SYNTHESIS, ENZYMATIC RESOLUTION AND TRANSFORMATIONS OF ALICYCLIC *CIS*- AND *TRANS*-1,2-DIFUNCTIONAL COMPOUNDS

Ph.D. Thesis

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PUBLICATIONS RELATED TO THE THESIS

Full papers

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ABBREVIATIONS

Ac	acetyl
Boc	*tert*-butoxycarbonyl
t-Bu	*tert*-butyl
c	conversion
CAL-A	lipase from *Candida antarctica*
CAL-B	lipase from *Candida antarctica*
CDI	*N*, *N*'-carbonyldiimidazole
Cp	cyclopentyl
CSI	chlorosulfonyl isocyanate
DCC	dicyclohexylcarbodiimide
DMAP	4-(dimethylamino)pyridine
DMF	dimethylformamide
EDC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
ee	enantiomeric excess
ee_s	enantiomeric excess of substrate
ee_p	enantiomeric excess of product
E	enantiomeric ratio
Et	ethyl
GC	gas chromatography
HPLC	high-performance liquid chromatrographyy
lipase AK	lipase from *Pseudomonas fluorescens*
lipase PS	lipase from *Pseudomonas cepacia*
Me	methyl
MS	mass spectroscopy
NMR	nuclear magnetic resonance spectroscopy
Ph	phenyl
PPA	polyphosphoric acid
PPL	porcine pancreatic lipase
*i*Pr	*iso*propyl
PTAB	phenyltrimethylammonium perbromide
TEA	triethyl amine
THF	tetrahydrofuran
TMS	tetramethysilane
Ts	*p*-toluenesulfonyl
p-TSA	*p*-toluenesulfonic acid
VA	vinyl acetate
VB	vinyl butyrate

1. INTRODUCTION

Much attention has recently been focused on the alicyclic β-amino acids because a number of their derivatives exhibit interesting pharmacological effects[1,2]. β-Amino acids are also key structural elements of important medical compounds such as the promising anti-cancer agent Taxol, where the side-chain containing β-amino acid is essential for its biological activity[3]. The synthesis and transformations of β-amino acids with five- and six-membered rings have been widely reviewed[4-9], but very few papers on cycloheptane and cyclooctane derivatives are known[10-12], and preparations of the higher-ring homologous β-amino acids have not been published yet. Important β-amino acid derivatives (and precursors) are the β-lactams, which have been found in antibiotics[13], human leukocyte elastase inhibitors[14], and cholesterol uptake inhibitors[15]. This stimulated us to synthetize enantiopure β-amino acids and β-lactams.

Pyridopyrimidinones are of pharmaceutical importance: they possess analgesic, antipyretic, antiarteriosclerotic, antibiotic, *etc*. effects[16]. The syntheses and chemical reactivities of a great number of bicyclic and tricyclic pyridopyrimidinones have been reported[17-20]. Tricyclic pyridopyrimidinones were prepared via the reactions of ethyl 2-oxo-cycloalkanecarboxylates and 2-aminopyridines. Merely the formation of linearly-condensed products was observed[21]. In the course of the present work, both linearly- and angularly-fused homoadamantane pyridopyrimidinones were synthetized.

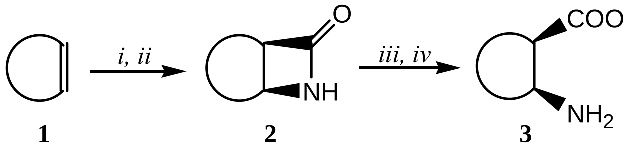
11*H*-Pyrido[2,1-*b*]quinazolin-11-ones have have been evaluated for their antiallergy activities, their effects in inhibiting passive cutaneous anaphylaxis in rats and their analgesic activities in mice[22,23]. Their derivatives saturated in ring **A** are convenient intermediates for rutecarpine alkaloids[24]. In our work some 11*H*-pyrido[2,1-*b*]quinazolin-11-one derivatives were prepared.

The *cis*- and *trans*-2-hydroxycycloalkanecarboxylic acids and carboxamide derivatives are used as starting materials for the synthesis of cycloalkane-condensed saturated or partly saturated heterocycles. While several procedures are known for the synthesis of mixtures of *cis* and *trans* isomers, predominantly containing the *cis* isomer, preparation of the *trans* isomer is problematic. The basic isomerization of homologous *cis*- and *trans*-2-hydroxy-cycloalkanecarboxylic acids was therefore examined in 30% KOH. Additionally, these compounds can serve as model compounds for the study of hydrogen-bonded associations in crystals. Changing the ring size and the stereochemistry allows investigation of the effects of steric constraints on hydrogen-bonding networks.

2. SYNTHESIS AND ENZYMATIC RESOLUTION OF ALICYCLIC β-AMINO ACIDS AND THEIR DERIVATIVES

2.1. Synthesis of β-amino acids and their esters

Cycloalkane-*cis*-1,2-dicarboxylic acid anhydrides have been used as starting materials for the preparation of *cis*-2-aminocycloalkanecarboxylic acids, which, via monoamide formation and subsequent Hofmann degradation, yield β-amino acids[10,25,26]. This method is suitable for the synthesis of *cis*-2-aminocyclohexane- and *cis*-2-aminocyclohex-4-ene-carboxylic acids, because the starting dicarboxylic anhydrides are readily available. A suitable general method, chlorosulfonyl isocyanate (CSI) addition to cycloalkenes and subsequent hydrolysis of the azetidinone derivatives obtained, has also been applied[11,27-29]. This method is used for the preparation of 2-aminocycloheptane-, 2-aminocyclooctane-, 2-aminocyclododecanecarboxylic acids and 5-aminotricyclo[4.3.1.1^{3,8}]undecane-4-carboxylic acid.



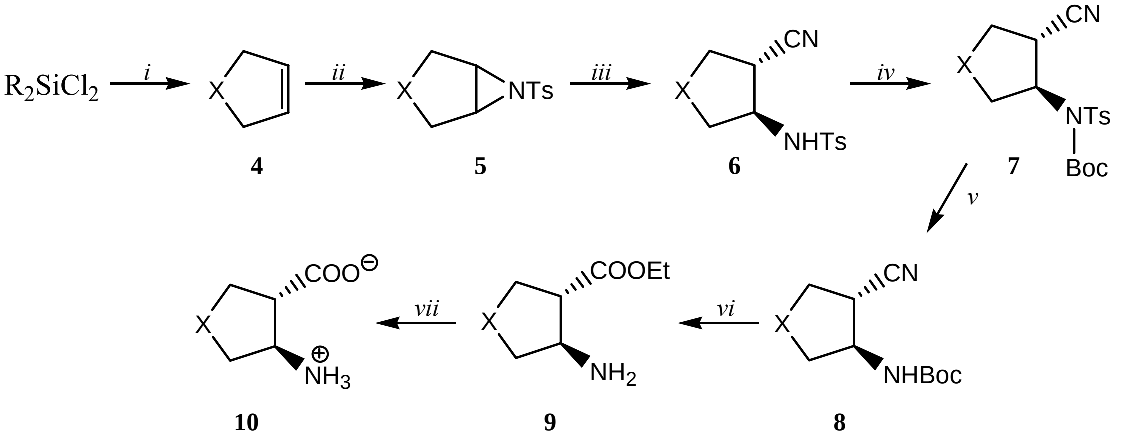
i: CSI, CH_2Cl_2; *ii*: Na_2SO_3, NaOH; *iii*: cc. HCl;
i*v:* ion-exchange chromatography or propylene oxide

Scheme 1

Starting from a mixture of *cis*- and *trans*-cyclododecene, the obtained β-lactam is a mixture of the *cis* and *trans* isomers. These *cis*- and *trans*-β-lactams were separated on silica gel by column chromatography.

For the synthesis of the *trans* isomers, several further methods can be used. *trans*-Hexahydrophtalic anhydride was transformed to the monoamide with NH_4OH, and Hofmann degradation afforded *trans*-2-aminocyclohexanecarboxylic acid[30]. For the preparation of alicyclic 2-aminocarboxylic acids, a well-known method is the Michael addition of NH_3 to cycloalkene-1-carboxylic acids at high pressure and temperature[13,31]. The yields of this reaction are moderate. A new method for the preparation of the unnatural amino acids was achieved by following the route outlined in Scheme 2, which was used to synthetize *trans*-2-aminocyclopentanecarboxylic acid (**10d**) by MATTHEWS *et al.*[32].

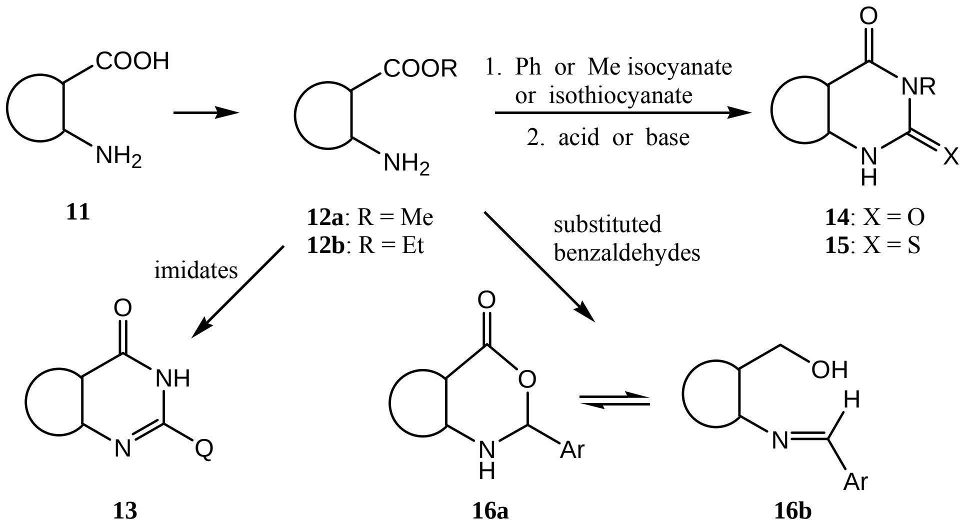
From 2-aminocarboxylic acids, the corresponding esters are prepared by treatment with $SOCl_2$ in absolute EtOH below −10 °C[33-35] or with absolute EtOH and HCl[36]. **12a,b** are starting materials of several heterocyclic compounds[5,37,38] (Scheme 3). 2-Substituted pyrimidinones (**13**) have been synthetized from **12** with imidates. The reaction of **12** with phenyl or methyl isocyanate or isothiocyanate afforded the urea or thiourea, which, in the presence of acid or base, resulted in *N*-substituted pyrimidinones (**14, 15**). Ring-chain tautomerism **16a**$\rightleftharpoons$**16b** is a typical process for 1,3-oxazines**,** which has been studied in detail[38].



a: X = $SiMe_2$; **b**: X = $SiPh_2$; **c**: X = $Si(CH_2)CH_2$; **d**: X = CH_2

i: Cp_2TiCl_2, $H_2C{=}CHMgBr$, THF; *ii*: chloramine-T, PTAB, MeCN; *iii*: Et_2AlCN, toluene; *iv*: Boc_2O, DMAP, MeCN, *v*: Mg, MeOH, sonication; *vi*: saturated HCl in EtOH; *vii*: NaOH

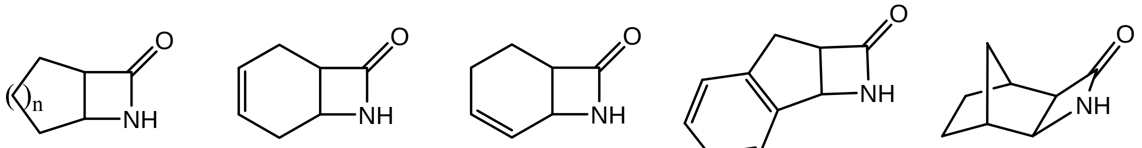
Scheme 2



Scheme 3

2.2. Synthesis of β-lactams and their derivatives

β-Lactams are of pharmaceutical importance[13-15]. One of the several synthetic methods for the preparation of these compounds[39] is shown in Scheme 1. CSI addition to the corresponding alkene takes place regio- and stereoselectively, in accordance with the Markovnikov rule, resulting in β-lactams[27-29]. Several bicyclic and tricyclic β-lactams have been prepared by the 1,2-dipolar cycloaddition of CSI to cycloalkene in CH_2Cl_2 and subsequent reduction with KH_2PO_4[27b] or Na_2SO_3[6,11,12,40] (Figure 1).

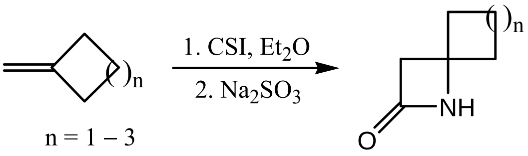


17: n = 1; **18**: n = 2
19: n = 3; **20**: n = 4

21 **22** **23** **24**

Figure 1

This method is also suitable for the preparation of spiro-β-lactams[41] (Scheme 4).

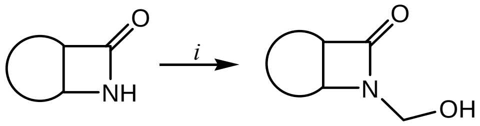


n = 1 – 3

25 **26**

Scheme 4

N-Substituted derivatives of β-lactams (*e.g.* *N*-hydroxymethyl β-lactams) are key compounds in several enzymatic resolution processes. In the presence of the corresponding enzyme, the enantioselective acylation of *N*-hydroxymethyl-β-lactams is a general method for the preparation of enantiopure β-amino acids. The β-amino acids are currently widely used. They are introduced into peptides in order to increase their stability and biological activities[40]. *N*-Hydroxymethyl-β-lactams are prepared in good yields from the corresponding β-lactams by reaction with paraformaldehyde in the presence of K_2CO_3 and H_2O under sonication[6,7,11,40,42] (Scheme 5).



2 **27**

i: paraformaldehyde, H_2O, K_2CO_3

Scheme 5

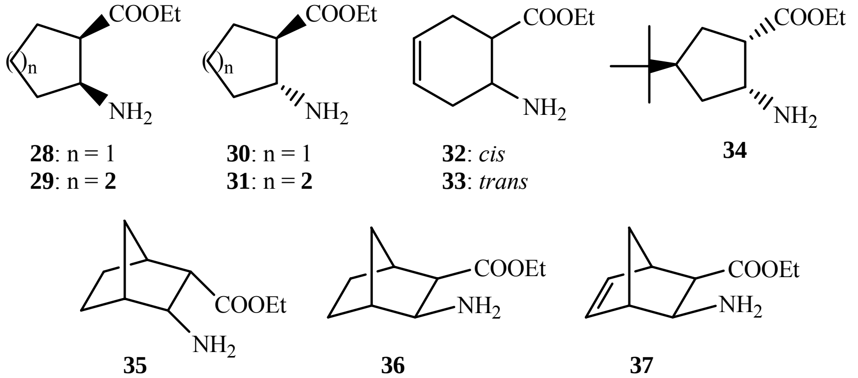
2.3. Enzymatic resolutions

2.3.1. Lipases

Hydrolytic enzymes, such as esterases, proteases and, in particular, lipases, have received much attention because of their effectiveness in chemo-, regio- and enantioselective transformations of different acids, alcohols, amines, amides and esters. These reactions are often performed in organic solvents[43]. Lipase-catalysed biotransformations are applied to prepare enantiopure pharmaceuticals and synthetic intermediates, and to modify natural lipids. A major advantages of lipases is that they act efficiently on water-insoluble substrates. This ability is required, because the natural substrates of lipases (triglycerides) are insoluble in water. Lipases bind to the water-organic interface and catalyse the hydrolysis. This binding places the lipase close to the substrate and increases the catalytic power of the lipase[44]. In the present work *Candida antarctica A* (CAL-A)*,* *Candida antarctica B* (CAL-B) and *Pseudomonas cepacia* (lipase PS) were used. CAL-B comes from the *Rhizomucor* family and lipase PS from the *Pseudomonas* family. CAL-A is unclassified.

2.3.2. Enzymatic resolution of β-amino esters

The potential of lipases as chiral catalysts is widely exploited for the kinetic resolution of racemic mixtures[45]. Use was earlier made of lipase PS- and CAL-A-catalysed asymmetric amide formation to prepare the enantiomers of various alicyclic β-amino esters from the racemic mixtures (Figure 2) with the aid of an appropriate 2,2,2-trifluoroethyl carboxylate in *i*Pr_2O[46]. The acylation of the amino group occurred preferentially at the (*R*) centre.



28: n = 1
29: n = 2

30: n = 1
31: n = 2

32: *cis*
33: *trans*

34

35

36

37

Figure 2

In most cases (resolution of **28-33**, **35** and **36**), 2,2,2-trifluoroethyl chloroacetate was used as acyl donor in Et_2O for gram-scale resolutions. With lipase PS, high enantioselectivity was attainable (ee > 90). In the cases of **34** and **37**, 2,2,2-trifluoroethyl hexanoate with CAL-A was used.

