Dissertation zur Erlangung des Doktorgrades
Der Fakultät für Chemie und Pharmazie
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Development of New GABA Uptake Inhibitors Derived from Proline or from Pyrrolidin-2-yl Acetic Acid

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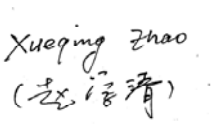
Erklärung

Diese Dissertation wurde im Sinne von § 13 Abs. 3 bzw. 4 der Promotionsordnung vom 29. Januar 1998 von Mr. Prof. Dr. K. Th. Wanner betreut.

Ehrenwörtliche Versicherung:

Diese Dissertation wurde selbständig, ohne unerlaubte Hilfe erarbeitet.

München, am April 30th. 2002



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(Xueqing Zhao □□□)

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1. Gutacher Prof. Dr. K. Th. Wanner

2. Gutacher Prof. Dr. Hans-Dietrich Stachel

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Fakultät fur Chemie und Pharmazie
der Ludwig-Maximilians Universität München.

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This is dedicated to all the ones who love me.

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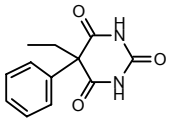
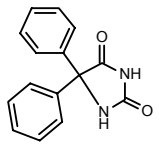
CONTENTS

1. Introduction: Antiepileptic Drugs

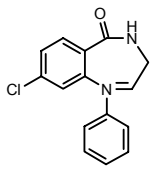
Epilepsy is a relatively common neurological disorder affecting 0.4-1.0% of world's population [1]. In 1912, the first antiepileptic drug (AED) phenobarbital (1) [2] was used in clinics, and then phenytoin (2) [3] was found in 1938 for overcoming the serious side effects of the barbitals-like. Since 1960s some AEDs such as diazepam (3) (1965) [4], carbamazepine (4) (1974) [5] and valproic acid (5) [5] (1978), etc. have been widely prescribed but patients still suffer from a range of side effects. A significant part of patients (20-30%) is still resistant to the currently available therapeutics [6].



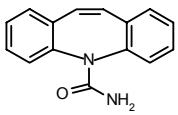
Phenobartibal (**1**)



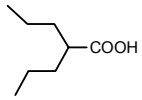
Phenytoin (**2**)



Diazepam (**3**)

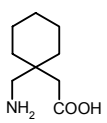


Carbamazepine (**4**)

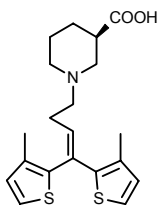


Valproic acid (**5**)

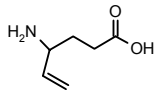
In the past decade several new drugs have been launched on market, e.g. gabapentin (**6**) [7], tiagabine (**7**) [8], vigabatrin (**8**) [9] and progabide (**9**) [10]. Many of the new AEDs exhibit improved efficacies and relatively less side effects, but are still ineffective to some patients with intractable epilepsy. The diverse pathological profiles result in this neural disorder to be hard tackled. [11] Thus, there is a urgent need to establish new screening models for epilepsy and develop novel drugs with less severe side effects.



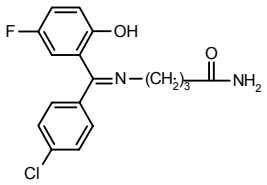
Gabapentin (**6**)



Tiagabine (**7**)

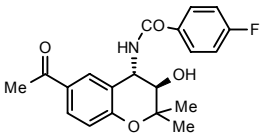


Vigabatrin (**8**)



Progabide (**9**)

AEDs comprise a huge number of structurally diverse compounds acting on a variety of different targets in the brain. In accordance with the present understanding of the different mechanisms, the ways by which AEDs exert their therapeutic effects, may be summarized as follows [12]: (a) by inhibiting the function of excitatory system (predominantly by the glutamate system); (b) by enhancing the inhibitory system function (predominantly by the GABA system); (c) by inhibiting excessive neuronal firing (modulation of membrane cation conductance of sodium, calcium or potassium channels). In addition, some drugs work through other or unknown mechanisms such as SB-204269 (**10**) [11].



SB-204269 (**10**)

(a): Glutamate system

Compounds which modulate glutamic acid receptors are frequently first evaluated for anticonvulsant activity. Glutamate receptors may be subdivided into two main classes: the iontropic channels (NMDA, kainic acid/AMPA receptors) and the metabotropic receptors (mGluRs) [13]. Their therapeutic potentials have been reviewed recently [14, 15, 16, 17]. Owing to their adverse effects, so far none of them has succeeded in clinics, but considerable research continues in this field.

(b): γ-Aminobutyric acid (GABA) system

γ-Aminobutyric acid (GABA) plays a significant role for the inhibitory function in the mammalian central nervous system (CNS), as approximate 40% of synapses in the CNS are GABA‘ergic. The dysfunctions of the central GABA system have been inferred to involve in the development and outbreak of several diseases such as anxiety, pain and epilepsy.

Decreased GABA'ergic activity results in the excessive excitement of CNS (namely neuronal firing) [18]. Each step of GABA'ergic transmission including metabolism, release, and transport as well as activation of specific receptors will affect seizures of epilepsy and may become a target for new drugs.

Several drugs, which influence the procedure of GABA transmission, have succeeded in clinics, e.g. valproic acid (**5**) (succinic semialdehyde dehydrogenase), *S*(+)-vigabatrin (**8**) (GABA transaminase inhibitor) [19], progabide (**9**) (a novel GABA agonist with a resemblance to benzodiazepine) [10]. But directly agonizing or increasing the delivery of the neurotransmittors always incurs the exhaustion of GABA in the synapse and exhibits unacceptable systematic side effects.

GABA uptake inhibitors

The discovery of highly selective inhibitors of GABA-transport-system (*Iversen et, al*, 1968) [20, 21] and the isolation of the transport proteins (*Kanner*, 1978) [22] provided new pathways for drug design. GABA-mediated inhibitory synaptic transmission is terminated by the rapid removal of GABA from synaptic cleft after its release [23]. Although diffusion can't be neglected, the majority of transmitter molecules are immediately recycled by a cellular uptake system of high affinity sodium and chloride-dependent transporter proteins [24, 25], which are located in the plasma membrane of glial cells and synaptic nervous terminals.

Despite of the limited understanding to termination of the synaptic and glial GABA, it is impossible to figure out their mechanism related to its pharmacological intervention. It has been known, however, that neuronal and glial GABA uptakes have dissimilar substrate specificities, which are also distinctly different from those of postsynaptic GABA receptors. [26, 27] Therefore, this makes it possible to develop selective inhibitors for GABA uptake for enhancing the inhibitory effects of synaptic released GABA so as to avoid adverse systematic side effects. As a result, GABA uptake inhibitors would be very promising in therapeutic use and so far much interest has been focused on the development to GABA uptake inhibitor.
Conformationally restrained GABA analogs such as (*R*)-nicopetic acid (**11**), guvacine (**12**), and (*RS*)-c*is*-4-hydroxynicopetic acid (**13**) are known to be potent GABA uptake inhibitors with no affinity for GABA receptors (*Johnston et al,* 1975) [28]. But these amino acids do not readily enter the CNS following peripheral administration due to their hydrophilic nature.

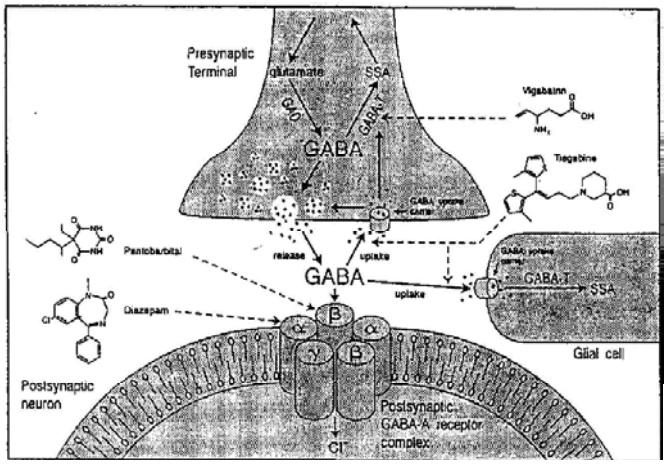
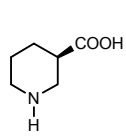
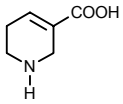


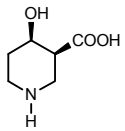
Fig. 1.1. Structures and sites of actions at a GABA'ergic synapse [29]
(SSA: Succinate semialdehyde; GAD: Glutamic acid decarboxylatase)



(*R*)-Nicopetic acid (**11**)
IC_{50}: 9 ± 1 μM



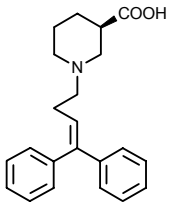
Guvacine (**12**)
8 ± 1 μM



(*RS*)-*cis*-4-hydroxynicopetic acid (**13**)
8 ± 1 μM

Some novel compounds such as (*R*)-SK&F 89976-A (**14**) and SK&F 100330-A (**15**) and (*RS*)-*cis*-SK&F 100591-A (**16**), which can cross the blood brain barrier following peripheral administration due to the introduction of appropriate bulky lipophilic groups to nitrogen atoms, showed approximately 20-fold more potent inhibition for GABA uptake than their precursors (*Ali et al*, 1985) [30]. These reports on the inhibition resulted in intensive investigation in this field.

Since the discovery of the first potent uptake inhibitor, many similar potent derivatives have been synthesized and intensively investigated for their pharmacology, such as CI-966 (**17**) (*M. R. Pavia*, 1992) [31] and Tiagabine (**7**) (*K. E. Andersen*, 1993) [18].

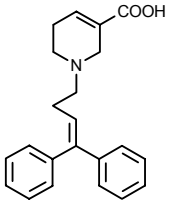


(*R*)-SK&F 89976-A (**14**)

IC_{50}: 0.11 μM

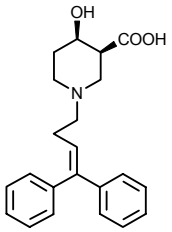
(*S*)-SK&F 89976-A

IC_{50}: 1.91 μM



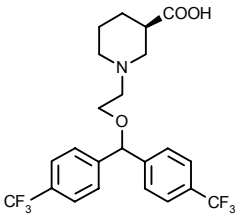
SK&F 100330-A (**15**)

0.30 μM



(*RS*)-*cis*-SK&F 100591 (**16**)

IC_{50}: 0.26 μM



(*R*)-CI-996 (**17**)

C 0.34 μM

Heterogenity of GABA transporter:

Three different GABA transporters have been cloned from animals of different species. They were termed GAT-1 [32], GAT-2 and GAT-3 [33] (nomenclature for transporters obtained from rat brain). BGT-1, which transports both the osmolyte betaine and GABA, was first cloned from dog kidney [34]. All these different transporters provide precise targets for study of the pharmacological profiles of GABA transmission and new drugs design.

GAT-1

After GAT-1 had been cloned [35], it has turned out that potent inhibitors developed so far (e.g. **14**-**17**) are selective combined for GAT-1. According to the data of many highly selective inhibitors for GAT-1, their common structural features may be depicted as follows:

1. The nitrogen atom should be situated in the mean plane of the pharmacophore.

2. The acidic group should be located at a distance of 4.2 Å from the center of the amine function.

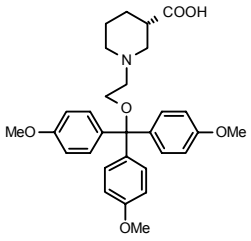
3. The two aromatic rings are beneficial to strong affinity.

GAT-2

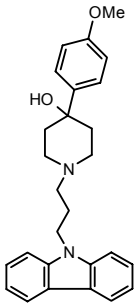
Up to now, a little is known about the characteristics and the pharmacological role of GAT-2, due in part to the lack of selective probes.

GAT-3

The first relatively selective GAT-3 inhibitor (*S*)-SNAP-5114 (**18**) was reported by *Dhar et al.* [35] in 1994. It displays an IC_{50} of 5 μM at GAT-3, 21 μM at GAT-2, > 200 μM at GAT-1 and 140 μM at BGT-1 (GAT-B); its (3*R*) enantiomer shows an IC_{50} of only 86 μM at GAT-3. Later a selective GAT-3 inhibitor NNC-05-2045 (**19**) was found, which proved to be a blocking agent for audiogenic seizure in genetically epilepsy-prone (GEP) rats and to be anticonvulsant in the maximal electroshock seizure (MES) test in amygdala kindled rats [12]. Compounds **18** and **19** should be useful tools for investigating the role of GAT-3 in the CNS. *Dhar et al.* suggested that the following structural features for the GAT-3 inhibitors of type **18** appear to affect inhibition and selectivity: (a) a chain of two-carbon length between.



(*S*)-SNAP-5114 (**18**)



NNC-05-2045 (**19**)

nitrogen and oxygen atom; (b) an oxygen atom linking the carbon chain to a tertiary carbon atom with three phenyl groups, and (c) lipophilic groups at the para position of three phenyl groups, with *p*-methoxy groups being preferred with respect to the nitrogen residue at the amino acid skeleton.

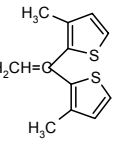
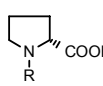
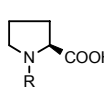
2. DESIGN OF GABA UPTAKE INHIBITORS:

2-Carboxylic acid and 2-acetic acid derivatives of 4-hydroxy-pyrrolidines and 4-hydroxy-4-(4-methoxy-phenyl)pyrrolidines

As described above, neuronal and glial GABA uptake proteins are different from postsynaptic GABA receptors with respect to their substrate specificities. Therefore, it is possible to develop compounds that are selective for GABA brains part without affecting GABA receptors. Since the first potent GAT-1 inhibitor was reported in the early 1980s [30], several compounds have been investigated in clinic trials and one (Tiagabine) has been put on market, but inhibitors with a higher potency and selectivity are still desirable. Furthermore, the pharmacological profiles of GAT-2 and GAT-3 remain less known, and no highly selective and potent inhibitor of the transporters has been discovered until now.

In our group, my former colleague Dr. Fülep had successfully prepared a series of pyrrolidine derivatives with three different N-substituents what are typically used for GABA uptake inhibitors. Some of these compounds are potent inhibitors as may be seen from Table 2.1 [36], e.g. (*S*)-**98** exhibits a relatively potent inhibition at GAT-1 (IC_{50} of 0.40 μM) as compared

Table 2.1 The binding test results of pyrrolidine derivatives prepared by Dr. Fülep.

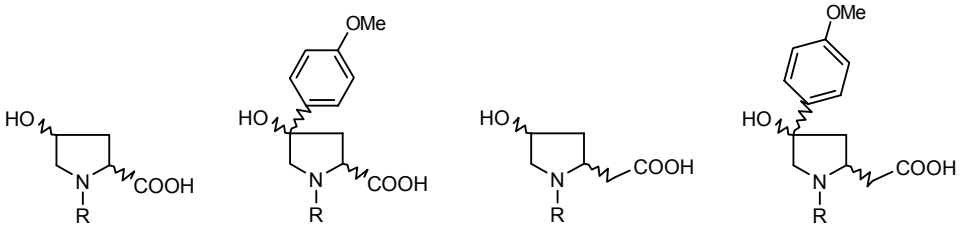
	H		$-CH_2CH_2C{=}CPh_2$				$-CH_2CH_2OC(C_6H_4OMe)_3$	
	GAT-1 IC_{50}μM	GAT-3 IC_{50}μM	GAT-1 IC_{50}μM	GAT-3 IC_{50}μM	GAT-1 IC_{50}μM	GAT-3 IC_{50}μM	GAT-1 IC_{50}μM	GAT-3 IC_{50}μM
	214±16	602±59	3.05±0.47	189±22	0.89±0.07	180±23.0	67.8±19.0	3.10±0.45 (*R*)-**100**
	482±39	74.2±6.2	0.40±0.03 (*S*)-**98**	64.8±12.1	0.34±0.0	26.6±4.4	35.4±1.8	28.7±9.4
	> 10 mM	6390±176	2.97±0.08	231±24	------	------	143±39	18.5±4.0
	875±57	1912±287	2.56±029	309±29	------	------	23±18	57.7±6.5

with (*R*)-SK&F 89976-A (0.11 μM). Furthermore, a relatively high and selective inhibition of (*R*)-**100** at GAT-3 (IC_{50} 3.10 μM) was found to be equivalent to (*S*)-SNAP-5114.

It may be seen from the comparison of (*R*)-SK&F 89976-A (**14**) with (*RS*)-*cis*-SK&F 100591 (**16**), the latter is still a potent inhibitor despite of the introduction of hydroxy group in the C-4 position. Accordingly, the hydroxy group in this position seems to be acceptable for the GAT-1 transporters.

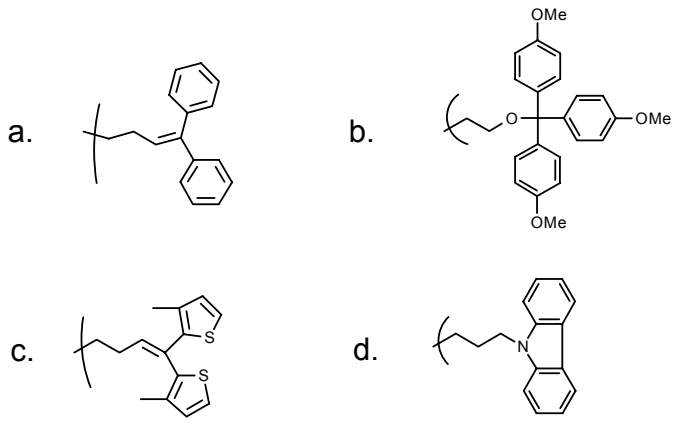
Following Dr. Fülep's work and referring to (*RS*)-*cis*-SK&F100591 (**16**) as well as NNC-05-2045 (**19**), my idea was to introduce hydroxy group or hydroxy and *p*-methoxyphenyl group to the C-4 position of the pyrrolidines with 2-carboxylic acid or 2-acetic acid in order to look into the impact of these different steric groups on the inhibition at GAT-1 and GAT-3 transporters. Thereby well-known N-substituents **a**, **b**, **c**, and **d**, which are typical for GAT-1 and GAT-3 inhibitors, should be applied for their study.

Thus, according to the present study it was my intention to prepare the following compounds (the general formula **20-23**) and to evaluate their biological activity.



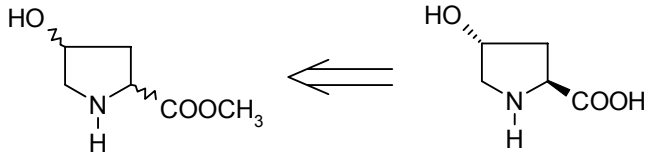
20 **21** **22** **23**

R = H and **24a-d**.

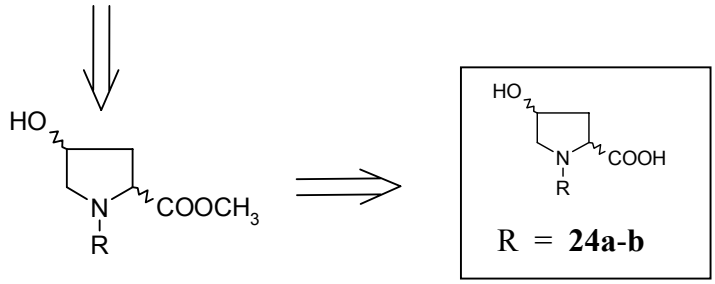


4. DISCUSSION OF SYTHETIC METHODS

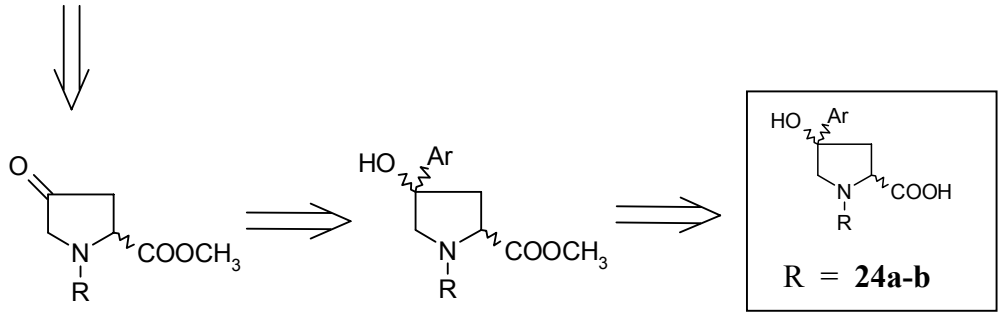
For my synthetic plan, commercially available L-*trans*-4-hydroxypyroline [(2*S*,4*R*)-**25**] appeared to be useful as a precursor. It bears two optically active centers and is an ideal chiral building block. It can be converted into its (2*R*)-isomer or (4*S*)-isomer and furthermore the carboxylic acid function can be extended to an acetic acid through several different routes.
The main synthetic routes, which I wanted to explore, are shown below. One arrow doesn't necessarily mean a single step and also the transformation of configurations is not noted here.
Scheme 1



26 **25**

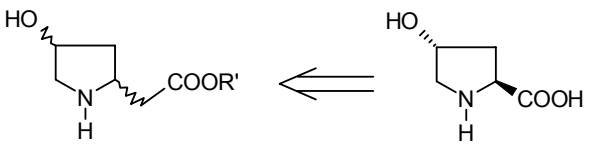


27 **28**

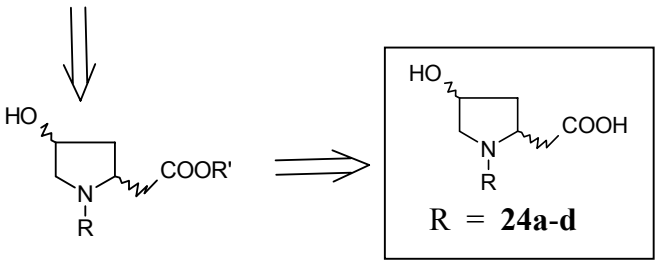


29 **30** **31**

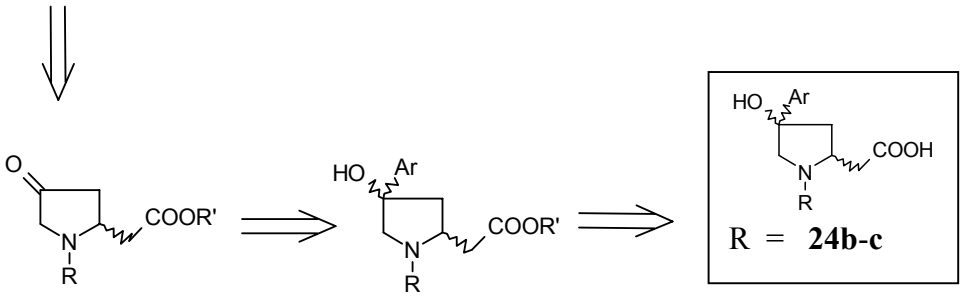
Scheme 2



32 **25**



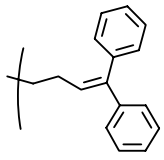
33 **34**



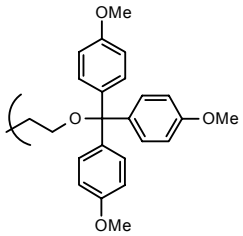
35 **36** **37**

Ar = 4-Methoxyphenyl **R** = **24**a-d

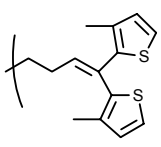
a.



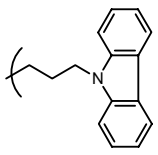
b.



c.



d.



Access to compounds of general formula 28:

From (2*S*,4*R*)-**25** exhibiting two stereocenters, each with a definite stereochemistry compounds **28** would be accessible via the configuration inversion of the respective stereocenter followed by esterification, alkylation and final hydrolysis.

Access to compounds of general formula **31**:

Upon oxidation of the hydroxy group of **27**, ketone **29** should be obtained. Subsequent addition of organometallic reagents to the ketone might yield a mixture of diastereomers **30**. Separation and final hydrolysis would lead to the single isomers of **31**.

Access to compounds of general formula **34**:

An Arndt-Eistert reaction should allow to prolong the carboxylic chain in (2*S*,4*R*)-**25**. The accession will require the protection and deprotection of the amino and hydroxy group. Acid-selective inversion of the configuration of stereocenters would give access to all stereomers.

Access to compounds of general formula **37**:

A procedure similar to the one for the preparation of **31** should lead to **37** starting from **32**.

Synthetic routes to N-unsubstituted derivatives of **28**, **31**, **34**, and **37** are not mentioned here. These will be discussed in the sections, which just follow those respectively about N-substituted derivatives.

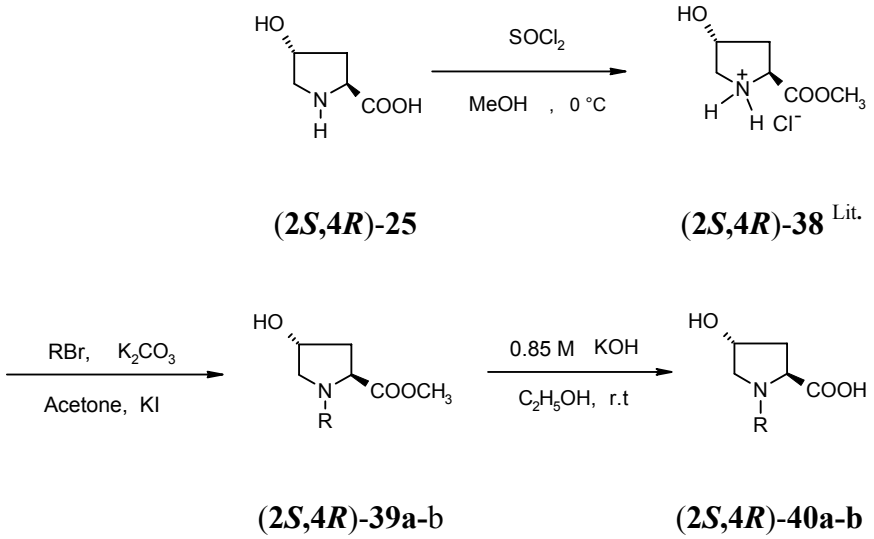
3.1 Preparation of N-substituted 4-hydroxypyrrolidine-2-carboxylic acids

3.1.1 Derivatives of N-substituted (2*S*)-4-hydroxypyrrolidine-2-carboxylic acids

Keeping the stereochemistry of the starting material unchanged, compound (2*S*,4*R*)-**25** was directly utilized to prepare (2*S*,4*R*)-**40a-b** via esterification of the 2-carboxylic acid, N-alkylation and final hydrolysis.

Thus upon the treatment of (2*S*,4*R*)-**25** in methanol with thionyl chloride, (2*S*,4*R*)-**38** was obtained in 96% yield [37, 38, 39]. The ester (2*S*,4*R*)-**38** was N-substituted with the bromides of **24a-b** in acetone at room temperature to give (2*S*,4*R*)-**39a-b** in moderate yields [30]. Final hydrolysis of the ester function with aqueous 0.85 M KOH at room temperature in ethanol afforded (2*S*,4*R*)-**40a-b** in good yields (Table 3.1).

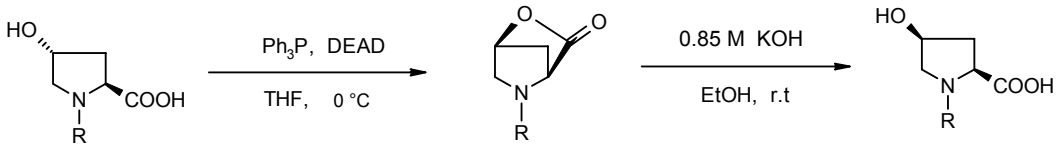
Scheme 3



R = **24a-b**. a. $-CH_2CH_2CH=CPh_2$ b. $-CH_2CH_2OC(p\text{-}MeOC_6H_4)_3$

The inversion of the stereochemistry in the 4-position of 4-hydroxypyrrolidine derivatives has been successfully achieved through classic methods: (1) Jones oxidation of the hydroxy group followed by reduction with $NaBH_4$ [40]; (2) intramolecular esterification of the hydroxy group affected by a proceeding tosylation and subsequent hydrolysis of the resulting lactone [41]. Also the Mitsunobu reaction has been widely applied for esterification process with complete inversion of the stereochemistry of alcohol function [42], the free alcohol is simply obtained by the hydrolysis of the resulting esters.

Scheme 4

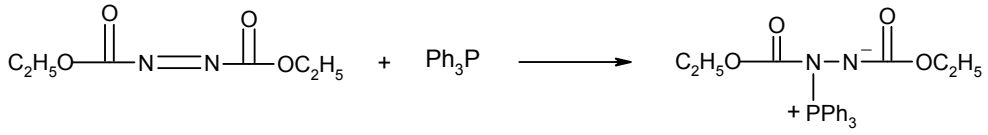


(2*S*,4*R*)-40a-b **(1*S*,4*S*)-41a** **(2*S*,4*S*)-40a-b**

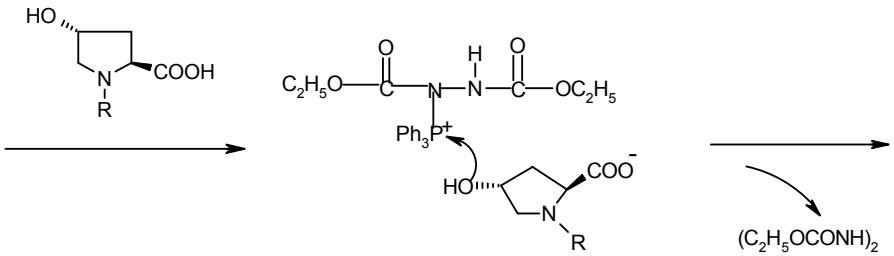
For the Mitsunobu reaction in my performance, (2*S*,4*R*)-**40a** was transformed to the lactone (1*S*,4*S*)-**41a** in 85% yield with the desired configuration [43, 44, 45]. Upon the hydrolysis of this lactone the stereoisomer (2*S*,4*S*)-**40a** was obtained (Table 3.1). But when the crude product from the Mitsunubo reaction of (2*S*,4*R*)-**40b** was purified by flash chromatography (packing: Al_2O_3 pH 7.5±0.5), (1*S*,4*S*)-**42b** was directly given in a overall 76% yield.

The Mitsunobu reaction [42] is believed to proceed through the following steps: (1) In the first step the addition of triphenylphosphine **43** to diethyl azodicarboxylate **42** gave the quaternary phosphonium salt **44**; (2) **44** is protonized by RCOOH; (3) Finally an alkoxyphosphonium salt **46** is formed; (4) **46** undergoes a S_N2 type displacement to give **41**.

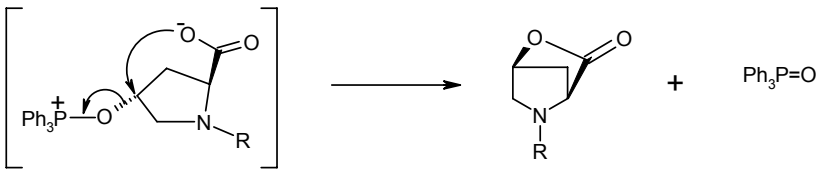
Scheme 5



42 **43** **44**



45



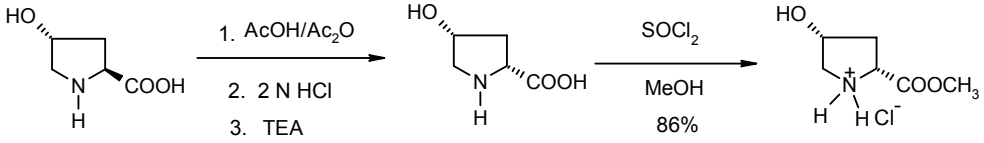
46 **41** **47**

3.1.2 Derivatives of N-substituted (2*R*)-4-hydroxypyrrolidine-2-carboxylic acids

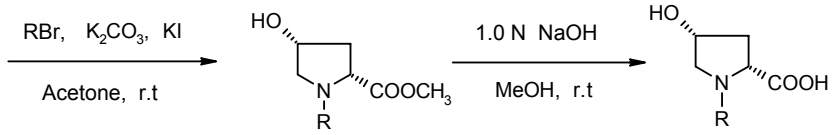
The inversion of the chiral center at the C-2 of (2*S*,4*R*)-**25** was affected by refluxing the starting material in a mixture of acetic anhydride and acetic acid, subsequent hydrolysis with aqueous 2 N hydrochloric acid. The recrystallization gave (2*R*,4*R*)-**25** in 58% yield [46]. The recrystallization procedure was considerably simplified by applying triethylamine to neutralize the epimeric hydoxyproline salt instead of silver carbonate [47].

In analogy to the preparation of (2*S*,4*R*)-**40a-b**, the target compounds (2*R*,4*R*)-**40a-b** (Table 3.1) were synthesized from (2*R*,4*R*)-**25** by the esterification of the 2-carboxylic acid, N-alkylation and final hydrolysis of the ester function.

Scheme 6



(2*S*,4*R*)-25 **(2*R*,4*R*)-25** Lit. **(2*R*,4*R*)-38** Lit.

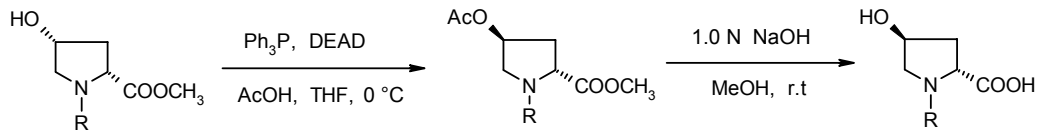


(2*R*,4*R*)-39a-b **(2*R*,4*R*)-40a-b**

R = **24a-b**. a. $-CH_2CH_2CH{=}CPh_2$ b. $-CH_2CH_2OC(p\text{-}MeOC_6H_4)_3$

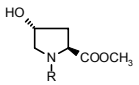
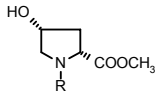
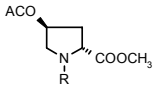
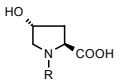
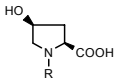
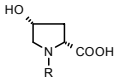
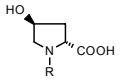
The preparation of the stereoisomers (2*R*,4*S*)-**40a-b** were accomplished by performing an intermolecular Mitsunobu reaction of (2*R*,4*R*)-**39a-b** followed by the hydrolysis of resulting ester (2*R*,4*S*)-**48a-b**. The cleavage in the side chain **b** by the reactant acetic acid was observed and the separation on prep. HPLC was needed for removing side $(EtOCONH)_2$ (see Scheme 5). The diastereomeric purity of the product (2*R*,4*S*)-**39a-b** was higher than that were reported in the literature [41] for the material that had been obtained by the tosylation of hydroxy group followed by hydrolysis under basic conditions. Hydrolysis of (2*R*,4*S*)-**48a-b** with aqueous 1.0 N NaOH in methanol at room temperature finally gave (2*R*,4*S*)-**40a-b** in medial yields (Table 3.1).

Scheme 7



(**2*R*,4*R*)-39a-b** (**2*R*,4*S*)-48a-b** (**2*R*,4*S*)-40a-b**

Table 3.1 The yields of new compounds **39a-b**, **40a-b**, **41a** and **48a-b**.

Structure	R: **a**	R: **b**
	-$CH_2CH_2CH{=}CPh_2$	-$CH_2CH_2OC(p\text{-}MeOC_6H_4)_3$
	52% (2*S*,4*R*)-**39a**	53% (2*S*,4*R*)-**39b**
	41% (2*R*,4*R*)-**39a**	33% (2*R*,4*R*)-**39b**
	85% (1*S*,4*S*)-**41a**	----------
	69% (2*R*,4*S*)-**48a**	56% (2*R*,4*S*)-**48b**
	92% (2*S*,4*R*)-**40a**	85% (2*S*,4*R*)-**40b**
	95% (2*S*,4*S*)-**40a**	76% (two steps) (2*S*,4*S*)-**40b**
	92% (2*R*,4*R*)-**40a**	67% (2*R*,4*R*)-**40b**
	92% (2*R*,4*S*)-**40a**	94% (2*R*,4*S*)-**40b**

For all pairs of enantiomers displayed in the Table 3.1, of course, identical data {^{1}H NMR, IR, MS} were obtained except for the changes of their optical rotations. Furthermore, all compounds that ever have the same pyrrolidine system and vary only in the side chain showed high similarities in their ^{1}H NMR spectra (see Table 3.2). The protons of (2*S*,4*R*)-**40a** could be unequivocally assigned by H,H-cosy spectra.

From a comparison of the ^{1}H NMR spectrum of (2*S*,4*S*)-**40a** (Fig.3.1) with that of its precursor (2*S*,4*R*)-**40a** (Fig. 3.2), it is evident that the Mitsunobu reaction has indeed led to the desired transformation, namely the inversion at C-4 of the pyrrolidine nucleus. The ^{1}H NMR

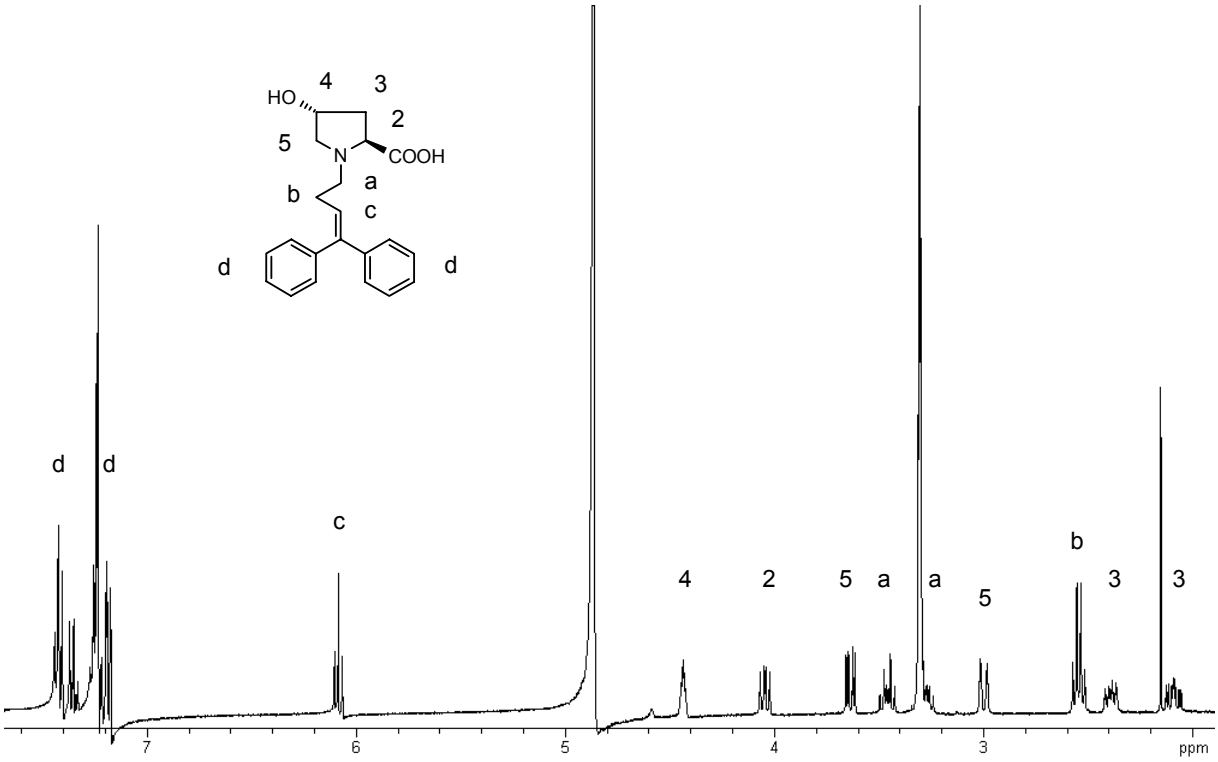


Fig. 3.1. The ^{1}H NMR spectrum of (2*S*,4*R*)-**40a** (CD_3OD, δ 2.0-7.6).

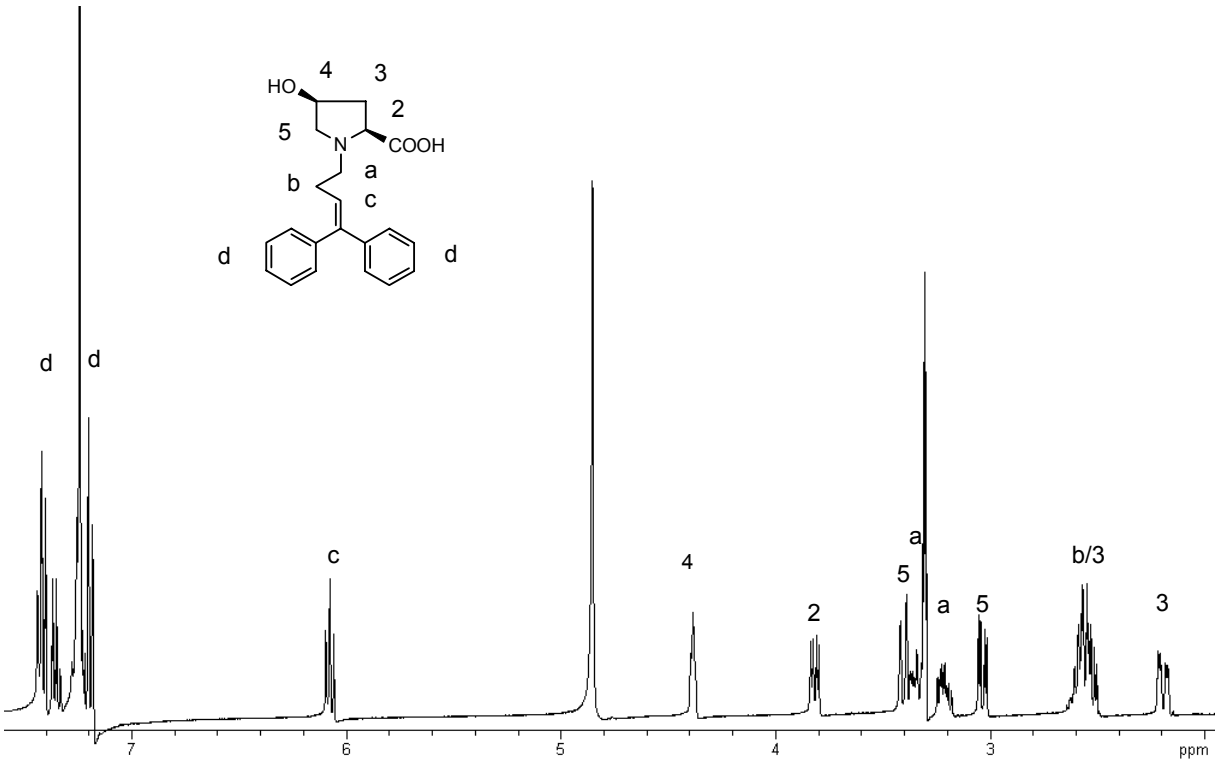


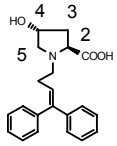
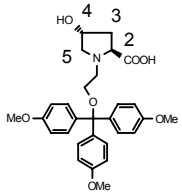
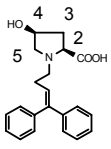
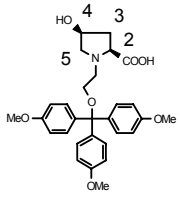
Fig. 3.2. The ^{1}H NMR spectrum of (2*S*,4*S*)-**40a** (CD_3OD, δ 2.0-7.6).

data of (2*S*,4*S*)-**40a-b** and (2*S*,4*R*)-**40a-b** are given in the Table 3.2. From these it can be easily seen that dependently on the stereochemistry, the NMR data on the pyrrolidine ring system are very similar for identical stereochemistry [(2*S*,4*R*)-**40a** and (2*S*,4*R*)-**40b**] or quite different for different stereochemistry [(2*S*,4*R*)-**40a** and (2*S*,4*S*)-**40a**].

(2*S*,4*R*)-**40a** and (2*S*,4*R*)-**40b**: The chemical shift values of the corresponding protons are very close, besides the peaks of the corresponding protons show the same shape and their coupling constants are very close, e.g H-2, H-3, H-5.

(2*S*,4*R*)-**40a** and (2*S*,4*S*)-**40a**: Significant changes of the chemical shifts have happened between the corresponding protons, e.g. H-2 (4.05), H-3 (2.39) and H-5 (3.64) for (2*S*,4*R*)-**40a**; H-2 (3.79), H-3 (2.48-2.63), H-5 (3.32-3.41) for (2*S*,4*S*)-**40a**.

Table 3.2 Chemical shift and multiplicity of their pyrrolidine ring protons of (2*S*,4*R*)-**40a-b** and (2*S*,4*S*)-**40a-b**.

^{1}HNMR (CD_3OD)	(2*S*,4*R*)-**40a**  $[\alpha]_D^{22} = -49.2$			(2*S*,4*R*)-**40b**  $[\alpha]_D^{28} = -24.8$		
Proton	δ	Peak	*J* Hz	δ	peak	*J* Hz
H-2	4.05	dd	10.6/7.6	4.19	dd	10.1/7.8
H-3	2.09	ddd	13.7/10.6/4.4	2.15	ddd	13.8/10.1/4.7
H-3	2.39	ddt	13.7/7.6/2.0	2.41	ddt	13.8/7.8/1.9
H-4	4.43-4.45	m		4.43-4.46	m	
H-5	3.00	dt	12.3/1.7	3.08	br. d	12.4
H-5	3.64	dd	12.3/4.4	3.40-3.61	m	
^{1}HNMR (CD_3OD)	(2*S*,4*S*)-**40a**  $[\alpha]_D^{20} = -42.8$			(2*S*,4*S*)-**40b**  $[\alpha]_D^{24} = -11.9$		
Proton	δ	Peak	*J* Hz	δ	Peak	*J* Hz
H-2	3.79	dd	10.7/4.4	3.98	dd	11.0/4.0
H-3	2.15-2.21	m		2.23-2.29	m	
H-3	2.48-2.63	m		2.54	ddd	13.9/11.0/4.4
H-4	4.36-4.39	m		4.38-4.41	m	
H-5	3.03	dd	11.6/3.8	3.06	dd	11.6/3.6
H-5	3.32-3.41	m		3.23-3.37	m	

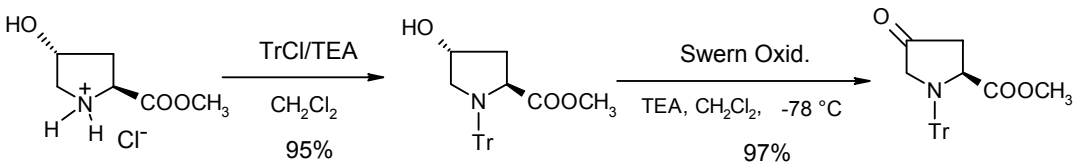
3.2 Preparation of 4-hydroxy-4-(4-methoxyphenyl)pyrrolidine-2-carboxylic acids and their N-substituted derivatives

3.2.1 Attempts towards the synthesis of methyl N-unsubstituted 4-hydroxy-4-(4-methoxyphenyl)-pyrrolidine-2-carboxylates

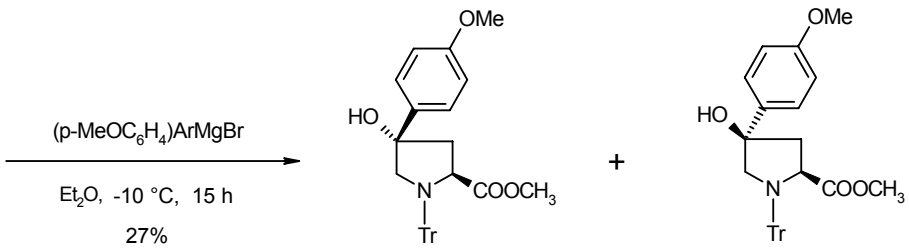
In order to get the pyrrolidine derivatives from (2*S*,4*R*)-**38** or (2*R*,4*R*)-**38**, the following steps seemed to be necessary: Protection of the amino function, oxidation of the 4-hydroxy group, addition of an organometallic reagent to the ketone and final N-deprotection. To the end the following efforts were made.

Triphenylmethyl group (trityl, Tr) was chosen for N-protection since it is labile to mild acid and hydrogenation, and provides an excellent stability for the α-carboxylic acid ester with respect to racemization [48, 49]. Selective N-tritylation of (2*S*,4*R*)-**38** was achieved with trityl chloride in 95% yield [50]. Swern oxidation of (2*S*,4*R*)-**49** led to (2*S*)-**50** in 97% yield. However, all attempts to add 4-methoxyphenylmagnesium bromide to **50** at low temperature (-78 °C ~ -30 °C) in ether or in THF as solvent, and in the presence of $CeCl_3$ did not meet any expectation. A mixture of diastereomers (2*S*,4*R*)-**51** and (2*S*,4*S*)-**51** was obtained [(2*S*,4*R*)-**51** and (2*S*,4*S*)-**51**: 9% and 18%] when the reaction temperature was raised to –10 °C, though the yield remained low and 56% of the starting ketone was recovered. Unfortunately the reaction was accompanied by simultaneous addition of the Grignard reagent to the ester group in THF with $CeCl_3$. The reason for this is unclear, but it has been reported that when trityl group is replaced with a 9-(9-phenylfluorenyl) group, a single diastereomer is achieved as addition product in a remarkable yield of 60%. This was thought to be due to a reduction of the steric hindrance, when going from a trityl to a 9-(9-phenylfluorenyl) group [51].

Scheme 8



(**2*S*,4*R*)-38** (**2*S*,4*R*)-49** Lit. (**2*S*)-50**



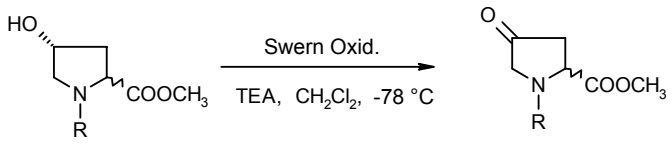
(2*S*,4*S*)-51 **(2*S*,4*R*)-51**

3.2.2 Preparation of 4-hydroxy-4-(4-methoxyphenyl)pyrrolidine-2-carboxylic acids and their N-substituted derivatives

As already indicated in the Scheme 1 (see page 9), it was my intention to introduce a 4-(4-methoxyphenyl) group into the C-4 position of 4-hydroxypyrrolidine derivatives via the corresponding. These should be accomplished by oxidation of the alcohol and addition of an organometallic reagent

When (2*S*,4*R*)-**39a-b** and (2*R*,4*R*)-**39a-b** underwent Swern oxidation at –78 °C [52], (2*S*)-**52a-b** and (2*R*)-**52a-b** were obtained in 83%-89% yield (Table 3.3). A cleavage of the C-O bond of (2*S*)-**52b** and (2*R*)-**52b** was not observed though this bond is highly sensitive to acid.

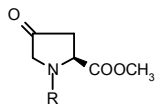
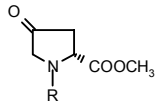
Scheme 9



(**2*S*,4*R***)-**39a-b** ▬ (**2*S***)-**52a-b** ▬

(**2*R*,4*R***)-**39a-b** ┈┈ (**2*R***)-**52a-b** ┈┈

Table 3.3 The yields of (2*S*)-**52a-b** and (2*R*)-**52a-b** by Swern oxidation

Structure	R: a	R: b
	-$CH_2CH_2CH{=}CPh_2$	-$CH_2CH_2OC(p\text{-}MeOC_6H_4)_3$
	87% (2*S*)-**52a**	83% (2*S*)-**52b**
	85% (2*R*)-**52a**	89% (2*R*)-**52b**

It is known for Grignard reagent that additives such as $MgBr_2$ [53], $LiClO_4$ [54], CuX and $CeCl_3$ [55, 56, 57] lead to a significant change in the reactivity of the organometallic compounds. For example, organocerium (III) reagent, generated from the reaction of organolithium or Grignard reagent with $CeCl_3$ is more efficient with respect to addition reaction to carbonyl groups, especially to sterically encumbered groups. It was recognized that side abnormal reactions such as enolization, reduction, condensation, conjugate addition and pinacol coupling were suppressed with organocerium (III) reagent. It was found, that especially for N-

protected 4-oxopyrrolidine derivatives the Grignard reagent in the presence of $CeCl_3$ could boost the stereoselectivity [58, 59]. In the absence of $CeCl_3$ as an additive, Grignard additions to the C-4 of N-benzyloxylcarbonyl-4-oxopyrrolidine derivatives gave only poor yields according to *J. E. Bvaldwin* and *M. Rudolph* [60], as enolization became the dominant process.

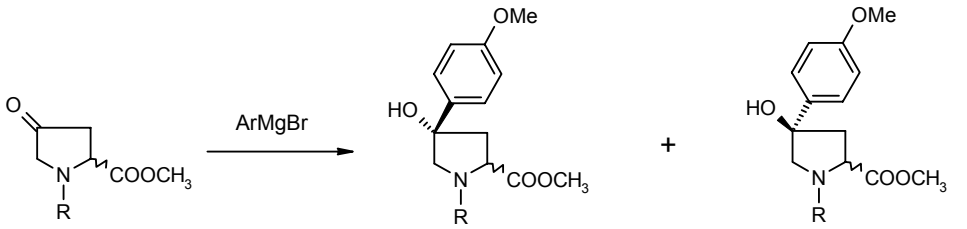
Therefore in my work these organometallic addition reactions were carried out in two different ways either with (4-$MeOC_6H_4$)MgBr at –78 °C in ether (A) or with (4-$MeOC_6H_4$)MgBr/$CeCl_3$ at – 60 °C~ -78 °C in THF (B), leading to two distinct results (Table 3.4):

Under the condition (A) the *cis* addition product (*cis* referred to the ester group) was obtained as the major diastereomer and a good diastereoselectivity was achieved [(2*S*,4*S*)-**53** / (2*S*,4*R*)-**53** or (2*R*,4*R*)-**53** / (2*R*,4*S*)-**53** range from 92:8 to 85:15 depending on the side chains].

Under the condition (B) the *trans* addition product (*trans* referred to the ester group) was formed as the major diastereomer and the ratio for the diastereoselectivity was rather low [(2*S*,4*S*)-**53** / (2*S*,4*R*)-**53** or (2*R*,4*R*)-**53** / (2*R*,4*S*)-**53** from 48:52 to 30:70 for the different side chains].

The configuration determination of the newly generated stereocenter will be discussed in section 3.5.1.

Scheme 10



(2*S*)-52a-b — **(2*S*,4*S*)-53a-b** — **(2*S*,4*R*)-53a-b** —

(2*R*)-52a-b ····· **(2*R*,4*S*)-53a-b** ····· **(2*R*,4*R*)-53a-b** ·····

R = a: $-CH_2CH_2CH{=}CPh_2$ b: $-CH_2CH_2OC(p\text{-}MeOC_6H_4)_3$

For my reactions no remarkable improvement on the diastereoselectivity or yields was achieved, when $CeCl_3$ as an additive and THF as a solvent were used. However, in contrast to the Grignard reagent that added *cis* to the ester function, here $CeCl_3$ desired reagent gave rise to a *trans* addition (Table 3.4)

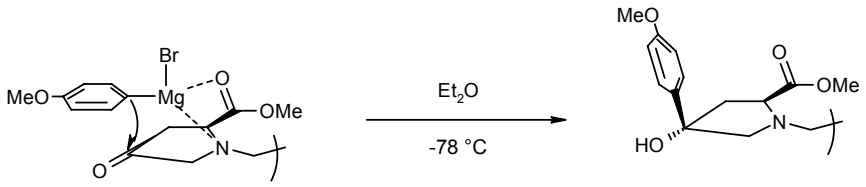
Table 3.4 Addition reactions of organometallic reagents to (2*S*)-**52a-b** and (2*R*)-**52a-b**.

	Starting material	solvent	$CeCl_3$ equiv.	Temp. °C	ArMgBr equiv.	Ratio of *d.s*	Yield (isolated)	
						(2*S*,4*S*)-**53** /(2*S*,4*R*)-**53**	(2*S*,4*S*)-**53**	(2*S*,4*R*)-**53**
1	(2*S*)-**52a**	THF	1.40	-60	1.40	39 : 61	15%	30%
2	(2*S*)-**52a**	THF	2.10	-60	2.10	41 : 59	25%	31%
3	(2*S*)-**52a**	THF	1.40	-78	1.40	30 : 70	12%	28%
4	(2*S*)-**52a**	THF	0.47	-78	1.40	39 : 61	10%	19%
5	(2*S*)-**52a**	Et_2O	-----	-78	1.80	89 : 11	56%	6%
6	(2*S*)-**52b**	THF	1.40	-60	1.40	48 : 52	24%	26%
7	(2*S*)-**52b**	Et_2O	-----	-78	1.80	85 : 15	40%	5%
						(2*R*,4*R*)-**53** /(2*R*,4*S*)-**53**	(2*R*,4*R*)-**53**	(2*R*,4*S*)-**53**
8	(2*R*)-**52a**	THF	1.40	-60	1.40	42 : 58	20%	28%
9	(2*R*)-**52b**	THF	1.40	-60	1.40	45 : 55	19%	21%

1. Reaction time: 20 h.

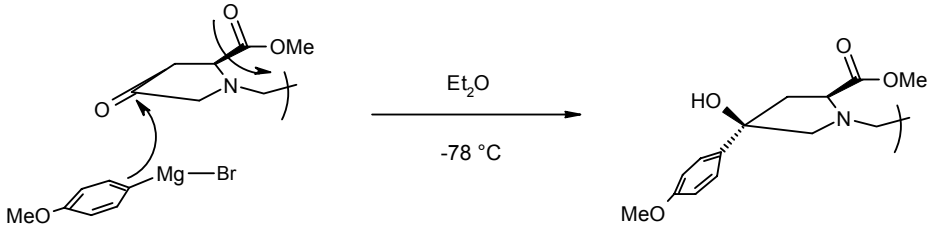
According to the description by *T. Imamoto, et al*. [57], the high efficiency of Grignard reagents that were modified with $CeCl_3$ in such addition reactions is due to the high oxophilicity of Ce^{3+}, which is supposed to be most important driving force for the promotion of carbonyl addition reaction. However this cannot explain the results I obtained with $CeCl_3$ as an additive. In my cases $CeCl_3$ as an additive resulted in a reversal of the stereoselectivity.
In contrast to the reactions described in literature [58, 59, 60] My starting materials **52a-b** always contain an amino group, the Grignard reagent may form a chelate as delineated in Scheme 11, which would result in the *cis* addition product (2*S*,4*S*)-**53a-b**. Alternatively, the Grignard reagent may add to the ketofunction by forming a complex as depicted in Scheme 12. In this complex (Scheme 12) the ester function at the chiral center of C-2 should direct the organometallic reagent to the opposite face. For structural reason, however, this complex might give rise only to low asymmetric induction and consequently low diastereoselectivity.

Scheme 11



(2S)-52a-b **(2*S*,4*S*)-53a-b**

Scheme 12

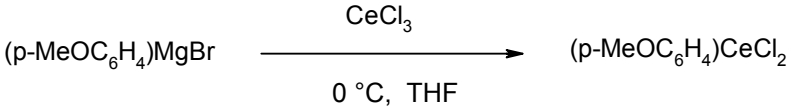


(2*S*)-52a-b **(2*S*,4*R*)-53a-b**

Compared with the transition state in Scheme 12, the one shown in Scheme 11 should prevail due to stronger binding with a lone pair of electrons of the amino group, and this would lead to (2*S*,4*S*)-**53a-b** as a major diastereomer,

As $CeCl_3$ and (4-$MeOC_6H_4$)MgBr were stirred at 0 °C in THF for one hour, it may be assumed that the following reagent **55** was formed: [55]

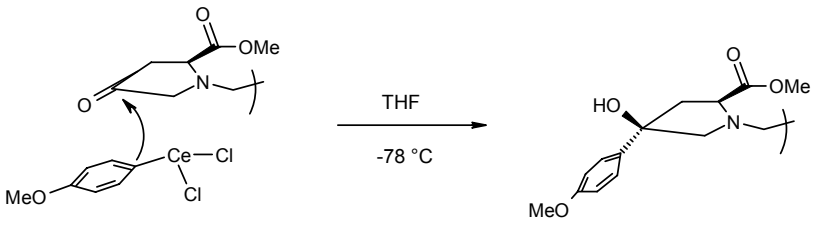
Scheme 13



54 55

The compound **55** is probably less suited to form a chelate similar to that shown for the Grignard reagent in Scheme 11. Therefore, the reagent should preferentially react via the convenient complex shown in Scheme 14, where the addition to the less barrier face should predominate to give (2*S*,4*R*)-**53a-b** from (2*S*)-**52a-b**. When the reaction temperature was lowered from – 60 °C to – 78 °C, the setereoselectivity slightly rose and the ratio of (2*S*,4*R*)-**53a** : (2*S*,4*S*)-**53a** increased from 61:39 to 70:30.

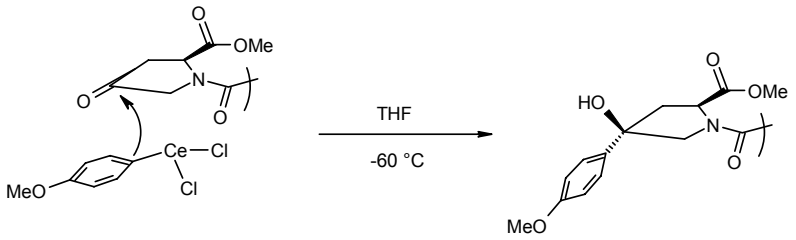
Scheme 14



(2*S*)-52a **(2*S*,4*R*)-53a**

When the amino group of the pyrrolidine cycle was protected with Cbz group (in the later Section 3.2.3 and 3.4.3), in this case with Grignard reagent (at -60 °C in ether), the (2*S*,4*R*) addition product was obtained as a major diastereomer. When $CeCl_3$ and THF were used in this case, a single (2*S*,4*R*)-**56** was obtained as a maijor diastereomer (see Scheme 15). These results about the addition to the C-4 of these pyrrolidine derivatives are in accord with those reported in literature [58, 59, 60].

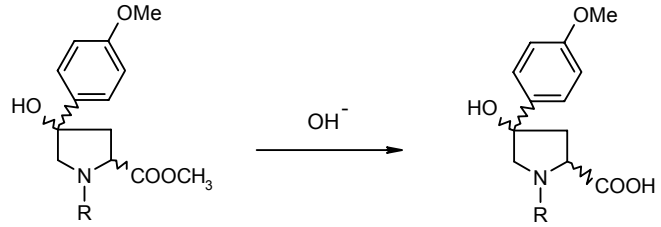
Scheme 15



(2*S*,4*R*)-56

In the final step the addition product **53a-b** purified to single diastereomers, were subjected to an alkaline hydrolysis in methanol or ethanol at room temperature to give the free amino acids (2*S*,4*R*)-**57a-b** and (2*S*,4*R*)-**57a-b**, (2*R*,4*S*)-**57a-b** and (2*R*,4*R*)-**57a-b**. The yields for these reactions ranged from 74% to 94% (Table 3.5).

Scheme 16



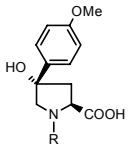
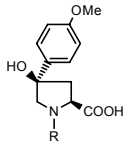
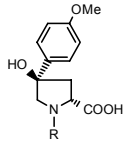
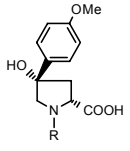
(2*S*,4*R*)-53a-b **(2*S*,4*R*)-57a-b**

(2*S*,4*S*)-53a-b **(2*S*,4*S*)-57a-b**

(2*R*,4*S*)-53a-b **(2*R*,4*S*)-57a-b**

(2*R*,4*R*)-53a-b **(2*R*,4*R*)-57a-b**

Table 3.5 **The yields of** 57a-b **from the hydrolysis of** 53a-b**.**

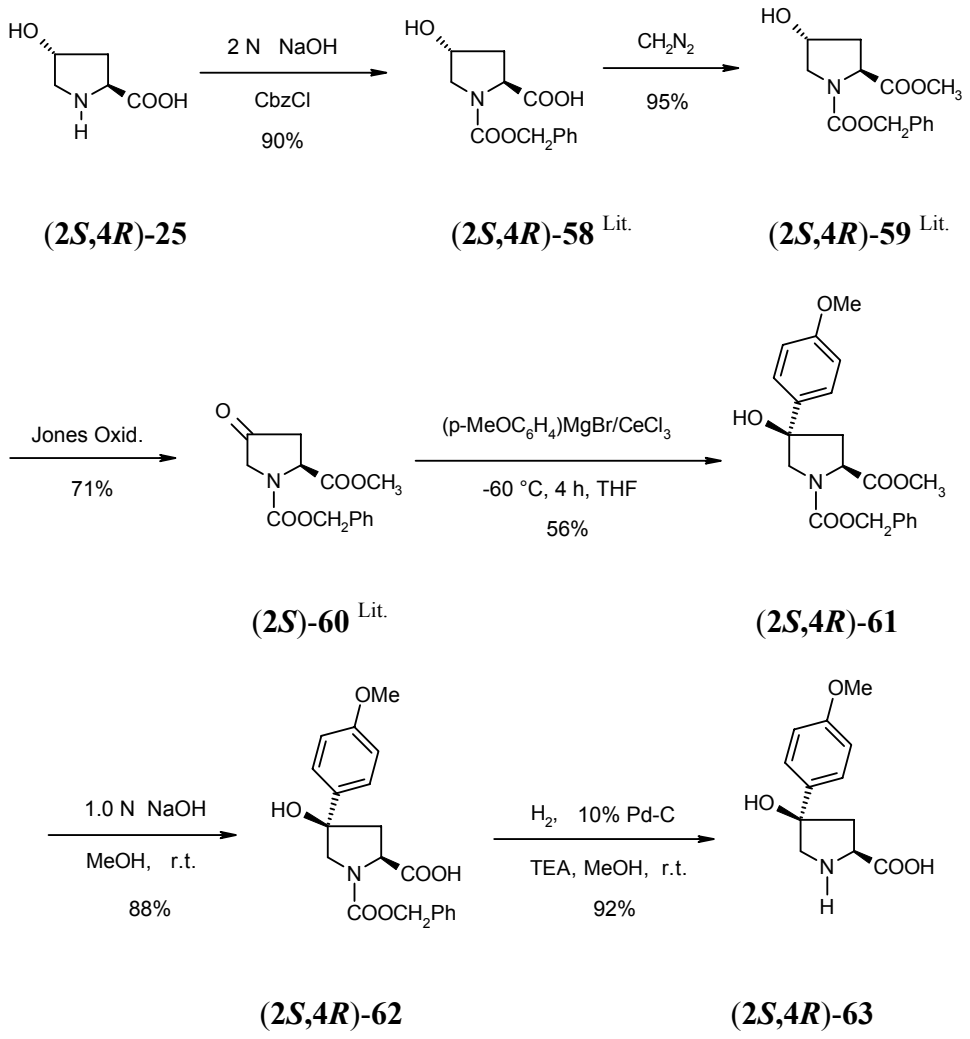
Structure	R: **a**	R: **b**
	$-CH_2CH_2CH=CPh_2$	$-CH_2CH_2OC(p\text{-}MeOC_6H_4)_3$
	74% (2*S*,4*S*)-**57a**	89% (2*S*,4*S*)-**57b**
	94% (2*S*,4*R*)-**57a**	88% (2*S*,4*R*)-**57b**
	88% (2*R*,4*R*)-**57a**	89% (2*R*,4*R*)-**57b**
	84% (2*R*,4*S*)-**57a**	89% (2*R*,4*S*)-**57b**

3.2.3 Preparation of 4-hydroxy-4-(4-methoxyphenyl)pyrrolidine-2-carboxylic acids

After the organometallic reagents had failed to be added to the C-4 position of the 4-oxopyrrolidine derivative (2*S*)-**50** (Section 3.2.1), the protected N-trityl group of **50** was replaced by a N-Cbz group, which was expected to solve the problem.

The required starting material (2S)-**60** was synthesized according to literature procedures by the N-protection of (2*S*,4*R*)-**25** with CbzCl at 0 °C (yield 90%) [61], by the esterification with diazomethane at 0 °C (yield 95%) [62, 63], and finally by Jones' oxidation (yield 71%) [41]. Interestingly, when the last step was performed by Swern oxidation, (2*S*)-**60** was obtained only in a very poor yield of 10%-27%.

Scheme 17



(2*S*,4*R*)-**25** (2*S*,4*R*)-**58** Lit. (2*S*,4*R*)-**59** Lit.

(2*S*)-**60** Lit. (2*S*,4*R*)-**61**

(2*S*,4*R*)-**62** (2*S*,4*R*)-**63**

In the case of (2*S*)-**60**, upon (4-$MeOC_6H_4$)MgBr (1.05 equiv.) pretreated with $CeCl_3$ (1.05 equiv.) in THF, only a single diastereomer (2*S*,4*R*)-**61** was formed (at –60 °C for 4 hours) and

18% of the starting (2*S*)-**60** was recycled. In contrast to the addition reactions of (4-$MeOC_6H_4$)$MgBr/CeCl_3$ to (2*S*)-**52a-b** and (2*R*)-**52a-b**, (1.40 equiv. For 20 hours) were less selective, as the addition to the C-4 ketone and to the ester group was occurred (31% yield). Hydrolysis of the ester group of (2*S*,4*R*)-**61** by aq.1.0 N NaOH (1.05 equiv.) gave (2*S*,4*R*)-**62** in 88% yield. To avoid a reactive removal of Cbz group, deprotection was performed by hydrogenolysis over Pd-C in the presence of triethylamine to afford (2*S*,4*R*)-**63** in 92% yield. Besides, triethylamine improved the solubility of the product in methanol.

The synthetic sequence shown in Scheme 17 was also applicable to (2*R*,4*R*)-**25** to give (2*R*,4*S*)-**63**.

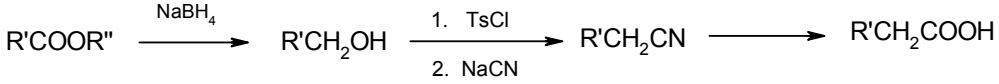
3.3 Preparation of 4-hydroxypyrrolidine-2-acetic acids and of their N-substituted derivatives

As illustrated in Scheme 2 (see page 10), the 4-hydroxypyrrolidine-2-acetic acid esters **32** are key intermediates for the synthesis of N-substituted 4-hydroxypyrrolidine-2-acetic acids **34** and N-substituted 4-hydroxy-4-(4-methoxyphenyl)pyrrolidine-2-acetic acids **37**. First in the following reactions the preparations of the 4-hydroxypyrrolidine-2-acetic acid esters **32** are discussed (Section 3.3.1-3.3.2).

3.3.1 Preparation of ethyl (2*R*,4*R*)-hydroxypyrrolidine-2-acetate via nucleophilic addition of a silyl ketene acetal to hydroxypyrrolidine derived N-acyliminium ions.

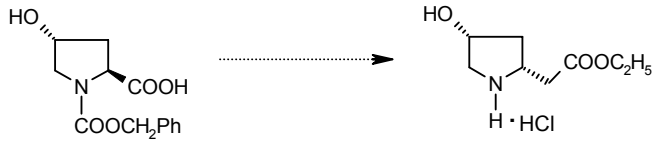
Two of the most common methods for the extension of carboxylic acid chain by one carbon are based on the Wolf rearrangement and on the Kolbe nitrile synthesis (see below). In both cases the configuration of a stereocenter adjacent to the carboxy function is retained.

Scheme 18



However, my intention was to accomplish the synthesis of the target compound **64** via N-acyliminium ions derived from optically active hydroxypyrrolidines like (2*S*,4*R*)-**58**. This might also allow the stereoselective construction of the desired compounds as the chiral center at C-4 still present in the N-acyliminium ion should give rise to asymmetric induction of a hopefully reasonable size.

Scheme 19



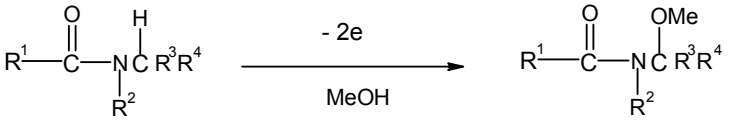
(**2*S*,4*R***)-**58** (**2*R*,4*R***)-**64**

For the conversion of (2*S*,4*R*)-**58** into (2*S*,4*R*)-**64**, the following synthetic steps were

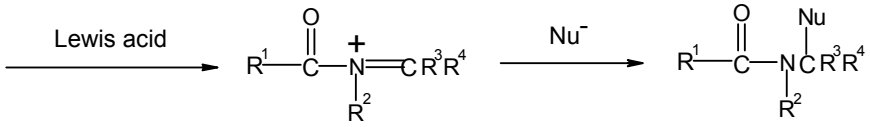
necessary: Electrolysis, protection of the 4-hydroxy group, nucleophilic addition to the N-acyliminium ion and final deprotection (Scheme 19).

1. Electrolysis: With the advantages of good yields and simple equipment in contrast to conventional chemical methods, the electrochemical oxidation of N-acylamines, also known as the *Ross-Eberson-Nyberg* reaction, is a unique approach to α-methoxy amides and α-methoxy carbamates [64]. Both, α-methoxy amides and carbamates have been shown to be versatile synthetic intermediates.

Scheme 20



65 **66**

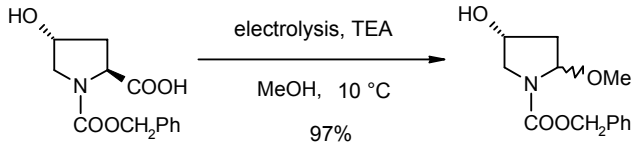


67 **68**

Upon their treatment with a Lewis acid such as BF_3 and $TiCl_4$, these α-methoxy products, in general, give access to N-acyliminium ions, which can be efficiently trapped with appropriate nucleophiles (Nu^-) to give the α-substituted products.

In addition to simple amides, N-acylated α-amino acids may be also subjected to anodic oxidation reaction, the latter being even more suitable. N-acyliminium ions, which are formed during the anodic decarboxylation reaction, are trapped by a solvent such as methanol to give the α-methoxylated product in most cases in high yield (Scheme 18) [65, 66, 67]. In my case the α-methoxy derivative **69** was obtained from (2*S*,4*R*)-**58** in 97% yield by anodic oxidation.

