Diploma Thesis

Synthesis of a New Class of Modulators of the NMDA-Receptor Function

Performed at the Faculty of Life Sciences - Department of Medicinal-Pharmaceutical Chemistry - University of Vienna

Submitted at the Faculty of Chemistry - Vienna University of Technology

Supervisor

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performed by

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Vienna, May 2005

Dedicated to my late grandfather Erich Stanetty

First of all I would like to thank Prof. Dr. Christian R. Noe for the interesting and challenging topic and the opportunity to include my own ideas into this thesis without allowing me to get lost and to forget the main target of this work. I wish to thank Prof. Dr. Ernst Urban for recording and processing many 1-D and 2-D NMR spectra on the 500 MHz spectrometer and his readiness to help in case there were problems in interpreting them. Furthermore I have to thank him for having given me the opportunity to gather first experiences in teaching ("Studienassistent" and FH-Tutor). Many thanks to Dr. Bodo Lachmann for the introduction into recording and processing of MS spectra on the ESI-MS and for all advice he provided me with in general and particularly in analytical fields.

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My special thank belongs to my parents, my sister, my grandparents and my girlfriend Sigrun Berger for making all this possible by their continuous support during the years of my studies and especially in the time of the diploma thesis.

Legend

All novel compounds prepared within this diploma thesis are labeled in bold and underscored Arabic numbers. All other compounds prepared within this diploma thesis are labeled in bold Arabic numbers.

Literature references are labeled in superscript Arabic numbers.

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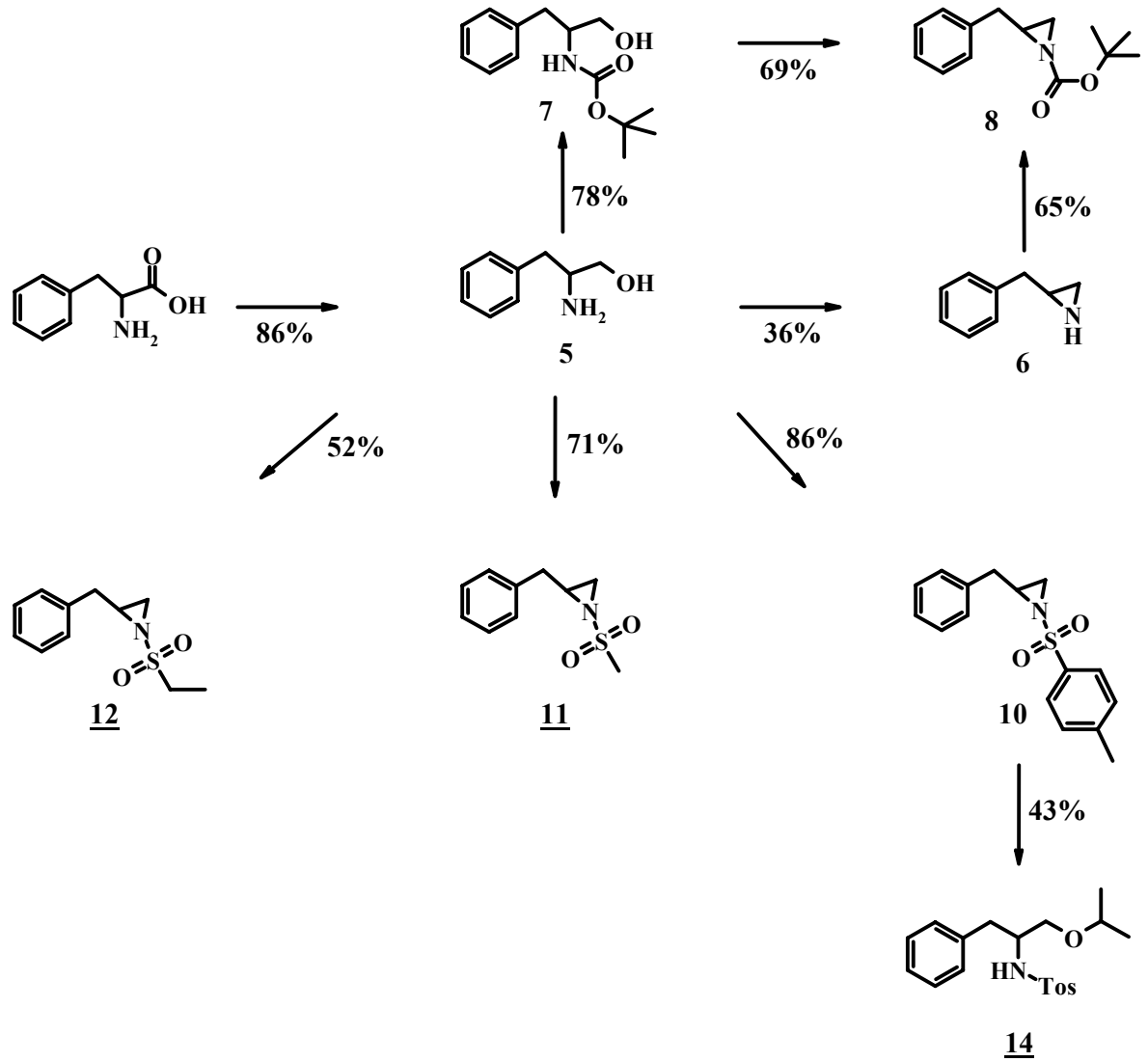
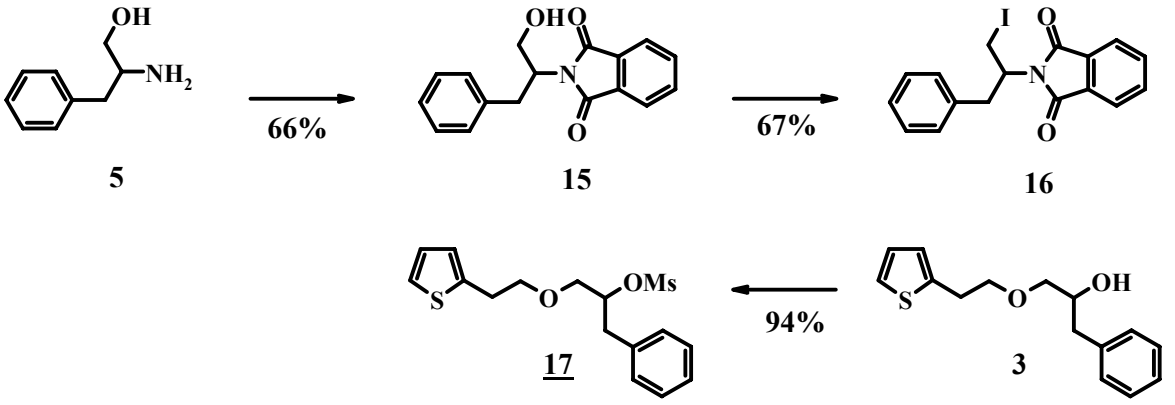
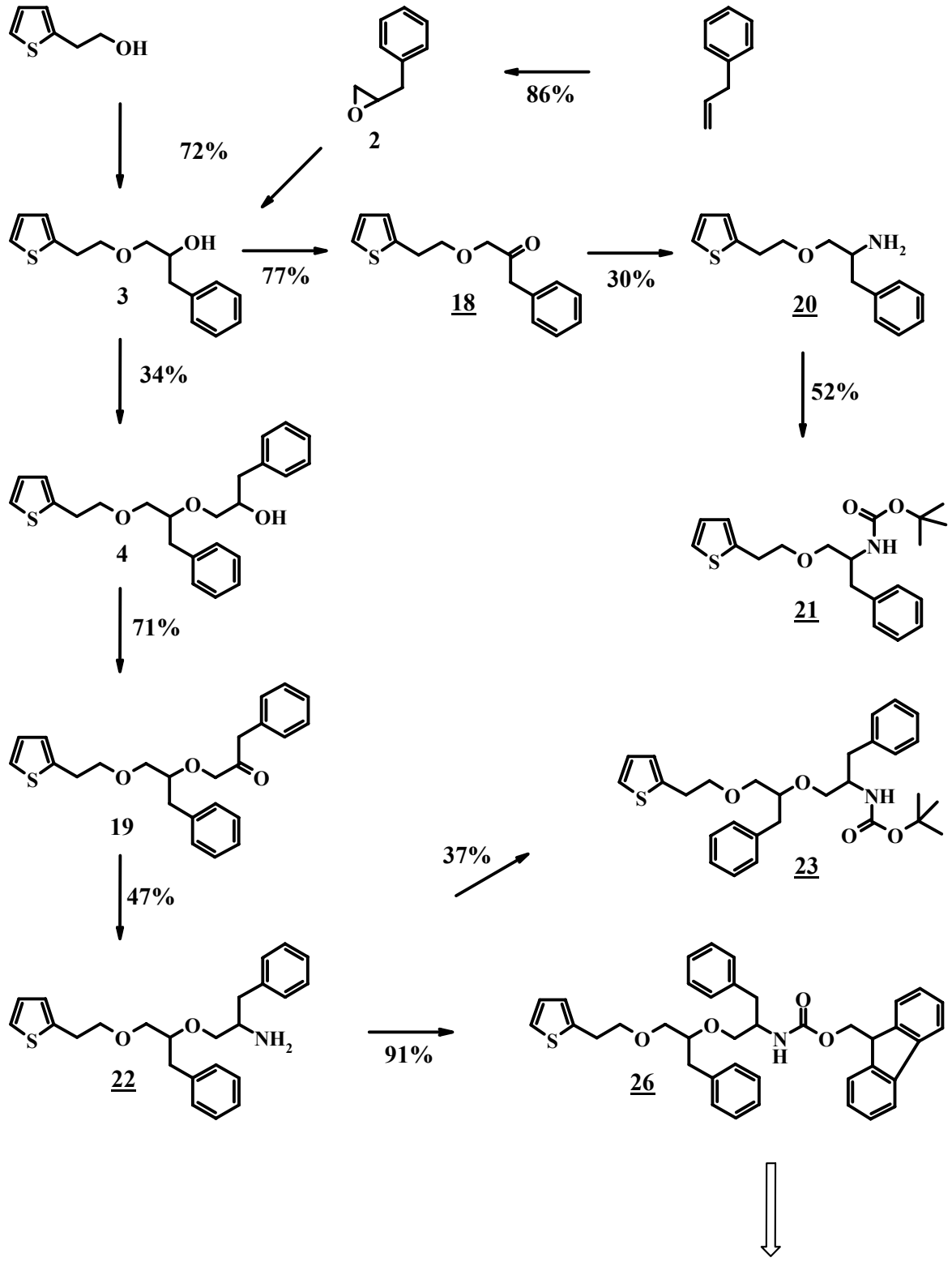
General Schemes



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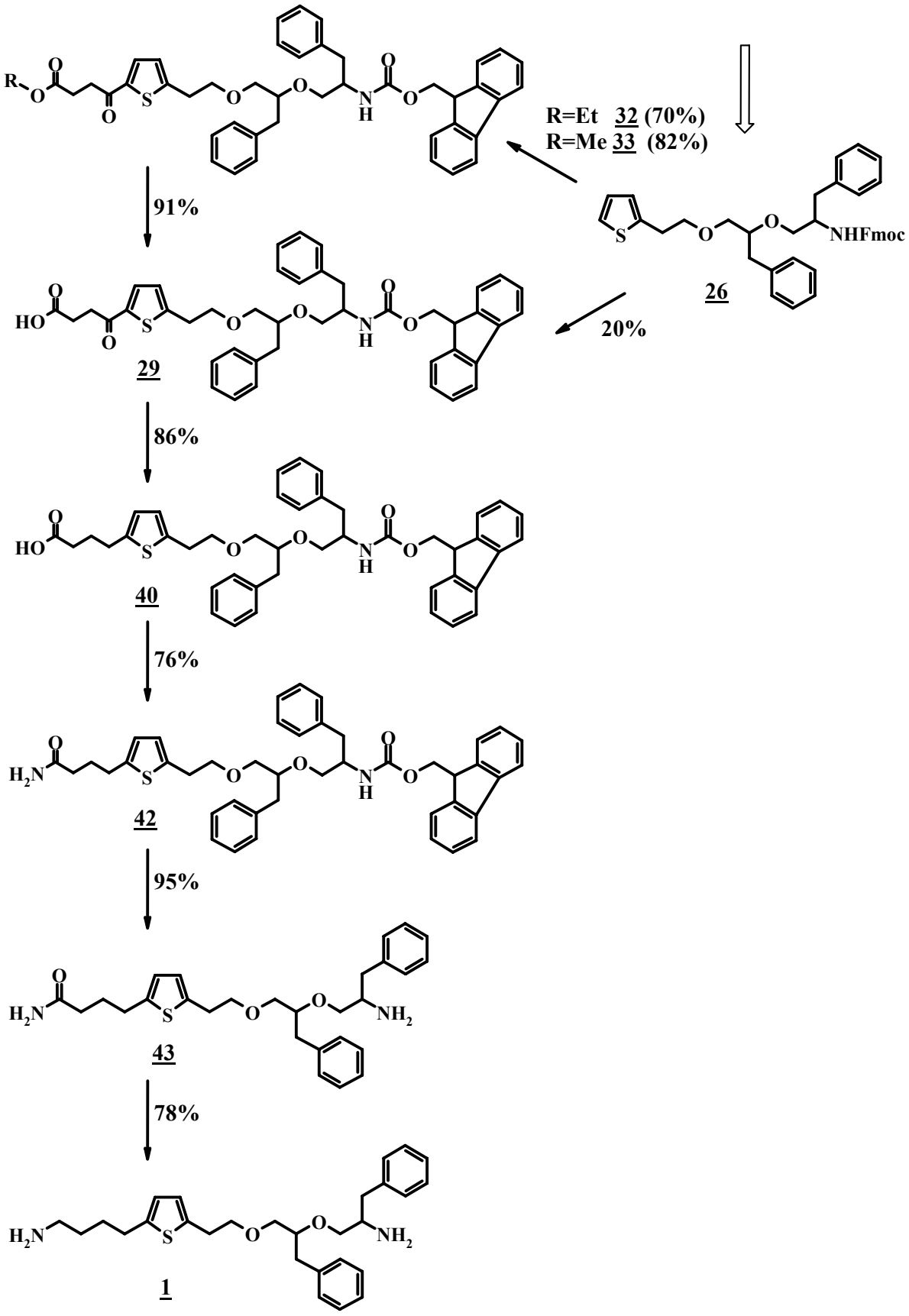
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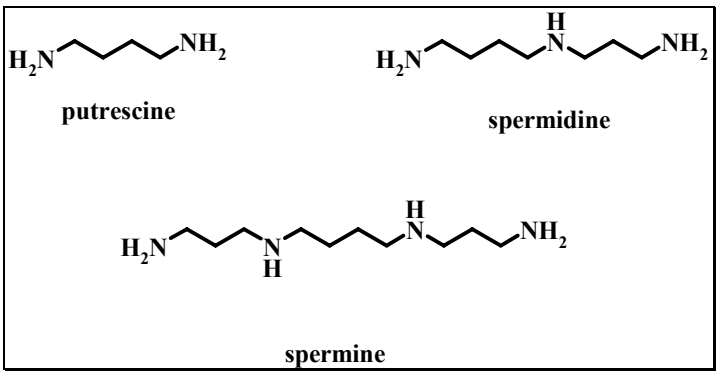
1 Introduction

1.1 Polyamines

The term polyamines – very general in chemical means – refers in concerns of cell biology to a rather small number of aliphatic di-, tri- and tetra-amines that occur at high molecular levels in almost all living organisms[1]: spermine, spermidine, their biosynthetical precursor putrescine in first place, and some similar structures that are found in natural sources less frequently. While in prokaryotic cells mostly putrescine and spermidine are found eukaryotic cells additionally use spermine. Actually spermine was the first one described - back in 1678 by Leeuwenhoeck[2] who crystallized it from drying sperm. Its structure however was not determined before 1924 and the multiple functions of polyamines in living cells are still a topic of growing interest.