2.3.3. Enzymatic resolution of primary alcohols (*N*-hydroxymethyl-β-lactams)

Lipases usually show low enantioselectivity toward primary alcohols [*except porcine pancreatic lipase* (PPL), lipase PS and *Pseudomonas fluorescence* (lipase AK)]. Although the chiral centre in these cases is two atoms removed from the reaction centre, high selectivities were observed in most of the lipase-catalysed transesterification reactions. Lipases from the *Pseudomonas* family (lipase PS and lipase AK) showed high enantioselectivity ($E > 40$) at room temperature towards alicycle-condensed *N*-hydroxymethyl-β-lactams (**38-45**) (Figure 3) with a primary alcoholic function (Table 1).

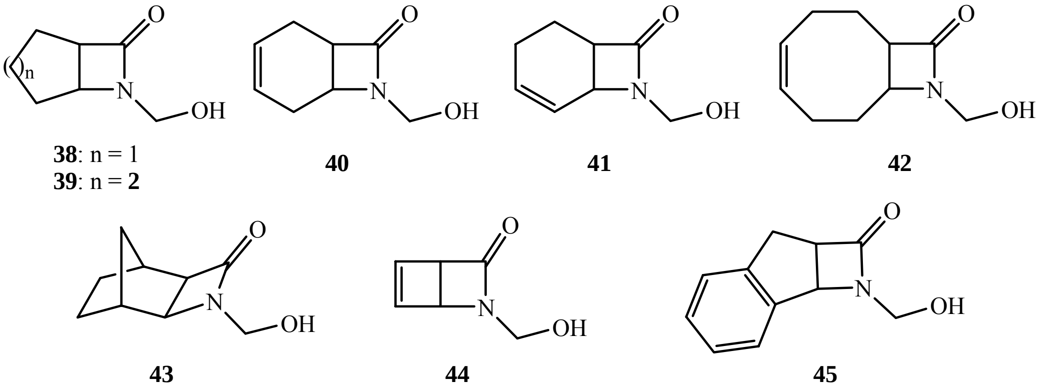


Figure 3

Table 1. Enzymatic resolution of alicycle-condensed *N*-hydroxymethyl-β-lactams (**38-45**) at room temperature

Compound	Enzyme	Acyl donor	Solvent	Idő (h)	*E*
38[40+]	lipase AK	VB	acetone	2.7	90
39[7++]	lipase PS	VB	acetone	5	> 200
40[7++]	lipase PS	VB	acetone	4	> 200
41[7++]	lipase PS	VB	acetone	6	> 200
42[11*++]	lipase PS	VB/VA	*i*Pr_2O	4/3	97/43
43[40+]	lipase AK	VB	acetone	3.5	62
44[6]	lipase PS	VA	*t*-BuOMe	4	78
	lipase AK			2	134
45[42++]	lipase AK	VB	THF	2.5	> 200

[*] The temperature was –15 °C

[+] Contains 10% (w/w) of the lipase adsorbed on Celite in the presence of sucrose

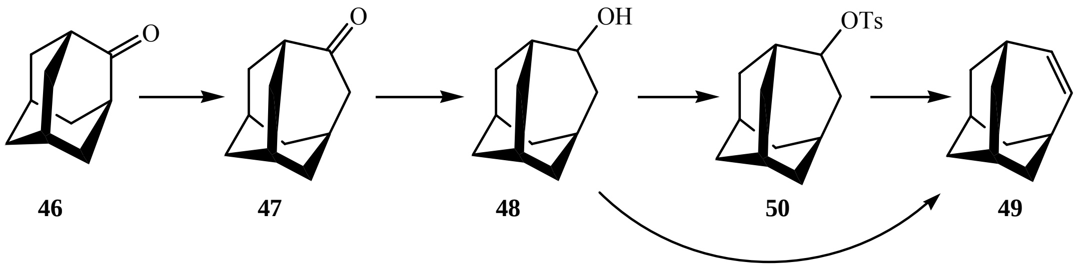
[++] Contains 20% (w/w) of the lipase adsorbed on Celite in the presence of sucrose

In each case vinyl acetate (VA) and vinyl butyrate (VB) were used as acyl donors. The chiral acyl donors can lead to an improved enantioselectivity in the lipase-mediated kinetic resolution of primary alcohols[47]. The most often used organic solvents are ethers (*i*Pr_2O, *t*-BuOMe and THF) and acetone. In the cases of **28-34,** (*S*) selectivity was found; this was not so for **35**.

3. SYNTHESIS AND TRANSFORMATIONS OF HOMOADAMANTANE DERIVATIVES

Homoadamantane, a slightly flexible homologue of adamantane, constitutes a family of compounds which are intriguing in organic chemistry. In particular, 4-homoadamantanone is easily prepared from adamantane[48], adamantanone[49,50] or 1-adamantanecarbaldehyde[51], and has frequently been used as a starting material for homoadamantane derivatives.

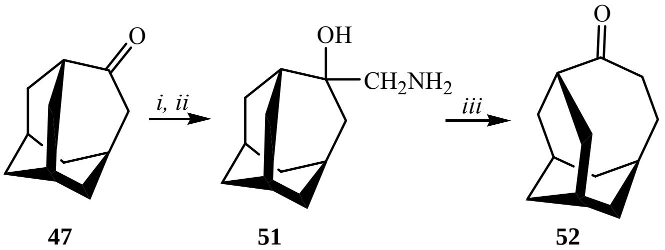
BLACK and GILL[50] converted adamantan-2-one (**46**) into homoadamantan-4-one (**47**) by reaction with CH_2N_2 in Et_2O in the presence of $BF_3{\cdot}Et_2O$ complex or $AlCl_3$ at 0 °C. **46** can be converted in good yield into homoadamantan-4-ol (**48**) by reduction with $NaBH_4$ or with $LiAlH_4$. For the preparation of homoadamant-4-ene (**49**), TsCl in pyridine in the presence of $POCl_3$ was used for the dehydration of **48**. **49** can be prepared from **48** in a higher yield in two steps[52]. First, 4-homoadamantyl tosylate (**50**) was generated by the reaction of homoadamantan-4-ol (**48**) with TsCl, and subsequent treatment of the tosylate with *t*BuOK in *t*BuOH furnished **49** (Scheme 6).



Scheme 6

The most widely used homoadamantane derivative is **47**, but in the literature only a few articles deal with the transformations of compounds **47-49**.

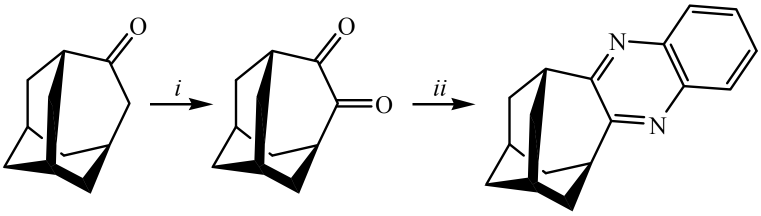
SASAKI *et al.*[53] prepared 4-hydroxy-4-aminomethylhomoadamantane (**51**) from homoadamantan-4-one (**47**) via cyanohydrin. The amino alcohol **51** was treated with $NaNO_2$ and, after purification, 1,1-bis(homoadamantan-4-one) (**52**) was obtained (Scheme 7).



i: HCN, pyridine; *ii*: $LiAlH_4$, THF; *iii*: $NaNO_2$, AcOH

Scheme 7

SCHLATMANN *et al.*[49] prepared quinoxaline derivative **54** from homoadamantan-4-one (**47**). This was the first example of the preparation of a homoadamantane-fused aromatic heterocycle (Scheme 8).



47 **53** **54**

i: SeO_2, dioxan, H_2O; *ii*: *o*-phenylenediamine, EtOH

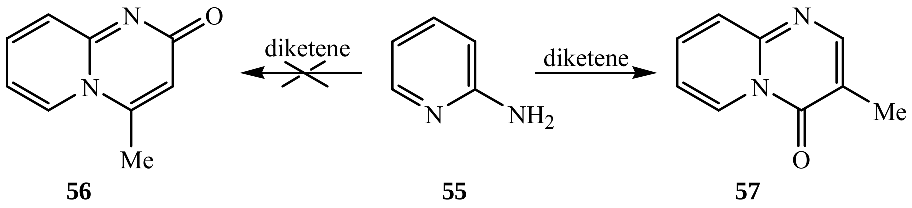
Scheme 8

EGUCHI *et al.*[54] prepared other homoadamantane-fused heterocycles, pyrimidine, pyridine and 1,4-diazepine derivatives from a 1,3-diketone, 5-trifluoroacetylhomoadamantan-4-one.

4. SYNTHESIS OF PYRIDO[1,2-*a*]PYRIMIDIN-4-ONES AND PYRIDO-[2,1-*b*]QUINAZOLINE DERIVATIVES

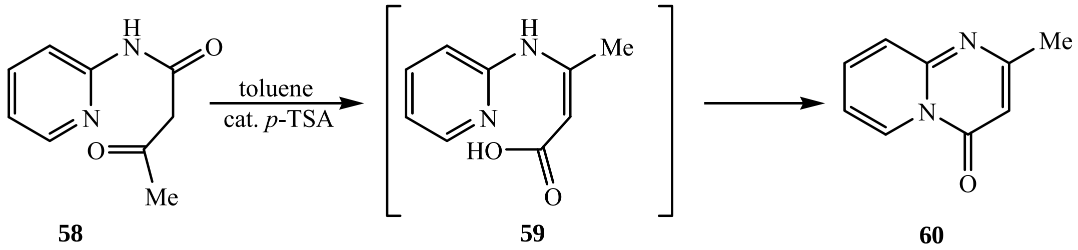
4.1. Synthesis of pyrido[1,2-*a*]pyrimidin-4-ones

KATO *et al.*[55] used 2-aminopyridine and diketene for the preparation of pyridopyrimidinones. In earlier work the 2-one structure (**56**) was presumed, but KATO *et al.* demonstrated that from this reaction compounds with the 4-one structure (**57**) can be prepared (Scheme 9).



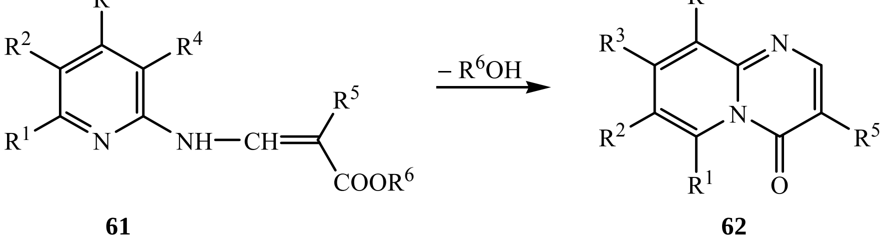
Scheme 9

A procedure has been developed by YALE and SPITZMILLER[56] for the conversion of 2-(acetoacetamido)pyridine (**58**) into 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones (Scheme 10). The reaction involves an acid-catalysed isomerization of the 2-(acetamido)pyridine derivative into an enamine (**59**), under conditions that permit the latter to undergo cyclization to the 4-one (**60**).



Scheme 10

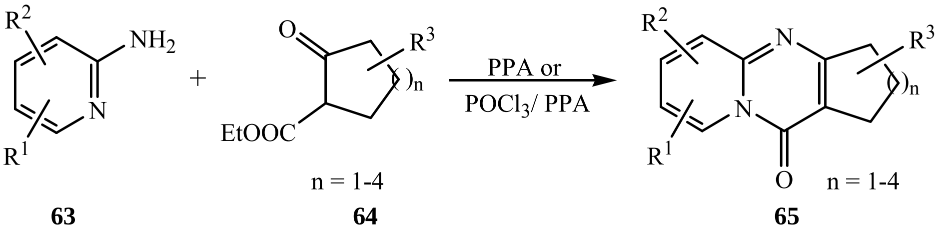
Cyclization of esters of type **61** in $POCl_3$/polyphosphoric acid (PPA) in the most cases affords the pyrido[1,2-*a*]pyrimidine derivatives (**62**) in good yields[57] (Scheme 11). PPA was first tried as a cyclocondensing agent, but the synthesis of nitrogen-bridgehead ring systems often failed.



Scheme 11

The reaction of 2-aminopyridines with malonic acid derivatives or ethyl acetoacetate (**64**) in $POCl_3$/PPA afforded bicyclic pyridopyrimidinones[57], but the reaction between 2-amino-6-hydroxypyridine and **64** did not give the expected pyridopyrimidine.

Through the condensation of alicyclic β-ketocarboxylates with substituted 2-amino-pyridines in PPA or in a mixture of PPA and $POCl_3$, numerous 2,3-tri-, tetra-, penta- and hexamethylene-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones have been synthetized for pharmacological purposes[17,19,58] (Scheme 12). In these cases, FÜLÖP *et al.*[58] did not find high differences in the yields when PPA or $POCl_3$/PPA was used.



Scheme 12

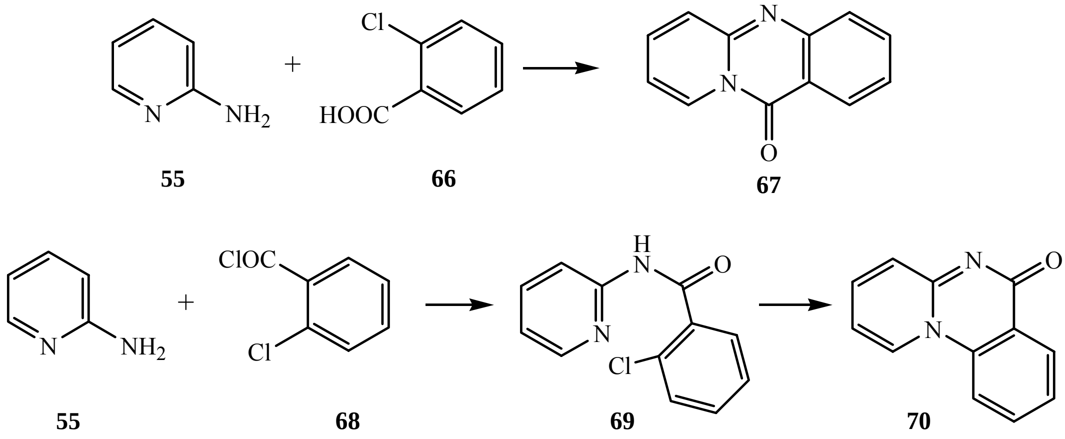
In the case of n = 2, compounds **65** contain the pyrido[2,1-*b*]quinazoline ring[18,20], which is an essential structural element of some plant alkaloids.

4.2. Synthesis of pyrido[2,1-*b*]quinazoline derivatives

As Scheme 12 shows, tetrahydro-11*H*-pyrido[2,1-*b*]quinazolin-11-ones can be prepared by the condensation of 2-aminopyridines and ethyl-(2-oxocyclohexanecarboxylate) in PPA[18].

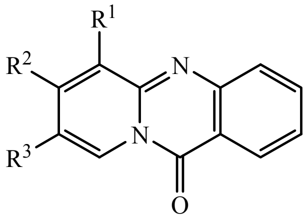
The reaction of 2-aminopyridine and 2-chlorobenzoic acid results in a linearly-condensed 11*H*-pyrido[2,1-*b*]quinazolin-11-one (**67**) in 75 % yield (Scheme 13)[59]. This compound is the starting material of the synthesis of the alkaloid rutecarpine[23]. Angularly-condensed pyridoquinazolones were prepared by TIMÁRI *et al.*[60]. 2-Aminopyridine was acylated with *o*-chlorobenzoyl chloride and the resulting amide was refluxed at elevated temperature (210 °C); after neutralization, the free base **70** was obtained (Scheme 13).

PATTERSON *et al.*[61] found that 3-(α-pyridyl)-1,2,3-benzotriazin-4-one undergoes thermal decomposition to form pyrido[2,1-*b*]quinazolin-11-one (**67**).



Scheme 13

The carboxylic acid derivatives of **67** (Figure 4) are often tested as potential anti-allergy agents. The preparation of these compounds is well known[21,62]. 11*H*-Pyrido[2,1-*b*]-quinazolin-11-one-6-carboxylic acid (**71**) was prepared by the reaction of ethyl anthranilate and 2-chloronicotinic acid in EtOH at 160 °C[62].



71: R^1 = COOH, $R^2 = R^3$ = H
72: R^2 = COOH, $R^1 = R^3$ = H
73: R^3 = COOH, $R^1 = R^2$ = H

Figure 4

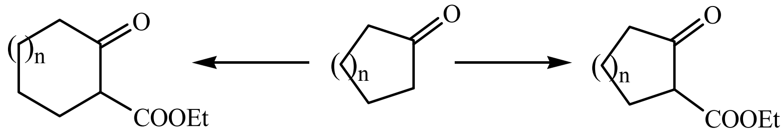
Carboxamides of 11*H*-pyrido[2,1-*b*]-quinazolin-11-one are of pharmacological importance. Their DNA-binding properties and antitumour activities have been tested[22]. In most cases, the carboxylic acid and amine were coupled with DCC[63,64], EDC[65,66] or $SOCl_2$ with TEA[67,68].

DMF to couple 11*H*-pyrido[2,1-*b*]quinazolin-11-one-6-carboxylic acid (73) with *N*,*N*-dimethylethylenediamine.

