$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.06 (br d, J = 8.6 Hz, 2H, Ph), 7.48 (m, 2H, Ph), 5.74 (d, 1H, $J_{2,3}$ = 4.9 Hz, H-2), 5.06 (ddd≈q, 1H, H-4), 4.91 (br t, 1H, NH), 4.68 (dd, 1H, $J_{3,4}$ = 6.8 Hz, H-3), 3.80-3.71 (m, 1H, H-5a), 3.67-3.58 (m, 1H, H-5b), 3.42 (s, 3H, OMe), 1.46 (s, 9H, Boc).



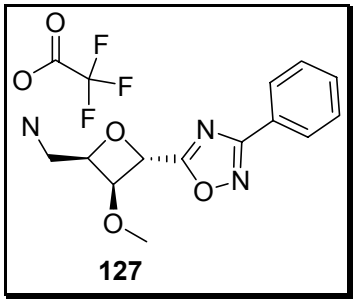
125

5-[(2*S*,3*S*,4*R*)-5-*N*-(*tert*-Butoxycarbonyl)amino-3-methoxy-oxetan-2-yl]-3-*p*-methylphenyl-1,2,4-oxadiazole (125). Starting with **61** (200.0 mg, 0.76 mmol) using general procedure 4.3.1.1 (cyclisation time 3 h), and after flash chromatography using heptane/EtOAc gradient, the title compound was obtained as colourless crystals (158.0 mg, 0.42 mmol, 55%). m.p. 78.4-78.8 ºC. $[\alpha]_D^{19.9}$ -45.62 (*c* 0.752, $CHCl_3$). MS: (ionspray) m/z 276.4 $[M\text{-Boc+H}]^+$, 320.1 $[M\text{-}t\text{-Bu+H}]^+$, 376.4 $[M+H]^+$, 398.1$[M+Na]^+$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.00 (br d, J = 8.2 Hz, 2H, Ph), 7.29 (br d, 2H, Ph), 5.74 (d, 1H, $J_{2,3}$ = 4.7 Hz, H-2), 5.06 (ddd≈q, 1H, H-4), 4.92 (br t, 1H, NH), 4.67 (dd, 1H, $J_{3,4}$ = 6.8 Hz, H-3), 3.80-3.71 (m, 1H, H-5a), 3.67-3.58 (m, 1H, H-5b), 3.42 (s, 3H, OMe), 2.42 (s, 3H, Me), 1.46 (s, 9H, Boc).



126

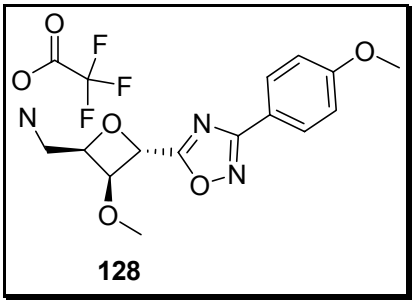
5-[(2*S*,3*S*,4*R*)-5-*N*-(*tert*-Butoxycarbonyl)amino-3-methoxy-oxetan-2-yl]-3-pyridinyl-1,2,4-oxadiazole (126). Starting with **61** (50.2 mg, 0.19 mmol) using general procedure 4.3.1.1 (cyclisation time 3 h), and after flash chromatography using heptane/EtOAc gradient, the title compound was obtained as colourless viscous oil (41.4 mg, 0.11 mmol, 59%). $[\alpha]_D^{20.0}$ -34.97 (*c* 0.643, $CHCl_3$). MS: (ionspray) m/z 263.1 $[M\text{-Boc+H}]^+$, 307.1 $[M\text{-}t\text{-Bu+H}]^+$, 363.4 $[M+H]^+$, 385.3 $[M+Na]^+$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.81-8.79 (m, 2H, Ph), 7.99-7.97 (m, 2H, Ph), 5.77 (d, 1H, $J_{2,3}$ = 4.9 Hz, H-2), 5.07 (ddd≈q, 1H, H-4), 4.94 (br t, 1H, NH), 4.68 (dd, 1H, $J_{3,4}$ = 6.6 Hz, H-3), 3.80-3.72 (m, 1H, H-5a), 3.68-3.59 (m, 1H, H-5b), 3.43 (s, 3H, OMe), 1.46 (s, 9H, Boc).



127

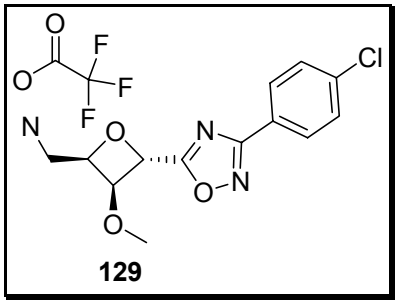
5-[(2*S*,3*S*,4*R*)-5'-Amonium-3'-methoxy-oxetan-2'-yl]-3-phenyl-1,2,4-oxadiazole Trifluoroacetate (127). Starting with **122** (90.0 mg, 0.25 mmol) using general procedure 4.3.1.2 (reaction time 1.5 h), and after crystallisation with EtOAc/*n*-Hex, the title compound was obtained as colourless crystals (80.1 mg, 0.21 mmol, 86%). $[\alpha]_D^{19.8}$ -38.31 (*c* 0.666, MeOH). MS: (ionspray) m/z 262.2 $[M\text{-TFA+H}]^+$, 284.1 $[M\text{-TFA+Na}]^+$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.06-8.03 (m, 2H, Ph), 7.51-7.44 (m, 3H, Ph), 5.78 (d, 1H, $J_{2,3}$ = 4.3 Hz, H-2), 5.36 (br td, 1H, H-4), 4.70 (dd, 1H, $J_{3,4}$ = 6.3 Hz,

H-3), 3.60 (A(ABX), 1H, $J_{4,5a}$ = 6.6 Hz, $J_{5a,5b}$ = 14.1 Hz, H-5a), 3.45 (br B(ABX), 1H, H-5b), 3.40 (s, 3H, OMe).



128

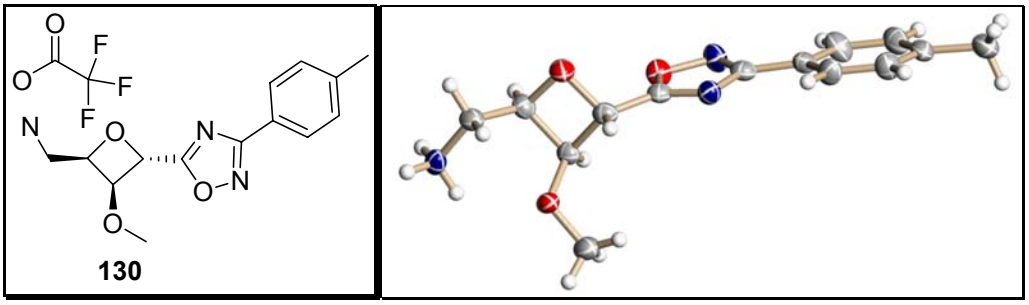
5-[(2*S*,3*S*,4*R*)-5-Amonium-3-methoxy-oxetan-2-yl]-3-*p*-methoxyphenyl-1,2,4-oxadiazole Trifluoroacetate (128). Starting with **123** (120.0 mg, 0.31 mmol) using general procedure 4.3.1.2 (reaction time 2 h), and after recrystallisation with EtOAc/n-Hex, the title compound was obtained as colourless crystals (102.0 mg, 0.25 mmol, 82%). m.p. 157.5-158.0 ºC. $[\alpha]_D^{19.9}$ -33.96 (*c* 0.716, MeOH). MS: (ionspray) m/z 292.2 $[M\text{-}TFA+H]^+$, 314.2 $[M\text{-}TFA+Na]^+$. ^{1}H NMR (300 MHz, MeOD): δ 7.93 (br d, J = 8.9 Hz, 2H, Ph), 6.98 (br d, 2H, Ph), 5.78 (dd, 1H, $J_{2,3}$ = 4.4 Hz, $J_{2,4}$ = 0.7 Hz, H-2), 5.17 (dtd, 1H, $J_{3,4}$ = 6.4 Hz, H-4), 4.78-4.74 (m, 1H+H_2O, H-3), 3.78 (s, 3H, OMe(Ph)), 3.45 (A(ABX), 1H, $J_{4,5a}$ = 6.8 Hz, $J_{5a,5b}$ = 13.9, H-5a), 3.26 (B(ABX), 1H, $J_{4,5b}$ = 4.2, H-5b), 3.37 (s, 3H, OMe).



129

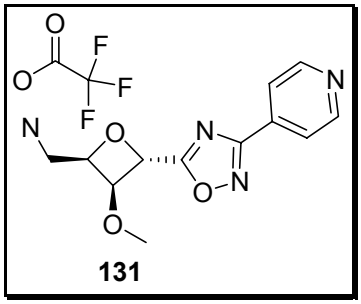
5-[(2*S*,3*S*,4*R*)-5-Amonium-3-methoxy-oxetan-2-yl]-3-*p*-chlorophenyl-1,2,4-oxadiazole Trifluoroacetate (129). Starting with **124** (112.2 mg, 0.28 mmol) using general procedure 4.3.1.2 (reaction time 2 h), and after recrystallisation with EtOAc/n-Hex, the title compound was obtained as colourless solid (101.4 mg, 0.25

mmol, 87%). $[\alpha]_D^{20.0}$ -35.35 (*c* 0.775, MeOH). MS: (ionspray) m/z 296.2 $[M\text{-}TFA+H]^+$, 318.0 $[M\text{-}TFA+Na]^+$. ^1H NMR (300 MHz, MeOD): δ 8.10 (d, J = 8.5 Hz, 2H, Ph), 7.59 (d, 2H, Ph), 5.93 (d, 1H, $J_{2,3}$ = 4.2 Hz, H-2), 5.30 (td, 1H, $J_{3,4}$ = 6.6 Hz, H-4), 4.97-4.81 (m, 1H+H_2O, H-3), 3.58 (A(ABX), 1H, $J_{4,5a}$ = 6.7 Hz, $J_{5a,5b}$ = 13.9, H-5a), 3.38 (B(ABX), 1H, $J_{4,5b}$ = 4.2, H-5b), 3.33 (s, 3H, OMe). Anal. Calcd. for $C_{15}H_{15}ClF_3N_3O_5$ (409.75): C, 43.97; H, 3.69; N, 10.26. Found: C, 43.70; H, 3.63; N, 10.04.



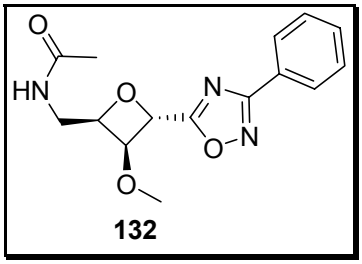
130

5-[(2*S*,3*S*,4*R*)-5-Amonium-3-methoxy-oxetan-2-yl]-3-*p*-methylphenyl-1,2,4-oxadiazole Trifluoroacetate (130). Starting with **125** (139.0 mg, 0.37 mmol) using general procedure 4.3.1.2 (reaction time 2 h), and after recrystallisation with EtOAc/n-Hex, the title compound was obtained as colourless crystals (124.9 mg, 0.32 mmol, 87%). m.p. 125.9-126.3 ºC. $[\alpha]_D^{20.0}$ -37.67 (*c* 0.775, MeOH). MS: (ionspray) m/z 276.2 $[M\text{-}TFA+H]^+$, 298.2 $[M\text{-}TFA+Na]^+$. ^1H NMR (300 MHz, MeOD): δ 7.88 (d, J = 8.2 Hz, 2H, Ph), 7.26 (d, 2H, Ph), 5.80 (d, 1H, $J_{2,3}$ = 4.4 Hz, H-2), 5.18 (br td, 1H, H-4), 4.82-4.73 (m, 1H+H_2O, H-3), 3.45 (A(ABX), 1H, $J_{4,5a}$ = 6.7 Hz, $J_{5a,5b}$ = 13.9, H-5a), 3.33 (s, 3H, OMe), 3.26 (B(ABX), 1H, $J_{4,5b}$ = 4.2, H-5b), 2.33 (s, 3H, Me(Ph)). Anal. Calcd. for $C_{16}H_{18}F_3N_3O_5$ (389.33): C, 49.36; H, 4.66; N, 10.79. Found: C, 49.35; H, 4.57; N, 10.76.



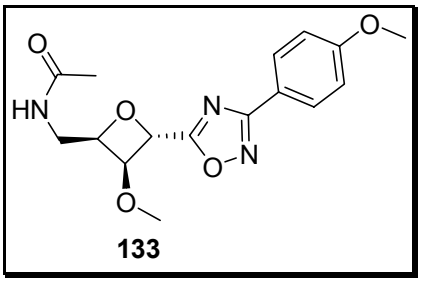
131

5-[(2*S*,3*S*,4*R*)-5-Amonium-3-methoxy-oxetan-2-yl]-3-pyridinyl-1,2,4-oxadiazole Trifluoroacetate (131). Starting with **126** (96.0 mg, 0.27 mmol) using general procedure 4.3.1.2 (reaction time 2 h), and after recrystallisation with EtOAc/n-Hex, the title compound was obtained as a light brown solid (83.0 mg, 0.22 mmol, 83%). $[\alpha]_D^{19.8}$ -41.48 (*c* 0.728, MeOH). MS: (ionspray) m/z 263.1 $[M\text{-}TFA+H]^+$. ^{1}H NMR (300 MHz, MeOD): δ 8.69-8.66 (m, 2H, Ph), 8.00-7.98 (m, 2H, Ph), 5.85 (dd, 1H, $J_{2,3}$ = 4.4 Hz, $J_{2,4}$ = 0.6 Hz, H-2), 5.19 (br td, 1H, H-4), 4.80 (dd, 1H, $J_{3,4}$ = 6.7 Hz, H-3), 3.47 (A(ABX), 1H, $J_{4,5a}$ = 6.7 Hz, $J_{5a,5b}$ = 13.9, H-5a), 3.32 (s, 3H, OMe), 3.27 (B(ABX), 1H, $J_{4,5b}$ = 4.1, H-5b).



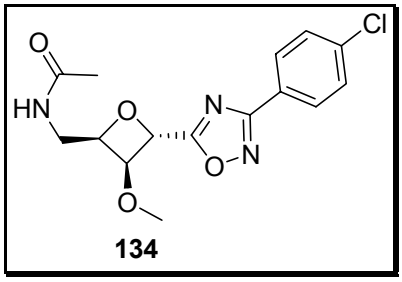
132

5-[(2*S*,3*S*,4*R*)-5-*N*-Acetyl-amino-3-methoxy-oxetan-2-yl]-3-phenyl-1,2,4-oxadiazole (132). Starting with **127** (29.0 mg, 0.08 mmol) using general procedure 4.3.1.3 (reaction time overnight), and after flash chromatography using heptane/EtOAc gradient, the title compound was obtained as colourless viscous oil (21.0 mg, 0.07 mmol, 90%). $[\alpha]_D^{20.0}$ -30.08 (*c* 1.227, $CHCl_3$). MS: (ionspray) m/z 304.2 $[M+H]^+$, 326.2 $[M+Na]^+$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.13-8.10 (m, 2H, Ph), 7.53-7.46 (m, 3H, Ph), 5.93 (br t, 1H, NH), 5.75 (d, 1H, $J_{2,3}$ = 4.8 Hz, H-2), 5.09 (br q, 1H, H-4), 4.69 (dd, 1H, $J_{3,4}$ = 6.7 Hz, H-3), 3.96 (ddd, 1H, $J_{4,5a}$ = 7.1 Hz, $J_{5a,5b}$ = 14.3 Hz, $J_{5a,NH}$ = 5.0 Hz, H-5a), 3.69 (ddd, 1H, $J_{4,5b}$ = 7.5 Hz, $J_{5b,NH}$ = 5.1 Hz, H-5b), 3.43 (s, 3H, OMe), 2.02 (s, 3H, Me(Ac)).



133

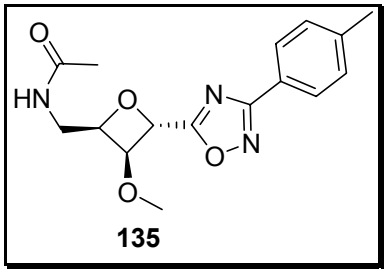
5-[(2*S*,3*S*,4*R*)-5-*N*-Acetyl-amino-3-methoxy-oxetan-2-yl]-3-*p*-methoxyphenyl-1,2,4-oxadiazole (133). Starting with **128** (120.0 mg, 0.31 mmol) using general procedure 4.3.1.3 (reaction time 3 h), and after recrystallisation with EtOAc/n-Hexane, the title compound was obtained as colourless solid (102.0 mg, 0.25 mmol, 82%). $[\alpha]_D^{20.0}$ -26.31 (*c* 0.844, $CHCl_3$). MS: (ionspray) m/z 334.1 $[M+H]^+$, 356.3 $[M+Na]^+$. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.15 (br d, J = 8.8 Hz, 2H, Ph), 7.26 (br d, 2H, Ph), 5.85 (br s, 1H, NH), 5.73 (d, 1H, $J_{2,3}$ = 4.7 Hz, H-2), 5.08 (q, 1H, $J_{3,4} \approx J_{4,5a} \approx J_{4,5b} \approx$ 7.0 Hz, H-4), 4.68 (br dd, 1H, H-3), 4.00-3.88 (m, 4 H, H-5a, OMe (Ph)), 3.69 (ddd, 1H, $J_{4,5b}$ = 7.0 Hz, $J_{5b,NH}$ = 5.4 Hz, $J_{5a,5b}$ = 13.8 Hz, H-5b), 3.43 (s, 3H, OMe), 2.02 (s, 3H, Me(Ac)).



134

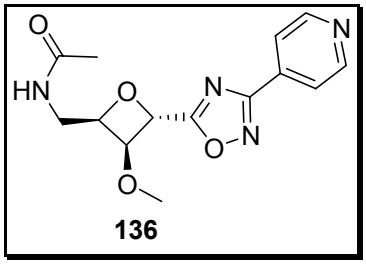
5-[(2*S*,3*S*,4*R*)-5-*N*-Acetyl-amino-3-methoxy-oxetan-2-yl]-3-*p*-chlorophenyl-1,2,4-oxadiazole (134). Starting with **129** (35.0 mg, 0.09 mmol) using general procedure 4.3.1.3 (reaction time 2 h), and after flash chromatography using heptane/EtOAc gradient, the title compound was obtained as colourless solid (28.8 mg, 0.09 mmol, 100%). $[\alpha]_D^{20.0}$ -28.96 (*c* 0.729, $CHCl_3$). MS: (ionspray) m/z 338.2 $[M+H]^+$, 360.1 $[M+Na]^+$. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (br d, J = 8.6 Hz, 2H, Ph), 7.47 (br d, 2H, Ph), 5.84 (br s , 1H, NH), 5.74 (d, 1H, $J_{2,3}$ = 4.8 Hz, H-2), 5.09 (br q, 1H, H-4), 4.67 (dd, 1H, $J_{3,4}$ = 6.7 Hz, H-3), 3.96 (ddd, 1H, $J_{4,5a}$ = 7.3 Hz, $J_{5a,5b}$ = 14.4 Hz, $J_{5a,NH}$ =

5.0 Hz, H-5a), 3.69 (ddd, 1H, $J_{4,5b}$ = 7.6 Hz, $J_{5b,NH}$ = 5.0 Hz, H-5b), 3.44 (s, 3H, OMe), 2.02 (s, 3H, Me(Ac)).



135

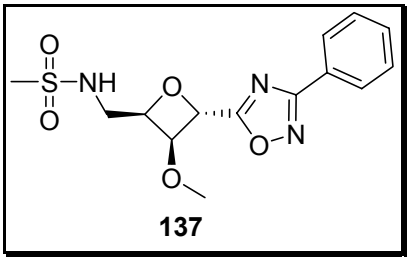
5-[(2*S*,3*S*,4*R*)-5-*N*-Acetyl-amino-3-methoxy-oxetan-2-yl]-3-*p*-methylphenyl-1,2,4-oxadiazole (135). Starting with **130** (40.0 mg, 0.10 mmol) using general procedure 4.3.1.3 (reaction time 3 h), and after flash chromatography using heptane/EtOAc gradient, the title compound was obtained as white waxy solid (28.6 mg, 0.09 mmol, 98%). $[\alpha]_D^{20.0}$ -32.45 (*c* 0.672, $CHCl_3$). MS: (ionspray) m/z 318.1 $[M+H]^+$, 340.1 $[M+Na]^+$. ^1H NMR (300 MHz, $CDCl_3$): δ 8.00 (br d, J = 8.1 Hz, 2H, Ph), 7.30 (br d, 2H, Ph), 5.83 (br s , 1H, NH), 5.73 (d, 1H, $J_{2,3}$ = 4.9 Hz, H-2), 5.08 (br q, 1H, H-4), 4.68 (dd, 1H, $J_{3,4}$ = 6.7 Hz, H-3), 3.96 (ddd, 1H, $J_{4,5a}$ = 7.4 Hz, $J_{5a,5b}$ = 14.5 Hz, $J_{5a,NH}$ = 5.0 Hz, H-5a), 3.69 (ddd, 1H, $J_{4,5b}$ = 7.5 Hz, $J_{5b,NH}$ = 4.9 Hz, H-5b), 3.43 (s, 3H, OMe), 2.43 (s, 3H, Me(Ph), 2.02 (s, 3H, Me(Ac)).



136

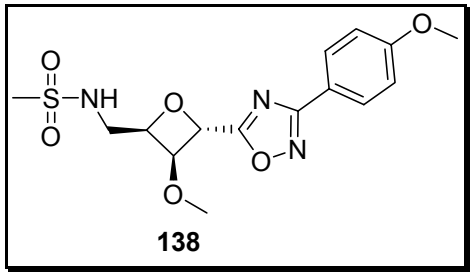
5-[(2*S*,3*S*,4*R*)-5-*N*-Acetyl-amino-3-methoxy-oxetan-2-yl]-3-pyridinyl-1,2,4-oxadiazole (136). Starting with **131** (41.2 mg, 0.11 mmol) using general procedure 4.3.1.3 (reaction time 3 h), and after flash chromatography using heptane/EtOAc gradient, the title compound was obtained as light brown solid (30.1 mg, 0.10 mmol, 90%). $[\alpha]_D^{20.0}$ -29.2 (*c* 0.823, $CHCl_3$). MS: (ionspray) m/z 305.2 $[M+H]^+$, 327.2

$[M+Na]^+$. ^1H NMR (300 MHz, $CDCl_3$): δ 8.91-8.89 (m, 2H, Ph), 8.28-8.26 (m, 2H, Ph), 6.00 (br t, 1H, NH), 5.79 (d, 1H, $J_{2,3}$ = 4.8 Hz, H-2), 5.12 (br q, 1H, H-4), 4.69 (dd, 1H, $J_{3,4}$ = 6.7 Hz, H-3), 3.97 (ddd, 1H, $J_{4,5a}$ = 7.1 Hz, $J_{5a,NH}$ = 5.0 Hz, $J_{5a,5b}$ = 14.5 Hz, H-5a), 3.71 (ddd, 1H, $J_{4,5b}$ = 7.4 Hz, $J_{5b,NH}$ = 5.2 Hz, H-5b), 3.45 (s, 3H, OMe), 2.05 (s, 3H, Me(Ac)).



137

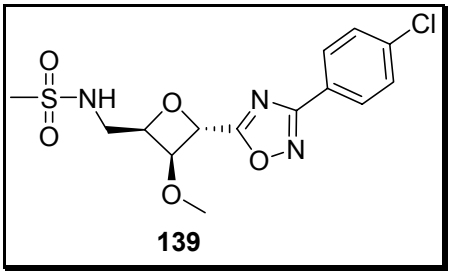
5-[(2*S*,3*S*,4*R*)-5-*N*-Mesyl-amino-3-methoxy-oxetan-2-yl]-3-phenyl-1,2,4-oxadiazole (137). Starting with **127** (50.0 mg, 0.13mmol) using general procedure 4.3.1.4 (reaction time 2 h), and after flash chromatography using heptane/EtOAc gradient, the title compound was obtained as a colourless viscous oil (42.0 mg, 0.12 mmol, 93%). $[\alpha]_D^{20.0}$ -51.94 (*c* 0.617, $CHCl_3$). MS: (ionspray) m/z 340.1 $[M+H]^+$, 362.2 $[M+Na]^+$. ^1H NMR (300 MHz, $CDCl_3$): δ 8.14-8.09 (m, 2H, Ph), 7.57-7.46 (m, 3H, Ph), 5.79 (d, 1H, $J_{2,3}$ = 4.8 Hz, H-2), 5.15 (br q, 1H, $J_{3,4} \approx J_{4,5a} \approx J_{4,5b} \approx$ 6.5 Hz, H-4), 5.03 (t, 1H, $J_{5a,NH} \approx J_{5b,NH} \approx$ 6.6 Hz, NH), 4.74 (dd, 1H, $J_{3,4}$ = 6.8 Hz, H-3), 3.77-3.60 (m, 2H, H-5a, H-5b), 3.44 (s, 3H, OMe), 3.06 (s, 3H, Me(Ms)).



138

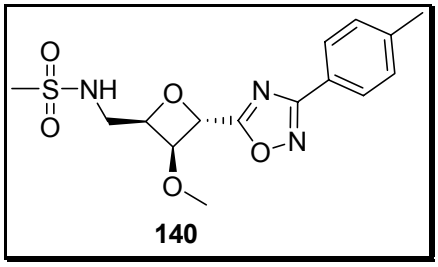
5-[(2*S*,3*S*,4*R*)-5-*N*-Mesyl-amino-3-methoxy-oxetan-2-yl]-3-*p*-methoxyphenyl-1,2,4-oxadiazole (138). Starting with **128** (35.0 mg, 0.09 mmol) using general procedure 4.3.1.4 (reaction time 1.5 h), and after flash chromatography using heptane/EtOAc gradient, the title compound was obtained as a colourless viscous oil

(23.0 mg, 0.06 mmol, 72%). $[\alpha]_D^{20.0}$ -45.26 (*c* 0.875, $CHCl_3$). MS: (ionspray) m/z 370.1 $[M+H]^+$, 392.2 $[M+Na]^+$. ^1H NMR (300 MHz, $CDCl_3$): δ 8.05 (br d, J = 8.7 Hz, 2H, Ph), 7.00 (br d, 2H, Ph), 5.77 (d, 1H, $J_{2,3}$ = 4.8 Hz, H-2), 5.15 (br q, 1H, $J_{3,4} \approx J_{4,5a} \approx J_{4,5b} \approx$ 6.5 Hz, H-4), 4.92 (t, 1H, $J_{5a,NH} \approx J_{5b,NH} \approx$ 6.6 Hz, NH), 4.73 (dd, 1H, $J_{3,4}$ = 6.8 Hz, H-3), 3.88 (s, 3H, OMe(Ph)), 3.77-3.60 (m, 2H, H-5a, H-5b), 3.44 (s, 3H, OMe), 3.06 (s, 3H, Me(Ms)).



139

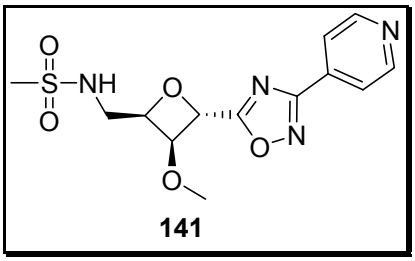
5-[(2*S*,3*S*,4*R*)-5-*N*-Mesyl-amino-3-methoxy-oxetan-2-yl]-3-*p*-chlorophenyl-1,2,4-oxadiazole (139). Starting with **129** (35.0 mg, 0.09 mmol) using general procedure 4.3.1.4 (reaction time 1.5 h), and after flash chromatography using heptane/EtOAc gradient, the title compound was obtained as a colourless oil (30.3 mg, 0.08 mmol, 95%). $[\alpha]_D^{20.0}$ -47.37 (*c* 0.758, $CHCl_3$). MS: (ionspray) m/z 374.2 $[M+H]^+$, 396.1 $[M+Na]^+$. ^1H NMR (300 MHz, $CDCl_3$): δ 8.05 (br d, J = 8.6 Hz, 2H, Ph), 7.58 (br d, 2H, Ph), 5.78 (d, 1H, $J_{2,3}$ = 4.8 Hz, H-2), 5.15 (br q, 1H, $J_{3,4} \approx J_{4,5a} \approx J_{4,5b} \approx$ 6.5 Hz, H-4), 4.95 (t, 1H, $J_{5a,NH} \approx J_{5b,NH} \approx$ 6.5 Hz, NH), 4.73 (dd, 1H, $J_{3,4}$ = 6.9 Hz, H-3), 3.77-3.60 (m, 2H, H-5a, H-5b), 3.44 (s, 3H, OMe), 3.06 (s, 3H, Me(Ms)).



140

5-[(2*S*,3*S*,4*R*)-5-*N*-Mesyl-amino-3-methoxy-oxetan-2-yl]-3-*p*-methylphenyl-1,2,4-oxadiazole (140). Starting with **130** (40.0 mg, 0.10 mmol) using general procedure

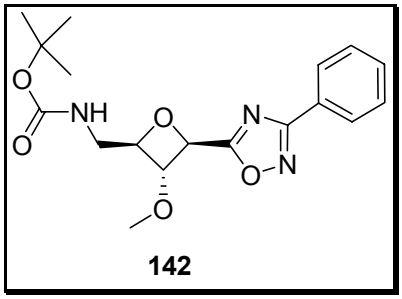
4.3.1.4 (reaction time 1.5 h), and after flash chromatography using heptane/EtOAc gradient, the title compound was obtained as a colourless oil (26.9 mg, 0.08 mmol, 74%). $[\alpha]_D^{20.0}$ -46.22 (*c* 0.738, $CHCl_3$). MS: (ionspray) m/z 354.2 $[M+H]^+$, 376.3 $[M+Na]^+$. ^1H NMR (300 MHz, $CDCl_3$): δ 8.00 (br d, J = 8.1Hz, 2H, Ph), 7.30 (br d, 2H, Ph), 5.78 (d, 1H, $J_{2,3}$ 4.8 Hz, H-2), 5.15 (br q, 1H, $J_{3,4} \approx J_{4,5a} \approx J_{4,5b} \approx$ 6.5 Hz, H-4), 4.94 (t, 1H, $J_{5a,NH} \approx J_{5b,NH} \approx$ 6.7 Hz, NH), 4.73 (dd, 1H, $J_{3,4}$ 6.8 Hz, H-3), 3.77-3.60 (m, 2H, H-5a, H-5b), 3.44 (s, 3H, OMe), 3.06 (s, 3H, Me(Ms)), 2.43 (s, 3H, Me(Ph)).



141

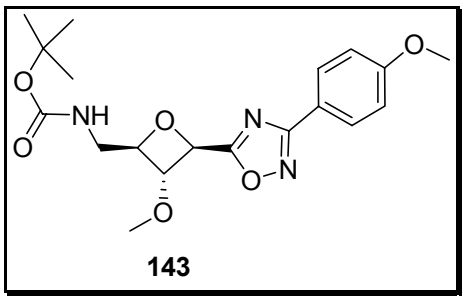
5-[(2*S*,3*S*,4*R*)-5-*N*-Mesyl-amino-3-methoxy-oxetan-2-yl]-3-pyridinyl-1,2,4-oxadiazole (141). Starting with **131** (128.2 mg, 0.34 mmol) using general procedure 4.3.1.4 (reaction time 2.5 h), and after flash chromatography using heptane/EtOAc gradient, the title compound was obtained as a white solid (70.7 mg, 0.21 mmol, 59%). $[\alpha]_D^{20.0}$ -34.25 (*c* 0.687, $CHCl_3$) . ^1H NMR (300 MHz, $CDCl_3$) δ 8.82-8.80 (m, 2H, Ph), 7.99-7.97 (m, 2H, Ph), 6.85 (br s, 1H, NH), 5.77 (d, 1H, $J_{2,3}$ 4.7 Hz, H-2), 5.18 (br q, 1H, H-4), 4.76 (dd, 1H, $J_{3,4}$ 6.8 Hz, H-3), 4.07 (ddd, 1H, $J_{5a,NH}$ = 5.0 Hz, $J_{4,5a}$ = 7.1Hz, $J_{5a,5b}$ = 14.4 Hz, H-5a), 3.81 (dt, 1H, $J_{4,5b} \approx J_{5b,NH} \approx$ 5.6 Hz, H-5b), 3.48 (s, 3H, OMe), 3.04 (s, 3H, Me(Ms)).