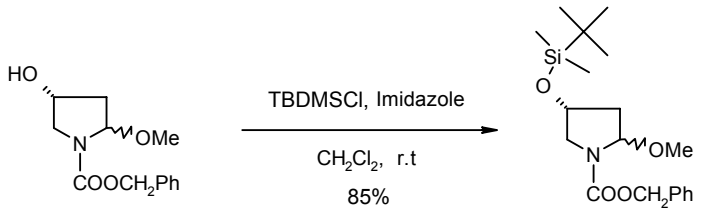
Scheme 21



(2*S*,4*R*)-58 **69**

2. Protection of the 4-hydroxy group: 1-Ethoxy-1-(trimethylsilyloxy)ethene was selected as a nucleophile to be added to the N-acyliminium ion that should form from (2*S*,4*R*)-**69** under the influence of a Lewis acid [68]. But despite of extensive variations of the reaction conditions, only small amounts of the desired products were obtained as a mixture of two diastereomers (determined by MS, IR, CHN analysis and analytical HPLC). As the failure was likely to arise from the free hydroxy group in the C-4 position, for this protection, **69** was treated with TBDMSCl in the presence of imidazole to provide **70** in 85% yield [69, 70].

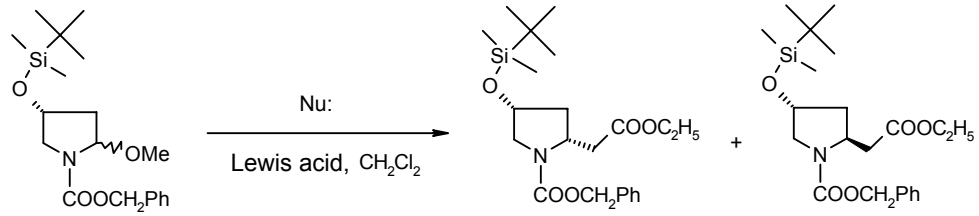
Scheme 22



69 **70**

3. Nucleophilic addition: For the substitution reactions the mixture of the diastereomers **70** was employed. While N-acyliminium ions are formed during the course of the reaction, it is unlikely that the stereochemistry at the C-2 of **70** will have any influence on diastereomeric composition of the final products, which has also been reported by *M. Thaning* and *Lars-G. Wistrand* [71]. For the transformation process of **70** to (2*R*,4*R*)-**71** and (2*S*,4*R*)-**71**, a series of experiments were made in order to optimize the yield and the stereoselectivity of this process. The reaction details are summarized in Table 3.6.

Scheme 23



70 *cis*-(**2*R*,4*R*)-71** *trans*-(**2*S*,4*R*)-71**

Table 3.6 Reactions of **70** with nucleophiles in the presence of Lewis acid.

No.	Nu:	Addition order	Temp.	Time	Ratio of *cis*/*trans*	Yield (isolated)	
						cis-(2*R*,4*R*)-**71**	*trans*-(2*S*,4*R*)-**71**
1	A	(**70** + A) + BF_3	20 °C	3 h	87:13	8%	54%
2	A	(**70** + A) + BF_3	-78 °C	4 h	92:8	5%	79%
3	A	(**70** + A) + BF_3	-78 °C	4 h	87:13	9%	79%
4	A	(**70** + A) + $TiCl_4$	-78 °C	16 h	80:20	5%	27%
5	A	(**70**+ BF_3) + A	-78 °C	4 h	97:3	1.7%	74%
6	A	(**70** + BF_3) + A	-78 °C	18 h	97:3	1.7%	62%
7	A	(**70** + $TiCl_4$) + A	-78 °C	16 h	89:11	7%	57%
8	B	(**70** + BF_3) + B	-78 °C	3 h	.....	0	0
9	B	(**70** + BF_3) + B	20 °C	19 h	.....	0	0

A: 1-Ethoxy-1-(trimethylsilyloxy)ethene, B: Ethyl bromozincacetate (0.50 M in CH_2Cl_2); Lewis acid $TiCl_4$ was used as a 1.0 M solution in CH_2Cl_2; the ratio of **70** : Nu : Lewis acid = 1 : 3.15 : 2.1, for all entrances except for No. 3 and 5, where the ratio was 1 : 4 : 2.1.

From the results displayed in Table 3.6, the following conclusion can be drawn.

(1) A raise in temperature and a prolongation of the reaction time led to a decrease in yields, possibly because of a cleavage of silyl protective group and Cbz group by the applied Lewis acids, compare No.1 with No.2, or No.5 with No.6; No dramatic change of the diastereoselectivity occurred when the temperature was varied, which is in concord with literature reports [71], compare No.1 with No.2 or with No.3,

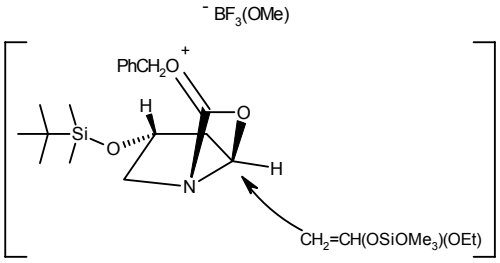
(2) The highest stereoselectivity was achieved when the starting material **70** was first mixed with the Lewis acid (15 minutes at –78 °C) before the nucleophile was added. This seems to

imply that the reaction may take place along a different pathway (S_N2-like reaction, ion pairs or free ions as intermediates) and that a more or less free N-acyliminium ion may be beneficial for a high stereoselectivity. On the other hand, one undergoes the risk of decomposition victim of the protective group when **70** is pretreated with a Lewis acid;

(3) $BF_3 \cdot Et_2O$ appeared to be slightly better for a higher stereoselectivity than $TiCl_4$;

(4) The Reformasky reagent (ethyl bromozincacetate 0.50 M in CH_2Cl_2) failed to undergo the desired reaction.

In all cases, the *cis* isomer (Table 3.6) was preferentially formed (for the confirmation of the configuration see Section 3.5.2). *Philippe Renaud* and *Dieter Seebach* [72] explained this high diastereoselectivity as the formation of **72**, in which the upper side of the cycle is occupied, and therefore the nucleophile preferentially attacks the compound from the bottom.

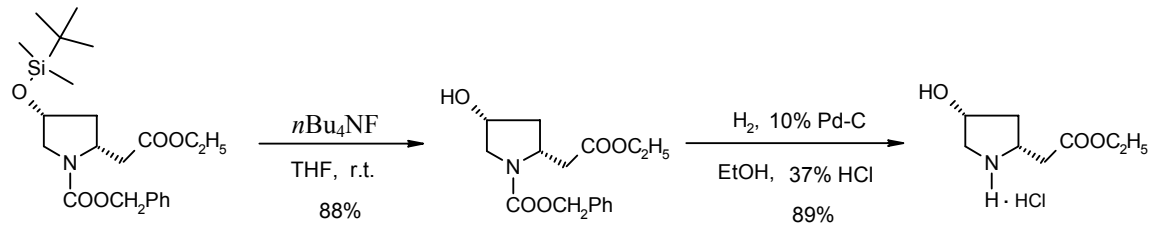


72

4. Deprotection:

(2*R*,4*R*)-**71** was liberated from the O-silyl group by means of *n*-Bu_4NF in THF at room temperature. The resulting compound (2*R*,4*R*)-**73** (88% yield) [71, 73, 74] was subjected to hydrogen over 10% Pd-C in conc. HCl/EtOH to give (2*R*,4*R*)-**64** (89% yield).

Scheme 24



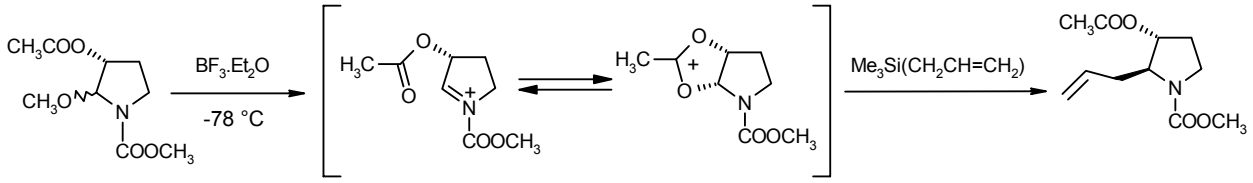
(**2*R*,4*R***)-**71** (**2*R*,4*R***)-**73** (**2*R*,4*R***)-**64**

3.3.2 Preparation of methyl (2*S*,4*R*)-4-hydroxypyrrolidine-2-acetate

3.3.2.1 Attempts of nucleophilic addition to N-acyliminium ions

A synthesis of **76** from **74** has been reported in literature [70, 71]. For this reaction a neighboring group effect (Scheme 25) is postulated to explain the observed *trans* selectivity.

Scheme 25

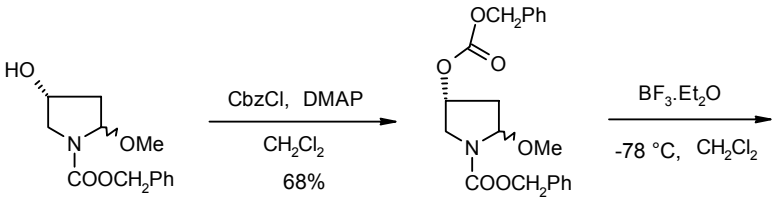


74 **75** **76** (major)

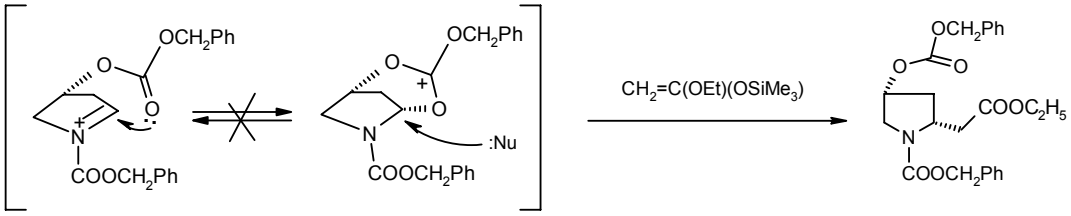
cis:*trans*~ 1:4 [Lit.]

My idea was to employ **77** as an α-amidoalkylation reagent, which might provide a convenient access to the desired 2,4-*trans* substituted pyrrolidine derivatives. Supposed that a similar neighboring group is effective (see **79**) as mentioned above, and then the addition reaction should proceed for **77** with *trans* selectivity as well.

Scheme 26



69 **77**



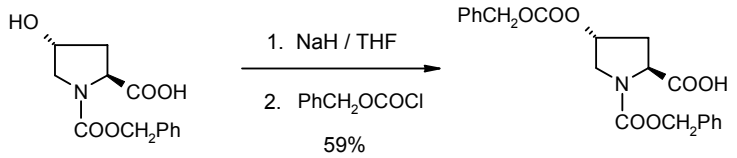
78 **79** *cis*-(**2*R*,4*R***)-**80**

The synthesis of the starting material **77** was easily accomplished by treating **69** with CbzCl in the presence of 4-dimethylaminopyridine (yield 68%). A series of amidoalkylation reactions were carried out with **77** at –78 °C for 4 h (yields of 3-13%), in which 1-ethoxy-1-(trimethylsilyloxy)ethene and Lewis acid $BF_3.Et_2O$ were used. These reactions were performed under various conditions and the addition order of the reagent was also changed. But in each case only the *cis*-(2*R*,4*R*)-**80** and no *trans* addition product (2*S*,4*R*)-**80** was found, while the yields remained low (3-13%). The *cis* configuration of (2*R*,4*R*)-**80** was ascertained by the comparison of the analytical data {^{1}H NMR, [α]} of this compound with those of (2*S*,4*R*)-**82** (see Scheme 27 and 34). Possibly, a neighboring predominated group effect arising from the carbamate function (similar to the complex **72**) predominated as compared to the one of the carbonate group in the 4-position of the pyrrolidine ring.

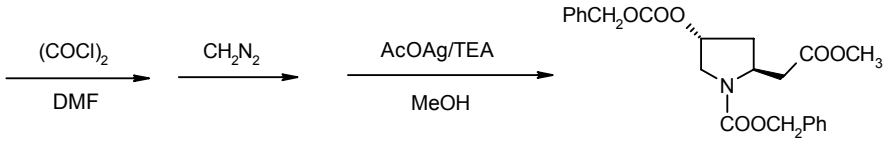
3.3.2.2 Preparation of methyl (2*S*,4*R*)-4-hydroxypyrrolidine-2-acetate via Wolf rearrangement

After the failure to get the *trans*-(2*S*,4*R*)-**80** by amidoalkylation reactions with **77** (Scheme 26), my attention turned to an alternative synthesis. I decided to start from a suitable pyrrolidine-2-carboxylic acid derivative with (2*S*)-configuration [see e.g. (2*S*,4*R*)-**81**] and to perform an elongation of the carboxylic acid side chain by a Wolff rearrangement, which is known to proceed with retention of configuration and should give the desired product. In order to be able to remove both protective groups in a single step by hydrogenation after the Wolff rearrangement, (2*S*,4*R*)-**81** was used as starting material. (2*S*,4*R*)-**81** was prepared by an literature method [44]. But only low yields were obtained from the Wolff rearrangement (overall yield of 12%). Evidence for the configuration at C-2 of (2*S*,4*R*)-**82** — that it had been retained — came from a comparison of its ^{1}H NMR data with related compounds.

Scheme 27



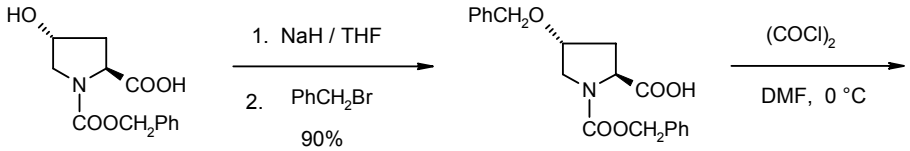
(2*S*,4*R*)-58 **(2*S*,4*R*)-81** Lit.



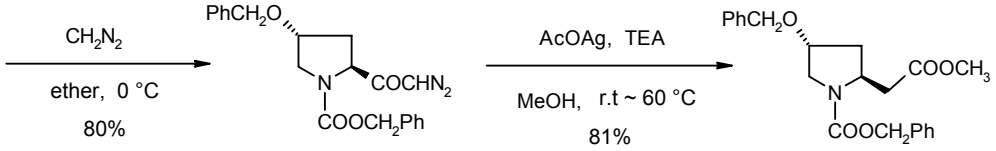
(2*S*,4*R*)-82

The acid sensitivity of the carbonate function was blamed to account for the low yield. Therefore, instead of the carbonate function a benzyl group seemed to be more appropriate for the protection of the hydroxy function. (2*S*,4*R*)-**58** was treated with NaH and subsequently refluxed with benzyl bromide in THF to give (2*S*,4*R*)-**83** in 90% yield [75]. Then (2*S*,4*R*)-**83** was transformed into the diazoketone (2*S*,4*R*)-**84** (80% yield) by means of $(COCl)_2$ (DMF as a catalyst) and diazomethane (at 0 °C). Finally, the rearrangement of **84** initiated by AcOAg-TEA as a catalyst, gave (2*S*,4*R*)-**85** in 81% yield.

Scheme 28



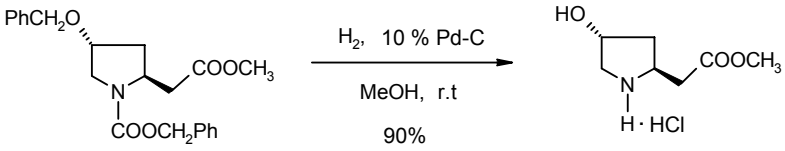
(2*S*,4*R*)-58 **(2*S*,4*R*)-83** [Lit.]



(2*S*,4*R*)-84 **(2*S*,4*R*)-85**

Hydrogenolysis over 10% Pd-C under ambient pressure provided the totally deprotected amino acid ester (2*S*,4*R*)-**86** in 90% yield [76, 77, 78].

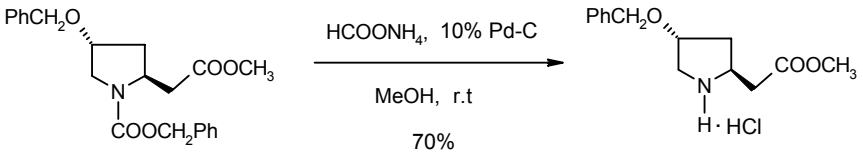
Scheme 29



(2*S*,4*R*)-85 **(2*S*,4*R*)-86**

But also a partial deprotection of (2*S*,4*R*)-**85** could be achieved, when ammonium formate was applied as a hydrogen donor in the presence of 10% Pd-C as a catalyst [79, 80]. Then, only the Cbz group was removed to yield the amino acid ester (2*S*,4*R*)-**87** [81].

Scheme 30



(2*S*,4*R*)-85 **(2*S*,4*R*)-87**

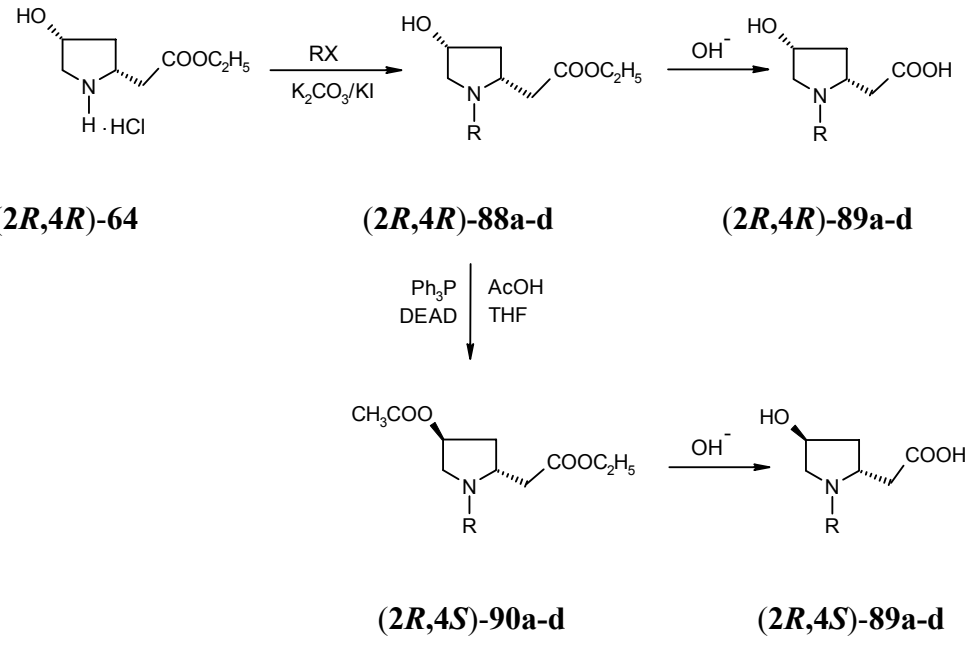
3.3.3 Preparation of 4-hydroxypyrrolidine-2-acetic acids and of their N-substituted derivatives

3.3.3.1 Preparation of N-substituted (2*R*)-4-hydroxypyrrolidine-2-carboxylic acids

In analogy to the preparation of (2*S*,4*R*)-**40a-b** (Scheme 3), (2*R*,4*R*)-**89a-d** were obtained via alkylation of (2*R*,4*R*)-**64** with the corresponding halides of **24a-d** and a subsequent hydrolysis of the ester group with aqueous 1.0 N NaOH (Table 3.7).

Furthermore, similar to the preparation of (2*R*,4*S*)-**40a-b** (Scheme 7), the configuration at C-4 of (2*R*,4*R*)-**88a-d** was inverted by a Mitsunobu reaction. Upon hydrolysis of the products (2*R*,4*S*)-**90a-d** with aqueous 1.0 N NaOH the final compounds (2*R*,4*S*)-**89a-d** were obtained (Table 3.7).

Scheme 31



(**2*R*,4*R***)-**64** (**2*R*,4*R***)-**88a-d** (**2*R*,4*R***)-**89a-d**

(**2*R*,4*S***)-**90a-d** (**2*R*,4*S***)-**89a-d**

R = **24a-c**, X = Br;

R = **24d**, X = I. (see Table 3.7)

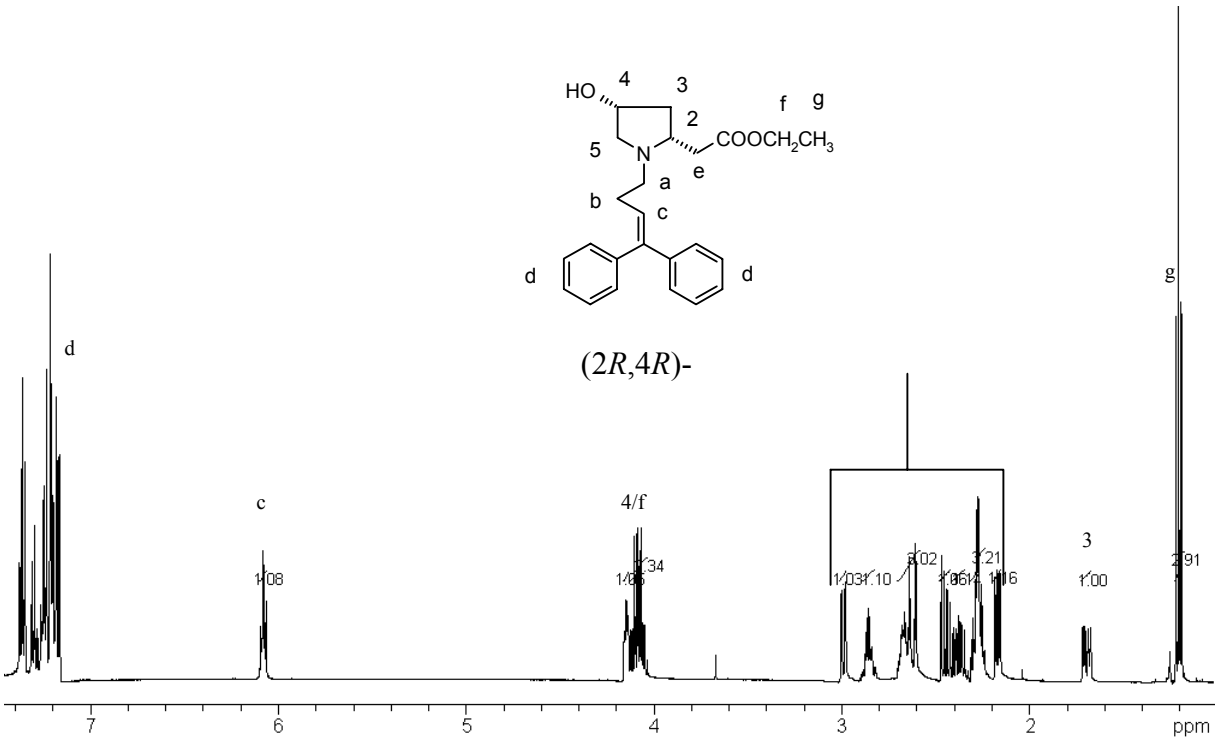


Fig. 3.3. The ^{1}H NMR spectrum of (2*R*,4*R*)-**88a** ($CDCl_3$, δ

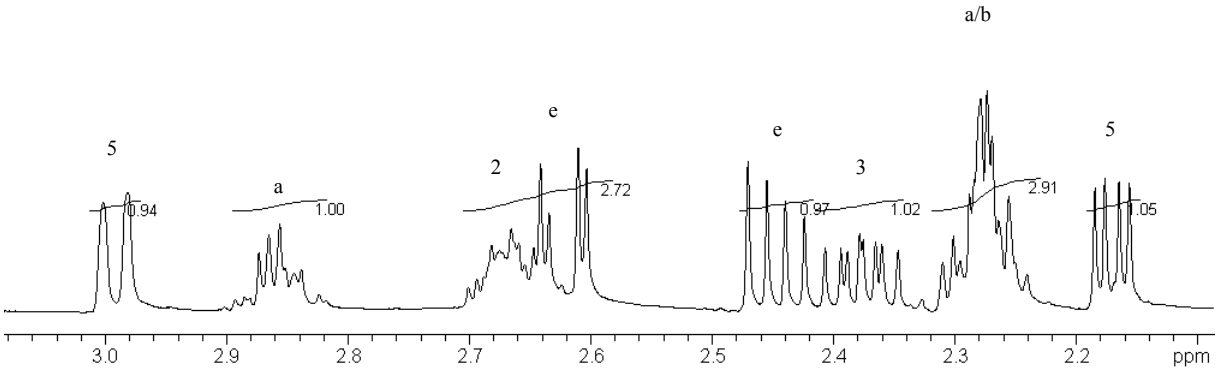
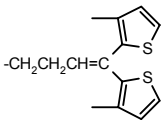
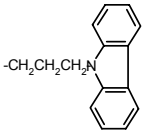
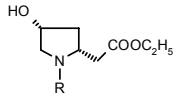
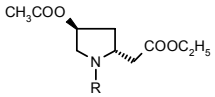
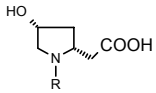
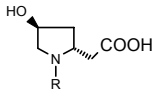


Fig. 3.4. The ^{1}H NMR spectrum of (2*R*,4*R*)-**88a** ($CDCl_3$, δ

The structures of the compounds mentioned above could be confirmed by the ^{1}H NMR and H,H-Cosy spectra in the combination with IR and MS spectra as well as by the combustion of analysis.

For (2*R*,4*R*)-**88a** the locations of the protons were also confirmed by the ^{1}H{^{13}C}-Cosy spectra. The ^{1}H NMR spectrum of (2*R*,4*R*)-**88a** is presented as an example in Fig. 3.3 and 3.4.

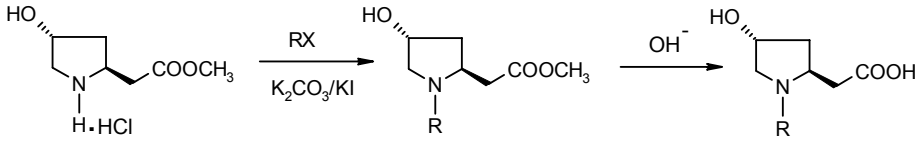
Table 3.7 The yields of **88a-d**, **89a-d** and **90a-d**.

Structure	R: **a**	**b**	**c** 	**d** 
	69% (2*R*,4*R*)-**88a**	52% (2*R*,4*R*)-**88b**	52% (2*R*,4*R*)-**88c**	87% (2*R*,4*R*)-**88d**
	72% (2*R*,4*S*)-**90a**	32% (2*R*,4*S*)-**90b**	63% (2*R*,4*S*)-**90c**	85% (2*R*,4*S*)-**90d**
	84% (2*R*,4*R*)-**89a**	78% (2*R*,4*R*)-**89b**	95% (2*R*,4*R*)-**89c**	90% (2*R*,4*R*)-**89d**
	93% (2*R*,4*S*)-**89a**	85% (2*R*,4*S*)-**89b**	94% (2*R*,4*S*)-**89c**	93% (2*R*,4*S*)-**89d**

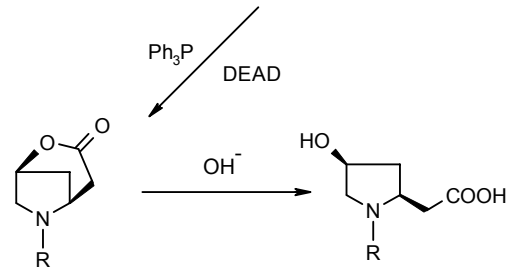
3.3.3.2 Preparation of N-substituted (2*S*)-4-hydroxypyrrolidine-2-acetic acids

(2*S*,4*R*)-**89a-d** and (2*S*,4*S*)-**89a-d** were synthesized in analogy to the preparation of (2*S*,4*R*)-**40a-b** and (2*S*,4*S*)-**40a-b** (Scheme 3 and 4). Thus, they started from (2*S*,4*R*)-**86** and went along (2*S*,4*R*)-**91a-d** and (1*S*,5*S*)-**92a-d** as intermediates. Also the compounds (2*S*,4*R*)-**94a** and **c** were prepared in a similar manner. In this case (2*S*,4*R*)-**87** as a starting material was N-alkylated with the bromides of **24a** and **c** to yield (2*S*,4*R*)-**93a** and **c**, from which the (2*S*,4*R*)-**94a** and **c** were obtained.

Scheme 32



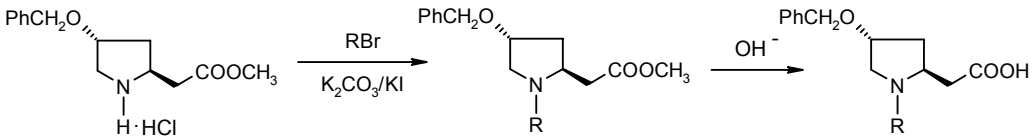
(2*S*,4*R*)-86 **(2*S*,4*R*)-91a-d** **(2*S*,4*R*)-89a-d**



(1*S*,5*S*)-92a-d **(2*S*,4*S*)-89a-d**

R = **24a-c**, X = Br; R = **24d**, X = I. (see Table 3.8)

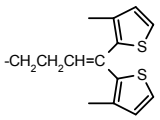
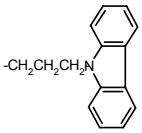
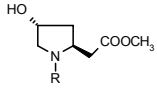
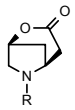
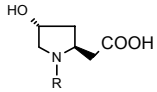
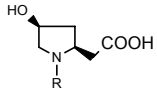
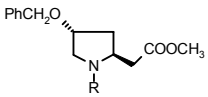
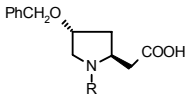
Scheme 33



(2*S*,4*R*)-87 **(2*S*,4*R*)-93a**, **c** **(2*S*,4*R*)-94a**, **c**

R = **24a**, **c** (see Table 3.8)

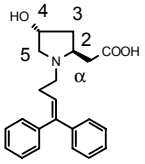
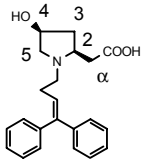
Table 3.8 The yields of **91a-d**, **92a-d**, **93a-d**, **93a** and **c, 94a** and **94c**.

Structure	R: **a**	**b**	**c**	**d**
	$-CH_2CH_2CH=CPh_2$	$-CH_2CH_2OC(p\text{-}MeOC_6H_4)_3$		
	59% (2*R*,4*R*)-**91a**	39% (2*R*,4*R*)-**91b**	41% (2*R*,4*R*)-**91c**	57% (2*R*,4*R*)-**91d**
	76% (1*S*,5*S*)-**92a**	70% (1*S*,5*S*)-**92b**	46% (1*S*,5*S*)-**92c**	41% (1*S*,5*S*)-**92d**
	83% (2*S*,4*R*)-**89a**	83% (2*S*,4*R*)-**89a**	92% (2*S*,4*R*)-**89c**	88% (2*S*,4*R*)-**89d**
	78% (2*S*,4*S*)-**89a**	96% (2*S*,4*S*)-**89b**	84% (2*S*,4*S*)-**89c**	95% (2*S*,4*S*)-**89d**
	45% (2*S*,4*R*)-**93a**	----------	51% (2*S*,4*R*)-**93a**	----------
	95% (2*S*,4*R*)-**94a**	----------	95% (2*S*,4*R*)-**94c**	----------

From the synthetic strategy shown above, I had obtained two sets of diastereomers that differed with respect to the configuration at C-4 of the pyrrolidine nucleus.

For these two sets of diastereomers e.g. (2*S*,4*R*)-**89a-d** and (2*S*,4*S*)-**89a-d**, remarked differences in ^{1}H NMR spectra for pairs of diastereomeric compounds were observed. In Table 3.9 the ^{1}H NMR data of (2*S*,4*R*)-**89a** and (2*S*,4*S*)-**89a** are shown as examples.

Table 3.9 **Chemical shift values of the partial protons of (2*S*,4*R*)-**89a **and (2*S*,4*S*)-**89a**.**

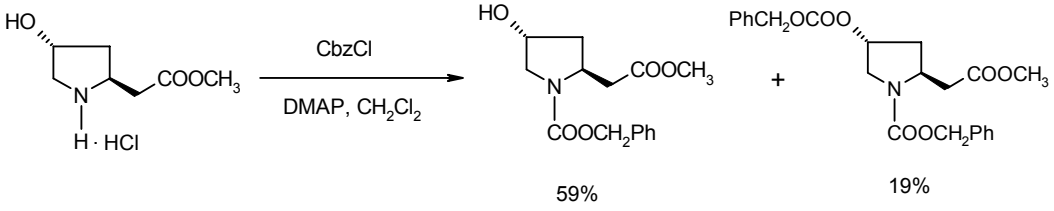
^{1}H NMR (CD_3OD)	(2*S*,4*R*)-**89a**  $[\alpha]_D^{20}$ = -69.4			(2*S*,4*S*)-**89a**  $[\alpha]_D^{20}$ = -51.5		
Proton	δ	Peak	*J* Hz	δ	Peak	*J* Hz
H-2	3.74-3.80	m		3.46-3.57	m	
H-3	1.93	ddd	13.6/11.4/5.1	1.71-1.77	m	
H-3	2.13	ddt	13.6/6.5/1.7	2.46-2.57	m	
H-4	4.38-4.41	m		4.35-4.40	m	
H-5	2.82	d	12.5	2.92-3.01	m	
H-5	3.46-3.53	m		3.17-3.29	m	
H-α	2.46	dd	16.5/3.0	2.46-2.57	m	
H-α	2.70	dd	16.5/5.9	2.63	dd	16.7/6.3

3.3.3.3 Preparation of 4-hydroxypyrrolidine-2-acetic acids

The intermediates (2*S*,4*R*)-**86** and (2*R*,4*R*)-**73** were employed in the preparation of the free amino acids (2*S*,4*R*)-**97** and (2*R*,4*R*)-**97**.

For the protection of the amino group, (2*S*,4*R*)-**86** was treated with CbzCl (in the presence of 4-dimethylaminopyridine) to give the known compound (2*S*,4*R*)-**95** [73] in 59% yield, which was identical with that one from Wolff rearrangement (Scheme 27). In addition, this reaction gave (2*S*,4*R*)-**82** in 19% yield. By a comparison of the analytical data of (2*S*,4*R*)-**95** and (2*S*,4*R*)-**96** with those in literature [73], also the configuration of (2*S*,4*R*)-**86** could be deduced.

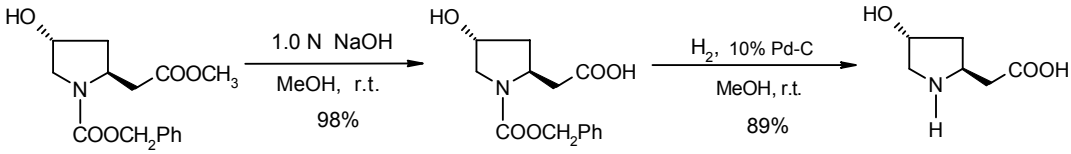
Scheme 34



(**2*S*,4*R***)-**86** (**2*S*,4*R***)-**95** Lit. (**2*S*,4*R***)-**82**

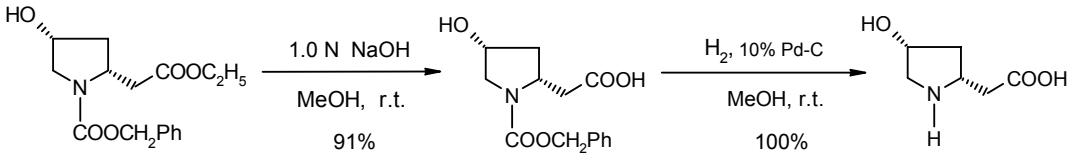
(2*S*,4*R*)-**95** and (2*R*,4*R*)-**73** were subjected to 1.0 N NaOH (1.05 equiv.) at room temperature in methanol to give (2*S*,4*R*)-**96** and (2*R*,4*R*)-**96**, and subsequent hydrogenolysis of (2*S*,4*R*)-**96** and (2*R*,4*R*)-**96** over Pd-C gave the respective free amino acids (2*S*,4*R*)-**97** and (2*R*,4*R*)-**97** in excellent yields.

Scheme 35



(**2*S*,4*R***)-**95** Lit (**2*S*,4*R***)-**96** Lit (**2*S*,4*R***)-**97**

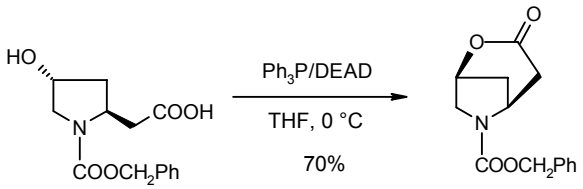
Scheme 36



(2*R*,4*R*)-73 **(2*R*,4*R*)-96** **(2*R*,4*R*)-97**

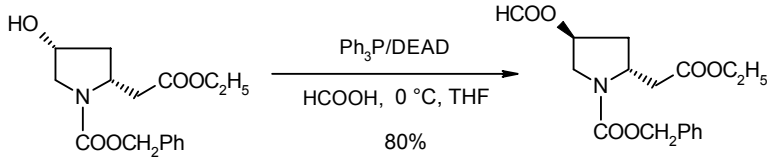
In a manner similar to the preparation of (1*S*,5*S*)-**90** and (2*R*,4*S*)-**92** (Scheme 31 and 32), the configuration at C-4 of (2*S*,4*R*)-**96** and (2*R*,4*R*)-**73** was inverted by a Mitsunobu reaction. In order to avoid that the carbamate group is affected during hydrolysis, a readily hydrolyzed formyl group was used in place of the acetyl group.

Scheme 37



(2*S*,4*R*)-96 **(1*S*,5*S*)-98**

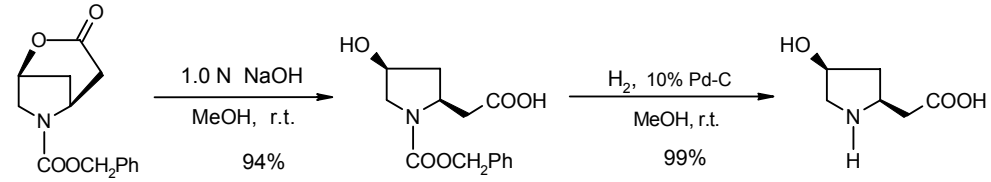
Scheme 38



(2*R*,4*R*)-73 **(2*R*,4*S*)-99**

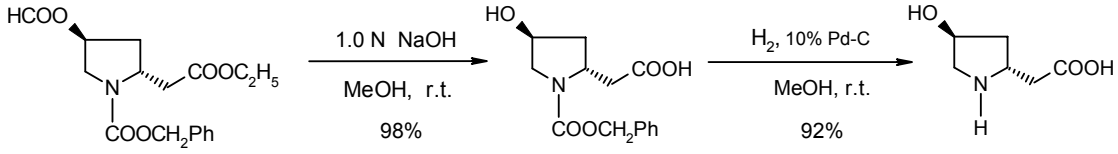
The controlled hydrolysis of (1*S*,5*S*)-**98** and (2*R*,4*S*)-**99**, and a subsequent hydrogenolysis yielded (2*S*,4*S*)-**97** and (2*R*,4*S*)-**97**, respectively.

Scheme 39



(1*S*,5*S*)-98 **(2*S*,4*S*)-96** **(2*S*,4*S*)-97**

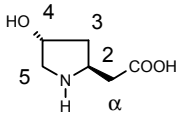
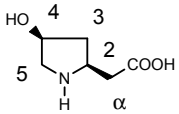
Scheme 40



(**2*R*,4*S*)-99** (**2*R*,4*S*)-96** (**2*R*,4*S*)-97**

The chemical shift differences of the two diastereomers (2*S*,4*S*)-**97** and (2*S*,4*R*)-**97** are reflected in Table 3.10. Remarkable differences of the chemical shifts of protons are seen for the C-3 and C-α positions.

Table 3.10 Chemical shift values of (2*S*,4*R*)-**97** and (2*S*,4*S*)-**97**.

^{1}H NMR (CD_3OD)	(2*S*,4*R*)-**97**  $[\alpha]_D^{20} = +1.3$			(2*S*,4*S*)-**97**  $[\alpha]_D^{20} = +5.3$		
Proton	δ	Peak	*J* Hz	δ	Peak	*J* Hz
H-2	4.02-4.08	m		3.93-3.99	m	
H-3	1.83	ddd	14.1/11.4/4.4	1.77	dddd	14.2/7.3/3.6/1.4
H-3	2.14-2.20	m		2.55	ddd	14.2/8.8/6.0
H-4	4.56-4.59	m		4.62-4.65	m	
H-5	3.22	dt	12.8/1.5	3.32	ddd	12.5/2.4/1.4
H-5	3.43	dd	12.8/4.2	3.38	dd	12.5/4.9
H-α	2.55	dd	16.6/7.7	2.72-2.74	m	
H-α	2.64	dd	16.6/5.5	2.72-2.74	m	

3.4 Preparation of 4-hydroxy-4-(4-methoxyphenyl)pyrrolidine-2-acetic acids and of their N-substituted derivatives

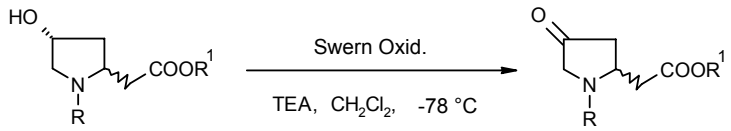
3.4.1 Preparation of N-substituted 4-hydroxy-4-(4-methoxyphenyl)pyrrolidine-2-acetic acids

As designed in Scheme 2 the four stereoisomers of **104b-c** could be prepared from (2*S*,4*R*)-**91b-c** and (2*R*,4*R*)-**88b-c** in analogy to the preparation of **57a-b** (Section 3.2.2) by a synthetic sequence: Swern oxidation of the 4-hydroxy group, addition of an organometallic reagent to the C-4 position and final hydrolysis.

Swern oxidation:

In the first step the 4-oxopyrrolidine-2-acetic acid esters (2*S*)-**100a-**c and (2*R*)-**101b-c** were prepared from (2*S*,4*R*)-**91a-c** and (2*R*,4*R*)-**88b-c** by Swern oxidation. The yields amounted to 81-92% yields.

Scheme 41

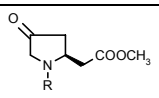
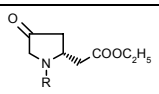


(**2*S*,4*R*)-91a-c** ▬ (**2*S*)-100a-c** ▬

(**2*R*,4*R*)-88b-c** ····· (**2*R*)-101b-c** ·····

(for R and R^1 see the following Table 3.11)

Table 3.11 Yields of (2*S*)-**100a-c** and (2*R*)-**101b-c** obtained by Swern oxidation

Structure	R: **a**	R: **b**	R: **c**
	-$CH_2CH_2CH{=}CPh_2$	-$CH_2CH_2OC(p\text{-}MeOC_6H_4)_3$	-$CH_2CH_2CH{=}C$ (2-thienyl)
	83% (2*S*)-**100a**	81% (2*S*)-**100b**	92% (2*S*)-**100c**
	----------	87% (2*R*)-**101b**	88% (2*R*)-**101c**

Addition of the organometallic reagent:

The addition of the organometallic reagent to (2*S*)-**100b-c** and (2*R*)-**101b-c** was carried out in two different ways. The reaction was either performed at –78 °C in ether without any additive (A), or at –78 °C in THF with $CeCl_3$ (B). Further details of the reactions are specified in Table 3.12 (for the determination of the configuration at C-4 of the products **102b-c** and **103b-c** see Section 3.5.3).

Scheme 42

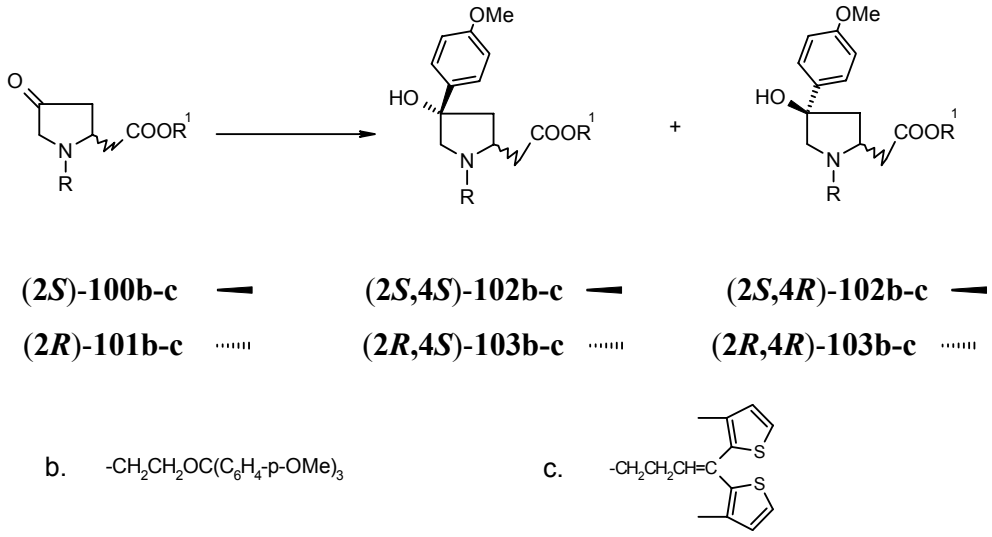


Table 3.12 Addition reactions of organometallic reagents to (2*S*)-**100b-c** and (2*R*)-**101b-c**

No.	Starting material	Solvent	$CeCl_3$ equiv.	ArMgBr equiv.	*d.s*	Yield (isolated)		Recovered (%)
						(2*S*,4*S*)-**102**	(2*S*,4*R*)-**102**	(2*S*)-**100**
1	(2*S*)-**100b**	Et_2O	……	1.80	81 : 19	47 %	14 %	33 %
2	(2*S*)-**100b**	THF	1.40	1.40	17 : 83	5 %	43 %	32 %
3	(2*S*)-**100c**	Et_2O	…….	1.80	87 : 13	47 %	11 %	24 %
4	(2*S*)-**100c**	THF	1.40	1.40	21 : 79	8 %	24 %	41 %
					d.s	(2*R*,4*R*)-**103**	(2*R*,4*S*)-**103**	(2*R*)-**101**
5	(2*R*)-**101b**	Et_2O	…….	1.80	79 : 21	50 %	15 %	31 %
6	(2*R*)-**101b**	THF	1.40	1.40		1 %	44 %	26 %
7	(2*R*)-**101c**	Et_2O	…….	1.80		54 %	10 %	10 %
8	(2*R*)-**101c**	THF	1.40	1.40	19 : 81	7 %	25 %	26 %

1. Reaction time: 20 hours; reaction temperature: -78 °C.
2. For the addition reactions performed with (2*S*)-**100c** and (2*R*)-**101c** in THF, a side product, possibly formed by intermolecular condensation reaction (determined by MS and ^{1}H NMR), was isolated in about 10% yield.

By comparison of Table 3.4 with Table 3.12 (for the reactions performed under the same conditions), it can be found that the addition reaction of organometallic reagent to (2*S*)-**100b-c** and (2*R*)-**101b-c** had proceeded with the same sense of asymmetric induction as those to **52a-b** (Scheme 10). Only slight changes in the stereoselectivities and yields occurred:

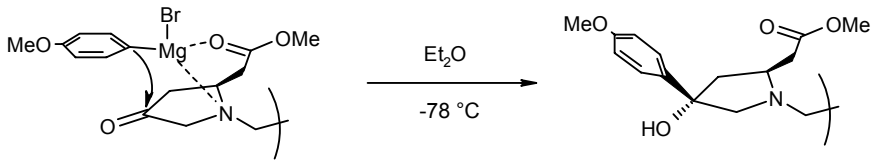
1) Under condition (A), the stereoselectivity slightly diminished, compare No.5 (89:11) and No.7 (85:15) in Table 3.4 with No.3 (87:13), No.1 (81:19) and No.5 (79:21) in Table 3.12.

2) Under condition (B), however, the stereoselectivity increased to a small extent, compare No.3 (30:70) in Table 3.4 with No.2 (17:83), No.4 (21:79), No.8 (19:81) in Table 3.12.

In accord with my assumptions regarding the reaction mechanism put forth in Section 3.2.2, these small variations might be explained as follows:

As claimed in Section 3.2.2, (4-$MeOC_6H_4$)MgBr formed a chelate with (2*S*)-**52a-b** in ether. The binding of (4-$MeOC_6H_4$)MgBr with (2*S*)-**100b-c** should be also preferentially located at the upper face of the molecule (Scheme 43), which would lead to the *cis* addition product (2*S*,4*S*)-**102b-c**. But this complexation might be a little weaker than that of (2*S*)-**52a-b** due to the elongated ester side chain, thus, the diastereoselectivity became a little bit lower.

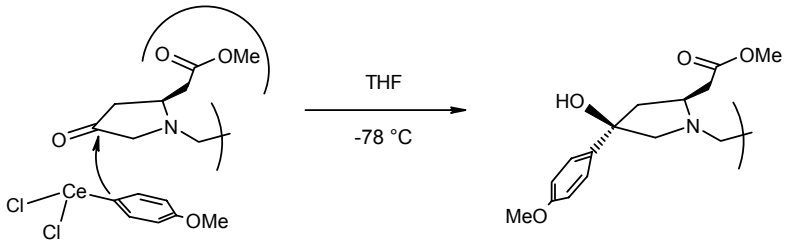
Scheme 43



(**2*S*)-100b-c** (**2*S*,4*S*)-102b-c**

The extension of the carboxylic acid side chain at C-2 also increased its bulkiness and thereby its ability to direct the attack to the opposite face as depicted in Scheme 44, thus, leading to a slightly enhanced stereoselectivity.

Scheme 44

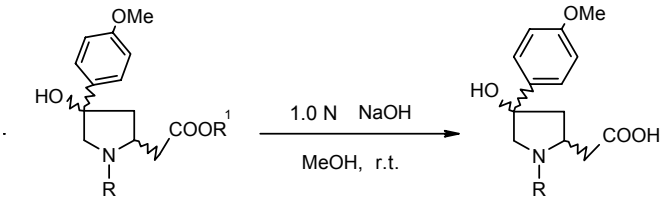


(**2*S*)-100b-c** (**2*S*,4*R*)-102b-c**

Hydrolysis:

All stereoisomers **102b-c** and **103b-c** were subjected to hydrolysis with aq. 1.0 N NaOH in methanol at room temperature to yield the free amino acids (2*S*,4*R*)-**104b-c**, (2*S*,4*S*)-**104b-c**, (2*R*,4*S*)-**104b-c** and (2*R*,4*R*)-**104b-c**. The yields ranged from 70%-98% (Table 3.13).

Scheme 45



R^1 = Me: (**2*S*,4*R*)-102b-c** (**2*S*,4*R*)-104b-c**

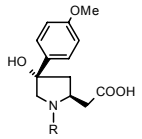
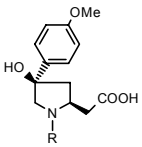
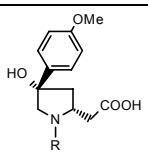
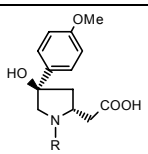
(**2*S*,4*S*)-102b-c** (**2*S*,4*S*)-104b-c**

R^1 = Et: (**2*R*,4*S*)-103b-c** (**2*R*,4*S*)-104b-c**

(**2*R*,4*R*)-103b-c** (**2*R*,4*R*)-104b-c**

R = 24b-c **(see Table 3.13)**

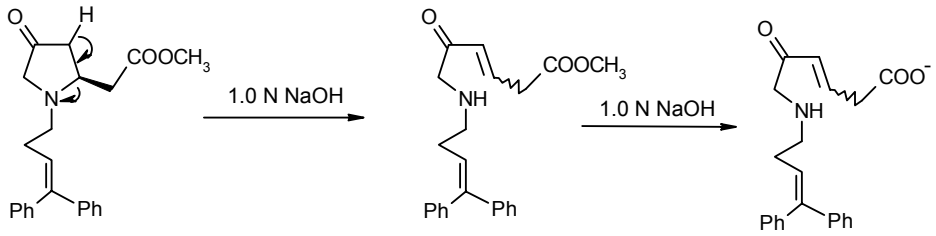
Table 3.13 The yields of **104b-c** from the hydrolysis of **102b-c** and **103b-c** series

Structure	R: **b**	R: **c**
	-$CH_2CH_2OC(C_6H_4$-p-OMe$)_3$	-CH_2CH_2CH=C(thienyl)
	73% (2*S*,4*S*)-**104b**	70% (2*S*,4*S*)-**104c**
	86% (2*S*,4*R*)-**104b**	98% (2*S*,4*R*)-**104c**
	89% (2*R*,4*S*)-**104b**	82% (2*R*,4*S*)-**104c**
	93% (2*R*,4*R*)-**104b**	95% (2*R*,4*R*)-**104c**

3.4.2 Attempts towards preparation of N-substituted 4-oxopyrrolidine-2-acetic acids

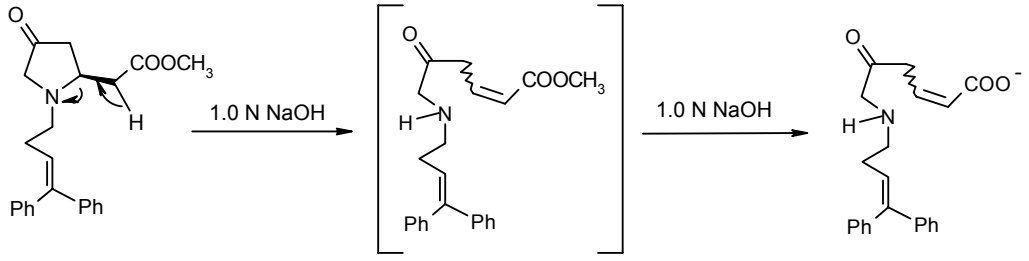
4-Oxopyrrolidine-2-acetic acid derivatives were of interest for biological evaluation. Therefore, (2*S*)-**100a** was subjected to an aqueous hydrolysis with 1.0 N NaOH in methanol at room temperature. But the amino acid (2*S*)-**105a** could be not obtained after neutralization of the reaction mixture. The reaction product had likely undergone reverse Michael reaction, for which following pathways may be considered:

Scheme 46



(2*S*)-100a **(2*S*)-105a** **106a**

Scheme 47

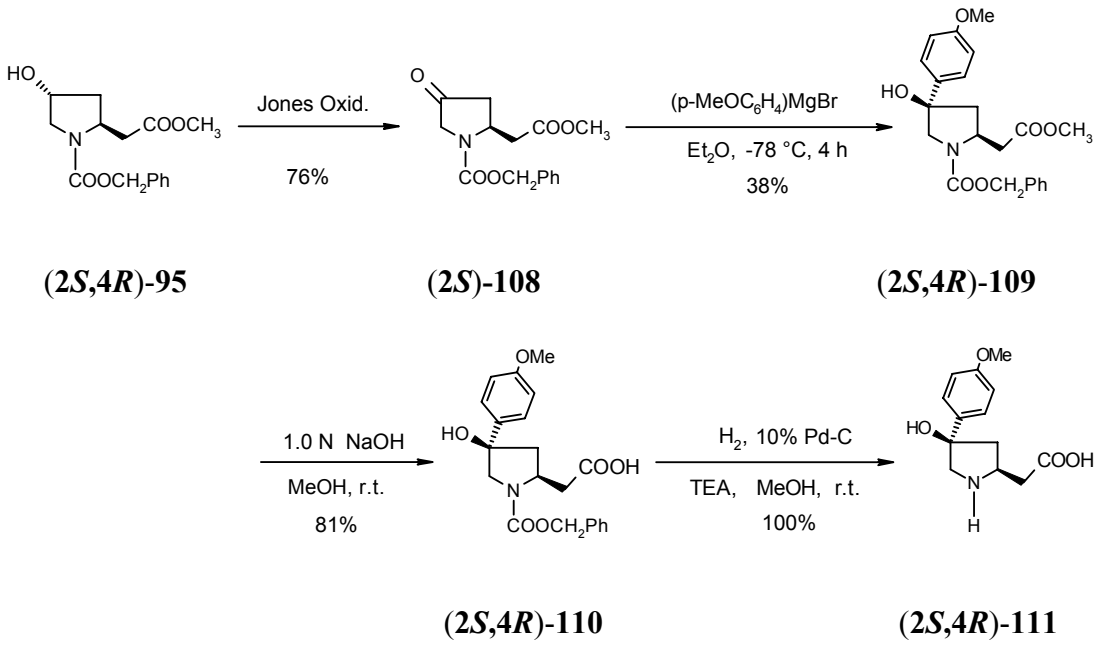


(2*S*)-100a **107a**

3.4.3 Preparation of N-unsubstituted 4-hydroxy-4-(4-methoxyphenyl)- pyrrolidine-2-acetic acids

A procedure similar to the preparation of **63** series (Scheme 17) was used for the synthesis of (2*S*,4*R*)-**111** from (2*S*,4*R*)-**95** (Scheme 48) and of (2*R*,4*S*)-**111** from (2*R*,4*R*)-**73** (Scheme 49). First Jones oxidation of (2*S*,4*R*)-**95** gave (2*S*)-**108** in 76% yield and then the addition of (4-$MeOC_6H_4$)MgBr/$CeCl_3$ (1.05 equiv.) in THF to (2*S*)-**108** led to (2*S*,4*R*)-**109** in 25% yield, thereby 52% of (2*S*)-**108** was recovered. However, this reaction led to 5% of a side product, which came from a simultaneous addition reaction to the ester group. Therefore, an addition reaction of a Grignard reagent (1.05 equiv.) to (2*S*)-**108** was carried out at –78 °C (for 4 hours in ether) and gave (2*S*,4*R*)-**109** in low yield (38%). After purification by column chromatography and subsequent prep. HPLC, no other stereoisomer could be found but some starting material (2*S*)-**108** could be recovered (52%). In the next step (2*S*,4*R*)-**109** was subjected to an hydrolysis with 1.0 N NaOH (1.05 equiv.) to yield (2*S*,4*R*)-**110** (81%). A final hydrogenolysis of (2*S*,4*R*)-**110** over Pd-C in the presence of triethylamine gave the target compound (2*S*,4*R*)-**111** in 100% yield.

Scheme 48

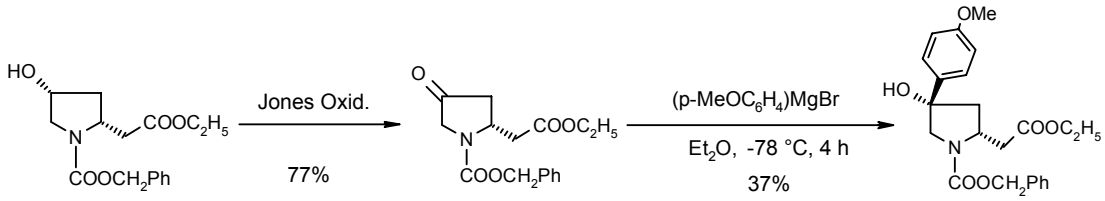


(2*S*,4*R*)-95 **(2*S*)-108** **(2*S*,4*R*)-109**

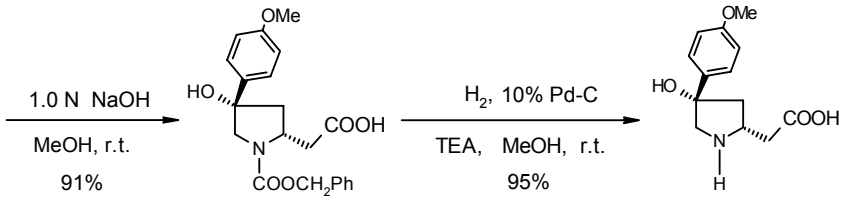
(2*S*,4*R*)-110 **(2*S*,4*R*)-111**

Along an analogous synthetic route to the one shown above the enantiomorphic (2*R*,4*S*)-**111** was prepared from (2*R*,4*R*)-**73** via (2*R*)-**112** and (2*R*,4*S*)-**113**. The overall yield (25%) was close to the one (overall yield 23%) obtained in the first sequence (Scheme 48).

Scheme 49



(2*R*,4*R*)-73 **(2*R*)-112** **(2*R*,4*S*)-113**



(2*R*,4*S*)-110 **(2*R*,4*S*)-111**

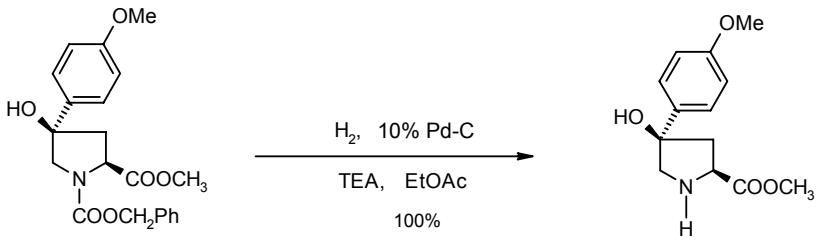
3.5 Determination of the stereochemistry of 4-arylsubstituted pyrrolidine derivatives obtained by addition of organometallic reagents to 4-oxopyrrolidines

3.5.1 Determination of the stereochemistry at C-4 of (2*S*,4*R*)-53a-b, (2*S*,4*S*)-53a-b and (2*S*,4*R*)-63.

The additions of the organometallic reagent to the C-4 position of (2*S*)-**52a-b** and (2*R*)-**52a-b** described in Section 3.2.2 yielded pairs of diastereomers of **53a-b**, from which a pair of diastereomers (2*S*,4*R*)-**53a** and (2*S*,4*S*)-**53a** were selected for further investigation of the stereochemistry at C-4 of these compounds. The stereochemistry found for (2*S*,4*R*)-**53a** and (2*S*,4*S*)-**53a** might finally serve as a basis, on which the stereochemistry of the remaining compounds **53a-b**, **57a-b** and **63** may be deduced. NOE (nuclear overhauser effect) technology is a very convenient method for the determination of the relative stereochemistry of a compound. According to the known configuration at C-2, NOE measurements for (2*S*,4*R*)-**53a** and (2*S*,4*S*)-**53a** might give a solution for their configuration at C-4. Unfortunately, the signals in the NOE spectra were too weak and not meaningful with respect to the configuration at C-4. But these measurements gave another information, which allowed the assignment of the signals that arose from the protons of the two-methoxy groups (COOCH_3 and ArOCH_3) in the ^{1}H NMR spectra.

Each of the **57a-b** series must exhibit the same stereochemistry as the corresponding one of the **53a-b** series**,** which was obtained from the basic hydrolysis of the formers without any influence on the stereochemistry. Thus, I attempted to determine the stereochemistry of these hydrolysis products. If one of two diastereomers (2*S*,4*R*)-**57a** and (2*S*,4*S*)-**57a** could be transformed to a lactone, then the hydrolysis of the obtained lactone under basic condition must give (2*S*,4*R*)-**57a**, which would be identical with one of the two diastereomers used as starting materials. Consequently, the stereochemistry of both **57a-b** and **53a-b** series would become known. However, all attempts from (2*S*,4*R*)-**57a** or (2*S*,4*S*)-**57a** employing CDI or Ph_3P/DEAD or DCC as a dehydrating agent failed to form a lactone.

Scheme 50



(2*S*,4*R*)-61 **(2*S*,4*R*)-114**

To eliminate the disturbance from the phenyl groups of the N-substituent in NOE measurements, finally I prepared (2*S*,4*R*)-**114** (100% yield) from (2*S*,4*R*)-**61** by hydrogenation over 10% Pd-C in the presence of triethylamine. The explicit ^{1}H NMR spectrum (Fig. 3.5) and the quantitative yield clearly indicate that the configuration at C-4 of (2*S*,4*R*)-**61** remained unchanged through the hydrogenation process. In a preliminary experiment, however, when the deprotection reaction had been carried out in methanol in the absence of triethylamine, a mixture consisting of **114** and its 4-dehydroxylated product were obtained, unluckily, they were not separable. A clear proof from the NOE spectrum of (2*S*,4*R*)-**114** (Fig. 3.6) reveals that the 4-aromatic group is located *cis* to H-2.

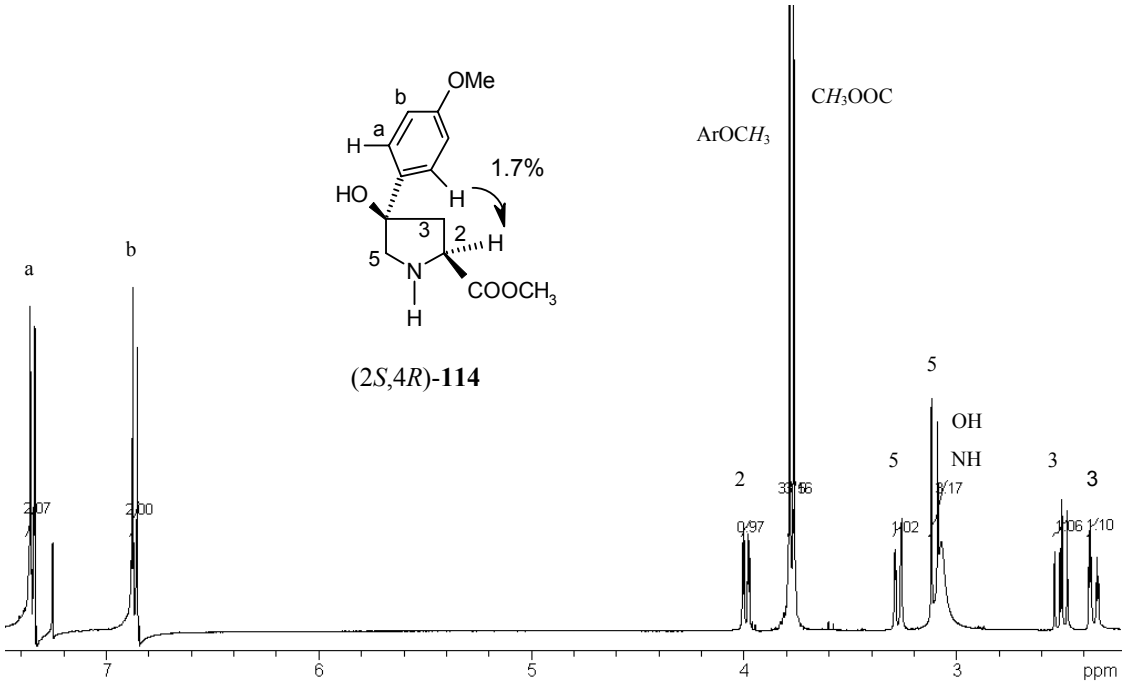


Fig. 3.5. The ^{1}H NMR spectrum of (2*S*,4*R*)-**114** ($CDCl_3$).

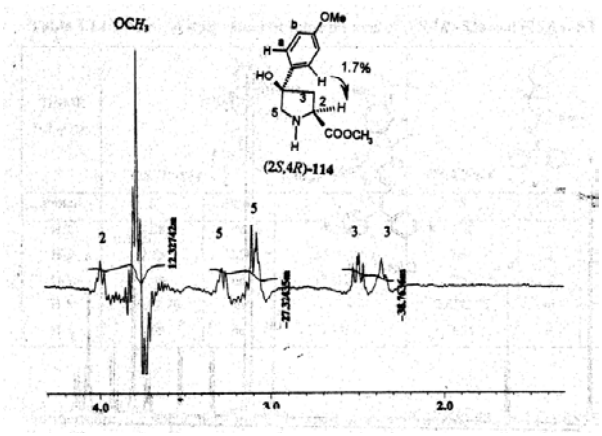
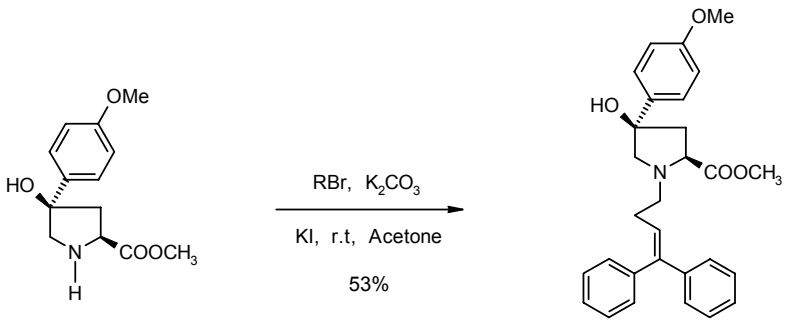


Fig. 3.6 The NOE spectrum of (2*S*,4*R*)-**114** ($CDCl_3$).

In analogy to the preparation of (2*S*,4*R*)-**39** (Scheme 3), (2*S*,4*R*)-**114** was N-alkylated with the bromide of **24a** to give (2*S*,4*R*)-**53a** in 53% yield. This product was found to be identical with the major diastereomer obtained from the addition reaction of (*p*-$MeOC_6H_4$)$MgBr/CeCl_3$ (THF) to (2*S*)-**52a** by comparison of their analytical data {^{1}H NMR, IR, MS, [α], M.p and elementary analysis}. Thus, the second isomer of this pair of diastereomers was unequivocally identified as (2*S*,4*S*)-**53a**.

Scheme 51



(**2*S*,4*R***)-**114** (**2*S*,4*R***)-**53a**

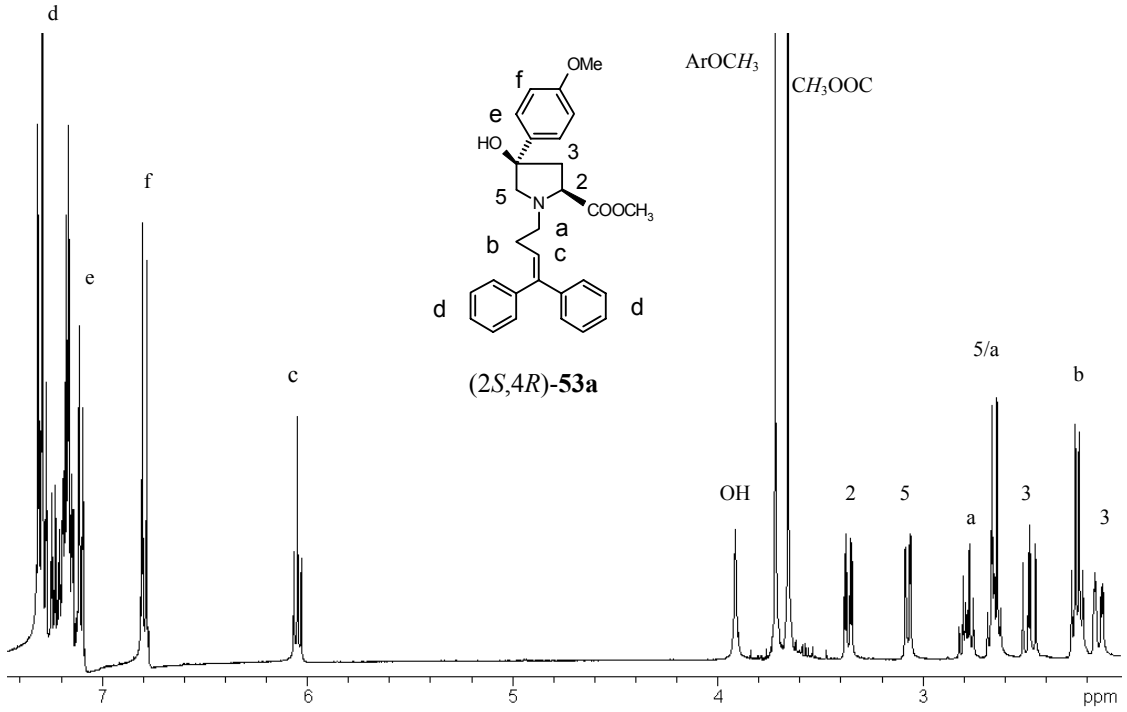


Fig. 3.7. The ^{1}H NMR spectrum of (2*S*,4*R*)-**53a** ($CDCl_3$).

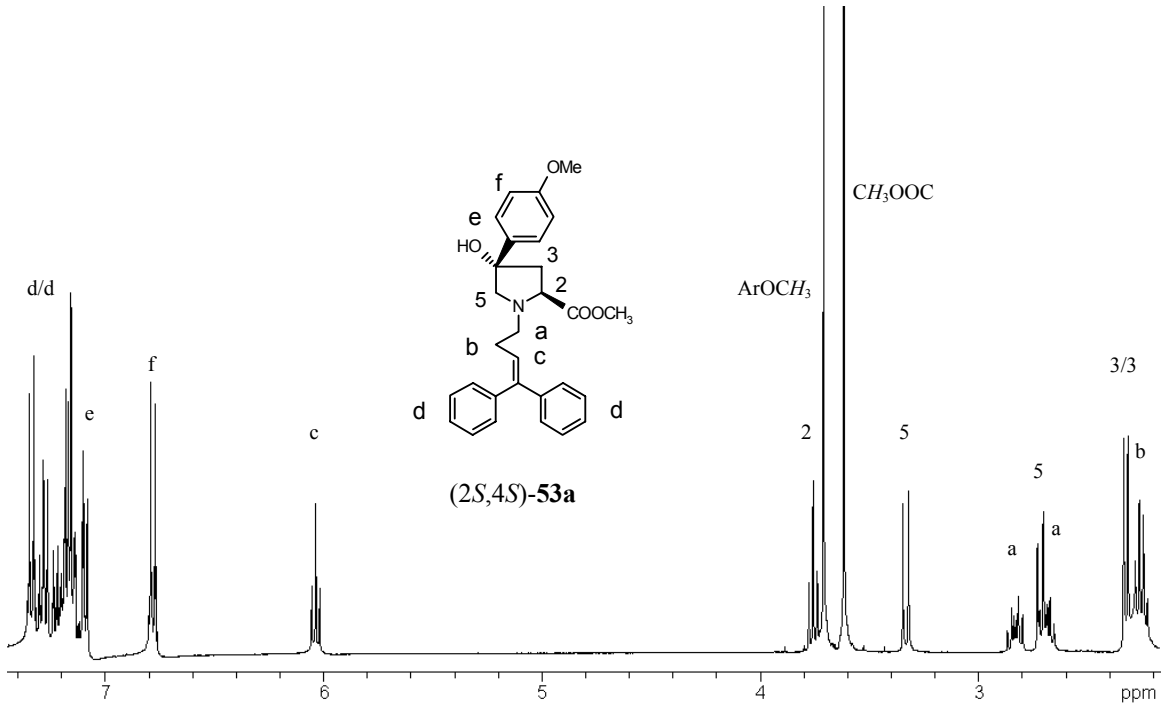
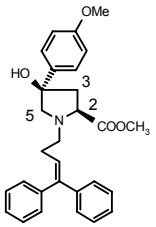
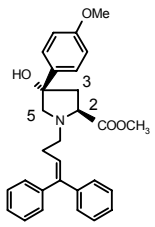


Fig. 3.8. The ^{1}H NMR spectrum of (2*S*,4*S*)-**53a** ($CDCl_3$).

Table 3.14 Chemical shift values of some protons of (2*S*,4*R*)-**53a** and (2*S*,4*S*)-**53a**.