5. 2-HYDROXYCYCLOALKANECARBOXYLIC ACIDS

5.1. Synthesis of 2-hydroxycycloalkanecarboxylic acids

The starting material for the preparation of 2-hydroxycycloalkanecarboxylic acids is the corresponding β-ketoester (**75**). This compound can be prepared by the Lewis acid-catalysed addition of diazotrifluoroethane (N_2CHCF_3), isopropyl diazoacetate ($N_2CHCO_2CH(CH_3)_2$)[69] or (most often) ethyl diazoacetate ($N_2CHCO_2C_2H_5$) to ketones (**74a-c**), which is a similar profile of rearrangement to that for the β-ketoesters[70] (Scheme 14). Another possibility is the condensation of cycloalkanone (**74a-c**) and Et_2CO_3 with NaH in Et_2CO_3 or in Et_2O[69]. For the synthesis of ethyl 2-ketocyclopentanecarboxylate (**76a**), diethyl adipate and Na are used in toluene, because diethyl adipate is an inexpensive starting material.



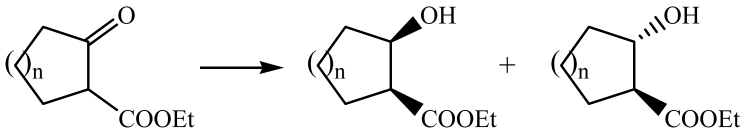
75 **74** **76**

a: n = 1; **b**: n = 2; **c**: n = 3

Scheme 14

Several compounds have been used as Lewis acid: $Rh(OAc)_3$[71], $AlCl_3$[72], $ZnCl_2$[72], $InCl_3$[73], $CrCl_2$[74], triethyloxonium fluoroborate[75], $BF_3{\cdot}Et_2O$[74,76,77] or $SnCl_2$[78]. The best results were obtained with $BF_3{\cdot}Et_2O$ and $SnCl_2$.

The reduction of ethyl 2-ketocycloalkanecarboxylates (**77, 80, 83, 86**) with Na/Hg[80], Adams' PtO_2[79,80], Raney Ni[81] or $NaBH_4$[79,81,82] gave a mixture of ethyl *cis*- and *trans*-2-hydroxycycloalkanecarboxylates (Scheme 15).



77: n = 1
80: n = 2
83: n = 3
86: n = 4

78: n = 1
81: n = 2
84: n = 3
87: n = 4

79: n = 1
82: n = 2
85: n = 3
88: n = 4

Scheme 15

The *cis* (**78**) and *trans* (**79**) isomers of ethyl 2-hydroxycyclopentanecarboxylates were earlier separated by fractional crystallization of their 3,5-dinitrobenzoates[80,83]. This tedious method is suitable for the separation of smaller quantities. For the separation of larger quantities of the *cis* and *trans* isomers of ethyl 2-hydroxycycloalkanecarboxylates (mixtures of **84** and **85,** or **87** and **88**), fractional vacuum distillation[79,81,83,84] on a column with a high number of theoretical plates was used. 2-Hydroxycycloalkanecarboxylic acids can be obtained by the hydrolysis of esters with NaOH[81,84]. BERNÁTH *et al.* separated *cis*- and *trans*-2-hydroxycyclohexane-[81], and *cis*- and *trans*-2-hydroxycycloheptanecarboxylic acid[79,83] by fractional crystallization.

Catalytic and $NaBH_4$ reduction of 2-carbethoxycycloheptanone (**83**) resulted in similar isomer ratios, though the formation of the *trans* isomer was predominant in the $NaBH_4$ reduction in the cases of the cyclopentane and cyclohexane homologues. In the reduction of 2-carbethoxycycloheptanone (**83**), the $NaBH_4$ method resulted in a lower amount of *trans* isomer than in the catalytic process. The same relation was observed in the reduction of 2-carbethoxycyclooctanone (**86**). The isomer ratios in the catalytic and $NaBH_4$ reductions are highly dependent on the ring size[79]. BERNÁTH *et al.*[84] found that, at lower temperature, formation of the *trans* isomer was more pronounced (the amount of **79** was 87.3 % when Raney Ni was used at 60 °C, and 60.4% at 25 °C). The amount of *trans* isomer in the mixture of the *cis* and *trans* isomers can be increased by isomerization of the carboxylic acids.

5.2. Isomerization of 2-hydroxycycloalkanecarboxylic acids

PASCUAL *et al.*[85] reported that *cis*-2-hydroxycyclohexanecarboxylic acid can be isomerized by prolonged refluxing with concentrated KOH solution, and the *trans* isomer can be obtained from the equilibrium mixture in good yields by fractional crystallization. In the course of the isomerization of *cis*-2-hydroxycyclopentanecarboxylic acid, besides the *trans* isomer, the formation of 1-cyclopentenecarboxylic acid was also observed[79]. Interestingly, in the isomerization of *cis*-2-hydroxy-*cis*-4-*t*-butylcyclopentanecarboxylic acid with 40% KOH, stereohomogeneous *trans*-2-hydroxy-*trans*-4-*t*-butylcyclopentanecarboxylic acid was obtained after fractional crystallization. No dehydration was observed during the isomerization[86], whereas 2-hydroxycyclopentanecarboxylic acid[79] also gave a considerable amount of 1-cyclopentenecarboxylic acid under similar conditions. When *cis*-2-hydroxycycloheptanecarboxylic acid was isomerized to the *trans* isomer[83], dehydration was not observed. For this reason we found it worthwhile to study the basic isomerization of the homologous alicyclic *cis*-2-hydroxycarboxylic acids.

5.3. Analysis of hydrogen-bonded networks

The properties of crystalline organic materials depend both on their molecular composition and on the crystal structure. While synthetic organic chemistry provides the means to design and control molecular composition, the design and control of crystal structures are unresolved problems. In particular, prediction of the crystal structure from the molecular structure is scarcely possible[87].

The arrangement of the molecules in the solid is determined by a subtle balance of a multitude of weak and mostly non-directional interactions between the molecules. The differences between the free energies of plausible molecular arrangements are usually smaller than the accuracy of our current models of these interactions. Accordingly, our knowledge permits only a listing of reasonable possibilities, but is not sufficient for the prediction of the stable crystal structure.

Hydrogen-bonds are among the strongest intermolecular interactions in organic crystals. The selectivity and directional nature of the hydrogen-bond make it an ideal tool for the manipulation of crystal structures[88]. An appropriate fit of donors and acceptors may outweigh the effects of weak non-directional forces and thus allow the introduction of rationally designed structural features into the crystal.

These structural features are best described in terms of graph sets assigned to hydrogen-bond motifs[89]. Each motif is represented by a designator of the form $M_d^a(n)$. M gives the type of the motif. It may be C (chain), R (ring), D (dimer or other finite set) or S (self, *i.e.* intramolecular hydrogen-bond). The numbers d and a give the numbers of donor (H) and acceptor atoms in the motif, while n is the total number of atoms in the pattern. For example, a ring joined by a carboxylic acid dimer is represented by the graph descriptor $R_2^2(8)$, and an infinite (...O=C-OH...) chain of the same molecules by $C_1^1(4)$.

A practical approach for the generation of such motifs is the identification of supramolecular synthons[90]. Supramolecular synthons are recurring spatial arrangements of intermolecular interactions between given molecular fragments. For example, phenolic OH groups frequently form $R_3^3(6)$ rings in crystals. The supramolecular synthon approach promises the design of crystal architectures in a retrosynthetic manner. It requires the identification of the representative/desired structural patterns as the first step. Appropriate supramolecular synthons are than selected. Finally, molecules are synthetized that contain the required functional groups in appropriate mutual arrangements. While this method does not permit the prediction of crystal structures in general, it has proved useful in the design of complicated crystalline architectures[91].

6. RESULTS AND DISCUSSION

6.1. Enzymatic resolutions

6.1.1. Materials and methods

Cycloalkenes, adamantan-2-one, CSI, propylene oxide, vinyl and methyl butanoates, 2,2,2-trifluoroethanol and the solvents were products of Aldrich or Fluka. 2,2,2-Trifluoroethyl butanoate was prepared from butanoyl chloride and 2,2,2-trifluoroethanol by a standard procedure. Homoadamant-4-ene was prepared from adamantan-2-one by a known method[51]. All solvents were of the highest analytical grade and were dried over molecular sieves (3 Å) before use. Lipase PS was purchased from Amano Europe, England, and CAL-A (Chirazyme L5) and CAL-B (Chirazyme L2, c.f. C2) from Roche. Before use, the lipase PS and CAL-A were adsorbed on Celite (17 g) by dissolving the enzyme (5 g) and sucrose (3 g) in Tris-HCl buffer (250 ml, 20 mM, pH = 7.9) as described previously[92]. The mixture was dried by allowing the water to evaporate. The final lipase content in the enzyme preparation was 20 % (w/w). Preparative chromatographic separations were performed by column chromatography on Merck Kieselgel 60 (0.063-0.200 μm). TLC was carried out with Merck Kieselgel 60F_{254} sheets. Spots were visualized with 5 % ethanolic phosphomolybdic acid solution and heating. Most of the enzymatic reactions were performed at room temperature (23-24 °C).

The ^{1}H and ^{13}C NMR spectra were recorded on a Brucker 400 spectrometer operating at 400 MHz and 100 MHz, respectively, and were referenced internally to TMS as internal standard. Elemental analyses were carried out with a Perkin-Elmer 2400 CHNS instrument. MS spectra were taken on a VG 7070E mass spectrometer. Optical rotations were determined with a JASCO Model DIP-360 digital polarimeter. $[\alpha]_D$ values are given in units of 10^{-1} deg cm^{2} g^{-1}. The determination of E was based on the equation $E = \ln[(1-c)(1-ee_S)]/\ln[(1-c)(1+ee_S)]$[93] with the use of linear regression, E being the slope of the line $\ln[(1-c)(1+ee_S)]$ vs. $\ln[(1-c)(1-ee_S)]$. Melting points were determined by a hot plate method and are uncorrected.

In a typical small-scale experiment, one of the substrates *rac*-**89a-c**, a mixture of *rac*-**89c** and *rac*-**89d** (0.2 mmol), and *rac*-**92** (0.1 mmol) in $i\text{Pr}_2\text{O}$ (2 ml), or one of the substrates *rac*-**95a-d** (0.1-0.2 mmol) and *rac*-**98** in dry acetone (2 ml), was added to a lipase preparation (10-150 mg, corresponding to 2-30 mg of lipase) or to a commercial lipase (5-100 mg), followed by the addition of an achiral acyl donor (2-4 equivalents) to the substrate. The progress of the reactions were followed and the ee values were found by taking samples (0.1 ml) at intervals and analysing them by gas chromatography (GC). For good baseline separation, the unreacted amino (substrates **89** and **92**) and hydroxy groups (substrates **95**) in the sample were derivatized with acetic anhydride in the presence of pyridine containing 1% DMAP before injection. The GC instrument was fitted with a Chrompack CP-Chirasil-DEX CB or Chrompack CP-Chirasil-L-Valine column. For high-performance liquid chromatography (HPLC) a Sumichiral OA-4900 (46 mm × 0.25 m, λ = 210 nm) column was used to obtain the ee$^{\mathbf{95d}}$ value. Conversions were calculated from the ee values $c = ee_S/(ee_S+ee_P)$, except in the cases of **95c** and **95d** as substrates, where hexadecane served as internal standard in the GC method.

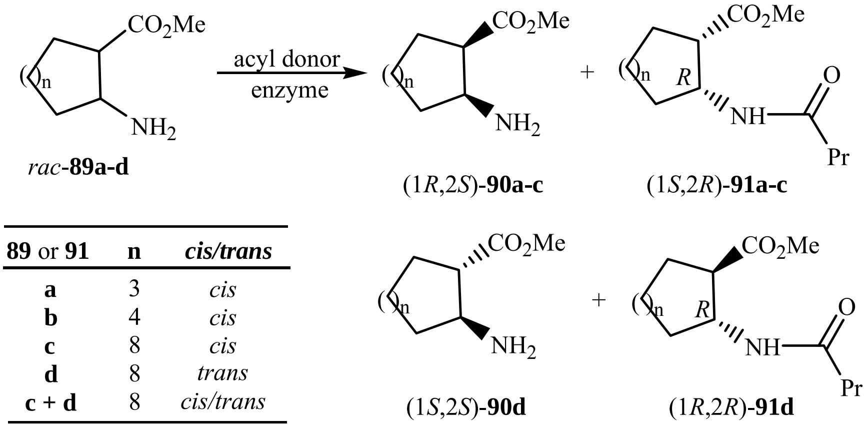
For X-ray crystallography, intensity data were collected on an Enraf-Nonius CAD4 diffractometer, with graphite-monochromated Cu-Kα radiation (λ = 1.54180 Å) at 293 K, in the range $3.58 \leq \theta \leq 75.92°$, using ω-2θ scans. Cell parameters were determined by least-squares refinements of 25 ($25.00 \leq \theta \leq 29.76°$) reflections. 5101 reflections were collected for **101**. The intensities of the standard reflections indicated a crystal decay of 1% (the data were corrected for decay). A psi-scan absorption correction was applied to the data (the minimum and maximum transmission factors were 0.8263 and 0.9704).

6.1.2. Enzymatic resolution of methyl 2-aminocycloalkanecarboxylates

6.1.2.1. Small-scale resolutions

In previous work, extensive lipase screening for the asymmetric acylation of 5- and 6-membered alicyclic *cis*- and *trans*-β-amino esters revealed that two lipases, lipase PS and CAL-A, display complementary behaviour, CAL-A proving to be more applicable for the *cis* isomers[46]. Later, it became clear that CAL-A is exceptional among the lipases by catalysing the *N*- and *O*-acylations of various sterically hindered substances in a highly enantioselective manner[94]. Previous solvent screening involved simple ethers, such as in *i*Pr$_2$O and *t*-BuOMe, which were the most favourable solvents for the enzymatic acylation of alicyclic β-amino esters[46].

Encouraged by the above findings, we subjected methyl 2-aminocycloheptane-, -cyclooctane- and -cyclododecanecarboxylates, *rac*-**89a-c** (*cis* isomers), and a mixture of methyl *cis*- and *trans*-2-aminocyclododecanecarboxylates, *rac*-(**89c** + **89d**) (*cis:trans* = 1:2) to acylation with a CAL-A preparation in the presence of 2,2,2-trifluoroethyl butanoate in *i*Pr$_2$O (Scheme 16).



rac-**89a-d**

(1*R*,2*S*)-**90a-c** (1*S*,2*R*)-**91a-c**

(1*S*,2*S*)-**90d** (1*R*,2*R*)-**91d**

89 or **91**	**n**	***cis/trans***
a	3	*cis*
b	4	*cis*
c	8	*cis*
d	8	*trans*
c + d	8	*cis/trans*

Scheme 16

Excellent enantioselectivity in terms of the *E* values is obvious for the present *cis*-amino esters (Table 2, entries 1-11 and 13), while the *trans* isomer **89d** in the *cis*/*trans* mixture (entry 13) reacted with negligible enantioselectivity.

Table 2. Enantioselectivity of the CAL-A preparation for the acylation of *rac*-**89a-c** (0.1 M) and *rac*-[**89c** + **89d**, (1:2)] (0.1 M) with 2,2,2-trifluoroethyl butanoate (0.2 M)[*]

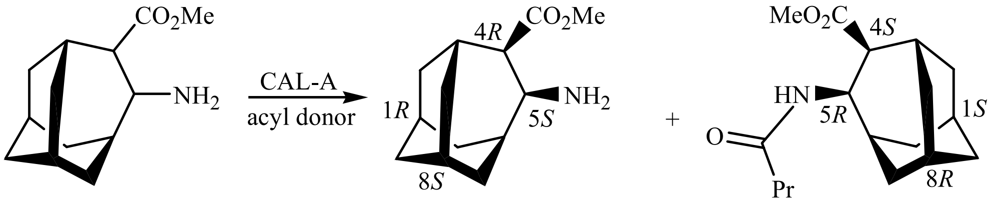
Entry	Compound	Enzyme content (mg/ml)	Time (h)	Conversion (%)	*E*
1	**89a**	10	1	28	>200
2	**89a**	20	1	48	>200
3	**89a**	25	1	49	>200
4	**89a**	50	1	48	>200
5	**89a**	75	1	46	>200
6	**89b**	5	1	24	130±7
7	**89b**	10	1	33	170±7
8	**89b**	20	1	34	>200
9	**89b**	40	1	18	>200
10	**89b**	75	1	17	>200
11	**89c**	50	24	50[a]	>200
12	**89c** + **89d**	50	48	-	-
13	**89c** + **89d**	50	24	50/8[a]	116±13/7

[*] Solvent: *i*Pr_2O (2 ml), room temperature
[a] Temperature 47 °C

The reactivity (reflected by the conversion reached after a certain time) of the *cis* isomers decreased considerably with increasing size of the alicyclic ring. Thus, conversions of 48 % for **89a** (entry 2) and 34 % for **89b** (entry 8) were reached after 1 h when 20 mg/ml of the enzyme preparation was used, whereas there was no reaction in the case of **89c** + **89d** as substrate (entry 12) after 2 days at room temperature, even though the enzyme content was high (50 mg/ml of the enzyme preparation). In the case of **89c** + **89d**, the replacement of *i*Pr$_2$O with acetone, MeCN, toluene or Et$_2$O as solvent did not improve the reactivity. When lipase PS, lipase AK, CAL-B or PPL was used in place of CAL-A in *i*Pr$_2$O, negligible reactivity (conversion 0-7% after 1 day) with practically no enantioselectivity was observed. When 2,2,2-trifluoroethyl chloroacetate was used with lipase PS in *i*Pr$_2$O, a chemical reaction strongly disturbed the enzymatic acylation. For the *cis* substrate **89c** (entry 11) and the *cis*/*trans* mixture **89c** + **89d** (entry 13) an elevated temperature (47 °C) was necessary for the acylation to proceed.

