A New Synthesis of enantiopure C-3-substituted Glutamates by Utilization of Ortho Ester protected (S)-Pyroglutamic acid

Dissertation

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aus
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FOR MY PARENTS.

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I GENERAL SECTION

1 INTRODUCTION

Amino acids are one of the most important elements, occurring in nature as building blocks for proteins and peptides. Among the 20 natural amino acids used as elements for proteins there are numerous non-proteinogenic amino acids, either as D- or L-enantiomeric compounds for peptides, involved in several physiological processes.
Recently, since high-throughput sequential analysis of peptides, especially for receptors, has been improved, non-proteinogenic amino acids gain more and more influence, on the one hand to investigate and understand physiological processes, and on the other hand to develop new substances for medicinal purposes. Therefore, it is important to obtain enantiomerically pure non-proteinogenic amino acids for the synthesis of active pharmaceutical ingredients (API), e.g. HIV protease inhibitors.

Glutamic acid is one of the most important excitatory neurotransmitter in the mammalian central nervous system (CNS) and plays a major role in essential physiological processes such as learning, memory and is supposed to be involved in neurodegenerative disorders like Parkinson`s and Alzheimer`s disease and Huntington`s chorea [1,2]. Furthermore, recent reports consider glutamate to be involved in cocaine-seeking behaviour [3], and in opiate tolerance and dependence [4,5]. Hence, for comprehension and examination of mentioned processes it is necessary to synthesize glutamic acid analogues, either as agonist, or antagonist of glutamatergic receptors.
On the other hand, glutamic acid also serves as a precursor in the physiological synthesis of other important amino acids, e.g. γ-aminobutyric acid (GABA). An important structural representative of GABA is (R)-baclofen, an antispastic agent, showing a similar agonistic activity comparable to GABA.

Nevertheless, object of this work was to find a new entrance to enantiomerically pure C-3-substituted pyroglutamic acid derivatives starting from (2S)-pyroglutamic acid as an ex-chiral-pool educt. Additionally, a new strategy for synthesis of (R)-baclofen was envisaged. For this purpose, an ortho ester derivative as protecting group for the carboxylate moiety according to Corey’s procedure was supposed to be suitable.

2 IMPORTANCE AND AVAILABILITY

Glutamic acid or rather pyroglutamic acid and its derivatives occur in peptides, proteins and as free amino acids in most organism. Therefore, some important pharmacological connections concerning these compounds are described in the following.

2.1 GLUTAMIC ACID DERIVATIVES

Glutamic acid is the most important neurotransmitter at excitatory synapses in the CNS. Glutamate is involved in essential processes such as learning, memory and neurodegenerative disorders, e.g. epilepsy [6], as well as in many psychiatric disorders such as anxiety [7] and schizophrenia [8]. It shows an activity at two types of receptors, termed as ionotropic and the metabotropic ones.

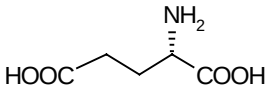
The ionotropic receptors, which have been characterized a long time ago, are multimeric glutamate-gated channels permeable to cations, and responsible for fast depolarization. Three types of ionotropic receptors, named after their preferred agonists [see:Figure 2.1-1], are known and subdivided into NMDA (N-methyl-D-aspartic acid), KA (kainic acid), and AMPA (α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid) receptors [9].

The metabotropic receptors (mGluRs) have been characterized and explored recently, and their physiological role seems to be more important than previously expected. They correspond to receptors coupled to G-proteins, which modulate the activity of ionic channels or enzymes producing second messengers [10], and they are involved in fast synaptic transmission [11]. Eight mGluRs have been characterized yet, and are divided into three classes (Group-I up to Group-III), depending on signal transduction mechanism, pharmacological properties, and sequence homology. Group-I receptors activate phospholipase C, producing diacylglycerol and inositol triphosphate as second messengers, whereas group-II and group-III receptors are negatively coupled to the enzyme adenylyl cyclase. Group-I receptors, containing mGluR1 and 5, posses sensivity to quisqualic acid and (1S,3R)-ACPD [(1S,3R)-1-aminocyclopentane-1,3-dicarboxylic acid] as well as group-II receptors, containing mGluR1 and 5. Group-III receptors, including mGluR4, 6, 7, and 8, are most sensitive to L-AP4 (2-amino-4-phosphonobutyric acid) [12].

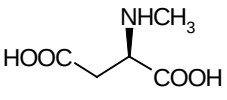
On the one hand, therapeutical applications are expected for group-I mGlu receptor antagonist activity, because they seem to inhibit glutamate-induced neuronal toxicity, and on

the other hand for group-II and III mGlu receptor agonist activity [13a], which means interaction with the glutamatergic system [13b].

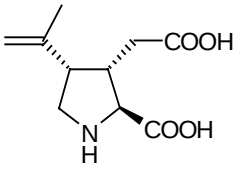
Figure 2.1-1



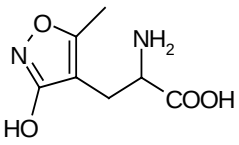
S-glutamic acid



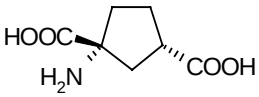
NMDA



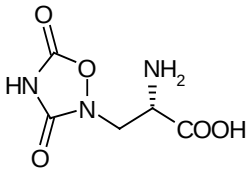
kainic acid



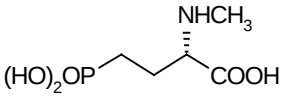
AMPA



(1S,3R)-ACDP



quisqualic acid



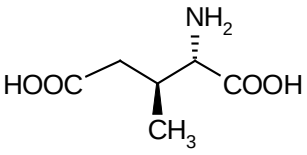
L-AP4

In order to better characterize the pivotal role of mGluRs and ionotropic receptors respectively in physiological processes, there is a need to find compounds with exquisite agonist as well as antagonist selectivity for each subtype.

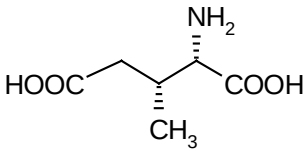
Furthermore, for physiological glutamate there exists an active transporting system, the so-called Excitatory Amino Acid Transporters, termed EAAT1-5 [14]. Extracellular glutamate can be removed from the synaptic cleft by transporters located at pre- and postsynaptic sites. If glutamate has diffused out of the synapse, it may be taken by transporters that are located in the glia cell membrane. Therefore, analogues of glutamate can inhibit EAATs by being transported themselves and thus act as competitive substrates of glutamate; alternatively, they can inhibit transport by blocking the EAATs without being transported themselves.

Recently, analogues with a methyl group at position 2, 3, and 4 on glutamate [see: Figure 2.1-2] have been investigated intensively on their various glutamatergic effects, which is shown exemplarily in fhe following. Their affinity to the corresponding receptors depends on the conformation, which is mainly influenced by the substitution pattern, and the pH value of the solution [15].

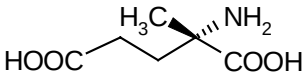
Figure 2.1-2



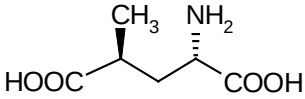
(2S,3S)-3-Me-Glu



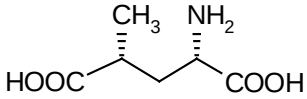
(2S,3R)-3-Me-Glu



(2S)-2-Me-Glu



(2S,4S)-4-Me-Glu



(2S,4R)-4-Me-Glu

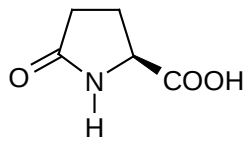
Jullian et. al [16] reported that (2S,4S)-4-methyl-glutamate [(2S,4S)-4-Me-Glu] showed an agonistic activity to mGluR1 (group-I) and mGluR2 (group-II) receptors comparable to that of glutamate, whereas (2S,4R)-4-methyl-glutamate [(2S,4R)-4-Me-Glu] has a lower affinity even comparable to that of (2S,3S)-3-methyl-glutamate [(2S,3S)-3-Me-Glu] and (2S,3R)-3-methyl-glutamate [(2S,3R)-3-Me-Glu], respectively. However, (2S)-2-methyl-glutamate [(2S)-2-Me-Glu] had no detectable affinity to mGluR1 and mGluR2 receptors.
Glutamates, substituted with a methyl group at position 2 and 3, had negligible low activity at KA and AMPA receptors, whereas location of the methyl group at position 4, namely the (2S,4R)-methyl-glutamate, expressed high agonistic activity at KA receptors [15,17,18].

Inspecting the Excitatory Amino Acid Transporting system, Vandenberg et al. [19] reported that EAAT2 is potently blocked by (2S,4R)-4-Me-Glu as well as by (±)-threo-3-methylglutamic acid (racemic (2S*,3R*)-3-methyl-glutamate), whereas EAAT1 is not influenced by (±)-threo-3-methylglutamic acid.

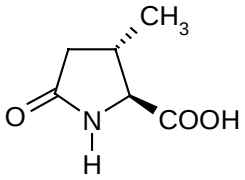
2.2 PYROGLUTAMIC ACID DERIVATIVES

The cyclic form of glutamic acid, pyroglutamic acid, is used as a starting material of choice for the synthesis of enantiomerically pure 3- and 4-substituted analogues [20,21,22] or of 3,4-di-substituted ones, respectively. Hence, (2S)-pyroglutamic acid serves as a template for stereospecific synthesis of a variety of new and highly functionalized amino acids [23,24,25,26] and, of course, as an intermediate of previously described corresponding substituted glutamates.

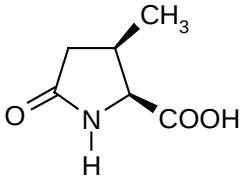
Figure 2.2-1



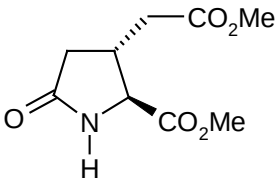
(2S)-Pyroglutamic acid



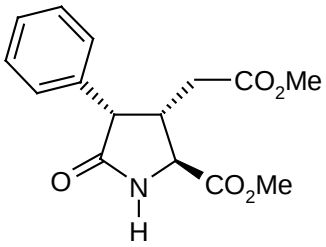
(2S,3S)-3-Methyl-pyroglutamic acid



(2S,3R)-3-Methyl-pyroglutamic acid



(2S,3R)-3-Methoxycarbonyl-methyl-5-oxo-pyrrolidine-2-carboxylic acid methyl ester



(2S,3S,4S)-3-Methoxycarbonyl-methyl-5-oxo-4-phenyl-pyrrolidine -2-carboxylic acid methyl ester

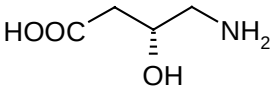
Pyroglutamic acid can be considered as a conformationally restricted form of glutamic acid, thus pyroglutamates are of importance as excitatory amino acid analogues [27], formally designed as compounds with glutamergic activity [28], and as conformationally controlling peptidomimetics [29], which means that pyroglutamate (here termed as Glp) works as N-terminal amino acid compound in a bradykinin potentiating peptide analogue with sequence Glp-Trp-Pro-Arg-Pro-Lysφ(NHCO)-(R,S)-Phe-Ala-Pro that exhibited in vivo activity [29b].

Enantiomerically pure 3-substituted analogues of pyroglutamate [33], e.g. (2S,3R)-3-methoxycarbonylmethyl-pyroglutamic acid methyl ester [see: Figure 2.2-1], considered as a conformationally constrained glutamate, have been synthesized to perform CPAA [(2S,3R)-2-carboxypyrrolidine-3-acetic acid], which shows NMDA receptor agonistic activity [30].
Beani et al. [31] reported that 3-methyl-subsitituted analogues of pyroglutamate, especially (2S,3S)-methyl- and (2S,3R)-methyl-pyroglutamic acid, can protect glutamate-induced convulsion in CNS, however, these substances had to be injected i.p. (intra peritoneal). There was no activity against NMDA-induced convulsion, therefore, they expected pyroglutamic acid to be an starting point for synthesis of excitatory amino acid antagonists at non-NMDA receptors.
Furthermore, 3,4-di-substituted pyroglutamates were synthesized to obtain conformationally constrained kainoid analogues [33]. Corresponding pyrrolidinones, for example (2S,3S,4S)-3-methoxycarbonylmethyl-4-phenyl-pyroglutamic acid methyl ester, shows desired stereochemistry of kainoid analogues [27] (for kainic acid see: Figure 2.1-1). Therefore, this compound can be considered as a template of proline-containing analogues of kainic acid.

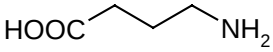
2.3 BACLOFEN

For about 30 years the racemic form of baclofen, (RS)-4-amino-3-(4-chlorophenyl)butanoic acid, has been commercially available, whereas only the enantiomerically pure (R)-form mainly exhibits desired pharmacological activity. It is used for treatment of spasticity associated with spinal cord injuries [34], normally, corresponding symptoms are associated with multiple sclerosis, and furthermore, for treatment of neuropathic chronic pain. Recently, report of pre-clinical trials suggest that baclofen may constitute a novel therapeutic agent for alcohol abuse, because it is supposed to decrease intensity of ethanol withdrawal symptoms [35]. Nevertheless, a mulifactorial view on neurotransmitter actions of GABA and glutamate gains important more and more [36].
Baclofen itself was developed as an analogue of 4-aminobutanoic acid (GABA), which is the most important inhibitory amino acid in the CNS.
GABA is a physiological product derived from glutamic acid by decarboxylation, and possesses affinity to $GABA_A$, $GABA_B$ [37], and $GABA_C$ receptors ($GABA_X$-Rs). Conformationally restricted analogues of GABA have been used to help identify these receptors [see: Figure 2.3-1].

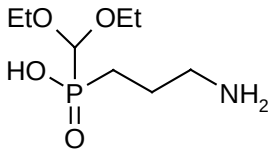
Figure 2.3-1



(R)-3-OH-GABA



GABA



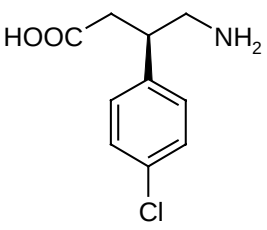
CGP35348

$GABA_A$ and $GABA_C$ receptors are transmitter-gated ion channels being permeable to chloride ions, and including nicotinic acetylcholine, strychnine-sensitive glycine and 5-hydroxy-tryptamine receptors. $GABA_A$–Rs are blocked competitively and selectively by the alkaloid bicuculline [see: Figure 2.3-2] and modulated by some steroids, barbiturates and benzodiazepines, whereas $GABA_C$–Rs are not blocked or rather modulated by these substances.

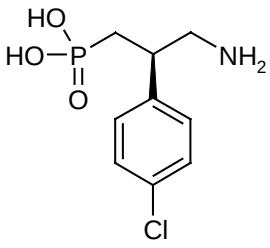
Instead, $GABA_B$-Rs are seven transmembrane-containing receptors that are coupled to G-proteins activating a second messenger system, and calcium and potassium channels, which resemble previously mentioned metabotropic glutamate receptors (mGluRs). Selective agonists for the interesting $GABA_B$-Rs site are (R)-baclofen and (R)-4-amino-3-hydroxybutanoic acid [(R)-3-OH-GABA], and corresponding blockers, which means competitive $GABA_B$-R antagonist, are represented by CGP35348 and phaclofen [38, 39], the phosphonic acid analogue of (R)-baclofen.

Therefore, it is still interesting to develop compounds possessing agonistic and antagonistic affinity to $GABA_X$-Rs for pharmacological tools as well as therapeutic targets [40].

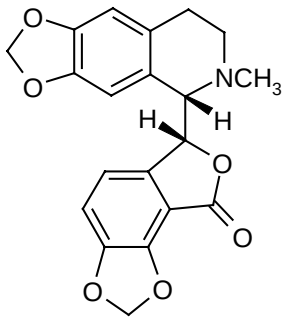
Figure 2.3-2



(R)-Baclofen



(R)-Phaclofen



Bicucullin

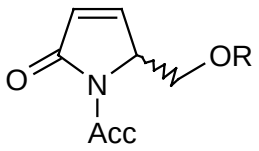
3 PUBLISHED SYNTHESIS

3.1 GLUTAMIC ACID DERIVATIVES

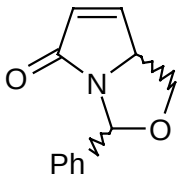
There are several synthesis of racemic (±)-3-substituted glutamates, known especially for methyl- and phenyl-derivatives [41], but enantiomerically pure compounds gain important more and more.

Principally, enantiomerically pure 3-substituted glutamic acid derivatives can be obtained via functionalized pyroglutamates derived from L-glutamic acid and D-glutamic acid, respectively, in which it is necessary for stereoselective alkylation at C-3 atom to use the 3,4-didehydroderivative of pyroglutaminol as a silylated compound **1** or as related bicyclic compound **2** [see: Figure 3.1-1]. If L-glutamic acid serves as starting material, **1** and **2** are (S)-configurated and, respectively, if D-glutamic acid is used, **1** and **2** are (R)-configurated.

Figure 3.1-1



1

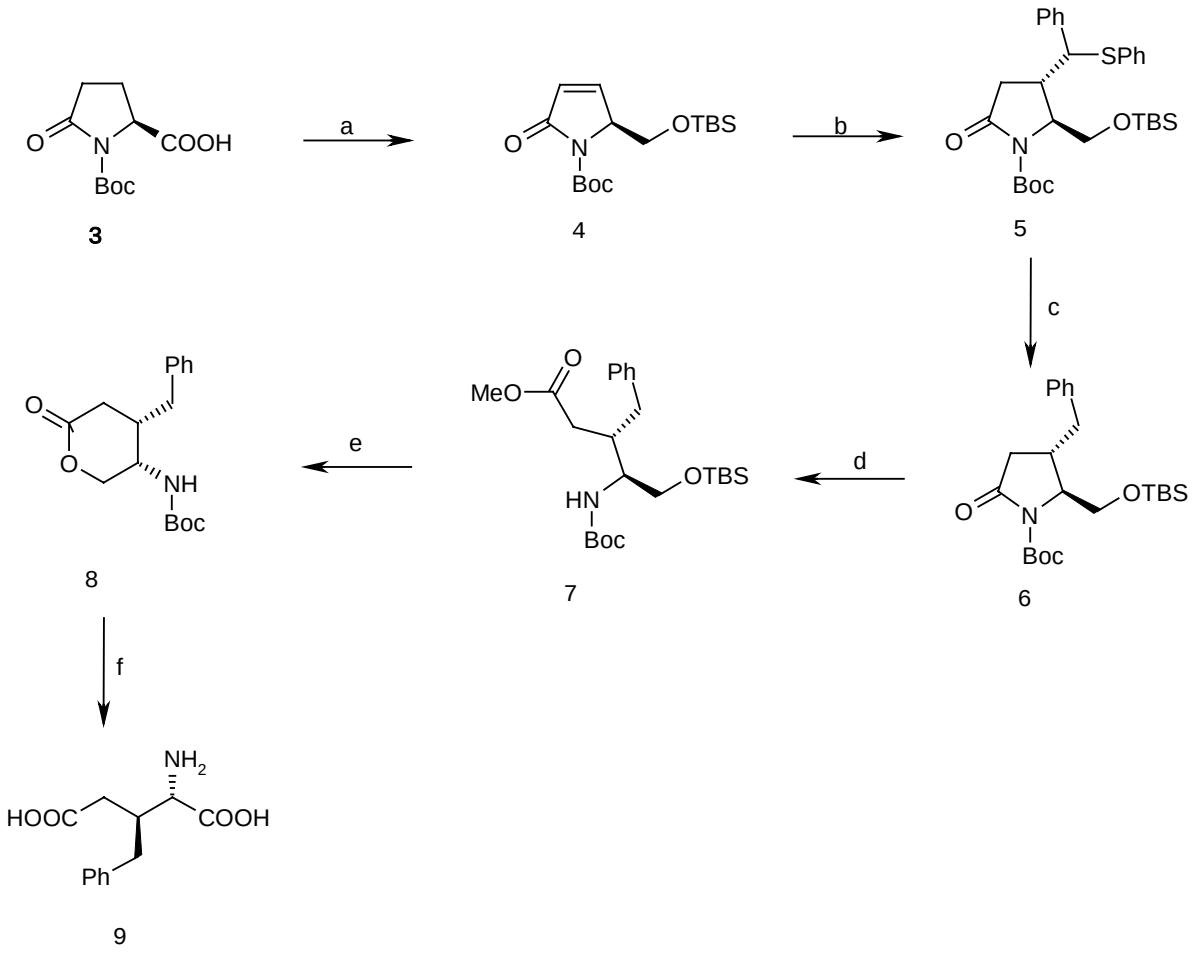


2

R = silyl, Acc = acceptor, Ph = phenyl

The lactam **4** [see: Scheme 3.1-1], as the corresponding N-Boc-protected and silylated compound of **1**, can be prepared from N-Boc-L-pyroglutamic acid (**3**) [42]. The lactam **4** is obtained by successive reduction of a mixed anhydride, followed by silylation of the corresponding alcohol, selenation at C-4 with final oxidative elimination. Afterwards, benzylphenyl sulfide is added to perform Michael-addition and the obtained trans-configurated adduct **5** is transformed to compound **6** by desulfurisation. After ring opening of the protected lactam **6** with sodium hydroxide solution and esterification with diazomethane, cyclisation to the lacton **8** occurs. Then, after cleavage of the silyl ether, the lacton **8** is hydrolized and, afterwards oxidized with aqueous potassium permanganate solution to furnish (2S,3S)-3-benzyl-glutamic acid (**9**). The corresponding enantiomer of the lactam **4** has been used for the preparation of (2R,3R)-3-benzyl-glutamic acid [43].

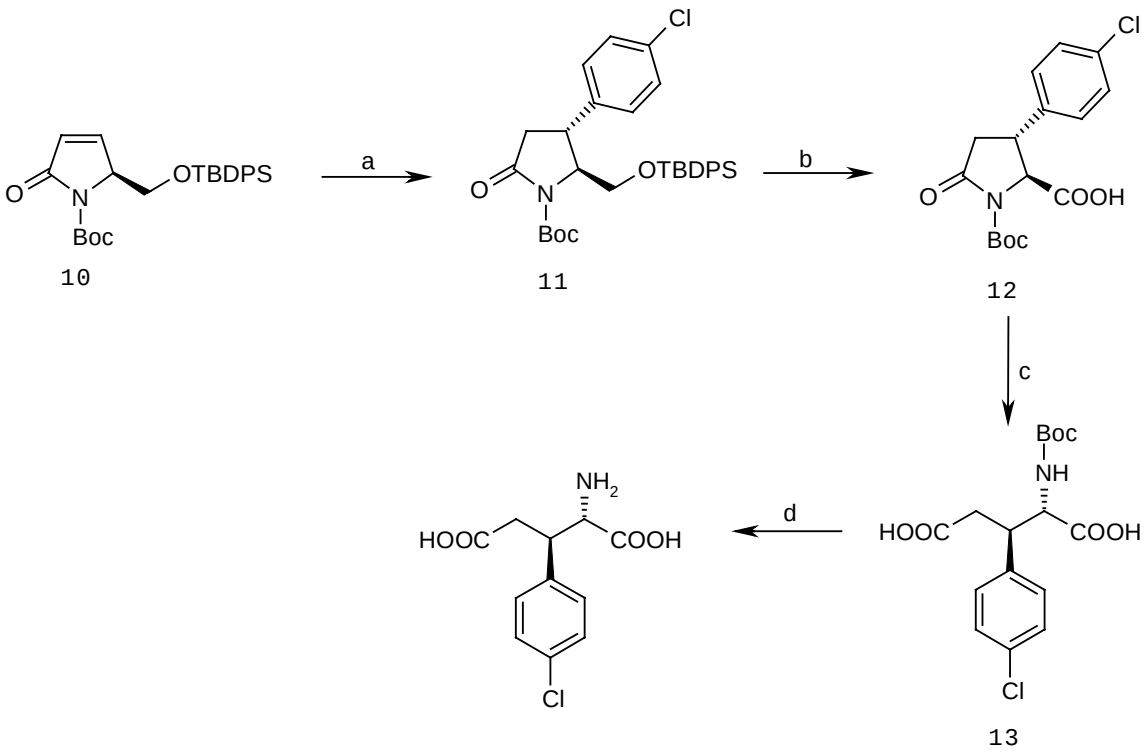
Scheme 3.1-1



a) 1.$ClCO_2Et$, 2.$NaBH_4$, 3.TBSCl 4.LDA, PhSeCl, 5.O_3 b) $PhCH_2SPh$, TMEDA, n-BuLi, THF, -78°C c) Raney-nickel, acetone, water, reflux d) 1. 1M NaOH, MeOH 2.CH_2N_2, MeOH e) HF aq., MeCN f) 1.$KMnO_4$, 1M NaOH 2. TFA.

(2R,3S)-3-(4-Chlorophenyl)-glutamic acid [see: Scheme 3.1-2] was synthesized by Hubmann [44,45b] via a derivative similar to **4**, derived from (2S)-pyroglutamate as starting material. Therefore, the silylated N-protected 3,4-didehydro-derivative of pyroglutaminol (**10**) is converted to the trans-configurated compound **11** by a cuprate addition using p-chlorophenylmagnesium bromide as reactant. Afterwards, cleavage of the silyl ether occurs, followed by a Sharpless oxidation [46] to obtain the intermediate **12**. The N-protected lactam **12** is opened carefully and finally deprotected by TFA to yield the desired enantiomerically pure (2R,3S)-3-(4-chlorophenyl)-glutamic acid.

Scheme 3.1-2

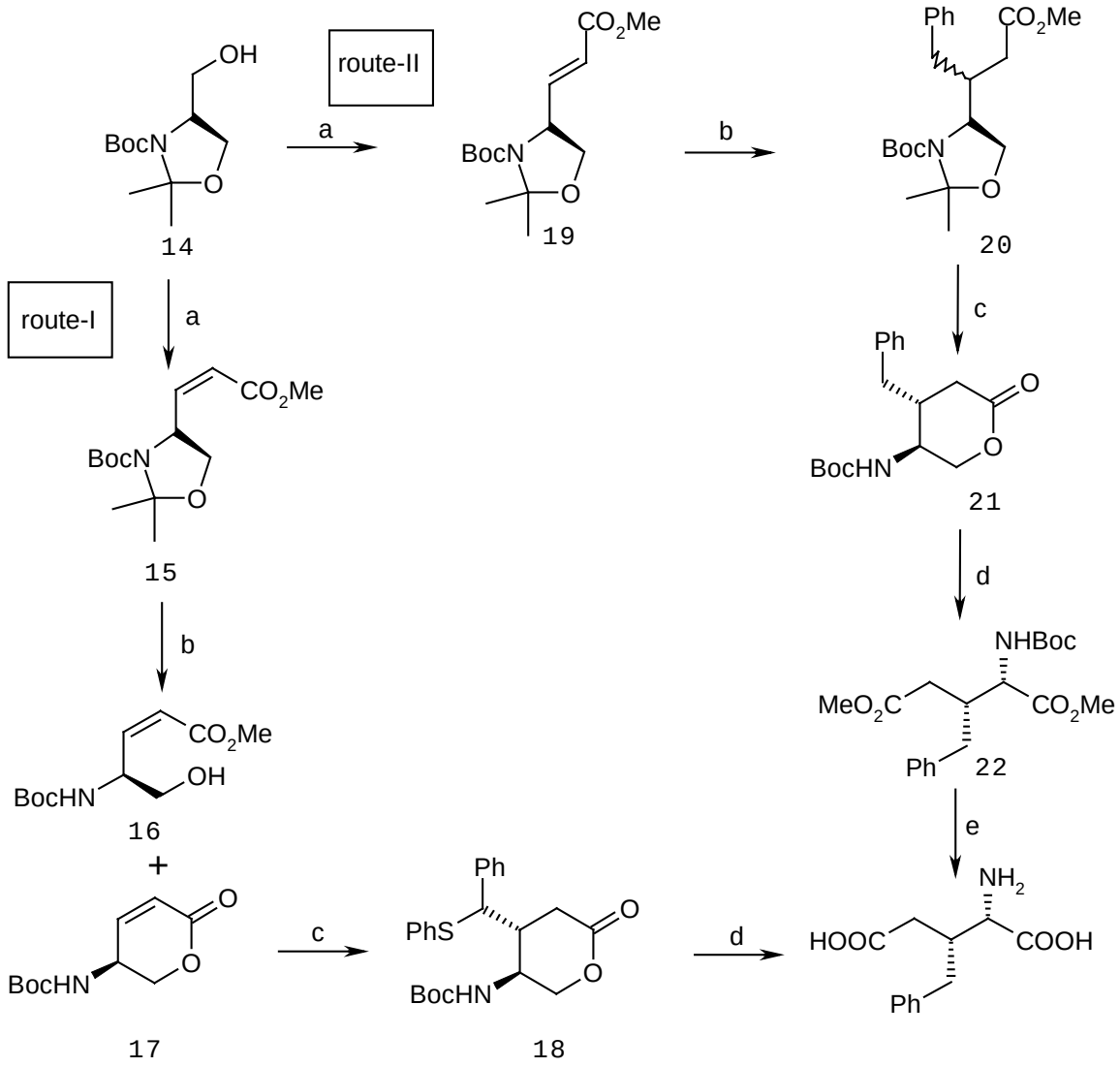


a) p-Chlorophenylmagnesium bromide, CuBr•S(CH_3)$_2$, TMSCl, Et_2O, THF, -78°C b) 1.Et_3N-HF, THF 2.$RuCl_3$, $NaIO_4$, MeCN, water; c) 1 M LiOH, THF, water; d) TFA aqueous.

Furthermore, for (2S,3R)- and (2R,3S)-3-benzylglutamic acids, respectively, there exist two strategies using the N-protected oxazolidine derivative **14** as an intermediate derived from L-serine or D-serine [43], respectively, whereas Jako et al. [47] prepared (2S,3R)-3-benzylglutamic acid from D-serine in a similar way. Both routes (**route-I** for [43] and **route-II** for [47], see: Scheme 3.1-3) start with **14** to yield (2S,3R)-3-benzyl-glutamic acid as a final product.

Via **route-I** [43] the N-protected oxazolidine **14** is transformed to the corresponding aldehyd by Swern-oxidation followed by a Wittig-Horner-reaction to obtain the Z-configurated α,β-unsaturated methyl ester **15**. The treatment with p-toluenesulfonic acid in methanol gives a mixture of the ring-opened compound **16** and the α,β-unsaturated lacton **17**. The cyclisation of **16** is favoured in this mixture, so that the lacton **17** is converted stereoselectively to mainly trans-configurated **18** by Michael-addition. After desulfurisation with tributyltin hydride, the same procedure as previously described [see: Scheme 3.1-1] is applied to give finally (2S,3R)-3-benzylglutamic acid.

Scheme 3.1-3



Via **route-I** : a) 1. Swern ox., -78°C 2. $(CF_3CH_2O)_2P(O)CH_2CO_2Me$, KH, $(TMS)_2NH$, 18-crown-6, THF, -78°C; b) 1. p-TsOH, MeOH 2. p-TsOH, CH_2Cl_2; c) 1. $PhCH_2SPh$, TMEDA, n-BuLi, -78°C; d) 1. n-Bu_3SnH, AIBN, benzene, reflux 2. $KMnO_4$, 1M NaOH 3. TFA.

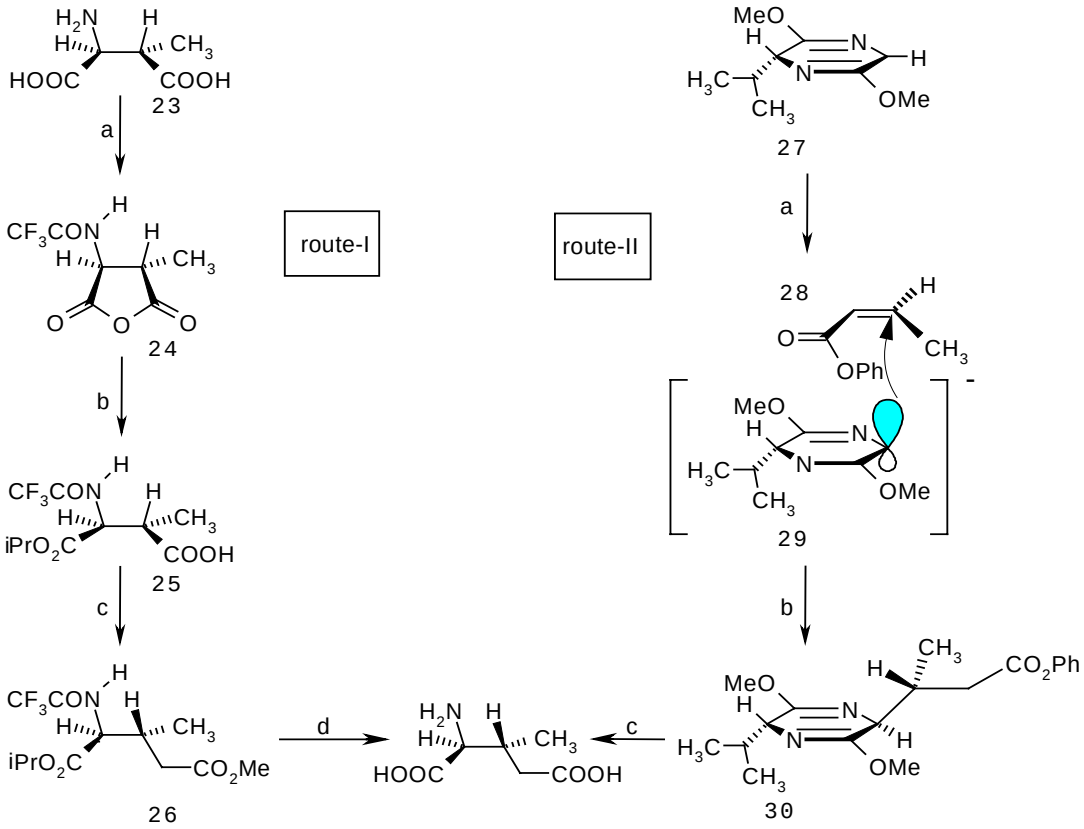
Via **route-II**: a) $(MeO)_2POCH_2CO_2Me$, 3M K_2CO_3, 20°C; b) $(Benzyl)_2CuLi$, TMSCl, -30°C; c) p-TsOH, toluene, refux; d) 1. K_2CO_3, MeOH 2. pH 4, water 3. CH_2N_2, 4. PDC, DMF, 20°C 5. CH_2N_2; e) 6N HCl, reflux.

Via **route-II** [47] the N-protected oxazolidine **14** is converted to the mainly trans-configurated α,β-unsaturated methyl ester **19** (ratio 95:5) by Swern-oxidation followed by a Wittig-Horner-reaction under protic conditions with trimethyl phosphonoacetate. Then, the benzyl residue is introduced by a 1,4–lithium dibenzylcuprate addition to get the favoured syn-adduct **20** (ratio 4:1), which is hydrolized and, furthermore, converted to the trans-configurated lacton **21** by

the treatment with p-toluenesulfonic acid in toluene. After compound **21** was hydrolized, treatment with diazomethane gives an intermediate as monomethyl ester, which is oxidized and converted to the corresponding N-protected dimethylester **22**. Then, (2S,3R)-3-benzylglutamic acid as the target compound is prepared by hydrolisation in refluxing 6 N HCl.

Another possibility for synthesis of enantiomerically pure 3-substituted glutamic acids was developed by Hartzoulakis and Gani [48].

Scheme 3.1-4



Via **route-I** : a) $(CF_3CO)_2O$, THF; b) iPrOH, 30°C; c) 1. $SOCl_2$, CH_2Cl_2 , reflux 2. CH_2N_2, ether 3. Ag_2O, MeOH; d) 1. 6N HCl 2. propylen oxide, EtOH, reflux.
Via **route-II**: a)+b) BuLi, then crotonate, -78°C; c) 1.6N HCl, reflux 2. NH_3 to pH 1.5, then recrystallization.

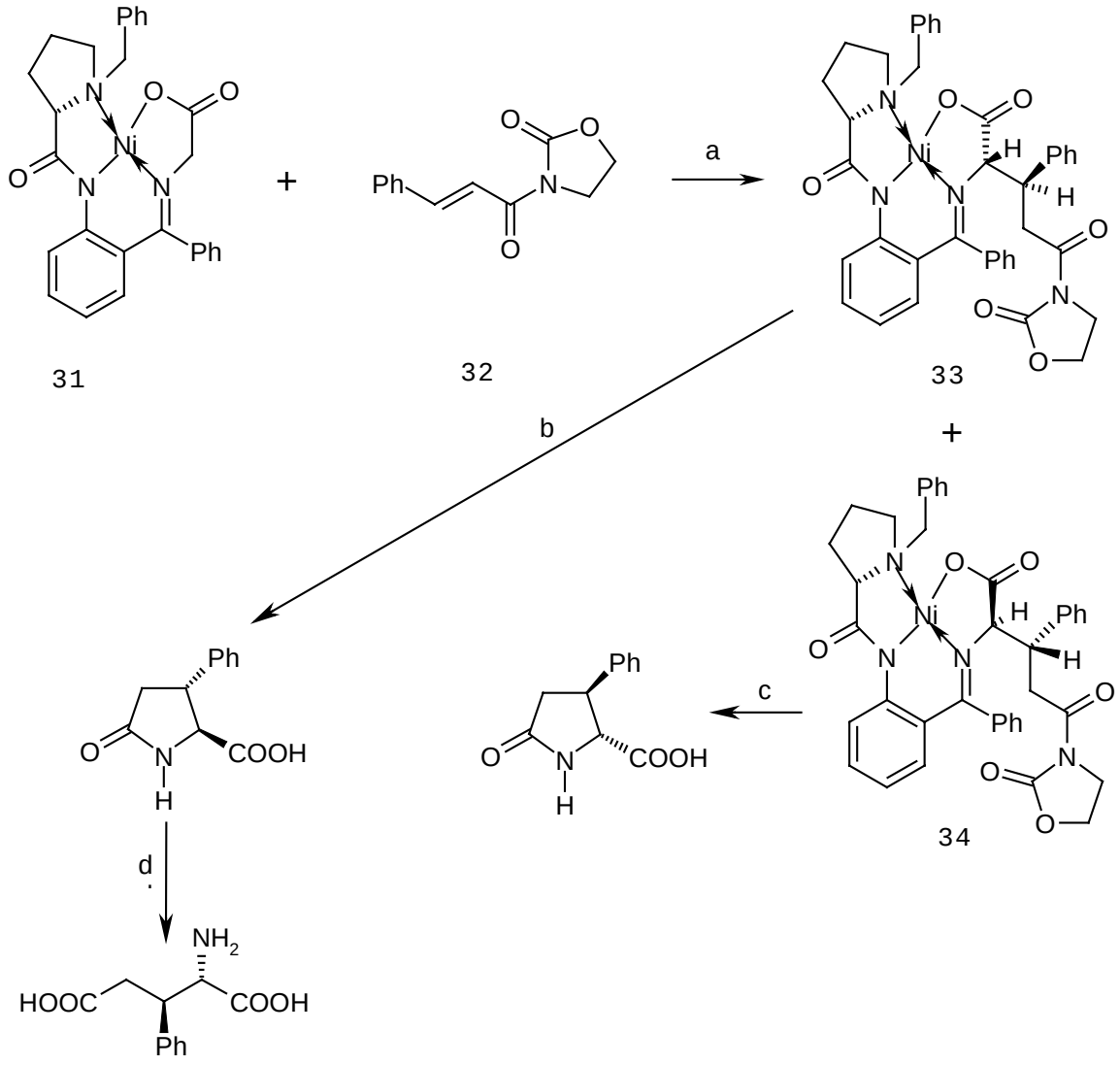
Herein, they used suitably protected (2S,3S)-3-methylaspartic acid **23** as a starting material to perform (2S,3R)-3-methylglutamate via Arndt-Eistert homologation (see: **route-I**, Scheme 3.1-4) as well as via a conjugate addition of a lithiated anion of a bis-lactim ether of cyclo-(R-Val-Gly) to methyl trans-butenoate (see: **route-II**, Scheme 3.1-4). This bis-lactim ether methodology particulary bases on the previous work of Schöllkopf et al. [49].

Via **route-I**, (2S,3S)-3-methylaspartic acid (**23**) is treated with TFA to give the cyclic anhydride **24** which is hydrolized with propan-2-ol to the ring-opened mono ester **25**. This β-carboxylic ester is treated successively with thionyl chloride, diazomethane, and finally with silver oxide in the presence of methanol to obtain exclusively the N-trifluoroacetyl-3-methylglutamate diester **26**, which is deprotected under acidic conditions followed by the treatment with propylen oxide to yield exclusively (2S,3R)-3-methylglutamate.
Via **route-II**, the anion **29**, generated by treatment of the bis-lactim ether **27** with butylithium, attacks the corresponding cis-configurated methyl crotonate **28** to give the desired dihydropyrazine derivative **30**. Afterwards, **30** is treated successively with refluxing hydrochloric acid, and NH_3 to adjust pH 1.5 for recrysallisation of (2S,3R)-3-methylglutamate. Additionally, synthesis of the diastereomere (2S,3S)-3-methylglutamate is reported to be possible via route-II using trans-configurated methyl crotonate.
Based on this bis-lactim ether methodology, diastereoselective synthesis of all four isomers of 3-(4-chlorophenyl)glutamic acid, as an analogue of 3-phenylglutamate, has been reported [50a,b], but the diastereomeres, (2S,3R)- and (2S,3S)-3-(4-chlorophenyl)glutamate and the corresponding pair, (2R,3S)- and (2R,3R)-3-(4-chlorophenyl)glutamate, have to be separated by column chromatography.

Further similar syntheses of enantiomerically pure 3-substituted glutamic acids using Michael addition systems are reported [51,52,53].

The latest variant of Michael addition reactions [see: Scheme 3.1-5] between a chiral Ni(II)-complex of glycine, as donor group, and various 3-(trans-enoyl)oxazolidin-2-ones, as acceptor molecule, is reported from Soloshonok and Hruby [54], improving a method, first developed by Belokon et al. [55,56].
Improving their previously published methodology [57], they use the Ni(II)-complex **31** of the chiral Schiff base glycine with (S)-o-[N-(N-benzylprolyl)amino] benzophenone (BPB) [56,58], and the N-trans-crotonyl-derived oxazolidin-2-one derivative, which is here demonstrated for 3-(trans-3´-phenylpropenoyl)oxazolidin-2-one **32**, forming a mixture of the Ni(II)-complexes **33** and **34** in a diastereomeric ratio of 4:1. The major product, in this case compound **33**, is isolated in enantiomerically pure form by recrystallization without chromatographic separation. After decomposition of **33** with hydrochloric acid and successively treatment with ammonium hydroxide and Dowex, (2S,3R)-3-phenylpyroglutamate is obtained with recovery of corresponding byproducts (not listed). Afterwards, (2S,3R)-3-phenylpyroglutamate is hydrolized with hydrochloric acid to yield (2S,3R)-3-phenylglutamate. The corresponding minor product, in this case (2R,3R)-3-phenylpyroglutamate, is isolated from the recrystallized Ni(II)-complex **34** using the same procedure.

Scheme 3.1-5



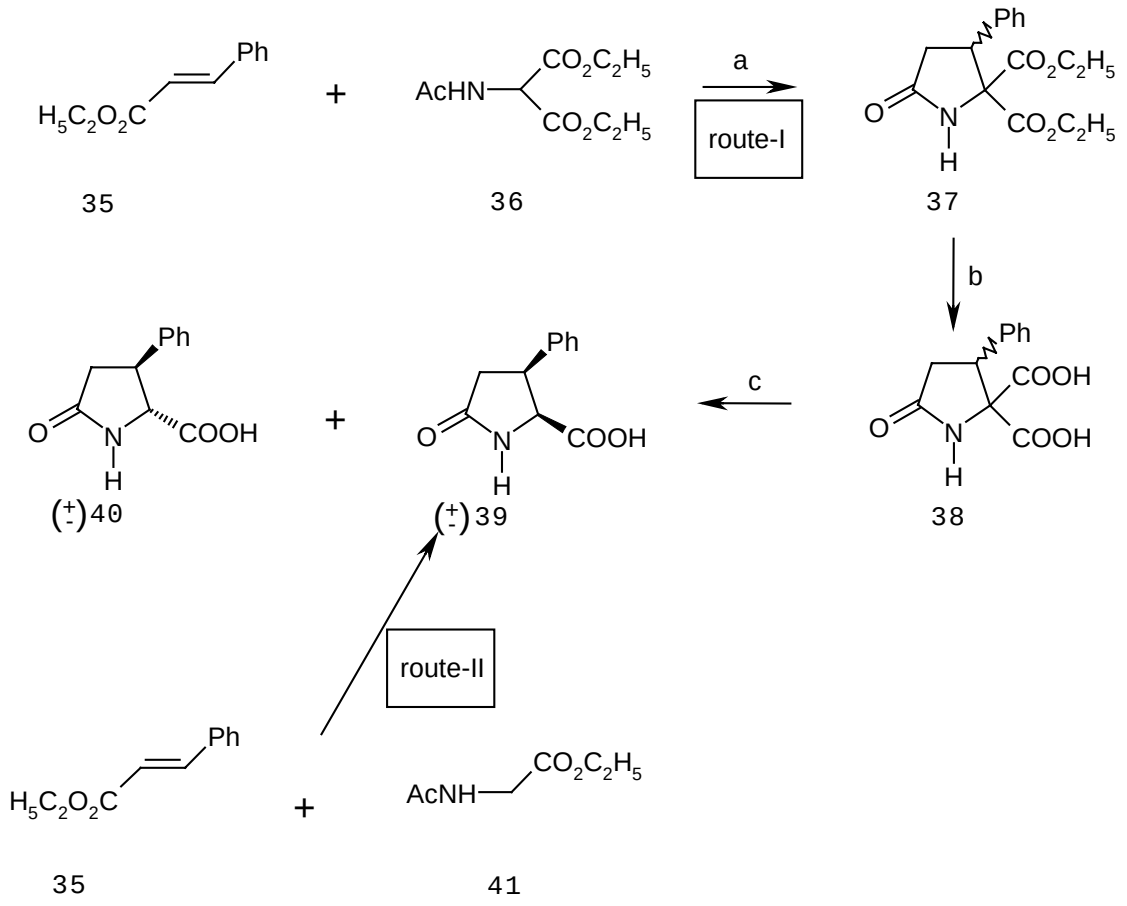
a) DMF, cat. DBU; b) and c) 1. HCl, MeOH 2. NH_4OH 3. Dowex; d) 3N HCl.

3.2 PYROGLUTAMIC ACIDS DERIVATIVES

Functionalized pyroglutamates at carbon C-3, both as racemic 3-substituted pyroglutamic acid derivatives [59], and as enantiomerically pure ones [60], can be synthesized and isolated as intermediates according to previously descibed procedures (see: Scheme 3.1-2 and Scheme 3.1-5).

Pachaly [61,62] reported that synthesis of cis- and trans-configurated pyroglutamic acids [see: Scheme 3.2-1] can be performed via condensation of the cinnamate ester **35** and the N-acetylmalonic acid ester **36** using sodium in ethanol to yield the 3-phenyl substituted pyrrolidinone dicarboxylic ester compound **37** (**route-I**).

Scheme 3.2-1



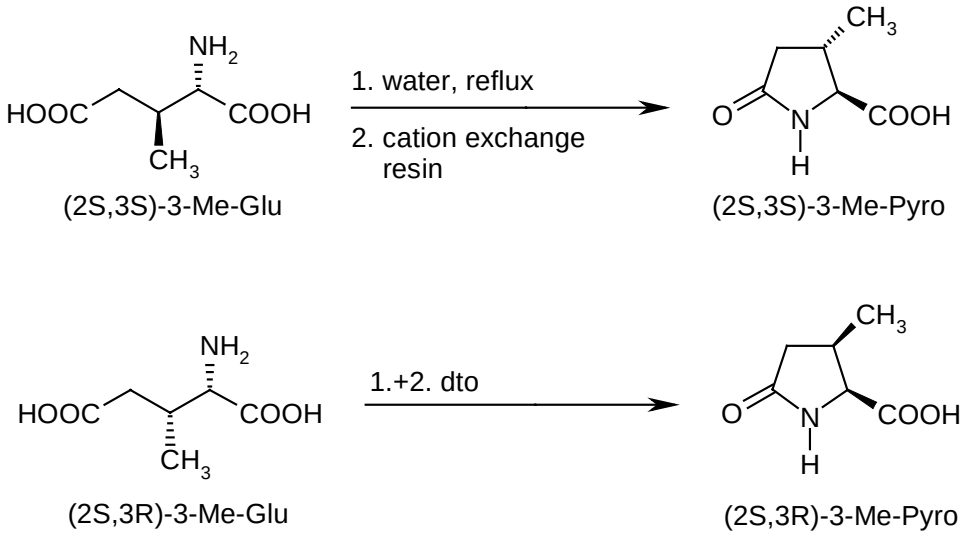
Via **route-I**: a) Na, EtOH, reflux; b) KOH, H_2O, EtOH; c) 1. collidine, reflux, then pH1; 2. recrystall. acetone-petroleum ether.

Via **route-II**: NaH, benzene, ambient temp.

After basic hydrolisation and decarboxylation in collidine, the corresponding mixture of the isomers **39** and **40** is obtained in a ratio of 3:2. Separation is performed by selective recrystallization from acetone/petroleum ether, whereas successively (2S*,3S*)- and (2R*,3S*)-3-phenylpyroglutamic acid (**39** and **40**, respectively) can be isolated.
Alternatively, the trans-configurated target compound **39** can be prepared in an one-pot procedure (**route-II**). Herein, the cinnamate ester **35** and the N-acetyl-glycinate **41** are treated with sodium hydride in benzene to give exclusively (2R*,3S*)-3-phenylpyroglutamic acid (**39**) in racemic form.

A facile method for the synthesis of N-deprotected 3-substituted pyroglutamates is reported [48,51] according to the methodology of Hardy [63].
Herein, cyclisation of (2S,3S)- and (2S,3R)-3-methyl glutamates [see: Scheme 3.2-2] to the corresponding pyroglutamates occurs under neutral conditions. Therefore, glutamic acids are refluxed in water, passed through an acid ion exchange resin, and finally are recrystallized.
Nevertheless, synthesis with enantiomerically pure 3-substituted glutamates as educts seems to be tedious, and thus, this method mainly is used for determination of enantiomeric purity.

Scheme 3.2-2

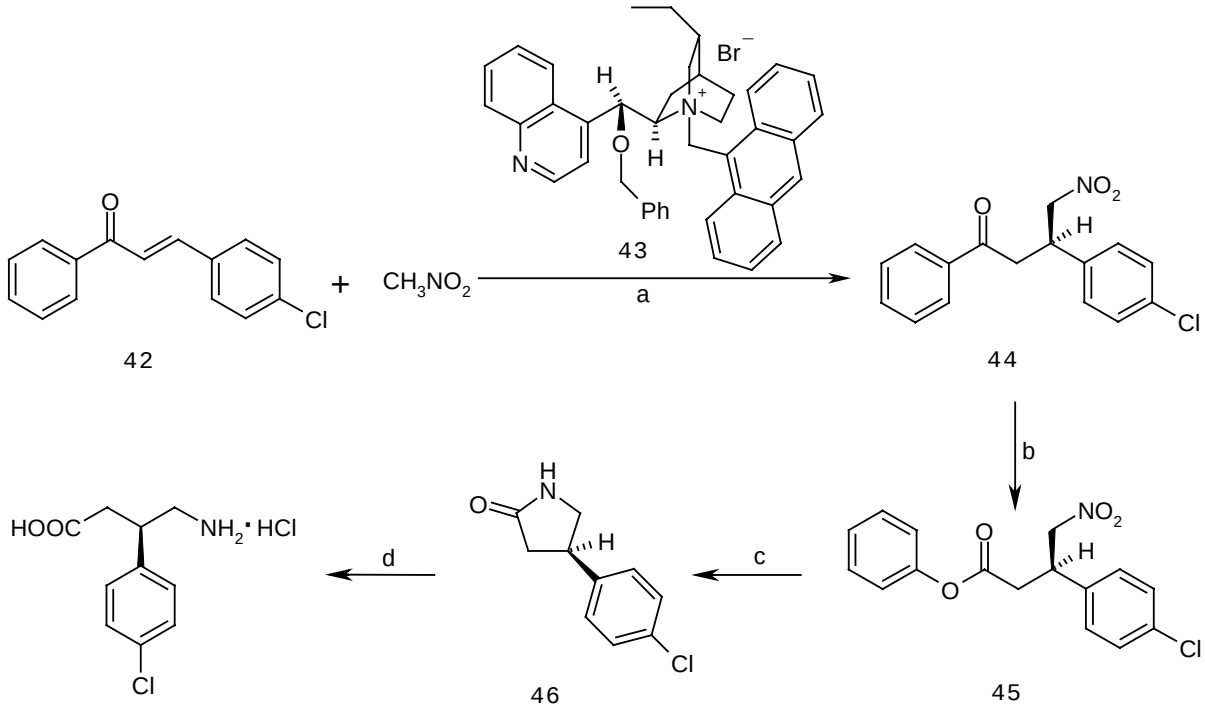


3.3 (R)-BACLOFEN

Besides the synthesis of racemic baclofen [64], importance of the enantiomerically pure product (R)-baclofen gains more and more interest. In addition to previously described methods for the synthesis of (2R,3S)-3-(4-chlorophenyl)-glutamic acid [see: Scheme 3.1-2], in which compound **12** serves as precursor of (R)-baclofen, there will be introduced two recently published strategies of synthesis. Despite this synthetic elegancy and reduced production steps, cost factors prevent the introduction of (R)-baclofen into the market.

Corey [65] reported on an enantioselective Michael addition [see: Scheme 3.3-1] of nitromethane in the presence of caesium fluoride to the α,β-enone **42**, to yield mainly selective R-configurated intermediate **44** (ratio R/S: 85/15). The reaction is catalyzed by the chiral cinchonidine derivative **43**.

Scheme 3.3-1



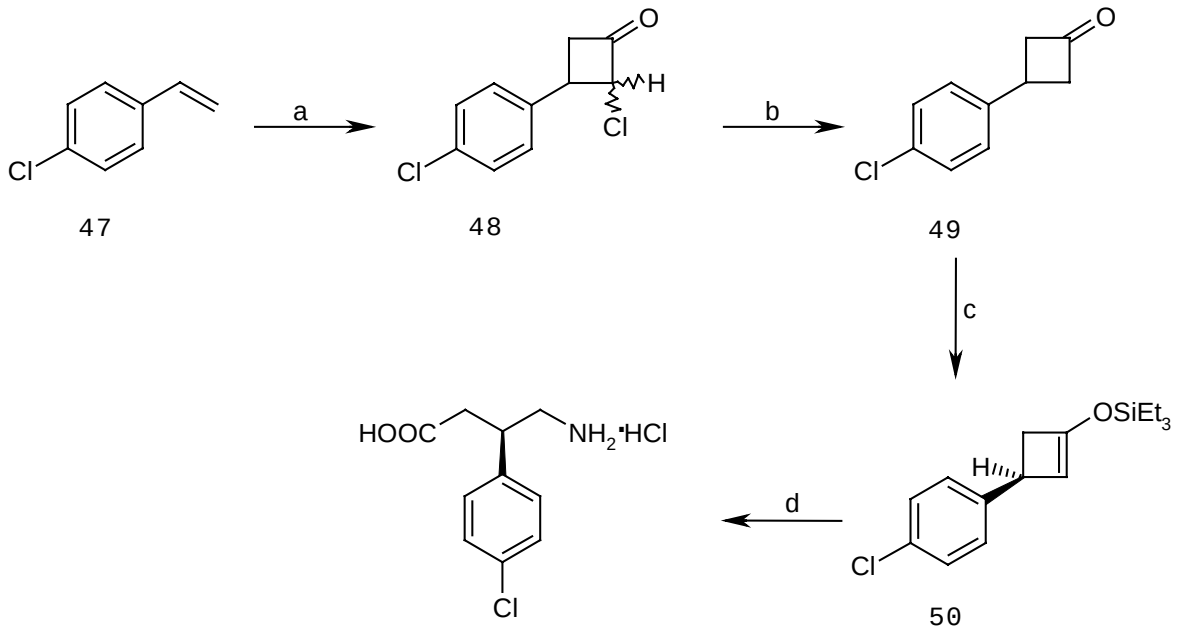
a) 1. CsF, toluene, -40°C, then recrystallization (EtOAc-hexane); b) m-CPBA, $ClCH_2CH_2Cl$, reflux; c) $NiCl_2/NaBH_4$, MeOH; d) 5N HCl, reflux.

Afterwards, recrystallization of **44** from ethyl acetate/hexane gives this compound with a ratio of 97.5:2.5 (R/S). The following Baeyer-Villiger oxidation affords the (R)-γ-nitro ester **45**,

which is converted to the corresponding (R)-γ-lactam **46** by reduction in the presence of nickel boride in methanol. Afterwards, acid hydrolysis of the (R)-γ-lactam **46** gives (R)-baclofen as the hydrochloride, in enantiopure form.

Another strategy of synthesis [see: Scheme 3.3-2] uses 4-chlorostyrene (**47**) as a starting material [66]. The racemic cycloadduct **48** is prepared utilizing dichloroketene, which is an in situ product of trichloroacetyl chloride and phosphorus oxychloride in the presence of powdered zinc and copper. After reductive dechlorination of **48** with zinc/acetic acid, the resulting cycloadduct **49** is deprotonated with lithium (S,S')-α,α'-dimethylbenzyl amide as a chiral base, and the generated enolate is quenched with triethylsilyl chloride to obtain the (S)-configurated silylenol ether **50**. After oxidative cleavage of the double bond with ozone and reductive work-up, the intermediate aldehyde is reductively aminated with ammonium acetate and sodium cyanoborohydride. Finally, acidification with hydrochloric acid provides (R)-baclofen hydrochloride as the target compound.

Scheme 3.3-2



a) 1. CCl_3COCl, $POCl_3$, Zn-Cu, Et_2O; b) Zn, AcOH; c) lithium (S,S')-α,α'-dimethylbenzyl amide, THF, TESCl, -100°C; d) 1. O_3, CH_2Cl_2, -78°C 2. Me_2S, amb. temp, $NaBH_3CN$, NH_4AcO 3. 6N HCl, 100°C.

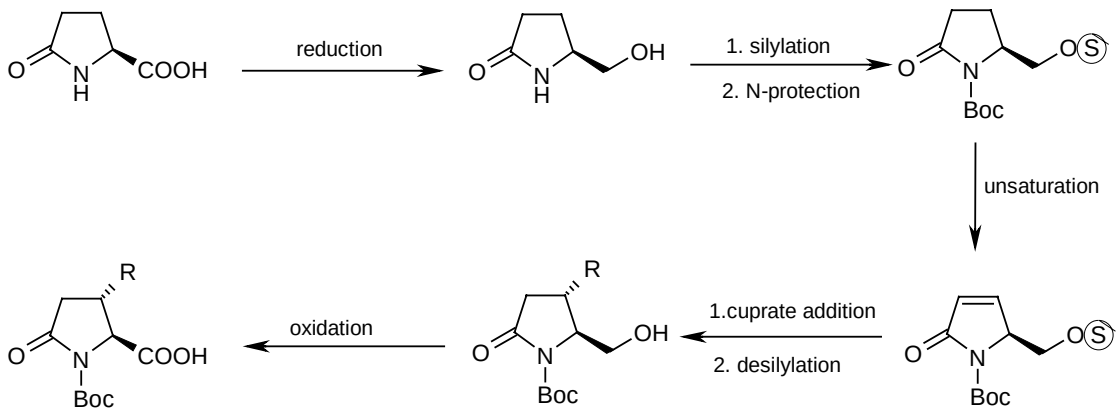
4 PLAN OF SYNTHESIS

As the starting compound was envisaged non-racemic (S)-pyroglutamic acid, which is a cheap and commercially available educt for ex-chiral-pool synthesis of C-3-substituted glutamic acid derivatives [see: Scheme 4.1-1].

In previous publications our group [45b] and others have shown that (S)- or (R)-pyroglutamic acid is a nearly ideal starting material for the synthesis of C-2- and C-3-substituted derivatives [see: Scheme 4-1]. But a serious drawback is the bad atom-economy in the reaction sequence of published procedures, including our own. To maintain stereochemical integrity at position 2 of pyroglutamic acid in the presence of a N-acceptor protecting group (Boc, Cbz), when a double bond is introduced, the carboxylic function has to be reduced to the alcohol. This has to be protected with a bulky group (trityl, silyl) to get perfect trans selectivity in the cuprate addition reaction to the Michael system.

After deprotection and re-oxidation, the N-Boc pyroglutamates can be transformed to glutamates or decarboxylated to enantiopure pyrrolidone derivatives [45b]. Obviously, the concept of atom-economy is not achieved.

Scheme 4.1



S = trityl, silyl

To accomplish this, the ortho ester functionality (OBO ester) developed by Corey [69] was introduced. Three following issues of critical importance have to be considered:
The OBO ester should be stable during the introduction of the double bond (1), the bulkiness should be large enough to get perfect stereoselection during Michael addition reaction (2), and (3) mild conditions for the hydrolysis of OBO ester should prevent ring opening reaction of the pyroglutamate derivatives.