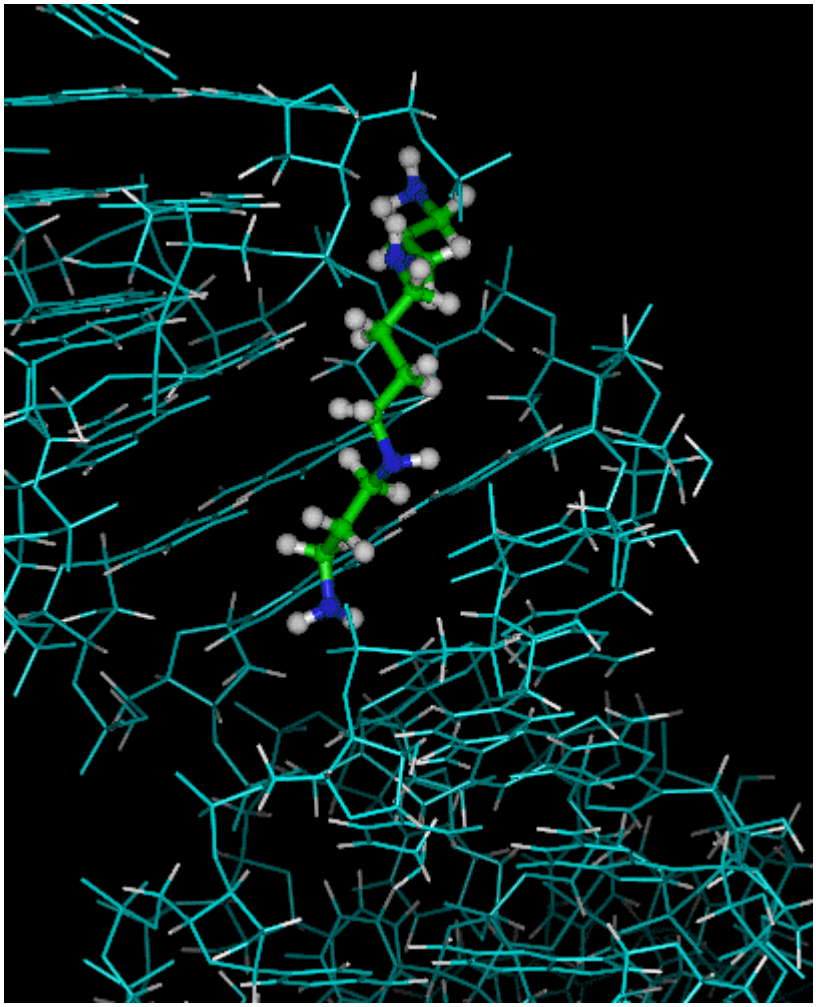
Scheme 1: Wide spread natural polyamines

1.1.1 Polyamines and their Interactions

At physiological pH both the primary as also the secondary amines exist in their protonated form and therefore biogenous amines are organic poly cations of small molecular weight. In contrast to inorganic cations which carry charges located at a particular atom the total charge of polyamines is distributed over a wider area. In this form they can have electrostatic interactions with anionic sites of biopolymers like DNA and RNA[3], membranes and

[1] Tabor, C.W.; Tabor, H. *Microbiol. Rev.*, **1985**, *49*, 81-99
[2] Leeuwenhoeck, A. *Philos. Trans. R. Soc. London*, **1678**, *12*, 1040
[3] Westhof, E.; Dumas, P.; Moras, D. *Acta Crystallogr., Sect.A* **1988**, *A44*, 112-123

phospholipids. A variety of modulations of cell function by polyamines have been investigated, including cell proliferation, differentiation and apoptosis[4,5]. The ligands described within this thesis should contribute to the knowledge about the polyamine binding site on the NMDA-receptor (for a recent review[6]). These specific interactions of polyamines with the NMDA receptor will discussed in Chapter 1.3.2.

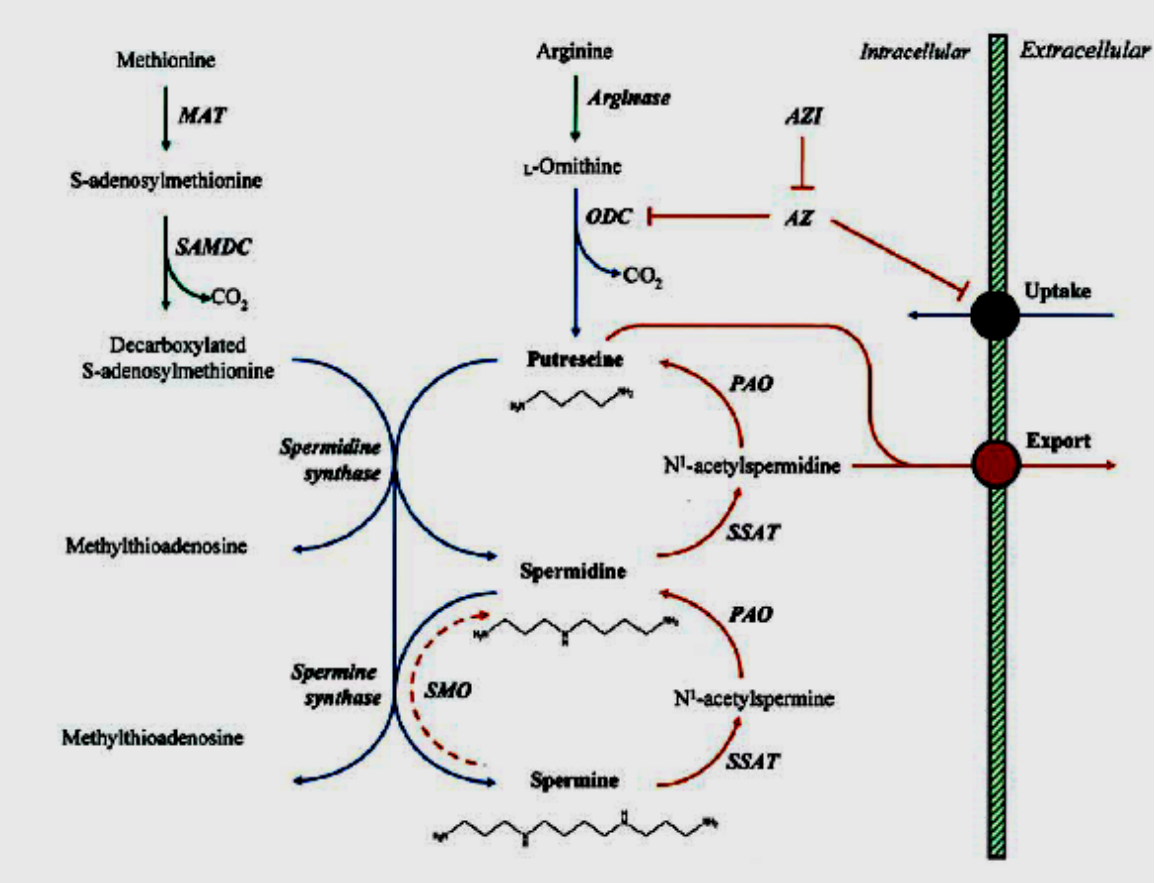


Scheme 2: Interaction of spermine with t-RNA (X-ray structure)[3]

[4] Pegg, A.E. *Cancer Res.* **1988**, *48*, 759
[5] Cohen, S.M. *Drug Metab. Rev.* **1998**, *30*, 339-
[6] Berger, M.L.; Noe, C.R. *Curr. Top. Med. Chem.* **2003**, *3*, 51-64

1.1.2 Polyamine Metabolisms

All endogenous polyamines are products of the ornithine metabolism[7]. Putrescine which is named after putrefying flesh, in which it is found in large quantities, is formed from ornithine by ornithine decarboxylase (ODC). By subsequent addition of an activated aminopropyl group by spermidine synthase and spermine synthase the larger polyamines are formed in living cells. The aminopropyl group is delivered in form of decarboxylated S-adenosylmethionine which is previously formed by S-adenosylmethione decarboxylase (SAMDC) from S-adenosylmethionine. The addition of the aminopropyl group is an irreversible step in the biosynthesis of spermine and spermidine. The degradation of natural polyamines in living organism is done *via* another path. After N-acetylation of the polyamine FAD-dependent polyamine oxidases (PAOs) remove the aminopropyl groups. Most of the PAOs are not selective and can react with N-acetyl spermine and N-acetyl spermidine.



Scheme 3: Pathways of polyamine biosynthesis and metabolism[7]

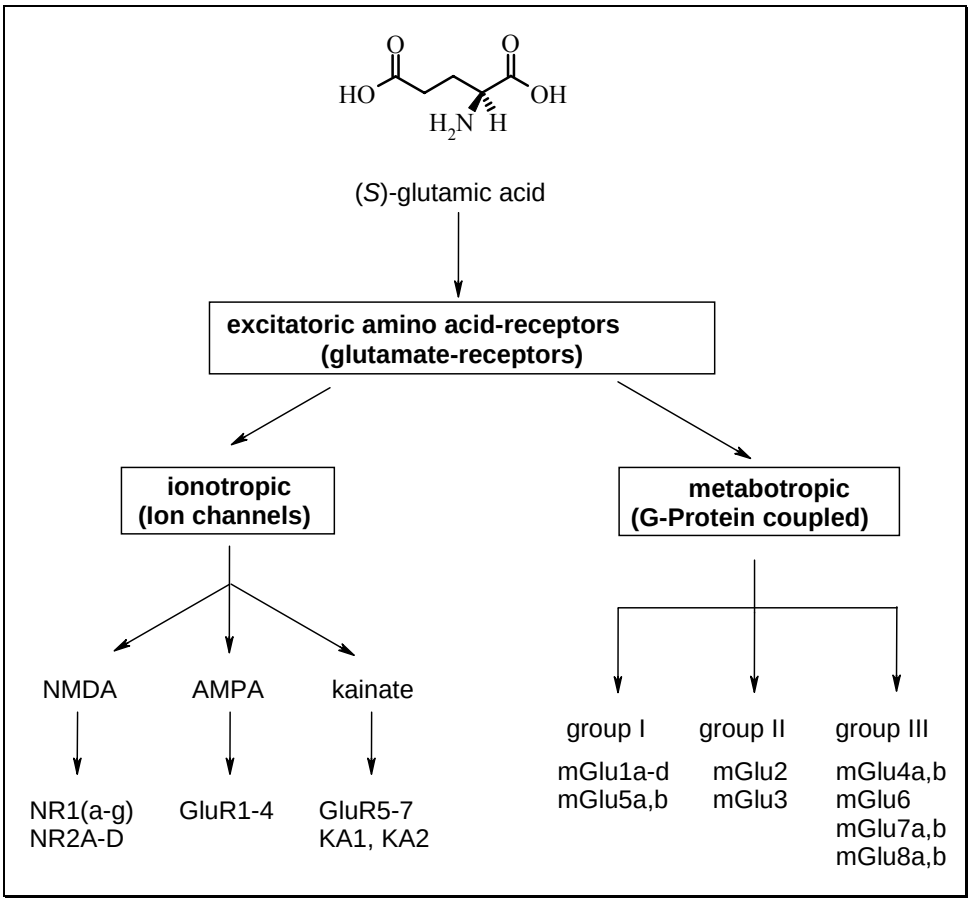
[7] Wallace, H.M.; Fraser, A., V. Hughes, A. *Biochem. J.* **2003**, *376*, 1-14

1.2 Glutamate Receptors

In the brain the signal transduction is provided by nervous cells. When a cell is stimulated the signal is transferred by so called neurotransmitters. They are released and after diffusion through the synaptic gap they modulate the corresponding receptors of the neighboring cell, activating it to further transport of the signal along the nervous system.

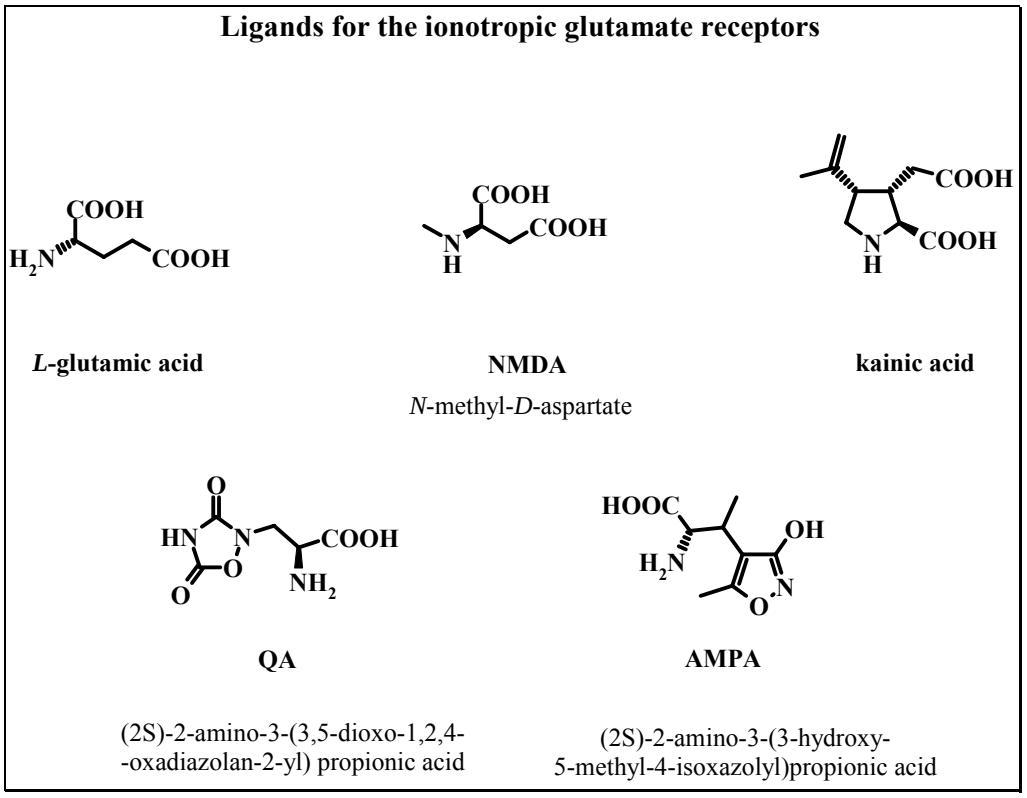
In the central nervous system of mammalian species besides the more prominent neurotransmitters like acetylcholine, dopamine or serotonin there are mainly amino acids that serve as neurotransmitters, both in excitatory (supporting the synaptic transmission) and in inhibitory manner (hindering the synaptic transmission). Most of the excitatory receptors in the mammalian brain can be stimulated by the natural amino acid S-glutamic acid (glutamate receptors).

1.2.1 Classification of Glutamate Receptors



Scheme 4: Classification of glutamate receptors

The glutamate receptors are classified in the first place into ionotropic (ion channel mediating) and metabotropic (G-protein coupled) receptors. The ionotropic receptors are further divided by their affinity towards N-methyl-D-aspartate (NMDA) into NMDA and non-NMDA receptors. The non-NMDA receptors have further been classified by their affinity to more selective ligands into AMPA and kainate receptors (Scheme 4).