For substrates **89a** and **89b**, 10 or 20 mg/ml of the enzyme preparation was taken as optimum enzyme content. For the acylation of **89b**, high enzyme contents tended to halt the reactivity (entries 9 and 10). Aggregation of the enzyme preparation under the given reaction conditions was taken as an explanation.

Methyl *cis*-5-aminotricyclo[4.3.1.1^{3,8}]undecane-4-carboxylate *(rac*-**92**) was subjected to *N*-acylation with 2,2,2-trifluoroethyl butanoate in *i*Pr$_2$O in the presence of the CAL-A preparation (Scheme 17).



rac-**92** **93** **94**

Scheme 17

Excellent enantioselectivity in terms of the *E* values is obvious from the results (Table 3). The high enantioselectivity is also indicated by the fact that the reaction stops at 50% conversion, with ee values of ~99% for both the unreacted **93** and the amide **94** formed. Interestingly, the reactivity (reflected by the conversion achieved after a certain time) of the bulky homoadamantyl derivative (the amino and ester fuctions attached to the 7-membered ring) is relatively high as compared with the reactivities of **89a** (entry 4) and **89c** (entry 5).

For the *N*-acylation of *rac*-**92** with 2,2,2-trifluoroethyl butanoate in *i*Pr$_2$O, the CAL-A content was optimized. As shown in Table 3, 50 mg/ml of the enzyme preparation led to a 50% conversion in 5 h (entry 3) while 10 h was needed when 10 mg/ml of the preparation was applied (entry 1).

Table 3. Acylation of *rac*-**92** (0.05 M) with 2,2,2-trifluoroethyl butanoate (0.1 M) in the presence of the CAL-A preparation[*]

Entry	CAL-A preparation (mg/ml)	Time (h)	Conversion (%)	*E*
1	10	5 (10)	38 (50)	>>200
2	25	5	46	>>200
3	50	5	50	>>200
4	50	1	48[a]	>200
5	50	24	50[b]	>200

[*] Solvent: *i*Pr$_2$O (2 ml); room temperature

[a] **89a** as substrate; [b] **89c** as substrate

6.1.2.2. Gram-scale resolutions

Successful gram-scale resolutions of **89a-c** with CAL-A in *i*Pr$_2$O were performed. As shown later, (1*S*,2*R*) enantiomers are the more reactive compounds.

Table 4. Acylation results for *rac*-**89** with CAL-A[*] using 2,2,2-trifluoroethyl butanoate

Substrate	Time (h)	Conversion (%)	ee$^{\mathbf{90}\text{ or }\mathbf{93}}$ (%) (Configuration)	ee$^{\mathbf{91}\text{ or }\mathbf{94}}$ (%) (Configuration)
rac-**89a**	1.8	50	98 (1*R*,2*S*)	97 (1*S*,2*R*)
rac-**89b**	4	50	99 (1*R*,2*S*)	95 (1*S*,2*R*)
rac-**89c**	24[a]	49	96 (1*R*,2*S*)	99 (1*S*,2*R*)
rac-**92**	10	50	> 99 (1*R*,4*R*,5*S*,8*S*)	> 99 (1*S*,4*S*,5*R*,8*R*)

[*] Concentration: 10-50 mg/ml of CAL-A; solvent: *i*Pr$_2$O, room temperature

[a] Temperature 47 °C

For the gram-scale resolution of *rac*-**92**, 10 mg/ml (corresponding to 2 mg/ml of CAL-A) was chosen. For economic reasons, a low enzyme content was preferred at the expense of the reaction time. The work-up after 10 h gave enantiopure (1*R*,4*R*,5*S*,8*S*)-**93** and (1*S*,4*S*,5*R*,8*R*)-**94** in close to quantitative isolated chemical yields (47% of each, the theoretical yields being 50%). Thus, in accordance with expectations, the amino group at the stereogenic (5*R*) centre was enzymatically acylated. The present results confirm the earlier suggestion that *N*-acylation mediated by CAL-A (a calcium-dependent, thermostable lipase)[95] provides an excellent method for the resolution of sterically hindered alicyclic and aliphatic β-amino esters[46,94d,94e].

6.1.2.3. Absolute configuration

In order to confirm the absolute configurations, the amino esters were subjected to hydrolysis in 18% HCl, followed by treatment of the acid hydrochlorides obtained with a basic Amberlite IRA 904 resin. The specific rotations, $[\alpha]_D^{25} = -4.6$ ($c = 0.5$, H_2O) for the free acid produced from ester **90a** and $[\alpha]_D^{25} = +11.0$ ($c = 0.5$, H_2O) for that produced from **90b**, are in accordance with the literature values[12], $[\alpha]_D^{25} = -7.2$ ($c = 0.5$, H_2O) and $+17.8$ ($c = 0.4$, H_2O) for the (1*R*,2*S*) acids. In consequence of the slight differences in our $[\alpha]_D^{25}$ values and the literature values, the enantiopurity was confirmed by transforming the free acids back to the amino esters and determining ee = 96% for the reproduced **90a** and **90b** (as compared with ee = 98 and 99% for the resolved products) by the GC method. Accordingly, the *N*-acylations by CAL-A proceeded at the stereogenic (2*R*) centre, as expected on the basis of the previous work[47]. There is every reason to presume that the same enantiopreference will hold for the CAL-A-catalysed *N*-acylation of **90c**. It is therefore concluded that the more reactive enantiomer of *rac*-**89a-c** has the (1*S*,2*R*) absolute configuration. By the same reasoning, the (1*R*,2*R*) enantiomer reacts in the case of *rac*-**89d**.

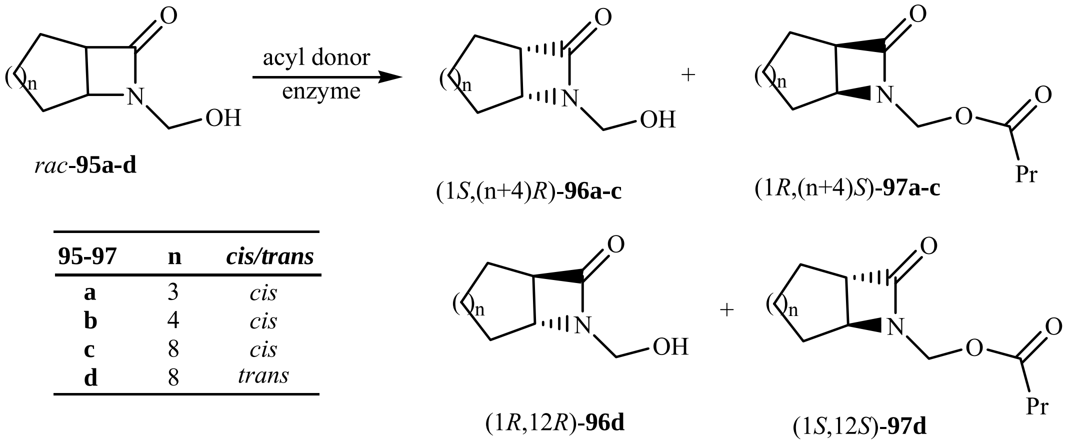
Determination of the absolute configurations of **93** and **94** is discussed below.

6.1.3. Enzymatic resolution of *N*-hydroxymethyl-β-lactams

6.1.3.1. Small-scale resolutions

As a second approach to the enantiomers of alicyclic β-amino acids, *N*-hydroxymethyl-β-lactams *rac*-**95a-d** were subjected to lipase-catalysed acylation in dry acetone (Scheme 18).

As concerns enzymatic enantioselectivity and suppression of the enzymatic hydrolysis (caused by the water adsorbed on the seemingly dry enzyme preparation) of new ester product **97** back to *N*-hydroxymethyl-β-lactams, acetone was previously found to be the most appropriate solvent for β-lactam substrates[40]. Vinyl esters were expected to be excellent as achiral acyl donors because the vinyl alcohol produced (another product of enzymatic acylation) is unstable and decomposes with the formation of acetaldehyde. Accordingly, the reverse enzymatic reactions of [1*R*,(n+4)*S*]-**97a-c** (n = 3, 4 and 8) and (1*S*,12*S*)-**97d** with the released vinyl alcohol and subsequent racemization can be avoided.



rac-**95a-d**

(1*S*,(n+4)*R*)-**96a-c**

(1*R*,(n+4)*S*)-**97a-c**

(1*R*,12*R*)-**96d**

(1*S*,12*S*)-**97d**

95-97	**n**	***cis/trans***
a	3	*cis*
b	4	*cis*
c	8	*cis*
d	8	*trans*

Scheme 18

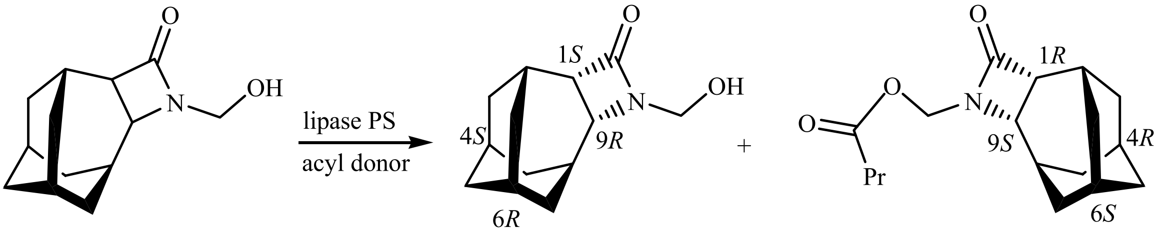
As expected on the basis of the earlier studies[6,7,11,40], lipase PS (Table 5, entries 1-6) and lipase AK (entry 7) smoothly catalyse the formation of (1*R*,7*S*)-**97a** with vinyl esters in dry acetone, the combination of lipase PS and VB (entry 5) being most enantioselective. For appropriate reactivity, 50 mg/ml of the enzyme preparation was chosen for further studies. In the cases of substrates *rac*-**95b-d**, the acylation reactions with VB tend to stop at an early stage (entries 9, 11 and 15). It is well known that aldehydes form hemiacetals under both acidic (the reaction continues to an acetal) and basic conditions. However, side-products were not detected by the GC method with the present primary alcohols. A drop in ee for the separated **95** in consequence of the decomposition of free hemiacetals (if present) during the work-up as compared with the ee for the resolved mixture was not detected either. The present observations do not exclude the possibility of the inactivation of lipase PS by unstable hemiacetal formation. It is worth emphasizing that vinyl esters are commonly accepted by lipase PS[44]. As a different possibility, an enzymatic reaction between the produced [1*R*,(n+4)*S*]-**97** and the less reactive primary alcohol [1*S*,(n+4)*R*]-**96** can become important in the reaction mixture at longer reaction times. In a positive case, a drop in ee is expected for both resolution products. Since the ee values in the resolution mixture remained practically unchanged for hours after the reaction had stopped and since the change of the vinyl ester to 2,2,2-trifluoroethyl butanoate as acyl donor (entries 8, 10 and 13) allowed us to complete the resolutions, the possibility was not studied further. The same reactions with CAL-B and PPL proceeded without difficulty, but unfortunately with low selectivities (entries 12, 16 and 17).

Table 5. Enzymatic acylation of *rac*-**95a-d** with acyl donors (0.2 M) in acetone (2 ml) at room temperature

Entry	Compound	Acyl donor	Enzyme content (mg/ml)	Time (h)	Conversion (%)	*E*
1	**95a** (0.1 M)	$MeCO_2CH=CH_2$	lipase PS (50)	1	48	50±10
2	**95a** (0.1 M)	$PrCO_2CH=CH_2$	lipase PS (10)	1	17	>200
3	**95a** (0.1 M)	$PrCO_2CH=CH_2$	lipase PS (30)	1	36	>200
4	**95a** (0.1 M)	$PrCO_2CH=CH_2$	lipase PS (40)	1	40	>200
5	**95a** (0.1 M)	$PrCO_2CH=CH_2$	lipase PS (50)	1	45	>200
6	**95a** (0.1 M)	$PrCO_2CH=CH_2$	lipase PS (75)	1	48	>200
7	**95a** (0.1 M)	$PrCO_2CH=CH_2$	lipase AK (50)	1	46	82±9
8	**95b** (0.1 M)	$PrCO_2CH_2CF_3$	lipase PS (50)	2	32	27±1
9	**95b** (0.1 M)	$PrCO_2CH=CH_2$	lipase PS (50)	2	30[b]	-
10	**95c** (0.05 M)	$PrCO_2CH_2CF_3$	lipase PS (50)	3	48	83±10
11	**95c** (0.05 M)	$PrCO_2CH=CH_2$[a]	lipase PS (25)	3	30[b]	-
12	**95c** (0.05 M)	$PrCO_2CH=CH_2$	CAL-B (2.5)	1	62	3±1
13	**95d** (0.1 M)	$PrCO_2CH_2CF_3$	lipase PS (50)	2	39	5±1
14	**95d** (0.1 M)	$PrCO_2CH_2CF_3$[a]	lipase PS-C (50)	2	49	10±2
15	**95d** (0.1 M)	$PrCO_2CH=CH_2$	lipase PS (50)	2	23[b]	-
16	**95d** (0.05 M)	$PrCO_2CH=CH_2$	PPL (25)	2	11	18±2
17	**95d** (0.05 M)	$PrCO_2CH=CH_2$	CAL-B (2.5)	2	54	26±2
18	**95d** (0.05 M)	$PrCO_2(CH_2)_3CH_3$	CAL-B (2.5)	2	40	15±5

[a] 0.4 M; [b] Reaction stops.

For the lipase-catalysed *O*-acylation of alicyclic *N*-hydroxymethyl-β-lactams, **95a-d**, lipase PS and CAL-B are the most suitable catalysts in dry acetone. Accordingly, *rac*-**98** was subjected to lipase-catalysed acylation with 2,2,2-trifluoroethyl butanoate and VB in dry acetone in the presence of the lipase PS preparation (Scheme 19, Table 6).



rac-**98** **99** **100**

Scheme 19

Table 6. Enzymatic acylation of *rac*-**98** (0.05 M) with achiral acyl donors (0.2 M)*

Entry	Acyl donor	Enzyme preparation (mg/ml)	Time (h)	Conversion (%)	ee$^{\mathbf{99}}$ (%)	ee$^{\mathbf{100}}$ (%)
1	$PrCO_2CH_2CF_3$	lipase PS (12.5)	3 (10)	47 (48)[a]	89 (93)	> 99
2	$PrCO_2CH_2CF_3$	lipase PS (25)	3 (5)	43 (44)[a]	76 (78)	> 99
3	$PrCO_2CH_2CF_3$	lipase PS (50)	3 (10)	34 (45)[a]	52 (81)	> 99
4	$PrCO_2CH{=}CH_2$	lipase PS (25)	3 (5)	43 (44)[a]	76 (78)	> 99
5	$PrCO_2CH{=}CH_2$	CAL-B (2.5)	5	55[b]	60	50

* Solvent: dry acetone; room temperature
[a] Estimated *E* >>200; reaction stops before 50 % conversion is reached; [b] *E* = 5

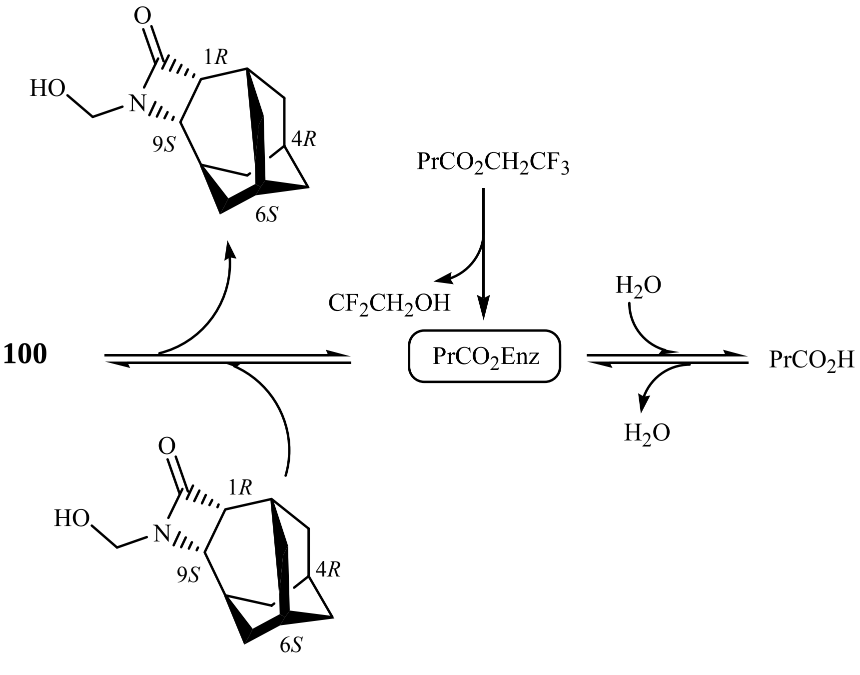
The results show that the acylation tends to stop at around 45 % conversion, especially at higher lipase PS contents (entries 2-4). For alicycle-fused *N*-hydroxymethyl-β-lactam substrates, enzymatic hydrolysis of the ester enantiomer produced and reaction between the product and unreacted primary alcohol enantiomers were suggested earlier, but not studied in detail[11,40]. When (1*R*,4*R*,6*S*,9*S*)-**100** (0.1 M) in acetone was reacted in the presence of the lipase PS preparation (50 mg/ml), 13 % (after 1 h) and 15% (after 6 h) of the substrate was hydrolysed to the corresponding alcohol. When a mixture of **99** (0.05 M, ee = 87 or 94 %) and **100** (0.05 M, ee = 99 %) as such or in the presence of 2,2,2-trifluoroethyl butanoate was treated under the same conditions, **99** was racemized as time passed while the enantiopurity of **100** remained almost unchanged (Table 7).