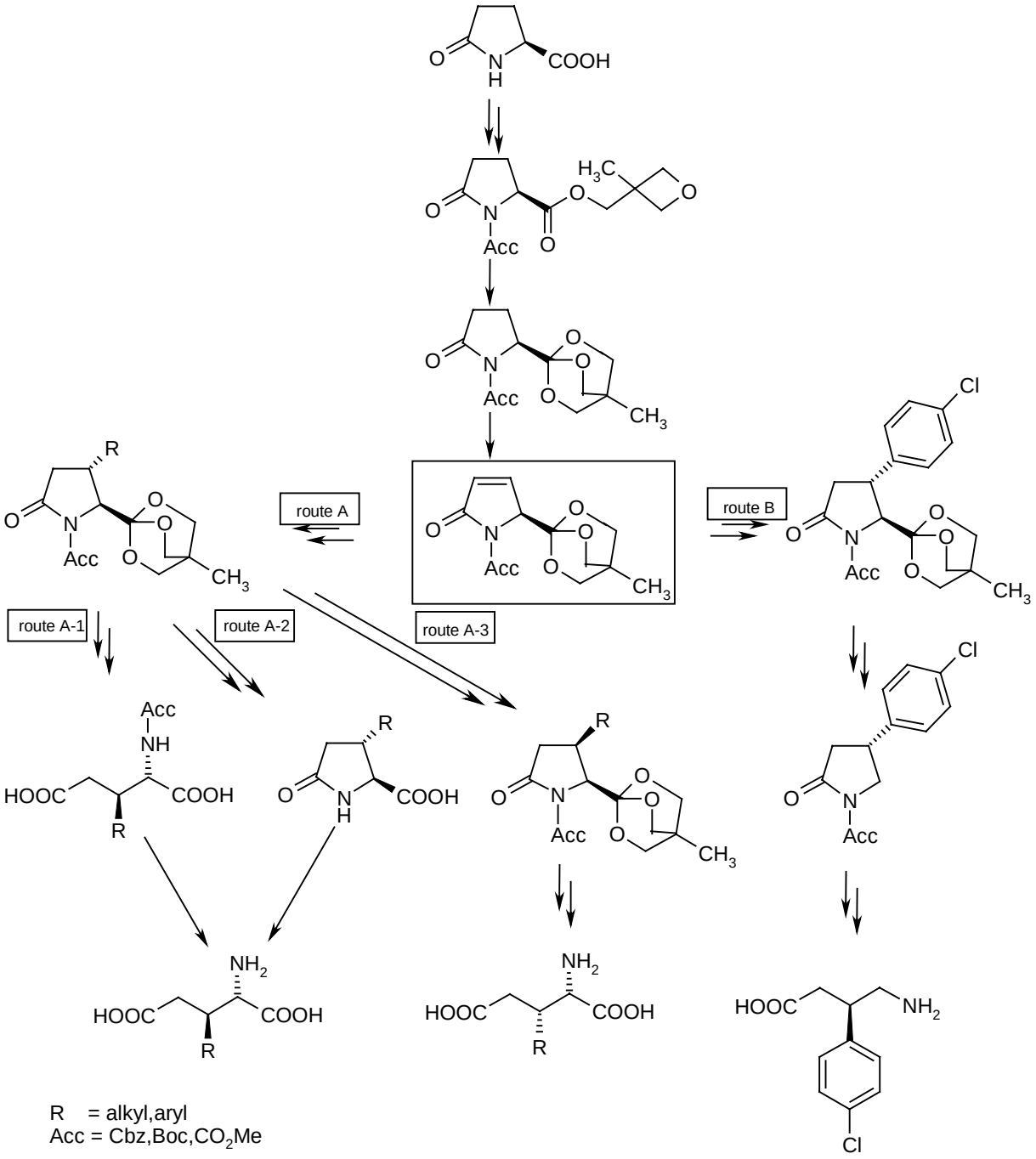
After esterification and N-protection of (S)-pyroglutamic acid, the corresponding oxetane ester should be obtained easily. It is necessary to reduce electron density at the lactam, to perform following steps, so an electron withdrawing protecting group for N-protection has to be introduced, e.g. Cbz and Boc, respectively. Furthermore, cleavage of N-protecting group should be carried out under mild conditions, to prevent epimerisation at the chiral center C-2.
The rearrangement of the oxetane to the ortho ester has to be accomplished according to a method developed by Corey [69]. It seems to be an advantage using an ortho ester instead of a “normal” ester compound, because of the absence of acceptor properties minimizing racemisation at C-1 (α-position). Additionally, the ortho ester is supposed to control stereoselective 1,4-addition at the following α,β-unsaturated moiety, to generate high diastereomeric ratio.
Two possible main routes lead from this α,β-unsaturated ortho ester to obtain desired target compounds via **routes A-1** until **A-3** and **route B**, respectively.

4.1 C-3-SUBSTITUTED PYROGLUTAMIC ACID DERIVATIVES

Via **route A-2:**
The plan for the introduction of substituents at position C-3 of the α,β-unsaturated ortho ester was to use C-nucleophiles, especially organo cuprates, which favour 1,4-additions. These compounds are, on the one hand comparatively non-nucleophilic, to prevent ring opening reactions of the N-acceptor substituted lactams, and on the other hand, easily available from organo lithium or Grignard compounds.
Therefore, corresponding intermediate products should be received as enantiomerically and diastereomerically pure (2S,3S)-alkyl or rather (2S,3R)-aryl substituted N-protected ortho ester derivatives of pyroglutamic acid.
Principally, there are two possible alternatives for cleavage of protecting groups to obtain desired (2S,3S)-alkyl, or rather (2S,3R)-aryl pyroglutamates via **route A-2**.

The first one includes the removal of the ortho ester, followed by the N-acceptor group, vice versa for the second alternative.

Scheme 4.1-1



4.2 C-3-SUBSTITUTED GLUTAMIC ACIDS DERIVATIVES

Via **route A-1** up to **route A-3:**

It was envisaged to synthesize trans-configurated (2S,3S)-alkyl, or rather (2S,3R)-aryl substituted glutamic acids via **route A-1** and **route A-2**, and cis-configurated (2S,3R)-alkyl, or rather (2S,3S)-aryl substituted glutamic acids via **route A-3**.

On the one hand, via **route A-2**, ring opening of (2S,3S)-alkyl, or rather (2S,3R)-aryl pyroglutamic acid derivatives, which were mentioned before, should lead to desired target compounds as enantiomerically pure (2S,3S)-alkyl, or rather (2S,3R)-aryl glutamic acid derivatives.

On the other hand, via **route A-1**, ring opening of the substituted lactam under mild conditions, followed by the cleavage of the ortho ester group, may furnish N-protected glutamates in an easier manner. After removal of the N-acceptor group, desired (2S,3S)-alkyl, or rather (2S,3R)-aryl glutamic acid derivatives, should be obtained easily.

Synthesis of (2S,3R)-alkyl, or rather (2S,3S)-aryl glutamic acid derivatives, via **route A-3** ("cis-compounds"), requires again introduction of a double bond which has to be hydrogenated from the less hindered α-side.

The methodology of deprotection is to be close to previously mentioned one for the trans-configurated (2S,3S)-alkyl, and (2S,3R)-aryl glutamic acid derivatives, respectively.

4.3 (R)-BACLOFEN

Via **route B:**

The ortho ester of 4-chlorophenyl compound has to be cleaved completely, as mentioned before, followed by a decarboxylation to get an enantiomerically pure N-protected lactam. Afterwards, ring opening reaction could be done carefully, to receive the N-protected γ-aminobutyric acid intermediate product. (R)-Baclofen, as target compound, is expected to be obtained, after removal of the acceptor group, without epimerisation at the carbon atom C-3.

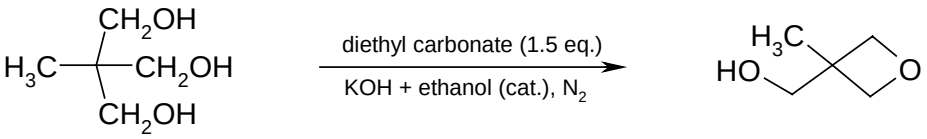
5 SEQUENCE OF PREPARATION

5.1 FORMATION OF PYROGLUTAMIC OXETANE ESTERS

The ortho ester (OBO) as protecting group was supposed to meet all mentioned requirements, and therefore decision was made to employ the oxetane **53** to finally perform synthesis of desired ortho ester compounds.

The necessary preparation of 3-(hydroxymethyl)oxetane (**53**) is already published and principally has been developed from a methodology using pyrolytic conditions to yield cyclic ethers [67], and from a methodology working with more moderate conditions [68], respectively. Further development of this preparation by Corey [69] shows an easy way to obtain 3-(hydroxymethyl)oxetane from commercially available 2,2-bishydroxymethyl-1-propanol (**52**). Corresponding to that synthesis, an excess of diethyl carbonate facilitated heating of the mixture, and additionally, improved outcome of the oxetane **53**. Therefore, an excess (50 %) of diethyl carbonate in the presence of a catalytic amount potassium hydroxide in ethanol was employed, to yield 90% of 3-(hydroxymethyl)oxetane after final destillation.
The analytical data of **53** correspond to ref.: [69] b.p. 122°C, 40 mmHg and ^{1}H-NMR spectroscopic data [71].

Scheme 5.1-1



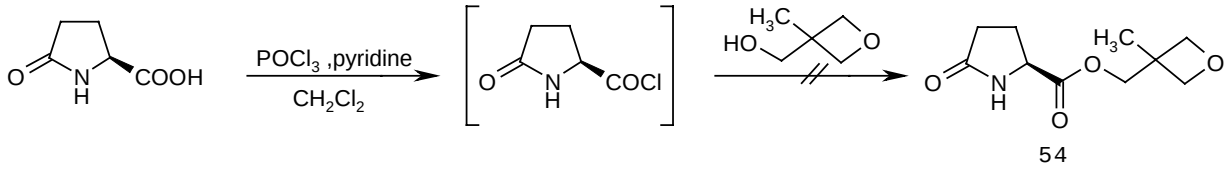
52 53

Principally, there are three published alternatives for the ester formation utilizing an oxetane as a reactant.
The first alternative gains oxetane esters employing an acid chloride as a starting material in the presence of pyridine in dichloromethane [69,70] or alternatively, an anhydride [71].

Hoffmann [72] improved this methodology working with an one-pot-synthesis, whereas the corresponding acid chloride is prepared in situ in the presence of $POCl_3$.

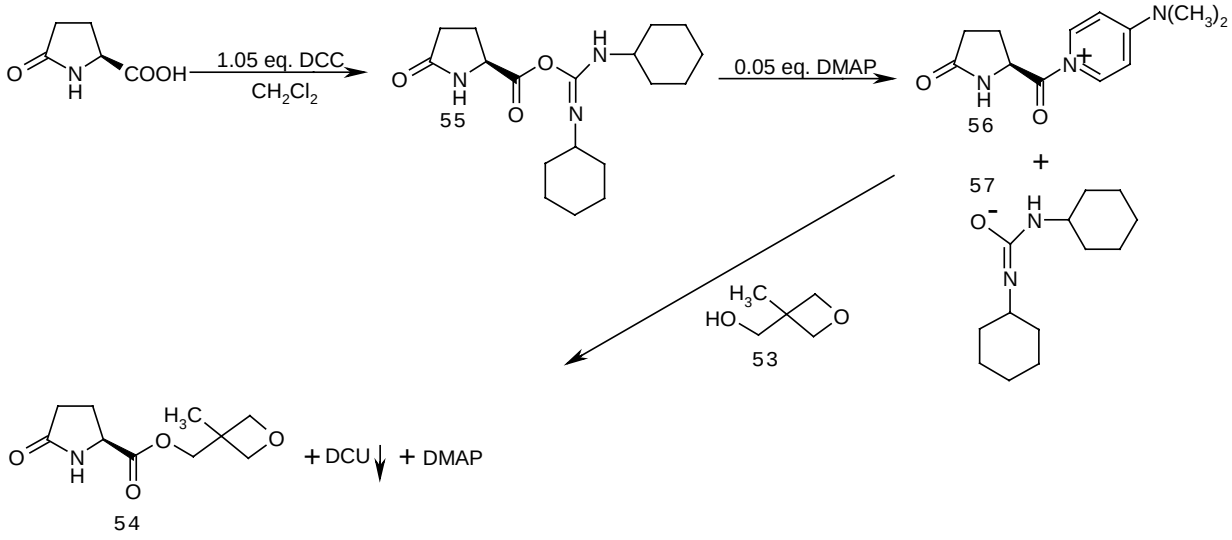
Hence, it was envisaged to generate in situ pyroglutamoyl chloride using $POCl_3$ in the presence of pyridine, and afterwards to complete esterification by the addition of 3-(hydroxymethyl)oxetane in dichloromethane. This procedure was supposed to be easier than the DCC-mediated alternative, but all efforts to obtain the desired pyroglutamic ester **54** failed because of decomposition. The predominant reason was that the oxetane is labile to acids, even in buffered solutions, and hence ring opening of the oxetane occurred. Additionally, it was difficult to extract the pyridine into saturated ammonium chloride solution and the hydrophilic product **54** into the organic phase.
Therefore, further experiments working with “hard” acids, like H_2SO_4 and HCl were not followed anymore [73].

Scheme 5.1-2



The next possibility showed the second alternative to prepare the desired pyroglutamic ester **54**. The methodology which is used for esterification of acids and oxetanes, bases on the coupling reaction of amides developed for the synthesis of peptides. Lajoie [74] and others [75] transformed the DCC-mediated coupling reaction to the requirements of N-protected amino acids to finally generate the desired oxetane esters.
The possible mechanism of the reaction [76] is outlined in Scheme 5.1-3. Thus, (2S)-pyroglutamic acid attacks dicyclohexylcarbodiimide (DCC) to form the intermediate species **55**, which interacts with 4-DMAP to give the acylpyridinium ion **56** and the anion of dicyclohexylurea (**57**). Interception of **56** is performed by the oxetane alcohol **53**, whereas the released proton is captured by the basic anion of dicyclohexylurea (**57**) to finally provide the observed oxetane ester **54**.

Scheme 5.1-3



This method seemed to be more adequate than the latter one, and finally afforded the pyroglutamic oxetane ester (**54**) in high yield (75 %). Therefore, (2S)-pyroglutamic acid and the oxetane alcohol **53** were suspended in CH_2Cl_2, then a solution of DCC and a catalytic amount of 4-DMAP in CH_2Cl_2 were added to this mixture, to yield dissolved (2S)-pyroglutamic acid oxetane ester **54**. Work-up of the reaction mixture was performed to the described procedure in the experimental section. The byproduct (dicyclohexyl urea (DCU)) was filtered off and then triturated in boiling ethanol. The DCU was recovered nearly quantitive (90 %) and can be re-converted to DCC. 4-Dimethylaminopyridine is not worth to be recycled because of its negligible amount.
It is worth mentioning that the desired product **54** was not available, if 4-DMAP is dissolved in the reaction mixture before DCC is added. This issue contradicts the general method of DCC-mediated esterification of amino acid reported from Lajoie [74].

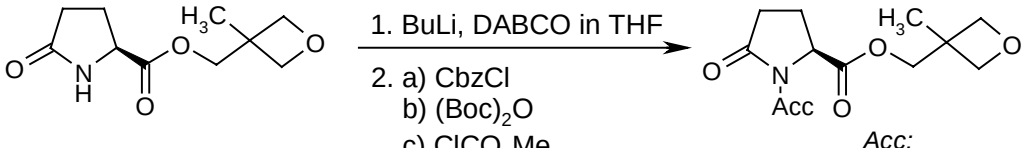
Recently, it was reported [77] that the esterification can be perfomed alternatively with an oxetane tosylate in a nucleophilic substitution reaction, whereas the corresponding pyroglutamic acid is employed as a caesium salt. The reaction is brought to completion by the addition of oxetane tosylate in the presence of sodium iodide, but unfortunately, DMF as a solvent is used, which causes problems with its removal. Therefore, this method did not seem to have an advantage over the DCC-mediated procedure.

5.2 N-PROTECTION OF PYROGLUTAMIC OXETANE ESTERS

The N-protection of pyroglutamatic acid esters was intended to be perfomed using an electron withdrawing protecting group, which should be removed easily in later stage of the synthesis. Hence, common N-acceptor protecting groups like benzyloxycarbonyl (Cbz), t-butoxycarbonyl (Boc), methoxycarbonyl (CO_2Me), and p-toluenesulfonyl (Tos) were regarded to be suitable. On the one hand, it was explored whether the bulkiness of the protecting group plays a significant role in the following rearrangement of the oxetane ester, and on the other hand, whether the following cuprate addition can be performed as expected.
The cleavage of Cbz or Boc protecting group is performed under mild conditions, namely Cbz can be cleaved by hydrogenation and Boc by mild acidic conditions [78]. Instead, CO_2Me needs more drastic conditions for its cleavage by hydrolization, and tosylate is exclusively removed under reductive conditions using sodium or lithium, in liquid ammonia, or by electrochemical methods [79].
Cbz, Boc and CO_2Me can be introduced using commercially available reagents like benzyloxycarbonylchloride (CbzCl), di-t-butyl-di-carbonate ($(Boc)_2O$), and methylchloro formate ($ClCO_2Me$), respectively, whereas the Tos-acceptor group, using tosylchloride (TosCl) as a reagent can not be introduced directly to the amide, and therefore will be described later [see: Scheme 5.2-2].

According to the method of Miller [80] and others [81] the corresponding lactam was deprotonated with butyllithium at -78°C in THF. Then, the resulting lithium amide was quenched with CbzCl, $(Boc)_2O$ and $ClCO_2Me$, respectively, in the presence of 1,4-diazabicyclooctane (DABCO) serving as an appropriate Lewis-base for the lithium cation. Aqueous work-up furnished the N-acceptor protected compounds **59**–**61** [see: Scheme 5.2-1].

Scheme 5.2-1



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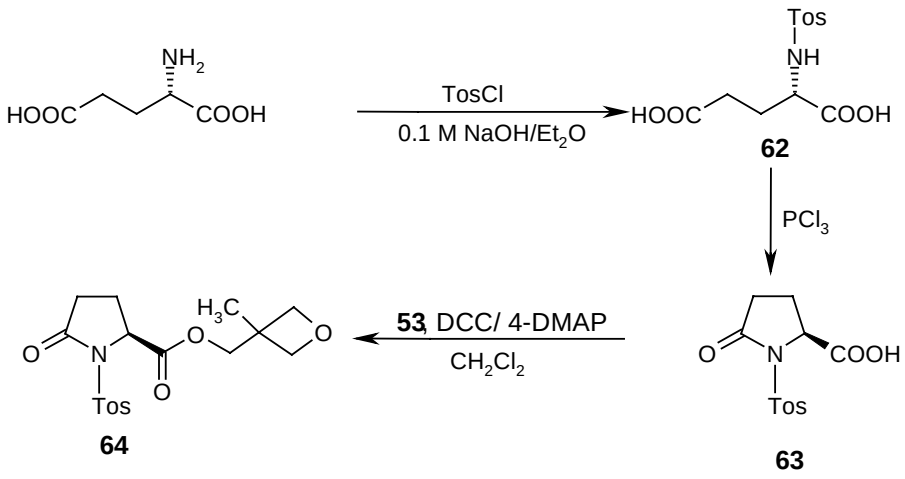
Unfortunately, the N-methoxycarbonyl protected pyroglutamic acid oxetane ester **61** was not available, when $ClCO_2Me$ was used. Therefore, the more toxic but less reactive methylcyano formate ($CNCO_2Me$), the so-called Mander's reagent, was used to provide compound **61**. Additional attempts were made to improve the yield of the N-Cbz derivative **59**, whereas benzyloxycarbonylcyanide (CbzCN) instead of CbzCl was employed. However, the high price was prohibiting, so that finally CbzCl was maintained as a reagent.

Further attempts to improve the outcome of the N-protected pyroglutamic oxetane esters **59**-**61** were made according to a method reported by Kikugawa [82] and Terashima [83]. The latter based on a procedure developed by Ohfune [42,84]. It is outlined that amides are transformed to the corresponding N-protected derivatives by using acylating reagents (i.e. CbzCN, $ClCO_2Me$, $(Boc)_2O$) in the presence of triethylamine/DMAP (in acetonitrile or dichloromethane, room temp.). However, the preparation of the N-protected derivatives **59**-**61** failed completely under these conditions, whereas decomposition was observed.
By using the method of Kikugawa [82] even lower yields were observed. According to the published method, a freshly prepared mixture of LiHMDS and the pyroglutamic ester **54** (THF, –78°C) was quenched with the acylating reagents (CbzCl, $(Boc)_2O$, and $CNCO_2Me$). However, the yields of expected compounds were disappointing. The main reason for this failure seems to be the lack of stabilization of the lithium amide like DABCO does, and therefore, these methods were dropped.

The previous mentioned tosylation [see: Scheme 5.2-2] of S-glutamic acid, to furnish the N-tosylated compound **62**, was carried out according to a procedure published by Rudinger [85].

Scheme 5.2-2

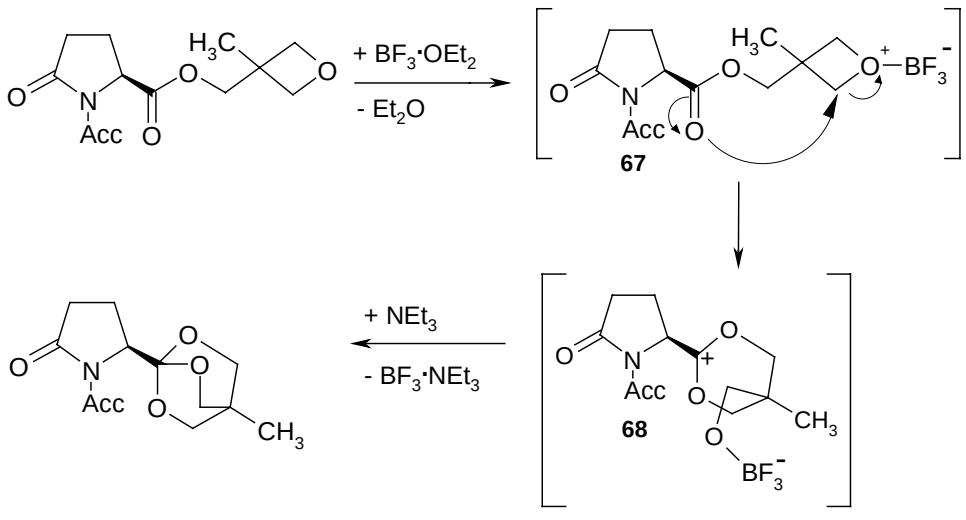


In this way S-glutamate was dissolved in a two-phase-system, containing diethyl ether and 0.1M sodium hydroxide solution, followed by the addition of tosyl chloride. The concluding cyclisation of compound **62** occurred under reflux in PCl_3 to furnish the N-tosylated pyroglutamate **63**. Unfortunately, the final esterification of **63**, employing previously described DCC-mediated [86] method [see: Scheme 5.2-1], gave yields of **64** below 10%, so that this route was abandoned, on the one hand with regard to the low outcome, and on the other hand with regard to expected problems with the cleavage of the protecting group (i.e. Tos).

5.3 REARRANGEMENT TO OBO ESTERS

The rearrangement of the oxetane esters (**59**, **60** and **61**) to the corresponding ortho esters was carried out according to the methodology of Corey [69].
The mechanism of the reaction [see: Scheme 5.3-1] is reported to take course via the Lewis acid-base adduct which rearranges to the final products, namely the 2,6,7-trioxabicyclo[2.2.2]octanes (i.e. OBO series).

Scheme 5.3-1



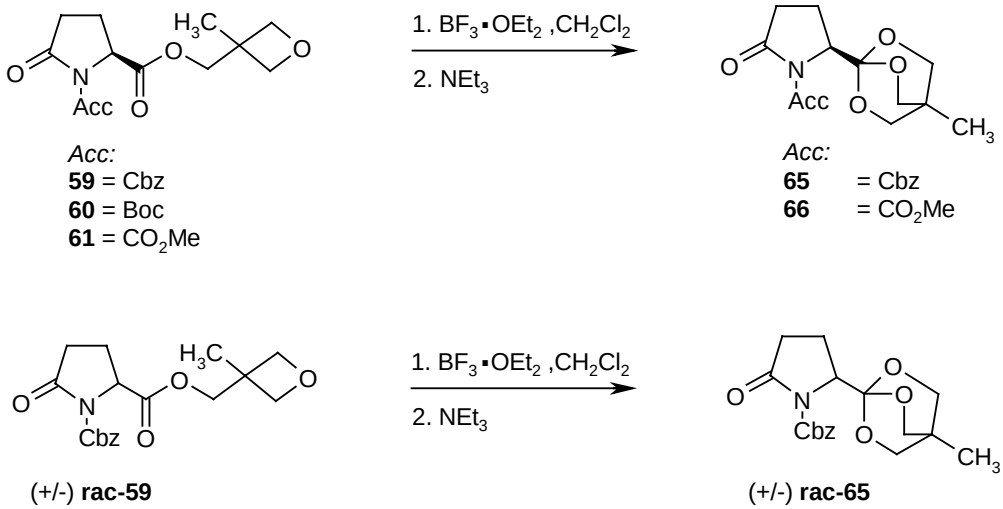
Acc = Cbz, CO_2Me

Boron trifluoride etherate interacts as a Lewis acid with the oxetane oxygen to form the intermediate **67**, then heterolysis of the C-O bond is induced to give the zwitterion **68**. The

thermodynamic driving force for the rearrangement to finally furnish the corresponding OBO esters is the result of the ring strain of the oxetane [71].

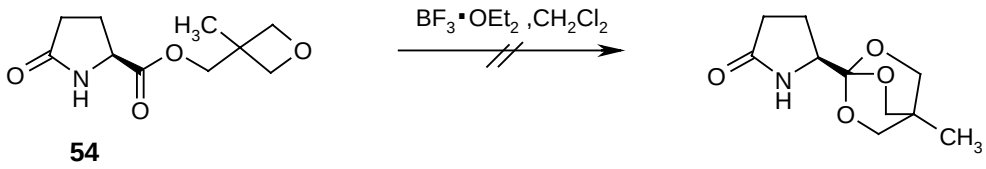
For this purpose, the N-protected oxetane esters (**59**, **60**, and **61**) were dissolved in dichloromethane and treated with boron trifluoride etherate at 0°C, then the reaction mixture was quenched with triethylamine to finally provide the N-Cbz and N-CO_2Me ortho ester compounds (**65** and **66**, respectively) [see: Scheme 5.3-2]. It turned out that BF_3 can not be removed by extraction anyway, hence it was indispensible to add an excess of 10 equivalents NEt_3, and to conclude work-up of **65** and **66** by column chromatography. Unfortunately, Boc as the protecting group of compound **60**, was attacked by BF_3 and immediately removed, so that the desired N-Boc-ortho ester was not available that way. Additionally, the racemic Cbz-derivative ((±) **rac-65**), derived from R,S-pyroglutamic acid, was prepared employing same procedure, whereas the corresponding intermediates 5-oxo-pyrrolidine-2-carboxylic acid 3-methyl-oxetan-3-ylmethyl ester ((±) **rac-54**, not listed) and benzyl oxycarbonyl-5-oxo-pyrrolidine-2-carboxylic acid 2-(3-methyl-oxetan-3-yl-methyl) ester ((±) **rac-59,** not listed) have not been isolated and characterized.

Scheme 5.3-2



Due to the loss of Boc as a protecting group, a further attempt was started to provide the ortho esters directly from the unprotected oxetane ester (**54**) after its esterification [see: Scheme 5.3-3]. Therefore, the same procedure for rearrangement was supposed to be suitable, but when BF_3•OEt_2 was added to the reaction mixture a colourless solid precipitated.

Scheme 5.3-3



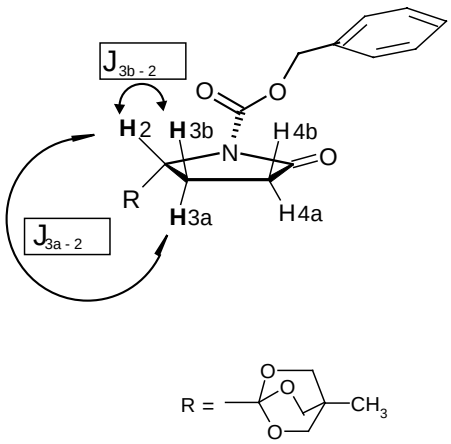
54

Further trials to dissolve this viscous precipitate failed, which may be the result of the high affinity of BF_3 to the lactam to form an insoluble adduct.

The characterization of **65** by ^{1}H-NMR spectroscopy is examplarily shown [see: Figure 5.3-2], whereas the racemic compound ((±) **rac-65**) naturally shows identical spectroscopic NMR-data, but has a different melting point, 145°C ((±) **rac-65**) compared to 165°C of **65**.

The determination of the diastereomeric excess finally can be performed by ^{1}H-NMR spectroscopy after the generation of the second stereogenic center at the carbon atom C-3, but in view of later characterization of the 3-substituted lactam derivatives [see: (2S,3R)- and (2S,3R)-N-protected pyroglutamic ortho ester in chapters 5.8 and 5.10, respectively), there is an indication for special coupling constants [see: Table 5.3-1].

Figure 5.3-1



Especially, the coupling between H-2 and the cis-configurated proton (H-3b) or rather the trans-configurated H-2 and H-3a, which differ significantly from each other, have to be

inspected. Whereas the trans-configurated hydrogens exhibit coupling constants (J_{3a-2}) [see: Figure 5.3-1] in a range between 0 and 1 Hz, the corresponding cis-configurated H-3b and H-2 (J_{3b-2}) range between 5 and 10 Hz. Observed coupling constants (J_{3a-2} = 0 Hz and J_{3b-2} = 8.6 Hz) are outlined in Table 5.3-1.

Measured chemical shifts, especially for ^{13}C-NMR (in $CDCl_3$, as internal standard) of the ortho ester carbon atoms of **65** [see: Figure 5.3-4], are very close to reported ones [74]. Significant shifts hence have been characterized, and are exhibited by the following carbons [in ppm, range ± 1]: 30.5 ($\underline{C}CH_3(CH_2O\text{-})_3$), 72.5 (3 x $\underline{C}H_2O$), 118.5 ($\underline{C}CH_3(OCH_2)_3$).

Figure 5.3-2 ^{1}H-NMR spectrum of **65**

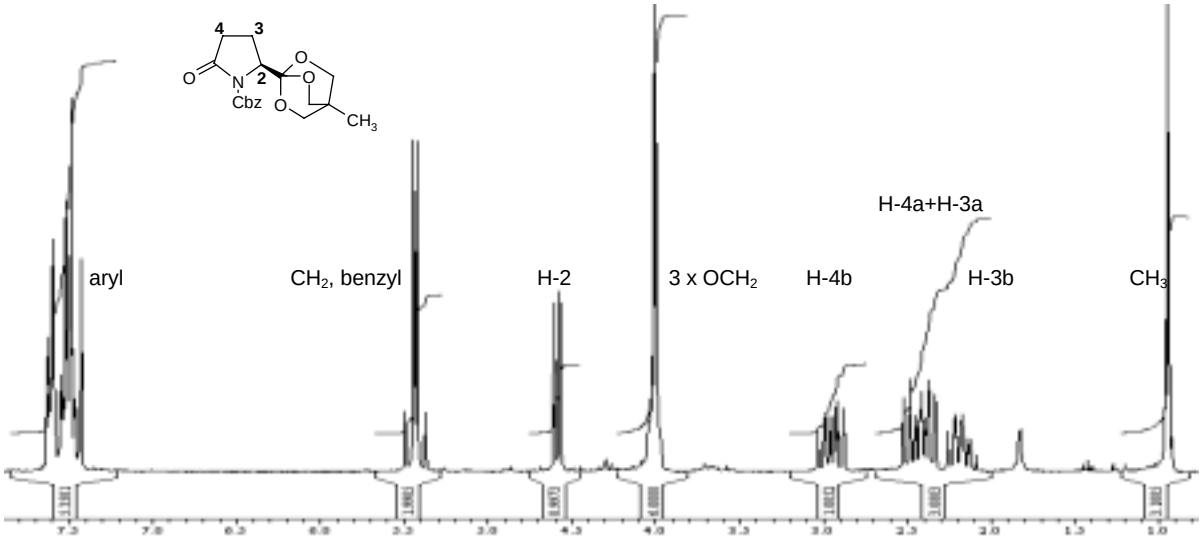


Table 5.3-1

x-H – y-H	J_{x-y} [Hz]
4a - 4b	17.4
3a - 3b	13.2
4a - 3a	11.6
4b - 3a	9.2
4a - 3b	9.7
4b - 3b	11.9
3b - 2	8.6
3a - 2	0.0

Figure 5.3-3 ^{1}H-NMR spectrum of **65** (detail)

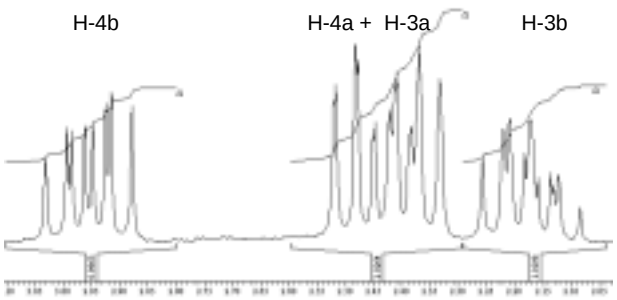
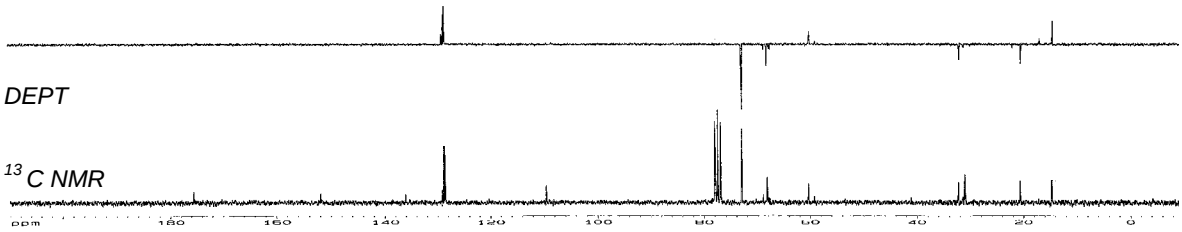


Figure 5.3-4 ^{13}C-NMR and DEPT spectra of **65**



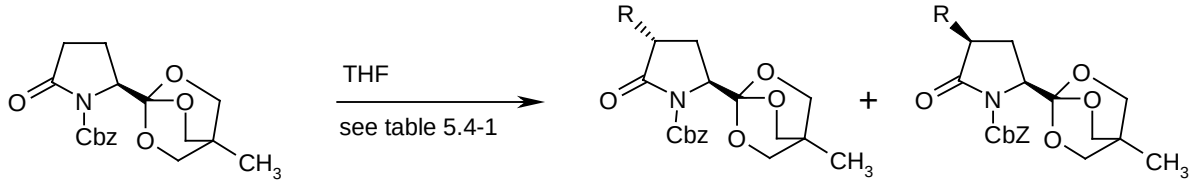
^{13}C NMR ($CDCl_3$): δ = 14.27 (CH_3), 20.24 (C-3), 30.62 ($\underline{C}CH_3(CH_2O\text{-})_3$), 31.85 (C-4), 59.89 (C-2), 67.90 (CH_2, benzyl), 72.63 (3 x CH_2O), 118.5 ($\underline{C}CH_3(OCH_2)_3$), 128.1, 128.2, 128.4, 135.1 (6 x C, aryl), 150.9 (C=O, urethane), 166.0 (C=O, lactam).

5.4 SUBSTITUTION AT C-4

After the rearrangement of the oxetanes to the ortho esters compounds, the substitution at the C-4 carbon atom was attempted to explore the diastereomeric ratio of the resulting 4-substituted products (cis/trans) also in view of the introduction of the double bond [see: chapter 5.5]. Additionally, the ability of the oxetane ester as a bulky protecting group was expected to be sufficient to favour mainly outcome of one diastereomere, namely of the trans-4-substituted one.

At first, for alkylation of the ortho ester **65**, a methyl group (R = methyl) was considered to be suitable [see: Scheme 5.4-1]. For instance, Jones [87] treated a N-Boc pyroglutaminol silyl ether with LDA in THF at –78°C to generate the corresponding lithium enolate. The addition of methyl iodide surprisingly afforded a mixture of the cis- and trans-configurated products (diastereomeric ratio 5:1). Charrier et al. [88] performed this alkylation in a similar manner, and thus used a N-Boc pyroglutamate ester that was treated with LiHMDS and methyl iodide to furnish a mixture of the cis- and trans-configurated products (diastereomeric ratio 6:1). Hence, the trans-alkylation is proposed to be favoured by S_N1-type electrophiles, whereas the cis-alkylation is favoured by S_N2-type electrophiles like CH_3I to form the thermodynamically less stable cis-products [88,89].

Scheme 5.4-1

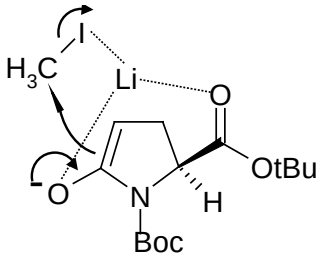


65

According to these methods the ortho ester **65** was treated in different ways [see: entry 1, Table 5.4-1] to undergo substitution at C-4, but surprisingly, either no reaction to the desired 4-substituted compounds took place and the educt **65** was recovered, or decomposition of **65** occurred. These results correspond to those reported by Baldwin [91], whereas enolates that are generated by LDA as well as by LiHMDS, did not undergo alkylation with methyl iodide

as an electrophile. Ezquerra et al. [90] obtained yields of less than 10% when CH_3I was used. A recent reinvestigation of the direct alkylation of pyroglutamate ester urethanes with methyl iodide by Charrier et al. [88] seems to confirm the lack of reactivity of compound **65**. They explored direct methylation at the N-Boc-tert-butyl pyroglutamic ester and summarized that chelation [see: Figure 5.4-1] of the intermediate enolate **69** seems to be essential for the alkylation of N-protected pyroglutamic acid derivatives.

Figure 5.4-1



69

Table 5.4-1

entry	reactant R-X	reactant	reaction conditions		product [a]	
			temp. (°C)	T (h)	cis (%)	trans (%)
1	CH_3I (1.0 up to 10.0 eq.)	LiHMDS	-78, then 25	2-12	educt	
		KHMDS	-78, then 25	2-12	educt	
		LDA	-78, then 25	2-4	educt	
		1.)LiHMDS 2.)TMSCl 3.)TBAF	-78, then 25	2-4	decomposition	
2	$PhCH_2Br$ (1.05 eq.)	LiHMDS	-78, then 25	2	**71** (10)	**71** (90)
3	PhSeCl (1.05 eq.)	LiHMDS	-78, then 25	2	**72** (30)	**72** (70)
4	$PhSO_2Me$ (1.05 eq.)	KH	20	1	**73** (30)	**73** (70)

[a] approximated diastereomeric ratio, measured in $CDCl_3$

Due to these results direct methylation of compound **65** was dropped and hence alkylation at the C-4 carbon atom was attempted with benzyl halides. Therefore, direct alkylation [90,91,92] of **65** was carried out with an excess of LiHMDS (2.3 eq.) in THF at –78 °C to generate the intermediate lithium enolates, and the following addition of the benzyl halide

$PhCH_2Br$ or the phenylselenenyl halide PhSeCl furnished a mixture of the products cis-**71**/trans-**71** and cis-**72**/trans- **72**, respectively [see: entries 2 and 3, Table 5.4-1].

The preparation of the product mixture cis-**73**/trans-**73** was carried out with KH (2.3 eq.) as a base (in THF at room temp.), and the following addition of methyl phenylsulfinate furnished the substitution. Final aqueous work-up provided the diastereomeric cis-**73**/trans-**73** mixture [see: entry 4, Table 5.4-1].

Due to the introduction of the double bond [see: chapter 5.5], the separation of the diastereomeric pairs cis-**72**/trans-**72** and cis-**73**/trans-**73** was dropped, whereas the 4-benzyl substituted derivatives (cis-**71**/trans-**71**) were attempted to undergo separation by column chromatography on silica gel (eluent: EtOAc-petroleum ether, 2+1). However, the retention indices of the diastereomeres cis-**71** and trans-**71** were to similar to allow complete separation. Hence, this diastereomeric mixture was supposed to undergo deprotection (cleavage of the ortho ester and Cbz protecting group, see: chapter 5.9). Work-up provided the corresponding 4-substituted pyroglutamic acids and concluding selective recrystallization exclusively afforded the trans-configurated pyroglutamic acid derivative **105** [see: Scheme 5.9-1].

5.5 INTRODUCTION OF DOUBLE BOND

The transformation of a carbonyl compound to α,β-unsaturated derivatives can be accomplished by several methods.
Theissen [93] reported that the preparation of α,β-unsaturated ketones can be carried out by the usage of oxygen in the presence of metallic catalysts, preferably Pd(II)-compounds [94]. But disadvantagely, drastic reaction conditions are necessary for successful transformation. This α,β-unsaturation requires a high reaction temperature of about 100°C, and there are liberated "hard" acids (e.g. hydrochloric acid). The latter procedure would lead to the undesired ring opening reaction of the ortho ester protecting group, and hence was left out of consideration.

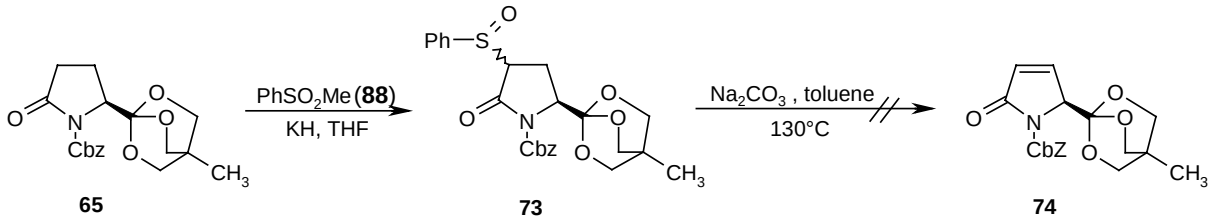
Alternatively, halogenation, and especially the bromination of an enolized α-position of carbonyl compounds in the presence of NBS is applied to transform carbonyl compounds to the α,β-unsaturated derivatives [95]. However, when the bromination is carried out, liberated HBr also would lead to a ring opening reaction of the ortho ester protecting group, and therefore has to be dropped.

Another reported reaction with the activated chinone 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) was supposed to provide the α,β-unsaturated lactam **74**, because the reaction temperature normally ranges between room temp. and that of refluxing toluene or dioxane [96]. The mechanism of the dehydrogenation under neutral conditions is to run via a charge-transfer-complex of the chinone and the carbonyl compound, whereas the benzochinone serves as a hydrid and proton acceptor, while the carbonyl compound functions as a donor [97]. According to this published procedure [98] the ortho ester compound **65** was treated with two equivalents of DDQ in toluene at room temp., to give the α,β-unsaturated lactam **74**. However, even under more drastic reaction conditions (reflux in toluene for several hours), compound **74** was not detectable and the educt **65** was partially recovered.

Another transformation reaction for carbonyl compounds to α,β-unsaturated ketones is reported [99,100] and has been employed successfully in our group [101] to generate the unsaturated compound **2** [see: Figure 3.1-1].
Therefore, the preparation of the methyl phenylsulfinate **88** was carried out according to a procedure reported by Meyers [99]. The formation of the α-sulfinyl lactam **73** (diastereomeric mixture of cis-**73**/trans-**73**, see: Scheme 5.4-1) was performed by subjection of compond **65** to potassium hydride (in THF at room temp.), to generate an enolized intermediate. The

electrophilic attack of compound **88** finished this addition reaction. Final work-up yielded the diastereomeric mixture of **73** (cis-**73**/trans-**73**, see: Table 5.4-1), which was supposed to undergo a syn-elimination reaction to provide the α,β-unsaturated lactam **74**.

Scheme 5.5-1



Hence, this diastereomeric mixture was dissolved in toluene and refluxed in the presence of sodium bicarbonate, until **73** was consumed (monitored by TLC). However, the pyrolysis of **73** failed and the desired α,β-unsaturated lactam **74** could not be provided that way. Thus, due to these drastic reaction conditions, an alternative procedure had to be chosen.

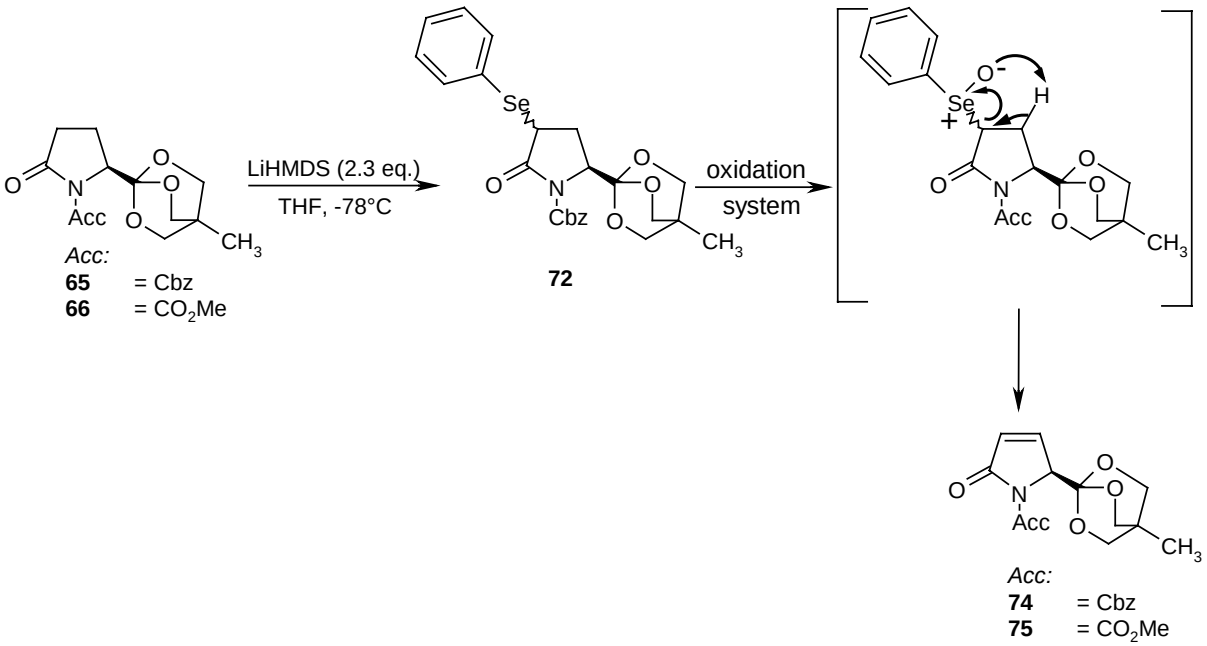
Instead of sulfinates, the corresponding selenoxides, as oxidized derivatives of the phenylselenenyl products, were supposed to promise a convenient transformation to the α,β-unsaturated lactam **74**. The higher efficacy of the syn-elimination process, compared to that of sulfoxides, is the result of a greater polarization of the Se-O and Se-C bond, respectively, and therefore, can occur at low temperature when a conjugate system is formed. This process is most commonly carried out through an efficient elimination of appropriate selenoxides developed by Reich [102], employing phenylselenenyl halides as alkylates (e.g. PhSeCl or PhSeBr). However, these selenium compounds normally should be avoided due to their costs and high toxicity, whereas in view of the costs, there exists an efficient procedure for the preparation of PhSeCl [103]. Alternatively, the corresponding phenylselenenyl halides directly can be generated in situ [104] from diphenyl diselenide, but this method has not been followed anymore because of its acidic reaction conditions.

According to the mentioned procedure, the selenenylation was carried out [see: Scheme 5.4-1]. The ortho esters (**65** and **66**) were treated with LiHMDS in THF at –78°C to generate an intermediate lithium enolate that undergoes nucleophilic reaction with PhSeCl, to afford the phenylselenenyl product **72** (diastereomeric ratio 3:7 cis- **72**/trans-**72**, see: entry 4, Table 5.4-1). Final chromatographic isolation yielded **72** (70%). Hence, the 4-substituted N-

methoxycarbonyl analogue was not available, however, detection utilizing ^{1}H-NMR spectroscopy as well as TLC took place to confirm its existence in the reaction mixture.
There are various proposals for the oxidation of organoseleno compounds to the form corresponding selenoxides. A common oxidation procedure employs aqueous solvent systems, as one- or two-phase-systems [105], whereas an excess of a water-soluble oxidizing agent is used, mainly H_2O_2 30 % [106,107,108] or sodium periodate [109]. Alternatively, the oxidation can be performed in organic solvents (THF or CH_2Cl_2), utilizing meta-chloroperbenzoic acid, peracetic acid or t-butyl hydroperoxide as oxidizing agents [110,111,112].

At first, the oxidation of compound **72** was carried out by a procedure mainly used for N-protected lactams [108,44], whereas **72** was dissolved in an appropriate amount of an organic solvent (i.e. EtOAc, THF or CH_2Cl_2), then conc. H_2O_2 is added to this solution at 0°C to complete syn-elimination. Finally, after extractive work-up the desired α,β-unsaturated compounds (**74** and **75**) should be obtained.
The mechanism of the in situ generated selenoxide is supposed to undergo a syn-elimination reaction to finally provide the desired α,β-unsaturated lactam **74** [see: Scheme 5.5-2].

Scheme 5.5-2



According to mentioned procedures various oxidation systems were tested, whereas the phenyselenenyl adduct **72** was dissolved in an appropriate solvent (solvent), then the

oxidizing reagent (ox. reagent) was added to this mixture in the presence of a buffered system (buffer). All tested oxidation systems are recorded in Table 5.5-1.
Unfortunately, compound **75** yet has not been available that way, neither emyloying aqueous systems nor organic solvent systems, whereas the N-Cbz-protected α,β-unsaturated lactam **74** exclusively was obtained in a basic buffered system (CH_2Cl_2/THF in the presence of DABCO) with a more or less satisfying yield (48%). Noteworthy is the essential excess of DABCO, otherwise decomposition (decomp.) occurred.

Table 5.5-1

oxidation system			reaction conditions		product	
solvent	ox.reagent	buffer	time [h]	temp. [°C]	**74** yield [%]	**75** yield [%]
EtOAc	H_2O_2 (30%)	no	1	0, then 20	decomp.	decomp.
CH_2Cl_2	H_2O_2 (30%)	Na_2CO_3/$NaHCO_3$ (pH8)	0.5	0, then 20	decomp.	decomp.
EtOAc	$NaIO_4$	no	0.5	0, then 20	decomp.	decomp.
MeOH/H_2O	$NaIO_4$	Na_2CO_3/$NaHCO_3$ (pH8)	0.5	0, then 20	decomp.	decomp.
CH_2Cl_2/THF	m-CPBA	no	2.0	-20, then 20	decomp.	decomp.
CH_2Cl_2/THF	m-CPBA	DABCO	2.0	-20, then 20	48	decomp.

On the one hand, these difficulties for the preparation of **74** suggest implicitly the involvement of intermediate formed PhSeOH [105], and on the other hand, the lack of stability of the ortho ester **65** against acids is demonstrated. Phenylselenenic acid, namely PhSeOH, which is generated during the selenoxide syn-elimination, are in equilibrium, that means disproportion, with diphenyl diselenide and phenylseleninic acid, and therefore, under neutral or acidic conditions they react with olefins and especially with conjugated systems. However, re-addition of PhSeOH to the conjugated system of compound **74**, and additionally, ring opening reaction of the ortho ester protecting group is inhibited in basic medium. It has to be pointed out that the N-benzyloxycarbonyl protecting group (Cbz) plays a major role for stabilization while the elimination occurs, whereas CO_2Me seems to favour the decomposition of the intermediate selenoxide due to the destabilizing activity of the CO_2Me moiety.

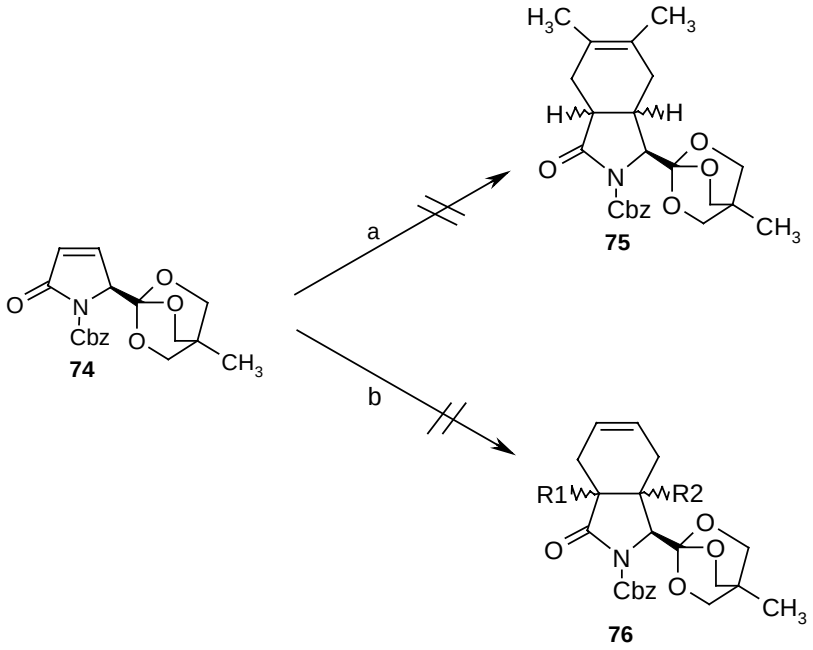
The structure determination of compound **74** utilizing ^{1}H- and ^{13}C-NMR spectroscopy provides characteristic chemical shifts (ppm, $CDCl_3$) for the protons H-3 (7.12) and H-4 (6.08)

[see: Figure 5.5-1], and for the carbon atoms C-3 (146.8) and C-4 (126.7) [see: Figure 5.5-3], respectively.

The allylic system, which is formed by H-2, H-3 and H-4, shows typical coupling constants ($J_{3\text{-}2}$ = 2.5 Hz, $J_{4\text{-}2}$ = 1.5 Hz and $J_{3\text{-}4}$ = 6.0 Hz) [see: Table 5.5-2]. Additionally, optical rotation of **74** ensured that no complete racemisation occurred ($[\alpha]_D^{20}$ = -190.5, c = 0.4, CH_2Cl_2). Hence, these data seemed to ensure the availability of compound **74**, and therefore the following 1,4-addition was envisaged to afford products with high diastereomeric excess.

To test the high reactivity of the N-Cbz-α,β-unsaturated lactam as an electron poor olefin, compound **74** was tested in an DA-reaction [see: Scheme 5.5-3].

Scheme 5.5-3



a) 2,3-dimethylbut-1,3-diene (10.0 eq.), toluene, reflux, argon; b) trimethylsiloxybuta-1,3-diene (10.0 eq.), toluene, reflux, argon; R1 = $OSi(CH_3)_3$ and R2 = H, or R1 = H and R2 = $OSi(CH_3)_3$.

Hence, compound **74** was treated with 2,3-dimethylbut-1,3-diene and trimethylsiloxybuta-1,3-diene under reflux in toluene to undergo [4+2] cycloaddition to the corresponding bicyclic lactam derivatives **75** and **76** [113]. But not surprisingly, even after 5 days under reflux compound **74** was partially recovered and either formation of **75** nor of **76** was observed.

Figure 5.5-1 ^{1}H-NMR spectrum of **74**

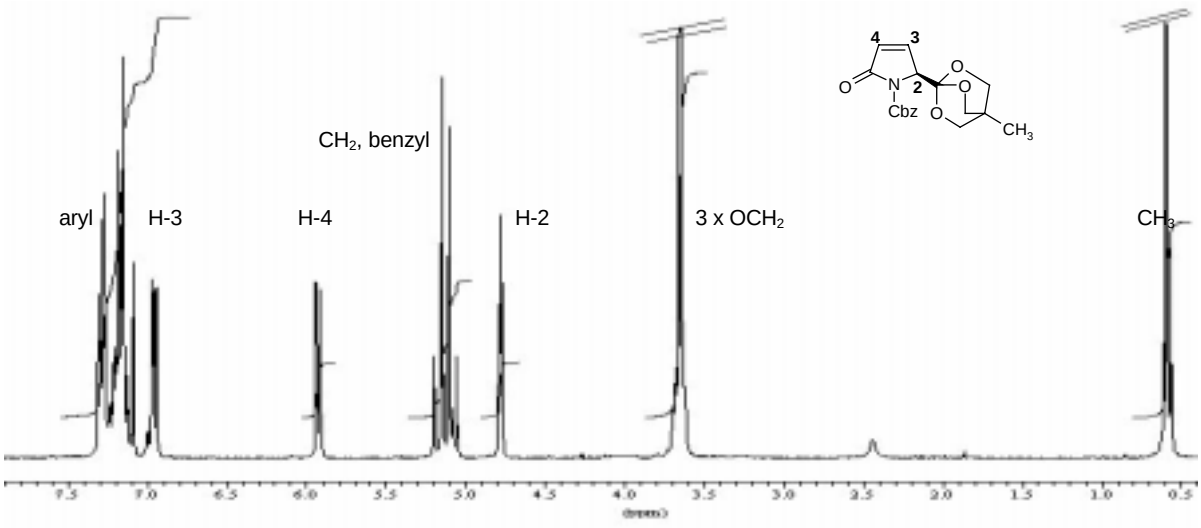


Table 5.5-2

x-H – y-H	J_{x-y} [Hz]
3 - 4	6.0
3 - 2	2.5
4 - 2	1.5
2 - 3	2.0
2 - 4	2.0

Figure 5.5-2 ^{1}H-NMR spectrum of **74** (detail)

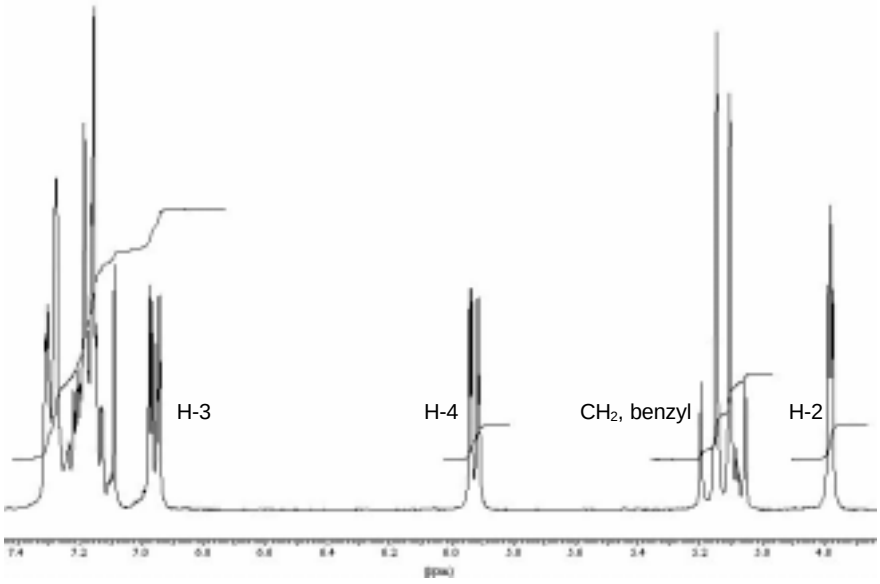
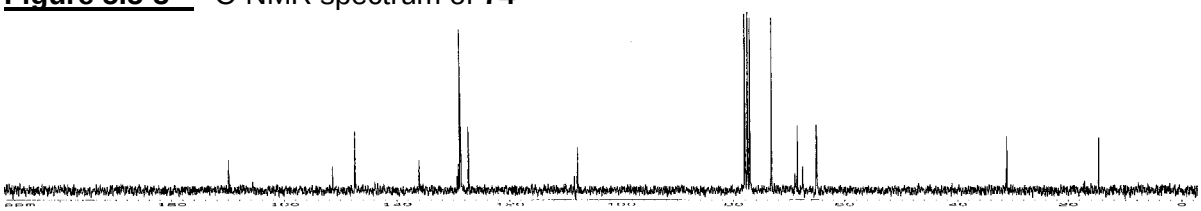


Figure 5.5-3 ^{13}C-NMR spectrum of **74**



^{13}C NMR ($CDCl_3$): δ = 14.07 (CH_3), 30.55 ($\underline{C}CH_3(CH_2O\text{-})_3$), 64.48 (C-2), 67.99 ($CH_2$, benzyl), 72.72 (3 x CH_2O), 107.3 ($\underline{C}CH_3(OCH_2)_3$), 126.7 (C-4), 128.0, 128.1, 128.3, 128.5, 135.5 (6 x C, aryl), 146.8 (C-3), 151.0 (C=O, urethane), 169.2 (C=O, lactam).