Scheme 5: Examples for ligands of ionotropic glutamate receptors

1.3 NMDA Receptors

The NMDA receptors are like all others glutamate receptors permeable for Na^+ and K^+ ions. In contrast to most of the mentioned non-NMDA receptors the NMDA receptor is moreover permeable for Ca^{2+} ions[8,9]. They induce signal transduction by depolarization of the cell membrane but can furthermore interact with intracellular enzymes by activation of second messenger systems. An outstanding property of the NMDA receptor compared to many other ion channels is that it is dependent on the transmembranal potential and needs stimulation of different ligands for its function. For opening the ion channel simultaneous stimulation by

[8] Danysz, W; Parson, A.C. *Pharmal. Rev.* **1998**, *50*, 597-664
[9] Stark, H.; Reichert, U.; Grassmann, S. *Pharmazie in unserer Zeit* **2000**, *29*, 228-236

agonist glutamate and co-agonist glycine is required. At normal membrane potential (-70mV) the ion channel is blocked by Mg^{2+}, although the receptor is stimulated by glutamate and glycine. Only at partial membrane depolarization Mg^{2+} is released from the pore opening the channel for other ions.

It was examined that dependent on the region in the brain and its state of development the NMDA receptors have different pharmacological and biochemical properties. Actually the NMDA receptor consists of NR-1 and NR-2 subunits each consisted of 900-1500 amino acids. Today many variants of both the NR-1 and the NR-2 subunit are known and their combination leads to great diversity of NMDA receptors. The NMDA receptor is involved in processes, which are referred to as long-term-potention as the basis for learning and memory and long–term-depression responsible for forgetting.[10]

Although the excitatory effect of glutamate is fundamentally essential for the signal transduction in the central nervous system, it was proofed by Olney *et al.*[11] that under different acute pathological incidents like stroke or epilepsy[12] over-excitation of NMDA receptor causes complex neurodegenerative processes leading to apoptosis of the neuronal nervous system. The NMDA receptor was also investigated in context with chronic neurodegenerative diseases like AIDS Dementia[13], Chorea Huntington[14], epilepsy[12], glaucoma[15], Morbus Alzheimer[16] or Morbus Parkinson[17].

1.3.1 Binding Regions and Corresponding Ligands

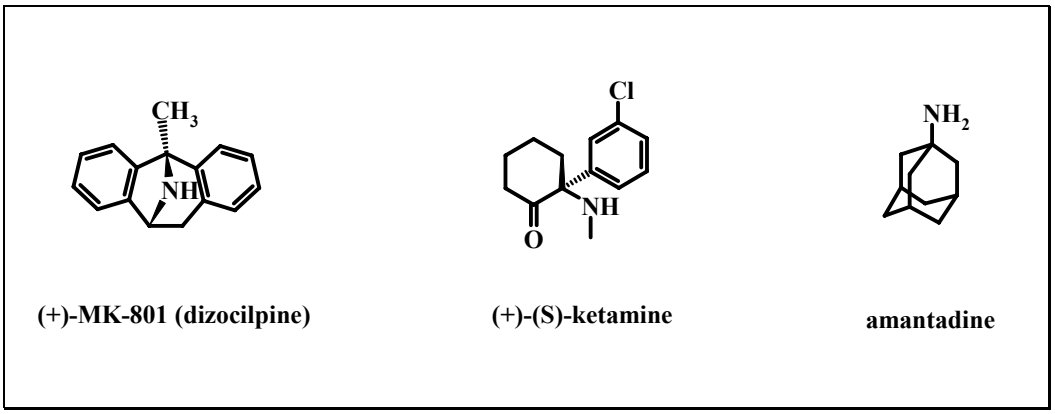
The NMDA receptor has a great variety of binding sites for substrates of different chemical identity. Besides the most important binding site for endogenous agonist and co-agonist, glutamate and glycine and the already mentioned Mg^{2+}-block, there have been found several other specific binding sites for natural and synthetic substrates, among them modulatory

[10] Collingridge, G.L.; Lester, R.A *Pharmacol. Rev.* **1989**, *41*, 143-210
[11] Olney, J.W.; Ho, O.L.; Rhee, V. *Exp. Brain Res.* **1971**, *14*, 61-76
[12] Meldrum, B.; Garthwaite, J. *Trends Pharmacol. Sci.* 1990, *11*, 379-387
[13] Lipton, S.A. *Mol. Neurobiol.***1994**, *8*, 181-196
[14] Young, A.B.; Greenamyre, J. T., Hollingworth, Z.; Albin R.; D'Amato, C.; Shoulson, I.; Penney, J.B. *Science* **1988**, *241*, 981-983
[15] Schroder, A.; Erb, C. *Klinische Monatsblätter für Augenheilkunde* **2002**, 219, 533-536
[16] Steele *et al*. *Brain Res.*, **1989**, *500*, 369-373
[17] Klockgether, T.; Turski, L. *Ann. Neurol.* **1993**, *34*, 585-593

binding sites for protons[18], redox active compounds[19] like dithiothreitol[20], Zn^{2+}ion[21] or ethanol[22] and a modulatory binding site for natural polyamines. There have been various efforts – involving projects of our research group[23,24,25] - to stimulate the NMDA function with synthetic ligands, to design agonists and antagonists and inverse agonists for most of the studied binding sites. Within this thesis the discussion is focused on the interaction of natural polyamines and synthetic ligands with the polyamine binding site of the NMDA receptor.

1.3.2 Interactions of Polyamines with the NMDA Receptor

In presence of glutamate and glycine and conditions of depolarization of the neuronal cell membrane the favorable state of the NMDA receptor ion channel is the active opened form. Open channel blockers like dizocilpine, (+)-(S)-ketamine or amantadine can only reach their binding site when the receptor is in his open channel form.



Scheme 6: Examples of open channel blockers

It is especially the tritiated form of dizocilpine ([^{3}H]-MK-801) that is regularly used in functional binding essays. The rate of the specific binding of an open channel block can easily be monitored in case of a radioactive labeled compound. Under conditions of non-saturating

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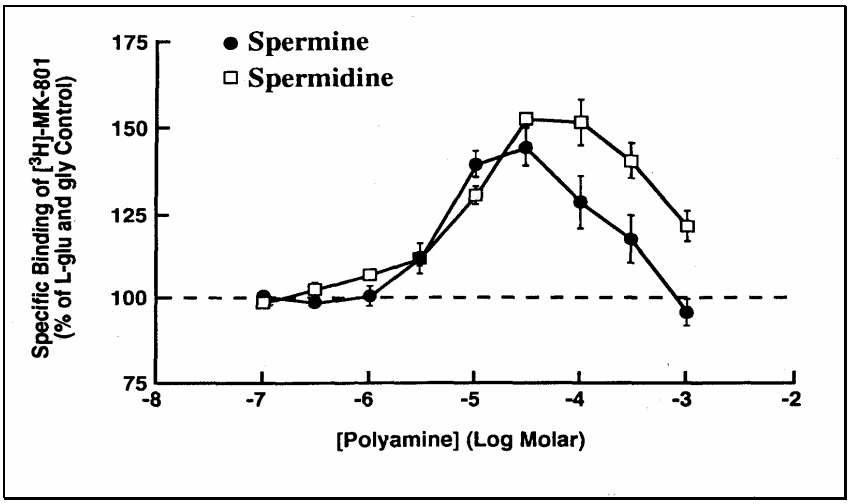
[18] Traynelis, S.F.; Cull-Candy, S.G. *Nature*, **1990**, *345*, 347-350
[19] Lipton, S.A.; Aizenman, E. *Neuron* **1989**, *2*, 1257-1263
[20] Reynolds, I.J.; Aizenman, E.; Rush, E.A. *Br. J. of Pharmacol.* **1990**, *101*, 178-182
[21] Christine, C.W.; Choi, D.W. *J. of Neurosci.* **1990**, *10*, 108-116
[22] Koltchine, V.; Anantharam, V.; Wilson, A.; Bayley, H.; Treistman, St.N. *Neurosci. Lett.* **1993**, *152*, 13-16
[23] Schödl, C. *PhD Thesis* **1994**, Vienna University of Technology
[24] Gottschlich, R.; Leibrock, J.; Noe, C.R.; Berger, M.; Buchstaller, H.-P. E*ur. Pat. Appl.* **1996** EP 95-119009
[25] Buchstaller, H.-P.; Siebert, C.D.; Lyssy, R.H.; Ecker, G.; Krug, M.; Berger, M.; Gottschlich, R.; Noe, C. R. *Sci. Pharm.* **2000**, *68*, 3-14

concentrations of the [^{3}H]-MK-801 the influence of additionally present ligands on this rate of specific binding can be determined. Ransom and Stec[26] have examined the effect of present spermine and spermidine under saturation concentrations of glycine and glutamate on the specific binding of [^{3}H]-MK-801 and found that the presence of polyamine is supportive. Closer examinations[27] showed that the positive effect on the channel opening has a certain maximum, meaning that higher concentrations of polyamine lead to decreasing binding of open channel blocker. They postulated two different modulatory binding sites for polyamines, an excitatory and an inhibitory one.



Scheme 7: Biphasic curve of the natural polyamines

Polyamines act on NMDA receptor channels to produce both stimulatory and inhibitory effects by at least four distinct mechanisms. The potentiating effects of the polyamines can be subdivided into glycine-independent[28] and glycine-dependent[29] stimulation, whereas the inhibitory effects can be divided into a decrease in the affinity for agonists[30] of their binding sites and a voltage-dependent inhibition[31]. All these effects have been shown to highly depend on the subtype of the NMDA receptor[32].

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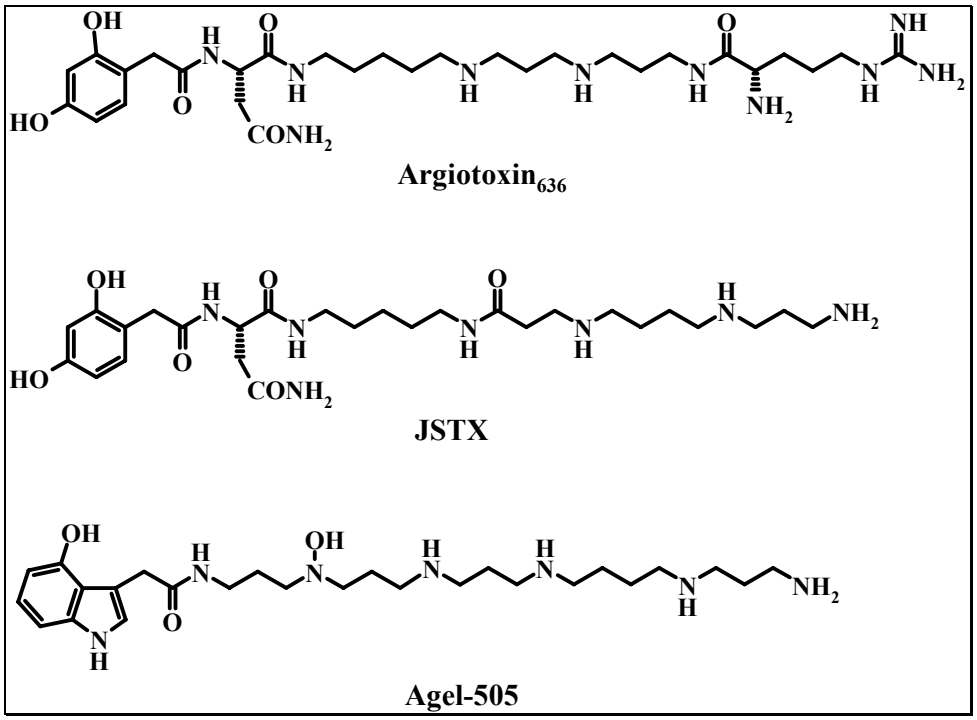
[26] Ransom, R.W.; Stec, N.L. *J. Neurochem.* **1988**, *51*, 830-836
[27] Brackley, P. Goodnow, R. Jr.; Nakanishi, K.; Sudan, H.L.; Usherwood, P.N.R. *Neurosci. Lett.* **1990**, *114*, 51-56
[28] Lerma, J. *Neuron* **1992**, *8*, 343-352
[29] Williams, K. *Neurosci. Lett.* **1995**, *184*, 181-184
[30] Williams, K. *Mol. Pharmacol.* **1994**, *46*, 161-168
[31] Kashiwagi, K.; Pahk, A. Jr.; Masuko, T.; Igarashi, K.; Williams, K. *Mol. Pharmacol.* **1997**, *52*, 701-713
[32] Williams, K. *Cell. Signal.* **1997**, *9*, 1-13

1.3.3 Ligands of the NMDA Polyamine Binding Site

Besides the endogenous polyamines several other classes of substances have been examined with respect to their interaction with the NMDA-receptor and were found to interact with polyamine binding regions of the receptor. Very interesting is the class of natural polyamine amides, toxins of natural poisons isolated from different wasps and spiders.



Scheme 8: Examples for spider and wasp toxins

Very soon after the examination of the stimulating effect of polyamines on the NMDA receptor ion channel, neuroscientists were able to show that these compounds inhibit ionotropic transmitter receptors. They exhibited strong voltage dependent channel blocking properties. In contrast to spermine and its inhibiting effect at higher concentrations these substances block the ion channel of the NMDA receptor at very low concentration (100μM). This inhibition of the ion flux of the NMDA receptor has been proposed to result from interactions with a polyamine binding site in the channel near the extracellular end. The structural similarity to natural polyamines shall be underlined with the following examples in Scheme 8.

Besides other classes of synthetic targets that have been examined in regard to the NMDA receptor polyamine binding site, α,ω alkyldiamines have been identified to exhibit activity towards the NMDA receptor. Derivatives containing more than eight methylene groups showed clearly inverse agonistic effects in the [^{3}H]-MK-801 binding essay. Various studies have been undertaken with this class of compounds in our research group in the last 15 years and will be discussed separately in Chapter 1.5.

1.4 Pharmacological Binding Studies

1.4.1 General Aspects

Receptors in biochemical concerns are intracellular or transmembrane proteins with specific binding sites for chemical substrates, normally of low molecular weight. Binding of the so called transmitter leads to a reaction, the so called cell answer. For the evaluation of new ligands there are two fundamentally different approaches. A functional binding study delivers the relationship between a ligand and its effect on the cell, for example the contraction of muscle cells or the opening of a channel. On the contrary, radio-ligand binding studies only evaluate the chemical affinity of a new ligand towards the receptor without any regard to the effect to the function. In these experiments it is determined to which degree a certain concentration of candidate can replace the known ligand (radioactive) on the receptor.

1.4.2 The used Binding Essay

For the polyamine binding site of the NMDA receptor by now no selective radio-ligand for the direct determination of affinity by competitive exchange experiments exists. For the evaluation of new ligands, agonist, inverse agonist or antagonist functional binding essays with [^{3}H-MK-801] are used. Applying saturation concentrations (maximum opening frequency of the channel) of glutamate and glycine the open channel blocker reaches its binding site with a certain rate. The presence of natural polyamines like spermine leads to an increase of this rate. Agonists of the polyamine binding site are compounds that have the same effect as the natural ligands increasing the opening frequency of the channel. Inverse agonists on the other hand have the opposite effect on the opening frequency of the channel, thus decrease the specific binding of [^{3}H-MK-801], while antagonists bind to the site but do not affect the function of the NMDA receptor. Antagonists can therefore in these experiments

only be examined in a competitive situation with the natural polyamines thus inhibiting their effect. The used binding essay is a functional binding essay in which the effect of the examined ligands is detected *via* a radioactive ligand.

The IC_{50} value (inhibitory concentration) for an inverse agonist is the concentration that lowers the specific binding of the open channel blocker to 50%. The lower the IC_{50} value is, the higher is the affinity of the ligand towards its binding site. Besides the affinity it is interesting whether the effect on the receptor is really based on interaction with the polyamine binding site or based on another interaction. This selectivity for the polyamine binding site is evaluated by performing analogous experiments with or without the natural agonist spermine present in the essay. If the inhibition is really a competitive one, the presence of spermine must have a strong influence on the inhibitory potential of the ligand.