4.3.2.3 Library on 2,4-Anhydro-5-*N*-(*tert*-butoxycarbonyl)amino-3-*O*-methyl-D-*ribonic* acid (71)



142

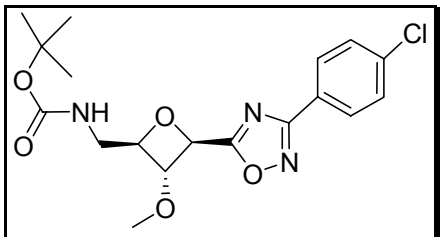
5-[(2*R*,3*R*,4*R*)-5-*N*-(*tert*-Butoxycarbonyl)amino-3-methoxy-oxetan-2-yl]-3-phenyl-1,2,4-oxadiazole (142). Starting with **71** (150.0 mg, 0.57 mmol) using general procedure 4.3.1.1 (cyclisation time 3 h), and after flash chromatography using heptane/EtOAc gradient, the title compound was obtained as a brown oil (124.0 mg, 0.34 mmol, 60%). $[\alpha]_D^{20.0}$ -51.85 (*c* 0.791, $CHCl_3$). MS: (ionspray) m/z 262.1 $[M\text{-Boc}+H]^+$, 306.1 $[M\text{-}t\text{-Bu}+H]^+$, 362.3 $[M+H]^+$, 384.2 $[M+Na]^+$. ^1H NMR (300 MHz, $CDCl_3$): δ 8.17-8.13 (m, 2H, Ph), 7.52-7.49 (m, 3H, Ph), 5.68 (br d, 2H, $J_{2,3}$ = 4.9 Hz, H-2, NH), 4.90 (br ddd, 1H, H-4), 4.42 (t, 1H, $J_{3,4} \approx J_{2,3} \approx 4.9$ Hz, H-3), 3.70 (ddd, 1H, $J_{4,5a}$ = 8.1 Hz, $J_{5a,NH}$ = 3.2 Hz, $J_{5a,5b}$ = 15.0 Hz, H-5a), 3.44 (ddd, 1H, $J_{4,5b} \approx J_{5b,NH} \approx 3.3$ Hz, H-5b), 3.39 (s, 3H, OMe), 1.40 (s, 9H, Boc).



143

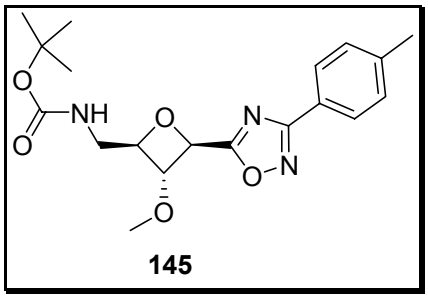
5-[(2*R*,3*R*,4*R*)-5-*N*-(*tert*-Butoxycarbonyl)amino-3-methoxy-oxetan-2-yl]-3-*p*-methoxyphenyl-1,2,4-oxadiazole (143). Starting with **71** (55.0 mg, 0.211 mmol) using general procedure 4.3.1.1 (cyclisation time 3 h), and after flash chromatography using heptane/EtOAc gradient, the title compound was obtained as

a light yellow oil (38.2 mg, 0.098 mmol, 46%). $[\alpha]_D^{20.0}$ -61.03 (*c* 1.039, $CHCl_3$). MS: (ionspray) m/z 292.1 $[M\text{-Boc+H}]^+$, 336.2 $[M\text{-}t\text{-Bu+H}]^+$, 392.2 $[M+H]^+$, 414.3 $[M+Na]^+$. ^1H NMR (300 MHz, $CDCl_3$), δ 8.08 (br d, J = 8.8 Hz, 2H, Ph), 6.99 (br d, 2H, Ph), 5.70 (br d, 1 H, NH), 5.65 (d, 1H, $J_{2,3}$ = 5.0 Hz, H-2), 4.89 (br ddd, 1H, H-4), 4.40 (t, 1H, $J_{2,3} \approx J_{3,4} \approx$ 5.0 Hz, H-3), 3.88 (s, 3H, Ph-OMe), 3.69 (ddd, 1H, $J_{4,5a}$ = 8.1 Hz, $J_{5a,NH}$ = 2.9 Hz, $J_{5a,5b}$ = 15.1 Hz, H-5a), 3.43 (ddd, 1H, $J_{4,5b} \approx J_{5b,NH} \approx$ 3.3 Hz, H-5b), 3.39 (s, 3H, OMe), 1.41 (s, 9H, Boc).



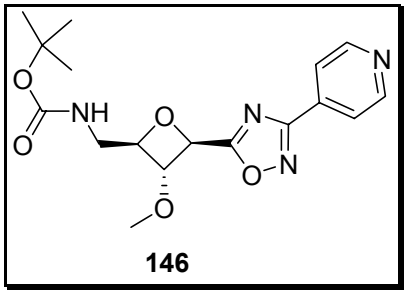
144

5-[(2*R*,3*R*,4*R*)-5-*N*-(*tert*-Butoxycarbonyl)amino-3-methoxy-oxetan-2-yl]-3-*p*-chlorophenyl-1,2,4-oxadiazole (144). Starting with **71** (193.0 mg, 0.739 mmol) using general procedure 4.3.1.1 (cyclisation time 3 h), and after flash chromatography using heptane/EtOAc gradient, the title compound was obtained as a colourless oil (218.0 mg, 0.551 mmol, 75%). $[\alpha]_D^{20.0}$ -62.60 (*c* 0.791, $CHCl_3$). MS: (ionspray) m/z 296.2 $[M\text{-Boc+H}]^+$, 340.0 $[M\text{-}t\text{-Bu+H}]^+$, 396.1 $[M+H]^+$, 418.2 $[M+Na]^+$. ^1H NMR (300 MHz, $CDCl_3$): δ 8.09 (br d, J = 8.5 Hz, 2H, Ph), 7.47 (br d, 2H, Ph), 5.67 (d, 1H, $J_{2,3}$ = 5.0 Hz, H-2), 5.62 (br d, 1 H, NH), 4.89 (br ddd, 1H, H-4), 4.41 (t, 1H, $J_{2,3} \approx J_{3,4} \approx$ 5.0 Hz, H-3), 3.69 (ddd, 1H, $J_{4,5a}$ = 8.1 Hz, $J_{5a,NH}$ = 2.7 Hz, $J_{5a,5b}$ = 15.0 Hz, H-5a), 3.43 (ddd, 1H, $J_{4,5b} \approx J_{5b,NH} \approx$ 3.5 Hz, H-5b), 3.40 (s, 3H, OMe), 1.41 (s, 9H, Boc). HRMS (ESI) *m/z* 396.13218 $[M+H]^+$, calcd. 396.13207 for $C_{18}H_{23}ClN_3O_5$.



145

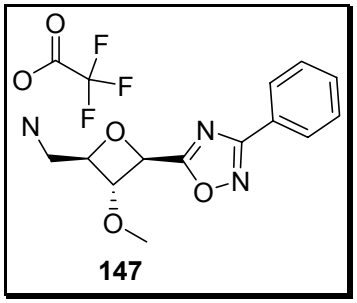
5-[(2*R*,3*R*,4*R*)-5-*N*-(*tert*-Butoxycarbonyl)amino-3-methoxy-oxetan-2-yl]-3-*p*-methylphenyl-1,2,4-oxadiazole (145). Starting with **71** (175.0 mg, 0.670 mmol) using general procedure 4.3.1.1 (cyclisation time 3 h), and after flash chromatography with heptane/EtOAc gradient, the title compound was obtained as a yellow oil (212.4 mg, 0.566 mmol, 84%). $[\alpha]_D^{20.0}$ -45.62 (*c* 0.752, $CHCl_3$). MS: (ionspray) m/z 276.1 $[M\text{-Boc}+H]^+$, 320.1 $[M\text{-}t\text{-Bu}+H]^+$, 376.4 $[M+H]^+$, 398.2 $[M+Na]^+$. ^1H NMR (300 MHz, $CDCl_3$): δ 8.03 (br d, J = 8.1 Hz, 2H, Ph), 7.29 (br d, 2H, Ph), 5.69 (br s, 1 H, NH), 5.66 (d, 1H, $J_{2,3}$ = 5.0 Hz, H-2), 4.89 (br ddd, 1H, H-4), 4.41 (t, 1H, $J_{2,3} \approx J_{3,4} \approx$ 5.0 Hz, H-3), 3.69 (ddd, 1H, $J_{4,5a}$ = 8.1 Hz, $J_{5a,NH}$ = 2.9 Hz, $J_{5a,5b}$ = 15.0 Hz, H-5a), 3.43 (ddd, 1H, $J_{4,5b} \approx J_{5b,NH} \approx$ 3.4 Hz, H-5b), 3.39 (s, 3H, OMe), 2.43 (s, 3H, Me), 1.41 (s, 9H, Boc).



146

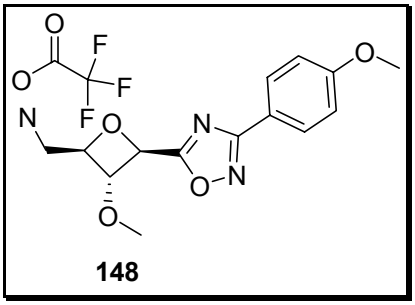
5-[(2*R*,3*R*,4*R*)-5-*N*-(*tert*-Butoxycarbonyl)amino-3-methoxy-oxetan-2-yl]-3-pyridinyl-1,2,4-oxadiazole (146). Starting with **71** (107.5 mg, 0.411 mmol) using general procedure 4.3.1.1 (cyclisation time 4 h), and after flash chromatography using heptane/EtOAc gradient, the title compound was obtained as a colourless oil (124.2 mg, 0.343 mmol, 83%). $[\alpha]_D^{20.0}$ -60.47 (*c* 0.744, $CHCl_3$). MS: (ionspray) m/z 263.1 $[M\text{-Boc}+H]^+$, 307.2 $[M\text{-}t\text{-Bu}+H]^+$, 363.2 $[M+H]^+$, 385.2 $[M+Na]^+$. ^1H NMR (300

MHz, $CDCl_3$): δ 8.81-8.79 (m, 2H, Ph), 8.02-8.00 (m, 2H, Ph), 5.70 (d, 1H, $J_{2,3}$ = 5.0 Hz, H-2), 5.67 (br s, 1H, NH), 4.90 (br ddd, 1H, H-4), 4.43 (t, 1H, $J_{2,3} \approx J_{3,4} \approx 5.0$ Hz, H-3), 3.69 (ddd, 1H, $J_{4,5a}$ = 8.3 Hz, $J_{5a,NH}$ = 2.9 Hz, $J_{5a,5b}$ = 15.1 Hz, H-5a), 3.45 (ddd, 1H, $J_{4,5a} \approx J_{5a,NH} \approx 3.7$ Hz, H-5b), 3.41 (s, 3H, OMe), 1.41 (s, 9H, Boc).



147

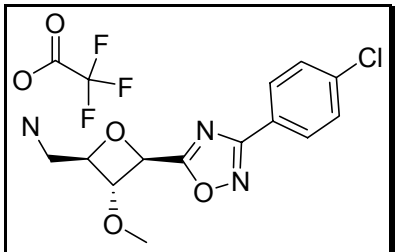
5-[(2*R*,3*R*,4*R*)-5-Amonium-3-methoxy-oxetan-2-yl]-3-phenyl-1,2,4-oxadiazole Trifluoroacetate (147). Starting with **142** (124.0 mg, 0.343 mmol) using general procedure 4.3.1.2 (reaction time 4 h), and after flash chromatography with EtOAc/MeOH gradient, the title compound was obtained as a light brown viscous oil (103.0 mg, 0.274 mmol, 80%). $[\alpha]_D^{20.0}$ 41.93 (*c* 0.854, MeOH). MS: (ionspray) m/z 262.1 $[M\text{-}TFA+H]^+$, 284.0 $[M\text{-}TFA+Na]^+$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.14-8.11 (m, 2H, Ph), 7.60-7.57 (m, 3H, Ph), 5.86 (d, 1H, $J_{2,3}$ = 4.9 Hz, H-2), 5.00 (ddd, 1H, $J_{3,4}$ = 5.0 Hz, H-4), 4.63 (t, 1H, H-3), 3.51 (A(ABX), 1H, $J_{4,5a}$ = 7.4 Hz, $J_{5a,5b}$ = 13.8 Hz, H-5a), 3.47 (s, 3H, OMe), 3.43 (B(ABX), 1H, $J_{4,5b}$ = 3.9 Hz, H-5b).



148

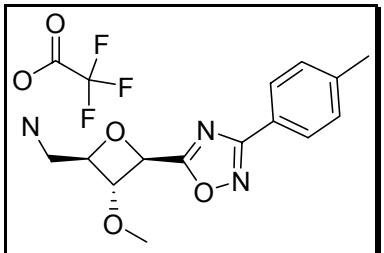
5-[(2*R*,3*R*,4*R*)-5-Amonium-3-methoxy-oxetan-2-yl]-3-*p*-methoxyphenyl-1,2,4-oxadiazole Trifluoroacetate (148). Starting with **143** (120.0 mg, 0.307 mmol) using general procedure 4.3.1.2 (reaction time 4 h), and after recrystallisation with

MeOH/DCM/n-Hex, the title compound was obtained as colourless crystals (122.0 mg, 0.301 mmol, 98%). m.p. 156.0-156.5 ºC. $[\alpha]_D^{20.0}$ 38.43 (*c* 0.752, MeOH). MS: (ionspray) m/z 292.1 $[M\text{-}TFA+H]^+$. ^1H NMR (300 MHz, MeOD): δ 7.94 (br d, J = 8.9 Hz, 2H, Ph), 6.97 (br d, 2H, Ph), 5.71 (d, 1H, $J_{2,3}$ = 4.9 Hz, H-2), 4.86 (ddd, 1H, $J_{3,4}$ = 5.0 Hz, H-4), 4.48 (t, 1H, H-3), 3.37 (A(ABX), 1H, $J_{4,5a}$ = 7.3 Hz, $J_{5a,5b}$ = 13.8 Hz, H-5a), 3.34 (s, 3H, OMe), 3.29 (B(ABX), 1H, $J_{4,5b}$ 3.9 Hz, H-5b).



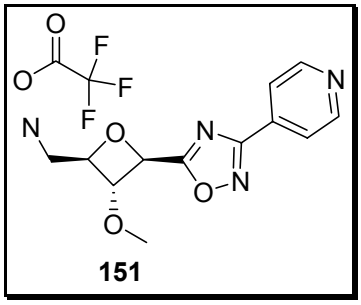
149

5-[(2*R*,3*R*,4*R*)-5-Amonium-3-methoxy-oxetan-2-yl]-3-*p*-chlorophenyl-1,2,4-oxadiazole Trifluoroacetate (149). Starting with **144** (178.0 mg, 0.450 mmol) using general procedure 4.3.1.2 (reaction time 4 h), and after recrystallisation with MeOH/DCM/n-Hex, the title compound was obtained as a white solid (157.0 mg, 0.383 mmol, 85%). $[\alpha]_D^{20.0}$ 41.53 (*c* 0.884, MeOH). MS: (ionspray) m/z 296.2 $[M\text{-}TFA+H]^+$, 318.0 $[M\text{-}TFA+Na]^+$. ^1H NMR (300 MHz, MeOD) δ 8.12 (br d, J = 8.6 Hz, 2H, Ph), 7.60 (br d, 2H, Ph), 5.86 (d, 1H, $J_{2,3}$ = 4.9 Hz, H-2), 5.99 (ddd, 1H, $J_{3,4}$ = 5.0 Hz, H-4), 4.99 (t, 1H, H-3), 3.50 (A(ABX), 1H, $J_{4,5a}$ = 7.4 Hz, $J_{5a,5b}$ = 13.8, H-5a), 3.47 (s, 3H, OMe), 3.42 (B(ABX), 1H, $J_{4,5b}$ = 3.9, H-5b). HRMS (ESI) *m/z* 296.07959 $[M\text{-}TFA+H]^+$, calcd. 296.07965 for $C_{13}H_{15}ClN_3O_3$.



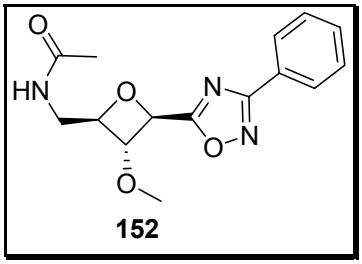
150

5-[(2*R*,3*R*,4*R*)-5-Amonium-3-methoxy-oxetan-2-yl]-3-*p*-methylphenyl-1,2,4-oxadiazole Trifluoroacetate (150). Starting with **145** (137.9 mg, 0.367 mmol) using general procedure 4.3.1.2 (reaction time 4 h), and after flash chromatography with EtOAc/MeOH, the title compound was obtained as a light yellow oil (128.6 mg, 0.330 mmol, 90%). $[\alpha]_D^{20.0}$ 37.67 (*c* 0.725, MeOH). MS: (ionspray) m/z 276.1 $[M\text{-}TFA+H]^+$, 298.2 $[M\text{-}TFA+Na]^+$. ^{1}H NMR (300 MHz, MeOD): δ 7.88 (br d, J = 8.2 Hz, 2H, Ph), 7.27 (br d, 2H, Ph), 5.72 (d, 1H, $J_{2,3}$ = 4.9 Hz, H-2), 4.86 (ddd, 1H, $J_{3,4}$ = 5.0 Hz, H-4), 4.49 (t, 1H, H-3), 3.37 (A(ABX), 1H, $J_{4,5a}$ = 7.4 Hz, $J_{5a,5b}$ = 13.8, H-5a), 3.34 (s, 3H, OMe), 3.30 (B(ABX), 1H, $J_{4,5b}$ = 4.0, H-5b), 2.33 (s, 3H, Me(Ph)).



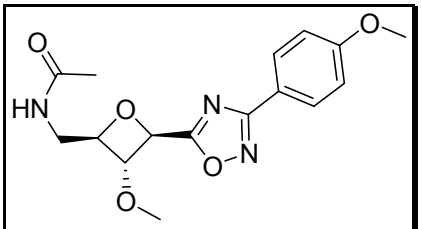
151

5-[(2*R*,3*R*,4*R*)-5-Amonium-3-methoxy-oxetan-2-yl]-3-pyridinyl-1,2,4-oxadiazole Trifluoroacetate (151). Starting with **146** (101.2 mg, 0.279 mmol) using general procedure 4.3.1.2 (reaction time 4 h), and after recrystallisation with MeOH/DCM/n-Hex, the title compound was obtained as a white solid (98.7 mg, 0.262 mmol, 94%). $[\alpha]_D^{20.0}$ 41.48 (*c* 0.921, MeOH). MS: (ionspray) m/z 263.1 $[M\text{-}TFA+H]^+$. ^{1}H NMR (300 MHz, MeOD): δ 8.73-8.71 (m, 2H, Py), 8.08-8.06 (m, 2H, Py), 5.79 (d, 1H, $J_{2,3}$ = 4.9 Hz, H-2), 4.89 (ddd, 1H, $J_{3,4}$ = 5.0 Hz, H-4), 4.52 (t, 1H, , H-3), 3.38 (A(ABX), 1H, $J_{4,5a}$ = 7.4 Hz, $J_{5a,5b}$ = 13.9 Hz, H-5a), 3.35 (s, 3H, OMe), 3.31 (B(ABX), 1H, $J_{4,5b}$ = 4.0 Hz, H-5b).



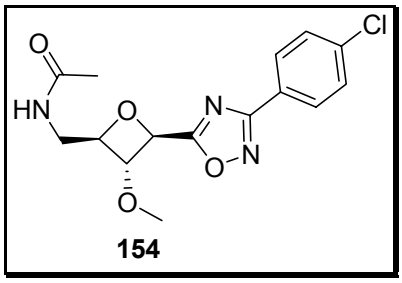
152

5-[(2*R*,3*R*,4*R*)-5-*N*-Acetyl-amino-3-methoxy-oxetan-2-yl]-3-phenyl-1,2,4-oxadiazole (152). Starting with **147** (50.0 mg, 0.133 mmol) using general procedure 4.3.1.3 (reaction time 4 h), and after flash chromatography using heptane/EtOAc gradient, the title compound was obtained as colourless solid (36.6 mg, 0.121 mmol, 91%). $[\alpha]_D^{20.0}$ -105.0 (*c* 0.923, $CHCl_3$). MS: (ionspray) m/z 304.1 $[M+H]^+$, 326.1 $[M+Na]^+$. ^1H NMR (300 MHz, $CDCl_3$): δ 8.14-8.07 (m, 2H, Ph), 7.59-7.47 (m, 3H, Ph), 6.61 (br s, 1H, NH), 5.71 (d, 1H, $J_{2,3}$ = 5.0 Hz, H-2), 4.94 (dt, 1H, H-4), 4.36 (t, 1H, $J_{3,4}$ = 5.0 Hz, H-3), 4.01 (ddd, 1H, $J_{4,5a}$ = 2.8 Hz, $J_{5a,5b}$ = 15.3 Hz, $J_{5a,NH}$ = 8.5 Hz, H-5a), 3.39 (ddd, 1H, $J_{4,5b} \approx J_{5b,NH} \approx$ 3.2 Hz, H-5b), 3.39 (s, 3H, OMe), 2.04 (s, 3H, Me(Ac)).



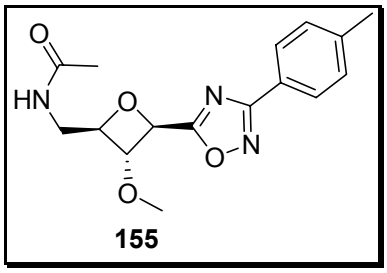
153

5-[(2*R*,3*R*,4*R*)-5-*N*-Acetyl-amino-3-methoxy-oxetan-2-yl]-3-*p*-methoxyphenyl-1,2,4-oxadiazole (153). Starting with **148** (45.0 mg, 0.111 mmol) using general procedure 4.3.1.3 (reaction time 4 h), and after flash chromatography using heptane/EtOAc gradient, the title compound was obtained as a white solid (30.5 mg, 0.091 mmol, 82%). $[\alpha]_D^{20.0}$ -102.9 (*c* 0.922, $CHCl_3$). MS: (ionspray) m/z 334.2 $[M+H]^+$, 356.1$[M+Na]^+$. ^1H NMR (300 MHz, $CDCl_3$): δ 8.04 (br d, J = 8.8 Hz, 2H, Ph), 7.01 (br d, 2H, Ph), 6.68 (br s, 1H, NH), 5.68 (d, 1H, $J_{2,3}$ = 4.9 Hz, H-2), 4.93 (br s, 1H, H-4), 4.34 (t, 1H, $J_{3,4}$ = 4.9 Hz, H-3), 4.00 (ddd, 1H, $J_{4,5a}$ = 2.3 Hz, $J_{5a,5b}$ = 15.2 Hz, $J_{5a,NH}$ = 8.4 Hz, H-5a), 3.88 (s, 3H, OMe(Ph)), 3.43-3.34 (m, 4H, H-5b, OMe), 2.03 (s, 3H, Me(Ac)).



154

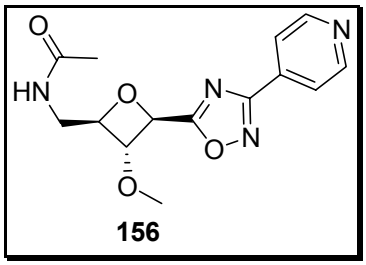
5-[(2*R*,3*R*,4*R*)-5-*N*-Acetyl-amino-3-methoxy-oxetan-2-yl]-3-*p*-chlorophenyl-1,2,4-oxadiazole (154). Starting with **149** (45.0 mg, 0.110 mmol) using general procedure 4.3.1.3 (reaction time 2 h), and after flash chromatography using heptane/EtOAc gradient, the title compound was obtained as a white solid (34.2 mg, 0.101 mmol, 92%). $[\alpha]_D^{20.0}$ -62.14 (*c* 0.917, $CHCl_3$). MS: (ionspray) m/z 338.1 $[M+H]^+$, 360.1 $[M+Na]^+$. ^1H NMR (300 MHz, $CDCl_3$): δ 8.04 (br d, J = 8.5 Hz, 2H, Ph), 7.49 (br d, 2H, Ph), 6.51 (br s , 1H, NH), 5.70 (d, 1H, $J_{2,3}$ = 5.1 Hz, H-2), 4.93 (dt, 1H, H-4), 4.35 (t, 1H, $J_{3,4}$ = 5.1 Hz, H-3), 3.99 (ddd, 1H, $J_{4,5a}$ = 3.0 Hz, $J_{5a,5b}$ = 15.3 Hz, $J_{5a,NH}$ = 8.4 Hz, H-5a), 3.40 (ddd, 1H, $J_{4,5b} \approx J_{5b,NH} \approx$ 3.3 Hz, H-5b), 3.39 (s, 3H, OMe), 2.03 (s, 3H, Me(Ac)). HRMS (ESI) *m/z* 338.09018 $[M+H]^+$, calcd. 338.09021 for $C_{15}H_{17}ClN_3O_4$.



155

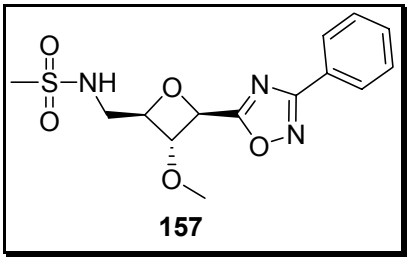
5-[(2*R*,3*R*,4*R*)-5-*N*-Acetyl-amino-3-methoxy-oxetan-2-yl]-3-*p*-methylphenyl-1,2,4-oxadiazole (155). Starting with **150** (30.4 mg, 0.078 mmol) using general procedure 4.3.1.3 (reaction time 3 h), and after flash chromatography using heptane/EtOAc gradient, the title compound was obtained as a colourless oil (20.6 mg, 0.065 mmol, 83%). $[\alpha]_D^{20.0}$ -68.44 (*c* 0.698, $CHCl_3$). MS: (ionspray) m/z 318.1 $[M+H]^+$, 340.1 $[M+Na]^+$. ^1H NMR (300 MHz, $CDCl_3$): δ 7.99 (br d, J = 8.1 Hz, 2H, Ph), 7.25 (br d, 2H, Ph), 6.67 (br s , 1H, NH), 5.70 (d, 1H, $J_{2,3}$ = 5.0 Hz, H-2), 4.93 (dt, 1H,

H-4), 4.35 (t, 1H, $J_{3,4}$ = 5.0 Hz, H-3), 4.01 (ddd, 1H, $J_{4,5a}$ = 2.7 Hz, $J_{5a,5b}$ = 15.3 Hz, $J_{5a,NH}$ = 8.5 Hz, H-5a), 3.39 (s, 3H, OMe), 3.38 (ddd, 1H, $J_{4,5b} \approx J_{5b,NH} \approx$ 3.0 Hz, H-5b), 2.43 (s, 3H, Me(Ph)), 2.03 (s, 3H, Me(Ac)).



156

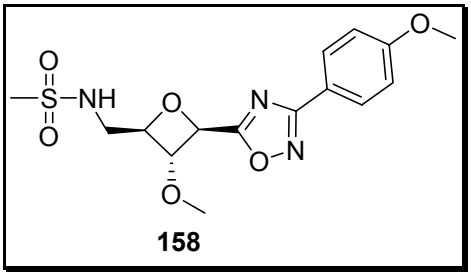
5-[(2*R*,3*R*,4*R*)-5-*N*-Acetyl-amino-3-methoxy-oxetan-2-yl]-3-pyridinyl-1,2,4-oxadiazole (156). Starting with **151** (40.0 mg, 0.106 mmol) using general procedure 4.3.1.3 (reaction time 3 h), and after flash chromatography using heptane/EtOAc gradient, the title compound was obtained as a colourless oil (29.7 mg, 0.098 mmol, 92%). $[\alpha]_D^{20.0}$ -62.23 (*c* 0.739, $CHCl_3$). MS: (ionspray) m/z 305.2 $[M+H]^+$, 327.2 $[M+Na]^+$. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.88-8.77 (m, 2H, Py), 8.13-8.11 (m, 2H, Py), 5.75 (d, 1H, $J_{2,3}$ = 5.1 Hz, H-2), 4.83 (q, 1H, H-4), 4.51 (t, 1H, $J_{3,4}$ = 5.1 Hz, H-3), 3.70 (ddd, 1H, $J_{4,5a} \approx J_{5a,NH} \approx$ 4.6 Hz, $J_{5a,5b}$ = 15.0 Hz, H-5a), 3.53 (ddd, 1H, $J_{4,5b} \approx J_{5b,NH} \approx$ 4.1 Hz, H-5b), 3.42 (s, 3H, OMe), 2.00 (s, 3H, Me(Ac)).



157

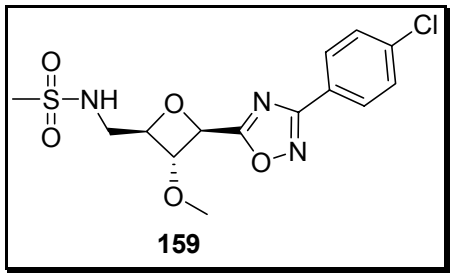
5-[(2*R*,3*R*,4*R*)-5-*N*-Mesyl-amino-3-methoxy-oxetan-2-yl]-3-phenyl-1,2,4-oxadiazole (157). Starting with **147** (30.0 mg, 0.080 mmol) using general procedure 4.3.1.4 (reaction time 2 h), and after flash chromatography using heptane/EtOAc gradient, the title compound was obtained as a colourless viscous oil (22.4 mg, 0.066 mmol, 83%). $[\alpha]_D^{20.0}$ 5.75 (*c* 0.695, $CHCl_3$). MS: (ionspray) m/z 340.0 $[M+H]^+$, 362.2 $[M+Na]^+$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.18-8.12 (m, 2H, Ph), 7.57-7.47 (m,

3H, Ph), 5.94 (t, 1H, $J_{5a,NH} \approx J_{5b,NH} \approx 5.7$ Hz, NH), 5.70 (d, 1H, $J_{2,3} = 4.9$ Hz, H-2), 4.97 (dt, 1H, $J_{4,5a} \approx J_{4,5b} \approx 5.7$ Hz, H-4), 4.63 (t, 1H, $J_{3,4} = 4.9$ Hz, H-3), 3.59-3.54 (m, 2H, H-5a, H-5b), 3.42 (s, 3H, OMe), 3.04 (s, 3H, Me(Ms)).



158

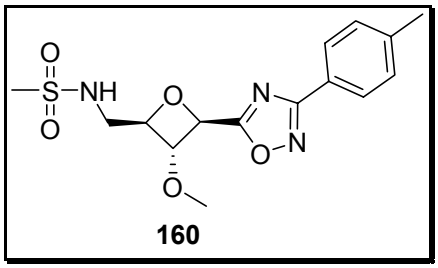
5-[(2*R*,3*R*,4*R*)-5-*N*-Mesyl-amino-3-methoxy-oxetan-2-yl]-3-*p*-methoxyphenyl-1,2,4-oxadiazole (158). Starting with **148** (45.0 mg, 0.111 mmol) using general procedure 4.3.1.4 (reaction time 2 h), and after flash chromatography using heptane/EtOAc gradient, the title compound was obtained as a light brown oil (31.2 mg, 0.084 mmol, 76%). $[\alpha]_D^{20.0}$ -0.771 (*c* 0.648, $CHCl_3$). MS: (ionspray) m/z 370.1 $[M+H]^+$, 392.2 $[M+Na]^+$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.09 (br d, J = 8.9 Hz, 2H, Ph), 7.02 (br d, 2H, Ph), 6.06 (t, 1H, $J_{5a,NH} \approx J_{5b,NH} \approx 5.2$ Hz, NH), 5.68 (d, 1H, $J_{2,3} = 5.2$ Hz, H-2), 4.96 (br dt, 1H, H-4), 4.62 (t, 1H, $J_{3,4} = 4.8$ Hz, H-3), 3.87 (s, 3H, OMe(Ph)), 3.57-3.54 (m, 2H, H-5a, H-5b), 3.41 (s, 3H, OMe), 3.04 (s, 3H, Me(Ms)).



159

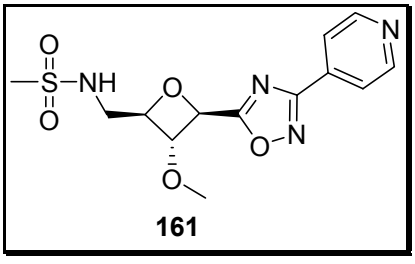
5-[(2*R*,3*R*,4*R*)-5-*N*-Mesyl-amino-3-methoxy-oxetan-2-yl]-3-*p*-chlorophenyl-1,2,4-oxadiazole (159). Starting with **149** (45.0 mg, 0.110 mmol) using general procedure 4.3.1.4 (reaction time 2 h), and after flash chromatography using heptane/EtOAc gradient, the title compound was obtained as a colourless viscous oil (40.6 mg,

0.109 mmol, 99%). $[\alpha]_D^{20.0}$ -0.610 (*c* 0.820, $CHCl_3$). MS: (ionspray) m/z 374.4 $[M+H]^+$, 396.3 $[M+Na]^+$. ^1H NMR (300 MHz, $CDCl_3$): δ 8.10 (d, 2H, J = 8.4 Hz, Ph), 7.49 (d, 2H, Ph), 5.95 (t, 1H, $J_{5a,NH} \approx J_{5b,NH} \approx$ 5.8 Hz, NH), 5.70 (d, 1H, $J_{2,3}$ = 4.8 Hz, H-2), 4.97 (br dt, 1H, H-4), 4.63 (t, 1H, $J_{3,4}$ = 4.9 Hz, H-3), 3.57-3.54 (m, 2H, H-5a, H-5b), 3.41 (s, 3H, OMe), 3.03 (s, 3H, Me(Ms)). HRMS (ESI) *m/z* 374.05708 $[M+H]^+$, calcd. 3374.05720 for $C_{14}H_{17}ClN_3O_5S$.