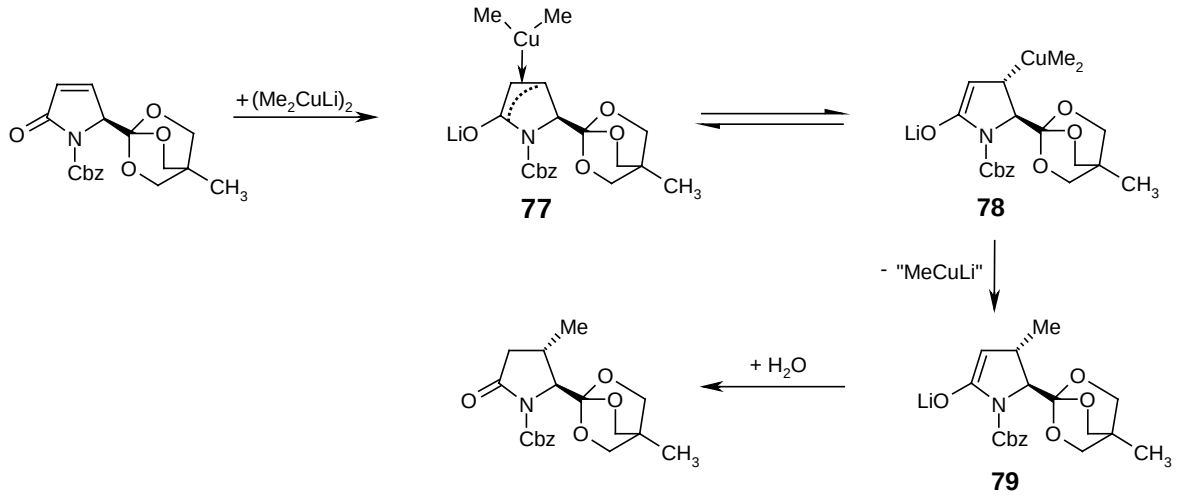
5.6 1,4-ADDITIONS WITH 74 VIA ROUTE A

Owing to the mentioned results compound **74** was supposed to undergo an 1,4-addition via a copper-mediated conjugate addition of a nucleophilic carbon compound to the α,β-enone system of **74**. This methodology of a C-C bond formation has been employed previously in our group [44,114], and therefore was considered to be suitable for stereoselective synthesis of the expected trans-configurated compounds.

The conjugate addition of organocopper compounds to α,β-enones was originally observed by Kharash [115], whereas he explored that 1,4-addition is favoured to 1,2-addition in the presence of a catalytic amount of Cu(I). Later development of the first organocuprate "Me_2CuLi", commonly known as "Gilman's cuprate" [116], lead to various applications of C-C bond formation [117]. Although organocuprates are one of the most popular organometal-containing reagents for structural elaboration, especially for C-C bond formation, but very little was actually known about the intermediate species involved. Besides these so-called LO ("low order") cuprate complexes like "Me_2CuLi", there exist the so-called HO ("higher order") cuprates, as "R_3CuLi_2" and "$R_2Cu(CN)Li_2$" [118,119,120d], which are derived from copper halides (i.e., 3Rli + CuX) and CuCN, respectively. Meanwhile the dispute or controversy between the two parties has been settled. The "higher order cuprates" have to be renamed after intensive spectroscopic investigations as cyano-Gilman cuprates [120e-g].
The existence of a monoanionic cuprate (LO cuprate) or of a dianionic one (HO cuprate) mainly depends on the choice of the solvent [121,122]. While diethyl ether favours formation of the dimeric complexes of LO cuprates, $(Me_2CuLi)_2$ [120a-c], THF gives equilibria between at least two cuprate clusters and methyllithium. However, THF should be avoided because of its Lewis basicity which decreases the rate of the reaction and the yield of the desired product.
It seems to be clear that the enone-cuprate conjugate addition requires initial coordination of the enone carbonyl with lithium or magnesium [117], and therefore the introduction of a nucleophilic carbon agent can be carried out via organo lithium or Grignard compounds.
The mechanism of the conjugate addition reaction of Gilman reagents, mainly of dimeric "Me_2CuLi", has been observed intensively [121,123]. The hypothetic mechanism is outlined in Scheme 5.6-1.
The complexation of the organocuprate with the α,β-enone is proposed to be an initial step, whereas the complex lithium or magnesium cation undergoes coordination with the oxygen of the carbonyl compound. Then, the enone's carbons (here: C-3, C-4 and C-5), acting as a

π-acid, allow the formation of the metastable (d,π^3 *)-complex **77** with the copper of the cuprate reagent, which acts as a d^{10}-base [124]. In the following reversible step, the copper(III) β-adduct **78** is generated which undergoes reductive elimination to furnish the β-substituted enolate **79**. The formation of an intermediate copper(III) β-adduct has been studied utilizing ^{13}C- and ^{1}H-NMR spectroscopy, and hence its existence seems to be ensured [125]. Final hydrolysis should provide the 3-methyl substituted ortho ester compound. However, direct oxidation of Cu(I) to the copper (III) β-adduct **78** is discussed, but experimental support of this single electron transfer (SET) is still lacking.

Scheme 5.6-1

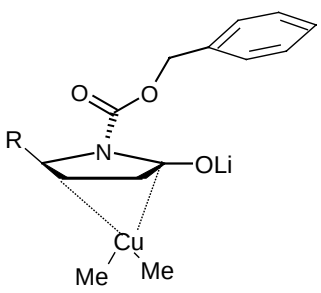


The combination of organocuprate reagents and chlorosilane (i.e.; chlorotrimethylsilane) has been pointed out to accelerate the conjugate addition reaction, especially in THF, although THF itself decreases rate of the reaction [123]. In addition, an excess of TMSCl enhances the stereochemical outcome of many conjugate addition reactions, i.e. in this case a high selectivity of the trans-substituted product could be predicted. Hence, an explanation for the stereochemical selectivity can give favoured anti-coordination of copper to the intermediate species **77**. The two possible complexes (anti-**77** and syn-**77**) are illustrated in Scheme 5.6-2. Clearly, syn-**77** is expected to be less favourable because of the repulsion between copper and the axial bulky ortho ester protecting group.

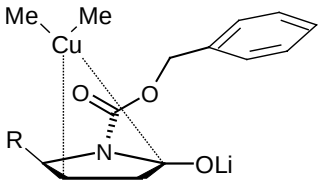
Besides mentioned aspects, the stereochemical selectivity as well as the acceleration of the conjugate addition reaction, on the one hand depends on the choice of the copper (I) compound [126], and on the other hand the substitution pattern of the α,β-enone is essential for its reactivity. The latter includes utilization of the bulky ortho ester protecting group and of

an electron withdrawing protecting group (Cbz) [87,127], which was a pre-condition in the plan of synthesis [see: chapter 4]. It has been pointed out that CuBr•$S(CH_3)_2$ and CuCN are to be favoured to other copper (I) reagents, because of kinetic aspects [126].

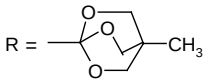
Scheme 5.6-2



anti-**77**

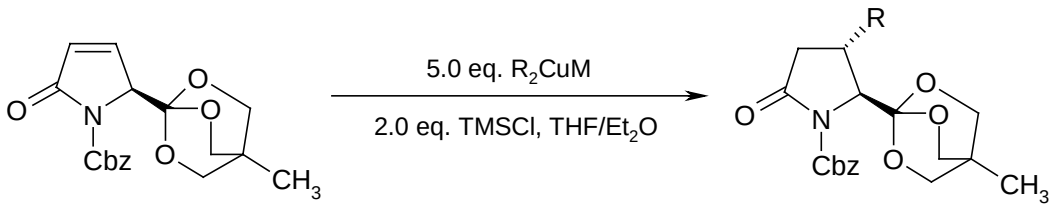


syn-**77**



Due to previous observations, especially in our group [44,114], it was decided to utilize an excess of the organo cuprate reagent (5.0 eq.) in the presence of TMSCl (2.0 eq.) to accomplish the conjugate 1,4-addition reaction via copper catalyzed Grignard reagents as well as via Gilman cuprates [see: Scheme 5.6-3].

Scheme 5.6-3



74 **80 - 88**

Therefore, the corresponding Grignard reagents were freshly prepared and added to the reaction mixture in one portion at a temperature below –20 °C, whereas the alkyl lithium compounds (MeLi and BuLi) have been employed as commercially available compounds.

For extractive work-up of the quenched reaction mixtures (see: Experimental Section **80**-**88**) it is noteworthy that the removal of the residue of copper compounds in the organic layers exceptionally required intensive washing (at least 4x with satd. NH_4Cl solution) until the blue colour of the water phases disappears. All prepared compounds yielded as colourless crystals [Table 5.6-1]. However, furnishment of compound **88** [see: entry 9, Table 5.6-1] failed due to the utilization of 2-thienylmagnesium bromide as a so-called “dummy-ligand”, and hence, its preparation was not followed anymore. Work-up of the arylcuprates [see: entries 5-8, Table 5.6-1] generally required purification by column chromatography to remove byproducts (i.e phenols). They are a result of decomposition of the arylcuprates (i.e. naphthol, biphenyl, phenol, and p-chlorophenol) in the presence of oxygen [128], but recrystallization after column chromatography afforded the pure crystalline products **84**-**87**.

Table 5.6-1

entry	R	M	compound	yield (%)
1	methyl	Li	**80**	75
2	ethyl	MgBr	**81**	62
3	1-butyl	Li	**82**	70
4	allyl	MgBr	**83**	48
5	phenyl	MgBr	**84**	50
6	p-chlorophenyl	MgBr	**85**	55
7	1-biphenyl	MgBr	**86**	30
8	1-naphthyl	MgBr	**87**	55
9	2-thienyl	MgBr	**88**	2

On the other hand, the alkyl compounds **80**-**82** [see: entries 1-3, Table 5.6-1] have been recrystallized from the crude product after their extractive work-up. However, the allylic compound **83** [see: entry 4, Table 5.6-1] required purification by column chromatography due to the formation of several byproduts (i.e. polymers) in the 1,4-addition reaction.

The structure determination of compounds **80**-**87** has been made on the basis of ^{1}H-NMR spectroscopy to ensure the expected trans diastereoselectivity of observed products. Therefore, the position of the substituent **R** [see: Figure 5.6-1] unambiguously can be

performed by the inspection of the corresponding coupling constants ($J_{2\text{-}3}$, $J_{4a\text{-}3}$, $J_{4b\text{-}3}$). Characteristically, the latter range between 0 and 3 Hz ($0 < J_{2\text{-}3} < 3$ Hz) for trans-configurated H-2 and H-3, whereas the cis-configurated products would show coupling constants between 8 and 10 Hz ($8 < J_{2\text{-}3} < 10$ Hz) [44,53,62a]. In addition, assignment of H-3, H-4a and H-4b also can be done inspecting their coupling constants. The coupling constants of cis-configurated H-3 and H-4a ($J_{4a\text{-}3}$) are expected to differ significantly from the corresponding coupling constants of trans-configurated H-3 and H-4b ($J_{4b\text{-}3}$) [see: Table 5.6-2].
Due to emphasize following arguments, several convincing ^{1}H-NMR spectra of the (2S,3S)-3-alkyl derivatives (see: entries 1,2 and 4, Table 5.6-2) and the (2S,3R)-3-aryl derivatives (see: entries 5 and 8, Table 5.6-2) are therefore outlined.

Figure 5.6-1

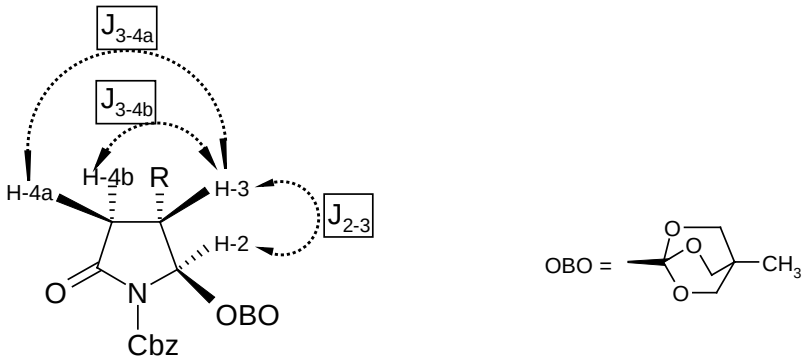


Table 5.6-2

entry	R	compound	coupling constants [Hz]				for spectrum see:
			$J_{2\text{-}3}$	$J_{4a\text{-}3}$	$J_{4b\text{-}3}$	$J_{4a\text{-}4b}$	
1	methyl	**80**	0	8.2	0	17.4	Figure 5.6-2
2	ethyl	**81**	0	8.5	0	17.7	Figure 5.6-5
3	1-butyl	**82**	0	8.5	0	17.7	-
4	allyl	**83**	0	8.5	0	17.1	Figure 5.6-8
5	phenyl	**84**	0	9.2	0	18.0	Figure 5.6-11
6	p-chlorophenyl	**85**	0	9.3	0	18.3	-
7	1-biphenyl	**86**	0	9.2	0	18.0	-
8	1-naphthyl	**87**	0	8.9	0	17.7	Figure 5.6-14

solvent: $CDCl_3$

Characteristically, the observed ^{1}H-NMR spectra of **80**-**87** provide signals for H-2 (s), H-4a (dd) and H-4b (d), whereas trans-configurated H-2/H-3 and H-3/H-4b do not couple with each other. Therefore, the corresponding coupling constants $J_{2\text{-}3}$ / $J_{4b\text{-}3}$ (0 Hz), $J_{4b\text{-}3}$ (range: 8.2–9.3 Hz) and J_{gem} (range: 17.1–18.3 Hz) are observed. These spectroscopic data are in accordance with reported ones [44,53,62a] and confirm the assumption that **80**-**87** are trans-configurated.

Additionally, the C-3-alkyl-substituted compounds **80**-**83** show coupling between H-3 and the vicinal protons of the alkyl moiety (**R** = methyl, ethyl, 1-butyl, allyl) with more or less complex coupling patterns [see: Table 5.6-3].

Table 5.6-3

entry	R	compound	coupling constants [Hz]			for spectra see:
			$J_{3\text{-}CH3}$			
1	methyl	**80**	7.3			Figure 5.6-3
			$J_{3\text{-}CH2}$	$J_{CH2\text{-}CH3}$		
2	ethyl	**81**	7.6	-[a)]		Figure 5.6-6
			$J_{3\text{-}CH2}$	$J_{CH2\text{-}CH3}$		
3	1-butyl	**82**	-[a)]	6.7		-
			$J_{3\text{-}1'}$	$J_{1'\text{-}2'}$	$J_{2'\text{-}3'}$	
4	allyl	**83**	7.3	-[a)]	-[a)]	Figure 5.6-9

a) overlapping signals

It is pointed out that inspection of the ^{1}H-NMR as well as ^{13}C-NMR spectra show one set of signals. Hence, assignment of all hydrogen and carbon atoms is unambiguously made on the basis of ^{1}H-NMR and ^{13}C-NMR spectra, whereas assignment of the carbon atoms C-2, C-3 and C-4 is ensured by utilizing DEPT spectroscopy. Examplarily, these arguments are emphasized by outlined spectra [see: Figure 5.6-4 for **80**, Figure 5.6-7 for **81**, Figure 5.6-10 for **83**, Figure 5.6-13 for **84**, and Figure 5.6-16 for **87**].

Hence, it can be recorded the fact that all prepared compounds (**80**-**87**) show expected trans substitution between H-2 and H-3. It was gratifying to notice that the bulkiness of the OBO group resulted in an exclusive trans diastereoselectivity of the conjugate 1,4-addition reaction.

Figure 5.6-2 ^{1}H-NMR spectrum of **80**

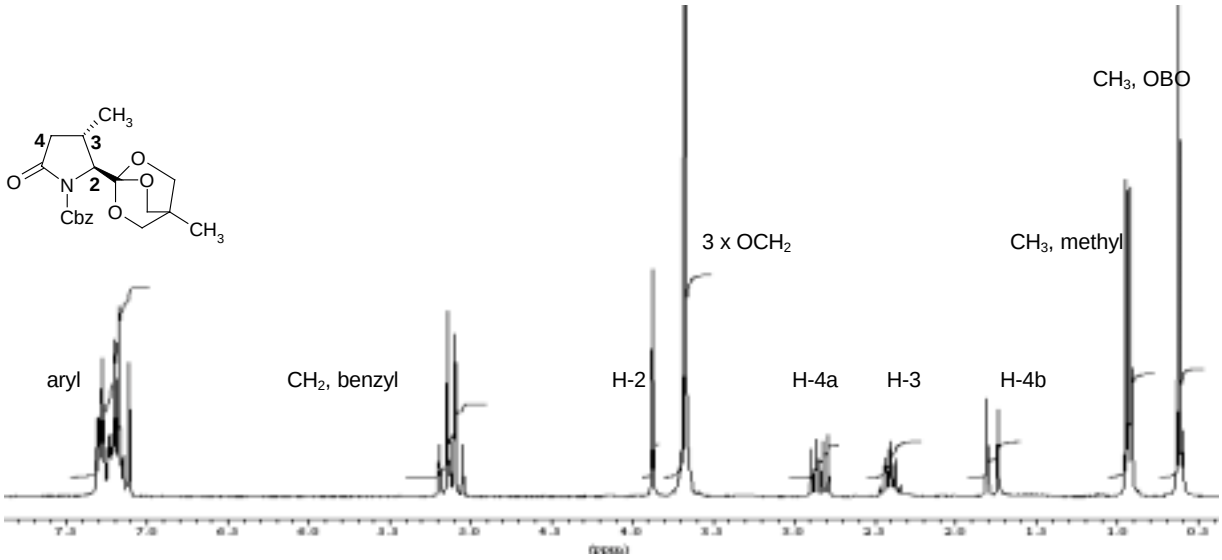


Figure 5.6-3 ^{1}H-NMR spectrum of **80** (detail)

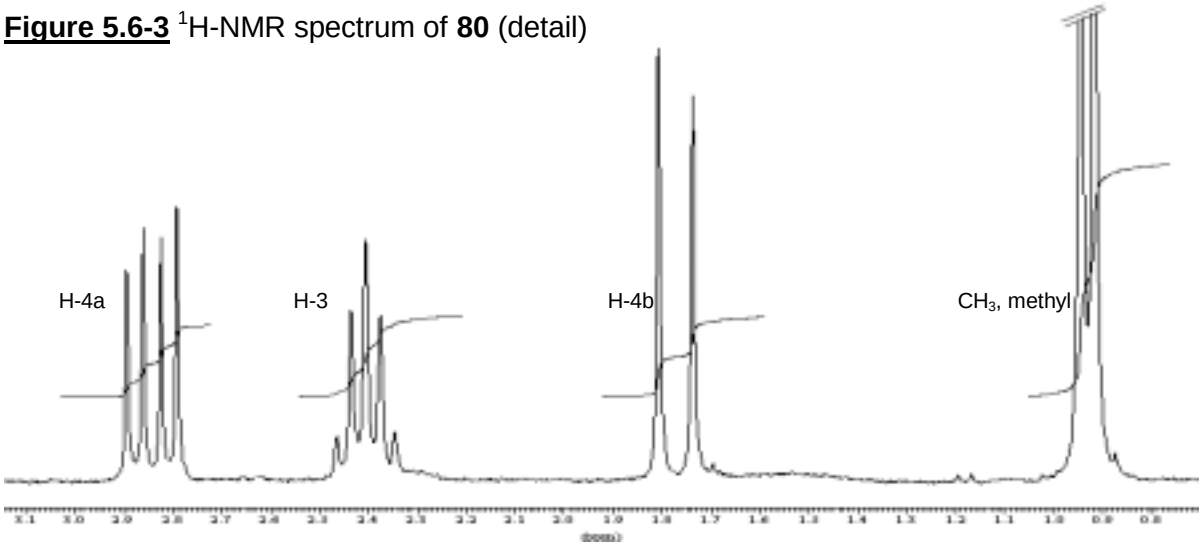
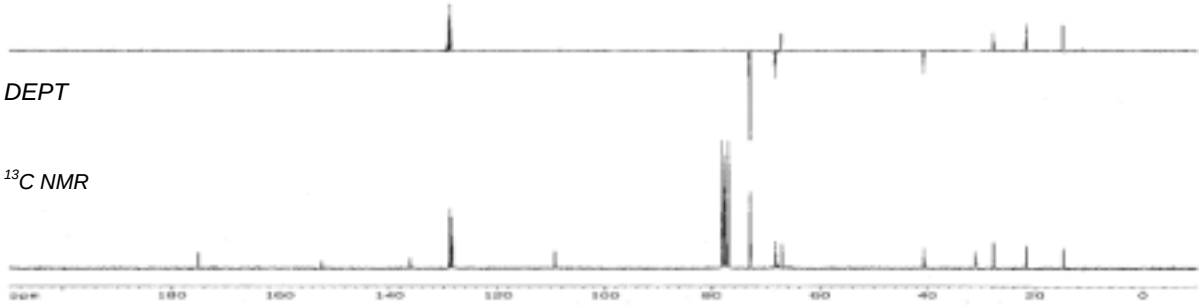


Figure 5.6-4 ^{13}C-NMR and DEPT spectra of **80**



^{13}C NMR ($CDCl_3$): δ = 14.72 (CH_3), ortho ester), 21.61 (CH_3, methyl), 27.66 (C-3), 31.04 ($\underline{C}CH_3(CH_2O\text{-})_3$), 40.51 (C-4), 67.22 (C-2), 68.36 (CH_2, benzyl), 73.04 (3 x CH_2O), 109.2 ($\underline{C}CH_3(OCH_2)_3$), 128.5, 128.6, 128.8, 129.0, 129.1, 136.0 (6 x C, aryl), 152.3 (C=O, urethane), 175.1 (C=O, lactam).

Figure 5.6-5 ^{1}H-NMR spectrum of **81**

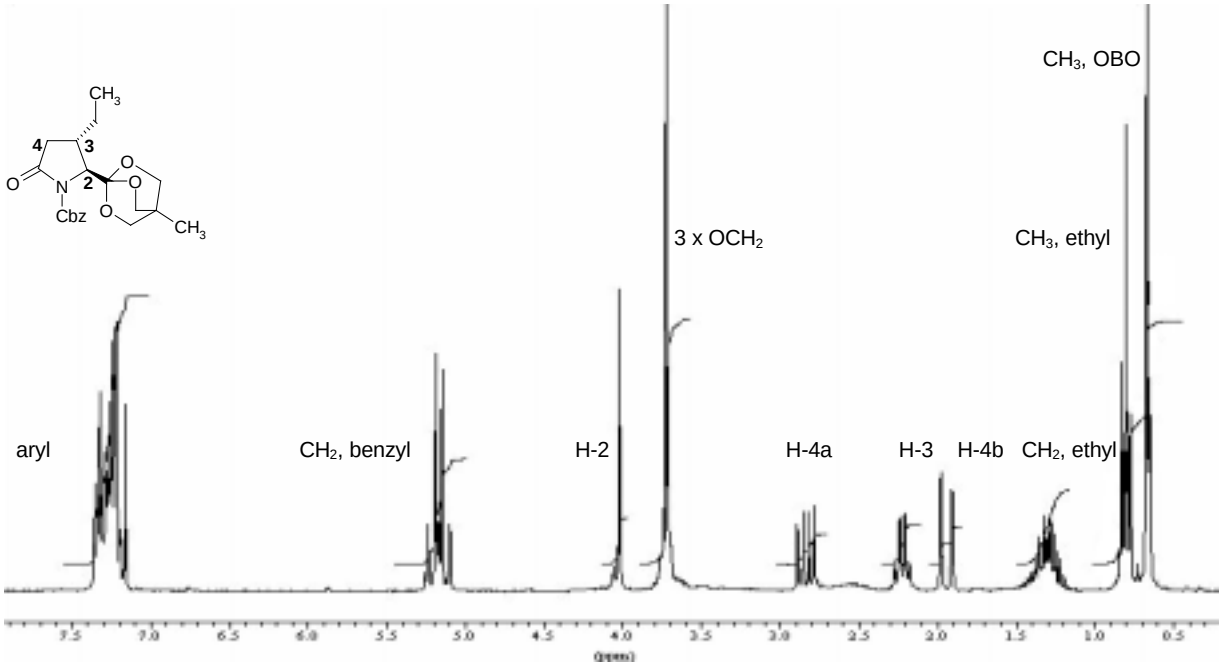


Figure 5.6-6 ^{1}H-NMR spectra of **81** (detail)

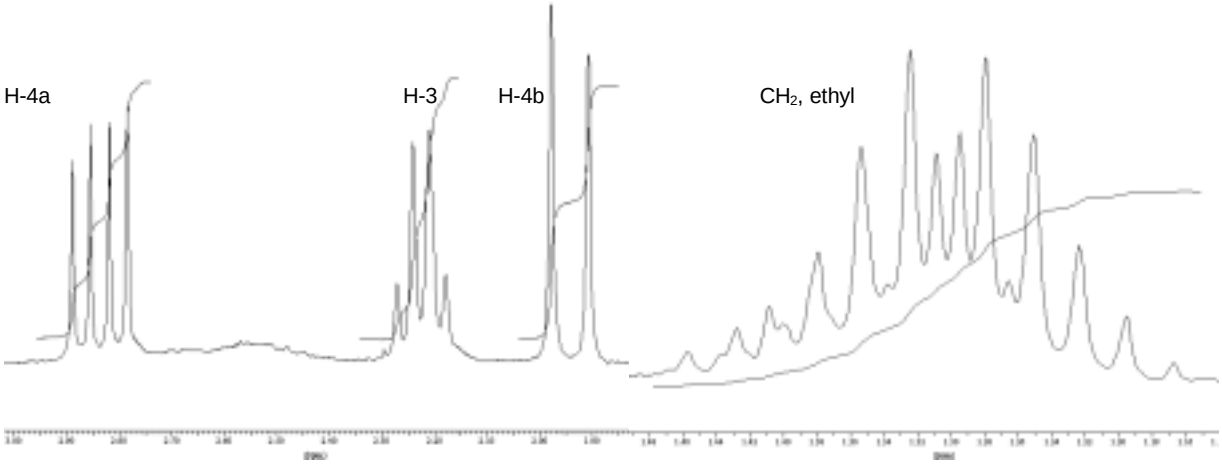
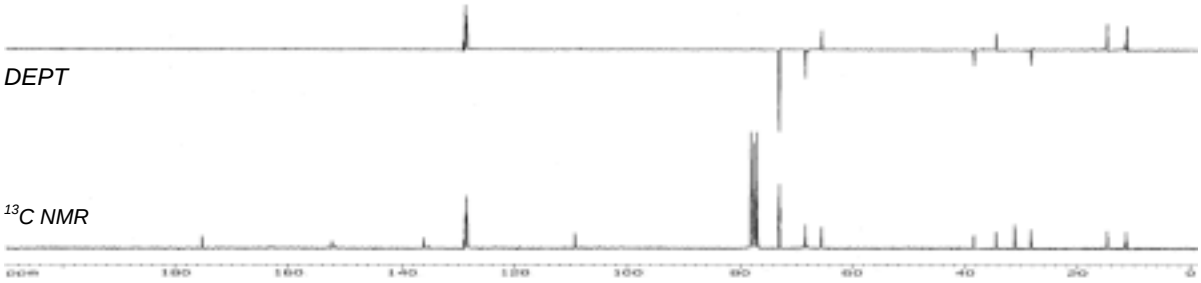


Figure 5.6-7 ^{13}C-NMR and DEPT spectra of **81**



^{13}C NMR ($CDCl_3$): δ = 11.42 (CH_3, ethyl), 14.74 (CH_3, ortho ester), 28.16 (CH_2, ethyl), 31.04 ($\underline{C}CH_3(CH_2O\text{-})_3$), 34.34 (C-3), 38.42 (C-4), 65.34 (C-2), 68.34 (CH_2, benzyl), 73.06 (3 x CH_2O), 109.3 ($\underline{C}CH_3(OCH_2)_3$), 128.4, 128.5, 128.6, 129.0, 136.1 (6 x C, aryl), 152.2 (C=O, urethane), 175.2 (C=O, lactam).

Figure 5.6-8 ^{1}H-NMR spectrum of **83**

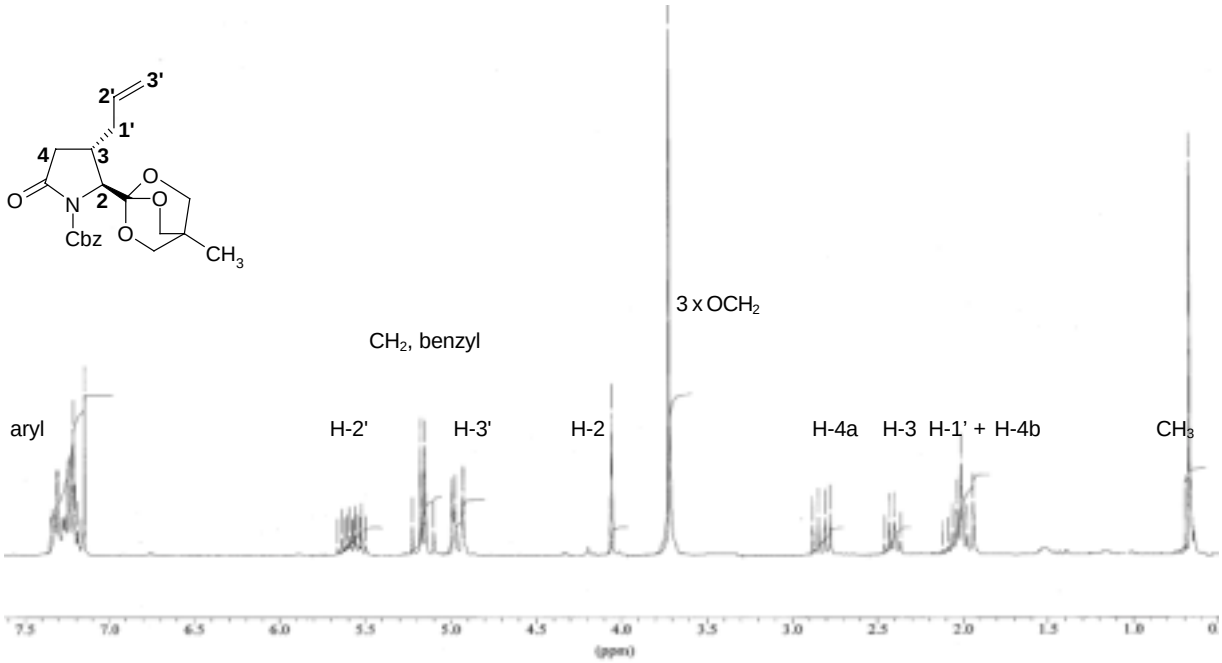


Figure 5.6-9 ^{1}H-NMR spectra of **83** (detail)

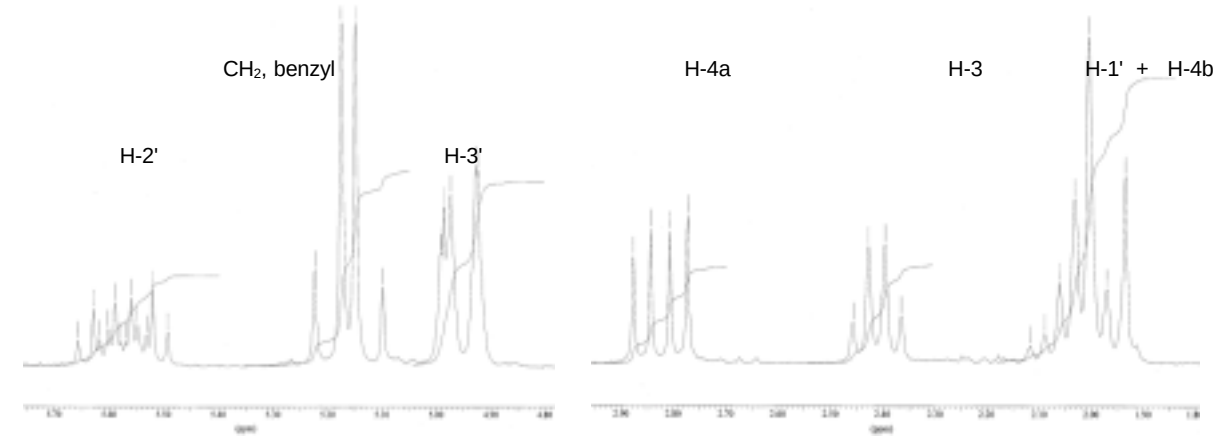
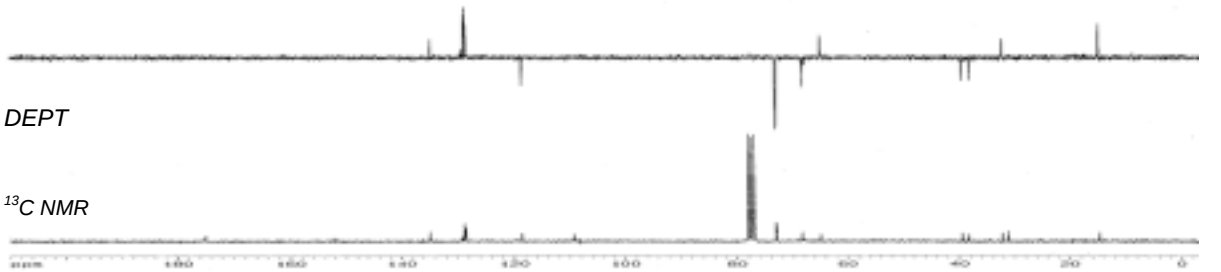


Figure 5.6-10 ^{13}C-NMR and DEPT spectra of **83**



^{13}C NMR ($CDCl_3$): δ = 14.73 (CH_3, ortho ester), 31.04 ($\underline{C}CH_3(CH_2O\text{-})_3$), 32.15 (C-3), 38.12 (C-4), 39.38 (C-1', allyl), 64.91 (C-2), 68.33 (CH_2, benzyl), 73.07 (3 x CH_2O), 109.3 ($\underline{C}CH_3(OCH_2)_3$), 118.6 (C-3', allyl), 128.5, 128.6, 128.8, 129.1 (6 x C, aryl), 134.8 (C-2', allyl), 152.0 (C=O, urethane), 175.0 (C=O, lactam).

Figure 5.6-11 ^{1}H-NMR spectrum of **84**

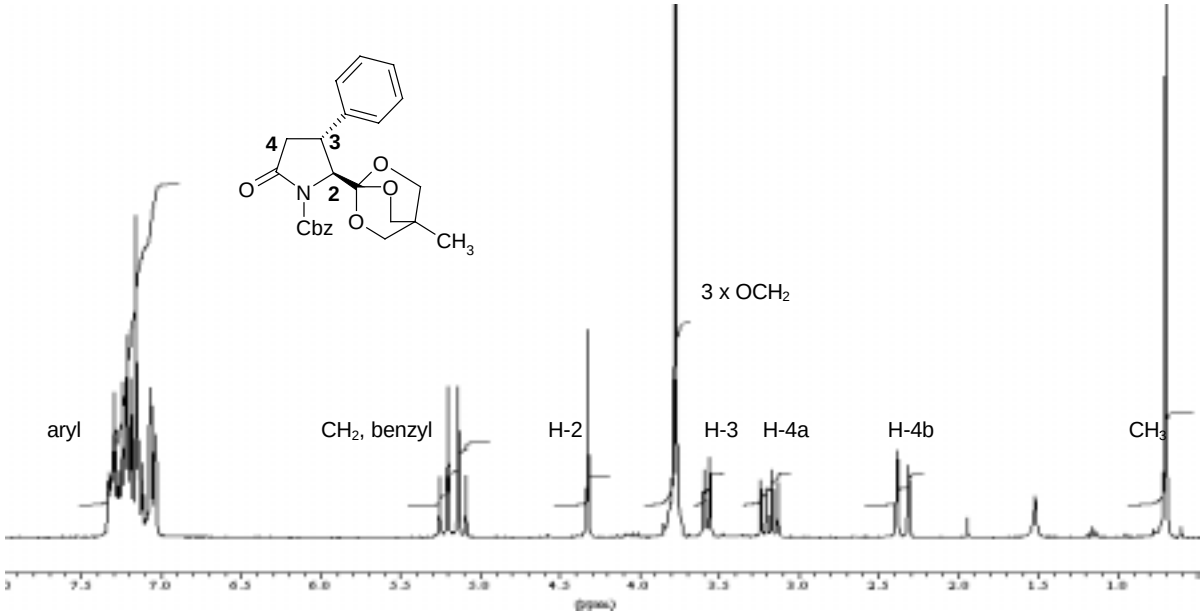


Figure 5.6-12 ^{1}H-NMR spectrum of **84** (detail)

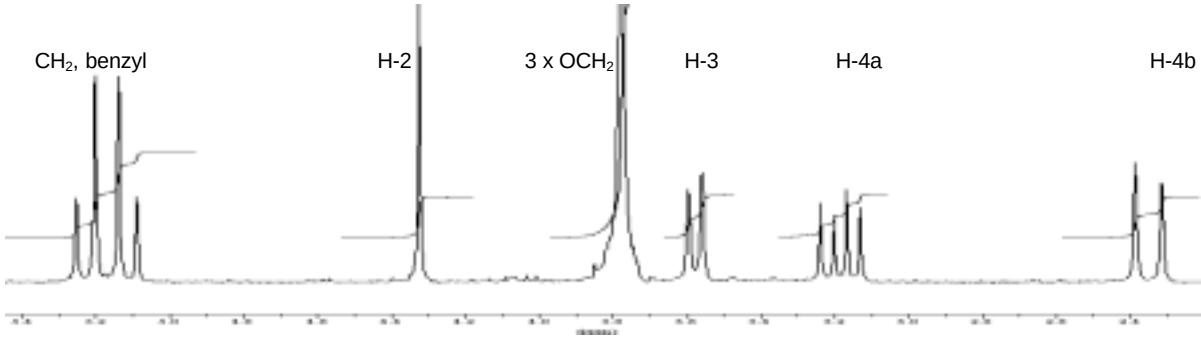
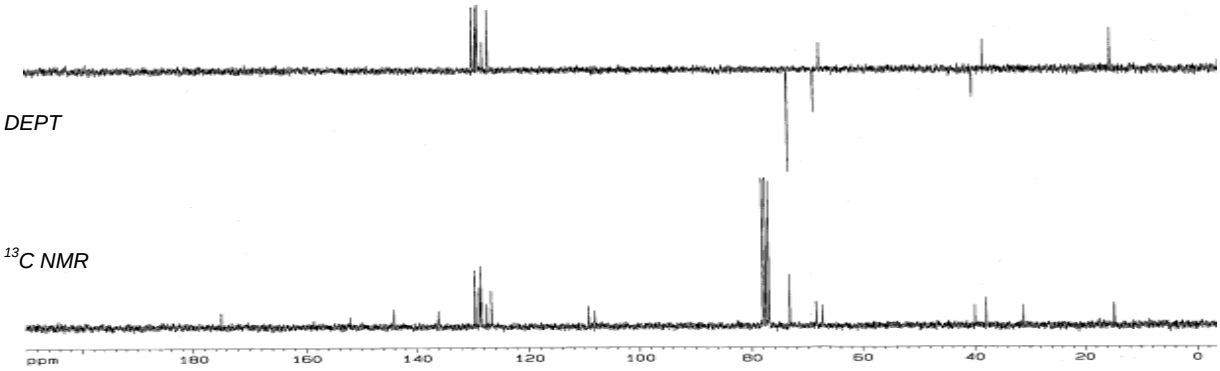


Figure 5.6-13 ^{13}C-NMR and DEPT spectra of **84**



^{13}C NMR ($CDCl_3$): δ = 14.74 (CH_3), 31.14 ($\underline{C}CH_3(CH_2O\text{-})_3$), 37.85 (C-3), 39.84 (C-4), 67.30 (C-2), 68.42 (CH_2, benzyl), 73.17 (3 x CH_2O), 109.2 ($\underline{C}CH_3(OCH_2)_3$), 126.7, 127.5, 128.5, 128.8, 129.4, 136.0, 144.1, (12 x C, aryl), 151.9 (C=O, urethane), 174.9 (C=O, lactam).

Figure 5.6-14 ^{1}H-NMR spectrum of **87**

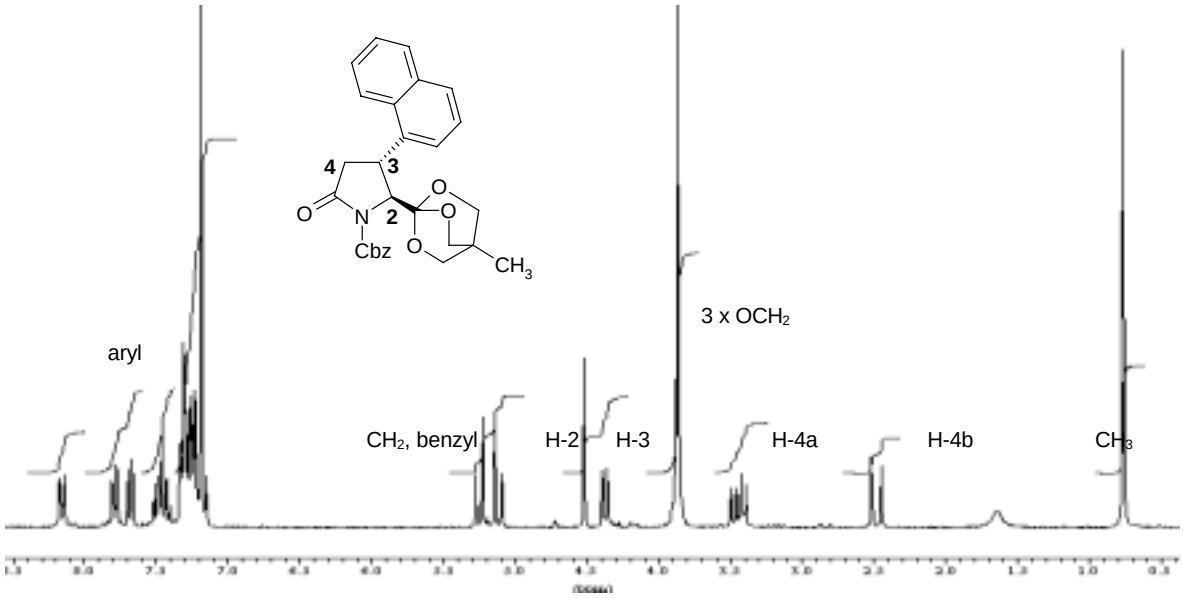


Figure 5.6-15 ^{1}H-NMR spectra of **87** (detail)

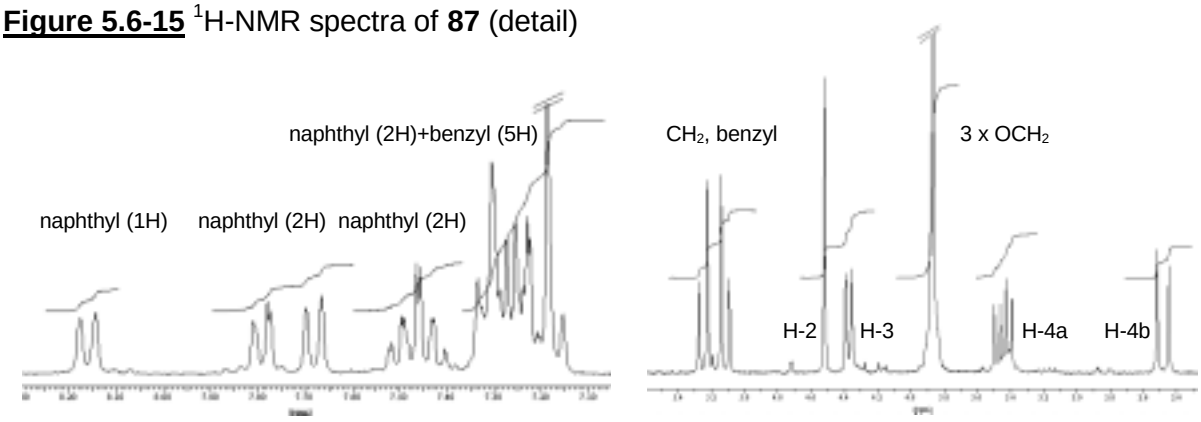
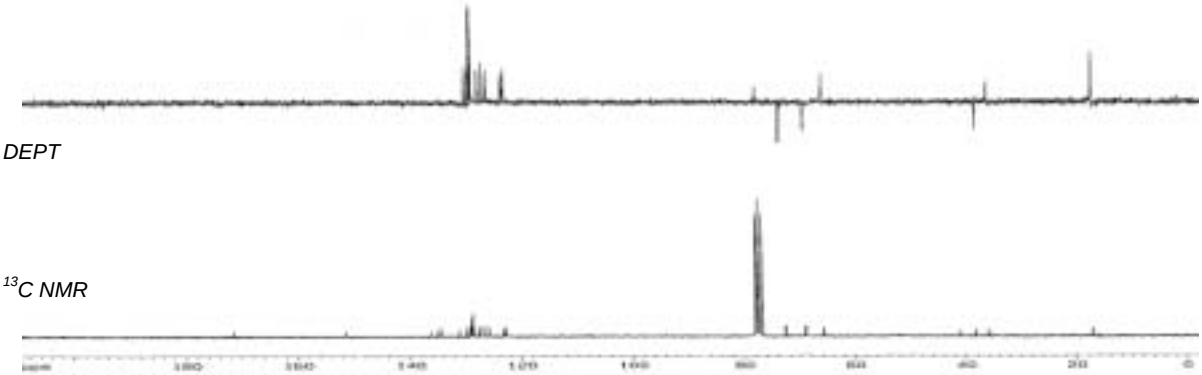


Figure 5.6-16 ^{13}C-NMR and DEPT spectra of **87**

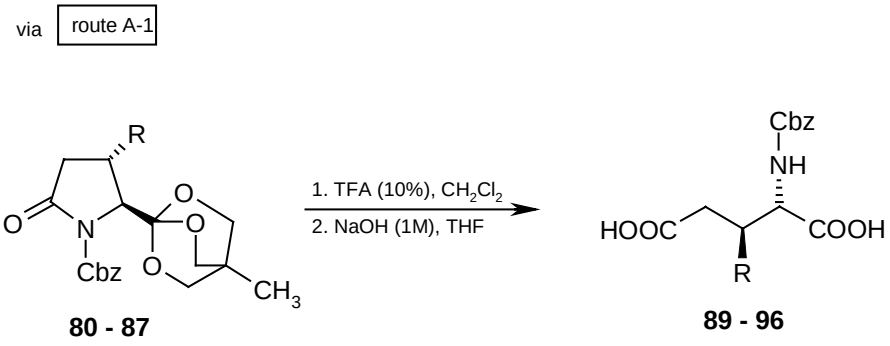


^{13}C NMR ($CDCl_3$): δ = 14.75 (CH_3), 31.12 ($\underline{C}CH_3(CH_2O\text{-})_3$), 35.98 (C-3), 38.12 (C-4), 65.80 (C-2), 68.70 (CH_2, benzyl), 73.24 (3 x CH_2O), 108.0 ($\underline{C}CH_3(OCH_2)_3$), 122.8, 123.2, 125.8, 126.7, 127.5, 128.6, 129.0, 129.2, 129.8, 131.1, 134.5, 135.1, 136.1 (16 x C, aryl), 151.6 (C=O, urethane), 171.5 (C=O, lactam).

5.7 CONVERSION OF COMPOUNDS 80-87 TO N-ACCEPTOR PROTECTED GLUTAMATES VIA ROUTE A-1

The deprotection of the compounds **80**-**87** via route A-1 was performed utilizing the methodology from Corey [69]. Therefore, the ortho ester protecting group was expected to undergo a ring opening reaction in the presence of aqueous TFA at room temperature. Normally, the following hydrolysis is carried out in aqueous caesium carbonate sol. (10%) to yield the corresponding N-Cbz pyroglutamates, but to save one step in the deprotection sequence, an aqueous sodium hydroxide sol. (1M) was employed. Hence, the hydrolysis of the ester and the ring opening reaction of the lactam was done at once [84,129]. Final acidic work-up procedure provided the N-protected glutamates **89**-**96** [see: Scheme 5.7-1].
However, the allyl derivative **92** was not available in this way, decomposition was observed [see: entry 4, Table 5.7-1].

Scheme 5.7-1



80 - 87 **89 - 96**

The naphthyl derivative **96** [see: entry 8, Table 5.7-1] was not available as a pure product. It is pointed out that **96** was contaminated with the unprotected glutamate **111** [see: enrty 6, Table 5.10-1]. Spectroscopic ^{1}H-NMR data approximately allowed the composition of this mixture (ratio **96**:**111** = 10:1). However, isolation of **96** by column chromatography as well as by extraction failed. Due to this issue, the mixture of **96** and **111** was employed in the further run of deprotection, to finally afford the glutamic acid derivative **111** [see: chapter 5.10].

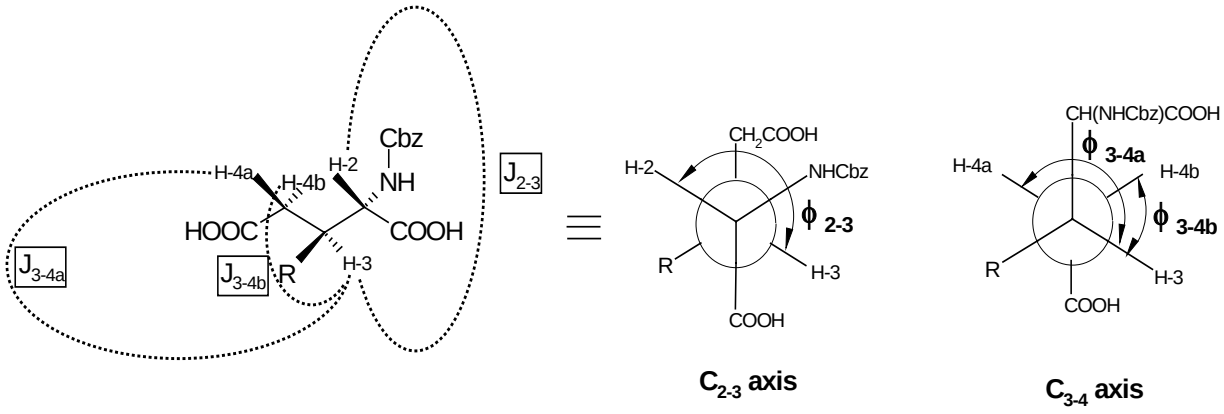
Table 5.7-1

entry	R	compound	yield (%)
1	methyl	**89**	75
2	ethyl	**90**	82
3	1-butyl	**91**	68
4	allyl	**92**	- [a]
5	phenyl	**93**	80
6	p-chlorophenyl	**94**	70
7	1-biphenyl	**95**	75
8	1-naphthyl	**96** [b]	75

[a] not available; [b] mixture

The structure determination of the N-Cbz derivatives [see: Table 5.7-2] has been made on the basis of ^{1}H-NMR as well as ^{13}C-NMR spectroscopy. The unambiguous assignment of the carbon atoms C-2, C-3 and C-4 utilizing ^{13}C-NMR and DEPT spectra, is therefore shown [see: Figure 5.7-4 for **89**, Figure 5.7-7 for **90**, and Figure 5.7-10 for **94**]. There is to be pointed out that these outlined spectra show one set of signals, namely those of the trans-substituted diastereomeres. The mild reaction conditions of the deprotection were supposed to maintain stereochemical integrity at the C-2 site, so that the observed products (**89**-**91** and **93**-**96**) possess expected trans substitution pattern between the hydrogen atoms H-2 and H-3.

Figure 5.7-1



This argument is confirmed by ^{1}H-NMR spectra, whereas the alkyl derivatives **89**-**91** [see: entries 1-3, Table 5.7-2] show overlapping signals of H-3, H-4a and H-4b, and additionally, coupling between H-3 and the alkyl moiety of the substituent **R** which leads to more complex coupling patterns [see: Table 5.7-3]. Hence, observation of the coupling constants J_{4a-3}, J_{4b-3} and J_{4a-4b} failed for alkyl derivatives, so that their structure has proved by mentioned ^{13}C-NMR and DEPT spectra. There can be drawn the conclusion from observed coupling constants of the aryl derivatives **93**-**95** [see: entries 5-7, Table 5.7-2] that the alkyl derivatives **89**-**91** are also trans-configurated.

Table 5.7-2

entry	R	compound	coupling constants [Hz]					for spectrum see:
			J_{2-3}	J_{4a-3}	J_{4b-3}	J_{4a-4b}	J_{NH-2}	
1	methyl [a)]	**89**	4.9	-[c)]	-[c)]	-[c)]	8.2	Figure 5.7-2
2	ethyl [a)]	**90**	3.0	-[c)]	-[c)]	-[c)]	8.5	Figure 5.7-5
3	1-butyl [a)]	**91**	-[c)]	-[c)]	-[c)]	-[c)]	8.6	-
5	phenyl [a)]	**93**	7.3	4.0	11.3	16.3	8.5	-
6	p-chlorophenyl [a)]	**94**	7.3	3.7[d)]	11.6	16.5	8.6	Figure 5.7-8
7	1-biphenyl [b)]	**95**	7.0	9.2	9.2	-[c)]	-[c)]	-

[a)] solvent: DMSO-d_6; [b)] CD_3OD; [c)] overlapping signals; [d)] partially overlapping signals.

The observed ^{1}H-NMR spectra of the 3-aryl substituted compounds **93**-**95** [see: entries 5-7, Table 5.7-2] allow unambiguous assignment of the hydrogen atoms (H-2, H-3 and H-4a/b) and their coupling constants (J_{2-3}, J_{4a-3} and J_{4a-3}). The Newman projections [see: Figure 5.7-1] along the axis of the carbons C-2/C-3 (C_{2-3} axis), and C-3/C-4 (C_{3-4} axis) give explanation for observed coupling constants. For this purpose, the torsion angles φ_{x-y} are approximated according to the Karplus curve. It is pointed out that corresponding coupling constants depend on employed solvents (here: DMSO-d_6 and CD_3OD, resp.), the pH value, and on the resulting equilibrium of rotameres. The conformation of the non-constrained compounds **89**-**95** is influenced by protonation or deprotonation. So DMSO-d_6 was used as a solvent to observe the coupling constants in a non-aqueous dipolar solvent [compare: chapter 5.10]. In this case the coupling between H-2 and N-H ($J_{NH-2} \approx 8.4$ Hz) is in accordance with references.

The bulky **R**-aryl moiety of these conformationally non-constrained aryl compounds (**93**–**95**) forces the hydrogen atoms H-2 and H-3 to form an torsion angle $\varphi_{2\text{-}3} \approx 140°$, which corresponds $J_{2\text{-}3} \approx 7$ Hz. Instead, the less bulky **R**-alkyl moiety of alkyl derivatives **89**–**91** results in $\varphi_{2\text{-}3} \approx 130°$, which corresponds $J_{2\text{-}3} \approx 4$ Hz. Hence, it is recorded the fact that the moiety (**R**) mainly influences the conformation of the observed compounds, i.e. the bulkiness of **R** plays a major role for the resulting torsion angle $\varphi_{2\text{-}3}$ along the $C_{2\text{-}3}$ axis. The torsion angles $\varphi_{4a\text{-}3} \approx 150°$ (accords to $J_{4a\text{-}3} \approx 12$ Hz) and $\varphi_{4b\text{-}3} \approx 30°$ (accords to $J_{4b\text{-}3} \approx 4$ Hz) show expected values for *anti* and *gauche* conformation of these hydrogens, respectively (see: $C_{3\text{-}4}$ axis, Figure 5.7-1). Hence, the *anti*-positioned hydrogens H-4a/H-3 exhibit characteristic coupling constants ($0 < J_{anti} < 5$ Hz), whereas the *gauche*-positioned hydrogens H-4b/H-3 show a different coupling constant ($8 < J_{gauche} < 15$ Hz).

Table 5.7-3

entry	R	compound	coupling constants [Hz]		for spectrum see:
			$J_{3\text{-}CH3}$		
1	methyl	**89**	6.1		Figure 5.7-3
			$J_{3\text{-}CH2}$	$J_{CH2\text{-}CH3}$	
2	ethyl	**90**	~6.7	7.0	Figure 5.7-6
			$J_{3\text{-}CH2}$	$J_{CH2\text{-}CH3}$	
3	1-butyl	**91**	-[a)]	-[a)]	-

[a)] overlapping signals

The inspection of ^{13}C-NMR and DEPT spectra for all prepared compounds (**89**-**91** and **93**-**96**) show one set of signals, i.e. one diastereomere. The assignment of the expected trans-substituted diastereomeres is unambiguously confirmed by spectroscopic ^{1}H-NMR data (coupling constants) for the aryl derivatives **93**-**96**. Despite of lack of specific coupling constants for the alkyl compounds **89**-**91** there is to be drawn the conclusion from observed data of **93**-**96** that the alkyl derivatives also are trans-substituted, i.e. they possess (2S,3S)-configuration.

Figure 5.7-2 ^{1}H-NMR spectrum of **89**

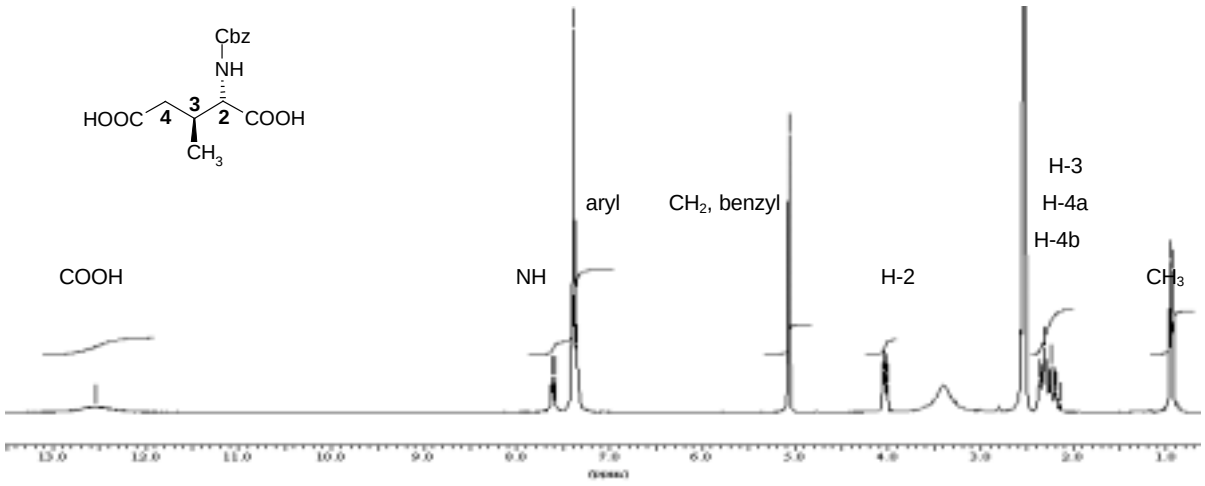


Figure 5.7-3 ^{1}H-NMR spectrum of **89** (detail)

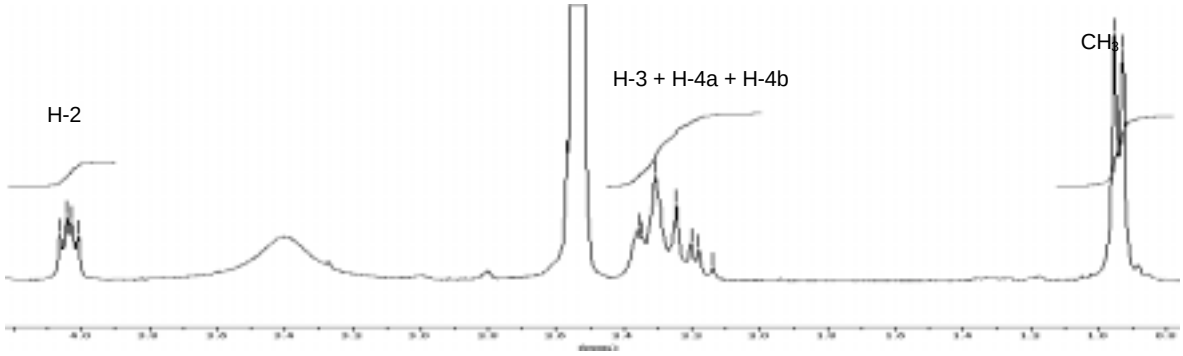
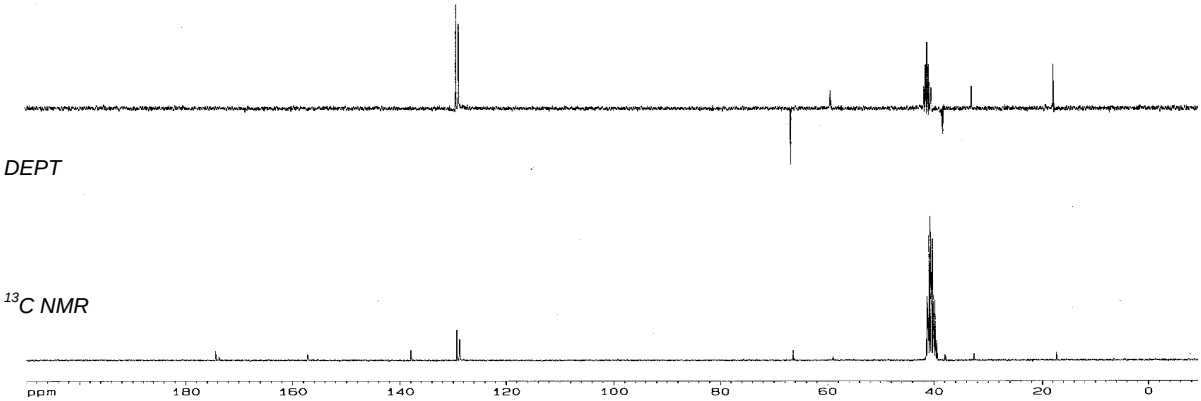


Figure 5.7-4 ^{13}C-NMR and DEPT spectra of **89**



^{13}C NMR (DMSO-d_6): δ = 17.18 (CH_3, methyl), 32.42 (C-3), 37.84 (C-4), 58.96 (C-2), 66.36 (benzyl), 128.6, 128.7, 129.2, 137.8 (6 x C, aryl), 157.2 (urethane), 173.7, 174.3 (2 x COOH, carboxylate).