^{1}HNMR (CD_3OD)	(2*S*,4*R*)-**53a**  $[\alpha]_D^{20}$ = -49.4			(2*S*,4*S*)-**53a**  $[\alpha]_D^{20}$ = -1.8		
Proton	δ	Peak	*J* Hz	δ	Peak	*J* Hz
H-2	3.38	dd	10.7/3.2	3.78	t	7.7
H-3	2.15	ddd	13.9/3.2/2.0	2.34	d	7.7
H-3	2.49	dd	13.9/10.7	2.34	d	7.7
H-5	2.63-2.70	m		2.67-2.75	m	
H-5	3.09	dd	9.2/2.0	3.35	d	10.3

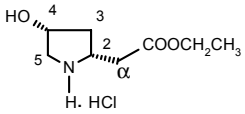
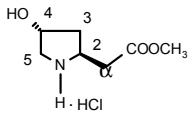
Furthermore, the phenomena in the ^{1}H NMR spectra of (2*S*,4*R*)-**53a** and (2*S*,4*S*)-**53a** (Fig. 3.7 and 3.8, and Table 3.12) support the above conclusions. H-2 (δ 3.38) of (2*S*,4*R*)-**53a** is situated at higher field than H-2 (δ 3.78) of (2*S*,4*S*)-**53a**. The aromatic group of (2*S*,4*R*)-**53a** might account for the result of a magnetic shielding when it is located *cis* to H-2. Moreover, the hydroxy proton of (2*S*,4*R*)-**53a** was found to be at lower field than that of (2*S*,4*S*)-**53a**, which might be attributed to an intramolecular hydrogen bond between the 4-hydroxy group and the carbonyl group.

Finally the configuration of the products (2*S*,4*R*)-**63** and (2*R*,4*S*)-**63** must be as given. These compounds have been prepared from (2*S*,4*R*)-**61** and (2*R*,4*S*)-**61**, respectively, by a synthetic sequence — hydrolysis of the ester function, reductive removal of the Cbz group — that should not affect the stereocenters. Thus, the stereochemistry assigned for (2*S*,4*R*)-**61** and (2*R*,4*S*)-**61** (see Scheme 17) must apply to (2*S*,4*R*)-**63** and (2*R*,4*S*)-**63**.

3.5.2 Elucidation of the stereochemistry of (2*S*,4*R*)-86 and (2*R*,4*R*)-64.

The proof for the stereochemistry of (2*S*,4*R*)-**86** has been presented in section 3.3.3.3. It seems reasonable that the relative configuration of (2*R*,4*R*)-**64** at C-2 can be deduced by a comparison of its ^{1}H NMR spectrum with the data of (2*S*,4*R*)-**86** (Fig.3.9 and 3.10). The chemical shifts and coupling constants for some protons of (2*S*,4*R*)-**86** and (2*R*,4*R*)-**64** are distinctly different. These manifest that **64** must be of *cis* stereochemistry because (2*S*,4*R*)-**86** is *trans* substituted,

Table 3.15 Chemical shift values of some protons of (2*S*,4*R*)-**86** and (2*R*,4*R*)-**64**.

^{1}H NMR (CD_3OD)	 (2*R*,4*R*)-**64** $[\alpha]_D^{20}$ = -34.0			 (2*S*,4*R*)-**86** $[\alpha]_D^{20}$ = +42.8		
Proton	δ	Peak	*J* Hz	δ	Peak	*J* Hz
H-2	4.00-4.08	m		3.99-4.07	m	
H-3	1.79	ddt	14.1/4.7/1.9	1.71	ddd	13.7/11.4/4.0
H-3	2.43	ddd	14.1/9.8/5.0	2.09	ddt	13.7/6.4/1.5
H-4	4.50-4.53	m		4.38-4.41	m	
H-5	3.22	dd	11.9/3.6	3.09	dd	12.2/1.5
H-5	3.27	dt	11.9/1.9	3.25	dd	12.2/3.7
H-α	2.92	dd	18.0/5.2	2.69	dd	18.0/9.9
H-α	2.98	dd	18.0/9.4	2.82	dd	18.0/4.0

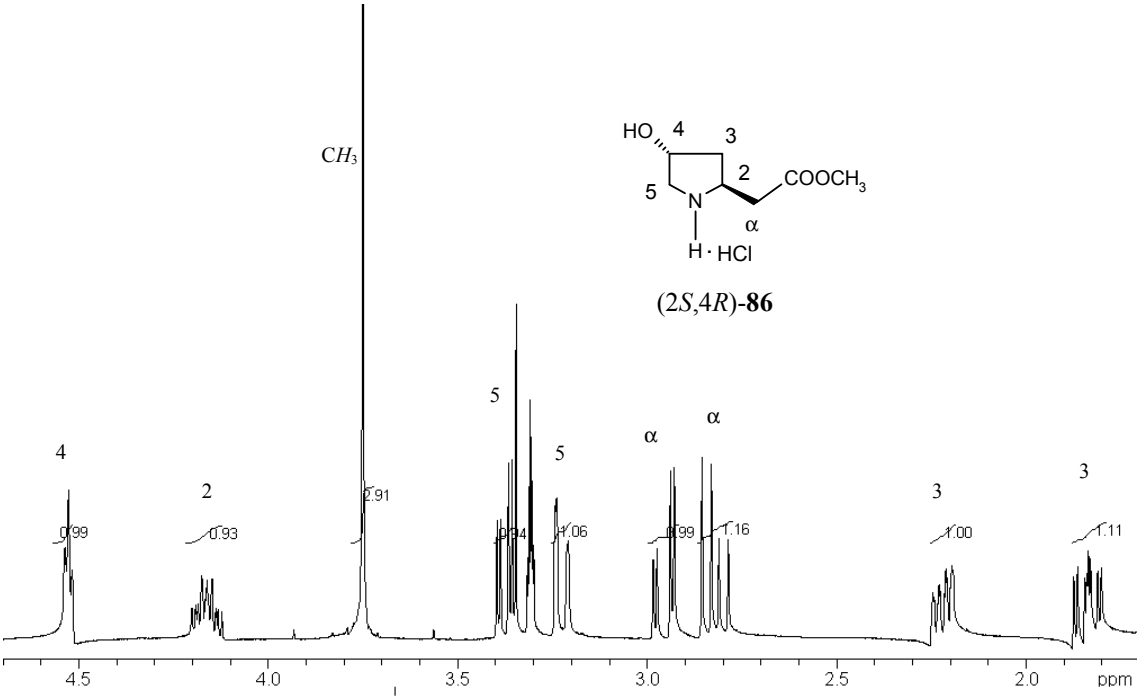


Fig. 3.9. The ^{1}H NMR spectrum of (2*S*,4*R*)-**86** (CD_3OD).

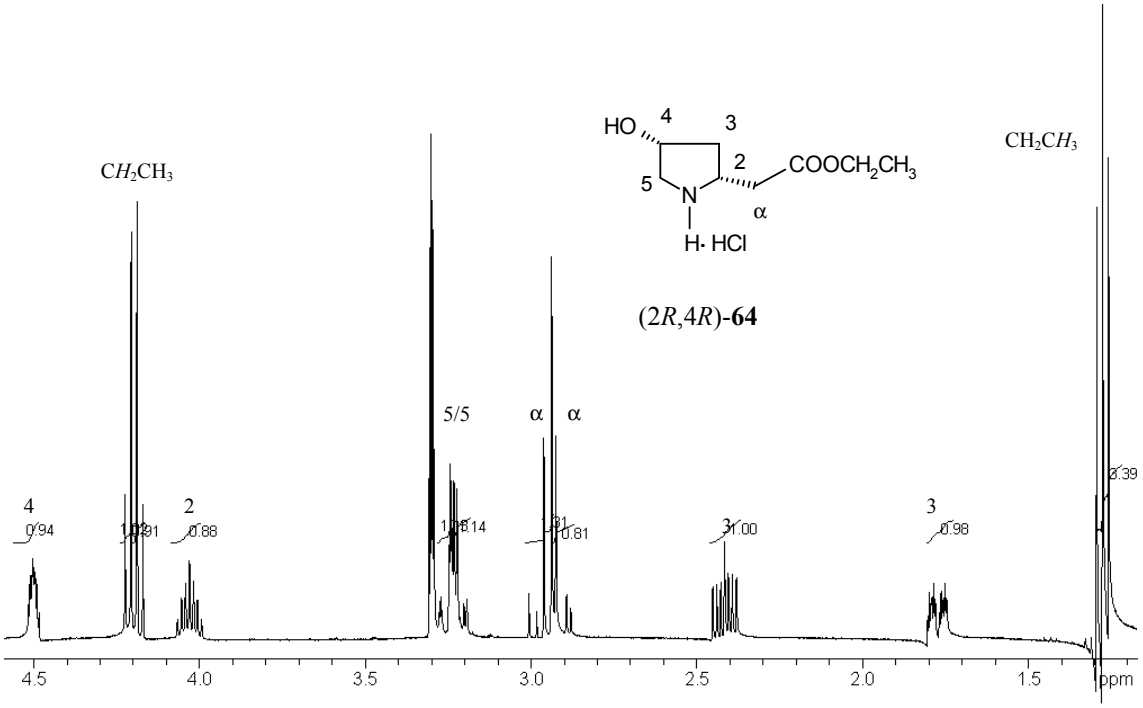
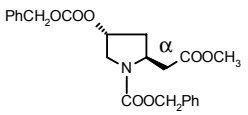
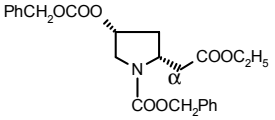


Fig. 3.10. The ^{1}H NMR spectrum of (2*R*,4*R*)-**64** (CD_3OD).

(2*S*,4*R*)-**82** (see Table 3.16) has been prepared from (2*S*,4*R*)-**58** via Wolf rearrangement (Scheme 27) as well as from (2S,4*R*)-**86** by O,N-protection (Scheme 34) and in both processes the configuration (2*S*,4*R*) remained unchanged. Thus, the known configuration of (2*S*,4*R*)-**86** must apply to (2*S*,4*R*)-**82** as well. Finally, the stereochemistry of (2*R*,4*R*)-**80** $\{[\alpha]_D^{20} = +21.2\}$ may be deduced from the configuration of (2*S*,4*R*)-**82** $\{[\alpha]_D^{20} = -43.0\}$. As a result of their synthesis (2*S*,4*R*)-**82** and (2*R*,4*R*)-**80** must be both of (2*R*)-configuration at C-4. ^{1}H NMR spectra of the two compounds are quite different regarding some signals (e.g. H-3 and H-5), demonstrating the opposite relation of their stereochemistry at C-2. Accordingly, (2*R*,4*R*)-**80** must be of the shown stereochemistry. The following Table 3.16 displays the ^{1}H NMR spectra of (2*S*,4*R*)-**82** and (2*R*,4*R*)-**80**.

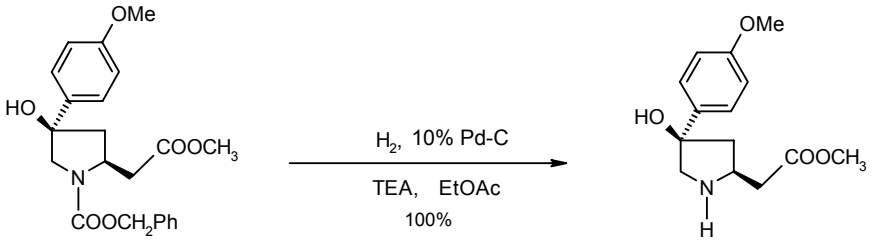
Table 3.16 Chemical shift values of some protons of (2*S*,4*R*)-**82** and (2*R*,4*R*)-**80**.

^{1}H NMR (CD_3OD)	 (2*S*,4*R*)-**82** $[\alpha]_D^{20}$ = -43.0			 (2*R*,4*R*)-**80** $[\alpha]_D^{20}$ = +21.2		
Proton	δ	Peak	*J* Hz	δ	Peak	*J* Hz
H-2	4.45-4.52	m		4.47-4.54		
H-3	2.25-2.32	m		2.29	br. d	15.4
H-3	2.49-2.56	m		2.49-2.57	m	
H-4	5.31-5.35	m		5.30-5.35	m	
H-5	3.79	dd	12.4/5.4	3.72	dd	12.6/1.1
H-5	3.98	dt	12.4/2.0	3.96	dd	12.6/5.3
H-α	2.68	dd	15.4/8.6	2.73	dd	15.2/9.7
H-α	3.06	dd	15.4/3.9	3.13	dd	15.2/3.7

3.5.3 Determination of the stereochemistry at C-4 of (2*S*,4*R*)-102b-c and (2*S*,4*S*)-102b-c

(2*S*,4*R*)-**109** was transformed into (2*S*,4*R*)-**115** in 100% yield by hydrogenation over 10% Pd-C in the presence of triethylamine. Unfortunately, the signal of H-2 (δ 3.61-3.83) overlapped with the signal of the ArOC*H*$_3$ (δ 3.69) in the ^{1}H NMR spectrum of (2*S*,4*R*)-**115** ($CDCl_3$ or CD_3OD as solvent), therefore, the NOE experiments could not provide any meaningful information.

Scheme 52



(**2*S*,4*R***)-**109** (**2*S*,4*R***)-**115**

It is likely practicable that the NOE experiments were performed with (2*S*,4*R*)-**102c** and (2*S*,4*S*)-**102c**. In the cases of these two compounds, the NOE signals were too weak to make a reliable decision for their stereochemistry.

There was an alternative way to determine the configuration at C-4 of (2*S*,4*R*)-**115**. (2*S*,4*R*)-**111** (Fig. 3.12), prepared from (2*S*,4*R*)-**109** by hydrolysis of the ester group under basic condition and subsequent hydrogenation for N-deprotection (in the presence of triethylamine, Scheme 48), possesses the same configuration at C-2 and C-4 as (2*S*,4*R*)-**115**. Owing to its poor solubility in common ^{1}H NMR solvents ($CDCl_3$, CD_3OD or DMSO-d_6), the ^{1}H NMR spectrum of (2*S*,4*R*)-**111** as a sodium salt was taken in CD_3OD. Fortunately, H-2 moved to a higher field (δ 3.54-3.61), away from the peak (δ 3.77) of C*H*$_3$OAr (Fig. 3.12). In an NOE experiment with (2*S*,4*R*)-**111**, irradiation of the signal pertaining to H-2 enhanced the H-a signal of the aromatic group by 2.4%, revealing that H-2 and the phenyl substituent are *cis* to each other (Fig. 3.13).

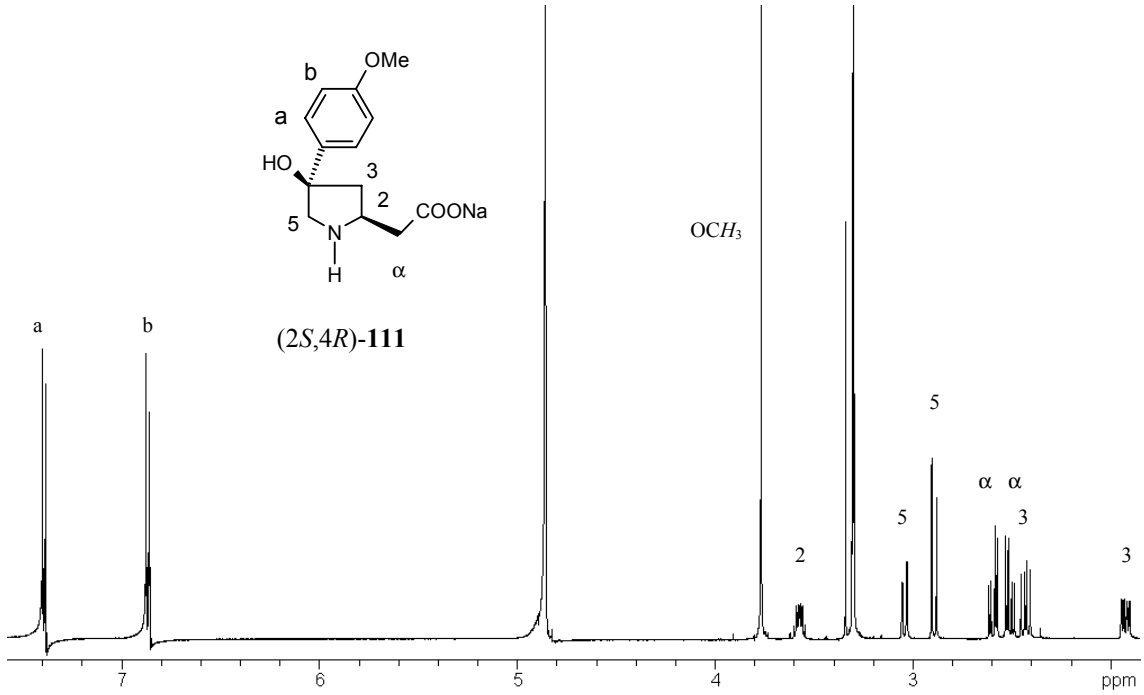


Fig. 3.12. The ^{1}H NMR spectrum of (2*S*,4*R*)-**111** (CD_3OD).

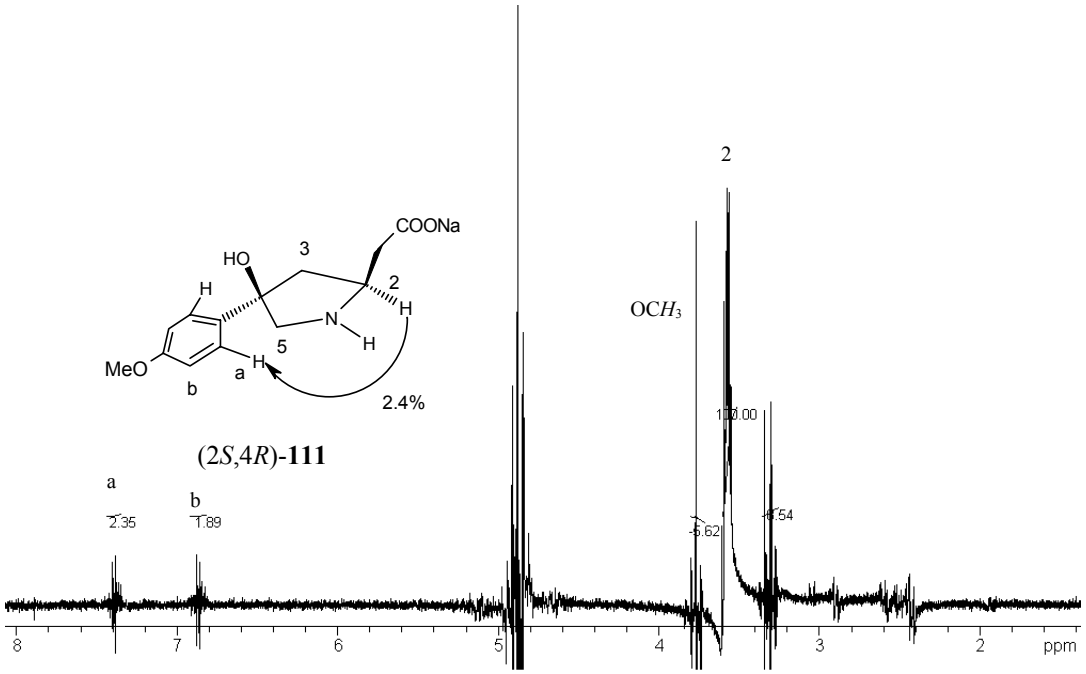
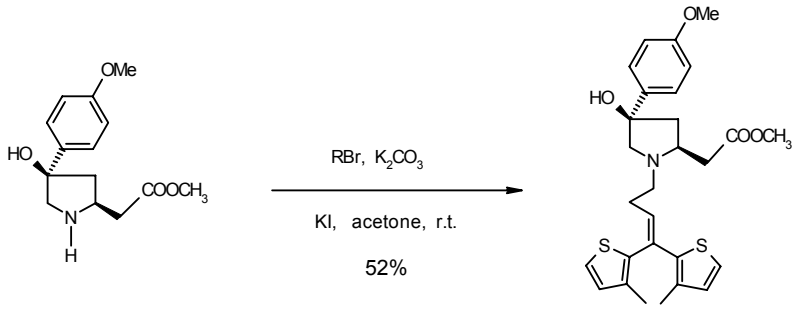


Fig. 3.13 The NOE spectrum of (2*S*,4*R*)-**111** (CD_3OD).

Analytical data {^{1}H NMR, IR, MS, [α]} of (2*S*,4*R*)-**102c** obtained by N-alkylation of (2*S*,4*R*)-**115** were identical with those of the major isomer formed by an addition of (4-$MeOC_6H_4$)$MgBr/CeCl_3$ (in THF) to (2*S*)-**100c**. Therefore, the minor isomer (2*S*,4*S*)-**102c** of this addition reaction may be assigned as the shown stereochemistry. The stereochemistry of the related compounds — (2*S*,4*R*)-**102b** and (2*S*,4*S*)-**102b**, (2*R*,4*S*)-**103b-c** and (2*R*,4*R*)-**103b-c** — became known from a comparison of their ^{1}H NMR data with those of (2*S*,4*R*)-**102c** and (2*S*,4*S*)-**102c**.

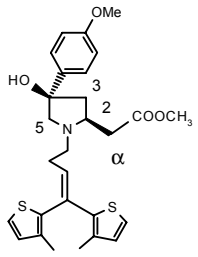
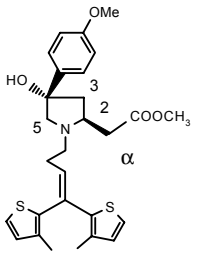
Scheme 53



(2*S*,4*R*)-115 **(2*S*,4*R*)-102c**

R = **24c**

Table 3.17 chemical shift values of some protons of (2*S*,4*R*)-**102c** and (2*S*,4*S*)-**102c**

^{1}H NMR (CD_3OD)	 (2*S*,4*R*)-**102c** $[\alpha]_D^{20}$ = +73.1			 (2*S*,4*S*)-**102c** $[\alpha]_D^{20}$ = -50.4		
Proton	δ	Peak	*J* Hz	δ	Peak	*J* Hz
H-2	2.90-3.02	m		3.35-3.42	m	
H-3	2.09	ddd	14.2/5.2/2.0	2.04	dd	13.2/9.5
H-3	2.50-2.60	m		2.27-2.35	m	
H-5	2.39-2.46	m		2.67-2.72	m	
H-5	3.13	dd	9.4/2.0	3.35-3.42	m	
H-α	2.50-2.60	m		2.27-2.35	m	
H-α	2.73	dd	15.7/3.5	2.67-2.72	m	

The above setereochemical assignment for (2*S*,4*R*)-**102c** and (2*S*,4*S*)-**102c** is also supported by the chemical shift values found for H-2. Because of the shielding effect of the aromatic group at C-4, H-2 (δ 2.90-3.02) of (2*S*,4*R*)-**102c** is located at higher field in the ^{1}H NMR spectrum than H-2 (δ 3.35-3.42) of (2*S*,4*S*)-**102c**.

4. DISCUSSION OF THE BIOLOGICAL RESULTS

4.1 Introduction

It is known for a long time that transport proteins for neurotransmitters mediating active uptake are present in the synapses in the CNS. As described before (Section 1), so far for GABA uptake four characteristic transport proteins have been discovered. The different genes as well as the corresponding transport proteins, which can be expressed in mammalian cells, have been respectively termed GAT-1, GAT-2, GAT-3 and BGT-1 [32, 33, 34]. It has been accepted that GAT-1 and GAT-3 are the most important GABA transporters. The functional differences of GAT-1 and GAT-3 are still unknown, but it has been detected that these transporters differ with respect to their distribution in distinct regions and subcelluar structures of the brain.

The GABA uptake experiments described below were performed to investigate the potency and selectivity of the synthesized compounds with respect to their inhibition of GABA uptake mediated by GAT-1 and GAT-3.

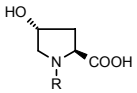
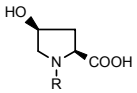
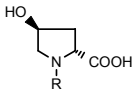
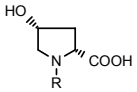
4.2 Procedure and evaluation

The experimental procedure for the inhibition of GABA uptake was developed on the basis of subcellular fractions from frontal cortex and brain stem of bovine brain (Experimental Section 5.2.1). Membrane fractions from frontal cortex were utilized to study the inhibitory potency of test compounds regarding GAT-1-mediated GABA-uptake. After the incubation of the prepared membrane fractions with a test compound, the incubation with [^{3}H] GABA and GABA followed.

To study the inhibitory potency of test compounds regarding GAT-3-mediated GABA-uptake, membrane fractions from brain stem were applied. Additionally, the incubation was performed in the presence of NNC-711, a GAT-1 selective inhibitor, to block GABA uptake mediated by GAT-1 so that the inhibitory effect on GAT-3 mediated GABA-uptake could be evaluated (Experimental Section 5.2.2.2). After the incubation of the prepared membrane fractions with a test compound, the incubation with [^{3}H] GABA and GABA followed.

The biological results are listed in Table 4.1, 4.2 and 4.3. All the results of the measurements were processed and evaluated in triplicate.

Table 4.1 The inhibition of GABA uptake by 4-hydroxypyrrolidine-2-carboxylic acid derivatives: **25** and **40a-b** series.

	H		-$CH_2CH_2CH{=}CPh_2$		-$CH_2CH_2OC(C_6H_4$-p-$OMe)_3$	
	IC_{50} μM		IC_{50} μM		IC_{50} μM	
	GAT-1	GAT-3	GAT-1	GAT-3	GAT-1	GAT-3
	4328±708 [a] (2*S*,4*R*)-**25**	1340±290 [b] (2*S*,4*R*)-**25**	79.6 [a] (2*S*,4*R*)-**40a**	> 100 [b] (2*S*,4*R*)-**40a**	> 100 [a] (2*S*,4*R*)-**40b**	> 100 [b] (2*S*,4*R*)-**40b**
	----------	----------	> 100 [a] (2*S*,4*S*)-**40a**	> 100 [b] (2*S*,4*S*)-**40a**	> 100 [a] (2*S*,4*S*)-**40b**	> 100 [b] (2*S*,4*S*)-**40b**
	----------	----------	> 100 [a] (2*R*,4*S*)-**40a**	> 100 [b] (2*R*,4*S*)-**40a**	> 100 [a] (2*R*,4*S*)-**40b**	> 100 [b] (2*R*,4*S*)-**40b**
	> 10 mM [a] (2*R*,4*R*)-**25**[1]	> 10 mM [b] (2*R*,4*R*)-**25**[1]	9.4±0.4 [a] (2*R*,4*R*)-**40a**	313±39 [b] (2*R*,4*R*)-**40a**	> 100 [a] (2*R*,4*R*)-**40b**	> 100 [b] (2*R*,4*R*)-**40b**

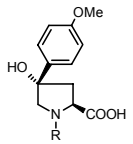
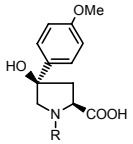
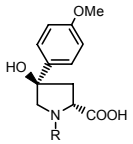
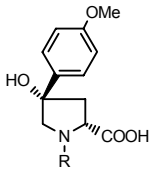
Note:

The abbreviations a-f specify the used biological material (for their entire names: see Section 5.2.1).

a. bfcP2B (from bovine brain)
b. bbsP2C (from bovine brain)
c. pfcP2B (from porcine brain)
d. pbsP2C (from porcine brain)
e. cfcP2B (from calf brain)
f. cbsP2C (from calf brain)

1. The concentration of the inhibitory substance was 10 mM for the test.
2. If not specified otherwise, the concentration of each test compound was 100 μM.
3. Each IC_{50} was given as mean±SEM. If the IC_{50} value was larger than 100 μM, no exact value was given.

Table 4.2 The inhibition of GABA uptake by 4-hydroxypyrrolidine-2-carboxylic acid derivatives: **57a-b** series, (2*S*,4*R*)-**63** and (2*R*,4*S*)-**63**.

	H		-CH_2CH_2CH=CPh_2		-$CH_2CH_2OC(C_6H_4$-p-$OMe)_3$	
	IC_{50} μM		IC_{50} μM		IC_{50} μM	
	GAT-1	GAT-3	GAT-1	GAT-3	GAT-1	GAT-3
	----------	----------	> 100 [a] (2*S*,4*S*)-**57a**	> 100 [b] (2*S*,4*S*)-**57a**	68.1±4.4 [a] (2*S*,4*S*)-**57b**	63.3±5.8 [b] (2*S*,4*S*)-**57b**
	> 100 [c] (2*S*,4*R*)-**63**	> 100 [d] (2*S*,4*R*)-**63**	> 100 [a] (2*S*,4*R*)-**57a**	237±160 [b] (2*S*,4*R*)-**57a**	45.1±2.7 [a] (2*S*,4*R*)-**57b**	29.7±0.8 [b] (2*S*,4*R*)-**57b**
	----------	----------	> 100 [e] (2*R*,4*R*)-**57a**	> 100 [f] (2*R*,4*R*)-**57a**	71±1.4 [c] (2*R*,4*R*)-**57b**	> 100 [b] (2*R*,4*R*)-**57b**
	> 100 [c] (2*R*,4*S*)-**63**	> 100 [d] (2*R*,4*S*)-**63**	> 100 [e] (2*R*,4*S*)-**57a**	> 100 [f] (2*R*,4*S*)-**57a**	56±4.3 [c] (2*R*,4*S*)-**57b**	38.0±5.8 [d] (2*R*,4*S*)-**57b**

Note:

The abbreviations a-f specify the used biological material (for their entire names: see Section 5.2.1.

a. bfcP2B (from bovine brain)

b. bbsP2C (from bovine brain)

c. pfcP2B from porcine brain)

d. pbsP2C (from porcine brain)

e. cfcP2B (from calf brain)

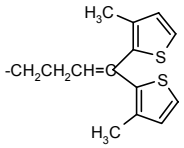
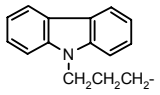
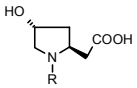
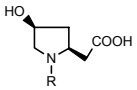
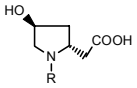
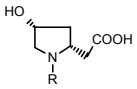
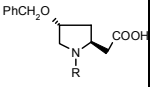
f. fcbsP2C (from calf brain)

1. The concentration of the inhibitory substance was 10 mM for the test.

2. If not specified, the concentration of each test compound was 100 μM.

3. Each IC_{50} was given as mean±SEM. If the IC_{50} value was larger than 100 μM, no exact value was given.

Table 4.3 The inhibition of GABA uptake by 4-hydroxypyrrolidine-2-acetic acid derivatives: **89a-d**, **94a** and c, and **97** series.

	H		-CH_2CH_2CH=CPh_2				-$CH_2CH_2OC(C_6H_4$-p-OMe$)_3$			
	IC_{50} μM		IC_{50} μM		IC_{50} μM		IC_{50} μM		IC_{50} μM	
	GAT-1	GAT-3	GAT-1	GAT-3	GAT-1	GAT-3	GAT-1	GAT-3	GAT-1	GAT-3
	>1.0 mM [c] (2*S*,4*R*)-**97** [1]	> 1.0 mM [d] (2*S*,4*R*)-**97** [1]	3.29 ±0.54[a] (2*S*,4*R*)-**89a**	> 100 [b] (2*S*,4*R*)-**89a**	3.15±0.30[a] (2*S*,4*R*)-**89c**	> 100 [b] (2*S*,4*R*)-**89c**	> 100 [a] (2*S*,4*R*)-**89b**	> 100 [b] (2*S*,4*R*)-**89b**	> 100 [a] (2*S*,4*R*)-**89d**	> 100 [b] (2*S*,4*R*)-**89d**
	> 100 [c] (2*S*,4*S*)-**97**	> 100 [d] (2*S*,4*S*)-**97**	4.92±0.42 [a] (2*S*,4*S*)-**89a**	> 100 [b] (2*S*,4*S*)-**89a**	5.14±2.8 [c] (2*S*,4*S*)-**89c**	> 100 [b] (2*S*,4*S*)-**89c**	> 100 [c] (2*S*,4*S*)-**89b**	58.6±17.1[d] (2*S*,4*S*)-**89b**	> 100 [e] (2*S*,4*S*)-**89d**	> 100 [f] (2*S*,4*S*)-**89d**
	>1.0 mM [c] (2*R*,4*S*)-**97** [1]	> 1.0 mM [d] (2*R*,4*S*)-**97** [1]	28.9±11.6[a] (2*R*,4*S*)-**89a**	> 100 [f] (2*R*,4*S*)-**89a**	6.56±0.7 [a] (2*R*,4*S*)-**89c**	> 100 [b] (2*R*,4*S*)-**89c**	> 100 [c] (2*R*,4*S*)-**89b**	19.9±1.1 [d] (2*R*,4*S*)-**89b**	> 100 [a] (2*R*,4*S*)-**89d**	> 100 [b] (2*R*,4*S*)-**89d**
	> 100 [c] (2*R*,4*R*)-**97**	> 100 [d] (2*R*,4*R*)-**97**	40.7±8 [a] (2*R*,4*R*)-**89a**	> 100 [b] (2*R*,4*R*)-**89a**	96.6 [a] n=1 (2*R*,4*R*)-**89c**	> 100 [b] (2*R*,4*R*)-**89c**	> 100 [a] (2*R*,4*R*)-**89b**	126±7.0 [b] (2*R*,4*R*)-**89b**	> 100 [a] (2*R*,4*R*)-**89d**	> 100 [b] (2*R*,4*R*)-**89d**
	----------	----------	87.6±11.1[a] (2*S*,4*R*)-**94a**	148±33[b] (2*S*,4*R*)-**94a**	70±5.8 [a] (2*S*,4*R*)-**94c**	104±16[b] (2*S*,4*R*)-**94c**	----------	----------	----------	---------

Note:

The abbreviations a-f specify the used biological material (for their entire names: see Section 5.2.1).

a. bfcP2B (from bovine brain) c. pfcP2B (from porcine brain) e. cfcP2B (from calf brain)

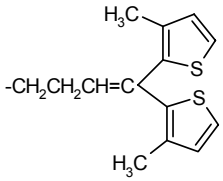
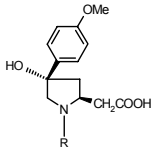
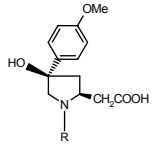
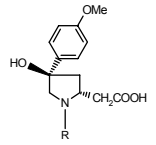
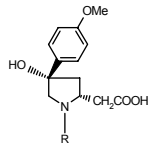
b. bbsP2C (from bovine brain) d. pbsP2C (from porcine brain) f. cbsP2C (from calf brain)

1. The concentration of the inhibitory substance was 10 mM for the test.

2. If not specified, the concentration of each test compound was 100 μM.

3. Each IC_{50} was given as mean±SEM. If the IC_{50} value was larger than 100 μM, no exact value was given.

Table 4.4 The inhibition of GABA uptake by 4-hydroxy-4-(4-methoxyphenyl)pyrrolidine-2-acetic acid derivatives: **104b-c** and **111** series.

	H				$-CH_2CH_2OC(C_6H_4\text{-}p\text{-}OMe)_3$	
	IC_{50} μM		IC_{50} μM		IC_{50} μM	
	GAT-	GAT-	GAT-1	GAT-	GAT-1	GAT-3
	----------	----------	> 100 [c] (2*S*,4*S*)-**104c**	122±9 [d] (2*S*,4*S*)-**104c**	75.2±8.8 [c] (2*S*,4*S*)-**104b**	78.9±18.5 [d] (2*S*,4*S*)-**104b**
	> 100 [c] (2*S*,4*R*)-**111**	> 100 [d] (2*S*,4*R*)-**111**	> 100 [c] (2*S*,4*R*)-**104c**	124±15 [d] (2*S*,4*R*)-**104c**	48.4±1.6 [c] (2*S*,4*R*)-**104b**	66.7±11.2 [d] (2*S*,4*R*)-**104b**
	----------	----------	> 100 [c] (2*R*,4*R*)-**104c**	> 100 [d] (2*R*,4*R*)-**104c**	64.54±3.07 [c] (2*R*,4*R*)-**104b**	65.4±5.1 [d] (2*R*,4*R*)-**104b**
	> 100 [c] (2*R*,4*S*)-**111**	> 100 [d] (2*R*,4*S*)-**111**	89.7 [c], n = 1 (2*R*,4*S*)-**104c**	> 100 [d] (2*R*,4*S*)-**104c**	57.3±7.0 [c], n = 2 (2*R*,4*S*)-**104b**	66.1±3.5 [d] (2*R*,4*S*)-**104b**

Note

The abbreviations a-f specify the used biological material (for their entire names: see Section 5.2.1).

c. pfcP2B (from porcine brain)

d. psP2C (from porcine brain)

1. If not described, the concentration of each test compound was 100 μM.

2. Each IC_{50} was given as mean±SEM. If the IC_{50} value was larger than 100 μM, no exact value was given.

4.3 Discussion of the biological results

Owing to BSE event, calf brain was temporarily used instead of the bovine brain material for the biological tests and finally porcine brain material was chosen. No significant differences could be detected for a set of standard GABA uptake inhibitors with respect to their potency evaluated with membrane fractions from different species.

The biological data of the 4-unsubstituted pyrrolidine derivatives mentioned in the following discussion are listed in Table 2.1 (page 7)

Table 4.1 and 4.2:

Compared with the corresponding 4-unsubstituted pyrrolidines, the stereoisomers of series **40a**-**b** containing a 4-hydroxy group showed a big loss of inhibitory potency at both GAT-1 and GAT-3, e.g. (2*S,*4*R*)-**40a** (an IC_{50} of 79.6 μM at GAT-1) and (2*S*,4*S*)-**40a** (an IC_{50} > 100 μM at GAT-1). Thus, they are much weaker than the corresponding compound without a 4-hydroxy group (IC_{50} 2.56 μM).

Only (2*R*,4*R*)-**40a** was found to be approximately three-fold less potent at GAT-1 (IC_{50} 9.4 μM) than the corresponding compound without a 4-hydroxy group (2.97 μM). The known compounds (2*S*,4*R*)-**25** and (2*R*,4*R*)-**25** showed a very weak inhibitory effect at GAT-1 and GAT-3, if any at all.

The introduction of a 4-methoxyphenyl group into the C-4 position of (2*R*,4*R*)-**40a** (9.4 μM) led to a big drop of inhibitory effect for (2*R*,4*S*)-**57a** and (2*R*,4*R*)-**57a** at GAT-1 (IC_{50} > 100 μM), but for the rest of the **57a** stereoisomers, no significant change in the inhibitory potency at GAT-1 or GAT-3 was observed. In one word, a drastic decrease of inhibition at GAT-1 as well as GAT-3 occurred for all the stereoisomers of the **40a**-**b** series in contrast to the corresponding compounds without any substituent at C-4.

Compared with the **40b** series, some of the stereoisomers of the **57b** series showed a significantly increased inhibition at GAT-1 and GAT-3, e.g. (2*S*,4*R*)-**57b** (an IC_{50} of 29.7 μM at GAT-3) and (2*R*,4*S*)-**57b** (an IC_{50} of 38.0 μM at GAT-3). But there were no big changes about their inhibition at GAT-1 and GAT-3 as compared to the 4-unsubstituted compound with the (2*S*) configuration (23.0 μM at GAT-1) and the 4-unsubstituted compound with the (2*R*) configuration (18.5 μM at GAT-3). But it should be mentioned here that (2*R*,4*S*)-**57b** (IC_{50} 38.0 μM) and (2*S*,4*R*)-**57b** (IC_{50} 29.7 μM) are much stronger inhibitors at GAT-3 than their isomer (2*R*,4*R*)-**57b** (IC_{50} > 100 μM), which is actually more or less inactive. In contrast, the inhibitory potency of these two compounds at GAT-1 is very close, thus, no significant stereoselectivity at GAT-1 is seen.

No inhibition at GAT-1 as well as GAT-3 was observed for (2*S*,4*R*)-**63** and for (2*R*,4*S*)-**63** at a concentration of 100 μM, thus, these compounds are devoid of any significant inhibitory potency.

Table 4.3:

All the stereoisomers **97** with the 4-hydroxypyrrolidine-2-acetic acid skeletons showed no inhibitory potency at GAT-1 and GAT-3, though they were tested up to a rather high concentration. On the contrary the 4-unsubstituted compounds with the (2*S*) configuration showed a considerable potency (IC_{50} 74.2 μM at GAT-1).

After the extension of the 2-carboxylic acid side chains of (2*S*,4*R*)-**40a** and (2*S*,4*S*)-**40a** by one carbon, the resulting compounds (2*S*,4*R*)-**89a** and (2*S*,4*S*)-**89a** became more potent inhibitors at GAT-1 with IC_{50} values of 3.29 μM and 4.92 μM, respectively. Interestingly, the inhibitory potency displayed by (2*S,*4*S*)-**89a**, (2*S*,4*R*)-**89a**, (2*R,*4*S*)-**89a** and (2*R*,4*R*)-**89a** was only one order of magnitude lower than those of the corresponding 4-unsubstituted compounds with (2*S*) configuration (IC_{50} 0.40 μM at GAT-1) and (2*R*) configuration (3.05 μM). No significant changes in their inhibitory potency were observed in the **89b** series at GAT-1 as compared with the **40b** series. Due to the introduction of a 4-hydroxy group, the **89c** series showed the same big losses of inhibitory potency at GAT-1 as the **89a** series. Compounds of the **89a** and **89c** series with the (2*S*) configuration showed an about 10-fold potency at GAT-1 as those of the **89a** and **89c** series with the (2*R*)-configuration except (2*R*,4*S*)-**89c**. All these biological results indicate that the introduction of a 4-hydroxy group is harmful to the potency of GABA uptake inhibitors, and that the (2*S*) configuration is crucial for the derivatives of the pyrrolidine-2-acetic acids to be potent at GAT-1.

It was found that the inhibitory potency at GAT-3 for the **89b** series had significantly increased as compared to the **40b** series due to the elongation of the carboxylic acid side chain by one carbon; (2*R*,4*S*)-**89b** appears to be the most potent one at GAT-3 (IC_{50} 19.9 μM) among the **89a-d** series and it is much more potent than its diastereomer (2*R*,4*R*)-**89b** (IC_{50} > 126 μM). Furthermore, the stereoisomer of the **89b** series with the (2*R*) configuration containing a 4-hydroxy group also showed a big decrease in inhibitory potency at both GAT-1 (100 μM) and GAT-3 (19.9 μM) as referred to the corresponding 4-unsubstituted compound at GAT-1 (67.8 μM) and GAT-3 (3.0 μM). Therefore, the 4-hydroxy group present in the compounds of **89b** series seems to be detrimental to a potent binding to GAT-3.

(2*S*,4*S*)-**89a** and (2*S*,4*S*)-**89c** are much weaker at GAT-1 than SK&F 100591 (0.26 μM), possibly due to a longer distance between the hydroxyl group and the carboxylic group in (2*S*,4*S*)-**89a** and (2*S*,4*S*)-**89c** as compared to SK&F 100591.

For the compounds of the **89d** series with a carbazole moiety, no inhibition of GAT-1 and GAT-3 was observed when tested at the concentrations of 100 μM.

In (2*S*,4*R*)-**94a** (IC_{50} 87.6 μM at GAT-1) and (2*S*,4*R*)-**94c** (70.0 μM), the substitution of the 4-hydroxy group by a 4-benzyloxy group led to a weaker potency at GAT-1 by a factor of about 25 as compared with (2*S*,4*R*)-**89a** (3.29 μM) and (2*S*,4*R*)-**89c** (3.15 μM). In contrast, their potency at GAT-3 was not affected by the change of the 4-substituent.

Table 4.4:

A comparison of the **104c** series with the **89c** series reveals that the introduction of a 4-methoxyphenyl group to C-4 gives rise to a sharp drop of the inhibitory potency at GAT-1, but a little enhancement at GAT-3 except that (2*R*,4*S*)-**104c** showed no significant variation. The situation is different when the 4-methoxyphenyl substituent is introduced into the **89b** series, in most cases, an increase of the inhibitory potency at both GAT-1 and GAT-3 is seen for the **104b** series except for (2*R*,4*R*)-**104b**.

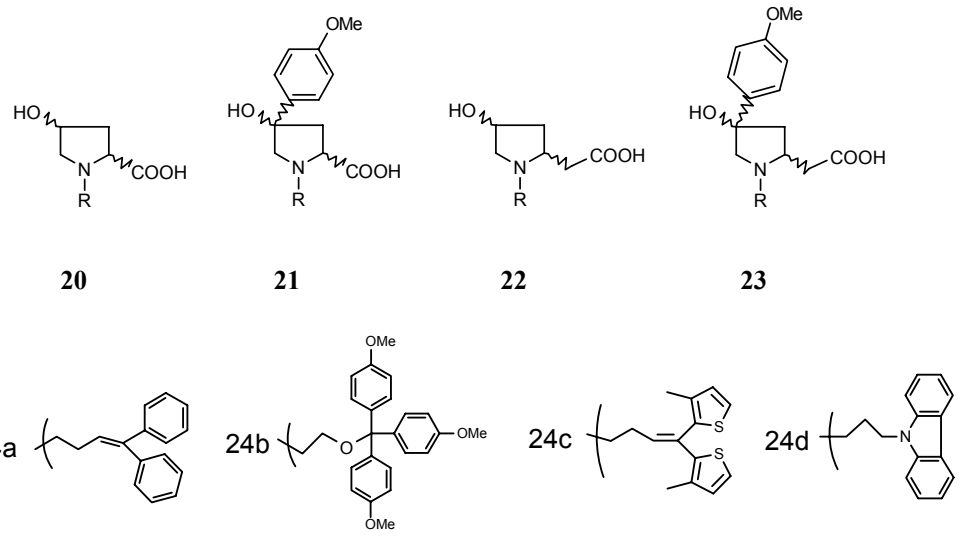
Finally for the basic compounds (2*S*,4*R*)-**111** and (2*R*,4*S*)-**111**, no inhibitory potency was observed at GAT-1 or GAT-3 up to the tested concentration. Thus, they behave the same as the compounds of series **97**

5. SUMMARY

GABA transporters GAT-1, GAT-2 and GAT-3 are new targets for drug design. The substitution of the nitrogen atoms in Nicopetic acid (**11**), Guvacine (**12**) and *cis*-4-Hydroxynicopetic acid (**13**) with appropriate bulky lipophilic groups resulted in very potent GABA uptake inhibitors for GAT-1 as well as for GAT-3. Pyrrolidine-2-acetic acid derivatives with the three N-substituents **24a-c** (Scheme 54) also showed a highly potent inhibition at GAT-1 and GAT-3, respectively.

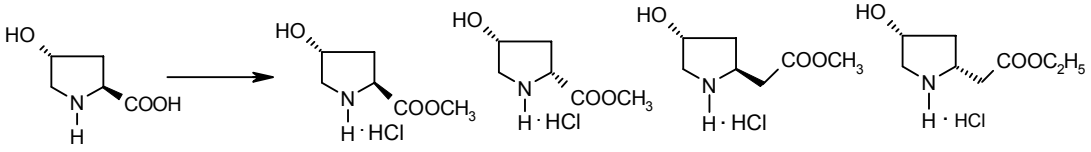
My intention was to investigate how the potency of pyrrolindine-2-carboxylic acid derivatives and of pyrrolidine-2-acetic acid derivatives at GAT-1 and GAT-3 is influenced by the introduction of a hydroxy group or both of a hydroxy and a (4-methoxy)phenyl group at C-4. For this study, the N-substituents **24a-d** were chosen. Thus, the four series of pyrrolidine derivatives **20-23** shown below were designed as potential GABA uptake inhibitors.

Scheme 54



L-*trans*-4-hydroxypyrrolidine [(2*S*,4*R*)-**25]** was chosen as a precursor, from which the four key intermediates (2*S*,4*R*)-**38**, (2*R*,4*R*)-**38**, (2*S*,4*R*)-**86** and (2*R*,4*R*)-**64** were synthesized.

Scheme 55

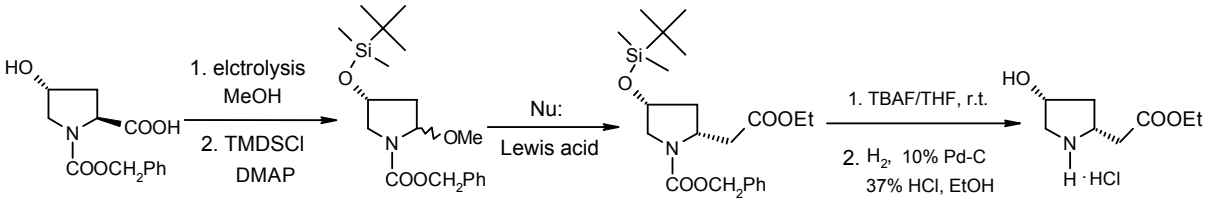


(**2*S*,4*R***)-**25** (**2*S*,4*R***)-**38** Lit. (**2*R*,4*R***)-**38** Lit. (**2*S*,4*R***)-**86** (**2*R*,4*R***)-**64**

The known compounds (2*S*,4*R*)-**38** and (2*R*,4*R*)-**38** were prepared from (2*S*,4*R*)-**25** according to literature procedures.

N-protection of (2*S*,4*R*)-**25** with Cbz group gave (2*S*,4*R*)-**58** (90% yield). After a series of reactions — electrolysis (97% yield), O-silyl protection (85%), nucleophilic addition of 1-ethoxy-1-(trimethylsilyloxy)ethene (*cis*-**71** 79%; *trans*-**71** 9%) and finally O-deprotection (88%) and N-deprotection (89%) — (2*R*,4*R*)-**64** was obtained in 46% overall yield [from (2*S*,4*R*)-**25**].

Scheme 56

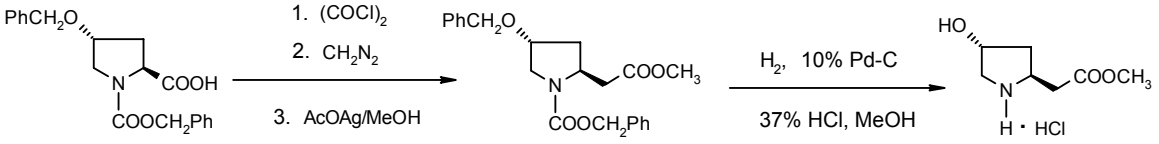


(**2*S*,4*R***)-**58** Lit. **70** *cis*-(**2*R*,4*R***)-**71 (major)** (**2*R*,4*R***)-**64**

After the reaction conditions for the conversion of **70** into **71** have been optimized, the best stereoselectivity [a ratio of *cis*/*trans* 97:3; yield *cis*-**71** 74%, *trans*-(2*S*,4*R*)-**71** 1.7%] and a good yield of 88% (*cis* 79%, *trans* 9%) were achieved. $BF_3{\cdot}Et_2O$ appeared to be slightly better for a higher stereoselectivity than $TiCl_4$.

(2*S*,4*R*)-**83** was obtained in 90% yield by protecting the hydroxy group of (2*S*,4*R*)-**58**. An *Arndt-Eistert* reaction (64% yield) starting from (2*S*,4*R*)-**83** followed by a simultaneous N,O-deprotection (90% yield) of (2*S*,4*R*)-**85** led to (2*S*,4*R*)-**86** in 47% overall yield [from (2*S*,4*R*)-**25**].

Scheme 57

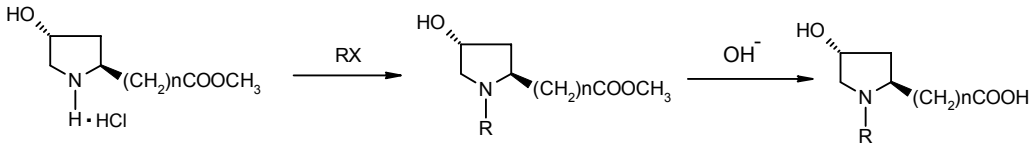


(**2*S*,4*R***)-**83** Lit. (**2*S*,4*R***)-**85** (**2*S*,4*R***)-**86**

As illustrated in Scheme 58 and 59, (2*S*,4*R*)-**38** and (2*S*,4*R*)-**86,** (2*R*,4*R*)-**38** and (2*R*,4*R*)-**64** were used as starting materials for the synthesis of the N-substituted target compounds (2*S*,4*R*)-**40a-b**, (2*S*,4*S*)-**40a-b**, (2*R*,4*S*)-**40a-b**, (2*R*,4*R*)-**40a-b**, (2*S*,4*R*)-**89a-d**, (2*S*,4*S*)-**89a-d**, (2*R*,4*R*)-**89a-d** and (2*R*,4*S*)-**89a-d**. N-alkylation of these four starting materials with the halides of **24a-d** yielded the corresponding tertiary amines. Mitsunobu reactions gave access

to the stereoisomers by inversion of the stereocenter at C-4 of the pyrrolidine ring. Finally upon hydrolysis, all the N-substituted pyrrolidine derivatives with a 2-carboxylic acid side chain or a 2-acetic acid side chain were obtained.

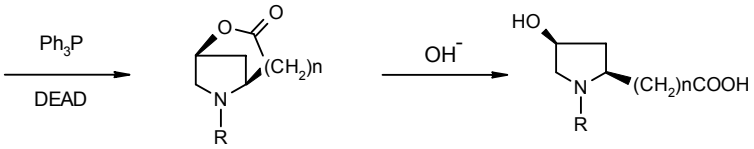
Scheme 58



(**2*S*,4*R*)-38**, n = 0
(**2*S*,4*R*)-86**, n = 1

(**2*S*,4*R*)-39a-b**
(**2*S*,4*R*)-91a-d**
(**2*S*,4*R*)-95** [Lit], R = Cbz, n = 1

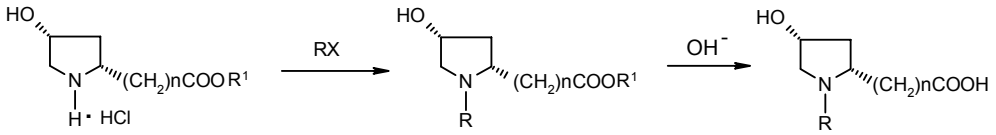
(**2*S*,4*R*)-40a-b**
(**2*S*,4*R*)-89a-d**
(**2*S*,4*R*)-96** [Lit]



(**1*S*,4*S*)-41a**
(**1*S*,5*S*)-92a-d**
(**1*S*,5*S*)-98**

(**2*S*,4*S*)-40a-b**
(**2*S*,4*S*)-89a-d**
(**2*S*,4*S*)-96**

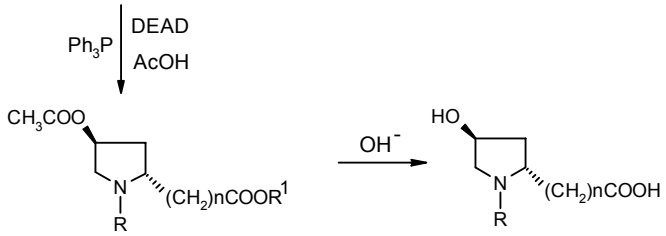
Scheme 59



(**2*R*,4*R*)-38**, n = 0
(**2*R*,4*R*)-64**, n = 1

(**2*R*,4*R*)-39a-b**
(**2*R*,4*R*)-88a-d**
(**2*R*,4*R*)-73**, R = Cbz, n = 1

(**2*R*,4*R*)-40a-b**
(**2*R*,4*R*)-89a-d**
(**2*R*,4*R*)-96**



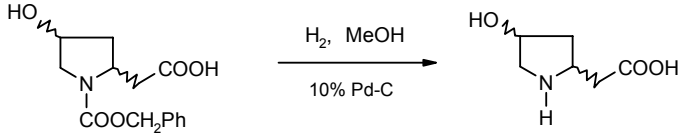
(**2*R*,4*S*)-48a-b**
(**2*R*,4*S*)-90a-d**
(**2*R*,4*S*)-99,** (4*S*)-HCOO-

(**2*R*,4*S*)-40a-b**
(**2*R*,4*S*)-89a-d**
(**2*R*,4*S*)-96**

(For the N-substituents **24a-d** see page 73)

In the same manners (scheme 58 and 59), the series **96** also were synthesized and finally their hydrogenolysis over Pd-C provided each of four stereoisomers **97**.

Scheme 60

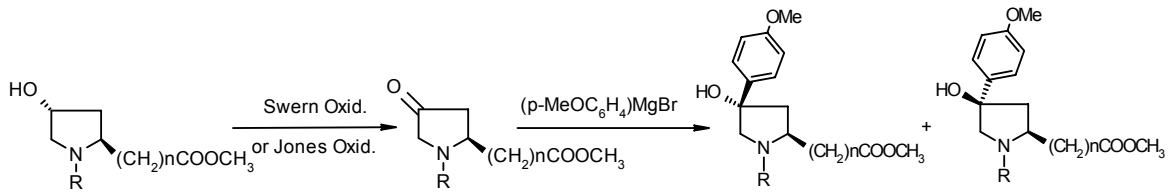


96 **97**

The N-substituted 4-oxopyrrolidine derivatives (2*S*)-**52a-b** and (2*S*)-**100a-c** (see Scheme 61) were prepared (81-92% yields) via Swern oxidation, and fortunately, the acid-sensitive N-substituent **24b** was not affected. The N-Cbz-protected 4-oxopyrrolidine derivatives **60** and **108** (Scheme 61) were prepared in good yield (71-78%) via Jones' oxidation, but in low yield (10-27%) via Swern oxidation.

The addition reactions of the organometallic reagents to the N-substituted pyrrolidine derivatives **52a-b** and (2*S*)-**100b-c** were carried out in two different ways. Depending on the starting material and the employed organometallic reagent, two different results were obtained: Under condition A [(4-$MeOC_6H_4$)MgBr at –78 °C in ether] the *cis* addition product (*cis* refers to the ester group) was formed as the major diastereomer and a good diastereoselectivity was achieved (*cis*/*trans* addition from 79:21 to 89:11; total yields 45-65%); Under condition B [(4-$MeOC_6H_4$)MgBr/$CeCl_3$ at –78 °C in THF], the *trans* addition product was obtained as a major diastereomer (*cis*/*trans* addition from 30:70 to 17:83; total yields 32-48%).

Scheme 61



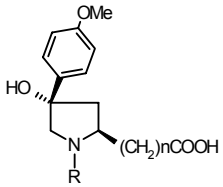
(**2*S*,4*R***)-**39a-b**, n = 0	(**2*S***)-**52a-b**	(**2*S*,4*S***)-**53a-b**	(**2*S*,4*R***)-**53a-b**
(**2*S*,4*R***)-**91a-c**, n = 1	(**2*S***)-**100a-c**	(**2*S*,4*S***)-**102b-c**	(**2*S*,4*R***)-**102b-c**
(**2*S*,4*R***)-**59** [Lit], R = Cbz, n = 0	(**2*S***)-**60** [Lit]	----------	(**2*S*,4*R***)-**61**
(**2*S*,4*R***)-**95** [Lit], R = Cbz, n =1	(**2*S***)-**108**	----------	(**2*S*,4*R***)-**109**

(For the N-substituents **24a-c** see page 73)

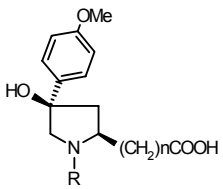
In the case of the N-Cbz-protected pyrrolidine derivative (2*S*)-**60**, a single diastereomer (2*S*,4*R*)-**61** was formed in 56% yield under condition B [(4-$MeOC_6H_4$)MgBr/$CeCl_3$ in THF at – 60 °C for 4 h]. However, for the homologous (2*S*)-**108** under the same conditions, (2*S*,4*R*)-**109** (25% yield) and a side product (5%) resulting from a simultaneous addition to the ester group were formed. The addition of (4-$MeOC_6H_4$)MgBr to (2*S*)-**108** (at –78 °C in ether for 4 h), however, led to (2*S*,4*R*)-**109** (38% yield) as a single diastereomer.

Each of the N-substituted stereoisomers from the reaction above was subjected to a basic hydrolysis, which was followed by hydrogenolysis over Pd-C, where necessary, to afford the free amino acids (70-98% yields).

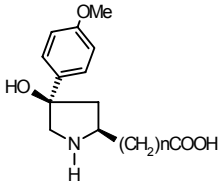
Scheme 62



(**2*S*,4*S*)-57a-b**, n = 0
(**2*S*,4*S*)-104b-c**, n =1



(**2*S*,4*R*)-57a-b**
(**2*S*,4*R*)-104b-c**



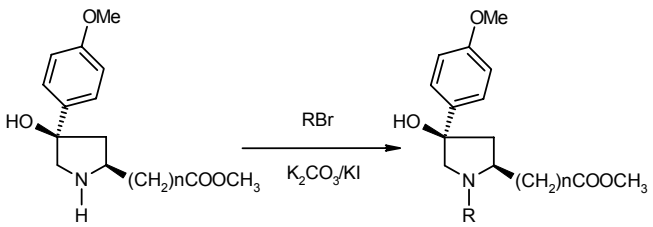
(**2*S*,4*R*)-63**
(**2*S*,4*R*)-111**

(For the N-substituents **24a-c** see page 73).

Via the similar synthetic procedures as described above, the rest of the stereoisomers (2*R*,4*R*)-**57a-b** and (2*R*,4*S*)-**57a-b**, (2*R*,4*R*)-**104b-c** and (2*R*,4*S*)-**104b-c**, (2*R*,4*S*)-**63** and (2*R*,4*S*)-**111** were obtained from (2*R*,4*R*)-**39a-b**, (2*R*,4*R*)-**88b-c**, (2*R*)-**60** and (2*R*,4*R*)-**73**.

The relative stereochemistry of the products obtained from the addition of the organometallic reagents to the 4-oxopyrrolidine derivatives was determined by chemical correlation and NOE measurements.

Scheme 63



(**2*S*,4*R*)-114**
(**2*S*,4*R*)-115**

(**2*S*,4*R*)-53a**
(**2*S*,4*R*)-102c**

(For the N-substituents **24a** and **c** see page 73)

NOE experiments performed with (2*S*,4*R*)-**114** revealed that the phenyl group and H-2 are *cis* to each other. As important signals for the assignment overlapped in the ^{1}H NMR spectrum of (2*S*,4*R*)-**115**, the NOE experiments were performed with (2*S*,4*R*)-**111**, which is the sodium salt of (2*S*,4*R*)-**115**. The NOE measurement revealed that the phenyl group is located *cis* to H-2, thus, (2*S*,4*R*)-**111** and (2*S*,4*R*)-**115** being of the stereochemistry shown.
The N-alkylation of (2*S*,4*R*)-**114** with the bromide of **24a**, and of (2*S*,4*R*)-**115** with the bromide of **24c** led to (2*S*,4*R*)-**53a** and (2*S*,4*R*)-**102c**, respectively. With these compounds as references, also the stereochemistry of all related compounds differing only in side chain on the amino nitrogen could be deduced.

The target compounds obtained in this study were evaluated for their biological activities. Membrane fractions from frontal cortex of bovine brain (or porcine brain) were utilized to study the inhibitory potency of the test compounds regarding the GAT-1-mediated GABA-uptake. For the determination of the potency as GAT-3 inhibitors, membrane fractions from brain stem of bovine brain (or porcine brain) were used.
As compared to the corresponding 4-unsubstituted compounds with (2*S*) configuration (IC_{50} 2.56 μM at GAT-1) and with (2*R*) configuration (IC_{50} 18.5 μM), the **40a-b** series containing a 4-hydroxy group showed a significant drop in the inhibitory potency at both GAT-1 and GAT-3, only one compound [(2*R,*4*R*)-**40a]** showed a reasonable potency at GAT-1 (IC_{50} 9.4 μM) and no one of them for GAT-3 (IC_{50} > 100 μM).
(2*S,*4*S*)-**89a (**IC_{50} 3.29 μM at GAT-1) and (2*S*,4*S*)-**89c** (5.14 μM), (2*S*,4*R*)-**89a (**4.92 μM) and (2*S*,4*R*)-**89c** (3.15 μM) exhibiting a 4-hydroxypyrrolidine-2-acetic acid skeleton showed an inhibitory potency at GAT-1, which was only one order of magnitude lower than the potency of corresponding compounds with (2*S*) configuration without the 4-hydroxy group (with N-substituent **24a**: IC_{50} 0.40 μM and with N-substituent **24c**: 0.34 μM).
(2*R*,4*S*)-**89b** was the most potent inhibitor at GAT-3 (IC_{50} 19.9 μM) of all the stereoisomers of series **89a-d** and showed a much higher potency than its isomer (2*R*,4*R*)-**89b** (126 μM). According to these data a 4-hydroxy group is detrimental to the potency at both GAT-1 and GAT-3, and (2*S*)-configuration of the pyrrolidine-2-acetic acid unit is crucial for a reasonable potency at GAT-1.
As compared to the **40b** series, some stereoisomers of the **57b** series, the latter exhibiting a (4-methoxy)phenyl group at C-4 of the pyrrolidine ring, showed an increased potency as inhibitors at GAT-1 and GAT-3 [e.g. (2*S*,4*R*)-**57b**: IC_{50} 29.7 μM at GAT-3; (2*R*,4*S*)-**57b**: IC_{50} of 38.0 μM at GAT-3]. In contrast, the introduction of a (4-methoxy)phenyl group into C-4 of

the **89b-c** series, resulting in the compounds of **104b-c**, gave rise to diverse biological results. As compared with (2*R*,4*S*)-**89b**, (2*R*,4*R*)-**104b** displayed a loss of inhibitory potency at GAT-3 but some enhancement at GAT-1.

6. EXPERIMENTAL SECTION

6.1 Synthetic section

General remarks

Reagents and solvents: Tetrahydrofuran, toluene, benzene and diisopropylamine were distilled from sodium under nitrogen. Acetonitrile was distilled from phosphorus pentoxide and then from potassium carbonate. Triethylamine was refluxed with benzoyl chloride and distilled under nitrogen. Methanol for anhydrous reactions was distilled from magnesium. Other common solvents for recrystallization, column chromatography, analytical HPLC and preparative HPLC were always distilled before use. Purchased chemical reagents were used without further purification.

Buffer: Aqueous buffer (pH 5.5, 0.42 M and pH 6.6, 0.42 M) was prepared from KH_2PO_4 and KOH.

TLC: TLC plates: silica gel 60 F_{254} on aluminum sheets (Merck); indicator: the aqueous solution containing 5% $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$, 0.2% $Ce(SO_4)_2\cdot 4H_2O$ and 5% conc. H_2SO_4.

Column chromatography (CC): If nothing else is stated, every packing for flash chromatography (ϕ mm; column length: mm) was silica gel (mesh 230-400, Merck).

Analytical HPLC: Column LiChrospher Si 60 (5 μm, 250 × 4 mm with precolumn 4 × 4 mm), Pump L-6000 (Hitachi), UV-VIS Detector L-4000 (275 nm, Merck-Hitachi), Integrator D-2000 (Merck-Hitachi).

Preparative HPLC: Column LiChrospher Si 60 (7 μm, 250 × 25 mm), Pump L-6200 (Hitachi), UV-VIS Detector L-4000 (275 nm, Hitachi), Integrator D-7500 (Merck-Hitachi).

Optical rotations: Polarimeter 241 MC at λ 589 cm^{-1} of Na light.

Melting points: M.p (uncorrected) were determined with a Büchi 510 Melting Point apparatus.

Elementary analysis: Elementaranalysator Rapid (Heraeus).

IR spectrum: FI-IR Spectometer 1600 and Paragon 1000 (Perkin Elmer), oily samples as film, solid samples as pellets for measurements.

Mass spectra: Mass Spectrometer 5989 A with 59980 B particle beam LC/MS interface (Hewlett Packard), method: Chemical ionization (CH_5^+: CI) (not specified); API 2000 (PE-Biosystem), method: electric spray ionization (N_2).

NMR Spectra: NMR spectra were recorded on JNMR-GX (Jeol, 400 MHz and 500 MHz) with TMS as internal standard and integrated with the program of NMR-software Nuts (2D Version 5.097, Acorn NMR, 1995). If nothing else is stated, measurements were performed at 400 MHz at room temperature.

It was not specified that some reactions needed absolute solvents or other absolute conditions, or protective gas such as nitrogen. For every reaction, stirring was always necessary despite of no mention.

Abbreviations:

Ac	acetyl
Cbz	carboxylate benzyl
CDI	carbonyldiimidazole
DCC	N,N'-dicyclohexyldiimide
DEAD	diethyl azodicarboxylate
DMAP	4-(dimethylamino)pyridine
Decomp.	decomposition
DMSO	dimethyl sulfoxide
DMF	dimethyl formamide
Ether	diethylether
Et	ethyl
LDA	lithium diisopropylamide
Me	methyl
Oxid.	Oxidation

prep.	preparative
r.t.	room temperature
sat.	saturated
TBAF	tetrabutylammonium fluoride
TEA	triethylamine
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	tetramethylsilane
TMSCl	trimethylchlorosilane
TBDMSCl	(*tert*-butyl)dimethylsilylchloride
Tr	triphenyl
t_R	retention time
Ph	phenyl

6.1.1 Preparation of the esters of the amino acids

(2*R*,4*R*)-4-Hydroxypyrrolidine-2-carboxylic acid [(2*R*,4*R*)-25]

According to ref. [47] 9.30 g (70.9 mmol) of (2*S*,4*R*)-**25** in 71 ml (76.7 g, 75.1 mmol) of Ac_2O and 142 ml of AcOH were refluxed for 5.5 h. After the solvent had been distilled off, the residual dark oil was refluxed in 180 ml (0.36 mol) of aq. 2 M HCl for 3 h. The reaction mixture was decolorized with charcoal. Water was removed under reduced pressure, the resulting colorless crystals were dissolved in 21 ml of H_2O and the solution was slowly neutralized by the addition of 10.4 ml (7.27 g, 72.0 mmol) of TEA in 200 ml of EtOH to give colorless crystals. Recrystallization was repeated twice with H_2O and EtOH to yield 5.41 g (58%) of (2*R*,4*R*)-**25** as colorless crystals. – M.p. 250-256 °C (decomp.). – $[\alpha]_D^{20}$ = +59.3 (*c* = 2.00, H_2O). {ref. [47]: M.p. 250-254 °C; $[\alpha]_D^{23}$ = +58.6 (*c* = 2.0, H_2O)}.

Methyl (2*S*,4*R*)-4-hydroxypyrrolidine-2-carboxylate hydrochloride [(2*S*,4*R*)-38]

According to ref. [37] A solution of 4.5 g (34.3 mmol) of (2*S*,4*R*)-**25** and 2.80 ml (4.57 g, 38.4 mmol) of $SOCl_2$ in 45 ml of MeOH was stirred at r.t. for 15 h and then 60 ml of Et_2O was added to give 5.50 g (96%) of (2*S*,4*R*)-**38** as colorless crystals. – M.p. 168-171 °C (MeOH). – $[\alpha]_D^{20}$ = -21.3 (*c* = 1.00, MeOH). {ref. [37]: M.p. 168-170 °C (MeOH); $[\alpha]_D^{20}$ = -19.5 (*c* = 1, MeOH)}.

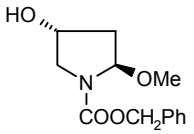
Methyl (2*R*,4*R*)-4-hydroxypyrrolidine-2-carboxylate hydrochloride [(2*R*,4*R*)-38]

According to ref. [37] To a mixture of 2.03 g (15.5 mmol) of (2*R*,4*R*)-**25** in 23 ml of MeOH, 1.20 ml (1.94 g, 16.3 mmol) of $SOCl_2$ was added at r.t. The mixture was stirred at r.t. for 1 h, then refluxed for 4 h and finally cooled down. 25 ml of iPr_2O was added and the mixture gave 2.43 g (86%) of (2*R*,4*R*)-**38** as colorless crystals. – M.p. 120-122 °C. – $[\alpha]_D^{20}$ = +9.8 (*c* = 1.00, MeOH). {ref. [82]: M.p. 121-123 °C}.

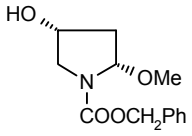
(2*S*,4*R*)-1-Benzyloxycarbonyl-4-hydroxypyrrolidine-2-carboxylic acid [(2*S*,4*R*)-58]

As described by ref. [41]: To a solution of 1.31 g (10 mmol) of (2*S*,4*R*)-2**5** in 5.0 ml (10 mmol) of aq. 2.0 M NaOH, 1.41 ml (1.70 g, 10.0 mmol) of CbzCl and 5.0 ml (10 mmol) of aq. 2.0 M NaOH were by turn added at 0 °C within 45 min. The mixture was stirred overnight, and then acidified to pH 1-2 with aq. 4.0 M HCl and finally extracted with EtOAc. Combined extract was dried (Na_2SO_4) and evaporated. Yield: 2.39 g (90%); colorless oil. – $[\alpha]_D^{20}$ = -44.1 (*c* = 1.00, MeOH). {ref. [61]: $[\alpha]_D^{24}$ = -41 (*c* = 1.0, MeOH)}

Benzyl (2*R*,4*R*)-4-hydroxy-2-methoxypyrrolidine-1-carboxylate [(2*R*,4*R*)-69] and benzyl (2*S*,4*R*)-4-hydroxy-2-methoxypyrrolidine-1-carboxylate [(2*S*,4*R*)-69]



(**2*R*,4*R*)-69**



(**2*S*,4*R*)-69**

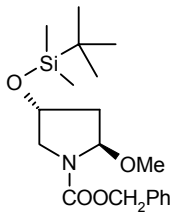
In 60 ml of MeOH containing 145 mg (1.44 mmol) of TEA, 1.90 g (7.17 mmol) of (2*S*,4*R*)-**58** was electrolyzed at 10~15 °C at the voltage of 13 v, a slim stick of platinum as an anode and a wire grate of platinum as a cathode) until no bubble appeared on the surface of platinum wire in 7 h. After MeOH was removed (T < 25 °C), the resulting oil was subjected to analytical HPLC (the ratio of *d.s* = 41:59; respective t_R = 9.4 min, 10.5 min; *n*-heptane/EtOAc, 40:60; 1.5 ml/min) and purificated by CC (ϕ 40 × 245; *i*Pr_2O/EtOH, 92:8) gave 1.74 g (97%) of **69**. It was possible to get optically pure diastereomers via the above CC.