IC_{50} [Agonist] = IC_{50} ([Agonist] = 0) x (1 + [Agonist] / EC_{50}) (**Cheng-Prusoff-Equation**)

The Cheng-Prusoff equation[33] describes the linear increase of the IC_{50} value of an inhibitor with increasing concentrations of competitive agonist and is the basis of the evaluation for the data obtained in the [^{3}H-MK-801] binding experiments.
The stimulating effect of spermine in the [^{3}H-MK-801] binding experiment provides an EC_{50}-value (effective concentration) of 4.2±1.9µM. The EC_{50}-value is the necessary concentration to provide 50% of the maximum effect on the specific binding. Therefore the addition of 30µM spermine in the essay should raise the IC_{50} value of a competitive inhibitor of same affinity by the factor 8.1 = (1+30/4.2). In practice the IC_{50}-value for a new ligand is determined with and without a certain amount of spermine present in the medium. The so called spermine factor (the ratio of these two IC_{50} values) is an indicator for the selectivity of the new ligand for the polyamine binding site. For a selective inhibitor the spermine factor must be high. More detailed information about the experimental methods for the determination of affinity and selectivity can be retrieved from reports from Dr. Michael Berger[34] with whom the pharmacological experiments were carried out.

[33] Cheng, Y.-C.; Prusoff, W.H. *Biochem. Pharmacol*. **1973**, *22*, 3099-3108
[34] Berger, M.L. *J. Pharmacol. Toxicol. Meth*. **1995**, *34*, 79-88

1.5 Progress in Polyamine Inverse Agonist Design

The research project investigating the observed[35,36,37] weak inhibitory effects of alkyl diamines in the [^{3}H]-MK-801 binding essay of the polyamine binding site of the NMDA receptor started several years ago in our research group. Compounds showing these inhibitory effects are referred to as "polyamine inverse agonists"[38]. Clemens Schödl systematically examined the influence of the length of the alkyl chain finding an optimum in compound N-14-N. Within his PhD thesis he discovered that the insertion of a thiophene structure into the chain can further increase affinity and selectivity[39]. The optimization of the relative position of the thiophene within the chain delivered compound N-4-T-8-N, the lead compound for the following optimization efforts in due course.

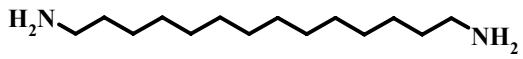
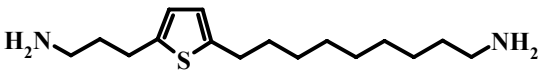
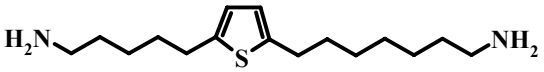
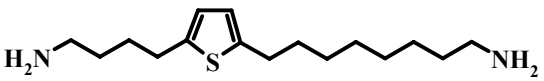
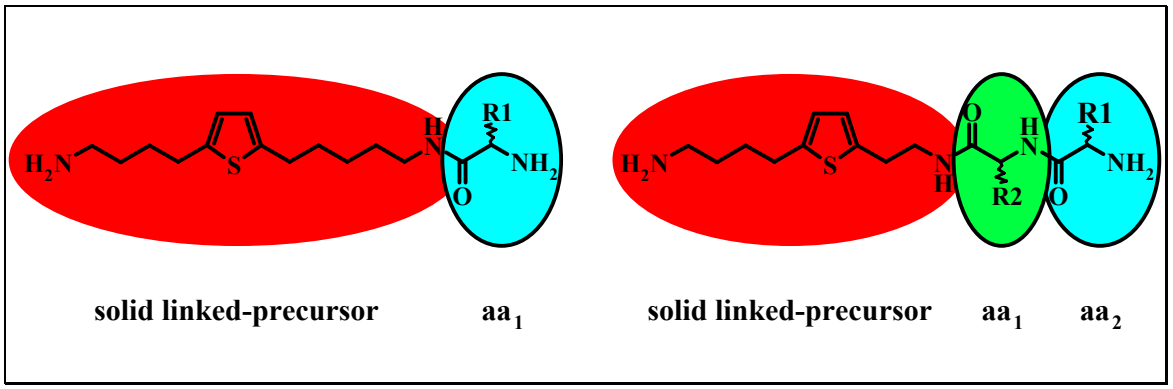
structure	IC_{50} [μM]	$\frac{IC_{50}\text{ (Spn) [μM]}}{IC_{50}\text{[μM]}}$
 **N-14-N**	4.72	6.92
 **N-3-T-9-N**	4.98	5.35
 **N-5-T-7**	1.59	7.85
 **N-4-T-8-N**	0.33	12.0

Table 1: T…thiophene, N...primary amino group, number…of methylene groups

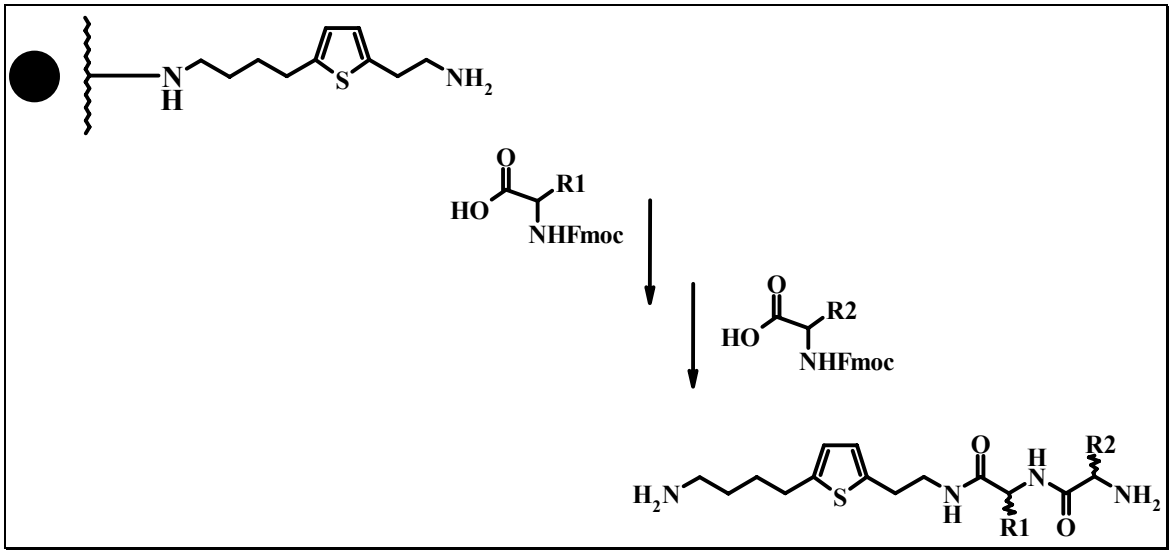
[35] Reynolds, I.J. *J. Pharmacol. Exp. Ther.* **1990,** *255*, 1001-1007
[36] Sacaan, A.I.; Johnson, K.M. *Mol. Pharmacol.* **1990**, *37*, 572-577
[37] Yoneda, Y.; Ogita, K; Enomoto, R. J. *J. Pharmacol. Exp. Ther.* **1991,** *256*, 1161-1172
[38] Williams, K.; Dawson, V.L.; Romano, C.; Dichter, M.A.; Molinoff, P.B. *Neuron* **1990**, *4*, 199-208
[39] Berger, M.L.; Schödl, C.; Noe, C.R. *Eur. J. Med. Chem.* **1998**, *33*, 3-14

Many different variations of this lead structure are described in the PhD thesis of Oliver Schadt[40] affording structures with an amide functionality included into the longer chain as the most promising ones for further investigations. A loss of affinity was compensated by an interesting rise of the spermine factor. On the basis of these first examinations towards amide functionality Thomas Pöhler worked out a methodology to create a small library of substrates with the following general structures to further investigate the influence of different substituents along the longer chain with one or two amide moieties included[41].



Scheme 9: General structure of substrate libraries

The synthetic concept to create these libraries was based on combinatorial chemistry using a solid linked precursor onto that one or two amino acids (aa) were coupled. He used the Fmoc-methodology on a Trityl-resin or a Wang®-resin on a 1mmol scale.



Scheme 10: Principle procedure of the solid phase synthesis

[40] Schadt, O. *PhD Thesis* **1998**, University of Frankfurt
[41] Pöhler T. *PhD Thesis* **2003**, University of Frankfurt and references therein

The preparation of these libraries allowed interesting structure activity relationship studies. Within this combinatorial survey the influence of the absolute configuration was investigated and it was found that in general its impact on the pharmacological properties is low. However, the evaluation of the pharmacological data also made clear that the rigidity of the right chain, introduced by the amide functionalities, was in general not supporting good affinity. On the other hand it turned out to be beneficial to have aromatic lipophilic substituents along the right chain. With respect to the subject of this thesis representative results of the work of Thomas Pöhler and Oliver Schadt highlighting the positive effect of lipophilic groups along the chain are compiled in Table 2 and Table 3.

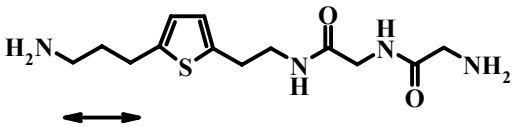
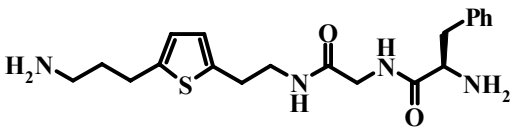
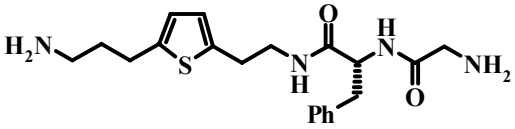
structure	IC_{50} [μM]	$\frac{IC_{50}\ (Spn)\ [\mu M]}{IC_{50}[\mu M]}$
 C_3 **gly-gly**	328	9.6
 C_3 **gly-(D)-phe**	60.2	n.d.
 C_3 **(D)-phe-gly**	24.9	n.d.

Table 2: Amino acids in three letter code

It is obvious that the introduction of a benzyl group close to one terminus of the longer chain, in form of phenylalanine, leads to an increase of affinity compared to the unsubstituted di-amide structure, whether as the first or the second amino acid (Table 2).

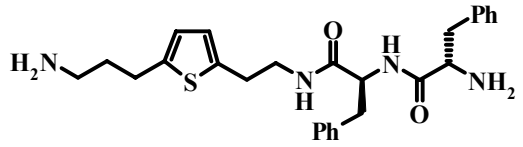
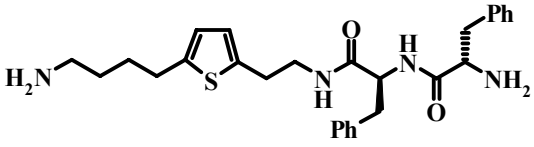
structure	IC_{50} [μM]	$\frac{IC_{50}\ (Spn)\ [\mu M]}{IC_{50}[\mu M]}$
 C_3 (L)-phe-(L)-phe	113±44	5.83
 C_4 (L)-phe-(L)-phe	28	7.85

Table 3: Amino acids in three letter code

Although the introduction of two phenylalanine equivalents seems to have no beneficial effect in case of the C_3 derivative, the corresponding C_4 derivative shows a relatively high affinity and good selectivity for a compound of this general structure (Table 3). The introduction of lipophilic groups along the longer chain analogous to compound N-4-T-2-phe-phe-N will be one of the structural motifs of the present thesis.

The second structural motif was delivered from investigations of the influence of heteroatom substitution in the longer chain that has been undertaken by Daniela Niepel within her PhD thesis[42]. She synthesized and pharmacologically tested compounds with the principal structure of N-**4**-T-8-N but inserted ether, amide and amine functionalities into the longer, right sided chain.

[42] Niepel, D.I *PhD Thesis*, **2004** University of Vienna and references therein

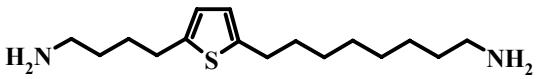
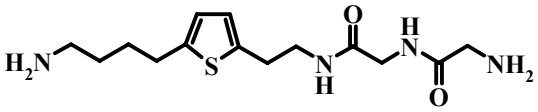
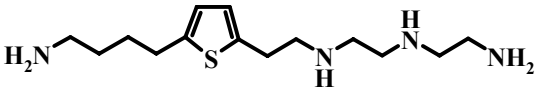
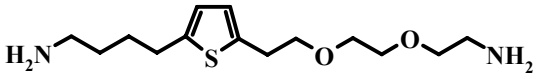
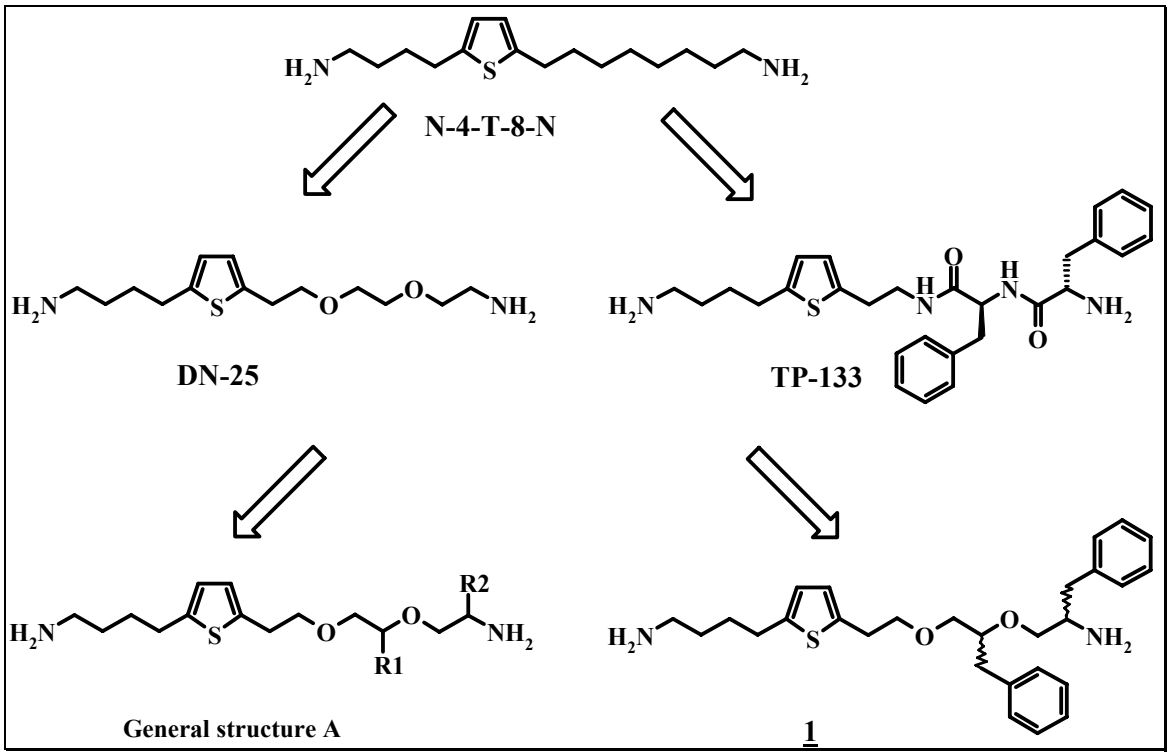
structure	IC_{50} [μM]	$\frac{IC_{50}\ (Spn)\ [\mu M]}{IC_{50}[\mu M]}$
 **N-4-T-8-N**	0.39 ± 0.12	9 ± 6
 **DN-71**	122.1	5.48
 **DN-80**	Agonist	
 **DN-25**	5.04	16.1

Table 4: Influence of inserted heteroatoms in the longer chain

The most exciting investigation was that the insertion of oxygen atoms (DN-25, Table 4) into the longer right sided chain lead to no big loss in affinity compared to that of lead structure N-4-T-8-N but afforded a higher spermine factor, indicating that the additional sites of interaction have a positive effect on the selectivity. The diether pattern of compound DN-25 is the second structural motif of the synthesis that will be reported in this thesis.