Table 7. Enantiopurities in dry acetone in the presence of lipase PS (50 mg/ml) in the mixture of (a), (b) and (c)*, followed by the addition of **100** (0.05 M) after 2 h at room temperature

Time (h)	ee$^{\mathbf{99}}$ (%)			ee$^{\mathbf{100}}$ (%)		
	(a)	(b)	(c)	(a)	(b)	(c)
0	95	87	87	99	99	99
3		68			98	
5	68		54	98		99
10	59	46		98	98	
24	52			96		

* (a): **99** (0.05 M) and **100** (0.05 M);
(b): **99** (0.05 M), **100** (0.05 M) and 2,2,2-trifluoroethyl butanoate (0.2 M);
(c): **99** (0.05 M) and 2,2,2-trifluoroethyl butanoate (0.2 M)

The system was stable without the enzyme. These results draw attention to enzymatic hydrolysis as an explanation. However, the question of the origin of the water arises because the partial hydrolysis of alkyl-activated achiral esters detected (2,2,2-trifluoroethyl butanoate or VB used in molar excess) can be assumed to consume the water in the seemingly dry enzyme preparation at the very beginning of the resolution reaction. Esterification is known to produce water. When the mixture of the more reactive (1*R*,4*R*,6*S*,9*S*)-alcohol (0.05 M) and butanoic acid (0.05 M) in acetone was subjected to the presence of the lipase PS preparation (50 mg/ml) the formation of (1*R*,4*R*,6*S*,9*S*)-**100** was clear, though the reaction seemed to stop at 3% conversion. Competing ester hydrolysis due to the water in the enzyme preparation is evident in this test reaction. Accordingly, for the enzymatic resolution of *rac*-**98**, competition for the enzyme between the activated achiral ester, (1*R*,4*R*,6*S*,9*S*)-**100** and butanoic acid explains the difficulty in reaching the theoretical 50% conversion and the racemization of **99** as result of the complicated equilibria, where the water produced in the system plays a role (Scheme 20).



Scheme 20

6.1.3.2. Gram-scale resolutions

Gram-scale resolutions with lipase PS and VB (*rac*-**95a**) or 2,2,2-trifluoroethyl butanoate (*rac*-**95b** and **95c**) in acetone were performed. The results are shown in Table 8.

In accordance with the relatively low enantioselectivity of lipase PS for *rac*-**95b** and *rac*-**95c** (Table 5, entries 8 and 10), the resolution products (1*S*,8*R*)-**96b** and (1*R*,8*S*)-**97b,** and (1*S*,12*R*)-**96c** and (1*R*,12*S*)-**97c** are not enantiopure at 50% conversion. For resolution of the *trans*-β-lactam analogue **95d**, CAL-B-catalysed acylation with VB in acetone is most appropriate (Table 5, entry 17).

Table 8. Acylation results for *rac*-**95** with lipase PS*, using 2,2,2-trifluoroethyl butanoate (VB in the case of *rac*-**95a**)

Substrate	Time (h)	Conversion (%)	ee$^{\mathbf{96}\text{ or }\mathbf{99}}$ (%) (Configuration)	ee$^{\mathbf{97}\text{ or }\mathbf{100}}$ (%) (Configuration)
rac-**95a**	2	49	93 (1*S*,7*R*)	97 (1*R*,7*S*)
rac-**95b**	24	52	90 (1*S*,8*R*)	82 (1*R*,8*S*)
rac-**95c**	10	50	90 (1*S*,12*R*)	-[b]
rac-**95d**[a]	2.5	50	85 (1*R*,12*R*)	-[b]
rac-**98**	10	48	94 (1*S*,4*S*,6*R*,9*R*)	>99 (1*R*,4*R*,6*S*,9*S*)

*Concentration: 50 mg/ml lipase PS; solvent: dry acetone; room temperature

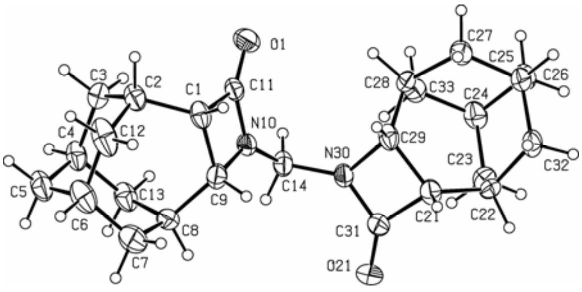
[a] CAL-B as enzyme; [b] Determination of ee for the resolution mixture was not possible.

The gram-scale resolution of *rac*-**98** with 2,2,2-trifluoroethyl butanoate was performed in dry acetone with 12.5 mg/ml of the lipase PS preparation in 2 ml of dry acetone. After 10 h, 48% conversion was reached and the work-up afforded (1*S*,4*S*,6*R*,9*R*)-**99** and (1*R*,4*R*,6*S*,9*S*)-**100** in almost quantitative chemical yields.

6.1.3.3. Absolute configuration

Opposite enantiodiscrimination was previously reported[40,47] for the acylation of alicyclic β-amino esters and the corresponding *N*-hydroxymethyl-β-lactams by lipases. This likewise holds in this work, where **96b** and **96d** were first transformed to the amino esters **90b** and **90d** by treatment with MeOH/HCl and NH_3, after which the positions of the peaks in the GC chromatograms were compared with those for the CAL-A-catalysed acylations of the amino esters. The result justifies the conclusion concerning the absolute configurations (1*S*,8*R*) for the unreacted enantiomer of *rac*-**95b** and (1*R*,12*R*) for *rac*-**95d**. More generally, the [1*R*,(n+4)*S*] enantiomers (n = 3, 4 and 8) are more reactive for the lipase-catalysed acylation of racemic *cis* isomers **95a-c**.

The absolute configurations of **99** and **100** were obtained by X-ray structure elucidation. For this purpose, *N*-hydroxymethyl-β-lactam **99** was transformed to the dimer **101** by stirring in aqueous HCl (18%) solution for 24 h at room temperature. Under such conditions, the corresponding β-lactam enantiomer is formed and reacts with the **99** present in the reaction mixture, leading to formation of the dimer **101**.



101

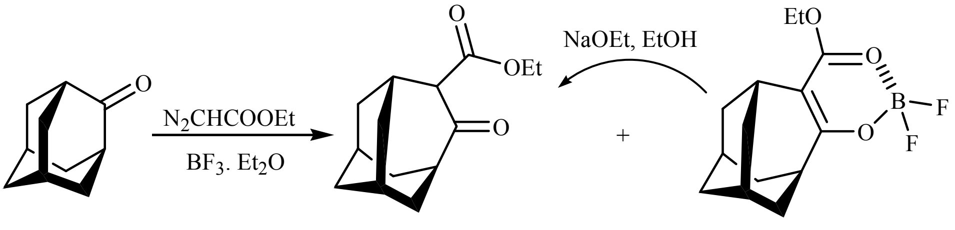
Figure 5

The X-ray structure (Figure 5) clearly indicates the (1*S*,4*S*,6*R*,9*R*) configuration for **99**. In accord with the earlier cases[6,7,11,40], the enantiomer that reacts is the one in which the *N*-hydroxymethyl group is attached to the carbon with the (*S*) absolute configuration. After separation, **99** was transformed to the amino ester **93** by treatment with MeOH/HCl and NH_3, the positions of the peaks in the GC chromatograms then being compared with those for the CAL-A-catalysed resolution of *rac*-**92**. The results confirm the absolute configuration (1*R*,4*R*,5*S*,8*S*) for **93** and (1*S*,4*S*,5*R*,8*R*) for **94**.

6.2. Homoadamantane-fused pyridopyrimidinones

6.2.1. Synthesis

The starting material (**102**) for the preparation of homoadamantane-fused pyridopyrimidinones was obtained by the reaction between adamantan-2-one (**46**) and ethyl diazoacetate ($N_2CHCOOEt$) in the presence of $BF_3{\cdot}Et_2O$[75,96,97] (Scheme 21).



Scheme 21

The main product (**102**) was always accompanied by a high yield of the difluoroborate complex of its enol form (**103**). This complex seemed to be more stable than the analogous complexes of other β-ketocarboxylates. In earlier papers[75,97], such boron complexes were decomposed by treating the reaction mixture with aqueous $NaHCO_3$ or dilute aqueous

NH$_4$OH solution. However, these methods were not applicable for the decomposition of complex **103**; a stronger nucleophile, ethanolic NaOEt, was required. Its structure was determined by X-ray study (Figure 6).

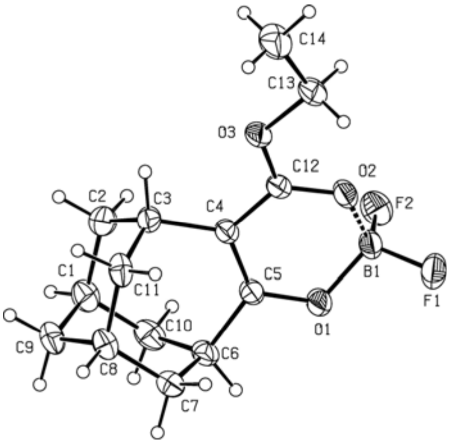
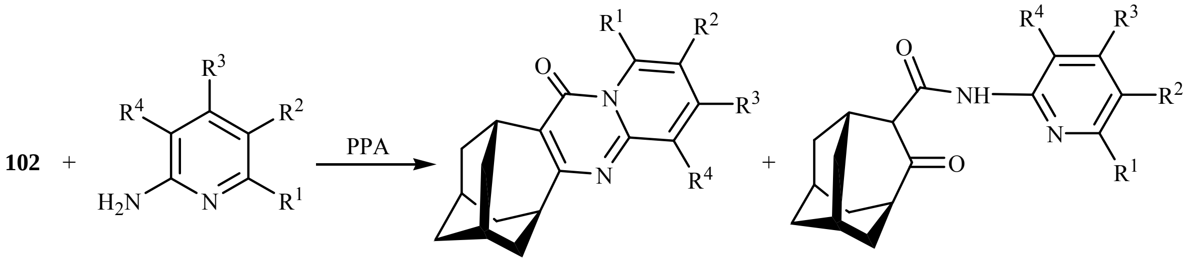


Figure 6

In fact, NMR analyses revealed that **102** consisted of the oxo and enol forms in almost equal amounts (51:49). However, the various reactions can still proceed unaffected, since the forms are in equilibrium with each other in solution.

The reactions of **102** with methyl-substituted 2-aminopyridines in PPA gave both linearly-condensed pyridopyrimidinones (**104a–c**) and 2-pyridylcarboxamides (**105a–c**) (Scheme 22).



104a-c **105a-c**

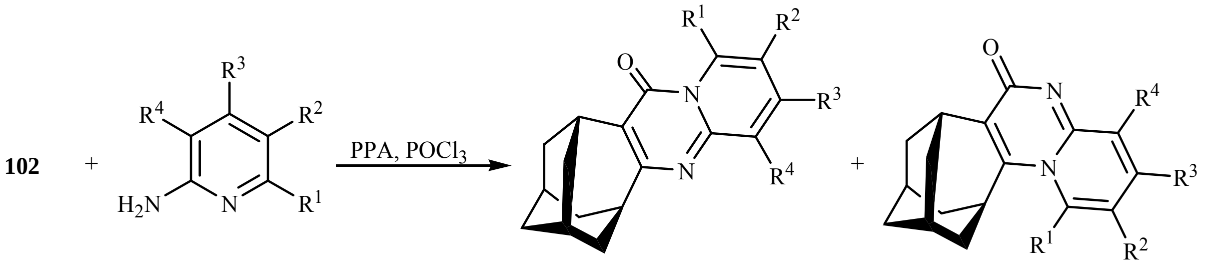
104	105	R^1	R^2	R^3	R^4
a	**a**	H	H	Me	H
b	**b**	H	Me	H	H
c	**c**	Me	H	H	H

Scheme 22

Carboxamides **105a-c** were expected to undergo cyclization in PPA to furnish the angularly-condensed pyridopyrimidinones, but even at elevated temperatures the yields were low, and finally almost complete decomposition occurred.

Use of a mixture of PPA and POCl$_3$ (Scheme 23) instead of PPA alone (Scheme 22) afforded both linearly-condensed (**104a-c**, **e**, **f**) and angularly-condensed (**106a-c**, **e**, **f**) pyridopyrimidinones.

Angularly-condensed pyridopyrimidinones were obtained only when the carboxamide was formed from the corresponding β-oxocarboxylate and 2-aminopyridine in the course of the reaction. Accordingly, these carboxamides were synthetized and their reactivities were studied under different conditions.

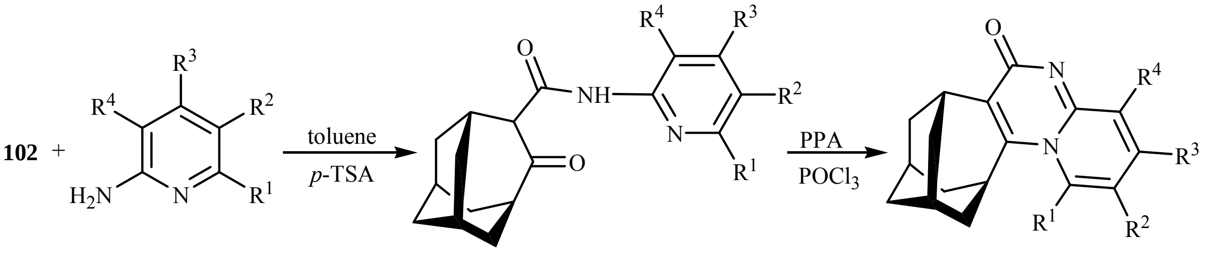


104a-c, e, f **106a-c, e, f**

104	**106**	R^1	R^2	R^3	R^4
a	**a**	H	H	Me	H
b	**b**	H	Me	H	H
c	**c**	Me	H	H	H
e	**e**	H	Br	H	H
f	**f**	H	Cl	H	H

Scheme 23

Carboxamides **105a-f** were prepared by the reactions of β-oxocarboxylate **102** with 2-aminopyridines in toluene with *p*-TSA as catalyst at reflux temperature. In a mixture of PPA and $POCl_3$, **105a-f** yielded angularly-condensed pyridopyrimidinones **106a-f** (Scheme 24) as the only products at 80-120 °C, while the cyclization of carboxamides in PPA alone failed.

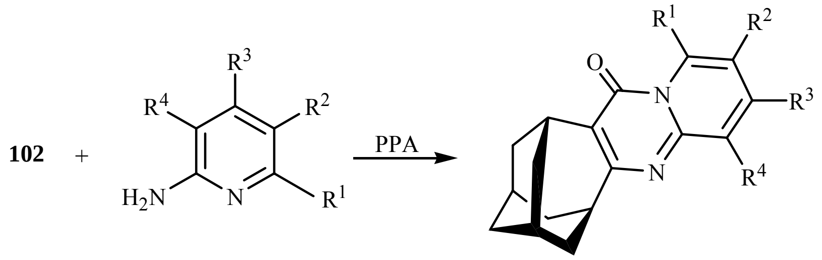


105a-f **106a-f**

105	**106**	R^1	R^2	R^3	R^4
a	**a**	H	H	Me	H
b	**b**	H	Me	H	H
c	**c**	Me	H	H	H
d	**d**	H	H	H	H
e	**e**	H	Br	H	H
f	**f**	H	Cl	H	H

Scheme 24

In fact, we first studied the reactions of **2** with amino, hydroxy and nitro derivatives of 2-aminopyridine in PPA. It was found that, in agreement with the literature data[20], these reactions gave a single product, the linearly-condensed pyridopyrimidinones, **104g–j** (Scheme 25).