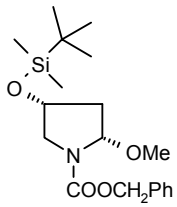
Major diastereomer: Colorless oil. TLC: R_f = 0.36 (*i*Pr_2O/EtOH, 9:1). – $[\alpha]_D^{20}$ = +1.2 (*c* = 1.76, EtOH). – ^{1}H NRM ($CDCl_3$): Two rotamers δ = 1.91-2.01 (m, 1 H, NCHCH_2), 2.15-2.19 (m, 1 H, NCHCH_2), 3.23, 3.37 (2s, 3 H, OCH_3), 3.45-3.49, 3.67-3.71 (m, 2 H, NCH_2), 4.60-4.64 (m, 1 H, C*H*OH), 5.11-5.31 (m, 3 H, NC*H* and OCH_2Ph), 7.29-7.36 (m, 5 H, H_{aromat}). – IR: $\tilde{\nu}$ = 3429, 2947, 2834, 1704, 1416, 1088, 774, 698 cm^{-1}. – MS; *m*/*z* (%): 252 (1) $[M+1]^+$, 220 (92), 176 (100), 91 (62), 86 (29). – $C_{13}H_{17}NO_4$ (251.28): calcd. C 62.14, H 6.82, N 5.57; found C 62.00, H 7.00, N 5.53.

Minor diastereomer: Colorless oil. TLC: R_f = 0.27 (*i*Pr_2O/EtOH, 9:1). – $[\alpha]_D^{20}$ = -31.7 (*c* = 1.20, EtOH). – ^{1}H NMR ($CDCl_3$): two rotamers δ = 1.91-1.97 (m, 1 H, NCHCH_2), 2.12-2.18

(m, 1 H, NCHCH_2), 3.10-3.24, 3.58-3.71 (m, 2 H, NCH_2), 3.31-3.44 (m, 3 H, OCH_3), 4.34-4.37 (m, 1 H, C*H*OH), 5.13-5.38 (m, 3 H, NC*H* and OCH_2Ph), 7.30-7.38 (m, 5 H, H_{aromat}). – IR: $\tilde{\nu}$ = 3466, 2946, 2834, 1708, 1410, 1084, 754, 699 cm^{-1}. – MS; *m*/*z* (%): 252 (1) $[M+1]^+$, 220 (100), 176 (100), 91 (79), 86 (52). – $C_{13}H_{17}NO_4$ (251.28): calcd. C 62.14, H 6.82, N 5.57; found C 61.98, H 6.85, N 5.70.

Benzyl (2*R*,4*R*)-4-(*tert*-butyl)dimethylsilyloxy-2-methoxypyrrolidine-1-carboxylate [(2*R*,4*R*)-70] and
benzyl (2*S*,4*R*)-4-(*tert*-butyl)dimethylsilyloxy-2-methoxypyrrolidine-1-carboxylate [(2*S*,4*R*)-70]





(**2*R*,4*R*)-70** (**2*S*,4*R*)-70**

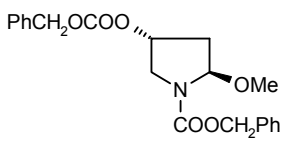
To a solution of 0.986 g (3.93 mmol) of **27** and 0.401 g (5.89 mmol) of imidazole in 14 ml of CH_2Cl_2, a solution of 0.770 g (5.11 mmol) of TBDMSCl in 6 ml of CH_2Cl_2 was added at r.t. After stirring for 16 h, the mixture was washed with H_2O, dried (Na_2SO_4), and then evaporated to afford colorless oil. Purification by CC (ϕ 25 × 95; *n*-heptane/EtOAc, 7:1) gave 1.22 g (85%) of **70** as colorless oil and separation by prep. HPLC (*n*-heptane/EtOAc, 7:1; 12 ml/min) gave pure diastereomers.

Diastereomer I: Colorless oil. – t_R = 24.6 min. – TLC: R_f = 0.35 (*n*-heptane/EtOAc, 7:1). – $[\alpha]_D^{20}$ = -10.9 (*c* = 0.82, EtOAc). – ^{1}H NMR ($C_6D_5NO_2$, 120 °C): δ = 0.11 (s, 3 H, $SiCH_3$), 0.12 (s, 3 H, $SiCH_3$), 0.93 [s, 9 H, $SiC(CH_3)_3$], 2.00 (dt, *J* = 13.9/1.5 Hz, 1 H, NCHCH_2), 2.35 (dt, *J* = 13.9/6.4 Hz, 1 H, NCHCH_2), 3.41-3.45 (m, 4 H, NCH_2 and 3 H of OCH_3), 3.99 (dd, *J* = 11.2/6.6 Hz, 1 H, NCH_2), 4.44-4.49 (m, 1 H, CHOSi), 5.24 (d, *J* = 12.6 Hz, 1 H, CH_2Ph), 5.28 (d, *J* = 12.6 Hz, 1 H, CH_2Ph), 5.36 (dd, *J* = 6.4/1.5 Hz, 1 H, NCH), 7.25-7.44 (m, 5 H, H_{aromat}). – IR: $\tilde{\nu}$ = 3034, 2930, 2857, 1714, 1410, 1098, 837, 775, 698 cm^{-1}. – MS; *m*/*z* (%):

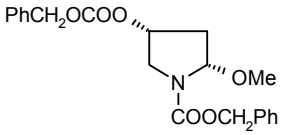
364 (1) $[M-1]^+$, 334 (65), 290 (74), 264 (23), 234 (21), 158 (22), 91 (100). – $C_{19}H_{31}NO_4Si$ (365.55): calcd. C 62.43, H 8.55, N 3.83; found C 62.33, H 8.73, N 3.94.

Diastereomer II: Colorless oil. – t_R = 21.6 min. – TLC: R_f = 0.42 (*n*-heptane/EtOAc, 7:1). – $[\alpha]_D^{20}$ = +14.4 (*c* = 1.07, EtOAc). – ^{1}H NMR ($C_6D_5NO_2$, 120 °C): δ = 0.10 (s, 3 H, $SiCH_3$), 0.11 (s, 3 H, $SiCH_3$), 0.91 [s, 9 H, $SiC(CH_3)_3$], 2.00 (dd, *J* = 12.9/7.2 Hz, 1 H, NCHC*H*$_2$), 2.20 (ddd, *J* = 12.9/5.8/1.5 Hz, 1 H, NCHC*H*$_2$), 3.38 (s, 3 H, OCH_3), 3.50 (dd, *J* = 11.1/5.2 Hz, 1 H, NCH_2), 3.72 (dd, *J* = 11.1/6.3 Hz, 1 H, NCH_2), 4.66-4.73 (m, 1 H, CHOSi), 5.25 (d, *J* = 12.7 Hz, 1 H, C*H*$_2$Ph), 5.29 (d, *J* = 12.7 Hz, 1 H, C*H*$_2$Ph), 5.38 (dd, *J* = 7.2/1.5 Hz, 1 H, NCH), 7.26-7.35, 7.42-7.44 (m, 5 H, H_{aromat}). – IR: $\tilde{\nu}$ = 3040, 2954, 2991, 1714, 1408, 1096, 900, 777, 698 cm^{-1}. – MS; *m*/*z* (%): 364 (1) $[M-1]^+$, 334 (49), 290 (61), 264 (19), 234 (19), 158 (22), 91 (22). – $C_{19}H_{31}NO_4Si$ (365.55): calcd. C 62.43, H 8.55, N 3.83; found C 62.59, H 8.64, N 3.93.

Benzyl (2*S*,4*R*)-4-(benzyloxycarbonyl)oxy-2-methyoxypyrrolidine-1-carboxylate [(2*S*,4*R*)-77] and
benzyl (2*R*,4*R*)-4-(benzyloxycarbonyl)oxy-2-methyoxypyrrolidine-1-carboxylate [(2*R*,4*R*)-77]



(**2*R*,4*R*)-77**



(**2*S*,4*R*)-77**

To a solution of 518 mg (2.06 mmol) of **69** and 377 mg (3.07 mmol) of DMAP in 20 ml of CH_2Cl_2, 0.407 ml (493 mg, 2.89 mmol) of CbzCl was added at 0 °C. The mixture was stirred at 0 °C for 19 h, and then neutralized with aq. 1.2 N HCl to ~ pH 8, finally washed with water. The CH_2Cl_2 layer was separated, dried ($MgSO_4$), and evaporated to give yellow oil. The two diastereomers were obtained by CC (ϕ 25 × 250; EtOAc/*n*-heptane, 1:4).

Major diastereomer: 322 mg (41%); colorless oil. – TLC: R_f = 0.22 (EtOAc/*n*-heptane, 1:3). – $[\alpha]_D^{20}$ = -25.6 (*c* = 1.00, EtOAc). – ^{1}H NMR ($C_6D_5NO_2$, 120 °C): δ = 2.26 (dt, *J* = 13.9/5.9 Hz, 1 H, NCHC*H*$_2$), 2.41 (ddd, *J* = 13.9/6.6/2.0 Hz, 1 H, NCHC*H*$_2$), 3.37 (s, 3 H, OCH_3), 3.83-3.85 (m, 2 H, NCH_2), 5.22 (d, *J* = 12.6 Hz, 1 H, OCOOC*H*$_2$Ph), 5.22 (s, 2 H,

NCOOC*H*$_2$Ph), 5.27 (d, *J* = 12.6 Hz, 1 H, OCOOC*H*$_2$Ph), 5.36-5.42 (m, 1 H, NCH$_2$C*H*O), 5.45 (dd, *J* = 5.9/2.0 Hz, 1 H, NC*H*), 7.25-7.42 (m, 10 H, H$_{aromat}$). – IR: $\tilde{\nu}$ = 3034, 2950, 1746, 1714, 1410, 1270, 1085, 792, 753, 698 cm^{-1}. – MS; *m*/*z* (%): 354 (1) [M-OCH$_3$]$^+$, 202 (100), 158 (34), 91 (66). – $C_{21}H_{23}NO_6$ (385.42): calcd. C 65.44, H 6.02, N 3.63; found C 65.17, H 6.08, N 3.63.

Minor diastereomer: 228 mg (27%); colorless oil. – TLC: R_f = 0.32 (EtOAc/*n*-heptane, 1:3). – $[\alpha]_D^{20}$ = +16.5 (*c* = 1.00, EtOAc). – ^{1}H NMR ($C_6D_5NO_2$, 120 °C): δ = 2.32 (br. d, *J* = 14.8 Hz, 1 H, NCHC*H*$_2$), 2.39 (dt, *J* = 14.8/5.5 Hz, 1 H, NCHC*H*$_2$), 3.40 (s, 3 H, OCH$_3$), 3.70 (dd, *J* = 12.5/2.5 Hz, 1 H, NCH$_2$), 4.08 (dd, *J* = 12.5/6.4 Hz, 1 H, NCH$_2$), 5.22 (s, 2 H, NCOOC*H*$_2$Ph), 5.26 (d, *J* = 4.4, 2 H, OCOOC*H*$_2$Ph), 5.29-5.34 (m, *1* H, NCH$_2$C*H*O), 5.41 (dd, *J* = 5.5/1.0 Hz, 1 H, NCH), 7.26~7.44 (m, 10 H, H$_{aromat}$). – IR: $\tilde{\nu}$ = 3034, 2950, 1747, 1714, 1416, 1265, 1085, 791, 754, 698 cm^{-1}. – MS; *m*/*z* (%): 354 (1) [M-OCH$_3$]$^+$, 202 (100), 158 (33), 91 (77). – $C_{21}H_{23}NO_6$ (385.42): cal. C 65.44, H 6.02, N 3.63; found C 65.24, H 6.05, N 3.63.

1-Ethoxy-1-(trimethylsilyloxy)ethene (116)

According to ref. [82] To a solution of 3.08 ml (22.0 mmol) of *i*Pr$_2$NH in 20 ml of THF, 13.8 ml (1.6 M in *n*-heptane, 22 mmol) of *n*-BuLi was added at –5 °C. After stirring for 20 min at 0 °C, the mixture was cooled down to –78°C, and then 2.95 ml (1.76 g, 20.0 mmol) of EtOAc was added. After 30 min, 3.00 ml (2.58 g, 24.0 mmol) of TMSCl was added and stirring was continued for 1 h. The mixture was poured into a mixture of 100 ml of pentane and 40 ml of H_2O. The organic layer was washed with H_2O, dried ($MgSO_4$) and then distilled under reduced pressure (75-80 °C/118-122 mbr). Yield: 1.73 g (51%) (*Si-O*/*Si-C* = 75:25, purity 75%, determined by ^{1}H NMR); colorless liquid.

General procedure (GP1)

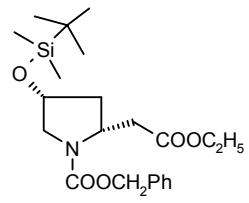
A)

To a solution of **70** (1 equiv.) and the nucleophile (**116** or ethyl bromozincacetate, 3.2-4.0 equiv.) in CH_2Cl_2 (3 ml/mmol), the solution of Lewis acid ($BF_3{\cdot}Et_2O$ or $TiCl_4$, 2.1 equiv.) was added at the temperature given. The mixture was allowed to stir at this temperature for the time given, before it was quenched with aq. 5% K_2CO_3 (2.3-2.6 equiv.). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined extracts were dried ($MgSO_4$) and concentrated to yield a colorless oil. The ratio of *d.s* was determined by analytical HPLC gave Purification by CC and separation by prep. HPLC yielded pure diastereomers.

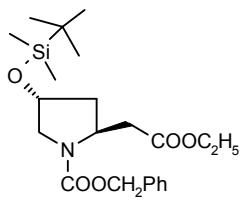
B)

To a solution of **70** (1 equiv.) in CH_2Cl_2 (3 ml/mmol), Lewis acid ($BF_3{\cdot}Et_2O$ or $TiCl_4$, 2.1 equiv.) was added. After this mixture had been stirred for 15 min, the nucleophile (**116** or ethyl bromozincacetate, 3.2-4.0 equiv.) was added. This mixture was allowed to stir at this temperature for the time given. The reaction mixture was quenched with aq. 5% K_2CO_3 (2.3-2.6 equiv.). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. the combined extract was dried ($MgSO_4$) and concentrated to yield a colorless oil. Assay on analytical HPLC gave the ratio of *d.s*. Purification by CC and separation by prep. HPLC yielded pure diastereomers.

Ethyl (2*R*,4*R*)-1-benzyloxycarbonyl-4-(*tert*-butyl)dimethylsilyloxypyrrolidine-2-acetate [(2*R*,4*R*)-71] and
ethyl (2*S*,4*R*)-1-benzyloxycarbonyl-4-(*tert*-butyl)dimethylsilyloxypyrrolidine-2-acetate [(2*S*,4*R*)-71]



cis-(**2*R*,4*R*)-71**



trans-(**2*S*,4*R*)-71**

2) According to GP1-A from 124 mg (0.339 mmol) of **70**, 228 mg (purity: 75%, 1.07 mmol) of **116** and 101 mg (0.711 mmol) of $BF_3 \cdot Et_2O$ in 3 ml of CH_2Cl_2; reaction: at –78 °C for 4 h; 3.2 ml (2.3 mmol) of aq. 5% K_2CO_3; analytical HPLC (*n*-heptane/EtOAc, 7:1; 1.5 ml/min) *cis*/*trans* = 92:8 (*cis* t_R = 10.8 min, *trans* t_R = 8.8 min). Purification by CC (ϕ 12 × 220; *n*-heptane/EtOAc, 9:1) and separation by prep. HPLC (*n*-heptane/EtOAc, 7:1; 12.0 ml/min) gave (2*R*,4*R*)-**71** (t_R = 31.7 min) and (2*S*,4*R*)-**71** (t_R = 26.8 min).

(2*R*,4*R*)-**71**: 113 mg (79%); colorless oil. – TLC: R_f = 0.40 (*n*-heptane/EtOAc, 3:1). – $[\alpha]_D^{20}$ = +13.0 (*c* = 1.02, EtOAc). – ^{1}H NMR ($C_6D_5NO_2$, 120 °C): δ = 0.13 (s, 3 H, $SiCH_3$), 0.14 (s, 3 H, $SiCH_3$), 0.94 [s, 9 H, $C(CH_3)_3$], 1.25 (t, *J* = 7.0 Hz, 3 H, CH_2CH_3), 2.04 (dt, *J* = 13.5/2.4 Hz, 1 H, CH_2CHCH_2COO), 2.32 (ddd, *J* = 13.5/8.1/5.4 Hz, 1 H, CH_2CHCH_2COO), 2.91 (dd, *J* = 15.1/9.6 Hz, 1 H, CH_2COO), 3.18 (dd, *J* = 15.1/4.0 Hz, 1 H, CH_2COO), 3.50 (ddd, *J* = 11.4/2.9/1.1 Hz, 1 H, NCH_2), 3.82 (dd, *J* = 11.4/5.4 Hz, 1 H, NCH_2), 4.14-4.22 (m, 2 H, CH_2CH_3), 4.43-4.53 (m, 2 H, CHOSi and NCH), 5.26 (s, 2 H, CH_2Ph), 7.24-7.45 (m, 5 H, H_{aromat}). – IR: $\tilde{\nu}$ = 3034, 2955, 2858, 1738, 1704, 1415, 1357, 1098, 838, 775, 698 cm^{-1}. – MS; *m*/*z* (%): 422 (36) $[M+1]^+$, 364 (8), 314 (7), 163 (7), 91 (100). – $C_{22}H_{35}NO_5$ (421.61): calcd. C 62.67, H 8.37, N 3.32; found C 62.47, H 8.28, N 3.25.

(2*S*,4*R*)-**71**: 7 mg (5%); colorless oil. – TLC: R_f = 0.43 (*n*-heptane/EtOAc, 3:1). – $[\alpha]_D^{20}$ = -40.3 (*c* = 1.00, EtOAc). – ^{1}H NMR ($C_6D_5NO_2$, 120 °C): δ = 0.06 (s, 6 H, 2 $SiCH_3$), 0.90 [s, 9 H, $Si(CH_3)_3$], 1.24 (t, *J* = 7.0 Hz, 3 H, CH_2CH_3), 2.06-2.12 (m, 1 H, CH_2CHCH_2COO), 2.22-2.28 (m, 1 H, CH_2CHCH_2COO), 2.62 (dd, *J* = 15.1/8.5 Hz, 1 H, CH_2COO), 3.08 (dd, J = 15.1/2.2 Hz, 1 H, CH_2COO), 3.62 (dt, *J* = 11.3/2.2 Hz, 1 H, NCH_2), 3.69 (br. d, *J* = 11.3 Hz, 1 H, NCH_2), 4.17 (q, *J* = 7.0 Hz, 2 H, CH_2CH_3), 4.50-4.56 (m, 2 H, NCH and CHOSi), 5.23 (d, *J* = 12.9 Hz, 1 H, CH_2Ph), 5.27 (d, *J* = 12.9 Hz, 1 H, CH_2Ph), 7.25-7.43 (m, 5 H, H_{aromat}). – IR: $\tilde{\nu}$ = 3034, 2955, 2857, 1735, 1705, 1413, 1110, 838, 776, 697 cm^{-1}. – MS; *m*/*z* (%): 422 (72) $[M+1]^+$, 378 (13), 314 (16), 91 (100). – $C_{22}H_{35}NO_5$ (421.61): calcd. C 62.67, H 8.37, N 3.32; found C 62.48, H 8.47, N 3.36.

1) According to GP1-A from 124 mg (0.339 mmol) of **70** and 228 mg (purity: 75%, 1.07 mmol) of **116** in 3 ml of CH_2Cl_2, 101 mg (0.711 mmol) of $BF_3 \cdot Et_2O$; reaction: at 20 °C for 3 h; 3.2 ml (2.3 mmol) of aq. 5% K_2CO_3; analytical HPLC (*n*-heptane/EtOAc, 88/12; 1.5 ml/min) *cis*/*trans* = 87:13 (*cis* t_R = 9.4 min, *trans* t_R = 7.6 min); purification by CC (ϕ 12 × 200; *n*-heptane/EtOAc, 87.5:12.5) and separation by prep. HPLC (*n*-heptane/EtOAc,

87.5:12.5; 12 ml/min). Yield: 11 mg (8%) of (2*S*,4*R*)-**71** (t_R = 23.5 min) and 77 mg (54%) of (2*R*,4*R*)-**71** (t_R = 27.3 min).

3) According to GP1-A from 3.00 (8.20 mmol) of **70** and 8.60 g (purity: 61%, 32.8 mmol) of **116** in 83 ml of CH_2Cl_2, 2.43 g (17.2 mmol) of $BF_3{\cdot}Et_2O$; reaction: at –78 °C for 4 h; 66.7 ml (48.3 mmol) of aq. 5% K_2CO_3; analytical HLPC (*n*-heptane/EtOAc, 88/12; 1.3 ml/min) *cis*/*trans* = 87:13 (*cis* t_R = 12.0 min, *trans* t_R = 9.5 min); purification by CC (*n*-heptane/EtOAc, 88:12) and separation by prep. HPLC (*n*-heptane/EtOAc, 88:12; 12 ml/min). Yield: 314 mg (9%) of (2*S*,4*R*)-**71** (t_R = 27.0 min) and 2.72 g (79%) of (2*R*,4*R*)-**71** (t_R = 32.7 min).

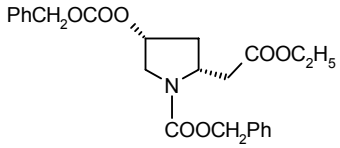
4) According to GP1-A from 124 mg (0.339 mmol) of **70** and 228 mg (purity: 75%, 1.07 mmol) of **116** in 3 ml of CH_2Cl_2, 0.71 ml (1.0 M in CH_2Cl_2, 0.71 mmol) of $TiCl_4$; reaction: at –78 °C for 48 h; 3.5 ml (2.5 mmol) of aq. 5% K_2CO_3; analytical HPLC (*n*-heptane/EtOAc, 87.5/12.5; 1.3 ml/min) *cis*/*trans* = 80:20 (*cis* t_R = 13.1 min, *trans* t_R = 10.1 min); purification by CC (ϕ 18 × 230; *n*-heptane/EtOAc, 87.5:12.5) and separation by prep. HPLC (*n*-heptane/EtOAc, 87.5:12.5; 12 ml/min). Yield: 7 mg (5%) of (2*S*,4*R*)-**71** and 38 mg (27%) of (2*R*,4*R*)-**71**.

5) According to GP1-B from 124 mg (0.339 mmol) of **70** and 101 mg (0.711 mmol) of $BF_3{\cdot}Et_2O$ in 3 ml of CH_2Cl_2, 357 mg (purity: 61%, 1.36 mmol) of **116**; reaction: at -78 °C for 4 h; 3.2 ml (2.3 mmol) of aq. 5% K_2CO_3; analytical HPLC (*n*-heptane/EtOAc, 88/12; 1.3 ml/min) *cis*/*trans* = 97:3 (*cis* t_R = 12.3 min, *trans* t_R = 9.6 min); purification by CC (ϕ 18 × 220; *n*-heptane/EtOAc, 88:12) and separation by prep. HPLC (*n*-heptane/EtOAc, 88:12; 12 ml/min). Yield: 2.4 mg (1.7%) of (2*S*,4*R*)-**71** (t_R = 27.6 min) and 106 mg (74%) of (2*R*,4*R*)-**71** (t_R = 33.0 min).

6) According to GP1-B from 124 mg (0.339 mmol) of **70** and 101 mg (0.711 mmol) of $BF_3{\cdot}Et_2O$ in 3 ml of CH_2Cl_2, 228 mg (purity: 75%, 1.07 mmol) of **116**; reaction: at -78 °C for 18 h; 3.2 ml (2.3 mmol) of aq. 5% K_2CO_3; analytical HPLC (*n*-heptane/EtOAc, 87.5:12.5; 1.3 ml/min) *cis*/*trans* = 97:3 (*cis* t_R = 12.6 min, *trans* t_R = 10.2 min); purification by CC (ϕ 18 × 240; *n*-heptane/EtOAc, 87.5:12.5) and separation by prep. HPLC (*n*-heptane/EtOAc, 88:12; 12 ml/min). Yield: 2.5 mg (2%) of (2*S*,4*R*)-**71** (t_R = 26.6 min) and 89 mg (62%) of (2*R*,4*R*)-**71** (t_R = 30.8 min).

7) According to GP1-B from 124 mg (0.339 mmol) of **70** and 0.71 ml (1.0 M in CH_2Cl_2, 0.71 mmol) of $TiCl_4$ in 3 ml of CH_2Cl_2, 228 mg (purity: 75%, 1.07 mmol) of **116**; reaction: at -78 °C for 16 h; 3.2 ml (2.3 mmol) of aq. 5% K_2CO_3; analytical HPLC (*n*-heptane/EtOAc, 87.5:12.5; 1.3 ml/min) *cis*/*trans* = 89:19 (*cis* t_R = 11.72 min, *trans* t_R = 9.40 min); purification by CC (ϕ 18 × 245; *n*-heptane/EtOAc, 87.5:12.5) and separation by prep. HPLC (*n*-heptane/EtOAc, 88:12; 12 ml/min). Yield: 10 mg (7%) of (2*S*,4*R*)-**71** (t_R = 23.2 min) and 82 mg (57%) of (2*R*,4*R*)-**71** (t_R = 27.7 min).

Ethyl (2*R*,4*R*)-1-benzyloxycarbonyl-4-(benzyloxycarbonyl)oxypyrrolidine-2-acetate [(2*R*,4*R*)-80]

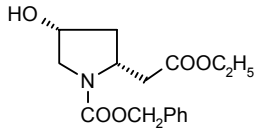


1) According to GP1-A from 131 mg (0.339 mmol) of **77**, 400 mg (purity: 57%, 1.42 mmol) of **116** and 101 mg (0.711 mmol) of $BF_3{\cdot}Et_2O$ in 3 ml of CH_2Cl_2; reaction: at –78 °C for 4 h; 3.2 ml (2.3 mmol) of aq. 5% K_2CO_3. Purification by CC (ϕ 25 × 210; *iso*-hexane/acetone, 4:1) and separation by prep. HPLC (*n*-heptane/EtOAc, 7:3; 12 ml/min) gave (2*R*,4*R*)-**80**. And 36 mg (24%) of the starting material **77** (t_R = 28.5 min) was recycled.

(2*R*,4*R*)-**80**: 19 mg (13%); colorless oil. – t_R = 26.5 min. – TLC: R_f = 0.33 (*n*-heptane/ EtOAc, 3:1). – $[\alpha]_D^{20}$ = +21.2 (*c* = 0.50, EtOAc). – ^{1}H NMR ($C_6D_5NO_2$, 120 °C): δ = 1.22 (t, *J* = 7.1 Hz, 3 H, CH_2CH_3), 2.29 (br. d, *J* = 15.4 Hz, 1 H, CH_2CHCH_2COO), 2.49-2.57 (m, 1 H, CH_2CHCH_2COO), 2.73 (dd, *J* = 15.2/9.7 Hz, 1 H, CH_2COO), 3.13 (dd, *J* = 15.2/3.7 Hz, 1 H, CH_2COO), 3.72 (dd, *J* = 12.6/1.1 Hz, 1 H, NCH_2CHO), 3.96 (dd, *J* = 12.6/5.3 Hz, 1 H, NCH_2CHO), 4.15 (q, *J* = 7.1 Hz, 2 H, CH_2CH_3), 4.47-4.54 (m, 1 H, NCH), 5.23-5.29 (m, 4 H, CH_2Ph), 5.30-5.35 (m, 1 H, NCH_2CHO), 7.26-7.44 (m, 10 H, H_{aromat}). – IR: $\tilde{\nu}$ = 3034, 2956, 1732, 1705, 1498, 1415, 1268, 770, 752, 698 cm^{-1}. – MS; *m*/*z* (%): 442 $[M+1]^+$ (100), 398 (14), 181 (14), 154 (37). – $C_{24}H_{27}NO_7$ (441.48): calcd. C 65.29, H 6.16, N 3.17; found C 65.24, H 6.16, N 3.17.

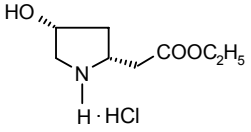
2) According to GP1-B from 131 mg (0.339 mmol) of **77**, 101 mg (0.711 mmol) of $BF_3 \cdot Et_2O$; 400 mg (purity: 57%, 1.42 mmol) of **116** in 3 ml of CH_2Cl_2; reaction: at –78 °C for 4 h; 3.2 ml (2.3 mmol) of aq. 5% K_2CO_3. Purification by CC (ϕ 25 × 200; *iso*-hexane/acetone, 4:1) and separation by prep. HPLC (*n*-heptane/EtOAc, 7:3; 12 ml/min) gave 5.6 mg (4%) of (2*R*,4*R*)-**80** (t_R = 27.2 min). And 20 mg (15%) of the starting material **77** (t_R = 28.7 min) was recycled.

Ethyl (2*R*,4*R*)-1-benzyloxycarbonyl-4-hydroxypyrrolidine-2-acetate [(2*R*,4*R*)-73]



To a solution of 90 mg (0.21 mmol) of (2*R*,4*R*)-**71** in 2 ml of THF, 0.26 ml (1.0 M in THF, 0.26 mmol) of TBAF was added, then resulting solution was stirred at r.t. for 4.5 h. 2.0 ml of 0.1% K_2CO_3 was added. The organic layer was separated, dried (Na_2SO_4), and evaporated to give pale yellow oil, which was purified by CC (ϕ 12 × 100; *i*Pr_2O/EtOH, 95:5). Yield: 58 mg (88%); colorless oil. – TLC: R_f = 0.54 (*i*Pr_2O/EtOH, 9:1). – $[\alpha]_D^{22}$ = +23.4 (*c* = 0.7, EtOAc). – ^{1}H NMR ($C_6D_5NO_2$, 120 °C): δ = 1.24 (t, *J* = 7.1 Hz, 3 H, CH_2CH_3), 2.09 (dtd, *J* = 13.8/3.1/1.3 Hz, 1 H, CH_2CHCH_2COO), 2.39 (ddd, *J* = 13.8/8.4/5.6 Hz, 1 H, CH_2CHCH_2COO), 2.60 (s, 1 H, OH), 2.93 (dd, *J* = 15.4/9.2 Hz, 1 H, CH_2COO), 3.17 (dd, *J* = 15.4/4.1 Hz, 1 H, CH_2COO), 3.57 (ddd, *J* = 11.8/2.9/1.3 Hz, 1 H, NCH_2), 3.83 (dd, *J* = 11.8/5.4 Hz, 1 H, NCH_2), 4.17 (q, *J* = 7.1 Hz, 2 H, CH_2CH_3), 4.41-4.48 (m, 1 H, NCH), 4.54-4.58 (m, 1 H, CHOH), 5.25 (s, 2 H, CH_2Ph), 7.25-7.45 (m, 5 H, H_{aromat}). – IR: $\tilde{\nu}$ = 3442, 3034, 2944, 1731, 1682, 1416, 1119, 770, 750, 698 cm^{-1}. – MS; *m*/*z* (%): 308 (93) $[M+1]^+$, 264 (44), 262 (36), 172 (23), 91 (100). – $C_{16}H_{21}NO_5$ (307.35): calcd. C 62.53, H 6.89, N 4.56; found C 62.39, H 6.92, N 4.49.

Ethyl (2*R*,4*R*)-4-hydroxypyrrolidine-2-acetate hydrochloride [(2*R*,4*R*)-64]

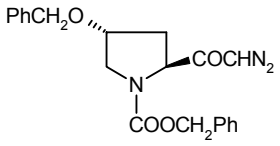


To a solution of 187 mg (0.608 mmol) of (2*R*,4*R*)-**73** in 10 ml of EtOH, 93 mg (0.087 mmol) of 10% Pd-C and 55 µl (0.66 mmol) of aq. 37% HCl were added. The mixture was hydrogenated at r.t. under ambient pressure for 2 h, and then filtrated and finally concentrated. The residue was recrystallized from EtOH/iPr$_2$O. Yield: 114 mg (89%); colorless crystals. – M.p. 150-151 °C (EtOH/iPr$_2$O). – $[\alpha]_D^{20}$ = -34.0 (c = 1.00, EtOH). – ^{1}H NMR (CD_3OD): δ = 1.29 (t, J = 7.4 Hz, 3 H, CH_2CH_3), 1.79 (ddt, J = 14.1/4.7/1.9 Hz, 1 H, CH_2CHCH_2COO), 2.43 (ddd, J = 14.1/9.8/5.0 Hz, 1 H, CH_2CHCH_2COO), 2.92 (dd, J = 18.0/5.2 Hz, 1 H, CH_2COO), 2.98 (dd, J = 18.0/9.4 Hz, 1 H, CH_2COO), 3.22 (dd, J = 11.9/3.6 Hz, 1 H, NCH_2), 3.27 (dt, J = 11.9/1.9 Hz, 1 H, NCH_2), 4.00-4.08 (m, 1 H, NCH), 4.21 (q, J = 7.4 Hz, 2 H, CH_2CH_3), 4.50-4.53 (m, 1 H, CHOH). – IR: $\tilde{\nu}$ = 3303, 2934, 2758, 1721, 1585, 1259, 1104, 1033 cm^{-1}. – MS; m/z (%): 174 (100). – $C_8H_{16}ClNO_3$ (209.67): calcd. C 45.83, H 7.69, N 6.68, Cl 16.91; found C 45.76, H 7.72, N 6.64, Cl 16.68.

(2*S*,4*R*)-4-Benzyloxy-1-benzyloxycarbonylpyrrolidine-2-carboxylic acid [(2*S*,4*R*)-83]

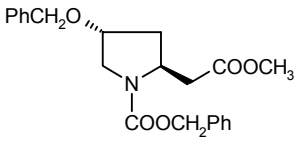
According to ref. [75]: To a solution of 5.0 g (19 mmol) of (2*S*,4*R*)-**58** in 200 ml of THF, 1.61 g (55~60% in oil, 40 mmol) of NaH was added at r.t, the mixture was stirred over night and then 7.42 g (43.4 mmol) of benzyl bromide was added. After refluxing for 11.5 h, the reaction mixture was cooled down, quenched with ice-water and extracted with 300 ml of *n*-heptane. The aqueous layer was acidified with aq. 2 M HCl to pH 1~2 and extracted with Et_2O (4 × 100 ml). The combined extracts were dried ($MgSO_4$) and concentrated. Yield: 6.07 g (90%); colorless oil. – $[\alpha]_D^{20}$ = -34.9 (*c* = 1.27, EtOH). {ref. [75]: $[\alpha]_D^{20}$ = -23.2 (*c* = 0.2, EtOH)}

Benzyl (2*S*,4*R*)-4-benzyloxy-2-diazoacetylpyrrolidine-1-carboxylate [(2*S*,4*R*)-84]



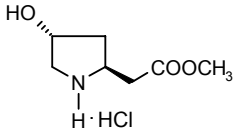
To a solution of 3.90 g (11.0 mmol) of (2*S*,4*R*)-**83** and 50 µl of DMF as a catalyst in 26 ml of CH_2Cl_2 2.10 g (16.5 mmol) of $(COCl)_2$ was added at 0 °C. After the mixture had been stirred for 1 h at 0 °C, the solvent was removed under vacuo to afford the acid chloride as a yellow oil. To a solution of 2.22 g (52.8 mmol) of CH_2N_2 in 150 ml of Et_2O the acid chloride was diluted in 4.5 ml of Et_2O and slowly added at 0 °C. After the resulting yellow solution had been stirred for 1 h, excessive CH_2N_2 was decomposed by the addition of AcOH and then the mixture was neutralized with aq. 1% K_2CO_3, dried (Na_2SO_4) and evaporated to give a yellow oil. Purification by CC (ϕ 45 × 230; *iso*-hexane/acetone, 7:3). Yield: 3.33 g (80%); yellow oil. – TLC: R_f = 0.41 (*n*-heptane/acetone, 3:2). – $[\alpha]_D^{20}$ = -55.5 (*c* = 1.00, EtOAc). – ^{1}H NMR ($CDCl_3$, -30 °C): Two rotamers (the chemical shift small one to the large one 43:57) δ = 2.01-2.07, 2.10-2.16 (m, 1 H, NCHCH_2), 2.30-2.37, 2.41-2.48 (m, 1 H, NCHCH_2), 3.55-3.59, 3.61-3.65 (m, 1 H, NCH_2), 3.69-3.73, 3.88-3.92 (m, 1 H, NCH_2), 4.14-4.23 (m, 1 H, NCH_2CHO), 4.37-4.53 (m, 3 H, NC*H* and PhCH_2OCH), 5.00-5.23 (m, 2 H, PhCH_2OCO), 5.26, 5.54 (s, 1 H, CHN_2), 7.28-7.38 (m, 10 H, H_{aromat}). – IR: $\tilde{\nu}$ = 3090, 3033, 2943, 2107, 1704, 1650, 1416, 1357, 1119, 770, 740, 698 cm $^{-1}$. – MS; *m*/*z* (%): 380 (2) $[M+1]^+$, 352 (100), 310 (34), 266 (29), 181 823), 107 (5). – $C_{21}H_{21}N_3O_4$ (379.42): calcd. C 66.48, H 5.58, N 11.08; found C 66.82, H 5.71, N 10.63.

Methyl (2*S*,4*R*)-4-benzyloxy-1-benzyloxycarbonylpyrrolidine-2-acetate [(2*S*,4*R*)-85]



To a solution of 390 mg (1.03 mmol) of (2*S*,4*R*)-**84** in 3 ml of MeOH, a solution of 17 mg (0.10 mmol) of AgOAc and 61 mg (0.61 mmol) of TEA in 1.5 ml of MeOH was added at r.t. The mixture turned to be brown within a few minutes, and then was warmed to 60 °C for 30 min. The reaction mixture was decolorized with charlcoal and concentrated. The resulting oil was purified by CC (ϕ 15 × 210; *n*-heptane/acetone, 3:1). Yield: 317 mg (81%); colorless oil. – TLC: R_f = 0.45 (*n*-heptane/acetone, 3:2). – $[\alpha]_D^{20}$ = -33.8 (*c* = 0.95, EtOAc). – ^{1}H NMR ($C_6D_5NO_2$, 120 °C): δ = 2.07-2.13 (m, 1 H, C*H*$_2$CHCH$_2$COO), 2.41-2.47 (m, 1 H, C*H*$_2$CHCH$_2$COO), 2.62 (dd, *J* = 15.4/8.4 Hz, 1 H, CH$_2$COO), 3.07 (dd, *J* = 15.4/3.7 Hz, 1 H, CH$_2$COO), 3.62 (dd, *J* = 11.8/4.8 Hz, 1 H, NCH$_2$), 3.66 (s, 3 H, CH$_3$), 3.91 (br. d, *J* = 11.8 Hz, 1 H, NCH$_2$), 4.24-4.29 (m, 1 H, NCH$_2$C*H*O), 4.50-4.54 (m, 1 H, NCH), 4.56 (s, 2 H, PhC*H*$_2$OCH), 5.26 (s, 2 H, COOC*H*$_2$Ph), 7.25-7.45 (m, 10 H, H$_{aromat}$). – IR: $\tilde{\nu}$ = 3092, 3034, 2109, 1746, 1712, 1644, 1416, 1125, 770, 754, 698 cm^1. – MS; *m*/*z* (%): 384 (22) $[M+1]^+$, 340 (26), 248 (32), 148 (17), 91 (100). – $C_{22}H_{25}NO_5$ (383.44): calcd. C 68.91, H 6.57, N 3.65; found C 68.80, H 6.59, N 3.52.

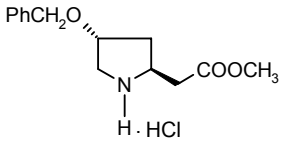
Methyl (2*S*,4*R*)-4-hydroxypyrrolidine-2-acetate hydrochloride [(2*S*,4*R*)-86]



To a solution of 325 mg (0.848 mmol) of (2*S*,4*R*)-**85** and 80 µl (0.96 mmol) of aq. 37% HCl in 10 ml of MeOH , 162 mg (0.153 mmol) of 10% Pd-C was added. The mixture was hydrogenated under ambient pressure at r.t. for 5 d, then filtrated. The filtrate was evaporated and its residue was dissolved in a small amount of MeOH and then crystallized from *i*Pr$_2$O. Yield: 149 mg (90%); colorless crystals. – M.p. 116-117 °C. – $[\alpha]_D^{20}$ = +42.8 (*c* = 0.43, MeOH). – ^{1}H NMR (CD$_3$OD): δ = 1.71 (ddd, *J* = 13.7/11.4/4.0 Hz, 1 H, C*H*$_2$CHCH$_2$COO), 2.09 (ddt, *J* = 13.7/6.4/1.5 Hz, 1 H, C*H*$_2$CHCH$_2$COO), 2.69 (dd, *J* = 18.0/9.9 Hz, 1 H, CH$_2$COO), 2.82 (dd, *J* = 18.0/4.0 Hz, 1 H, CH$_2$COO), 3.09 (dd, *J* = 12.2/1.5 Hz, 1 H, NCH$_2$),

3.25 (dd, J = 12.2/3.7 Hz, 1 H, NCH_2), 3.62 (s, 3 H, CH_3), 3.99-4.07 (m, 1 H, NCH), 4.38-4.41 (m, 1 H, C*H*OH). – IR: $\tilde{\nu}$ = 3333, 2955, 1735, 1588, 1202, 1163 cm^{-1}. – MS; *m*/*z* (%): 160 (100), 142 (8). – $C_7H_{14}ClNO_3$ (195.46): calcd. C 42.97, H 7.21, N 7.16, Cl 18.12; found C 42.78, H 7.42, N 7.16, Cl 18.16.

Methyl (2*S*,4*R*)-4-benzyloxypyrrolidine-2-acetate hydrochloride [(2*S*,4*R*)-87]



1) To a solution of 298 mg (0.778 mmol) of (2*S*,4*R*)-**85** and 196 mg (3.11 mmol) of $HCOONH_4$ in 5 ml of MeOH, 100 mg (0.047 mmol) of 5% Pd-C was added. The mixture was hydrogenated at r.t. under ambient pressure for 2 h, then filtrated and evaporated. The resulting residue was dissolved in a small amount of H_2O and the mixture was extracted with Et_2O. the combined extract was dried (Na_2SO_4) and concentrated to give an oil, which was bubbled by dry HCl gas in iPr$_2$O to give 151 mg (70%) of (2*S*,4*R*)-**87** as colorless crystals. – M.p. 128-129 °C (iPr$_2$O). – $[\alpha]_D^{20}$ = +18.4 (c = 1.02, MeOH). – ^{1}H NMR (CD_3OD): δ = 1.71 (ddd, J = 14.0/11.5/4.0 Hz, 1 H, C*H*$_2$CHCH$_2$COO), 2.33-2.39 (m, 1 H, C*H*$_2$CHCH$_2$COO), 2.71 (dd, J = 18.0/9.9 Hz, 1 H, CH_2COO), 2.86 (dd, J = 18.0/4.0 Hz, 1 H, CH_2COO), 3.28 (dd, J = 12.7/3.8 Hz, 1 H, NC*H*$_2$CHO), 3.36 (br. d, J = 12.7 Hz, 1 H, NC*H*$_2$CHO), 3.63 (s, 3 H, CH_3), 3.96-4.04 (m, 1 H, NCH), 4.22-4.25 (m, 1 H, NCH$_2$C*H*O), 4.45 (s, 2 H, C*H*$_2$Ph), 7.15-7.27 (m, 5 H, H_{aromat}). – IR: $\tilde{\nu}$ = 3456, 3031, 2900, 2732, 1735, 1209, 1166, 740, 700 cm^{-1}. – MS; *m*/*z* (%): 250 (100), 176 (9), 143 (5), 119 (1). – $C_{14}H_{20}ClNO_3$ (285.77): calcd. C 58.84, H 7.05, N 4.90, Cl 12.41; found C 58.67, H 7.22, N 4.91, Cl 12.57.

2) To a solution of 300 mg (0.783 mmol) of (2*S*,4*R*)-**85** and 24 mg (0.23 mmol) of TEA in 15 ml of MeOH, 150 mg (0.141 mmol) of 10% Pd-C was added. The mixture was hydrogenated under ambient pressure at r.t. for 23 h, and then filtrated and evaporated. The resulting residue was bubbled by dry HCl gas in iPr$_2$O to give 203 mg (91%) of (2*S*,4*R*)-**87**.

6.1.2 Preparation of alkyl halides

Cyclopropyldiphenylmethanol (117)

To a solution of 5.70 g (0.115 mmol) of ethyl cyclopropanecarboxylate in 85 ml of THF, PhMgBr, prepared from 18.0 g (0.115 mmol) of C_6H_5Br and 2.80 g (0.115 mmol) of Mg powder in 90 ml of THF, was added at 0 °C. The mixture was allowed to stir at r.t. for 1 h and sat. aq. NH_4Cl was added. Organic layer was isolated, and dried (Na_2SO_4) and evaporated. The residual oil was crystallized to give 9.19 g (82%) of **117** as colorless crystals. – M.p. 82-84 °C (petroleum ether). {ref. [83]: M.p. 82-83 °C}.

4-Bromo-1,1-dipheny-1-butene (118)

According to ref. [35]: 7.40 g (33 mmol) of **117** in 10 ml of CH_2Cl_2 was treated with 30 ml (0.26 mol) of 47% hydrobromic acid at 0 °C for 4 h. The mixture was extracted with CH_2Cl_2, washed with sat. $NaHCO_3$, H_2O, dried (Na_2SO_4) and evaporated to give 8.63 g (86%) of **118** as colorless oil.

Tris(4-methoxyphenyl)methanol (119)

According to ref. [84]: To a solution of 6.65 g (40 mmol) of methyl 4-methoxybenzoate in 105 ml of THF 4-methoxyphenyl magnesium bromide, prepared from 2.07 g (86.0 mmol) of Mg and 15.7 g (84.0 mmol) of 4-methoxyphenylbromide, was added at 0 °C. The mixture was stirred at r.t. for 3 h and the reaction was quenched with sat. aq. NH_4Cl. The organic layer was separated, dried (Na_2SO_4) and concentrated to yield an oil, which was crystallized from *i*Pr_2O to give 11.5 g (82%) of **119** as colorless crystals. – M.p. 81-84 °C (*n*-heptane). {ref. [85]: M.p. 82-82.5 °C (*n*-pentane)}.

1-Bromo-2-[tris(4-methoxyphenyl)]methoxyethane (120)

According to ref. [85]: Tris(4-methoxyphenyl)chloromethane as violet solid was prepared from 4.15 g (11.8 mmol) of **119** and 2.04 g (1.85 ml, 26.0 mmol) of AcCl in 20 ml of CH_2Cl_2. 1.56 g (0.880 ml, 11.8 mmol) of 2-bromoethanol was dropwise added at 0 °C to the solution of the above violet solid in 20 ml of CH_2Cl_2, and followed by the addition of 1.74 g (17.2 mmol) of

TEA. After 1 h, this mixture was washed with H_2O, and dried (Na_2SO_4) and concentrated to yield a yellow oil. Purification by CC (Al_2O_3, mesh 70-230, pH 9.5 ± 0.5; *n*-heptane/EtOAc, 9:1) gave 4.87 g (90%) of **120** [35] as colorless oil.

2-Bromo-3-methylthiophene (121)

According to ref. [86]: To a solution of 4.80 ml (4.91 g, 50.0 mmol) of 3-methylthiophene in 38 ml of EtOAc, a suspension of 9.53 g (52.0 mmol) of NBS in 61 ml of EtOAc-$CHCl_3$ (1:1, v/v) was stepwise added at r.t. within 12 min. After 1.5 h, the mixture was washed with aq. 1% K_2CO_3, dried ($MgSO_4$), and finally evaporated. The residual oil was purified by azeotropic distillation. Yield: 7.13 g (81%); yellow oil.

Cyclopropyldi(3-methyl-2-thienyl)methanol (122) [18]

To a solution of 3-methyl-2-thienylmagnesium bromide in 50 ml of Et_2O, which was prepared from 7.10 g (40.1 mmol) of **121** and 1.01 g (42.1 mmol) of Mg in 60 ml of Et_2O, 1.89 ml (1.83 g, 16.0 mmol) of ethyl cyclopropanecarboxylate in 10 ml of Et_2O was slowly added below 10 °C. The mixture was stirred over night and then quenched with aq. sat. NH_4Cl. The organic layer was isolated, dried ($MgSO_4$), and concentrated. Yield: 4.1 g (39%); yellow oil.

4-Bromo-1,1-di(3-methyl-2-thienyl)-1-butene (123)

According to ref. [62]: To a solution of 4.08 g (12.5 mmol) of **122** and 6 ml of AcOH, 30 ml (0.56 mmol) of aq. 47% HBr was added at 0-5 °C. The resulting mixture was stirred for 1.5 h, and then diluted with 80 ml of H_2O and extracted with Et_2O (2 × 40 ml). The combined extracts were washed, in turn, with H_2O, aq. 1% K_2CO_3, H_2O, dried (Na_2SO_4), and evaporated. The residue was purified by CC (ϕ 25 × 100, *n*-heptane). Yield 3.93 g (78%); yellow oil.

9-(3-Chloropropyl)carbazole (124)

According to ref. [87]: To a solution of 13.8 g (82.8 mmol) of carbazole and 15.8 g (101 mmol) of 1-bromo-3-chloropropane in 180 ml of DMF, 16.2 g (405 mmol) of NaOH powder was slowly added. The mixture was stirred at r.t. for 3 h, and then mixed with 500 ml of ice-water

and extracted with *i*Pr_2O (2 × 200 ml). The combined extracts were washed with H_2O, dried ($MgSO_4$), and evaporated. The residue was purified by CC (ϕ 50 × 200; *n*-heptane/EtOAc, 75:25). Yield: 13.6 g (68%); slightly yellow oil.

9-(3-Iodopropyl)carbazole (125)

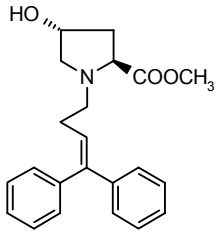
A mixture of 8.0 g (33 mmol) of **124** and 10 g (60 mmol) of KI was stirred in 100 ml of acetone at r.t. for 15 d, and then filtrated and evaporated. Yield: 8.2 g; yellow oil [purity: 70% (w/w); I/Cl = 1.6:1 (mol/mol), determined by ^1H NMR].

6.1.3 Preparation of N-Substituted pyrrolidine derivatives

General procedure 2 (GP2) [30]

The respective alkyl halide RX (1.0 equiv.) and KI (0.2 equiv.) were added to a mixture of the pyrrolidine derivative (1.0 equiv. hydrochloride) and K_2CO_3 (5.0 equiv.) in acetone (4~8 ml/mmol). It was stirred at r.t. for the time indicated. Inorganic salts were removed by filtration and the filtrate was evaporated in vacuuo. The residue was purified by CC.

Methyl (2*S*,4*R*)-1-(4,4-diphenylbut-3-en-1-yl)-4-hydroxypyrrolidine-2-carboxylate [(2*S*,4*R*)-39a]

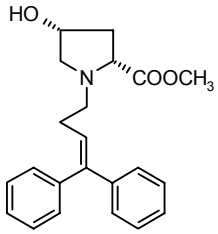


According to GP2 from 50 mg (0.30 mmol) of KI, 454 mg (1.50 mmol) of **118,** 274 mg (1.0 mmol) of (2*S*,4*R*)-**38** and 691 mg (5.0 mmol) of K_2CO_3 in 8 ml of acetone; reaction time: 144 h; purification by CC (ϕ 20 × 310; *n*-heptane/acetone, 4:1). Yield: 273 mg (52%); colorless oil. – TLC: R_f = 0.39 (*n*-heptane/acetone, 3:2). – $[\alpha]_D^{20}$ = -53.3 (*c* = 0.6, EtOAc). – ^{1}H NMR ($CDCl_3$): δ = 2.03 (ddd, *J* = 13.7/7.6/3.1 Hz, 1 H, NCHC*H*$_2$), 2.19 (dd, *J* = 13.7/7.6 Hz, 1 H, NCHC*H*$_2$), 2.30 (q, *J* = 7.5 Hz, 2 H, NCH$_2$C*H*$_2$), 2.41 (dd, *J* = 10.1/3.6 Hz, 1 H, NC*H*$_2$CHOH), 2.62 (dt, *J* = 12.2/7.5 Hz, 1 H, NC*H*$_2$CH$_2$), 2.82 (dt, *J* = 12.2/7.5 Hz, 1 H, NC*H*$_2$CH$_2$), 3.33 (dd, *J* = 10.1/5.5 Hz, 1 H, NC*H*$_2$CHOH), 3.53 (t, *J* = 7.6 Hz, 1 H, NC*H*), 3.67 (s, 3 H, OCH$_3$), 4.40-4.45 (m, 1 H, C*H*OH), 6.07 (t, *J* = 7.5 Hz, 1 H, =C*H*CH$_2$), 7.15-7.38 (m, 10 H, H$_{aromat}$). – IR: $\tilde{\nu}$ = 3418, 3055, 2949, 1738, 1443, 763, 701 cm^{-1}. – MS; *m*/*z* (%): 352 (67) $[M+1]^+$, 351 (100), 207 (18), 129 (58). – $C_{22}H_{25}NO_3$ (351.45): calcd. C 75.19, H 7.17, N 4.00; found C 74.83, H 7.22, N 3.94.

The oily product described above was treated in acetone with anhydrous HCl to give its hydrochloride as colorless crystals. – M.p. 125-127 °C (acetone). – $[\alpha]_D^{20}$ = -39.9 (*c* = 1.00, EtOH). – ^{1}H NMR (CD_3OD): δ = 2.20 (ddd, *J* = 13.6/12.4/4.3 Hz, 1 H, NCHC*H*$_2$), 2.45 (dd, *J* = 13.6/7.2 Hz, 1 H, NCHC*H*$_2$), 2.51-4.61 (m, 2 H, NCH$_2$C*H*$_2$), 3.19 (d, *J* = 12.4 Hz, 1 H, NC*H*$_2$CHOH), 3.34-3.41 (m, 1 H, NC*H*$_2$CH$_2$), 3.54-3.62 (m, 1 H, NC*H*$_2$CH$_2$), 3.76 (dd, *J* =

12.4/4.3 Hz, 1 H, NC*H*$_2$CHOH), 3.85 (s, 3 H, OCH$_3$), 4.50-4.54 (m, 1 H, C*H*OH), 4.61 (dd, *J* = 12.4/7.2 Hz, 1 H, NC*H*), 6.09 (t, *J* = 7.2 Hz, 1 H, =C*H*CH$_2$), 7.18-7.47 (m, 10 H, H$_{aromat}$). – IR: $\tilde{\nu}$ = 3254, 2935, 1749, 772, 703 cm^{-1}. – MS; *m*/*z* (%): 353 (27), 352 (100) [M-Cl]$^+$, 158 (13). – $C_{22}H_{26}ClNO_3$ (387.91): calcd. C 68.12, H 6.76, N 3.61; found C 68.15, H 6.85, N 3.49.

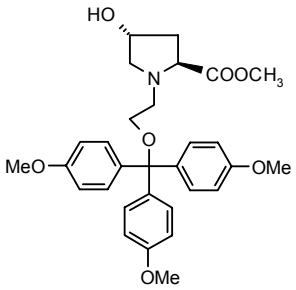
Methyl (2*R*,4*R*)-1-(4,4-diphenylbut-3-en-1-yl)-4-hydroxypyrrolidine-2-carboxylate [(2*R*,4*R*)-39a]



According to GP2 from 50 mg (0.30 mmol) of KI, 936 mg (3.09 mmol) of **118**, 549 mg (3.00 mmol) of (2*R*,4*R*)-**38**, 2.07 g (15.0 mmol) of K_2CO_3 in 12 ml of acetone; reaction time: 72 h; purification by CC (ϕ 25 × 260; *n*-heptane/EtOAc, 3:2). Yield: 432 mg (41%); colorless oil. – TLC: R_f = 0.28 (*n*-heptane/EtOAc, 3:2). – $[\alpha]_D^{20}$ = +45.4 (*c* = 1.00, EtOAc). – ^{1}H NMR ($CDCl_3$): δ = 1.92 (ddt, *J* = 14.2/3.6/1.5 Hz, 1 H, NCHC*H*$_2$), 2.30 (q, *J* = 7.5 Hz, 2 H, NCH$_2$C*H*$_2$), 2.29-2.37 (m, 1 H, NCHC*H*$_2$), 2.58 (dd, 1 H, *J* = 9.9/4.0 Hz, NC*H*$_2$CHOH), 2.63 (dt, *J* = 12.0/7.5 Hz, 1 H, NC*H*$_2$CH$_2$), 2.81 (dt, *J* = 12.0/7.5 Hz, 1 H, NC*H*$_2$CH$_2$), 3.00 (dt, *J* = 9.9/1.5 Hz, 1 H, NC*H*$_2$CHOH), 3.26 (dd, *J* = 9.9/3.6 Hz, 1 H, NC*H*), 3.70 (s, 3 H, OCH$_3$), 4.23-4.26 (m, 1 H, C*H*OH), 6.08 (t, *J* = 7.5 Hz, 1 H, =C*H*CH$_2$), 7.16-7.40 (m, 10 H, H$_{aromat}$). – IR: $\tilde{\nu}$ = 3424, 3023, 2950, 1732, 1598, 1494, 1443, 1203, 1075, 867, 764, 700 cm^{-1}.– MS; *m*/*z* (%): 352 (100) [M+1]$^+$, 320 (34), 158 (39). – $C_{22}H_{25}NO_3$ (351.45): calcd. C 75.19, H 7.17, N 4.00; found C 74.90, H 7.18, N 3.82.

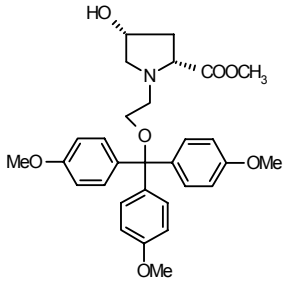
Methyl (2*S*,4*R*)-4-hydroxy-1-{2-[tris(4-methoxyphenyl)methoxy]-1-ethyl}pyrrolidine-2-carboxylate [(2*S*,4*R*)-39b]

According to GP2 from 50 mg (0.30 mmol) of KI, 682 mg (1.49 mmol) of **120**, 273 mg (1.49 mmol) of (2*S*,4*R*)-**38**, 680 mg (6.85 mmol) of K_2CO_3 in 6 ml of acetone; reaction time: 72 h; purification by CC (Al_2O_3, pH 7.5, mesh 70-230; ϕ 20 × 250; *n*-heptane/acetone, 2:1). Yield: 414 mg (53%); colorless oil. – TLC: R_f = 0.16 (*n*-heptane/acetone, 3:2). – $[\alpha]_D^{22}$ = -24.5 (*c* =



0.55, EtOH). – ^{1}H NMR ($CDCl_3$): δ = 2.00-2.07 (m, 1 H, NCHCH_2), 2.16 (ddt, *J* = 13.6/7.2/3.3 Hz, 1 H, NCHCH_2), 2.57 (dd, *J* = 10.2/3.4 Hz, 1 H, NCH_2CHOH), 2.83 (m, 1 H, NCH_2CH$_2$), 2.95 (m, 1 H, NCH_2CH$_2$), 3.20 (t, *J* = 6.1 Hz, 2 H, NCH$_2$CH_2), 3.38 (dd, *J* = 10.2/5.4 Hz, 1 H, NCH_2CHOH), 3.64-3.66 (m, 1 H, NC*H*), 3.65 (s, 3 H, COOCH_3), 3.78 (s, 9 H, ArOCH_3), 4.40-4.44 (m, 1 H, C*H*OH), 6.83-6.79 (m, 6 H, H_{aromat}), 7.29-7.33 (m, 6 H, H_{aromat}). – IR: $\tilde{\nu}$ = 3418, 3031, 2952, 1740, 1608, 1582, 1504, 1250, 1035, 828 cm^{-1}. – MS (ESI$^+$); *m*/*z* (%): 522 $[M+1]^+$ (1), 333 (67), 266 (22), 146 (42). – $C_{30}H_{35}NO_7$ (521.61): calcd. C 69.08, H 6.76, N 2.69; found C 68.85, H 7.04, N 2.65.

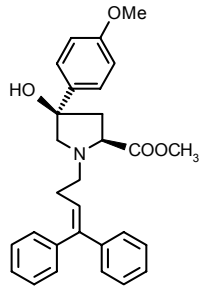
Methyl (2*R*,4*R*)-4-hydroxy-1-{2-[tris(4-methoxyphenyl)methoxy]-1-ethyl}pyrrolidine-2-carboxylate [(2*R*,4*R*)-39b]



According to GP2 from 42 mg (0.25 mmol) of KI, 1.14 g (2.50 mmol) of **120**, 458 mg (2.50 mmol) of (2*R*,4*R*)-**38**, 1.73 g (12.5 mmol) of K_2CO_3 in 12 ml of acetone; reaction time: 72 h; purification by CC (ϕ 25 × 220; *n*-heptane/acetone, 3:2). Yield: 429 mg (33%); colorless oil. – TLC: R_f = 0.32 (*n*-heptane/acetone, 3:2). – $[\alpha]_D^{20}$ = +30.8 (*c* = 1.45, EtOH). – ^{1}H NMR ($CDCl_3$): δ = 1.88-1.93 (m, 1 H, NCHCH_2), 2.32 (ddd, *J* = 14.2/10.0/5.9 Hz, 1 H, NCHCH_2), 2.67 (dd, *J* = 9.9/4.1 Hz, 1 H, NCH_2CHOH), 2.79 (dt, *J* = 12.4/6.0 Hz, 1 H, NCH_2CH$_2$), 2.94 (dt, *J* = 12.4/6.0 Hz, 1 H, NCH_2CH$_2$), 3.03 (s, 1 H, OH), 3.06 (dt, *J* = 9.9/1.4 Hz, 1 H, NCH_2CHOH), 3.12-3.21 (m, 2 H, NCH$_2$CH_2), 3.38 (dd, *J* = 10.0/3.9 Hz, 1 H, NCH), 3.66 (s, 3 H, COOCH_3), 3.77 (s, 9 H, ArOCH_3), 4.20-4.24 (m, 1 H, C*H*OH), 6.78-6.82 (m, 6 H, H_{aromat}), 7.28-7.32 (m, 6 H, H_{aromat}). – IR: $\tilde{\nu}$ = 3444, 2952, 2836, 1732, 1607, 1504, 1249,

1034, 827, 787 cm^{-1}. – MS (ESI^+); *m*/*z* (%): 522 (1), 333 (100). – $C_{30}H_{35}NO_7$ (521.61): calcd. C 69.08, H 6.76, N 2.69; found C 69.41, H 7.16, N 2.48.

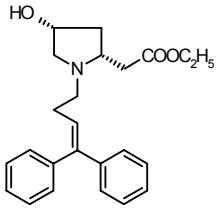
Methyl (2*S*,4*R*)-1-(4,4-diphenylbut-3-en-1-yl)-4-hydroxy-4-(4-methoxyphenyl)-pyrrolidine-2-carboxylate [(2*S*,4*R*)-53a]



According to GP2 from 76 mg (0.30 mmol) of (2*S*,4*R*)-**114**, 93 mg (0.30 mmol) of **118**, 167 mg (0.906 mmol) of K_2CO_3 and 10 mg of KI in 3 ml of acetone; reaction time: 2 d; purification by CC (ϕ 18 × 240; *n*-heptane/EtOAc, 7:3). Yield: 73 mg (53%); colorless crystals. – M.p. 106-107 °C (*i*Pr_2O). – TLC: R_f = 0.23 (*n*-heptane/EtOAc, 7:3). – $[\alpha]_D^{20}$ = -47.8 (*c* = 0.95, $CHCl_3$). – ^1H NMR ($CDCl_3$, 500 MHz): δ = 2.15 (ddd, *J* = 13.9/3.2/2.1 Hz, 1 H, NCHCH_2), 2.26 (q, *J* = 7.5 Hz, 2 H, NCH_2CH_2), 2.49 (dd, *J* = 13.9/10.8 Hz, 1 H, NCHCH_2), 2.64-2.69 (m, 2 H, NCH_2CH_2 and NCH_2CO), 2.80 (dt, *J* = 12.0/7.5 Hz, 1 H, NCH_2CH_2), 3.08 (dd, *J* = 9.1/2.1 Hz, 1 H, NCH_2CO), 3.37 (dd, *J* = 10.8/3.2 Hz, 1 H, NCH), 3.67 (s, 3 H, COOCH_3), 3.73 (s, 3 H, ArOCH_3), 3.91 (s, 1 H, OH), 6.05 (t, *J* = 7.5 Hz, 1 H, =C*H*CH_2), 6.79-6.82 (m, 2 H, H_{aromat}), 7.10-7.33 (m, 12 H, H_{aromat}). – IR: $\tilde{\nu}$ = 3474, 3060, 2955, 1720, 1608, 1515, 1274, 1031, 834, 770, 752, 720 cm^{-1}. – MS; *m*/*z* (%): 458 (58) $[M+1]^+$, 440 (66), 426 (33), 380 (46), 264 (100), 207 (93), 167 (71), 109 (8). – $C_{29}H_{31}NO_4$ (457.57): calcd. C 76.12, H 6.83, N 3.06; found C 76.15, H 7.04, N 3.04. All analytical data were identical with those of one diastereomer which was prepared via the organometallic addition to (2*S*)-**52a**.

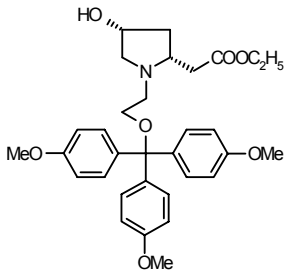
Ethyl (2*R*,4*R*)-1-(4,4-diphenylbut-3-en-1-yl)-4-hydroxypyrrolidine-2-acetate [(2*R*,4*R*)-88a]

According to GP2 from 92 mg (0.44 mmol) of (2*R*,4*R*)-**64**, 132 mg (0.439 mmol) of **118**, 298 mg (2.16 mmol) of K_2CO_3 and 10 mg of KI in 2.7 ml of acetone; purification by CC (ϕ 18 × 230; *n*-heptane/acetone, 3:1). Yield: 115 mg (69%); colorless oil. – TLC: R_f = 0.39 (*n*-



heptane/acetone, 3:2). – $[\alpha]_D^{20}$ = +58.9 (*c* = 0.85, EtOAc). – ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.20 (t, *J* = 7.1 Hz, 3 H, CH_2CH_3), 1.69 (ddt, *J* = 14.3/6.1/1.7 Hz, 1 H, CH_2CHCH_2COO), 2.16 (dd, *J* = 10.0/4.2 Hz, 1 H, NCH_2CHOH), 2.23-2.33 (m, 3 H, NCH_2CH_2 and 2 H of NCH_2CH_2), 2.37 (ddd, *J* = 14.3/9.2/6.5 Hz, 1 H, CH_2CHCH_2COO), 2.43 (dd, *J* = 15.3/7.8 Hz, 1 H, CH_2COO), 2.62 (dd, *J* = 15.3/3.3 Hz, 1 H, CH_2COO), 2.63-2.70 (m, 2 H, NC*H* and O*H*), 2.80-2.90 (m, 1 H, NCH_2CH_2), 2.99 (d, *J* = 10.0 Hz, 1 H, NCH_2CHOH), 4.05-4.15 (m, 3 H, C*H*OH and 2 H of CH_2CH_3), 6.05-6.09 (m, 1 H, =C*H*CH_2), 7.14-7.37 (m, 10 H, H_{aromat}). – ^{13}C {^{1}H} (decoupling: X-freq. ^{1}H 500 MHz; Y-freq. ^{13}C 125.8 MHz): δ = 14.2 (CH_3), 28.8 (NCH_2CH_2), 38.8 (CH_2COO), 40.9 (1 C, CH_2CHCH_2COO), 53.3 (NCH_2CH_2), 59.5 (NCH), 60.4 (OCH_2CH_3), 62.1 (NCH_2CHO), 70.1 (CHOH), 127.0, 127.1 (2 C, C_{aromat}), 127.3 (=$CHCH_2$), 128.2, 128.3 (4 C, C_{aromat}), 129.9 (4 C, C_{aromat}), 140.0 (2 C, C=$CHCH_2$), 142.5 142.7 (2 C, C_{aromat}), 172.3 (COO). – IR: $\tilde{\nu}$ = 3415, 3025, 2976, 1731, 1598, 1444, 1031, 762, 702 cm^{-1}. – MS; *m*/*z* (%): 380 (82) $[M+1]^+$, 334 (100), 292 (17), 186 (43), 140 (18). – $C_{24}H_{29}NO_3$ (379.50): calcd. C 75.96, H 7.70, N 3.69; found C 75.64, H 7.74, N 3.57.

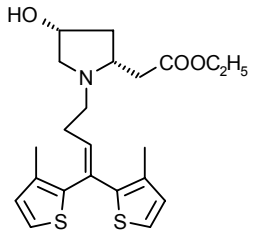
Ethyl (2*R*,4*R*)-4-hydroxy-1-{2-[tris(4-methoxyphenyl)methoxy]-1-ethyl}pyrrolidine-2-acetate [(2*R*,4*R*)-88b]



According to GP2 from 136 mg (0.608 mmol**)** of (2*R*,4*R*)-**64**, 278 mg (0.608 mmol) of **120**, 420 mg (3.04 mmol) of K_2CO_3 and 15 mg of KI in 4 ml of acetone; purification by CC (ϕ 18 × 250; *n*-heptane/acetone, 3:1). Yield: 175 mg (52%); colorless oil. – TLC: R_f = 0.32 (*n*-heptane/acetone, 3:2). – $[\alpha]_D^{20}$ = +22.5 (*c* = 1.65, EtOAc). – ^{1}H NMR ($CDCl_3$): δ = 1.20 (t, *J* = 7.1 Hz, 3 H, CH_2CH_3), 1.69 (ddt, *J* = 14.2/6.2/1.7 Hz, 1 H, CH_2CHCH_2COO), 2.29 (dd, *J* =

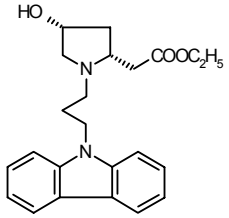
10.1/4.2 Hz, 1 H, NC*H*$_2$CHOH), 2.38 (ddd, *J* = 14.2/9.5/6.6 Hz, 1 H, C*H*$_2$CHCH$_2$COO), 2.41-2.48 (m, 2 H, NC*H*$_2$CH$_2$ and C*H*$_2$COO), 2.64 (dd, *J* = 15.8/3.4 Hz, 1 H, CH$_2$COO), 2.70-2.77 (m, 1 H, NCH), 2.96 (dt, *J* = 12.6/6.3 Hz, 1 H, NC*H*$_2$CH$_2$), 3.05 (br. d, *J* = 10.1 Hz, 1 H, NC*H*$_2$CHOH), 3.12 (dt, *J* = 9.5/5.8 Hz, 1 H, NCH$_2$C*H*$_2$), 3.19 (dt, *J* = 9.5/6.1 Hz, 1 H, NCH$_2$C*H*$_2$), 3.77 (s, 9 H, ArOC*H*$_3$), 4.01-4.14 (m, 2 H, C*H*$_2$CH$_3$), 4.13-4.18 (m, 1 H, C*H*OH), 6.79-6.82 (m, 6 H, H$_{aromat}$), 7.30-7.33 (m, 6 H, H$_{aromat}$). – IR: $\tilde{\nu}$ = 3440, 2955, 2875, 1731, 1607, 1506, 1250, 1035, 828, 732 cm^{-1}. – MS; *m*/*z* (%): 333 (100) [Ar$_3$C]$^+$, 227 (5), 186 (8). – $C_{32}H_{39}NO_7$ (549.66): calcd. C 69.92, H 7.15, N 2.55; found C 69.70, H 7.31, N 2.42.

Ethyl (2*R*,4*R*)-1-[4,4-di(3-methyl-2-thienyl)but-3-en-1-yl]-4-hydroxypyrrolidine-2-acetate [(2*R*,4*R*)-88c]



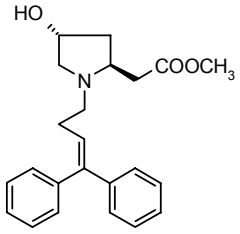
According to GP2 from 92 mg (0.44 mmol) of (2*R*,4*R*)-**64**, 143 mg (0.439 mmol) of **123**, 298 mg (2.16 mmol) of K_2CO_3 and 10 mg of KI in 2.7 ml of acetone; purification by CC (ϕ 18 × 230; *n*-heptane/acetone, 2:1). Yield: 95 mg (52%); yellow oil. – TLC: R_f = 0.32 (*n*-heptane/acetone, 3:2). – $[\alpha]_D^{20}$ = +69.8 (*c* = 0.80, EtOAc). – ^{1}H NMR ($CDCl_3$): δ = 1.23 (t, *J* = 7.3 Hz, 3 H, CH$_2$C*H*$_3$), 1.69 (ddt, *J* = 14.3/6.1/1.7 Hz, 1 H, C*H*$_2$CHCH$_2$COO), 1.99 (s, 3 H, thienyl-C*H*$_3$), 2.04 (s, 3 H, thienyl-C*H*$_3$), 2.20 (dd, *J* = 10.0/4.1 Hz, 1 H, NC*H*$_2$CHOH), 2.25-2.40 (m, 4 H, NC*H*$_2$CH$_2$, C*H*$_2$CHCH$_2$COO and 2 H of NCH$_2$C*H*$_2$), 2.43 (dd, *J* = 15.4/ 7.8 Hz, 1 H, CH$_2$COO), 2.52 (br. s, 1 H, OH), 2.62-2.72 (m, 2 H, NC*H* and C*H*$_2$COO), 2.81-2.92 (m, 1 H, NC*H*$_2$CH$_2$), 3.01 (br. d, *J* = 10.0 Hz, 1 H, NC*H*$_2$CHOH), 4.05-4.18 (m, 3 H, C*H*OH and 2 H of C*H*$_2$CH$_3$), 6.03-6.07 (m, 1 H, =C*H*CH$_2$), 6.75 (d, *J* = 5.2 Hz, 1 H, SCH), 6.84 (d, *J* = 5.2 Hz, 1 H, SCH), 7.04 (d, *J* = 5.2 Hz, 1 H, SCH=C*H*), 7.21 (d, *J* = 5.2 Hz, 1 H, SCH=C*H*). – IR: $\tilde{\nu}$ = 3433, 2937, 1732, 1456, 1156, 1032, 711, 668 cm^{-1}. – MS; *m*/*z* (%): 420 (29) [M+1]$^+$, 374 (35), 186 (57), 140 (100). – $C_{22}H_{29}NO_3S_2$ (419.60): calcd. C 62.98, H 6.97, N 3.34, S 15.28; found C 62.87, H 6.95, N 3.28, S 15.31.