160

5-[(2*R*,3*R*,4*R*)-5-*N*-Mesyl-amino-3-methoxy-oxetan-2-yl]-3-*p*-methylphenyl-1,2,4-oxadiazole (160). Starting with **150** (32.0 mg, 0.082 mmol) using general procedure 4.3.1.4 (reaction time 2 h), and after flash chromatography using heptane/EtOAc gradient, the title compound was obtained as a colourless oil (21.4 mg, 0.061 mmol, 74%). $[\alpha]_D^{20.0}$ -0.573 (*c* 0.782, $CHCl_3$). MS: (ionspray) m/z 354.1 $[M+H]^+$, 376.2 $[M+Na]^+$. ^1H NMR (300 MHz, $CDCl_3$): δ 8.04 (d, 2H, J = 8.0 Hz, Ph), 7.31 (d, 2H, Ph), 6.00 (t, 1H, $J_{5a,NH} \approx J_{5b,NH} \approx$ 5.5 Hz, NH), 5.69 (d, 1H, $J_{2,3}$ = 4.8 Hz, H-2), 4.97 (br dt, 1H, H-4), 4.63 (t, 1H, $J_{3,4}$ = 4.9 Hz, H-3), 3.58-3.55 (m, 2H, H-5a, H-5b), 3.41 (s, 3H, OMe), 3.03 (s, 3H, Me(Ms)), 2.42 (s, 3H, Me(Ph)).

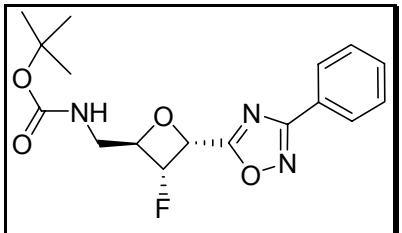


161

5-[(2*R*,3*R*,4*R*)-5-*N*-Mesyl-amino-3-methoxy-oxetan-2-yl]-3-*p*-pyridinyl-1,2,4-oxadiazole (161). Starting with **151** (40.0 mg, 0.106 mmol) using general procedure

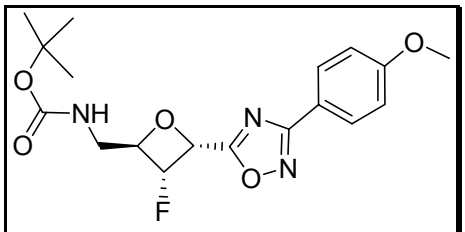
4.3.1.4 (reaction time 2 h), and after flash chromatography using heptane/EtOAc gradient, the title compound was obtained as a colourless viscous oil (30.8 mg, 0.090 mmol, 85%). $[\alpha]_D^{20.0}$ -0.633 (*c* 0.832, $CHCl_3$). MS: (ionspray) m/z 341.1 $[M+H]^+$, 363.2 $[M+Na]^+$. ^1H NMR (300 MHz, MeOD): δ 8.79 (br d, 2H, J = 6.1 Hz, Py), 8.14-8.10 (m, 2H, Py), 5.76 (t, 1H, $J_{5a,NH} \approx J_{5b,NH} \approx 5.5$ Hz, NH), 4.91-4.88 (m, H-2+H_2O), 4.80 (br dt, 1H, H-4), 4.54 (t, 1H, $J_{3,4}$ = 5.2 Hz, H-3), 3.75-3.71 (m, 1H, H-5a), 3.51-3.43 (m, 4H, H-5b, OMe), 3.34-3.32 (m, Me(Ms)+MeOH).

4.3.2.4 Library on 2,4-Anhydro-5-*N*-(*tert*-butoxycarbonyl)amino-3-fluoro-D-*arabinonic* acid (79)



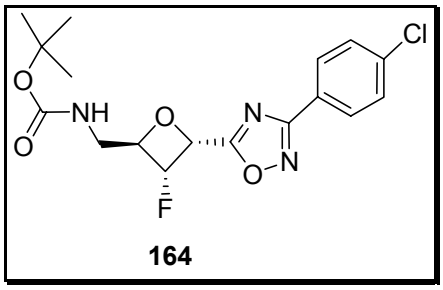
162

5-[(2*S*,3*R*,4*R*)-5-*N*-(*tert*-Butoxycarbonyl)amino-3-fluoro-oxetan-2-yl]-3-phenyl-1,2,4-oxadiazole (162). Starting with **79** (134.1 mg, 0.54 mmol) using general procedure 4.3.1.1 (cyclisation time 3 h), and after flash chromatography using heptane/EtOAc gradient, the title compound was obtained as a light yellow viscous oil (152.2 mg, 0.44 mmol, 81%). $[\alpha]_D^{20.0}$ -54.03 (*c* 0.602, $CHCl_3$). MS: (ionspray) m/z 250.1 $[M-Boc+H]^+$, 294.1 $[M-t\text{Bu}+H]^+$, 350.3 $[M+H]^+$, 367.2 $[M+NH_4]^+$, 372.2$[M+Na]^+$. ^1H NMR (300 MHz, $CDCl_3$): δ 8.15-8.11 (m, 2H, Ph), 7.54-7.45 (m, 3H, Ph), 5.95 (ddd, 1H, $J_{2,F}$ = 11.8 Hz, $J_{2,3}$ = 6.6 Hz, $J_{2,4}$ = 0.8 Hz, H-2), 5.56 (ddd, $J_{3,F}$ = 54.8 Hz, $J_{3,4}$ = 5.1 Hz, H-3), 5.35 (dqd, 1H, $J_{4,F}$ = 18.0 Hz, H-4), 4.96 (br s, 1H, NH), 3.74-3.66 (m, 1H, H-5a), 3.50 (dt, 1H, $J_{4,5b} \approx J_{5b,NH} \approx 4.7$ Hz, $J_{5a,5b}$ = 15.2 Hz, H-5b), 1.46 (s, 9H, Boc).



163

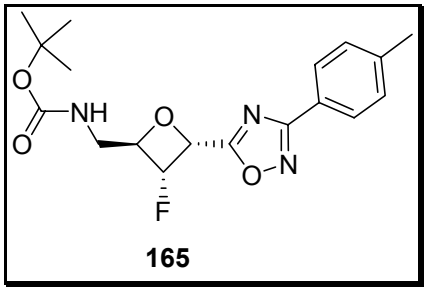
5-[(2*S*,3*R*,4*R*)-5-*N*-(*tert*-Butoxycarbonyl)amino-3-fluoro-oxetan-2-yl]-3-*p*-methoxyphenyl-1,2,4-oxadiazole (163). Starting with **79** (175.0 mg, 0.70 mmol) using general procedure 4.3.1.1 (cyclisation time 3 h), and after flash chromatography using heptane/EtOAc gradient, the title compound was obtained as a light yellow viscous oil (222.1 mg, 0.58 mmol, 83%). $[\alpha]_D^{20.0}$ -56.45 (*c* 0.953, $CHCl_3$). MS: (ionspray) m/z 324.3 $[M\text{-}t\text{-}Bu+H]^+$, 380.2 $[M+H]^+$, 397.3 $[M+NH_4]^+$, 402.4 $[M+Na]^+$. ^1H NMR (300 MHz, $CDCl_3$): δ 8.08-8.03 (m, 2H, Ph), 7.02-6.97 (m, 2H, Ph), 5.92 (ddd, 1H, $J_{2,F}$ = 11.8 Hz, $J_{2,3}$ = 6.5 Hz, $J_{2,4}$ = 1.0 Hz, H-2), 5.56 (ddd, $J_{3,F}$ = 54.9 Hz, $J_{3,4}$ = 4.9 Hz, H-3), 5.34 (dqd, 1H, $J_{4,F}$ = 18.0 Hz, H-4), 4.97 (br s, 1H, NH), 3.87 (s, 3H, OMe(Ph)) 3.74-3.65 (m, 1H, H-5a), 3.49 (dt, 1H, $J_{4,5b} \approx J_{5b,NH} \approx 4.8$ Hz, $J_{5a,5b}$ = 15.4 Hz, H-5b), 1.49 (s, 9H, Boc).



164

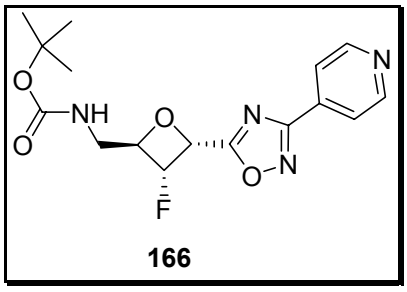
5-[(2*S*,3*R*,4*R*)-5-*N*-(*tert*-Butoxycarbonyl)amino-3-fluoro-oxetan-2-yl]-3-*p*-chlorophenyl-1,2,4-oxadiazole (164). Starting with **79** (200.0 mg, 0.80 mmol) using general procedure 4.3.1.1 (cyclisation time 4 h), and after flash chromatography using heptane/EtOAc gradient, the title compound was obtained as a light yellow viscous oil (260.0 mg, 0.67 mmol, 84%). $[\alpha]_D^{20.0}$ -58.04 (*c* 0.789, $CHCl_3$). MS: (ionspray) m/z 328.2 $[M\text{-}t\text{Bu}+H]^+$, 384.3 $[M+H]^+$, 401.3 $[M+NH_4]^+$, 406.3 $[M+Na]^+$. ^1H

NMR (300 MHz, $CDCl_3$): δ 8.07 (br d, J = 8.6 Hz, 2H, Ph), 7.47 (br d, 2H, Ph), 5.94 (ddd, 1H, $J_{2,F}$ = 11.6 Hz, $J_{2,3}$ = 6.5 Hz, $J_{2,4}$ = 0.7 Hz, H-2), 5.57 (ddd, $J_{3,F}$ = 54.9 Hz, $J_{3,4}$ = 4.9 Hz, H-3), 5.34 (dqd, 1H, $J_{4,F}$ = 18.0 Hz, H-4), 4.96 (br s, 1H, NH), 3.74-3.65 (m, 1H, H-5a), 3.49 (dt, 1H, $J_{4,5b} \approx J_{5b,NH} \approx$ 4.6 Hz, $J_{5a,5b}$ = 15.2 Hz, H-5b), 1.49 (s, 9H, Boc). Anal. Calcd. for $C_{17}H_{19}ClFN_3O_4$ (383.81): C, 53.20; H, 4.99; N, 10.95. Found: C, 53.09; H, 4.80; N, 10.88.



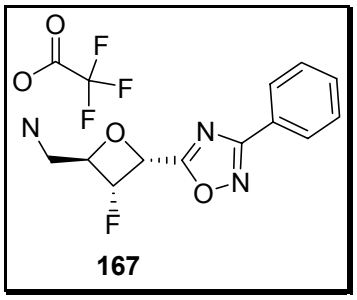
165

5-[(2*S*,3*R*,4*R*)-5-*N*-(*tert*-Butoxycarbonyl)amino-3-fluoro-oxetan-2-yl]-3-*p*-methylphenyl-1,2,4-oxadiazole (165). Starting with **79** (200.0 mg, 0.80 mmol) using general procedure 4.3.1.1 (cyclisation time 4 h), and after flash chromatography using heptane/EtOAc gradient, the title compound was obtained as a yellow oil (208.2 mg, 0.57 mmol, 71%). $[\alpha]_D^{20.0}$ -54.55 (*c* 0.836, $CHCl_3$). MS: (ionspray) m/z 308.2 $[M\text{-}t\text{Bu}+H]^+$, 364.3 $[M+H]^+$, 381.3 $[M+NH_4]^+$, 386.2 $[M+Na]^+$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.01 (br d, J = 8.2 Hz, 2H, Ph), 7.30 (br d, 2H, Ph), 5.93 (dd, 1H, $J_{2,F}$ = 11.8 Hz, $J_{2,3}$ = 6.5 Hz, H-2), 5.55 (ddd, $J_{3,F}$ = 54.9 Hz, $J_{3,4}$ = 5.0 Hz, H-3), 5.34 (dqd, 1H, $J_{4,F}$ = 18.0 Hz, $J_{2,4}$ = 0.9 Hz, H-4), 4.96 (br s, 1H, NH), 3.74-3.65 (m, 1H, H-5a), 3.49 (dt, 1H, $J_{4,5b} \approx J_{5b,NH} \approx$ 4.6 Hz, $J_{5a,5b}$ = 15.3 Hz, H-5b), 2.42 (s, 3H, Me(Ph)), 1.49 (s, 9H, Boc).



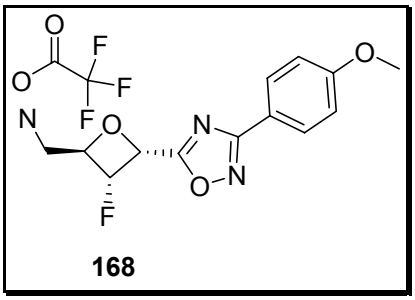
166

5-[(2*S*,3*R*,4*R*)-5-*N*-(*tert*-Butoxycarbonyl)amino-3-fluoro-oxetan-2-yl]-3-pyridinyl-1,2,4-oxadiazole (166). Starting with **79** (204.2 mg, 0.82 mmol) using general procedure 4.3.1.1 (cyclisation time 5 h), and after flash chromatography using heptane/EtOAc gradient, the title compound was obtained as a light yellow foam (159.4 mg, 0.46 mmol, 56%). $[\alpha]_D^{20.0}$-68.23 (*c* 0.922, $CHCl_3$). MS: (ionspray) m/z 351.3 $[M+H]^+$, 373.3 $[M+Na]^+$. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.80 (br d, J = 6.0 Hz, 2H, Ph), 7.99 (br d, 2H, Ph), 5.97 (dd, 1H, $J_{2,F}$ = 11.8 Hz, $J_{2,3}$ = 6.4 Hz, H-2), 5.58 (ddd, $J_{3,F}$ = 54.8 Hz, $J_{3,4}$ = 5.0 Hz, H-3), 5.35 (dq, 1H, $J_{4,F}$ = 18.1 Hz, H-4), 4.98 (br s, 1H, NH), 3.75-3.66 (m, 1H, H-5a), 3.50 (dt, 1H, $J_{4,5b} \approx J_{5b,NH} \approx$ 4.7 Hz, $J_{5a,5b}$ = 15.3 Hz, H-5b), 1.49 (s, 9H, Boc).



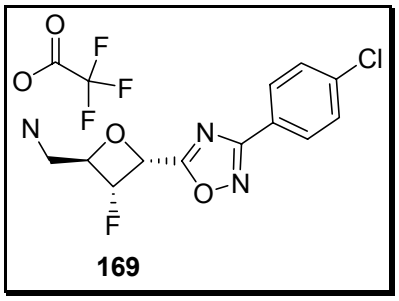
167

5-[(2*S*,3*R*,4*R*)-5-Amonium-3-fluoro-oxetan-2-yl]-3-phenyl-1,2,4-oxadiazole Trifluoroacetate (167). Starting with **162** (144.6 mg, 0.41 mmol) using general procedure 4.3.1.2 (reaction time 5 h), and after recrystallisation with MeOH/DCM/n-Hex, the title compound was obtained as a colourless solid (141.4 mg, 0.39 mmol, 94%). $[\alpha]_D^{19.8}$-37.48 (*c* 0.984, MeOH). MS: (ionspray) m/z 250.1 $[M\text{-}TFA+H]^+$, 272.4 $[M\text{-}TFA+Na]^+$. ^{1}H NMR (300 MHz, MeOD): δ 8.02-7.98 (m, 2H, Ph), 7.49-7.42 (m, 3H, Ph), 6.08 (ddd, 1H, $J_{2,3}$ = 6.5 Hz, $J_{2,4}$ = 1.0 Hz, $J_{2,F}$ = 12.2 Hz, H-2), 5.53 (ddd, 1H, $J_{3,4}$ = 5.0 Hz, $J_{3,F}$ = 54.3 Hz, H-3), 5.36 (dqd, 1H, $J_{3,4} \approx J_{4,5a} \approx J_{4,5b} \approx$ 5.0 Hz, $J_{4,F}$ = 18.3 Hz, H-4), 3.40-3.37 (m, 2H, H-5a, H-5b).



168

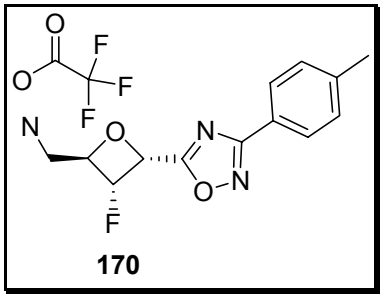
5-[(2*S*,3*R*,4*R*)-5-Amonium-3-fluoro-oxetan-2-yl]-3-*p*-methoxyphenyl-1,2,4-oxadiazole Trifluoroacetate (168). Starting with **163** (165.2 mg, 0.43 mmol) using general procedure 4.3.1.2 (reaction time 5 h), and after recrystallisation with MeOH/DCM/n-Hex, the title compound was obtained as colourless solid (107.7 mg, 0.27 mmol, 63%). $[\alpha]_D^{20.0}$ -47.62 (*c* 0.754, MeOH). MS: (ionspray) m/z 280.3 [M-TFA+H]$^+$, 302.4 [M-TFA+Na]$^+$. ^{1}H NMR (300 MHz, MeOD): δ 7.93 (br d, J = 8.9 Hz, 2H, Ph), 6.98 (br d, 2H, Ph), 6.05 (ddd, 1H, $J_{2,3}$ = 6.5 Hz, $J_{2,4}$ = 1.0 Hz, $J_{2,F}$ = 12.1 Hz, H-2), 5.63 (ddd, 1H, $J_{3,4}$ = 5.0 Hz, $J_{3,F}$ = 54.3 Hz, H-3), 5.35 (dqd, 1H, $J_{3,4} \approx J_{4,5a} \approx J_{4,5b} \approx$ 5.0 Hz, $J_{4,F}$ = 18.2 Hz, H-4), 3.78 (s, 3H, OMe), 3.39-3.37 (m, 2H, H-5a, H-5b).



169

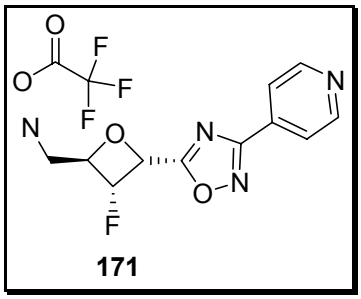
5-[(2*S*,3*R*,4*R*)-5-Amonium-3-fluoro-oxetan-2-yl]-3-*p*-chlorophenyl-1,2,4-oxadiazole Trifluoroacetate (169). Starting with **164** (200.3 mg, 0.52 mmol) using general procedure 4.3.1.2 (reaction time 5 h), and after recrystallisation with MeOH/DCM/n-Hex, the title compound was obtained as colourless solid (155.1 mg, 0.39 mmol, 75%). $[\alpha]_D^{20.0}$ -43.95 (*c* 0.876, MeOH). MS: (ionspray) m/z 284.0 [M-TFA+H]$^+$, 306.0 [M-TFA+Na]$^+$. ^{1}H NMR (300 MHz, MeOD): δ 7.99 (br d, J = 8.6 Hz, 2H, Ph), 7.48 (br d, 2H, Ph), 6.08 (ddd, 1H, $J_{2,3}$ = 6.4 Hz, $J_{2,4}$ = 0.6 Hz, $J_{2,F}$ = 12.2

Hz, H-2), 5.64 (ddd, 1H, $J_{3,4}$ = 5.1 Hz, $J_{3,F}$ = 54.3 Hz, H-3), 5.35 (dqd, 1H, $J_{3,4} \approx J_{4,5a} \approx J_{4,5b} \approx$ 5.1 Hz, $J_{4,F}$ = 18.5 Hz, H-4), 3.39-3.37 (m, 2H, H-5a, H-5b). Anal. Calcd. for $C_{14}H_{12}ClF_4N_3O_4$ (397.71): C, 42.28; H, 3.04; N, 10.57. Found: C, 42.05; H, 3.00; N, 10.57.



170

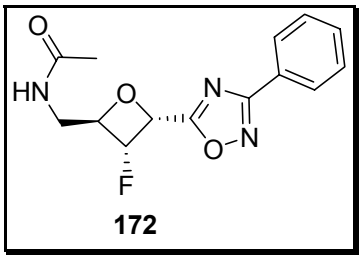
5-[(2*S*,3*R*,4*R*)-5-Amonium-3-fluoro-oxetan-2-yl]-3-*p*-methylphenyl-1,2,4-oxadiazole Trifluoroacetate (170). Starting with **165** (158.0 mg, 0.43 mmol) using general procedure 4.3.1.2 (reaction time 5 h), and after recrystallisation with MeOH/DCM/n-Hex, the title compound was obtained as colourless solid (125.1 mg, 0.33 mmol, 76%). $[\alpha]_D^{20.0}$ -48.59 (*c* 0.792, MeOH). MS: (ionspray) m/z 264.3 [M-TFA+H]$^+$, 286.1 [M-TFA+Na]$^+$. ^{1}H NMR (300 MHz, MeOD) δ 7.88 (br d, J = 8.3 Hz, 2H, Ph), 7.27 (br d, 2H, Ph), 6.06 (ddd, 1H, $J_{2,3}$ = 6.5 Hz, $J_{2,4}$ = 0.9 Hz, $J_{2,F}$ = 12.2 Hz, H-2), 5.63 (ddd, 1H, $J_{3,4}$ = 5.0 Hz, $J_{3,F}$ = 54.3 Hz, H-3), 5.35 (dqd, 1H, $J_{3,4} \approx J_{4,5a} \approx J_{4,5b} \approx$ 5.0 Hz, $J_{4,F}$ = 18.2 Hz, H-4), 3.39-3.37 (m, 2H, H-5a, H-5b), 2.33 (s, 3H, Me(Ph)).



171

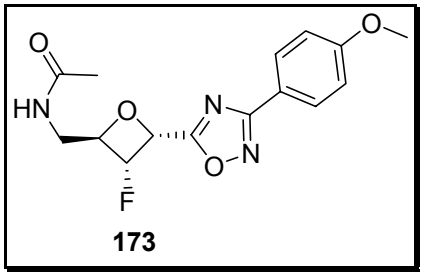
5-[(2*S*,3*R*,4*R*)-5-Amonium-3-fluoro-oxetan-2-yl]-3-pyridinyl-1,2,4-oxadiazole Trifluoroacetate (171). Starting with **166** (120.0 mg, 0.34 mmol) using general

procedure 4.3.1.2 (reaction time 5 h), and after recrystallisation with MeOH/DCM/n-Hex, the title compound was obtained as a light yellow solid (110.6 mg, 0.30 mmol, 89%). $[\alpha]_D^{20.0}$ -38.04 (*c* 0.831, MeOH). MS: (ionspray) m/z 251.1 $[M\text{-}TFA+H]^+$. ^1H NMR (300 MHz, MeOD): δ 8.69-8.67 (m, 2H, Ph), 8.00-7.98 (m, 2H, Ph), 6.12 (ddd, 1H, $J_{2,3}$ = 6.5 Hz, $J_{2,4}$ = 0.9 Hz, $J_{2,F}$ = 12.2 Hz, H-2), 5.66 (ddd, 1H, $J_{3,4}$ = 5.0 Hz, $J_{3,F}$ = 54.2 Hz, H-3), 5.36 (dqd, 1H, $J_{3,4} \approx J_{4,5a} \approx J_{4,5b} \approx$ 5.0 Hz, $J_{4,F}$ = 18.4 Hz, H-4), 3.39-3.37 (m, 2H, H-5a, H-5b).



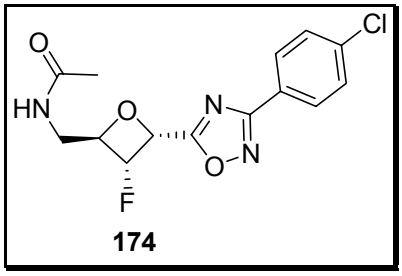
172

5-[(2*S*,3*R*,4*R*)-5-*N*-Acetyl-amino-3-fluoro-oxetan-2-yl]-3-phenyl-1,2,4-oxadiazole (172). Starting with **167** (57.2 mg, 0.16 mmol) using general procedure 4.3.1.3 (reaction time overnight), and after flash chromatography using heptane/EtOAc gradient, the title compound was obtained as colourless solid (32.7 mg, 0.112 mmol, 71%). $[\alpha]_D^{20.0}$ -92.46 (*c* 0.787, $CHCl_3$). MS: (ionspray) m/z 292.1 $[M+H]^+$, 314.0 $[M+Na]^+$. ^1H NMR (300 MHz, $CDCl_3$): δ 8.13-8.10 (m, 2H, Ph), 7.52-7.49 (m, 3H, Ph), 5.94 (br dd, 2H, $J_{2,3}$ = 6.1 Hz, $J_{2,F}$ = 11.6 Hz, H-2, NH), 5.51 (br dt, 1H, $J_{3,4} \approx$ 5.7 Hz, $J_{3,F}$ = 54.9 Hz, H-3), 5.37 (br dq, 1H, H-4), 3.84 (ddd, 1H, $J_{4,5a}$ = 4.5 Hz, $J_{5a,NH}$ = 6.1 Hz, $J_{5a,5b}$ = 14.9 Hz, H-5a), 3.64 (dt, 1H, $J_{4,5b} \approx J_{5b,NH} \approx$ 4.6 Hz, H-5b), 2.09 (s, 3H, Me(Ac)). Anal. Calcd. for $C_{14}H_{14}FN_3O_3$ (291.28): C, 57.73; H, 4.84; N, 14.43. Found: C, 57.52; H, 4.78; N, 14.11.



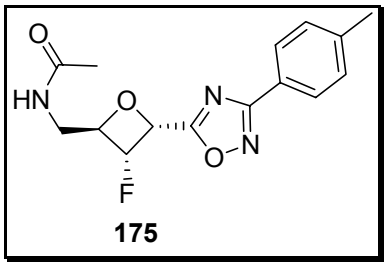
173

5-[(2*S*,3*R*,4*R*)-5-*N*-Acetyl-amino-3-fluoro-oxetan-2-yl]-3-*p*-methoxyphenyl-1,2,4-oxadiazole (173). Starting with **168** (40.0 mg, 0.102 mmol) using general procedure 4.3.1.3 (reaction time 3 h), and after flash chromatography using heptane/EtOAc gradient, the title compound was obtained as colourless solid (32.1 mg, 0.100 mmol, 98%). $[\alpha]_D^{20.0}$ -76.42 (*c* 0.781, $CHCl_3$). MS: (ionspray) m/z 322.2 $[M+H]^+$, 344.1$[M+Na]^+$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.06 (br d, J = 8.7 Hz, 2H, Ph), 7.00 (br d, 2H, Ph), 5.92 (br dd, 2H, $J_{2,3}$ = 5.9 Hz, $J_{2,F}$ = 11.5 Hz, H-2, NH), 5.51 (br dt, 1H, $J_{3,4}$ = 5.9 Hz, $J_{3,F}$ = 54.9 Hz, H-3), 5.36 (br dq, 1H, H-4), 3.88-3.80 (m, 4H, H-5a, OMe), 3.64 (dt, 1H, $J_{4,5b} \approx J_{5b,NH} \approx$ 4.6 Hz, $J_{5a,5b}$ = 15.0 Hz, H-5b), 2.09 (s, 3H, Me(Ac)).



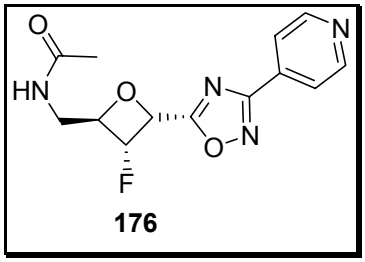
174

5-[(2*S*,3*R*,4*R*)-5-*N*-Acetyl-amino-3-fluoro-oxetan-2-yl]-3-*p*-chlorophenyl-1,2,4-oxadiazole (174). Starting with **169** (49.6 mg, 0.124 mmol) using general procedure 4.3.1.3 (reaction time 3 h), and after flash chromatography using heptane/EtOAc gradient, the title compound was obtained as colourless solid (40.0 mg, 0.123 mmol, 98%). $[\alpha]_D^{20.0}$ -77.85 (*c* 0.787, $CHCl_3$). MS: (ionspray) m/z 326.1$[M+H]^+$, 348.2$[M+Na]^+$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.07 (br d, J = 8.6 Hz, 2H, Ph), 7.48 (br d, 2H, Ph), 5.93 (br dd, 2H, $J_{2,3}$ = 6.5 Hz, $J_{2,F}$ = 11.6 Hz, H-2, NH), 5.52 (br dt, 1H, $J_{3,4}$ = 5.0 Hz, $J_{3,F}$ = 54.6 Hz, H-3), 5.36 (br dq, 1H, $J_{4,F}$ = 17.8 Hz, H-4), 3.84 (ddd, 1H, 1H, $J_{4,5a}$ = 4.8 Hz, $J_{5a,NH}$ = 6.7 Hz, $J_{5a,5b}$ = 15.0 Hz, H-5a), 3.64 (dt, 1H, $J_{4,5b} \approx J_{5b,NH} \approx$ 4.8 Hz, H-5b), 2.09 (s, 3H, Me(Ac)). Anal. Calcd. for $C_{14}H_{13}ClFN_3O_3$ (325.73): C, 51.62; H, 4.02; N, 12.90. Found: C, 51.74; H, 4.03; N, 12.30.



175

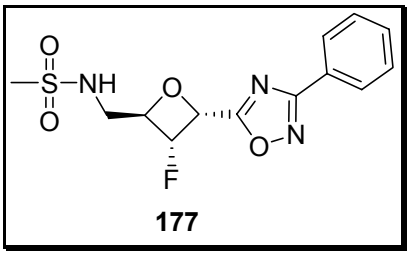
5-[(2*S*,3*R*,4*R*)-5-*N*-Acetyl-amino-3-fluoro-oxetan-2-yl]-3-*p*-methylphenyl-1,2,4-oxadiazole (175). Starting with **170** (32.1 mg, 0.085 mmol) using general procedure 4.3.1.3 (reaction time 3 h), and after flash chromatography using heptane/EtOAc gradient, the title compound was obtained as a light yellow solid (23.5 mg, 0.077 mmol, 91%). $[\alpha]_D^{20.0}$ -81.55 (*c* 0.820, $CHCl_3$). MS: (ionspray) m/z 306.2 $[M+H]^+$, 328.2 $[M+Na]^+$. ^1H NMR (300 MHz, $CDCl_3$): δ 8.00 (br d, J = 8.2 Hz, 2H, Ph), 7.30 (br d, 2H, Ph), 6.14 (br t , 1H, NH), 5.93 (ddd, 1H, $J_{2,3}$ = 6.6 Hz, $J_{2,4}$ = 0.8 Hz, $J_{2,F}$ = 11.8 Hz, H-2), 5.51 (ddd, 1H, $J_{3,4}$ = 5.0 Hz, $J_{3,F}$ = 54.7 Hz, H-3), 5.35 (br dq, 1H, $J_{4,F}$ = 18.0 Hz, H-4), 3.82 (ddd, 1H, 1H, $J_{4,5a}$ = 5.0 Hz, $J_{5a,NH}$ = 6.7 Hz, $J_{5a,5b}$ = 15.0 Hz, H-5a), 3.63 (ddd≈dt, 1H, $J_{4,5b} \approx J_{5b,NH} \approx$ 5.0 Hz, H-5b), 2.42 (s, 3H, Me(Ph)), 2.08 (s, 3H, Me(Ac)).



176

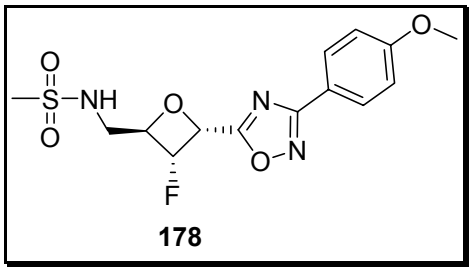
5-[(2*S*,3*R*,4*R*)-5-*N*-Acetyl-amino-3-fluoro-oxetan-2-yl]-3-pyridinyl-1,2,4-oxadiazole (176). Starting with **171** (37.0 mg, 0.102 mmol) using general procedure 4.3.1.3 (reaction time 3 h), and after flash chromatography using heptane/EtOAc gradient, the title compound was obtained as a white solid (29.3 mg, 0.101 mmol, 99%). $[\alpha]_D^{20.0}$ -79.23 (*c* 0.746, $CHCl_3$). MS: (ionspray) m/z 293.1 $[M+H]^+$, 315.0 $[M+Na]^+$. ^1H NMR (300 MHz, MeOD): δ 8.68-8.66 (m, 2H, Ph), 8.00-7.98 (m, 2H, Ph), 6.01 (ddd, 1H, $J_{2,3}$ = 6.5 Hz, $J_{2,4}$ = 0.9 Hz, $J_{2,F}$ = 12.4 Hz, H-2), 5.50 (ddd, 1H, $J_{3,4}$ =

5.0 Hz, $J_{3,F}$ = 55.0 Hz, H-3), 5.15 (br dq, 1H, $J_{4,F}$ = 19.0 Hz, H-4), 3.62 (A(ABX), 1H, 1H, $J_{4,5a}$ = 5.0 Hz, $J_{5a,5b}$ = 14.7 Hz, H-5a), 3.46 (B(ABX), 1H, $J_{4,5b}$ = 5.0 Hz, H-5b), 1.93 (s, 3H, Me(Ac)).