104	R¹	R²	R³	R⁴
g	NH_2	H	H	H
h	H	H	H	OH
i	OH	H	H	H
j	H	NO_2	H	H

104g-j

Scheme 25

6.2.2. Structure elucidation

NMR

The molecules in sub-series **104** and **106** contain a plane of symmetry, in which the pyridopyrimidinone moiety lies. This is evident from the chemical equivalence of the protons and carbons at positions 13/19, 17/18 and 14/16. In series **106**, the irradiation of H1 resulted in a strong NOE in H4 (or Me in the case of **106c**), thereby proving the angular fusion. For series **104**, a similar enhancement was not observed, which confirmed the linear condensation. As a whole, comparison of the chemical shifts demonstrated the differences expected on the basis of the linear and angular structures. Some special features deserve mention. In general, H1 and C1 resonate at clearly higher or lower field, respectively, in linear compounds **104** than in angular compounds **106**. In compounds **104**, in consequence of the coplanarity with the carbonyl groups, H8 resonates at exceptionally low field. It is therefore relatively easy to distinguish linearly- (**104**) and angularly-condensed (**106**) compounds from each other on the basis of their ^{1}H and ^{13}C NMR spectra.

Carboxamides **105** have an additional chiral carbon (C4) in the homoadamantane moiety, and consequently, they have no plane of symmetry; therefore, all the protons and carbons in the carbocyclic moiety are chemically inequivalent. The irradiation of H4 demonstrated an NOE enhancement in H11eq (for **105f**), allowing correct assignment of the signals within the pairs 2/11, 1/8 and 7/10. All of compounds **105** exhibited the presence of small amounts of the enol form of the homoadamantone moiety. The carbon signals corresponding to this minor form could not be resolved because of its small concentration. In the ^{1}H spectra, however, some of the signals of the enol forms were resolved as follows: 2.51–

2.53 ppm (H6), 2.62–2.66 ppm (H3) and 14.46–14.64 ppm (5-OH). The tautomeric ratios (keto/enol) were in all cases ≥ 20.

The ^{1}H spin subsystem of the homoadamantane moiety is relatively complex as a result of the overlapping strongly coupled signals, and the reported chemical shifts of these signals may be inaccurate.

X-ray structures

During crystallization, **104c** undergoes spontaneous resolution, which results in an enantiomeric space group $P4_12_12$. Additionally, it contains linear ring junctions, lying on the twofold axes, which are the plane diagonals of the tetragonal unit cell. Since the overall C_2 molecular symmetry is violated by the three heteroatoms N3, N9 and O10 and the Me group, the crystallographic twofold symmetry can be maintained by rotational disorder of the planar pyridopyrimidinone tail. While the homoadamantyl moiety is located on the twofold axis, the aromatic rings are significantly displaced from it (Figure 7). The twofold axis is defined by the positions of C15 and C7. Along the twofold rotor, N9 is displaced.

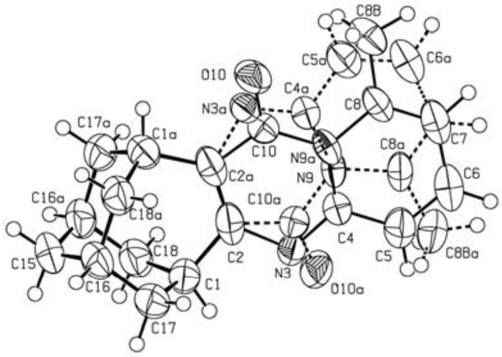


Figure 7

Compounds **106e** and **106f** differ only in their halogen (Br *vs* Cl) substituent, and their monoclinic crystals therefore exhibit a rather high degree of isostructurality[98]. Their intramolecular bonding and conformation hardly differ. In both structures (Figure 8a and 8b), the angular ring junctions give rise to a rather short H$\cdots$H contact between the sp^3-C1 and the aromatic C4. The planarity of the pyridopyrimidinone moieties [the torsion angles C1-C2-N3-C4 are 4.4(2)º (Cl) and 5.4(4)º (Br)] does not allow a greater separation of H1 and H4 than 1.84 Å (Cl) and 1.89 Å (Br).

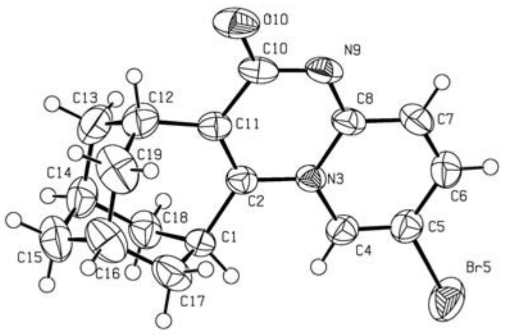


Figure 8a

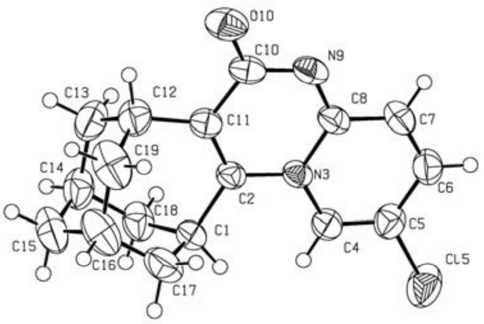
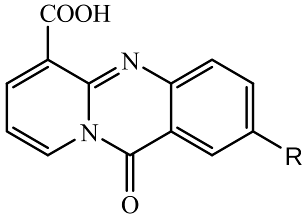


Figure 8b

6.3. Synthesis of 11-oxo-11*H*-pyrido[2,1-*b*]quinazoline-6-carboxamides

As a continuation of our work on fused-skeleton saturated and partially saturated heterocycles[37], we performed the preparation and investigation of homoadamantane-fused pyridopyrimidinones (see above). Carboxamide derivatives of 11-oxo-11*H*-pyrido[2,1-*b*]-quinazoline-6-carboxylic acid (**107**) and 14-chloro-11-oxo-11*H*-pyrido[2,1-*b*]quinazoline-6-carboxylic acid (**108**) were prepared for pharmacological investigation, primary of their antiallergy and anaphylaxis inhibitor activities.

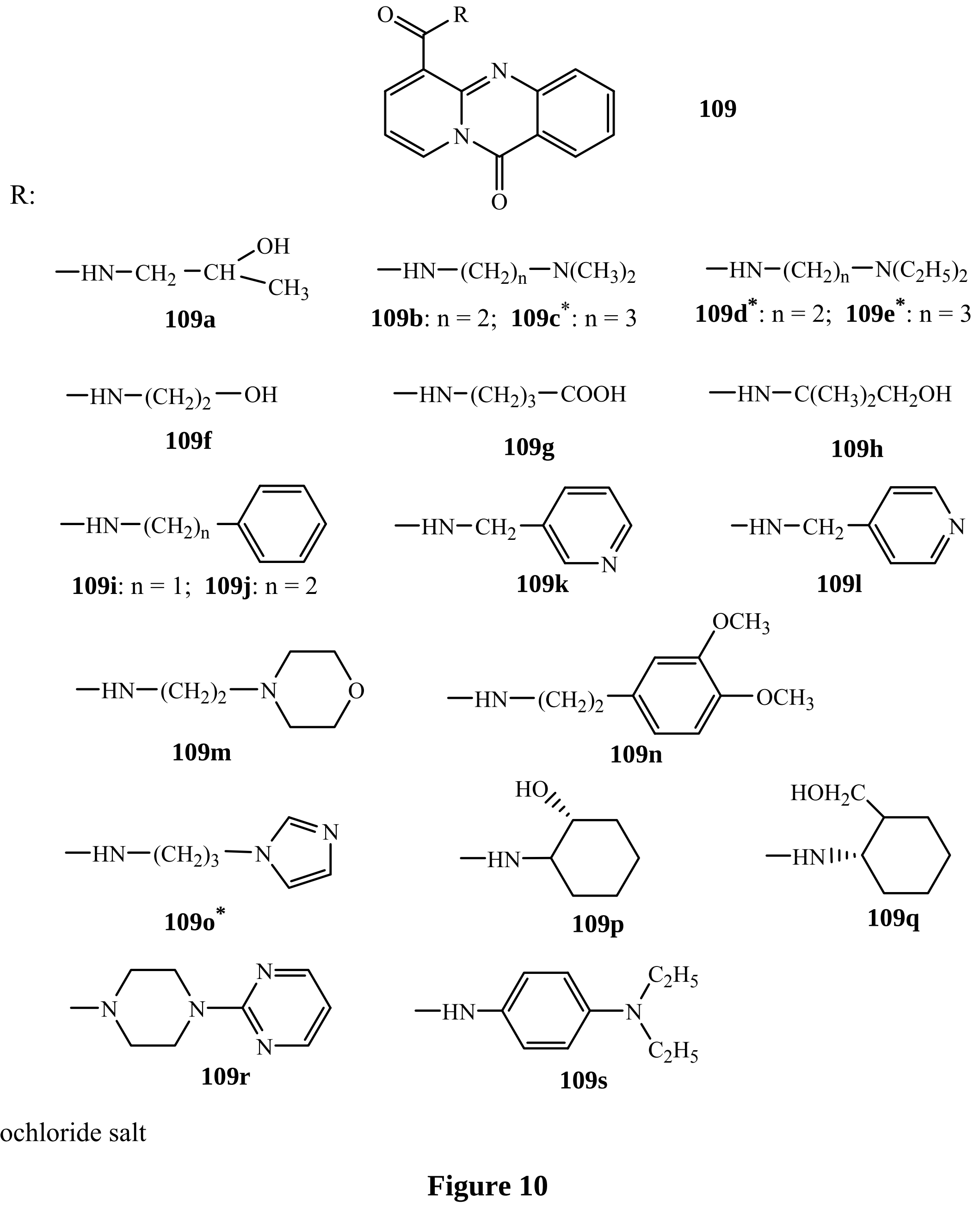
The key compounds of the syntheses, **107** and **108** (Figure 9), were synthetized from 2-chloronicotinic acid with anthranilic acid or with 5-chloroanthranilic acid at elevated temperature (130 °C and 160 °C), respectively.



107: R = H; **108**: R = Cl

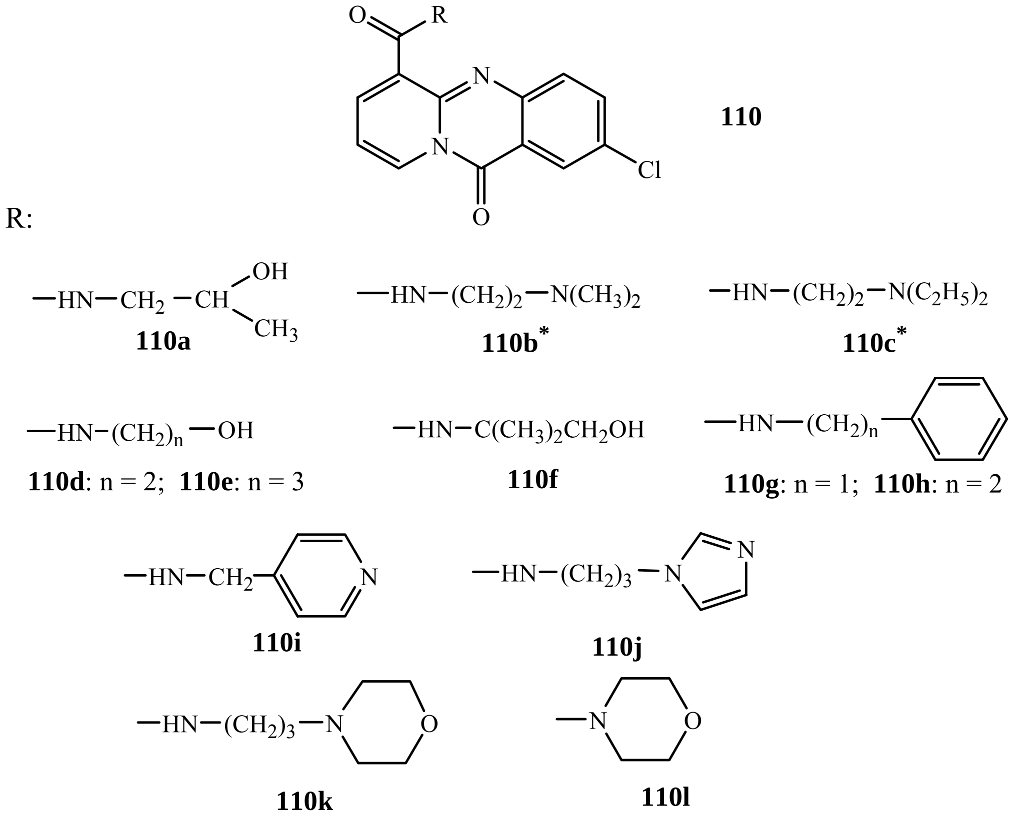
Figure 9

The pyrido[2,1-*b*]carboxylic acids (**107**, **108**) were reacted with primary or secondary amines to give **109a-s** and **110a-l** carboxamides (Scheme 26). In the carboxamide formation, the application of DCC (1 eq) in THF resulted in low yields, and therefore isobutyl chloroformate and triethyl amine (TEA) were used. For the synthesis of carboxamides (**109a-s**), 11-oxo-11*H*-pyrido[2,1-*b*]quinazoline-6-carboxylic acid (**107**) was dissolved in DMF at −15 °C, isobutyl chloroformate and TEA were added dropwise, the mixture was stirred at this temperature for 1 h, and the corresponding amine was then added. After stirring for further 4 hs at −15 °C and standing at room temperature overnight, the solvent was evaporated off and the residue was purified by recrystallization or by column chromatography. The compounds obtained, **109a, 109b, 109f-n, 109p-s**, were yellow crystals. Four compounds were light-brown oils, which were transformed to hydrochlorides with ethanolic HCl (**109c-e, 109o**) (Figure 10). In a similar way, 14-chloro-11-oxo-11*H*-pyrido[2,1-*b*]quinazoline-6-carboxamides **110a**, **110d-l** were synthetized from **108**. **110b** and **110c** were prepared as hydrochlorides, because the carboxamides were oils (Figure 11).



* Hydrochloride salt

Figure 10



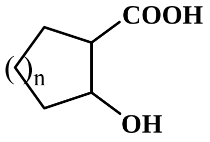
* Hydrochloride salt

Figure 11

6.4. 2-Hydroxycycloalkanecarboxylic acids and β-lactams

6.4.1. Isomerization of 2-hydroxycycloalkanecarboxylic acids

As part of our extensive synthetic work on saturated heterocycles for pharmacological and theoretical investigations[37], a convenient method of obtaining the *trans* isomers in relatively large quantities was required.



111-114

111: n = 1; **a**: *cis*; **b**: *trans*
112: n = 2; **a**: *cis*; **b**: *trans*
113: n = 3; **a**: *cis*; **b**: *trans*
114: n = 4; **a**: *cis*; **b**: *trans*

Figure 12

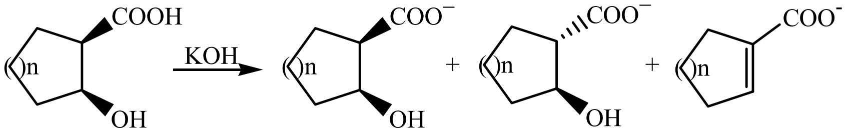
It was earlier found that the isomerization of *cis*-2-hydroxycyclohexanecarboxylic acid (**112a**) in boiling aqueous KOH solution produced an appreciable amount of the *trans* isomer (**112b**), and the two isomers could be separated by crystallization[87]. Since the alkaline isomerization of the other homologues had not been applied for synthetic purposes nor studied kinetically, and the *cis-trans* isomerization had not been investigated in detail even for 2-hydroxycyclohexanecarboxylic acid, we considered it reasonable to explore the *cis-trans* isomerization of the cyclopentane, cyclohexane, cycloheptane and cyclooctane homologues (Figure 12) from both preparative and theoretical aspects.

6.4.1.1. Basic screening

In a search for the optimum reaction conditions, the concentration of the KOH solution was varied between 5 w/w% and 40 w/w%. Significant isomerization proceeded only when concentrated (30 w/w% or 40 w/w%) KOH solutions were applied. Of these two possibilities, the more dilute solution was used, because the more concentrated alkaline solution rapidly attacked the glassware, making the work very inconvenient.

6.4.1.2. Kinetic investigations

Soon after the start of the isomerization reaction, the *trans* isomer could be detected, as could the olefinic carboxylic acid formed by water elimination. The *cis-trans* isomerization leads to an equilibrium mixture, containing the *cis* isomer (**111a-114a**), the *trans* isomer (**111b-114b**) and the olefinic carboxylic acid (**111c-114c**) (Scheme 26), the composition of this mixture varying with the ring size.