Figure 5.7-5 ^{1}H-NMR spectrum of **90**

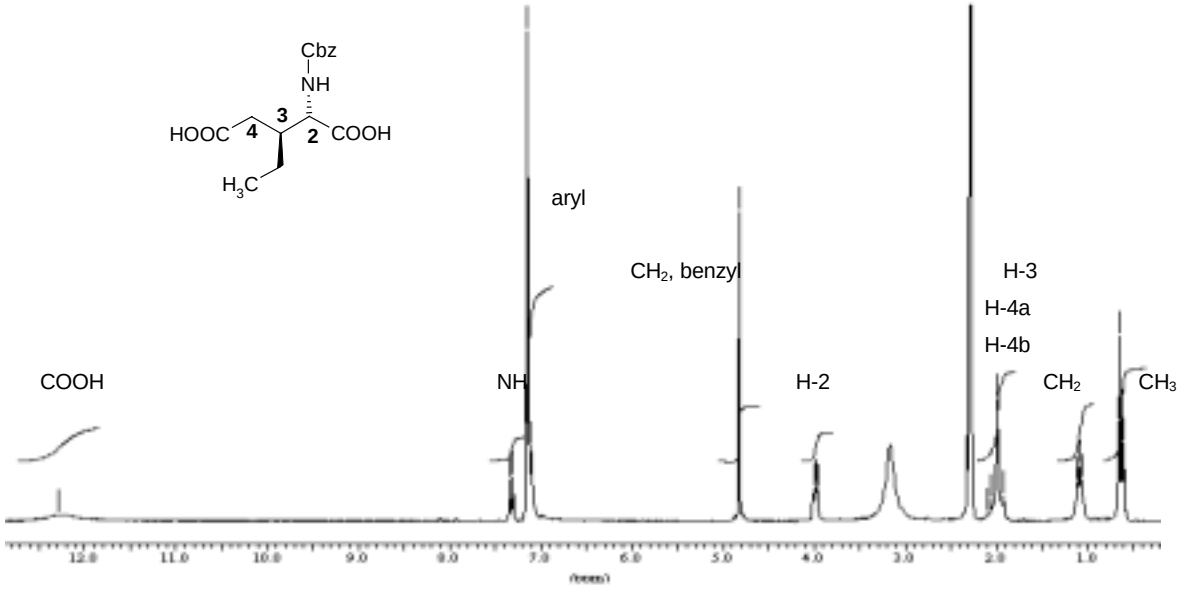


Figure 5.7-6 ^{1}H-NMR spectrum of **90** (detail)

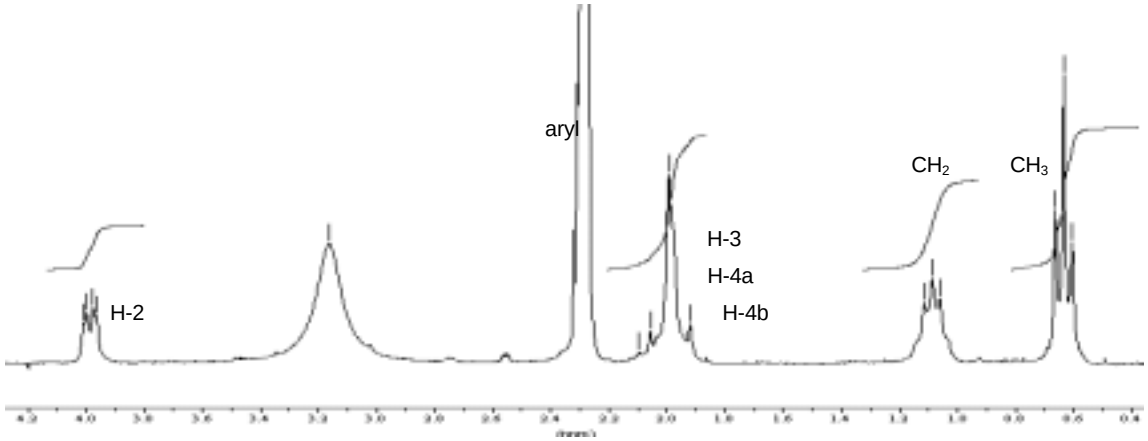
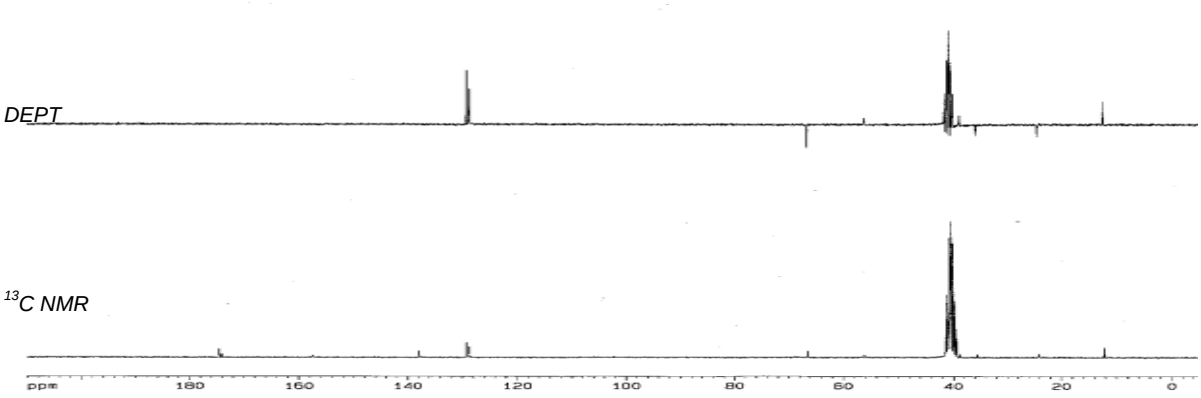


Figure 5.7-7 ^{13}C-NMR and DEPT spectra of **90**



^{13}C NMR (DMSO-d_6): δ = 12.17 (CH_3, ethyl), 24.11 (CH_2, ethyl), 35.58 (C-4), 38.78 (C-3), 56.09 (C-2), 66.39 (benzyl), 128.6, 128.7, 129.2, 137.8 (6 x C, aryl), 157.4 (urethane), 174.2, 174.6 (2 x COOH, carboxylate).

Figure 5.7-8 ^{1}H-NMR spectrum of **94**

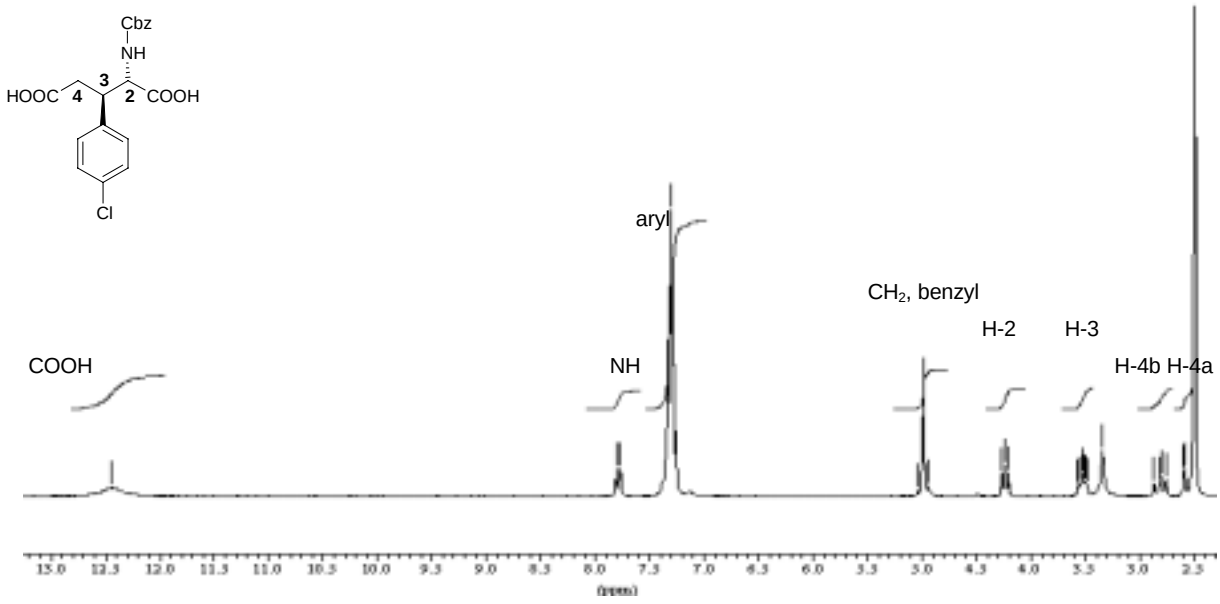


Figure 5.7-9 ^{1}H-NMR spectrum of **94** (detail)

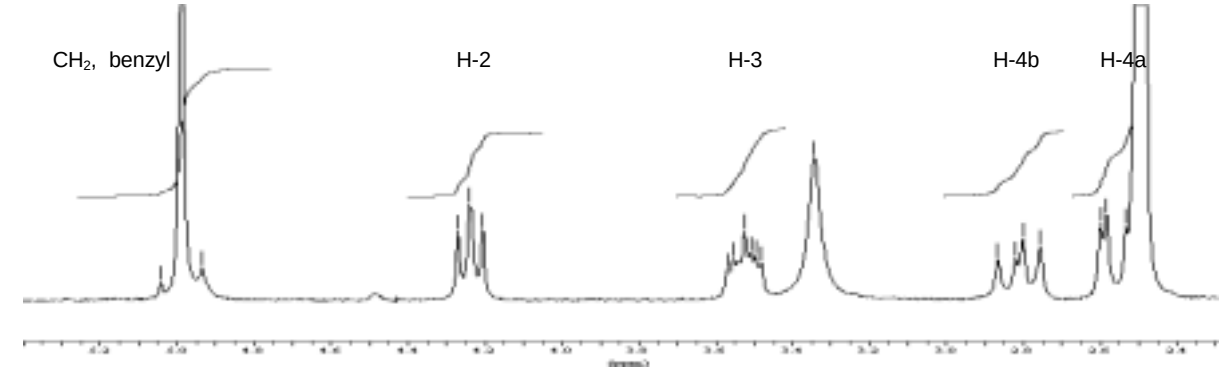
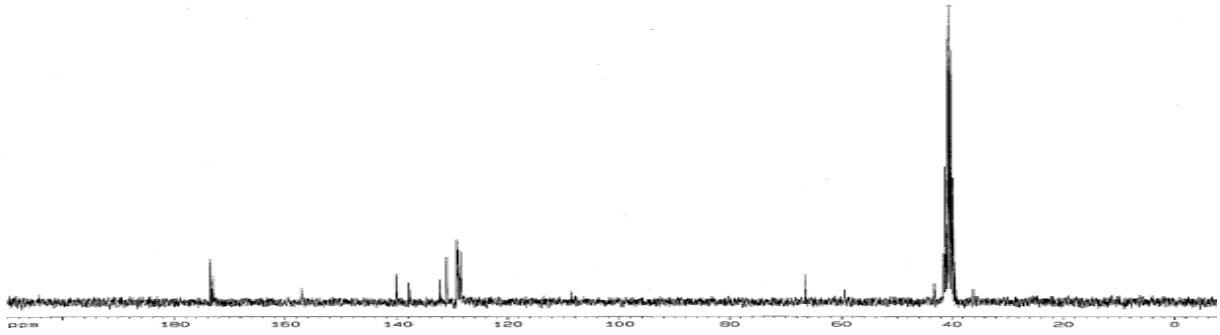


Figure 5.7-10 ^{13}C-NMR spectrum of **94**

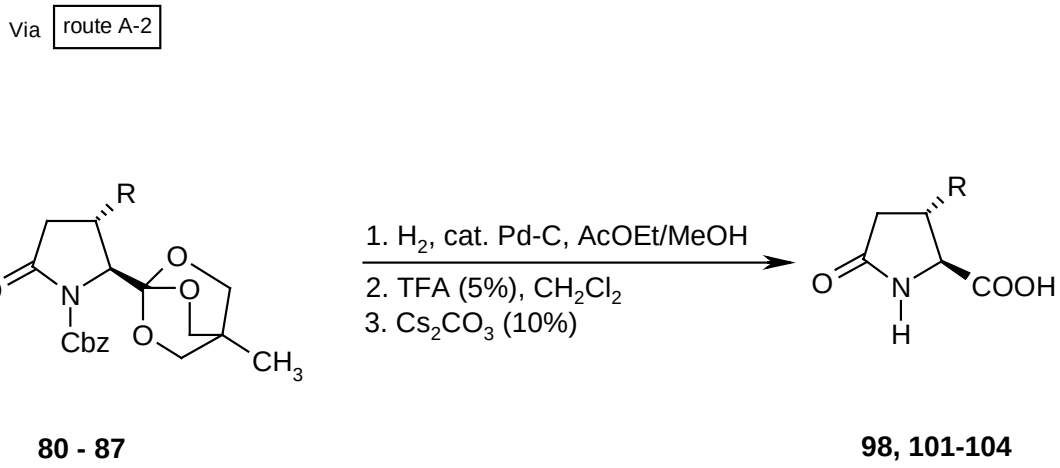


^{13}C NMR (DMSO-d_6): δ = 36.06 (C-4), 43.17 (C-3), 59.46 (C-2), 66.33 (benzyl), 128.4, 128.6, 128.9, 129.2, 131.0, 132.3, 137.8 140.1, (12 x C, aryl), 157.0 (urethane), 173.0, 173.4 (2 x COOH, carboxylate).

5.8 CONVERSION OF COMPOUNDS 80-87 TO PYROGLUTAMATES VIA ROUTE A-2

According to the plan of synthesis the conversion of **80**-**87** to the corresponding 3-substituted pyroglutamates was envisaged to be accomplished via route A-2 [see: Scheme 4.1-1]. The first alternative for deprotection suggests the removal of the ortho ester group [69] and following cleavage of the Cbz residue. Instead, the second alternative runs vice versa. Hence, both alternatives were tested, whereas exclusively the second alternative succeeded. It is to be pointed out that the 3-aryl substituted derivatives **101**-**104** did not undergo hydrolysis to the corresponding N-Cbz pyroglutamic acids. This issue will be demonstrated on the basis of compound **85** [see chapter 5.13].

Scheme 5.8-1



80 - 87 **98, 101-104**

Therefore, general procedure for the preparation of the 3-substituted pyroglutamates **98**, **101**-**104** [see: Scheme 5.8-1] was found by the hydrogenation in the presence of a catalytic amount of palladium on charcoal. Then, the intermediates (i.e. N-deprotected ortho ester pyroglutamtes) successively were treated with aq. trifluoro acetic acid (5%)/dichloromethane and caesium carbonate solution (10%) to finally give the pyroglutamic acid derivatives **98**, **101**-**104** [see: Table 5.8-1]. However, the preparation of **97** and **99** failed. The allyl derivative **100** was not available due to the hydrogenation. The undesired 3-propyl pyroglutamate was

isolated. Due to the loss of the allylic functionality, the 3-propyl substituted derivative was not regarded anymore.

Table 5.8-1

entry	R	compound	yield (%)
1	methyl	**97**	- [a)]
2	ethyl	**98**	65
3	1-butyl	**99**	- [a)]
4	allyl	**100**	- [a)]
5	phenyl	**101**	70
6	p-chlorophenyl	**102**	65
7	1-biphenyl	**103**	- [b)]
8	1-naphthyl	**104**	58

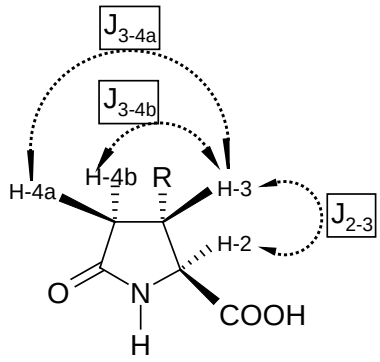
[a)] not available; [b)] not listed.

The structure determination of the pyroglutamic acid derivatives [see:Table 5.8-1] has been made on the basis of ^{1}H-NMR as well as ^{13}C-NMR spectroscopy. These conformationally constrained analogues of the 3-substituted glutamates allow unambiguous assignment of the carbon atoms (C-2, C-3 and C-4) utilizing the ^{13}C-NMR and DEPT spectra for **98** [see: Figure 5.8-3], and utilizing ^{13}C-NMR spectra for **102** [see: Figure 5.8-6] and **104** [see: Figure 5.8-9], respectively. However, the signal of C-4 of the naphthyl compound **104** partially overlaps with the signal of DMSO-d_6. There is to be pointed out that these outlined spectra exceptionally show one set of signals, namely the expected trans-substituted diastereomeres. Due to the mild reaction conditions of deprotection, the stereochemical integrity at the sites of C-2 and C-3 is supposed to be maintained, so that observed products (**98**, **101**-**104**) possess the expected trans substitution pattern between the hydrogen atoms H-2 and H-3.

This argument is confirmed by ^{1}H-NMR spectroscopy and the inspection of the coupling constants of the hydrogens H-2, H-3, H-4a, and H-4b [see: Figure 5.8-1]. The assignment of the observed signals for the expected (2S,3S)-3-ethyl derivative **98** [see: entry 2, Table 5.8-2] can be done unambiguously [see: Figure 5.8-2]. The hydrogen atoms H-2, H-3, H-4a and H-4b are therefore assigned, whereas the signals of H-3 and H-4a partially overlap.

Additionally, coupling between H-3 and the alkyl moiety of the substituent **R** (ethyl) leads to more complex coupling patterns [see: Figure 5.8-2]. The diastereotopic methylen protons (H-a_{ethyl} and H-b_{ethyl}) of the alkyl moiety give splitted multiplets with the observed coupling constants $Ja_{ethyl-3}$, $Jb_{ethyl-3}$, J_{CH3}-a_{ethyl}, and J_{CH3}-b_{ethyl} [see: Table 5.8-3]. The corresponding coupling constants (J_{2-3}, J_{4a-3}, J_{4b-3} and J_{4a-4b}) of **98** [see: entry 1, Table 5.8-2] are very close to reported ones of the (2S,3S) 3-methyl pyroglutamate, which therefore serves as structural analogue of compound **98** [31,52,54,62a]. It is outlined that J_{2-3} of the trans-configurated hydrogen atoms H-2 and H-3 range between 5.0 and 6.3 Hz ($5.0 < J_{2-3} < 6.3$ Hz), instead the hydrogens of the the cis-configurated diastereomeric (2S,3**R**) 3-methyl derivative significantly show a different coupling constant of $J_{2-3} \approx 8.0$ Hz. The published constants J_{4a-3} of the cis-configurated hydrogens H-4a and H-3 range about 8.5 Hz ($J_{4a-3} \approx 8.5$ Hz), whereas corresponding J_{4b-3} is about 5.0 Hz. The diastereomeric (2S,3**R**) 3-methyl derivative is reported to exhibit $J_{4a-3} \approx 7.0$ Hz (for cis-configurated H-4a and H-3), and $J_{4b-3} \approx 8.5$ Hz (for trans-configurated H-4b and H-3). According to reported and observed data there can be drawn the firm conclusion that the alkyl derivative **98** is trans-configurated, i.e. possesses the expected (2S,3S)-configuration.

Figure 5.8-1



The C-3-substituted aryl derivatives **101**–**104** are supposed to possess the expected (2S,3R)-configuration (i.e. trans configuration). Hence, the hydrogens H-2, H-3, H-4a, and H-4b are assigned utilizing the corresponding ^{1}H-NMR spectra [see: Figure 5.8-4 for **102**, and Figure 5.8-7 for **104**]. The observed coupling constants of **101** and **102** [see: entries 5 and 6, Table 5.8-2] are very close to reported ones for the trans-configurated (2S,3R) 3-phenyl pyroglutamate [54,61b]. It is outlined that J_{2-3} for the expected trans-configurated hydrogens H-2 and H-3 range between 5.0 and 5.5 Hz ($5.0 < J_{2-3} < 5.5$ Hz), whereas the cis-configurated hydrogens of the diastereomeric (2S,3**S**) 3-phenyl derivative significantly show

a different coupling constant of $J_{2\text{-}3} \approx 8.0$ Hz. The reported constants $J_{4a\text{-}3}$ of the cis-configurated hydrogens H-4a and H-3 range about 9.0 Hz, whereas the corresponding $J_{4b\text{-}3}$ is about 6.3–7.0 Hz. Instead, the (2S,3**S**) 3-phenyl derivative is reported to exhibit $J_{4a\text{-}3} \approx J_{4b\text{-}3} \approx$ 8.0 Hz (for cis-configurated H-4a and H-3 and trans-configurated H-4b and H-3). According to published and observed NMR-data there can be drawn the conclusion that the aryl derivatives **101** and **102** are trans-configurated, i.e. possess expected (2S,3S)-configuration.

Table 5.8-2

entry	R	compound	coupling constants [Hz]				for spectrum see:
			$J_{2\text{-}3}$	$J_{4a\text{-}3}$	$J_{4b\text{-}3}$	$J_{4a\text{-}4b}$	
2	ethyl	**98**	4.0	8.5	4.7	16.2	Figure 5.8-2
5	phenyl	**101**	5.6	9.2	6.7	16.8	-
6	p-chlorophenyl	**102**	6.1	9.2	7.1	16.8	Figure 5.8-4
8	naphthyl	**104**	3.4	6.7	4.3	16.8	Figure 5.8-7

solvent: DMSO-d_6

An explanation for the different coupling constants ($J_{2\text{-}3}$, $J_{4a\text{-}3}$, and $J_{4b\text{-}3}$) of compound **104** [see: entry 8, Table 5.8-2] can be given by the influence of the aryl substituent. On the one hand, the bulkiness of the naphthyl moiety forces the hydrogen atom H-3 to a different torsion angle $\varphi_{x\text{-}y}$ ($\varphi_{2\text{-}3}$ along $C_{2\text{-}3}$ axis, and $\varphi_{3\text{-}4a}/\varphi_{3\text{-}4a}$ along $C_{3\text{-}4}$ axis) in comparison with those of **101** and **102**. In other words: the naphthyl ring forces the pyrrolidone-ring in a different conformation. On the other hand, the electron negativity of the substituent **R** plays a major role for the value of the coupling constants $J_{x\text{-}y}$. It is known that an increasing electron withdrawal activity of the substituent **R** decreases the value of the corresponding coupling constants $J_{x\text{-}y}$. The naphthyl moiety of **104** exhibits an insignificant different electron withdrawal activity in comparison with the monocyclic aryl substituents of **101** and **102**. Hence, this effect can be disregarded. The decreased values of the coupling constants of compound **104** mainly depend on the sterical effect of the naphthyl moiety.

Obviously, observed spectroscopic data on the basis of ^{1}H-NMR, ^{13}C-NMR, and DEPT spectra, allow to drawn the firm conclusion that the alkyl derivative **98**, and the aryl derivatives **101**-**104** are trans-configurated.

Figure 5.8-2 ^{1}H-NMR spectra of **98** (details)

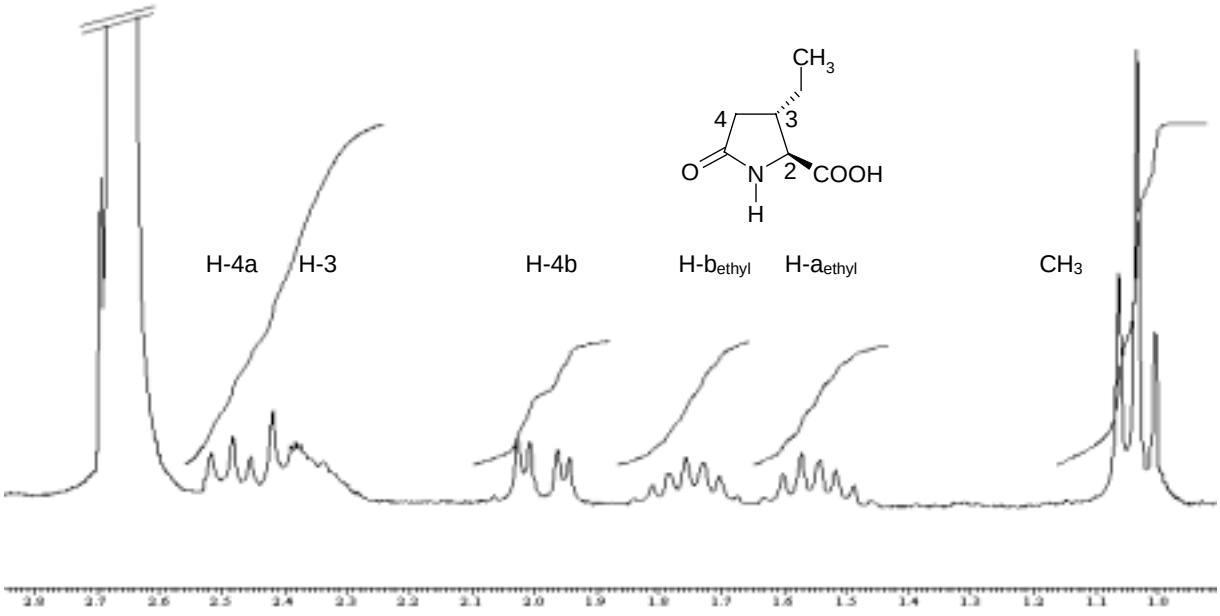


Table 5.8-3

x-H – y-H	J_{x-y} [Hz]
a_{ethyl} - 3	6.1
b_{ethyl} - 3	6.1
CH_3 - a_{ethyl}	7.3
CH_3 - b_{ethyl}	7.3

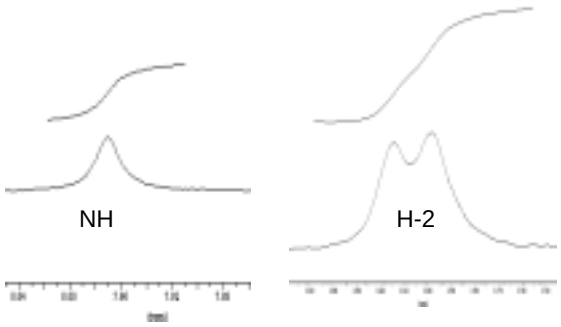
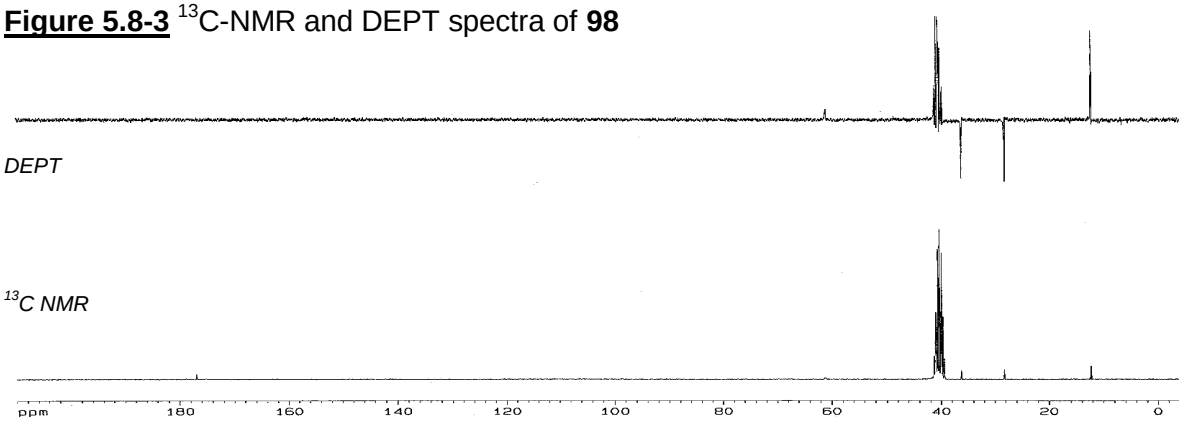


Figure 5.8-3 ^{13}C-NMR and DEPT spectra of **98**



^{13}C NMR (DMSO-d_6): δ = 12.30 (CH_3), 28.24 (CH_2), 36.28 (C-3), 40.96 (C-4), 61.17 (C-2), 176.8 (C=O, lactam), 176.9 (COOH, carboxylate).

Figure 5.8-4 ^{1}H-NMR spectrum of **102**

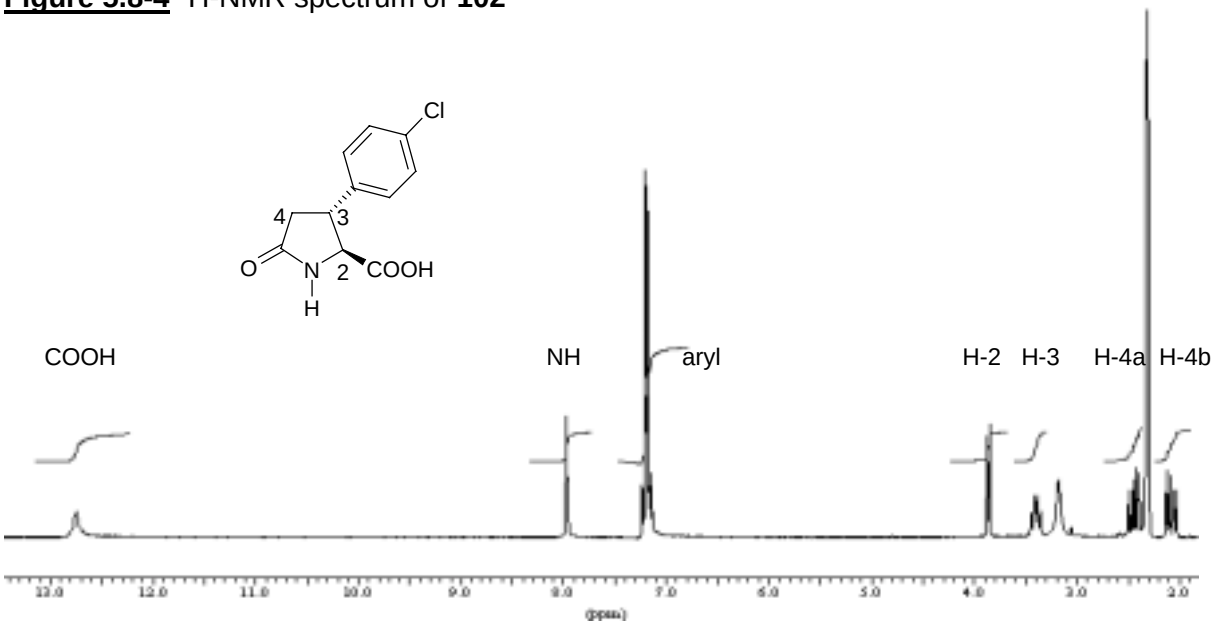


Figure 5.8-5 ^{1}H-NMR spectrum of **102** (detail)

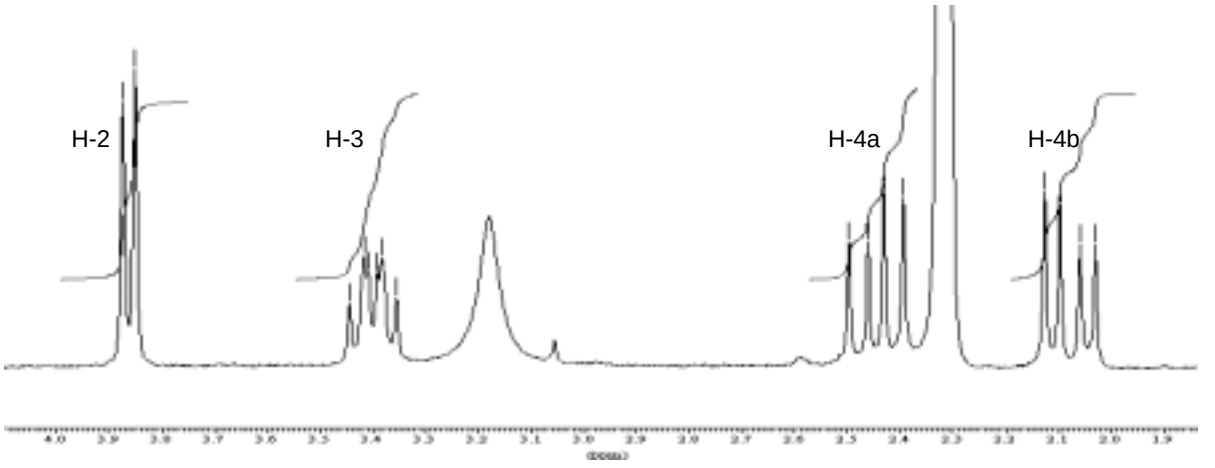
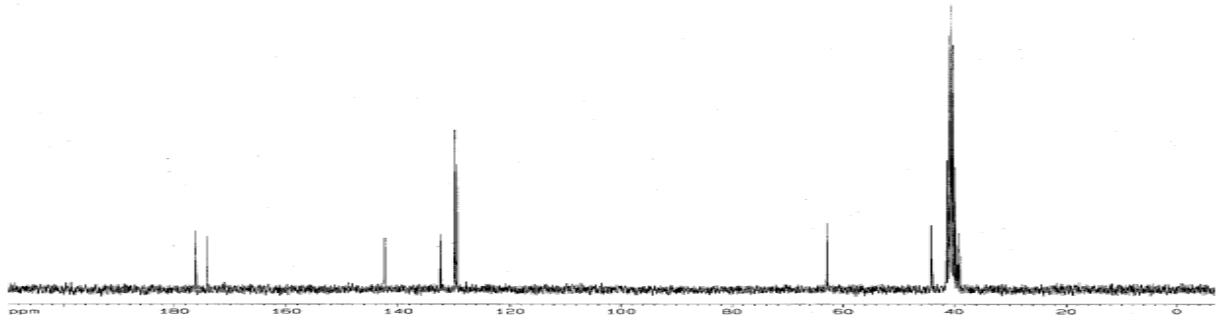


Figure 5.8-6 ^{13}C-NMR spectrum of **102**



^{13}C NMR (DMSO-d_6): δ = 38.91 (C-3), 44.00 (C-4), 62.92 (C-2), 129.4, 129.9, 132.4, 142.3, (6 x C, aryl), 174.0 (COOH, carboxylate), 176.1 (C=O, lactam).

Figure 5.8-7 ^{1}H-NMR spectrum of **104**

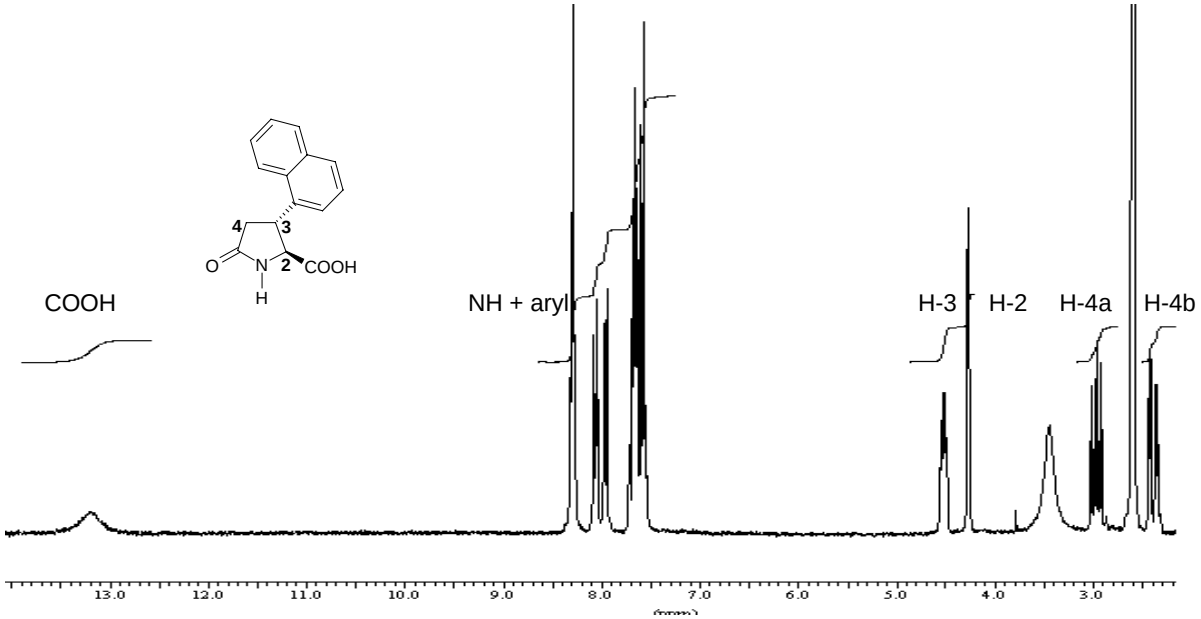


Figure 5.8-8 ^{1}H-NMR spectrum of **104** (detail)

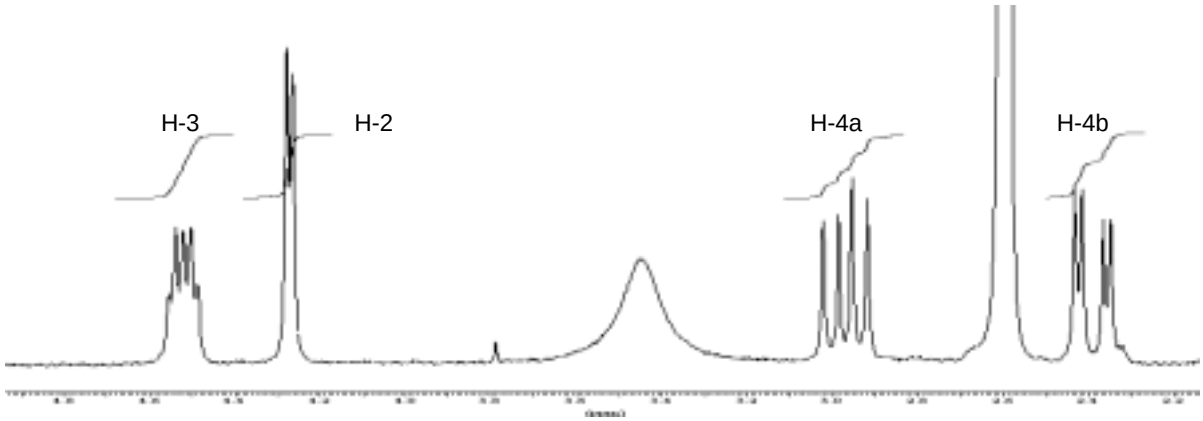
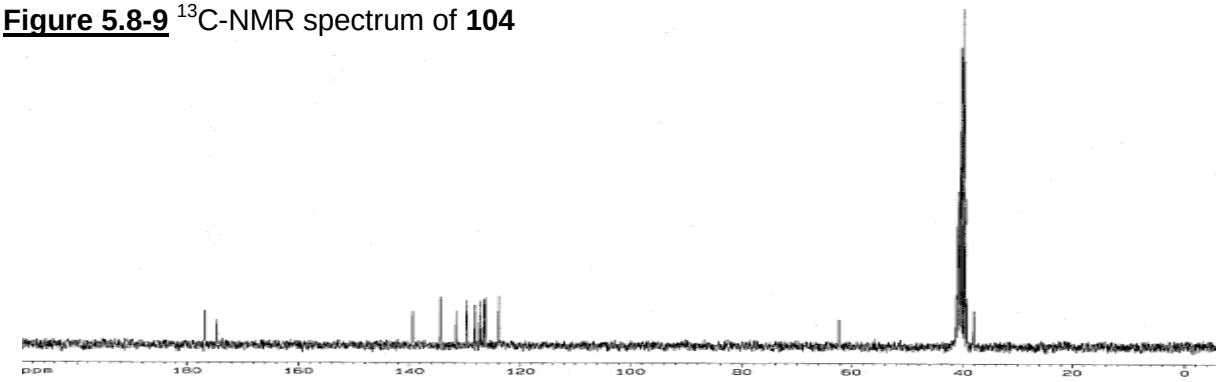


Figure 5.8-9 ^{13}C-NMR spectrum of **104**

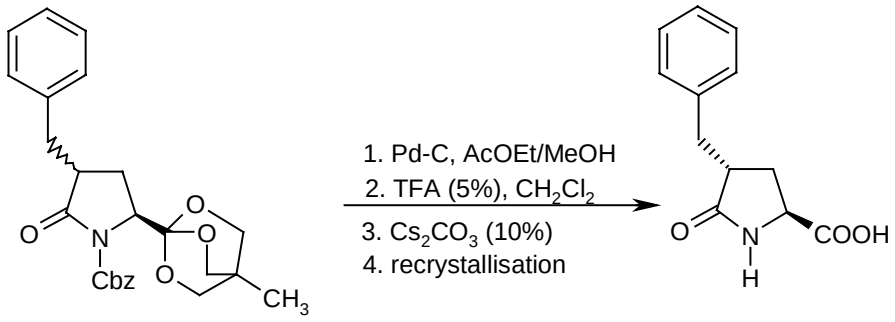


^{13}C NMR (DMSO-d_6): δ = 38.11 (C-3), ~ 40 (C-4, overlapping signal with DMSO-d_6), 62.35 (C-2), 123.9, 124.0, 126.5, 126.7, 127.4, 128.3, 129.8, 131.6, 134.5, 139.4 (10 x C, aryl), 174.6 (COOH, carboxylate), 176.8 (C=O, lactam).

5.9 CONVERSION OF 71 TO THE PYROGLUTAMATE 105

The mixture of the 4-benzyl substituted derivatives cis-**71**/trans-**71** [see: entry 2, Table 5.4-1] was supposed to be deprotected to the corresponding pyroglutamate **105** [see: Scheme 5.9-1]. Hence, this mixture was treated according to the described procedure in chapter 5.8. Careful recrystallization yielded **105** as diastereomerically pure compound.

Scheme 5.9-1

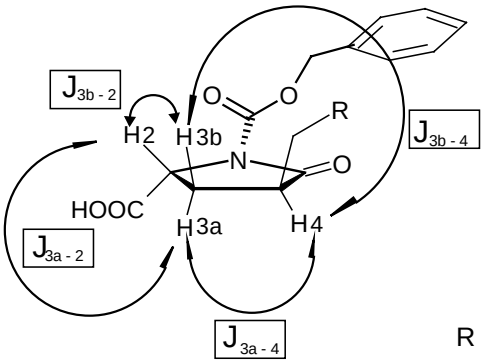


cis/trans-**71** **105**

The structure determination of **105** has been made on the basis of ^{1}H-NMR as well as ^{13}C-NMR and DEPT spectroscopy. The latter unambiguously allow the assignment of the carbon atoms C-2, C-3 and C-4 [see: Figure 5.9-4], whereas one set of signals was observed.
In order to confirm the stereochemical assignment of **105**, observed coupling constants [see: entry 1, Table 5.9-1] are compared to reported ones [90,91,130]. Therefore, characteristic coupling, especially between the hydrogen atoms H-2/H-3a ($J_{2\text{-}3a}$ = 4.4 Hz) and H-2/H-3b ($J_{2\text{-}3b}$= 8.1 Hz) [see: Figure 5.9-1] was supposed to draw the firm conclusion, that compound **105** is trans-configurated, i.e. possesses expected (2S,4R)-configuration. Unfortunately, the signals of H-4 overlap with those of H_{benzyl}, so that available NMR-data [see: entry 1, Table 5.9-1] was compared to literature data. Latter are contradictory [see: entries 3-6, Table 5.9-1] and specific coupling constants (i.e. $J_{2\text{-}3a}$ and $J_{2\text{-}3b}$) for compound **105** are lacking [see: entry 2, Table 5.9-1]. Instead, observed NMR-data (i.e. coupling constants) of **105** is very close to the structural analogue t-butyl (2S,4R)-1-(t-butoxycarbonyl)-4-benzyl pyroglutamate [see: entry 3, Table 5.9-1], whereas it is pointed out that the coupling constants $J_{2\text{-}3a}$ and $J_{2\text{-}3b}$ of the corresponding **cis**-configurated diastereomere (t-butyl (2S,4**S**)-1-(t-butoxycarbonyl)-4-benzyl pyroglutamate) significantly differ from those of the trans-configurated one. The cis-

configurated diastereomere t-butyl (2S,4**S**)-1-(t-butoxycarbonyl)-4-benzyl pyroglutamate shows coupling between H-2/H-3a ($J_{2\text{-}3a} \approx 7.0$Hz) and H-2/H-3b ($J_{2\text{-}3b} \approx 8.5$ Hz) [90].

Figure 5.9-1



R = **105**

According to these results, it can be concluded that the observed trans substitution of compound **105** is confirmed on the basis of available ^{1}H-NMR, ^{13}C-NMR and DEPT spectroscopic data in comparison with literature data, namely [90]. This assumption should be confirmed by further data of diastereomerically pure C-4-substituted analogues or X-ray.

Table 5.9-1

entry	compound	coupling constants [Hz]				
		$J_{2\text{-}3a}$	$J_{2\text{-}3b}$	$J_{a\text{-benzyl-4}}$	$J_{b\text{-benzyl-4}}$	$J_{gem,\ benzyl}$
1	(2S,4R) **105**	4.4	8.1	3.8	- [f]	13.6
2	(2S,4R) **105** [a]	-	-	3.9	10.3	13.6
3	t-Butyl (2S,4R)-4-benzyl pyroglutamate [b]	7.9	7.9	-	-	-
4	t-Butyl (2S,4R)-1-(t-butoxycarbonyl)-4-benzyl pyroglutamate [c]	3.7	7.6	4.0	9.5	13.7
5	t-Butyl (2S,4R)-1-(t-butoxycarbonyl)-4-benzyl pyroglutamate [d]	8.3	10.7	-	-	-
6	t-Butyl (2S,4R)-1-(t-butoxycarbonyl)-4-benzyl pyroglutamate [e]	5.0	6.6	-	-	-

[a] in CD_3OD [91]; [b] in $CDCl_3$ [91]; [c] in $CDCl_3$ [90]; [d] in C_6D_6 [91]; [e] in $CDCl_3$ [130]; [f] overlapped signals.
*t-Butyl (2S,4R)-4-benzyl-pyroglutamate [see: entry 3] and t-butyl (2S,4R)-1-(t-butoxycarbonyl)-4-benzyl pyroglutamate [see: entries 4-6] are employed to serve as structural analogues of **105**.*

Figure 5.9-2 ^{1}H-NMR spectrum of **105**

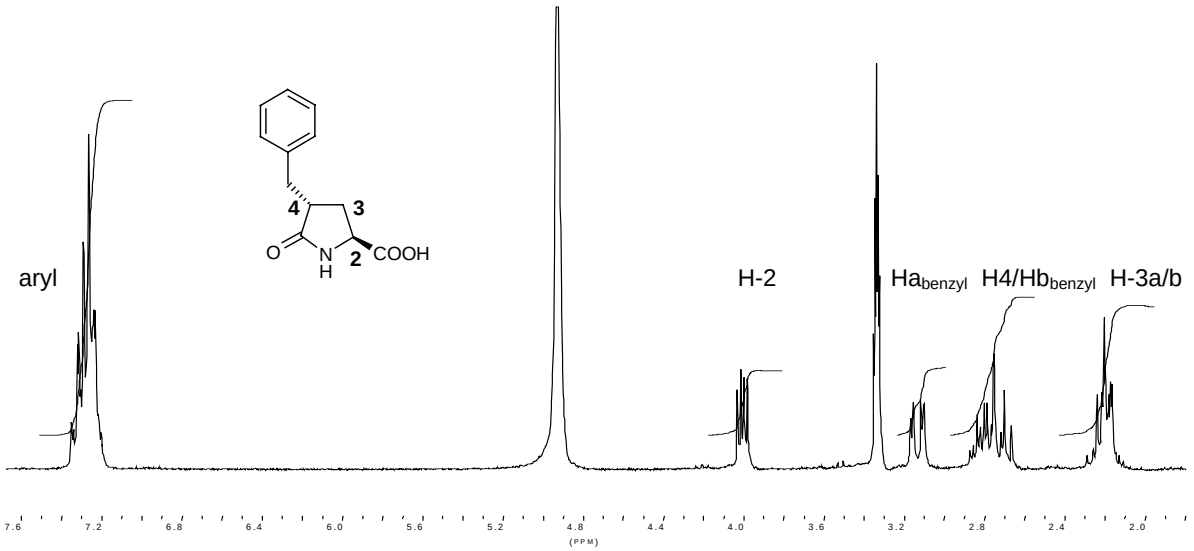


Figure 5.9-3 ^{1}H-NMR spectrum of **105** (detail)

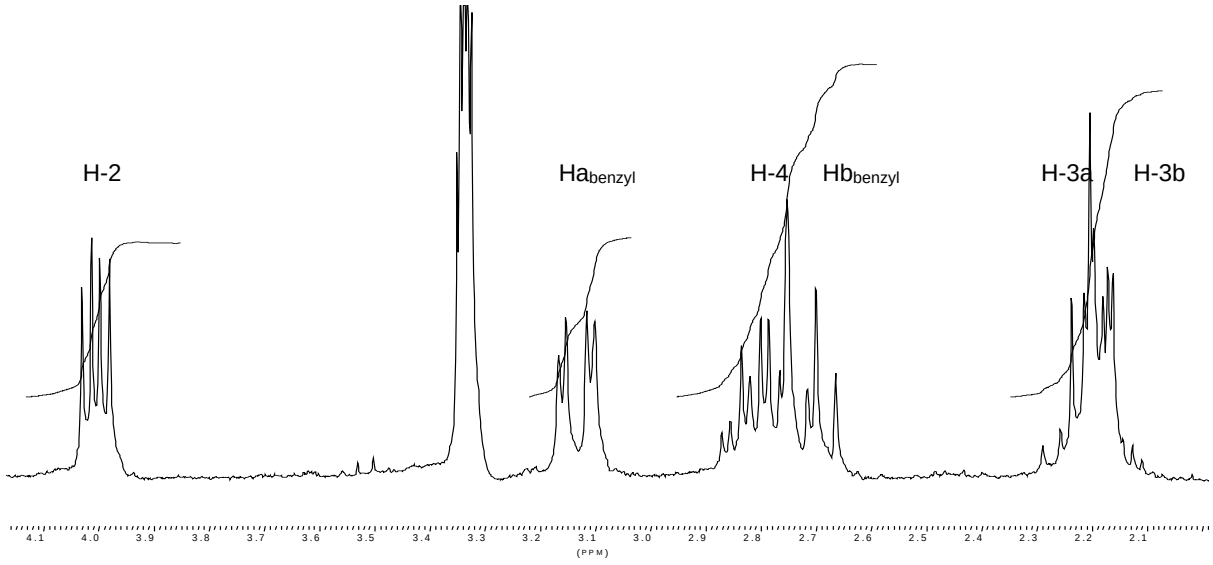
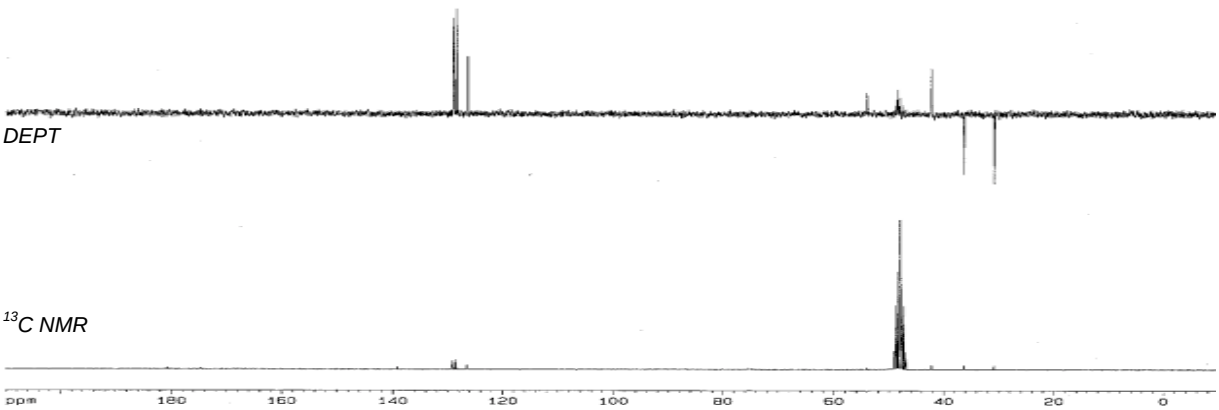


Figure 5.9-4 ^{13}C-NMR and DEPT spectra of **105**

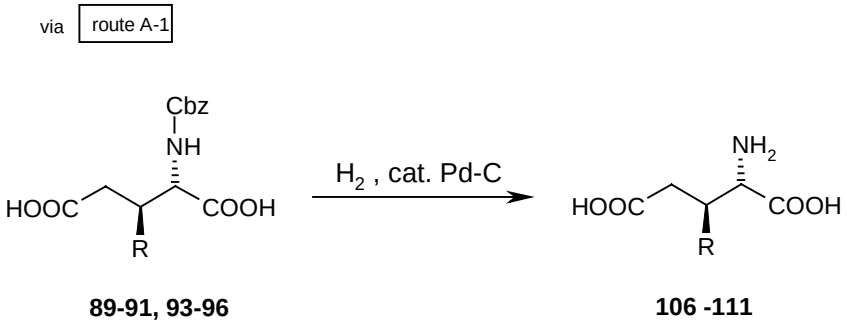


^{13}C NMR (CD_3OD): δ = 30.72 (benzyl), 36.27 (C-3), 42.19 (C-4), 54.01 (C-2), 126.5, 128.6, 129.1, 139.1 (6 x C, aryl), 174.8 (C=O, lactam), 180.7 (COOH, carboxylate).

5.10 PREPARATION OF TRANS-CONFIGURATED GLUTAMATES VIA ROUTE A-1

The last step for the preparation of C-3-substituted glutamates via route A-1, afforded the cleavage of the Cbz-protection group to provide the enantiomerically pure compounds **106**-**111**. The mild reaction conditions for the removal of Cbz are supposed to maintain the stereochemical integrity at position two and four (C-2 and C-4). Therefore, the N-Cbz glutamic acid derivatives **89**-**91** and **93**-**96** were treated with hydrogen in the presence of a catalytic amount of Pd/C at room temperature [see: Scheme 5.10-1], [78]. However, usage of alcoholic solvents (e.g. methanol, ethanol, 1-propanol) should be avoided, otherwise autocatalytic esterification of the carboxylic site takes place. For example, about 10% of the monomethyl ester of compound **106** have been detected, when methanol was employed instead of 2-propanol.

Scheme 5.10-1



89-91, 93-96 **106 -111**

Work-up of the C-3-substituted glutamates did not require chromatographic purification to separate byproducts. In addition, due to the absence of acids (i.e. HCl) it is not expected that the products **106**-**111** are provided as conjugate acids.
It was gratifying to notice that all compounds (**106**-**111**) yielded as pure crystalline compounds [see: Table 5.10-1]. However, due to the lack of further quantities the 3-substituted biphenyl derivative has not been isolated until now.

To confirm the assumption that **106**-**108** possess (2S,3S)-, and **109**-**111** (2S,3R)-configuration (i.e. they are trans-configurated), the structure determination has been made on the basis of ^{1}H-NMR, ^{13}C-NMR and Dept spectroscopic data. Hence, ^{13}C-NMR and Dept

spectra allow assignment of C-2, C-3, and C-4. It is recorded that exclusively one set of signals was observed, namely the expected trans-substituted one.
Outlined spectra examplarily illustrate this assumption for the 3-alkyl glutamates **106** [see: Figure 5.10-4], **107** [see: Figure 5.10-7], and for the 3-aryl glutamates **110** [see: Figure 5.10-14], **111** [see: Figure 5.10-17], respectively.

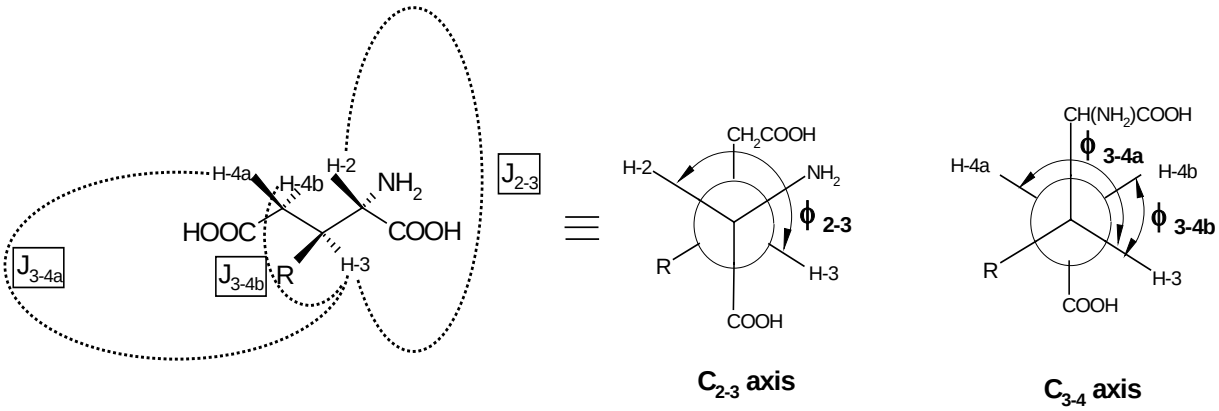
Table 5.10-1

entry	R	compound	yield (%)
1	methyl	**106**	78
2	ethyl	**107**	62
3	1-butyl	**108**	75
4	phenyl	**109**	63
5	p-chlorophenyl	**110**	70
6	naphthyl	**111**	60

The assignment of the hydrogen atoms H-2, H-3, and H-4a/b [see: Figure 5.10-1] has been made utilizing ^{1}H-NMR spectroscopic data. The analysis of the coupling constants $J_{2\text{-}3}$, $J_{4a\text{-}3}$, and $J_{4b\text{-}3}$, gives evident information about the configuration of the C-3-substituted glutamates **106**-**111**.
The conformation of these conformationally non-constrained compounds especially influences corresponding coupling constants [compare: chapter 5.7]. Hence, the influence of the chosen solvent as well as the pH-value have to taken into consideration [15]. Outlined Newman projections [see: Figure 5.10-1] along the axis of the carbons C-2/C-3 ($C_{2\text{-}3}$ axis), and C-3/C-4 ($C_{3\text{-}4}$ axis) give explanation for the pH value depending coupling constants. The torsion angles $\varphi_{x\text{-}y}$ are mainly influenced by the protonated and deprotonated, respectively, α-carboxylate and α-amino (position 1) as well as by the γ-carboxylate (position 3) moiety. Thus, an equilibrium of possible rotameres at various pH values decisively influences resulting coupling constants. Additionally, coupling between H-3 and the alkyl moiety (methyl, ethyl, butyl) leads to more complex coupling patterns [see: Table 5.10-3]. The individual diastereotopic methylen protons (H-a_{ethyl} and H-b_{ethyl}) of compound **107** give splitted multiplets [see: Figure 5.10-6] with the observed coupling constants $Ja_{ethyl\text{-}3} \approx Jb_{ethyl\text{-}3}$, and $J_{CH3}.a_{ethyl} \approx J_{CH3}.b_{ethyl}$ [see: entry 2, Table 5.10-3].

Obviously, ^{1}H-NMR measuring and comparison with literature data provided unambiguous spectroscopic data, which ensure the availability of the expected diastereomeric purity of the (2S,3S)-3-alkyl glutamates **106**-**108** [see: Table 5.10-2].

Figure 5.10-1



The coupling constants ($J_{2\text{-}3}$, $J_{4a\text{-}3}$, $J_{4b\text{-}3}$) of **106** and **108** measured in D_2O/NaOD solution [see: entries 1, 3; Table 5.10-2] significantly differ from those of **107** [see: entry 2]. These results correspond to reported data for D_2O solution measurement at different pH values [15]. For compound **106** it is reported that its $J_{2\text{-}3}$ and $J_{4b\text{-}3}$ increase, when the pH value increases ($J_{2\text{-}3}$ = 3.5 Hz ≅ pH 3, $J_{2\text{-}3}$ = 4.0 Hz ≅ pH 7, $J_{2\text{-}3}$ = 5.0 Hz ≅ pH 10) and ($J_{4b\text{-}3}$ = 8.0 Hz ≅ pH 3, $J_{4b\text{-}3}$ = 8.3 Hz ≅ pH 7, $J_{4b\text{-}3}$ = 11.4 Hz ≅ pH 10) , whereas $J_{4a\text{-}3}$ behaves reciprocally ($J_{4a\text{-}3}$ = 5.1 Hz ≅ pH 3, $J_{4a\text{-}3}$ = 4.6 Hz ≅ pH 7, $J_{4a\text{-}3}$ = 3.4 Hz ≅ pH 10). Due to an existing pH ≈ 12 in D_2O/NaOD solution, observed data [see: entries 1, 3; Table 5.10-2] unambiguously conform to published data [15]. It has to be pointed out that the unexpected (2S,3**R**)-configurated diastereomere **116** (i.e. cis-configurated) shows significantly different coupling constants (at pH 10: $J_{2\text{-}3}$ = 3.2 Hz, $J_{4a\text{-}3}$ = 5.0 Hz, $J_{4b\text{-}3}$ = 9.6 Hz) [see: chapter 5.12].