1.6 Subject of this Thesis

Based on the structure of lead compound N-4-T-8-N various efforts have been described in the preceding chapter aiming at compounds with increased affinity as well as selectivity towards the polyamine binding site of the NMDA receptor.



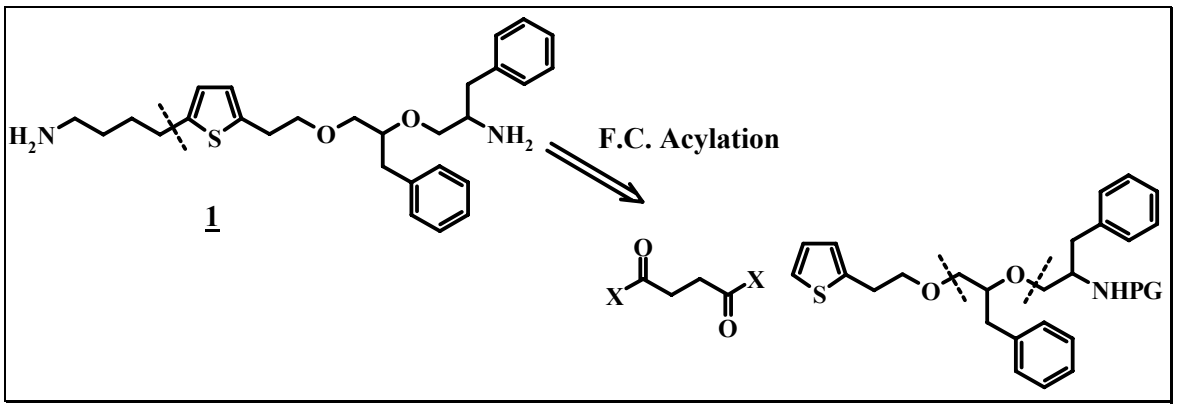
Scheme 11: Genesis of the subject of the thesis

The obtained results - especially those for N-4-T-8-N-related compounds TP-133 and DN-25 - have made a combination of the tentatively crucial structural elements of these two compounds an interesting lead structure for new, hopefully more potent ligands of the polyamine binding site of the NMDA receptor (general structure **A**). It was the target of this thesis to establish a synthetic route towards compound **1**, a prototype of this interesting class of products with general structure **A**. During the synthesis the general applicability to other derivatives should always be kept in mind to obtain methods that allow faster synthesis of more examples of general structure **A**. - in case that the pharmacological results are promising. A ligand with high affinity and selectivity would allow the development of a radiomarker for direct binding experiments, simplifying subsequent screening for new agonists, inverse agonists and antagonist candidates.

2 Results and Discussion

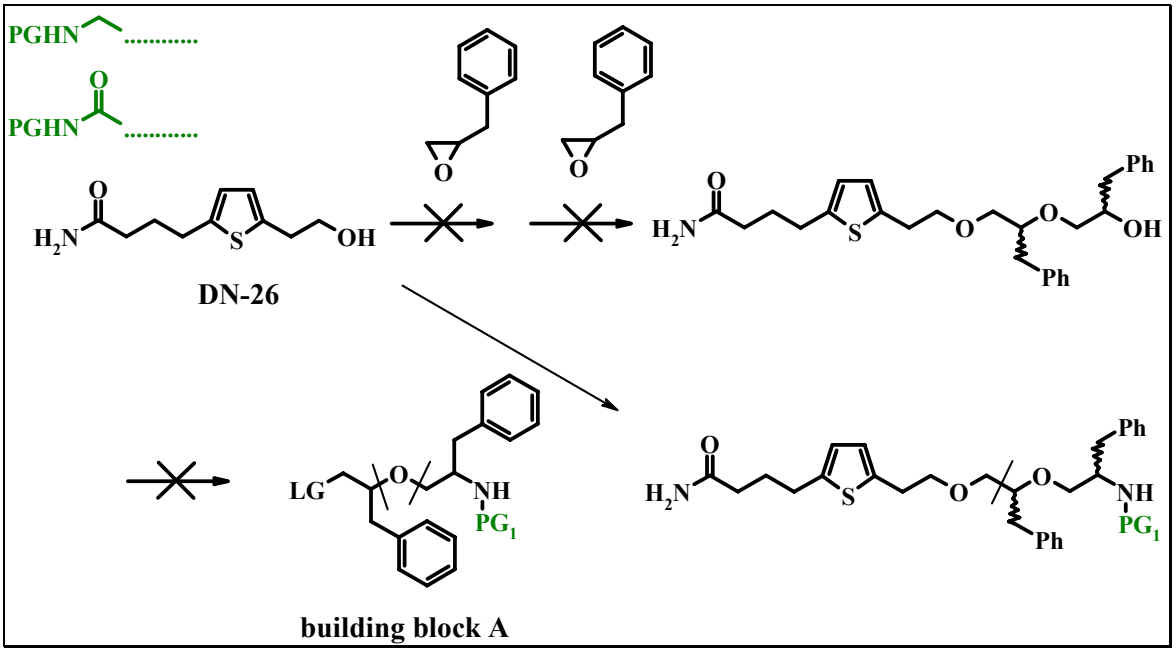
2.1 Preliminary Results

Due to the relatively high number of functionalities in compound **1** there are some prominent positions of strategic cleavage within a retrosynthetic analysis. Methods for the introduction of the shorter left side chain into the thiophene are based on Friedel-Crafts acylation and further transformation to the aliphatic amine and were in principle well established in the group and should be applicable to the current problem at the appropriate step of the synthetic sequence.



Scheme 12: Retrosynthetic considerations

The first decision considered was whether it was better to start with the synthesis of the right or the left chain. Starting to attach the shorter aliphatic chain to some suitable thiophene derivative building up a kind of precursor for the synthesis of the right chain (**Strategy A**) has the advantage of allowing in principle the application of combinatorial chemistry. On the other hand it might be advantageous to solve the problems associated with the assembly of the longer right sided chain with its new structural elements of the substituted diether as early as possible in the sequence (**Strategy B**).

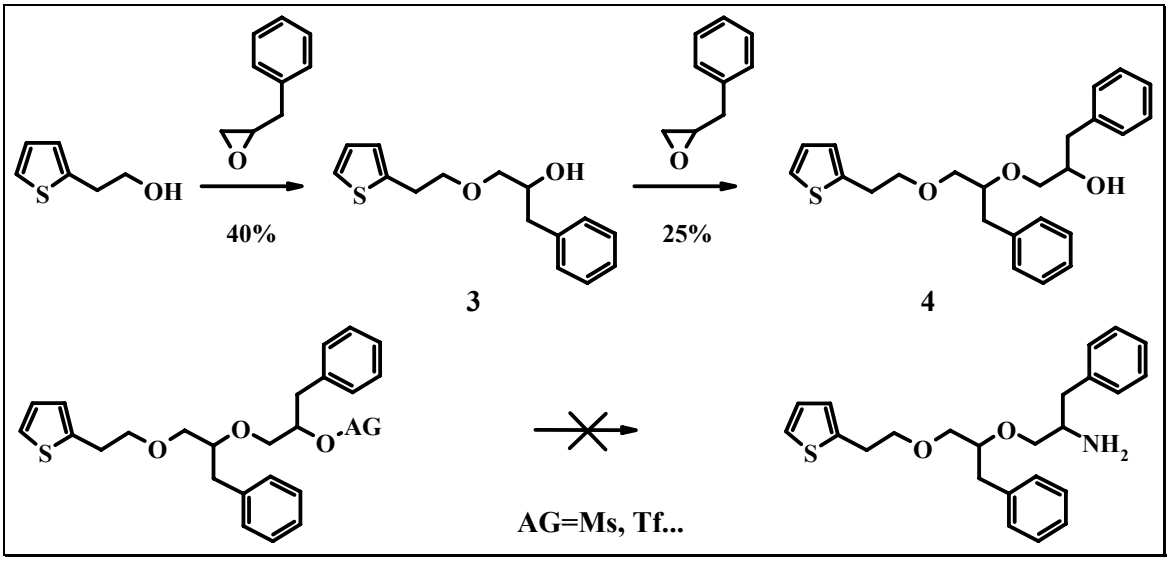


Scheme 13: Strategy A

Actually, several approaches based on precursor DN-26 (**Strategy A**) were attempted but reported as unsuccessful in the PhD thesis of Daniela Niepel[42]:

1) Sequential addition of two equiv. of benzyloxirane to precursor DN-26
2) Attempted synthesis of different type **A** building blocks envisioning to subsequently attach this preformed fragment to the precursor **DN-26**

Consequently a synthetic concept for the initial assembly of the long sided chain was developed.

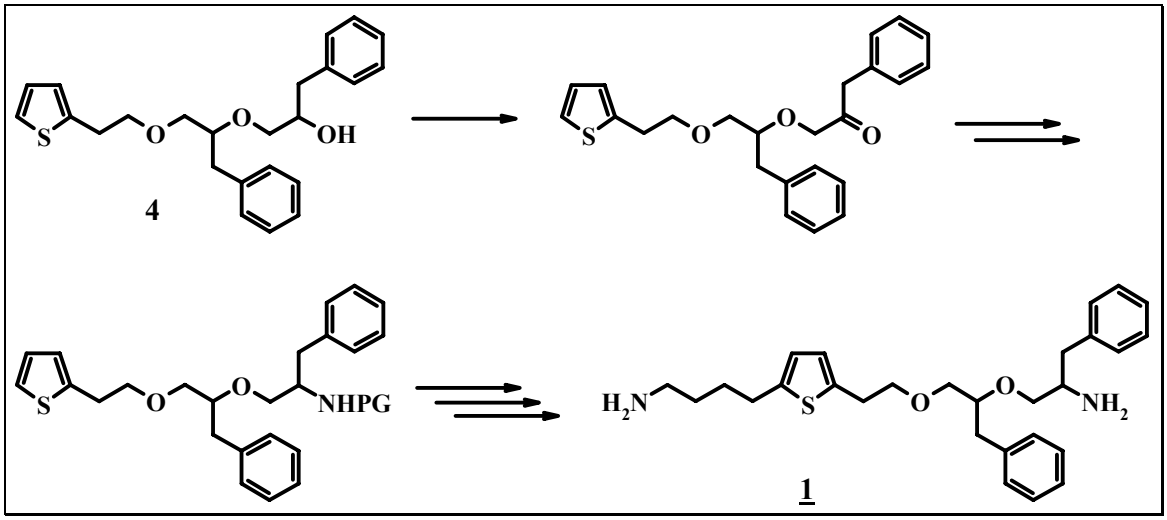


Scheme 14: Strategy B

In her PhD thesis Daniela Niepel reported two sequential ring opening reactions of benzyloxirane starting with commercially available thiophene-2-ethanol leading to alcohols **3** and **4.** Equimolar amounts of thiophene-2-ethanol and benzyloxirane **2** were reacted in substance with catalytic amounts of solid Na at 90°C overnight to give **3** in up to 40% yield and subsequently under the same conditions alcohol **4** in a yield of 25%. Besides the low yield the second addition suffers from difficult separation of the similar alcohols **3** and **4.** The attempted transformation to the primary amine however was not successful. Various approaches to introduce the amine moiety *via* hydroxyl activation and nucleophilic substitution are reported: Activation as mesylate or triflate followed by reaction with liquid ammonia, a Mitsunobu type protocol with potassium phthalimide as well as activation with 2-fluoro-N-methylpyridinium tosylate and reaction with LiN_3. Unfortunately none of the desired nitrogen bearing compounds was obtained.

2.2 Synthetic Approach within this Thesis

Structural variations of precursor **DN-26** or the nitrogen protecting group PG_1 were considered as possible efforts based on strategy A. These envisioned strategies are indicated in Scheme 13 in green color. However, the difficulties described by Daniela Niepel, promising challenges interesting and tough enough associated with the functionalities of the right chain were the basis of the decision to exclusively follow strategy **B** within this thesis**.**



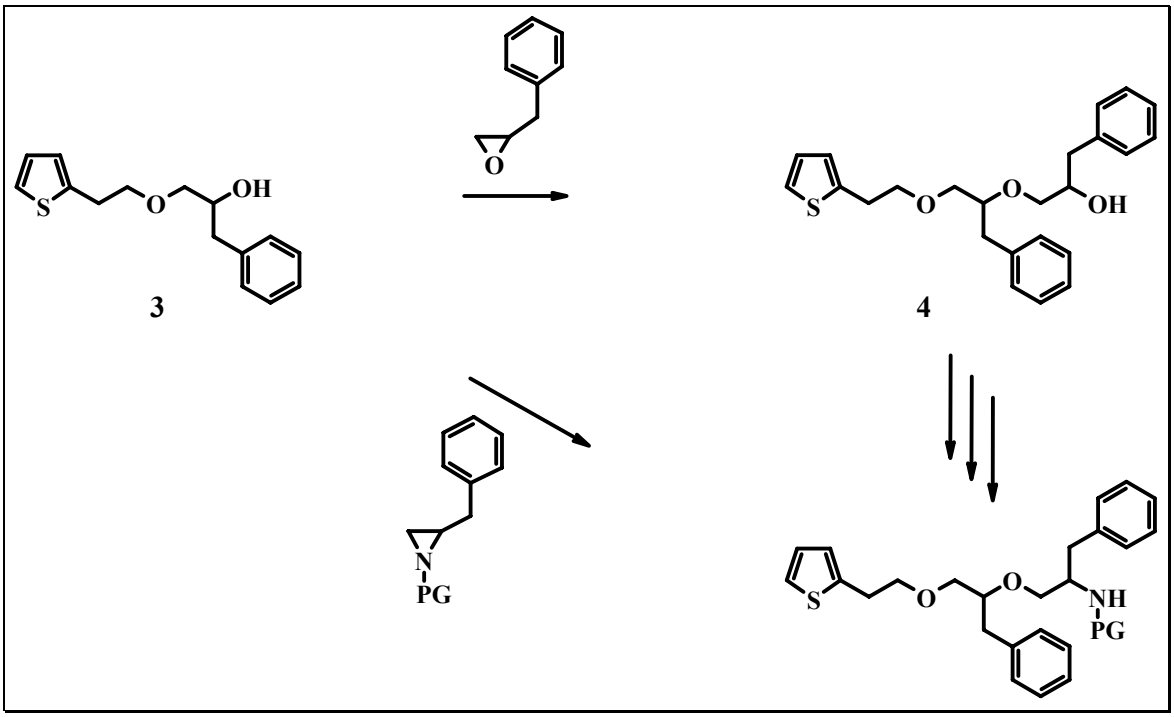
Scheme 15: Planned synthetic strategy

Based on the reported results of the initial formation of the two ether bridges affording alcohol **4** the investigation whether the introduction of amine moiety *via* oxidation and reductive amination could be achieved was considered. Afterwards the selection of a suitable protecting group for the amine moiety should hopefully allow the introduction of the shorter chain based on synthetic concepts established by former group members. However at the beginning of the thesis another approach was favored.

In general, based on the results of the investigation of effects of absolute configuration (Chapter 2.1) racemic starting material was used in all approaches. In steps where a second stereogenic center was formed no effort to achieve diastereoselectivity was undertaken. The distribution of diastereomers was evaluated by NMR only and found to be about 1:1.