177

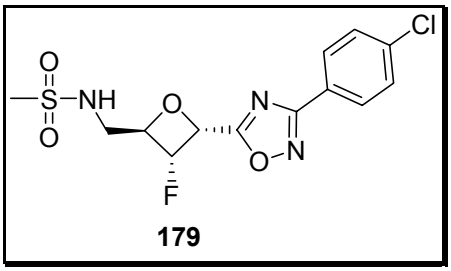
5-[(2*S*,3*R*,4*R*)-5-*N*-Mesyl-amino-3-fluoro-oxetan-2-yl]-3-phenyl-1,2,4-oxadiazole (177). Starting with **167** (43.1 mg, 0.119 mmol) using general procedure 4.3.1.4 (reaction time 1.5 h), and after flash chromatography using heptane/EtOAc gradient, the title compound was obtained as a white solid (28.8 mg, 0.088 mmol, 74%). $[\alpha]_D^{20.0}$ -85.01 (*c* 0.775, $CHCl_3$). MS: (ionspray) m/z 328.2 $[M+H]^+$, 345.0 $[M+NH_4]^+$. ^1H NMR (300 MHz, $CDCl_3$): δ 8.13-8.11 (m, 2H, Ph), 7.51-7.49 (m, 3H, Ph), 5.99 (dd, 1H, $J_{2,3}$ = 6.4 Hz, $J_{2,F}$ = 11.6 Hz, H-2), 5.75 (br dt, 1H, $J_{3,4} \approx$ 5.0 Hz, $J_{3,F}$ = 54.8 Hz, H-3), 5.42 (br dd, 1H, $J_{4,F}$ = 17.5 Hz, H-4), 5.04 (br t, 1H, NH), 3.64-3.54 (m, 2H, H-5a, H-5b), 3.07 (s, 3H, Me(Ms)). Anal. Calcd. for $C_{13}H_{14}FN_3O_4$ (327.34): C, 47.70; H, 4.31; N, 12.84. Found: C, 47.73; H, 4.31; N, 12.53.



178

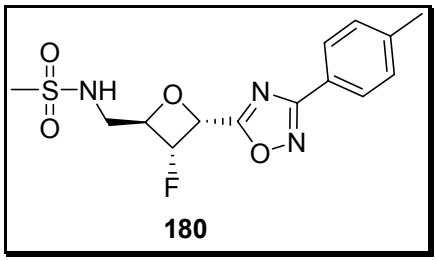
5-[(2*S*,3*R*,4*R*)-5-*N*-Mesyl-amino-3-fluoro-oxetan-2-yl]-3-*p*-methoxyphenyl-1,2,4-oxadiazole (178). Starting with **168** (40.0 mg, 0.102 mmol) using general procedure 4.3.1.4 (reaction time 2 h), and after flash chromatography using heptane/EtOAc gradient, the title compound was obtained as a colourless solid (34.8 mg, 0.097 mmol, 96%). $[\alpha]_D^{20.0}$ -72.32 (*c* 0.781, $CHCl_3$). MS: (ionspray) m/z 358.3 $[M+H]^+$, 380.1

$[M+Na]^+$. ^1H NMR (300 MHz, $CDCl_3$) δ 8.06 (br d, J = 8.6 Hz, 2H, Ph), 7.00 (br d, 2H, Ph), 5.96 (dd, 1H, $J_{2,3}$ = 6.6 Hz, $J_{2,F}$ = 11.6 Hz, H-2), 5.75 (ddd, 1H, $J_{3,4}$ = 5.1 Hz, $J_{3,F}$ = 54.8 Hz, H-3), 5.42 (dq, 1H, $J_{4,F}$ = 17.3 Hz, H-4), 4.88 (br t, 1H, NH), 3.87 (s, 3H, OMe), 3.67-3.52 (m, 2H, H-5a, H-5b), 3.07 (s, 3H, Me(Ms)).



179

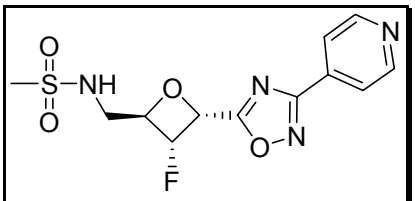
5-[(2*S*,3*R*,4*R*)-5-*N*-Mesyl-amino-3-fluoro-oxetan-2-yl]-3-*p*-chlorophenyl-1,2,4-oxadiazole (179). Starting with **169** (50.0 mg, 0.126 mmol) using general procedure 4.3.1.4 (reaction time 2 h), and after flash chromatography using heptane/EtOAc gradient, the title compound was obtained as a colourless solid (38.0 mg, 0.105 mmol, 84%). $[\alpha]_D^{20.0}$ -68.37 (*c* 0.775, $CHCl_3$). MS: (ionspray) m/z 362.1 $[M+H]^+$, 384.1 $[M+Na]^+$. ^1H NMR (300 MHz, $CDCl_3$): δ 8.07 (br d, J = 8.5 Hz, 2H, Ph), 7.48 (br d, 2H, Ph), 5.98 (ddd, 1H, $J_{2,3}$ = 6.5 Hz, $J_{2,4}$ = 0.7 Hz, $J_{2,F}$ = 11.6 Hz, H-2), 5.77 (ddd, 1H, $J_{3,4}$ = 5.0 Hz, $J_{3,F}$ = 54.8 Hz, H-3), 5.42 (br dq, 1H, $J_{4,F}$ = 17.4 Hz, H-4), 4.92 (br t, 1H, NH), 3.67-3.53 (m, 2H, H-5a, H-5b), 3.08 (s, 3H, Me(Ms)). Anal. Calcd. for $C_{13}H_{13}ClFN_3O_4S$ (361.78): C, 43.16; H, 3.62; N, 11.61. Found: C, 42.89; H, 3.69; N, 11.31.



180

5-[(2*S*,3*R*,4*R*)-5-*N*-Mesyl-amino-3-fluoro-oxetan-2-yl]-3-*p*-methylphenyl-1,2,4-oxadiazole (180). Starting with **170** (35.9 mg, 0.095 mmol) using general procedure 4.3.1.4 (reaction time 2 h), and after flash chromatography using heptane/EtOAc

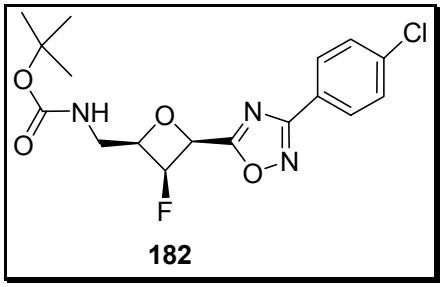
gradient, the title compound was obtained as a white solid (17.7 mg, 0.052 mmol, 55%). $[\alpha]_D^{20.0}$ -69.25 (*c* 0.742, $CHCl_3$). MS: (ionspray) m/z 342.1 $[M+H]^+$, 364.1 $[M+Na]^+$. ^1H NMR (300 MHz, $CDCl_3$): δ 8.00 (br d, J = 8.1 Hz, 2H, Ph), 7.30 (br d, 2H, Ph), 5.98 (dd, 1H, $J_{2,3}$ = 6.5 Hz, $J_{2,F}$ = 11.8 Hz, H-2), 5.74 (ddd, 1H, $J_{3,4}$ = 5.0 Hz, $J_{3,F}$ = 54.7 Hz, H-3), 5.41 (br dq, 1H, $J_{4,F}$ = 17.6 Hz, H-4), 5.14 (t, 1H, $J_{5a,NH} \approx J_{5b,NH} \approx$ 6.2 Hz, NH), 3.60-3.56 (m, 2H, H-5a, H-5b), 3.07 (s, 3H, Me(Ms)), 2.42 (s, 3H, Me(Ph)).



181

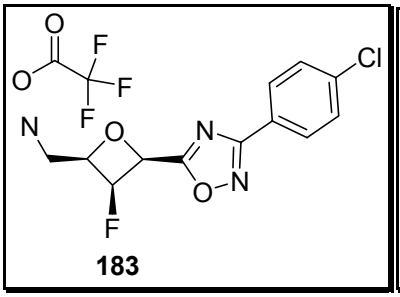
5-[(2*S*,3*R*,4*R*)-5-*N*-Mesyl-amino-3-fluoro-oxetan-2-yl]-3-*p*-pyridinyl-1,2,4-oxadiazole (181). Starting with **171** (23.8 mg, 0.065 mmol) using general procedure 3.1.5. (reaction time 3 h), and after flash chromatography using heptane/EtOAc gradient, the title compound was obtained as a colourless solid (15.4 mg, 0.047 mmol, 72%). $[\alpha]_D^{20.0}$ -71.34 (*c* 0.758, $CHCl_3$). MS: (ionspray) m/z 329.2 $[M+H]^+$. ^1H NMR (300 MHz, $CDCl_3$): 8.80 (d, 2H, J = 5.9 Hz, Py), 8.13 (br d, 2H, Py), 6.02 (dd, 1H, $J_{2,3}$ = 6.3 Hz, $J_{2,F}$ = 11.6 Hz, H-2), 5.73 (ddd, 1H, $J_{3,4}$ = 5.0 Hz, $J_{3,F}$ = 54.5 Hz, H-3), 5.43 (br dq, 1H, $J_{4,F}$ = 17.6 Hz, H-4), 5.17 (t, 1H, $J_{5a,NH} \approx J_{5b,NH} \approx$ 6.1 Hz, NH), 3.62-3.57 (m, 2H, H-5a, H-5b), 3.06 (s, 3H, Me(Ms)).

4.3.2.5 Derivatisation of 2,4-Anhydro-5-N-(*tert*-butoxycarbonyl)amino-3-fluoro-D-*xylonic* acid (91)

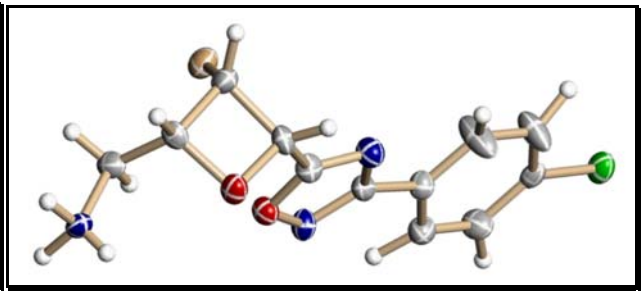


182

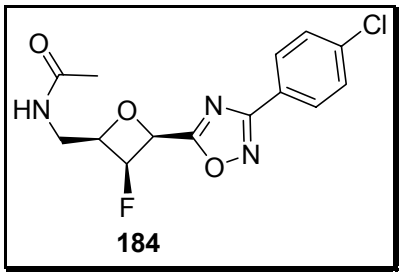
5-[(2*R*,3*S*,4*R*)-5-*N*-(*tert*-Butoxycarbonyl)amino-3-fluoro-oxetan-2-yl]-3-*p*-chlorophenyl-1,2,4-oxadiazole (182). Starting with **91** (81.3 mg, 0.326 mmol) using general procedure 4.3.1.1 (cyclisation time 4 h), and after flash chromatography using heptane/EtOAc gradient, the title compound was obtained as a colourless solid (98.1 mg, 0.256 mmol, 79%). $[\alpha]_D^{20.0}$ 57.04 (*c* 0.569, $CHCl_3$). MS: (ionspray) m/z 328.1 $[M\text{-}t\text{Bu}+H]^+$, 384.1 $[M+H]^+$, 406.2 $[M+Na]^+$. H^1 NMR (300 MHz, $CDCl_3$): δ 8.07 (d, 2H, J = 8.4 Hz, Ph), 7.48 (d, 2H, Ph), 6.11 (dd, 1H, $J_{2,3}$ = 5.9 Hz, $J_{2,F}$ = 16.0 Hz, H-2), 5.78 (dt, 1H, $J_{2,3} \approx J_{3,4} \approx$ 5.9 Hz, $J_{3,F}$ = 55.9 Hz, H-3), 5.23-5.08 (m, 2H, H-4, NH), 3.89-3.72 (m, 2H, H-5a, H-5b), 1.43 (s, 9H, Boc). HRMS (NSI) *m/z* 384.11195 $[M+H]^+$, calcd. 384.11209 for $C_{17}H_{20}ClFN_3O_4$.



183

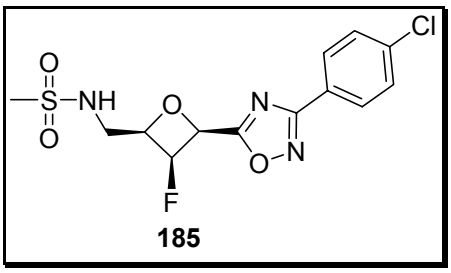


5-[(2*R*,3*S*,4*R*)-5-Amonium-3-fluoro-oxetan-2-yl]-3-*p*-chlorophenyl-1,2,4-oxadiazole Trifluoroacetate (183). Starting with **182** (79.2 mg, 0.206 mmol) using general procedure 4.3.1.2 (reaction time 7 h), and after recrystallisation with MeOH/Et_2O/n-Hex, the title compound was obtained as colourless crystals (74.2 mg, 0.187 mmol, 90%). m.p. 165.3-165.7 ºC. $[\alpha]_D^{20.0}$ 58.20 (*c* 0.667, MeOH). ^1H NMR (300 MHz, MeOD): δ 8.12 (dt, 2H, J = 8.7 Hz, J = 2.2 Hz, Ph), 7.60 (dt, 2H, Ph), 6.38 (ddd, 1H, $J_{2,3}$ = 5.8 Hz, $J_{2,F}$ = 16.3 Hz, H-2), 6.01 (dt, 1H, $J_{2,3} \approx J_{3,4} \approx$ 5.7 Hz, $J_{3,F}$ = 55.5 Hz, H-3), 5.35 (dddd, 1H, $J_{4,F}$ = 16.1 Hz, H-4), 3.77 (A(ABX), 1H, $J_{4,5a}$ = 8.5 Hz, $J_{5a,5b}$ = 13.8 Hz, H-5a), 3.46 (B(ABX), 1H, $J_{4,5b}$ = 4.2 Hz, H-5b). HRMS (NSI) *m/z* 284.05949 $[M\text{-}TFA+H]^+$, calcd. 284.05966 for $C_{12}H_{12}ClFN_3O_4$.



184

5-[(2*R*,3*S*,4*R*)-5-*N*-Acetyl-amino-3-fluoro-oxetan-2-yl]-3-*p*-chlorophenyl-1,2,4-oxadiazole (184). Starting with **183** (25.8 mg, 0.065 mmol) using general procedure 4.3.1.3 (reaction time 2 h), and after flash chromatography using heptane/EtOAc gradient, the title compound was obtained as colourless solid (17.4 mg, 0.053 mmol, 82%). $[\alpha]_D^{20.0}$ 67.27 (*c* 0.837, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.05 (br d, 2H, J =8.8 Hz, Ph), 7.49 (br d, 2H, Ph), 6.13 (br dd, 2H, $J_{2,3}$ = 5.8 Hz, $J_{2,F}$ = 16.0 Hz, H-2, NH), 5.79 (dt, 1H, $J_{2,3} \approx J_{3,4} \approx$ 5.8 Hz, $J_{3,F}$ = 55.9 Hz, H-3), 5.21 (br dq, 1H, $J_{4,5a} \approx J_{4,5b} \approx$ 5.8 Hz, $J_{4,F}$ = 17.0 Hz, H-4), 3.99-3.85 (m, 2H, H-5a, H-5b), 2.05 (s, 3H, Me(Ac)). HRMS (NSI) *m/z* 326.07007 $[M+H]^+$, calcd. 326.07022 for $C_{14}H_{14}ClFN_3O_3$.

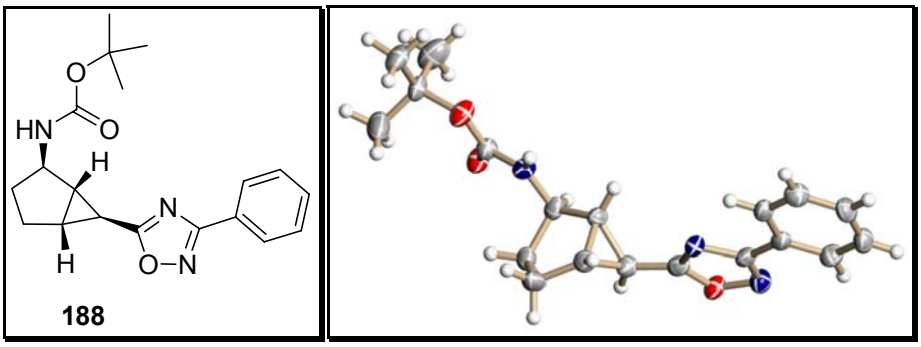


185

5-[(2*R*,3*S*,4*R*)-5-*N*-Mesyl-amino-3-fluoro-oxetan-2-yl]-3-*p*-chlorophenyl-1,2,4-oxadiazole (185). Starting with **183** (28.4 mg, 0.071 mmol) using general procedure 4.3.1.4 (reaction time 2 h), and after flash chromatography using heptane/EtOAc gradient, the title compound was obtained as a colourless solid (21.7 mg, 0.060 mmol, 84%). $[\alpha]_D^{20.0}$ 62.57 (*c* 0.674, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.09 (d, 2H, J = 8.0 Hz, Ph), 7.49 (d, 2H, Ph), 6.15 (dd, 1H, $J_{2,3}$ = 5.9 Hz, $J_{2,F}$ = 15.7 Hz, H-2), 5.84 (dt, 1H, $J_{2,3} \approx J_{3,4} \approx$ 5.9 Hz, $J_{3,F}$ = 55.2 Hz, H-3), 5.30-5.10 (M, 2H, H-4, NH), 3.90-3.73 (m, 2H, H-5a, H-5b), 3.05 (s, 3H, Me(Ms)). HRMS (NSI) *m/z* 362.03702 $[M+H]^+$, calcd. 362.03721 for $C_{13}H_{14}ClFN_3O_4S$.

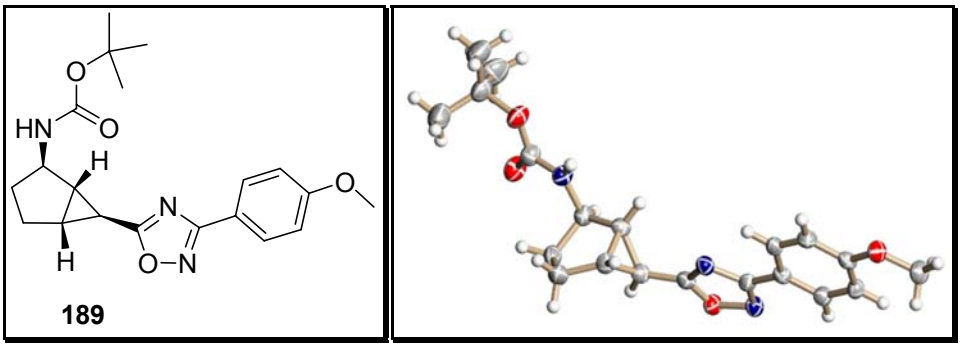
4.3.3 Library Construction on Bicyclic δ-Amino Acid Scaffolds

4.3.3.1 Library on *rac*-(1*S*,2*R*,5*R*,6*S*)-2-(*tert*-Butoxycarbonyl)amino-6-carboxylic acid-bicyclo[3.1.0]hexane (186)



188

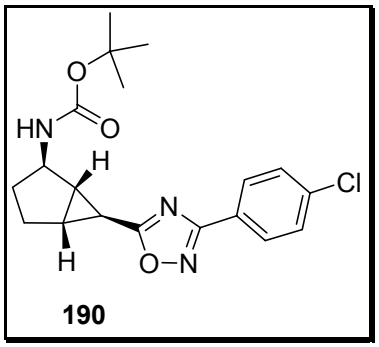
***rac*-(1S,2R,5R,6S)-2-(*tert*-Butoxycarbonyl)amino-6-(3-phenyl-1,2,4-oxadiazol-5-yl)bicyclo[3.1.0]hexane (188).** Starting with **186** (150.0 mg, 0.62 mmol) using general procedure 4.3.1.1 (cyclisation time overnight), and after flash chromatography using heptane/EtOAc gradient, the title compound was obtained as a colourless crystals (113.3 mg, 0.33 mmol, 53%). m.p. 126.3-126.7 ºC. MS: (ionspray) m/z 286.1 $[M\text{-}t\text{-}Bu+H]^+$, 342.2 $[M+H]^+$, 364.2 $[M+Na]^+$. ^1H NMR (300 MHz, $CDCl_3$): δ 8.04-8.01 (m, 2H, Ph), 7.50-7.43 (m, 3H, Ph), 4.62 (br s, 1 H, NH), 4.26 (br s, 1H, H-2), 2.24 (br s, 2H, H-1, H-5), 2.06-1.98 (m, 3H, H-6, H-4a, H-4b), 1.71-1.55 (m, 2H, H-3a, H-3b), 1.46 (s, 9H, Boc).



189

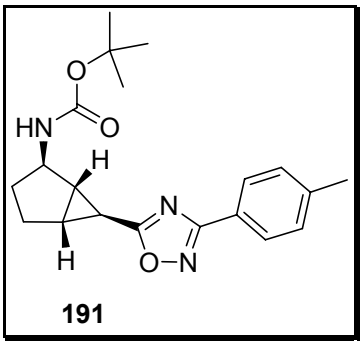
***rac*-(1S,2R,5R,6S)-2-(*tert*-Butoxycarbonyl)amino-6-(3-*p*-methoxyphenyl-1,2,4-oxadiazol-5-yl)bicyclo[3.1.0]hexane (189).** Starting with **186** (50.0 mg, 0.21 mmol)

using general procedure 4.3.1.1 (cyclisation time overnight), and after flash chromatography using heptane/EtOAc gradient, the title compound was obtained as a colourless crystals (51.1 mg, 0.14 mmol, 66%). m.p. 128.8-129.3 ºC. MS: (ionspray) m/z 316.2 $[M\text{-}t\text{-}Bu+H]^+$, 372.3 $[M+H]^+$, 394.2 $[M+Na]^+$. ^1H NMR, COSY, HMQC (300 MHz, $CDCl_3$): δ 7.96 (br d, J = 8.9 Hz, 2H, Ph), 6.96 (br d, 2H, Ph), 4.62 (br s, 1 H, NH), 4.25 (br s, 1H, H-2), 3.86 (s, 3H, OCH_3), 2.22 (br s, 2H, H-1, H-5), 2.04-1.97 (m, 3H, H-6, H-4a, H-4b), 1.70-1.54 (m, 2H, H-3a, H-3b), 1.46 (s, 9H, Boc).



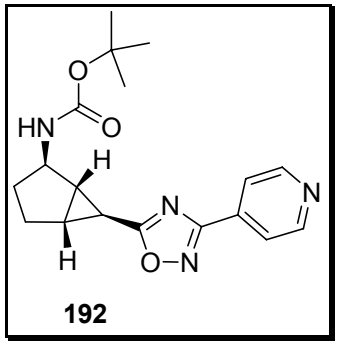
190

***rac*-(1S,2R,5R,6S)-2-(*tert*-Butoxycarbonyl)amino-6-(3-*p*-chlorophenyl-1,2,4-oxadiazol-5-yl)bicyclo[3.1.0]hexane (190).** Starting with **186** (200.0 mg, 0.83 mmol) using general procedure 4.3.1.1 (cyclisation time overnight), and after flash chromatography using heptane/EtOAc gradient, the title compound was obtained as a colourless solid (116.8 mg, 0.31 mmol, 38%). MS: (ionspray) m/z 320.1 $[M\text{-}t\text{-}Bu+H]^+$, 376.4 $[M+H]^+$, 393.3 $[M+NH_4]^+$, 398.3 $[M+Na]^+$. ^1H NMR (300 MHz, $CDCl_3$): δ 7.95 (br d, J = 8.7 Hz, 2H, Ph), 7.44 (br d, 2H, Ph), 4.62 (br s, 1 H, NH), 4.26 (br s, 1H, H-2), 2.23 (br s, 2H, H-1, H-5), 2.05-1.94 (m, 3H, H-6, H-4a, H-4b), 1.71-1.56 (m, 2H, H-3a, H-3b), 1.46 (s, 9H, Boc). Anal. Calcd. for $C_{19}H_{22}ClN_3O_3$ (375.85): C, 60.72; H, 5.90; N, 11.18. Found: C, 60.44; H, 5.91; N, 11.19.



191

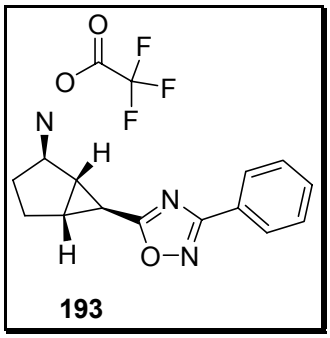
***rac*-(1S,2R,5R,6S)-2-(*tert*-Butoxycarbonyl)amino-6-(3-*p*-methylphenyl-1,2,4-oxadiazol-5-yl)bicyclo[3.1.0]hexane (191).** Starting with **186** (250.0 mg, 1.04 mmol) using general procedure 4.3.1.1 (cyclisation time overnight), and after flash chromatography using heptane/EtOAc gradient, the title compound was obtained as a colourless solid (209.4 mg, 0.59 mmol, 57%). MS: (ionspray) m/z 300.1 [M-*t*-Bu+H]$^+$, 356.2 [M+H]$^+$, 378.3 [M+Na]$^+$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.91 (d, J = 8.2 Hz, 2H, Ph), 7.26 (d, 2H, Ph), 4.62 (br s, 1 H, NH), 4.26 (br s, 1H, H-2), 2.40 (s, 3H, Me(Ph)), 2.23 (br s, 2H, H-1, H-5), 2.05-1.93 (m, 3H, H-6, H-4a, H-4b), 1.68-1.55 (m, 2H, H-3a, H-3b), 1.46 (s, 9H, Boc).



192

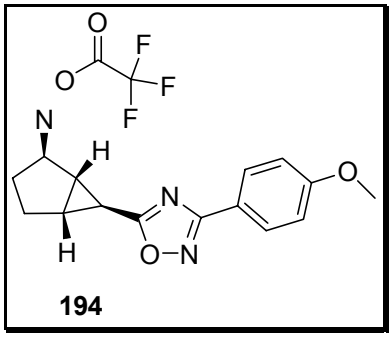
***rac*-(1S,2R,5R,6S)-2-(*tert*-Butoxycarbonyl)amino-6-(3-pyridinyl-1,2,4-oxadiazol-5-yl)bicyclo[3.1.0]hexane (192).** Starting with **186** (250.0 mg, 1.04 mmol) using general procedure 4.3.1.1 (cyclisation time overnight), and after flash chromatography using heptane/EtOAc gradient, the title compound was obtained as a colourless solid (203.1 mg, 0.59 mmol, 57%). MS: (ionspray) m/z 287.1 [M-*t*-Bu+H]$^+$, 343.2 [M+H]$^+$, 365.3 [M+Na]$^+$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.77-8.75 (m, 2H, Ph), 7.90-7.88 (m, 2H, Ph), 4.65 (br s, 1H, NH), 4.27 (br s, 1H, H-2), 2.26 (br s,

2H, H-1, H-5), 2.10-1.96 (m, 3H, H-6, H-4a, H-4b), 1.72-1.56 (m, 2H, H-3a, H-3b), 1.46 (s, 9H, Boc).



193

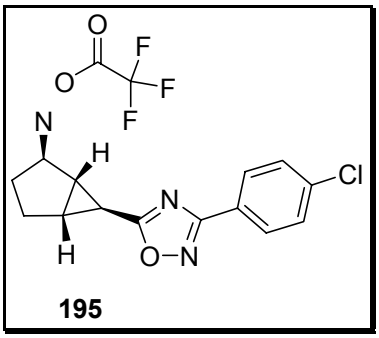
***rac*-(1S,2R,5R,6S)-2-Amonium-6-(3-phenyl-1,2,4-oxadiazol-5-yl)bicyclo[3.1.0]hexane Trifluoroacetate (193).** Starting with **188** (113.3 mg, 0.33 mmol) using general procedure 4.3.1.2 (reaction time 6 h), and after crystallization with DCM/n-Hex the title compound was obtained as a white solid (72.8 mg, 0.20 mmol, 62%). MS: (ionspray) m/z 242.3 $[M\text{-}TFA+H]^+$. ^1H NMR (300 MHz, $CDCl_3$): δ 8.04-8.01 (m, 2H, Ph), 7.57-7.50 (m, 3H, Ph), 3.94-3.91 (m, 1H, H-2), 2.44-2.33 (m, 3H, H-1, H-5, H-6), 2.31-2.09 (m, 2H, H-4a, H-4b), 1.94-1.83 (m, 2H, H-3a, H-3b).



194

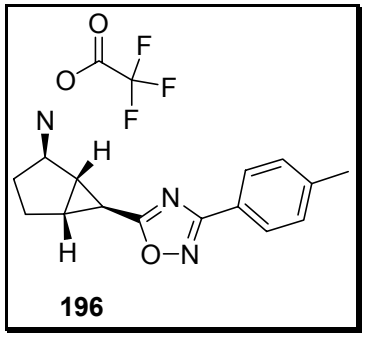
***rac*-(1S,2R,5R,6S)-2-Amonium-6-(3-*p*-methoxyphenyl-1,2,4-oxadiazol-5-yl)bicyclo[3.1.0]hexane Trifluoroacetate (194).** Starting with **189** (128.0 mg, 0.38 mmol) using general procedure 4.3.1.2 (reaction time 6 h), and after recrystallisation with DCM/ n-Hex the title compound was obtained as a colourless solid (129.1 mg, 0.33 mmol, 89%). MS: (ionspray) m/z 272.1 $[M\text{-}TFA+H]^+$. ^1H NMR (300 MHz, $CDCl_3$): δ 7.84 (br d, J = 8.8 Hz, 2H, Ph), 6.94 (br d, 2H, Ph), 3.80-3.76 (m, 4H, H-2,

OMe), 2.28-2.20 (m, 3H, H-1, H-5, H-6), 2.16-1.94 (m, 2H, H-4a, H-4b), 1.79-1.71 (m, 2H, H-3a, H-3b).



195

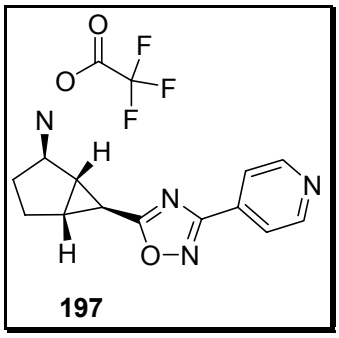
***rac*-(1S,2R,5R,6S)-2-Amonium-6-(3-*p*-chlorophenyl-1,2,4-oxadiazol-5-yl)bicyclo[3.1.0]hexane Trifluoroacetate (195).** Starting with **190** (110.0 mg, 0.293 mmol) using general procedure 4.3.1.2 (reaction time 5 h), and after recrystallisation with DCM/n-Hex the title compound was obtained as a colourless solid (112.3 mg, 0.288 mmol, 98%). MS: (ionspray) m/z 276.1 $[M\text{-}TFA+H]^+$. ^1H NMR (300 MHz, $CDCl_3$): δ 7.90 (br d, J = 8.5 Hz, 2H, Ph), 7.43 (br d, 3H, Ph), 3.80 (br d, 1H, H-2), 2.30-2.22 (m, 2H, H-1, H-5), 2.18-1.96 (m, 3H, H-6, H-4a, H-4b), 1.79-1.74 (m, 2H, H-3a, H-3b). Anal. Calcd. for $C_{16}H_{15}ClF_3N_3O_3$ (389.76): C, 49.31; H, 3.88; N, 10.78. Found: C, 49.11; H, 3.90; N, 10.71.