The coupling constants of compound **107** [see: entry 2; Table 5.10-2], which were measured in D_2O solution (pH ≈ 3-4), conform for observed $J_{2\text{-}3}$, but differ for observed $J_{4a\text{-}3}$ and $J_{4b\text{-}3}$. The observed values of $J_{4a\text{-}3}$ and $J_{4b\text{-}3}$ are averaged ($J_{4a\text{-}3}$ ≈ $J_{4b\text{-}3}$ = 6.4 Hz) in comparison with those of compound **106** ($J_{4a\text{-}3}$ = 3.1 Hz, $J_{4b\text{-}3}$ = 11.3 Hz) and compound **108** ($J_{4a\text{-}3}$ = 3.5 Hz, $J_{4b\text{-}3}$ = 10.6 Hz). The averaged coupling constants for compound **107** are a result of the existing pH value at the isoelectric point (pH ≈ 3-4). Herein, a different equilibrium of rotameres is favoured [15] to give different $J_{4a\text{-}3}$ and $J_{4b\text{-}3}$ in comparison with those of **106** and **108**. However, observed coupling constants of **107** are closer to those reported by

Soloshonok et al. [60a] (for compound **106**, as monoammonium salt). Therefore, outlined J_{2-3} = 3.4 Hz, J_{4a-3} = 5.1 Hz, and J_{4b-3} = 7.2 Hz data (measured in D_2O solution [60a]) show clearly the variability of the coupling constants (i.e. J_{4a-3} and J_{4b-3}) by measurement at various pH values.

Obviously, due to observed spectroscopic data of **106**-**108** [see: entries 1-3, Table 5.10-2] and comparison with published data of compound **106** [15,60a] it can be recorded that the trans configuration of the 3-alkyl glutamates **106**-**108** is ensured.

Table 5.10-2

entry	R	comp.	solvent	coupling constants [Hz]				for spectrum see:
				J_{2-3}	J_{4a-3}	J_{4b-3}	J_{4a-4b}	
1	methyl	**106**	D_2O/NaOD	5.5	3.1	11.3	12.9	Figure 5.10-2
2	ethyl	**107**	D_2O	3.4	6.4	6.4	16.5	Figure 5.10-5
3	1-butyl	**108**	D_2O/NaOD	4.2	3.5	10.6	13.2	-
			CD_3OD	3.2	8.0	-[a)]	18.2	-
4	phenyl	**109**	DMSO-d_6	-[a)]	6.4	9.5	16.7	-
			D_2O/NaOD	-[a)]	-[a)]	-[a)]	-[a)]	-
5	p-chlorophenyl	**110**	CD_3OD	5.2	6.4	9.2	17.1	Figure 5.10-8
			DMSO-d_6	5.8	7.1	9.4	16.8	Figure 5.10-9
			D_2O/NaOD	-[a)]	-[a)]	-[a)]	-[a)]	Figure 5.10-10
6	naphthyl	**111**	CD_3OD	3.1	3.7	8.9	17.2	Figure 5.10-15
			DMSO-d_6	-[a)]	1.5	9.2	17.2	-

[a)] overlapping signals.

To confirm the trans configuration of the 3-aryl glutamates **109**-**111** [see: entries 4-6, Table 5.10-1], assignment of H-2, H-3, and H-4a/b was deduced from the corresponding ^{1}H-NMR spectra. Due to their solubility, measurement was performed in various solvents. Thus, the 3-aryl glutamates **109**-**111** were expected to show similar coupling constants in non-aqueous

polar solvents (CD_3OD, DMSO-d_6), whereas the D_2O/NaOD solvent system [see: entries 4 and 5 for compounds **109** and **110**, Table 5.10-1] did not allow assignment of the coupling constants $J_{2\text{-}3}$, $J_{4a\text{-}3}$, and $J_{4b\text{-}3}$. The latter result corresponds to reported data of compound **111** [50a]. It turned out that the protic D_2O/NaOD solvent system was not suitable for spectroscopic structure determination of the aryl compounds **109**-**111**, and hence was dropped.

Instead, measurement of **109** and **110** [see: entries 4,5; Table 5.10-2] in non-aqueous polar solvents (CD_3OD and DMSO-d_6) unambiguously allow assignment of the coupling constants $J_{2\text{-}3}$, $J_{4a\text{-}3}$, and $J_{4b\text{-}3}$. Their comparison with published data of the trans-3-phenyl glutamate **109** ([53]: CD_3OD, $J_{2\text{-}3}$ = 4.8 Hz, $J_{4a\text{-}3}$ = 5.7 Hz, $J_{4b\text{-}3}$ = 9.2 Hz) confirms the assumption that **109** and the analogue **110** are trans-configurated. It has to be pointed out that the cis-configurated diastereomere (2S,3**S**)-3-phenyl glutamate shows significantly different coupling constants ([53]: CD_3OD, $J_{2\text{-}3}$ = 8.2 Hz, $J_{4a\text{-}3}$ = 8.3 Hz, $J_{4b\text{-}3}$ = 8.3 Hz).

Table 5.10-3

entry	R	compound	coupling constants [Hz]		for spectrum see:
			$J_{3\text{-}CH3}$		
1	methyl	**106**	6.7		Figure 5.10-3
			$J_{3\text{-}CH2}$	$J_{CH2\text{-}CH3}$	
2	ethyl	**107**	7.0	7.3	Figure 5.10-6
			$J_{3\text{-}CH2}$	$J_{CH2\text{-}CH3}$	
3	1-butyl	**108**	-[a)]	6.7	-

[a)] overlapping signals

The explanation for decreased coupling constants ($J_{2\text{-}3}$, $J_{4a\text{-}3}$, and $J_{4b\text{-}3}$) of compound **111** [see: entry 8, Table 5.10-2] can be given by the influence of the naphthyl substituent. On the one hand, the bulkiness of the naphthyl moiety forces the hydrogen atom H-3 to different torsion angles $\varphi_{x\text{-}y}$ ($\varphi_{2\text{-}3}$ along $C_{2\text{-}3}$ axis, and $\varphi_{3\text{-}4a}$/$\varphi_{3\text{-}4a}$ along $C_{3\text{-}4}$ axis) in comparison with those of **109** and **110**, and thus favours other equilibration of predominant conformeres. On the other hand, the electron negativity of the substituent **R** plays a major role for the value of the coupling constants $J_{x\text{-}y}$ [compare: page 63]. The naphthyl moiety of **111** exhibits an

insignificant different electron withdrawal activity in comparison with the monocyclic aryl substituents of **109** and **110**. Hence, this effect can be disregarded. The decreased values of the coupling constants of compound **111** mainly depend on the sterical effect of the naphthyl moiety. These assumptions explain observed spectroscopic data of compound **111** and correspond mentioned observation of the (2S,3R)-3-naphthyl pyroglutamate **104**.

Conclusively, it is recorded the fact that observation from the interpretation of ^{13}C-NMR and DEPT spectra for the trans-configurated compounds (i.e. (2S,3S)-configuration for **106**-**108** and (2S,3R)-configuration for **109**-**111**) show one set of signals of diastereomeres, and that assignment of expected trans-substituted diastereomeres is unambiguously confirmed by spectroscopic ^{1}H-NMR data (coupling constants). In addition, it has been pointed out that the cis-configurated diastereomeres (i.e. (2S,3**R**)-3-methyl glutamate [15,60a] and (2S,3**S**)-3-phenyl glutamate [53]) significantly differ from the observed trans-configurated compounds **106** or rather **109** with regard to corresponding coupling constants. Despite of the lack of specific published coupling constants for the analogous alkyl derivatives **107** and **108** as well as for the analogous aryl derivatives **110** and **111**, there can be drawn the conclusion from observed and published data of **106** and **109**, respectively, that these derivatives also are trans-configurated.

Figure 5.10-2 ^{1}H-NMR spectrum of **106**

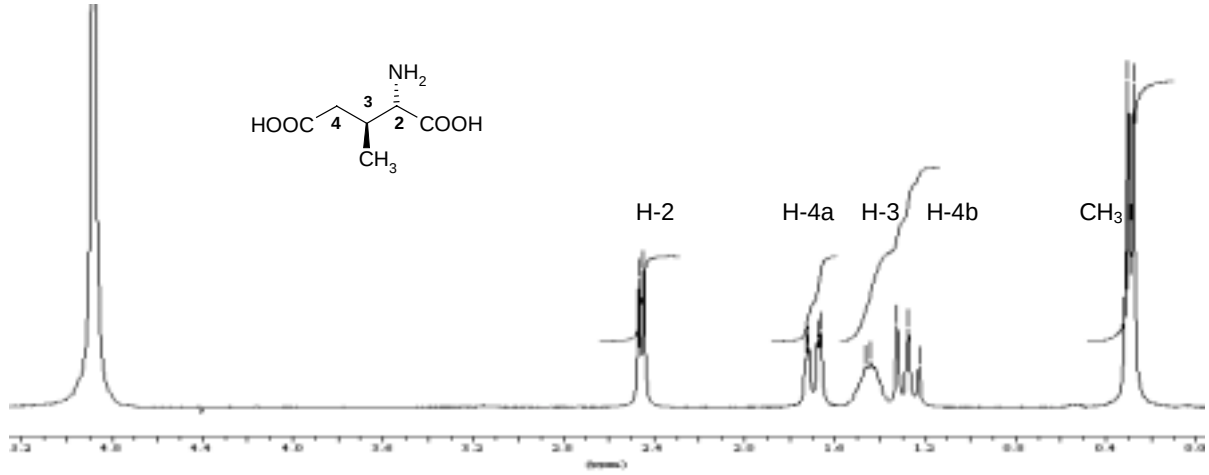


Figure 5.10-3 ^{1}H-NMR spectrum of **106** (detail)

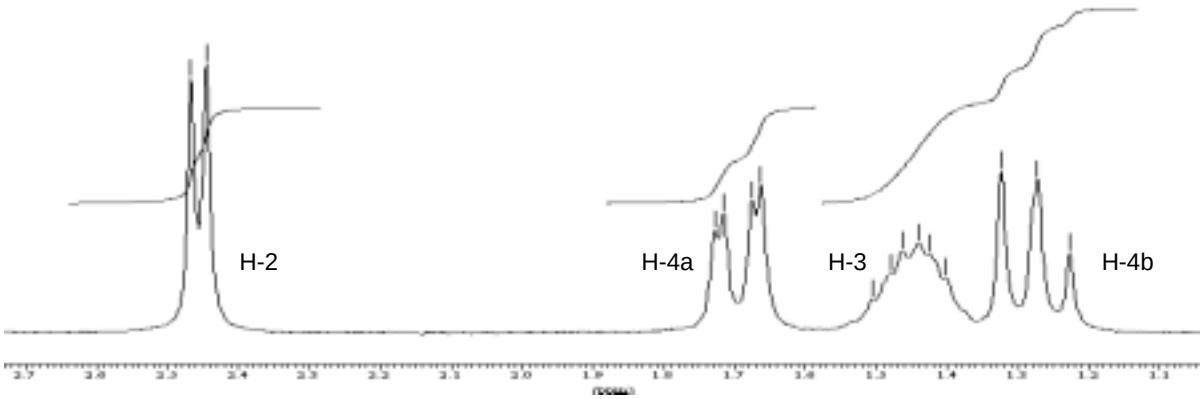
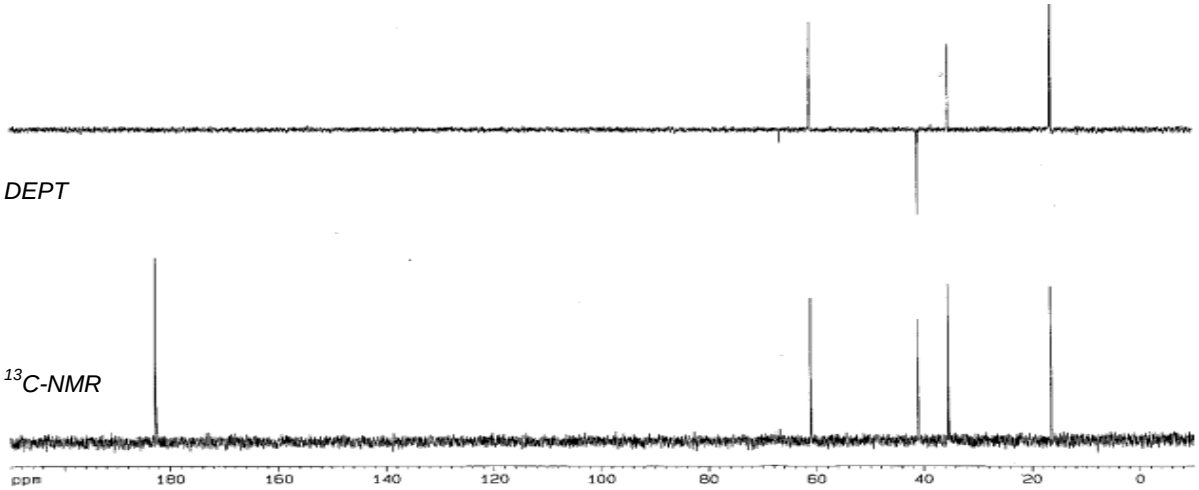


Figure 5.10-4 ^{13}C-NMR and DEPT spectra of **106**



^{13}C NMR (D_2O/NaOD, dioxane): δ = 16.47 (CH_3), 35.32 (C-3), 40.96 (C-4), 61.11 (C-2), 182.4 (COO^-), 182.6 (COO^-).

Figure 5.10-5 ^{1}H-NMR spectrum of **107**

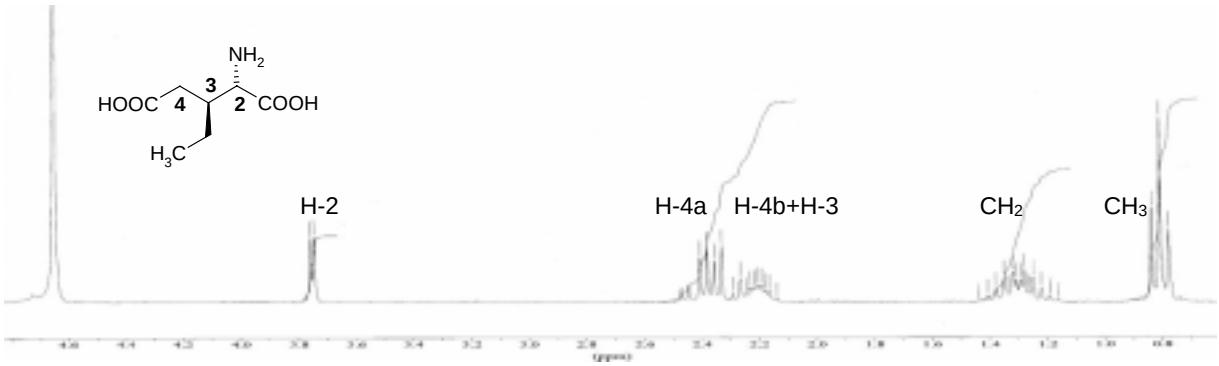


Figure 5.10-6 ^{1}H-NMR spectra of **107** (details)

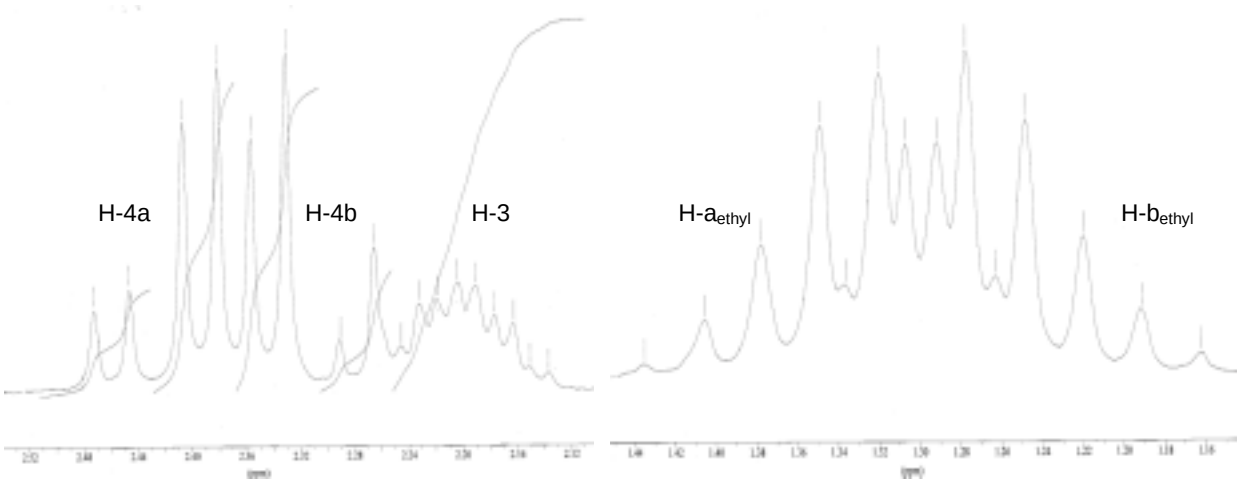
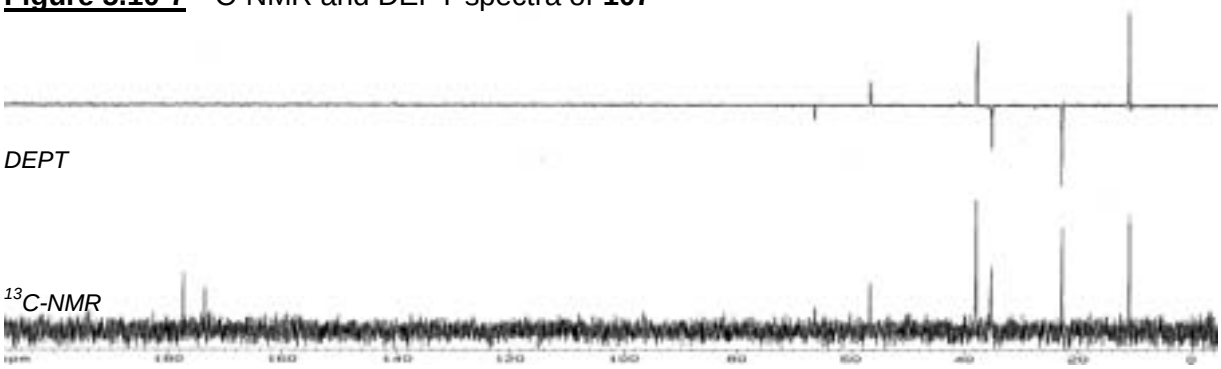


Figure 5.10-7 ^{13}C-NMR and DEPT spectra of **107**



^{13}C NMR (D_2O, dioxane): δ = 11.19 (CH_3), 22.84 (CH_2), 35.27 (C-4), 37.86 (C-3), 56.80 (C-2), 173.6 (COOH), 177.4 (COOH).

Figure 5.10-8 ^{1}H-NMR spectrum of **110** (CD_3OD)

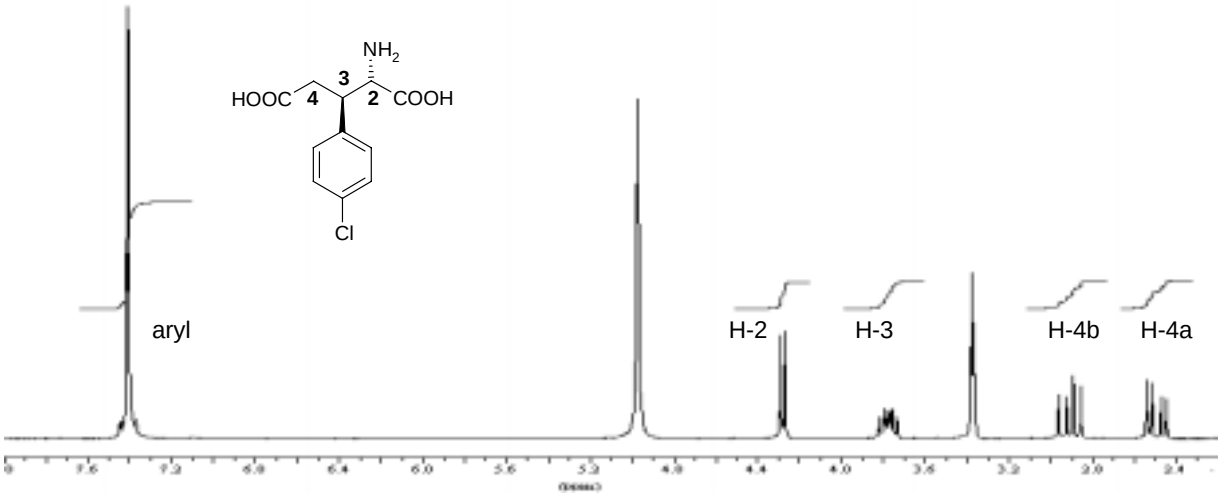


Figure 5.10-9 ^{1}H-NMR spectrum of **110** (DMSO-d_6)

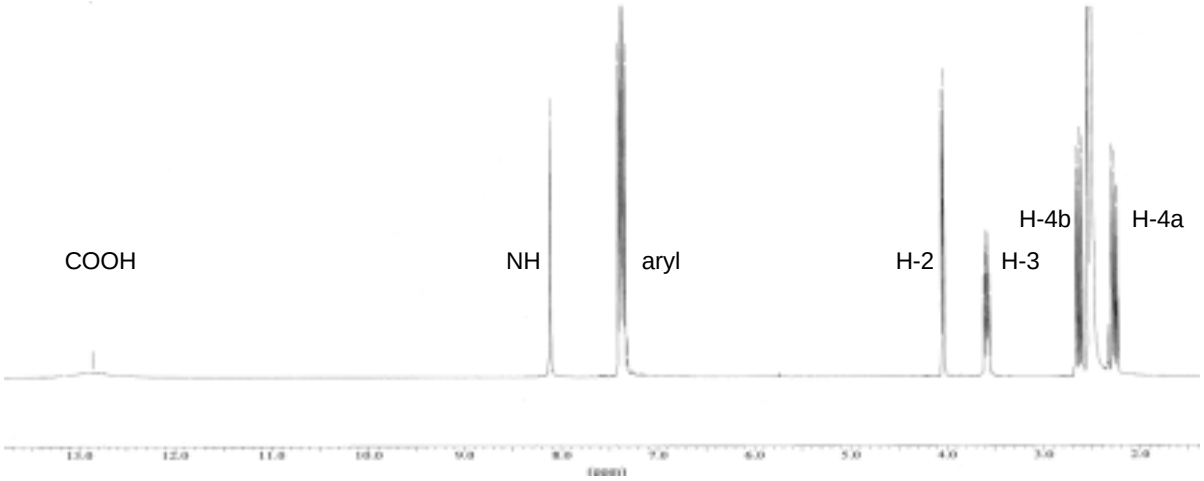


Figure 5.10-10 ^{1}H-NMR spectrum of **110** (D_2O/NaOD)

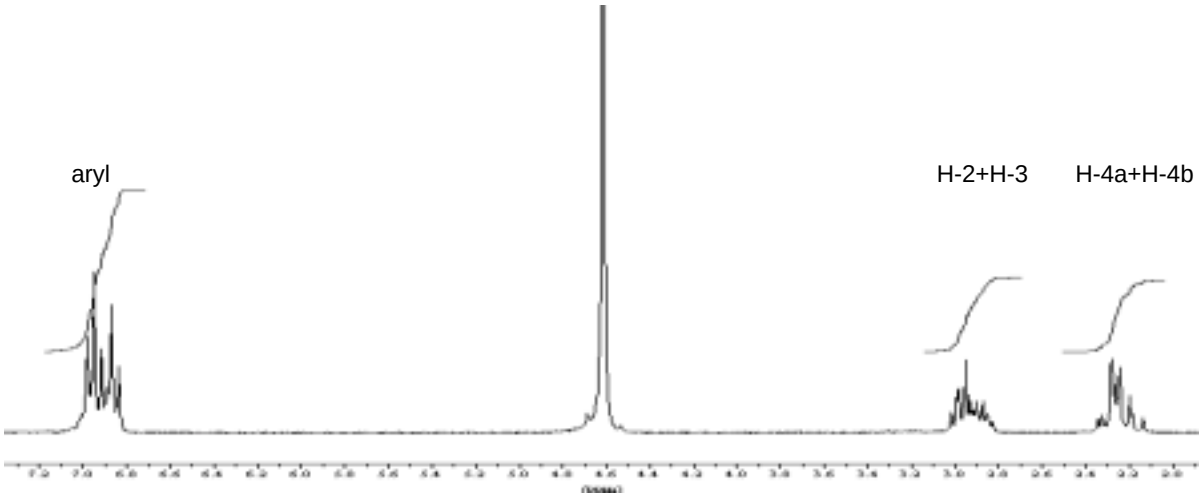


Figure 5.10-11 ^{1}H-NMR spectra of **110** (detail, CD_3OD)

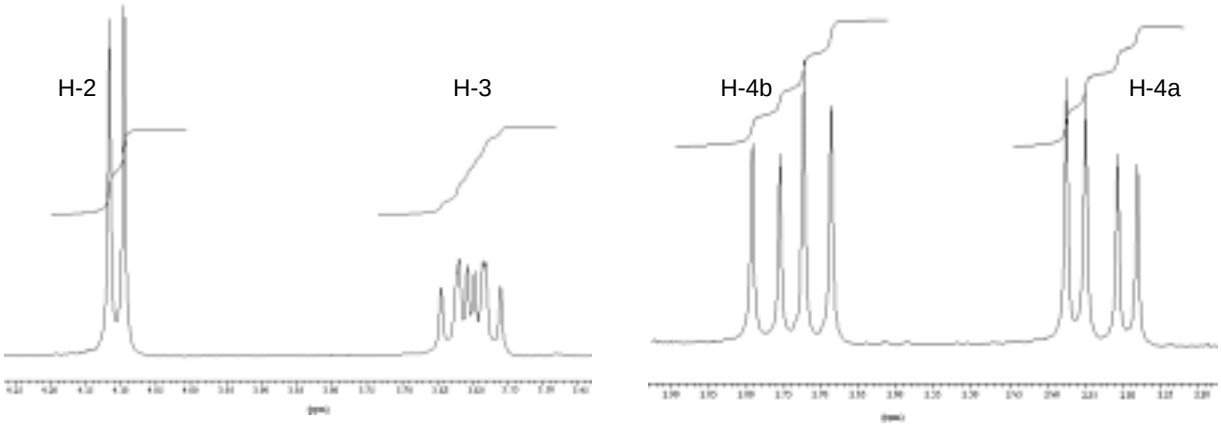


Figure 5.10-12 ^{1}H-NMR spectra of **110** (detail,DMSO-d_6); **Figure 5.10-13** (detail,D_2O/NaOD)

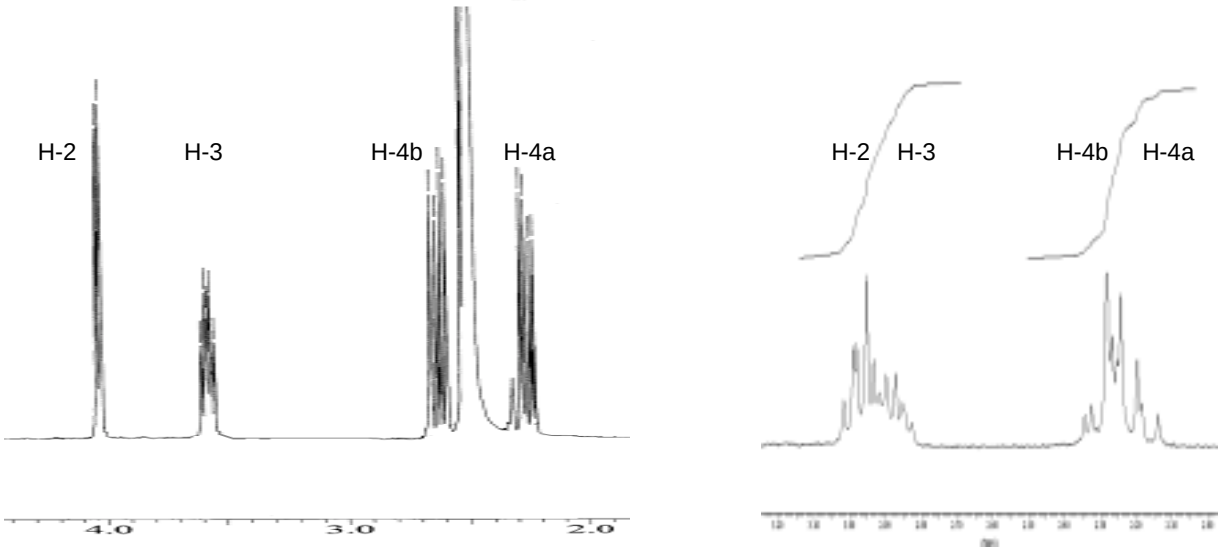
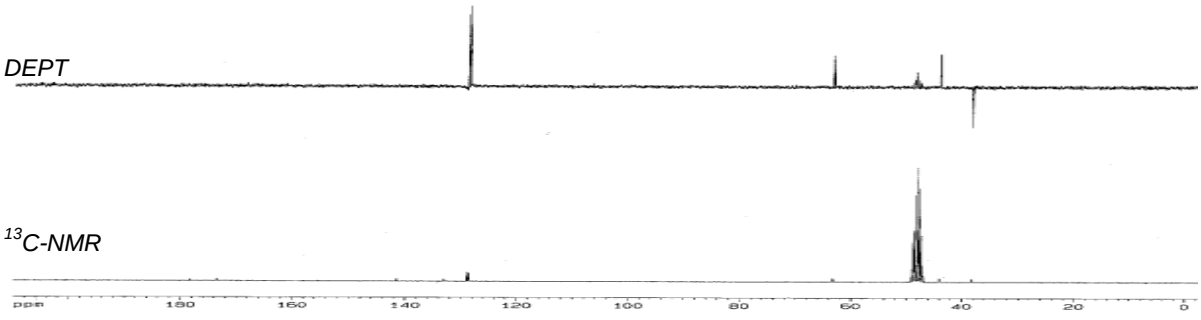


Figure 5.10-14 ^{13}C-NMR and DEPT spectra of **110**



^{13}C NMR (CD_3OD): δ = 38.16 (C-4), 43.97 (C-3), 63.31 (C-2), 128.7, 129.0, 133.1, 141.5 (6 x C, aryl), 173.6 (COOH), 178.3 (COOH).

Figure 5.10-15 ^{1}H-NMR spectrum of **111** (CD_3OD)

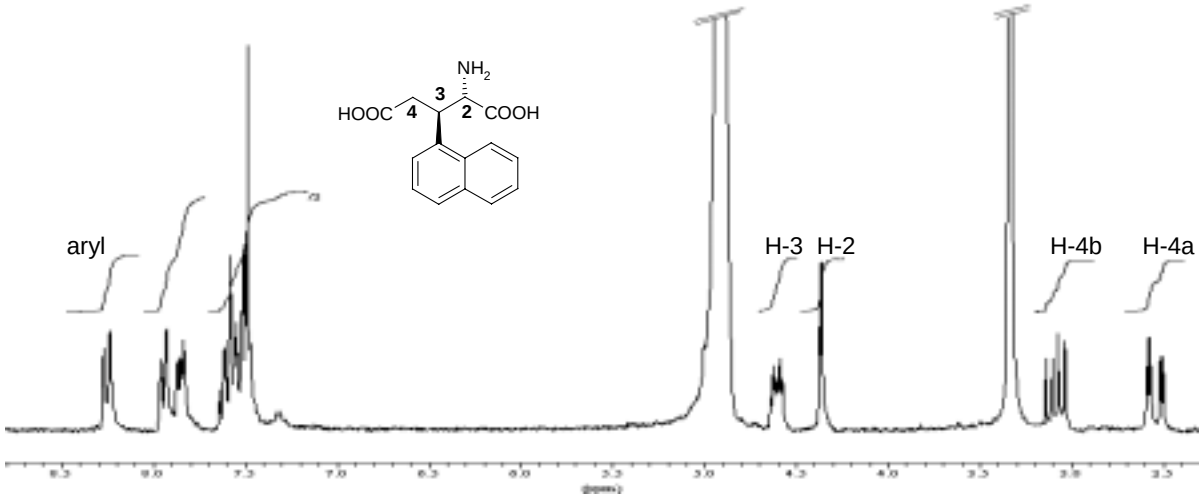


Figure 5.10-16 ^{1}H-NMR spectra of **111** (detail, CD_3OD)

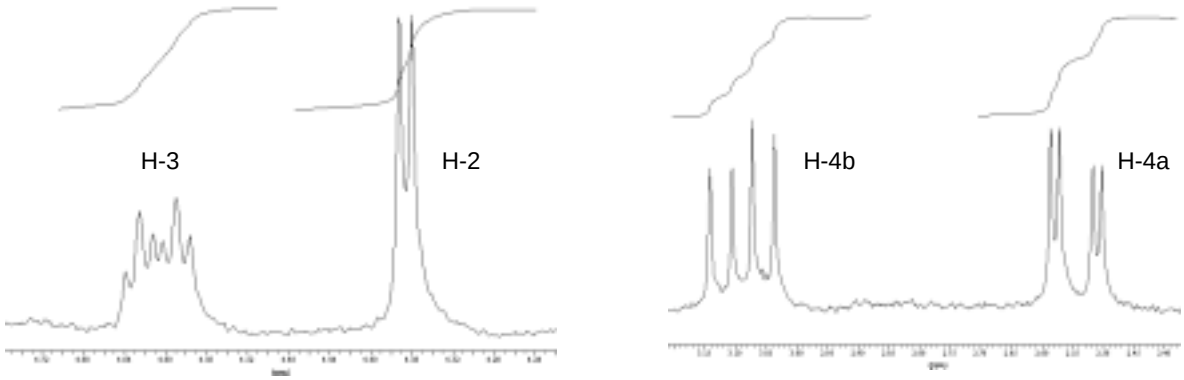
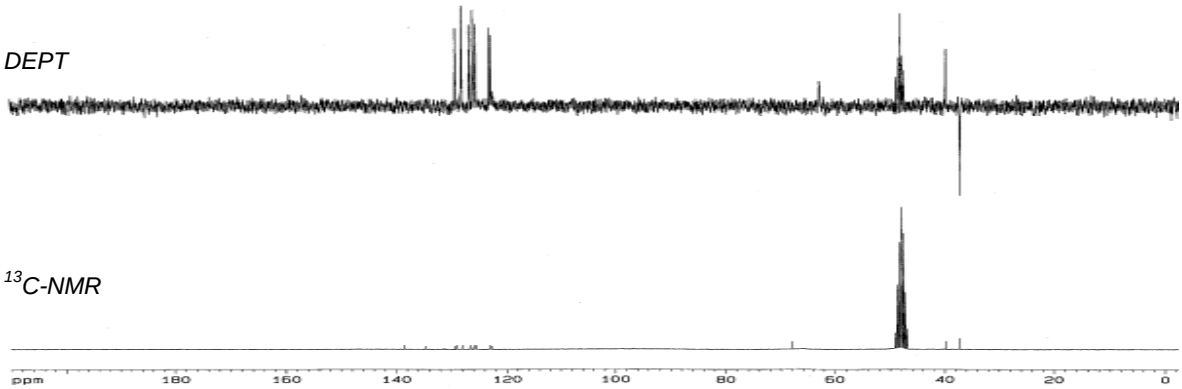


Figure 5.10-17 ^{13}C-NMR and DEPT spectra of **111**

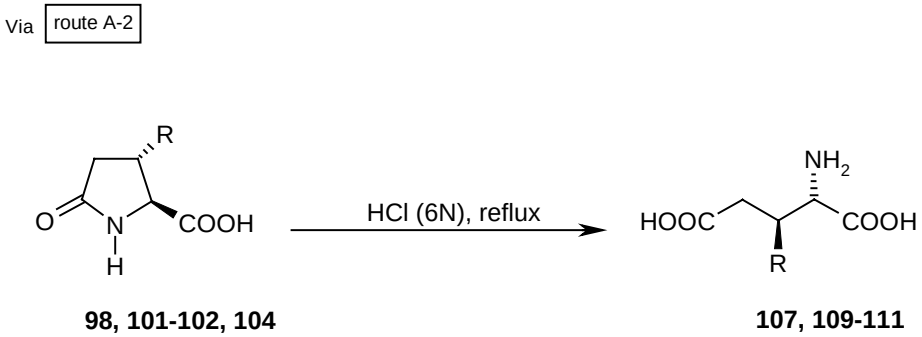


^{13}C NMR (CD_3OD): δ = 37.24 (C-4), 39.83 (C-3), 66.30 (C-2), 122.9, 123.1, 125.5, 126.0, 126.6, 128.0, 129.1, 131.9, 134.7, 138.5 (10 x C, aryl), 177.0 (COOH, weak), 178.0 (COOH, weak).

5.11 PREPARATION OF TRANS-CONFIGURATED GLUTAMATES VIA ROUTE A-2

According to the plan of synthesis, the 3-substituted pyroglutamates **98**, **101-102**, and **104** were supposed to undergo a ring opening reaction via route A-2. To accomplish this, the corresponding pyroglutamates were refluxed in hydrochloric acid (6 N) for several hours to afford the glutamic acid derivatives **107**, **109**-**111** [see: Scheme 5.11-1].

Scheme 5.11-1



98, 101-102, 104 **107, 109-111**

Final work-up yielded pure crystalline compounds [see: Table 5.11-1]. It has to be pointed out that work-up procedure is essential, i.e. the removal of hydrochloric acid was done carefully under reduced pressure. Additionally, an autocatalytic re-cyclization has to be avoided [63]. Hence, further treatment with aqueous solution was omitted to prevent cyclization of compounds **107**, and **109**-**111**.

Table 5.11-1

entry	R	compound	yield (%)
1	ethyl	**107**	49
2	phenyl	**109**	52
3	p-chlorophenyl	**110**	58
4	naphthyl	**111**	50

Although more drastic conditions were utilized (i.e. 6 N HCl, reflux), the stereochemical integrity at C-2 and C-3 should be maintained. In addition, due to the employment of HCl it has to be checked, whether **107**, **109**-**111** are afforded as free amino acids, or as corresponding hydrochlorides.
Therefore, spectroscopic data of **107** and **109**-**111** were compared to those obtained via route A-2 [see: entries 2, and 4-6, Table 5.10-2]. Observed data (^{1}H-, ^{13}C-NMR and DEPT) unambiguously confirmed that the free amino acids **107**, **109**-**111** were at hand.

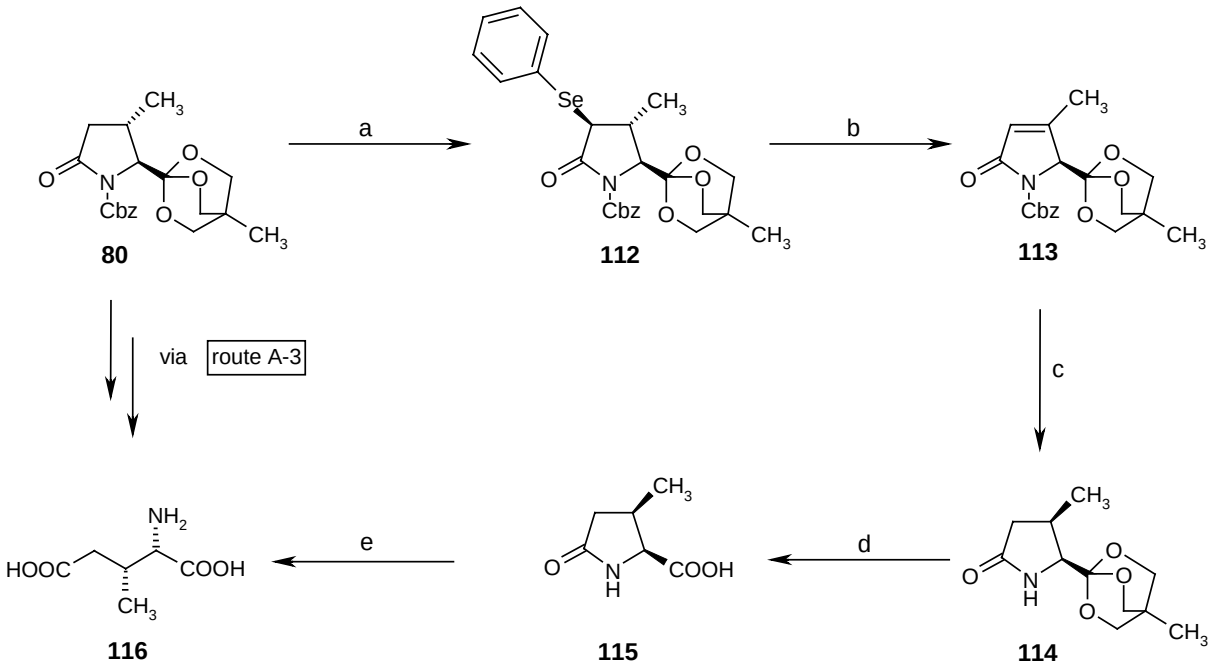
However, it is recorded the fact that **107** and **109**-**111**, which had been prepared via route A-2, were afforded with lower yields [compare: entries 2 and 4-6, Table 5.10-1]. Due to this issue, the preparation via route A-1 is to be favoured towards route A-2, and therefore the preparation of the C-3-substituted glutamic acid compounds (**106**-**111**) exclusively is outlined for the procedure via route A-1. Nevertheless, observed spectroscopic data and comparison with alternatively provided compounds via route A-2 [see: chapter 5.10], unambiguously ensured the availability of the expected trans configuration of **107** and **109**-**111**.

5.12 PREPARATION OF CIS-CONFIGURATED GLUTAMATES VIA ROUTE A-3

The C-3-substituted ortho ester compounds **80**-**87** [see: chapter 5.6, Table 5.6-1] were supposed to be transformed to cis-configurated glutamates via route A-3 [see: Scheme 4.1-1]. However, it turned out that the 3-aryl substituted derivatives (**84**-**87**) did not undergo necessary substitution reaction at position C-4 for the introduction of the phenylselenenyl substituent. The repulsion between the bulky substituent (i.e. phenyl, p-chlorophenyl, biphenyl, and naphthyl) and the phenylselenenyl residue prevented the preparation of the desired (2S,3S)-aryl glutamic acid derivatives.

Hence, it was decided to convert exemplarily compound **80** into the corresponding (2S,3R)-configurated glutamate **116** [see: step a, Scheme 5.12-1]. On the one hand, the less bulky moiety (i.e. methyl) of **80** should not cause mentioned steric strain, and on the other hand available spectroscopic NMR-data of the expected cis-configurated compound **116** would prove the (2S,3S)-configuration of the trans diastereomere **106** [see: chapter 5.10].

Scheme 5.12-1



steps a-e see: Table 5.12-1

The conversion of compound **80** to the phenylselenenyl product **112** [see: entry 1, Table 5.12-1] was performed utilizing the reaction conditions which correspond to the preparation of the mixture cis-**72**/trans-**72** [see: entry 3, Table 5.4-1]. Compound **112** was provided as a pure diastereomeric compound.

Table 5.12-1

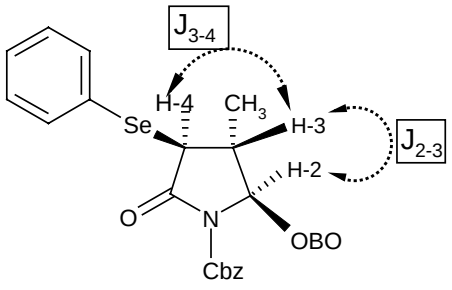
entry	educt	step	reaction conditions	product	yield (%)
1	**80**	a	LiHMDS, PhSeCl, THF, - 78°C	**112**	55
2	**112**	b	m-CPBA, DABCO, CH_2Cl_2/THF, 0 °C	**113**	79
3	**113**	c	H_2 (4 bar), Pd-C, EtOAc	**114**	80
4	**114**	d+e	HCl (6 N), reflux	**116**	52

The expected all-trans (2S,3R,4S)-configuration of compound **112** was determined on the basis of ^{1}H-NMR spectra [see: Figure 5.12-5, Figure 5.12-6] as well as ^{13}C-NMR and DEPT spectra [see: Figure 5.12-7]. The latter allowed unambiguous assignment of C-2, C-3, and C-4. It is pointed out that compound **112** exclusively showed one set of signals for all carbon atoms.

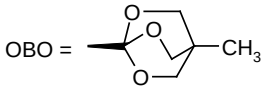
Table 5.12-2

x-H – y-H	J_{x-y} [Hz]
2 – 3	1.0
3 – 4	2.0
CH_3 – 3	7.3

Figure 5.12-1



112



To ensure the all-trans configuration of **112**, the coupling constants (J_{2-3} and J_{4-3}) utilizing ^{1}H-NMR spectroscopic data were inspected [see: Table 5.12-2]. Characteristically, J_{2-3} and J_{4-3}

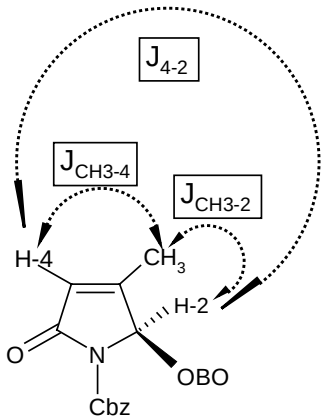
range between 0 and 3 Hz ($0 < J_{2-3} \approx J_{4-3} < 3$ Hz) for the trans-configurated H-2/H-3 and H-3/H-4, whereas the cis-configurated diastereomeres would show coupling constants between 8 and 10 Hz ($8 < J_{2-3} \approx J_{4-3} < 10$ Hz) [44,53,62a]. Hence, measurement of J_{2-3} and J_{4-3} unambiguously allow assignment of the trans-configurated pairs H-2/H-3 and H-3/H-4.
It can be concluded that observed spectroscopic data and comparison with published data [44,53,62a] confirm the availability of the expected (2S,3R,4S)-configurated phenylselenenyl derivative **112**. For better illustration, convincing ^{1}H-NMR spectra of **112** are therefore documented [see: Figure 5.12-5 and Figure 5.12-6].

The next step was to generate the α,β-unsaturated lactam **113** [see: step b, Scheme 5.12-1]. Therefore, the same successful methodology was utilized as for the preparation of compound **74** [see: chapter 5.5]. However, it turned out that the syn-elimination of **113** at least required 48 h, compared to 2 h of the analogue **74**. Thus, the syn-elimination was envisaged to be performed in the aqueous oxidation system [compare: Table 5.5-1] to afford compound **113** in an easier manner. Unfortunately, decomposition of the educt **112** was observed, whereas the desired product **113** was not detectable by in-process-controll (TLC).
At least the successful preparation via the anhydrous methodology was applied to yield **113** [see: entry 2, Table 5.12-1].

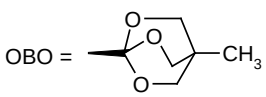
Table 5.12-3

R – y-H	J_{x-y} [Hz]
CH_3 – 2	0.8
4-H – 2	0.9
CH_3 – 4	1.3

Figure 5.12-2



113



The structure of compound **113** was determined on the basis of spectroscopic NMR data (^{1}H-, and ^{13}C-NMR spectra). The outlined ^{13}C-NMR spectrum [see: Figure 5.12-10] was

compared to that of the analogue **74** [see: Figure 5.5-3]. Observed chemical shifts of C-2, C-3, and C-4 are in accordance with the structure of compound **113**. The optical activity $[\alpha]_D^{20}$ = -113 (c = 0.42, CH_2Cl_2) showed that no racemisation occurred under these reaction conditions.

The allylic system, formed by H-2, H-4 and the methyl group, provides characteristic coupling constants [see: Table 5.12-3]. It is pointed out that the methyl substituent decreases the value of the coupling constant $J_{4\text{-}2}$ = 0.9 Hz, compared to those of analogue **74** ($J_{4\text{-}2}$ = 1.5 Hz, see: Table 5.5-2). In addition, there is observed a multiplet [see: Figure 5.12-9] for the diastereotopic protons of the OBO moiety (3 x O$C\underline{H}_2$) instead of a singulet observed for compound **74**.

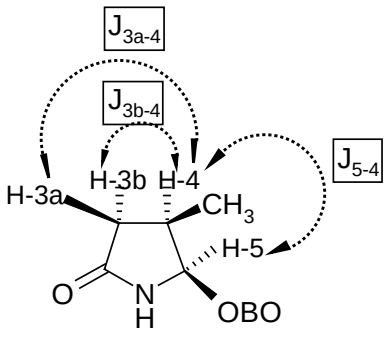
The spectroscopic NMR data are in full accordance with the strucuture of **113**, and therefore the following hydrogenation of the double bond was envisaged to afford **114** hopefully in perfect cis selectivity.

The conversion of the α,β-unsaturated lactam **113** to the cis-configurated compound **114** was done via hydrogenation with palladium on charcoal [see: step c, Scheme 5.12-1]. The hydrogenation of the Michael system from the less hindered α-side is accompanied by the loss of the Cbz group. It was gratifying to notice that the bulkiness of the OBO group resulted in an exclusive hydrogenation of the double bond from the α-side. Compound **114** was obtained in high yield [see: entry 3, Table 5.12-1].

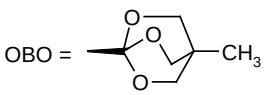
Table 5.12-4

x-H – y-H	$J_{x\text{-}y}$ [Hz]
3a – 4	7.9
3b – 4	8.2
5 – 4	7.9
3a – 3b	16.8
CH_3 – 4	7.0

Figure 5.12-3



114



The expected cis configuration of compound **114** was proved by spectroscopic data (^{1}H-, ^{13}C-NMR, and DEPT spectra). The carbon atoms C-3, C-4, and C-5 were unambiguously

assigned utilizing the corresponding ^{13}C-NMR and DEPT spectra [see: Figure 5.12-13]. The observed data of **114** were compared to that of the trans-configurated N-Cbz protected compound **80** [see: Figure 5.6-4]. It is pointed out that numbering of **114** differs due to the priority of the substituents (IUPAC). There was not observed any trans diastereomere in the crude reaction product. However, comparison of the chemical shifts utilizing the ^{13}C-NMR spectra of **80** and **114**, did not allow unambiguous assignment of expected cis configuration for compound **114**.

Therefore, comparison of H-H coupling constants (**80** and **114**) were employed [see: Table 5.12-5]. The H-H coupling constants of compound **114** [see: entry 1, Table 5.12-5] significantly differ from those of the trans-configurated compound **80** [see: entry 2, Table 5.12-5].

Table 5.12-5

entry	compound	coupling constants [Hz]					for spectra see:
		$J_{5\text{-}4}$	$J_{3a\text{-}4}$	$J_{3b\text{-}4}$	$J_{4\text{-}CH3}$	$J_{3a\text{-}3b}$	
1	**114**	7.9	7.9	8.2	7.0	16.8	Figure 5.12-11, Figure 5.12-12
		$J_{2\text{-}3}$	$J_{4a\text{-}3}$	$J_{4b\text{-}3}$	$J_{3\text{-}CH3}$	$J_{4a\text{-}4b}$	
2	**80**	0	8.2	0	7.3	17.4	Figure 5.6-2, Figure 5.6-3

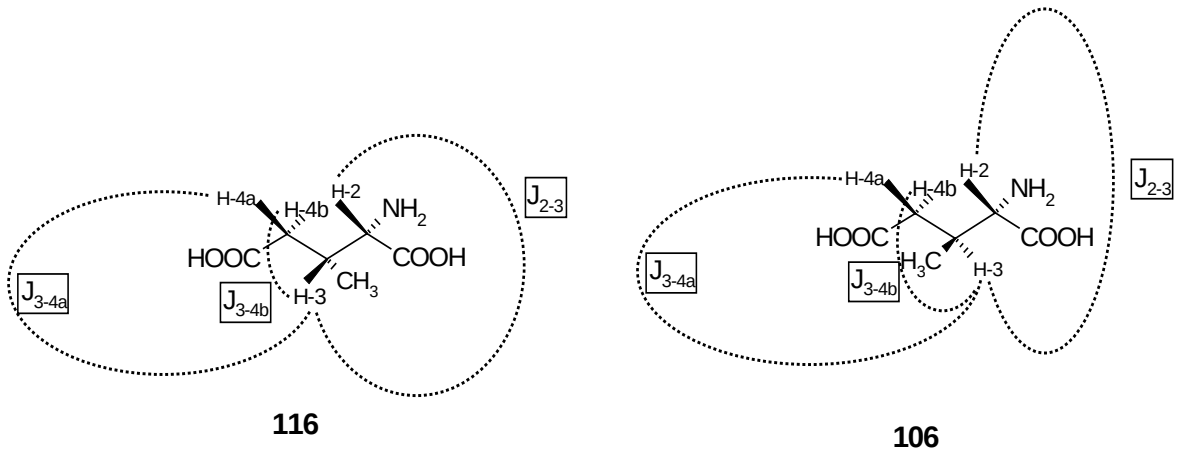
Hence, it is recorded the fact that especially cis-$J_{5\text{-}4}$ = 7.9 Hz of **114** is different to corresponding trans-$J_{2\text{-}3}$ = 0 Hz of **80**. These data are in accordance to published ones [44,53,62a]. Additionally, observed trans-$J_{3a\text{-}4}$ = 7.9 Hz and cis-$J_{3b\text{-}4}$ = 8.2 Hz emphasize expected cis configuration of **114**. These coupling constants differ from the corresponding cis-$J_{4a\text{-}3}$ = 8.2 Hz and trans-$J_{4b\text{-}3}$ = 0 Hz of compound **80**. Comparison of chemical shifts show that the diastereotopic methylen protons H-3a (δ_{3a} = 2.19 ppm) and H-3b (δ_{3b} = 2.59 ppm) of **114** are shifted to lower and higher field, respectively (compare **80**: δ_{4b} = 1.89 ppm and δ_{4a} = 2.96 ppm).

Due to observed and published data [44,53,62a], the exclusive availability of the cis-configurated diastereomere **114** is proved. There can be drawn the conclusion that the observed spectroscopic data and their comparison with **80**, unambiguously prove that the OBO group is an excellent steering group for both reactions, namely the introduction of alkyl and aryl substituents to the Michael system and the hydrogenation of the double bond.

The last step for the generation of the (2S,3R)-methyl glutamate (**116**) included the removal of the ortho ester protecting group followed by the ring opening reaction of the intermediate **115** [see: steps d and e, Scheme 5.12-1]. The isolation of the pyroglutamate derivative **115** failed [compare: diastereomere **97**, chapter 5.8]. Due to this issue, it was decided to carry out the corresponding steps (d and e) in an one-reaction sequence.

Hence, compound **114** was supposed to undergo complete deprotection reaction (i.e. OBO and lactam) in 6 N HCl under reflux. This one-pot-synthesis succeeded and final work-up afforded the diastereomerically pure (2S,3R)-3-methyl glutamate **116** [see: entry 4, Table 5.12-1].

Figure 5.12-4



116 and **106** are illustrated as extended conformeres

The structure determination of **116** has been made on the basis of ^{1}H-NMR, ^{13}C-NMR, and DEPT spectra. The latter allow the assumption that exclusively one diastereomere was observed [see: Figure 5.12-16]. However, comparison of the chemical shifts of **116** with the diastereomeric compound **106** [compare: Figure 5.10-4] did not show significant differences for C-2, C-3 and C-4, so that the expected (2S,3R)-configuration of **116** has to be proved on the basis of available ^{1}H-NMR spectroscopic data. Therefore, assignment of the hydrogen atoms H-2, H-3, and H-4a/b [see: Figure 5.12-14] has been made, and especially the inspection of the coupling constants $J_{2\text{-}3}$, $J_{4a\text{-}3}$, and $J_{4b\text{-}3}$, was envisaged to give evident information about the configuration of compound **116**.

However, the conformation of **116** as a conformationally non-constrained compound is influenced by the chosen solvent (here: D_2O/NaOD) as well as the existing pH-value

[compare: chapter 5.7 and 5.10]. The Newman projections along the axis of the carbons C-2/C-3 (C_{2-3} axis), and C-3/C-4 (C_{3-4} axis) give explanation for pH value depending coupling constants. The torsion angles φ_{x-y} are mainly influenced by the protonated and deprotonated, respectively, α-carboxylate and α-amino (position 1) as well as by the γ-carboxylate (position 3) moiety. Thus, equilibrium of possible rotameres at various pH values decisively influences resulting coupling constants. The explanation for the resulting torsion angles of compound **106** was given in chapter 5.10. The torsion angles φ_{x-y} of compound **116** can also be approximated employing the Karplus curve [$\varphi_{2-3} \approx 60°(+180°)$, $\varphi_{3-4a} \approx 50°(+180°)$, and $\varphi_{3-4b} \approx 180°$].

Table 5.12-6

entry	comp.	solvent	coupling constants [Hz]					for spectra see:
			J_{2-3}	J_{4a-3}	J_{4b-3}	J_{4a-4b}	J_{3-CH3}	
1	**116**	D_2O/NaOD	3.4	5.0	9.6	12.1	7.0	Figure 5.12-14, Figure 5.12-15
2	**116**[a)]	D_2O/NaOD	3.2	5.0	9.6	-	-	-
3	**106**	D_2O/NaOD	5.5	3.1	11.3	12.9	6.7	Figure 5.10-2, Figure 5.10-3
4	**106**[a)]	D_2O/NaOD	5.0	3.4	11.4	-	-	-
5	**106**[b)]	D_2O	3.4	5.1	7.2	15.0	6.6	-

Ref.: [a)] [15]; [b)] [60a], as monoammonium salt.

The coupling constants (J_{2-3}, J_{4a-3}, and J_{4b-3}) of **116** were compared to those of compound **106** as well as to published ones [15,60a]. Obviously, the coupling constants of **116** [see: entries 1-2, Table 5.12-6] and **106** [see: entries 3-4, Table 5.12-6] significantly differ from each other. It is pointed out that **106**, as a monoammonium salt, [see: entry 5, Table 5.12-6] was measured in D_2O [60a] and therefore shows different coupling constants [compare: chapter 5.10].

These spectroscopic data allow the firm conclusion that compound **116** possesses the observed (2S,3R)-configuration. The comparison of observed [see: entry 1, Table 5.12-6] and published data [see: entry 2, Table 5.12-6] of compound **116** unambiguously prove the availability of the cis configuration of compound **116** and the trans configuration of the diastereomere **106**.

Figure 5.12-5 ^{1}H-NMR spectrum of **112**

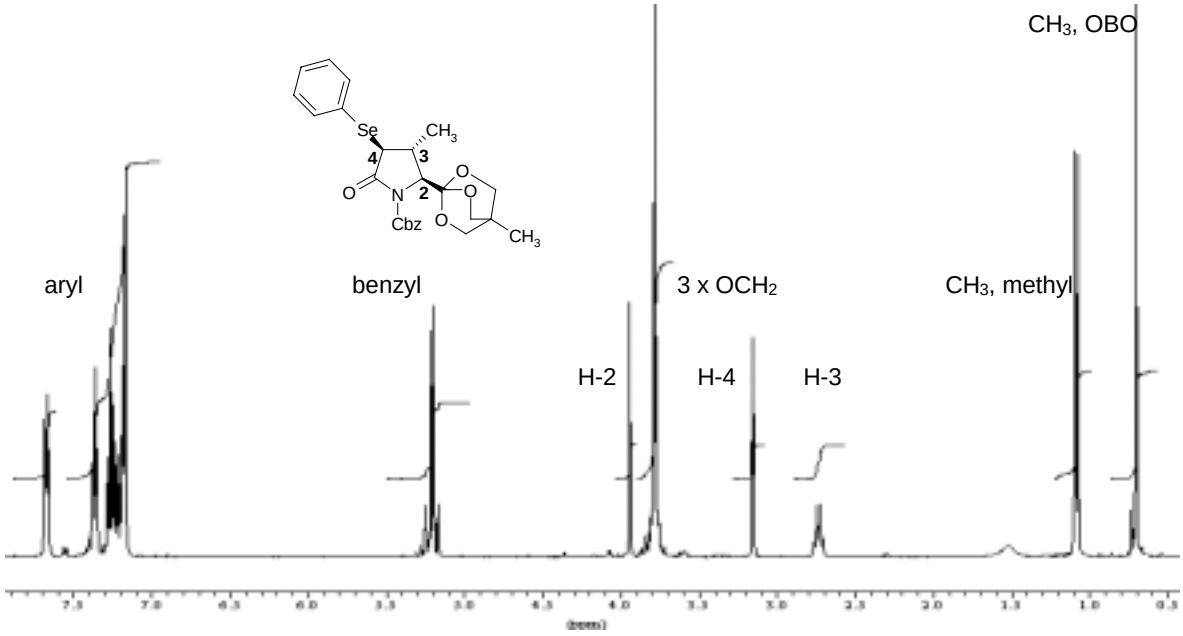


Figure 5.12-6 ^{1}H-NMR spectra of **112** (detail)

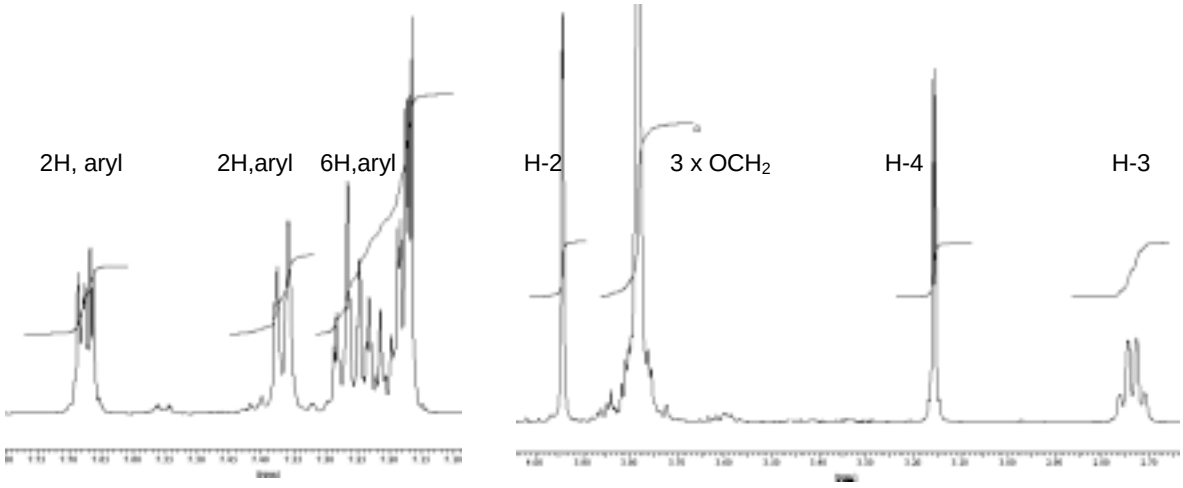
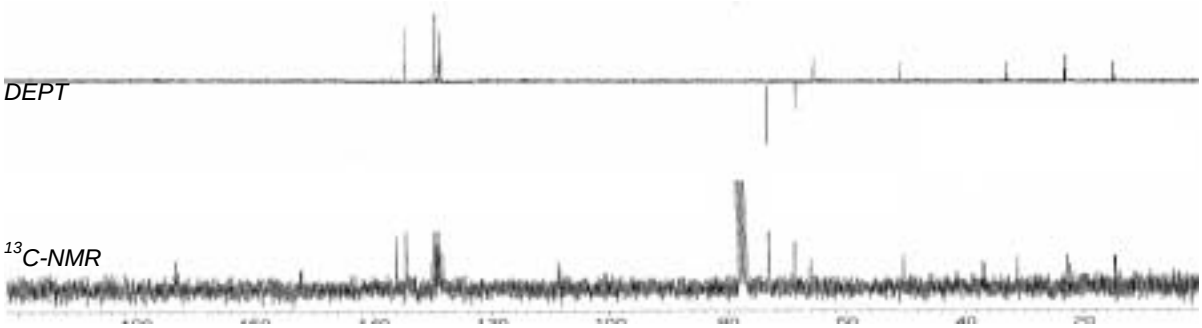


Figure 5.12-7 ^{13}C-NMR and DEPT spectra of **112**



^{13}C NMR ($CDCl_3$): δ = 14.67 (CH_3 , ortho ester), 22.60 (CH_3, methyl), 31.50 ($\underline{C}CH_3(CH_2O\text{-})_3$), 36.81 (C-3), 50.24 (C-4), 66.04 (C-2), 68.71 (CH_2, benzyl), 73.04 (3 x CH_2O), 109.2 ($\underline{C}CH_3(OCH_2)_3$), 127.9, 128.5 (2x), 128.6, 128.8, 128.9, 129.0 (2x), 129.3, 129.4, 134.2, 135.9 (18 x C, aryl), 152.1 (C=O, urethane), 175.6 (C=O, lactam).