2.3 Addition to activated Benzylaziridines

In respect to the unsatisfactory results reported for the epoxide approach and the attempted introduction of the amine moiety at the beginning of the thesis an alternative methodology for the formation of the second ether functionality and the simultaneous - so far unsuccessful - introduction of the amine moiety was envisioned.



Scheme 16: Benefits of an "aziridine concept"

By replacing the epoxide benzyloxirane by its nitrogen analogue, benzylaziridine the second ether moiety and the amine functionality could simultaneously be introduced saving at least two steps that are reported as very difficult to establish before. An epoxide concept suffers based on its mechanism from subsequent side reactions, which will be described below. For the aziridine ring opening this is not the case and in contrast to the reported difficult separation between the similar alcohols **3** and **4** starting material and product of the aziridine cleavage should differ enough in chemical and physical properties to make separation easy. In Scheme 16 it is highlighted how many steps would be saved if the "aziridine concept" could be realized, compared to the synthetic strategy involving epoxide addition, oxidation, reductive amination and nitrogen protection as described above. Circumventing both the

second epoxide addition and the introduction of the amine moiety in one step would be a great achievement in the applicability of the synthesis towards derivatives of general structure **A**.

Aziridine Rings

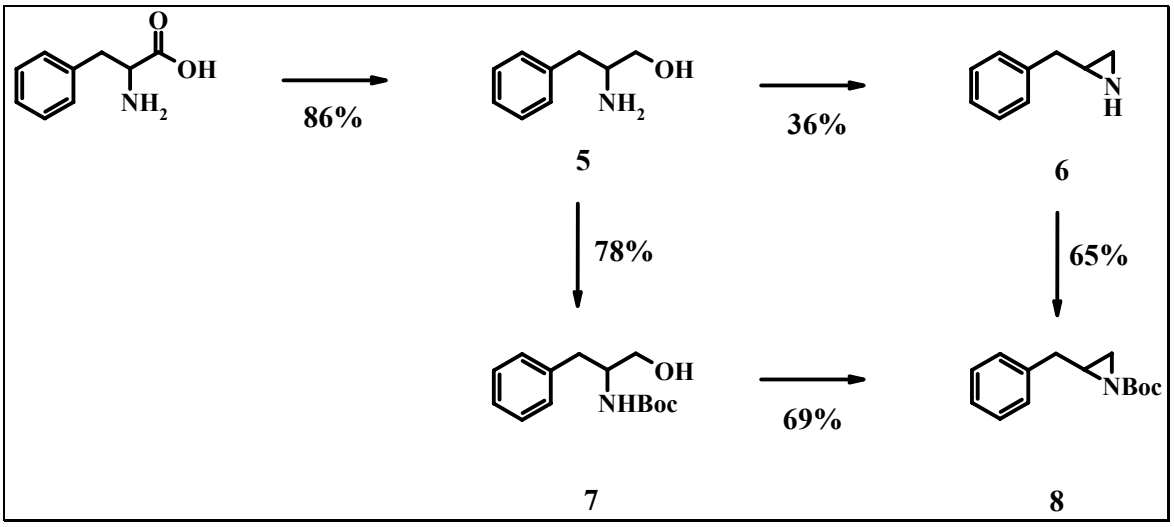
Compared with oxiranes aziridines are more stable three membered rings in the neutral form and also in the positively charged aziridinium form. The activation with e.g. Lewis acids does not automatically lead to the cleavage of one of the two possible nitrogen-carbon bonds and it is also not possible to cleave N-unsubstituted aziridines by nucleophiles in the same manner as it is possible with epoxides. The regioselectivity of the ring opening reactions is not as predictable as in case of oxirane where nucleophiles in general lead to addition at the less substituted carbon and Lewis acidic catalysis normally leads - *via* formation of the more stable carbocation - to addition at the higher substituted carbon atom.

Beside the activating catalyst and the nucleophile the protecting group at the nitrogen has substantial influence on the ring opening properties. In the present problem the group must be activating enough to allow the ring opening by a secondary aliphatic alcohol and must be on the other hand of temporary character and removable under conditions where other functionalities of the molecule are not affected. The most restrictive moiety in this context is the thiophene ring, which excludes groups that are cleaved by hydrogenolysis. In addition the homobenzylic ethers prohibit the use of strong base and ether cleaving Lewis acids.

Unfortunately, although extensive reviews[43,44,45] about the ring opening of aziridines exist, only little literature was found about reactions with alcohols other than MeOH, EtOH or *i*-PrOH, which can be offered in large excess.

[43] Stamm, H. *J. Prakt. Chem.* **1999**, *341*, 319-331
[44] Hu, X.E. *Tetrahedron* **2004**, *60*, 2701-2743
[45] Prasad, B.A.B.; Sanghi, R.; Singh, V.K. *Tetrahedron* **2002**, *58*, 7355-7363

2.3.1 Preparation of N-Boc-2-benzylaziridine 8



Scheme 17: Possible routes towards Boc-aziridine 8

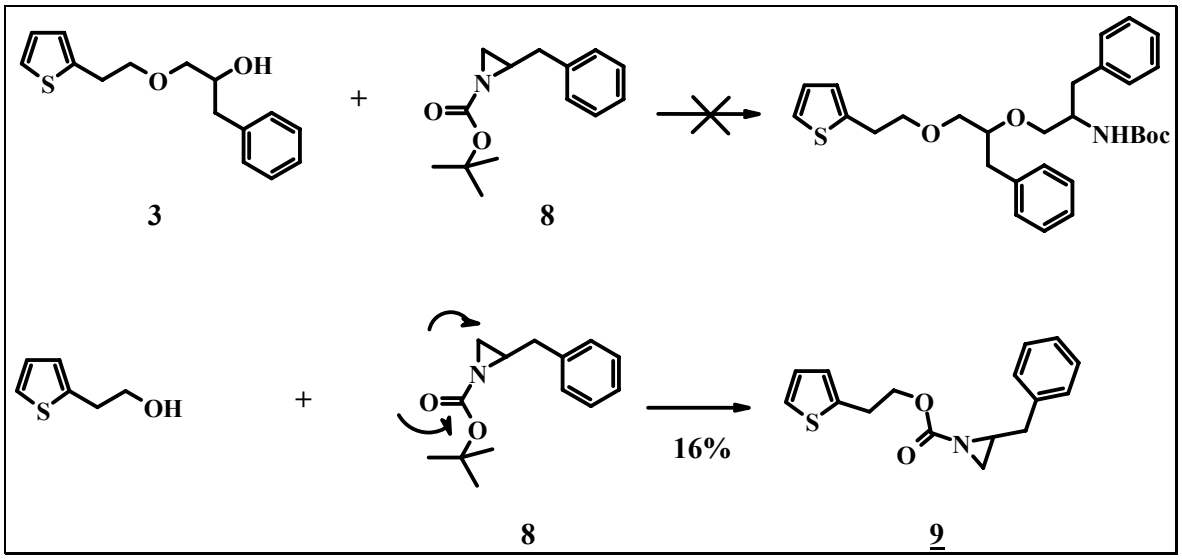
With special regard to its easy removal - cleavable under different mild acidic conditions - more than to its activating properties the first group that was tested was the Boc-group.
All aziridine compounds within this thesis were prepared from phenylalaninol. Phenylalaninol **5** has been prepared by reduction from racemic phenylalanine with $LiAlH_4$[46] in 86.6% yield. Besides the classical $LiAlH_4$ reduction a very interesting protocol using $NaBH_4/I_2$ was found in the literature and was tested. The conditions have been optimized by Gooding *et al*[47] for the preparation of phenylalaninol in a synthesis robot. Simulating the reported conditions in a standard reaction flask as far as possible phenylalaninol was obtained in a good yield of 74%. The benefits of the latter method are the possibility to work in concentrated solution (15 %) and the homogenous workup.

Boc-aziridine **8** is a compound previously reported in the literature and was prepared starting from the phenylalaninol **5** either by initial ring closure[48] to give aziridine **6** and subsequent introduction of the Boc-group[49] or *vice versa* by initially protecting the amine moiety to give intermediate **7**[64] and subsequent ring closure[50] to yield Boc-aziridine **8**. In both cases the ring closure can be performed according to literature protocols *via* a Mitsunobu type reaction with

[46] Granander, J.; Sott, R.; Hilmersson, G. *Tetrahedron* **2002**, *58*, 4717-4725
[47] Vo, L.; Ciula, J.; Gooding, O.W. *Org. Process Res. Dev.* **2003**, *7*, 514-520
[48] Xu, J. *Tetrahedron: Asymmetry* **2002**, *13*, 1129-1134
[49] analogous to: Ziegler, F.E.; Belema, M. *J. Org. Chem.* **1994**, *59*, 7962-7967
[50] analogous to: Hillier, M.C.; Davidson, J.P.; Stephen F.M. *J. Org. Chem.* **2001**, *66*, 1657-1671

triphenylphosphine and DEAD. Actually both paths have been investigated and the second variant was favored in the present case. The ring closure can be performed under milder conditions with the Boc-amino group. The obtained yields were higher and the crystalline intermediate **7** was easier to purify than the unsubstituted aziridine **6**, which has to be submitted to chromatography. According to the mechanism of Mitsunobu type reactions the deprotonated form of the nucleophile attacks the activated hydroxyl group and therefore the acidity of the NH bond and not the nucleophilicity is important for higher reactivity and milder conditions.

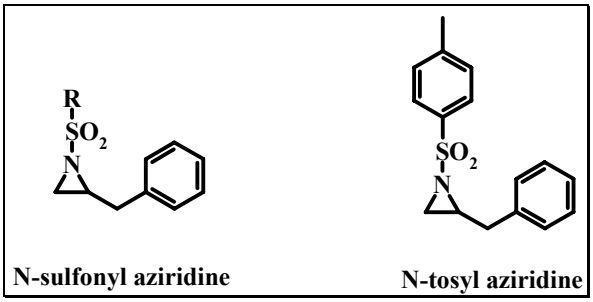
2.3.2 Attempted Ring Opening of N-Boc-aziridine 8



Scheme 18

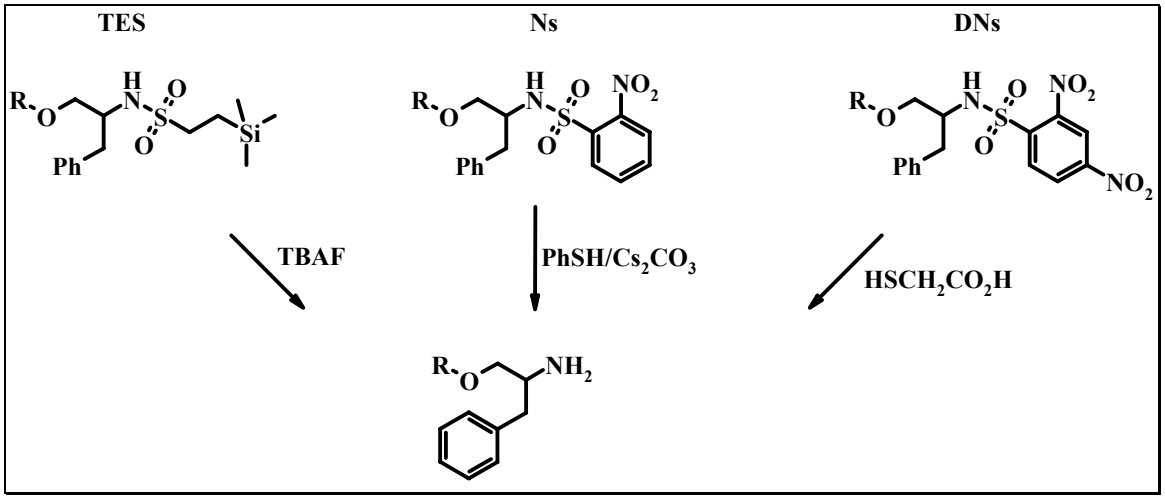
Attempts to open N-Boc-benzylaziridine **8** by alcohol **3** and by thiophene-2-ethanol using literature procedures were unsuccessful. Only in the latter case a reaction was observed but the isolated product **9** was that of a transesterification. Carbonyl attack as side reaction is known in the literature[43] but is normally observed to happen on carbamates less bulky than a Boc-amine. The fact, that even a primary alcohol did attack the sterically hindered carbamate rather than open the aziridine was interpreted as indication that the Boc group was not activating enough.

2.3.3 N-Sulfonyl-protected Aziridines



Scheme 19: N-Sulfonylaziridines

N-Sulfonylaziridines in general and especially tosylaziridines are described in the literature as particularly activated aziridine derivatives due to the good leaving group quality of the sulfonamide[43]. A problematic feature of sulfonamides as PG for amines in general is that the cleavage of the S-N bond can normally only be accomplished under harsh conditions of dissolving metal reduction[51,52], conditions tentatively incompatible with the thiophene or the ether moieties. Certainly more sophisticated sulfonamide PGs have been developed and used to prevent the protection from being almost irreversible.



Scheme 20: Easily removable N-sulfonyl protecting groups

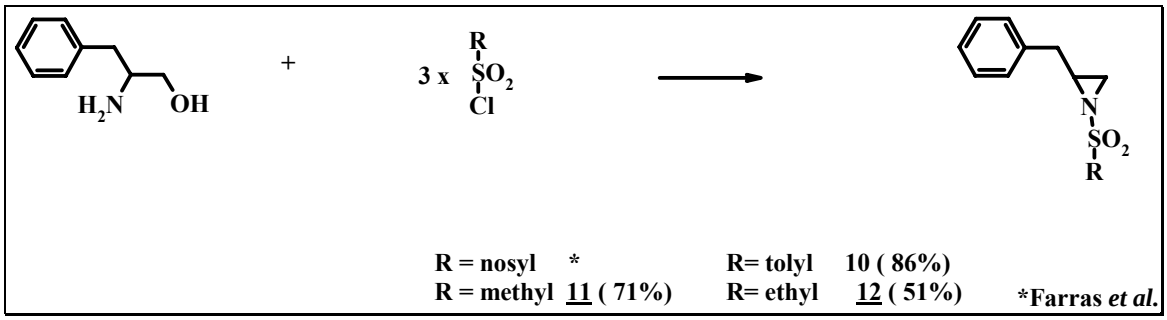
Examples that should be mentioned in this context are the 2-nitrophenylsulfonyl (Ns) and the 2,4 dinitrophenylsulfonyl group (DNs), which can be cleaved by mercaptoacetic acid or

[51] Kocienski, P.J. *Protecting Groups,* Georg Thieme Verlag, Stuttgart **2000** and references therein
[52] Alonso, A.A.; Andersson, P.G. *J. Org. Chem.* **1998**, *63*, 9455-9461

thiophenol, respectively[53] and Weinreb's so called TES-group[54,55] that can be cleaved by treatment with fluoride releasing agents.

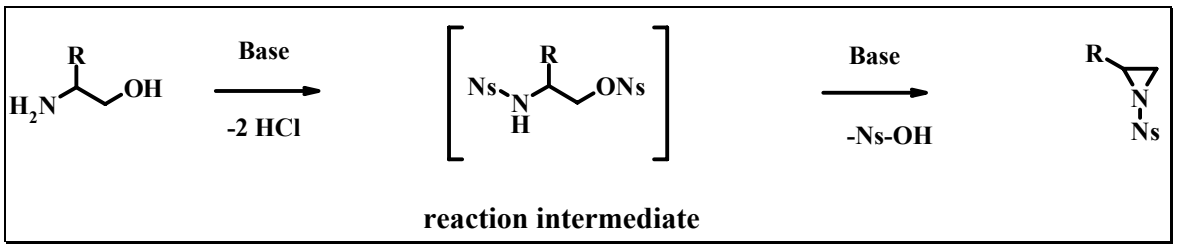
However, the tosyl group is the most cited PG regarding aziridine opening and tosyl chloride is readily available right in contrast to the alternative groups, which are either expensive or have to be synthesized. These facts led to the decision to develop a method for the ring opening reaction starting N-tosylaziridine **10** and only after success the same conditions were planned to be applied to one of the other, more sophisticated protection groups.