196

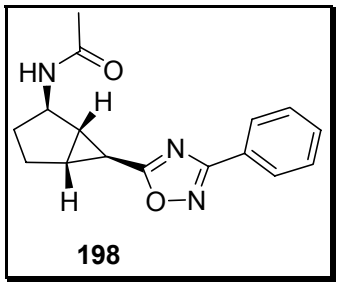
***rac*-(1S,2R,5R,6S)-2-Amonium-6-(3-*p*-methylphenyl-1,2,4-oxadiazol-5-yl)bicyclo[3.1.0]hexane Trifluoroacetate (196).** Starting with **191** (165.0 mg, 0.46 mmol) using general procedure 4.3.1.2 (reaction time 5 h), and after recrystallisation with DCM/n-Hex the title compound was obtained as colourless crystals (131.2 mg,

0.36 mmol, 77%). m.p. 218.9-219.4 ºC. MS: (ionspray) m/z 256.4 $[M\text{-}TFA+H]^+$. ^1H NMR (300 MHz, $CDCl_3$): δ 7.91 (br d, J = 8.2 Hz, 2H, Ph), 7.34 (br d, 2H, Ph), 3.92 (br d, 1H, H-2), 2.45-2.32 (m, 6H, H-1, H-5, H-6, Me(Ph)), 2.28-2.06 (m, 2H, H-4a, H-4b), 1.93-1.82 (m, 2H, H-3a, H-3b).



197

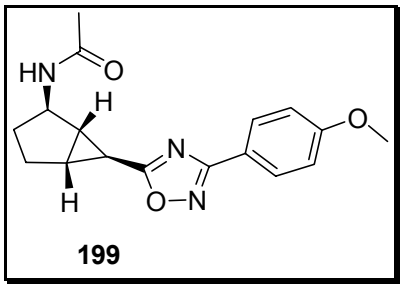
***rac*-(1S,2R,5R,6S)-2-Amonium-6-(3-pyridinyl-1,2,4-oxadiazol-5-yl)bicyclo[3.1.0]hexane Trifluoroacetate (197).** Starting with **192** (125.0 mg, 0.365 mmol) using general procedure 4.3.1.2 (reaction time 5 h), and after recrystallisation with EtOAc/n-Hex the title compound was obtained as a colourless solid (117.2 mg, 0.329 mmol, 90%). MS: (ionspray) m/z 243.1 $[M\text{-}TFA+H]^+$. ^1H NMR (300 MHz, $CDCl_3$): δ 8.65-8.63 (m, 2H, Py), 7.94-7.92 (m, 2H, Py), 3.81 (br d, 1H, H-2), 2.36 (t, 1H, $J_{1,6} \approx J_{5,6} \approx 3.2$ Hz, H-6), 2.33-2.24 (m, 2H, H-1, H-5), 2.20-1.97 (m, 2H, H-4a, H-4b), 1.81-1.73 (m, 2H, H-3a, H-3b).



198

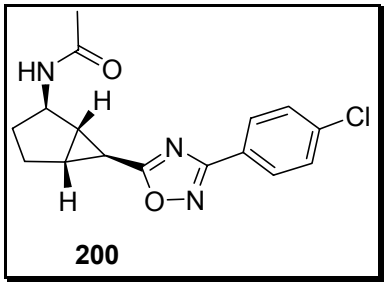
***rac*-(1S,2R,5R,6S)-2-*N*-Acetyl-amino-6-(3-*p*-methoxyphenyl-1,2,4-oxadiazol-5-yl)bicyclo[3.1.0]hexane (198).** Starting with **193** (35.0 mg, 0.099 mmol) using general procedure 4.3.1.3 (reaction time 2 h), and after flash chromatography using heptane/EtOAc gradient, the title compound was obtained as a white solid (27.9 mg,

0.098 mmol, 99%). MS: (ionspray) m/z 284.1 $[M+H]^+$. ^1H NMR (300 MHz, $CDCl_3$): δ 8.06-7.97 (m, 2H, Ph), 7.53-7.41 (m, 3H, Ph), 5.70 (br s, 1 H, NH), 4.52 (t, 1H, $J_{2,3}$ = 6.3 Hz, H-2), 2.25 (br s, 2H, H-1, H-5), 2.12-1.95 (m, 6H, H-4a, H-4b, H-6, CH_3 (Ac)), 1.73-1.57 (m, 2H, H-3a, H-3b).



199

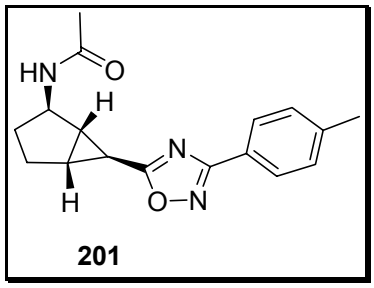
***rac*-(1S,2R,5R,6S)-2-*N*-Acetyl-amino-6-(3-*p*-methoxyphenyl-1,2,4-oxadiazol-5-yl)bicyclo[3.1.0]hexane (199).** Starting with **194** (40.0 mg, 0.104 mmol) using general procedure 4.3.1.3 (reaction time 2 h), and after flash chromatography using heptane/EtOAc gradient, the title compound was obtained as a white waxy solid (32.3 mg, 0.103 mmol, 99%). MS: (ionspray) m/z 314.0 $[M+H]^+$, 336.3 $[M+Na]^+$. ^1H NMR, COSY, HMQC (300 MHz, $CDCl_3$): δ 7.96 (br d, J = 8.9 Hz, 2H, Ph), 6.98-6.95 (m, 2H, Ph), 5.57 (br d, 1 H, $J_{2,NH}$ = 6.8 Hz, NH), 4.52 (t, 1H, $J_{2,3}$ = 6.7 Hz, H-2), 3.86 (s, 3H, OCH_3), 2.23-2.20 (m, 2H, H-1, H-5), 2.06 (t, 1H, $J_{5,6} \approx J_{1,6} \approx$ 2.7 Hz), 2.04-2.00 (m, 5H, H-4a, H-4b, CH_3 (Ac)), 1.73-1.53 (m, 2H, H-3a, H-3b).



200

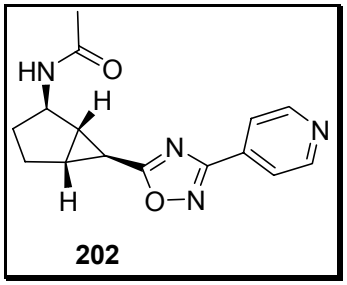
***rac*-(1S,2R,5R,6S)-2-*N*-Acetyl-amino-6-(3-*p*-chlorophenyl-1,2,4-oxadiazol-5-yl)bicyclo[3.1.0]hexane (200).** Starting with **195** (40.0 mg, 0.103 mmol) using general procedure 4.3.1.3 (reaction time 2 h), and after flash chromatography using heptane/EtOAc gradient, the title compound was obtained as a colourless solid (31.3

mg, 0.099 mmol, 96%). MS: (ionspray) m/z 318.1 $[M+H]^+$. ^1H NMR (300 MHz, $CDCl_3$): δ 7.95 (br d, J = 8.6 Hz, 2H, Ph), 7.44 (br d, 2H, Ph), 5.58 (br s, 1 H, NH), 4.52 (t, 1H, $J_{2,3}$ = 6.2 Hz, H-2), 2.24 (br s, 2H, H-1, H-5), 2.08-1.99 (m, 6H, H-4a, H-4b, H-6, Me(Ac)), 1.81-1.56 (m, 2H, H-3a, H-3b).



201

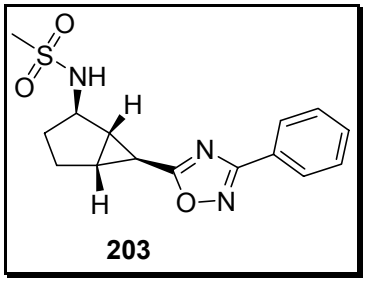
***rac*-(1S,2R,5R,6S)-2-*N*-Acetyl-amino-6-(3-*p*-methylphenyl-1,2,4-oxadiazol-5-yl)bicyclo[3.1.0]hexane (201).** Starting with **196** (40.0 mg, 0.108 mmol) using general procedure 4.3.1.3 (reaction time 3 h), and after flash chromatography using heptane/EtOAc gradient, the title compound was obtained as a colourless solid (32.1 mg, 0.108 mmol, 100%). MS: (ionspray) m/z 298.2 $[M+H]^+$. ^1H NMR (300 MHz, $CDCl_3$): δ 7.95 (br d, J = 8.1 Hz, 2H, Ph), 7.27 (br d, 2H, Ph), 5.70 (br s, 1 H, NH), 4.52 (t, 1H, $J_{2,3a}$ = 6.3 Hz, H-2), 2.44-2.38 (m, 4H, H-1, Me(Ph)), 2.24 (br s, 2H, H-1, H-5), 2.08-1.96 (m, 6H, H-4a, H-4b, H-6, Me(Ac)), 1.76-1.57 (m, 2H, H-3a, H-3b).



202

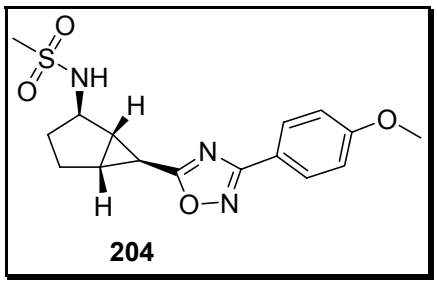
***rac*-(1S,2R,5R,6S)-2-*N*-Acetyl-amino-6-(3-pyridinyl-1,2,4-oxadiazol-5-yl)bicyclo[3.1.0]hexane (202).** Starting with **197** (40.0 mg, 0.112 mmol) using general procedure 4.3.1.3 (reaction time 3 h), and after flash chromatography using heptane/EtOAc gradient, the title compound was obtained as a colourless solid (31.4 mg, 0.110 mmol, 98%). MS: (ionspray) m/z 285.1 $[M+H]^+$. ^1H NMR (300 MHz,

$CDCl_3$): δ 8.80 (br d, J = 5.5 Hz, 2H, Ph), 8.00 (br d, 2H, Ph), 5.54 (br s, 1 H, NH), 4.54 (t, 1H, $J_{2,3a}$ = 6.2 Hz, H-2), 2.29 (br s, 2H, H-1, H-5), 2.11 (t, 1H, $J_{5,6} \approx J_{1,6} \approx 3.1$, H-6), 2.08-2.01 (m, 5H, H-4a, H-4b, Me (Ac)), 1.73-1.62 (m, 2H, H-3a, H-3b).



203

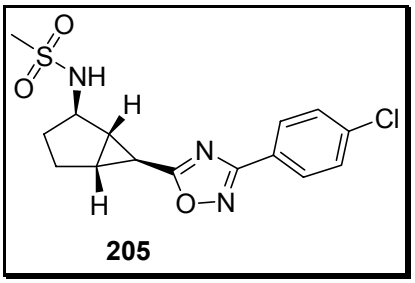
***rac*-(1S,2R,5R,6S)-2-*N*-Mesyl-amino-6-(3-phenyl-1,2,4-oxadiazol-5-yl)bicyclo[3.1.0]hexane (203).** Starting with **193** (35.0 mg, 0.099 mmol) using general procedure 4.3.1.4 (reaction time 2 h), and after flash chromatography using heptane/EtOAc gradient, the title compound was obtained as a colourless solid (30.2 mg, 0.095 mmol, 96%). MS: (ionspray) m/z 320.1 $[M+H]^+$. ^1H NMR (300 MHz, $CDCl_3$): δ 8.05-8.00 (m, 2H, Ph), 7.50-7.43 (m, 3H, Ph), 4.50 (d, 1 H, $J_{2,NH}$ = 8.2 Hz, NH), 4.13 (dd, 1H, $J_{2,3b}$ = 6.4 Hz, H-2), 3.04 (s, 3H, Me(Ms)), 2.35-2.28 (m, 2H, H-1, H-5), 2.10-2.03 (m, 3H, H-4a, H-4b, H-6), 1.85 (dd, 1H, $J_{3,4}$ = 7.0, $J_{3a,3b}$ = 14.8 Hz, H-3a), 1.70-1.60 (m, 1H, H-3b).



204

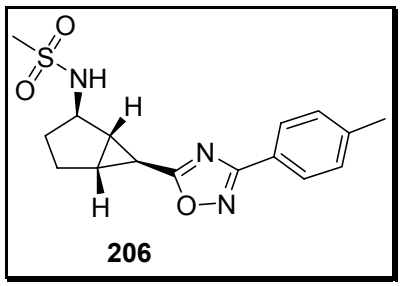
***rac*-(1S,2R,5R,6S)-2-*N*-Mesyl-amino-6-(3-*p*-methoxyphenyl-1,2,4-oxadiazol-5-yl)bicyclo[3.1.0]hexane (204).** Starting with **194** (40.0 mg, 0.104 mmol) using general procedure 4.3.1.4 (reaction time 2 h), and after flash chromatography using heptane/EtOAc gradient, the title compound was obtained as a colourless solid (35.1 mg, 0.101 mmol, 97%). MS: (ionspray) m/z 350.3 $[M+H]^+$. ^1H NMR, COSY, HSQC

(400 MHz, $CDCl_3$): δ 7.96 (br d, 2H, J = 9.0 Hz, Ph), 6.97 (br d, 2H, Ph), 4.49 (d, 1 H, $J_{2,NH}$ = 8.4 Hz, NH), 4.13 (dd, 1H, $J_{2,3b}$ = 6.3 Hz, H-2), 3.86 (s, 3H, OMe), 3.04 (s, 3H, Me(Ms)), 2.32-2.27 (m, 2H, H-1, H-5), 2.11-1.99 (m, 3H, H-4a, H-4b, H-6), 1.85 (dd, 1H, $J_{3,4}$ = 6.8, $J_{3a,3b}$ = 15.0 Hz, H-3a), 1.70-1.60 (m, 1H, H-3b).



205

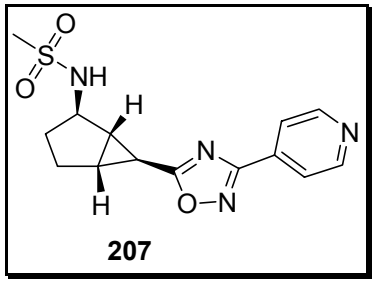
***rac*-(1S,2R,5R,6S)-2-*N*-Mesyl-amino-6-(3-*p*-chlorophenyl-1,2,4-oxadiazol-5-yl)bicyclo[3.1.0]hexane (205).** Starting with **195** (40.0 mg, 0.103 mmol) using general procedure 4.3.1.4 (reaction time 2 h), and after flash chromatography using heptane/EtOAc gradient, the title compound was obtained as a colourless solid (32.4 mg, 0.092 mmol, 89%). MS: (ionspray) m/z 354.2 $[M+H]^+$. ^1H NMR (300 MHz, $CDCl_3$): δ 7.96 (d, 2H, J = 8.4 Hz, Ph), 7.44 (br d, 2H, Ph), 4.48 (d, 1 H, $J_{2,NH}$ = 8.2 Hz, NH), 4.13 (dd, 1H, $J_{2,3b}$ = 6.3 Hz, H-2), 3.04 (s, 3H, Me(Ms)), 2.32-2.29 (m, 2H, H-1, H-5), 2.08-2,02 (m, 3H, H-4a, H-4b, H-6), 1.85 (dd, 1H, $J_{3,4}$ = 6.5, $J_{3a,3b}$ = 14.7 Hz, H-3a), 1.73-1.61 (m, 1H, H-3b).



206

***rac*-(1S,2R,5R,6S)-2-*N*-Mesyl-amino-6-(3-*p*-methylphenyl-1,2,4-oxadiazol-5-yl)bicyclo[3.1.0]hexane (206).** Starting with **196** (40.0 mg, 0.108 mmol) using general procedure 4.3.1.4 (reaction time 2 h), and after flash chromatography using heptane/EtOAc gradient, the title compound was obtained as a colourless solid (35.6

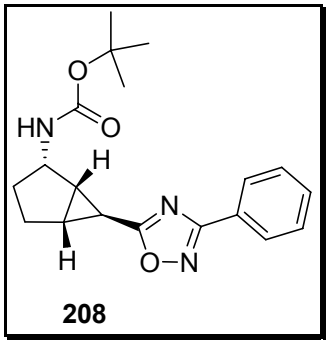
mg, 0.107 mmol, 99%). MS: (ionspray) m/z 334.2 $[M+H]^+$. ^1H NMR (300 MHz, $CDCl_3$): δ 7.91 (d, 2H, J = 8.1 Hz, Ph), 7.27 (br d, 2H, Ph), 4.51 (d, 1 H, $J_{2,NH}$ = 8.1 Hz, NH), 4.12 (dd, 1H, $J_{2,3b}$ = 6.4 Hz, H-2), 3.04 (s, 3H, Me(Ms)), 2.41 (s, 3H, Me(Ph)), 2.32-2.27 (m, 2H, H-1, H-5), 2.08-2,01 (m, 3H, H-4a, H-4b, H-6), 1.85 (dd, 1H, $J_{3,4}$ = 6.6, $J_{3a,3b}$ = 14.3 Hz, H-3a), 1.72-1.58 (m, 1H, H-3b).



207

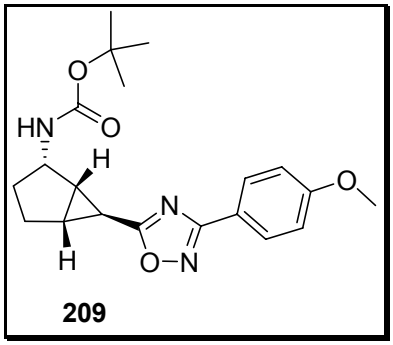
***rac*-(1S,2R,5R,6S)-2-*N*-Mesyl-amino-6-(3-*p*-pyridinyl-1,2,4-oxadiazol-5-yl)bicyclo[3.1.0]hexane (207).** Starting with **197** (10.3 mg, 0.029 mmol) using general procedure 4.3.1.4 (reaction time 2 h), and after flash chromatography using heptane/EtOAc gradient, the title compound was obtained as a colourless solid (7.3 mg, 0.0.023 mmol, 79%). MS: (ionspray) m/z 321.1 $[M+H]^+$. ^1H NMR (300 MHz, $CDCl_3$): δ 8.72-8.69 (m, 2H, Py), 8.02-7.98 (m, 2H, Ph), 4.53 (d, 1 H, $J_{2,NH}$ = 8.3 Hz, NH), 4.12 (dd, 1H, $J_{2,3b}$ = 6.4 Hz, H-2), 3.03 (s, 3H, Me(Ms)), 2.31-2.25 (m, 2H, H-1, H-5), 2.06-2.02 (m, 3H, H-4a, H-4b, H-6), 1.85 (dd, 1H, $J_{3,4}$ = 6.6, $J_{3a,3b}$ = 14.3 Hz, H-3a), 1.71-1.58 (m, 1H, H-3b).

4.3.3.2 Library on *rac*-(1*S*,2*S*,5*R*,6*S*)-2-(*tert*-Butoxycarbonyl)amino-6-carboxylic acid-bicyclo[3.1.0]hexane (187)



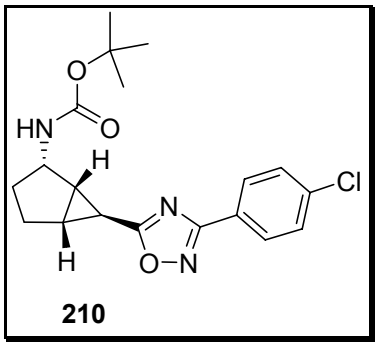
208

***rac-(1S,2S,5R,6S)*-2-(*tert*-Butoxycarbonyl)amino-6-(3-phenyl-1,2,4-oxadiazol-5-yl)bicyclo[3.1.0]hexane (208).** Starting with **187** (210.0 mg, 0.87 mmol) using general procedure 4.3.1.1 (cyclisation: overnight at 100 ºC), and after flash chromatography using heptane/EtOAc gradient, the title compound was obtained as light yellow crystals (141.9 mg, 0.42 mmol, 48%). m.p. 148.2-148.5 ºC. MS: (ionspray) m/z 286.0 $[M\text{-}t\text{-Bu+H}]^+$, 342.1 $[M+H]^+$, 364.4 $[M+Na]^+$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.04-8.01 (m, 2H, Ph), 7.48-7.45 (m, 3H, Ph), 4.62 (br s, 1 H, NH), 4.45 (br s, 1H, H-2), 2.41 (ddd, 1H, $J_{1,2}$ = 6.9 Hz, $J_{1,6} \approx J_{1,5} \approx$ 3.4 Hz, H-1), 2.28 (t, 1H, $J_{1,6} \approx J_{5,6} \approx$ 3.1 Hz, H-6), 2.20-1.92 (m, 4H, H-3a, H-4a, H-4b, H-5), 1.44 (s, 9H, Boc), 1.08-0.93 (m, 1H, H-3b).



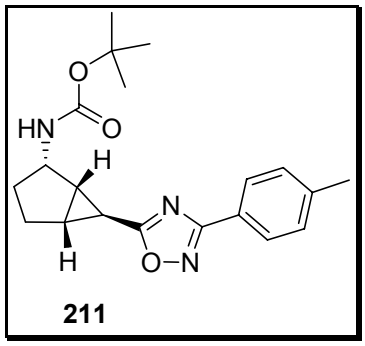
209

***rac-(1S,2S,5R,6S)*-2-(*tert*-Butoxycarbonyl)amino-6-(3-*p*-methoxyphenyl-1,2,4-oxadiazol-5-yl)bicyclo[3.1.0]hexane (209).** Starting with **187**(250.0 mg, 1.04 mmol) using general procedure 4.3.1.1 (cyclisation: 5 h at 100 ºC), and after flash chromatography using heptane/EtOAc gradient, the title compound was obtained as a colourless solid (258.4 mg, 0.70 mmol, 67%). MS: (ionspray) m/z 316.3 $[M\text{-}t\text{-Bu+H}]^+$, 372.4 $[M+H]^+$, 394.3 $[M+Na]^+$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.96 (br d, J = 8.9, 2H, Ph), 6.97 (br d, 2H, Ph), 4.63 (br s, 1H, NH), 4.44 (br s, 1H, H-2), 2.39 (ddd, 1H, $J_{1,2}$ = 6.9 Hz, $J_{1,6} \approx J_{1,5} \approx$ 3.3 Hz, H-1), 2.26 (t, 1H, $J_{1,6} \approx J_{5,6} \approx$ 3.1 Hz, H-6), 2.19-1.91 (m, 4H, H-3a, H-4a, H-4b, H-5), 1.44 (s, 9H, Boc), 1.07-0.93 (m, 1H, H-3b).



210

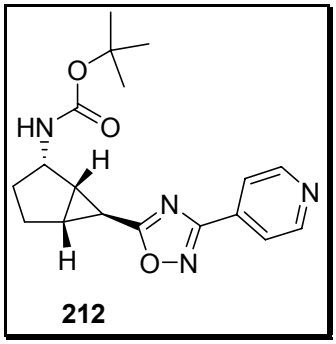
***rac-(1S,2S,5R,6S)*-2-(*tert*-Butoxycarbonyl)amino-6-(3-*p*-chlorophenyl-1,2,4-oxadiazol-5-yl)bicyclo[3.1.0]hexane (210).** Starting with **187** (250.0 mg, 1.04 mmol) using general procedure 4.3.1.1 (cyclisation: 5 h at 100 ºC), and after flash chromatography using heptane/EtOAc gradient, the title compound was obtained as colourless crystals (248.4 mg, 0.66 mmol, 64%). MS: (ionspray) m/z 320.3 [M-*t*-Bu+H]$^+$, 376.5 [M+H]$^+$, 398.1 [M+Na]$^+$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.97 (br d, J = 8.6 Hz, 2H, Ph), 7.44 (br d, 2H, Ph), 4.62 (br s, 1 H, NH), 4.44 (br s, 1H, H-2), 2.41 (ddd, 1H, $J_{1,2}$ = 6.9 Hz, $J_{1,6} \approx J_{1,5} \approx$ 3.3 Hz, H-1), 2.26 (t, 1H, $J_{1,6} \approx J_{5,6} \approx$ 3.1 Hz, H-6), 2.19-1.92 (m, 4H, H-3a, H-4a, H-4b, H-5), 1.44 (s, 9H, Boc), 1.07-0.93 (m, 1H, H-3b).



211

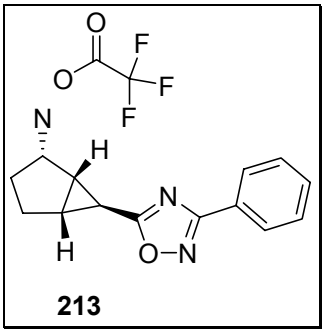
***rac-(1S,2S,5R,6S)*-2-(*tert*-Butoxycarbonyl)amino-6-(3-*p*-methylphenyl-1,2,4-oxadiazol-5-yl)bicyclo[3.1.0]hexane (211).** Starting with **187** (250.0 mg, 1.04 mmol) using general procedure 4.3.1.1 (cyclisation: 7 h at 100 ºC), and after flash chromatography using heptane/EtOAc gradient, the title compound was obtained as colourless solid (190.2 mg, 0.54 mmol, 52%). MS: (ionspray) m/z 300.4 [M-*t*-Bu+H]$^+$, 356.3 [M+H]$^+$, 378.3 [M+Na]$^+$. ^{1}H NMR, COSY, HSQC (400 MHz, $CDCl_3$): δ 7.91 (br

d, J = 8.1 Hz, 2H, Ph), 7.27 (br d, 2H, Ph), 4.63 (br s, 1 H, NH), 4.44 (br s, 1H, H-2), 2.42-2.37 (m, 4H, H-1, Me(Ph)), 2.27 (t, 1H, $J_{1,6} \approx J_{5,6} \approx 2.8$ Hz, H-6), 2.19-1.94 (m, 4H, H-3a, H-4a, H-4b, H-5), 1.44 (s, 9H, Boc), 1.07-0.93 (m, 1H, H-3b). Anal. Calcd. for $C_{20}H_{25}N_3O_3$ (355.44): C, 67.58; H, 7.09; N, 11.82. Found: C, 67.26; H, 6.86; N, 11.78.



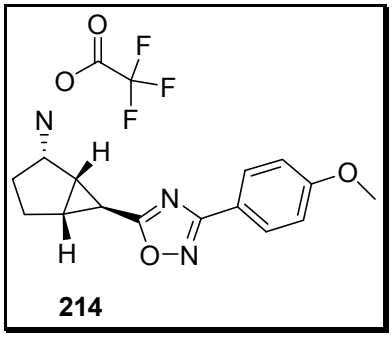
212

***rac-(1S,2S,5R,6S)*-2-(*tert*-Butoxycarbonyl)amino-6-(3-pyridinyl-1,2,4-oxadiazol-5-yl)bicyclo[3.1.0]hexane (212).** Starting with **187** (200.0 mg, 0.83 mmol) using general procedure 4.3.1.1 (cyclisation: overnight at 100 ºC), and after flash chromatography using heptane/EtOAc gradient, the title compound was obtained as colourless solid (114.6 mg, 0.33 mmol, 40%). MS: (ionspray) m/z 287.0 $[M\text{-}t\text{-}Bu+H]^+$, 343.3 $[M+H]^+$, 365.3 $[M+Na]^+$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.77-8.75 (m, 2H, Ph), 7.91-7.88 (m, 2H, Ph), 4.65 (d, 1 H, $J_{2,NH}$ = 7.6 Hz, NH), 4.45 (br s, 1H, H-2), 2.44 (ddd, 1H, $J_{1,2}$ = 6.8 Hz, $J_{1,6} \approx J_{1,5} \approx 3.4$ Hz, H-1), 2.29 (t, 1H, $J_{1,6} \approx J_{5,6} \approx 3.1$ Hz, H-6), 2.22-1.92 (m, 4H, H-3a, H-4a, H-4b, H-5), 1.44 (s, 9H, Boc), 1.09-0.94 (m, 1H, H-3b).



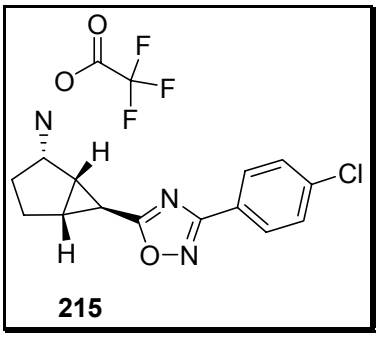
213

***rac-(1S,2S,5R,6S)*-2-Amonium-6-(3-phenyl-1,2,4-oxadiazol-5-yl)bicyclo[3.1.0]hexane Trifluoroacetate (213).** Starting with **208** (100.0 mg, 0.29 mmol) using general procedure 4.3.1.2 (reaction time 5 h), and after flash chromatography eluting with EtOAc/MeOH gradient the title compound was obtained as light yellow solid (101.2 mg, 0.28 mmol, 97%). MS: (ionspray) m/z 242.3 $[M\text{-}TFA+H]^+$. ^1H NMR (300 MHz, MeOD): δ 8.04-8.01 (m, 2H, Ph), 7.56-7.50 (m, 3H, Ph), 4.11-4.04 (m, 1H, H-2), 2.68 (t, 1H, $J_{1,6} \approx J_{5,6} \approx 3.2$ Hz, H-3), 2.47 (ddd, 1H, $J_{1,5} = 4.2$ Hz, $J_{1,2} = 6.7$ Hz, H-1), 2.39-2.34 (m, 1H, H-5), 2.23-2.13 (m, 3H, H-3a, H-4a, H-4b), 1.49-1.33 (m, 1H, H-3b).



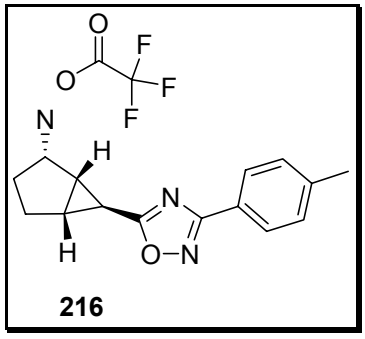
214

***rac-(1S,2S,5R,6S)*-2-Amonium-6-(3-*p*-methoxyphenyl-1,2,4-oxadiazol-5-yl)bicyclo[3.1.0]hexane Trifluoroacetate (214).** Starting with **209** (120.1 mg, 0.32 mmol) using general procedure 4.3.1.2 (reaction time 5 h), and after flash chromatography using EtOAc/MeOH gradient, the title compound was obtained as a yellow oil (101.3 mg, 0.26 mmol, 81%). MS: (ionspray) m/z 272.2 $[M\text{-}TFA+H]^+$. ^1H NMR (300 MHz, MeOD): δ 7.98-7.93 (m, 2H, Ph), 7.08-7.03 (m, 2H, Ph), 4.12-4.00 (m, 1H, H-2), 2.66 (t, 1H, $J_{1,6} \approx J_{5,6} \approx 3.1$ Hz, H-6), 2.45 (ddd, 1H, $J_{1,5} = 4.0$ Hz, $J_{1,2} = 6.7$ Hz, H-1),2.36-2.31 (m, 1H, H-5), 2.23-2.13 (m, 3H, H-3a, H-4a, H-4b), 1.47-1.31 (m, 1H, H-3b).



215

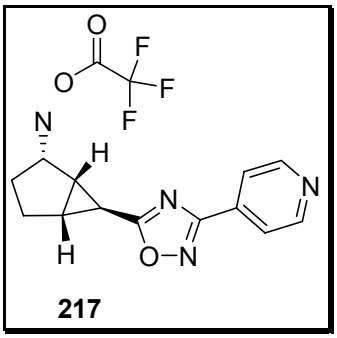
***rac-(1S,2S,5R,6S)*-2-Amonium-6-(3-*p*-chlorophenyl-1,2,4-oxadiazol-5-yl)bicyclo[3.1.0]hexane Trifluoroacetate (215).** Starting with **210** (204.6 mg, 0.54 mmol) using general procedure 4.3.1.2 (reaction time 5 h), and after recrystallisation with DCM/n-Hex the title compound was obtained as a colourless solid (177.4 mg, 0.46 mmol, 84%). MS: (ionspray) m/z 276.1 $[M\text{-}TFA+H]^+$. ^1H NMR (300 MHz, MeOD): δ 8.01 (br d, 2H, J = 8.5 Hz, Ph), 7.54 (br d, 2H, Ph), 4.10-4.03 (m, 1H, H-2), 2.68 (br t, 1H, $J_{1,6} \approx J_{5,6} \approx 3.0$ Hz, H-6), 2.47-2.43 (m, 1H, H-1), 2.37-2.32 (m, 1H, H-5), 2.21-2.12 (m, 3H, H-3a, H-4a, H-4b), 1.46-1.31 (m, 1H, H-3b).