Figure 5.12-8 ^{1}H-NMR spectrum of **113**

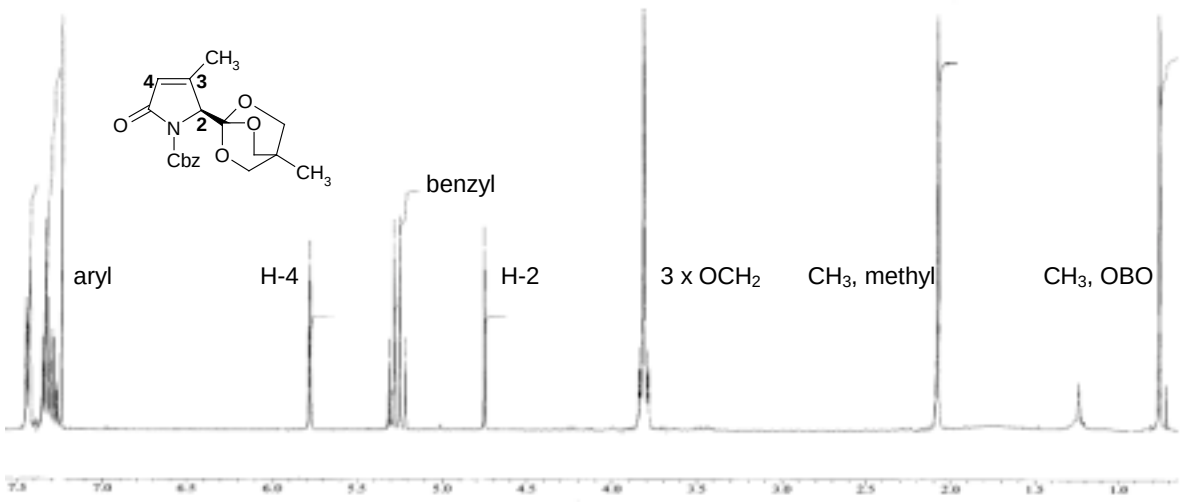


Figure 5.12-9 ^{1}H-NMR spectra of **113** (details)

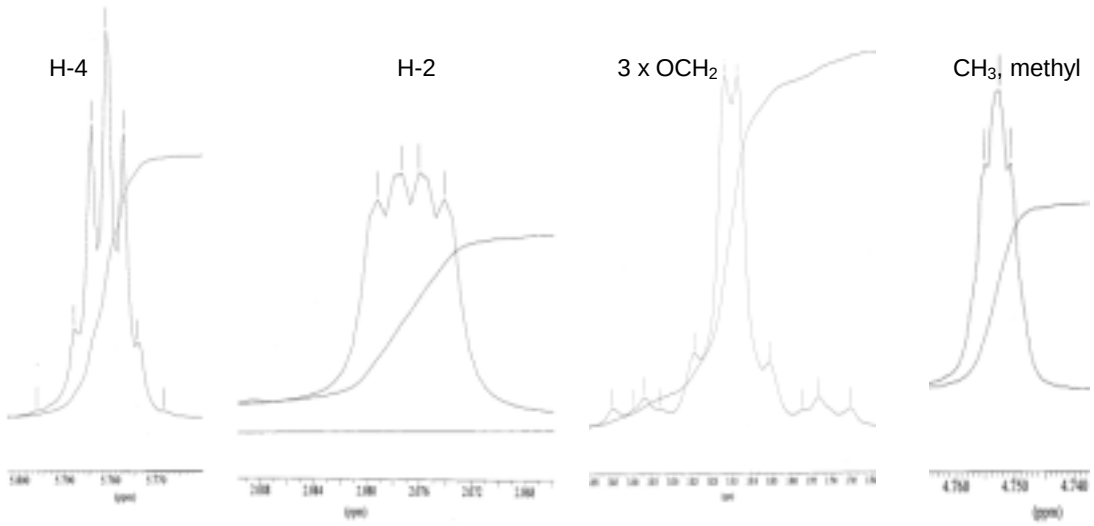
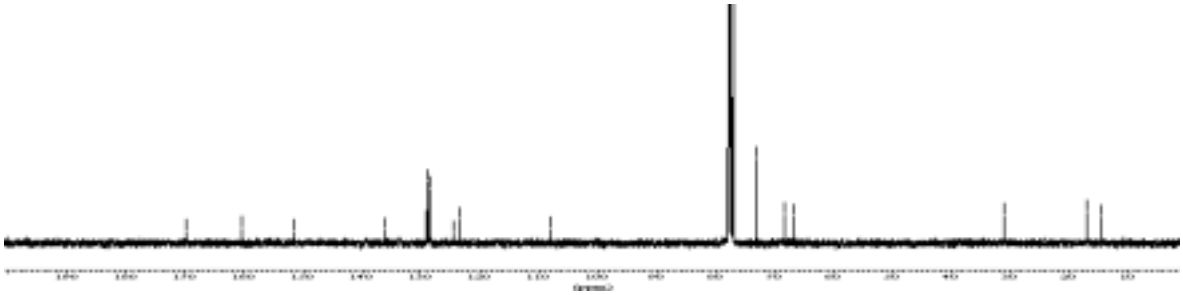


Figure 5.12-10 ^{13}C-NMR spectrum of **113**



^{13}C NMR ($CDCl_3$): δ = 14.62 (CH_3, ortho ester), 16.92 (CH_3), 31.09 ($\underline{C}CH_3(CH_2O\text{-})_3$), 66.77 (C-2), 68.39 ($CH_2$, benzyl), 73.15 (3 x CH_2O), 107.9 ($\underline{C}CH_3(OCH_2)_3$), 123.4 (C-4), 128.5, 128.6 (2x), 128.8, 129.0, 136.1 (6 x C, aryl), 151.5 (C=O, urethane), 160.2 (C-3), 169.8 (C=O, lactam).

Figure 5.12-11 ^{1}H-NMR spectrum of **114**

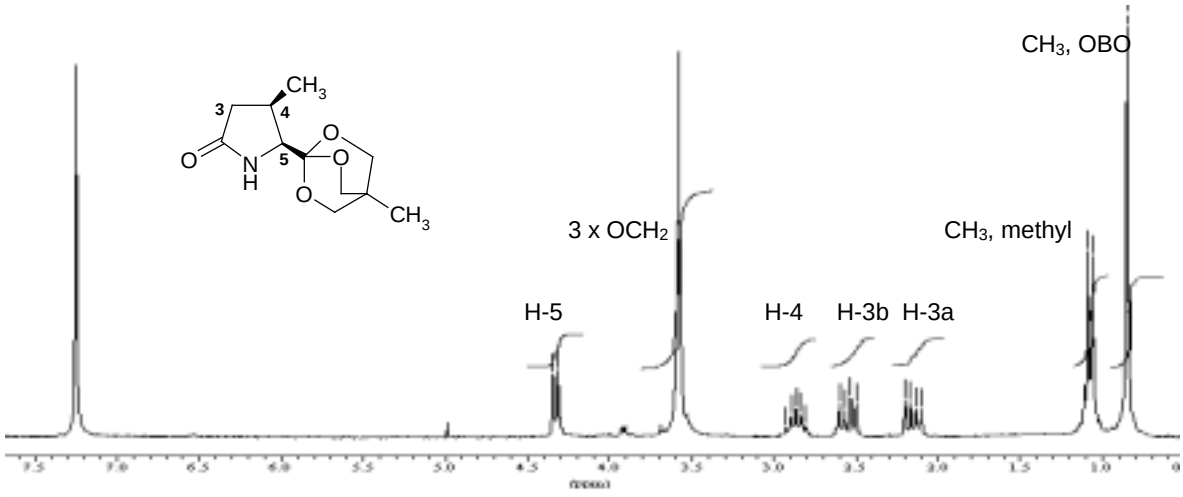


Figure 5.12-12 ^{1}H-NMR spectrum of **114** (detail)

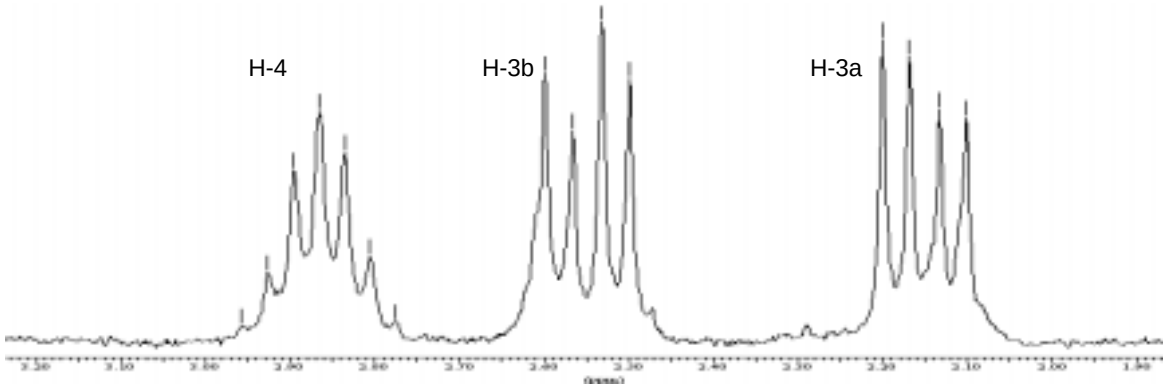
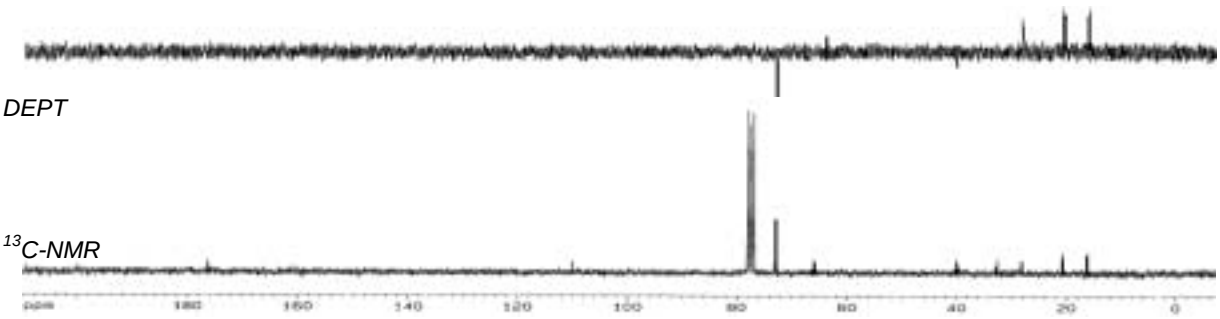


Figure 5.12-13 ^{13}C-NMR and DEPT spectra of **114**



^{13}C NMR ($CDCl_3$): δ = 14.70 (CH_3, ortho ester), 21.81 (CH_3, methyl), 28.20 (C-4), 31.67 ($\underline{C}CH_3(CH_2O\text{-})_3$), 40.51 (C-3), 66.22 (C-5), 72.80 (3 x CH_2O), 109.1 ($\underline{C}CH_3(OCH_2)_3$), 176.1 (C=O, lactam).

Figure 5.12-14 ^{1}H-NMR spectrum of **116**

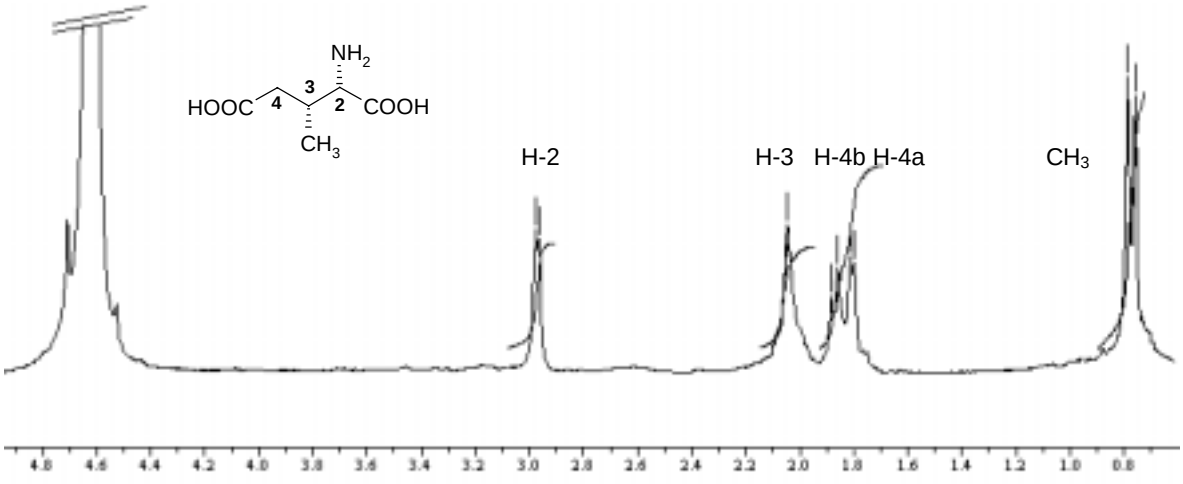


Table 5.12-7

x-H – y-H	J_{x-y} [Hz]
2 – 3	3.4
4a – 3	5.0
4b – 3	9.6
4a – 4b	12.1
CH_3 – 3	7.0

Figure 5.12-15 ^{1}H-NMR spectrum of **116** (detail)

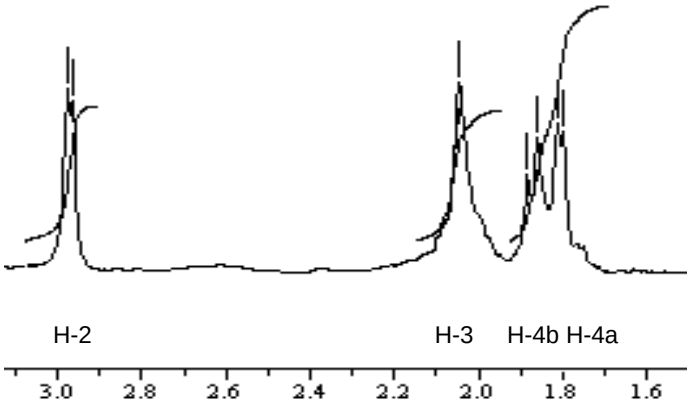
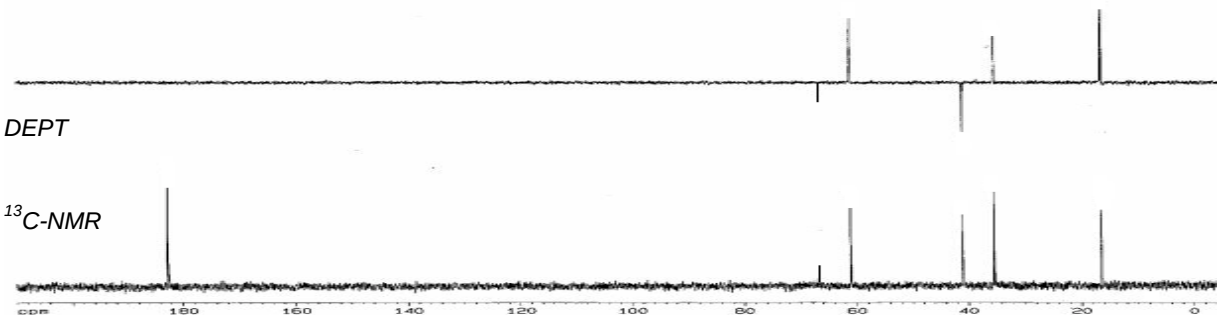


Figure 5.12-16 ^{13}C-NMR and DEPT spectra of **116**

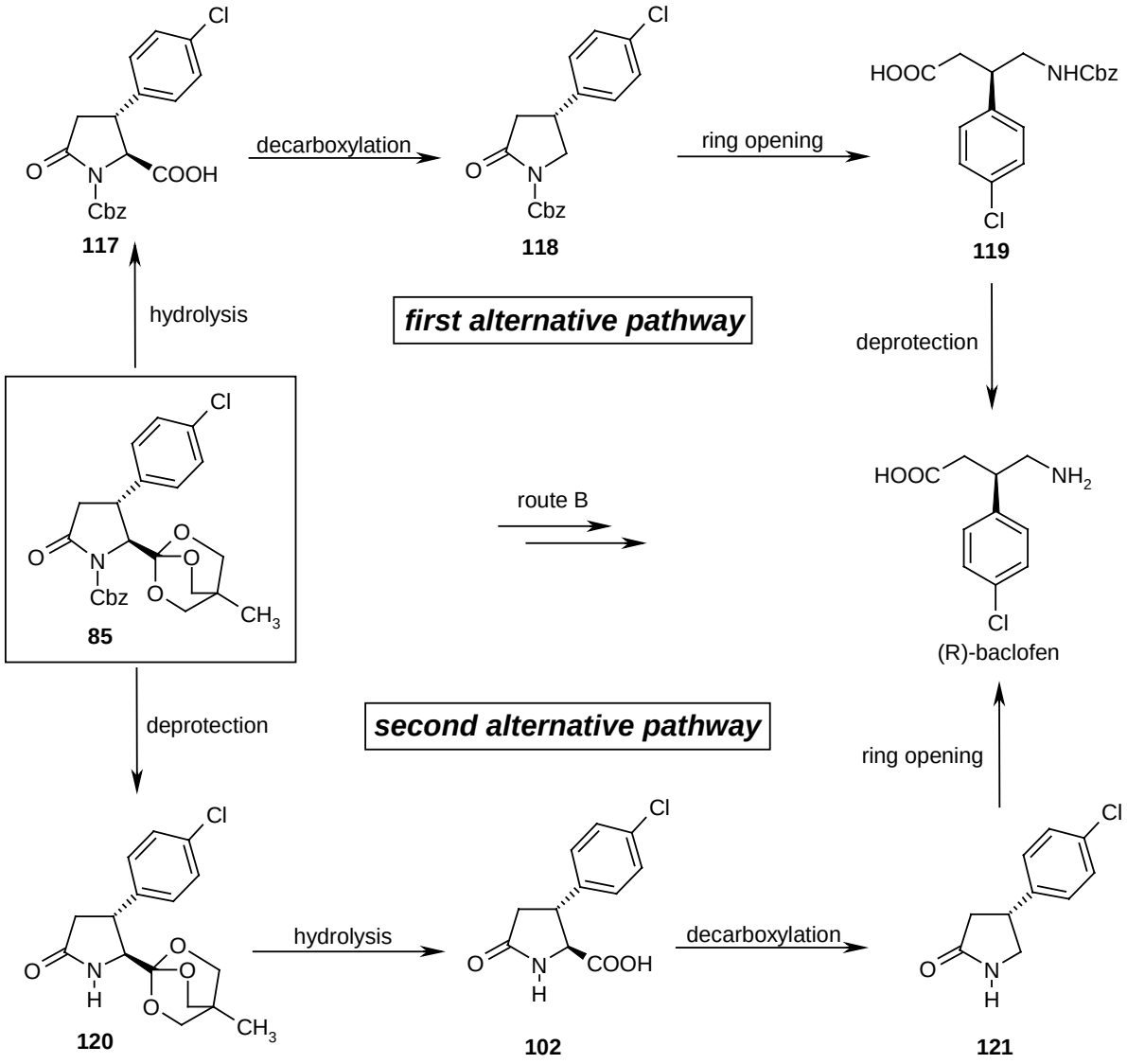


^{13}C NMR (D_2O/NaOD, dioxane): δ = 16.40 (CH_3), 35.85 (C-3), 40.90 (C-4), 61.10 (C-2), 182.8 (COO^-), 183.0 (COO^-).

5.13 CONVERSION OF COMPOUND 85 VIA ROUTE B

According to the plan of synthesis [see: chapter 4], compound **85** was supposed to be converted to (R)-baclofen via route B. For this purpose, two alternative pathways were considered to be suitable [see: Scheme 5.13-1].

Scheme 5.13-1

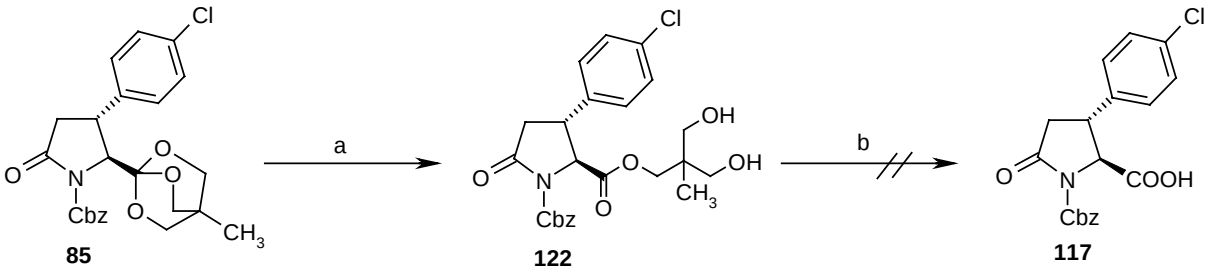


The first alternative path suggests hydrolysis of compound **85** to the N-Cbz protected pyroglutamic acid derivative **117**. The following key step reaction (i.e. decarboxylation) was supposed to provide the decarboxylated compound **118**. The conversion of latter to the ring

opened γ-amino butyric acid derivative **119** should be performed in the presence of lithium hydroxide [compare: chapter 5.7]. Finally, compound **119** was supposed to undergo hydrogenation with palladium on charcoal to yield (R)-baclofen.

An attempt was made to generate (R)- baclofen via the first alternative pathway. Hence, compound **85** succesively was treated with aqueous TFA and caesium carbonate sol. (10%) [see: ref. 69, and chapter 5.8] to hopefully give **117**.

Scheme 5.13-2



However, hydrolysis to the N-Cbz protected pyroglutamate **117** did not succeed anyway. It is pointed out that exclusively the ring opened oxetane ester derivative **122** was available, whereas further conversion to compound **117** failed [see: Scheme 5.13-2].
All attempts for hydrolysis conditions of **85** as well as of the intermediate **122** are outlined in Table 5.13-1.

Table 5.13-1

entry	educt	reaction conditions		product (yield [%])
		a	b	
1	**85**	TFA (5%), 1 h, r. t.	Cs_2CO_3 (10%), up to 7d, r. t.	**122** (95)
2	**85**	TFA (5%), 1 h, r. t.	Li_2CO_3 (10%), up to 7d, r. t.	**122** (90)
3	**85**	HCl (6M), up to 7d, r. t.		**122** (60)
4	**85**	HCl (6M), up to 12 h), reflux		decomp.
5	**85**	TFA (5%), 1 h, r. t.	LiOH (1M), 4 h, r. t.	**94** (70)

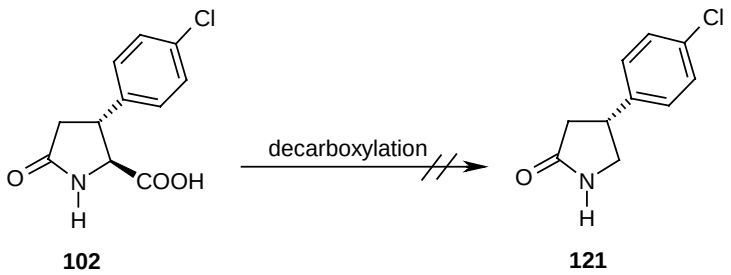
Clearly, hydrolysis of the intermediate **117** in aqueous lithium hydroxide solution (see: b, entry 5, Table 5.13-1) was accompanied by the ring opening reaction of the N-Cbz protected

lactam. Thus, generation of the N-Cbz glutamic acid derivative **94** was observed [compare: chapter 5.7].
An explanation for the failure of the hydrolysis can be given by steric hinderance. The combination of the two bulky residues (i.e. Cbz and the p-chorophenyl substituent of **122**) does not permit hydrolysis at the carboxylic site of **85**. Due to this issue, the second alternative pathway was envisaged to yield (R)-baclofen.

The second alternative pathway [see: Scheme 5.13-1] runs in a different manner. Thus, compound **85** has to be converted to the ortho ester derivative **120** via hydrogenation with palladium on charcoal. According to the described procedure in chapter 5.8, the latter should be hydrolized to afford the C-3-substituted pyroglutamate **102**. Then, compound **102** was supposed to be decarboxylated, to yield the pyrrolidone derivative **121**, that should be ring opened in the presence of aqueous hydrochloric acid to finally provide (R)-baclofen.

According to the deprotection procedure [see: chapter 5.8], compound **85** successfully was converted to the (2S,3R)-3-(4-chorophenyl) pyroglutamate **102**.
Attempts for decarboxylation of **102** utilizing bacteria [132], as well as drastic reaction conditions (i.e. high temperature) [133], have not been regarded, due to their availability and the hazards of decomposition.
Another possibilty for an efficient decarboxylation of α-amino acids was employed [134]. Thus, the educt **102** was refluxed in cyclohexanol/2-cyclohexenone (cat.) for several hours. It pointed out that even after 10 h the starting material **102** partially was recovered, while the generation of the product **121** was not observed.

Scheme 5.13-3



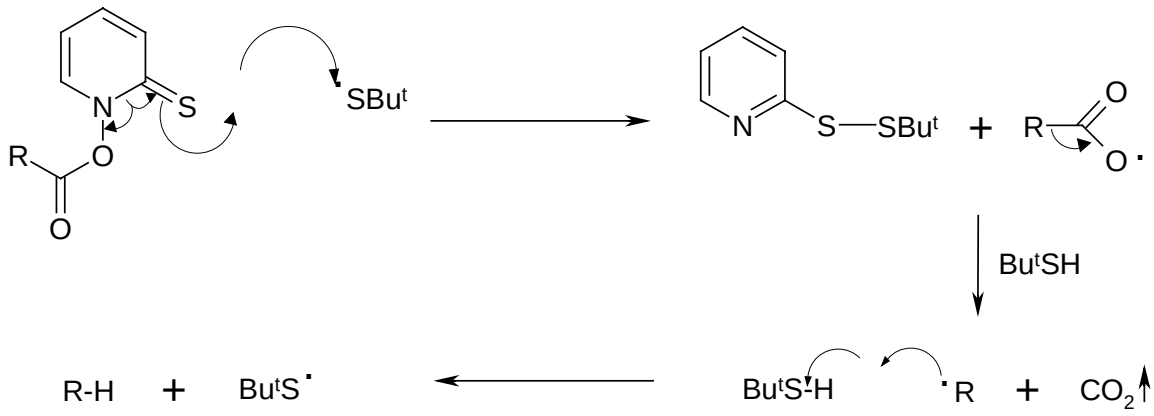
102 **121**

Barton et al. [135] developed a reductive radical decarboxylation reaction for α-amino acids and peptides. Due to the utilization in our group [44,45b] and by others [136] as well as due

to the moderate reaction conditions, this methodology was supposed to provide the decarboxylated compound **121**.

Scheme 5.13-4 shows the radical mechanism of the so-called Barton decarboxylation. This procedure starts with the formation of a mixed anhydride of the amino acid using isobutyl chloroformate and N-methylmorpholine (NMM) at -15 °C in THF (not illustrated). The following addition of N-hydroxypyridinethione and triethylamine affords an intermediate ester of N-hydroxypyridine-2-thione. The latter is kept under UV light in the presence of an excess of t-butyl thiol, to give the radical of the amino acid ($RCO_2\bullet$). This intermediate radical undergoes decarboxylation in the presence of further t-butyl thiol, to finally afford the decarboxylated product (R-H). It is pointed out that the success of this decarboxylation reaction mainly depends on the protection of the amino functionality [135].

Scheme 5.13-4



The pyroglutamate **102** was treated according to this procedure. Unfortunately, conversion to the decarboxylated product **121** failed, even in the presence of a suitable initiation reagent (AIBN).

Furthermore, the usage of the DCC-mediated methodology [135c, and chapter 5.1] to form the intermediate ester of N-hydroxypyridine-2-thione did not succeed. Due to the lack of quantities of compounds, further variants utilizing for example the mixed anhydride methodology [137] were not followed anymore.

Conclusively, it is recorded the fact that the intermediate ester formation between N-hydroxypyridinethione and the unprotected pyroglutamate **102** has not been observed yet.

6 CONCLUSION AND PREVIEW

The introductory chapters of this work present an overview of importance and availability of glutamic acid, pyroglutamic acid, and GABA derivatives. Especially, the pivotal role of glutamate as one of the most important excitatory neurotransmitter in the mammalian central nervous system is described. For this purpose, there are introduced several therapeutical targets physiological glutamate seems to be involved. In order to better characterize the pivotal role of glutamatergic effects, it is pointed out that there is a need to find compounds acting as competitive as well as non-competitive substrates of glutamate.

In the following, there are mentioned published synthesis of C-3-substituted pyroglutamates, C-3-substituted glutamates, and (R)-baclofen representing an important GABA analogue, whereas priority especially is given to the enantiomeric purity as well as stereoselective outcome of described compounds.

The plan of synthesis bases on the idea to generate enantiomerically pure C-3-substituted pyroglutamates and C-3-substituted glutamates, as well as non-racemic (R)-baclofen, derived from (S)-pyroglutamic acid as a starting material. The objective of this ex-chiral-pool synthesis was to ameliorate the serious drawback of the bad atom-economy in the reaction sequence of previously published procedures. To meet all mentioned requirements, the ortho ester functionality (OBO ester) developed by Corey [69] was introduced.

According to the plan of synthesis, the starting material, non-racemic (S)-pyroglutamic acid, was converted to the corresponding oxetane ester **54** via a DCC-mediated esterification. In the following step, the latter was N-protected to provide the N-acceptor substituted pyroglutamic acid oxetane esters **59**-**61**.
The rearrangement of these esters was performed by the methodology of Corey [69] to yield the ortho ester derivatives **65**, **66**, and the racemic compound (±) **rac-65**. Due to the action of boron trifluoride in the rearrangement, the N-Boc ortho ester derivative was not available.
Then, substitution reactions at the C-4 carbon atom of compound **65** were attempted to explore the diastereomeric ratio of resulting C-4-substituted products (cis/trans), also in view of the following introduction of the double bond. The ability of the OBO ester as a bulky protecting group was expected to be sufficient to favour mainly the outcome of one diastereomere, namely of the trans-4-substituted ones. To demonstrate this, corresponding

ratios of the diastereomeric mixtures of the 4-benzyl product cis-**71**/trans-**71** (10:90), and of the 4-phenylselenenyl product cis-**72**/trans-**72** (30:70) were synthesized.
The introduction of the bouble bond was envisaged to provide the N-methoxycarbonyl and N-benzyloxycarbonyl α,β-unsaturated lactams, respectively. The introduction succeeded utilizing compound **72** which was oxidized to undergo a syn-elimination reaction. However, it turned out that the Cbz protecting group plays a pivotal role for stabilization while the syn-elimination occurs, whereas CO_2Me seems to favour decomposition of the intermediate selenoxide derivative. In addition, it is noteworthy that the ortho ester functionality shows instability towards aqueous as well as organic acids. Therefore, employment of anhydrous bases turned out to prevent the ring opening reaction of the OBO functionality. Finally, the α,β-unsaturated lactam **74** was obtained in moderate yield (48 %).

The formation of the trans-configurated compounds **80**-**87** was performed via a copper-mediated conjugate addition to the α,β-enone system of the α,β-unsaturated lactam **74**. The OBO functionality hence was envisaged to support perfect trans selectivity in this cuprate addition to the Michael system of **74**. Spectroscopic NMR-data, on the basis of ^{1}H-, ^{13}C- and DEPT spectra, proved the assumption that the C-3-substituted ortho ester derivatives **80**-**87** exclusively are trans-configurated (i.e. the alkyl derivatives **80**-**83** are (2S,3S)-configurated and the aryl derivatives **84**-**87** are (2S,3R)-configurated).

The conversion of compound **85** to (R)-baclofen via route B yet failed. Both introduced alternative pathways did not succeed. On the one hand, hydrolysis of **85** to the N-Cbz-3-(4-chlorophenyl) pyroglutamate **117** failed due to combination of the two bulky residues (i.e. Cbz and the p-chorophenyl substituent), which prevent for steric reasons hydrolysis at the carboxylic site of **85**. On the other hand, decarboxylation of the 3-(4-chlorophenyl) pyroglutamate **102** to the corresponding pyrrolidine **121** did not succeed. The essential ester formation between compound **102** and N-hydroxypyridine-2-thione has not been observed yet.

Chapter 5.7 describes the conversion of the lactams **80**-**87** to the ring opened N-Cbz-3-alkyl glutamates **89**-**91** and N-Cbz-3-aryl glutamates **93**-**95** via route A-1. However, the N-Cbz-3-naphthyl glutamate **96** turned out to be partially N-deprotected, so that an inseparable mixture of **96** and **111** (ratio 10:1) was observed. This mixture was employed in the further step for the preparation of the unprotected glutamate **111**.
Then, the conversion of the lactams **80**-**87** to the 3-alkyl pyroglutamate **98** and 3-aryl pyroglutamates **101**-**102**, and **104** via route A-2 was introduced. To prove the assumption that the 3-ethyl derivative **98** possesses (2S,3S)-configuration, and the 3-aryl substituted

derivatives **101**-**102**,**104** possess (2S,3R)-configuration, respectively, the unambiguous assignment of the protons as well as carbon atoms was performed, utilizing available ^{1}H-, ^{13}C- and DEPT spectra.

In the following, the preparation of the trans-configurated (2S,3S)-3-alkyl glutamates **106**-**108** and (2S,3R)-3-aryl glutamates **109**-**111** was described. According to the plan of synthesis, both alternative routes (route A-1 and route A-2) were explored and observed results were compared. On the one hand, the N-Cbz-C-3-substituted glutamates (**89**-**91**, **93**-**96**) were transformed via route A-1, and on the other hand the C-3-substituted pyroglutamates (**98**, **101**-**102**, **104**) were reacted via route A-2, to finally provide the corresponding C-3-substituted glutamates. It turned out that route A-1 in comparison with route A-2 provided higher yields, and furthermore is to be prefered due to its more elegant way of preparation.

According to route A-3, the ortho ester compound **80** was supposed to undergo a transformation sequence to give the cis-configurated glutamic acid derivative **116**. Therefore, the introduction of the double bond was carried out utilizing successively the C-4 substitution with phenylselenyl chloride and the syn-elimination reaction to give the α,β-unsaturated lactam **113**. The availability of the all-trans 3,4-disubstituted phenyselenenyl derivative **112** as well as of compound **113** was proved on the basis of spectroscopic NMR-data. The following hydrogenation with palladium on charcoal exclusively yielded the cis-configurated ortho ester compound **114**. Finally, hydrolysis of **114** provided the cis-configurated (2S,3R)-3-methyl glutamate **116**. The comparison of the diastereomeres **106** and **116** unambiguously proved their (2S,3S)- and (2S,3R)-configuration, respectively.

Conclusively, there can be recorded the fact that the serious drawback of the bad atom-economy in the reaction sequence previously used can be circumvented by the introduction of the OBO functionality, so the concept of an improved atom-economy is achieved. Additionally, in comparison to the silyl-ether-mediated synthesis, the OBO functionality provided crystalline ortho ester derivatives, which facilitated their purification as well as characterization. Due to mentioned issues, the preparation of (R)-baclofen failed until now.

The employment of the ortho ester functionality in this work shows an opportunity to synthesize enantiopure C-3-substituted proline derivatives [138]. Especially, the 3-alkyl ortho ester derivatives **80**-**83** allow substitution at C-4 to generate further all-trans 3,4-disubstituted pyroglutamic acid as well as all-trans 3,4-disubstituted proline derivatives.

6 ZUSAMMENFASSUNG UND AUSBLICK

Die Eingangskapitel dieser Arbeit vermitteln einen Überblick über die Bedeutung und das Vorkommen von Glutaminsäuren, Pyroglutaminsäuren und GABA-Derivaten. Im Besonderen wird hierbei die herausragende Rolle des Glutamats als einen der wichtigsten exzitatorischen Neurotransmitter im ZNS beschrieben. Zu diesem Zweck werden einige therapeutische Ansätze vorgestellt, bei denen physiologisch vorkommendes Glutamat involviert zu sein scheint. Um die bedeutende Rolle glutamerger Effekte besser darstellen zu können, ist es von großem Interesse sowohl Substanzen mit kompetetiven als auch nicht-kompetetiven Eigenschaften des Substrats Glutamat zu finden.
Im Folgenden wird auf publizierte Synthesen von C-3-substituierten Pyroglutamaten und Glutamaten, sowie (R)-Baclofen eingegangen, wobei letzteres ein wichtiges GABA-Analoges repräsentiert. Hierbei wird das Augenmerk besonders auf Enantiomerenreinheit und die stereoselektive Ausbeute der beschriebenen Substanzen gelenkt.

Der Syntheseplan basiert auf der Idee C-3-substituierte Pyroglutamate und Glutamate, sowie nicht-razemisches (R)-Baclofen aus (S)-Pyroglutaminsäure als Ausgangsmaterial zu gewinnen. Das Ziel dieser Ex-chiral-pool-Synthese war die unzulängliche Wirtschaftlichkeit bereits bekannter Verfahren zu verbessern. Um diesen Anforderungen gerecht zu werden, wurde die von Corey [69] entwickelte Orthoester-Funktionalität (OBO Ester) eingeführt.

Dem Syntheseplan entsprechend wurde die Ausgangskomponente, nicht-razemische (S)-Pyroglutaminsäure, über eine DCC-vermittelte Veresterung zum Oxetanester **54** umgesetzt. Der Oxetanester wurde daraufhin N-geschützt, wobei die N-Akzeptor-substituierten Pyroglutaminsäureoxetanester **59**-**61** erhalten wurden.
Die Umlagerung dieser Ester wurde der Methode von Corey entsprechend ausgeführt, wobei die Orthoester Derivate **65**, **66** und die razemische Komponente (±) **rac-65** als Produkte gewonnen wurden. Das N-Boc-Orthoester-Derivat konnte aufgrund des hohen lewissauren Potentials von Bortrifluorid während der Umlagerung nicht erhalten werden.
Anschließend wurden Substitutionsreaktionen am C-4 Kohlenstoff von Komponente **65** durchgeführt, um das Diastereomerenverhältnis der resultierenden C-4-substituierten Produkte (cis/trans) zu untersuchen. Dies erfolgte auch im Hinblick auf die noch einzuführende Doppelbindung. Die Fähigkeit des OBO Esters als eine voluminöse Schutzgruppe sollte entscheidend zur Gewinnung eines Diastereomers beitragen, nämlich der des trans-4-substituierten. Um dies zu demonstrieren wurden die entsprechenden

Verhältnisse der Diastereomerenmischungen des 4-Benzyl Produkts cis-**71**/trans-**71** (10:90) und des 4-Phenylselenenyl Produkts cis-**72**/trans-**72** (30:70) synthetisiert.
Das N-Methoxycarbonyl- bzw. N-Benzyloxycarbonyl-α,β-ungesättigte Lactam sollte bei der Einführung der Doppelbindung erhalten werden. Den Erfolg erzielte man durch den Einsatz von **72**, welches nach Oxidation und syn-Eliminierung erhalten wurde. Jedoch stellte sich heraus, daß die Cbz-Gruppe entscheidend zur Stabilisierung während der syn-Eliminierung beitrug, wohingegen CO_2Me die Zersetzung des intermediär auftretenden Selenoxidderivats zu unterstützen schien. Zusätzlich ist die Instabilität der Orthoester-Funktionalität gegenüber wäßrigen und organischen Säuren zu beachten. Aufgrund dessen wurden nichtwäßrige Basen eingesetzt, um eine Ringöffnungsreaktion des OBO Esters zu verhindern. Schließlich wurde das α,β-ungesättigte Lactam **74** in einer moderaten Ausbeute von 48 % erhalten.

Die trans-konfigurierten Substanzen **80**-**87** wurden über eine kupferkatalysierte 1,4-Addition an das α,β-Enon-System von **74** erhalten. Hiebei war zu erwarten, daß die OBO-Funktionalität ausschließlich trans-Selektivität bei der Cuprat-Addition an das Michael System von **74** gewährleistet. ^{1}H-, ^{13}C- und DEPT-Spektren und die daraus erhaltenen Daten lieferten den Beweis, daß die C-3-substituierten Orthoester-Derivate **80**-**87** nur trans-Konfiguration aufwiesen, d.h. die Alkylderivate **80**-**83** sind (2S,3S)-konfiguriert bzw. die Arylderivate **84**-**87** (2S,3R)-konfiguriert.

Die Umwandlung von **85** zum (R)-Baclofen über Route B gelang bisher nicht. Die dargestellten Alternativen schlugen fehl. Einerseits misslang die Hydrolyse von **85** zum N-Cbz-3-(4-chlorphenyl)pyroglutamat **117**, wobei sich dies auf die Kombination der beiden voluminösen Reste (N-Cbz und p-Chlorphenyl) und der sich daraus ergebenden sterischen Hinderung zurückführen läßt. Andererseits brachten Decarboxylierungsversuche des 3-(4-Chlorphenyl)pyroglutamats **102** zum entsprechenden Pyrrolidon **121** ebenso keinen Erfolg. Hierbei konnte die notwendige Veresterung zwischen **102** und N-Hydroxypyridin-2-thion bisher nicht beobachtet werden.

Kapitel 5.7 beschreibt die Umwandlung der Lactame **80**-**87** zu den ringoffenen N-Cbz-3-alkylglutamaten **89**-**91** und N-Cbz-3-arylglutamaten **93**-**95** über Route A-1.
Dabei stellte sich heraus, daß das N-Cbz-3-naphthylglutamat teilweise entschützt war, wodurch ein untrennbares Gemisch aus **96** und **111** (Verhältnis 10:1) entstand. Dieses Gemisch konnte jedoch im weiteren Verlauf der Synthese zum ungeschützten Glutamat **111** umgesetzt werden.
Daraufhin wurde die Umwandlung der Lactame **80**-**87** zum 3-Alkylpyroglutamat **98** und den 3-Arylpyroglutamaten **101**-**102** und **104** über Route A-2 vorgestellt. Um die Vermutung zu

bestätigen, daß das 3-Ethylderivat **98** (2S,3S)-konfiguriert bzw. die Derivate **101**-**102**, **104** (2S,3R)-konfiguriert sind, wurden sowohl die entsprechenden Wasserstoff- als auch Kohlenstoffatome zweifelsfrei auf der Basis vorhandener ^{1}H-, ^{13}C- und DEPT-Spektren zugeordnet.

Die Gewinnung der trans-konfigurierten (2S,3S)-3-Alkylglutamate **106**-**108** und der (2S,3R)-3-Arylglutamate **109**-**110** wurde im Folgenden beschrieben. Beide Alternativrouten, Route A-1 und Route A-2, wurden dem Syntheseplan entsprechend getestet und resultativ miteinander verglichen. Zum einen wurden die N-Cbz-C-3-substituierten Glutamate (**89**-**91**, **93**-**96**) über Route A-1, zum anderen die C-3-substituierten Pyroglutamate (**98**, **101**-**102**, **104**) über Route A-2 zu den entsprechenden C-3-substituierten Glutamaten transformiert. Aufgrund höherer Ausbeuten und einer eleganteren Darstellungsweise ist hierbei Route A-1 zu bevorzugen.

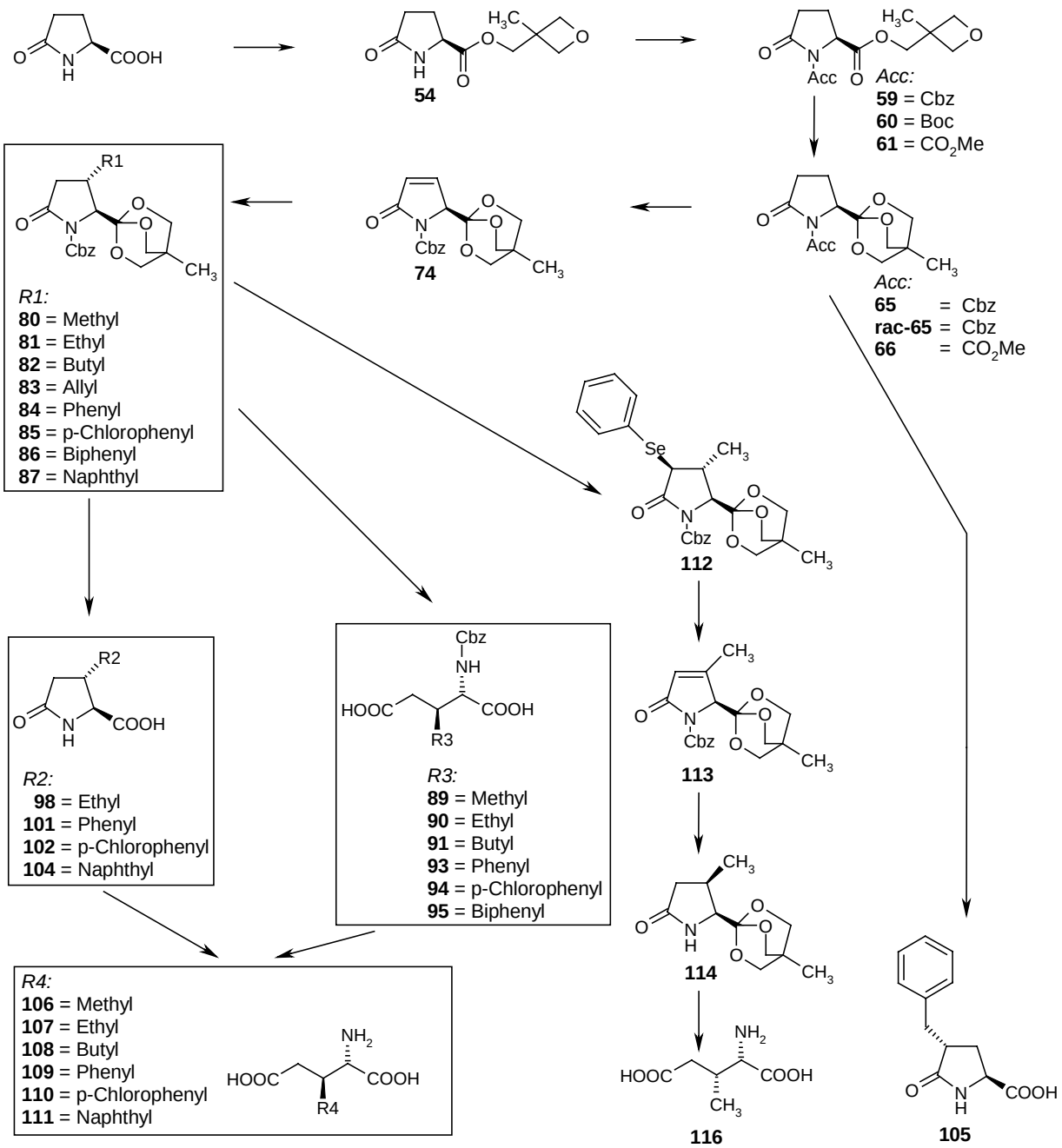
Über Route A-3 sollte dementsprechend das cis-konfigurierte Glutaminsäurederivat **116** aus dem Orthoester-Derivat **80** über mehrere Syntheseschritte erhalten werden. Das α,β-ungesättigte Lactam **113** wurde sukzessiv durch C-4-Substitution mit Phenylselenylchlorid und einer syn-Eliminierungsreaktion aus Komponente **80** erhalten. Die Existenz des all-trans 3,4-disubstituierten Phenylselenenyl-Derivats **112** und der Komponente **113** wurde anhand spektroskopischer NMR-Daten bewiesen. Die anschließende Hydrierung mit Pd/Aktivkohle lieferte ausschließlich den cis-konfigurierten Orthoester **114**. Dieser wurde letztendlich zum (2S,3R)-3-Methylglutamat **116** hydrolisiert. Der Vergleich der Diastereomeren **106** und **116** bewies eindeutig ihre (2S,3S)- bzw. (2S,3R)-Konfiguration.

Zusammenfassend läßt sich feststellen, daß der Nachteil der unzulänglichen Wirtschaftlichkeit früherer Synthesen durch die Einführung der OBO-Funktionalität umgangen werden kann, so daß letztendlich das Konzept einer verbesserten „atom-economy“ erreicht wurde. Zusätzlich lieferte die OBO-Funktionalität im Vergleich mit Silylether-Synthesen den Vorteil kristalliner Orthoester-Produkte, was sowohl die Aufarbeitung als auch deren Charakterisierung erleichterte. Aufgrund der bereits erörterten Probleme ist die Synthese des (R)-Baclofen bisher noch nicht gelungen.

Der Einsatz der Orthoester-Funktionalität in dieser Arbeit eröffnet somit eine weitere Möglichkeit enantiomerenreine C-3-substituierte Prolin-Derivate zu synthetisieren [138]. Die 3-Alkylorthoester-Derivate **80**-**83** bieten hierbei insbesondere die Möglichkeit der Substitution an C-4, um sowohl all-trans 3,4-disubstituierte Pyroglutamate als auch all-trans 3,4-disubstituierte Proline zu gewinnen.

7 OVERVIEW

Scheme 7-1



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9 LIST OF ABBREVIATIONS

Acc	=	acceptor
AcOH	=	acetic acid
AIBN	=	α,α'-azo-isobutyronitrile
b.p.	=	boiling point
Boc	=	t-butoxycarbonyl
Bu	=	butyl
c	=	concentration
Cbz	=	benzyloxycarbonyl
CH_2N_2	=	diazomethane
conc.	=	concentrated
δ	=	chemical shift
d	=	duplet, day
DABCO	=	1,4-diazabicyclo[2.2.2]octan
DCC	=	dicylohexyl carbodiimide
DCU	=	dicylohexyl urea
dd	=	duplet of duplet
DDQ	=	2,3-dichloro-5,6-dicyanobenzochinone
de	=	diastereomeric excess
DMAP	=	4-dimethylaminopyridine
DMF	=	dimethylformamide
DMSO	=	dimethylsulfoxide
Et	=	ethyl
Et_2O	=	diethyl ether
EtOAc	=	ethyl acetate
EtOH	=	ethanol
h	=	hour
iPr	=	2-propanol
J	=	coupling constant
LDA	=	lithiumdiisopropyl amide
m	=	meta, multiplet
m.p.	=	melting point
m-CPBA	=	meta-chloroperbenzoic acid
Me	=	methyl
MeCN	=	acetonitrile
MeOH	=	methanol

n-BuLi	=	butyllithium
NEt_3	=	triethylamine
OBO	=	2,6,7-trioxobicyclo[2.2.2]octane
p	=	para
PhSeCl	=	phenylselenenyl chloride
q	=	quartet
r.t	=	room temperature
s	=	second, singulet
satd.	=	saturated
t	=	triplet
TBDPS	=	tert.-butyldiphenyl silane
TFA	=	trifluoro acetic acid
THF	=	tetrahydrofurane
TLC	=	thin-layer chromatography
TMEDA	=	N,N,N',N'-tetramethylenediamine
TMSCl	=	trimethylsilyl chloride
Tos	=	p-toluenesulfonyl (tosyl)

II EXPERIMENTAL SECTION

1 GENERAL DATA

1.1 NOMENCLATURE

Compounds in the Experimental Section are conform to IUPAC nomenclature. Therefore, numbering of the unprotected lactam **114** differs due to priority of substituents. In order to facilitate description, compounds in the General Section mainly were named after their protection group (i.e. Cbz and Boc as prefix, ortho ester as suffix) as well as after their heterocyclic backbone (i.e. lactam etc).

1.2 GENERAL PROCEDURES

Thin-layer chromatography (TLC) was performed on Merck precoated silica gel 60 F_{254} sheets. Compounds were visualized on TLC sheets utilizing UV light (254 nm) and/or iodine vapor.

Column chromatography (CC) was performed on Merck silica gel 60 (0.0063-0.200 mm).

Melting points are uncorrected and were determined with a Büchi 510 apparatus.

IR-spectra were recorded on a Perkin-Elmer spectrophotometer 681 and on a Bio-Rad FT-IR Pharmalyzir spectrophotometer.

Optical rotations were determined with a Perkin-Elmer polarimeter 241 at 589 nm (20 °C).

NMR-spectra were measured on a Bruker AC200 instrument (200 MHz for ^{1}H-NMR and 50 MHz for ^{13}C-NMR), Bruker AC250 instrument (250 MHz for ^{1}H-NMR and 62.5 MHz for ^{13}C-NMR), and Bruker AVANCE 400 instrument (400 MHz for ^{1}H-NMR and 100 MHz for ^{13}C-NMR). For ^{1}H-NMR, TMS (δ = 0.00 ppm) or 1,2-dioxane (δ = 3.70 ppm) was used as internal standard for spectra recorded in organic solvents or D_2O, respectively. For ^{13}C-NMR, corresponding organic solvents were used as internal standard ($CDCl_3$: 77.0 ppm; DMSO-d_6:

39.5 ppm; CD_3OD: 49.0 ppm) or 1,2-dioxane (δ = 67.6 ppm) for measurement in D_2O, respectively.

Eletron impact mass spectra (MS) were determined by the Mass Spectrometry Laboratory of the Department of Organic Chemistry at the University of Würzburg on a Finnigan MAT 8200 instrument at 70 eV.

Elemental analyses were carried out at the Microanalytical Laboratory of the Department of Inorganic Chemistry at the University of Würzburg.

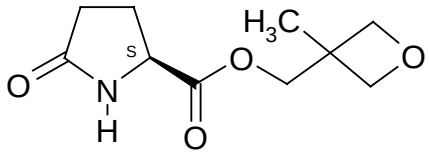
Evaporations were performed under vacuo (with a specific vacuo for each solvent at a temperature of approx. 40°C for water-bath) on a rotary evaporator.

Reactions were performed under a positive pressure of nitrogen or argon.

Solvents and **reagents** were purchased from commercial sources (Fluka, Sigma-Aldrich, Merck, Riedel de Haen, Janssen) and used as received, unless otherwise indicated.
Solvents were generally destilled prior to use. Following procedures for purification were applied: Tetrahydrofuran (THF) was dried over KOH, then refluxed, afterwards destilled from oil-free sodium hydride. Diethyl ether was dried over calcium chloride, then destilled from sodium. Acetonitril was destilled from calcium chloride. Dichloromethane was destilled from phosphorus pentoxide.

2 PREPARATION OF COMPOUNDS

(2S)-5-Oxo-pyrrolidine-2-carboxylic acid 3-methyl-oxetan-3-ylmethyl ester (54)



To a suspension of L-pyroglutamic acid (20.00 g, 0.155 mol) and 3-hydroxymethyl-3-methyl-oxetane (15.82 g, 0.155 mol) in dichloromethane (300 ml), was added a solution of DMAP (0.950 g, 0.008 mol) and DCC (31.96 g, 0.155 mol) in CH_2Cl_2 (180 ml) over 30 min at ambient temperature. The suspension was stirred for 2 h and the colourless solid was removed by suction and rinsed with CH_2Cl_2. The organic phases were concentrated to 200 ml and extracted with water (2 x 250 ml). The combined water extracts were concentrated under reduced pressure to give **54** as a colourless oil, which was purified by column chromatography on silica gel using EtOAc as an eluent. Yield: 24.7 g (75 %).

TLC: $R_f \sim 0.2$ (EtOAc).- $[\alpha]_D^{20} = -6.72$ (c = 6.1, EtOAc).

$C_{10}H_{15}NO_4$ (213.23): calcd. C 56.33, H 7.09, N 6.57; found C 56.68, H 7.08, N 6.23.

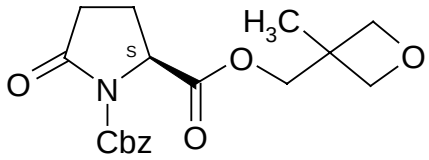
IR (neat): ν = 3250 cm^{-1}, 2970, 2890 (C-H), 1750, 1700 (C=O), 1470 (C-H), 1200.

^{1}H-NMR ($CDCl_3$): δ = 1.31 (s, 3 H, CH_3), 2.10–2.65 (m, 4 H, H-3a/b and H-4a/b), 4.20 and 4.25 (d, 2 H, J = 12.0 Hz, $COOCH_2$), 4.20–4.35 (m, 1 H, H-2), 4.38 (d, J = 7.0 Hz, 2 H, CH_2OCH_2), 4.47 and 4.48 (2d, 2 H, J = 7.0 Hz, CH_2OCH_2), 7.08 (s, 1H, NH).

^{13}C-NMR ($CDCl_3$): δ = 20.81 ($\underline{C}H_3$), 24.79 (C–3), 29.12 (C–4), 39.98 ($\underline{C}CH_3(CH_2O)_2$), 55.41 (C–2), 69.27 ($COO\underline{C}H_2$), 79.11 (2 x $\underline{C}H_2O$), 172.1 (C=O, ester), 178.2 (C=O, lactam).

MS (70 eV), m/z (%): 213 (2) [M^+], 169 (1), 84 (100) [M^+ - oxetylate], 56 (11), 41 (11).

(2S)-1-Benzyloxycarbonyl-5-oxo-pyrrolidine-2-carboxylic acid 2-(3-methyl-oxetan-3-yl-methyl) ester (59)



To a solution of **54** (7.74 g, 0.036 mol) and DABCO (4.07 g, 0.036 mol) in THF (100 ml) was added butyllithium (25.0 ml, 0.040 mol, 1.6 M in hexane) at –78 °C. The mixture was stirred for 30 min, then benzyloxycarbonylchloride (6.81 g, 0.040 mol) was added. After stirring for 3 h at –78 °C and then room temp., the reaction was quenched with satd. ammonium chloride solution (100 ml) and the organic layer was diluted with ethylacetate (100 ml). The organic phase was washed with satd. ammonium chloride solution, brine, dried over sodium sulfate and concentrated. The residue was column chromatographed on silica gel with EtOAc/petroleum ether (10+1) to give **59** as a colourless oil. Yield: 4.74 g (39 %).

TLC: R_f ~ 0.4, EtOAc/petroleum ether (10+1).- $[\alpha]_D^{20}$ = -19.9 (c = 3.0, CH_2Cl_2).

$C_{18}H_{21}NO_6$ (347.37): calcd. C 62.24, H 6.09, N 4.03; found C 62.19, H 6.15, N 3.93.

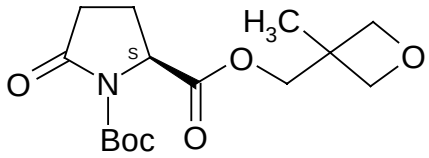
IR (neat): ν = 2960 cm^{-1}, 2880, 1470 (C-H), 1800, 1750 (C=O).

^{1}H-NMR ($CDCl_3$): δ = 1.24 (s, 3 H, CH_3), 2.05–2.75 (m, 4 H, H-3a/b, H-4a/b), 4.14 and 4.20 (2d, 2 H, J = 11.0 Hz, $COOCH_2$), 4.31 and 4.32 (2d, 2 H, J = 8.0 Hz, CH_2OCH_2), 4.39 and 4.40 (2d, 2 H, J = 8.0 Hz, CH_2OCH_2), 4.72 (m, 1 H, H-2), 5.22 (d, 1 H, J = 12.1 Hz, CH_2, benzyl), 5.30 (d, 1H, J = 12.1 Hz, CH_2, benzyl), 7.39–7.31 (m, 5 H, aryl).