Ethyl (2*R*,4*R*)-1-[3-(9-carbazolyl)-1-propyl]-4-hydroxypyrrolidine-2-acetate [(2*R*,4*R*)-88d]



According to GP2 from 122 mg (0.528 mmol) of (2*R*,4*R*)-**64**, 279 mg (purity: 70.0%, 0.528 mmol) of **125** and 400 mg (2.91 mmol) of K_2CO_3 in 3 ml of acetone; purification by CC (ϕ 18 × 260; *n*-heptane/acetone, 1:3). Yield: 193 mg (87%); colorless oil. – TLC: R_f = 0.31 (*n*-heptane/acetone, 3:2). – $[\alpha]_D^{20}$ = +56.8 (*c* = 0.96, EtOAc). – ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.23 (t, *J* = 7.2 Hz, 3 H, CH_2CH_3), 1.74 (ddt, *J* = 14.3/6.2/1.7 Hz, 1 H, CH_2CHCH_2COO), 1.99-2.14 (m, 2 H, $CHNCH_2CH_2$), 2.21 (dd, *J* = 10.0/4.1 Hz, 1 H, NCH_2CHOH), 2.23-2.29 (m, 1 H, CH_2NCH), 2.38-2.46 (m, 2 H, CH_2CHCH_2COO and CH_2COO), 2.56 (dd, *J* = 15.6/3.6 Hz, 1 H, CH_2COO), 2.64-2.71 (m, 1 H, NCH), 2.84 (ddd, *J* = 15.9/8.7/7.3 Hz, 1 H, CH_2NCH), 3.11 (br. d, *J* = 10.0 Hz, 1 H, NCH_2CHOH), 4.07-4.17 (m, 2 H, CH_2CH_3), 4.19-4.23 (m, 1 H, CHOH), 4.28-4.35 (m, 1 H, CH_2-carbazole), 4.42-4.49 (m, 1 H, CH_2-carbazole), 7.25 (ddd, *J* = 8.0/6.9/1.1 Hz, 2 H, H_{aromat}), 7.44 (br. d, *J* = 8.0 Hz, 2 H, H_{aromat}), 7.49 (ddd, *J* = 8.0/6.9/1.1 Hz, 2 H, H_{aromat}), 8.12 (br. d, *J* = 8.0 Hz, 2 H, H_{aromat}). – IR: $\tilde{\nu}$ = 3427, 3052, 2938, 1732, 1597, 1454, 1326, 751, 725, 616 cm^{-1}. – MS; *m*/*z* (%): 381 (27) $[M+1]^+$, 363 (4), 335 (100), 293 (12), 180 (8), 140 (8). – $C_{23}H_{28}N_2O_3$ (380.49): calcd. C 72.60, H 7.42, N 7.36; found C 72.27, H 7.65, N 7.13.

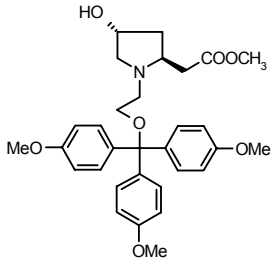
Methyl (2*S*,4*R*)-1-(4,4-diphenylbut-3-en-1-yl)-4-hydroxypyrrolidine-2-acetate [(2*S*,4*R*)-91a]



According to GP2 from 81 mg (0.41 mmol) of (2*S*,4*R*)-**86**, 129 mg (0.426 mmol) of **118**, 228 mg (1.65 mmol) of K_2CO_3 and 10 mg of KI; reaction time: 3 d; purification by CC (ϕ 18 × 230; *iso*-hexane/acetone, 3:1). Yield: 89 mg (59%); colorless oil. – TLC: R_f = 0.31 (*n*-heptane/acetone, 3:2). – $[\alpha]_D^{20}$ = -72.8 (*c* = 0.87, $CHCl_3$). – ^{1}H NMR ($CDCl_3$): δ = 1.83 (ddd, *J* = 13.6/8.4/7.0 Hz, 1 H, CH_2CHCH_2COO), 1.93 (ddd, *J* = 13.6/7.0/3.1 Hz, 1 H,

CH_2CHCH$_2$COO), 2.16 (dd, *J* = 10.1/4.4 Hz, 1 H, NCH_2CHOH), 2.19-2.33 (m, 3 H, CH_2COO and 2 H of NCH$_2$CH_2), 2.39 (ddd, *J* = 12.0/8.8/4.9 Hz, 1 H, NCH_2CH$_2$), 2.58 (dd, *J* = 15.0/4.2 Hz, 1 H, CH$_2$COO), 2.81 (dt, *J* = 12.0/7.3 Hz, 1 H, NCH_2CH$_2$), 3.02-3.09 (m, 1 H, NCH), 3.29 (dd, *J* = 10.1/6.0 Hz, 1 H, NCH_2CHOH), 3.62 (s, 3 H, OCH$_3$), 4.29-4.35 (m, 1 H, C*H*OH), 6.06 (t, *J* = 7.2 Hz, 1 H, =C*H*CH$_2$), 7.14-7.37 (m, 10 H, H$_{aromat}$). – IR: $\tilde{\nu}$ = 3064, 3023, 2950, 1738, 1598, 1443, 763, 701 cm^{-1}. – MS; *m*/*z* (%): 366 (57) [M+1]$^+$, 292 (17), 172 (100). – $C_{23}H_{27}NO_3$ (365.47): calcd. C 75.59, H 7.45, N 3.83; found C 75.31, H 7.30, N 3.63.

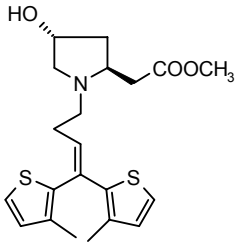
Methyl (2*S*,4*R*)-4-hydroxy-1-{2-[tris(4-methoxyphenyl)methoxy]-1-ethyl}pyrrolidine-2-acetate [(2*S*,4*R*)-91b]



According to GP2 from 195 mg (1.00 mmol) of (2*S*,4*R*)-**86**, 457 mg (1.00 mmol) of **120**, 690 mg (5.00 mmol) of K_2CO_3 and 16 mg of KI in 3 ml of acetone; reaction time: 3 d; purification by CC (ϕ 18 × 230, *n*-heptane/acetone, 7:3). Yield: 210 mg (39%); colorless oil. – TLC: R_f = 0.25 (*n*-heptane/acetone, 3:2). – $[\alpha]_D^{20}$ = -28.2 (*c* = 1.00, EtOAc). – ^{1}H NMR ($CDCl_3$): δ = 1.81 (ddd, *J* = 13.5/8.4/7.0 Hz, 1 H, CH_2CHCH$_2$COO), 1.95 (ddd, *J* = 13.5/7.0/3.1 Hz, 1 H, CH_2CHCH$_2$COO), 2.23 (dd, *J* = 15.0/9.1 Hz, 1 H, CH$_2$COO), 2.32 (dd, *J* = 10.4/4.4 Hz, 1 H, NCH_2CHOH), 2.56-2.66 (m, 2 H, CH_2COO and NCH_2CH$_2$), 2.93 (dt, *J* = 12.6/6.3 Hz, 1 H, NCH_2CH$_2$), 3.10-3.20 (m, 3 H, NC*H* and 2 H of NCH$_2$CH_2), 3.36 (dd, *J* = 10.4/5.8 Hz, 1 H, NCH_2CHOH), 3.63 (s, 3 H, COOCH$_3$), 3.77 (s, 9 H, ArOCH_3), 4.33-4.38 (m, 1H, C*H*OH), 6.78-6.82 (m, 6 H, H$_{aromat}$), 7.30-7.34 (m, 6 H, H$_{aromat}$). – IR: $\tilde{\nu}$ = 3444, 3036, 2950, 1735, 1608, 1504, 1435, 1173, 1033, 829 cm^{-1}. – MS; *m*/*z* (%): 333 (100) [Ar$_3$C]$^+$, 227 (76), 204 (52), 186 (16), 172 (60), 130 (12), 79 (37). – $C_{31}H_{37}NO_7$ (535.64): calcd. C 69.51, H 6.96, N 2.62; found C 69.58, H 7.28, N 2.63.

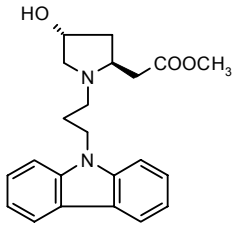
Methyl (2*S*,4*R*)-1-[4,4-di(3-methyl-2-thienyl)but-3-en-1-yl]-4-hydroxypyrrolidine-2-acetate [(2*S*,4*R*)-91c]

According to GP2 from 94 mg (0.48 mmol) of (2*S*,4*R*)-**86**, 156 mg (0.480 mmol) of **123**, 330



mg (2.40 mmol) of K_2CO_3 and 11 mg of KI in 3 ml of acetone; reaction time: 3 d; purification by CC (ϕ 20 × 300; *n*-heptane/acetone, 3:1). Yield: 80 mg (41%); slight yellow oil. – TLC: R_f = 0.32 (*n*-heptane/acetone 2:3). – $[\alpha]_D^{20}$ = -84.6 (*c* = 1.00, EtOAc). – ^{1}H NMR ($CDCl_3$): δ = 1.83 (ddd, *J* = 13.5/8.3/7.1 Hz, 1 H, C*H*$_2$CHCH$_2$COO), 1.95 (ddd, *J* = 13.5/7.1/3.2 Hz, 1 H, C*H*$_2$CHCH$_2$COO), 2.00 (s, 3 H, thienyl-C*H*$_3$), 2.03 (s, 3 H, thienyl-C*H*$_3$), 2.16-2.32 (m, 4 H, NC*H*$_2$CHOH, C*H*$_2$COO and 2 H of NCH$_2$C*H*$_2$), 2.41 (ddd, *J* = 11.9/8.2/5.0 Hz, 1 H, NC*H*$_2$CH$_2$), 2.62 (dd, *J* = 15.0/4.0 Hz, 1 H, CH$_2$COO), 2.83 (dt, *J* = 11.9/8.2 Hz, 1 H, NC*H*$_2$CH$_2$), 3.05-3.12 (m, 1 H, NCH), 3.33 (dd, *J* = 10.2/6.1 Hz, 1 H, NC*H*$_2$CHOH), 3.65 (s, 3 H, OCH$_3$), 4.32-4.37 (m, 1 H, C*H*OH), 6.04 (t, *J* = 7.3 Hz, 1 H, =C*H*CH$_2$), 6.75 (d, *J* = 5.1 Hz, 1 H, SCH), 6.83 (d, *J* = 5.1 Hz, 1 H, SCH), 7.04 (d, *J* = 5.1 Hz, 1 H, SCH=C*H*), 7.20 (d, *J* = 5.1 Hz, 1 H, SCH=C*H*). – IR: $\tilde{\nu}$ = 3410, 3100, 2949, 1738, 1436, 713 cm^{-1}. – MS; *m*/*z* (%): 406 (46) $[M+1]^+$, 388 (4), 332 (10), 172 (100), 158 (2). – $C_{21}H_{27}NO_3S_2$ (405.57): calcd. C 62.19, H 6.71, N 3.45, S 15.81; found C 62.43, H 6.99, N 3.35, S 15.64.

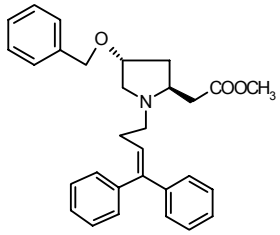
Methyl (2*S*,4*R*)-1-[3-(9-carbazolyl)-1-propyl]-4-hydroxypyrrolidine-2-acetate [(2*S*,4*R*)-91d]



According to GP2 from 166 mg (0.847 mmol) of (2*S*,4*R*)-**86**, 406 mg (purity: 70.0%, 0.847 mmol) of **125**, 574 mg (1.24 mmol) of K_2CO_3 in 3.5 ml of acetone; reaction time: 3 d; purification by CC (ϕ 18 × 240; *n*-heptane/acetone, 3:1). Yield: 170 mg (57%); yellowish oil. – TLC: R_f = 0.21 (*n*-heptane/acetone, 3:2). – $[\alpha]_D^{20}$ = -51.0 (*c* = 1.05, EtOAc). – ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.89 (ddd, *J* = 13.6/8.2/7.0 Hz, 1 H, C*H*$_2$CHCH$_2$COO), 1.94-2.11 (m, 3 H, C*H*$_2$CHCH$_2$COO and 2 H of CHNCH$_2$C*H*$_2$), 2.17-2.24 (m, 2 H, C*H*$_2$COO and NC*H*$_2$CHOH), 2.38 (ddd, *J* = 12.0/7.1/4.7 Hz, 1 H, C*H*$_2$NCH), 2.50 (dd, *J* = 15.0/4.9 Hz, 1 H,

CH_2COO), 2.78 (dt, J = 12.0/7.9 Hz, 1 H, CH_2NCH), 3.05-3.11 (m, 1 H, NCH), 3.40 (dd, J = 10.2/6.0 Hz, 1 H, NCH_2CHOH), 3.61 (s, 3 H, OCH_3), 4.30 (dt, J = 14.9/7.4 Hz, 1 H, CH_2-carbazole), 4.37-4.43 (m, 2 H, C*H*OH and CH_2-carbazole), 7.23 (t, J = 7.4 Hz, 2 H, H_{aromat}), 7.41 (br. d, J = 7.9 Hz, 2 H, H_{aromat}), 7.44-7.47 (m, 2 H, H_{aromat}), 8.10 (br. d, J = 7.9 Hz, 2 H, H_{aromat}). – IR: $\tilde{\nu}$ = 3417, 3051, 2949, 1732, 1597, 1454, 1327, 752, 725, 682 cm^{-1}. – MS; *m*/*z* (%): 367 (100) $[M+1]^+$, 293 (24), 180 (6), 172 (10), 97 (3). – $C_{22}H_{26}N_2O_3$ (366.46): calcd. C 72.11, H 7.15, N 7.64; found C 72.56, H 7.46, N 7.53.

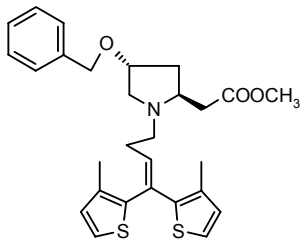
Methyl (2*S*,4*R*)-4-benzyloxy-1-(4,4-diphenylbut-3-en-1-yl)pyrrolidine-2-acetate [(2*S*,4*R*)-93a]



According to GP2 from 207 mg (0.723 mmol) of (2*S*,4*R*)-**87**, 239 mg (0.723 mmol) of **118**, 200 mg (1.43 mmol) of K_2CO_3 and 12 mg of KI in 6 ml of CH_3CN; reaction time: 3 d; purification by CC (ϕ 18 × 240; *n*-heptane/EtOAc, 1:3). Yield: 147 mg (45%); colorless oil. – TLC: R_f = 0.17 (*n*-heptane/EtOAc, 3:1). – $[\alpha]_D^{20}$ = -60.0 (*c* = 1.34, EtOAc). – ^{1}H NMR ($CDCl_3$): δ = 1.73 (dt, J = 13.3/7.9 Hz, 1 H, CH_2CHCH$_2$COO), 2.05 (ddd, J = 13.3/7.4/3.3 Hz, 1 H, CH_2CHCH$_2$COO), 2.14-2.24 (m, 4 H, CH_2COO, NCH_2CHO and 2 H of NCH$_2$CH_2), 2.27-2.34 (m, 1 H, NCH_2CH$_2$), 2.54 (dd, J = 14.6/3.8 Hz, 1 H, CH_2COO), 2.73-2.81 (m, 1 H, NCH_2CH$_2$), 2.91-2.98 (m, 1 H, NCH), 3.26 (dd, J = 10.1/6.4 Hz, 1 H, NCH_2CHO), 3.57 (s, 3 H, OCH_3), 3.97-4.02 (m, 1 H, NCH$_2$C*H*O), 4.33 (d, J = 12.0 Hz, 1 H, CH_2Ph), 4.40 (d, J = 12.0 Hz, 1 H, CH_2Ph), 6.01 (t, J = 7.4 Hz, 1 H, =C*H*CH$_2$), 7.09-7.31 (m, 15 H, H_{aromat}). – IR: $\tilde{\nu}$ = 3056, 3028, 2948, 1737, 1443, 1098, 762, 737, 699 cm^{-1}. – MS; *m*/*z* (%): 456 (32) $[M+1]^+$, 382 (9), 262 (100), 175 (11), 148 (25), 91 (61). – $C_{30}H_{33}NO_3$ (455.60): calcd. C 79.09, H 7.30, N 3.07; found C 78.73, H 7.38, N 3.09.

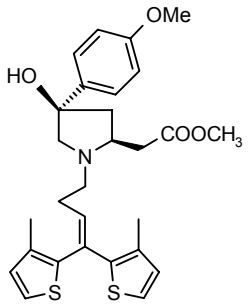
Methyl (2*S*,4*R*)-4-benzyloxy-1-[4,4-di(3-methyl-2-thienyl)but-3-en-1-yl]pyrrolidine-2-acetate [(2*S*,4*R*)-93c]

According to GP2 from 69 mg (0.21 mmol) of (2*S*,4*R*)-**87**, 68 mg (0.21 mmol) of **123**, 145



mg (1.05 mmol) of K_2CO_3 and 10 mg of KI in 3 ml of acetone; purification by CC (ϕ 18 × 200; *n*-heptane/acetone, 6:1). Yield: 53 mg (51%); colorless oil. – TLC: R_f = 0.21 (*n*-heptane/EtOAc, 3:1). – $[\alpha]_D^{21}$ = -43.5 (*c* = 1.19, EtOAc). – ^{1}H NMR ($CDCl_3$): δ = 1.72 (dt, *J* = 13.4/8.1 Hz, 1 H, C*H*$_2$CHCH$_2$COO), 1.94 (s, 3 H, theinyl-C*H*$_3$), 1.97 (s, 3 H, thienyl-C*H*$_3$), 2.05 (ddd, *J* = 13.4/7.1/3.2 Hz, 1 H, C*H*$_2$CHCH$_2$COO), 2.12-2.26 (m, 4 H, NC*H*$_2$CHO, C*H*$_2$COO and 2 H of NCH$_2$C*H*$_2$), 2.27-2.34 (m, 1 H, NC*H*$_2$CH$_2$), 2.56 (dd, *J* = 14.8/4.1 Hz, 1 H, CH$_2$COO), 2.77 (dt, *J* = 11.5/8.1 Hz, 1 H, NC*H*$_2$CH$_2$), 2.91-2.98 (m, 1 H, NCH), 3.28 (dd, *J* = 9.9/6.2 Hz, 1 H, NC*H*$_2$CHO), 3.58 (s, 3 H, OCH$_3$), 3.97-4.02 (m, 1 H, NCH$_2$C*H*O), 4.34 (d, *J* = 12.0 Hz, 1 H, C*H*$_2$Ph), 4.40 (d, *J* = 12.0 Hz, 1 H, C*H*$_2$Ph), 5.97 (t, *J* = 7.2 Hz, 1 H, =C*H*CH$_2$), 6.69 (d, *J* = 5.2 Hz, 1 H, SCH), 6.76 (d, *J* = 5.2 Hz, 1 H, SCH), 6.98 (d, *J* = 5.2 Hz, 1 H, SCH=C*H*), 7.13 (d, *J* = 5.2 Hz, 1 H, SCH=C*H*), 7.20-7.28 (m, 5 H, H_{aromat}). – IR: $\tilde{\nu}$ = 3050, 3030, 2949, 1736, 1702, 1413, 1112, 769, 735, 697 cm^{-1}. – MS; *m*/*z* (%): 496 (4) $[M+1]^+$, 384 (34), 340 (32), 248 (36), 91 (100), 79 (37). – $C_{28}H_{33}NO_3S_2$ (495.70): calcd. C 67.85, H 6.71, N 2.83; found C 67.85, H 6.60, N 3.06.

Methyl (2*S*,4*R*)-1-[4,4-di(3-methyl-2-thienyl)but-3-en-1-yl]-4-hydroxy-4-(4-methoxy-phenyl)pyrrolidine-2-acetate [(2*S*,4*R*)-102c]



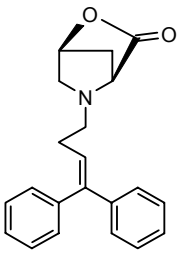
According to GP2 from 10 mg (0.038 mmol) of (2*S*,4*R*)-**115**, 12 mg (0.038 mmol) of **123**, 26 mg (0.19 mmol) of K_2CO_3 and 3 mg KI in 1.5 ml of acetone; purification by CC (ϕ 12 × 110; *iso*-hexane/acetone, 85:15). Yield: 11 mg (57%). – M.p. 96-98 (*i*Pr$_2$O). – TLC: R_f = 0.33 (*n*-heptane/acetone, 3:2). – $[\alpha]_D^{20}$ = -82 (*c* = 0.29, $CHCl_3$). All other analytical data (^{1}H NMR, IR, MS) were identical with that prepared from (2*S*)-**100c** (Section 5.1.7)

6.1.4 Stereochemical inversions of the 4-hydroxy groups of pyrrolidine derivatives by Mitsunobu reaction

General procedure 3 (GP3) [42, 43, 44, 45]

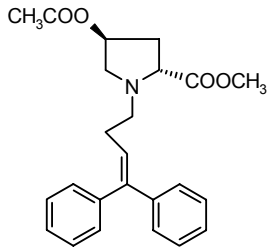
To a solution of the N-substituted or N-protected 4-hydroxy pyrrolidine derivative (1 equiv.) and Ph_3P (1.0-1.5 equiv.) in THF (10-50 ml/mmol), DEAD (1.2-1.5 equiv.) was added at 0 °C. The resulting yellow solution was stirred for 10 min and then AcOH or HCOOH (1.05-1.50 equiv.) was added at 0 °C (for intramolecular Mitsunobu reaction no additoinal acid was used). Stirring was continued at 0 °C for the time given. The solvent was evaporated in vacuo. and the residual oil was purified by CC. Some compounds needed separation on prep. HPLC.

(1*S*,4*S*)-5-(4,4-Diphenylbut-3-en-1-yl)-2-oxa-5-azabicyclo[2,2,1]heptane-3-one [(1*S*,4*S*)-41a]



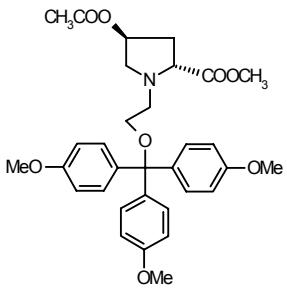
According to GP3 from 195 mg (0.578 mmol) of (2*S*,4*R*)-**40a** and 304 mg (1.16 mmol) of Ph_3P, 151 mg (0.867 mmol) of DEAD in 10 ml of THF; reaction time: 13 h; purification by CC (ϕ 20 × 250; *n*-heptane/acetone, 4:1). Yield: 157 mg (85%); colorless crystals. – TLC: R_f = 0.23 (*n*-heptane/acetone, 3:2). – M.p. 85-86 °C (*n*-heptane/acetone, 4:1). – $[\alpha]_D^{21}$ = -60.7 (*c* = 0.84, EtOH). – ^{1}H NMR ($CDCl_3$): δ = 1.85 (dd, *J* = 10.5/1.6 Hz, 1 H, NCHC*H*$_2$), 1.92-2.08 (m, 1 H, NCHC*H*$_2$), 2.15 (dd, *J* = 10.6/1.2 Hz, 1 H, NC*H*$_2$CHO), 2.17-2.31 (m, 2 H, NCH$_2$C*H*$_2$), 2.43 (dt, *J* = 11.8/6.6 Hz, 1 H, NC*H*$_2$CH$_2$), 2.68 (dt, *J* = 11.8/7.1 Hz, 1 H, NC*H*$_2$CH$_2$), 3.22 (dd, *J* = 10.6/0.9 Hz, 1 H, NC*H*$_2$CHO), 3.48 (br. s, 1 H, NCH), 4.78 (br. s, 1 H, NCH$_2$C*H*O), 6.02 (t, *J* = 7.3 Hz, 1 H, =C*H*CH$_2$), 7.09-7.30 (m, 10 H, H_{aromat}). – IR: $\tilde{\nu}$ = 3053, 1766, 1089, 926, 774, 757 cm^{-1}. – MS; *m*/*z* (%): 320 (100) $[M+1]^+$, 274 (11), 207 (10). – $C_{21}H_{21}NO_2$ (319.40): calcd. C 78.97, H 6.63, N 4.39; found C 78.92, H 6.71, N 4.36.

Methyl (2*R*,4*S*)-4-acetoxy-1-(4,4-diphenylbut-3-en-1-yl)pyrrolidine-2-carboxylate [(2*R*,4*S*)-48a]



According to GP3 from 120 mg (0.352 mmol) of (2*R*,4*R*)-**39a**, 134 mg (0.513 mmol) of Ph_3P, 243 µl (38-40% in $PhCH_3$, 0.513 mmol) of DEAD, 29 mg (0.51 mmol) of AcOH in 5 ml of THF; reaction time: for 6 h; purification by CC (ϕ 25 × 220; *n*-heptane/EtOAc, 3:1) and further separation on prep. HPLC (*n*-heptane/EtOAc, 75:25; t_R = 29.6 min; 12 ml/min). Yield: 92 mg (69%); colorless oil. – TLC: R_f = 0.26 (*n*-heptane/EtOAc, 1:3). – $[\alpha]_D^{20}$ = +43.1 (*c* = 1.02, EtOAc). – ^{1}H NMR ($CDCl_3$): δ = 2.02 (s, 3 H, CH_3COO), 2.12 (ddd, *J* = 13.9/7.5/2.9 Hz, 1 H, NCHCH_2), 2.25-2.33 (m, 3 H, NCHCH_2 and 2 H of NCH_2CH_2), 2.50 (dd, *J* = 10.8/3.3 Hz, 1 H, NCH_2CHO), 2.59 (dt, *J* = 12.0/7.6 Hz, 1 H, NCH_2CH_2), 2.79 (dt, *J* = 12.0/8.0 Hz, 1 H, NCH_2CH_2), 3.43 (dd, *J* = 10.8/6.2 Hz, 1 H, NCH_2CHO), 3.49 (t, *J* = 7.5 Hz, 1 H, NCH), 3.68 (s, 3 H, $COOCH_3$), 5.17-5.22 (m, 1 H, NCH_2CHO), 6.06 (t, *J* = 7.4 Hz, 1 H, =C*H*CH_2), 7.14-7.38 (m, 10 H, H_{aromat}). – IR: $\tilde{\nu}$ = 3055, 2951, 1738, 1718, 1495, 1243, 762, 702 cm^{-1}**.** – MS; *m*/*z* (%): 394 (64) $[M+1]^+$, 334 (11), 200 (100), 140 (8). – $C_{24}H_{27}NO_4$ (393.48): calcd. C 73.25, H 6.92, N 3.56; found C 73.04, H 6.83, N 3.79.

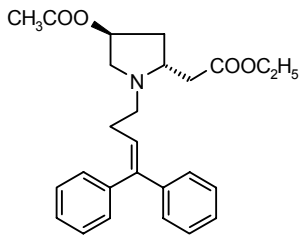
Methyl (2*R*,4*S*)-4-acetoxy-1-{2-[tris(4-methoxyphenyl)methoxy]-1-ethyl}pyrrolidine-2-carboxylate [(2*R*,4*S*)-48b]



According to GP3 from 100 mg (0.192 mmol) of (2*R*,4*R*)-**39b** and 79 mg (0.29 mmol) of Ph_3P, 139 µl (38-40% in $PhCH_3$, 0.288 mmol) of DEAD, 13 mg (0.22 mmol) of AcOH in 3.5 ml of THF; reaction time: 4 h; purification by CC (ϕ 18 × 260; *n*-heptane/acetone, 3:1) and

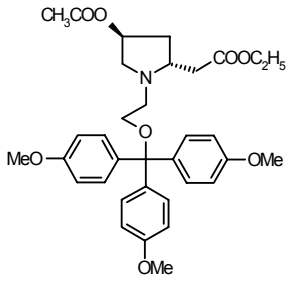
further separation on prep. HPLC (*n*-heptane/EtOAc, 60:40; t_R = 29.2 min; 12 ml/min,). Yield: 60 mg (56%); colorless oil. – TLC: R_f = 0.35 (*n*-heptane/acetone, 3:2). – $[\alpha]_D^{20}$ = +21.3 (*c* = 1.10, EtOAc). – ^{1}H NMR ($CDCl_3$): δ = 2.02 (s, 3 H, CH_3COO), 2.12 (ddd, *J* = 13.9/7.5/3.0 Hz, 1 H, NCHC*H*$_2$), 2.27 (dt, *J* = 13.9/7.5 Hz, 1 H, NCHC*H*$_2$), 2.64 (dd, *J* = 11.0/3.3 Hz, 1 H, NC*H*$_2$CHO), 2.79 (dt, *J* = 12.6/6.2 Hz, 1 H, NC*H*$_2$CH$_2$), 2.89-2.94 (m, 1 H, NC*H*$_2$CH$_2$), 3.19 (t, *J* = 6.2 Hz, 2 H, NCH$_2$C*H*$_2$), 3.48 (dd, *J* = 11.0/6.2 Hz, 1 H, NC*H*$_2$CHO), 3.59 (t, *J* = 7.5 Hz, 1 H, NC*H*), 3.67 (s, 3 H, $COOCH_3$), 3.78 (s, 9 H, ArOC*H*$_3$), 5.17-5.21 (m, 1 H, NCH$_2$C*H*O), 6.78-6.81 (m, 6 H, H_{aromat}), 7.29-7.32 (m, 6 H, H_{aromat}). – IR: $\tilde{\nu}$ = 3036, 2836, 1738, 1732, 1608, 1505, 1249, 1035, 828, 681 cm^{-1}. – MS; *m*/*z* (%): 333 (100) $[Ar_3C]^+$, 232 (12), 227 (35), 200 (42), 140 (10). – $C_{32}H_{37}NO_8$ (563.65): calcd. C 68.19, H 6.62, N 2.49; found C 67.96, H 6.58, N 2.48.

Ethyl (2*R*,4*S*)-4-acetoxy-1-(4,4-diphenylbut-3-en-1-yl)pyrrolidine-2-acetate [(2*R*,4*S*)-90a]



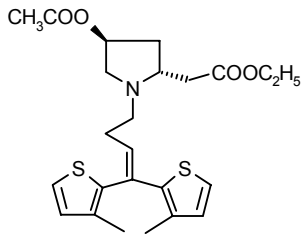
According to GP3 from 50 mg (0.13 mmol) of (2*R*,4*R*)-**88a** and 52 mg (0.20 mmol) of Ph_3P in 2 ml of THF, 94 µl (38-40% in $PhCH_3$, 0.20 mmol) of DEAD and 11 mg (0.18 mmol) of AcOH; reaction time: 23 h; purification (ϕ 18 × 220; *n*-heptane/EtOAc, 3:1) and separation by prep. HPLC (t_R = 37.8 min; *n*-heptane/EtOAc, 75:25; 12 ml/min). Yield: 40 mg (72%); colorless oil. – TLC: R_f = 0.27 (*n*-heptane/EtOAc, 3:1). – $[\alpha]_D^{20}$ = +57.9 (*c* = 0.98, EtOAc). – ^{1}H NMR ($CDCl_3$): δ = 1.24 (t, *J* = 7.0 Hz, 3 H, CH$_2$C*H*$_3$), 1.89 (ddd, *J* = 13.9/9.0/7.6 Hz, 1 H, C*H*$_2$CHCH$_2$COO), 2.01 (s, 3 H, CH_3COO), 2.06 (ddd, *J* = 13.9/6.6/2.6 Hz, 1 H, C*H*$_2$CHCH$_2$COO), 2.17-2.40 (m, 5 H, NC*H*$_2$CHO, NC*H*$_2$CH$_2$, C*H*$_2$COO and 2 H of NCH$_2$C*H*$_2$), 2.61 (dd, *J* = 15.0/4.2 Hz, 1 H, CH$_2$COO), 2.80-2.87 (m, 1 H, NC*H*$_2$CH$_2$), 2.97-3.04 (m, 1 H, NCH), 3.42 (dd, *J* = 10.8/6.4 Hz, 1 H, NC*H*$_2$CHO), 4.05-4.17 (m, 2 H, C*H*$_2$CH$_3$), 5.06-5.11 (m, 1 H, NCH$_2$C*H*O), 6.06 (t, *J* = 7.2 Hz, 1 H, =C*H*CH$_2$), 7.14-7.38 (m, 10 H, H_{aromat}). – IR: $\tilde{\nu}$ = 3056, 2979, 1740, 1732, 1495, 1369, 1256, 763, 702 cm^{-1}. – MS; *m*/*z* (%): 422 (46), $[M+1]^+$, 362 (10), 334 (13), 228 (100), 168 (10), 115 (4). – $C_{26}H_{31}NO_4$ (421.54): calcd. C 74.08, H 7.41, N 3.32; found C 74.16, H 7.38, N 3.32.

Ethyl (2*R*,4*S*)-4-acetoxy-1-{2-[tris(4-methoxyphenyl)methoxy]-1-ethyl}pyrrolidine-2-acetate [(2*R*,4*S*)-90b]



According to GP3 from 147 mg (0.267 mmol) of (2*R*,4*R*)-**88b** and 105 mg (0.401 mmol) of Ph_3P in 5 ml of THF, 190 µl (38-40% in $PhCH_3$, 0.40 mmol) of DEAD and 19 mg (0.32 mmol) of AcOH; reaction time: 2 h; purification by CC (ϕ 25 × 220; *n*-heptane/acetone, 3:1) and separation by prep. HPLC (*n*-heptane/EtOAc, 60:40; t_R = 32.1 min; 12 ml/min). Yield: 50 mg (32%); colorless oil. – TLC: R_f = 0.37 (*n*-heptane/acetone, 3:2). – $[\alpha]_D^{20}$ = +23.4 (*c* = 1.51, EtOAc). – ^{1}H NMR ($CDCl_3$): δ = 1.23 (t, *J* = 7.2 Hz, 3 H, CH_2CH_3), 1.86 (ddd, *J* = 13.9/9.1/7.4 Hz, 1 H, CH_2CHCH_2COO), 2.01 (s, 3 H, CH_3COO), 2.06 (ddd, *J* = 13.9/6.6/2.6 Hz, 1 H, CH_2CHCH_2COO), 2.21 (dd, *J* = 15.1/9.1 Hz, 1 H, CH_2COO), 2.34 (dd, *J* = 10.9/4.4 Hz, 1 H, NCH_2CHO), 2.48-2.55 (m, 1 H, NCH_2CH_2), 2.65 (dd, *J* = 15.1/4.1 Hz, 1 H, CH_2COO), 2.90-2.97 (m, 1 H, NCH_2CH_2), 3.03-3.18 (m, 3 H, NC*H* and 2 H of NCH_2CH_2), 3.46 (dd, *J* = 10.9/6.3 Hz, 1 H, NCH_2CHO), 3.78 (s, 3 H, $ArOCH_3$), 4.06-4.14 (m, 2 H, CH_2CH_3), 5.06-5.12 (m, 1 H, NCH_2CHO), 6.78-6.82 (m, 6 H, H_{aromat}), 7.29-7.33 (m, 6 H, H_{aromat}). – IR: $\tilde{\nu}$ = 2980, 1733, 1608, 1508, 1249, 828 cm^{-1}. – MS; *m*/*z* (%): 406 (12), 333 (100) $[Ar_3C]^+$, 287 (20), 258 (5), 184 (22), 94 (37). – $C_{34}H_{41}NO_8$ (591.70): calcd. C 69.02, H 6.99, N 2.37; found C 69.02, H 7.38, N 2.31.

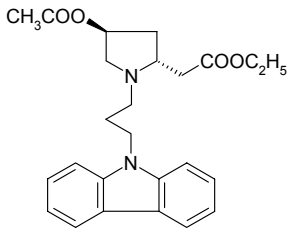
Ethyl (2*R*,4*S*)-4-acetoxy-1-[4,4-di(3-methyl-2-thienyl)but-3-en-1-yl]pyrrolidine-2-acetate [(2*R*,4*S*)-90c]



According to GP3 from 117 mg (0.279 mmol) of (2*R*,4*R*)-**88c** and 108 mg (0.419 mmol) of

Ph_3P in 4 ml of THF, 199 µl (38-40% in toluene, 0.42 mmol) of DEAD and 24 mg (0.40 mmol) of AcOH; reaction time: 3 h; purification by CC (ϕ 25 × 220; *n*-heptane/EtOAc, 4:1) nd separation by prep. HPLC (*n*-heptane/EtOAc, 75:25; t_R = 27.3 min; 12 ml/min). Yield: 81 mg (63%); colorless oil. – TLC: R_f = 0.38 (*n*-heptane/EtOAc, 3:1). – $[\alpha]_D^{20}$ = +86.8 (*c* = 0.94, EtOAc). – ^{1}H NMR ($CDCl_3$): δ = 1.24 (t, *J* = 7.1 Hz, 3 H, CH_2CH_3), 1.87 (ddd, *J* = 13.9/9.0/7.6 Hz, 1 H, CH_2CHCH_2COO), 2.00-2.09 (m, 10 H, 1 H of CH_2CHCH_2COO, 3 H of CH_3COO and 6 H of thienyl-CH_3), 2.18-2.42 (m, 5 H, NCH_2CHO, NCH_2CH_2, CH_2COO and 2 H of NCH_2CH_2), 2.63 (dd, *J* = 15.1/4.2 Hz, 1 H, CH_2COO), 2.83 (dt, *J* = 11.5/8.1 Hz, 1 H, NCH_2CH_2), 2.97-3.05 (m, 1 H, NCH), 3.44 (dd, *J* = 10.8/6.4 Hz, 1 H, NCH_2CHO), 4.12 (q, *J* = 7.1 Hz, 2 H, CH_2CH_3), 5.06-5.11 (m, 1 H, NCH_2CHO), 6.02 (t, *J* = 7.2 Hz, 1 H, $=CHCH_2$), 6.75 (d, *J* = 5.1 Hz, 1 H, SCH), 6.83 (d, *J* = 5.1 Hz, 1 H, SCH), 7.05 (d, *J* = 5.1 Hz, 1 H, SCH=C*H*), 7.20 (d, *J* = 5.1 Hz, 1 H, SCH=C*H*). – IR: $\tilde{\nu}$ = 3105, 2978, 1738, 1732, 1369, 1244, 713 cm^{-1}. – MS; *m*/*z* (%): 462 (12) $[M+1]^+$, 402 (2), 374 (4), 228 (100), 111 (5). – $C_{24}H_{31}NO_4S_2$ (461.64): calcd. C 62.44, H 6.77, N 3.03, S 13.89; found C 62.31, H 7.00, N 2.96, S 13.56.

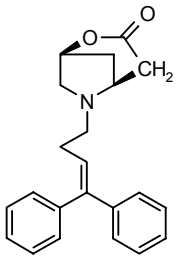
Ethyl (2*R*,4*S*)-4-acetoxy-1-[3-(9-carbazolyl)-1-propyl]pyrrolidine-2-acetate [(2*R*,4*S*)-90d]



According to GP3 from 110 mg (0.289 mmol) of (2*R*,4*R*)-**88d** and 152 mg (0.578 mmol) of Ph_3P in 4 ml of THF, 269 µl (38-40% in $PhCH_3$, 0.58 mmol) of DEAD and 26 mg (0.43 mmol) of AcOH; reaction time: 3 h; purification by CC (ϕ 18 × 210; *n*-heptane/acetone, 4:1) and separation by prep. HPLC (*n*-heptane/EtOAc, 60:40; t_R = 34.2 min; 12 ml/min). Yield: 104 mg (85%); colorless oil. – TLC: R_f = 0.43 (*n*-heptane/acetone, 3:2). – $[\alpha]_D^{20}$ = +43.6 (*c* = 1.04, EtOAc). – ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.22 (t, *J* = 7.1 Hz, 3 H, CH_2CH_3), 1.93-2.12 (m, 7 H, CH_2CHCH_2COO, $CHNCH_2CH_2$ and CH_3COO), 2.19 (dd, *J* = 15.0/8.6 Hz, 1 H, CH_2COO), 2.29 (dd, *J* = 10.8/4.3 Hz, 1 H, NCH_2CHO), 2.32-2.35 (m, 1 H, CH_2NCH), 2.48 (dd, *J* = 15.0/4.4 Hz, 1 H, CH_2COO), 2.77 (dt, *J* = 12.1/7.8 Hz, 1 H, CH_2NCH), 3.00-3.05 (m, 1 H, NCH), 3.53 (dd, *J* = 10.8/6.3 Hz, 1 H, NCH_2CHO), 4.08 (q, *J* = 7.1 Hz, 2 H, CH_2CH_3), 4.29-4.35 (m, 1 H, CH_2-carbazole), 4.37-4.43 (m, 1 H, CH_2-carbazole), 5.14-5.18 (m, 1 H,

NCH_2CHO), 7.21-7.25 (m, 2 H, H_{aromat}), 7.41-7.42 (m, 2 H, H_{aromat}), 7.45-7.48 (m, 2 H, H_{aromat}), 8.09-8.11 (m, 2 H, H_{aromat}). – IR: $\tilde{\nu}$ = 3051, 2978, 1737, 1732, 1597, 1246, 751, 725 cm^{-1}. – MS; *m/z* (%): 423 (100) $[M+1]^+$, 363 (13), 335 (25), 275 (11), 228 (9), 180 (12). – $C_{25}H_{30}N_2O_4$ (422.53): calcd. C 71.07, H 7.16, N 6.63; found C 71.01, H 7.29, N 6.54.

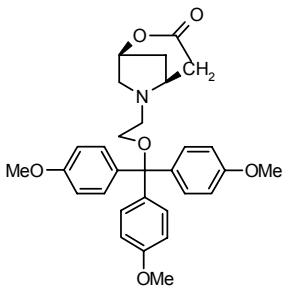
(1*S*,5*S*)-6-(4,4-Diphenylbut-3-en-1-yl)-2-oxa-6-azabicyclo[3,2,1]octane-3-one [(1*S*,5*S*)-92a]



According to GP3 from 97 mg (0.27 mmol) of (2*S*,4*R*)-**91a** and 112 mg (0.411 mmol) of Ph_3P in 5 ml of THF, 198 µl (38-40% in $PhCH_3$, 0.41 mmol) of DEAD; reaction time: 4 h; purification by CC (ϕ 18 × 24; *n*-heptane/acetone, 3:1) and separation by prep. HPLC (*n*-heptane/EtOAc, 1:1; t_R = 35.8 min; 12 ml/min). Yield: 65 mg (76%); colorless crystals. – M.p. 72-74 °C. – TLC: R_f = 0.41 (*n*-heptane/acetone, 3:2). – $[\alpha]_D^{20}$ = +4.6 (*c* = 1.00, EtOAc). – ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.98 (br. s, 2 H, CH_2CHCH_2COO), 2.26 (q, *J* = 7.3 Hz, 2 H, NCH_2CH_2), 2.43 (dd, *J* = 18.6/3.7 Hz, 1 H, CH_2COO), 2.67-2.78 (m, 3 H, CH_2COO and 2 H of NCH_2CH_2), 2.95 (d, *J* = 11.9 Hz, 1 H, NCH_2CHO), 3.06 (dd, *J* = 11.9/3.7 Hz, 1 H, NCH_2CHO), 3.37-3.41 (m, 1 H, NCH), 4.84-4.86 (m, 1 H, NCH_2CHO), 6.09 (t, *J* = 7.3 Hz, 1 H, $=CHCH_2$), 7.15-7.39 (m, 10 H, H_{aromat}). – IR: $\tilde{\nu}$ = 3054, 2969, 1732, 1598, 1494, 1372, 1203, 1068, 770, 702 cm^{-1}. – MS; *m/z* (%): 334 (100) $[M+1]^+$, 140 (40), 91 (3). – $C_{22}H_{23}NO_2$ (333.43): calcd. C 79.25, H 6.95, N 4.20; found C 79.14, H 7.10, N 4.08.

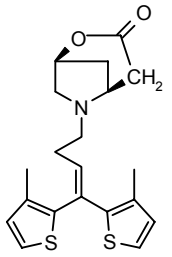
(1*S*,5*S*)-6-{2-[Tris(4-methoxyphenyl)methoxy]-1-ethyl}-2-oxa-6-azabicyclo[3,2,1]octane-3-one [(1*S*,5*S*)-92b]

According to GP3 from 96 mg (0.18 mmol) of (2*S*,4*R*)-**91b** and 97 mg (0.37 mmol) of Ph_3P in 4 ml of THF, 174 µl (38-40% in toluene, 0.37 mmol) of DEAD; reaction time: 4 h; purification by CC (ϕ 18 × 240; *n*-heptane/acetone, 3:1) and separation by prep. HPLC (t_R =



32.4 min; *n*-heptane/EtOAc, 8:2; 12 ml/min). Yield: 43 mg (46%); colorless oil. – TLC: R_f =0.27 (*n*-heptane/acetone, 3:2). – $[\alpha]_D^{20}$ = +2.4 (*c* = 0.55, EtOAc). – ^{1}H NMR ($CDCl_3$): δ = 1.99 (br. s, 2 H, CH_2CHCH$_2$COO), 2.47 (dd, *J* = 18.6/3.5 Hz, 1 H, CH$_2$COO), 2.82-2.88 (m, 3 H, CH_2COO, NCH_2CH$_2$ and NCH_2CHO), 3.07 (d, *J* = 12.0 Hz, 1 H, NCH_2CHO), 3.14-3.18 (m, 3 H, NCH_2CH$_2$ and 2 H of NCH$_2$CH_2), 3.48-3.51 (m, 1 H, NCH), 3.78 (s, 9 H, ArOCH_3), 4.85-4.87 (m, 1 H, NCH$_2$C*H*O), 6.79-6.83 (m, 6 H, H_{aromat}), 7.28-7.32 (m, 6 H, H_{aromat}). – IR: $\tilde{\nu}$ = 3049, 2943, 1737, 1595, 1453, 753, 726 cm^{-1}. – MS; *m*/*z* (%): 333 (100) $[Ar_3C]^+$, 227 (10), 172 (12), 109 (2). – $C_{30}H_{33}NO_6$ (503.59): calcd. C 71.55, H 6.61, N 2.78; found C 71.17, H 6.66, N 2.73.

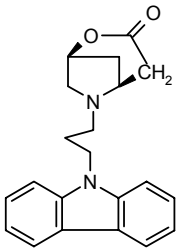
(1*S*,5*S*)-6-[4,4-Di(3-methyl-2-thienyl)but-3-en-1-yl]-2-oxa-6-azabicyclo[3,2,1]octane-3-one [(1*S*,5*S*)-92c]



According to GP3 from 111 mg (0.284 mmol) of (2*S*,4*R*)-**91c** and 154 mg (0.568 mmol) of Ph_3P in 6 ml of THF, 269 µl (38-40% in $PhCH_3$, 0.57 mmol) of DEAD; reaction time: 4 h; purification by CC (ϕ 18 × 250; *n*-heptane/acetone, 3:1) and separation by prep. HPLC (t_R = 42.7 min; *n*-heptane/EtOAc, 35:65; 12 ml/min). Yield: 74 mg (70%); colorless oil. – TLC: R_f = 0.38 (*n*-heptane/acetone, 3:2). – $[\alpha]_D^{22}$ = +6.9 (*c* = 1.00, EtOAc). – ^{1}H NMR ($CDCl_3$): δ = 1.97-2.00 (m, 2 H, CH_2CHCH$_2$COO), 2.00 (s, 3 H, thienyl-CH_3), 2.03 (s, 3 H, thienyl-CH_3), 2.28 (q, *J* = 7.3 Hz, 2 H, NCH$_2$CH_2), 2.45 (dd, *J* = 18.7/3.7 Hz, 1 H, CH_2COO), 2.68-2.81 (m, 3 H, CH_2COO and 2 H of NCH_2CH$_2$), 2.97 (br. d, *J* = 11.9 Hz, 1 H, NCH_2CHO), 3.06 (dd, *J* = 11.9/3.7 Hz, 1 H, NCH_2CHO), 3.38-3.41 (m, 1 H, NCH), 4.85-4.87 (m, 1 H, NCH$_2$C*H*O), 6.06 (t, *J* = 7.3 Hz, 1 H, =C*H*CH$_2$), 6.76 (d, *J* = 5.2 Hz, 1 H, SCH), 6.84 (d, *J* = 5.2 Hz, 1 H,

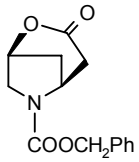
SCH), 7.05 (d, *J* = 5.2 Hz, 1 H, SCH=C*H*), 7.21 (d, *J* = 5.2 Hz, 1 H, SCH=C*H*). – IR: $\tilde{\nu}$ = 3103, 2946, 1738, 1444, 1204, 858, 834, 715 cm^{-1}. – MS; *m*/*z* (%): 374 (32) $[M+1]^+$, 307 (3), 172 (5), 140 (100). – $C_{20}H_{23}NO_2S_2$ (373.53): calcd. C 64.31, H 6.17, N 3.75, S 17.18; found C 64.24, H 6.31, N 3.70, S 16.94.

(1*S*,5*S*)-6-[3-(9-Carbazolyl)-1-propyl]-2-oxa-6-azabicyclo[3,2,1]octane-3-one [(1*S*,5*S*)-92d]



According to GP3 from 142 mg (0.403 mmol) of (2*S*,4*R*)-**91d** and 212 mg (0.806 mmol) of Ph_3P in 8 ml of THF, 383 µl (38-40% in $PhCH_3$, 0.81 mmol) of DEAD; reaction time: 3 h; purification by CC (ϕ 30 × 230; *n*-heptane/acetone, 3:2) and separation by prep. HPLC (t_R = 36.0 min; *n*-heptane/EtOAc, 20:80; 16.5 ml/min). Yield: 55 mg (41%); colorless oil. – TLC: R_f = 0.31 (*n*-heptane/acetone, 3:2). – $[\alpha]_D^{20}$ = +6.2 (*c* = 0.97, EtOAc). – ^{1}H NMR ($CDCl_3$): δ = 1.95-2.07 (m, 4 H, CH_2CHCH_2COO and CHNCH_2CH_2), 2.41-2.51 (m, 2 H, CH_2COO and CH_2NCH), 2.58-2.64 (m, 1 H, CH_2NCH), 2.73-2.79 (m, 1 H, CH_2COO), 3.00 (br. d, *J* = 11.8 Hz, 1 H, NCH_2CHO), 3.06 (dd, *J* = 11.8/3.5 Hz, 1 H, NCH_2CHO), 3.28-3.31 (m, 1 H, NCH), 4.36-4.49 (m, 2 H, CH_2-carbazole), 4.8-4.91 (m, 1 H, NCH_2C*H*O), 7.21-7.26 (m, 2 H, H_{aromat}), 7.41-7.48 (m, 4 H, H_{aromat}), 8.09-8.12 (m, 2 H, H_{aromat}). – IR: $\tilde{\nu}$ = 3036, 2952, 1738, 1607, 1505, 1249, 1034, 827, 628 cm^{-1}. – MS; *m*/*z* (%): 335 (100) $[M+1]^+$, 293 (5), 180 (7), 140 (7). – $C_{21}H_{22}N_2O_2$ (334.42): calcd. C 75.42, H 6.63, N 8.38; found C 75.05, H 6.83, N 8.05.

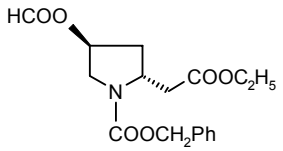
Benzyl (1*S*,5*S*)-2-oxa-6-azabicyclo[3,2,1]octane-3-one-6-carboxylate [(1*S*,5*S*)-98]



According to GP3 from 290 mg (1.04 mmol) of (2*S*,4*R*)-**96**, 491 mg (1.87 mmol) of Ph_3P in

25 ml of THF, 886 µl (38-40% in $PhCH_3$, 1.9 mmol) of DEAD; reaction time: 7 h; purification by CC (ϕ 25 × 250; *n*-heptane/acetone, 3:1) and separation by prep. HPLC (t_R = 53.8 min; *n*-heptane/EtOAc/*iso*-propanol, 55:45:1.0; 12 ml/min). Yield: 191 mg (70%); colorless oil. – TLC: R_f = 0.26 (*n*-heptane/acetone, 3:2). – $[\alpha]_D^{20}$ = -63.4 (*c* = 1.22, $CHCl_3$). – ^{1}H NMR ($C_6D_5NO_2$, 120 °C): δ = 2.19 (br. s, 2 H, C*H*$_2$CHCH$_2$COO), 2.70-2.77 (m, 1 H, CH$_2$COO), 3.04 (br. d, *J* = 18.5 Hz, 1 H, CH$_2$COO), 3.67-3.71 (m, 1 H, NCH$_2$), 3.88 (d, *J* = 12.2 Hz, 1 H, NCH$_2$), 4.52 (br. s, 1 H, NCH), 5.06 (br. s, 1 H, NCH$_2$C*H*O), 5.24 (br. s, 2 H, C*H*$_2$Ph), 7.25-7.44 (m, 5 H, H_{aromat}). – IR: $\tilde{\nu}$ = 3035, 2955, 1747, 1709, 1417, 1360, 1206, 1069, 767, 699 cm^{-1}. – MS; *m*/*z* (%): 262 (100) $[M+1]^+$, 218 (14), 105 (7). – $C_{14}H_{15}NO_4$ (261.28): calcd. C 64.36, H 5.79, N 5.36; found C 64.31, H 5.90, N 5.34.

Ethyl (2*R*,4*S*)-1-benzyloxycarbonyl-4-formyloxypyrrolidine-2-acetate [(*2R*,4*S*)-99]



According to GP3 from 106 mg (0.345 mmol) of (2*R*,4*R*)-**73** and 135 mg (0.517 mmol) of Ph_3P in 5 ml of THF, 245 µl (38-40% in $PhCH_3$, 0.72 mmol) of DEAD; reaction time: 16 h; purification by CC (ϕ 25 × 210; *n*-heptane/acetone, 3:1) and separation by prep. HPLC (t_R = 22.7 min; *n*-heptane/EtOAc/*iso*-propanol, 78:22:0.8; 12 ml/min). Yield: 92 mg (80%); colorless oil. – TLC: R_f = 0.40 (*n*-heptane/acetone, 3:2). – $[\alpha]_D^{20}$ = +36.4 (*c* = 1.64, $CHCl_3$). – ^{1}H NMR ($C_6D_5NO_2$, 120 °C): δ = 1.21-1.26 (m, 3 H, CH$_2$C*H*$_3$), 2.25-2.33 (m, 1 H, C*H*$_2$CHCH$_2$COO), 2.41-2.49 (m, 1 H, C*H*$_2$CHCH$_2$COO), 2.64-2.72 (m, 1 H, CH$_2$COO), 3.04-3.10 (m, 1 H, CH$_2$COO), 3.75-3.80 (m, 1 H, NCH$_2$), 3.89 (d, *J* = 12.1 Hz, 1 H, NCH$_2$), 4.13-4.20 (m, 2 H, C*H*$_2$CH$_3$), 4.45-4.52 (m, 1 H, NCH), 5.26 (s, 2 H, C*H*$_2$Ph), 5.45-5.49 (m, 1 H, NCH$_2$C*H*O), 7.27-7.36, 7.40-7.44 (m, 5 H, H_{aromat}), 8.03 (s, 1 H, HCOO). – IR: $\tilde{\nu}$ = 3030, 2982, 1728, 1705, 1416, 1174, 770, 699 cm^{-1}. – MS; *m*/*z* (%): 308 (79), 264 (31), 225 (63), 187 (16), 174 (26), 105 (100). – $C_{17}H_{21}NO_6$ (335.36): calcd. C 60.89, H 6.31, N 4.18; found C 60.55, H 6.40, N 4.27.

6.1.5 4-Oxopyrrolidine derivatives from Swern oxidation or Jones' oxidation

General procedure 4 (GP4)

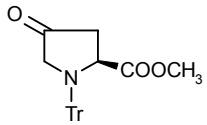
A) [52, 58]

To a solution of $(COCl)_2$ (1.5 equiv.) in CH_2Cl_2 (3~9 ml/mmol), DMSO (3 equiv.) was added at –78 °C over several minutes to give the oxidizing reagent. After 15 min the respective derivative of 4-hydroxypyrrolidine (1 equiv.) in CH_2Cl_2 (5~9 ml/mmol) was added to the above solution at –78 °C. After the mixture had been stirred between –78 °C ~ -70 °C for 15 min (10 min for the derivatives with side chain **b**), TEA (3.10-3.25 equiv.) was added. The reaction mixture was allowed to stir at r.t. for 15 min (10 min for the derivative with side chain b). After water and aq. dilute KOH or NaOH (3.2 equiv.) were added, the organic layer was isolated, the aqueous phase was extracted with CH_2Cl_2. The combined organic layers were washed with water, and then dried ($MgSO_4$) and evaporated. The residual oil was purified by CC.

B) [41]

To a solution of the respective derivative of N-protected 4-hydroxypyrroline (1 equiv.) in acetone (15 ml), 2.67 M chromic acid in aq. H_2SO_4 (8.50 equiv.) was added at r.t. over 5 min. The brown mixture was stirred at r.t. for 30 min and excessive oxidizing agent was destroyed by addition of MeOH (9 equiv.). The supernatant was decanted, diluted by CH_2Cl_2 (70 ml), washed with sat. aq. NH_4Cl, dried ($MgSO_4$) and evaporated. The residual oil was purified by CC.

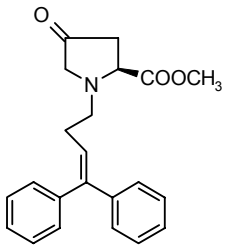
Methyl (2*S*)-4-oxo-1-triphenylmethylpyrrolidine-2-carboxylate [(2*S*)-50]



Accordingbto GP4-A form 397 mg (6.00 mmol) of $(COCl)_2$ and 0.426 ml (469 mg, 6.00 mmol) of DMSO in 8 ml of CH_2Cl_2, 775 mg (2.00 mmol) of (2*S*,4*R*)-**49** in 5 ml of CH_2Cl_2; 679 mg (6.60 mmol) of TEA, no strong base was used; purification by CC (ϕ 25 × 100; *n*-

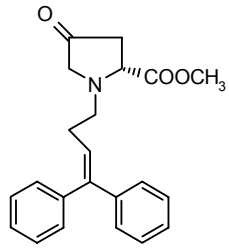
heptane/acetone, 4:1). Yield: 703 mg (97%), slightly yellow foam. – $[\alpha]_D^{20}$ = +83.4 (*c* = 1.22, EtOAc). – ^{1}H NMR ($CDCl_3$): δ = 1.11 (ddd, *J* = 18.7/10.2/1.6 Hz, 1 H, NCHC*H*$_2$), 1.87 (dt, *J* = 18.7/1.2 Hz, 1 H, NCHC*H*$_2$), 3.52 (dd, *J* = 19.8/0.7 Hz, 1 H, NC*H*$_2$), 3.76 (s, 3 H, OC*H*$_3$), 3.82 (d, *J* = 19.8 Hz, 1 H, NCH$_2$), 4.25 (d, *J* = 10.0 Hz, 1 H, CHCOO), 7.10-7.31 (m, 9 H, H_{aromat}), 7.54-7.57 (m, 6 H, H_{aromat}). – IR: $\tilde{\nu}$ = 3058, 2925, 1750, 1489, 1448, 1205, 746, 711 cm^{-1}. – MS; *m*/*z* (%): 243 (100) $[Ph_3C]^+$. – $C_{25}H_{23}NO_3$ (385.46): calcd. C 77.90, H 6.02, N 3.63; found C 77.39, H 6.30, N 3.26.

Methyl (2*S*)-1-(4,4-diphenylbut-3-en-1-yl)-4-oxopyrrolidine-2-carboxylate [(2*S*)-52a]



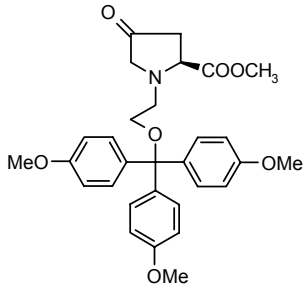
According to GP4-A from 227 mg (2.91 mmol) of DMSO and 193 mg (1.46 mmol) of $(COCl)_2$ in 4.5 ml of CH_2Cl_2, 357 mg (0.970 mmol) of (2*S*,4*R*)-**39a** in 1.5 ml of CH_2Cl_2; 304 mg (3.00 mmol) of TEA, 3.7 ml (3.2 mmol) of aq. 0.85 M KOH; purification by CC (ϕ 20 × 250; *n*-heptane/acetone, 4:1). Yield: 312 mg (87%); colorless oil. – TLC: R_f = 0.15 (*n*-heptane/acetone, 4:1). – $[\alpha]_D^{25}$ = -32.4 (*c* = 1.26, EtOH). – ^{1}H NMR ($CDCl_3$): δ = 2.26 (q, *J* = 7.4 Hz, 2 H, NCH$_2$C*H*$_2$), 2.43 (dd, *J* = 18.0/5.5 Hz, 1 H, NCHC*H*$_2$), 2.54-2.62 (m, 2 H, NCHC*H*$_2$ and NC*H*$_2$CH$_2$), 2.77 (dt, *J* = 12.1/7.4 Hz, 1 H, NC*H*$_2$CH$_2$), 2.91 (d, *J* = 17.2 Hz, 1 H, NCH$_2$CO), 3.29 (d, *J* = 17.2 Hz, 1 H, NCH$_2$CO), 3.65 (s, 3 H, OCH_3), 3.70 (dd, *J* = 7.8/5.5 Hz, 1 H, NCH), 6.03 (t, *J* = 7.4 Hz, 1 H, =C*H*CH$_2$), 7.07-7.34 (m, 10 H, H_{aromat}). – IR: $\tilde{\nu}$ = 3055, 3023, 2951, 1761, 1737, 762, 702 cm^{-1}. – MS; *m*/*z* (%): 350 (100) $[M+1]^+$, 207 (7), 156 (72). – $C_{22}H_{23}NO_3$ (349.43): calcd. C 75.62, H 6.64, N 4.01; found C 75.79, H 6.75, N 3.73.

Methyl (2*R*)-1-(4,4-diphenylbut-3-en-1-yl)-4-oxopyrrolidine-2-carboxylate [(2*R*)-52a]



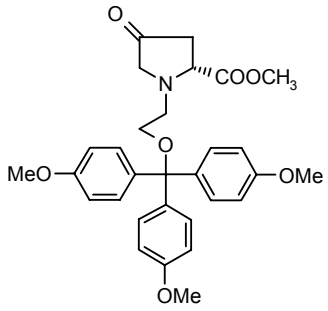
According to GP4-A from 62 mg (0.79 mmol) of DMSO and 50 mg (0.40 mmol) of $(COCl)_2$ in 2 ml of CH_2Cl_2, 92 mg (0.26 mmol) of (2*R*,4*R*)-**39a** in 2 ml of CH_2Cl_2; 83 mg (0.82 mmol) of TEA, 0.80 ml (0.80 mmol) of aq. 1.0 M NaOH; purification by CC (ϕ 18 × 230; *n*-heptane/EtOAc, 4:1). Yield: 78 mg (85%); colorless oil. – TLC: R_f = 0.28 (*n*-heptane/EtOAc, 3:1). – $[\alpha]_D^{20}$ = +33.2 (*c* = 0.60, EtOH). The spectra (^{1}H NMR, IR, and MS) were identical with those of (2*S*)-**52a**. – $C_{22}H_{23}NO_3$ (349.43): calcd. C 75.62, H 6.64, N 4.01; found C 75.51, H 6.66, N 3.87.

Methyl (2*S*)-4-oxo-1-{2-[tris(4-methoxyphenyl)methoxy]-1-ethyl}pyrrolidine-2-carboxylate [(2*S*)-52b]



According to GP4-A from 72 mg (0.92 mmol) of DMSO and 61 mg (0.46 mmol) of $(COCl)_2$ in 2 ml of CH_2Cl_2, 160 mg (0.307 mmol) of (2*S*,4*R*)-**39b** in 1.5 ml of CH_2Cl_2; 108 mg (1.07 mmol) of TEA, 1.2 ml (1.0 mmol) of aq. 0.85 M KOH; purification by CC (Al_2O_3, pH 7.5 ± 0.5; ϕ 20 × 180; *n*-heptane/EtOAc, 1:1). Yield: 132 mg (83 %); colorless viscous oil. – TLC: R_f = 0.40 (*n*-heptane/acetone, 3:2). – $[\alpha]_D^{29}$ = -6.4 (*c* = 1.83, EtOAc). – ^{1}H NMR ($CDCl_3$): δ = 2.48 (dd, *J* = 18.0/5.5 Hz, 1 H, NCHC*H*$_2$), 2.65 (dd, *J* = 18.0/7.8 Hz, 1 H, NCHC*H*$_2$), 2.83 (dt, *J* = 13.0/5.7 Hz, 1 H, NC*H*$_2$CH$_2$), 2.94 (dt, *J* = 13.0/5.7 Hz, 1 H, NC*H*$_2$CH$_2$), 3.13 (d, *J* = 17.4 Hz, 1 H, NCH$_2$CO), 3.24 (t, *J* = 5.7 Hz, 2 H, NCH$_2$C*H*$_2$), 3.44 (d, *J* = 17.4 Hz, 1 H, NCH$_2$CO), 3.72 (s, 3 H, COOCH$_3$), 3.78 (s, 9 H, ArOC*H*$_3$), 3.84 (dd, *J* = 7.8/5.5 Hz, 1 H, NCH), 6.79-6.83 (m, 6 H, H$_{aromat}$), 7.29-7.32 (m, 6 H, H$_{aromat}$). – IR: $\tilde{\nu}$ = 2953, 2840, 1754, 1604, 1504, 1254, 1028, 797 cm^{-1}. – MS; *m*/*z* (%): 333 (79) [Ar$_3$C]$^+$, 335 (19), 334 (59), 333 (79), 227 (100), 186 (5), 158 (62). – $C_{30}H_{33}NO_7$ (519.59): calcd. C 69.35, H 6.40, N 2.70; found C 69.53, H 6.59, N 2.33.

Methyl (2*R*)-4-oxo-1-{2-[tris(4-methoxyphenyl)methoxy]-1-ethyl}pyrrolidine-2-carboxylate [(2*R*)-52b]



According to GP4-A from 93 mg (1.2 mmol) of DMSO and 75 mg (0.59 mmol) of $(COCl)_2$ in 5 ml of CH_2Cl_2, 206 mg (0.395 mmol) of (2*R*,4*R*)-**39b** in 5 ml of CH_2Cl_2; 132 mg (1.30 mmol) of TEA, 1.2 ml (1.2 mmol) of aq. 1.0 M NaOH; purification (ϕ 18 × 230; *n*-heptane/acetone, 3:1). Yield: 183 mg (89%); colorless oil. – TLC: R_f = 0.40 (*n*-heptane/acetone, 3:2). – $[\alpha]_D^{20}$ = +4.3 (*c* = 1.5, EtOAc). The spectra (^{1}H NMR, IR, and MS) were identical with those of (2*S*)-**52b**. – $C_{30}H_{33}NO_7$ (519.59): calcd. C 69.35, H 6.40, N 2.70; found C 69.42, H 6.75, N 2.82.

Methyl (2*S*)-1-benzyloxycarbonyl-4-oxopyrrolidine-2-carboxylate [(2*S*)-60] [61]

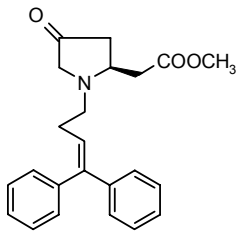
1) According to GP4-A from 148 mg (2.25 mmol) of $(COCl)_2$ and 352 mg (4.50 mmol) of DMSO in 6 ml of CH_2Cl_2, 419 mg (1.50 mmol) of (2*S*,4*R*)-**58**; 465 mg (4.70 mmol) of TEA, no strong base (NaOH or KOH) in use; purification by CC (ϕ 30 × 230; *n*-heptane/acetone, 3:1). Yield: 110 mg (26%); colorless oil. – $[\alpha]_D^{20}$ = +17.8 (*c* = 1.10, $CHCl_3$) {ref. [41]: $[\alpha]_D^{20}$ = +18.5 (*c* = 1.0, $CHCl_3$)}.

2) According to GP4-B from 500 mg (1.79 mmol) of (2*S*,4*R*)-**58** in 28 ml of acetone, 1.90 ml (15.2 mmol) of 2.67 M chromic acid in aq. H_2SO_4. Yield: 354 mg (71%); colorless oil.

Methyl (2*R*)-1-benzyloxycarbonyl-4-oxopyrrolidine-2-carboxylate [(2*R*)-60] [75]

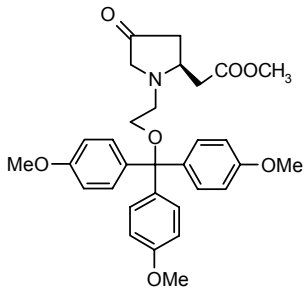
According to GP4-B from 800 mg (2.87 mmol) of (2*R*,4*R*)-**58**, 3.04 ml (24.3 mmol) of 2.67 M chromic acid in aq. H_2SO_4. Yield: 623 mg (78%); colorless oil. – $[\alpha]_D^{20}$ = -18.8 (*c* = 1.31, $CHCl_3$) {ref. [41]: $[\alpha]_D^{20}$ = -19.4 (*c* = 1.0, $CHCl_3$)}.

Methyl (2*S*)-1-(4,4-diphenylbut-3-en-1-yl)-4-oxopyrrolidine-2-acetate [(2*S*)-100a]



According to GP4-A from 54 mg (0.42 mmol) of $(COCl)_2$ and 66 mg (0.85 mmol) of DMSO in 1.5 ml of CH_2Cl_2, 103 mg (0.282 mmol) of (2*S*,4*R*)-**91a** in 1.5 ml of CH_2Cl_2; 101 mg (1.01 mmol) of TEA, 0.90 ml (0.90 mmol) of aq. 1.0 M NaOH; purification by CC (ϕ 18 × 210; *n*-heptane/acetone, 4:1). Yield: 86 mg (83%); colorless oil. – TLC: R_f = 0.43 (*n*-heptane/acetone, 3:2). – $[\alpha]_D^{20}$ = +63.5 (*c* = 1.06, EtOAc). – ^{1}H NMR ($CDCl_3$): δ = 2.21-2.38 (m, 4 H, C*H*$_2$COO, NC*H*$_2$CH$_2$, and 2 H of NCH$_2$C*H*$_2$), 2.43 (dd, *J* = 15.4/8.7 Hz, 1 H, C*H*$_2$CHCH$_2$COO), 2.57-2.63 (m, 2 H, C*H*$_2$COO and NC*H*$_2$CO), 2.78 (dd, *J* = 15.4/3.8 Hz, 1 H, C*H*$_2$CHCH$_2$COO), 2.98 (dt, *J* = 11.5/7.8 Hz, 1 H, NC*H*$_2$CH$_2$), 3.15-3.22 (m, 1 H, NCH), 3.32 (d, *J* = 17.5 Hz, 1 H, NCH$_2$CO), 3.66 (s, 3 H, OCH$_3$), 6.09 (t, *J* = 7.3 Hz, 1 H, =C*H*CH$_2$), 7.14-7.39 (m, 10 H, H_{aromat}). – IR: $\tilde{\nu}$ = 3055, 2951, 1760, 1738, 1598, 1495, 1442, 768, 702, 631 cm^{-1}. – MS; *m*/*z* (%): 364 (63) $[M+1]^+$, 290 (17), 183 (10), 170 (100) 134 (17), 91 (7). – $C_{23}H_{25}NO_3$ (363.46): calcd. C 76.00, H 6.93, N 3.85; found C 75.72, H 7.04, N 3.79.

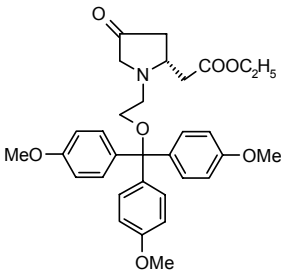
Methyl (2*S*)-4-oxo-1-{2-[tris(4-methoxyphenyl)methoxy]-1-ethyl}pyrrolidine-2-acetate [(*2S*)-100b]



According to GP4-A from 65 mg (0.51 mmol) of $(COCl)_2$ and 80 mg (1.0 mmol) of DMSO in 3 ml of CH_2Cl_2, 183 mg (0.342 mmol) of (2*S*,4*R*)-**91b** in 3 ml of CH_2Cl_2; 114 mg (1.14 mmol) of TEA, 1.1 ml (1.1 mmol) of aq. 1.0 M NaOH; purification by CC (ϕ 18 × 200; *n*-heptane/acetone, 3:2). Yield: 148 mg (81%); colorless oil. – TLC: R_f = 0.40 (*n*-heptane/acetone, 3:2). – $[\alpha]_D^{20}$ = -45.2 (*c* = 0.95, EtOAc). – ^{1}H NMR ($CDCl_3$): δ = 2.23 (dd, *J*

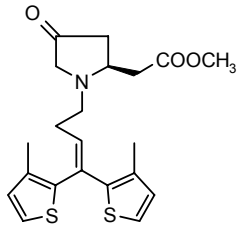
= 18.4/9.3 Hz, 1 H, CH_2COO), 2.41 (dd, *J* = 15.5/8.8 Hz, 1 H, C*H*$_2$CHCH$_2$COO), 2.49 (dt, *J* = 12.7/5.7 Hz, 1 H, NC*H*$_2$CH$_2$), 2.60 (dd, *J* = 18.4/6.7 Hz, 1 H, CH_2COO), 2.79 (d, *J* = 17.7 Hz, 1 H, NCH_2CO), 2.82 (dd, *J* = 15.5/3.8 Hz, 1 H, C*H*$_2$CHCH$_2$COO), 3.01-3.07 (m, 1 H, NC*H*$_2$CH$_2$), 3.12-3.28 (m, 3 H, NC*H* and 2 H of NCH_2CH_2), 3.45 (d, *J* = 17.7 Hz, 1 H, NCH_2CO), 3.65 (s, 3 H, $COOCH_3$), 3.77 (s, 9 H, ArOC*H*$_3$), 6.78-6.84 (m, 6 H, H_{aromat}), 7.28-7.32 (m, 6 H, H_{aromat}). – IR: $\tilde{\nu}$ = 3035, 2953, 1756, 1738, 1607, 1506, 1249, 1175, 1034, 828 cm^{-1}. – MS; *m*/*z* (%): 333 (100) $[Ar_3C]^+$, 227 (45), 202 (24), 170 (19), 160 (14), 128 (9). – $C_{31}H_{35}NO_7$ (533.62): calcd. C 69.78, H 6.61, N 2.62; found C 69.29, H 6.75, N 2.54.