216

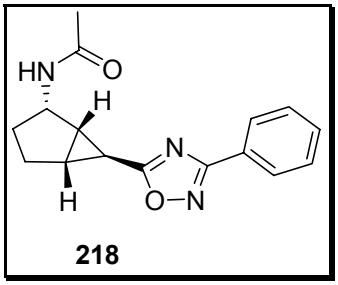
***rac-(1S,2S,5R,6S)*-2-Amonium-6-(3-*p*-methylphenyl-1,2,4-oxadiazol-5-yl)bicyclo[3.1.0]hexane Trifluoroacetate (216).** Starting with **211** (150.0 mg, 0.42 mmol) using general procedure 4.3.1.2 (reaction time 5 h), and after flash chromatography using EtOAc/MeOH gradient, the title compound was obtained as light yellow solid (111.1 mg, 0.30 mmol, 71%). MS: (ionspray) m/z 256.4 $[M\text{-}TFA+H]^+$. ^1H NMR, COSY, HMSQ (400 MHz, MeOD): δ 7.90 (br d, J = 8.2 Hz, 2H, Ph), 7.34 (br d, 2H, Ph), 4.09-4.02 (m, 1H, H-2), 2.66 (t, 1H, $J_{1,6} \approx J_{5,6} \approx 3.2$ Hz, H-6),

2.47-2.41 (m, 4H, H-1, Me(Ph)), 2.36-2.30 (m, 1H, H-5), 2.22-2.11 (m, 3H, H-3a, H-4a, H-4b), 1.46-1.30 (m, 1H, H-3b).



217

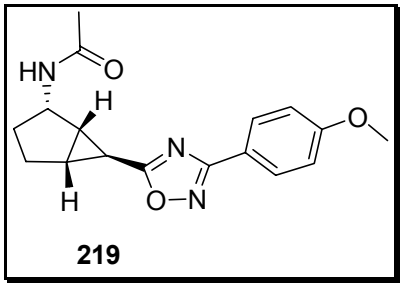
***rac-(1S,2S,5R,6S)*-2-Amonium-6-(3-piridinyl-1,2,4-oxadiazol-5-yl)bicyclo[3.1.0]hexane Trifluoroacetate (217).** Starting with **212** (188.8 mg, 0.55 mmol) using general procedure 4.3.1.2 (reaction time 5 h), and after flash chromatography using EtOAc/MeOH gradient, the title compound was obtained as light yellow viscous oil (166.2 mg, 0.47 mmol, 84%). MS: (ionspray) m/z 243.2 $[M\text{-}TFA+H]^+$. ^1H NMR (300 MHz, MeOD) δ 8.69-8.66 (m, 2H, Py), 7.99-7.97 (m, 2H, Py), 4.08-4.02 (m, 1H, H-2), 2.65 (t, 1H, $J_{1,6} \sim J_{5,6} \sim 3.3$ Hz, H-6), 2.47-2.42 (m, 4H, H-1, Me(Ph)), 2.36-2.30 (m, 1H, H-5), 2.22-2.11 (m, 3H, H-3a, H-4a, H-4b), 1.47-1.32 (m, 1H, H-3b).



218

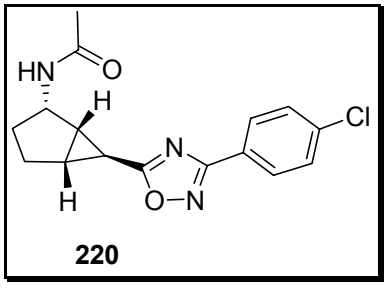
***rac-(1S,2S,5R,6S)*-2-*N*-Acetyl-amino-6-(3-phenyl-1,2,4-oxadiazol-5-yl)bicyclo[3.1.0]hexane. (218).** Starting with **213** (35.0 mg, 0.099 mmol) using general procedure 4.3.1.3 (reaction time 2 h), and after flash chromatography using EtOAc/MeOH gradient, the title compound was obtained as colourless crystals (17.5 mg, 0.062 mmol, 63%). m.p. 158.9-159.4 ºC. MS: (ionspray) m/z 284.1 $[M+H]^+$. ^1H

NMR (300 MHz, $CDCl_3$): δ 8.04-8.01 (m, 2H, Ph), 7.50-7.44 (m, 3H, Ph), 5.63 (br s, 1 H, NH), 4.75-4.65 (m, 1H, H-2), 2.45-2.39 (m, 1H, H-1), 2.30 (t, 1H, $J_{1,6} \approx J_{5,6} \approx 3.0$ Hz, H-6), 2.23-2.10 (m, 2H, H5, H3a), 2.06-1.98 (m, 5H, H-4a, H-4b, Me (Ac)), 1.07-0.93 (m, 1H, H-3b).



219

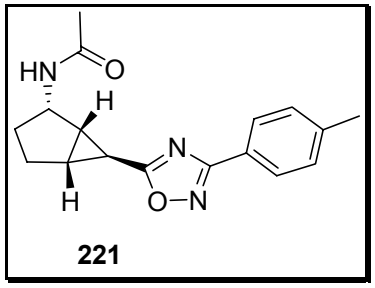
***rac-(1S,2S,5R,6S)*-2-*N*-Acetyl-amino-6-(3-*p*-methoxyphenyl-1,2,4-oxadiazol-5-yl)bicyclo[3.1.0]hexane. (219).** Starting with **214** (45.5 mg, 0.118 mmol) using general procedure 4.3.1.3 (reaction time 2 h), and after flash chromatography using EtOAc/MeOH gradient, the title compound was obtained as a light brown oil (35.8 mg, 0.114 mmol, 97%). MS: (ionspray) m/z 314.0 $[M+H]^+$. ^1H NMR (300 MHz, $CDCl_3$): δ 7.96 (br d, 2H, J = 8.9 Hz, Ph), 6.97 (br d, 2H, Ph), 5.63 (br s, 1 H, NH), 4.74-4.65 (m, 1H, H-2), 3.86 (s, 3H, OMe(Ph)), 2.43-2.38 (m, 1H, H-1), 2.28 (t, 1H, $J_{1,6} \approx J_{5,6} \approx 3.0$ Hz, H-6), 2.22-2.09 (m, 2H, H5, H3a), 2.05-1.96 (m, 5H, H-4a, H-4b, Me (Ac)), 1.07-0.92 (m, 1H, H-3b).



220

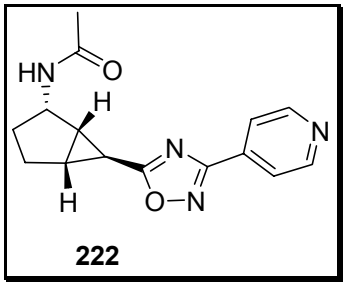
***rac-(1S,2S,5R,6S)*-2-*N*-Acetyl-amino-6-(3-*p*-chlorophenyl-1,2,4-oxadiazol-5-yl)bicyclo[3.1.0]hexane (220).** Starting with **215** (37.3 mg, 0.096 mmol) using general procedure 4.3.1.3 (reaction time 2 h), and after flash chromatography using

EtOAc/MeOH gradient, the title compound was obtained as a colourless solid (29.7 mg, 0.093 mmol, 98%). MS: (ionspray) m/z 318.1 $[M+H]^+$. ^1H NMR (300 MHz, $CDCl_3$): δ 7.96 (br d, 2H, J = 8.6 Hz, Ph), 7.44 (br d, 2H, Ph), 5.70 (br d, 1 H, NH), 4.75-4.65 (m, 1H, H-2), 2.45-2.40 (m, 1H, H-1), 2.29 (t, 1H, $J_{1,6} \approx J_{5,6} \approx 3.0$ Hz, H-6), 2.22-2.09 (m, 2H, H5, H3a), 2.05-1.98 (m, 5H, H-4a, H-4b, Me (Ac)), 1.08-0.94 (m, 1H, H-3b).



221

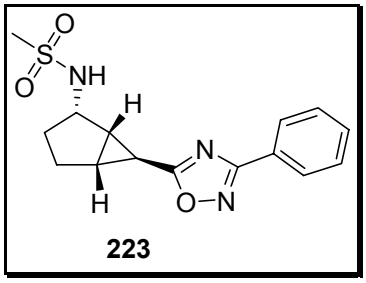
***rac-(1S,2S,5R,6S)*-2-*N*-Acetyl-amino-6-(3-*p*-methylphenyl-1,2,4-oxadiazol-5-yl)bicyclo[3.1.0]hexane (221).** Starting with **216** (32.8 mg, 0.089 mmol) using general procedure 4.3.1.3 (reaction time 2 h), and after flash chromatography using EtOAc/MeOH gradient, the title compound was obtained as a colourless solid (17.9 mg, 0.060 mmol, 68%). MS: (ionspray) m/z 298.2 $[M+H]^+$. ^1H NMR (300 MHz, $CDCl_3$): δ 7.91 (br d, 2H, J = 8.1 Hz, Ph), 7.27 (br d, 2H, Ph), 5.60 (br s, 1 H, NH), 4.75-4.65 (m, 1H, H-2), 2.43-2.39 (m, 1H, H-1, Me(Ph)), 2.29 (t, 1H, $J_{1,6} \approx J_{5,6} \approx 3.0$ Hz, H-6), 2.22-2.09 (m, 2H, H5, H3a), 2.06-1.96 (m, 5H, H-4a, H-4b, Me (Ac)), 1.07-0.92 (m, 1H, H-3b). Anal. Calcd. for $C_{17}H_{19}N_3O_2$ (297.36): C, 68.67; H, 6.44; N, 14.13. Found: C, 68.22; H, 6.38; N, 13.46.



222

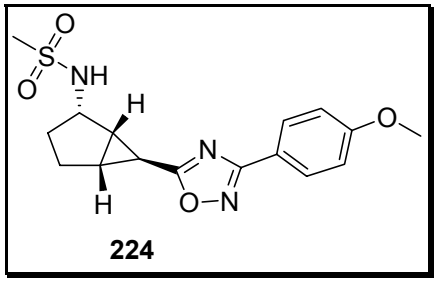
***rac-(1S,2S,5R,6S)*-2-*N*-Acetyl-amino-6-(3-*p*-pyridinyl-1,2,4-oxadiazol-5-yl)bicyclo[3.1.0]hexane (222).** Starting with **217** (45.6 mg, 0.128 mmol) using

general procedure 4.3.1.3 (reaction time 2 h), and after flash chromatography using EtOAc/MeOH gradient, the title compound was obtained as a light yellow viscous oil (36.2 mg, 0.127 mmol, 99%). MS: (ionspray) m/z 285.0 $[M+H]^+$. ^1H NMR (300 MHz, MeOD): δ 8.74 (br d, 2H, J = 5.9 Hz, Py), 8.02 (br d, 2H, Py), 4.66-4.58 (m, 1H, H-2), 2.52 (t, 1H, $J_{1,6} \approx J_{5,6} \approx 3.0$ Hz, H-6), 2.44-2.40 (m, 1H, H-1), 2.23-2.19 (m, 1H, H-5), 2.13-1.97 (m, 6H, H-3a, H-4a, H-4b, Me (Ac)), 1.30-1.14 (m, 1H, H-3b).



223

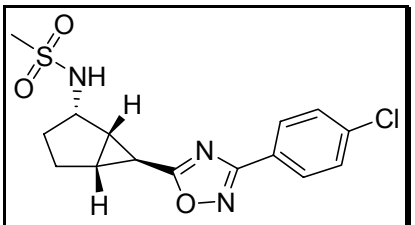
***rac-(1S,2S,5R,6S)*-2-*N*-Mesyl-amino-6-(3-phenyl-1,2,4-oxadiazol-5-yl)bicyclo[3.1.0]hexane (223).** Starting with **213** (31.4 mg, 0.088 mmol) using general procedure 4.3.1.4 (reaction time 2 h), and after flash chromatography using heptane/EtOAc gradient, the title compound was obtained as a colourless solid (20.0 mg, 0.063 mmol, 71%). MS: (ionspray) m/z 320.1 $[M+H]^+$. ^1H NMR (300 MHz, $CDCl_3$): δ 8.04-8.00 (m, 2H, Ph), 7.52-7.43 (m, 3H, Ph), 4.63 (d, 1H, $J_{2,NH}$ = 7.3 Hz, NH), 4.35-4.25 (m, 1H, H-2), 3.00 (s, 3H, Me(Ms)), 2.48-2.43 (m, 1H, H-1), 2.36 (t, 1H, $J_{1,6} \approx J_{5,6} \approx 3.1$ Hz, H-6), 2.26-1.94 (m, 4H, H-3a, H-4a, H-4b, H-5), 1.28-1.11 (m, 1H, H-3b).



224

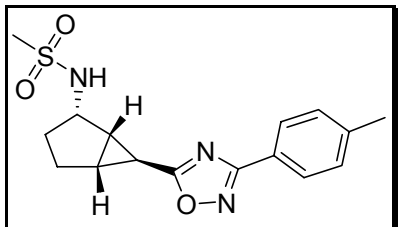
***rac-(1S,2S,5R,6S)*-2-*N*-Mesyl-amino-6-(3-*p*-methoxyphenyl-1,2,4-oxadiazol-5-yl)bicyclo[3.1.0]hexane (224).** Starting with **214** (45.5 mg, 0.118 mmol) using

general procedure 4.3.1.4 (reaction time 2 h), and after flash chromatography using heptane/EtOAc gradient, the title compound was obtained as a light yellow waxy solid (26.3 mg, 0.075 mmol, 64%). MS: (ionspray) m/z 350.4 $[M+H]^+$. ^1H NMR (300 MHz, $CDCl_3$): δ 7.96 (d, 2H, J = 8.9 Hz, Ph), 6.97 (d, 2H, Ph), 4.58 (br s, 1H, NH), 4.34-4.25 (m, 1H, H-2), 3.86 (s, 3H, OMe), 3.00 (s, 3H, Me(Ms)), 2.47-2.42 (m, 1H, H-1), 2.34 (t, 1H, $J_{1,6} \approx J_{5,6} \approx 3.0$ Hz, H-6), 2.24-1.98 (m, 4H, H-3a, H-4a, H-4b, H-5), 1.29-1.10 (m, 1H, H-3b).



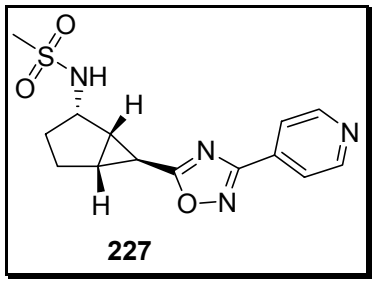
225

***rac-(1S,2S,5R,6S)*-2-*N*-Mesyl-amino-6-(3-*p*-chlorophenyl-1,2,4-oxadiazol-5-yl)bicyclo[3.1.0]hexane. (225).** Starting with **115** (93.1 mg, 0.239 mmol) using general procedure 4.3.1.4 (reaction time 2 h), and after flash chromatography using heptane/EtOAc gradient, the title compound was obtained as light brown crystals (78.6 mg, 0.222 mmol, 93%). m.p. 159.8-160.4 ºC. MS: (ionspray) m/z 354.2 $[M+H]^+$. ^1H NMR (300 MHz, $CDCl_3$): δ 7.96 (d, 2H, J = 8.6 Hz, Ph), 7.44 (d, 2H, Ph), 4.67 (d, 1H, $J_{2,NH}$ = 7.5 Hz, NH), 4.34-4.24 (m, 1H, H-2), 3.00 (s, 3H, Me(Ms)), 2.47-2.43 (m, 1H, H-1), 2.36 (t, 1H, $J_{1,6} \approx J_{5,6} \approx 3.0$ Hz, H-6), 2.25-1.94 (m, 4H, H-3a, H-4a, H-4b, H-5), 1.25-1.11 (m, 1H, H-3b).



226

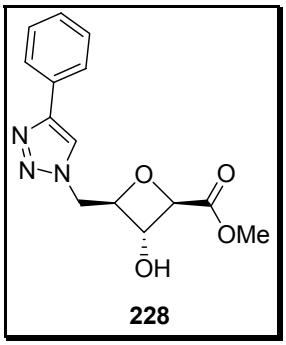
***rac-(1S,2S,5R,6S)*-2-*N*-Mesyl-amino-6-(3-*p*-methylphenyl-1,2,4-oxadiazol-5-yl)bicyclo[3.1.0]hexane (226).** Starting with **216** (35.0 mg, 0.095 mmol) using general procedure 4.3.1.4 (reaction time 2 h), and after flash chromatography using heptane/EtOAc gradient, the title compound was obtained as a colourless solid (25.3 mg, 0.076 mmol, 80%). MS: (ionspray) m/z 334.2 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$, COSY, HSQC): δ 7.91 (d, 2H, J = 8.1 Hz, Ph), 7.27 (br d, 2H, Ph), 4.52 (d, 1H, $J_{2,NH}$ = 7.4 Hz, NH), 4.34-4.26 (m, 1H, H-2), 3.00 (s, 3H, Me(Ms)), 2.46-2.40 (m, 4H, H-1, Me(Ph)), 2.34 (t, 1H, $J_{1,6} \approx J_{5,6} \approx$ 3.1 Hz, H-6), 2.25-1.96 (m, 4H, H-3a, H-4a, H-4b, H-5), 1.28-1.12 (m, 1H, H-3b).



227

***rac-(1S,2S,5R,6S)*-2-*N*-Mesyl-amino-6-(3-*p*-pyridinyl-1,2,4-oxadiazol-5-yl)bicyclo[3.1.0]hexane (227).** Starting with **217** (10.9 mg, 0.031 mmol) using general procedure 4.3.1.4 (reaction time 3 h), and after flash chromatography using heptane/EtOAc gradient, the title compound was obtained as a colourless solid (6.2 mg, 0.019 mmol, 63%). MS: (ionspray) m/z 321.2 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): δ 8.73-8.61 (m, 2H, Py), 8.08-8.06 (m, 2H, Py), 4.51 (d, 1H, $J_{2,NH}$ = 7.5 Hz, NH), 4.34-4.25 (m, 1H, H-2), 3.02 (s, 3H, Me(Ms)), 2.47-2.41 (m, 1H, H-1), 2.34 (t, 1H, $J_{1,6} \approx J_{5,6} \approx$ 3.3 Hz, H-6), 2.26-1.96 (m, 4H, H-3a, H-4a, H-4b, H-5), 1.28-1.11 (m, 1H, H-3b).

4.3.4 Triazole Library on Methyl 2,4-Anhydro-5-azido-5-deoxy-D-ribonate (88)

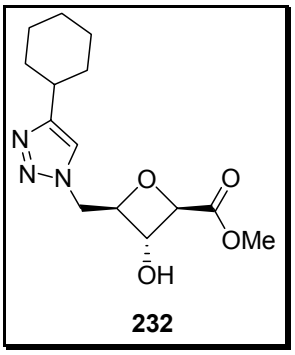


228

Methyl [(2*R*,3*R*,4*R*)-3-hydroxy-4-{[4-(phenyl)-triazol-1-yl]methyl}oxetan-2-yl]carboxylate (228). Procedure A: To a solution of **88** (20.0 mg, 0.107 mmol) in DMF (0.6 mL) was added phenylacetylene (13.0 mL, 0.118 mmol), sodium ascorbate (0.5 mg, 0.002 mmol) and $CuSO_4.5H_2O$ (0.5 mg, 0.003 mmol) and the mixture was stirred at rt for 3h. Water was added and the product was extracted with 3x diethyl ether. The organic layers were combined, dried over $MgSO_4$, filtered and concentrated. The product was purified by recrystallisation with diethylether/n-Hex to afford the desired compound as a colourless solid (23.9 mg, 0.082 mmol, 77%).

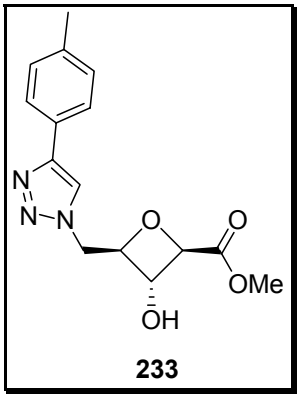
Procedure B: To a solution of methyl ester **88** (24.6 mg, 0.13 mmol) in DMF (0.6 mL) was added phenylacetylene (16.1 mL, 0.15 mmol), sodium ascorbate (0.6 mg, 0.002 mmol) and $CuSO_4.5H_2O$ (0.6 mg, 0.003 mmol) and the mixture was microwaved at 80 °C for 2 min. Water was added and the product was extracted with 3x diethyl ether. The organic layers were combined, dried over $MgSO_4$, filtered and concentrated. The product was purified by crystallization with ether/n-Hex to afford the desired compound as a colourless solid (27.7 mg, 0.096 mmol, 73%).

Analytical data: $[\alpha]_D^{20.0}$ 139.3 (*c* 0.352, $CHCl_3$. MS: (ionspray) m/z 290.1 $[M+H]^+$, 312.1 $[M+Na]^+$.). ^1H NMR (300 MHz, $CDCl_3$): δ 8.22 (s, 1H, CH(triazole)), 7.82 (d, 2H, J = 7.8 Hz, Ph), 7.45-7.31 (m, 3H, Ph), 5.54 (d, 1H, $J_{3,OH}$ = 5.4 Hz, OH-3), 5.07 (dt, 1H, $J_{3,4}$ = 5.5 Hz, $J_{4,5a} \approx J_{4,5b} \approx$ 3.3 Hz, H-4), 5.02 (d, 1H, $J_{2,3}$ = 5.9 Hz, H-2), 4.98 (A(ABX), 1H, H-5a), 4.61 (B(ABX), 1H, $J_{5a,5b}$ = 15.1 Hz, H-5b), 4.39 (q, 1H, H-3), 3.52 (s, 3H, OMe).



232

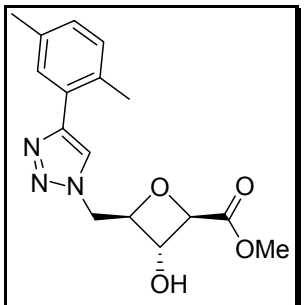
Methyl [(2*R*,3*R*,4*R*)-4-{[4-(cyclohexyl)-triazol-1-yl]-3-hydroxymethyl}oxetan-2-yl]carboxylate (232). To a solution of the azide **88** (20.9 mg, 0.112 mmol) and 1-ethynylcyclohexane (16.19 μL, 0.124 mmol) in DMF (0.5 mL) at rt was added a aq soln of sodium ascorbate (0.1 M, 0.1 mL) and $CuSO_4.5H_20$ (0.1 M, 0.1 mL). A suspension was formed and the mixture was stirred for 1 h while it became a clear solution. The mixture was injected directly on preparative HPLC and after fraction evaporation the title compound was obtained as colourless oil (20.4 mg, 0.069 mmol, 62%). MS: (ionspray) m/z 296.1 $[M+H]^+$, 318.1 $[M+Na]^+$. ^1H NMR (300 MHz, $CDCl_3$): δ 7.64 (s, 1H, CH(triazole)), 5.02-4.97 (m, 2H, H-2, H-4), 4.86 (A(ABX), 1H, $J_{4,5a}$ = 3.8 Hz, $J_{5a,5b}$ = 15.0 Hz, H-5a), 4.53 (B(ABX), 1H, H-5b), 4.32 (t, 1H, $J_{2,3} \approx J_{3,4} \approx$ 5.9 Hz, H-3), 3.69 (s, 3H, OMe), 2.70 (br s, 1H, CH(cyclohexyl)), 2.02-1.70 (m, 5H, CH_2(cyclohexyl)), 1.45-1.22 (m, 5H, CH_2(cyclohexyl)).



233

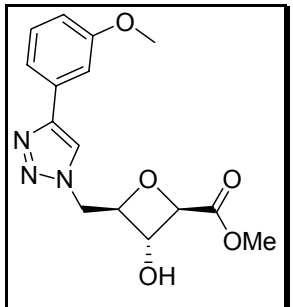
Methyl [(2*R*,3*R*,4*R*)-3-hydroxy-4-{[4-(4-methylphenyl)-triazol-1-yl]methyl}oxetan-2-yl]carboxylate (233). Using GP 4.3.1.5 with 4-ethynyltoluene

the desired compound was obtained in 77% yield. $[\alpha]_D^{20.0}$ 130.3 (*c* 0.344, $CHCl_3$). MS (HPLC-MS): m/z 304.1 $[M+H]^+$, 367.1 $[M+Na+MeCN]^+$. ^1H NMR (300 MHz, $CDCl_3$): δ 8.09 (s, 1H, CH(triazole)), 7.72 (d, 2H, J = 5.8 Hz, Ph), 7.24 (d, 2H, Ph), 5.03-4.97 (m, 2H, H-2, H-4), 4.89 (A(ABX), 1H, $J_{4,5a}$ = 3.5 Hz, $J_{5a,5b}$ = 15.0 Hz, H-5a), 4.60 (B(ABX), 1H, $J_{4,5a}$ = 3.6 Hz, H-5b), 4.42 (t, 1H, $J_{2,3} \approx J_{3,4} \approx$ 5.4 Hz, H-3), 3.56 (s, 3H, OMe), 2.38 (s, 3H, Me(Ph)).



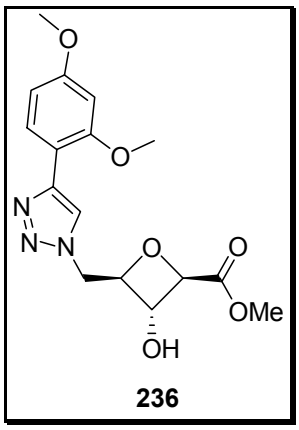
234

Methyl [(2*R*,3*R*,4*R*)-3-hydroxy-4-{[4-(2,5-dimethylphenyl)-triazol-1-yl]methyl}oxetan-2-yl]carboxylate (234). Using GP 4.3.1.5 with 1-ethynyl-2,4-dimethylbenzene the desired compound was obtained in 40% yield. $[\alpha]_D^{20.0}$ 62.64 (*c* 0.698, $CHCl_3$). MS (HPLC-MS): m/z 318.1 $[M+H]^+$, 381.1 $[M+Na+MeCN]^+$. ^1H NMR (300 MHz, $CDCl_3$): δ 7.98 (s, 1H, CH(triazole)), 7.57 (br s, 1H, Ph), 7.16;7.08 (AB, 2H, $J_{a,b}$ = 7.7 Hz, H-3', H-4', Ph), 5.06-5.01 (m, 1H, H-4), 4.99 (d, 1H, $J_{2,3}$ = 5.9 Hz, H-2), 4.91 (A(ABX), 1H, $J_{4,5a}$ = 3.6 Hz, $J_{5a,5b}$ = 15.0 Hz, H-5a), 4.63 (B(ABX), 1H, $J_{4,5b}$ = 3.6 Hz, H-5b), 4.49 (t, 1H, $J_{2,3} \approx J_{3,4} \approx$ 5.7 Hz, H-3), 3.58 (s, 3H, OMe), 2.43 (s, 3H, Me(Ph)), 2.36 (s, 3H, Me(Ph)).



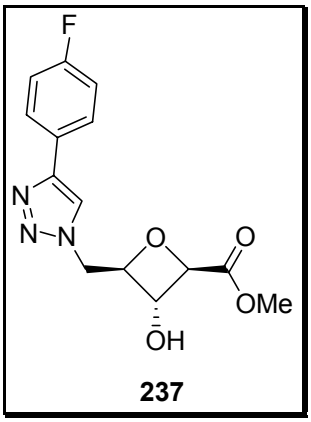
235

Methyl [(2*R*,3*R*,4*R*)-3-hydroxy-4-{[4-(3-methoxyphenyl)-triazol-1-yl]methyl}oxetan-2-yl]carboxylate (235). Using GP 4.3.1.5 with 1-ethynyl-3-methoxybenzene but proceeding to purification by flash chromatography (heptane/EtOAc gradient), the desired compound was obtained in 95% yield as colourless oil. $[\alpha]_D^{20.0}$ 142.01 (*c* 0.607, $CHCl_3$). MS (HPLC-MS): m/z 320.1 $[M+H]^+$, 383.1 $[M+Na+MeCN]^+$. ^1H NMR (300 MHz, $CDCl_3$): δ 8.24 (s, 1H, CH(triazole)), 7.38-7.32 (m, 3H, Ph), 6.90-6.86 (m, 1H, Ph), 5.10-5.06 (m, 1H, H-4), 5.02 (d, 1H, $J_{2,3}$ = 6.0 Hz, H-2), 4.97 (A(ABX), 1H, $J_{4,5a}$ = 3.4 Hz, $J_{5a,5b}$ = 15.0 Hz, H-5a), 4.59 (B(ABX), 1H, $J_{4,5b}$ = 3.0 Hz, H-5b), 4.36 (t, 1H, $J_{2,3} \approx J_{3,4} \approx$ 5.9 Hz, H-3), 3.86 (s, 3H, OMe(Ph)), 3.50 (s, 3H, OMe).



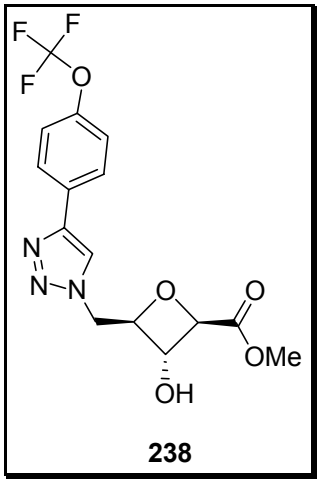
236

Methyl [(2*R*,3*R*,4*R*)-3-hydroxy-4-{[4-(2,4-dimethoxyphenyl)-triazol-1-yl]methyl}oxetan-2-yl]carboxylate (236). Using GP 4.3.1.5 with 1-ethynyl-2,4dimethoxybenzene the desired compound was obtained in 86% yield. $[\alpha]_D^{20.0}$ 80.97 (*c* 0.504, $CHCl_3$). MS (HPLC-MS): m/z 350.1 $[M+H]^+$, 413.1 $[M+Na+MeCN]^+$. ^1H NMR (300 MHz, $CDCl_3$): δ 8.16 (s, 1H, CH(triazole)), 7.43 (d, 1H, $J_{5',6'}$ = 1.9 Hz, H-6'), 7.34 (dd, 1H, $J_{3',5'}$ = 8.3 Hz, H-5'), 6.92 (d, 1H, H-3'), 5.07-5.03 (m, 1H, H-4), 5.00 (d, 1H, $J_{2,3}$ = 5.9 Hz, H-2), 4.94 (A(ABX), 1H, $J_{4,5a}$ = 3.3 Hz, $J_{5a,5b}$ = 15.1 Hz, H-5a), 4.59 (B(ABX), 1H, $J_{4,5b}$ = 3.2 Hz, H-5b), 4.35 (t, 1H, $J_{2,3} \approx J_{3,4} \approx$ 5.7 Hz, H-3), 3.97 (s, 3H, OMe(Ph)), 3.91 (s, 3H, OMe(Ph)), 3.54 (s, 3H, OMe).



237

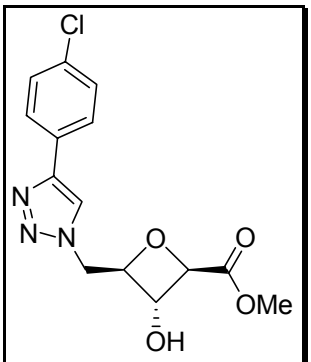
Methyl [(2*R*,3*R*,4*R*)-4-{[4-(4-fluorophenyl)-triazol-1-yl]methyl}-3-hydroxyoxetan-2-yl]carboxylate (237). Using GP 4.3.1.5 with 1-ethynyl-4-fluorobenzene the desired compound was obtained in 70% yield. $[\alpha]_D^{20.0}$ 94.91 (*c* 0.543, $CHCl_3$). MS (HPLC-MS): m/z 308.1 $[M+H]^+$, 371.0 $[M+Na+MeCN]^+$. ^1H NMR (300 MHz, $CDCl_3$): δ 8.18 (s, 1H, CH(triazole)), 7.80 (dd, 2H, $J_{2',3'} \approx J_{5',6'} \approx 8.5$ Hz, $J_{2',F} \approx J_{6',F} \approx 5.4$ Hz, H-2', H-6'), 7.12 (t, 2H, $J_{3',F} \approx J_{5',F} \approx 8.5$ Hz, H-3', H-5'), 5.22 (br s, 1H, OH), 5.07-5.03 (m, 1H, H-4), 5.01 (d, 1H, $J_{2,3} = 5.9$ Hz, H-2), 4.97 (A(ABX), 1H, $J_{4,5a} = 3.4$ Hz, H-5a), 4.60 (B(ABX), 1H, $J_{4,5b} = 3.1$ Hz, $J_{5a,5b} = 15.1$ Hz, H-5b), 4.36 (t, 1H, $J_{2,3} \approx J_{3,4} \approx 5.8$ Hz, H-3), 3.54 (s, 3H, OMe).



238

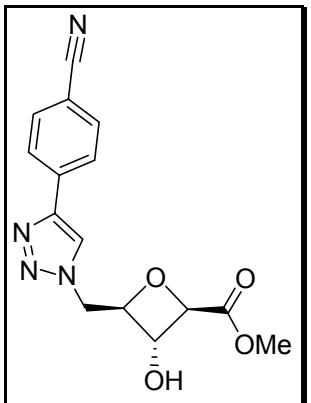
Methyl [(2*R*,3*R*,4*R*)-4-{[4-(4-trifluoromethoxyphenyl)-triazol-1-yl]methyl}-3-hydroxyoxetan-2-yl]carboxylate (238). Using GP 4.3.1.5 with 1-ethynyl-4-

trifluoromethoxybenzene the desired compound was obtained in 34% yield. $[\alpha]_D^{20.0}$ 75.93 (*c* 0.461, $CHCl_3$). MS (HPLC-MS): m/z 374.1 $[M+H]^+$, 437.1 $[M+Na+MeCN]^+$. ^1H NMR (300 MHz, $CDCl_3$): δ 8.23 (s, 1H, CH(triazole)), 7.86 (br d, 2H, $J_{2',3'} \approx J_{5',6'} \approx 8.8$ Hz, H-2', H-6'), 7.28 (d, 2H, H-3', H-5'), 5.07-4.99 (m, 3H, H-2, H-4, OH), 4.96 (A(ABX), 1H, $J_{4,5a}$ = 3.5 Hz, H-5a), 4.61 (B(ABX), 1H, $J_{4,5b}$ = 3.1 Hz, $J_{5a,5b}$ = 15.1 Hz, H-5b), 4.35 (br q, 1H, H-3), 3.54 (s, 3H, OMe).