^{13}C-NMR ($CDCl_3$): δ = 20.81 ($\underline{C}H_3$), 21.85 (C–3), 30.91 (C–4), 39.05 ($\underline{C}CH_3(CH_2O)_2$), 58.61 (C–2), 68.36 ($CH_2$, benzyl), 69.48 ($COO\underline{C}H_2$), 79.08 (2 x CH_2O), 128.1, 128.4, 128.5 (5 x C, aryl), 134.9 (1 x C, aryl), 150.9 (C=O, urethane), 171.0 (C=O, lactam), 172.5 (C=O, ester).

MS (70 eV), m/z (%): 347 (9) [M^+], 212 (4) [M^+- Cbz], 157 (25), 91 (100) [benzyl], 84 (53), 65 (7).

(2S)-1-(t-Butoxycarbonyl)-5-oxo-pyrrolidine-2-carboxylic acid 2-(3-methyl-oxetan-3-yl-methyl) ester (60)



To a solution of HMDS (6.57 g, 0.032 mol) in THF (25 ml) buthyllithium (11.10 ml, 0.030 mol, 2.7 M in heptane) was added with stirring at –78 °C for 15 min. Then a solution of **54** (6.20 g, 0.029 mol) in THF (25 ml) was added dropwise. After 15 min. $(Boc)_2O$ (9.38g, 0.043 mol) dissolved in THF (20 ml) was added slowly to the stirred suspension. After vigorous stirring for 3 h at –78 °C the reaction was quenched with satd. ammonium chloride solution (100 ml), the organic layer was diluted with ethylacetate (150 ml) and washed with satd. ammonium chloride solution, brine and water, dried over sodium sulfate and concentrated in vacuo. The oily residue was column chromatographed on silica gel with EtOAc/petroleum ether (10+1) to give **60** as a yellow oil. Yield. 6.10 g (66 %).

TLC: R_f ~ 0.45, EtOAc/petroleum ether (10+1).- $[\alpha]_D^{20}$ = -23.8 (c = 1.40, CH_2Cl_2).

$C_{15}H_{23}NO_6$ (313.35): calcd. C 57.50, H 7.40, N 4.47; found C 57.41, H 7.42, N 4.44.

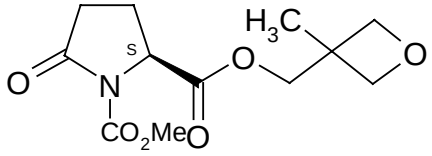
IR (neat): ν = 2960 cm^{-1}, 2880 (C-H), 1790, 1760, 1740 (C=O), 1470 (C-H).

^{1}H-NMR ($CDCl_3$): δ = 1.32 (s, 3 H, CH_3, oxetane), 1.48 (s, 9H, CH_3, Boc), 1.79–2.21 (m, 1H, H-4a/b), 2.23-2.73 (m, 3 H, H-3a/b and H-4a/b), 4.24 and 4.30 (2d, 2 H, J = 12.0 Hz, $COOCH_2$), 4.39 (d, 2 H, J = 6.1 Hz, CH_2OCH_2), 4.47 and 4.48 (2d, 2 H, J = 6.1 Hz, CH_2OCH_2), 4.62-4.68 (m, 1 H, H-2).

^{13}C-NMR ($CDCl_3$): δ = 20.93 (CH_3, oxetane), 21.64 (C–3), 27.85 ($C\underline{C}H_3)_3$, Boc), 31.09 (C–4), 39.18 ($\underline{C}CH_3$ $(CH_2O)_2$), 58.76 (C–2), 69.59 ($COO\underline{C}H_2$), 79.22 (2 x CH_2O), 83.66 ($\underline{C}(CH_3)_3$, Boc), 149.4 (C=O, urethane), 171.4 (C=O, lactam), 172.8 (C=O, ester).

MS (70 eV), m/z (%): 313 (0) [M^+], 213 (2) [M^+- Boc], 130 (16), 84 (100), 57 (49).

(2S)-1-(Methoxycarbonyl)-5-oxo-pyrrolidine-2-carboxylic acid 2-(3-methyl-oxetan-3-yl-methyl) ester (61)



To a suspension of **54** (8.74 g, 0.041 mol) and DABCO (5.05 g, 0.045 mol) in THF (150 ml) was added buthyllithium (16.60 ml, 0.045 mol, 2.7 M in heptane) at –78 °C. After 15 min methylcyano formate (3.87 ml, 0.049 mol) was added dropwise. After vigorous stirring for 3 h at –78 °C, the reaction was quenched with satd. ammonium chloride solution (100 ml). The mixture was diluted with ethylacetate (150 ml), and the organic phase was washed with satd. ammonium chloride solution, brine and water, dried over sodium sulfate and concentrated in vacuo. The oily residue was column chromatographed on silica gel with EtOAc/petroleum ether (10+1) to give **61** as a colourless oil. Yield: 5.40 g (49 %).

TLC: R_f ~ 0.4, EtOAc/petroleum ether (10+1).- $[\alpha]_D^{20}$ = -26.7 (c = 6.75, CH_2Cl_2).

$C_{12}H_{17}NO_6$ (271.26): calcd. C 53.13, H 6.32, N 5.16; found C 52.90, H 6.07, N 5.09.

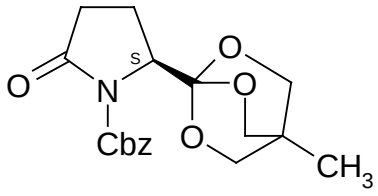
IR (neat): ν = 2960 cm^{-1}, 2875 (C-H), 1790, 1730 (C=O), 1440 (C-H), 1300.

^{1}H-NMR ($CDCl_3$): δ = 1.25 (s, 3 H, CH_3), 1.96–2.15 (m, 1H, H-4a/b), 2.23-2.63 (m, 3 H, H-3a/b, H-4a/b), 3.77 (s, 3 H, OCH_3), 4.17 and 4.23 (2d, 2 H, J = 12.1 Hz, $COOCH_2$), 4.30 (d, 2 H, J = 6.0 Hz, CH_2OCH_2), 4.40 and 4.41 (2d, 2 H, J = 6.0 Hz, CH_2OCH_2), 4.63-4.69 (m, 1 H, H-2).

^{13}C-NMR ($CDCl_3$): δ = 20.68 (CH_3, oxetane), 21.63 (C–3), 30.82 (C–4), 39.00 ($\underline{C}CH_3(CH_2O)_2$), 53.64 ($O\underline{C}H_3$), 58.50 (C–2), 69.26 ($COO\underline{C}H_2$), 79.93 (2 x CH_2O), 151.6 (C=O, urethane), 170.9 (C=O, lactam), 172.4 (C=O, ester).

MS (70 eV), m/z (%): 271 (1) [M^+], 188 (27), 142 (100) [M^+ - oxetylate], 98 (58), 70 (13).

(2S)-2-(4-Methyl-2,6,7-trioxa-bicyclo[2.2.2]oct-1-yl)-5-oxo-pyrrolidine-1-carboxylic acid benzyl ester (65)



To a solution of **59** (4.52 g, 0.013 mol) in dichloromethane (50 ml) was added $BF_3 \cdot OEt_2$ (1.85 g, 0.013 mol) at 0 °C under nitrogen. The mixture was allowed to reach room temperature, and was quenched with triethylamine (3.16 g, 0.130 mol). After 1 h the end of reaction was monitored by TLC. The reaction mixture was concentrated in vacuo to give an oily residue which was purified by column chromatography on silica gel with EtOAc/petroleum ether (10+1) to give **65** as colourless crystals. Yield: 2.71 g (60 %).

TLC: R_f ~ 0.6, EtOAc/petroleum ether (10+1).- m.p. 165 °C.- $[\alpha]_D^{20}$ = -77.5 (c = 5.0, $CHCl_3$).

$C_{18}H_{21}NO_6$ (347.37): calcd. C 62.24, H 6.09, N 4.03; found C 61.87, H 5.81, N 4.07.

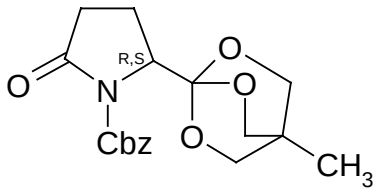
IR (KBr): ν = 2960 cm^{-1}, 2880 (C-H), 1760, 1680 (C=O), 1470 (C-H).

^{1}H-NMR ($CDCl_3$): δ = 0.77 (s, 3 H, CH_3), 2.17 (“m”, J_{gem} ~ 13.2 Hz, J_{3b-4b} ~ 11.9 Hz, J_{3b-4a} ~ 9.7 Hz, J_{3b-2} ~ 9.0 Hz, 1 H, H-3b), 2.37 (ddd, J_{gem} = 13.2 Hz, J_{3a-4a} = 11.6 Hz, J_{3a-4b} = 9.2 Hz 1 H, H-3a), 2.41 (ddd, J_{gem} = 17.4 Hz, J_{4a-3a} = 11.6 Hz, J_{4a-3a} = 9.7 Hz, 1 H, H-4a), 2.97 (ddd, J_{gem} = 17.4 Hz, J_{4b-3b} = 11.9 Hz, J_{4b-3a} = 9.2 Hz, 1 H, H-4b), 3.84 (s, 6 H, 3 x OCH_2, ortho ester), 4.42 (d, 1 H, J_{2-3b} = 9.0 Hz, H-2), 5.23 (d, 1 H, J = 7 Hz, CH_2, benzyl), 5.31 (d, 1 H, J = 7 Hz, CH_2, benzyl), 7.29–7.47 (m, 5 H, aryl).

^{13}C-NMR ($CDCl_3$): δ = 14.27 (CH_3), 20.24 (C–3), 30.62 ($\underline{C}CH_3(CH_2O\text{-})_3$), 31.85 (C–4), 59.89 (C–2), 67.90 (CH_2, benzyl), 72.63 (3 x CH_2O), 118.5 ($\underline{C}CH_3(OCH_2)_3$), 128.1, 128.2, 128.4, 135.1 (6 x C, aryl), 150.9 (C=O, urethane), 166.0 (C=O, lactam).

MS (70 eV), m/z (%): 347 (48) [M^+], 241 (21), 157 (78), 91 (100) [benzyl], 84 (30), 65 (7).

2-(4-Methyl-2,6,7-trioxa-bicyclo[2.2.2]oct-1-yl)-5-oxo-pyrrolidine-1-carboxylic acid benzyl ester ((±) **rac-65)**



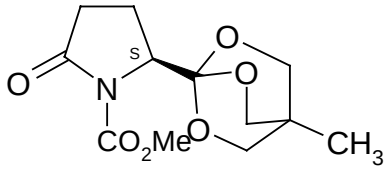
To a suspension of D,L-pyroglutamic acid (10.00 g, 0.078 mol) and 3-hydroxymethyl-3-methyl-oxetane (7.91 g, 0.078 mol) in dichloromethane (150 ml), was added a solution of DMAP (0.475 g, 0.004 mol) and DCC (15.98 g, 0.155 mol) in CH_2Cl_2 (100 ml) over 30 min at ambient temperature. The suspension was stirred for 2 h and the colourless solid was removed by suction and rinsed with CH_2Cl_2. The organic phases were concentrated to 100 ml and extracted with water (2 x 150 ml). The combined water extracts were concentrated under reduced pressure to give (±) **rac-54** (not listed) as a colourless oil. Then, to a solution of (±) **rac-54** (12.33 g, 0.057 mol) and DABCO (6.49 g, 0.057 mol) in THF (150 ml) was added butyllithium (40.0 ml, 0.064 mol, 1.6 M in hexane) at –78 °C. This mixture was stirred for 30 min, then benzyloxycarbonylchloride (10.85 g, 0.064 mol) was added. After stirring for 3 h at –78 °C and then room temp. the reaction was quenched with satd. ammonium chloride solution (150 ml) and the organic layer was diluted with ethylacetate (150 ml). The organic phase was washed with satd. ammonium chloride solution, brine, dried over sodium sulfate and concentrated. The residue was column chromatographed on silica gel with EtOAc/petroleum ether (10+1) to give (±) **rac-59** (not listed) as a colourless oil. Afterwards, to a solution of (±) **rac-59** (7.75 g, 0.022 mol) in dichloromethane (100 ml) was added $BF_3 \cdot OEt_2$ (3.17 g, 0.022 mol) at 0 °C under nitrogen. The mixture was allowed to reach room temperature, and was quenched with triethylamine (5.42 g, 0.222 mol), after the end of the reaction was monitored by TLC. The reaction mixture was concentrated in vacuo to give an oily residue which was purified by column chromatography on silica gel with EtOAc/petroleum ether (10+1) to give (±) **rac-65** as colourless crystals. Yield: 5.69 g (21 %).
TLC: R_f ~ 0.6 [EtOAc – petroleum ether (10 + 1)].- m.p. 145 °C.
$C_{18}H_{21}NO_6$ (347.37): calcd. C 62.24, H 6.09, N 4.03; found C 61.93, H 6.08, N 4.98.
IR (KBr): ν = 2960 cm^{-1}, 2880 (C-H), 1760, 1680 (C=O) 1470 (C-H).
^{1}H-NMR ($CDCl_3$): δ = 0.77 (s, 3 H, CH_3), 2.20 (“m”, J_{gem} ~ 13.2 Hz, J_{3b-4b} ~ 11.9 Hz, J_{3b-4a} ~ 9.7 Hz, J_{3b-2} ~ 9.0 Hz, 1 H, H-3b), 2.37 (ddd, J_{gem} = 13.2 Hz, J_{3a-4a} = 11.6 Hz, J_{3a-4b} = 9.2 Hz 1 H, H-3a), 2.41 (ddd, J_{gem} = 17.4 Hz, J_{4a-3a} = 11.6 Hz, J_{4a-3a} = 9.7 Hz, 1 H, H-4a), 2.97 (ddd,

J_{gem} = 17.4 Hz, J_{4b-3b} = 11.9 Hz, J_{4b-3a} = 9.2 Hz, 1 H, H-4b), 3.84 (s, 6 H, 3 x OCH_2, ortho ester), 4.42 (d, 1 H, J_{2-3} = 9.0 Hz, H-2), 5.23 (d, 1 H, J = 7 Hz, CH_2, benzyl), 5.31 (d, 1 H, J = 7 Hz, CH_2, benzyl), 7.29–7.47 (m, 5 H, aryl).

^{13}C-NMR ($CDCl_3$): δ = 14.27 (CH_3), 20.24 (C–3), 30.62 ($\underline{C}CH_3(CH_2O\text{-})_3$), 31.85 (C–4), 59.89 (C–2), 67.90 (CH_2, benzyl), 72.63 (3 x CH_2O), 118.5 ($\underline{C}CH_3(OCH_2)_3$), 128.1, 128.2, 128.4, 135.1 (6 x C, aryl), 150.9 (C=O, urethane), 166.0 (C=O, lactam).

MS (70 eV), m/z (%): 347 (20) [M^+], 241 (17), 157 (77), 91 (100) [benzyl], 84 (21), 65 (12).

(2S)-2-(4-Methyl-2,6,7-trioxa-bicyclo[2.2.2]oct-1-yl)-5-oxo-pyrrolidine-1-carboxylic acid methyl ester (66)



To a solution of **61** (4.52 g, 0.013 mol) in dichloromethane (50 ml) $BF_3{\cdot}OEt_2$ (1.85 g, 0.013 mol) was added dropwise under nitrogen at 0 °C. The mixture was allowed to reach room temperature. The end of the reaction was monitored by TLC (1h). To the mixture was added triethylamine (13.16 g, 0.130 mol) and the solution was concentrated in vacuo to give an oily residue which was diluted with EtOAc. The organic phase was washed with satd. ammoniumchloride solution, brine and water, then concentrated and purified by column chromatographie on silica gel with EtOAc/petroleum ether (10+1) to give **66** as colourless crystals. Yield: 2.03 g (56 %).

TLC: R_f ~ 0.5, EtOAc/petroleum ether (10+1).- m.p. 184 °C.- $[\alpha]_D^{20}$ = -79.1 (c = 2.5, CH_2Cl_2).

$C_{12}H_{17}NO_6$ (271.27): calcd. C 53.13, H 6.32, N 5.16; found C 52.30, H 5.89, N 4.90.

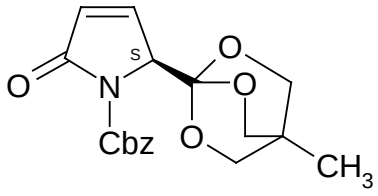
IR (KBr): ν = 2950 cm^{-1}, 2885 (C-H), 1750, 1730 (C=O), 1440 (C-H).

^{1}H-NMR ($CDCl_3$): δ = 0.77 (s, 3 H, CH_3, ortho ester), 1.90-2.34 (m, 3 H, H-3a/b and H-4a/b), 2.67-2.86 (m, 1 H, H-4a/b), 3.81 (s, 3H, $COOCH_3$), 3.86 (s, 6 H, 3 x OCH_2, ortho ester), 4.83 (d, 1 H, J_{2-3} = 8 Hz, H-2).

^{13}C-NMR ($CDCl_3$): δ = 14.20 (CH_3, ortho ester), 20.24 (C–3), 30.54 ($\underline{C}CH_3(CH_2O\text{-})_3$), 31.84 (C–4), 53.33 ($COO\underline{C}H_3$), 59.81 (C–2), 72.63 (3 x CH_2O, ortho ester), 109.1 ($\underline{C}CH_3(OCH_2)_3$), 152.2 (C=O, urethane), 174.9 (C=O, lactam).

MS (70 eV), m/z (%): 272 (2) [$M+1^+$], 241 (66), 142 (100), 98 (38), 85 (9), 70 (7).

(2S)-2-(4-Methyl-2,6,7-trioxa-bicyclo[2.2.2]oct-1-yl)-5-oxo-2,5-dihydro-pyrrole-1-carboxylic acid benzyl ester (74)



To a solution of HMDS (2.18 g, 0.013 mol) and butyllithium (4.92 ml, 0.013 mol, 2.7 M in heptane) in THF (40 ml) at –78 °C was added a solution of **65** (2.00 g, 0.006 mol) in THF (15 ml) under nitrogen over a period of 30 min. The reaction was allowed to warm to 0° C then it was cooled to –78 °C. and a solution of phenylselenenyl chloride (1.21 g, 0.006 mol) in THF (40 ml) was added and the reaction mixture was stirred for 2 h, then allowed to warm to room temperature. The reaction was quenched by adding satd. ammonium chloride solution (60 ml), and EtOAc (120 ml) and the organic phase was washed with satd. ammonium chloride sol. (2x). The organic layer was concentrated in vacuo to give a yellow oily residue. The residue was dissolved in THF (40 ml) and DABCO (2.92 g, 0.026 mol) was added under vigorous stirring at –20 °C. After 10 min a solution of m-chloroperbenzoic acid (6.73 g, 0.039 mol) in dichloromethane (150 ml) was added slowly to the reaction mixture over a period of 30 min. The reaction mixture was allowed to reach room temp., was diluted with EtOAc (600 ml) and the organic phase was washed with satd. sodium bisulfite, satd. sodium bicarbonate and satd. brine. The concentrated and dried organic phase gave an oily residue which was purified by column chromatography on silica gel with EtOAc/petroleum ether (2+1) to give **74** as colourless crystals. Yield 2.15 g (48 %).

TLC: R_f ~ 0.4, EtOAc/petroleum ether (2+1)].- m.p. 125 °C.- $[\alpha]_D^{20}$ = -190.5 (c = 0.4, CH_2Cl_2).

$C_{18}H_{19}NO_6$ (345.35): calcd. C 62.60, H 5.55, N 4.06; found C 62.51, H 5.52, N 4.06.

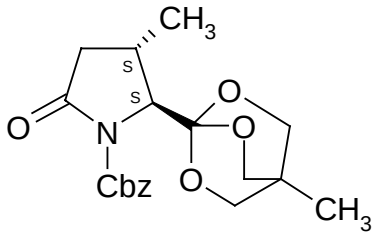
IR (KBr): ν = 3060 cm^{-1}, 2950, 2860 (C-H), 1760, 1680 (C=O), 1600, 1470 (C-H).

^{1}H-NMR ($CDCl_3$): δ = 0.76 (s, 3 H, CH_3), 3.81 (s, 6 H, 3 x OCH_2, ortho ester), 4.94 (t, 1 H, J_{2-3} ~ J_{2-4} = 2.0 Hz, H-2), 5.23 (d, 1 H, J = 12.0 Hz, CH_2, benzyl), 5.33 (d, 1 H, J = 12.0 Hz, CH_2, benzyl), 6.08 (dd, 1 H, J_{4-3} = 6.0 Hz, J_{4-2} = 1.5 Hz, H-4), 7.12 (dd, 1 H, J_{3-4} = 6.0 Hz, J_{3-2} = 2.5 Hz, H-3), 7.26–7.47 (m, 5 H, aryl).

^{13}C-NMR ($CDCl_3$): δ = 14.07 (CH_3), 30.55 ($\underline{C}CH_3(CH_2O\text{-})_3$), 64.48 (C–2), 67.99 ($CH_2$, benzyl), 72.72 (3 x CH_2O), 107.3 ($\underline{C}CH_3(OCH_2)_3$), 126.7 (C-4), 128.0, 128.1, 128.3, 128.5, 135.5 (6 x C, aryl), 146.8 (C-3), 151.0 (C=O, urethane), 169.2 (C=O, lactam).

MS (70 eV), m/z (%): 345 (6) [M^+], 301 (17), 239 (57), 109 (25), 91 (100) [benzyl], 85 (19), 65 (17).

(2S,3S)-2-(4-Methyl-2,6,7-trioxa-bicyclo[2.2.2]oct-1-yl)-5-oxo-3-methyl-pyrrolidine-1-carboxylic acid benzyl ester (80)



To a suspension of CuBr•$S(CH_3)_2$ (4.12 g, 20.00 mmol) in diethyl ether (30 ml) was added methyllithium (25.00 ml, 40.00 mmol, 1.6 M in diethyl ether) at -20 °C under nitrogen. After 10 min the reaction was cooled to –78 °C. Then a solution of trimethylsilyl chloride (1.02 ml, 8.00 mmol) and **74** (1.38 g, 4.00 mmol) in THF (20 ml) was added under vigorous stirring. After keeping the reaction temperature at –78 °C for 1 h the reaction mixture was allowed to reach –20 °C. The reaction was stopped by adding satd. ammonium chloride solution. The organic layer was diluted with diethyl ether, washed with satd. ammonium chloride (3x) and brine, then concentrated in vacuo to give an solid residue which was purified by column chromatography on silica gel using EtOAc/petroleum ether (1+1) to give **80** as colourless crystals. Recrystallization from dichloromethane/ethanol yielded 1.09 g (75 %).

TLC: R_f ~ 0.50, EtOAc/petroleum ether (2+1).- m.p. 192 °C.- $[\alpha]_D^{20}$ = -63.6 (c = 0.50, CH_2Cl_2).

$C_{19}H_{23}NO_6$ (361.39): calcd. C 63.15, H 6.41, N 3.88; found C 62.93, H 6.15, N 4.16.

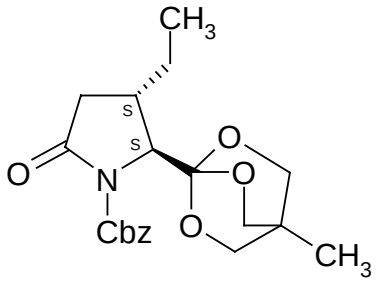
IR (KBr): ν = 2960 cm^{-1}, 2940 (C-H), 2870, 1770 (C=O), 1490 (C-H).

^{1}H-NMR ($CDCl_3$): δ = 0.74 (s, 3 H, CH_3, ortho ester), 1.05 (d, 3 H, J_{CH3-3} = 7.3 Hz, CH_3), 1.89 (d, 1 H, J_{gem} = 17.4 Hz, H-4b), 2.53 (dt, 1 H, J_{3-4a} = 8.2 Hz, J_{3-CH3} = 7.3 Hz, H-3), 2.96 (dd, 1 H, J_{gem} = 17.4 Hz, J_{4a-3} = 8.2 Hz, H-4a), 3.80 (s, 6 H, 3 x OCH_2, ortho ester), 4.00 (s, 1 H, H-2), 5.19 (d, 1 H, J = 12.5 Hz, CH_2, benzyl), 5.29 (d, 1 H, J = 12.2 Hz, CH_2, benzyl), 7.23–7.44 (m, 5 H, aryl).

^{13}C-NMR ($CDCl_3$): δ = 14.72 (CH_3), ortho ester), 21.61 (CH_3, methyl), 27.66 (C-3), 31.04 ($\underline{C}CH_3(CH_2O\text{-})_3$), 40.51 (C–4), 67.22 (C–2), 68.36 (CH_2, benzyl), 73.04 (3 x CH_2O), 109.2 ($\underline{C}CH_3(OCH_2)_3$), 128.5, 128.6, 128.8, 129.0, 129.1, 136.0 (6 x C, aryl), 152.3 (C=O, urethane), 175.1 (C=O, lactam).

MS (70 eV), m/z (%): 361 (21) [M^+], 317 (3) [M^+-carboxylate], 255 (11), 226 (7), 172 (9), 171 (82) [M^+-benzyl], 144 (5), 98 (18), 91 (100) [benzyl], 85 (7), 69 (20), 65 (11).

(2S,3S)-2-(4-Methyl-2,6,7-trioxa-bicyclo[2.2.2]oct-1-yl)-5-oxo-3-ethyl-pyrrolidine-1-carboxylic acid benzyl ester (81)



To a suspension of CuBr•$S(CH_3)_2$ (8.94 g, 43.43 mmol) in diethyl ether (90 ml) was added freshly prepared Grignard solution of ethylmagnesium bromide (11.57 g, 86.84 mmol) in diethyl ether (120 ml) at -40 °C under nitrogen in one portion. After 30 min reaction was cooled –78 °C. Then a solution of trimethylsilyl chloride (3.53 ml, 27.79 mmol) and **74** (3.00 g, 8.68 mmol) in THF (30 ml) was added under vigorous stirring. After keeping the reaction temperature at –78 °C for 1 h the reaction mixture was allowed to reach –20 °C. The reaction was stopped by adding satd. ammonium chloride solution. The organic layer was diluted with diethyl ether, washed with satd. ammonium chloride solution (3x) and brine, then concentrated in vacuo to give an solid residue which was purified by column chromatography on silica gel using EtOAc/petroleum ether (2+1) to give **81** as colourless crystals. Recrystallization from dichloromethane/ethanol yielded 2.02 g (62 %).

TLC: R_f ~ 0.55, EtOAc/petroleum ether (2+1).- m.p. 183 °C.- $[\alpha]_D^{20}$ = -60.7 (c = 0.29, CH_2Cl_2).

$C_{20}H_{25}NO_6$ (375.42): calcd. C 63.99, H 6.71, N 3.73; found C 63.45, H 6.36, N 3.93.

IR (KBr): ν = 2960 cm^{-1}, 2940 (C-H), 2880, 1770 (C=O), 1460 (C-H).

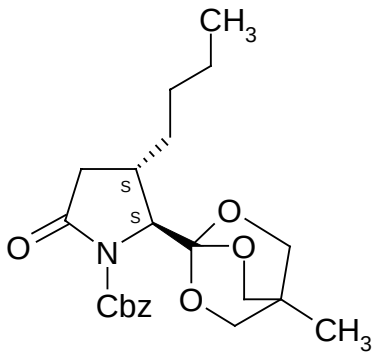
^{1}H-NMR ($CDCl_3$): δ = 0.74 (s, 3 H, CH_3, ortho ester), 0.87 (t, 3 H, J = 7.3 Hz, CH_3, ethyl), 1.27–1.48 (m, 2 H, CH_2, ethyl), 2.01 (d, 1 H, J_{gem} = 17.7 Hz, H-4b), 2.30 (2d, 1 H, $J_{3\text{-}4a}$ ~ 8.5 Hz, $J_{3\text{-}CH2,\ ethyl}$ = 7.6 Hz, H-3), 2.91 (dd, 1 H, J_{gem} = 17.7 Hz, $J_{4a\text{-}3}$ = 8.5 Hz, H-4a), 3.79 (s, 6 H, 3 x OCH_2, ortho ester), 4.09 (s, 1 H, H-2), 5.19 (d, 1 H, J = 12.5 Hz, CH_2, benzyl), 5.28 (d, 1 H, J = 12.5 Hz, CH_2, benzyl), 7.27–7.38 (m, 5 H, aryl).

^{13}C-NMR ($CDCl_3$): δ = 11.42 (CH_3, ethyl), 14.74 (CH_3, ortho ester), 28.16 (CH_2, ethyl), 31.04 ($\underline{C}CH_3(CH_2O\text{-})_3$), 34.34 (C-3), 38.42 (C–4), 65.34 (C–2), 68.34 (CH_2, benzyl), 73.06 (3 x

CH_2O), 109.3 ($\underline{C}CH_3(OCH_2)_3$), 128.4, 128.5, 128.6, 129.0, 136.1 (6 x C, aryl), 152.2 (C=O, urethane), 175.2 (C=O, lactam).

MS (70 eV), m/z (%): 375 (18) [M^+], 269 (15), 240 (14), 185 (53) [M^+-benzyl], 144 (4), 112 (15), 107 (6), 91 (100) [benzyl], 85 (8), 65 (11).

(2S,3S)-2-(4-Methyl-2,6,7-trioxa-bicyclo[2.2.2]oct-1-yl)-5-oxo-3-butyl-pyrrolidine-1-carboxylic acid benzyl ester (82)



To a suspension of CuBr•$S(CH_3)_2$ (7.43 g, 36.19 mmol) in diethyl ether (70 ml) was added butyllithium (26.00 ml, 72.38 mmol, 2.7 M in heptane) at -40 °C under nitrogen. After 30 min the reaction was cooled to –78 °C. Then a solution of trimethylsilyl chloride (2.94 ml, 23.16 mmol) and **74** (2.50 g, 7.24 mmol) in THF (30 ml) was added under vigorous stirring. After keeping the reaction temperature at –78 °C for 1 h the reaction mixture was allowed to warm to –20 °C. The reaction was stopped by adding satd. ammonium chloride solution and the organic layer was diluted with diethyl ether, washed with satd. ammonium chloride sol. (3 x) and brine, then concentrated in vacuo to give an oily yellow residue which was purified by column chromatography on silica gel using EtOAc/petroleum ether (1+1) as eluent to give **82** as colourless crystals. Yield 2.04 g (70 %).

TLC: R_f ~ 0.50, EtOAc/petroleum ether (2+1).- m.p. 126 °C.- $[\alpha]_D^{20}$ = -61.0 (c = 0.39, CH_2Cl_2).

$C_{22}H_{29}NO_6$ (403.47): calcd. C 65.49, H 7.24, N 3.47; found C 64.62, H 7.39, N 3.38.

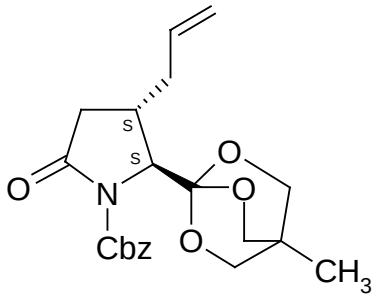
IR (KBr): ν = 2930 cm^{-1} (C-H), 1790 (C=O), 1490 (C-H).

^{1}H-NMR ($CDCl_3$): δ = 0.74 (s, 3 H, CH_3, ortho ester), 0.84 (t, 3 H, J = 6.7 Hz, CH_3, butyl), 0.89–1.03 (m, 6 H, 3 x CH_2, butyl), 2.01 (d, 1 H, J_{gem} = 17.7 Hz, H-4b), 2.36 (m, 1 H, H-3), 2.91 (dd, 1 H, J_{gem} = 17.7 Hz, J_{4a-3} = 8.5 Hz, H-4a), 3.80 (s, 6 H, 3 x OCH_2, ortho ester), 4.09 (s, 1 H, H-2), 5.20 (d, 1 H, J = 12.5 Hz, CH_2, benzyl), 5.29 (d, 1 H, J = 12.5 Hz, CH_2, benzyl), 7.23–7.36 (m, 5 H, aryl).

^{13}C-NMR ($CDCl_3$): δ = 14.36 (CH_3, ortho ester), 14.72 (CH_3, butyl), 22.87 (CH_2, butyl), 29.05 (CH_2, butyl), 31.02 ($\underline{C}CH_3(CH_2O\text{-})_3$), 32.76 (C-3), 35.00 ($CH_2$, butyl), 38.75 (C–4), 65.57 (C–2), 68.31 (CH_2, benzyl), 73.04 (3 x CH_2O), 109.0 ($\underline{C}CH_3(OCH_2)_3$), 128.5, 128.6, 128.8, 129.0, 136.1 (6 x C, aryl), 152.2 (C=O, urethane), 175.3 (C=O, lactam).

MS (70 eV), m/z (%): 403 (19) [M^+], 269 (15), 240 (11), 213 (34) [M^+-benzyl], 144 (35), 140(39), 111 (10), 91 (100) [benzyl], 85 (10), 65 (9).

(2S,3S)-2-(4-Methyl-2,6,7-trioxa-bicyclo[2.2.2]oct-1-yl)-5-oxo-3-allyl-pyrrolidine-1-carboxylic acid benzyl ester (83)



To a suspension of $CuBr{\bullet}S(CH_3)_2$ (5.96 g, 28.95 mmol) in diethyl ether (60 ml) was added a freshly prepared Grignard solution of allylmagnesium bromide (8.41 g, 57.89 mmol) in diethyl ether (80 ml) at -40 °C under nitrogen in one portion. After 30 min the reaction was cooled to –78 °C. Then a solution of trimethylsilyl chloride (2.35 ml, 18.53 mmol) and **74** (2.00 g, 5.79 mmol) in THF (20 ml) was added under vigorous stirring. After keeping the reaction temperature at –78 °C for 1 h, the reaction mixture was allowed to warm to –20 °C. The reaction was stopped by adding satd. ammonium chloride sol. The organic layer was diluted with diethyl ether, washed with satd. ammonium chloride (3x) and brine, then concentrated in vacuo to give an oily residue which was purified by column chromatography on silica gel using EtOAc/petroleum ether (2+1) to give **83** as colourless crystals. Recrystallization from dichloromethane/ethanol yielded 1.33 g (48 %).

TLC: R_f ~ 0.55, EtOAc/petroleum ether (1+1).- m.p. 93 °C.- $[\alpha]_D^{20}$ = -49.1 (c = 0.21, CH_2Cl_2).

$C_{21}H_{25}NO_6$ (387.43): calcd. C 65.10, H 6.50, N 3.62; found C 64.61, H 6.58, N 3.62.

IR (KBr): ν = 3060 cm^{-1}, 2960, 2940 (C-H), 2880, 1770 (C=O), 1690, 1460 (C-H).

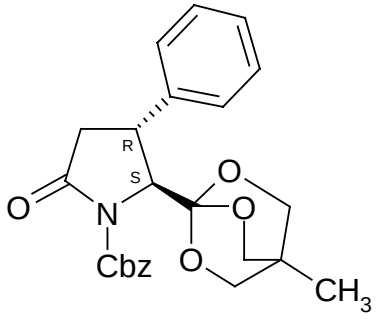
^{1}H-NMR ($CDCl_3$): δ = 0.74 (s, 3 H, CH_3, ortho ester), 1.98–2.20 (m, 2 H, H-1'), 2.05 (d, 1 H, J_{gem} = 17.1 Hz, H-4b), 2.49 (2d, 1 H, $J_{3\text{-}4a}$ ~ 8.5 Hz, $J_{3\text{-}1'}$ = 7.3 Hz, H-3), 2.90 (dd, 1 H, J_{gem} = 17.7 Hz, $J_{4a\text{-}3}$ = 8.5 Hz, H-4a), 3.80 (s, 6 H, 3 x OCH_2, ortho ester), 4.14 (s, 1 H, H-2), 5.01

("d", 1 H, J_{gem} = 1 Hz, H-3'), 5.06 ("d", 1 H, J_{gem} = 1 Hz, H-3'), 5.20 (d, 1 H, J = 12.5 Hz, CH_2, benzyl), 5.28 (d, 1 H, J = 12.5 Hz, CH_2, benzyl), 5.57–5.74 (m, 1 H, H-2'), 7.25–7.40 (m, 5 H, aryl).

^{13}C-NMR ($CDCl_3$): δ = 14.73 (CH_3, ortho ester), 31.04 ($\underline{C}CH_3(CH_2O\text{-})_3$), 32.15 (C-3), 38.12 (C–4), 39.38 (C–1', allyl), 64.91 (C–2), 68.33 (CH_2, benzyl), 73.07 (3 x CH_2O), 109.3 ($\underline{C}CH_3(OCH_2)_3$), 118.6 (C–3', allyl), 128.5, 128.6, 128.8, 129.1 (6 x C, aryl), 134.8 (C–2', allyl), 152.0 (C=O, urethane), 175.0 (C=O, lactam).

MS (70 eV), m/z (%): 387 (21) [M^+], 281 (8), 280 (5), 240 (57), 197 (3) [M^+-benzyl], 138 (7), 107 (6), 91 (100) [benzyl], 85 (11), 65 (10).

(2S,3R)-2-(4-Methyl-2,6,7-trioxa-bicyclo[2.2.2]oct-1-yl)-5-oxo-3-phenyl-pyrrolidine-1-carboxylic acid benzyl ester (84)



To a suspension of CuBr•$S(CH_3)_2$ (5.96 g, 27.95 mmol) in diethyl ether (50 ml) was added a freshly prepared Grignard solution of phenylmagnesium bromide (10.50 g, 57.89 mmol) in diethyl ether (50 ml) at -40 °C under nitrogen in one portion. After 30 min the mixture was cooled to -78 °C. Then a solution of trimethylsilyl chloride (2.35 ml, 18.53 mmol) and **74** (2.00 g, 5.79 mmol) in THF (25 ml) was added under vigorous stirring. After keeping the reaction temperature at -78 °C for 1 h, the reaction mixture was allowed to warm to -20 °C. The reaction was quenched by adding satd. ammonium chloride solution and the organic layer was diluted with diethyl ether, washed with satd. ammonium chloride (3x) and brine, then concentrated in vacuo, to give an oily yellow residue which was purified by column chromatography on silica gel using EtOAc/petroleum ether (1+1) to give **84** as colourless crystals. Yield 1.00 g (50 %).

TLC: R_f ~ 0.45 EtOAc/petroleum ether (1+1).- m.p. 181 °C.- $[\alpha]_D^{20}$ = -23.4 (c = 0.41, CH_2Cl_2).

$C_{24}H_{25}NO_6$ (423.46): calcd. C 68.07, H 5.95, N 3.31; found C 67.72, H 6.00, N 3.35.

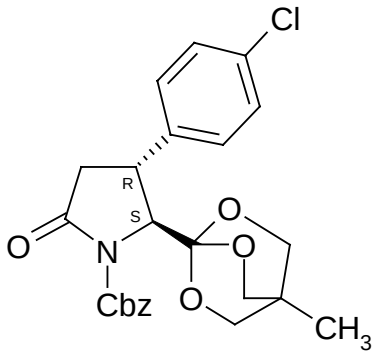
IR (KBr): ν = 2920 cm^{-1}, 2880 (C-H), 1770 (C=O), 1690 (urethane), 1450 (C-H).

^{1}H-NMR ($CDCl_3$): δ = 0.80 (s, 3 H, CH_3), 2.46 (d, 1 H, J_{gem} = 18.0 Hz, H-4b), 3.29 (dd, 1 H, J_{gem} = 17.7 Hz, J_{4a-3} = 9.2 Hz, H-4a), 3.68 (d, 1 H, J_{3-4a} = 9.2 Hz, H-3), 3.80 (s, 6 H, 3 x OCH_2, ortho ester), 4.42 (s, 1 H, H-2), 5.22 (d, 1 H, J = 12.5 Hz, CH_2, benzyl), 5.32 (d, 1 H, J = 12.5 Hz, CH_2, benzyl), 7.14–7.33 (m, 9 H, aryl).

^{13}C-NMR ($CDCl_3$): δ = 14.74 (CH_3), 31.14 ($\underline{C}CH_3(CH_2O\text{-})_3$), 37.85 (C-3), 39.84 (C–4), 67.30 (C–2), 68.42 (CH_2, benzyl), 73.17 (3 x CH_2O), 109.2 ($\underline{C}CH_3(OCH_2)_3$), 126.7, 127.5, 128.5, 128.8, 129.4, 136.0, 144.1, (12 x C, aryl), 151.9 (C=O, urethane), 174.9 (C=O, lactam).

MS (70 eV), m/z (%): 423 (19) [M^+], 288 (7), 233 (51) [M^+-benzyl], 185 (8), 131(25), 104 (11), 91 (100) [benzyl], 85 (8), 77 (5), 65 (9).

(2S,3R)-2-(4-Methyl-2,6,7-trioxa-bicyclo[2.2.2]oct-1-yl)-5-oxo-3-(4-chlorophenyl)-pyrrolidine-1-carboxylic acid benzyl ester (85)



To a suspension of CuBr•$S(CH_3)_2$ (1.49 g, 7.24 mmol) in diethyl ether (15 ml) was added a freshly prepared Grignard solution of para-chlorophenylmagnesium bromide (2.77 g, 14.48 mmol) in diethyl ether (10 ml) at -40 °C under nitrogen in one portion. After 30 min the mixture was cooled to–78 °C. Then a solution of trimethylsilyl chloride (0.59 ml, 4.63 mmol) and **74** (0.50 g, 1.45 mmol) in THF (15 ml) was added under vigorous stirring. After keeping the reaction temperature at -78 °C for 1 h, the reaction mixture was allowed to reach -20 °C. The reaction was quenched by adding satd. ammonium chloride solution. The organic layer was diluted with diethyl ether, washed with satd. ammonium chloride (3 x) and brine, then concentrated in vacuo to give an oily yellow residue which was purified by column chromatography on silica gel using EtOAc/petroleum ether (1+1) give **85** as colourless crystals. Yield 0.37 g (55 %).

TLC: R_f ~ 0.45, EtOAc/petroleum ether (1+1).- m.p. 166 °C.- $[\alpha]_D^{20}$ = -20.4 (c = 0.5, CH_2Cl_2).

$C_{24}H_{24}ClNO_6$ (457.91): calcd. C 62.95, H 5.28, N 3.06; found C 62.88, H 5.42, N 3.08.

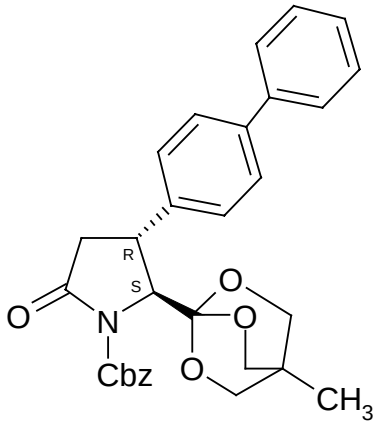
IR (KBr): ν = 2950 cm^{-1}, 2870 (C-H), 1780, 1690 (C=O) 1490 (C-H).

^{1}H-NMR ($CDCl_3$): δ = 0.80 (s, 3 H, CH_3), 2.39 (d, 1 H, J_{gem} = 18.3 Hz, H-4b), 3.28 (dd, 1 H, J_{gem} = 17.7 Hz, J_{4a-3} = 9.2 Hz, H-4a), 3.66 (d, 1 H, J_{3-4a} = 9.3 Hz, H-3), 3.87 (s, 6 H, 3 x OCH_2, ortho ester), 4.35 (s, 1 H, H-2), 5.21 (d, 1 H, J = 12.5 Hz, CH_2, benzyl), 5.32 (d, 1 H, J = 12.5 Hz, CH_2, benzyl), 7.06–7.41 (m, 9 H, aryl).

^{13}C-NMR ($CDCl_3$): δ = 14.25 (CH_3), 30.70 ($\underline{C}CH_3(CH_2O\text{-})_3$), 36.89 (C-3), 39.16 (C–4), 66.80 (C–2), 68.08 (CH_2, benzyl), 72.73 (3 x CH_2O), 108.7 ($\underline{C}CH_3(OCH_2)_3$), 127.6, 128.1, 128.3, 128.4, 129.1, 132.9, 135.4, 142.0, (12 x C, aryl), 151.3 (C=O, urethane), 174.0 (C=O, lactam).

MS (70 eV), m/z (%): 457 (17) [M^+], 267 (45) [M^+-benzyl], 165 (18), 138 (13), 91 (100) [benzyl], 85 (11), 65 (10).

(2S,3R)-2-(4-Methyl-2,6,7-trioxa-bicyclo[2.2.2]oct-1-yl)-5-oxo-3-biphenyl-pyrrolidine-1-carboxylic acid benzyl ester (86)



To a suspension of CuBr•$S(CH_3)_2$ (2.98 g, 14.47 mmol) in abs. diethyl ether (30 ml) was added a freshly prepared Grignard solution of 4-biphenylmagnesium bromide (6.75 g, 28.95 mmol) in abs. diethyl ether (60 ml) at -40 °C under nitrogen in one portion. After 30 min the mixture was cooled to -78 °C. Then, a solution of trimethylsilyl chloride (1.18 ml, 9.23 mmol) and **74** (1.00 g, 2.90 mmol) in abs. THF (10 ml) was added under vigorous stirring. After keeping the reaction temperature at -78 °C for 1 h the mixture was allowed to warm to 0 °C. The reaction was quenched by adding satd. ammonium chloride solution. The organic layer was diluted with diethyl ether, washed with satd. ammonium chloride sol. (3 x) and brine, then concentrated in vacuo to give an oily yellow residue which was purified by column

chromatography on silica gel using EtOAc/petroleum ether (1+1) as an eluent to give **86** as colourless crystals. Yield 0.43 g (30 %).

TLC: R_f ~ 0.50 (EtOAc/petroleum ether (1+1).- m.p. 219 °C.- $[\alpha]_D^{20}$ = +18.2 (c = 0.32, CH_2Cl_2).

$C_{30}H_{29}NO_6$ (499.56): calcd. C 72.13, H 5.85, N 2.80; found C 71.20, H 5.61, N 2.78.

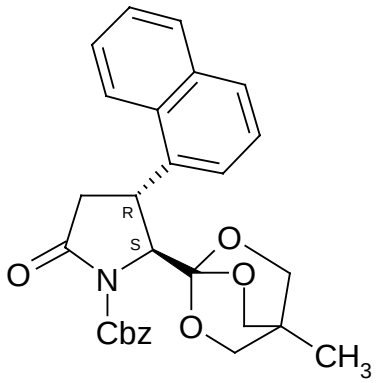
IR (KBr): ν = 3047 cm^{-1} (aryl), 2938, 2880 (C-H), 1785 (C=O), 1705 (urethane).

^{1}H-NMR ($CDCl_3$): δ = 0.80 (s, 3 H, CH_3), 2.48 (d, 1 H, J_{gem} = 18.0 Hz, H-4b), 3.31 (dd, 1 H, J_{gem} = 17.7 Hz, J_{4a-3} = 9.2 Hz, H-4a), 3.71 (d, 1 H, J_{3-4a} = 8.9 Hz, H-3), 3.88 (s, 6 H, 3 x OCH_2, ortho ester), 4.45 (s, 1 H, H-2), 5.22 (d, 1 H, J = 12.5 Hz, CH_2, benzyl), 5.33 (d, 1 H, J = 12.5 Hz, CH_2, benzyl), 7.18–7.62 (m, 14 H, aryl).

^{13}C-NMR ($CDCl_3$): δ = 17.09 (CH_3), 39.28 ($\underline{C}CH_3(CH_2O\text{-})_3$), 40.35 (C-4), 41.02 (C–3), 66.56 (C–2), 67.77 (CH_2, benzyl), 73.20 (3 x CH_2O), 108.0 ($\underline{C}CH_3(OCH_2)_3$), 127.3, 127.4, 128.0, 128.4, 128.5, 128.7, 128.8, 129.0, 129.1, 129.2, 129.3, 135.1, 139.9, 140.6, 141.5 (18 x C, aryl), 151.5 (C=O, urethane), 172.3 (C=O, lactam).

MS (70 eV), m/z (%): 499 (18) [M^+], 364 (46), 309 (20) [M^+-benzyl], 262 (11), 207 (12), 180 (28), 147 (12), 91 (100) [benzyl], 85 (13), 65 (6).

(2S,3R)-2-(4-Methyl-2,6,7-trioxa-bicyclo[2.2.2]oct-1-yl)-5-oxo-3-naphthyl-pyrrolidine-1-carboxylic acid benzyl ester (87)



To a suspension of $CuBr{\bullet}S(CH_3)_2$ (5.96 g, 28.95 mmol) in diethyl ether (20 ml) was added a freshly prepared Grignard solution of 1-naphthylmagnesium bromide (13.34 g, 57.91 mmol) in diethyl ether (80 ml) at -40 °C under nitrogen. After 30 min the mixture was cooled down to –78 °C and a solution of trimethylsilyl chloride (2.35 ml, 18.53 mmol) and **74** (2.00 g, 5.79 mmol) in THF (25 ml) was added under vigorous stirring. After keeping the reaction temperature at -78 °C for 1 h the mixture was allowed to warm to -20 °C. The reaction was quenched by adding satd. ammonium chloride solution and the organic layer was diluted with

diethylether, washed with satd. ammonium chloride (3x) and brine, then concentrated in vacuo to give an oily yellow residue which was purified by column chromatography on silica gel using EtOAc/petroleum ether (1+1) to give **87** as colourless crystals. Yield 1.34 g (55 %).

TLC: R_f ~ 0.50, EtOAc/petroleum ether (1+1).- m.p. 190 °C.- $[\alpha]_D^{20}$ = -61.8 (c = 0.44, CH_2Cl_2).

$C_{28}H_{27}NO_6$ (473.52): calcd. C 71.02, H 5.75, N 2.96; found C 67.64, H 5.62, N 2.87.

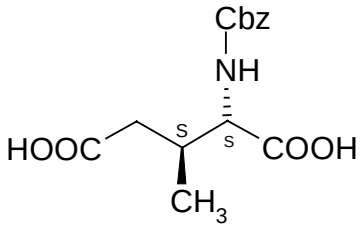
IR (KBr): ν = 3040 cm^{-1} (aryl), 2930, 2870 (C-H), 1780 (C=O), 1690 (urethane).

^{1}H-NMR ($CDCl_3$): δ = 0.77 (s, 3 H, CH_3), 2.48 (d, 1 H, J_{gem} = 17.7 Hz, H-4b), 3.45 (dd, 1 H, J_{gem} = 17.7 Hz, J_{4a-3} = 8.9 Hz, H-4a), 3.87 (s, 6 H, 3 x OCH_2, ortho ester), 4.37 (d, 1 H, J_{3-4a} = 8.9 Hz, H-3), 4.52 (s, 1 H, H-2), 5.12 (d, 1 H, J = 12.5 Hz, CH_2, benzyl), 5.25 (d, 1 H, J = 12.5 Hz, CH_2, benzyl), 7.14 – 7.34 (m, 2 H, naphthyl, 5 H, benzyl), 7.40-7.52 (m, 2 H, naphthyl), 7.68 (d, 1 H, J = 8.5 Hz, naphthyl), 7.78 (m, 1 H, J = 8.5 Hz, naphthyl), 8.15 (d, 1 H, J = 8.5 Hz, naphthyl).

^{13}C-NMR ($CDCl_3$): δ = 14.75 (CH_3), 31.12 ($\underline{C}CH_3(CH_2O\text{-})_3$), 35.98 (C-3), 38.12 (C–4), 65.80 (C–2), 68.70 (CH_2, benzyl), 73.24 (3 x CH_2O), 108.0 ($\underline{C}CH_3(OCH_2)_3$), 122.8, 123.2, 125.8, 126.7, 127.5, 128.6, 129.0, 129.2, 129.8, 131.1, 134.5, 135.1, 136.1 (16 x C, aryl), 151.6 (C=O, urethane), 171.5 (C=O, lactam).

MS (70 eV), m/z (%): 473 (32) [M^+], 338 (30), 283 (29) [M^+-benzyl], 236 (12), 181 (19), 165 (9), 154 (37), 153 (25), 152 (13), 91 (100) [benzyl], 85 (11), 65 (7).

(2S,3S)-1-(Benzyloxycarbonyl)-3-methyl-glutamic acid (89)



To a solution of **80** (1.00 g, 2.77 mmol) in dichloromethane (10 ml) was added a 10 % aqueous solution of trifluoro acetic acid (10 ml). After stirring for 1 h the solvent was removed in vacuo to give a colourless oily residue which was dissolved in a mixture of THF (5 ml) and 1 M aqueous sodium hydroxide (15 ml). This solution was stirred for 12 h, then THF was removed in vacuo and the reaction mixture was adjusted with hydrochloric acid (6 N) to pH 1. The aqueous phase was extracted with diethyl ether (3 x 20 ml) and the combined and dried organic phases were concentrated in vacuo to give **89** as colourless crystals after recrystallization from chloroform/diethyl ether. Yield 0.61 g (75 %).

TLC: R_f ~ 0.7, EtOAc/acetic acid (10+1).- m.p. 133 °C.- $[\alpha]_D^{20}$ = +7.4 (c = 0.34, EtOAc).

$C_{14}H_{27}NO_6$ (295.29): calcd. C 56.95, H 5.80, N 4.74; found C 56.95, H 5.48, N 4.69.

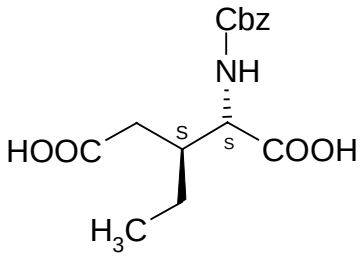
IR (KBr): ν = 3330 cm^{-1} (NH), 3100 (COOH), 2960 (C-H), 1700 (C=O), 1530 (C-H).

^{1}H-NMR (DMSO-d_6): δ = 0.99 (d, 3 H, J_{CH3-3} = 6.1 Hz, CH_3, methyl), 2.19–2.41 (m, 3 H, H-3 and H-4a/b), 4.08 (2d, 1 H, J_{2-NH} = 8.2 Hz, J_{2-3} = 4.9 Hz, H-2), 5.12 (s, 2 H, CH_2, benzyl), 7.30–7.44 (m, 5 H, aryl), 7.65 (d, 1 H, J_{NH-2} = 8.2 Hz, N-H), 12.6 (s, 2 H, carboxylate).

^{13}C-NMR (DMSO-d_6): δ = 17.18 (CH_3, methyl), 32.42 (C-3), 37.84 (C-4), 58.96 (C–2), 66.36 (benzyl), 128.6, 128.7, 129.2, 137.8 (6 x C, aryl), 157.2 (urethane), 173.7, 174.3 (2 x COOH, carboxylate).

MS (70 eV), m/z (%): 295 (2) [M^+], 277 (3), 160 (5), 144 (17), 109 (3), 108 (44), 107 (29), 98 (21), 91 (100), 79 (19), 77 (10).

(2S,3S)-1-(Benzyloxycarbonyl)-3-ethyl-glutamic acid (90)



To a solution of **81** (1.00 g, 2.66 mmol) in dichloromethane (10 ml) was added a 10 % aqueous solution of trifluoro acetic (10 ml). After stirring for 1 h the solvent was removed in vacuo to give a colourless oily residue which was dissolved in a mixture of THF (5 ml) and 1 M aqueous sodium hydroxide (15 ml). This solution was stirred for 12 h, then THF was removed in vacuo and the reaction mixture was adjusted with hydrochloric acid (6 N) to pH 1. The water phase was extractred with diethyl ether (3 x 20 ml) and the combined and dried organic phases were concentrated in vacuo to give **90** as colourless crystals after recrystallization from chloroform/diethyl ether. Yield 0.68 g (82 %).

TLC: R_f ~ 0.7, EtOAc/acetic acid (10+1).- m.p. 156 °C.- $[\alpha]_D^{20}$ = +12.6 (c = 0.39, EtOAc).

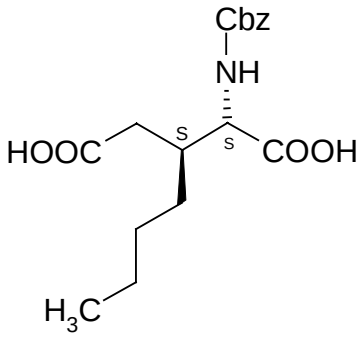
$C_{15}H_{19}NO_6$ (309.32): calcd. C 58.25, H 6.19, N 4.53; found C 57.68, H 6.04, N 4.43.

IR (KBr): ν = 3340 cm^{-1} (NH), 3150 (COOH), 2960 (C-H), 1720, 1650 (C=O), 1540 (C-H).

^{1}H-NMR (DMSO-d_6): δ = 0.88 (t, 3 H, J = 7.0 Hz, CH_3, ethyl), 1.33 (dt, 2 H, $J_{CH2–3}$ = 6.7 Hz, J ~ 7.0 Hz, CH_2, ethyl), 2.17–2.33 (m, 3 H, H-3, H-4a/b), 4.14 (2d, 1 H, J_{2-NH} = 8.2 Hz, $J_{2–3}$ = 3.0

Hz, H-2), 5.04 (d, 1 H, J_{gem} ~ 15.0 Hz, CH_2, benzyl), 5.10 (d, 1 H, J_{gem} ~ 15.0 Hz, CH_2, benzyl), 7.27–7.32 (m, 5 H, aryl), 7.57 (d, 1 H, J_{NH-2} = 8.5 Hz, N-H), 12.5 (s, 2 H, carboxylate).
^{13}C-NMR (DMSO-d_6): δ = 12.17 (CH_3, ethyl), 24.11 (CH_2, ethyl), 35.58 (C-4), 38.78 (C-3), 56.09 (C–2), 66.39 (benzyl), 108.6, 128.6, 128.7, 129.2, 137.8 (6 x C, aryl), 157.4 (urethane), 174.2, 174.6 (2 x COOH, carboxylate).
MS (70 eV), m/z (%): 309 (1) [M^+], 291 (4), 158 (20), 112 (35), 109 (3), 108 (35), 107 (28), 91 (100), 79 (17), 77 (9).

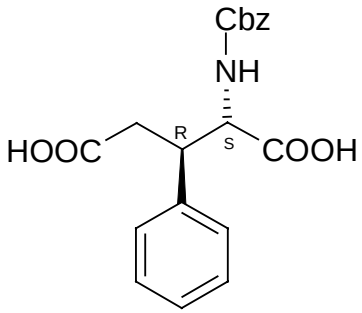
(2S,3S)-1-(Benzyloxycarbonyl)-3-butyl-glutamic acid (91)



To a solution of **82** (1.00 g, 2.49 mmol) in dichloromethane (10 ml) was added trifluoro acetic acid (10 % in water) (10 ml). After stirring for 1 h the solvent was removed under vacuo to give a colourless oily residue which was dissolved in a mixture of THF (5 ml) and 1 M sodium hydroxide sol. (15 ml). This solution was stirred for 12 h, then THF was removed under vacuo and the mixture was treated with 6 M hydrochloric acid to reach pH 1. The water phase was extractred with diethyl ether (3 x 20 ml) and the combined and dried organic phases were concentrated under vacuo to give **91** as colourless crystals after recrystallization from chloroform/diethyl ether. Yield 0.57 g (68 %).
TLC: R_f ~ 0.7, EtOAc/acetic acid (10+1).- m.p. 131 °C.- $[\alpha]_D^{20}$ = +10.3 (c = 0.58, EtOAc).
$C_{17}H_{23}NO_6$ (337.37): calcd. C 60.52, H 6.87, N 4.15; found C 60.30, H 6.74, N 4.20.
IR (KBr): ν = 3300 cm^{-1} (NH), 2980 (COOH), 2900 (C-H), 1700 (C=O), 1560 (C-H).
^{1}H-NMR (DMSO-d_6): δ = 0.79 (s, 3 H, CH_3, butyl), 1.20–1.25 (m, 6 H, 3 x CH_2, butyl), 2.04–2.23 (m, 3 H, H-3, H-4a/b), 4.14 (dd, 1 H, J_{2-NH} ~ 8.6 Hz, H-2), 4.98 (d, 1 H, J_{gem} ~ 15.0 Hz, CH_2, benzyl), 5.04 (d, 1 H, J_{gem} ~ 15.0 Hz, CH_2, benzyl), 7.27–7.32 (m, 5 H, aryl), 7.42 (d, 1 H, J_{NH-2} = 8.6 Hz, N-H), 12.4 (s, 2 H, carboxylate).

^{13}C-NMR (DMSO-d_6): δ = 14.67 (CH_3, butyl), 22.95 (CH_2, butyl), 29.30 (CH_2, butyl), 31.00 (CH_2, butyl), 36.00 (C-4), 37.50 (C-3), 56.30 (C–2), 66.32 (benzyl), 128.5, 129.2, 137.9 (6 x C, aryl), 157.0 (urethane), 173.0, 174.6 (2 x COOH, carboxylate).
MS (70 eV), m/z (%): 337 (1) [M^+], 319 (5), 186 (23), 140 (45), 109 (2), 108 (24), 107 (23), 91 (100), 79 (12), 77 (12).