Ethyl (2*R*)-4-oxo-1-{2-[tris(4-methoxyphenyl)methoxy]-1-ethyl}pyrrolidine-2-acetate [(2*R*)-101b]



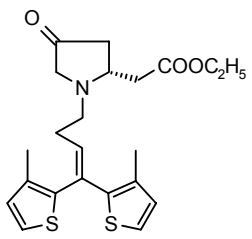
According to GP4-A from 69 mg (0.54 mmol) of $(COCl)_2$ and 85 mg (1.0 mmol) of DMSO in 2 ml of CH_2Cl_2, 149 mg (0.271 mmol) of (2*R*,4*R*)-**88b** in 2.5 of ml CH_2Cl_2; 121 mg (1.19 mmol) of TEA, 1.1 ml (1.1 mmol) of aq. 1.0 M NaOH; purification by CC (ϕ 18 × 100; *n*-heptane/acetone, 3:2). Yield: 130 mg (87%); pale yellow oil. – TLC: R_f = 0.40 (*n*-heptane/acetone, 3:2). – $[\alpha]_{578}^{20}$ = +56.9 (*c* = 1.53, EtOAc). – ^{1}H NMR ($CDCl_3$): δ = 1.23 (t, *J* = 7.2 Hz, 1 H, CH_2CH_3), 2.23 (dd, *J* = 18.4/9.3 Hz, 1 H, CH_2COO), 2.40 (dd, *J* = 15.5/8.8 Hz, 1 H, C*H*$_2$CHCH$_2$COO), 2.48 (dt, *J* = 12.7/5.7 Hz, 1 H, NC*H*$_2$CH$_2$), 2.60 (dd, *J* = 18.4/6.7 Hz, 1 H, CH_2COO), 2.79 (d, *J* = 17.7 Hz, 1 H, NCH_2CO), 2.81 (dd, *J* =15.5/3.8 Hz, 1 H, C*H*$_2$CHCH$_2$COO), 3.02-3.08 (m, 1 H, NC*H*$_2$CH$_2$), 3.13-3.29 (m, 3 H, NC*H* and 2 H of NCH_2CH_2), 3.45 (d, *J* = 17.7 Hz, 1 H, NCH_2CO), 3.77 (s, 9 H, ArOC*H*$_3$), 4.06-4.17 (m, 2 H, C*H*$_2$CH$_3$), 6.79-6.82 (m, 6 H, H_{aromat}), 7.29-7.23 (m, 6 H, H_{aromat}). – IR: $\tilde{\nu}$ = 3031, 2955, 1760, 1732, 1608, 1505, 1250, 1176, 1034, 828 cm^{-1}. – MS; *m*/*z* (%): 333 (100) $[Ar_3C]^+$, 198 (6), 184 (4), 89 (5). – $C_{32}H_{37}NO_7$ (547.65): calcd. C 70.18, H 6.81, N 2.56; found C 69.98, H 6.79, N 2.43.

Methyl (2*S*)-1-[4,4-di(3-methyl-2-thienyl)but-3-en-1-yl]-4-oxopyrrolidine-2-acetate [(2*S*)-100c]



According to GP4-A from 56 mg (0.44 mmol) of $(COCl)_2$ and 69 mg (0.87 mmol) of DMSO in 2.5 ml of CH_2Cl_2, 118 mg (0.291 mmol) of (2*S*,4*R*)-**91c** in 2.5 ml f CH_2Cl_2; 98 mg (0.96 mmol) of TEA, 0.92 ml (0.92 mmol) of aq. 1.0 M NaOH; purification by CC (ϕ 18 × 260; *n*-heptane/acetone, 3:1). Yield: 108 mg (92%); slightly yellow oil. – TLC: R_f = 0.28 (*n*-heptane/acetone, 4:1). $-[\alpha]_D^{20}$ = +68.3 (*c* = 0.75, EtOAc). – ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 2.00 (s, 3 H, thienyl-C*H*$_3$), 2.02 (s, 3 H, thienyl-C*H*$_3$), 2.23-2.43 (m, 5 H, C*H*$_2$COO, NC*H*$_2$CH$_2$, C*H*$_2$CHCH$_2$COO and 2 H of NCH$_2$C*H*$_2$), 2.59-2.66 (m, 2 H, NC*H*$_2$CO and C*H*$_2$COO), 2.80 (dd, *J* = 15.4/3.9 Hz, 1 H, C*H*$_2$CHCH$_2$COO), 2.99 (dt, *J* = 11.6/7.9 Hz, 1 H, NC*H*$_2$CH$_2$), 3.17-3.23 (m, 1 H, NCH), 3.35 (d, *J* = 17.5 Hz, 1 H, NCH$_2$CO), 3.67 (s, 3 H, OCH$_3$), 6.05 (t, *J* = 7.3 Hz, 1 H, =C*H*CH$_2$), 6.76 (d, *J* = 5.2 Hz, 1 H, SCH), 6.84 (d, *J* = 5.2 Hz, 1 H, SCH), 7.05 (d, *J* = 5.2 Hz, 1 H, SCH=C*H*), 7.21 (d, *J* = 5.2 Hz, 1 H, SCH=C*H*). – IR: $\tilde{\nu}$ = 3104, 2950, 1760, 1732, 1435, 715 cm^{-1}. – MS; *m*/*z* (%): 404 (30) $[M+1]^+$, 330 (4), 247 (3), 170 (100), 156 (8), 79 (3). – $C_{21}H_{25}NO_3S_2$ (403.56): calcd. C 62.50, H 6.24, N 3.47; found C 62.25, H 5.97, N 3.40.

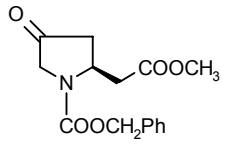
Ethyl (2*R*)-1-[4,4-di(3-methyl-thienyl)but-3-en-1-yl]-4-oxopyrrolidine-2-acetate [(2*R*)-101c]



According to GP4-A from 140 mg (1.10 mmol) of $(COCl)_2$ and 173 mg (2.20 mmol) of DMSO in 3 ml of CH_2Cl_2, 230 mg (0.548 mmol) of (2*R*,4*R*)-**88c** in 3 ml of CH_2Cl_2; 246 mg (2.42 mmol) of TEA, 2.3 ml (2.3 mmol) of aq. 1.0 M NaOH; purification by CC (ϕ 25 × 170;

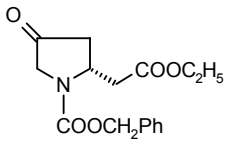
n-heptane/acetone, 3:1). Yield: 201 mg (88%); yellow oil. –TLC: R_f = 0.45 (*n*-heptane/acetone, 3:2). – $[\alpha]_D^{20}$ = -59.4 (*c* = 2.00, EtOAc). – ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.25 (t, *J* = 7.2 Hz, 1 H, CH_2CH_3), 2.00 (s, 3 H, thienyl-CH_3), 2.02 (s, 3 H, thienyl-CH_3), 2.22-2.42 (m, 5 H, CH_2COO, NCH_2CH_2, CH_2CHCH_2COO and 2 H of NCH_2CH_2), 2.59-2.66 (m, 2 H, NCH_2CO and CH_2COO), 2.80 (dd, *J* = 15.4/3.9 Hz, 1 H, CH_2CHCH_2COO), 2.99 (dt, *J* = 11.6/7.9 Hz, 1 H, NCH_2CH_2), 3.17-3.23 (m, 1 H, NCH), 3.35 (d, *J* = 17.5 Hz, 1 H, NCH_2CO), 4.09-4.18 (m, 2 H, CH_2CH_3), 6.05 (t, *J* = 7.3 Hz, 1 H, =$CHCH_2$), 6.76 (d, *J* = 5.2 Hz, 1 H, SCH), 6.84 (d, *J* = 5.2 Hz, 1 H, SCH), 7.05 (d, *J* = 5.2 Hz, 1 H, SCH=C*H*), 7.21 (d, *J* = 5.2 Hz, 1 H, SCH=C*H*). – IR: $\tilde{\nu}$ = 3100, 2974, 1759, 1732, 1184, 1027, 714 cm^{-1}. – MS; *m*/*z* (%): 418 (46) $[M+1]^+$, 329 (9), 225 (48), 184 (100), 165 (26), 105 (78). – $C_{22}H_{27}NO_3S_2$ (417.59): calcd. C 63.28, H 6.52, N 3.35, S 15.35; found C 63.20, H 6.53, N 3.20, S 14.92.

Methyl (2*S*)-1-benzyloxycarbonyl-4-oxopyrrolidine-2-acetate [(2*S*)-108]



According to GP4-B from 300 mg (1.02 mmol) of (2*S*,4*R*)-**95** in 16 ml of acetone, 1.08 ml (8.7 mmol) of 2.67 M chromic acid in aq. H_2SO_4; purification by CC (ϕ 25 × 200; *n*-heptane/acetone, 3:1). Yield: 225 mg (76%); colorless crystals. – M.p. 53-54 °C. – TLC: R_f = 0.36 (*n*-heptane/acetone, 3:2). – $[\alpha]_D^{20}$ = +10.7 (*c* = 1.06, $CHCl_3$). – ^{1}H NMR ($C_6D_5NO_2$, 120 °C): δ = 2.59 (d, *J* = 18.4 Hz, 1 H, CH_2COO), 2.83-2.99 (m, 3 H, CH_2COO and 2 H of CH_2CHCH_2COO), 3.63 (s, 3 H, OCH_3), 3.88 (d, *J* = 18.1 Hz, 1 H, NCH_2), 4.02 (d, *J* = 18.1 Hz, 1 H, NCH_2), 4.75-4.82 (m, 1 H, NCH), 5.27 (s, 2 H, CH_2Ph), 7.27-7.44 (m, 5 H, H_{aromat}). – IR: $\tilde{\nu}$ = 3033, 1765, 1732, 1698, 1416, 1106, 742, 700 cm^{-1}. – MS; *m*/*z* (%): 292 (100) $[M+1]^+$, 248 (45), 156 (25), 119 (3). – $C_{15}H_{17}NO_5$ (291.31): calcd. C 61.85, H 5.88, N 4.81; found C 61.77, H 6.07, N 4.74.

Ethyl (2*R*)-1-benzyloxycarbonyl-4-oxopyrrolidine-2-acetate [(2*R*)-112]



According to GP4-B from 192 mg (0.625 mmol) of (2*R*,4*R*)-**73**, 0.69 ml (5.5 mmol) of 2.67 M chromic acid in aq. H_2SO_4; purification by CC (ϕ 25 × 210; *n*-heptane/acetone, 3:1). Yield: 147 mg (77%); colorless oil. – TLC: R_f = 0.36 (*n*-heptane/acetone, 3:2). – $[\alpha]_D^{20}$ = -11.3 (*c* = 1.38, $CHCl_3$). – ^{1}H NMR ($CDCl_3$): δ = 1.66-1.70 (m, 3 H, CH_2CH_3), 3.06-3.12 (m, 1 H, CH_2COO), 3.31-3.37 (m, 1 H, CH_2COO), 3.39-3.47 (m, 2 H, CH_2CHCH_2COO), 4.36 (d, *J* = 18.6 Hz, 1 H, NCH_2), 4.50 (d, *J* = 18.6 Hz, 1 H, NCH_2), 4.58-4.64 (m, 2 H, CH_2CH_3), 5.23-5.29 (m, 1 H, NCH), 5.74 (s, 2 H, CH_2Ph), 7.72-7.84 (m, 5 H, H_{aromat}). – IR: $\tilde{\nu}$ = 3031, 2982, 1766, 1732, 1698, 1416, 1027, 768, 740, 699 cm^{-1}. – MS; *m*/*z* (%): 306 (100) $[M+1]^+$, 262 (30), 198 (3), 170 (15). – $C_{16}H_{19}NO_5$ (305.34): calcd. C 62.94, H 6.27, N 4.59; found 62.76, H 6.28, N 4.55.

6.1.6 Organometallic addition reaction to the C-4 positions of 4-oxopyrrolidine derivatives

General procedure 5 (GP5)

A) [51, 55, 56, 57, 59, 60]

To a mixture of 266 mg (11.1 mmol) of Mg in 22 ml of THF, 1.43 ml (2.08 g, 11.1 mmol) of 4-$MeOC_6H_5Br$ was added over 40 min at r.t. to give a gray solution of 4-$MeOC_6H_4MgBr$ (0.48 M) in THF , which was stored in a freezer at –35 °C.

$CeCl_3 \cdot 7H_2O$ was heated at 140 °C under high vacuo for 3.5 h to yield anhydrous $CeCl_3$ as white powder.

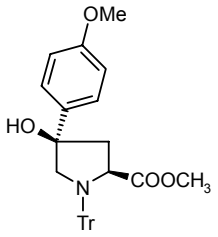
Anhydrous $CeCl_3$ (0.33-2.0 equiv.) was dried in vacuo with a heatgun for 15 min and then cooled to 0 °C. THF (10-20 ml/mmol) and 4-$MeOC_6H_4MgBr$ (1.0-2.1 equiv.) in THF were added and the resulting white suspension was stirred for 1 h at 0 °C and then cooled down to the temperature given. A solution of the respective 4-oxopyrrolidine (1 equiv.) in THF (10-20 ml/mmol) was added. Stirring was continued at the same temperature for the time given. The reaction was quenched with aq. sat. NH_4Cl. The organic layer was separated and the aqueous layer was extracted with Et_2O. The combined organic phases were dried ($MgSO_4$) and concentrated. The resulting oil was subjected to analytical HPLC, purified by CC and finally separated by prep. HPLC. Thereby some starting ketone was also recovered.

B) [58]

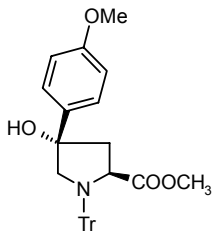
To a mixture of 266 mg (11.1 mmol) of Mg in 25 ml of Et_2O, 1.43 ml (2.08 g, 11.1 mmol) of 4-$MeOC_6H_4Br$ was added over 40 min at r.t. to give 4-$MeOC_6H_4MgBr$ (0.44 M) in Et_2O, which was stored at –35 °C.

To a solution of the respective 4-oxopyrrolidine (1 equiv.) in Et_2O (35 ml/mmol), a solution of 4-$MeOC_6H_4MgBr$ (1.80 equiv.) in Et_2O was dropwise added at the temperature given. Stirring was continued at the temperature for the time given. The reaction was quenched with aq. sat. NH_4Cl. The organic layer was separated and the aqueous layer was extracted with Et_2O. The combined organic phases were dried ($MgSO_4$) and concentrated. The resulting oil was subjected to analytical HPLC, purified by CC and finally separated by prep. HPLC. Thereby some starting ketone was also recovered.

Methyl (2*S*,4*R*)-4-hydroxy-4-(4-methoxyphenyl)-1-triphenylmethylpyrrolidine-2-carboxylate [(2*S*,4*R*)-51] and
methyl (2*S*,4*S*)-4-hydroxy-4-(4-methoxyphenyl)-1-triphenylmethylpyrrolidine-2-carboxylate [(2*S*,4*S*)-51]



(2*S*,4*R*)-51



(2*S*,4*S*)-51

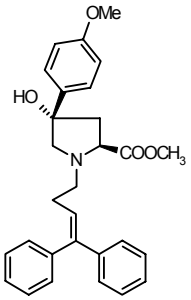
Accodording GP5-B from 2.61 ml (2.74 mmol) of 4-$MeOC_6H_4MgBr$ (1.05 M in Et_2O) was added to 530 mg (1.38 mmol) of (2*S*)-**50** in 60 ml of Et_2O; reaction: at –10 °C fro 15 h. Purification by CC (ϕ 25 × 240; *n*-heptane/EtOAc, 3:1,) and separation on prep. HPLC (*n*-heptane/EtOAc, 85:15; 12 ml/min) gave pure diastereomers. 299 mg (55%) of (2*S*)-**50** was recycled.

The minor *ds*: 58 mg (9%); colorless crystals. – t_R = 34.1 min. – M.p: 65-67 °C. – $[\alpha]_D^{20}$ = +28.3 (*c* = 0.70, EtOAc). – TLC: R_f = 0.26 (*n*-heptane/EtOAc, 2:1). – ^{1}H NMR ($CDCl_3$): δ = 1.59 (dd, *J* = 13.5/10.3 Hz, 1 H, NCHCH_2), 1.79 (dd, *J* = 13.5/1.1 Hz, 1 H, NCHCH_2), 2.78 (d, *J* = 10.7 Hz, 1 H, NCH_2), 3.57-3.61 (m, 1 H, NCH_2), 3.57 (s, 3 H, $COOCH_3$), 3.66 (s, 3 H, ArOCH_3), 3.98 (dd, *J* = 10.3/1.1 Hz, 1 H, CHCOO), 5.06 (s, 1 H, O*H*), 6.64-6.67 (m, 2 H, H_{aromat}), 6.89-6.93 (m, 2 H, H_{aromat}), 7.10-7.14 (m, 3 H, H_{aromat}), 7.19-7.24 (m, 6 H, H_{aromat}), 7.50-7.54 (m, 6 H, H_{aromat}). – IR: $\tilde{\nu}$ = 3445, 3056, 2951, 1739, 1610, 1514, 1251, 1177, 832, 745, 712 cm^{-1}. – MS; *m*/*z* (%): 310 (10), 243 (100) $[Ph_3C]^+$, 165 (50), 135 (21). – $C_{32}H_{31}NO_4$ (493.60): calcd. C 77.87, H 6.33, N 2.84; found C 77.74, H 6.62, N 2.67.

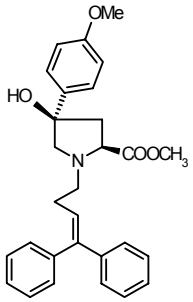
The major *ds*: 118 mg (18%); colorless crystals. – t_{RT} = 41.7 min. – M.p: 108-110 °C. – $[\alpha]_D^{20}$ = -59.1 (*c* = 1.16, EtOAc). – TLC: R_f = 0.22 (*n*-heptane/EtOAc, 2:1). – ^{1}H NMR ($CDCl_3$): δ = 2.14 (ddd, *J* = 13.2/6.9/2.2 Hz, 1 H, NCHCH_2), 2.45 (dd, *J* = 13.2/9.2 Hz, 1 H, NCHCH_2), 3.19 (d, *J* = 13.0/2.2 Hz, 1 H, NCH_2), 3.42 (s, 3 H, $COOCH_3$), 3.76 (s, 3 H, ArOCH_3), 3.97 (d, *J* = 13.0 Hz, 1 H, NCH_2), 4.07 (dd, *J* = 9.2/6.9 Hz, 1 H, CHCOO), 6.79-6.83 (m, 2 H, H_{aromat}), 7.18-7.22 (m, 3 H, H_{aromat}), 7.29-7.33 (m, 8 H, H_{aromat}), 7.60-7.63 (m, 6 H, H_{aromat}). – IR: $\tilde{\nu}$ =

3446, 3056, 3031, 2951, 1722, 1611, 1515, 1448, 1253, 1178, 832, 746, 712 cm^{-1}. – MS; *m*/*z* (%): 354 (4), 243 (100) $[Ph_3C]^+$, 165 (41). – $C_{32}H_{31}NO_4$ (493.60): calcd. C 77.87, H 6.33, N 2.84; found C 77.58, H 6.66, N 2.80.

Methyl (2S,4S)-1-(4,4-diphenylbut-3-en-1-yl)-4-hydroxy-4-(4-methoxyphenyl)-pyrrolidine-2-carboxylate [(2S,4S)-53a] and
methyl (2*S*,4*R*)-1-(4,4-diphenylbut-3-en-1-yl)-4-hydroxy-4-(4-methoxyphenyl)-pyrrolidine-2-carboxylate [(2*S*,4*R*)-53a]



(**2*S*,4*S*)-53a**



(**2*S*,4*R*)-53a**

1) According to GP5-A from 99 mg (0.40 mmol) of anhydrous $CeCl_3$ and 0.83 ml (0.48 M in THF, 0.40 mmol) of 4-$MeOC_6H_4MgBr$ in 5 ml of THF; 100 mg (0.286 mmol) of (2*S*)-**52a** in 5 ml of THF; reaction: at –60 °C for 20 h. Analytical HPLC (*n*-heptane/EtOAc/*iso*-propanol, 88:12:0.77; 1.3 ml/min) *d.s*: (2*S*,4*R*) / (2*S*,4*S*) = 61:39 [(2*S*,4*R*) t_R = 21.4 min, (2*S*,4*S*) t_R = 26.8 min]. Purification by CC (ϕ 18 × 240; *n*-heptane/EtOAc, 75:25) and separation by prep. HPLC (*n*-heptane/EtOAc/*iso*-propanol, 90:10:1.0; 12 ml/min) yielded (2*S*,4*R*)-**53a** (t_R = 40.8 min) and (2*S*,4*S*)-**53a** (t_R = 49.3 min).

(2*S*,4*R*)-**53a**: 39 mg (30%); colorless crystals. – M.p. 105-106 °C (*i*Pr_2O). – TLC: R_f = 0.23 (*n*-heptane/EtOAc, 70:30). – $[\alpha]_D^{20}$ = -49.4 (*c* = 0.815, $CHCl_3$). – ^{1}H NMR ($CDCl_3$): δ = 2.15 (ddd, *J* = 13.9/3.2/2.0 Hz, 1 H, NCHCH_2), 2.25 (q, *J* = 7.5 Hz, 2 H, NCH_2CH_2), 2.49 (dd, *J* = 13.9/10.7 Hz, 1 H, NCHCH_2), 2.63-2.70 (m, 2 H, NCH_2CH_2 and NCH_2CO), 2.80 (dt, *J* = 12.1/7.5 Hz, 1 H, NCH_2CH_2), 3.09 (dd, *J* = 9.2/2.0 Hz, 1 H, NCH_2CO), 3.38 (dd, *J* = 10.7/3.2 Hz, 1 H, NCH), 3.66 (s, 3 H, $COOCH_3$), 3.72 (s, 3 H, $ArOCH_3$), 3.92 (s, 1 H, OH), 6.05 (t, *J* = 7.5 Hz, 1 H, =C*H*CH_2), 6.78-6.81 (m, 2 H, $H_{aromat.}$), 7.09-7.33 (m, 12 H, $H_{aromat.}$). – IR: $\tilde{\nu}$ = 3471, 3026, 2956, 2808, 1720, 1604, 1509, 1248, 770, 694 cm^{-1}. – MS; *m*/*z* (%): 458 (19)

$[M+1]^+$, 440 (25), 426 (85), 381 (35), 380 (100), 207 (96), 171 (38). – $C_{29}H_{31}NO_4$ (457.57): calcd. C 76.12, H 6.83, N 3.06; found C 76.03, H 6.89, N 3.09.

(2*S*,4*S*)-**53a**: 20 mg (15%); colorless crystals. – M.p. 103-104 °C (*i*Pr_2O). – TLC: R_f = 0.18 (*n*-heptane/EtOAc, 70:30). – $[\alpha]_D^{20}$ = -1.8 (*c* = 1.00, $CHCl_3$). – ^{1}H NMR ($CDCl_3$): δ = 2.27 (q, *J* = 7.5 Hz, 2 H, NCH_2CH_2), 2.34 (d, *J* = 7.7 Hz, 2 H, $NCHCH_2$), 2.67-2.75 (m, 2 H, NCH_2CH_2 and NCH_2CO), 2.85 (dt, *J* = 12.0/7.5 Hz, 1 H, NCH_2CH_2), 3.35 (d, *J* = 10.3 Hz, 1 H, NCH_2CO), 3.63 (s, 3 H, $COOCH_3$), 3.71 (s, 3 H, $ArOCH_3$), 3.78 (t, *J* = 7.7 Hz, 1 H, NCH), 6.05 (t, *J* = 7.5 Hz, 1 H, $=CHCH_2$), 6.76-6.81 (m, 2 H, $H_{aromat.}$), 7.09-7.37 (m, 12 H, $H_{aromat.}$). – IR: $\tilde{\nu}$ = 3424, 3025, 2948, 1742, 1610, 1518, 1248, 762, 700 cm^{-1}. – MS; *m*/*z* (%): 458 (55) $[M+1]^+$, 440 (100), 264 (82), 246 (86), 183 (15). – $C_{29}H_{31}NO_4$ (457.57): calcd. C 76.12, H 6.83, N 3.06; found C 76.23, H 6.86, N 2.92.

2) According to GP5-A from 222 mg (0.901 mmol) of $CeCl_3$ and 1.88 ml (0.48 M in THF, 0.90 mmol) of 4-$MeOC_6H_4MgBr$ in 8 ml of THF; 150 mg (0.429 mmol) of (2*S*)-**52a** in 6 ml of THF; reaction: at –60 °C for 20 h; analytical HPLC *d.s*: (2*S*,4*R*) / (2*S*,4*S*) = 59:41 [(2*S*,4*R*) t_R = 21.7 min, (2*S*,4*S*) t_R = 26.8 min]; prep. HPLC yield: 60 mg (31%) of (2*S*,4*R*)-**53a** (t_R = 40.7 min) and 48 mg (25%) of (2*S*,4*S*)-**53a** (t_R = 48.8 min).

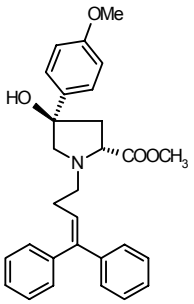
3) According to GP5-A from 148 mg (0.601 mmol) of $CeCl_3$ and 1.25 ml (0.48 M in THF, 0.60 mmol) of 4-$MeOC_6H_4MgBr$ in 8 ml of THF; 150 mg (0.429 mmol) of (2*S*)-**52a** in 7 ml of THF; reaction: at –78 °C for 20 h; analytical HPLC *d.s*: (2*S*,4*R*) / (2*S*,4*S*) = 70:30 [(2*S*,4*R*) t_R = 22.8 min, (2*S*,4*S*) t_R = 28.4 min]; prep. HPLC yield: 54 mg (28%) of (2*S*,4*R*)-**53a** (t_R = 39.7 min) and 24 mg (12%) of (2*S*,4*S*)-**53a** (t_R = 49.5 min).

4) According to GP5-A from 50 mg (0.20 mmol) of $CeCl_3$ and 1.37 ml (0.48 M in THF, 0.60 mmol) of 4-$MeOC_6H_4MgBr$ in 8 ml of THF; 150 mg (0.429 mmol) of (2*S*)-**52a** in 7 ml of THF; reaction: at –78 °C for 20 h; analytical HPLC *d.s*: (2*S*,4*R*) / (2*S*,4*S*) = 61:39 [(2*S*,4*R*) t_R = 21.9 min, (2*S*,4*S*) t_R = 29.0 min]; prep. HPLC yield: 37 mg (19%) of (2*S*,4*R*)-**53a** (t_R = 37.4 min) and 19 mg (10%) of (2*S*,4*S*)-**53a** (t_R = 49.2 min).

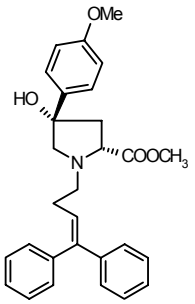
5) According to GP5-B from 150 mg (0.429 mmol) of (2*S*)-**52a** in 15 ml of Et_2O, 1.76 ml (0.44 M in Et_2O, 0.77 mmol) of 4-$MeOC_6H_4MgBr$; reaction: at –78 °C for 20 h; analytical

HPLC *d.s*: (2*S*,4*R*) / (2*S*,4*S*) = 89:11 [(2*S*,4*R*) t_R = 23.1 min, (2*S*,4*S*) t_R = 28.4 min]; prep. HPLC yield: 12 mg (6%) of (2*S*,4*R*)-**53a** (t_R = 39.0 min) and 109 mg (56%) of (2*S*,4*S*)-**53a** (t_R = 53.6 min).

Methyl (2*R*,4*R*)-1-(4,4-diphenylbut-3-en-1-yl)-4-hydroxy-4-(4-methoxyphenyl)-pyrrolidine-2-carboxylate [(2*R*,4*R*)-53a] and methyl (2*R*,4*S*)-1-(4,4-diphenylbut-3-en-1-yl)-4-hydroxy-4-(4-methoxyphenyl)-pyrrolidine-2-carboxylate [(2*R*,4*S*)-53a]



(**2*R*,4*R*)-53a**



(**2*R*,4*S*)-53a**

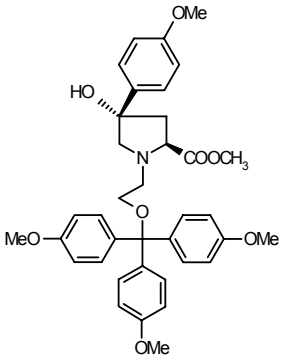
8) According to GP5-A from 315 mg (1.28 mmol) of $CeCl_3$ and 2.67 ml (0.48 M in THF, 1.3 mmol) of 4-$MeOC_6H_4MgBr$ in 14 ml of THF; 320 mg (0.915 mmol) of (2*R*)-**52a** in 10 ml of THF; reaction: at –60 °C for 20 h; analytical HPLC (*n*-heptane/EtOAc/*iso*-propanol, 88:12:0.77; 1.3 ml/min) *d.s*: (2*R*,4*S*) / (2*R*,4*R*) = 58:42 [(2*R*,4*S*) t_R = 21.8 min, (2*R*,4*R*) t_R = 27.2 min]. Purification by CC (ϕ 25 × 290; *n*-heptane/EtOAc, 3:1) and separation by prep. HPLC (*n*-heptane/EtOAc/*iso*-propanol, 86:14:0.9; 12 ml/min) yielded (**2*R*,4*S***)-**53a** (t_R = 26.0 min) and (2*R*,4*R*)-**53a** (t_R = 37.1 min); 25 mg of (2*R*)-**52a** was recovered.

(2*R*,4*S*)-**53a**: 116 mg (28%); colorless crystals. – M.p. 105-107 °C (*i*Pr_2O). – TLC: R_f = 0.23 (*n*-heptane/EtOAc, 7:3).– $[\alpha]_D^{20}$ = +47.9 (*c* = 0.90, $CHCl_3$). The spectra (^{1}H NMR, IR, and MS) were identical with those of (2*S*,4*R*)-**53a**. – $C_{29}H_{31}NO_4$ (457.57): calcd. C 76.12, H 6.83, N 3.06; found C 76.03, H 6.86, N 3.02.

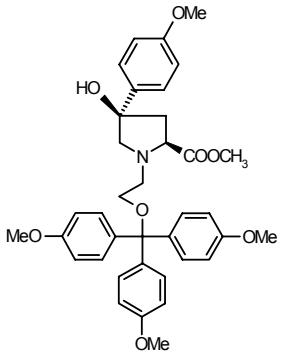
(2*R*,4*R*)-**53a**: 82 mg (20%); colorless crystals. – M.p. 103-104 °C (*i*Pr_2O). – TLC: R_f = 0.18 (*n*-heptane/EtOAc, 7:3). – $[\alpha]_D^{20}$ = +1.6 (*c* = 0.80, $CHCl_3$). The spectra (^{1}H NMR, IR, and

MS) were identical with those of (2*S*,4*S*)-**53a**. – $C_{29}H_{31}NO_4$ (457.57): calcd. C 76.12, H 6.83, N 3.06; found 76.07, H 6.83, N 3.09.

Methyl (2*S*,4*S*)-4-hydroxy-4-(4-methoxyphenyl)-1-{2-[tris(4-methoxyphenyl)-methoxy]-1-ethyl}pyrrolidine-2-carboxylate [(2*S*,4*S*)-53b] and methyl (2*S*,4*R*)-4-hydroxy-4-(4-methoxyphenyl)-1-{2-[tris(4-methoxyphenyl)-methoxy]-1-ethyl}pyrrolidine-2-carboxylate [(2*S*,4*R*)-53b]



(**2*S*,4*S*)-53b**



(**2*S*,4*R*)-53b**

6) According to GP5-A from 130 mg (0.527 mmol) of $CeCl_3$ and 0.80 ml (0.67 M in THF, 0.53 mmol) of 4-$MeOC_6H_4MgBr$ in 5 ml of THF; 196 mg (0.377 mmol) of (2*S*)-**52b** in 6 ml of THF; reaction: at –60 °C for 20 h; analytical HPLC (*n*-heptane/EtOAc, 50:50; 1.3 ml/min) *d.s*: (2*S*,4*S*)-**53b** / (2*S*,4*R*)-**53b** = 48:52 [(2*S*,4*S*) t_R = 7.6 min, (2*S*,4*R*) t_R = 11.9 min]. Purification by CC (ϕ 20 × 320; *n*-heptane/EtOAc, 3:2) and separation by prep. HPLC (*n*-heptane/EtOAc, 55:45; 12 ml/min) afforded (2*S*,4*S*)-**53b** (t_R = 19.7 min) and (2*S*,4*R*)-**53b** (t_R = 24.6 min).

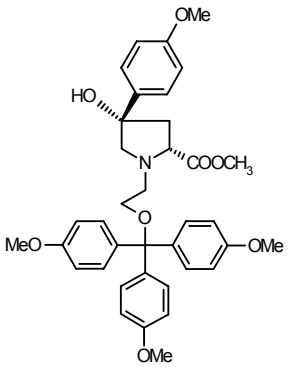
(2*S*,4*S*)-**53b**: 57 mg (24%); colorless viscous oil. – TLC: R_f = 0.19 (*n*-heptane/EtOAc, 1:1). – $[\alpha]_D^{20}$ = -7.1 (*c* = 1.10, acetone). – ^{1}H NMR ($CDCl_3$): δ = 2.34-2.44 (m, 2 H, NCHCH_2), 2.54 (s, 1 H, OH), 2.94-3.00 (m, 2 H, NCH_2CO and NCH_2CH_2), 3.04-3.10 (m, 1 H, NCH_2CH_2), 3.17-3.26 (m, 2 H, NCH_2CH_2), 3.49 (d, *J* = 10.7 Hz, 1 H, NCH_2CO), 3.69 (s, 3 H, COOCH_3), 3.78 (s, 9 H, ArOCH_3), 3.79 (s, 3 H, Ar'OCH_3), 3.94 (t, *J* = 7.6 Hz, 1 H, NCH), 6.79-6.83 (m, 6 H, H_{aromat}), 6.85-6.88 (m, 2 H, H_{aromat}), 7.31-7.34 (m, 6 H, H_{aromat}), 7.38-7.42 (m, 2 H, H_{aromat}). – MS; *m*/*z* (%): 333 (100) $[Ar_3C]^+$, 296 (15), 227 (38). – IR: $\tilde{\nu}$ = 3478, 3036, 2953, 1738, 1608, 1583, 1505, 1251, 1036, 829 cm^{-1}. – $C_{37}H_{41}NO_8$ (627.73): calcd. C 70.80, H

6.58, N 2.23; found C 70.33, H 7.07, N 2.22.

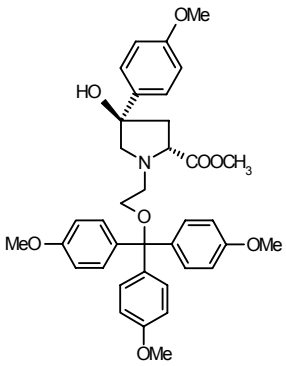
(2*S*,4*R*)-**53b**: 62 mg (26%); colorless viscous oil. – TLC: R_f = 0.23 (*n*-heptane/EtOAc, 1:1). – $[\alpha]_D^{20}$ = -22.7 (*c* = 1.66, acetone). – ^{1}H NMR ($CDCl_3$): δ = 2.23 (dt, *J* = 13.9/3.0 Hz, 1 H, NCHCH_2), 2.56 (dd, *J* = 13.9/10.7 Hz, 1 H, NCHCH_2), 2.87-2.95 (m, 2 H, NCH_2CO and NCH_2CH$_2$), 2.98-3.05 (m, 1 H, NCH_2CH$_2$), 3.19-3.24 (m, 3 H, NCH_2CO and 2 H of NCH$_2$CH_2), 3.63 (dd, *J* = 10.7/3.0 Hz, 1 H, NCH), 3.71 (s, 3 H, COOCH_3), 3.79 (s, 9 H, ArOCH_3), 3.81 (s, 3 H, Ar'OCH_3), 6.81-6.84 (m, 6 H, H_{aromat}), 6.86-6.90 (m, 2 H, H_{aromat}), 7.31-7.35 (m, 6 H, H_{aromat}), 7.37-7.40 (m, 2 H, H_{aromat}). – MS; *m*/*z* (%): 333 (100) $[Ar_3C]^+$, 296 (11), 227 (34). – IR: $\tilde{\nu}$ = 3476, 3036, 2950, 1733, 1608, 1582, 1508, 1250, 1034, 829 cm^{-1}. – $C_{37}H_{41}NO_8$ (627.73): calcd. C 70.80, H 6.58, N 2.23; found C 70.51, H 6.62, N 2.15.

7) According to GP5-B from 113 mg (0.218 mmol) of (2*S*)-**52b** in 6 ml of Et_2O and 0.78 ml (0.50 M in Et_2O, 0.39 mmol) of 4-MeOC$_6$H$_4$MgBr; reaction: at –78 °C for 20 h; analytical HPLC (*n*-heptane/EtOAc/*iso*-propanol, 70:30:1.0; 1.3 ml/min) *d.s*: (2*S*,4*S*) / (2*S*,4*R*) = 85:15 [(2*S*,4*S*) t_R = 17.7 min, (2*S*,4*R*) t_R = 23.5 min]; purification by CC (ϕ 18 × 230; *n*-heptane/acetone, 2:1) and separation by prep. HPLC (*n*-heptane/EtOAc, 60:40; 12 ml/min) gave 55 mg (40%) of (2*S*,4*S*)-**53b** (t_R = 31.1 min) and 7 mg (5%) of (2*S*,4*R*)-**53b** (t_R = 45.2 min).

Methyl (2*R*,4*S*)-4-hydroxy-4-(4-methoxyphenyl)-1-{2-[tris(4-methoxyphenyl)-methoxy]-1-ethyl}pyrrolidine-2-carboxylate [(2*R*,4*S*)-53b] and methyl (2*R*,4*R*)-4-hydroxy-4-(4-methoxyphenyl)-1-{2-[tris(4-methoxyphenyl)-methoxy]-1-ethyl}pyrrolidine-2-carboxylate [(2*R*,4*R*)-53b]



(2*R*,4*S*)-**53b**



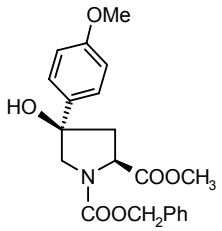
(2*R*,4*R*)-**53b**

9) According to GP5-A from 165 mg (0.669 mmol) of $CeCl_3$ and 1.40 ml (0.48 M in THF, 0.67 mmol) of 4-$MeOC_6H_4MgBr$ in 10 ml of THF; 248 mg (0.478 mmol) of (2*R*)-**52b** in 10 ml of THF; reaction: at –60 °C for 20 h. Analytical HPLC (*n*-heptane/EtOAc/*iso*-propanol, 70:30:1.0; 1.3 ml/min) *d.s*: (2*R*,4*R*) / (2*R*,4*S*) = 45:55 [(2*R*,4*R*) t_R = 17.5 min, (2*R*,4*S*) t_R = 22.9 min]. Purification by CC (ϕ 25 × 265; *n*-heptane/acetone, 2:1) and separation by prep. HPLC (*n*-heptane/EtOAc, 60:40; 12 ml/min) yielded (2*R*,4*R*)-**53b** (t_R = 29.3 min) and (2*R*,4*S*)-**53b** (t_R = 43.7 min); 19 mg of the starting ketone was recovered.

(2*R*,4*R*)-**53b**: 57 mg (19%); colorless viscous oil. – TLC: R_f = 0.19 (*n*-heptane/EtOAc, 50:50). – $[\alpha]_D^{23}$ = +7.6 (*c* = 0.93, acetone). The spectra (^{1}H NMR, IR, and MS) were identical with those of (2*R*,4*R*)-**53b**. – ($C_{37}H_{41}NO_8$ (627.73): calcd. C 70.80, H 6.58, N 2.23; found C 70.47, H 6.62, N 2.13.

(2*R*,4*S*)-**53b**: 63 mg (21%); colorless oil. – TLC: R_f = 0.23 (*n*-heptane/EtOAc, 50:50). – $[\alpha]_D^{24}$ = +22.9 (*c* = 1.12, acetone). The spectra (^{1}H NMR, IR, and MS) were identical with those of (2*S*,4*R*)-**53b**. – $C_{37}H_{41}NO_8$ (627.73): calcd. C 70.80, H 6.58, N 2.23; found C 70.61, H 6.58, N 2.15.

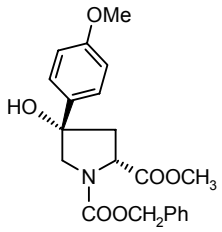
Methyl (2*S*,4*R*)-1-benzyloxycarbonyl-4-hydroxy-4-(4-methoxyphenyl)pyrrolidine-2-carboxylate [(2*S*,4*R*)-61]



According to GP5-A from 330 mg (1.34 mmol) of $CeCl_3$ and 2.80 ml (0.48 M in THF, 1.34 mmol) of 4-$MeOC_6H_4MgBr$ in 20 ml of THF, 354 mg (1.28 mmol) of (2*S*)-**60** in 5 ml of THF; reaction: at – 60 °C for 4.5 h; purification by CC (ϕ 25 × 270; *n*-heptane/acetone, 3:1). 61 mg of the starting ketone was recovered. Yield: 276 mg (56%); colorless oil. – TLC: R_f = 0.35 (*n*-heptane/acetone, 3:2). – $[\alpha]_D^{20}$ = -23.5 (*c* = 1.36, EtOAc). – ^{1}H NMR ($C_6D_5NO_2$, 120 °C): δ = 2.51 (dd, *J* = 13.6/1.8 Hz, 1 H, NCHCH_2), 2.83 (ddd, *J* = 13.6/9.7/1.5 Hz, 1 H, NCHCH_2), 3.78-3.81 (m, 6 H, COOCH_3 and ArOCH_3), 3.93 (dd, *J* = 11.4/1.5 Hz, 1 H, NCH_2), 4.07 (dd, *J* = 11.4/1.3 Hz, 1 H, NCH_2), 4.77 (dd, *J* = 9.7/1.3 Hz, 1 H, NCH), 5.23 (d, *J* = 12.6 Hz, 1 H, PhCH_2), 5.32 (d, *J* = 12.6 Hz, 1 H, PhCH_2), 6.89-6.94 (m, 2 H, H_{aromat}), 7.27-

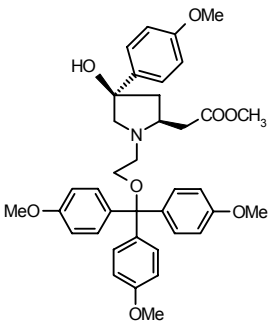
7.50 (m, 7 H, H_{aromat}). – IR: $\tilde{\nu}$ = 3438, 3063, 2951, 1756, 1706, 1610, 1514, 1418, 1251, 832, 770, 699 cm^{-1}. – MS; *m*/*z* (%): 385 (2) $[M+1]^+$, 368 (62), 324 (100), 250 (18), 234 (21), 135 (18), 91 (90). – $C_{21}H_{23}NO_6$ (385.42): calcd. C 65.44, H 6.02, N 3.63; found C 65.11, H 6.19, N 3.70.

Methyl (2*R*,4*S*)-1-benzyloxycarbonyl-4-hydroxy-4-(4-methoxyphenyl)pyrrolidine-2-carboxylate [(2*R*,4*S*)-61]

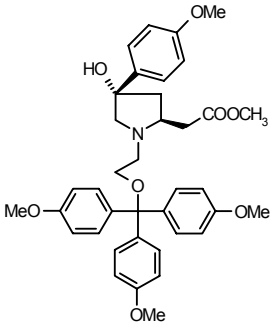


According to GP5-A from 399 mg (1.62 mmol) of $CeCl_3$ and 3.38 ml (0.48 M in THF, 1.62 mmol) of 4-$MeOC_6H_4MgBr$ in 25 ml of THF, 427 mg (1.54 mmol) of (2*R*)-**60**; reaction: at – 60 °C for 5.5 h; purification by CC (ϕ 30 × 250; *n*-heptane/acetone, 3:1). 84 mg of the starting ketone was recovered. Yield: 265 mg (45%); colorless oil. – TLC: R_f = 0.35 (*n*-heptane/acetone, 3:2). – $[\alpha]_D^{20}$ = +24.8 (*c* = 1.08, EtOAc). The spectra (^{1}H NMR, IR, and MS) were identical with those of (2*S*,4*R*)-**61**. – $C_{21}H_{23}NO_6$ (385.42): calcd. C 65.44, H 6.02, N 3.63; found C 65.48, H 6.16, N 3.57.

Methyl (2*S*,4*R*)-4-hydroxy-4-(4-methoxyphenyl)-1-{2-[tris(4-methoxyphenyl)methoxy]-1-ethyl}pyrrolidine-2-acetate [(2*S*,4*R*)-102b] and
methyl (2*S*,4*S*)-4-hydroxy-4-(4-methoxyphenyl)-1-{2-[tris(4-methoxyphenyl)methoxy]-1-ethyl}pyrrolidine-2-acetate [(2*S*,4*S*)-102b]



(2*S*,4*R*)-102b



(2*S*,4*S*)-102b

1) According to GP5-B from 115 mg (0.216 mmol) of (2*S*)-**100b** in 11 ml of Et_2O, 0.88 ml (0.44 M in Et_2O, 0.39 mmol) of 4-$MeOC_6H_4MgBr$; reaction: at –78 °C for 20 h; analytical HPLC (*n*-heptane/EtOAc/*iso*-propanol, 54:45:1.2; 1.3 ml/min) *d.s*: (2*S*,4*S*) / (2*S*,4*R*) = 81:19 [(2*S*,4*S*) t_R = 9.1 min, (2*S*,4*R*) t_R = 13.8 min]. Purification by CC (ϕ 25 × 210; *n*-heptane/acetone, 3:1) and separation by prep. HPLC (*n*-heptane/EtOAc/*iso*-propanol, 54:45:1.2; 12 ml/min) yielded (2*S*,4*S*)-**102b** (t_R = 19.4 min) and (2*S*,4*R*)-**102b** (t_R = 29.0 min). 38 mg of (2*S*)-**100b** was recovered.

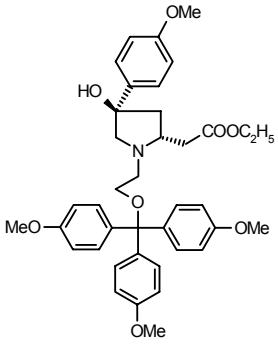
(2*S*,4*S*)-**102b**: 65 mg (47%); colorless oil. – TLC: R_f = 0.28 (*n*-heptane/EtOAc/*iso*-propanol, 54:45:1.2). – $[\alpha]_D^{20}$ = -14.4 (*c* = 0.95, acetone). – ^{1}H NMR ($CDCl_3$): δ = 2.05 (dd, *J* = 13.0/9.6 Hz, 1 H, C*H*$_2$CHCH$_2$COO), 2.28-2.37 (m, 2 H, C*H*$_2$CHCH$_2$COO and C*H*$_2$COO), 2.69-2.77 (m, 2 H, NC*H*$_2$CH$_2$ and C*H*$_2$COO), 2.82 (d, *J* = 10.9 Hz, 1 H, NCH$_2$CO), 2.99-3.06 (m, 1 H, NC*H*$_2$CH$_2$), 3.10-3.20 (m, 2 H, NCH$_2$C*H*$_2$), 3.43 (d, *J* = 10.9 Hz, 1 H, NCH$_2$CO), 3.44-3.51 (m, 1 H, NCH), 3.63 (s, 3 H, COOC*H*$_3$), 3.77 (s, 9 H, Ar'OC*H*$_3$), 3.79 (s, 3 H, ArOC*H*$_3$), 6.78-6.82 (m, 6 H, H$_{aromat}$), 6.83-6.86 (m, 2 H, H$_{aromat}$), 7.31-7.35 (m, 6 H, H$_{aromat}$), 7.36-7.40 (m, 2 H, H$_{aromat}$). – IR: $\tilde{\nu}$ = 3462, 3030, 2951, 1732, 1608, 1581, 1509, 1249, 1176, 1034, 829 cm^{-1}. – MS; *m*/*z* (%): 333 (100) [Ar_3C]$^+$, 260 (14), 227 (41), 186 (5), 101 (12). – $C_{38}H_{43}NO_8$ (641.77): calcd. C 71.12, H 6.75, N 2.18; found C 71.10, H 6.86, N 2.11.

(2*S*,4*R*)-**102b**: 20 mg (14%); colorless oil. – TLC: R_f = 0.23 (*n*-heptane/EtOAc/*iso*-propanol,

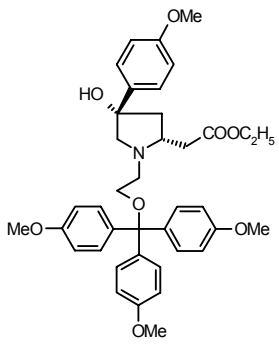
54:45:1.2). – $[\alpha]_D^{20}$ = -36.8 (*c* = 0.88, acetone). – ^{1}H NMR ($CDCl_3$): δ = 2.08 (ddd, *J* = 14.1/5.2/1.8 Hz, 1 H, C*H*$_2$CHCH$_2$COO), 2.51-2.61 (m, 4 H, C*H*$_2$CHCH$_2$COO, C*H*$_2$COO, NC*H*$_2$CH$_2$ and NC*H*$_2$CO), 2.72 (dd, *J* = 16.0/3.5 Hz, 1 H, CH$_2$COO), 2.99-3.08 (m, 2 H, NC*H*$_2$CH$_2$ and NC*H*), 3.12-3.25 (m, 3 H, NC*H*$_2$CO and 2 H of NCH$_2$C*H*$_2$), 3.55 (s, 1 H, OH), 3.64 (s, 3 H, COOC*H*$_3$), 3.77 (s, 9 H, Ar'OC*H*$_3$), 3.79 (s, 3 H, ArOC*H*$_3$), 6.80-6.88 (m, 8 H, H_{aromat}), 7.30-7.34 (m, 6 H, H_{aromat}), 7.35-7.39 (m, 2 H, H_{aromat}). – IR: $\tilde{\nu}$ = 3481, 3000, 1732, 1607, 1580, 1508, 1248, 1034, 829 cm^{-1}. – MS; *m*/*z* (%): 334 (41), 333 (100) $[Ar_3C]^+$, 280 (16), 260 (12), 227 (100), 218 (25), 101 (7). – $C_{38}H_{43}NO_8$ (641.77): calcd. C 71.12, H 6.75, N 2.18; found C 71.06, H 7.08, N 2.14.

2) According to GP5-A from 110 mg (0.45 mmol) of $CeCl_3$ and 0.93 ml (0.48 M in THF, 0.45 mmol) of 4-MeOC$_6$H$_4$MgBr in 8 ml of THF; 170 mg (0.320 mmol) of (2*S*)-**100b** in 4 ml of THF; reaction: at –78 °C for 20 h; analytical HPLC (*n*-heptane/EtOAc/*iso*-propanol, 54:45:1.2; 1.3 ml/min) *d.s*: (2*S*,4*S*) / (2*S*,4*R*) = 17:83 [(2*S*,4*S*) t_R = 10.0 min, (2*S*,4*R*) t_R = 14.1 min]; purification by CC (ϕ 25 × 220; *n*-heptane/acetone, 3:1) and separation by prep. HPLC yielded 11 mg (5%) of (2*S*,4*S*)-**102b** (t_R = 20.4 min) and 88 mg (43%) of (2*S*,4*R*)-**102b** (t_R = 28.0 min). 35 mg of (2*S*)-**100b** was recovered.

Ethyl (2*R*,4*R*)-4-hydroxy-4-(4-methoxyphenyl)-1-{2-[tris(4-methoxyphenyl)methoxy]-1-ethyl}pyrrolidine-2-acetate [(2*R*,4*R*)-103b] and
ethyl (2*R*,4*S*)-4-hydroxy-4-(4-methoxyphenyl)-1-{2-[tris(4-methoxyphenyl)methoxy]-1-ethyl}pyrrolidine-2-acetate [(2*R*,4*S*)-103b]



(2*R*,4*R*)-**103b**



(2*R*,4*S*)-**103b**

1) According to GP5-B from 185 mg (0.338 mmol) of (2*R*)-**101b** in 12 ml of Et$_2$O, 1.38 ml (0.44 M in Et$_2$O, 0.61 mmol) of 4-MeOC$_6$H$_4$MgBr; reaction: at –78 °C for 20 h; analytical

HPLC (*n*-heptane/EtOAc/*iso*-propanol, 60:40:1.2; 1.3 ml/min) *d.s*: (2*R*,4*R*) / (2*R*,4*S*) = 79:21 [(2*R*,4*R*) t_R = 10.5 min, (2*R*,4*S*) t_R = 12.4 min]. Purification by CC (ϕ 25 × 230; *n*-heptane/acetone, 3:2) and separation by prep. HPLC (*n*-heptane/EtOAc/*iso*-propanol, 60:40:0.88; 12 ml/min) yielded (2*R*,4*R*)-**103b** (t_R = 22.5 min) and (2*R*,4*S*)-**103b** (t_R = 31.3 min). 58 mg of (2*R*)-**101b** was recovered.

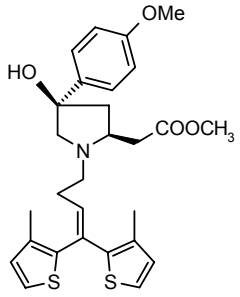
(2*R*,4*R*)-**103b**: 111 mg (50%); colorless oil. – TLC: R_f = 0.31 (*n*-heptane/acetone, 3:2). – $[\alpha]_D^{20}$ = +14.6 (*c* = 2.18, EtOAc). – ^{1}H NMR ($CDCl_3$): δ = 1.25 (t, *J* = 7.1 Hz, 3 H, CH_2CH_3), 2.10 (br. s, 1 H, OH), 2.05 (dd, *J* = 13.1/9.7 Hz, 1 H, CH_2CHCH_2COO), 2.28-2.35 (m, 2 H, CH_2CHCH_2COO and CH_2COO), 2.67-2.77 (m, 2 H, NCH_2CH_2 and CH_2COO), 2.82 (d, *J* = 10.8 Hz, 1 H, NCH_2CO), 3.00-3.07 (m, 1 H, NCH_2CH_2), 3.10-3.20 (m, 2 H, NCH_2CH_2), 3.42 (d, *J* = 10.8 Hz, 1 H, NCH_2CO), 3.44-3.51 (m, 1 H, NCH), 3.77 (s, 9 H, Ar'OCH_3), 3.79 (s, 3 H, ArOCH_3), 4.05-4.13 (m, 2 H, CH_2CH_3), 6.77-6.81 (m, 6 H, H_{aromat}), 6.82-6.86 (m, 2 H, H_{aromat}), 7.31-7.35 (m, 6 H, H_{aromat}), 7.36-7.40 (m, 2 H, H_{aromat}). – IR: $\tilde{\nu}$ = 3492, 2933, 1729, 1608, 1508, 1249, 1034, 828 cm^{-1}. – MS; *m*/*z* (%): 333 (100) $[Ar_3C]^+$, 227 (52), 105 (24). – $C_{39}H_{45}NO_8$ (655.80): calcd. C 71.43, H 6.92, N 2.14; found C 71.17, H 6.92, N 2.08.

(2*R*,4*S*)-**103b**: 33 mg (15%); colorless oil. – TLC: R_f = 0.31 (*n*-heptane/acetone, 3:2). – $[\alpha]_D^{20}$ = +36.5 (*c* = 0.85, EtOAc). – ^{1}H NMR ($CDCl_3$): δ = 1.22 (t, *J* = 7.2 Hz, 3 H, CH_2CH_3), 2.08 (dd, *J* = 14.1/5.2/1.8 Hz, 1 H, CH_2CHCH_2COO), 2.51-2.60 (m, 4 H, CH_2CHCH_2COO, CH_2COO, NCH_2CH_2 and NCH_2CO), 2.72 (dd, *J* = 15.9/3.3 Hz, 1 H, CH_2COO), 2.99-3.08 (m, 2 H, NCH_2CH_2 and NC*H*), 3.12-3.25 (m, 3 H, NCH_2CO and 2 H of NCH_2CH_2), 3.54 (s, 1 H, OH), 3.77 (s, 9 H, Ar'OCH_3), 3.79 (s, 3 H, ArOCH_3), 4.05-4.16 (m, 2 H, CH_2CH_3), 6.80-6.88 (m, 8 H, H_{aromat}), 7.30-7.34 (m, 6 H, H_{aromat}), 7.35-7.39 (m, 2 H, H_{aromat}). – IR: $\tilde{\nu}$ = 3462, 3036, 2952, 1728, 1608, 1508, 1249, 1176, 1034, 828 cm^{-1}. – MS; *m*/*z* (%): 333 (100) $[Ar_3C]^+$, 324 (10), 227 (55), 105 (74). – $C_{39}H_{45}NO_8$ (655.80): calcd. C 71.43, H 6.92, N 2.14; found C 71.43, H 7.17, N 2.05.

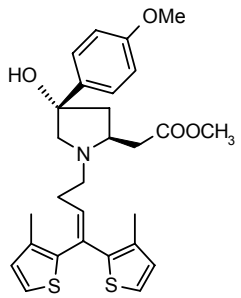
2) According to GP5-A from 76 mg (0.31 mmol) of $CeCl_3$ and 0.63 ml (0.48 M in THF, 0.30 mmol) of 4-$MeOC_6H_4MgBr$ in 5 ml of THF, 119 mg (0.217 mmol) of (2*R*)-**101b** in 4 ml of THF; reaction: at –78 °C for 20 h. Purification by CC (ϕ 25 × 260; *iso*-hexane/acetone, 3:1) and separation by prep. HPLC (*n*-heptane/EtOAc/*iso*-propanol, 60:40:0.88; 12 ml/min.) yielded 2 mg (1%) of (2*R*,4*R*)-**103b** (t_R = 23.0 min) and 63 mg (44%) of (2*R*,4*S*)-**103b** (t_R =

30.4 min). 20 mg of (2*R*)-**101b** was recovered.

Methyl (2*S*,4*R*)-1-[4,4-di(3-methyl-2-thienyl)but-3-en-1-yl]-4-hydroxy-4-(4-methoxyphenyl)pyrrolidine-2-acetate [(2*S*,4*R*)-102c] and methyl (2*S*,4*S*)-1-[4,4-di(3-methyl-2-thienyl)but-3-en-1-yl]-4-hydroxy-4-(4-methoxyphenyl)pyrrolidine-2-acetate [(2*S*,4*S*)-102c]



(**2*S*,4*R*)-102c**



(**2*S*,4*S*)-102c**

1) According to GP5-B from 136 mg (0.337 mmol) of (2*S*)-**100c** in 17 ml of Et_2O, 1.53 ml (0.44 M in Et_2O, 0.67 mmol) of 4-$MeOC_6H_4MgBr$; reaction: at -78 °C for 20 h; analytical HPLC (*n*-heptane/EtOAc/*iso*-propanol, 75:25:0.5; 1.3 ml/min) *d.s*: (2*S*,4*S*) / (2*S*,4*R*) = 87:13 [(2*S*,4*S*) t_R = 17.0 min, (2*S*,4*R*) t_R = 20.5 min]. Purification by CC (ϕ 25 × 200; *n*-heptane/acetone, 3:1) and separation by prep. HPLC (*n*-heptane/EtOAc/*iso*-propanol, 75:25:0.5; 12 ml/min) yielded (2*S*,4*S*)-**102c** (t_R = 36.5 min) and (2*S*,4*R*)-**102c** (t_R = 49.6 min). 33 mg of (2*S*)-**100c** was recovered.

(2*S*,4*S*)-**102c**: 81 mg (47%); colorless oil. – TLC: R_f = 0.36 (*n*-heptane/acetone, 3:2). – $[\alpha]_D^{20}$ = -50.4 (*c* = 1.09, $CHCl_3$). – ^{1}H NMR ($CDCl_3$): δ = 2.00 (s, 3 H, thienyl-CH_3), 2.02 (s, 3 H, thienyl-CH_3), 2.04 (dd, *J* = 13.2/9.5 Hz, 1 H, CH_2CHCH_2COO), 2.27-2.35 (m, 4 H, CH_2CHCH_2COO, CH_2COO and 2 H of NCH_2CH_2), 2.54-2.61 (m, 1 H, NCH_2CH_2), 2.67-2.72 (m, 2 H, CH_2COO and NCH_2CO), 2.90 (dt, *J* = 12.0/8.0 Hz, 1 H, NCH_2CH_2), 3.35-3.42 (m, 2 H, NCH_2CO and NC*H*), 3.64 (s, 3 H, $COOCH_3$), 3.78 (s, 3 H, ArOCH_3), 6.09 (t, *J* = 7.2 Hz, 1 H, =C*H*CH_2), 6.76 (d, *J* = 5.2 Hz, 1 H, SCH), 6.82-6.86 (m, 3 H, SC*H* and 2 H of H_{aromat}), 7.05 (d, *J* = 5.2 Hz, 1 H, SCH=C*H*), 7.19 (d, *J* = 5.2 Hz, 1 H, SCH=C*H*), 7.37-7.41 (m, 2 H, H_{aromat}). – IR: $\tilde{\nu}$ = 3493, 3090, 2950, 1732, 1613, 1514, 1249, 833, 713 cm^{-1}. – MS; *m*/*z* (%):

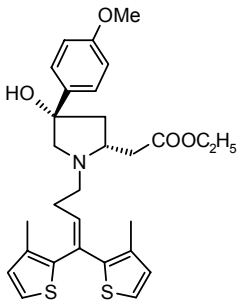
512 (13) $[M+1]^+$, 494 (10), 480 (2), 278 (100), 260 (24), 248 (10), 101 (2). – $C_{28}H_{33}NO_4S_2$ (511.70): calcd. C 65.72, H 6.50, N 2.74, S 12.53; found C 65.97, H 6.84, N 2.56, S 12.35.

(2*S*,4*R*)-**102c**: 19 mg (11%); colorless crystals. – M.p. 99-100 °C (*i*Pr_2O). – TLC: R_f = 0.33 (*n*-heptane/acetone, 3:2). – $[\alpha]_D^{20}$ = +73.1 (*c* = 1.00, $CHCl_3$). – ^{1}H NMR ($CDCl_3$): δ = 2.00 (s, 3 H, thienyl-C*H*$_3$), 2.03 (s, 3 H, thienyl-C*H*$_3$), 2.09 (ddd, *J* = 14.2/5.2/2.0 Hz, 1 H, C*H*$_2$CHCH$_2$COO), 2.29-2.37 (m, 2 H, NCH$_2$C*H*$_2$), 2.39-2.46 (m, 2 H, NC*H*$_2$CH$_2$ and NC*H*$_2$CO), 2.50-2.60 (m, 2 H, C*H*$_2$CHCH$_2$COO and C*H*$_2$COO), 2.73 (dd, *J* = 15.7/3.5 Hz, 1 H, CH$_2$COO), 2.90-3.02 (m, 2 H, NC*H*$_2$CH$_2$ and NC*H*), 3.13 (dd, *J* = 9.4/2.0 Hz, 1 H, NCH$_2$CO), 3.42 (s, 1 H, OH), 3.66 (s, 3 H, COOCH$_3$), 3.79 (s, 3 H, ArOC*H*$_3$), 6.08 (t, *J* = 7.2 Hz, 1 H, =C*H*CH$_2$), 6.76 (d, *J* = 5.2 Hz, 1 H, SCH), 6.83 (d, *J* = 5.2 Hz, 1 H, SCH), 6.84-6.88 (m, 2 H, H_{aromat}), 7.05 (d, *J* = 5.2 Hz, 1 H, SCH=C*H*), 7.20 (d, *J* = 5.2 Hz, 1 H, SCH=C*H*), 7.36-7.40 (m, 2 H, H_{aromat}). – MS; *m*/*z* (%): 512 (14), 494 (15), 480 (5), 420 (18), 278 (100), 260 (43), 248 (12), 186 (6). – IR: $\tilde{\nu}$ = 3523, 3090, 2938, 1731, 1514, 1511, 1246, 1167, 838, 806, 710 cm^{-1}. – $C_{28}H_{33}NO_4S_2$ (511.70): calcd. C 65.72, H 6.50, N 2.74, S 12.53; found C 66.07, H 6.70, N 2.70, S 12.48.

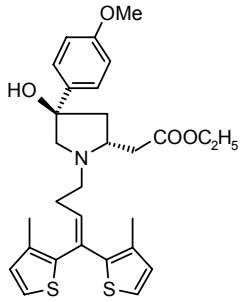
2) According to GP5-A from 127 mg (0.521 mmol) of $CeCl_3$ and 1.1 ml (0.48 M in THF, 0.52 mmol) of 4-MeOC_6H_4MgBr in 8 ml of THF, 150 mg (0.372 mml) of (2*S*)-**100c** in 7 ml of THF; reaction: at –78 °C for 20 h; analytical HPLC (*n*-heptane/EtOAc/*iso*-propanol, 75:25:0.5; 1.3 ml/min) *d.s*: (2*S*,4*S*) / (2*S*,4*R*) = 21:79 [(2*S*,4*S*) t_R = 16.7 min, (2*S*,4*R*) t_R 19.6 min;]. Purification by CC (ϕ 25 × 230; *n*-heptane/acetone, 3:1) and separation by prep. HPLC (*n*-heptane/EtOAc/*iso*-propanol, 75:25:0.5; 12 ml/min) yielded 16 mg (8%) of (2*S*,4*S*)-**102c** (t_R = 39.1 min), and 45 mg (24%) of (2*S*,4*R*)-**102c** (t_R = 46.2 min). 52 mg of (2*S*)-**100c** was recovered.

Ethyl (2*R*,4*S*)-1-[4,4-di(3-methyl-2-thienyl)but-3-en-1-yl]-4-hydroxy-4-(4-methoxyphenyl)pyrrolidine-2-acetate [(2*R*,4*S*)-103c] and
ethyl (2*R*,4*R*)-1-[4,4-di(3-methyl-2-thienyl)but-3-en-1-yl]-4-hydroxy-4-(4-methoxyphenyl)pyrrolidine-2-acetate [(2*R*,4*R*)-103c]

1) According to GP5-A from 117 mg (0.280 mmol) of (2*R*)-**101c** in 10 ml of Et_2O, 1.2 ml (0.44 M in Et_2O, 0.51 mmol) of 4-MeOC_6H_4MgBr; reaction: at –78 °C for 20 h. Purification



(**2*R*,4*S*)-103c**



(**2*R*,4*R*)-103c**

by CC (ϕ 25 × 210; *n*-heptane/acetone, 3:1) and separation by prep. HPLC (*n*-heptane/ EtOAc/*iso*-propanol, 80:20:0.5; 12 ml/min) yielded (2*R*,4*R*)-**103c** (t_R = 38.6 min) and (2*R*,4*S*)-**103c** (t_R = 45.9 min). 12 mg of (2*R*)-**101c** was recovered.

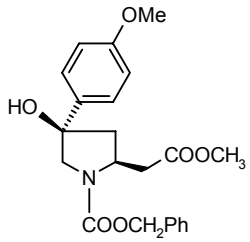
(2*R*,4*R*)-**103c**: 79 mg (54%); colorless oil. – TLC: R_f = 0.36 (*n*-heptane/acetone, 3:2). – $[\alpha]_D^{20}$ = +51.0 (*c* = 1.07, $CHCl_3$). – ^{1}H NMR ($CDCl_3$): δ = 1.23 (t, *J* = 7.1 Hz, 3 H, CH_2CH_3), 2.00 (s, 3 H, thienyl-CH_3), 2.02 (s, 3 H, thienyl-CH_3), 2.00-2.07 (m, 1 H, CH_2CHCH_2COO), 2.26-2.34 (m, 4 H, CH_2COO, CH_2CHCH_2COO and 2 H of NCH_2CH_2), 2.53-2.61 (m, 1 H, NCH_2CH_2), 2.65-2.72 (m, 2 H, CH_2COO and NCH_2CO), 2.91 (dt, *J* = 12.0/8.0 Hz, 1 H, NCH_2CH_2), 3.34-3.42 (m, 2 H, NCH_2CO and NCH), 3.78 (s, 3 H, $ArOCH_3$), 4.11 (q, *J* = 7.1 Hz, CH_2CH_3), 6.09 (t, *J* = 7.2 Hz, 1 H, $=CHCH_2$), 6.76 (d, *J* = 5.2 Hz, 1 H, SCH), 6.82-6.87 (m, 3 H, SCH and H_{aromat}), 7.05 (d, *J* = 5.2 Hz, 1 H, SCH=CH), 7.19 (d, *J* = 5.2 Hz, 1 H, SCH=CH), 7.37-7.41 (m, 2 H, H_{aromat}). – IR: $\tilde{\nu}$ = 3482, 3061, 2932, 1732, 1611, 1513, 833, 714 cm^{-1}. – MS; *m*/*z* (%): 526 (18) $[M+1]^+$, 508 (22), 292 (100), 274 (56), 105 (21). – $C_{29}H_{35}NO_4S_2$ (525.73): calcd. C 66.25, H 6.71, N 2.66, S 12.20; found C 66.50, H 6.79, N 2.51, S 11.89.

(2*R*,4*S*)-**103c**: 14 mg (10%); colorless oil. – TLC: R_f = 0.36 (*n*-heptane/acetone, 3:2). – $[\alpha]_D^{20}$ = -77.9 (*c* = 0.67, $CHCl_3$). – ^{1}H NMR ($CDCl_3$): δ = 1.24 (t, *J* = 7.3 Hz, 3 H, CH_2CH_3), 1.99 (s, 3 H, thienyl-CH_3), 2.03 (s, 3 H, thienyl-CH_3), 2.09 (ddd, *J* = 14.2/5.2/2.0 Hz, 1 H, CH_2CHCH_2COO), 2.30-2.37 (m, 2 H, NCH_2CH_2), 2.39-2.46 (m, 2 H, NCH_2CH_2 and NCH_2CO), 2.50-2.60 (m, 2 H, CH_2CHCH_2COO and CH_2COO), 2.73 (dd, *J* = 15.7/3.5 Hz, 1 H, CH_2COO), 2.90-3.02 (m, 2 H, NCH_2CH_2 and NCH), 3.12 (dd, *J* = 9.4/2.0 Hz, 1 H, NCH_2CO), 3.43 (s, 1 H, OH), 3.79 (s, 3 H, $ArOCH_3$), 4.09-4.17 (m, 2 H, CH_2CH_3), 6.07 (t, *J*

= 7.2 Hz, 1 H, =C*H*CH_2), 6.76 (d, *J* = 5.0 Hz, 1 H, SCH), 6.82-6.88 (m, 3 H, SC*H* and 2 H of H_{aromat}), 7.05 (d, *J* = 5.0 Hz, 1 H, SCH=C*H*), 7.20 (d, *J* = 5.0 Hz, 1 H, SCH=C*H*), 7.36-7.40 (m, 2 H, H_{aromat}). – IR: $\tilde{\nu}$ = 3468, 3061, 2932, 1713, 1611, 1513, 833, 713 cm^{-1}. – MS; *m*/*z* (%): 527.1 (100) $[M+1]^+$, 526.7 (80), 508 (63), 494.3 (18), 420 (29). – $C_{29}H_{35}NO_4S_2$ (525.73): calcd. C 66.25, H 6.71, N 2.66, S 12.20; found C 66.28, H 6.86, N 2.56, S 11.99.

2) According to GP5-A from 146 mg (0.601 mmol) of $CeCl_3$ and 1.30 ml (0.48 M in THF, 0.60 mmol) of 4-$MeOC_6H_4MgBr$ in 12 ml of THF, 176 mg (0.421 mmol) of (2*R*)-**101c** in 6 ml of THF; reaction: at –78 °C for 20 h; analytical HPLC *d.s*: (2*R*,4*R*) / (2*R*,4*S*) = 19:81 [(2*R*,4*R*) t_R = 13.9 min, (2*R*,4*S*) t_R = 17.7 min; *n*-heptane/EtOAc/*iso*-propanol, 75:25:0.5; 1.3 ml/min]. Purification by CC (ϕ 25 × 200; *iso*-hexane/acetone, 3:1) and separation by prep. HPLC (*n*-heptane/EtOAc/*iso*-propanol, 80:20:0.5, 12 ml/min.) yielded 16 mg (7%) of (2*R*,4*R*)-**103c** (t_R = 40.5 min), and 55 mg (25%) of (2*R*,4*S*)-**103c** (t_R = 45.6 min). 46 mg of (2*R*)-**101c** was recovered.

Methyl (2*S*,4*R*)-1-benzyloxycarbonyl-4-hydroxy-4-(4-methoxyphenyl)pyrrolidine-2-acetate [(2*S*,4*R*)-109]

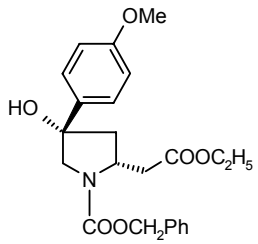


1) According to GP5-B from 168 mg (0.611 mmol) of (2*S*)-**108** in 30 ml of Et_2O, 1.53 ml (0.44 M in Et_2O, 0.67 mmol) of 4-$MeOC_6H_4MgBr$; reaction: at –78 °C for 4 h; purification by CC (ϕ 25 × 220; *n*-heptane/acetone, 80:20) and separation by prep. HPLC (*n*-heptane/EtOAc/*iso*-propanol, 78:22:0.5; t_R = 64.2 min; 12 ml/min). 91 mg of (2*S*)-**108** was recovered. Yield: 92 mg (38%); colorless oil. – TLC: R_f = 0.35 (*n*-heptane/acetone, 3:2). – $[\alpha]_D^{20}$ = -29.1 (*c* = 0.95, $CHCl_3$). – ^{1}H NMR ($C_6D_5NO_2$, 120 °C): δ = 2.40 (d, *J* = 13.7 Hz, 1 H, C*H*$_2$CHCH_2COO), 2.68 (dd, *J* = 13.7/9.1 Hz, 1 H, C*H*$_2$CHCH_2COO), 2.78 (s, 1 H, OH), 3.17 (dd, *J* = 15.4/3.3 Hz, 1 H, CH_2COO), 3.32 (dd, *J* = 15.4/3.3 Hz, 1 H, CH_2COO), 3.70 (s, 3 H, ArOC*H*$_3$), 3.76 (s, 3 H, $COOCH_3$), 3.90-4.00 (m, 1 H, NCH), 4.56-4.64 (m, 1 H, C*H*OH), 5.29, 5.34 (2s, 2 H, C*H*$_2$Ph), 6.86-6.91 (m, 2 H, H_{aromat}), 7.25-7.48 (m, 7 H, H_{aromat}). – IR: $\tilde{\nu}$ = 3440, 3031, 2952, 1734, 1700, 1610, 1515, 1416, 1252, 832, 771, 698 cm^{-1}. – MS;

m/*z* (%): 382 (100), 368 (78), 338 (31), 324 (83), 15 (11). – $C_{22}H_{25}NO_6$ (399.45): calcd. C 66.15, N 3.51, H 6.31; found C 66.45, N 3.44, H 6.67.