111a-114a **111a'-114a'** **111b'-114b'** **111c'-114c'**

111a, **a'**, **b'**, **c'**: n = 1; **112a**, **a'**, **b'**, **c'**: n = 2; **113a**, **a'**, **b'**, **c'**: n = 3; **114a**, **a'**, **b'**, **c'**: n = 4

Scheme 26

The reaction rates in the homologous series differed. The measured composition *vs* time points were fitted numerically according to a pseudo-first-order reaction scheme (Scheme 27).

$$\begin{tikzcd}
\textit{cis}\text{-2-hydroxycycloalkanecarboxylic acid} \arrow[rr, shift left, "k_{11}"] \arrow[dr, shift left, "k_{21}"] & & \textit{trans}\text{-2-hydroxycycloalkanecarboxylic acid} \arrow[ll, shift left, "k_{12}"] \arrow[dl, shift left, "k_{31}"] \\
& \text{1-cycloalkenecarboxylic acid} \arrow[ul, shift left, "k_{22}"] \arrow[ur, shift left, "k_{32}"] &
\end{tikzcd}$$

Scheme 27

The curves are depicted in Figure 13a-d.

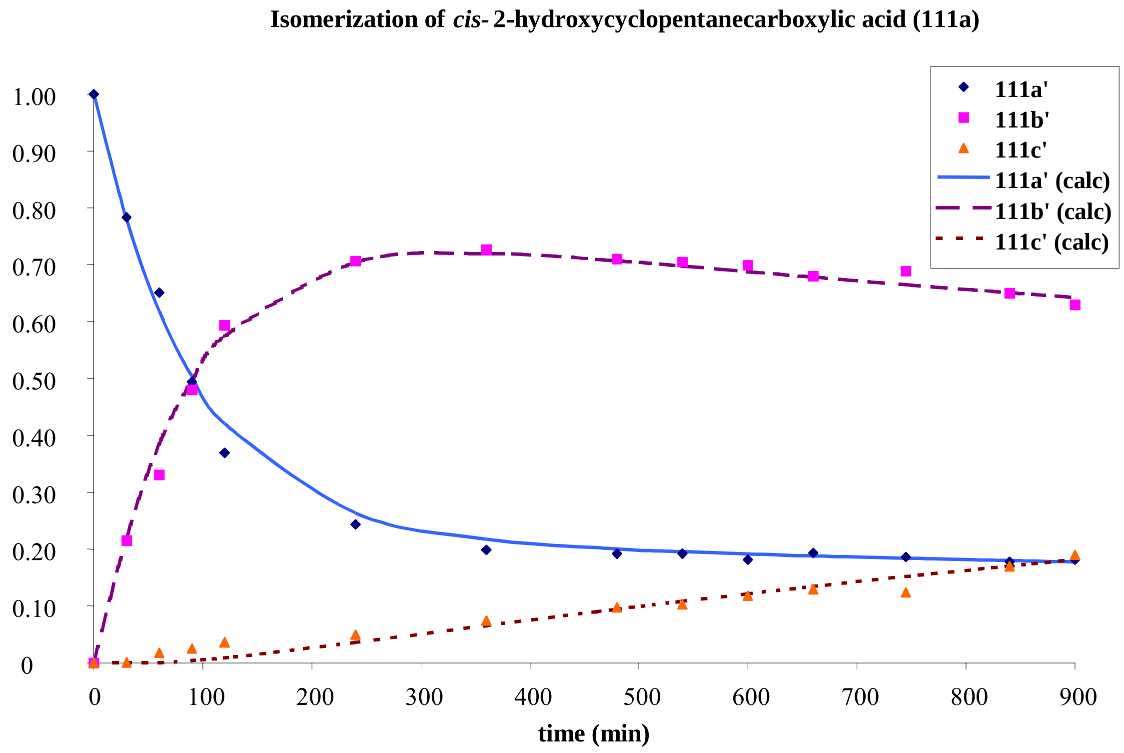


Figure 13a

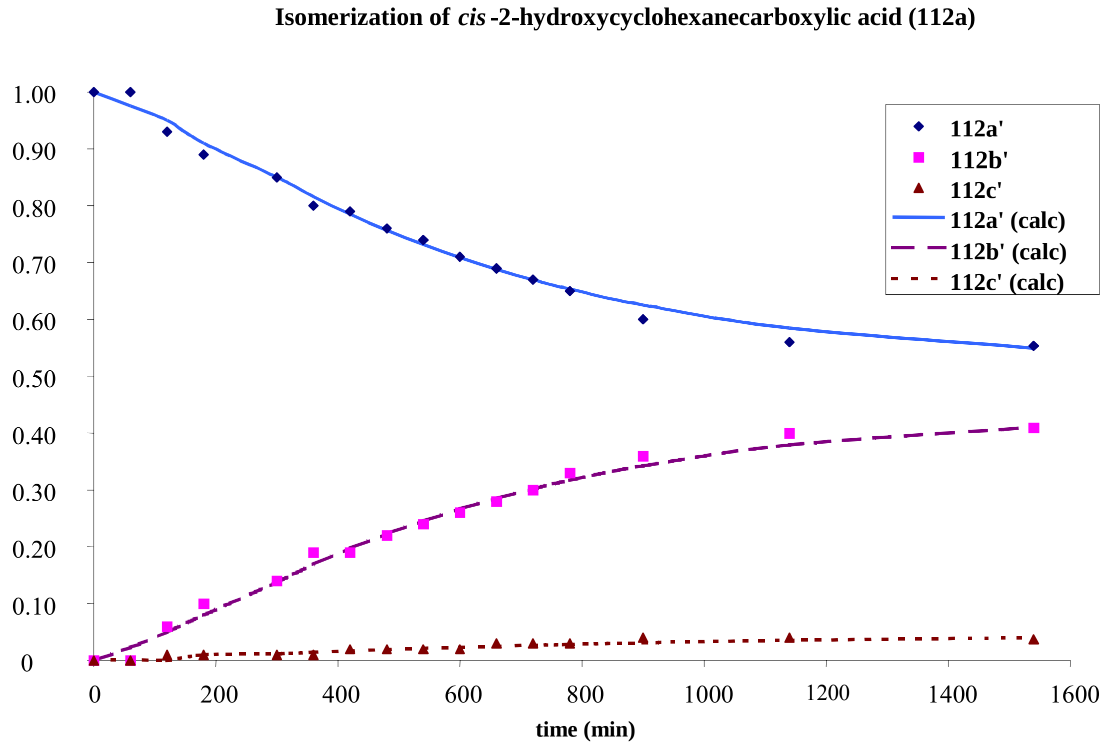


Figure 13b

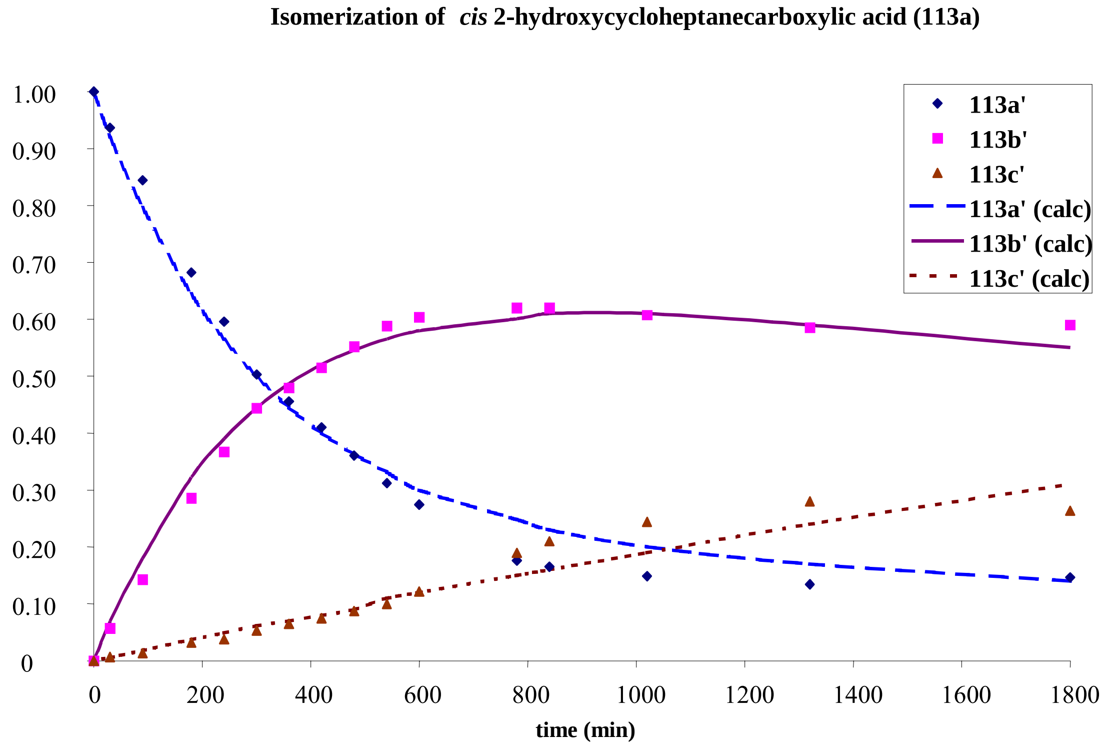


Figure 13c

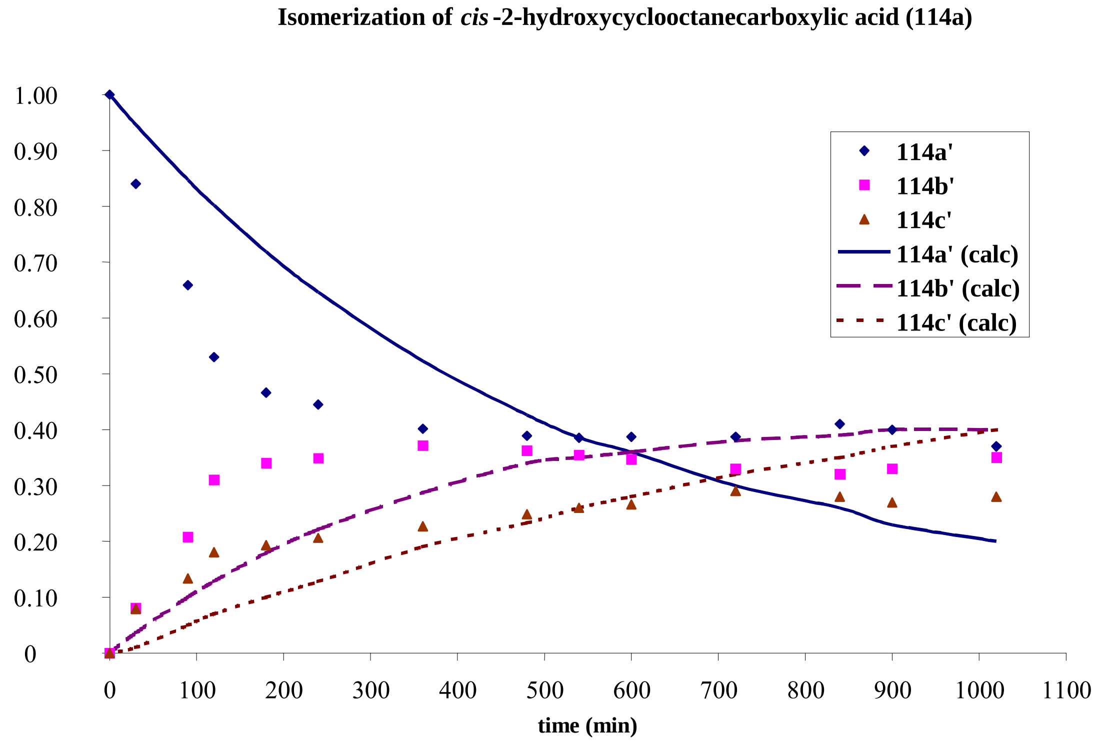


Figure 13d

The fit to the experimental points ranged from excellent to fair, except for 2-hydroxy-cyclooctanecarboxylic acid; the rate constants derived for the reactions of **114a** are somewhat vague.

Both the kinetic behaviour and the thermodynamic (equilibrium) data are worthy of consideration from a synthetic viewpoint. When the formation of the elimination side-product is slow, as for **112a**, waiting for equilibrium to be attained may make sense if the aim is to obtain the highest possible amount of the *trans* isomer. Otherwise, there is an optimum time to obtain the highest possible amount of the *trans* isomer, when the formation of side-product (olefinic acid) is minimal (Table 9).

Table 9. Composition of the equilibrium mixtures when the reaction starts from the alicyclic *cis*- or *trans*-2-hydroxycycloalkanecarboxylic acids

Starting compound	Time for equilibration (h)	Equilibrium composition (%) **a' – b' – c'**	Starting compound	Time for equilibration (h)	Equilibrium composition (%) **a' – b' – c'**
111a	15	14 – 72 – 14	**111b**	25	15 – 55 – 30
112a	20	55 – 41 – 4	**112b**	33	10 – 89 –1
113a	25	10 – 67 – 23	**113b**	50	10 – 46 – 45
114a	10	37 – 35 – 28	**114b**	30	6 – 37 – 57

It is to be seen that **111a** and **113a** afforded the highest amounts of the *trans* isomers, though dehydration was appreciable in both cases. After the given reaction time, the amount of **112b'** (produced from **112a**) was still less than that of **112a'**, though the amount of the dehydration side-product was particularly low here. This means that the reaction may be used well for the preparation of *trans*-2-hydroxycyclohexanecarboxylic acid. After the reaction of **114a** for the given time, **114a'**, **114b'** and **114c'** were present in roughly similar amounts. These results suggest that these isomerization reactions might be suitable for the preparation of **111b**, **112b** and **113b** from **111a**, **112a** and **113a**, respectively, but that isomerization under alkaline conditions is not suitable for the larger-scale preparation of the *trans* compound **114b**.

The isomerization reactions were also studied by using the *trans* compounds (**111b-114b**) as the starting molecules (Table 9). The same basic conditions were used for **111a-114a** and **111b-114b**. The differences in the amounts of **111c-114c** formed in the reactions in the two different directions are due to the fact that the rates of dehydration are different for the *cis* and the *trans* isomers.

As regards the kinetics of the various reactions, the pseudo-first-order rate constants are given in Table 10.

Table 10. Pseudo-first-order rate constants (1/min) for the reactions outlined in Scheme 27

	k_{11}	k_{12}	k_{21}	k_{22}	k_{31}	k_{32}
111	$8.88*10^{-3}$	$2.33*10^{-3}$	$1.05*10^{-4}$	$5.80*10^{-5}$	$4.06*10^{-4}$	$5.80*10^{-5}$
112	$7.73*10^{-4}$	$6.58*10^{-5}$	$6.26*10^{-5}$	$9.49*10^{-3}$	$2.63*10^{-6}$	$9.49*10^{-3}$
113	$2.44*10^{-3}$	$7.45*10^{-4}$	$1.99*10^{-4}$	$2.84*10^{-4}$	$2.55*10^{-4}$	$2.84*10^{-4}$
114	$1.24*10^{-3}$	$8.83*10^{-5}$	$5.85*10^{-4}$	$2.17*10^{-4}$	$6.95*10^{-4}$	$2.17*10^{-4}$

It may be seen that the rate of the *cis* → *trans* isomerization decreases in the sequence **111** > **113** > **114** > **112**, and the $K_{trans/cis}$ ratios are **111b**/**111a**: 3.8, **112b**/**112a**: 11.8, **113b**/**113a**: 3.3 and **114b**/**114a**: 14.1. Thus, the reaction **114a** → **114b** should be suitable for obtaining the *trans* isomer. However, the formation of the olefinic carboxylic acid from the *cis* isomer is relatively fast for **114a** (similarly as for the reaction **113a** → **113c**), and it would therefore not be reasonable to continue the isomerization to equilibrium if the *trans* isomer is to be obtained in appreciable quantities.

6.4.2. Hydrogen-bonding patterns in the crystals of 2-hydroxycycloalkanecarboxylic acids and β-lactams

The stereohomogeneous alicyclic *cis*- and *trans*-β-aminocarboxylic acids, β-hydroxy acids and their carboxamides were used for the study and prediction of hydrogen-bonding patterns and other supramolecular phenomena (*e.g.* isostructurality and polymorphism).

KÁLMÁN *et al.*[99] reported on the crystal structures of six related cyclopentane derivatives, which exhibit five forms of close-packing governed by two vicinal functions (either OH *vs* COOH or OH *vs* $CONH_2$). Our work extended to the homologous 2-hydroxycyclohexanecarboxylic acids, 2-hydroxycycloheptanecarboxylic acids and 2-hydroxycyclooctanecarboxylic acids (Figure 12).

Both the *cis* and *trans* isomers of these carboxylic acids were crystallized and subjected to X-ray crystallography. **111b**, **112a** and **113a** crystallized in the space group *C*2/*c*. These 3 structures exhibit deterministic isostructurality.

Each structure possesses a tetramer arranged in an $R_4^4(12)$ ring; such tetramers are formed whenever the two $R_2^2(12)$ dimers are joined laterally (Figure 14).

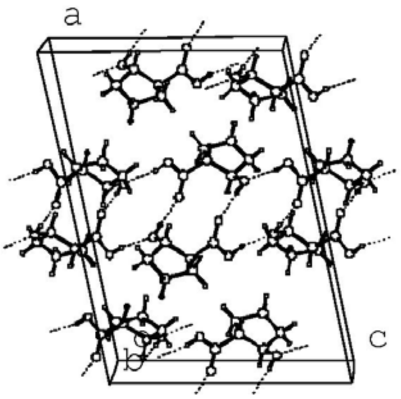


Figure 14

The $R_2^2(12)$ rings are held together by either O–H···O=C (**111b**) or O–H···O–H bonds (**113a**). The structure of **112a** comprises a disordered mixture of the two kinds of dimers.