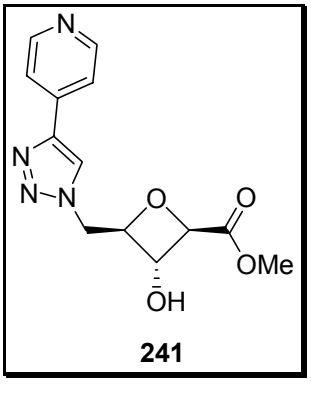
239

Methyl [(2*R*,3*R*,4*R*)-4-{[4-(4-chlorophenyl)-triazol-1-yl]methyl}-3-hydroxyoxetan-2-yl]carboxylate (239). Using GP 4.3.1.5 with 1-ethynyl-4-chlorobenzene the desired compound was obtained in 41% yield. $[\alpha]_D^{20.0}$ 83.37 (*c* 0.623, $CHCl_3$). MS (HPLC-MS): m/z 324.0 $[M+H]^+$, 387.0 $[M+Na+MeCN]^+$. ^1H NMR (300 MHz, $CDCl_3$): δ 8.20 (s, 1H, CH(triazole)), 7.77 (d, 2H, $J_{2',3'} \approx J_{5',6'} \approx 8.4$ Hz, H-2', H-6'), 7.40 (d, 2H, H-3', H-5'), 5.06-5.02 (m, 1H, H-4), 5.00 (d, 1H, $J_{2,3}$ = 6.0 Hz, H-2), 4.95 (A(ABX), 1H, $J_{4,5a}$ = 3.3 Hz, H-5a), 4.61 (B(ABX), 1H, $J_{4,5b}$ = 3.1 Hz, $J_{5a,5b}$ = 15.1 Hz, H-5b), 4.35 (t, 1H, $J_{2,3} \approx J_{3,4} \approx 5.6$ Hz, H-3), 3.54 (s, 3H, OMe).



240

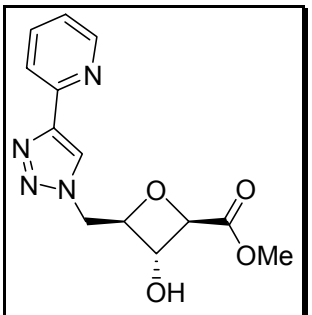
Methyl [(2*R*,3*R*,4*R*)-4-{[4-(4-cyanophenyl)-triazol-1-yl]methyl}-3-hydroxyoxetan-2-yl]carboxylate (240). Using GP 4.3.1.5 with 4-ethynylbenzonitrile but proceeding to flash chromatography (heptane/EtOAc gradient), the desired compound was obtained in 98% yield as colourless oil. $[\alpha]_D^{20.0}$ 106.2 (*c* 0.769, $CHCl_3$). MS (HPLC-MS): m/z 315.1 $[M+H]^+$, 356.1 $[M+H+MeCN]^+$. ^1H NMR (300 MHz, $CDCl_3$): δ 8.33 (s, 1H, CH(triazole)), 7.96 (d, 2H, $J_{2',3'} \approx J_{5',6'} \approx 8.6$ Hz, H-2', H-6'), 7.73 (d, 2H, H-3', H-5'), 5.07-5.00 (m, 1H, H-4), 5.00 (d, 1H, $J_{2,3} = 6.0$ Hz, H-2), 4.96 (A(ABX), 1H, $J_{4,5a} = 3.6$ Hz, H-5a), 4.64 (B(ABX), 1H, $J_{4,5b} = 3.1$ Hz, $J_{5a,5b} = 15.1$ Hz, H-5b), 4.44 (d, 1H, $J_{3,OH} = 5.6$ Hz, OH), 4.35 (q, 1H, $J_{2,3} \approx J_{3,4} \approx J_{3,OH} \approx 5.6$ Hz, H-3), 3.56 (s, 3H, OMe).



241

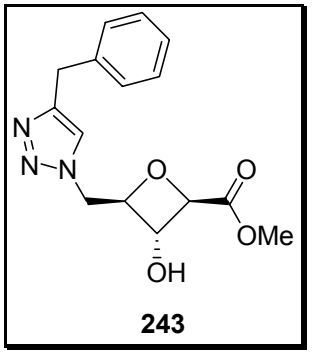
Methyl [(2*R*,3*R*,4*R*)-3-hydroxy-4-{[4-(pyridi-4-yl)-triazol-1-yl]methyl}oxetan-2-yl]carboxylate (241). Using GP 4.3.1.5 with 4-ethynylpyridine but proceeding to prep-HPLC on basic mode, the desired compound was obtained in 71% yield.

$[\alpha]_D^{20.0}$ 100.6 (*c* 0.617, MeOH). MS (HPLC-MS): m/z 391.3 $[M+H]^+$, 354.3 $[M+Na+MeCN]^+$. ^1H NMR (300 MHz, $CDCl_3$): δ 8.66 (br d, 2H, $J_{2',3'} \approx J_{5',6'} \approx 6.1$ Hz, H-2', H-6'), 8.31 (s, 1H, CH(triazole)), 7.75 (br d, 2H, H-3', H-5'), 5.05-5.01 (m, 1H, H-4), 4.98 (d, 1H, $J_{2,3}$ = 5.9 Hz, H-2), 4.91 (A(ABX), 1H, $J_{4,5a}$ = 3.8 Hz, $J_{5a,5b}$ = 15.0 Hz, H-5a), 4.65 (B(ABX), 1H, $J_{4,5b}$ = 3.5 Hz, H-5b), 4.36 (t, 1H, $J_{2,3} \approx J_{3,4} \approx 5.9$ Hz, H-3), 3.58 (s, 3H, OMe).



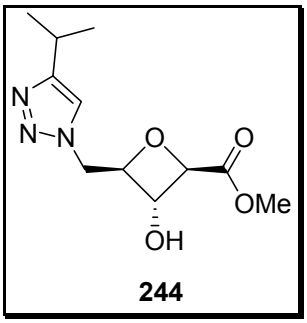
242

Methyl [(2*R*,3*R*,4*R*)-3-hydroxy-4-{[4-(pyridi-2-yl)-triazol-1-yl]methyl}oxetan-2-yl]carboxylate (242). Using GP 4.3.1.5 with 2-ethynylpyridine the desired compound was obtained in 59% yield. $[\alpha]_D^{20.0}$ 107.8 (*c* 0.589, MeOH). MS (HPLC-MS): m/z 291.1 $[M+H]^+$, 354.0 $[M+Na+MeCN]^+$. ^1H NMR (300 MHz, $CDCl_3$): δ 8.58 (br s, 1H, Py), 8.39 (s, 1H, CH(triazole)), 8.07 (d, 1H, J = 7.6 Hz, Py), 7.78 (t, 1H, J = 7.6 Hz, Py), 7.28-7.22 (m, $CDCl_3$+1H, Py), 5.05-5.01 (m, 1H, H-4), 4.99 (d, 1H, $J_{2,3}$ = 5.5 Hz, H-2), 4.87 (A(ABX), 1H, $J_{4,5a}$ = 4.1 Hz, $J_{5a,5b}$ = 14.9 Hz, H-5a), 4.68 (B(ABX), 1H, $J_{4,5b}$ = 4.2 Hz, H-5b), 4.56 (t, 1H, $J_{2,3} \approx J_{3,4} \approx 5.6$ Hz, H-3), 3.60 (s, 3H, OMe).



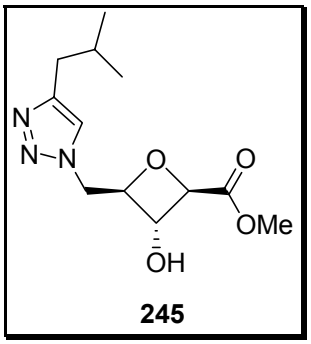
243

Methyl [(2*R*,3*R*,4*R*)-4-{[4-(benzyl)-triazol-1-yl]-3-hydroxymethyl}oxetan-2-yl]carboxylate (243). Using GP 4.3.1.5 with 3-phenyl-1-propyne the desired compound was obtained in 72% yield. $[\alpha]_D^{20.0}$ 89.21 (*c* 0.703, MeOH). MS (HPLC-MS): m/z 304.1 $[M+H]^+$, 367.0 $[M+Na+MeCN]^+$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.53 (s, 1H, CH(triazole)), 7.32-7.19 (m, 5H, Ph+$CHCl_3$), 4.95-4.91 (m, 2H, H-2, H-4), 4.72 (A(ABX), 1H, $J_{4,5a}$ = 4.2 Hz, $J_{5a,5b}$ = 14.9 Hz, H-5a), 4.49 (B(ABX), 1H, $J_{4,5b}$ = 4.1 Hz, H-5b), 4.39 (t, 1H, $J_{2,3} \approx J_{3,4} \approx$ 5.7 Hz, H-3), 4.05 (br s, 2H, CH_2Ph), 3.65 (s, 3H, OMe).



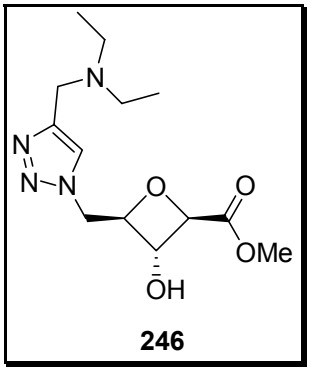
244

Methyl [(2*R*,3*R*,4*R*)-3-hydroxy-4-{[4-(isopropyl)-triazol-1-yl]methyl}oxetan-2-yl]carboxylate (244). Using GP 4.3.1.5 with 3-methyl-1-butyne the desired compound was obtained in 78% yield. $[\alpha]_D^{20.0}$ 62.07 (*c* 0.628, $CDCl_3$). MS (HPLC-MS): m/z 256.1 $[M+H]^+$, 319.0 $[M+Na+MeCN]^+$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.63 (s, 1H, CH(triazole)), 5.01-4.95 (m, 2H, H-2, H-4), 4.94 (A(ABX), 1H, $J_{4,5a}$ = 3.8 Hz, $J_{5a,5b}$ = 15.0 Hz, H-5a), 4.52 (B(ABX), 1H, $J_{4,5b}$ = 3.3 Hz, H-5b), 4.32 (t, 1H, $J_{2,3} \approx J_{3,4} \approx$ 5.8 Hz, H-3), 3.69 (s, 3H, OMe), 3.11-2.97 (m, 1H, CH(*i*-prop)), 1.30 (br s, 3H, Me(*i*-prop)), 1.28 (br s, 3H, Me(*i*-prop)).



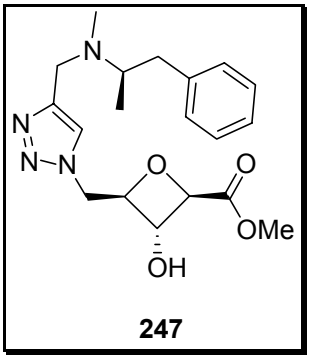
245

Methyl [(2*R*,3*R*,4*R*)-3-hydroxy-4-{[4-(isobutyl)-triazol-1-yl]methyl}oxetan-2-yl]carboxylate (244). Using GP 4.3.1.5 with 4-methyl-1-pentyne the desired compound was obtained in 66% yield. $[\alpha]_D^{20.0}$ 62.07 (*c* 0.628, $CDCl_3$). MS (HPLC-MS): m/z 270.3 $[M+H]^+$, 333.1 $[M+Na+MeCN]^+$. ^1H NMR (300 MHz, $CDCl_3$): δ 7.65 (s, 1H, CH(triazole)), 5.01-4.97 (m, 2H, H-2, H-4), 4.85 (A(ABX), 1H, $J_{4,5a}$ = 3.7 Hz, $J_{5a,5b}$ = 15.1 Hz, H-5a), 4.53 (B(ABX), 1H, $J_{4,5b}$ = 3.3 Hz, H-5b), 4.31 (t, 1H, $J_{2,3} \approx J_{3,4} \approx$ 5.8 Hz, H-3), 3.69 (s, 3H, OMe), 2.56;2.53 (2s, 2H, CH_2(*i*-but)), 2.00-1.87 (m, 1H, CH(*i*-but)), 1.70 (br s, 1H, OH), 0.92-0.89 (m, 6H, 2Me(*i*-but)).



246

Methyl [(2*R*,3*R*,4*R*)-4-({4-[(diethylamino)methyl]-triazol-1-yl} methyl)-3-hydroxy oxetan-2-yl]carboxylate (246). Using GP 4.3.1.5 with *N,N*-diethylpropargylamine the desired compound was obtained in 66% yield. $[\alpha]_D^{20.0}$ 83.42 (*c* 0.547, $CHCl_3$). MS (HPLC-MS): m/z 299.1 $[M+H]^+$, 362.1 $[M+Na+MeCN]^+$. ^1H NMR (300 MHz, MeOD): δ 8.07 (s, 1H, CH(triazole)), 5.05-4.99 (m, 2H, H-2, H-4), 4.88-4.85 (A(ABX), 1H+H_2O, H-5a), 4.68 (B(ABX), 1H, $J_{4,5b}$ = 3.0 Hz, H-5b), 3.96 (t, 1H, $J_{2,3} \approx J_{3,4} \approx$ 5.5 Hz, H-3), 3.78 (br s, 2H, CH_2N), 3.70 (s, 3H, OMe), 2.79 (q, 4H, J = 7.2 Hz, CH_2(Et)), 1.35 (t, 6H, Me(Et)).



247

Methyl [(2*R*,3*R*,4*R*)-4-({4-[(*R*)-deprenyl]-triazol-1-yl}methyl)-3-hydroxyoxetan-2-yl]carboxylate (247). Using GP 4.3.1.5 with R-(-)-deprenyl hydrochloride but using a amine basic flash chromatography the desired compound was obtained in 58% yield. $[\alpha]_D^{20.0}$ -24.52 (*c* 0.461, $CHCl_3$). MS: (ionspray) m/z 375.3 $[M+H]^+$. ^1H NMR (300 MHz, $CDCl_3$): δ 7.49 (s, 1H, CH(triazole)), 7.30-7.14 (m, 5H, Ph+$CHCl_3$), 4.97-4.90 (m, 2H, H-2, H-4), 4.70 (A(ABX), 1H, $J_{4,5a}$ = 4.4 Hz, $J_{5a,5b}$ = 14.7 Hz, H-5a), 4.55 (B(ABX), 1H, $J_{4,5b}$ = 4.6 Hz, H-5b), 4.47 (t, 1H, $J_{2,3} \approx J_{3,4} \approx$ 5.7 Hz, H-3), 3.75 (br s, 2H, CH_2N), 3.69 (s, 3H, OMe), 3.02-2.91 (m, 2H, CHN+C*Ha*HbPh), 2.47 (B(ABX), 1H, $J_{CH,CHb}$ = 10.4Hz, $J_{a,b}$ = 14.6 Hz, CHa*Hb*Ph), 2.30 (s, 3H, MeN), 1.01 (d, 3H, $J_{CH,Me}$ = 6.5 Hz, Me).

5. Appendix

Table A1- NMR data for compounds **34**,**38**, **45-47,49 and 51.**

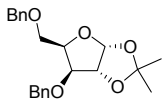
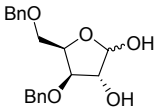
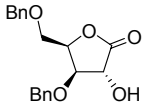
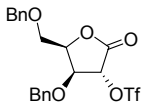
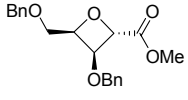
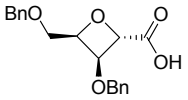
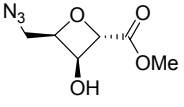
	 **45**	 **46**		 **47**	 **34**	 **38**	 **49**	 **51**
		a	**b**					
	$CDCl_3$	$CDCl_3$	$CDCl_3$	$CDCl_3$	$CDCl_3$	$CDCl_3$	$CDCl_3$	$CDCl_3$
H-1	5.93 d	5.50 t	5.10 d	-	-	-		
H-2	4.62 d	4.22 brddd	4.26 dd	4.81 d	5.89 d	5.06 dd	5.10 dd	5.08 d
H-3	3.97 brdd	4.00 dd	4.02 dd	4.37 t	4.52 t	4.62 dd	4.64 dd	4.87 dd
H-4	4.40 ddd	4.42 q	4.71-4.47 m	4.58 dt	4.51 ddd	5.00 dddd	5.03 dq	4.05 ddd
H-5a	3.78 A(ABX)	3.78 dd	3.68 dd	3.79 dd	3.74 dd	4.42 A(ABX)	3.96 A(ABX)	3.85 A(ABX)
H-5b	3.73 B(ABX)	3.73 dd	3.67 dd	3.71 dd	3.66 dd	3.94 B(ABX)	3.92 B(ABX)	3.62 b(ABX)
CH_2	4.52/4.61 4.51/4.68	4.71-4.47 m		4.83, 4.66, 4.58, 4.52 4d	4.79, 4.59, 4.59, 4.52 4d	4.60-4.53 4d	4.62,4.56 2d 4.65,4.50 2d	
Ph	7.26-7.36 m 2xPh	7.38-7.26 m 2xPh		7.39-7.29 m 2xPh	7.43-7.26 m 2xPh	7.32-7.27 m 2xPh	7.28-7.38 m 2x Ph	
NH		-	-	-	-	-		
OH		3.63(1) 2.80(2)	3.86 (1) 2.13 (2)	-	-	-		
others	1.31 s (*i*-prop) 1.48 s (*i*-prop)			-	-	3.81 s OMe		3.83 s OMe
$J_{1,2}$	3.8	4.8	0	-	-	-	-	-
$J_{2,3}$	3.0	2.4	2.4	8.0	7.9	5.1	5.1	5.3
$J_{2,4}$	-	-	-	-	-	0.4	0.8	-
$J_{3,4}$	6.1	5.0	5.0	8.0	7.9	6.6	6.5	7.0
$J_{4,5a}$	3.0	5.0	5.5	2.2	1.2	5.6	5.7	4.3
$J_{4,5b}$	3.0	4.8	3.8	2.8	2.4	6.0	6.1	3.3
$J_{5a,5b}$	6.1	9.8	7.0	11.0	11.0	10.9	11.0	13.6
	$J_{a,b}$ 11.8 Hz $J_{b',a'}$ 12.2 Hz							

Table A2- NMR data for compounds **52**, **53**, **95-97**.

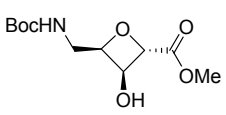
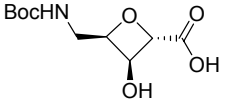
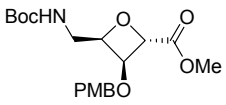
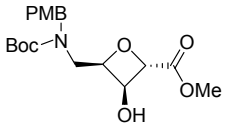
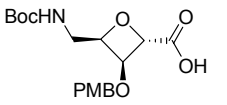
	 **52**	 **53**	 **95**	 **96**	 **97**
	$CDCl_3$	MeOD	$CDCl_3$	$CDCl_3$	MeOD
H-1	-	-	-	-	-
H-2	4.81 d	4.78 d	5.04 d	4.85-4.80 m	5.03 d
H-3	4.76 dd	4.64 br dd	4.57 dd	4.70 br td	4.57 dd
H-4	4.79 ddd	4.61 ddd	4.89-4.78 m	4.85-4.80 m	4.64-4.69 m
H-5a	3.78 ddd~dd	3.44 A(ABX)	3.73-3.62 m	4.00 br dd	3.50 d (2H)
H-5b	3.30 ddd~dd	3.36 B(ABX)	3.57-3.49 m	3.10 d	
CH_2			4.58 A(AB) 4.42 B(AB)	4.50 A(AB) 4.30 B(AB)	4.64-4.69 m 4.46 B(AB)
NH	br t NH		4.89-4.78 m		4.89-4.78 m
OH				5.82 br s	
	3.83 s OMe		7.24 br d 2H(Ph) 6.99 br d 2H(Ph)	7.14 br d 2H(Ph) 6.87 br d 2H(Ph)	7.31 br d 2H(Ph) 6.93 br d 2H(Ph)
			3.81 s 2xOMe	3.80 s 2xOMe	3.81 s 6H 2xOMe
	1.44 s Boc	1.34 s Boc	1.43 s Boc	1.48 s Boc	
$J_{1,2}$	-	-	-		
$J_{2,3}$	3.8	5.7	4.9	4.5	5.0
$J_{2,4}$	-	-	-	-	-
$J_{3,4}$	3.2	6.9	6.7	5.7	
$J_{4,5a}$	7.1	4.9			6.4
$J_{4,5b}$	6.2	6.2		0	6.4
$J_{5a,5b}$	13.4	14.5		14.9	
			$J_{a',b'}$ = 11.5	$J_{3,OH}$ = 5.7 $J_{a,b}$ = 15.4	$J_{a,b}$ = 11.5

Table A3- NMR data for compounds **54**-**61**.

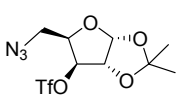
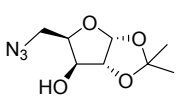
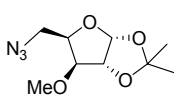
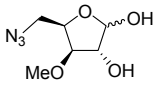
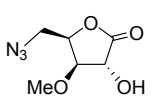
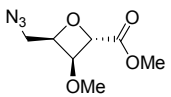
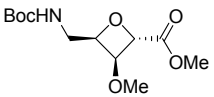
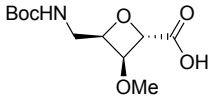
	 **54**	 **55**	 **56**	 **57** **a**	**b**	 **58**	 **59**	 **60**	 **61**
	$CDCl_3$	$CDCl_3$	$CDCl_3$	$CDCl_3$		$CDCl_3$	$CDCl_3$	$CDCl_3$	COC_2D_6
H-1	6.02 d	5.95 d	5.90 d	5.50 d	5.10 d	-	-	-	-
H-2	4.76 d	4.53 d	4.60 d	4.22 brt	4.31 brs	4.66 d	5.05 dd	4.99 d	4.93 d
H-3	5.18 d	4.31 – 4.25 m	3.73 d	3.83 dd	3.79 d	4.20 t	4.44 dd	4.39 dd	4.46 dd
H-4	4.43 dt		4.30 dt	4.46-4.38 m		4.73 dt	4.92 ddd	4.96- 4.76 m	4.79 q
H-5a	3.72 A(ABX)	3.65 A(ABX)	3.53 A(ABX)	3.57- 3.38 m		3.66-3.64 m	3.69 A(ABX)	3.61 ddd	3.56-3.40 m
H-5b	3.50 B(ABX)	3.61 B(ABX)	3.49 B(ABX)				3.64 B(ABX)	3.56-3.49 m	
OMe	-	-	3.43 s	3.46 s	3.50 s	3.56 s	3.43 s, 3.86 s		3.39
Isop	1.53; 1.35	1.51; 1.33	1.51; 1.33	-	-	-	-	3.83 COOMe	-
NH	-	-	-	-	-	-	-	4.96- 4.76 m	5.82 brs
OH	-	2.25 s	-	-	m	2.97 s	-	-	-
Boc	-	-	-	-	-	-	-	1.44	1.40
$J_{1,2}$	3.6	3.7	3.8	4.0	0	-	-	-	-
$J_{2,3}$	0	0	0	3.1	0	7.6	4.8	4.9	4.7
$J_{3,4}$	1.8	2.8	3.1	5.1	4.4	7.6	6.6	6.5	6.3
$J_{4,5a}$	7.0	6.1	6.8	-	-	3.7	6.1	6.8	6.5
$J_{4,5b}$	6.1	5.7	6.3	-	-	3.7	6.3	-	6.5
$J_{5a,5b}$	12.6	12.8	12.4	-	-	-	13.2	12.8	-
C-1	104.7	104.9	105.2	96.1	103.4	174.9	170.7	170.8	170.2
C-2	83.2	85.5	81.5	75.4	80.8, 77.4	71.9	84.0	83.7	83.7
C-3	87.9	75.6	83.9	85.4, 84.6		81.6	77.1	77.4	77.9
C-4	77.3	78.3	78.8	80.8, 77.4		76.8	82.5	82.4	82.2
C-5	48.6	49.4	49.0	50.7, 50.4		50.0	50.4	40.5	40.9
OMe	-	-	57.8	58.6, 58.0		58.6	57.5	52.5	57.3
	113.41 Cq-isop 120.10 CF_3	112.2 Cq-isop	112.0 Cq-isop					155.83 C=O Boc 79.5 Cq Boc, 28.4 Me 57.6 COOMe	156.7 78.8 28.3 Me *t*-Bu

Table A4- NMR data for compounds **64**-**72**.

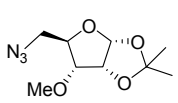
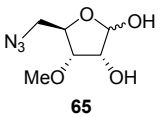
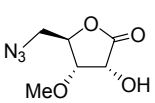
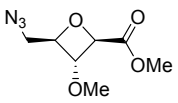
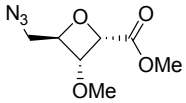
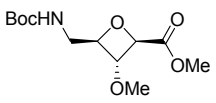
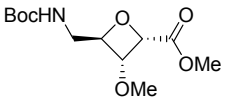
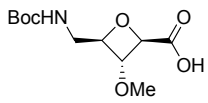
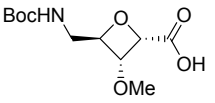
	 **64**	 **65** **a**	**b**	 **66**	 **67**	 **68**	 **69**	 **70**	 **71**	 **72**
	$CDCl_3$	$CDCl_3$		$CDCl_3$	$CDCl_3$	$CDCl_3$	$CDCl_3$	$CDCl_3$	COC_2D_6	COC_2D_6
H-1	5.80 d	5.37-5.32 m		-	-	-	-	-	-	-
H-2	4.71 t	4.18 brt	m	4.63 d	4.95 d	5.17 d	4.93 d	5.09 d	5.59 d	5.18 d
H-3	3.65 dd	3.70 t	4.0 dd	3.90 d	4.27 t	4.51 dd	4.13 t	4.36 dd	4.92 t	4.54 dd
H-4	4.14 dt	4.21 q	m	4.55 dd ≈ t	4.72 brq	4.95 brddd	4.7 brq	4.85 brq	5.31 q	4.81 q
H-5a	3.72 A(ABX)	3.56A(ABX)	3.61A(ABX)	3.74 A(ABX)	3.61 A(ABX)	3.65 A(ABX)	3.52 brddd	3.5 ddd	3.21-4.04 m 5H	3.47 d 2H
H-5b	3.32 B(ABX)	3.32B(ABX)	3.39B(ABX)	3.65 B(ABX)	3.44 B(ABX)	3.39 B(ABX)	3.33 dt	3.39 dt		
OMe	3.50	3.49	3.46	3.52	3.84; 3.40	3.86; 3.35	3.84; 3.37	3.85;3.33		
Isop	1.59; 1.38	-	-	-	-	-	-	-		3.41
NH	-	-	-	-	-	-	5.31 brs	4.93 brs	6.96 brs	----
OH	-	-	-	-	-	-	-	-	-	-
Boc	-	-	-	-	-	-	1.45	1.46 s	1.42	1.39
$J_{1,2}$	3.6	4.5	0	-	-	-	-	-	-	-
$J_{2,3}$	4.1	4.5	4.6	5.9	5.1	6.9	5.0	7.2	4.7	7.3
$J_{3,4}$	8.0	5.5	6.9	0	5.0	5.5	4.9	5.9	4.9	5.0
$J_{4,5a}$	2.5	4.0	3.7	4.3	4.0	3.7	---	4.5	4.9	5.0
$J_{4,5b}$	3.8	3.9	5.2	3.7	4.0	3.4	3.9	4.5	4.9	5.0
$J_{5a,5b}$	13.5	13.2	13.1	13.4	13.8	13.9	15.1	15.0	---	-
							$J_{5b,NH}$ 3.9	$J_{5a,NH}$ 7.0, $J_{5b,NH}$ 4.5		
C-1	104.1	97.1	102.3	174.5	170.2	169.8	170.1	169.9	171.5	171.5
C-2	77.0	70.1	73.2	68.1	81.7	81.4	81.6	81.0	81.6	81.6
C-3	80.6	80.4	81.1	78.0	78.4	75.9	78.7	75.8	80.2	80.2
C-4	77.4	79.1	80.0	79.4	84.2	87.5	85.7	88.6	85.6	85.6
C-5	50.7	52.2	53.3	51.91	52.7	52.8	42.8	42.8	43.3	43.3
OMe	58.6	59.0	58.6	58.5	57.1;52.5	58.4; 52.4	57.3; 52.6	58.0; 52.2	56.6	56.8
	113.4 Cq isop 26.9; 26.6 isop						155.8 C=O Boc 79.1 Cq Boc 27.9 Me *t*-Bu	156.1 C=O Boc 79.8 Cq Boc 28.3 Me *t*-Bu	157.1 C=O Boc 79.1 Cq Boc 28.4 Me *t*-Bu	157.1 C=O Boc 79.1 Cq Boc 28.4 Me *t*-Bu

Table A5- NMR data for compounds **80**-**88**.

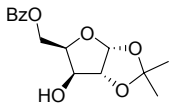
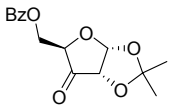
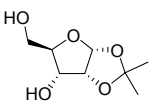
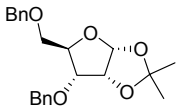
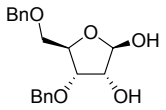
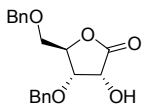
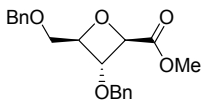
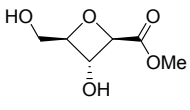
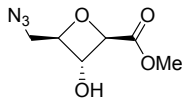
	 **80**	 **81**	 **82**	 **83**	 **84**	 **85**	 **86**	 **87**	 **88**
	$CDCl_3$	$CDCl_3$	$CDCl_3$	$CDCl_3$	$CDCl_3$	$CDCl_3$	$CDCl_3$	$CDCl_3$	$CDCl_3$
H-1	5.96 d	6.14 d	5.83 d	5.76 d	5.23 d	-	-	-	-
H-2	4.60 d	4.44 d	4.59 t	4.56 t	4.03 t	4.67 dd	5.01 dd	4.95 d	4.95 d
H-3	4.17 br dd	-	4.01 dt	3.86 dd	4.28 t	4.19 d	4.52 t	4.74 t	4.76-4.69 m
H-4	4.37 ddd	4.69 br s	3.84 br ddd	4.18 ddd	4.21 ddd	4.50 t	4.76 ddd	4.71 ddd	4.76-4.69 m
H-5a	4.81 A(ABX)	4.71 A(ABX)	3.97 ddd	3.76 A(ABX)	3.64 A(ABX)	3.67 A(ABX)	3.61 A(ABX)	3.84 A(ABX)	3.63 A(ABX)
H-5b	4.38 B(ABX)	4.47 B(ABX)	3.76 ddd	3.57 B(ABX)	3.55 B(ABX)	3.56 B(ABX)	3.55 B(ABX)	3.65 B(ABX)	3.44 B(ABX)
Others	7.46-8.04 m Ph 3.23 d OH 1.51; 1.33 2s Isop	7.44-7.95 m Ph 1.52; 1.44 2s Isop	2.38 d OH-3 2.05 br s OH-5 1.58; 1.38 2s Isop	7.36-7.26 m Ph 4.73 A(AB) Ha 4.54 B(AB) Hb 4.57 A(AB) Ha' 4.49 B(AB) Hb' 1.59; 1.36 2s Isop	7.39-7.26 m Ph 4.61 A(AB) Ha 4.56 B(AB) Hb 4.51 A(AB) Ha' 4.48 B(AB) Hb' 3.36 d OH-1 2.69 s OH-2	7.38-7.22 m Ph 4.72-4.64 AB Ha, Hb 4.55-4.23 AB Ha', Hb' 2.82 d OH-2	7.36-7.28 m Ph 4.67 – 4.60 AB Ha, Hb 4.67 – 4.60 AB Ha', Hb' 3.25 s OMe	3.80 s OMe	3.84 s OMe 3.26 br d OH
$J_{1,2}$	3.6	4.4	3.9	3.8	~ 0	-	-	-	-
$J_{2,3}$	0	-	5.1	4.3	4.7	5.9	5.2	4.9	4.8
$J_{3,4}$	2.2	-	9.0	8.9	5.9	~ 0	4.9	5.1	
$J_{4,5a}$	9.4	2.8	2.4	2.2	3.0	3.0	3.7	2.5	3.0
$J_{4,5b}$	4.5	4.7	3.6	3.8	2.9	2.5	4.0	2.0	3.3
$J_{5a,5b}$	12.7	13.4	12.0	11.3	10.3	10.9	11.5	13.4	13.7
	$J_{3,OH3}$ 4.0		$J_{3,OH3}$ 10.5	$J_{a',b'}$ 12.2 $J_{a,b}$ 11.9	$J_{a',b'}$ 8.3 $J_{a,b}$ 5.6 $J_{1,OH1}$ 7.4	$J_{a',b'}$ 12.0 $J_{a,b}$ 11.9 $J_{2,OH2}$ 9.5	$J_{a',b'}$ 11.6 $J_{a,b}$ 11.6		

Table A6- NMR data for compounds **74**-**79**, **89**-**91**.