2) According to GP5-A from 193 mg (0.784 mmol) of $CeCl_3$, 1.63 mmol (0.48 M in THF, 0.78 mmol) of 4-$MeOC_6H_4MgBr$ in 10 ml of THF, 198 mg (0.680 mmol) of (2*S*)-**108** in 5 ml of THF; reaction: at –60 °C for 20 h; purification by (ϕ 25 × 230; *n*-heptane/acetone, 3:1) and separation by prep. HPLC (*n*-heptane/EtOAc/*iso*-propanol, 78:22:0.5; t_R = 64.6 min; 12 ml/min). 22 mg of (2*S*)-**108** was recovered. Yield: 91 mg (34%).

Ethyl (2*R*,4*S*)-1-benzyloxycarbonyl-4-hydroxy-4-(4-methoxyphenyl)pyrrolidine-2-acetate [(2*R*,4*S*)-113]



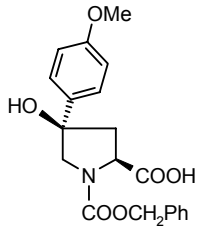
According to GP5-B from 120 mg (0.393 mmol) of (2*R*)-**112** and 0.94 ml (0.44 M in Et_2O, 0.41 mmol) of 4-$MeOC_6H_4MgBr$ in 20 ml of Et_2O; reaction: at –78 °C for 20 h; purification by CC (ϕ 25 × 195; *n*-heptane/acetone, 3:1) and separation by prep. HPLC (*n*-heptane/EtOAc/*iso*-propanol, 78:22:0.5; t_R = 47.4 min; 12 ml/min). 54 mg of (2*R*)-**112** was recovered. Yield: 60 mg (37%); colorless oil. – TLC: R_f = 0.35 (*n*-heptane/acetone, 3:2). – $[\alpha]_D^{20}$ = +26.1 (*c* = 1.05, $CHCl_3$). – ^{1}H NMR ($C_6D_5NO_2$, 120 °C): δ = 1.22-1.29 (m, 3 H, CH_2CH_3), 2.43 (d, *J* = 13.7 Hz, 1 H, CH_2CHCH_2COO), 2.65-2.72 (m, 1 H, CH_2CHCH_2COO), 2.80 (s, 1 H, OH), 3.18 (dd, *J* = 15.4/3.3 Hz, 1 H, CH_2COO), 3.27-3.34 (m, 1 H, CH_2COO), 3.76, 3.78 (2s, 3 H, $ArOCH_3$), 3.91-4.00 (m, 1 H, NCH), 4.17-4.24 (m, 2 H, CH_2CH_3), 4.57-4.65 (m, 1 H, CHOH), 5.30, 5.34 (2s, 2 H, CH_2Ph), 6.86-6.90 (m, 2 H, H_{aromat}), 7.26-7.48 (m, 7 H, H_{aromat}). – IR: $\tilde{\nu}$ = 3440, 3034, 2954, 1730, 1700, 1610, 1416, 831, 770, 698 cm^{-1}. – MS; *m*/*z* (%): 396 (43), 368 (34), 324 (42), 105 (15). – $C_{23}H_{27}NO_6$ (413.48): calcd. C 66.81, H 6.58, N 3.39; found C 66.95, H 6.77, N 3.20.

6.1.7 Hydrolysis of ester functions of N-protected pyrrolidine derivatives

General procedure 6 (GP6):

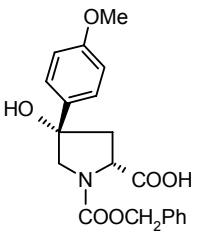
The respective ester (1 equiv.) was hydrolyzed with 1.0 M NaOH (2.05-4.10 equiv.) in MeOH (10-50 ml/mmol) at r.t. for the time given. After MeOH had been removed in vacuo, the residue was dissolved in a small amount of water and then acidified to pH 1-2 with aq. 1.0 M HCl. The mixture was extracted with CH_2Cl_2 and the combined extracts were dried (Na_2SO_4) and evaporated to yield the carboxylic acid.

(2*S*,4*R*)-1-Benzyloxycarbonyl-4-hydroxy-4-(4-methoxyphenyl)pyrrolidine-2-carboxylic acid [(2*S*,4*R*)-62]



According to GP6 from 131 mg (0.340 mmol) of (2*S*,4*R*)-**61**, 1.02 ml (1.02 mmol) of aq. 1.0 M NaOH in 4 ml of MeOH; reaction time: 3 h. Yield: 111 mg (88%); colorless foam. – M.p. 62-65 °C. – $[\alpha]_D^{20}$ = -25.0 (*c* = 1.00, MeOH). – ^{1}H NMR ($C_6D_5NO_2$, 120 °C): δ = 2.74-2.89 (m, 2 H, NCHC*H*$_2$), 3.77 (s, 3 H, ArOC*H*$_3$), 3.91 (d, *J* = 11.0 Hz, 1 H, NCH$_2$), 4.09 (d, *J* = 11.0 Hz, 1 H, NCH$_2$), 4.88 (d, *J* = 9.4 Hz, 1 H, NCH), 5.29-5.36 (m, 2 H, C*H*$_2$Ph), 6.89-6.93 (m, 2 H, H$_{aromat}$), 7.26-7.52 (m, 7 H, H$_{aromat}$). – IR: $\tilde{\nu}$ = 3420, 3060, 2955, 1705, 1611, 1516, 1425, 1252, 832, 771, 698 cm^{-1}. – MS; *m*/*z* (%): 370 (1) [M-1]$^+$, 355 (10), 354 (46), 310 (100), 236 (14), 220 (45), 218 (38), 174 (15), 135 (16). – $C_{20}H_{21}NO_6$ (371.40): calcd. C 64.68, H 5.70, N 3.77; found C 64.85, H 5.42, N 3.53.

(2*R*,4*S*)-1-Benzyloxycarbonyl-4-hydroxy-4-(4-methoxyphenyl)pyrrolidine-2-carboxylic acid [(2*R*,4*S*)-62]

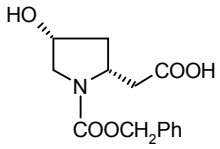


According to GP6 from 107 mg (0.278 mmol) of (2*R*,4*S*)-**61**, 0.83 ml (0.83 mmol) of aq. 1.0 M NaOH in 4.2 ml of MeOH; reaction time: 4 h. Yield: 83 mg (80%); colorless foam. – M.p. 58-62 °C. – $[\alpha]_D^{20}$ = +25.8 (*c* = 0.64, MeOH). The spectra (^{1}H NMR, IR, and MS) were identical with those of (2*S*,4*R*)-**62**. – $C_{20}H_{21}NO_6$ (371.40): calcd. C 64.68, H 5.70, N 3.77; found C 64.74, H 5.93, N 3.56.

(2*S*,4*R*)-1-Benzyloxycarbonyl-4-hydroxypyrrolidine-2-acetic acid [(2*S*,4*R*)-96]

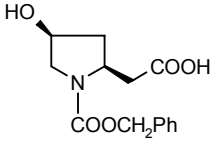
According to GP6 from 312 mg (1.06 mmol) of (2*S*,4*R*)-**95**. Yield: 290 mg (98%); colorless oil. – $[\alpha]_D^{20}$ = -61.2 (*c* = 1.22, MeOH). All its analytical data were identical with those in the literature [40]. {ref. [40]: $[\alpha]_D^{20}$ = - 62.4 (*c* = 3, MeOH)}.

(2*R*,4*R*)-1-Benzyloxycarbonyl-4-hydroxypyrrolidine-2-acetic acid [(2*R*,4*R*)-96]



According to GP6 from 86 mg (0.28 mmol) of (2*R*,4*R*)-**73**, 0.57 ml (0.57 mmol) of aq. 1.0 M NaOH in 3 ml of MeOH; reaction time: 23 h. Yield: 75 mg (91%); colorless oil. – $[\alpha]_D^{20}$ = +17.2 (*c* = 1.41, MeOH). – ^{1}H NMR ($C_6D_5NO_2$, 120 °C): δ = 2.11-2.17 (m, 1 H, C*H*$_2$CHCH$_2$COO), 2.37-2.46 (m, 1 H, C*H*$_2$CHCH$_2$COO), 3.04 (dd, *J* = 15.8/8.9 Hz, 1 H, CH$_2$COO), 3.28 (dd, *J* = 15.8/3.1 Hz, 1 H, CH$_2$COO), 3.59-3.67 (m, 1 H, NCH$_2$), 3.79-3.85 (m, 1 H, NCH$_2$), 4.44-4.51 (m, 1 H, NCH), 4.57-4.62 (m, 1 H, C*H*OH), 5.27 (s, 2 H, C*H*$_2$Ph), 7.25-7.46 (m, 5 H, H$_{aromat}$). – IR: $\tilde{\nu}$ = 3296, 2956, 1716, 1498, 1069, 769 cm^{-1}. – MS; *m*/*z* (%): 279 (10) M$^+$, 262 (100), 250 (17), 218 (20), 158 (7), 151 (12), 105 (16). – $C_{14}H_{17}NO_5$ (279.30): calcd. C 60.21, H 6.14, N 5.02; found C 60.41, H 6.34, N 4.82.

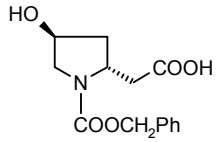
(2*S*,4*S*)-1-Benzyloxycarbonyl-4-hydroxypyrrolidine-2-acetic acid [(2*S*,4*S*)-96]



According to GP6 from 98 mg (0.38 mmol) of (1*S*,5*S*)-**98**, 0.77 ml (0.77 mmol) of aq. 1.0 M

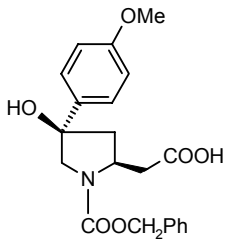
NaOH in 8.3 ml of MeOH; reaction time: 4 d. Yield: 98 mg (94%); colorless oil. – $[\alpha]_D^{20}$ = -17.6 (*c* = 1.03, MeOH). The spectra (^{1}H NMR, IR, and MS) were identical with those of (2*R*,4*R*)-45. – $C_{14}H_{17}NO_5$ (279.30): calcd. C 60.21, H 6.14, N 5.02; found C 60.41, H 6.62, N 4.86.

(2*R*,4*S*)-1-Benzyloxycarbonyl-4-hydroxypyrrolidine-2-acetic acid [(2*R*,4*S*)-96]



According to GP6 from 73 mg (0.22 mmol) of (2*R*,4*S*)-**99**, 0.89 ml (0.89 mmol) of aq. 1.0 M NaOH in 9.1 ml of MeOH; reaction time: 3 d. Yield: 60 mg (98%); colorless oil. – $[\alpha]_D^{20}$ = +59.6 (*c* = 1.05, MeOH). – ^{1}H NMR ($C_6D_5NO_2$, 120 °C): δ = 2.10-2.20 (m, 1 H, C*H*$_2$CHCH$_2$COO), 2.36-2.44 (m, 1 H, C*H*$_2$CHCH$_2$COO), 2.72 (dd, *J* = 15.6/8.2 Hz, 1 H, CH$_2$COO), 3.20 (dd, *J* = 15.6/3.8 Hz, 1 H, CH$_2$COO), 3.70 (dd, *J* = 11.5/4.4 Hz, 1 H, NCH$_2$), 3.79 (d, *J* = 11.5 Hz, 1 H, NCH$_2$), 4.53-4.62 (m, 2 H, C*H*OH and NC*H*), 5.25 (s, 2 H, C*H*$_2$Ph), 7.24-7.45 (m, 5 H, H_{aromat}). – IR: $\tilde{\nu}$ = 3423, 3032, 2926, 1704, 1418, 749 cm^{-1}. – MS; *m*/*z* (%): 280 (44) $[M+1]^+$, 250 (20), 236 (100), 146 (58), 128 (29). – $C_{14}H_{17}NO_5$ (279.30): calcd. C 60.21, H 6.14, N 5.02; found C 60.37, H 6.65, N 4.87.

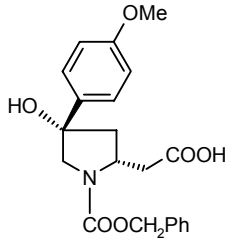
(2*S*,4*R*)-1-Benzyloxycarbonyl-4-hydroxy-4-(4-methoxyphenyl)pyrrolidine-2-acetic acid [(2*S*,4*R*)-110]



According to GP6 from 93 mg (0.23 mmol) of (2*S*,4*R*)-**109** and 0.48 ml (0.48 mmol) of aq. 1.0 M NaOH in 4.5 ml of MeOH; reaction time: 4 d. Yield: 73 mg (81%); colorless foam. – $[\alpha]_D^{20}$ = -30.0 (*c* = 0.80, MeOH). – ^{1}H NMR ($C_6D_5NO_2$, 120 °C): δ = 2.40-2.51 (m, 1 H, C*H*$_2$CHCH$_2$COO), 2.68-2.74 (m, 1 H, C*H*$_2$CHCH$_2$COO), 3.27 (dd, *J* = 16.0/8.9 Hz, 1 H, CH$_2$COO), 3.41 (dd, *J* = 16.0/3.8 Hz, 1 H, CH$_2$COO), 3.77 (s, 3 H, ArOC*H*$_3$), 3.93 (d, *J* =

11.5 Hz, 1 H, NCH_2), 4.00 (d, J = 11.5 Hz, 1 H, NCH_2), 4.59-4.68 (m, 1 H, NCH), 5.26-5.33 (m , 2 H, CH_2Ph), 6.85-6.91 (m, 2 H, H_{aromat}), 7.25-7.51 (m, 7 H, H_{aromat}). – IR: $\tilde{\nu}$ = 3424, 3031, 2954, 1702, 1677, 1611, 1421, 832, 770, 698 cm^{-1}. – MS; *m*/*z* (%): 368 (80), 324 (100), 300 (46), 256 (70), 234 (48), 174 (31). – $C_{21}H_{23}NO_6$ (385.42): calcd. C 65.44, H 6.02, N 3.63; found C 65.22, H 6.14, N 3.40.

(2*R*,4*S*)-1-Benzyloxycarbonyl-4-hydroxy-4-(4-methoxyphenyl)pyrrolidine-2-acetic acid [(2*R*,4*S*)-110]



According to GP6 from 40 mg (0.097 mmol) of (2*R*,4*S*)-**112** and 0.20 ml (0.20 mmol) of aq. 1.0 M NaOH in 2.8 ml of MeOH; reaction: 4 d. Yield: 34 mg (91%); colorless foam. – $[\alpha]_D^{20}$ = +29.2 (*c* = 0.49, MeOH). The spectra (^{1}H NMR, IR, and MS) were identical with those of (**2*S*,4*R***)-**56**. – $C_{21}H_{23}NO_6$ (385.42): calcd. C 65.44, H 6.02, N 3.63; found C 65.56, H 6.32, N 3.37.

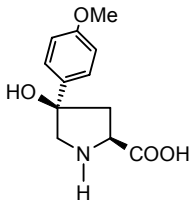
6.1.8 N-Deprotection of pyrrolidine derivatives by hydrogenolysis

General procedure 8 (GP8)

A) To a solution of the respective N-protected pyrrolidine (1 equiv.) and TEA (0.33-20 equiv.) in MeOH or EtOAc (40-50 ml/mmol)), 10% Pd-C (0.5-1.0 to the substrate, w/w) was added. This mixture was subjected to hydrogen at r.t. under ambient pressure for the time given. The reaction mixture was filtrated and evaporated to give its N-deprotected amine.

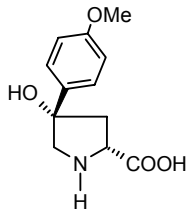
B) General procedure B (GP8-B) was identical with A (GP8-A) except that no TEA was used.

(2*S*,4*R*)-4-Hydroxy-4-(4-methoxyphenyl)pyrrolidine-2-carboxylic acid [(2*S*,4*R*)-63]



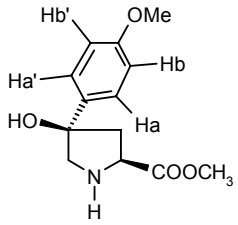
According to GP8-A from 140 mg (0.377 mmol) of (2*S*,4*R*)-**62** and 12 mg (0.12 mmol) of TEA in 17 ml of MeOH, 70 mg (0.066 mmol) of 10% Pd-C; reaction time: 1.5 h. Yield: 82 mg (92%); colorless crystals. – M.p. 244-247 °C (MeOH, decomp.). – $[\alpha]_D^{20}$ = +0.7 (*c* = 0.45, H_2O). – ^{1}H NMR (D_2O): δ = 2.47 (dt, *J* = 14.0/2.2 Hz, 1 H, NCHCH_2), 2.63 (dd, *J* = 14.0/11.0 Hz, 1 H, NCHCH_2), 3.40 (d, *J* = 12.2, 1 H, NCH_2), 3.55 (dd, *J* = 12.2/2.2 Hz, 1 H, NCH_2), 3.67 (s, 3 H, ArOCH_3), 4.23 (dd, *J* = 11.0/2.2 Hz, 1 H, NCH), 6.85-6.89 (m, 2 H, H_{aromat}), 7.26-7.30 (m, 2 H, H_{aromat}). – IR: $\tilde{\nu}$ = 3383, 3040, 2950, 1614, 1516, 1404, 1255, 830 cm^{-1}. – MS; *m*/*z* (%): 237 (11) M^+, 234 (25), 220 (100), 208 (38), 190 (63), 174 (69), 151 (55), 109 (15). – $C_{12}H_{15}NO_4$ (237.26): calcd. C 60.75, H 6.37, N 5.90; $C_{12}H_{15}NO_4 \cdot 0.2MeOH$: calcd. C 60.13, H 6.53, N 5.74; found C 60.00, H 6.47, N 5.76.

(2*R*,4*S*)-4-Hydroxy-4-(4-methoxyphenyl)pyrrolidine-2-carboxylic acid [(2*R*,4*S*)-63]



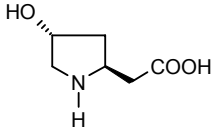
According to GP8-A from 66 mg (0.17 mmol) of (2*R*,4*S*)-**62** and 5.8 mg (0.056 mmol) of TEA in 8 ml of EtOAc, 33 mg (0.031 mmol) of 10% Pd-C; reaction time: 4 h. Yield: 38 mg (96%); colorless crystals. – M.p. 244-246 °C (MeOH, decomp.). – $[\alpha]_D^{20}$ = -0.9 (*c* = 0.76, H_2O). The spectra (^{1}H NMR (500 MHz), IR, and MS) were identical with those of (2*R*,4*S*)-**63**. – $C_{12}H_{15}NO_4 \cdot 0.4MeOH$: calcd. C 59.56, H 6.69, N 5.60; found C 59.32, H 6.54, N 5.68.

Methyl (2*S*,4*R*)-4-hydroxy-4-(4-methoxyphenyl)pyrrolidine-2-carboxylate [(2*S*,4*R*)-114]



According to GP8-A from 144 mg (0.374 mmol) of (2*S*,4*R*)-**61** and 11 mg (0.11 mmol) of TEA in 15 ml of EtOAc, 74 mg (0.070 mmol) of 10% Pd-C; reaction time: 6 h. Yield: 94 mg (100%); colorless crystals. – TLC: R_f = 0.25 (*i*Pr_2O/MeOH, 4:1). – M.p. 96-97 °C (EtOAc). – $[\alpha]_D^{20}$ = +27.3 (*c* = 1.00, $CHCl_3$). – ^{1}H NMR ($CDCl_3$, NOE for the determination of the C-4 configuration): δ = 2.35 (dt, *J* = 13.7/2.5 Hz, 1 H, NCHC*H*$_2$), 2.51 (dd, *J* = 13.7/10.0 Hz, 1 H, NCHC*H*$_2$), 3.07 (br. s, 1 H, OH), 3.10 (d, *J* = 11.8 Hz, 1 H, NCH_2), 3.27 (dd, *J* = 11.8/2.1 Hz, 1 H, NCH_2), 3.77 (s, 3 H, $COOCH_3$), 3.79 (s, 3 H, ArOC*H*$_3$), 3.99 (dd, *J* = 10.0/2.5 Hz, 1 H, NCH), 6.85-6.88 (m, 2 H, H_a and H_a'), 7.33-7.37 (m, 2 H, H_b and H_b'). – IR: $\tilde{\nu}$ = 3303, 3034, 2954, 1740, 1612, 1514, 1256, 1115, 831 cm^{-1}. – MS; *m*/*z* (%): 252 (7) $[M+1]^+$, 235 (15), 234 (100), 220 (10), 192 (10), 135 (4). – $C_{13}H_{17}NO_4$ (251.29): calcd. C 62.14, H 6.82, N 5.57; found C 62.11, H 6.97, N 5.53.

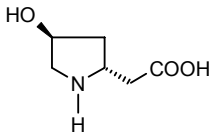
(2*S*,4*R*)-Hydroxypyrrolidine-2-acetic acid [(2*S*,4*R*)-97]



According to GP8-B from 76 mg (0.27 mmol) of (2*S*,4*R*)-**96** and 38 mg (0.036 mmol) of 10% Pd-C in 10 ml of MeOH; reaction time: 1 h. Yield: 35 mg (89%); colorless crystals. – M.p. 238-240 °C (decomp.). – $[\alpha]_D^{20}$ = +1.3 (*c* = 0.31, H_2O). – ^{1}H NMR (D_2O): δ = 1.83 (ddd, *J* = 14.1/11.4/4.4 Hz, 1 H, C*H*$_2$CHCH_2COO), 2.14-2.20 (m, 1 H, C*H*$_2$CHCH_2COO), 2.55 (dd, *J* =

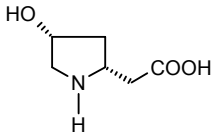
16.6/7.7 Hz, 1 H, CH_2COO), 2.64 (dd, *J* = 16.6/5.5 Hz, 1 H, CH_2COO), 3.22 (dt, *J* = 12.8/1.5 Hz, 1 H, NCH_2), 3.43 (dd, *J* = 12.8/4.2 Hz, 1 H, NCH_2), 4.02-4.08 (m, 1 H, NCH), 4.56-4.59 (m, 1 H, C*H*OH). – IR: $\tilde{\nu}$ = 3231, 2931, 2783, 1643, 1558, 1401, 732, 666 cm^{-1}. – MS; *m*/*z* (%): 146 (100) $[M+1]^+$, 145 (19), 128 (17), 102 (8). – $C_6H_{11}NO_3$ (145.16): calcd. C 49.65, H 7.64, N 9.65; found C 49.37, H 7.62, N 9.44.

(2*R*,4*S*)-4-Hydroxypyrrolidine-2-acetic acid [(2*R*,4*S*)-97]



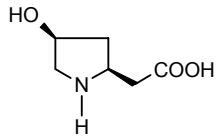
According to GP8-B from 50 mg (0.18 mmol) of (2*R*,4*S*)-**96** and 25 mg of 10% Pd-C in 8 ml of MeOH; reaction time 1 h. Yield: 24 mg (92%); colorless crystals. – M.p. 235-237 °C (MeOH, decomp.). – $[\alpha]_D^{20}$ = -2.6 (*c* = 0.23, H_2O). The spectra (^{1}H NMR, IR, and MS) were identical with those of (2*S*,4*R*)-**97**. – $C_6H_{11}NO_3$ (145.16): calcd. C 49.65, H 7.63, N 9.65; found C 49.10, H 7.50, N 9.49.

(2*R*,4*R*)-4-Hydroxypyrrolidine-2-acetic acid [(2*R*,4*R*)-97]



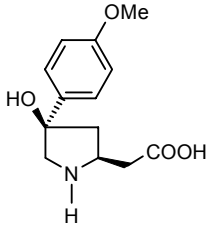
According to GP8-B from 59 mg (0.21 mmol) of (2*R*,4*R*)-**96** and 30 mg of 10% Pd-C in 10 ml of MeOH, reaction time: 1 h. Yield: 31 mg (100%); colorless crystals. – M.p. 210-212 °C (MeOH, decomp.). – $[\alpha]_D^{20}$ = -4.8 (*c* = 0.33, H_2O). – ^{1}H NMR (D_2O): δ = 1.77 (dddd, *J* = 14.2/7.3/3.6/1.4 Hz, 1 H, C*H*$_2$CHCH$_2$COO), 2.55 (ddd, *J* = 14.2/8.8/6.0 Hz, 1 H, C*H*$_2$CHCH$_2$COO), 2.72-2.74 (m, 2 H, CH_2COO), 3.32 (ddd, *J* = 12.5/2.4/1.4 Hz, 1 H, NCH_2), 3.38 (dd, *J* =12.5/4.9 Hz, 1 H, NCH_2), 3.93-3.99 (m, 1 H, NCH), 4.62-4.65 (m, 1 H, C*H*OH). – IR: $\tilde{\nu}$ = 3175, 2958, 1662, 1560, 1412, 1089, 722 cm^{-1}. – MS; *m*/*z* (%): 146 (100) $[M+1]^+$. – $C_6H_{11}NO_3$ (145.16): calcd. C 49.65, H 7.63, N 9.65; found C 49.71, H 7.91, N 9.47.

(2*S*,4*S*)-4-Hydroxypyrrolidine-2-acetic acid [(2*S*,4*S*)-97]



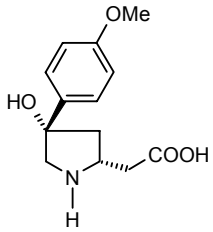
According to GP8-B from 80 mg (0.29 mmol) of (2*S*,4*S*)-**96** and 40 mg of 10% Pd-C in 8 ml of MeOH; reaction time 1 h. Yield: 41 mg (99%); colorless crystals. – M.p. 238-240 °C (MeOH, decomp.). – $[\alpha]_D^{20}$ = +5.3 (*c* = 0.32, H_2O). The spectra [^{1}H NMR (500 MHz), IR, and MS] were identical with those of (2*R*,4*R*)-**97**. – $C_6H_{11}NO_3$ (145.16): calcd. C 49.65, H 7.63, N 9.65; found C 49.27, H 7.75, N 9.73.

(2*S*,4*R*)-4-(4-Methoxyphenyl)-4-hydroxypyrrolidine-2-acetic acid [(2*S*,4*R*)-111]



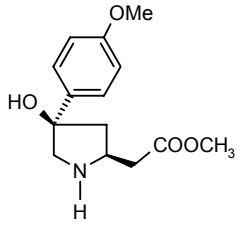
According to GP8-A from 59 mg (0.15 mmol) of (2*S*,4*R*)-**110**, 0.20 ml (1.4 mmol) of TEA in 5 ml of MeOH, 40 mg (0.038 mmol) of 10% Pd-C; reaction time: 3 h. Yield: 38 mg (100%); colorless crystals. – M.p. 261-262 °C (MeOH, decomp.). – $[\alpha]_D^{20}$ = +5.6 (*c* = 0.50, 0.05 M NaOH in MeOH). – ^{1}H NMR (its sodium salt in CD_3OD, 500 MHz; NOE): δ = 1.93 (ddd, *J* = 13.9/6.4/1.8 Hz, 1 H, C*H*$_2$CHCH$_2$COO), 2.43 (dd, *J* = 13.9/9.3 Hz, 1 H, C*H*$_2$CHCH$_2$COO), 2.51 (dd, *J* = 15.4/6.8 Hz, 1 H, CH_2COO), 2.60 (15.4/5.4 Hz, 1 H, CH_2COO), 2.90 (d, *J* = 12.0 Hz, 1 H, NCH_2), 3.04 (dd, *J* = 12.0/1.8 Hz, 1 H, NCH_2), 3.54-3.61 (m, 1 H, NCH), 3.77 (s, 3 H, ArOC*H*$_3$), 6.85-6.89 (m, 2 H, H_{aromat}), 7.38-7.41 (m, 2 H, H_{aromat}). – IR: $\tilde{\nu}$ = 3424, 3147, 2958, 1648, 1610, 1548, 1412, 1250, 1099, 828 cm^{-1}. – MS; *m*/*z* (%): 252 (8) $[M+1]^+$, 235 (18), 234 (100), 192 (16), 174 (46), 135 (18), 102 (16). – $C_{13}H_{17}NO_4$ (251.29): calcd. C 62.14, H 6.82, N 5.57; found C 61.62, H 6.68, N 5.45.

(2*R*,4*S*)-4-Hydroxy-4-(4-methoxyphenyl)pyrrolidine-2-acetic acid [(2*R*,4*S*)-111]



According to GP8-A from 73 mg (0.19 mmol) of (2*R*,4*S*)-**110** and 0.50 ml (3.5 mmol) of TEA in 10 ml of MeOH, 38 mg (0.036 mmol) of 10% Pd-C; reaction time: 1 h. Yield: 45 mg (95%); colorless crystals. – M.p. 251-253 °C (MeOH, decomp.). – $[\alpha]_D^{20}$ = -5.1 (*c* = 0.685, 0.04 M NaOH in MeOH). The spectra [^{1}H NMR (its sodium salt), IR, and MS] were identical with those of (2*S*,4*R*)-**111**. – $C_{13}H_{17}NO_4$ (251.29): calcd. C 62.14, H 6.82, N 5.57; found C 62.11, H 7.08, N 5.31.

Methyl (2*S*,4*R*)-4-hydroxy-4-(4-methoxyphenyl)pyrrolidine-2-acetic acid [(2*S*,4*R*)-115]



According to GP8-A from 40 mg (0.10 mmol) of (2*S*,4*R*)-**109** and 1.0 ml (7.0 mml) of TEA in 5 ml of EtOAc, 20 mg of 10% Pd-C (0.019 mmol); reaction time: 1 h. Yield: 26 mg (100%); colorless crystals. – TLC: R_f = 0.27 (*i*Pr$_2$O/MeOH, 4:1). – M.p. 83-84 °C (*i*Pr$_2$O). – $[\alpha]_D^{20}$ = + 5.4 (*c* = 0.59, $CHCl_3$). – ^{1}H NMR ($CDCl_3$, NOE): δ = 1.90 (ddd, *J* = 14.1/5.7/2.0 Hz, 1 H, C*H*$_2$CHCH$_2$COO), 2.47 (dd, *J* = 14.1/9.6 Hz, 1 H, C*H*$_2$CHCH$_2$COO), 2.69 (dd, *J* = 16.3/5.7 Hz, 1 H, CH$_2$COO), 2.75 (dd, *J* = 16.3/7.5 Hz, 1 H, CH$_2$COO), 3.10 (d, *J* = 11.0 Hz, 1 H, NCH$_2$), 3.22 (dd, *J* = 11.0/2.0 Hz, 1 H, NCH$_2$), 3.28 (br. s, 2 H, N*H* and O*H*), 3.61-3.83 (m, 1 H, NCH), 3.69 (s, 3 H, ArOC*H*$_3$), 3.77 (s, 3 H, COOCH$_3$), 6.85-6.89 (m, 2 H, H_{aromat}), 7.36-7.39 (m, 2 H, H_{aromat}). – IR: $\tilde{\nu}$ = 3305, 3063, 1733, 1610, 1252, 828 cm^{-1}. – MS; *m*/*z* (%): 266 (37) $[M+1]^+$, 248 (100), 192 (14), 158 (14). – $C_{14}H_{19}NO_4$ (265.32): calcd. C 63.38, H 7.22, N 5.28; found

6.1.9 Hydrolysis of ester functions of N-substituted pyrrolidine derivatives and of related lactone derivatives

General procedure 7 (GP7)

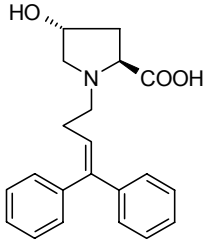
The respective ester (1 equiv.) was hydrolyzed in EtOH or MeOH (10-50 ml/mmol) at r.t. with aq. 0.85 M KOH or 1.0 M NaOH (3 equiv.; 6 equiv. for the derivatives with two ester groups) and for the time given. The mixture was neutralized with aq. 1.0 M HCl to pH 7 before buffer (pH 6.6 or pH 5.5) was added.

Two diferent procedures were used to isolate the final compounds:

A): The mixture was evaporated and the residue was purified by CC and recrystallization.

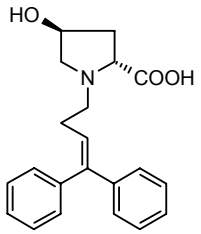
B): The mixture was diluted with some water to give white crystal; the product was collected by filtration.

(2*S*,4*R*)-1-(4,4-Diphenylbut-3-en-1-yl)-4-hydroxypyrrolidine-2-carboxylic acid [(2*S*,4*R*)-40a]



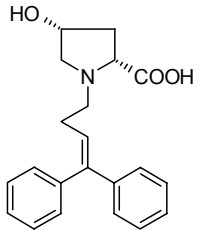
According to GP7-A from 185 mg (0.527 mmol) of (2*S*,4*R*)-**39a**, 1.85 ml (1.58 mmol) of aq. 0.85 M KOH in 7 ml of EtOH; reaction time: 1.5 h; 1 ml (pH 6.6) of buffer; purification by CC (ϕ 20 × 74; *n*-heptane/EtOAc, 1:1 → EtOH) and recrystallization in acetone. Yield: 170 mg (96%); colorless crystals. – M.p. 162-165 °C (acetone). – $[\alpha]_D^{22}$ = –49.2 (*c* = 0.85, EtOH). – ^{1}H NMR (CD_3OD): δ = 2.09 (ddd, *J* = 13.7/10.6/4.4 Hz, 1 H, NCHC*H*$_2$), 2.39 (ddt, *J* = 13.7/7.6/1.9 Hz, 1 H, NCHC*H*$_2$), 2.55 (q, *J* = 7.6 Hz, 2 H, NCH$_2$C*H*$_2$), 3.00 (dt, *J* = 12.3/1.9 Hz, 1 H, NC*H*$_2$CHOH), 3.35 (dt, *J* = 12.4/7.6 Hz, 1 H, NC*H*$_2$CH$_2$), 3.46 (dt, *J* = 12.4/7.6 Hz, 1 H, NC*H*$_2$CH$_2$), 3.64 (dd, *J* = 12.3/4.4 Hz, 1 H, NC*H*$_2$CHOH), 4.05 (dd, *J* = 10.6/7.6 Hz, 1 H, NC*H*), 4.43-4.45 (m, 1 H, C*H*OH), 6.09 (t, *J* = 7.6 Hz, 1 H, =C*H*CH$_2$), 7.17-7.43 (m, 10 H, H$_{aromat}$). – IR: $\tilde{\nu}$ = 3424, 3051, 2858, 1628, 1394, 775, 702 cm^{-1}. – MS; *m*/*z* (%): 338 (100) $[M+1]^+$, 274 (68), 144 (39). – $C_{21}H_{23}NO_3$ (337.42): calcd. C 74.75, H 6.87, N 4.15; found C 74.61, H 7.07, N 4.09.

(2*R*,4*S*)-1-(4,4-Diphenylbut-3-en-1-yl)-4-hydroxypyrrolidine-2-carboxylic acid [(2*R*,4*S*)-40a]



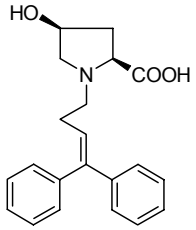
According to GP7-A from 85 mg (0.21 mmol) of (2*R*,4*S*)-**48a**, 1.26 ml (1.26 mmol) of aq. 1.0 M NaOH in 6 ml of EtOH; reaction time: 3 d; 3 ml of buffer (pH 6.6); purification by CC (ϕ 12 × 100, EtOH) and recrystallization in EtOH/*i*Pr_2O. Yield: 65 mg (92%); colorless crystals. – M.p. 181-184 °C (EtOH/*i*Pr_2O). – $[\alpha]_D^{20}$ = +50.6 (*c* = 0.93, EtOH). The spectra (^{1}H NM, IR, and MS) were identical with those of (2*S*,4*R*)-**40a**. – $C_{21}H_{23}NO_3$ (337.43)·H_2O: calcd. C 70.96, H 7.09, N 3.94; found C 71.07, H 7.12, N 3.95.

(2*R*,4*R*)-1-(4,4-Diphenylbut-3-en-1-yl)-4-hydroxypyrrolidine-2-carboxylic acid [(2*R*,4*R*)-40a]



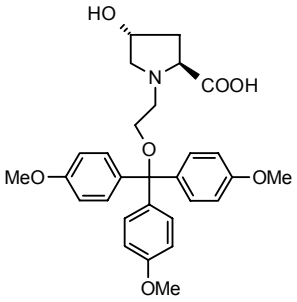
According to GP7-A from 68 mg (0.19 mmol) of (2*R*,4*R*)-**39a**, 0.58 ml (0.58 mmol) of aq. 1.0 M NaOH in 3 ml of EtOH; reaction time: 3 h; 1 ml (pH 6.6) of buffer; purification by CC (ϕ 12 × 100, EtOH) and recrystallization in C_6H_6/*i*Pr_2O. Yield: 58 mg (92%); colorless crystals. – M.p. 112-116 °C (C_6H_6/*i*Pr_2O). – $[\alpha]_D^{20}$ = +43.1 (*c* = 0.90, EtOH). – ^{1}H NMR (CD_3OD, 500 MHz): δ = 2.15-2.21 (m, 1 H, NCHC*H*$_2$), 2.48-2.63 (m, 3 H, NCHC*H*$_2$ and 2 H of NCH$_2$C*H*$_2$), 3.03 (dd, *J* = 11.5/3.8 Hz, 1 H, NC*H*$_2$CHOH), 3.18-3.24 (m, 1 H, NC*H*$_2$CH$_2$), 3.32-3.41 (m, 2 H, NC*H*$_2$CH$_2$ and NC*H*$_2$CHOH), 3.79 (dd, *J* = 10.6/4.4 Hz, 1 H, NC*H*), 4.36-4.39 (m, 1 H, C*H*OH), 6.07 (dd, *J* = 7.9/6.9 Hz, 1 H, =C*H*CH$_2$), 7.17-7.44 (m, 10 H, H_{aromat}). – IR: $\tilde{\nu}$ = 3274, 3053, 2851, 1633, 1494, 1400, 764, 702, 632 cm^{-1}. – MS; *m*/*z* (%): 338 (36) $[M+1]^+$, 320 (40), 274 (16), 213 (100), 195 (87), 183 (10), 126 (61), 91 (10). – $C_{21}H_{23}NO_3$ (337.42): calcd. C 74.75, H 6.87, N 4.15; $C_{21}H_{23}NO_3 \cdot 1.2H_2O$: calcd. C 70.25, H 7.13, N 3.90; found C 69.99, H 6.95, N 3.83.

(2*S*,4*S*)-1-(4,4-Diphenylbut-3-en-1-yl)-4-hydroxypyrrolidine-2-carboxylic acid [(2*S*,4*S*)-40a]



According to GP7-A from 157 mg (0.491 mmol) of (1*S*,4*S*)-**41a**, 2.1 ml (1.8 mmol) of aq. 0.85 M KOH in 12 ml of EtOH; reaction time: 40 min; 2.5 ml of buffer (pH 6.6); purification (ϕ 20 × 70; *n*-heptane/acetone, 1:1 → EtOH) and recrystallization in acetone. Yield: 158 mg (95%); colorless crystals. – M.p. 138-140 °C (acetone). – $[\alpha]_D^{24}$ = -42.8 (*c* = 1.00, EtOH). The spectra (^{1}H NMR, IR, and MS) were identical with those of (2*R*,4*R*)-**40a**. – $C_{21}H_{23}NO_3$ (337.42): calcd. C 74.75, H 6.87, N 4.15; found C 74.65, H 7.12, N 4.01.

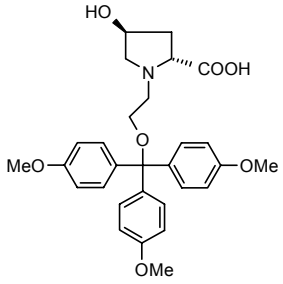
(2*S*,4*R*)-4-Hydroxy-1-{2-[tris(4-methoxyphenyl)methoxy]-1-ethyl}pyrrolidine-2-carboxylic acid [(2*S*,4*R*)-40b]



According to GP7-A from 299 mg (0.574 mmol) of (2*S*,4*R*)-**39b**, 1.7 ml (1.5 mmol) of aq. 0.85 M KOH in 23 ml of EtOH; reaction time: 4 h. 2.0 ml of buffer (pH 6.6); purification by CC (ϕ 25 × 70; Al_2O_3, pH 7.5; *n*-heptane/acetone, 3:2→EtOH/H_2O, 4:1) and recrystallization in acetone. Yield: 243 mg (85%); colorless crystals. – M.p. 142-144 °C (acetone). – $[\alpha]_D^{28}$ = -24.8 (*c* = 1.12, EtOH). – ^{1}H NMR (CD_3OD): δ = 2.15 (ddd, *J* = 13.8/10.1/4.7 Hz, 1 H, NCHC*H*$_2$), 2.41 (ddt, *J* = 13.8/7.8/1.9 Hz, 1 H, NCHC*H*$_2$), 3.08 (br. d, *J* = 12.4 Hz, 1 H, NC*H*$_2$CHOH), 3.29-3.35 (m, 1 H, NC*H*$_2$CH$_2$), 3.40-3.61 (m, 4 H, NC*H*$_2$CH$_2$, NC*H*$_2$CHOH and 2 H of NCH$_2$C*H*$_2$), 3.76 (s, 9 H, ArOC*H*$_3$), 4.19 (dd, *J* = 10.1/7.8 Hz, 1 H, NCH), 4.43-4.46 (m, 1 H, C*H*OH), 6.85-6.88 (m, 6 H, H_{aromat}), 7.32-7.36 (m, 6 H, H_{aroma}). – IR: $\tilde{\nu}$ = 3464,

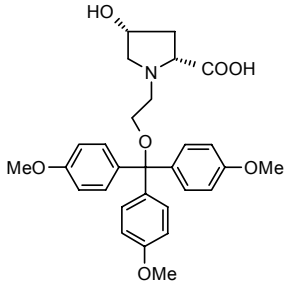
3213, 1640, 1607, 1509, 831 cm^{-1}. – MS (ESI); *m*/*z* (%): 333 (100). – $C_{29}H_{33}NO_7$ (507.58): calcd. C 68.62, H 6.55, N 2.76; found C 68.54, H 6.79, N 2.60.

(2*R*,4*S*)-4-Hydroxy-1-{2-[tris(4-methoxyphenyl)methoxy]-1-ethyl}pyrrolidine-2-carboxylic acid [(2*R*,4*S*)-40b]



According to GP7-A from 80 mg (0.14 mmol) of (2*R*,4*S*)-**48b**, 0.85 ml (0.85 mmol) of aq. 1.0 M NaOH in 3.5 ml of MeOH; reaction time: 3 d. 0.8 ml of buffer (pH 6.6); purification by recrystallization in C_6H_6/*i*Pr_2O. Yield: 68 mg (94%); colorless crystals. – M.p. 135-137 °C (C_6H_6/*i*Pr_2O). – $[\alpha]_D^{20}$ = +20.6 (*c* = 0.90, EtOH). The spectra (^{1}H NMR, IR, and MS) were identical with those of (2*S*,4*R*)-**40b**. – $C_{29}H_{33}NO_7$ (507.58): calcd. C 68.62, H 6.55, N 2.76; $C_{29}H_{33}NO_7 \cdot H_2O$ (525.60): calcd. C 66.27, H 6.71, N 2.67; found C 64.99, H 6.50, N 2.76.

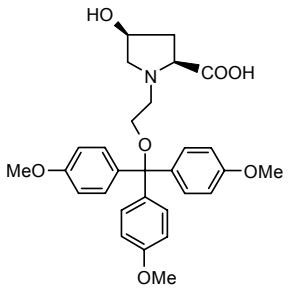
(2*R*,4*R*)-4-Hydroxy-1-{2-[tris(4-methoxyphenyl)methoxy]-1-ethyl}pyrrolidine-2-carboxylic acid [(2*R*,4*R*)-40b]



According to GP7-A from 66 mg (0.13 mmol) of (2*R*,4*R*)-**39b**, 0.38 ml (0.38 mmol) of aq. 1.0 M NaOH in 2.5 ml of EtOH; reaction time: 2 h; purification by CC (ϕ 12 × 110; Al_2O_3, pH 7 ± 0.5; EtOH/H_2O, 4:1) and recrystallization (petroleum ether). Yield: 43 mg (67%); colorless crystals. – M.p. 126-130 °C (petroleum ether). – $[\alpha]_D^{20}$ = +12.1 (*c* = 0.7, EtOH). – ^{1}H NMR (CD_3OD): δ = 2.23-2.29 (m, 1 H, NCHC*H*$_2$), 2.54 (ddd, *J* = 13.9/11.0/4.4 Hz, 1 H, NCHC*H*$_2$), 3.06 (dd, *J* = 11.6/3.6 Hz, 1 H, NC*H*$_2$CHOH), 3.23-3.37 (m, 3 H, NC*H*$_2$CHOH and 2 H of NC*H*$_2$CH$_2$), 3.51-3.61 (m, 2 H, NCH$_2$C*H*$_2$), 3.77 (s, 9 H, OCH_3), 3.98 (dd, *J* = 11.0/4.0 Hz, 1

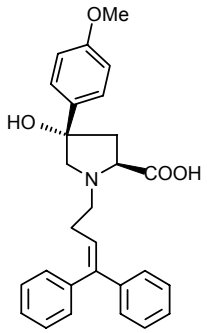
H, NCH), 4.38-4.41 (m, 1 H, C*H*OH), 6.86-6.90 (m, 6 H, H_{aromat}), 7.34-7.38 (m, 6 H, H_{aromat}). – IR: $\tilde{\nu}$ = 3414, 2956, 1638, 1608, 1250, 1176, 1033, 828 cm^{-1}. – MS (ESI); *m*/*z* (%): 333 (100), 185 (9), 149 (14). – $C_{29}H_{33}NO_7$ (507.58): calcd. C 68.62, H 6.55, N 2.76; $C_{29}H_{33}NO_7 \cdot H_2O$ (525.60): calcd. C 66.27, H 6.71, N 2.67; found C 66.26, H 6.77, N 2.59.

(2*S*,4*S*)-4-Hydroxy-1-{2-[tris(4-methoxyphenyl)methoxy]-1-ethyl}pyrrolidine-2-carboxylic acid [(2*S*,4*S*)-40b]



According to GP2 from 151 mg (0.298 mmol) of (2*S*,4*R*)-**40b** and 161 mg (0.596 mmol) of PPh_3, (67 mg, 0.39 mmol) of DEAD in 6.5 ml of THF; reaction time: 20 h. Purification by CC (Al_2O_3, pH 7.5 ±0.5; ϕ 25 × 180; gradient elution, *n*-heptane/acetone, 2:1 → EtOH/H_2O, 4:1) directly yielded (2*S*,4*S*)-**40b**. Yield: 115 mg (76% for two steps); colorless crystals. – M.p. 147-149 °C (EtOH/H_2O). – $[\alpha]_D^{24}$ = -11.9 (*c* = 0.75, EtOH). The spectra (^{1}H NMR, IR, and MS) were identical with those of (2*R*,4*R*)-**40b**. – $C_{29}H_{33}NO_7$ (507.58): calcd. C 68.62, H 6.55, N 2.76; found C 68.73, H 6.72, N 2.48.

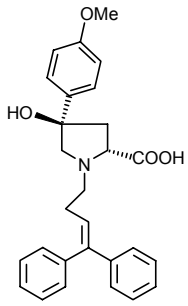
(2*S*,4*S*)-1-(4,4-Diphenylbut-3-en-1-yl)-4-hydroxy-4-(4-methoxyphenyl)pyrrolidine-2-carboxylic acid [(2*S*,4*S*)-57a]



According to GP7-A from 50 mg (0.11 mmol) of (2*S*,4*S*)-**53a**, 0.39 ml (0.33 mmol) of aq. 0.85 M KOH in 1.7 ml of EtOH; reaction time: 1 h; purification by CC (ϕ 10 × 70, gradient elution, *i*Pr_2O → EtOH). Yield: 36 mg (74%); colorless crystals. – M.p. 173-175 °C (MeOH).

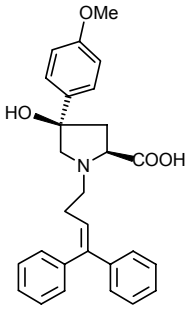
– $[\alpha]_D^{20}$ = -28.0 (*c* = 0.64, MeOH). – ^{1}H NMR (CD_3OD): δ = 2.42 (dd, *J* = 13.3/12.0 Hz, 1 H, NCHC*H*$_2$), 2.57 (q, *J* = 7.6 Hz, 2 H, NCH$_2$C*H*$_2$), 2.65 (ddd, *J* = 13.3/6.7/2.0 Hz, 1 H, NCHC*H*$_2$), 3.26-3.33 (m, 1 H, NCH$_2$CO), 3.36-3.40 (m, 1 H, NC*H*$_2$CH$_2$), 3.55 (dt, *J* = 12.2/7.6 Hz, 1 H, NC*H*$_2$CH$_2$), 3.68 (d, *J* = 12.3 Hz, 1 H, NCH$_2$CO), 3.78 (s, 3 H, ArOC*H*$_3$), 4.25 (dd, *J* = 12.0/6.7 Hz, 1 H, NCH), 6.12 (t, *J* = 7.6 Hz, 1 H, =C*H*CH$_2$), 6.90-6.93 (m, 2 H, H$_{aromat}$), 7.17-7.44 (m, 12 H, H$_{aromat}$). – IR: $\tilde{\nu}$ = 3254, 3023, 2960, 2862, 1622, 1516, 1260, 834, 764, 700 cm^{-1}. – MS; *m*/*z* (%): 444 (6) $[M+1]^+$, 382 (42), 381 (34), 380 (92), 207 (100), 188 (39), 127 (15). – $C_{28}H_{29}NO_4$ (443.54): calcd. C 75.82, H 6.59, N 3.16; found C 76.04, H 6.84, N 3.06.

(2*R*,4*R*)-1-(4,4-Diphenylbut-3-en-1-yl)-4-hydroxy-4-(4-methoxyphenyl)pyrrolidine-2-carboxylic acid [(2*R*,4*R*)-57a]



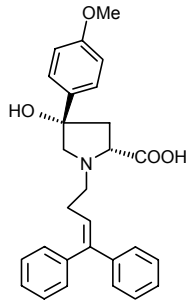
According to GP7-A from 62 mg (0.14 mmol) of (2*R*,4*R*)-**53a**, 0.42 ml (0.42 mmol) of aq. 1 M NaOH in 3.6 ml of MeOH; reaction time: 12 h; purification by recrystallization from MeOH. Yield: 56 mg (94%); colorless crystals. – M.p. 179-181 °C (MeOH). – $[\alpha]_D^{20}$ = +28.0 (*c* = 0.50, MeOH). The spectra (^{1}H NMR, IR, and MS) were identical with those of (2*S*,4*S*)-**57a**. – $C_{28}H_{29}NO_4$ (443.54)·H_2O: C 72.86, H 6.77, N 3.03; found C 72.77, H 6.57, N 2.95.

(2*S*,4*R*)-1-(4,4-Diphenylbut-3-en-1-yl)-4-hydroxy-4-(4-methoxyphenyl)pyrrolidine-2-carboxylic acid [(2*S*,4*R*)-57a]



According to GP7-B from 20 mg (0.044 mmol) of (2*S*,4*R*)-**53a**, 0.15 ml (0.13 mmol) of aq. 0.85 M KOH in 1 ml of EtOH; reaction time: 1 h; purification by CC (ϕ 10 × 80, gradient elution *i*Pr_2O → EtOH). Yield: 17 mg (88%); colorless crystals. – M.p. 168-173 °C. – $[\alpha]_D^{20}$ = -39.3 (*c* = 0.81, MeOH). – ^{1}H NMR (CD_3OD): δ = 2.54-2.71 (m, 3 H, NCHCH_2 and 2 H of NCH_2CH_2), 2.92 (dd, *J* = 13.5/11.4 Hz, 1 H, NCHCH_2), 3.33-3.53 (m, 3 H, NCH_2CO and 2 H of NCH_2CH_2), 3.62 (dd, *J* = 11.2/1.8 Hz, 1 H, NCH_2CO), 3.78 (s, 3 H, $ArOCH_3$), 4.39 (dd, *J* = 11.4/1.8 Hz, 1 H, NCH), 6.09 (t, *J* = 7.5 Hz, 1 H, =C*H*CH_2), 6.90-6.95 (m, 2 H, H_{aromat}), 7.16-7.45 (m, 12 H, H_{aromat}). – IR: $\tilde{\nu}$ = 3431, 3022, 2955, 2835, 1612, 1515, 1252, 832, 764, 702 cm^{-1}. – MS; *m*/*z* (%): 444 (5) $[M+1]^+$, 426 (47), 381 (33), 380 (100), 207 (87), 75 (67). – $C_{28}H_{29}NO_4$ (443.54): calcd. C 75.82, H 6.59, N 3.16; found: C 75.71, H 6.82, N 2.96;

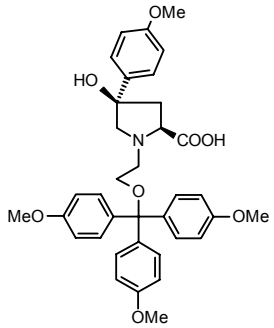
(2*R*,4*S*)-1-(4,4-Diphenylbut-3-en-1-yl)-4-hydroxy-4-(4-methoxyphenyl)pyrrolidine-2-carboxylic acid [(2*R*,4*S*)-57a]



According to GP7-A from 88 mg (0.19 mmol) of (2*R*,4*S*)-**53a**, 0.57 ml (0.57 mmol) of aq. 1 M NaOH in 6 ml of MeOH; reaction time: 12 h; purification by recrystallization from MeOH/*i*Pr_2O. Yield: 72 mg (84%); colorless crystals. – M.p. 165-170 °C (MeOH/*i*Pr_2O). – $[\alpha]_D^{20}$ = +40.4 (*c* = 1.55, MeOH). The spectra (^{1}H NMR, IR, and MS) were identical with those of (2*R*,4*S*)-**57a**. – $C_{28}H_{29}NO_4 \cdot 0.4H_2O$: C 74.56, H 6.62, N 2.92; found C 74.61, H 6.66, N 3.11.

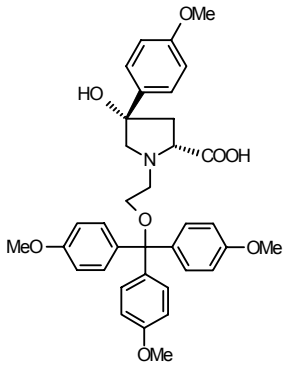
(2*S*,4*R*)-4-Hydroxy-4-(4-methoxyphenyl)-1-{2-[tris(4-methoxyphenyl)methoxy]-1-ethyl}-pyrrolidine-2-carboxylic acid [(2*S*,4*R*)-57b]

According to GP7-B from 62 mg (0.099 mmol) of (2*S*,4*R*)-**53b**, 0.47 ml (0.40 mmol) of aq. 0.85 M KOH in 2 ml of EtOH; reaction time: 3.5 h; 2.0 ml of buffer (pH 6.6). Yield: 54 mg (89%); colorless crystals. – M.p. 105-108 °C. – $[\alpha]_D^{20}$ = +1.5 (*c* = 1.15, MeOH). – ^{1}H NMR (CD_3OD): δ = 2.48 (dd, *J* = 13.5/2.1 Hz, 1 H, NCHCH_2), 2.75 (dd, *J* = 13.5/11.5 Hz, 1 H,



NCHCH_2), 3.16-3.22 (m, 2 H, NCH_2CO), 3.25-3.32 (m, 2 H, NCH_2CH_2), 3.49-3.62 (m, 2 H, NCH_2CH_2), 3.67 (s, 9 H, ArOCH_3), 3.70 (s, 3 H, Ar'OCH_3), 4.06 (dd, J = 11.5/2.1 Hz, 1 H, NCH), 6.77-6.84 (m, 8 H, H_{aromat}), 7.22-7.25 (m, 2 H, H_{aromat}), 7.28-7.32 (m, 6 H, H_{aromat}). – IR: $\tilde{\nu}$ = 3421, 2999, 2955, 2830, 1637, 1609, 1509, 1251, 1034, 830 cm^{-1}. – MS (ESI); *m*/*z* (%): 614 $[M+1]^+$ (4), 333 (100). – $C_{36}H_{39}NO_8 \cdot H_2O$: calcd. C 68.45, H 6.54, N 2.22; found C 68.62, H 6.40, N 2.18.

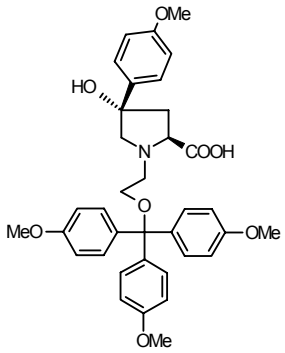
(2*R*,4*S*)-4-Hydroxy-(4-methoxyphenyl)-1-{2-[tris(4-methoxyphenyl)methoxy]-1-ethyl}-pyrrolidine-2-carboxylic acid [(2*R*,4*S*)-57b]



According to GP7-B from 60 mg (0.096 mmol) of (2*R*,4*S*)-**53b**, 0.29 ml (0.29 mmol) of aq. 1.0 M NaOH in 3 ml of MeOH; reaction time: 3 h; 0.5 ml of buffer (pH 6.6). Yield: 52 mg (89%); colorless crystals. – M.p. 158-160 °C (MeOH/H_2O). – $[\alpha]_D^{20}$ = -1.6 (*c* = 0.75, MeOH). The spectra (^{1}H NMR, IR, and MS) were identical with those of (2*S*,4*R*)-**57b**. – $C_{36}H_{39}NO_8 \cdot 0.5H_2O$ calcd. C 69.44, H 6.68, N 2.25; found: C 69.31, H 6.51, N 2.17.

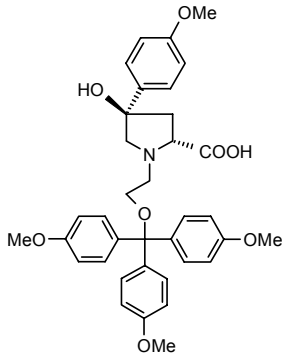
(2*S*,4*S*)-4-Hydroxy-4-(4-methoxyphenyl)-1-{2-[tris(4-methoxyphenyl)methoxy]-1-ethyl}-pyrrolidine-2-carboxylic acid [(2*S*,4*S*)-57b]

According to GP7-B from 30 mg (0.048 mmol) of (2*S*,4*S*)-**53b**, 0.39 ml (0.33 mmol) of aq.



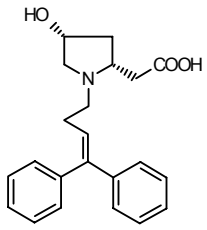
0.85 M KOH in 1 ml of EtOH; reaction time: 1.75 h; 1 ml of buffer (pH 6.6). Yield: 26 mg (89%); colorless crystals. – M.p. 138-139 °C (EtOH/H_2O). – $[\alpha]_D^{20}$ = -3.9 (*c* = 0.85, MeOH). – ^{1}H NMR (CD_3OD): δ = 2.32 (dd, *J* = 13.3/11.6 Hz, 1 H, NCHCH_2), 2.57 (ddd, *J* = 13.3/7.1/1.5 Hz, 1 H, NCHCH_2), 3.14 (dd, *J* = 12.5/2.1 Hz, 1 H, NCH_2CO), 3.30-3.51 (m, 5 H, NCH_2CO and 2 H of NCH_2CH_2 and 2 H of NCH_2CH_2), 3.65 (s, 9 H, Ar'OCH_3), 3.69 (s, 3 H, ArOCH_3), 4.29 (dd, *J* = 11.6/7.1 Hz, 1 H, NCH), 6.73-6.76 (m, 6 H, H_{aromat}), 6.78-6.81 (m, 2 H, H_{aromat}), 7.23-7.27 (m, 8 H, H_{aromat}). – IR: $\tilde{\nu}$ = 3425, 2839, 1630, 1609, 1509, 1250, 1175, 830 cm^{-1}. – MS (ESI); *m*/*z* (%): 614 $[M+1]^+$ (6), 333 (100). – $C_{36}H_{39}NO_8$ (613.71): calcd. C 70.46, H 6.41, N 2.28; found C 70.18, H 6.62, N 2.35.

(2*R*,4*R*)-4-Hydroxy-(4-methoxyphenyl)-1-{2-[tris(4-methoxyphenyl)methoxy]-1-ethyl}-pyrrolidine-2-carboxylic acid [(2*R*,4*R*)-57b]



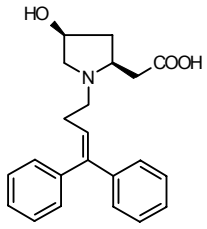
According to GP7-B from 56 mg (0.089 mmol) of (2*R*,4*R*)-**53b**, 0.27 ml (0.27 mmol) of aq. 1.0 M NaOH in 3 ml of MeOH; reaction time: 5 h; 0.5 ml of buffer (pH 6.6). Yield: 48 mg (88%); colorless crystals. – M.p. 158-160 °C (MeOH/H_2O). – $[\alpha]_D^{20}$ = +3.6 (*c* = 0.50, MeOH). The spectra (^{1}H NMR, IR, and MS) were identical with those of (2*S*,4*S*)-**57b**. – $C_{36}H_{39}NO_8 \cdot 0.3H_2O$ calcd. C 69.84, H 6.45, N 2.26; found C 69.76, H 6.67, N 2.15.

(2*R*,4*R*)-1-(4,4-Diphenylbut-3-en-1-yl)-4-hydroxypyrrolidine-2-acetic acid [(2*R*,4*R*)-89a]



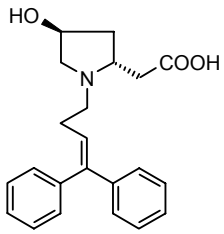
According to GP7-A from 53 mg (0.14 mmol) of (2*R*,4*R*)-**88a**, 0.42 ml (0.42 mmol) of aq. 1.0 M NaOH in 2 ml of MeOH; reaction time: 41 h; 1 ml of buffer (pH 5.5); purification by CC (ϕ 12 × 100, MeOH). Yield: 41 mg (84%); colorless crystals. – M.p. 70-76 °C (MeOH/*i*Pr_2O). – $[\alpha]_D^{20}$ = +52.2 (*c* = 0.50, MeOH). – ^{1}H NMR (CD_3OD): δ = 1.71-1.77 (m, 1 H, C*H*$_2$CHCH$_2$COO), 2.46-2.57 (m, 4 H, C*H*$_2$COO, C*H*$_2$CHCH$_2$COO and 2 H of NCH$_2$C*H*$_2$), 2.63 (dd, *J* = 16.7/6.3 Hz, 1 H, CH$_2$COO), 2.92-3.01 (m, 2 H, NC*H*$_2$CH$_2$ and NC*H*$_2$CHO), 3.17-3.29 (m, 1 H, NC*H*$_2$CHO), 3.46-3.57 (m, 2 H, NC*H*$_2$CH$_2$ and NC*H*), 4.35-4.40 (m, 1 H, C*H*OH), 6.02 (t, *J* = 7.3 Hz, 1 H, =C*H*CH$_2$), 7.14-7.40 (m, 10 H, H_{aromat}). – IR: $\tilde{\nu}$ = 3388, 3055, 2952, 1608, 1444, 1361, 773, 701 cm^{-1}. – MS; *m*/*z* (%): 352 (23) $[M+1]^+$, 334 (100), 292 (10), 158 (11), 140 (18), 89 (7), 75 (22) cm^{-1}. – $C_{22}H_{25}NO_3$ (351.45) · 1.0 H_2O: calcd. C 71.52, H 7.37, N 3.79; found C 71.72, H 7.01, N 3.49.

(2*S*,4*S*)-1-(4,4-Diphenylbut-3-en-1-yl)-4-hydroxypyrrolidine-2-acetic acid [(2*S*,4*S*)-89a]



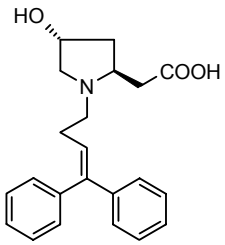
According to GP7-A from 60 mg (0.18 mmol) of (1*S*,5*S*)-**92a**, 0.54 ml (0.54 mmol) of aq. 1.0 M NaOH in 3 ml of MeOH; reaction time: 20 h; 0.7 ml of buffer (pH 6.6); purification by CC (ϕ 12 × 110, MeOH) and recrystallization from C_6H_6. Yield: 49 mg (78%); colorless crystals. – M.p. 95-97 °C (C_6H_6). – $[\alpha]_D^{20}$ = -51.5 (*c* = 0.47, MeOH). The spectra (^{1}H NMR, IR, and MS) were identical with those of (2*R*,4*R*)-**89a**.

(2*R*,4*S*)-1-(4,4-Diphenylbut-3-en-1-yl)-4-hydroxypyrrolidine-2-acetic acid [(2*R*,4*S*)-89a]



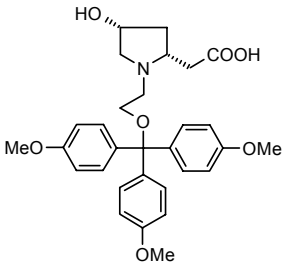
According to GP7-A from 36 mg (0.085 mmol) of (2*R*,4*S*)-**90a**, 0.51 ml (0.51 mmol) of aq. 1.0 M NaOH in 4.5 ml of MeOH; reaction time: 3 d; 0.3 ml of buffer (pH 6.6); purification by recrystallization (C_6H_6/*i*Pr_2O). Yield: 28 mg (93%); colorless crystals. – M.p. 57-60 °C (C_6H_6/*i*Pr_2O). – $[\alpha]_D^{20}$ = +65.6 (*c* = 0.5, MeOH). – ^{1}H NMR (CD_3OD): δ = 1.93 (ddd, *J* = 13.6/11.4/5.1 Hz, 1 H, C*H*$_2$CHCH$_2$COO), 2.13 (ddt, *J* = 13.6/6.5/1.7 Hz, 1 H, C*H*$_2$CHCH$_2$COO), 2.46 (dd, *J* = 16.5/3.0 Hz, 1 H, CH$_2$COO), 2.56 (q, *J* = 7.4 Hz, 2 H, NCH$_2$C*H*$_2$), 2.70 (dd, J = 16.5/5.9 Hz, 1 H, CH$_2$COO), 2.82 (d, *J* = 12.5 Hz, 1 H, NC*H*$_2$CHO), 3.03-3.10 (m, 1 H, NC*H*$_2$CH$_2$), 3.46-3.53 (m, 2 H, NC*H*$_2$CH$_2$ and NC*H*$_2$CHO), 3.74-3.80 (m, 1 H, NCH), 4.38-4.41 (m, 1 H, C*H*OH), 6.09 (t, *J* = 7.4 Hz, 1 H, =C*H*CH$_2$), 7.21-7.46 (m, 10 H, H_{aromat}). – IR: $\tilde{\nu}$ = 3295, 3055, 1718, 1624, 1444, 1396, 764, 702 cm^{-1}. – MS; *m*/*z* (%): 352 (19) $[M+1]^+$, 334 (26), 279 (26), 207 (47), 195 (35), 183 (95), 158 (39), 145 (100), 91 (31). – $C_{22}H_{25}NO_3$ (351.45).1.3 H_2O; calcd. C 70.50, H 7.42, N 3.74; found C 70.34, H 7.47, N 3.53.

(2*S*,4*R*)-1-(4,4-Diphenylbut-3-en-1-yl)-4-hydroxypyrrolidine-2-acetic acid [(2*S*,4*R*)-89a]



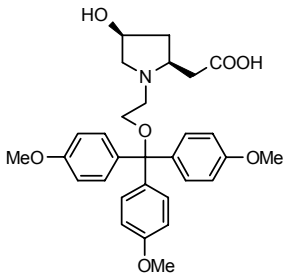
According to GP7-A from 50 mg (0.14 mmol) of (2*S*,4*R*)-**91a**, 0.42 ml (0.42 mmol) of aq. 1.0 M NaOH in 3 ml of EtOH; reaction time: 3 h; 2 ml of buffer (pH 6.6); purification by CC (ϕ 10 × 70, EtOH). Yield: 40 mg (83%); colorless oil. – $[\alpha]_D^{20}$ = -69.4 (*c* = 0.95, MeOH). The spectra (^{1}H NMR, IR, and MS) were identical with those of (2*R*,4*S*)-**89a**. – $C_{22}H_{25}NO_3$ (351.45): calcd. C 75.19, H 7.17, N 4.00; found C 74.70, H 7.48, N 3.79.

(2*R*,4*R*)-4-Hydroxy-1-{2-[tris(4-methoxyphenyl)methoxy]-1-ethyl}pyrrolidine-2-acetic acid [(2*R*,4*R*)-89b]



According to GP7-A from 54 mg (0.098 mmol) of (2*R*,4*R*)-**88b**, 0.30 ml (0.30 mmol) of aq. 1.0 M NaOH in 2 ml of MeOH; reaction time: 2 d; purification by CC (Al_2O_3, pH 7.0 ± 0.5, mesh 0.05-0.15 mm; ϕ 12 × 70; MeOH/H_2O, 7:3) and recrystallization (C_6H_6/*i*Pr_2O). Yield: 40 mg (78%); colorless crystals. – M.p. 85-88 °C. – $[\alpha]_D^{20}$ = +17.9 (*c* = 0.90, MeOH). – ^{1}H NMR (CD_3OD): δ = 1.83 (ddd, *J* = 13.4/9.0/4.3 Hz, 1 H, C*H*$_2$CHCH$_2$COO), 2.50-2.62 (m, 2 H, C*H*$_2$COO and C*H*$_2$CHCH$_2$COO), 2.74 (dd, *J* = 16.7/6.2 Hz, 1 H, CH$_2$COO), 2.98-3.04 (m, 1 H, NC*H*$_2$CH$_2$), 3.14 (dd, *J* = 11.9/5.7 Hz, 1 H, NC*H*$_2$CHO), 3.28-3.34 (m, 1 H, NC*H*$_2$CHO), 3.39-3.60 (m, 4 H, NC*H*$_2$CH$_2$, NC*H* and 2 H of NCH$_2$C*H*$_2$), 3.77 (s, 9 H, ArOC*H*$_3$), 4.41-4.46 (m, 1 H, C*H*OH), 6.85-6.89 (m, 6 H, H_{aromat}), 7.32-7.36 (m, 6 H, H_{aromat}). – IR: $\tilde{\nu}$ = 3420, 3050, 3025, 2933, 1607, 1508, 1250, 1176, 1034, 828 cm^{-1}. – MS (ESI$^+$); *m*/*z* (%): 522 [M+1]$^+$ (6), 333 (100). – $C_{30}H_{35}NO_7$ (521.61)·1.0 H_2O: calcd. C 66.78, H 6.91, N 2.60; found C 66.93, H 6.71, N 2.46.

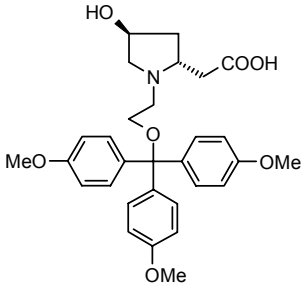
(2*S*,4*S*)-4-Hydroxy-1-{2-[tris(4-methoxyphenyl)methoxy]-1-ethyl}pyrrolidine-2-acetic aicd [(2*S*,4*S*)-89b]



According to GP7-A from 112 mg (0.227 mmol) of (1*S*,5*S*)-**92b**, 0.67 ml (0.67 mmol) of aq. 1.0 M NaOH in 7.3 ml of MeOH; reaction time: 2 d; purification by recrystallization from MeOH/*i*Pr_2O. Yield: 102 mg (96%); colorless powder. – M.p. 95-103 °C (C_6H_6/*i*Pr_2O). –

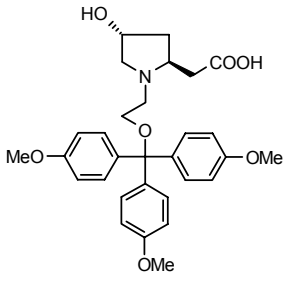
$[\alpha]_D^{20}$ = -16.8 (*c* = 0.75, MeOH). The spectra (^{1}H NMR, IR, and MS) were identical with those of (2*R*,4*R*)-**89b**. – $C_{30}H_{35}NO_7$ (521.61): calcd. C 69.08, H 6.76, N 2.69; found

(2*R*,4*S*)-4-hydroxy-1-{2-[Tris(4-methoxyphenyl)methoxy]-1-ethyl}pyrrolidine-2-acetic acid [(2*R*,4*S*)-89b]



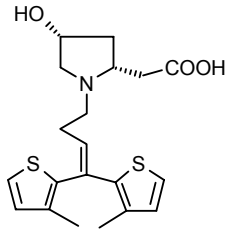
According to GP7-A from 70 mg (0.12 mmol) of (2*R*,4*S*)-**90b**, 0.71 ml (0.71 mmol) of aq. 1.0 m NaOH in 6.3 ml of MeOH; reaction time: 48 h; purification by recrystallization (C_6H_6/*i*Pr_2O). Yield: 52 mg (85%); colorless crystals. – M.p. 98-105 °C (C_6H_6/*i*Pr_2O). – $[\alpha]_D^{20}$ = +31.5 (*c* = 0.60, MeOH). – ^{1}H NMR (CD_3OD): δ = 1.93 (ddd, *J* = 13.5/11.5/4.6 Hz, 1 H, C*H*$_2$CHCH$_2$COO), 2.12 (ddt, *J* = 13.5/6.5/1.6 Hz, 1 H, C*H*$_2$CHCH$_2$COO), 2.39 (dd, *J* = 16.9/2.4 Hz, 1 H, CH$_2$COO), 2.72 (dd, *J* = 16.9/5.3 Hz, 1 H, CH$_2$COO), 3.00 (dt, *J* =12.6/1.6 Hz, 1 H, NC*H*$_2$CHO), 3.10-3.16 (m, 1 H, NC*H*$_2$CH$_2$), 3.38-3.53 (m, 4 H, NC*H*$_2$CHO, NC*H*$_2$CH$_2$ and 2 H of NCH$_2$C*H*$_2$), 3.75 (s, 9 H, ArOC*H*$_3$), 3.79-3.86 (m, 1 H, NCH), 4.39-4.43 (m, 1 H, C*H*OH), 6.83-6.87 (m, 6 H, H_{aromat}), 7.29-7.33 (m, 6 H, H_{aromat}). – IR: $\tilde{\nu}$ = 3398, 2933, 1607, 1506, 1251, 1176, 1033, 828, 583 cm^{-1}. – MS (ESI$^+$); *m*/*z* (%): 522 $[M+1]^+$ (16), 333 (100). – $C_{30}H_{35}NO_7$ (521.61)·0.8 H_2O: calcd. C 67.22, H 6.88, N 2.61; found C 67.34, H 7.19, N 2.45.