The *trans* stereoisomer **114b** exemplifies another mode of association of heterochiral dimers. Its crystal structure com-prises linear arrays of the two kinds of heterochiral dimers. The crystals of the *cis* stereoisomer, **114a** are built up from antiparallel hydrogen-bonded helices. Between the helices $R_2^2(12)$ rings are formed. The hydrogen-bond donors and acceptors of the helices and dimers alternate in the same way as in the two dimer types of **114b** ribbons. In the course of crystallization, the homochiral OH dimers of **114a** are presumably polymerized into antiparallel helices.

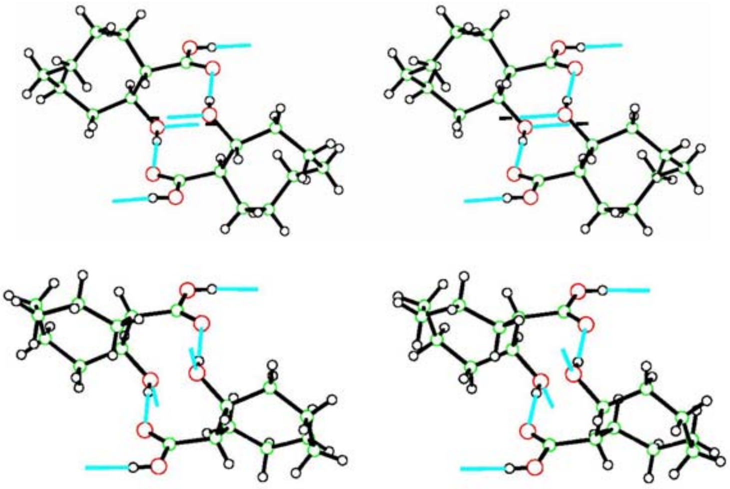


Figure 15

Thus, the OC dimers (Figure 15) remain the common building blocks of the two structures. The conformations of the OC dimers of the *cis* and *trans* isomers are similar. Both of them are folded along the O–H···O=C hydrogen-bond pairs.

If crystals are built up by parallel chains of hydrogen-bonds, large antidromic hydrogen-bonded rings are formed instead of dimers. The polymorphism of **113b** can be attributed to two different modes of dipole cancellation. Dipoles are formed in the antidromic rings of hydrogen-bonded molecules (Figure 16).

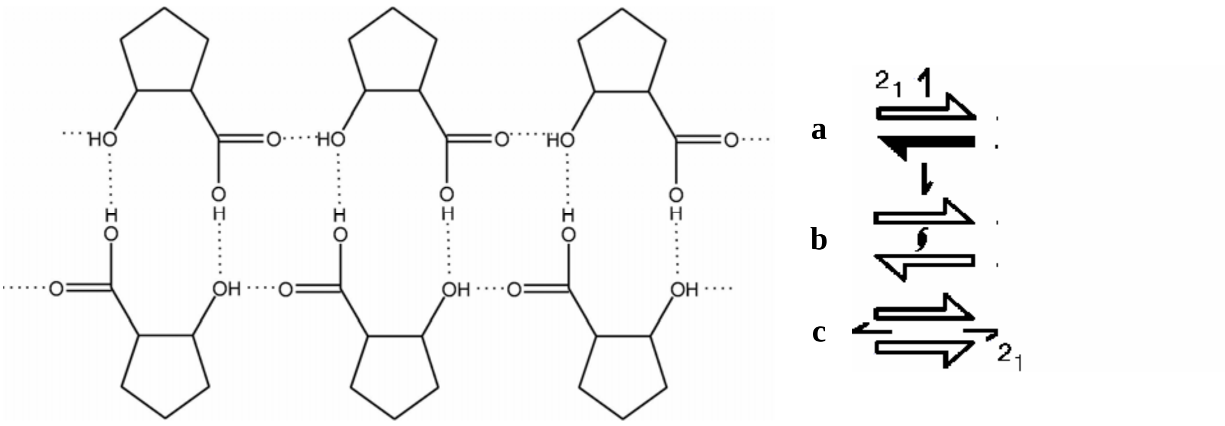


Figure 16

These dipoles must cancel out over the whole crystal by antiparallel stacking of either molecular layers or crystal domains. In one of the dimorphs (**II**) [crystallized from butan-2-one and a few drops of *n*-hexane], the layer stacking is antiparallel, whereas in the unit cell of the second form (**I**) [crystallized from Bu_2O and a few drops of *n*-hexane], the layers are parallel. In the second crystal, the antiparallel alignment of the domains cancels out the dipole moment. However, the dimorphs **I** and **II** (Figure 17) possess virtually the same cell, indicating a special form of isomorphism.

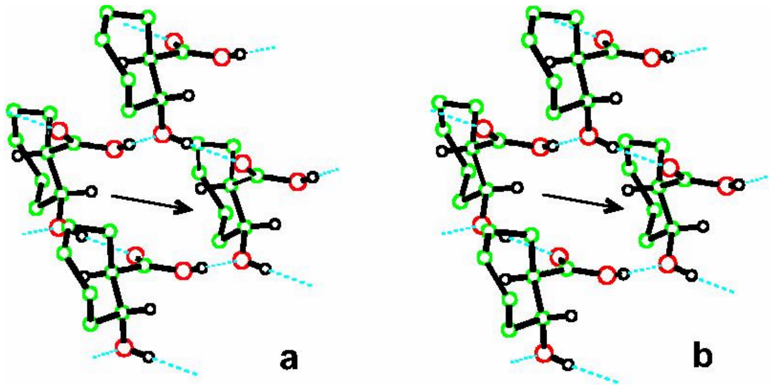


Figure 17

The layers of the antidromic rings may be rotated in three ways. The ring dipoles may be cancelled out by the sheets turning upon each other through 180° (Figure 16a) and generating screw axes perpendicular to the dipole vector.

This arrangement was observed by KÁLMÁN *et al.*[99] for compound **VI**, which forms layers of hydrogen-bonded tetramers joined by antidromic $R_4^4(18)$ rings. The dimorphs of **113b** demonstrate the two other modes of layer rotation. In both forms, screw axes turn the infinite layers upside down, but either perpendicular to (Figure 16b) or parallel with (Figure 16c) the direction of the dipole vector. In the perpendicular mode, the layer stacking becomes antiparallel, whereas in the parallel array, the new and the old dipoles in the layers remain parallel.

The isostructurality of dimorphs **I** and **II** can be understood if their unit cells are compared (Figure 18).

The upper halves of the cells are identical, while the lower halves are related to the upper ones by mutually perpendicular rotations. As a result, the lower halves are related to each other by a two-fold axis assigned along the *a* axis. It follows that a 180° turn of one of the cells around the *a* axis reveals the isostructural relationship between the lower layers and *vice versa*. Accordingly, independently from the upper halves, they are also isostructural. Thus, dimorphs **II** *vs* **I,** possessing virtually the same unit cell, involve an unprecedented form of both polymorphism and isostructurality.

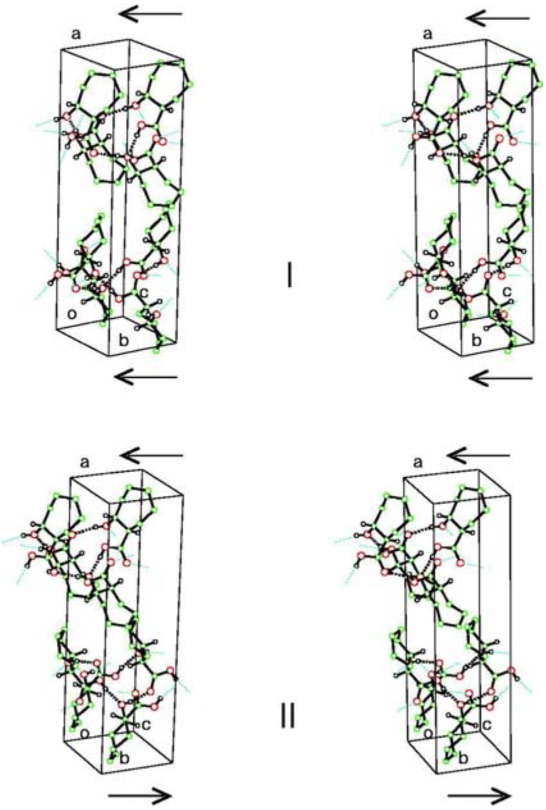


Figure 18

The racemic crystals of alicyclic (cyclopentane, cyclohexane, cycloheptane and cyclooctane) β-amino acids are isostructural[100]. The corresponding β-lactams contain only one hydrogen-bond.

The crystals of the cyclopentane[101] (**17**) and cyclohexane (**18**) homologues are isostructural. In the racemic crystals of **17** and **18**, the enantiomers are organized in homochiral helices with antiparallel orientation. In contrast with these results, the crystals of *cis*-8-azabicyclo[5.2.0]nonan-9-one (**19**) hallmarked by antiparallel helices of the homochiral molecules held together by N–H··O=C hydrogen-bonds, reveal spontaneous resolution. The length of their common, helix-bearing axis increases monotonously in the interval 6.147–6.683 Å.

In the polymorphs of *trans*-13-azabicyclo[10.2.0]tetradecan-14-one (**115**) (crystallized from MeOH and acetone), the lengths of the helices differ considerably. This can be attributed to the different orientations of the *O* lone-pair electrons that accept the hydrogen-bonds. The hydrogen-bonding arrangement may be either *anti*periplanar (**III**) or *syn*periplanar (**IV**) with respect to the endocyclic amide bond of the planar β-lactam ring (Figure 19a,b).

III

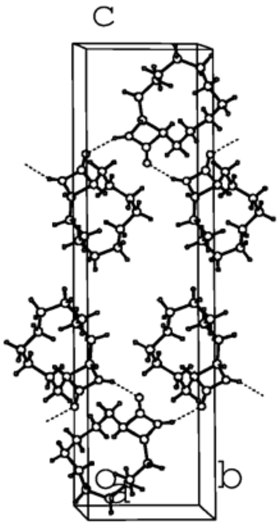


Figure 19a

IV

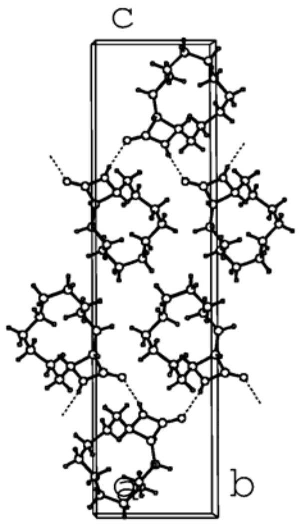


Figure 19b

Crystals **III** and **IV** exhibit isostructural polymorphism, revealed first by the dimorphs of **113b**, with virtually the same unit cell.

7. SUMMARY

The present work extends the known enzymatic kinetic resolution methods for the preparation of alicyclic β-amino acids with medium or large rings and *cis*-5-amino-tricyclo[4.3.1.1^{3,8}]undecane-4-carboxylic acid derivatives[40,46], in addition to normal-ring analogues[7,40]. The *N*-acylation of alicyclic β-amino esters *rac*-**89a-c** (*cis* isomers) and *rac*-**92** with 2,2,2-trifluoroethyl butanoate has been studied. The reactions in *i*Pr_2O proceed with excellent enantioselectivity (usually *E*>200) in the presence of CAL-A, allowing enantioseparation as a one-pot acylation at 50% conversion. The alicyclic ring size does not exert an effect on the enantioselectivity, and an amide product **91**. The above method with *E*>>200 is the most convenient route to **93** and **94**. In accordance with the previous results[46], the method works only poorly (*E* = 7) for the resolution of *trans* isomer **89d**.

Via enzymatic *O*-acylation of the *N*-hydroxymethyl-β-lactam *rac*-**95** and **98**, acylated with VB or 2,2,2-trifluoroethyl butanoate in dry acetone with lipase PS as catalyst, the [1*R*,(n+4)*S*] enantiomers (n = 3, 4 and 8) are more reactive for the lipase-catalysed acylation of racemic *cis* isomers **95a-c** and (1*R*,4*R*,6*S*,9*S*) of **98**. The enantioselectivity of lipase PS is highly dependent on the molecular size of the substrate alcohol (for **95a**: *E*>200, and for **95b**: *E* = 27). The method with CAL-B acting as the catalyst and VB as the acyl donor is suitable for resolution of the *trans*-β-lactam analogue (**95d**).

Opposite enantiodiscrimination was found for the acylation of β-amino esters (**89a-d**, **92**) and for the lipase-catalysed acylation of the corresponding *N*-hydroxymethyl-β-lactams (**95a-d**, **98**). On the basis of these data the more reactive enantiomer of *rac*-**89a-c** is (1*S*,2*R*), of *rac*-**92** is (1*S*,4*S*,5*R*,8*R*), while that of *rac*-**89d** is (1*R*,2*R*).

In connection with homoadamantane derivatives, homoadamantane-fused pyrido-pyrimidinones were synthetized from **102**. The reactions of substituted 2-aminopyridines and the β-ketocarboxylate (**102**) in PPA or in a mixture of PPA and $POCl_3$ afforded only linearly- (with carboxamides) or both linearly- and angularly-condensed pyridopyrimidinones, respectively. Only carboxamides were prepared by the reaction of **102** and 2-aminopyridines in toluene in the presence of *p*-TSA as catalyst. In a mixture of PPA and $POCl_3$, **105a-f** yielded angularly-condensed pyridopyrimidinones **106a-f.** In contrast with earlier data[21], which indicated only the formation of the linearly-condensed pyridopyrimidinones, we synthetized both the linearly- and the angularly-condensed pyridopyrimidinones The preparation of 11-oxo-11*H*-pyrido[2,1-*b*]quinazoline-6-carboxamides was also described.

As a continuation of the preparation and investigation of homoadamantane-fused pyridopyrimidinones, we prepared 11-oxo-11*H*-pyrido[2,1-*b*]quinazoline-6-carboxylates for pharmaceutical investigation. The key compounds (**107**, **108**) were reacted with primary and secondary amines in DMF with isobutyl chloroformate and TEA to give carboxamides (**109a-s** and **110a-l**).

Alicyclic *cis*- and *trans*-β-hydroxy acids (**111a-114a** and **111b-114b**) were used for basic isomerization, and the study and prediction of hydrogen-bond patterns and other supramolecular phenomena.

Alkaline isomerization of *cis*- and *trans*-2-hydroxycycloalkanecarboxylic acids (**111a-114a** and **111b-114b**) was studied from both preparative and theoretical aspects. Whereas the reduction of ethyl 2-oxocycloalkanecarboxylates (**77**, **80**, **83**, **86**) resulted in less than 10% of ethyl *trans*-2-hydroxycycloalkanecarboxylates (**79**, **82**, **85**, **88**) in most cases, the alkaline isomerization of *cis*-2-hydroxycycloalkanecarboxylic acids (**111a-114a**) for appropriate periods of time furnished much higher quantities of the *trans* isomers. The *cis-trans* isomerization leads to an equilibrium mixture containing the *cis* isomer (**111a-114a**), the *trans* isomer (**111b-114b**) and the olefinic carboxylic acid (**111c-114c**), the compositin of this mixture varying with the ring size. The reaction rates in the homologous series differed. The measured composition *vs* time points were fitted numerically according to a pseudo-first-order reaction scheme. Both the kinetic and the thermodynamic data are worthy of consideration from a synthetic viewpoint. When the formation of the elimination side-product is slow, as for **112a**, waiting for equilibrium to be attained may make sense if the aim is to obtain the highest possible amount of the *trans* isomer. Otherwise, there is an optimum time for getting the highest possible amount of the *trans* isomer when the formation of side-product (olefinic acid) is minimal.

In accordance with our previous results, the crystals of **111b**, **112a** and **113a** are isostructural and are built up by the antiparallel association of heterochiral chains. The dimers joined by the hydrogen-bonds that cross-link the chains may also be regarded as basic building blocks. This approach led to the derivation of a further possible structure, which was exhibited by the crystal structures of *trans*-2-hydroxycyclooctanecarboxylic acid (**114b**) and *trans*-2-hydroxycyclooctanecarboxamide. Two polymorphs of *trans*-2-hydroxycycloheptanecarboxylic acid (**113b**) were prepared.

The influence of steric factors on hydrogen-bonding was modelled in the case of β-lactams. **17** and **18** form isostructural racemic crystals, while their cycloheptane analogue (**19**) undergoes spontaneous resolution. The hydrogen-bonds link the molecules into helices in all three crystals. The unit lengths of these helices increase with increasing ring size. In the polymorphs of *trans*-13-azabicyclo[10.2.0]tetradecan-14-one (**115**) (crystallized from MeOH and acetone), the lengths of the helices differ considerably. The difference results from the different roles of the acceptor *O* lone pairs.

8. ACKNOWLEDGEMENTS

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