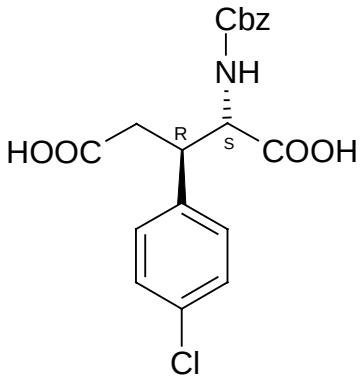
(2S,3R)-1-(Benzyloxycarbonyl)-3-phenyl-glutamic acid (93)



To a solution of **84** (1.00 g, 2.36 mmol) in dichloromethane (10 ml) was added a 10 % aqueous solution of trifluoro acetic (10 ml). After stirring for 1 h the solvent was removed under vacuo to give a colourless oily residue which was dissolved in a mixture of THF (5 ml) and 1 M sodium hydroxide sol. (15 ml). This solution was stirred for 12 h, then THF was removed under vacuo and the mixture was treated with 6 M hydrochloric acid to reach pH 1. The water phase was extractred with diethyl ether (3 x 20 ml) and the combined and dried organic phases were concentrated under vacuo to give **93** as colourless crystals after recrystallization from chloroform/diethyl ether. Yield 0.68 g (80 %).
TLC: R_f ~ 0.75, EtOAc/acetic acid (10+1).- m.p. 171 °C.- $[\alpha]_D^{20}$ = +4.6 (c = 0.24, EtOAc).
$C_{19}H_{18}ClNO_6$ (357.36): calcd. C 63.86, H 6.36, N 3.92; found C 62.33, H 5.21, N 3.90.
IR (KBr): ν = 3310 cm^{-1} (NH), 3010 (COOH), 1700 (C=O), 1550 (C-H).
^{1}H-NMR (DMSO-d_6): δ = 2.55 (dd, 1 H, J_{gem} ~16.5 Hz, J_{4a-3} = 4.0 Hz, H-4a), 2.80 (dd, 1 H, J_{gem} = 16.3 Hz, J_{4b-3} = 11.3 Hz, H-4b), 3.54 (dt, 1 H, J_{3-4a} ~ 4.0 Hz, J_{3-4b} ~ 11.3 Hz, J_{3-2} ~ 7.3 Hz, H-3), 4.24 (dd, 1 H, J_{2-3} = 7.3 Hz, J_{2-NH} = 8.5 Hz, H-2), 4.92 (d, 1 H, J = 12.8 Hz, CH_2, benzyl), 5.02 (d, 1 H, J = 12.8 Hz, CH_2, benzyl), 7.25–7.36 (m, 10 H, aryl), 7.69 (d, 1 H, J_{NH-2} = 8.5 Hz, N-H), 12.5 (s, 2 H, carboxylate).
^{13}C-NMR (DMSO-d_6): δ = 38.10 (C-4), 45.42 (C-3), 61.41 (C–2), 68.04 (benzyl), 129.4, 130.2, 130.4, 130.7, 130.9, 131.0, 139.6, 142.8 (12 x C, aryl), 158.7 (urethane), 174.9, 175.3 (2 x COOH, carboxylate).

MS (70 eV), m/z (%): 357 (1) [M^+], 339 (7), 206 (18), 160 (34), 149 (8), 117 (14), 108 (14), 107 (40), 104 (17), 92 (10), 91 (100), 79 (17), 78 (6), 77 (15).

(2S,3R)-1-(Benzyloxycarbonyl)-3-(4-chlorophenyl)-glutamic acid (94)



To a solution of **85** (0.80 g, 1.75 mmol) in dichloromethane (10 ml) was added a 10 % aqueous solution of trifluoro acetic (10 ml). After stirring for 1 h the solvent was removed in vacuo to give a colourless oily residue which was dissolved in a mixture of THF (5 ml) and 1 M aqueous sodium hydroxide (15 ml). This solution was stirred for 12 h, then THF was removed in vacuo and the reaction mixture was adjusted with hydrochloric acid (6 N) to pH 1. The water phase was extracted with diethylether (3 x 20 ml) and the combined and dried organic phases were concentrated in vacuo to give **94** as colourless crystals after recrystallization from chloroform/diethy lether. Yield 0.59 g (70 %).

TLC: R_f ~ 0.7, EtOAc/acetic acid (10+1).- m.p. 176 °C.- $[\alpha]_D^{20}$ = +1.2 (c = 0.44, EtOAc).

$C_{19}H_{18}ClNO_6$ (391.81): calcd. C 58.24, H 4.63, N 3.57; found C 58.24, H 4.74, N 3.57.

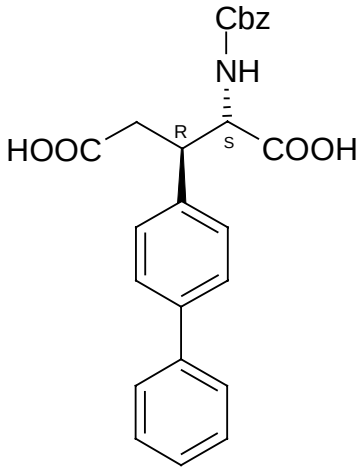
IR (KBr): ν = 3310 cm^{-1} (NH), 2950 (COOH), 1720 (C=O), 1560, 1520 (C-H).

^{1}H-NMR (DMSO-d_6): δ = 2.59 (dd, 1 H, J_{gem} = 16.5 Hz, J_{4a-3} = 3.7 Hz, H-4a), 2.81 (dd, 1 H, J_{gem} = 16.3 Hz, J_{4b-3} = 11.6 Hz, H-4b), 3.51 (dt, 1 H, J_{3-4a} ~ 3.7 Hz, J_{3-4b} ~ 11.6 Hz, J_{3-2} ~ 7.3 Hz, H-3), 4.24 (dd, 1 H, J_{2-3} = 7.3 Hz, J_{2-NH} = 8.6 Hz, H-2), 4.96 (d, 1 H, J = 15.0 Hz, CH_2, benzyl), 5.02 (d, 1 H, J = 15.0 Hz, CH_2, benzyl), 7.25–7.33 (m, 9 H, aryl), 7.79 (d, 1 H, J_{NH-2} = 8.6 Hz, N-H), 12.4 (s, 2 H, carboxylate).

^{13}C-NMR (DMSO-d_6): δ = 36.06 (C-4), 43.17 (C-3), 59.46 (C–2), 66.33 (benzyl), 128.4, 128.6, 128.9, 129.2, 131.0, 132.3, 137.8 140.1, (12 x C, aryl), 157.0 (urethane), 173.0, 173.4 (2 x COOH, carboxylate).

MS (70 eV), m/z (%): 391 (0) [M^+], 374 (10), 342 (21), 341 (16), 340 (65), 239 (12), 194 (27), 170 (12), 151 (21), 141 (10), 109 (6), 108 (75), 107 (55), 91 (39), 89 (10), 79 (100), 78 (12), 77 (57).

(2S,3R)-1-(Benzyloxycarbonyl)-3-biphenyl-glutamic acid (95)



To a solution of **86** (0.30 g, 0.60 mmol) in 5 ml dichloromethane was added 5 ml of trifluoro acetic acid (10 % in water). After stirring for 1 h the solvent was removed under vacuo to give a colourless oily residue which was dissolved in a mixture of 2 ml THF and 8 ml sodium hydroxide (1 M in water). This solution was stirred for 12 h, then THF was removed carefully under vacuo and the reaction mixture was adjusted with hydrochloric acid (6 N) to pH 1. The water phase was extractred with diethyl ether (3 x 10 ml) and the combined and dried organic phases were concentrated under vacuo to give **95** as colourless crystals after recrystallization from chloroform/diethyl ether. Yield 0.20 g (75 %).

TLC: R_f ~ 0.75 EtOAc/acetic acid (10+1).- m.p. 196 °C.- $[\alpha]_D^{20}$ = +5.6 (c = 0.30, EtOAc).

$C_{25}H_{23}NO_6$ (433.46): calcd. C 69.27, H 5.35, N 3.23; found C 68.80, H 5.86, N 3.33.

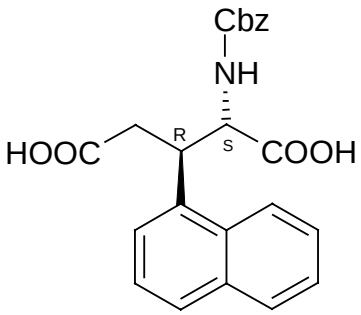
IR (KBr): ν = 3310 cm^{-1} (NH), 3020 (COOH), 2920, 2880 (C-H), 1790 (C=O), 1530 (C-H).

^{1}H-NMR (CD_3OD): δ = 2.80–2.95 (m, 2 H, H-4a/b), 3.73 (dt, 1 H, $J_{3\text{-}4a/b}$ ~ 9.2 Hz, $J_{3\text{-}2}$ ~ 6.7 Hz, H-3), 4.54 (d, 1 H, $J_{2\text{-}3}$ = 7.0 Hz, H-2), 5.06 (d, 1 H, J = 12.5 Hz, CH_2, benzyl), 5.15 (d, 1 H, J = 12.8 Hz, CH_2, benzyl), 7.31–7.63 (m, 14 H, aryl).

^{13}C-NMR (CD_3OD): δ = 36.10 (C-4), 44.02 (C-3), 59.40 (C-2), 66.75 (benzyl), 126.9, 127.0, 127.3, 127.8, 128.0, 128.5, 128.8, 128.9, 139.1, 140.4, 141.1, 141.8 (18 x C, aryl), 158.2 (urethane), 173.0, 174.0 (2 x COOH, carboxylate).

MS (70 eV), m/z (%): 433 (0) [M^+], 371 (12), 326 (6), 281 (13), 280 (55), 279 (11), 236 (100), 208 (20), 193 (38), 191 (10), 180 (35), 179 (12), 178 (41), 165 (18), 152 (8), 108 (10), 107 (14), 92 (7), 91 (90).

(2S,3R)-1-(Benzyloxycarbonyl)-3-naphthyl-glutamic acid (96): mixture with **(111)** [appr. relation: **96**:**111** = 10:1]

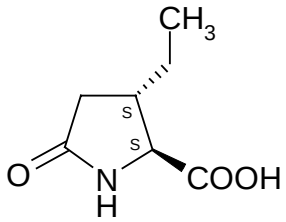


To a solution of (0.50 g, 1.06 mmol) **87** in 10 ml dichloromethane was added a 10 % aqueous solution of trifluoro acetic (10 ml). After stirring for 1 h the solvent was removed under vacuo to give a colourless oily residue which was dissolved in a mixture of 5 ml THF and 15 ml sodium hydroxide (1 M in water).This solution was stirred for 12 h, then THF was removed carefully under vacuo and the reaction mixture was adjusted with hydrochloric acid (6 N) to pH 1. The water phase was extractred with diethyl ether (3 x 30 ml) and the combined and dried organic phases were concentrated under vacuo to give a colourless solid mixture of **96** + **111** (appr. relation: **96**:**111** = 10:1). Yield (75 %).

^{1}H-NMR (DMSO-d_6): δ = 2.56 (dd, 1 H, J_{gem} = 17.1 Hz, J_{4a-3} = 3.6 Hz, H-4a, **111**), 2.89 (dd, 1 H, J_{gem} = 15.9 Hz, J_{4a-3} = 4.3 Hz, H-4a, **96**), 3.05–3.18 („m“, 1 H, H-4b, **96**; 1 H, H-4b, **111**), 4.63 (m, 1 H, H-2, **111**), 4.78–4.84 (m, 2 H, H-2 and H-3, **96**; 1H, H-3, **111**), 4.93 (d, 1 H, J = 12.9 Hz, CH_2, benzyl, **96**), 5.03 (d, 1 H, J = 12.9 Hz, CH_2, benzyl, **96**), 7.30–7.95 (m, 12 H, aryl, **96**; 7 H, aryl, **111**), 8.24 (m, 2 H, N-H, **111**), 8.35 (d, 1 H, J = 6.8 Hz, N-H, **96**), 12.3 (s, ~ 2 H, carboxylate, **96**; ~ 2 H, carboxylate, **111**)

^{13}C-NMR (DMSO-d_6): δ = 36.10 (C-4, **96**), 37.24 (C-4, **111**), 39.83 (C-3, **111**), 42.02 (C-3, **96**), 59.40 (C-2, **96**), 66.30 (C-2, **111**), 66.75 (benzyl, **96**), 122.9, 123.1, 125.5, 126.0, 126.6, 126.9, 127.0, 127.3, 127.8, 128.0, 128.5, 128.8, 128.9, 129.1, 131.9, 134.7, 138.5, 139.1, 140.4, 141.1, 141.8 (26 x C, aryl, **96**+**111**), 158.2 (urethane, **96**), 173.3 (COOH, **96**), 174.8 (COOH, **96**), 177.0 (COOH, **111**), 178.0 (COOH, **111**).

(2S,3S)-3-Ethyl-5-oxo-pyrrolidine-2-carboxylic acid (98)



To a solution of **81** (0.50 g, 1.47 mmol) in EtOAc/methanol (2+1) (70 ml) was added palladium on charcoal. This suspension was stirred for 2 h under hydrogen (4 bar). The catalyst was filtered off and the organic phase was concentrated in vacuo to give an oily colourless residue. The residue was treated with a mixture of trifluoro acetic acid (1 ml), water (20 ml) and dichloromethane (5 ml) for 1 h. The organic layer was diluted with dichloromethane, and the aqueous layer was extracted with dichloromethane (2x). The combined organic layers were concentrated in vacuo and the oily residue was treated with a 10 % caesium carbonate solution (10 ml) for 3 h. The reaction mixture was acidified with hydrochloric acid (pH < 2) and extracted with EtOAc (3 x 25 ml). The organic layers were dried and concentrated in vacuo to give **98** as colourless crystals. Recrystallization from chloroform/petroleum ether. Yield 0.15 g (65 %).

TLC: R_f ~ 0.40, EtOAc/acetic acid (10+1).- m.p. 115 °C.- $[\alpha]_D^{20}$ = +50.5 (c = 0.44, acetone).

$C_7H_{11}NO_3$ (157.17): calcd. C 53.49, H 7.05, N 8.91; found C 53.06, H 7.26, N 8.97.

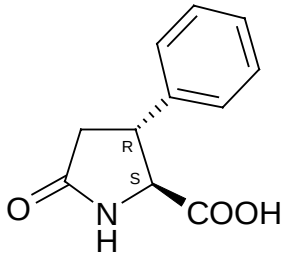
IR (KBr): ν = 3380 cm^{-1}(NH), 3010, 2940 (C-H), 1930, 1720 (C=O), 1650 (C=O, lactam), 1420 (C-H).

^{1}H-NMR (DMSO-d_6): δ = 0.87 (t, 3 H, J = 7.3 Hz, CH_3), 1.39 (dq, 1 H, J = 7.3 Hz, J = 6.1 Hz, Ha-ethyl), 1.59 (dq, 1 H, J = 7.3 Hz, J = 6.1 Hz, Hb-ethyl), 1.82 (dd, 1 H, J_{gem} = 16.2 Hz, J_{4b-3} = 4.7 Hz, H-4b), 2.21 (m, 1 H, J_{3-4a} ~ 8.5 Hz, J_{3-CH2} ~ 6.1 Hz, J_{3-4b} ~ 4.7 Hz, J_{3-2} ~ 4.0 Hz, H-3), 2.32 (dd, 1 H, J_{gem} = 16.2 Hz, J_{4a-3} = 8.5 Hz, H-4a), 3.64 (d, 1 H, J_{2-3} = 4.0 Hz, H-2), 7.80 (s, 1 H, N-H).

^{13}C-NMR (DMSO-d_6): δ = 12.30 (CH_3), 28.24 (CH_2), 36.28 (C-3), 40.96 (C-4), 61.17 (C-2), 176.8 (C=O, lactam), 176.9 (COOH, carboxylate).

MS (70 eV), m/z (%): 157 (3) [M^+], 113 (6) [M^+ - carboxylate], 112 (100), 98 (7), 84 (2), 83 (3), 70 (5), 69 (51).

(2S,3R)-3-Phenyl-5-oxo-pyrrolidine-2-carboxylic acid (101)



To a solution of **84** (1.00 g, 2.36 mmol) in EtOAc/methanol (2+1) (100 ml) was added 10 % palladium on charcoal. After the suspension was stirred for 2 h under hydrogen (4 bar), the catalyst was fitered off and the organic phase was concentrated in vacuo to give an oily colourless residue. The residue was treated with a mixture of trifluoro acetic acid (1 ml), water (20 ml) and dichloromethane (5 ml) for 1 h. The organic layer was diluted with CH_2Cl_2 and the aqueous phase was extracted with CH_2Cl_2 (2x). The combined organic layers were concentrated in vacuo and the oily residue was treated with of a 10 % caesium carbonate solution (10 ml) for 3 h. The reaction mixture was acidified with hydrochloric acid (pH < 2) and extracted with EtOAc (3 x 25 ml). The organic layers were dried and concentrated in vacuo to give **101.** Recrystallization from chloroform/petroleum ether gave colourless crystals. Yield 0.34 g (70 %).

TLC: R_f ~ 0.4, EtOAc/acetic acid (10+1).- m.p. 162 °C.- $[\alpha]_D^{20}$ = +86.7 (c = 0.27, acetone), $[\alpha]_D^{20}$ = +84.3 (c = 0.70, methanol).

Ref.: m.p. 139.0-140.0 °C [54].- $[\alpha]_D^{20}$ = +82.5 (c = 1.11, methanol) [54].- $[\alpha]_D^{20}$ = +82.8 (c = 1.10, methanol) [60d].

$C_{11}H_{11}NO_3$ (205.21): calcd. C 64.38, H 5.40, N 6.83; found C 63.23, H 5.62, N 6.44.

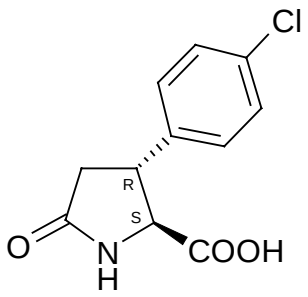
IR (KBr): ν = 3280 cm^{-1} (NH), 2960 (C-H), 1750 (C=O), 1650 (C=O, lactam).

^{1}H-NMR (DMSO-d_6): δ = 2.05 (dd, 1 H, J_{gem} = 16.8 Hz, J_{4b-3} = 6.7 Hz, H-4b), 2.43 (dd, 1 H, J_{gem} = 16.8 Hz, J_{4a-3} = 9.2 Hz, H-4a), 3.34 (dt, 1 H, J_{3-4b} ~ 6.7 Hz, J_{3-4a} ~ 9.2 Hz, J_{3-2} ~ 5.5 Hz, H-3), 3.82 (d, 1 H, J_{2-3} = 5.6 Hz, H-2), 7.03–7.10 (m, 5 H, aryl), 7.92 (s, 1 H, N-H), 12.7 (s, 1H, carboxylate).

^{13}C-NMR (DMSO-d_6): δ = 38.95 (C-3), 44.59 (C-4), 63.16 (C–2), 127.8, 129.5, 143.5, (6 x C, aryl), 174.3 (COOH, carboxylate), 176.3 (C=O, lactam).

MS (70 eV), m/z (%): 205 (26) [M^+], 162 (17), 161 (13) [M^+ - carboxylate],160 (100), 118 (11), 117 (75), 116 (6), 115 (26), 104 (74),103 (16), 91 (14), 77 (18).

(2S,3R)-3-(4-Chlorophenyl)-5-oxo-pyrrolidine-2-carboxylic acid (102)



To a solution of **85** (1.04 g, 2.27 mmol) in EtOAc/MeOH (2+1) (125 ml) was added palladium (10%) on charcoal. The suspension was stirred for 3 h under hydrogen (4 bar), the catalyst was filtered off and the solvent was evaporated to give an oily colourless residue. The residue was treated with a mixture of trifluoro acetic acid (1 ml), water (20 ml) and dichloromethane (5 ml) for 2 h. The organic layer was diluted with CH_2Cl_2 and the aqueous phase was extracted with CH_2Cl_2. The combined organic layers were concentrated in vacuo and the oily residue was stirred with a 10 % caesium carbonate solution (10 ml) for 3 h. The reaction mixture was acidified with hydrochloric acid (pH < 2) and extracted with EtOAc (3 x 25 ml). The organic layers were dried and concentrated in vacuo to give **102** as colourless crystals. Yield 0.35 g (65 %).

TLC: R_f ~ 0.4, isopropanol/CH_2Cl_2/acetic acid (5+1+1).- m.p. 191 °C.- $[\alpha]_D^{20}$ = +85.8 (c = 0.60, acetone).

$C_{11}H_{10}ClNO_3$ (239.66): calcd. C 55.13, H 4.21, N 5.84; found C 55.44, H 4.32, N 6.00.

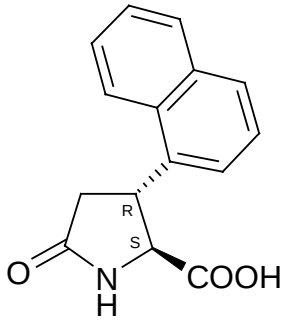
IR (KBr): ν = 3220 cm^{-1} (NH), 2950, 2870 (C-H), 1730 (C=O), 1640, 1490 (C-H).

^{1}H-NMR (DMSO-d_6): δ = 2.07 (dd, 1 H, J_{gem} = 16.8 Hz, J_{4b-3} = 7.1 Hz, H-4b), 2.45 (dd, 1 H, J_{gem} = 16.8 Hz, J_{4a-3} = 9.2 Hz, H-4a), 3.40 (dt, 1 H, J_{3-4b} ~ 7.1 Hz, J_{3-4a} ~ 9.3 Hz, J_{3-2} ~ 6.1 Hz, H-3), 3.86 (d, 1 H, J_{2-3} = 6.1 Hz, H-2), 7.13–7.24 (m, 4 H, aryl), 7.97 (s, 1 H, N-H), 12.7 (s, 1H, carboxylate).

^{13}C-NMR (DMSO-d_6): δ = 38.91 (C-3), 44.00 (C-4), 62.92 (C-2), 129.4, 129.9, 132.4, 142.3, (6 x C, aryl), 174.0 (COOH, carboxylate), 176.1 (C=O, lactam).

MS (70 eV), m/z (%): 241 (13) [M+1$^+$], 240 (6) [M$^+$], 239 (40) [M-1$^+$], 196 (54) [M$^+$ - carboxylate], 195 (13), 194 (92), 153 (15), 152 (6), 151 (47), 140 (32), 139 (10), 138 (100), 117 (19), 116 (26), 115 (23), 103 (33).

(2S,3R)-3-Naphthyl-5-oxo-pyrrolidine-2-carboxylic acid (104)



To a solution of **87** (0.75 g, 1.59 mmol) in EtOAc/methanol (2+1) (100 ml) was added 10 % palladium on charcoal. This suspension was stirred for 2 h under hydrogen (4 bar), then the catalyst was filtered off and the organic phase was concentrated in vacuo to give an oily colourless residue. The residue was treated with a mixture of trifluoro acetic acid (1 ml), water (20 ml) and dichloromethane (5 ml) for 1 h. The organic layer was diluted with CH_2Cl_2 and the aqueous phase was extracted with dichloromethane (2x). The combined organic layers were concentrated in vacuo and the oily residue was treated with a 10 % caesium carbonate solution (10 ml) for 3 h. The reaction mixture was acidified with hydrochloric acid (pH < 2) and extracted with EtOAc (3 x 25 ml). The organic layers were dried and concentrated in vacuo to give **104** as colourless crystals. Recrystallization from chloroform/petroleum ether yielded 0.41 g (58 %).

TLC: R_f ~ 0.45, EtOAc/acetic acid (10+1).- m.p. 210 °C.- $[\alpha]_D^{20}$ = -20.8 (c = 0.077, $CHCl_3$).

$C_{15}H_{13}NO_3$ (255.27): calcd. C 70.58, H 5.13, N 5.49; found C 70.27, H 5.63, N 5.37.

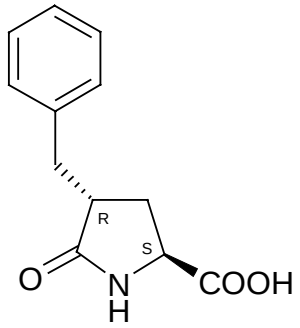
IR (KBr): ν = 3280 cm^{-1} (NH), 3050, 2920 (C-H), 1750 (C=O), 1650 (C=O, lactam), 1440 (C-H).

^{1}H-NMR (DMSO-d_6): δ = 2.39 (dd, 1 H, J_{gem} = 16.8 Hz, J_{4b-3} = 4.3 Hz, H-4b), 2.94 (dd, 1 H, J_{gem} = 19.7 Hz, J_{4a-3} = 6.7 Hz, H-4a), 4.27 (d, 1 H, J_{2-3} = 3.4 Hz, H-2), 4.52 (dt, 1 H, J_{3-4a} = 6.7 Hz, J_{3-4b} ~ 4.3 Hz, J_{3-2} ~ 3.4 Hz, H-3), 7.54 – 7.72 (m, 4 H, aryl), 7.96 (d, 1 H, J = 7.3 Hz, aryl), 8.07 (dd, 1 H, J = 7.3 Hz, J = 2.1 Hz, aryl), 8.29 (s, 1 H, N-H), 8.31 (”s”, 1 H, aryl), 13.2 (s, 1H, carboxylate).

^{13}C-NMR (DMSO-d_6): δ = 38.11 (C-3), ~ 40 (C-4), 62.35 (C–2), 123.9, 124.0, 126.5, 126.7, 127.4, 128.3, 129.8, 131.6, 134.5, 139.4 (10 x C, aryl), 174.6 (COOH, carboxylate), 176.8 (C=O, lactam).

MS (70 eV), m/z (%): 255 (40) [M^+], 211 (3) [M^+ - carboxylate], 210 (16), 167 (25), 165 (20), 155 (13), 154 (94), 153 (68), 152 (34), 128 (100), 103 (16), 91 (6), 77 (5), 76 (12).

(2S,4R)-4-Benzyl-5-oxo-pyrrolidine-2-carboxylic acid (105)



To a solution of HMDS (2.18 g, 0.013 mol) and butyllithium (4.92 ml, 0.013 mol, 2.7 M in heptane) in THF (40 ml) at –78 °C was added a solution of **65** (2.00 g, 0.006 mol) in THF (15 ml) under nitrogen over a period of 30 min. The reaction mixture was allowed to warm to 0° C then it was cooled to –78 °C. A solution of benzyl bromide (1.03 g, 0.006 mol) in THF (40 ml) was added and the reaction mixture was stirred for 2 h, and then allowed to warm to room temperature. The reaction was quenched by adding satd. ammonium chloride solution (60 ml), and EtOAc (120 ml), and the organic phase was washed with satd. ammonium chloride sol. (2x). The dried organic phase was concentrated in vacuo to give an oily colourless residue, that was purified by column chromatography to provide an colourless solid (cis-**71**/trans-**71**, not listed, chapter 5.4). This solid residue was dissolved in EtOAc/methanol (2+1, 100 ml) and was kept under hydrogen (4 bar) in the presence of palladium on charcoal for 5h. The catalyst was filtered off and the organic phase was concentrated in vacuo to give an oily colourless residue. This residue was treated with a mixture of trifluoro acetic acid (0.5 ml), water (20 ml) and dichloromethane (5 ml) for 1 h. The organic layer was diluted with dichloromethane, and the aqueous layer was extracted with dichloromethane (2x). The combined organic layers were concentrated in vacuo and the oily residue was treated with 10 % caesium carbonate solution (10 ml) for 3 h. The reaction mixture was acidified with hydrochloric acid (pH < 2) and extracted with EtOAc (3 x 25 ml). The organic layers were dried and concentrated in vacuo to give **105** as colourless crystals. Recrystallization from chloroform/petroleum ether. Yield 0.68 g (52 %).

TLC: R_f ~ 0.45, EtOAc/acetic acid (10+1).- m.p. 168 °C.- $[\alpha]_D^{20}$ = -3.4 (c = 0.32, methanol).

Ref.: m.p. 161 °C [91].- $[\alpha]_D^{20}$ = -96.3 (c = 0.77, methanol) [91].

$C_{12}H_{13}NO_3$ (219.24): calcd. C 65.75, H 5.98, N 6.39; found C 64.84, H 5.94, N 6.06.

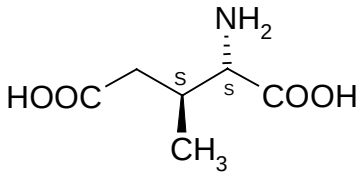
IR (KBr): ν = 3360 cm^{-1}(NH), 3230, 2940 (C-H), 1930, 1725 (C=O), 1640 (C=O, lactam), 1420 (C-H).

^{1}H-NMR (CD_3OD): δ = 2.21–2.29 (m, 2 H, H-3a and H-3b), 2.66–2.88 (m, 2 H, H-4 and H-b_{benzyl}), 3.13 (dd, 1 H, J_{gem} = 13.6 Hz, $J_{H\text{-}abenzyl\text{-}4}$ = 3.8 Hz, H-a_{benzyl}), 4.01 (dd, 1 H, $J_{2\text{-}3a}$ = 4.4 Hz, $J_{2\text{-}3b}$ = 8.1 Hz, H-2), 7.20–7.31 (m, 5 H, aryl).

^{13}C-NMR (CD_3OD): δ = 30.72 (benzyl), 36.27 (C-3), 42.19 (C-4), 54.01 (C-2), 126.5, 128.6, 129.1, 139.1 (6 x C, aryl), 174.8 (C=O, lactam), 180.7 (COOH, carboxylate).

MS (70 eV), m/z (%): 220 (8) [$M+1^+$], 219 (52) [M^+], 201 (14) [$M^+ - H_2O$], 174 (42), 131 (16), 129 (14), 128 (16), 119 (7), 118 (10), 117 (13), 96 (8), 91 [$benzyl^+$] (100), 78 (6), 65 (14).

(2S,3S)-3-Methyl-glutamic acid (106)



To a solution of **89** (0.74 g, 2.51 mmol) in H_2O/isopropanol (1+1) (50 ml) was added palladium on charcoal. This suspension was stirred for 3 h under hydrogen (4 bar). The catalyst was removed by filtration and the mixture was concentrated in vacuo to give a solid colourless residue. Recrystallization from H_2O/isopropanol gave **106** as colourless crystals. Yield 0.32 g (78 %).

m.p. 182-184 °C.- $[\alpha]_D^{20}$ = +41.9 (c = 0.82, 6M HCl).

Ref.: m.p. 169.5-170 °C [60a].- $[\alpha]_D^{20}$ = +42.8 (c = 0.97, 6M HCl) [60a].- m.p. 169-171 °C (for monoammonium salt) [60a].- $[\alpha]_D^{20}$ = +36.8 (c = 1.02, 6M HCl, for 0.75 hydrate) [48].- m.p. 180 °C [131].- $[\alpha]_D^{20}$ = +15.2 (c = 1, H_2O) [131].

$C_6H_{11}NO_4$ (161.16): calcd. C 44.72, H 6.88, N 8.69; found C 43.93, H 6.77, N 8.56.

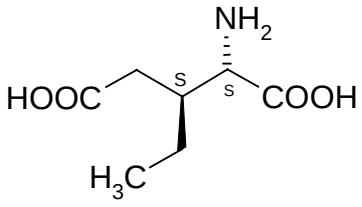
IR (KBr): ν = 3040 cm^{-1} (NH), 2940, 2870 (C-H), 2620-2500 (COOH), 1690 (COO^-), 1490 (C-H), 1420 (COO^-).

^{1}H-NMR (D_2O/NaOD): δ = 0.85 (d, 3H, $J_{CH3\text{-}3}$ = 6.7 Hz, CH_3), 1.83 (dd, 1 H, J_{gem} = 12.8 Hz, $J_{4b\text{-}3}$ = 11.3 Hz, H-4b), 1.91–2.15 („m“, 1 H, $J_{3\text{-}4a}$ ~ 3.1 Hz, $J_{3\text{-}4b}$ ~ 11.3 Hz, $J_{3\text{-}2}$ ~ 5.5 Hz, $J_{3\text{-}CH3}$ ~ 6.7 Hz, H-3), 2.25 (dd, 1 H, J_{gem} = 13.1 Hz, $J_{4a\text{-}3}$ = 3.1 Hz, H-4a), 3.01 (d, 1 H, $J_{2\text{-}3}$ = 5.5 Hz, H-2).

^{13}C-NMR (D_2O/NaOD): δ = 16.47 (CH_3), 35.32 (C-3), 40.96 (C-4), 61.11 (C-2), 182.4 (COO^-), 182.6 (COO^-).

MS (70 eV), m/z (%): 161 (0) [M^+], 144 (4) [$M^+ - H_2O$], 99 (6), 98 (100), 70 (3), 55 (69).

(2S,3S)-3-Ethyl-glutamic acid (107)



To a solution of **90** (0.50 g, 1.62 mmol) in EtOAc/methanol (1+5) (100 ml) was added palladium on charcoal. This suspension was stirred for 6 h under hydrogen (4 bar). The catalyst was removed by filtration and the mixture was concentrated in vacuo to give a solid colourless residue. This residue was treated diethyl ether to give **107** as colourless crystals. Yield 0.18 g (62 %).

m.p. 139 °C.- $[\alpha]_D^{20}$ = +49.3 (c = 0.78, 6M HCl).

$C_7H_{13}NO_4$ (175.18): calcd. C 47.99, H 7.48, N 8.00; found C 46.12, H 7.04, N 7.66.

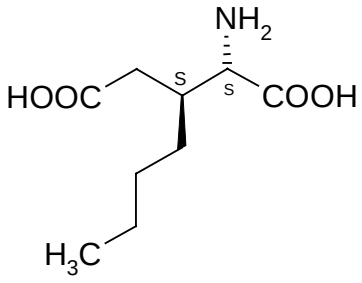
IR (KBr): ν = 3050 cm^{-1} (NH), 2970, 2940, 2880 (C-H), 2620-2500 (COOH), 1700 (COO^-), 1485 (C-H), 1420 (COO^-).

^{1}H-NMR (D_2O): δ = 0.81 (t, 3 H, J = 7.3 Hz, CH_3), 1.26 (dq, 1 H, J = 7.3 Hz, J_{CH2-3} = 7.0 Hz, CH_2), 1.32 (dq, 1 H, J = 7.3 Hz, J_{CH2-3} = 7.0 Hz, CH_2), 2.13–2.29 („m“, 1 H, H-3), 2.31 (dd, 1 H, J_{gem} = 16.5 Hz, J_{4b-3} = 6.4 Hz, H-4b), 2.43 (dd, 1 H, J_{gem} = 16.5 Hz, J_{4a-3} = 6.4 Hz, H-4a), 3.75 (d, 1 H, J_{2-3} = 3.4 Hz, H-2).

^{13}C-NMR (D_2O): δ = 11.19 (CH_3), 22.84 (CH_2), 35.27 (C-4), 37.86 (C-3), 56.80 (C-2), 173.6 (COOH), 177.4 (COOH).

MS (70 eV), m/z (%): 175 (0) [M^+], 157 (3) [M^+ - H_2O], 113 (7), 112 (100), 84 (2), 83 (3), 69 (50).

(2S,3S)-3-(1-Butyl)-glutamic acid (108)



To a solution of **91** (1.00 g, 2.96 mmol) in EtOAc/methanol (1+5) (100 ml) was added palladium on charcoal. This suspension was stirred for 5 h under hydrogen (4 bar). The catalyst was removed by filtration. The mixture was concentrated in vacuo to give a solid colourless residue. This residue was treated diethyl ether to give **108** as colourless crystals. Yield 0.52 g (75 %).

m.p. 122-123 °C; $[\alpha]_D^{20}$ = +7.90 (c = 0.42, methanol).

$C_9H_{17}NO_4$ (203.24): calcd. C 53.19, H 8.43, N 6.89; found C 52.34, H 8.03, N 6.71.

IR (KBr): ν = 3240 cm^{-1} (NH), 2950, 2930,2860 (C-H), 2620-2500 (COOH), 1710, 1680 (COO^-), 1520, 1500 (C-H), 1440 (COO^-).

^{1}H-NMR (CD_3OD, 27 °C): δ = 0.98 (t, 3 H, J = 6.7 Hz, CH_3), 1.37–1.48 (m, 4 H, 2 x CH_2), 1.51–1.57 (m, 2 H, 1 x CH_2), 2.45–2.50 (m, 3 H, H-4b and H-3), 2.70 (dd, 1 H, J_{gem} = 18.2 Hz, J_{4a-3} = 8.0 Hz, H-4a), 3.79 (d, 1 H, J_{2-3} = 3.2 Hz, H-2).

^{1}H-NMR (CD_3OD, 50 °C): δ = 0.97 (t, 3 H, J = 6.8 Hz, CH_3), 1.37–1.50 (m, 4 H, 2 x CH_2), 1.51–1.58 (m, 2 H, 1 x CH_2), 2.41–2.51 (m, 3 H, H-4b and H-3), 2.71 (dd, 1 H, J_{gem} = 18.3 Hz, J_{4a-3} = 6.9 Hz, H-4a), 3.79 (d, 1 H, J_{2-3} = 3.3 Hz, H-2).

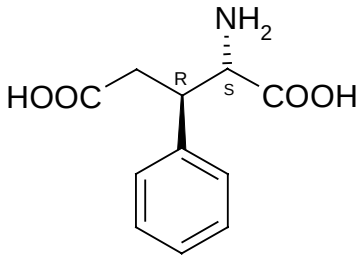
^{1}H-NMR (D_2O/NaOD, 27 °C): δ = 0.86 (t, 3H, J = 6.7 Hz, CH_3), 1.27–1.32 (m, 6H, 3 x CH_2), 1.96 (dd, 1 H, J_{gem} = 13.1 Hz, J_{4b-3} = 10.6 Hz, H-4b), 2.05–2.13 („m“, 1 H, J_{3-4a} ~ 3.5 Hz, J_{3-4b} ~ 10.6 Hz, J_{3-2} ~ 5.5 Hz, H-3), 2.16 (dd, 1 H, J_{gem} = 13.3 Hz, J_{4a-3} = 3.5 Hz, H-4a), 3.29 (d, 1 H, J_{2-3} = 4.2 Hz, H-2).

^{1}H-NMR (D_2O/NaOD, 50 °C): δ = 1.12 (t, 3H, J = 6.6 Hz, CH_3), 1.50–1.60 (m, 6H, 3 x CH_2), 2.23 (dd, 1 H, J_{gem} = 13.4 Hz, J_{4b-3} = 10.3 Hz, H-4b), 2.30–2.38 („m“, 1 H, J_{3-4a} ~ 3.5 Hz, J_{3-4b} ~ 10.3 Hz, J_{3-2} ~ 4.4 Hz, H-3), 2.43 (dd, 1 H, J_{gem} = 13.4 Hz, J_{4a-3} = 3.5 Hz, H-4a), 3.53 (d, 1 H, J_{2-3} = 4.4 Hz, H-2).

^{13}C-NMR (D_2O/NaOD): δ = 13.75 (CH_3, butyl), 22.46 (CH_2, butyl), 28.75 (CH_2, butyl), 30.47 (CH_2, butyl), 38.94 (C-4), 39.83 (C-3), 57.93 (C-2), 182.6 (COO^-), 182.8 (COO^-)

MS (70 eV), m/z (%): 203 (0) [M^+], 185 (2) [M^+ - H_2O], 141 (9), 140 (100), 98 (3), 97 (11).

(2S,3R)-3-Phenyl-glutamic acid (109)



To a solution of **93** (2.00 g, 5.60 mmol) in EtOAc/methanol (2+1) (120 ml) was added palladium on charcoal. This suspension was stirred for 4 h under hydrogen (4 bar). The catalyst was removed by filtration and the mixture was concentrated in vacuo to give an oily colourless residue. This residue was treated with diethyl ether to give **109** as colourless crystals. Yield 0.79 g (63 %).

m.p. 197 °C.- $[\alpha]_D^{20}$ = +16.7 (c = 0.60, 6M HCl).

Ref.: m.p. 158.0-158.6 °C [54].- $[\alpha]_D^{20}$ = +16.7 (c = 1.36, 6N HCl) [54].- $[\alpha]_D^{20}$ = +11.1 (c = 0.81, 6M DCl) [55].

$C_{11}H_{13}NO_4$ (223.23): calcd. C 59.19, H 5.87, N 6.27; found C 57.91, H 6.08, N 5.77.

IR (KBr): ν = 3150 cm^{-1} (NH), 2940 (C-H), 2620-2500, 1700 (COOH), 1620 (COO^-), 1500 (C-H), 1410 (COO^-).

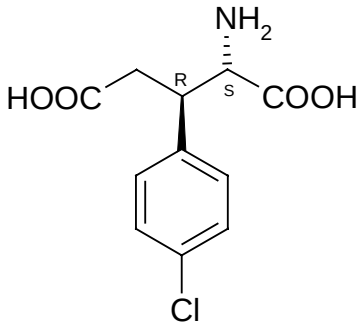
^{1}H-NMR (DMSO-d_6): δ = 2.31 (dd, 1 H, J_{gem} = 16.8 Hz, J_{4a-3} = 6.4 Hz, H-4a), 2.72 (dd, 1 H, J_{gem} = 16.5 Hz, J_{4b-3} = 9.5 Hz, H-4b), 3.64 (dt, 1 H, J_{3-4a} ~ 6.4 Hz, J_{3-4b} ~ 9.5 Hz, H-3), 4.08 („s“, 1 H, H-2), 7.21–7.45 (m, 5 H, aryl), 8.15 (s, ~1 H, N-H), 12.5 (s, ~2 H, carboxylate).

^{1}H-NMR (D_2O/NaOD): δ = 2.53–2.69 (m, 2 H, H-4), 3.21 – 3.56 (m, 2 H, H-2 and H-3), 7.19–7.38 (m, 5 H, aryl).

^{13}C-NMR (D_2O/NaOD): δ = 39.14 (C-4), 47.65 (C-3), 62.26 (C-2), 127.1, 128.6, 128.8, 141.6 (6 x C, aryl), 181.5 (COO^-), 181.7 (COO^-).

MS (70 eV), m/z (%): 223 (0) [M^+], 205 (25) [$M^+ - H_2O$], 162 (16), 161 (13), 160 (100), 118 (10), 117 (73), 115 (20), 104 (63), 103 (13).

(2S,3R)-3-(4-Chlorophenyl)-glutamic acid (110)



To a solution of **94** (2.00 g, 5.10 mmol) in EtOAc/methanol (2+1) (100 ml) was added palladium on charcoal. After the suspension was stirred for 3 h under hydrogen (4 bar), the catalyst was removed by filtration and the organic phase was concentrated in vacuo to give an oily colourless residue. This residue was treated with diethyl ether to give **110** as colourless crystals. Yield 0.92 g (70 %).

m.p. 197 °C.- $[\alpha]_D^{20}$ = +60.9 (c = 0.14, 1M HCl), $[\alpha]_D^{20}$ = +129 (c = 0.07, 1M NaOH).

Ref.: m.p. 182 °C [44].- m.p. 194.7–194.9 °C [50a].- $[\alpha]_D^{20}$ = +21.5 (c = 0.39, 1N NaOH) [50a].

$C_{11}H_{12}ClNO_4$ (257.67): calcd. C 51.28, H 4.69, N 5.44; found C 52.69, H 4.17, N 5.36.

IR (KBr): ν = 3350 cm^{-1} (NH), 2940, 2870 (C-H), 2620-2500, 1740 (COOH), 1650 (COO^-), 1490 (C-H), 1430 (COO^-).

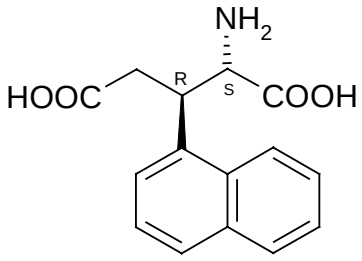
^{1}H-NMR (DMSO-d_6): δ = 2.25 (dd, 1 H, J_{gem} = 16.7 Hz, J_{4a-3} = 7.1 Hz, H-4a), 2.62 (dd, 1 H, J_{gem} = 16.9 Hz, J_{4b-3} = 9.4 Hz, H-4b), 3.56 (dt, 1 H, J_{3-4a} ~ 7.1 Hz, J_{3-4b} ~ 9.4 Hz, J_{3-2} ~ 5.8 Hz, H-3), 4.03 (d, 1 H, J_{2-3} = 5.8 Hz, H-2), 7.31–7.40 (m, 4 H, aryl), 8.11 (s, 1 H, N-H), 12.7 (s, ~2 H, carboxylate).

^{1}H-NMR (CD_3OD): δ = 2.33 (dd, 1 H, J_{gem} = 17.1 Hz, J_{4a-3} = 6.4 Hz, H-4a), 2.74 (dd, 1 H, J_{gem} = 17.1 Hz, J_{4b-3} = 9.2 Hz, H-4b), 3.59 (dt, 1 H, J_{3-4a} ~ 6.4 Hz, J_{3-4b} ~ 9.2 Hz, J_{3-2} ~ 5.2 Hz, H-3), 4.11 (d, 1 H, J_{2-3} = 5.2 Hz, H-2), 7.20–7.28 (m, 4 H, aryl).

^{13}C-NMR (CD_3OD): δ = 38.16 (C-4), 43.97 (C-3), 63.31 (C-2), 128.7, 129.0, 133.1, 141.5 (6 x C, aryl), 173.6 (COOH), 178.3 (COOH).

MS (70 eV), m/z (%): 257 (0) [M^+], 241 (10), 239 (36), 196 (55), 195 (14), 194 (100), 151 (51), 140 (31), 139 (9), 138 (97), 117 (19), 116 (28), 115 (21), 103 (29).

(2S,3R)-3-(1-Naphthyl)-glutamic acid (111)



To a solution of **96**+**111** [ratio 10:1] (0.40 g, ~ 0.98 mmol) in EtOAc/methanol (1+1) (50 ml) was added palladium on charcoal. This suspension was stirred for 8 h under hydrogen (4 bar). The catalyst was removed by filtration and the mixture was concentrated in vacuo to give an oily colourless residue. This residue was treated with diethyl ether to give **111** as colourless crystals. Yield 0.16 g (60 %).

m.p. 197 °C; $[\alpha]_D^{20}$ = -3.23 (c = 0.31, methanol).

$C_{15}H_{15}NO_4$ (273.29): calcd. C 65.92, H 5.53, N 5.13; found C 65.04, H 5.80, N 4.87.

IR (KBr): ν = 3350 cm^{-1} (NH), 2925, 2850 (C-H), 1750 (COOH), 1650 (COO^-), 1510 (C-H), 1420, 1400 (COO^-).

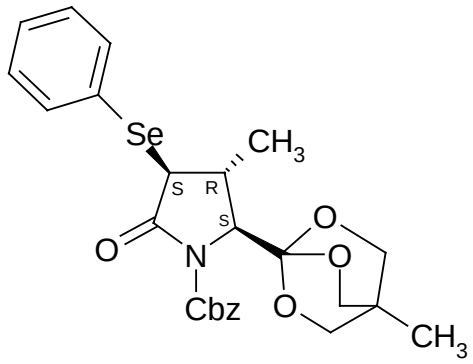
^{1}H-NMR (CD_3OD): δ = 2.56 (dd, 1 H, J_{gem} = 17.4 Hz, J_{4a-3} = 3.7 Hz, H-4a), 3.10 (dd, 1 H, J_{gem} = 17.1 Hz, J_{4b-3} = 9.2 Hz, H-4b), 4.38 (d, 1 H, J_{2-3} = 3.1 Hz, H-2), 4.62 („dt“, 1 H, J_{3-4b} = 8.9 Hz, J_{3-4a} ~ J_{3-2} ~ 3.4 Hz, H-3), 7.48–8.28 (m, 7 H, aryl).

^{1}H-NMR (DMSO-d_6): δ = 2.25 (dd, 1 H, J_{gem} = 17.4 Hz, J_{4a-3} = 1.5 Hz, H-4a), 2.84 (dd, 1 H, J_{gem} = 16.8 Hz, J_{4b-3} = 9.2 Hz, H-4b), 4.08 („s“, 1 H, H-2), 4.40 („m“, 1 H, H-3), 7.47-8.05 (m, 7 H, aryl), 8.24 (d, 1 H, J = 6.4 Hz, N-H).

^{13}C-NMR (CD_3OD): δ = 37.24 (C-4), 39.83 (C-3), 66.30 (C-2), 122.9, 123.1, 125.5, 126.0, 126.6, 128.0, 129.1, 131.9, 134.7, 138.5 (10 x C, aryl), 177.0 (COOH), 178.0 (COOH).

MS (70 eV), m/z (%): 273 (1) [M^+], 267 (16), 266 (35), 238 (10), 224 (14), 223 (15), 222 (21), 210 (36), 195 (11), 193 (16), 185 (14), 181 (24), 168 (15), 167 (59), 166 (17), 165 (35), 155 (16), 154 (100), 153 (68), 152 (42), 131 (17), 129 (17), 128 (83).

(2S,3R,4S)-3-Methyl-2-(4-methyl-2,6,7-trioxa-bicyclo[2.2.2]oct-1-yl)-5-oxo-4-phenylselenenyl-pyrrolidine-1-carboxylic acid benzyl ester (112)



To a solution of HMDS (1.54 g, 9.55 mmol) and butyllithium (3.54 ml, 9.55 mmol, 2.7 M in heptane) in abs. THF (10 ml) at -78 °C was added **80** (1.50 g, 4.15 mmol) dissolved in THF (25 ml) under nitrogen over a period of 30 min. The reaction mixture was allowed to warm to 0° C, then again cooled to -78 °C and phenylselenenyl chloride (0.83 g, 4.36 mmol) dissolved in abs. THF (10 ml) was added. After 2 h the mixture was allowed to warm to room temperature. The reaction was quenched by adding satd. ammonium chloride sol. (15 ml), diluted with diethyl ether (180 ml) and the organic phase was washed with satd. ammonium chloride sol. (2x). The dried organic layer was concentrated in vacuo to give an yellow oily residue, which was purified by column chromatography on silica gel using EtOAc/petroleum ether (1+1) as an eluent to give **112** as colourless crystals. Recrystallization from dichloromethane/ethanol. Yield 1.18 g (55 %).

TLC: R_f ~ 0.55, EtOAc/ petroleum ether (1+1).- m.p. 174 °C.- $[\alpha]_D^{20}$ = -88.6 (c = 0.50, CH_2Cl_2).

$C_{25}H_{27}NO_6Se$ (516.45): calcd. C 58.14, H 5.27, N 2.71; found C 58.80, H 5.50, N 2.72.

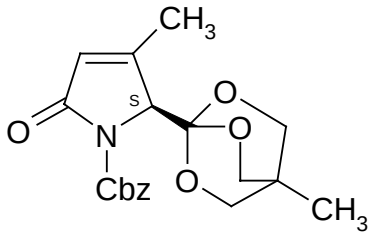
IR (KBr): ν = 2965 cm^{-1}, 2945 (C-H), 2882, 1720 (C=O), 1496 (C-H).

^{1}H-NMR ($CDCl_3$): δ = 0.78 (s, 3 H, CH_3, ortho ester), 1.16 (d, 3 H, J_{CH3-3} = 7.3 Hz, CH_3, methyl), 2.81 (ddq, 1 H, J_{3-4} = 2.0 Hz, J_{3-CH3} = 7.3 Hz, J_{3-2} = 1.0 Hz, H-3), 3.23 (d, 1 H, J_{4-3} = 2.0 Hz, H-4), 3.86 (s, 6 H, 3 x OCH_2, ortho ester), 4.01 (d, 1 H, J_{2-3} = 1.0 Hz, H-2), 5.26 (d, 1 H, J = 12.6 Hz, CH_2, benzyl), 5.31 (d, 1 H, J = 12.6 Hz, CH_2, benzyl), 7.21–7.38 (m, 6 H, aryl), 7.41–7.47 (m, 2 H, aryl) 7.72–7.77 (m, 2 H, aryl).

^{13}C-NMR ($CDCl_3$): δ = 14.67 (CH_3, ortho ester), 22.60 (CH_3, methyl), 31.50 ($\underline{C}CH_3(CH_2O\text{-})_3$), 36.81 (C-3), 50.24 (C-4), 66.04 (C-2), 68.71 (CH_2, benzyl), 73.04 (3 x CH_2O), 109.2 ($\underline{C}CH_3(OCH_2)_3$), 127.9, 128.5 (2x), 128.6, 128.8, 128.9, 129.0 (2x), 129.3, 129.4, 134.2, 135.9 (18 x C, aryl), 152.1 (C=O, urethane), 175.6 (C=O, lactam).

MS (70 eV), m/z (%): 517 (11) [M^+ +1], 515 (6) [M^+ -1], 382 (3), 316 (3), 254 (4), 224 (3), 186 (5), 171 (12), 144 (3), 96 (6), 91 (100) [benzyl], 85 (6), 69 (10).

(2S)-3-Methyl-2-(4-methyl-2,6,7-trioxa-bicyclo[2.2.2]oct-1-yl)-5-oxo-2,5-dihydro-pyrrole-1-carboxylic acid benzyl ester (113)



Compound **112** (1.00 g, 1.94 mmol) and DABCO (0.43 g, 3.87 mmol) were dissolved in abs. THF (25 ml) at 0 °C. After 10 min a solution of 3-chloroperbenzoic acid (1.00 g, 5.82 mol) in dichloromethane (50 ml) was given carefully to the reaction mixture over a period of 30 min. Then, the reaction was allowed to warm up and stirred for further 48h to complete the reaction (monitored by TLC). Afterwards, the reaction mixture was diluted with EtOAc (125 ml) and washed with satd. sodium bisulfite, satd. sodium bicarbonate and satd. brine. The dried and concentrated organic phase gave an oily residue which was purified by column chromatography on silica gel using EtOAc/petroleum ether (2 + 1) as an eluent to give **113** as colourless crystals. Yield 0.55 g (79 %).

TLC: R_f ~ 0.45, EtOAc/petroleum ether (2+1).- m.p. 130 °C.- $[\alpha]_D^{20}$ = -113 (c = 0.42, CH_2Cl_2).

$C_{19}H_{21}NO_6$ (359.38): calcd. C 63.50, H 5.89, N 3.90; found C 63.47, H 6.02, N 3.61.

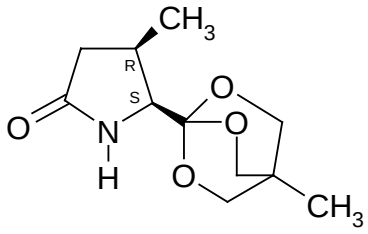
IR (KBr): ν = 2985 cm^{-1}, 2925, 2880, 2850 (C-H), 1760, 1700 (C=O), 1640, 1470, 1450 (C-H).

^{1}H-NMR ($CDCl_3$): δ = 0.76 (s, 3 H, CH_3, ortho ester), 2.08 (dd, 3 H, J_{CH3-4} = 1.3 Hz, J_{CH3-2} = 0.8 Hz, CH_3), 3.82 (m, 6 H, 3 x OCH_2, ortho ester), 4.75 („t“, 1 H, $J_{2-CH3} \sim J_{2-4}$ = 1.0 Hz, H-2), 5.23 (d, 1 H, J = 12.4 Hz, CH_2, benzyl), 5.30 (d, 1 H, J = 12.4 Hz, CH_2, benzyl), 5.78 (dq, 1 H, J_{4-CH3} = 1.3 Hz, J_{4-2} = 0.9 Hz, H-4), 7.26–7.45 (m, 5 H, aryl).

^{13}C-NMR ($CDCl_3$): δ = 14.62 (CH_3, ortho ester), 16.92 (CH_3), 31.09 ($\underline{C}CH_3(CH_2O\text{-})_3$), 66.77 (C-2), 68.39 ($CH_2$, benzyl), 73.15 (3 x CH_2O), 107.9 ($\underline{C}CH_3(OCH_2)_3$), 123.4 (C-4), 128.5, 128.6 (2x), 128.8, 129.0, 136.1 (6 x C, aryl), 151.5 (C=O, urethane), 160.2 (C-3), 169.8 (C=O, lactam).

MS (70 eV), m/z (%): 359 (11) [M^+], 315 (12), 253 (31), 211 (24), 123 (18), 109 (10), 96 (17), 91 (100) [benzyl], 85 (159), 65 (14).

(4R,5S)-4-Methyl-5-(4-methyl-2,6,7-trioxa-bicyclo[2.2.2]oct-1-yl)-pyrrolidin-2-one (114)



To a solution of **113** (0.20 g, 0.56 mmol) in EtOAc (50 ml) was added palladium on charoal. This suspension was stirred for 2 h under hydrogen (4 bar). The catalyst was removed by filtration and the mixture was concentrated in vacuo to give an oily colourless residue. This residue was treated with diethyl ether to give **114** as colourless crystals. Recrystallization from chloroform/petroleum ether. Yield 0.10 g (80 %).

TLC: R_f ~ 0.25, EtOAc.- m.p. 134 °C; $[\alpha]_D^{20}$ = +28.0 (c = 0.15, EtOAc).

$C_{11}H_{17}NO_4$ (227.26): calcd. C 58.14, H 7.54, N 6.16; found C 59.09, H 8.10, N 5.63.

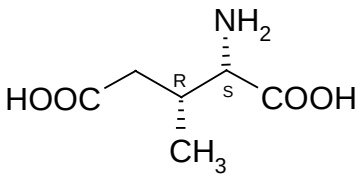
IR (KBr): ν = 3390 cm^{-1} (NH), 3220, 2930, 2880 (C-H), 1680 (C=O, lactam), 1420, 1400 (C-H).

^{1}H-NMR ($CDCl_3$): δ = 0.89 (s, 3 H, CH_3, ortho ester), 1.11 (d, 3 H, J = 7.0 Hz, CH_3), 2.19 (dd, 1 H, J_{gem} = 16.8 Hz, J_{3a-4} = 7.9 Hz, H-3a), 2.59 (dd, 1 H, J_{gem} = 16.8 Hz, J_{3b-4} = 8.2 Hz, H-3b), 2.91 (“septett”, 1 H, J_{4-3a} ~ J_{4-3b} ~ J_{4-CH3} ~ J_{4-5} = 7.6 Hz, H-4), 3.82 (s, 6 H, 3 x OCH_2, ortho ester), 4.37 (d, 1 H, J_{5-4} = 7.9 Hz, H-5).

^{13}C-NMR ($CDCl_3$): δ = 14.70 (CH_3, ortho ester), 21.81 (CH_3, methyl), 28.20 (C-4), 31.67 ($\underline{C}CH_3(CH_2O\text{-})_3$), 40.51 (C-3), 66.22 (C-5), 72.80 (3 x CH_2O), 109.1 ($\underline{C}CH_3(OCH_2)_3$), 176.1 (C=O, lactam).

MS (70 eV), m/z (%): 227 (7) [M^+], 185 (4), 131 (7), 99 (6), 98 (100) [M^+ - oxetylate], 97 (5), 85 (4), 83 (2), 55 (36).

(2S,3R)-3-Methyl-glutamic acid (116)



Compound **114** (0.09 g, 0.40 mmol) was dissolved in 6N HCl (10 ml) and this solution was allowed to reflux for 6 h. The reaction mixture was concentrated in vacuo (up to appr. 5 ml), followed by careful treatment with satd. sodium bicarbonate solution to adjust pH 2. After addition of isopropanol (5 ml), this solution was kept at 8 °C to yield **116** as colourless crystals. Yield 0.03 g (52 %).

m.p. 170-173 °C.- $[\alpha]_D^{20}$ = +6.0 (c = 0.25, 1M NaOH).

Ref.: m.p. 165-167 °C [48].- $[\alpha]_D^{20}$ = +22.6 (c = 1.03, 6M HCl) [48].- m.p. 163 °C [131].- $[\alpha]_D^{20}$ = +14.4 (c = 1, H_2O) [131].- $[\alpha]_D^{20}$ = +6.0 (for monoammonium salt, c = 1.07, H_2O) [52].

$C_6H_{11}NO_4$ (161.16): calcd. C 44.72, H 6.88, N 8.69; found C 44.05, H 6.70, N 8.52.

IR (KBr): ν = 3040 cm^{-1} (NH), 2940, 2870 (C-H), 2620-2500 (COOH), 1690 (COO^-), 1490 (C-H), 1420 (COO^-).

^{1}H-NMR (D_2O/NaOD): δ = 0.82 (d, 3H, J_{CH3-3} = 7.0 Hz, CH_3), 1.81 (d, 1 H, J_{gem} = 12.1 Hz, J_{4a-3} = 5.0 Hz, H-4a), 1.89 (d, 1 H, J_{gem} = 12.1 Hz, J_{4b-3} = 9.6 Hz, H-4b), 2.15 (m, 1 H, H-3), 2.99 (d, 1 H, J_{2-3} = 3.4 Hz, H-2).

^{13}C-NMR (D_2O/NaOD): δ = 16.40 (CH_3), 35.85 (C-3), 40.90 (C-4), 61.10 (C-2), 182.8 (COO^-), 183.0 (COO^-).

MS (70 eV), m/z (%): 161 (0) [M^+], 144 (5) [M^+ - H_2O], 99 (7), 98 (100), 70 (3), 55 (72).

BERND KELM

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- **01/98 - 04/98**

University of Heidelberg, Germany: "SYNTHESIS OF NUCLEOPHILIC SUBSTITUTED 2,2-SPIROCYCLO-2,3-DIHYDRO-1H-IMIDAZO[4,5-B]PYRIDINE DERIVATIVES"

Other Professional Experiences

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