2.3.4 Preparation of N-Sulfonyl-2-benzylaziridines.



Scheme 21

A very convenient way for the preparation of N-(4-nitrophenylsulfonyl)-2-benzylaziridine from phenylalaninol was described by Farras *et al*[56]. In a one pot reaction the amino alcohol was treated with an excess of nosyl chloride in DCM/Pyridine = 2:1 at room temperature. The nosyl chloride serves as activation for the hydroxyl group and as protection and activation of the nitrogen, which than reacts with the sulfonated hydroxyl group.



Scheme 22: Mechanism of the one-pot strategy towards N-sulfonylaziridines

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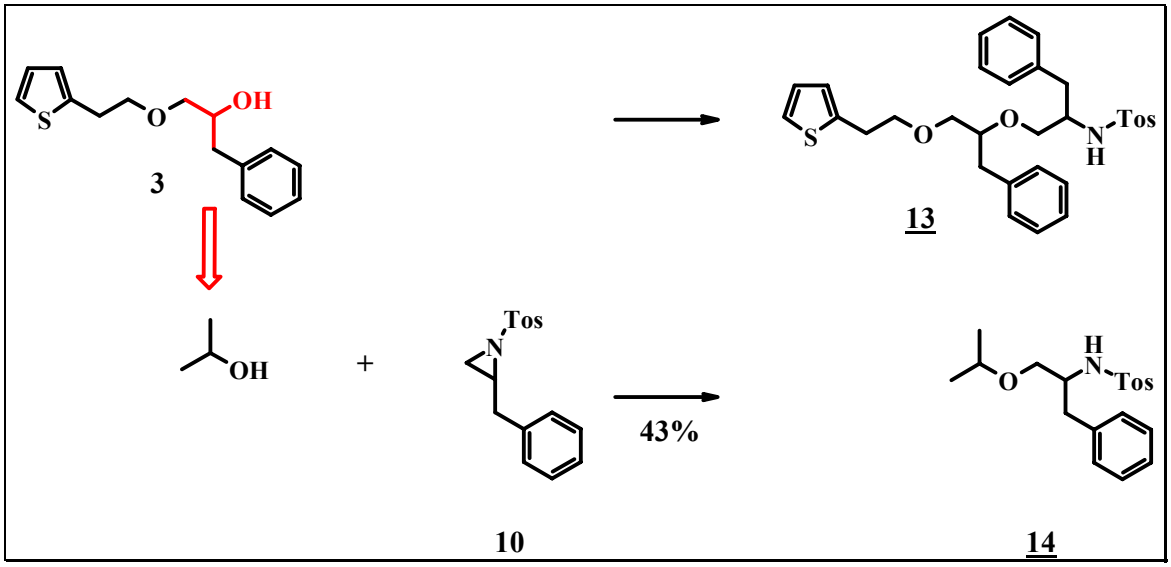
[53] Fukuyama, T.; Cheung, M.; Jow, C.-K.; Hidai, Y.; Kan, T. *Tetrahedron Lett.* **1997**, *38*, 5831-5834
[54] Weinreb, S.M.; Chase, C.E.; Wipf, P.; Venkatraman, S. *Organic Syntheses* **1998**, 75, 161-169
[55] Parker, L.L.; Gowans, N.D.; Jones, S.W.; Robins, D.J. *Tetrahedron*, **2003**, *59*, 10165-10171
[56] Farras, J.; Ginesta, X.; Sutton, P.W.; Taltavull, J.; Egeler, F.; Romea, P.; Urpi, F.; Vilarrasa, J. *Tetrahedron* **2001**, *57*, 7665-7674

With the exact reproduction of the reaction conditions (with tosyl chloride instead of nosyl chloride) a mixture of tosyl chloride, starting material, traces of target product and as the major compound a by-product which was identified as the postulated reaction intermediate (Scheme 22), was isolated. It was suggested that due to electronic effects the reaction was much slower without the 4-nitro group in the phenyl ring. Therefore the crude mixture was stirred in DCM/Pyridine = 2:1 overnight, affording compound **10** in an equimolar mixture with tosyl chloride. (An attempt to use only two equivalents of tosyl chloride - sufficient according to the mechanism - led to incomplete cyclisation) Compound **10** was isolated after column chromatography in high purity in a yield of 86 % as white crystals. This very convenient method was in an analogous manner successfully applied to the preparation of N-mesylaziridine **11** (71%) and N-ethansulfonylaziridine **12** (52%). These experiments were meant to prove the wide applicability of the method and should serve as model compounds for future attempts with aliphatic TES-Cl.

2.3.5 Ring Opening of N-Tosylaziridine 10

Expecting problems with regioselectivity or other side reactions and avoiding the complex analysis of compound **13** a model reaction with i-PrOH was carried out first.



Scheme 23: Isopropanol as model substrate

The addition of *i*-PrOH to the aziridine was attempted analogous to the literature[57] where benzylic alcohol was deprotonated with NaH and added to aziridine **10** in dry dioxane in good yield. Actually, after optimization of reaction time the method could be successfully applied to the addition of *i*-PrOH. It is advisable to follow the reaction with ^{1}H-NMR to avoid any starting material in the crude product that could not be separated by column chromatography. Target compound **14** can be obtained in pure form after column chromatography in a yield of 43%.

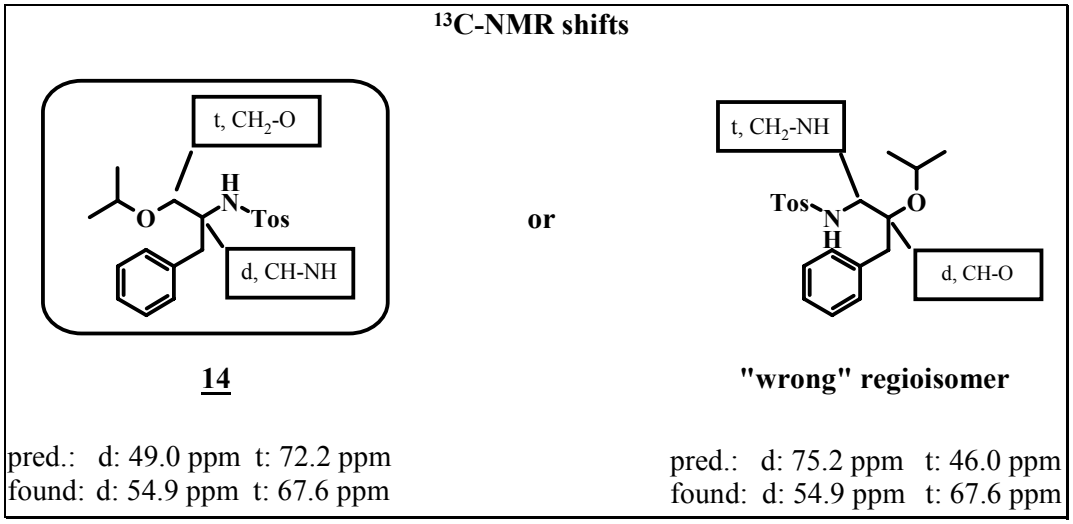
Proving the Correct Regiochemistry

It was necessary to confirm that the correct regioisomer was formed – proving that the nucleophilic attack occurred at the less substituted carbon.

In the NMR analysis all signals of the former aziridine systems can clearly be assigned to their position. The difference of the two possible regioisomers is the substitution pattern of the two former aziridine ring carbons. For these two positions the chemical shifts for the ^{13}C-

[57] Wipf, P.; Venkatraman, S.; Miller, C.P. *Tetrahedron Lett.* **1995**, *36*, 3639-3642

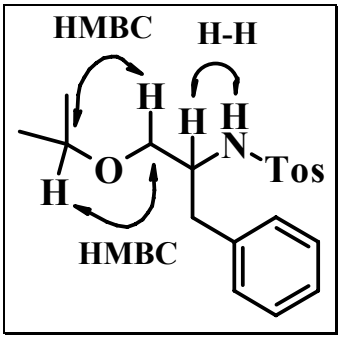
NMR were calculated[58] and compared with the signals of the APT (attached proton test) spectrum.



Scheme 24: NMR Analysis in concerns of regioselectivity of the ring opening

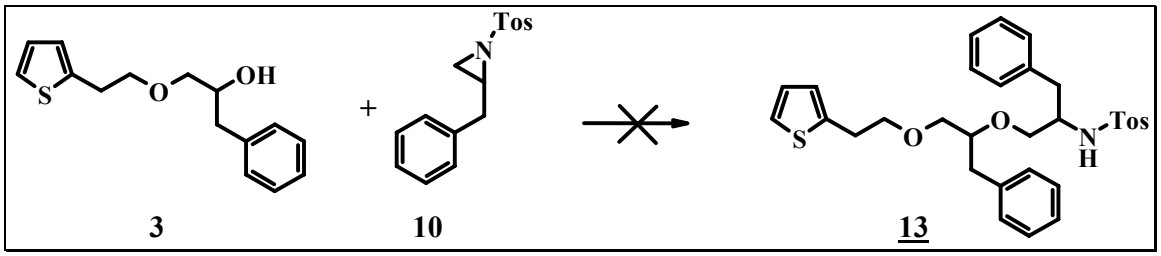
This comparison strongly indicates that regioisomer **14**, formed by reaction at the less substituted aziridine carbon, was the isolated product.

Structure **14** was further supported by correlation of the sulfonamide NH and the H-2 in the H-H COSY spectrum. Proton H-2 was correlated to doublet 54.9ppm *via* HSQC. Further more, there is a reciprocal correlation in the HMBC-spectrum between the CH of the propoxy group and the CH_2 at 67.6 ppm.



[58] Chem Draw

After the successful test reaction the same reaction conditions were applied to alcohol **3.**

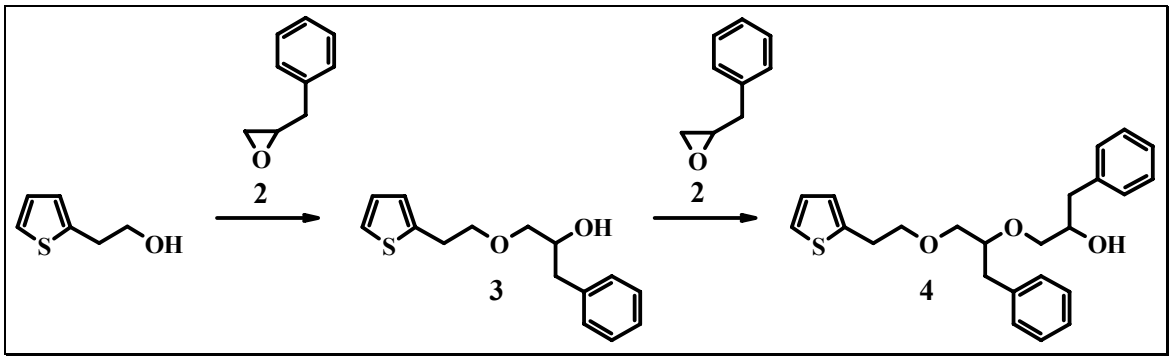


Scheme 25

It has to be reported that at different temperatures (55°C, 65°C, 75°C, 100°C) only decomposition of aziridine **10** was observed and no formation of compound **13** was obtained. Unfortunately, this very interesting and promising approach towards β-amino ether structures had to be abandoned for the time of the thesis in order to be able to reach the synthetic target in an appropriate time. Nevertheless the "aziridine approach" will definitely be further investigated as soon as possible in case that more derivatives of general structure A will be targets of future synthesis.

Accepting that within this thesis a synthesis of target compound **1** based on aziridine cleavage methodology will not be accomplished, it was decided to closely investigate the reasons for the poor yields reported in the "epoxide approach" and optimize the reaction conditions.

2.4 Preparation of Diether Alcohol 4



Scheme 26

Benzyloxirane 2

Benzyloxirane **2** was prepared from allylbenzene in 100g scale by epoxidation with m-CPBA in DCM according to the literature[59] and was purified by distillation to give pure compound **2** in over 85% yield.

2.4.1 By-products and their Minimization

After the protocols[42] were reproduced with comparably low yields, the reaction conditions were optimized to minimize the by-products. The general problems and by-products obtained in the epoxide addition reactions will be discussed in general before the differences of the two steps will be explained separately. What was decided right at the beginning was to generate the alkoxides with NaH instead of elemental Na. In comparison to pieces of solid Na. NaH is easier to handle, has a larger surface and it is possible to get a quantitative reaction with the alcohol.

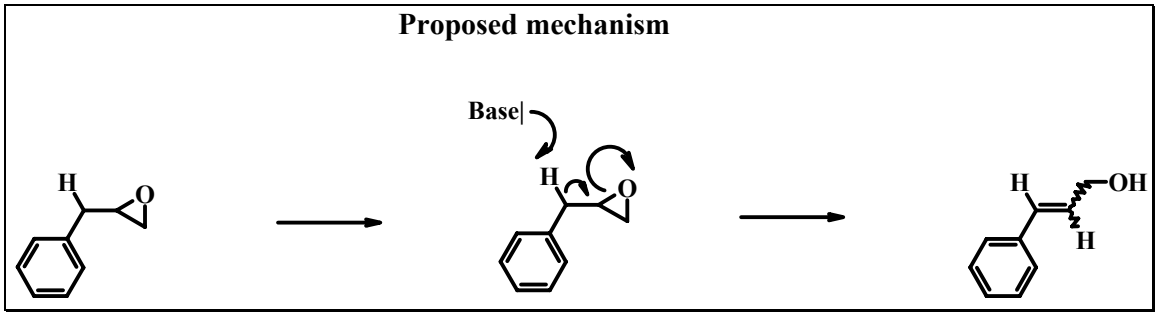
Elimination Tendency

It was observed that it is important to wait until all NaH is consumed before benzyloxirane **2** was added at temperatures lower then the optimal reaction temperature of 65°C. It was examined that benzyloxirane tends to eliminate otherwise, thus forming cinnamic alcohol as a mixture of E/Z isomers. It was obtained in almost all experiments(<5%) but in much higher

[59] Fuhrer, W.; Ostermayer, F.; Zimmermann, M.; Meier, M.; Mueller, H. *J. Med. Chem.* **1984**, *27*, 831-836

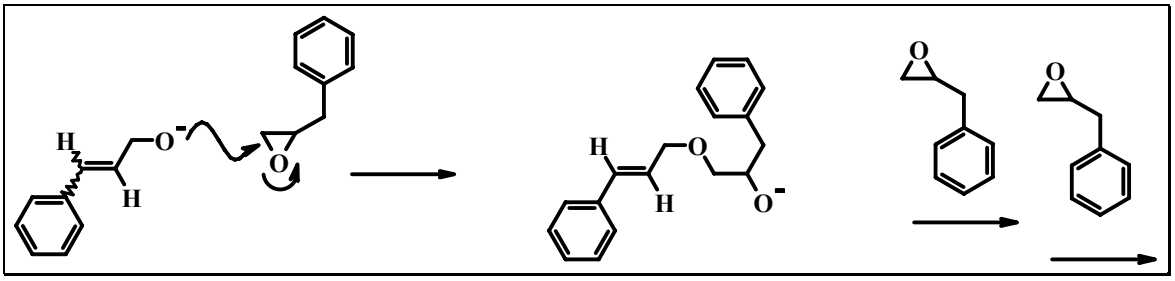
amounts if the temperature at the addition was higher than 40°C or direct contact of benzyloxirane **2** with unreacted NaH was not avoided. Therefore no more than 0.25 equiv. NaH relative to the alcohol can be used since otherwise the mixture does not get homogenous until the addition of the epoxide.