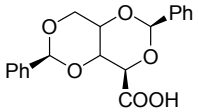
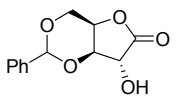
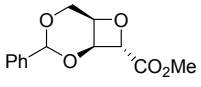
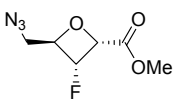
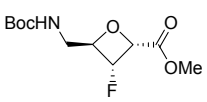
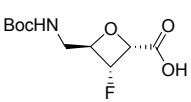
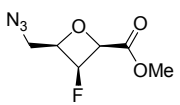
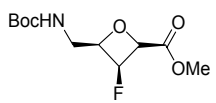
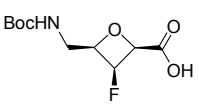
	 **75**	 **74**	 **76**	 **77**	 **78**	 **79**	 **89**	 **90**	 **91**
	DMSO	$CDCl_3$	$CDCl_3$	$CDCl_3$	$CDCl_3$	COC_2D_6	$CDCl_3$	$CDCl_3$	$CDCl_3$
H-2	4.78 d	4.59-4.53 m	4.99 d	5.23 dd	5.13 dd	5.18 dd	5.30 dd	5.28 dd	5.29 dd
H-3	4.37 br t	4.32 br s	4.92 dd	5.53 ddd	5.37 ddd	5.41 ddd	5.65 dt	5.60 dt	5.64 dt
H-4	4.04 br q	4.59-4.53 m	4.89 dd	5.14 dddd	5.03 dddd	5.03 br dq	5.02-4.91 m	5.04-4.91 m	5.01-4.86 m
H-5a	4.21 A(ABX)		4.30 d	3.72 A(ABX)	3.58 ddd	3.54-3.39 m	3.80 A(ABX)	3.59-3.54 m	4.08-3.95 m
H-5b	4.16 A(ABX)	4.19 B(ABX)	3.99 dd	3.48 B(ABX)	3.41 ddd		3.67 B(ABX)		3.29-3.19 m
Ph	7.52-7.50 m 2H 7.44-7.35 m 8H	7.46-7.44 m 2H 7.38-7.36 m 3H	7.48-7.29 m	-	-		-	-	-
CHPh	5.75 s, 5.69 s	5.54 s	5.42 s	-	-		-	-	-
NH	-	-	-	-	4.93 br s		-	5.04-4.91 m	5.01-4.86 m
OH	12.90	3.41 br s	-	-	-		-	-	-
OMe	-	-	-	3.87 s	3.86 s		3.86 s	3.84 s	-
Boc	-	-	-	-	1.46 s	1.47 s	-	1.44 s	1.46 s
$J_{2,3}$	2.1	-	2.2	6.7	6.8	6.7	5.8	5.6	6.0
$J_{2,F}$	-	-	-	15.2	14.8	15.3	18.4	18.9	17.8
$J_{3,4}$	1.8	-	5.1	4.5	4.8	4.7	5.8	5.6	6.0
$J_{3,F}$	-	-	-	56.1	56.0	55.7	56.2	56.6	56.1
$J_{4,F}$	-	-	-	19.1	19.1	19.5	15.5	-	-
$J_{4,5a}$	1.8	-	0	3.4	3.4	4.3	1.7	-	-
$J_{4,5b}$	1.3	1.8	2.5	3.0	3.0	4.3		-	-
$J_{5a,5b}$	12.8	13.5	14.0	14.2	14.8		13.0	-	-
$J_{5a,NH}$	-	-	-	-	7.2			-	-
$J_{5b,NH}$	-	-	-	-	4.7			-	-

Table A7- In silico results for compounds **102**-**121**.

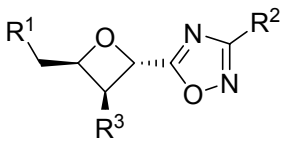
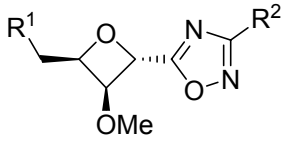
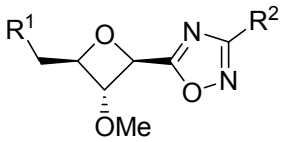
				MW	ClogP	ROF alerts	HBD	HBA	RotB	PSA	Peff	logBB	Andrew Binding	PKa ACID	PKa BASE
	R^1	R^2	R^3												
102	NHBoc	Ph	OPMB	467.52	3.94	0	1	9	8	92.62	-3.91	-0.86	8.61	*	*
103	NHBoc	*p*-OMePh	OPMB	497.55	4.0	0	1	10	9	101.04	-4.00	-0.99	9.81	*	*
104	NHBoc	*p*-ClPh	OPMB	501.97	4.7	0	1	9	8	92.62	-3.83	-0.75	9.91	*	*
105	NHBoc	*p*-MePh	OPMB	481.55	4.4	0	1	9	8	92.62	-3.84	-0.77	9.41	*	*
106	NHBoc	Py	OPMB	468.51	2.5	0	1	10	8	103.59	-4.19	-1.25	9.11	*	*
107	NH_2	Ph	OH	361.28	0.3	0	3	6	2	82.77	-4.84	-1.46	-0.46	13.48	9.03
108	NH_2	*p*-OMePh	OH	391.30	0.4	0	3	7	3	91.17	-4.93	-1.59	0.87	13.51	9.03
109	NH_2	*p*-ClPh	OH	395.72	1.1	0	3	6	2	82.79	-4.76	-1.35	0.96	13.45	9.03
110	NH_2	*p*-MePh	OH	375.30	0.8	0	3	6	2	82.77	-4.77	-1.37	0.46	13.52	9.03
111	NH_2	Py	OH	362.26	-1.1	0	3	7	2	93.75	-5.13	-1.85	0.16	13.34	9.03
112	NHAc	Ph	OH	289.29	0.4	0	2	7	3	87.11	-4.67	-1.54	3.17	13.53	*
113	NHAc	*p*-OMePh	OH	319.32	0.5	0	2	8	4	95.6	-4.76	-1.67	4.38	13.56	*
114	NHAc	*p*-ClPh	OH	323.74	1.2	0	2	7	3	87.11	-4.58	-1.43	4.47	13.50	*
115	NHAc	*p*-MePh	OH	303.32	0.9	0	2	7	3	87.11	-4.60	-1.45	3.97	13.56	*
116	NHAc	Py	OH	290.28	-1.0	0	2	8	3	98.09	-4.95	-1.94	3.67	13.38	*
117	NHMs	Ph	OH	325.34	0.6	0	2	8	4	103.72	-4.85	-1.81	13.07	10.91	*
118	NHMs	*p*-OMePh	OH	355.36	0.6	0	2	9	5	112.91	-4.95	-1.95	14.28	10.91	*
119	NHMs	*p*-ClPh	OH	359.78	1.3	0	2	8	4	103.68	-4.77	-1.70	14.37	10.91	*
120	NHMs	*p*-MePh	OH	339.37	1.1	0	2	8	4	103.72	-4.78	-1.72	13.87	10.91	*
121	NHMs	Py	OH	326.33	-0.9	0	2	9	4	114.7	-5.13	-2.20	13.57	10.91	*

Table A8- In silico results for compounds **122**-**141**.



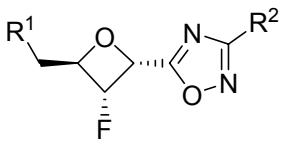
	R^1	R^2	MW	ClogP	ROF alerts	HBD	HBA	RotB	PSA	Peff	logBB	Andrew Binding	PKa ACID	PKa BASE
122	NHBoc	Ph	361.40	2.2	0	1	8	5	84.49	-4.05	-1.03	4.69	*	*
123	NHBoc	*p*-OMePh	391.42	2.2	0	1	9	6	92.82	-4.13	-1.16	5.90	*	*
124	NHBoc	*p*-ClPh	395.84	2.9	0	1	8	5	84.4	-3.96	-0.92	5.99	*	*
125	NHBoc	*p*-MePh	375.42	2.7	0	1	8	5	84.42	-3.97	-0.94	5.49	*	*
126	NHBoc	Py	362.38	0.8	0	1	9	5	95.35	-4.33	-1.42	5.19	*	*
127	NH_2	Ph	375.30	0.4	0	2	6	3	74.72	-4.42	-1.20	-1.06	*	8.94
128	NH_2	*p*-OMePh	405.33	0.4	0	2	7	4	83.17	-4.51	-1.33	0.27	*	8.94
129	NH_2	*p*-ClPh	409.75	1.1	0	2	6	3	74.67	-4.34	-1.09	0.36	*	8.94
130	NH_2	*p*-MePh	389.33	0.9	0	2	6	3	74.7	-4.35	-1.11	-0.26	*	8.94
131	NH_2	Py	376.29	-1.0	0	2	7	3	85.65	-4.70	-1.59	-0.56	*	8.94
132	NHAc	Ph	303.32	0.2	0	1	7	4	78.97	-4.24	-1.28	2.57	*	*
133	NHAc	*p*-OMePh	333.34	0.3	0	1	8	5	87.5	-4.33	-1.42	3.78	*	*
134	NHAc	*p*-ClPh	337.76	0.9	0	1	7	4	79.04	-4.16	-1.17	3.87	*	*
135	NHAc	*p*-MePh	317.34	0.7	0	1	7	4	79.04	-4.17	-1.19	3.37	*	*
136	NHAc	Py	304.30	-1.2	0	1	8	4	89.94	-4.53	-1.68	3.07	*	*
137	NHMs	Ph	339.37	0.4	0	1	8	5	95.25	-4.42	-1.55	12.47	10.86	*
138	NHMs	*p*-OMePh	369.39	0.4	0	1	9	6	103.68	-4.51	-1.68	13.68	10.86	*
139	NHMs	*p*-ClPh	373.81	1.1	0	1	8	5	95.21	-4.34	-1.43	13.77	10.86	*
140	NHMs	*p*-MePh	353.39	0.9	0	1	8	5	95.21	-4.35	-1.45	13.27	10.86	*
141	NHMs	Py	340.35	-1.0	0	1	9	5	106.16	-4.71	-1.94	12.97	10.86	*

Table A9- In silico results for compounds **142**-**161**.



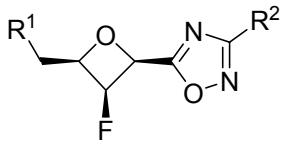
	R^1	R^2	MW	ClogP	ROF alerts	HBD	HBA	RotB	PSA	Peff	logBB	Andrew Binding	PKa ACID	PKa BASE
142	NHBoc	Ph	361.40	2.2	0	1	8	5	85.47	-4.06	-1.05	4.69	*	*
143	NHBoc	*p*-OMePh	391.42	2.2	0	1	9	6	93.93	-4.15	-1.18	5.90	*	*
144	NHBoc	*p*-ClPh	395.84	2.9	0	1	8	5	85.49	-3.97	-0.94	5.99	*	*
145	NHBoc	*p*-MePh	375.42	2.7	0	1	8	5	85.47	-3.99	-0.95	5.49	*	*
146	NHBoc	Py	362.38	0.8	0	1	9	5	96.44	-4.34	-1.44	5.19	*	*
147	NH_2	Ph	375.30	0.4	0	2	6	3	75.65	-4.43	-1.22	-1.06	*	8.94
148	NH_2	*p*-OMePh	405.33	0.4	0	2	7	4	84.35	-4.52	-1.35	0.27	*	8.94
149	NH_2	*p*-ClPh	409.75	1.1	0	2	6	3	75.67	-4.35	-1.11	0.36	*	8.94
150	NH_2	*p*-MePh	389.33	0.9	0	2	6	3	75.65	-4.36	-1.12	-0.26	*	8.94
151	NH_2	Py	376.29	-1.0	0	2	7	3	86.62	-4.72	-1.61	-0.56	*	8.94
152	NHAc	Ph	303.32	0.2	0	1	7	4	80.24	-4.26	-1.31	2.57	*	*
153	NHAc	*p*-OMePh	333.34	0.3	0	1	8	5	88.73	-4.35	-1.44	3.78	*	*
154	NHAc	*p*-ClPh	337.76	0.9	0	1	7	4	80.26	-4.17	-1.20	3.87	*	*
155	NHAc	*p*-MePh	317.34	0.7	0	1	7	4	80.24	-4.19	-1.21	3.37	*	*
156	NHAc	Py	304.30	-1.2	0	1	8	4	91.24	-4.54	-1.70	3.07	*	*
157	NHMs	Ph	339.37	0.4	0	1	8	5	96.46	-4.44	-1.57	12.47	10.86	*
158	NHMs	*p*-OMePh	369.39	0.4	0	1	9	6	104.95	-4.53	-1.70	13.68	10.86	*
159	NHMs	*p*-ClPh	373.81	1.1	0	1	8	5	96.46	-4.35	-1.46	13.77	10.86	*
160	NHMs	*p*-MePh	353.39	0.9	0	1	8	5	96.46	-4.37	-1.47	13.27	10.86	*
161	NHMs	Py	340.35	-1.0	0	1	9	5	107.45	-4.72	-1.96	12.97	10.86	*

Table A10- In silico results for compounds **162**-**181**.



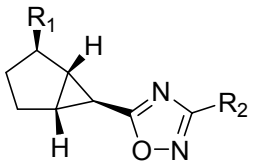
	R^1	R^2	MW	ClogP	ROF alerts	HBD	HBA	RotB	PSA	Peff	logBB	Andrew Binding	PKa ACID	PKa BASE
162	NHBoc	Ph	349.36	2.5	0	1	7	4	76.40	-3.86	-0.77	4.78	*	*
163	NHBoc	*p*-OMePh	379.39	2.5	0	1	8	5	84.77	-3.95	-0.90	5.99	*	*
164	NHBoc	*p*-ClPh	383.81	3.2	0	1	7	4	76.40	-3.78	-0.66	6.08	*	*
165	NHBoc	*p*-MePh	363.39	3.0	0	1	7	4	76.40	-3.79	-0.68	5.58	*	*
166	NHBoc	Py	350.35	1.1	0	1	8	4	87.35	-4.14	-1.16	5.28	*	*
167	NH_2	Ph	363.27	0.7	0	2	5	2	66.97	-4.24	-0.95	-0.95	*	8.66
168	NH_2	*p*-OMePh	393.29	0.7	0	2	6	3	75.02	-4.32	-1.07	0.36	*	8.66
169	NH_2	*p*-ClPh	397.71	1.4	0	2	5	2	66.60	-4.15	-0.83	0.45	*	8.66
170	NH_2	*p*-MePh	377.29	1.2	0	2	5	2	66.60	-4.16	-0.85	-0.15	*	8.66
171	NH_2	Py	364.26	-0.7	0	2	6	2	77.55	-4.52	-1.33	-0.45	*	8.66
172	NHAc	Ph	291.28	0.5	0	1	6	3	70.94	-4.06	-1.03	2.66	*	*
173	NHAc	*p*-OMePh	321.31	0.6	0	1	7	4	79.38	-4.15	-1.16	3.87	*	*
174	NHAc	*p*-ClPh	325.73	1.3	0	1	6	3	70.94	-3.97	-0.92	3.96	*	*
175	NHAc	*p*-MePh	305.31	1.0	0	1	6	3	70.89	-3.98	-0.93	3.46	*	*
176	NHAc	Py	292.27	-0.9	0	1	7	3	81.91	-4.34	-1.42	3.16	*	*
177	NHMs	Ph	327.33	0.7	0	1	7	4	87.18	-4.24	-1.29	12.56	10.73	*
178	NHMs	*p*-OMePh	357.36	0.7	0	1	8	5	95.65	-4.33	-1.42	13.77	10.73	*
179	NHMs	*p*-ClPh	361.77	1.4	0	1	7	4	87.18	-4.15	-1.18	13.86	10.73	*
180	NHMs	*p*-MePh	341.36	1.2	0	1	7	4	87.18	-4.17	-1.19	13.36	10.73	*
181	NHMs	Py	328.32	-0.7	0	1	8	4	98.48	-4.52	-1.68	13.06	10.73	*

Table A11- In silico results for compounds **182**-**185**.



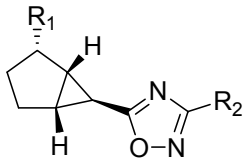
	R^1	R^2	MW	ClogP	ROF alerts	HBD	HBA	RotB	PSA	Peff	logBB	Andrew Binding	PKa ACID	PKa BASE
182	NHBoc	*p*-ClPh	383.81	3.2	0	1	7	4	76.51	-3.78	-0.66	6.08	*	*
183	NH_2	*p*-ClPh	397.71	1.4	0	2	5	2	66.92	-4.15	-0.84	0.45	*	8.66
184	NHAc	*p*-ClPh	325.73	1.3	0	1	6	3	71.26	-3.98	-0.92	3.96	*	*
185	NHMs	*p*-ClPh	361.77	1.4	0	1	7	4	87.46	-4.16	-1.18	13.86	10.73	*

Table A12- In silico results for compounds **188**-**207**.



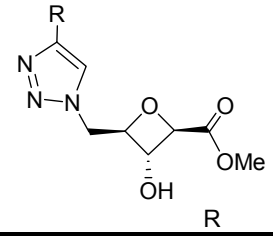
	R^1	R^2	MW	ClogP	ROF alerts	HBD	HBA	RotB	PSA	Peff	logBB	Andrew Binding	PKa ACID	PKa BASE
188	NHBoc	Ph	341.41	2.9	0	1	6	3	65.50	-3.46	-0.22	4.67	*	*
189	NHBoc	*p*-OMePh	371.44	3.0	0	1	7	4	73.95	-3.55	-0.35	5.88	*	*
190	NHBoc	*p*-ClPh	375.85	3.7	0	1	6	3	65.50	-3.37	-0.11	5.97	*	*
191	NHBoc	*p*-MePh	355.44	3.4	0	1	6	3	65.50	-3.39	-0.13	5.47	*	*
192	NHBoc	Py	342.40	1.5	0	1	7	3	76.48	-3.74	-0.61	5.17	*	*
193	NH_2	Ph	355.32	1.2	0	2	4	1	55.75	-3.83	-0.39	-1.04	*	10.72
194	NH_2	*p*-OMePh	385.34	1.2	0	2	5	2	64.20	-3.92	-0.52	0.25	*	10.72
195	NH_2	*p*-ClPh	389.76	1.9	0	2	4	1	55.75	-3.75	-0.28	0.34	*	10.72
196	NH_2	*p*-MePh	369.34	1.7	0	2	4	1	55.75	-3.76	-0.30	-0.24	*	10.72
197	NH_2	Py	356.30	-0.2	0	2	5	1	66.73	-4.12	-0.79	-0.54	*	10.72
198	NHAc	Ph	283.33	2.4	0	1	5	2	60.02	-3.65	-0.48	2.55	*	*
199	NHAc	*p*-OMePh	313.36	2.5	0	1	6	3	68.47	-3.74	-0.61	3.76	*	*
200	NHAc	*p*-ClPh	317.77	3.1	0	1	5	2	60.02	-3.57	-0.37	3.85	*	*
201	NHAc	*p*-MePh	297.36	3.0	0	1	5	2	60.02	-3.58	-0.38	3.35	*	*
202	NHAc	Py	284.32	1.3	0	1	6	2	71.00	-3.94	-0.87	3.05	*	*
203	NHMs	Ph	319.38	2.5	0	1	6	3	76.21	-3.83	-0.74	12.45	11.71	*
204	NHMs	*p*-OMePh	349.40	2.6	0	1	7	4	84.66	-3.92	-0.87	13.66	11.71	*
205	NHMs	*p*-ClPh	353.82	3.2	0	1	6	3	76.21	-3.75	-0.63	13.75	11.71	*
206	NHMs	*p*-MePh	333.40	3.1	0	1	6	3	76.21	-3.76	-0.64	13.25	11.71	*
207	NHMs	Py	320.37	-0.4	0	1	7	3	87.19	-4.12	-1.13	12.95	11.71	*

Table A13- In silico results for compounds **208**-**227**.



	R^1	R^2	MW	ClogP	ROF alerts	HBD	HBA	RotB	PSA	Peff	logBB	Andrew Binding	PKa ACID	PKa BASE
208	NHBoc	Ph	341.41	2.9	0	1	6	3	65.50	-3.46	-0.22	4.66	*	*
209	NHBoc	*p*-OMePh	371.44	3.0	0	1	7	4	73.95	-3.55	-0.35	5.88	*	*
210	NHBoc	*p*-ClPh	375.85	3.7	0	1	6	3	65.50	-3.37	-0.11	5.97	*	*
211	NHBoc	*p*-MePh	355.44	3.4	0	1	6	3	65.50	-3.39	-0.13	5.47	*	*
212	NHBoc	Py	342.40	1.5	0	1	7	3	76.48	-3.74	-0.61	5.17	*	*
213	NH_2	Ph	355.32	1.2	0	2	4	1	55.75	-3.83	-0.39	-1.04	*	10.72
214	NH_2	*p*-OMePh	385.34	1.2	0	2	5	2	63.19	-3.91	-0.51	0.25	*	10.72
215	NH_2	*p*-ClPh	389.76	1.9	0	2	4	1	55.75	-3.75	-0.28	0.34	*	10.72
216	NH_2	*p*-MePh	369.34	1.7	0	2	4	1	54.74	-3.75	-0.28	-0.24	*	10.72
217	NH_2	Py	356.30	-0.2	0	2	5	1	65.71	-4.10	-0.77	-0.54	*	10.72
218	NHAc	Ph	283.33	0.8	0	1	5	2	60.04	-3.65	-0.48	2.55	*	*
219	NHAc	*p*-OMePh	313.36	0.8	0	1	6	3	68.49	-3.74	-0.61	3.76	*	*
220	NHAc	*p*-ClPh	317.77	1.5	0	1	5	2	60.04	-3.57	-0.37	3.85	*	*
221	NHAc	*p*-MePh	297.36	1.3	0	1	5	2	60.04	-3.58	-0.38	3.35	*	*
222	NHAc	Py	284.32	-0.6	0	1	6	2	71.00	-3.94	-0.87	3.05	*	*
223	NHMs	Ph	319.38	1.0	0	1	6	3	76.15	-3.83	-0.74	12.45	11.71	*
224	NHMs	*p*-OMePh	349.40	1.0	0	1	7	4	84.59	-3.92	-0.86	13.66	11.71	*
225	NHMs	*p*-ClPh	353.82	1.7	0	1	6	3	76.15	-3.75	-0.62	13.75	11.71	*
226	NHMs	*p*-MePh	333.40	1.5	0	1	6	3	76.15	-3.76	-0.64	13.25	11.71	*
227	NHMs	Py	320.37	-0.4	0	1	7	3	87.12	-4.12	-1.13	12.95	11.71	*

Table A14- In silico results for compounds **233**-**247**.

	MW	ClogP	ROF alerts	HBD	HBA	RotB	PSA	Peff	logBB	Andrew Binding	PKa ACID	PKa BASE
233	303.32	1.2	0	1	7	3	80.13	-4.05	-1.03	3.97	12.61	*
234	317.34	1.4	0	1	7	3	77.65	-3.95	-0.89	4.77	12.61	*
235	319.32	0.6	0	1	8	4	88.62	-4.21	-1.25	4.38	12.59	*
236	349.34	0.3	0	1	9	5	97.09	-4.36	-1.47	5.59	12.61	*
237	307.28	0.8	0	1	7	3	80.13	-4.09	-1.09	4.47	12.59	*
238	373.29	1.7	0	1	8	5	88.62	-4.08	-1.09	7.59	12.59	*
239	323.74	1.4	0	1	7	3	80.11	-4.03	-1.01	4.47	12.58	*

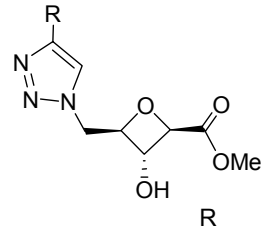
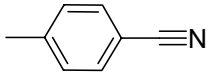
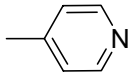
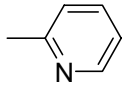
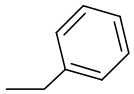
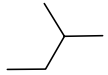
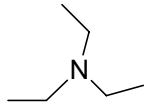
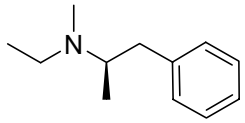
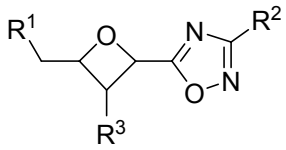
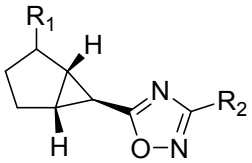
	MW	ClogP	ROF alerts	HBD	HBA	RotB	PSA	Peff	logBB	Andrew Binding	PKa ACID	PKa BASE
240 	314.30	0.2	0	1	8	3	100.84	-4.42	-1.55	3.68	12.59	*
241 	290.28	-0.7	0	1	8	3	91.08	-4.40	-1.51	3.67	12.54	*
242 	290.28	-0.5	0	1	8	3	90.44	-4.39	-1.50	3.67	12.49	*
243 	303.32	0.4	0	1	7	5	80.31	-4.06	-1.04	3.28	12.64	*
244 	255.27	-0.3	0	1	7	4	80.57	-4.16	-1.18	0.67	12.68	*
245 	269.30	0.3	0	1	7	5	78.54	-4.08	-1.06	1.47	12.66	*
246 	298.34	-0.6	0	1	8	7	84.26	-4.35	-1.43	2.09	12.62	10.27
247 	374.44	0.8	0	1	8	8	85.18	-4.17	-1.20	5.51	12.62	9.25

Table A15- MDO assays for oxetane derived 1,2,4-oxadiazole libraries.



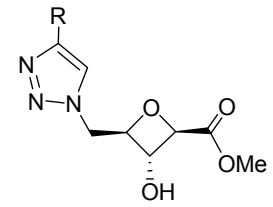
	R^1	R^2	R^3	Stereochem.	CEpKa	logD	lysa	Pampa predicted	Pampa measured	hCL_{int}	mCL_{int}
104	NHBoc	*p*-ClPh	OPMB	D-*lyxo*		4.0	1	M2H	-	-	-
109	NH_2	*p*-ClPh	OH	D-*lyxo*	8.3	2.1	375	L	M2H	12(M)	10(L)
114	NHAc	*p*-ClPh	OH	D-*lyxo*		2.0	479	L	M2H	18(M)	23(M)
119	NHMs	*p*-ClPh	OH	D-*lyxo*		1.9	325	L	M2H	42(H)	53(M)
122	NHBoc	Ph	OMe	D-*lyxo*		3.3	47	M2H	M2H	19 (M)	27 (L)
124	NHBoc	*p*-ClPh	OMe	D-*lyxo*		4.0	1	M2H	M2H	0 (L)	6 (L)
127	NH_2	Ph	OMe	D-*lyxo*	8.5	0.4	375	L	M2H	-	-
129	NH_2	*p*-ClPh	OMe	D-*lyxo*	8.5	1.1	455	L	M2H	-	-
132	NHAc	Ph	OMe	D-*lyxo*		1.6	360	borderline	M2H	6 (L)	9 (L)
134	NHAc	*p*-ClPh	OMe	D-*lyxo*		2.3	385	borderline	M2H	11 (M)	11 (L)
137	NHMs	Ph	OMe	D-*lyxo*		1.8	365	L	M2H	5(L)	12(L)
139	NHMs	*p*-ClPh	OMe	D-*lyxo*		2.2	200	L	M2H	0 (L)	0 (L)
144	NHBoc	*p*-ClPh	OMe	D-*ribo*		>3	1	M2H	M2H	-	-
146	NHBoc	*p*-Py	OMe	D-*ribo*		2.1	400	borderline	M2H	-	-
149	NH_2	*p*-ClPh	OMe	D-*ribo*	7.8	1.5	525	L	M2H	0 (L)	11(L)
151	NH_2	*p*-Py	OMe	D-*ribo*		-	435	L	M2H	18(M)	54(M)
154	NHAc	*p*-ClPh	OMe	D-*ribo*		2.2	340	borderline	M2H	20(M)	0(L)
156	NHAc	*p*-Py	OMe	D-*ribo*		0.2	295	L	M2H	13(M)	21(M)
159	NHMs	*p*-ClPh	OMe	D-*ribo*		-	205	L	M2H	22(M)	27(M)
161	NHMs	*p*-Py	OMe	D-*ribo*		0.5	355	L	M2H	7(M)	27(M)
162	NHBoc	Ph	F	D-*arabino*		3.0	41	M2H	-	-	-
163	NHBoc	*p*-OMePh	F	D-*arabino*		3.2	17	M2H	-	-	-
167	NH_2	Ph	F	D-*arabino*		1.0	370	L	M2H	3(L)	14(M)
168	NH_2	*p*-OMePh	F	D-*arabino*	7.6	1.0	385	L	M2H	24(M)	14(M)
172	NHAc	Ph	F	D-*arabino*		1.6	290	M2H	-	27(M)	44(M)
173	NHAc	*p*-OMePh	F	D-*arabino*		1.7	170	borderline	M2H	5(L)	43(M)
177	NHMs	Ph	F	D-*arabino*		1.5	355	borderline	M2H	1(L)	12(L)
178	NHMs	*p*-OMePh	F	D-*arabino*		1.6	17	borderline	M2H	0(L)	7(L)
182	NHBoc	*p*-ClPh	F	D-*xylo*		3.7	1	M2H	-	-	-
183	NH_2	*p*-ClPh	F	D-*xylo*		1.2	395	L	M2H	-	-
184	NHAc	*p*-ClPh	F	D-*xylo*		2.2	71	M2H	-	15(M)	20(M)
185	NHMs	*p*-ClPh	F	D-*xylo*		2.1	23	M2H	-	6(L)	0(L)

Table A16- MDO assays for bicyclic 1,2,4-oxadiazole libraries.

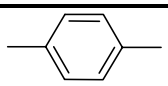
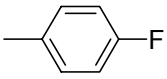
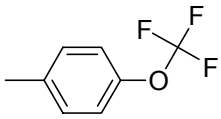
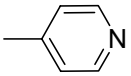
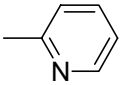
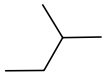
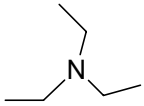
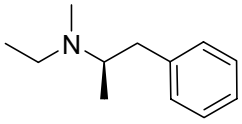


	R^1		R^2	CEpKa	logD	lysa	Pampa predicted	Pampa mesured	hCL_{int}	mCL_{int}
104	NHBoc	up	Ph		>3	1	M2H	-	-	-
109	NH_2	up	Ph		0.6	395	L	M2H	4.90(L)	73.41(H)
114	NHAc	up	Ph		2.4	275	M2H	-	0.00(L)	5.28(L)
119	NHMs	up	Ph		2.2	20	M2H	-	5.03(L)	20.88(M)
122	NHBoc	down	Ph		>3	1	M2H	-	-	-
124	NHBoc	down	*p*-MePh		>3	1	M2H	-	-	-
127	NH_2	down	Ph	9.2	0.5	390	L	M2H	6.01(L)	66.63(M)
129	NH_2	down	*p*-MePh	9.2	1.1	380	L	M2H	15.24(M)	34.26(M)
132	NHAc	down	Ph		2.5	295	M2H	-	3.90(L)	178.82(H)
134	NHAc	down	*p*-MePh		2.9	260	M2H	-	4.14(L)	123.16(H)
137	NHMs	down	Ph		2.2	43	M2H	-	0.00(L)	32.03(M)
139	NHMs	down	*p*-MePh		2.7	1	M2H	-	14.24(M)	157.18(H)

Table A17- MDO assays for oxetane 1,2,3-triazole library.



R

	R	logD	Lysa	Pampa predicted	Pampa measured	hCL_{int}	mCL_{int}
233		0.6	270	M2H	-	1946 (H)	3873(H)
237		-	275	M2H	-	-	-
238		1.6	27	M2H	-	-	-
241		-0.8	-	L	M2H	-	-
242		-0.6	240	L	M2H	-	-
245		-	245	M2H	-	-	-
246		-	-	L	no UV detection	-	-
247		-	260	L	M2H	-	-