(2*S*,4*R*)-4-Hydroxy-1-{2-[tris(4-methoxyphenyl)methoxy]-1-ethyl}pyrrolidine-2-acetic acid [(2*S*,4*R*)-89b]



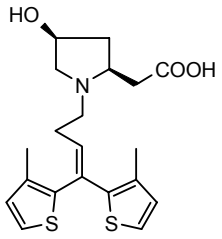
According to GP7-A from 149 mg (0.279 mmol) of (2*S*,4*R*)-**91b**, 0.85 ml (0.85 mmol) of aq. 1.0 M NaOH in 5 ml of MeOH; reaction time: 4 h; 2.5 ml of buffer (pH 6.6); purification by CC (Al_2O_3, pH 7 ± 0.5; ϕ 12 × 100; H_2O/MeOH, 1:4) and recrystallization from C_6H_6/petroleum ether. Yield: 120 mg (83%); colorless crystals. – M.p. 95-103 °C (C_6H_6/petroleum ether). – $[\alpha]_D^{20}$ = -33.2 (*c* = 1.00, MeOH). The spectra (^{1}H NMR, IR, and MS) were identical with those of (2*R*,4*S*)-**89b**. – $C_{30}H_{35}NO_7 \cdot 0.5\ H_2O$: calcd. C 67.90, H 6.84, N 2.64; found C 68.01, H 7.11, N 2.33.

(2*R*,4*R*)-1-[4,4-Di(3-methyl-2-thienyl)but-3-en-1-yl]-4-hydroxypyrrolidine-2-acetic acid [(2*R*,4*R*)-89c]



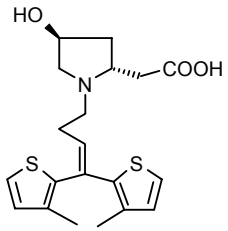
According to GP7-A from 47 mg (0.12 mmol) of (2*R*,4*R*)-**88c**, 0.56 ml (0.56 mmol) of aq. 1.0 M NaOH in 2 ml of MeOH; reaction time: 2 d; purification by CC (ϕ 12 × 120, MeOH) and recrystallization (C_6H_6/petroleum ether). Yield: 43 mg (95%); slightly yellow powder. – M.p. 69-74 °C (C_6H_6/petroleum ether). – $[\alpha]_D^{20}$ = +34.8 (*c* = 0.46, MeOH). – ^{1}H NMR (CD_3OD): δ = 1.72-1.78 (m, 1 H, C*H*$_2$CHCH$_2$COO), 1.97 (s, 3 H, thienyl-C*H*$_3$), 2.03 (s, 3 H, theinyl-C*H*$_3$), 2.46-2.60 (m, 5 H, C*H*$_2$CHCH$_2$COO, 2 H of C*H*$_2$COO and 2 H of NCH$_2$C*H*$_2$), 2.95-3.04 (m, 1 H, NC*H*$_2$CH$_2$), 3.08 (dd, *J* = 11.9/5.5 Hz, 1 H, NC*H*$_2$CHO), 3.30-3.60 (m, 3 H, NC*H*$_2$CHO, NC*H*$_2$CH$_2$ and NC*H*), 4.38-4.44 (m, 1 H, NCH$_2$C*H*O), 6.05 (t, *J* = 7.3 Hz, 1 H, =C*H*CH$_2$), 6.78 (d, *J* = 5.2 Hz, 1 H, SCH), 6.91 (d, *J* = 5.2 Hz, 1 H, SCH), 7.16 (d, *J* = 5.2 Hz, 1 H, SCH=C*H*), 7.35 (d, *J* = 5.2 Hz, 1 H, SCH=C*H*). – IR: $\tilde{\nu}$ = 3396, 3105, 2921, 1591, 1399, 1097, 713 cm^{-1}. – MS; *m*/*z* (%): 392 (12) $[M+1]^+$, 374 (24), 328 (25), 263 (19), 223 (49), 183 (18), 165 (40), 140 (100), 127 (41), 91 (10). – $C_{20}H_{25}NO_3S_2$ (391.54)·0.8 H_2O: calcd. C 59.17, H 6.60, N 3.45; found C 59.29, H 6.42, N 3.10.

(2*S*,4*S*)-1-[4,4-Di(3-methyl-2-thienyl)but-3-en-1-yl]-4-hydroxypyrrolidine-2-acetic acid [(2*S*,4*S*)-89c]



According to GP7-A from 67 mg (0.18 mmol) of (1*S*,5*S*)-**92c**, 0.54 ml (0.54 mmol) of aq. 1.0 M NaOH in 4.5 ml of MeOH; reaction time: 25 h; 1 ml of buffer (pH 6.6); purification by CC (ϕ 12 × 100, MeOH) and rescrystallization from MeOH/*i*Pr_2O. Yield: 59 mg (84%); colorless powder. – M.p. 72-78 °C (C_6H_5/*i*Pr_2O). – $[\alpha]_D^{20}$ = -34.4 (*c* = 0.52, MeOH). The spectra (^{1}H NMR, IR, and MS) were identical with those of (2*R*,4*R*)-**89c**. – $C_{20}H_{25}NO_3S_2 \cdot 1.1\ H_2O$: calcd. C 58.39, H 6.67, N 3.40; found C 58.33, H 6.64, N 3.08.

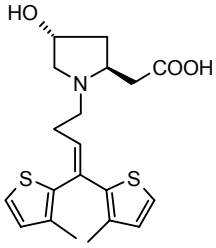
(2*R*,4*S*)-1-[4,4-Di(3-methyl-2-thienyl)but-3-en-1-yl]-4-hydroxypyrrolidine-2-acetic acid [(2*R*,4*S*)-89c]



According to GP7-A from 70 mg (0.15 mmol) of (2*R*,4*S*)-**90c**, 0.91 ml (0.91 mmol) of aq. 1.0 M NaOH in 4 ml of MeOH; reaction time: 3 d; 1.5 ml of buffer (pH 6.6); purification by CC (ϕ 12 × 110, MeOH). Yield: 56 mg (94%); pale yellow powder. – M.p. 58-62 °C (C_6H_6/*i*Pr_2O). – $[\alpha]_D^{20}$ = +57.5 (*c* = 0.52, MeOH). – ^{1}H NMR (CD_3OD): δ = 1.87-1.94 (m, 1 H, C*H*$_2$CHCH$_2$COO), 1.99 (s, 3 H, thienyl-C*H*$_3$), 2.04 (s, 3 H, thienyl-C*H*$_3$), 2.13 (dd, *J* = 13.6/6.5 Hz, 1 H, C*H*$_2$CHCH$_2$COO), 2.49 (dd, *J* = 16.6/3.2 Hz, 1 H, CH$_2$COO), 2.50-2.61 (m, 2 H, NCH$_2$C*H*$_2$), 2.63 (dd, *J* = 16.6/6.0 Hz, 1 H, CH$_2$COO), 2.85 (br. d, *J* = 12.1 Hz, 1 H, NC*H*$_2$CHO), 2.99-3.05 (m, 1 H, NC*H*$_2$CH$_2$), 3.42 (dt, *J* = 12.4/8.2 Hz, 1 H, NC*H*$_2$CH$_2$), 3.60 (dd, *J* = 12.1/4.9 Hz, 1 H, NC*H*$_2$CHO), 3.68-3.76 (m, 1H, NCH), 4.40-4.43 (m, 1H, C*H*OH), 6.05 (t, *J* = 7.4 Hz, 1 H, =C*H*CH$_2$), 6.77 (d, *J* = 5.2 Hz, 1 H, SCH), 6.91 (d, *J* = 5.2 Hz, 1 H, SCH), 7.15 (d, *J* = 5.2 Hz, 1 H, SCH=C*H*), 7.36 (d, *J* = 5.2 Hz, 1 H, SCH=C*H*). – IR: $\tilde{\nu}$ = 3380, 3102, 2921, 1588, 1401, 834, 713 cm^{-1}. – MS; *m*/*z* (%): 392 (45) $[M+1]^+$, 374 (13), 330

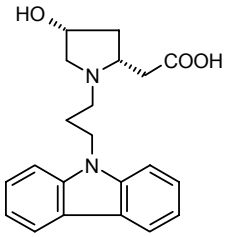
(14), 306 (13), 247 (25), 174 (37), 158 (100), 140 (39), 97 (13), 87 (50). – $C_{22}H_{25}NO_3S_2$ (391.54)·1.0 H_2O: calcd. C 58.65, H 6.65, N 3.42; found C 58.75, H 6.80, N 3.48.

(2*S*,4*R*)-1-[4,4-Di(3-methyl-2-thienyl)but-3-en-1-yl]-4-hydroxypyrrolidine-2-acetic acid [(2*S*,4*R*)-89c]



According to GP7-A from 90 mg (0.22 mmol) of (2*S*,4*R*)-**91c**, 0.67 ml (0.67 mmol) of aq. 1.0 M NaOH in 3.5 ml of MeOH; reaction time: 3 h; 2 ml of buffer (pH 6.6); purification by CC (ϕ 12 × 100, MeOH). Yield: 80 mg (92%); yellow foam. – M.p. 74-80 °C (C_6H_6/*i*Pr_2O). – $[\alpha]_D^{20}$ = -58.3 (*c* = 1.00, MeOH). The spectra (^{1}H NMR, IR, and MS) were identical with those of (2*R*,4*S*)-**89c**. – $C_{20}H_{25}NO_3S_2$·1.0 H_2O (391.54): calcd. C 58.65, H 6.65, N 3.42; found C 58.75, H 6.89, N 3.18.

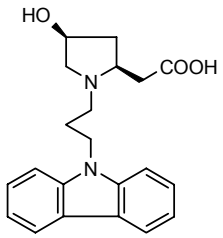
(2*R*,4*R*)-1-[3-(9-Carbazolyl)-1-propyl]-4-hydroxypyrroidine-2-acetic acid [(2*R*,4*R*)-89d]



According to GP7-A from 88 mg (0.23 mmol) of (2*R*,4*R*)-**88d**, 0.70 ml (0.70 mmol) of aq. 1.0 M NaOH in 3 ml of MeOH; reaction time: 14 h; 1 ml of buffer (pH 5.5); purification by CC (ϕ 12 × 100, MeOH) and recrystallization (MeOH/EtOAc). Yield: 73 mg (90%); colorless crystals. – M.p. 93-97 °C (MeOH/EtOAc). – $[\alpha]_D^{20}$ = +31.2 (*c* = 0.26, MeOH). – ^{1}H NMR (CD_3OD): δ = 1.71-1.78 (m, 1 H, C*H*$_2$CHCH$_2$COO), 2.18-2.32 (m, 2 H, CHNCH$_2$C*H*$_2$), 2.43-2.51 (m, 1 H, C*H*$_2$CHCH$_2$COO), 2.58-2.62 (m, 2 H, CH$_2$COO), 2.90-3.02 (m, 2 H, C*H*$_2$NCH and NC*H*$_2$CHO), 3.41-3.55 (m, 3 H, NC*H*, C*H*$_2$NCH and NC*H*$_2$CHO), 4.34-4.51 (m, 3 H, C*H*OH and 2 H of C*H*$_2$-carbazole), 7.17-7.21 (m, 2 H, H_{aromat}), 7.46-7.53 (m, 4 H, H_{aromat}),

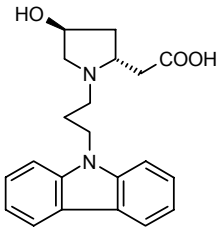
8.05-8.08 (m, 2 H, H_{aromat}). – IR: $\tilde{\nu}$ = 3385, 3049, 2946, 1595, 1454, 1387, 753, 726 cm^{-1}. – MS; *m*/*z* (%): 353 (2) $[M+1]^+$, 335 (100), 289 (21), 275 (16), 180 (19), 168 (18), 159 (17), 151 (21). – $C_{21}H_{24}N_2O_3$ (352.44): calcd. C 71.57, H 6.86, N 7.95; found

(2*S*,4*S*)-1-[3-(9-Carbazolyl)-1-propyl]-4-hydroxypyrrolidine-2-acetic acid [(*2S*,4*S*)-89d]



According to GP7-A from 54 mg (0.16 mmol) of (1*S*,5*S*)-**92d**, 0.49 ml (0.49 mmol) of aq. 1 M NaOH in 4.5 ml of MeOH; reaction time: 12 h; purification by CC (ϕ 12 × 90; CH_3OH/H_2O, 9:1) and recrystallization in MeOH/EtOAc. Yield: 54 mg (95%); colorless crystals. – M.p. 102-108 °C (MeOH/EtOAc). – $[\alpha]_D^{20}$ = -31 (*c* = 0.51, MeOH). The spectra (^{1}H NMR, IR, and MS) were identical with those of (2*R*,4*R*)-**89d**. – $C_{21}H_{24}N_2O_3 \cdot 1.0\ H_2O$ (370.46): calcd. C 68.09, H 7.05, N 7.56; found

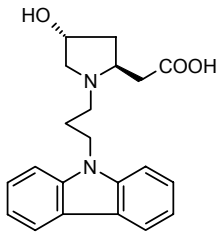
(2*R*,4*S*)-1-[3-(9-Carbazolyl)-1-propyl]-4-hydroxypyrrolidine-2-acetic acid [(2*R*,4*S*)-89d]



According to GP7-A from 94 mg (0.22 mmol) of (2*R*,4*S*)-**90d**, 1.3 ml (1.3 mmol) of aq. 1.0 M NaOH in 6.5 ml of MeOH; reaction time: 3 d; purification by recrystallization (MeOH/*i*Pr_2O). Yield: 73 mg (93%); colorless crystals. – M.p. 175-177 °C (MeOH/*i*Pr_2O). – $[\alpha]_D^{22}$ = +44.4 (*c* = 0.80, MeOH). – ^{1}H NMR (CD_3OD, 500 MHz): δ = 1.93 (ddd, *J* = 13.7/11.3/4.7 Hz, 1 H, C*H*$_2$CHCH$_2$COO), 2.13 (ddt, *J* = 13.7/6.4/1.7 Hz, 1 H, C*H*$_2$CHCH$_2$COO), 2.21-2.37 (m, 2 H, CHNCH$_2$C*H*$_2$), 2.45 (dd, *J* = 16.5/3.0 Hz, 1 H, CH$_2$COO), 2.65 (dd, *J* = 16.5/6.0 Hz, 1 H, CH$_2$COO), 2.93 (br. d, *J* = 12.4 Hz, 1 H, NC*H*$_2$CHO), 2.96-3.03 (m, 1 H, C*H*$_2$NCH), 3.36-3.42 (m, 1 H, C*H*$_2$NCH), 3.64-3.74 (m, 2 H, NC*H*$_2$CHO and NC*H*), 4.39-4.43 (m, 1 H, C*H*OH), 4.45-4.55 (m, 2 H, C*H*$_2$-carbazole), 7.21-7.26 (m, 2 H, H_{aromat}), 7.49-7.55 (m, 2 H,

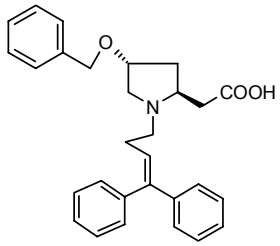
H_{aromat}), 7.62-7.67 (m, 2 H, H_{aromat}), 8.08-8.10 (m, 2 H, H_{aromat}). – IR: $\tilde{\nu}$ = 3405, 3053, 2949, 1594, 1401, 752, 725 cm^{-1}. – MS; *m*/*z* (%): 353 (3) $[M+1]^+$, 305 (38), 291 (100), 267 (14), 225 (21), 180 (7), 168 (24). – $C_{21}H_{24}N_2O_3$ (370.46)·1.0 H_2O: calcd. C 68.09, H 7.05, N 7.56; found C 67.91, H 6.77, N 7.37.

(2*S*,4*R*)-1-[3-(9-Carbazolyl)-1-propyl]-4-hydroxypyrrolidine-2-acetic acid [(2*S*,4*R*)-89d]



According to GP7-A from 105 mg (0.286 mmol) of (2*S*,4*R*)-**91d**, 0.86 ml (0.86 mmol) of aq. 1.0 M NaOH in 4 ml of MeOH; reaction time: 6 h; 1.5 ml of buffer (pH 6.6); purification by CC (ϕ 12 × 100, MeOH) and recrystallization from MeOH/iPr$_2$O. Yield: 89 mg (88%); colorless crystals. – M.p. 207-209 °C (MeOH/iPr$_2$O). – $[\alpha]_D^{20}$ = -43.5 (*c* = 0.93, MeOH). The spectra (^{1}H NMR, IR, and MS) were identical with those of (2*R*,4*S*)-**89d**. – $C_{21}H_{24}N_2O_3$ (352.44): calcd. C 71.57, H 6.86, N 7.95; found C 71.21, H 6.79, N 7.91.

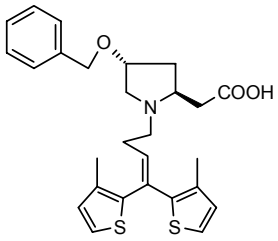
(2*S*,4*R*)-4-Benzyloxy-1-(4,4-diphenylbut-3-en-1-yl)pyrrolidine-2-acetic acid [(2*S*,4*R*)-94a]



According to GP7-B from 40 mg (0.088 mmol) of (2*S*,4*R*)-**93a**, 0.26 ml (0.26 mmol) of aq. 1.0 M NaOH in 1.5 ml of MeOH; reaction time: 4 h; 2 ml of buffer (pH 6.6). The residue was dissolved in C_6H_6, then filtrated, finally concentrated. Yield: 37 mg (95%); colorless oil. – $[\alpha]_D^{20}$ = -79.0 (*c* = 1.24, MeOH). – ^{1}H NMR (CD_3OD): δ = 1.90 (ddd, *J* = 13.9/11.5/4.8 Hz, 1 H, C*H*$_2$CHCH$_2$COO), 2.37-2.41 (m, 1 H, C*H*$_2$CHCH$_2$COO), 2.44 (dd, *J* = 17.0/2.9 Hz, 1 H, CH$_2$COO), 2.51-2.57 (m, 2 H, NCH$_2$C*H*$_2$), 2.74 (dd, *J* = 17.0/5.3 Hz, 1 H, CH$_2$COO), 3.03-

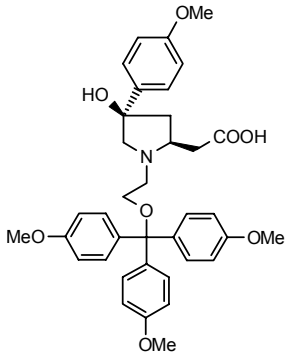
3.12 (m, 2 H, NCH_2CHO and NCH_2CH$_2$), 3.44-3.50 (m, 1 H, NCH_2CH$_2$), 3.53 (dd, J = 12.8/4.8 Hz, 1 H, NCH_2CHO), 3.74-3.80 (m, 1 H, NCH), 4.20-4.24 (m, 1 H, NCH$_2$CHO), 4.44 (d, J = 11.9 Hz, 1 H, CH_2Ph), 4.53 (d, J = 11.9 Hz, 1 H, CH_2Ph), 6.07 (t, J = 7.4 Hz, 1 H, =CHCH$_2$), 7.17-7.43 (m, 15 H, H$_{aromat}$). – IR: $\tilde{\nu}$ = 3394, 3030, 2932, 1698, 1595, 1397, 1094, 764, 736, 699 cm^{-1}. – MS; *m/z* (%): 444 (19) [M+1]$^+$, 443 (69), 382 (14), 274 (19), 248 (100), 91 (78). – $C_{29}H_{31}NO_3$ (441.57)·0.4 H_2O: calcd. C 77.62, H 7.14, N 3.12; found C 77.53, H 7.00, N 2.80.

(2*S*,4*R*)-4-Benzyloxy-1-[4,4-di(3-methyl-2-thienyl)but-3-en-1-yl]pyrrolidine-2-acetic acid [(2*S*,4*R*)-94c]



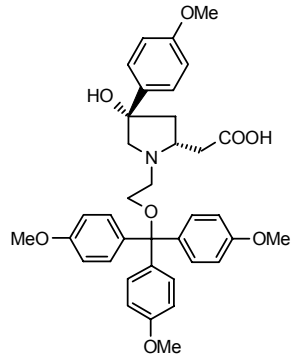
According to GP7-B from 39 mg (0.079 mmol) of (2*S*,4*R*)-**93c** and 0.32 ml (0.32 mmol) of aq. 1.0 M NaOH in 2 ml of MeOH; purification by CC (ϕ 12 × 70, MeOH). Yield: 36 mg (95%); yellow oil. – $[\alpha]_D^{20}$ = -53.8 (c = 1.03, MeOH). – ^{1}H NMR (CD$_3$OD): δ = 1.87 (ddd, J = 13.9/11.0/5.6 Hz, 1 H, CH_2CHCH$_2$COO), 1.98 (s, 3 H, thienyl-CH_3), 2.01 (s, 3 H, thienyl-CH_3), 2.35 (dd, J = 13.9/6.3 Hz, 1 H, CH_2CHCH$_2$OO), 2.46-2.60 (m, 4 H, NCH$_2$CH_2 and CH_2COO), 2.92-2.98 (m, 2 H, NCH_2CHO and NCH_2CH$_2$), 3.32-3.38 (m, 1 H, NCH_2CH$_2$), 3.57-3.67 (m, 2 H, NCH_2CHO and NCH), 4.20-4.23 (m, 1 H, NCH$_2$CHO), 4.46 (d, J = 11.8 Hz, 1 H, CH_2Ph), 4.54 (d, J = 11.8 Hz, 1 H, CH_2Ph), 6.05 (t, J = 7.4 Hz, 1 H, =CHCH$_2$), 6.77 (d, J = 5.2 Hz, 1 H, SCH), 6.89 (d, J = 5.2 Hz, 1 H, SCH), 7.15 (d, J = 5.2 Hz, 1 H, SCH=CH), 7.25-7.37 (m, 6 H, H$_{aromat}$). – IR: $\tilde{\nu}$ = 3407, 3056, 3021, 2922, 1592, 1093, 698 cm^{-1}. – MS; *m/z* (%): 482 (49) [M+1]$^+$, 422 (10), 336 (40), 248 (100), 91 (35). – $C_{27}H_{31}NO_3S_2$ (481.68)·1.0 H_2O: calcd. C 64.90, H 6.70, N 2.80; found C 64.70, H 6.37, N 2.90.

(2*S*,4*R*)-4-Hydroxy-4-(4-methoxyphenyl)-1-{2-[tris(4-methoxyphenyl)methoxy]-1-ethyl}-pyrrolidine-2-acetic acid [(2*S*,4*R*)-104b]



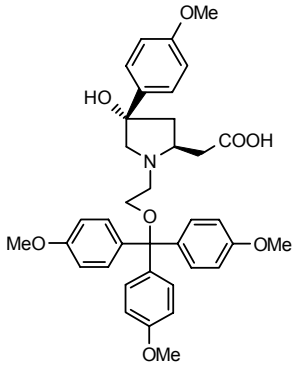
According to GP7-A from 115 mg (0.179 mmol) of (2*S*,4*R*)-**102b**, 0.54 ml (0.54 mmol) of aq. 1.0 M NaOH in 4.5 ml of MeOH; reaction time: 48 h; purification by recrystallization from C_6H_6/*i*Pr_2O. Yield: 97 mg (86%); colorless powder. – M.p. 106-111 °C (C_6H_6/*i*Pr_2O). – $[\alpha]_D^{20}$ = -20.5 (*c* = 0.81, MeOH). – ^{1}H NMR (CD_3OD, 500 MHz): δ = 2.19 (ddd, *J* = 14.1/6.0/1.4 Hz, 1 H, C*H*$_2$CHCH_2COO), 2.70 (dd, *J* = 16.5/4.1 Hz, 1 H, CH_2COO), 2.74-2.82 (m, 2 H, C*H*$_2$CHCH_2COO and C*H*$_2$COO), 3.19-3.25 (m, 1 H, NC*H*$_2$CH_2), 3.33 (d, *J* = 11.1 Hz, NCH_2CO), 3.44-3.49 (m, 3 H, NC*H*$_2$CO and 2 H of NCH_2C*H*$_2$), 3.62-3.67 (m, 1 H, NC*H*$_2$CH_2), 3.74 (s, 9 H, Ar'OC*H*$_3$), 3.78 (s, 3 H, ArOC*H*$_3$), 3.87-3.93 (m, 1 H, NCH), 6.83-6.86 (m, 6 H, H_{aromat}), 6.89-6.92 (m, 2 H, H_{aromat}), 7.31-7.38 (m, 8 H, H_{aromat}). – IR: $\tilde{\nu}$ = 3421, 3037, 2956, 1608, 1580, 1508, 1251, 1176, 1034, 829 cm^{-1}. – MS (ESI$^+$): *m*/*z* (%): 628 $(M+1)^+$ (51), 333 (100). – $C_{37}H_{41}NO_8$ (627.74)·0.7 H_2O: calcd. C 69.40, H 6.67, N 2.19; found C 69.45, H 6.94, N 2.19.

(2*R*,4*S*)-4-Hydroxy-4-(4-methoxyphenyl)-1-{2-[tris(4-methoxyphenyl)methoxy]-1-ethyl}-pyrrolidine-2-acetic acid [(2*R*,4*S*)-104b]



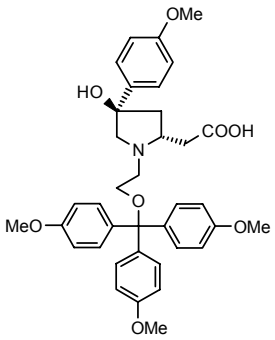
According to GP7-A from 125 mg (0.191 mmol) of (2*R*,4*S*)-**103b**, 0.58 ml (0.58 mmol) of aq. 1.0 M NaOH in 6.4 ml of MeOH; reaction time: 48 h; purification by CC (ϕ 18 × 120; MeOH-H_2O, 4:1) and recrystallization from C_6H_6/*i*Pr_2O. Yield: 107 mg (89%); colorless crystal. – M.p. 116-122 °C (C_6H_6/*i*Pr_2O). – $[\alpha]_D^{20}$ = +20.3 (*c* = 0.69, MeOH). The spectra (^{1}H NMR, IR, and MS) were identical with those of (2*S*,4*R*)-**104b**. – $C_{37}H_{41}NO_8$ (627.74)·0.6 H_2O: calcd. C 69.60, H 6.66, N 2.19; found C 69.50, H 6.75, N 2.08.

(2*S*,4*S*)-4-Hydroxy-4-(4-methoxyphenyl)-1-{2-[tris(4-methoxyphenyl)methoxy]-1-ethyl}-pyrrolidine-2-acetic acid [(2*S*,4*S*)-104b]



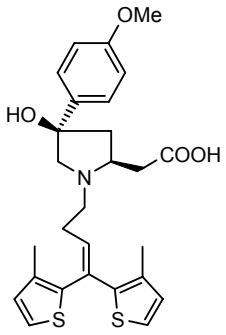
According to GP7-A from 70 mg (0.11 mmol) of (2*S*,4*S*)-**102b**, 0.33 ml (0.33 mmol) of aq. 1.0 M NaOH in 2.7 ml of MeOH; reaction time: 48 h; purification by CC (ϕ 12 × 90; MeOH-H_2O, 4:1) and recrystallization from C_6H_6/*i*Pr_2O. Yield: 50 mg (73%); colorless powder. – M.p. 117-121 °C (C_6H_6/*i*Pr_2O). – $[\alpha]_D^{20}$ = -9.4 (*c* = 0.50, MeOH). – ^{1}H NMR (CD_3OD): δ = 2.28-2.42 (m, 2 H, C*H*$_2$CHCH$_2$COO), 2.46 (dd, *J* = 16.9/1.5 Hz, 1 H, CH$_2$COO), 2.85 (dd, *J* = 16.9/5.1 Hz, CH$_2$COO), 3.23 (dd, *J* = 12.4/1.5 Hz, 1 H, NCH$_2$CO), 3.30-3.34 (m, 1 H, NC*H*$_2$CH$_2$), 3.38 (d, *J* = 12.4 Hz, 1 H, NCH$_2$CO), 3.43-3.68 (m, 3 H, NC*H*$_2$CH$_2$ and 2 H of NCH$_2$C*H*$_2$), 3.74 (s, 9 H, Ar'OC*H*$_3$), 3.79 (s, 3 H, ArOC*H*$_3$), 4.05-4.12 (m, 1 H, NCH), 6.84-6.88 (m, 6 H, H_{aromat}), 6.90-6.94 (m, 2 H, H_{aromat}), 7.31-7.37 (m, 8 H, H_{aromat}). – IR: $\tilde{\nu}$ = 3422, 3037, 2957, 1608, 1509, 1251, 1177, 1034, 829 cm^{-1}. – MS (ESI$^+$); *m*/*z* (%): 628 [M+1]$^+$ (26) 333 (100). – $C_{37}H_{41}NO_8$ (627.74)·0.8 H_2O: calcd. C 69.21, H 6.69, N 2.18; found C 69.22, H 6.78, N 2.02.

(2*R*,4*R*)-4-Hydroxy-4-(4-methoxyphenyl)-1-{2-[tris(4-methoxyphenyl)]methoxy-1-ethyl}pyrrolidine-2-acetic acid [(2*R*,4*R*)-104b]



According to GP7-A from 42 mg (0.065 mmol) of (2*R*,4*R*)-**103b**, 0.20 ml (0.20 mmol) of aq. 1.0 M NaOH in 3 ml of MeOH; reaction time: 2 d; purification by recrystallization from C_6H_6/*i*Pr_2O. Yield: 38 mg (93%); colorless powder. – M.p. 110-117 °C (C_6H_6/*i*Pr_2O). – $[\alpha]_D^{20}$ = +9.5 (*c* = 0.62, MeOH). The spectra [^{1}H NMR (500 MHz), IR, and MS] were identical with those of (2*S*,4*S*)-**104b**. – $C_{37}H_{41}NO_8$ (627.74)·0.9 H_2O: calcd. C 69.01, H 6.67, N 2.18; found C 68.85, H 6.56, N 2.21.

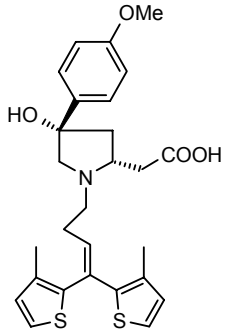
(2*S*,4*R*)-1-[4,4-Di(3-methyl-2-thienyl)but-3-en-1-yl]-4-hydroxy-4-(4-methoxyphenyl)-pyrrolidine-2-acetic acid [(2*S*,4*R*)-104c]



According to GP7-A from 83 mg (0.16 mmol) of (2*S*,4*R*)-**102c**, 0.49 ml (0.49 mmol) of aq. 1.0 M NaOH in 4.5 ml of MeOH; reaction time: 3 d; purification by CC (ϕ 12 × 110, MeOH) and recrystallization from C_6H_6/*i*Pr_2O. Yield: 56 mg (70%); colorless powder. – M.p. 73-76 °C (C_6H_6/*i*Pr_2O). – $[\alpha]_D^{20}$ = -37.9 (*c* = 0.61, MeOH). – ^{1}H NMR (CD_3OD, 500 MHz): δ = 1.96 (s, 3 H, thienyl-C*H*$_3$), 2.02 (s, 3 H, thienyl-C*H*$_3$), 2.13-2.18 (m, 1 H, C*H*$_2$CHCH$_2$COO), 2.60 (q, *J* = 7.4 Hz, 2 H, NCH$_2$C*H*$_2$), 2.69-2.81 (m, 3 H, C*H*$_2$CHCH$_2$COO and 2 H of C*H*$_2$COO), 3.08-3.12 (m, 1 H, NC*H*$_2$CH$_2$), 3.18-3.22 (m, 1 H, NCH$_2$CO), 3.54-3.62 (m, 2 H, NC*H*$_2$CH$_2$ and NC*H*$_2$CO), 3.77 (s, 3 H, ArOC*H*$_3$), 3.86-3.90 (m, 1 H, NCH), 6.04 (t, *J* = 7.4 Hz, 1 H, =C*H*CH$_2$), 6.78 (d, *J* = 5.2 Hz, 1 H, SCH), 6.88-6.93 (m, 3 H, SC*H* and 2 H of

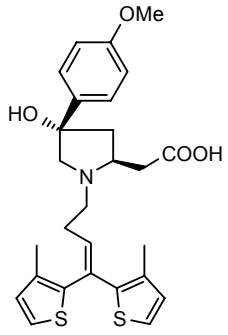
H_{aromat}), 7.16 (d, *J* = 5.2 Hz, 1 H, SCH=C*H*), 7.34 (d, *J* = 5.2 Hz, 1 H, SCH=C*H*), 7.38-7.40 (m, 2 H, H_{aromat}). – IR: $\tilde{\nu}$ = 3385, 3102, 2953, 1609, 1515, 1400, 1251, 1034, 832, 714 cm^{-1}. – MS; *m*/*z* (%): 498 (100) $[M+1]^+$, 480 (47), 434 (62), 276 (12), 186 (13). – $C_{27}H_{31}NO_4S_2$ (497.67)·0.5 H_20: calcd. C 64.00, H 6.37, N 2.76; found C 63.84, H 6.67, N 2.54.

(2*R*,4*S*)-1-[4,4-Di(3-methyl-2-thienyl)but-3-en-1-yl]-4-hydroxy-4-(4-methoxyphenyl)-pyrrolidine-2-acetic acid [(2*R*,4*S*)-104c]



According to GP7-A from 87 mg (0.17 mmol) of (2*R*,4*S*)-**103c**, 0.50 ml (0.50 mmol) of aq. 1.0 M NaOH in 4.5 ml of MeOH; reaction time: 2 d; purification by recrystallization from C_6H_6/*i*Pr_2O. Yield: 68 mg (82%); slightly yellow powder. – M.p. 69-73 °C (C_6H_6/*i*Pr_2O). – $[\alpha]_D^{20}$ = +34.0 (*c* = 0.85, MeOH). The spectra [^{1}H NMR (500 MHz), IR, and MS] were identical with those of (2*S*,4*R*)-**104c**. – $C_{27}H_{31}NO_4S_2$ (497.67)·0.6 H_2O: calcd. C 63.78, H 6.38, N 2.75, S 12.61; found C 63.60, H 6.38, N 2.67, S 12.43.

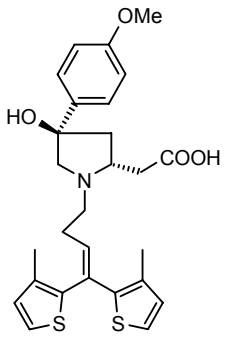
(2*S*,4*S*)-1-[4,4-Di(3-methyl-2-thienyl)but-3-en-1-yl]-4-hydroxy-4-(4-methoxyphenyl)-pyrrolidine-2-acetic acid [(2*S*,4*S*)-104c]



According to GP7-A from 60 mg (0.12 mmol) of (2*S*,4*S*)-**102c**, 0.35 ml (0.35 mmol) of aq. 1.0 M NaOH in 3.6 ml of MeOH; reaction time: 3 d; purification by recrystallization from

C_6H_6/*i*Pr_2O. Yield: 57 mg (98%); colorless powder. – M.p. 73-76 °C (C_6H_6/*i*Pr_2O). – $[\alpha]_D^{20}$ = -38.6 (*c* = 0.70, MeOH). – ^{1}H NMR (CD_3OD, 500 MHz): δ = 1.98 (s, 3 H, thienyl-C*H*$_3$), 2.03 (s, 3 H, thienyl-C*H*$_3$), 2.24-2.31 (m, 1 H, C*H*$_2$CHCH$_2$COO), 2.39 (ddd, *J* = 13.3/6.0/1.9 Hz, 1 H, C*H*$_2$CHCH$_2$COO), 2.51 (dd, *J* = 16.7/2.3 Hz, 1 H, CH$_2$COO), 2.61 (q, *J* = 7.4 Hz, 2 H, NCH$_2$C*H*$_2$), 2.79 (dd, *J* = 16.7/5.8 Hz, CH$_2$COO), 3.25-3.31 (m, 2 H, NC*H*$_2$CH$_2$ and NC*H*$_2$CO), 3.52-3.61 (m, 1 H, NC*H*$_2$CH$_2$), 3.64 (d, *J* = 12.4 Hz, 1 H, NCH$_2$CO), 3.77 (s, 3 H, ArOC*H*$_3$), 4.05-4.12 (m, 1 H, NCH), 6.07 (t, *J* = 7.4 Hz, 1 H, =C*H*CH$_2$), 6.77 (d, *J* = 5.2 Hz, 1 H, SCH), 6.89-6.92 (m, 3 H, SC*H* and 2 H of H_{aromat}), 7.15 (d, *J* = 5.2 Hz, 1 H, SCH=C*H*), 7.34-7.39 (m, 3 H, SCH=C*H* and H_{aromat}). – IR: $\tilde{\nu}$ = 3420, 3102, 2926, 1610, 1514, 1382, 1250, 1034, 833, 715 cm^{-1}. – MS: *m*/*z* (%): 498 (17) $[M+1]^+$, 480 (20), 420 (53), 412 (34), 264 (62), 236 (95), 178 (41), 146 (100), 128 (35). – $C_{27}H_{31}NO_4S_2$ (497.67)·0.5 H_20: calcd. C 64.00, H 6.37, N 2.76; found C 64.27, H 6.59, N 2.47.

(2*R*,4*R*)-1-[4,4-Di(3-methyl-2-thienyl)but-3-en-1-yl]-4-hydroxy-4-(4-methoxyphenyl)-pyrrolidine-2-acetic acid [(2*R*,4*R*)-104c]



According to GP7-A from 61 mg (0.12 mmol) of (2*R*,4*R*)-**103c**, 0.35 ml (0.35 mmol) of aq. 1.0 M NaOH in 4 ml of MeOH; reaction time: 2 d; purification by recrystallization from C_6H_6/*i*Pr_2O. Yield: 55 mg (95%); slight yellow powder. – M.p. 70-74 °C (C_6H_6/*i*Pr_2O). – $[\alpha]_D^{20}$ = +40.1 (*c* = 0.7, MeOH). The spectra [^{1}H NMR (500 MHz), IR, and MS] were identical with those of (2*S*,4*S*)-**104c.** – $C_{27}H_{31}NO_4S_2$ (497.67)·0.9 H_2O: calcd. C 65.11, H 6.43, N 2.73; found C 65.09, H 6.24, N 2.64.

6.1.10 Miscellaneous

Methyl (2S,4R)-4-hydroxy-1-triphenylmethylpyrrolidine-2-carboxylate [(2S,4R)-49] [45]

1.00 g (5.51 mmol) of (2*S*,4*R*)-**38** was dissolved in 55 ml of CH_2Cl_2 containing 1.34 g (13.3 mmol) of TEA to give a clear solution, and then 1.54 g (5.51 mmol) of TrCl was added at 0~5 °C. After the mixture had been stirred at this temperature for 20 min, the organic layer was washed with H_2O (3 × 60 ml), dried (Na_2SO_4), and evaporated to give a viscous oil, which was recrystallized from 4 ml of *i*Pr_2O and 8 ml of petroleum ether. Yield: 2.03 g (95%); colorless crystals. – M.p. 139-142 °C. – $[\alpha]_D^{20}$ = -26.2 (*c* = 1.01, MeOH) {ref. [45]: M.p: 144-145 °C; $[\alpha]_D^{30}$ = -24.2 (*c* = 1.00, MeOH)}.

(2*R*,4*R*)-1-Benzyloxycarbonyl-4-hydroxypyrrolidine-2-carboxylic acid [(2*R*,4*R*)-58]

As described by ref. [61] from 7.41 g (56.6 mmol) of (2*R*,4*R*)-**25** in 28 ml (57 mmol) of aq. 2.0 M NaOH, 7.98 ml (9.62 g, 56.6 mmol) of CbzCl and 28 ml (57 mmol) of aq. 2.0 M NaOH. Yield: 12.0 g (80%); colorless crystals. – M.p. 106-110 °C. – $[\alpha]_D^{22}$ = +27.1 (*c* = 1.00, $CHCl_3$) {ref. [41]: M.p. 110.5-11.5 °C (EtOAc/petroleum ether); $[\alpha]_D^{20}$ = +26.3 (*c* = 1.0, $CHCl_3$)}.

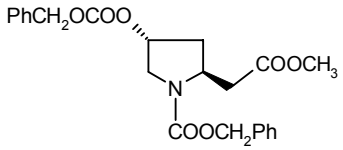
Methyl (2*S*,4*R*)-1-benzyloxycarbonyl-4-hydroxypyrrolidine-2-carboxylate [(2*S*,4*R*)-59]

As described by ref. [62, 63]: To a solution of 1.86 g (7.00 mmol) of (2*S*,4*R*)-**58** in 25 ml of EtOAc, 3.0 g (7.2 mmol) of CH_2N_2 in 20 ml of Et_2O was slowly added at 0 °C until yellow color persisted in 15 min. Excessive CH_2N_2 was decomposed by slow addition of AcOH. This solution was washed with aq. 0.1% K_2CO_3, dried ($MgSO_4$), and evaporated. Yield: 1.80 g (95%); colorless oil. – $[\alpha]_D^{20}$ = -58.0 (*c* = 0.90, $CHCl_3$) {ref. [37]: $[\alpha]_D^{20}$ = -58.8 (*c* = 1.04, $CHCl_3$)}.

Methyl (2*R*,4*R*)-1-benzyloxycarbonyl-4-hydroxypyrrolidine-2-carboxylate [(2*R*,4*R*)-59] [88]

As described by ref. [62, 63]: 1.86 g (7.00 mmol) of (2*R*,4*R*)-**58** in 30 ml of CH_2Cl_2 was esterified at 0 °C by 3.0 g (7.2 mmol) of CH_2N_2 in 20 ml of Et_2O. Yield: 1.97 g (100%); colorless crystals. – M.p. 82-84 °C. – $[\alpha]_D^{20}$ = +39.5 (*c* = 1.00, $CHCl_3$).

Methyl (2*S*,4*R*)-1-benzyloxycarbonyl-4-hydroxypyrrolidine-2-acetate [(2*S*,4*R*)-95][74] **and methyl (2*S*,4*R*)-1-benzyloxycarbonyl-4-(benzyloxycarbonyl)oxypyrrolidine-2-acetate [(2*S*,4*R*)-82]**



(**2*S*,4*R*)-82**

According to ref. [89, 90]: To a solution of 525 mg (2.68 mmol) of (2*S*,4*R*)-**86** and 1.08 g (8.87 mmol) of DMAP in 20 ml of CH_2Cl_2, 688 mg (4.03 mmol) of CbzCl was added at – 23 °C. This solution was continued to stir for 48 h, and then washed with H_2O, dried ($MgSO_4$) and evaporated. The residual oil was purified by CC (ϕ 25 × 220; *n*-heptane/acetone, 3:1) to yield (2*S*,4*R*)-**95** and (2*S*,4*R*)-**82**.

(2*S*,4*R*)-**95**: 462 mg (59%); $[\alpha]_D^{20}$ = -55.3 (*c* = 1.21, $CHCl_3$); colorless oil.

(2*S*,4*R*)-**82**: 184 mg (17%); colorless oil. – TLC: R_f = 0.42 (*n*-heptane/acetone, 3:2). – $[\alpha]_D^{20}$ = -43.0 (*c* = 0.90, EtOAc). – ^{1}H NMR ($C_6D_5NO_2$, 120 °C): δ = 2.25-2.32 (m, 1 H, C*H*$_2$CHCH$_2$COO), 2.49-2.56 (m, 1 H, C*H*$_2$CHCH$_2$COO), 2.68 (dd, *J* = 15.4/8.6 Hz, 1 H, CH$_2$COO), 3.06 (dd, *J* = 15.4/3.9 Hz, 1 H, CH$_2$COO), 3.66 (s, 3 H, OCH$_3$), 3.79 (dd, *J* = 12.4/5.4 Hz, 1 H, NCH$_2$), 3.98 (dt, *J* = 12.4/2.0 Hz, 1 H, NCH$_2$), 4.45-4.52 (m, 1 H, NCH), 5.22 (s, 4 H, C*H*$_2$Ph), 5.31-5.35 (m, 1 H, NCH$_2$C*H*O), 7.23-7.40 (m, 10 H, H$_{aromat}$). – IR: $\tilde{\nu}$ = 3034, 2954, 1738, 1704, 1416, 1265, 1230, 753, 698 cm^{-1}. – MS; *m*/*z* (%): 428 (12) [M+1]$^+$, 384 (14), 186 (15), 181 (13), 158 (10), 140 (39), 91 (100). – $C_{22}H_{25}NO_7$ (427.45): calcd. C 64.63, H 5.89, N 3.28; found C 65.01, H 5.84, N 3.17.

(2*S*,4*R*)-1-Benzyloxycarbonyloxy-4-(bezyloxycarbonyl)oxypyrrolidine-2-carboxylic acid [(2*S*,4*R*)-81] [91]

To a solution of 1.62 g (6.11 mmol) of (2*S*,4*R*)-**58** in 40 ml of THF, 490 mg (12.2 mmol) of NaH (55~60% in oil) was added at r.t. The resulting mixture was stirred for 1.5 h and then

1.15 g (6.73 mmol) of CbzCl was added at 0 °C. The reaction mixture was stirred at r.t. for 20 h, quenched with ice-water, acidified with aq. 2 N HCl to pH 1~2, and extracted (Et_2O). The extract was dried (Na_2SO_4) and concentrated. Yield: 1.45 g (59%); colorless oil.

Methyl (2*S*,4*R*)-1-Benzyloxycarbonyl-4-(benzyloxycarbonyl)oxypyrrolidine-2-acetate [(2*S*,4*R*)-82]

To a solution of 1.05 g (2.63 mmol) of (2*S*,4*R*)-**81** and 8 µl of DMF in 8 ml of CH_2Cl_2, 502 mg (3.95 mmol) of $(COCl)_2$ was added at 0 °C. After 20 min, the solution was stirred at r.t for 1 h. The solvent was removed in vacuo to give the acid chloride as colorless oil. The above acid chloride in 8 ml of Et_2O was slowly added to 365 mg (8.30 mmol) of CH_2N_2 in 35 ml of Et_2O at 0 °C. After 1 h, the excessive CH_2N_2 was decomposed with AcOH, and then the reaction mixture was evaporated to give yellow oil. Purification by CC (ϕ 25 × 300; *iso*-hexane/acetone, 3:1) yielded 210 mg (19%) of the diazoketone as yellow oil.

To a solution of 200 mg (0.473 mmol) of the above diazoketone in 1.0 ml of MeOH, a solution of 10 mg (0.06 mmol) of silver acetate and 37 mg (0.36 mmol) of TEA in 1.0 ml of MeOH was added at r.t. The new solution turned to be brown in several minutes, and then was warmed to 60 °C in 50 min, finally decolorized with active carbon. The reaction mixture was concentrated to yellow oil. Purification by CC (ϕ 18 × 340; *n*-heptane/acetone, 3:1). Yield: 110 mg (59%); colorless oil. All analytical data were identical with the about product prepared from (2*S*,4*R*)-**86**.

6.2 Biological experiments:

6.2.1 The Subcellular fractions from frontal cortex and brain stem

Subcellular fractions of frontal cortex and brain stem were obtained from freshly bovine brains according to a known procedure that has been slightly modified [92]. 10 g of each region (frontal cortex or brain stem) were homogenized in 100 ml of 0.32 M sucrose with a potter (PotterS 800 rpm, 12 up-and-down strokes) and then centrifuged at 3000 × *g* for 10 min in a Sorvall SS34 rotor. The supernatant was diluted with 0.32 M sucrose to 140 ml. 6 Aliquots of the resulting suspension were layered on 1.2 M sucrose. Centrifugation at 257 000 × *g* for 16 min in a Hitachi P70AT rotor gave a pellet, termed P2A. The interphase at the gradient was collected and then diluted with 0.32 M sucrose to 140 ml. 6 Aliquots of the resulting suspension were layered on 1.2 M sucrose 12 ml of 0.8 M sucrose. Centrifugation as described above yielded a pellet, termed P2B. The interphase at the gradient was collected and diluted again with 0.32 M sucrose. Centrifugation as above yielded a pellet, termed P2C. All the above procedures were carried out at 4 °C.

P2B from bovine frontal cortex (= bfcP2B) and P2C from bovine brain stem (= bbsP2C) were suspended in buffer I (119 mM NaCl, 2.5 mM $CaCl_2$, 1.2 mM $MgSO_4$, 1.2 mM KH_2PO_4, 4.7 mM KCl, 11 mM Glucose and 25 mM Tris HCl pH 7.2) or buffer II (2.5 mM $CaCl_2$ 1.2 mM $MgSO_4$, 1.2 mM KH_2PO_4, 4.7 mM KCl, 11 mM Glucose and 144 mM Tris HCl pH 7.2). The protein concentration was determined with bovine serum albumin as a standard as described by *Bradford* [93].

The preparations of P2B from frontal cortex and P2C from brain stem using porcine brains or calf brains were completely performed in the same way as above. The final membrane fractions for uptake experiments were termed as follows:

bfcP2B (P2B from bovine frontal cortex), cfcP2B (P2B from frontal cortex), pfcP2B (from porcine frontal cortex);

bbsP2C (P2C from bovine brain stem), cbcP2C (P2C from calf brain stem), pbsP2C (from porcine brain stem).

6.2.2 Inhibition of GABA-uptake

6.2.2.1 Inhibition of GAT-1 mediated GABA-uptake

Aliquots of about 50-100 µg protein bfcP2B (alternatively cfcP2B or pfcP2B) were preincubated with 10 µM aminooxyacetic acid and a test compound in 200 µl of buffer I for 10 min at 37 °C. After the addition of 25 µl of 12.5 nM [^{3}H] GABA and 25 µl of 250 nM GABA, the sample was incubated at 37 °C for 4 min. Then the incubation was terminated by the filtration in a Brandel M-24R Harvester through Whatman GF/C filters, which had been immersed in 0.9% NaCl for 1 h. The filters were washed with 0.9% NaCl (4 × 2 ml) and then measured in 3 ml of Rotiszint Eco Plus by the use of a Packard TriCarb 1600 Counter. Specific uptake was defined as difference between entire-uptake and non-specific uptake, which was determined with identical samples lacking NaCl (buffer II).

6.2.2.2 Inhibition of GAT-3 mediated GABA-uptake

Aliquots of about 50-100 µg protein bbsP2C (alternatively cbsP2C or pbsP2C) were preincubated with 10 µM aminooxyacetic acid, 10 µM NNC-711 and a test compound in 200 µl of buffer I for 10 min at 37 °C. After the addition of 25 µl of 50 nM [^{3}H] GABA and 25 µl of 1 µM GABA, the sample was incubated at 37 °C for 4 min. Then the incubation was terminated by the filtration in a Brandel M-24R Harvester through Whatman GF/C filters, which had been immersed in 0.9% NaCl for 1 h. The filters were washed with 0.9% NaCl (4 × 2 ml) and then measured in 3 ml of Rotiszint Eco Plus by the use of a Packard TriCarb 1600 Counter. Specific uptake was defined as difference between entire-uptake and non-specific uptake, which was determined with identical samples lacking NaCl (buffer II).

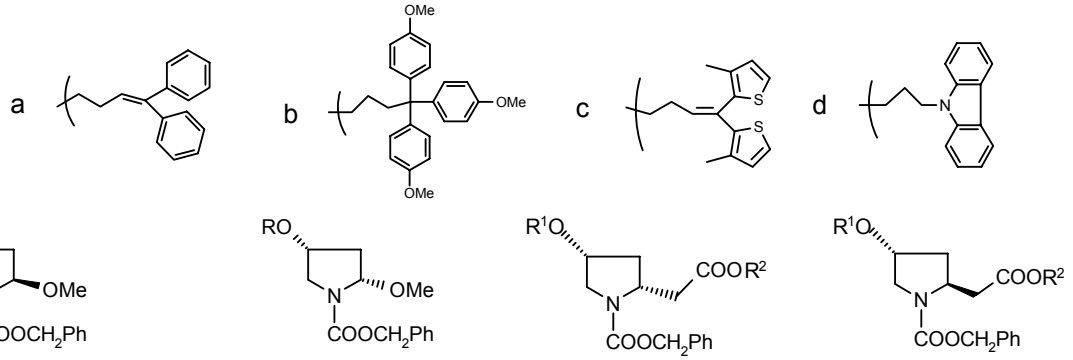
6.2.3 Evaluation

IC_{50} values were calculated by nonlinear regression analysis using Prism 2 (GraphPad Software ^{TM}). All the results were given as means ± SEM from three experiments if not stated otherwise.

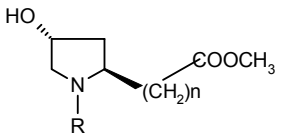
7 SRUCTURE LIST OF NEW COMPOUNDS AND MAIN SYNTHETIC ROUTES

7.1 List of new compounds:

All the compounds in my thesis listed below were synthesized at the first time and their page numbers where they are mentioned rank below. The suffix of each compound number respectively represents the following residues **a-d** if not illustrated otherwise.



R = H	R = H	R^1 = Cbz, R^2 = Et	R^1 = Cbz, R^2 = Me
(**2*S*,4*R*)-69** 30,33-34,85,87	(**2*R*,4*R*)-69** 30,33-34,85,87	(**2*R*,4*R*)-80** 33-34,59-60, 92	(**2*S*,4*R*)-82** 35 43,59,181
R = Cbz-	R = Cbz-	R^1 = TBDMS- R^2 = Et	R^1 = TBDMS- R^2 = Et
(**2*S*,4*R*)-77** 33-34, 87-88	(**2*R*,4*R*)-77** 33-34, 87-88	(**2*S*,4*R*)-71** 31-32, 89-92	(**2*R*,4*R*)-71** 31-32, 89-92
R = TBDMS-	R = TBDMS-	R^1 = H R^2 = Et	
(**2*S*,4*R*)-70** 30-31, 86-87	(**2*R*,4*R*)-70** 30-31, 86-87	(**2*R*,4*R*)-73** 32, 43-44, 51-52	



n = 0

(**2*S*,4*R*)-39a** 12, 15, 20, 101-102, 156

(**2*S*,4*R*)-39b** 12, 15, 20, 102-123, 158

n = 1

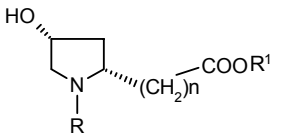
(**2*S*,4*R*)-86** (R = -H·HCl) 36, 40, 43, 58, 96, 107-109, 181

(**2*S*,4*R*)-91a** 40-41, 46, 107, 125, 166

(**2*S*,4*R*)-91b** 40-41, 46, 108, 125, 168

(**2*S*,4*R*)-91c** 40-41, 46, 108, 127, 171

(**2*S*,4*R*)-91d** 40-41, 109, 173



n = 0, R^1 = Me

(**2*R*,4*R*)-39a** 14, 15, 20, 102, 113, 122, 157

(**2*R*,4*R*)-39b** 14, 15, 20, 103, 113, 123, 159

n = 1 R^1 = Et

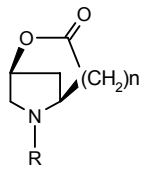
(**2*R*,4*R*)-64** (R = -H·HCl) 28,32,37,58, 93, 104-107

(**2*R*,4*R*)-88a** 37-39, 104, 114, 165

(**2*R*,4*R*)-88b** 37, 39, 46, 105, 115, 125, 167

(**2*R*,4*R*)-88c** 37, 39, 46, 106, 115, 127, 169

(**2*R*,4*R*)-88d** 37, 39, 107, 116, 171



n = 0

(**1*S*,4*S*)-41a** 13, 15, 112, 158

n = 1

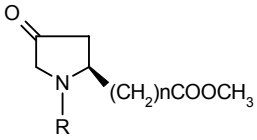
(**1*S*,5*S*)-92a** 40-41, 117, 165

(**1*S*,5*S*)-92b** 40-41, 117, 167

(**1*S*,5*S*)-92c** 40-41, 118, 170

(**1*S*,5*S*)-92d** 40-41, 119, 172

(**1*S*,5*S*)-98** (R = -Cbz) 44, 119, 148



n = 0

(**2*S*)-50** (R = -Tr) 18, 121, 131

(**2*S*)-52a** 20-24, 27, 48, 53, 55, 122, 132-134

(**2*S*)-52b** 20-23, 27, 48, 53, 123, 135-136

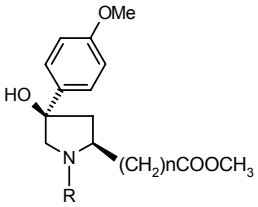
n = 1

(**2*S*)-100a** 46-47, 50, 125

(**2*S*)-100b** 46-48, 125, 139-140

(**2*S*)-100c** 46-48, 127, 142-143

(**2*S*)-108** (R = -Cbz) 51, 128, 145



n = 0

(**2*S*,4*R*)-51** (R = -Tr) 19, 131

(**2*S*,4*R*)-53a** 21-25, 53, 55-57, 104, 132-134, 162

(**2*S*,4*R*)-53b** 21-25, 53, 135-136, 162

(**2*S*,4*R*)-61** (R = -Cbz) 26-27, 54, 57, 137, 147

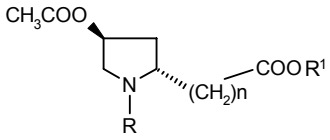
(**2*S*,4*R*)-114** (R = -H) 54-55, 104, 152

n = 1

(**2*S*,4*R*)-102b** 47-49, 139-140, 175

(**2*S*,4*R*)-102c** 47-49, 142-143, 177

(**2*S*,4*R*)-109** (R = -Cbz) 51, 62-64, 145, 149, 155



n = 0, R^1 = Me

(**2*R*,4*S*)-48a** 15, 113, 157

(**2*R*,4*S*)-48b** 15, 113, 159

n = 1, R^1 = Et

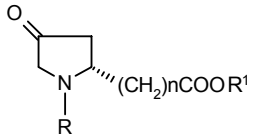
(**2*R*,4*S*)-90a** 37, 39, 114, 166

(**2*R*,4*S*)-90b** 37, 39, 115, 168

(**2*R*,4*S*)-90c** 37, 39, 115, 170

(**2*R*,4*S*)-90d** 37, 39, 116, 172

(**2*R*,4*S*)-99** [R = -Cbz , (4*S*)-HCOO] 44,45,120,149



n = 0, R^1 = Me

(**2*R*)-52a** 20-22, 53, 122-123, 135-136

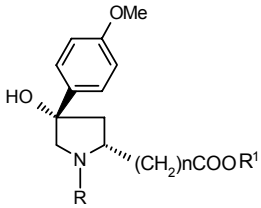
(**2*R*)-52b** 20-22, 53, 123-124, 136-137

n = 1, R^1 = Et

(**2*R*)-101b** 46-48, 126, 140-142

(**2*R*)-101c** 46-48, 127, 143-145

(**2*R*)-112** (R = -Cbz) 51-52, 128, 146



n = 0, R^1 = Me

(**2*R*,4*S*)-53a** 21-22, 53, 134-135, 162

(**2*R*,4*S*)-53b** 21-22, 53, 136-137, 163

(**2*R*,4*S*)-61** (R = -Cbz) 57, 138, 147

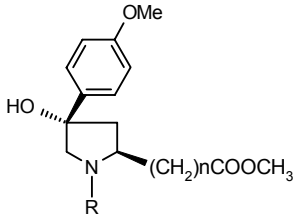
n = 1, R^1 = Et

(**2*R*,4*S*)-102b** 47-49, 140-142, 175

(**2*R*,4*S*)-102c** 47-49, 143-145, 178

(**2*R*,4*S*)-113** (R = -Cbz) 51-52, 146, 150

(**2*S*,4*R*)-115** (R = -H) 61, 63, 111, 155



n = 0

(**2*S*,4*S*)-51** (R = -Tr) 19, 131

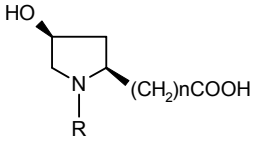
(**2*S*,4*S*)-53a** 21-25, 53, 56-57, 132-134, 166

(**2*S*,4*S*)-53b** 21-25, 53, 135-136, 163

n = 1

(**2*S*,4*S*)-102b** 47-49, 139-140, 176

(**2*S*,4*S*)-102c** 47-49, 142-143, 178



n = 0

(**2*S*,4*S*)-40a** 12-13, 15-17, 158

(**2*S*,4*S*)-40b** 12-13, 15, 17, 160

n = 1

(**2*S*,4*S*)-89a** 40-42, 165

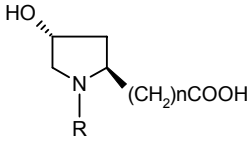
(**2*S*,4*S*)-89b** 40-41, 167

(**2*S*,4*S*)-89c** 40-41, 169-170

(**2*S*,4*S*)-89d** 40-41, 172

(**2*S*, 4*S*)-96** (R = -Cbz) 44**,** 148, 153-154

(**2*S*,4*S*)- 97** (R = -H) 44-45, 153-154



n = 0

(**2*S*,4*R*)-40a** 12-13, 15-17, 112, 156

(**2*S*,4*R*)- 40b** 12-13, 15-17, 158, 160

n = 1

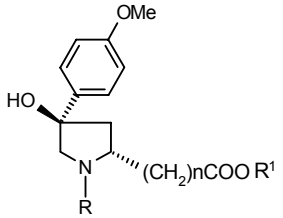
(**2*S*,4*R*)-89a** 40-42, 117, 166

(**2*S*,4*R*)-89b** 40-41, 117-118, 168-169

(**2*S*,4*R*)-89c** 40-41, 118-119, 171

(**2*S*,4*R*)-89d** 40-41, 119, 173

(**2*S*,4*R*)-97** (R = -H) 44-45, 152



n = 0, R^1 = Me

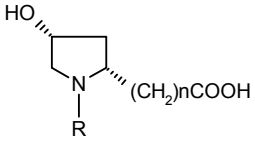
(**2*R*,4*R*)-53a** 21-22, 53, 134-135, 161

(**2*R*,4*R*)-53b** 21-22, 53, 136, 137, 164

n = 1, R^1 = Et

(**2*R*,4*R*)-103b** 47, 49, 140-142, 176-177

(**2*R*,4*R*)-103c** 47, 49, 143-145, 179



n = 0

(**2*R*,4*R*)-40a** 14-15, 157

(**2*R*,4*R*)-40b** 14-15, 159

n = 1

(**2*R*,4*R*)-89a** 37-39, 165

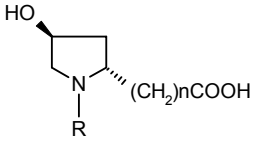
(**2*R*,4*R*)-89b** 37, 39, 167

(**2*R*,4*R*)-89c** 37, 39, 169

(**2*R*,4*R*)-89d** 37, 39, 171

(**2*R*,4*R*)-96** (R = -Cbz) 43, 148, 153

(**2*R*,4*R*)-97** (R = -H) 43, 153



n = 0

(**2*R*,4*S*)-40a** 14-15, 157

(**2*R*,4*S*)-40b** 14-15, 159

n = 1

(**2*R*,4*S*)-89a** 37, 39, 166

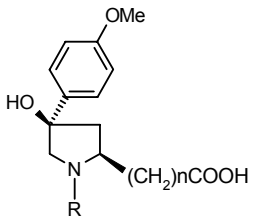
(**2*R*,4*S*)-89b** 37, 39, 168

(**2*R*,4*S*)-89c** 37, 39, 170

(**2*R*,4*S*)-89d** 37, 39, 172

(**2*R*,4*S*)-96** (R = -Cbz) 45, 149

(**2*R*,4*S*)-97** (R = -H) 45, 153



n = 0

(**2*S*,4*R***)-**57a** 25, 53, 161-162

(**2*S*,4*R***)-**57b** 25, 53, 162-163

(**2*S*,4*R***)-**62** (R = -Cbz) 26-27, 147, 151

(**2*S*,4*R***)-**63** (R = H) 26-27, 57, 151

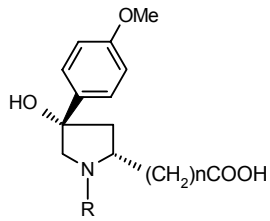
n = 1

(**2*S*,4*R***)-**104b** 49, 175

(**2*S*,4*R***)- **104c** 49, 177

(**2*S*,4*R***)-**110** (R = -Cbz) 51, 149-150, 154

(**2*S*,4*R***)-**111** (R = -H) 51, 61-62, 153



n = 0

(**2*R*,4*S***)-**57a** 25, 53, 162

(**2*R*,4*S***)-**57b** 25, 53, 163

(**2*R*,4*S***)-**62** (R = -Cbz) 147-148, 151-152

(**2*R*,4*S***)-**63** (R = -H) 27, 57, 151-152

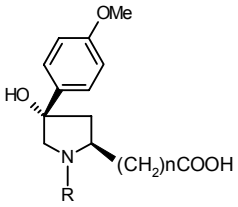
n = 1

(**2*R*,4*S***)-**104b** 49, 175-176

(**2*R*,4*S***)-**104c** 49, 179

(**2*R*,4*S***)-**110** (R = -Cbz) 52, 150

(**2*R*,4*S***)-**111** (R = -H) 52, 154-155



n = 0

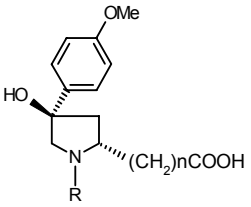
(**2*S*,4*S***)-**57a** 25, 53, 160-161

(**2*S*,4*S***)-**57b** 25, 53, 163-164

n = 1

(**2*S*,4*S***)-**104b** 49, 176

(**2*S*,4*S***)-**104c** 49, 178-179



n = 0

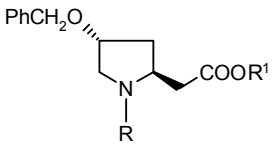
(**2*R*,4*R***)-**57a** 25, 53, 161

(**2*R*,4*R***)-**57b** 25, 53, 164

n = 1

(**2*R*,4*R***)-**104b** 49, 176-177

(**2*R*,4*R***)-**104c** 49, 179



R^1 = Me

(**2*S*,4*R***)-**85** (R = -Cbz) 36, 96-97

(**2*S*,4*R***)-**87** (R = -H·HCl) 36, 40, 110-111

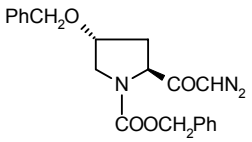
(**2*S*,4*R***)-**93a** 40-41, 110, 173

(**2*S*,4*R***)-**93c** 40-41, 110-111, 174

R^1 = H

(**2*S*,4*R***)-**94a** 40-41, 173

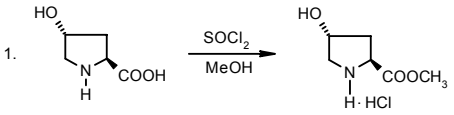
(**2*S*,4*R***)-**94c** 40-41, 1



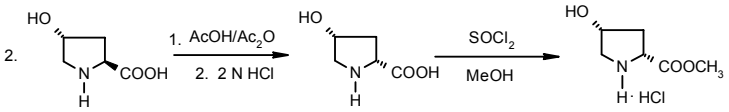
(**2*S*,4*R***)-**84** 36, 95

7.2 Main synthetic routes:

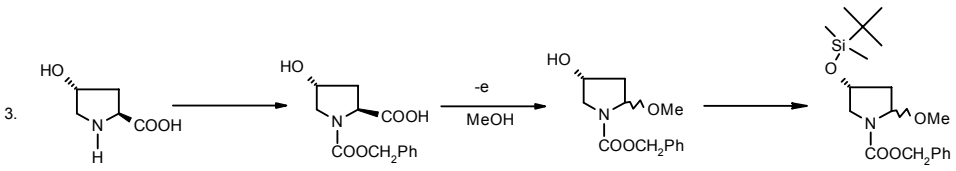
7.2.1. N-Unsubstituted 4-hydroxypyrrolidine derivatives.



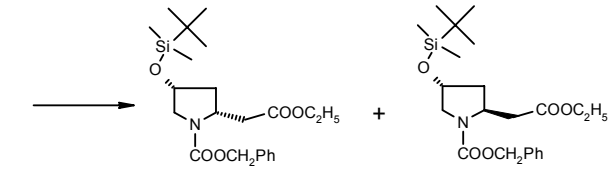
Lit.



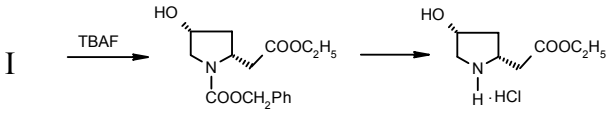
Lit. Lit.

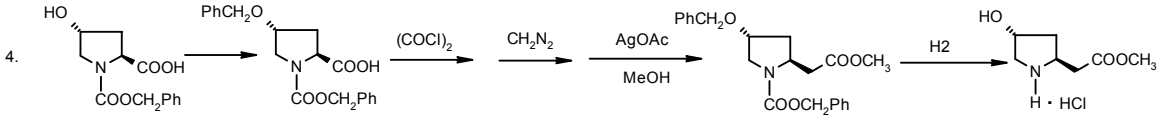


Lit.



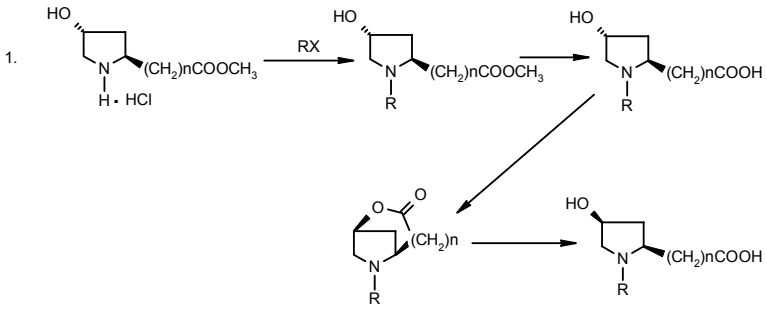
I II





Lit.

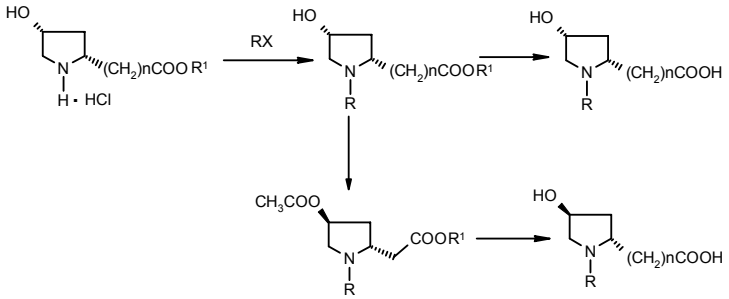
7.2.2. 4-Hydroxy pyrrolidine derivatives.



1). n = 0, R = **24a-b**, X = Br

2). n = 1, R = **24a-c**, X = Br; R = **24d**, X = I; R = Cbz, X = Cl.

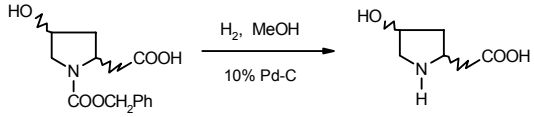
2.



1). n = 0, R^1 = Me, R = **24a-b**.

2). n = 1, R^1 = Et, R = **24a-c**, X = Br; R = **24d**, X = I; R = Cbz, (4*S*)-HCOO-.

3.



7.2.3. 4-Hydroxy-4-(4-methoxyphenyl)pyrrolidine derivatives.

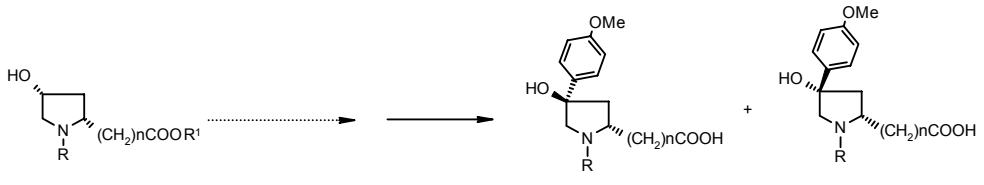
1.

I II

1). n = 0, R = **24a-b**; R = Cbz (no compound I).

2). n = 1, R = **24b-c**; R = Cbz (no compound I).

2.



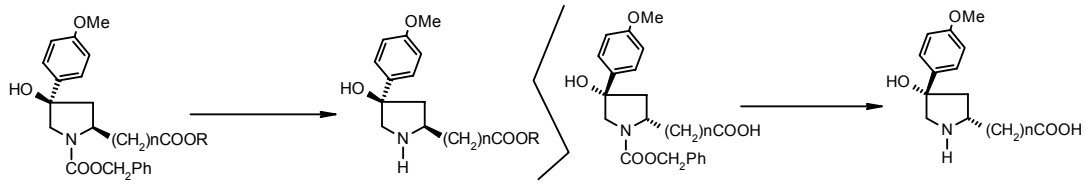
I II

The same procedure as above gave the corresponding (2*R*) stereoisomers.

1). n = 0, R^1 = Me, R = **24a-b**; R = Cbz (no compound I).

2). n = 1, R^1 = Et, R = **24b-c**; R = Cbz (no compound I).

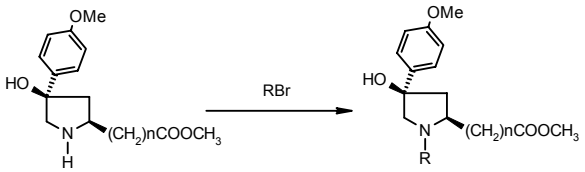
3.



1). n = 0, R = H, Me.
2). n = 1, R = H, Me.

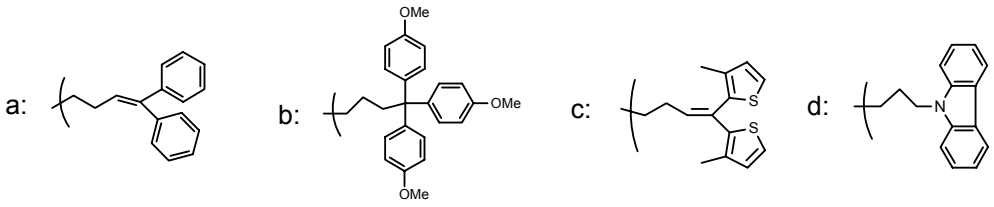
1). n = 0.
2). n = 1.

4.



1). n = 0, R = **24a**.
2). n = 1, R = **24c.**

R = **24a-d**



Lebenlauf [94]

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