In one experiment thiophene-2-ethoxide was generated with NaOMe by evaporation from MeOH. The residue was dissolved in dry DMF before benzyloxirane was added. In this case cinnamic alcohol was the only product isolable and was formed very quickly at the addition. These results were explained with the proposed mechanism in Scheme 27 that is also supported by results in the literature[60,61].



Scheme 27: Basic elimination of benzyl oxirane

The formation of a few percent of cinnamic alcohol is not a problem in principle but the cinnamic alcohol can and does react with benzyloxirane in the same manner as the desired alkoxide. The vinylic system was detected and quantified *via* its prominent signals in the ^{1}H-NMR also in the following synthetic steps.



Scheme 28: Side reactions of benzyl oxirane

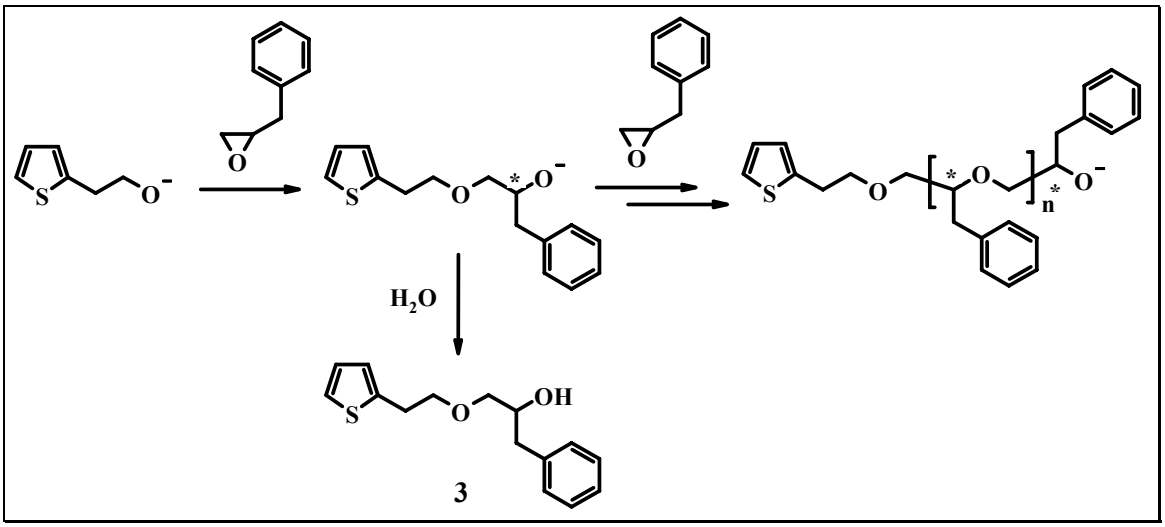
[60] Murayama, E.; Kikuchi, T.; Nishio, H.; Uematasu, M.; Sasaki, K.; Saotome, N.; Sato, T. *Nippon Kagaku Kaishi* **1985**, *3*, 350-361

[61] Haynes, L.; Heilbron, I.M.; Jones, E.R.H.; Sondheimer, F.; *J. Chem. Soc.* **1947**, 1583-1585

The elimination tendency of benzyloxirane **2** is troublesome but it can be minimized by following strictly the optimized procedure. All by-products that are formed containing the phenyl vinyl group instead of the thiophene ethyl group are eliminated latest in the Friedel-Crafts acylation step due to the lower activity of the phenyl ring in these reactions. (see also Chapter 2.10)

Oligoether Formation

The second type of by-products which are formed in both addition steps is unfortunately more difficult to avoid and might be the reason for the low yields reported especially for the second addition step.



Scheme 29: Mechanistic drawback of the oxirane concept

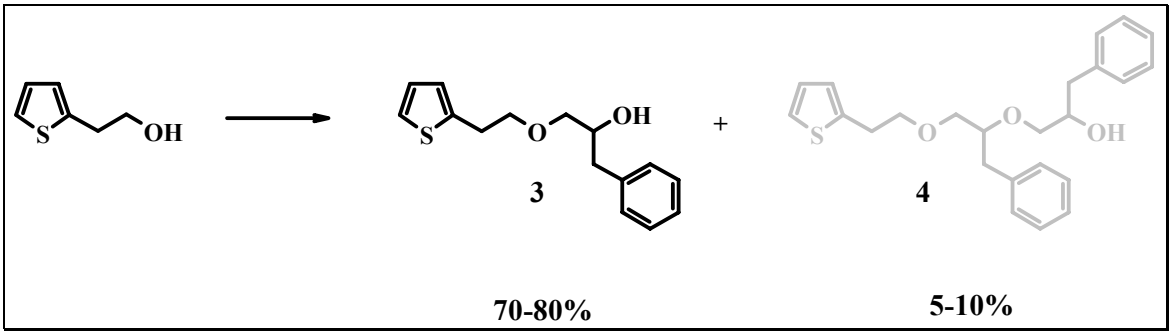
It was observed that always more benzyloxirane than alcohol was consumed. This evidence can reasonably be explained by the formation of oligoethers, products of multiple additions to benzyloxirane **2** in one reaction pot. Since the by-products are structurally very similar to the target compounds and because they are obtained as two or more diastereomers they were at the beginning hard to detect by TLC or NMR in mixtures.

Scheme 29 shall emphasize that the reason for the low yields lies inherently in the mechanism of nucleophilic epoxide ring opening. The addition of initially formed alkoxide to the oxirane affords another alkoxide of similar chemical reactivity.

Although oligoethers longer then compound **4** were not isolated in a pure form at the alcohol step they were identified in mixtures *via* mass spectroscopy and detected by ^{13}C-NMR. After the oxidation (Chapter 2.6) of contaminated alcohol **4** however the triether ketone was isolated and identified by NMR and MS as will be discussed later.

After considering the nature of the side reaction it seemed reasonable to try to establish a one pot procedure to yield alcohol **4** directly from commercially available thiophene-2-ethanol. Thus 2.2 equivalents of benzyloxirane **2** were added to one equivalent of thiophene-2-ethanol and 0.2 equivalent of NaH. The result agreed the above hypotheses and a similar distribution of products was obtained in the crude mixture as after the second step of the two-pot sequence. Nevertheless, since the only possibility to shift the distribution of products towards the target compounds was expected in offering an excess of starting alcohol, the two pot sequence was favored. The success of this "excess strategy" will be discussed for the two steps separately.

2.4.2 Preparation of Alcohol 3



Scheme 30

One equivalent of benzyloxirane **2** was added to 1.5 equiv. of thiophene-2-ethanol and 0.3 equiv. of NaH. After stirring 6 hours at 65°C total consumption of benzyloxirane was determined *via* TLC and after acidic workup the mixture of starting material and target product can be purified by column chromatography or bulb to bulb distillation (purification by normal distillation was attempted, but did only lead to decomposition and no pure fractions). Actually, alcohol **3** was formed almost exclusively, contaminated only with small amounts of alcohol **4.** It is reasonable to suppose that the steric hindrance of the formed secondary alkoxide **3** is strong enough to mainly avoid subsequent reactions. Thus, a reasonable selectivity to give one major product was achieved.

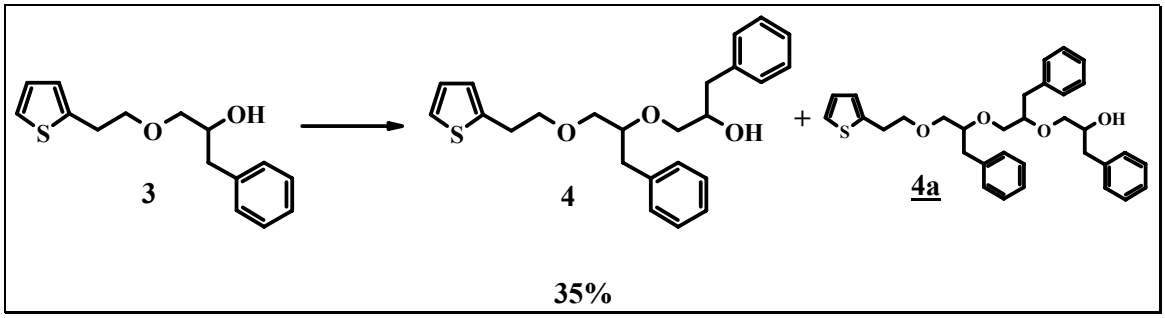
***Kugelrohr* Distillation**

At 150°C/0.1mbar the excess of thiophene-2-ethanol was distilled off and was successfully recycled as starting material. After 30 minutes the temperature was raised to 205°C/0.1mbar affording the target compound **3** in good purity. By raising the temperature to 250°C/0.1mbar, a second fraction was isolated containing a few percent of diether **4** in very good purity, which can be combined with the target product of the second step.

Summary

By small variations of the conditions the yield of the first addition was raised from 40% to over 70% (up to 80 % taking in account the diether alcohol **4**). A simplified purification procedure allowing the isolation of pure product also on a larger scale was a first satisfying result.

2.4.3 Preparation of Alcohol 4



Scheme 31

The second addition was performed under identical conditions like the first one but was more problematic due to several reasons:

1) Oligoethers with more than two benzyl groups are formed in a larger amount. This most probably occurs due to the fact that in contrast to step one, the steric hindrance of the corresponding alkoxides (**3** and **4**) is very similar.

2) While in step one the major by-product was the desired compound **4**, none of the by-products in the second addition step are useful.

3) Moreover the purification methods established in step one did not afford higher amounts of **4** in good purity. Due to very similar R_f-values of starting material **3** and

target compound **4,** column chromatography was not effective. *Kugelrohr* distillation also did not afford diether **4** in sufficient purity.

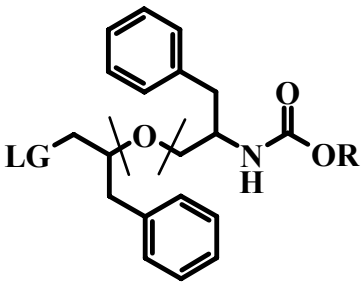
***Kugelrohr* Distillation**

The excess of alcohol **3** can be distilled off (200°/0.1mbar) under conditions reported above and afterwards target compound **4** was isolated (250°C/0.1mbar) as second fraction in 35% yield. In general the obtained material was contaminated with 10-15% triether **4a.** The separation of these oligoether impurities was achieved at the following ketone step and will be discussed later.

2.5 Attempted Alternatives for the Introduction of the Second Ether

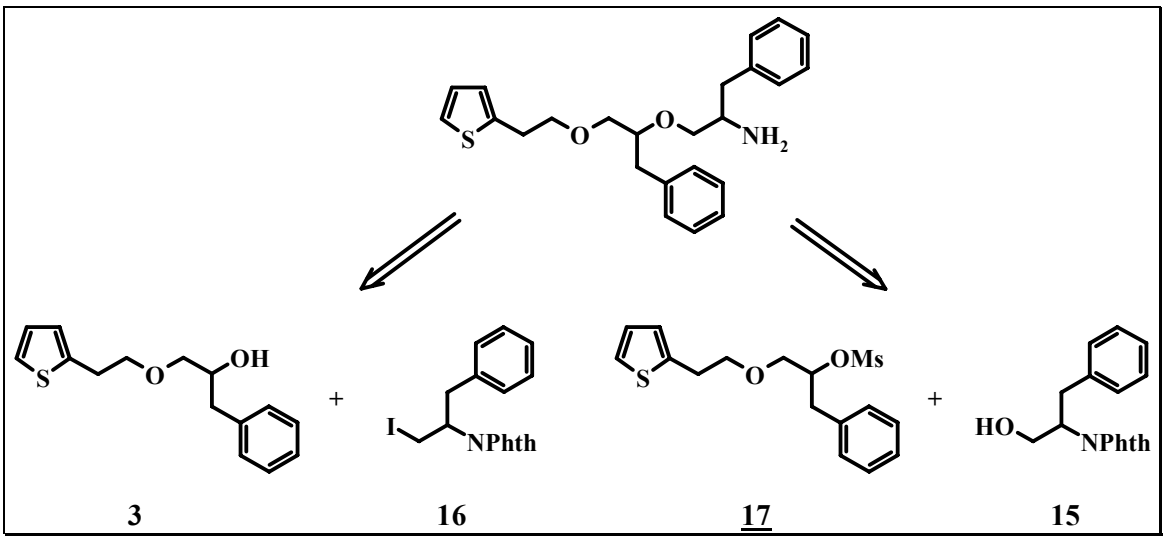
While the first epoxide addition could be optimized to give reproducible high yields the formation of the second ether moiety *via* the epoxide concept is very unlikely to be further improved significantly. Worse than the low yields, which could be accepted in one step is the fact that no methods of purification were found to obtain material that would for example allow exact combustion analysis. The impurities have so similar structures that a complete separation by means of chromatography is difficult also in the subsequent steps.
The aziridine approach has already been introduced as one possible short cut in the synthetic strategy that would have solved the problem. Additionally one more short survey into an alternative strategy was started aiming at the formation of the problematic ether bond.

2.5.1 Approaches *via* Williamson's Ether Synthesis



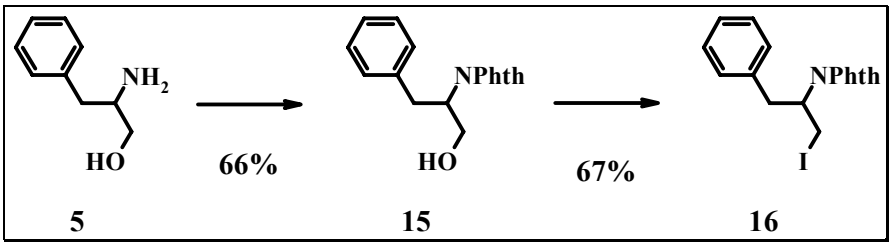
building block A

The reported[42] attempts to synthesize building blocks of type A (see Chapter 2.1) have been attempts *via* Williamson's ether synthesis. In all described experiments the PG for the amine moiety has been a NH-carbamate, the Boc group or the Cbz group respectively. Since these approaches suffered from predominant side reactions it was decided to use the phthalyl group in this case to end up with phenylalaninol derivatives **15** and **16** with a fully protected non nucleophilic nitrogen. These intermediates were envisioned for attachment to compound **3**, which is now according to the optimized synthesis readily available in larger quantities.



Scheme 32: Planned Williamson's Ether synthesis

As presented in Scheme 32 both directions of nucleophilic attack have been envisioned. The necessary building blocks were prepared according or analogous to the literature.

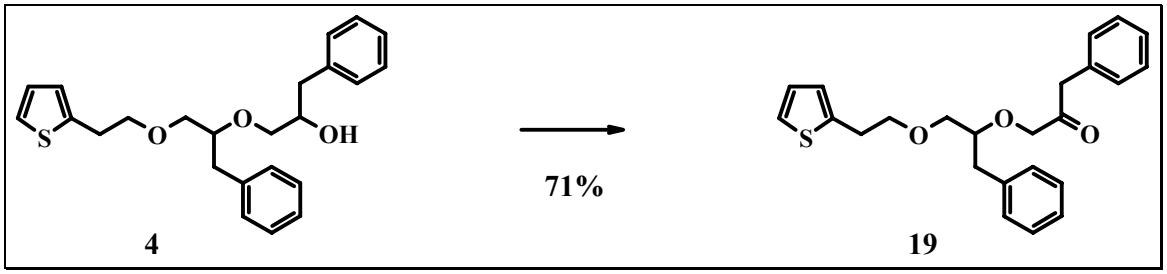


Scheme 33

Compound **15** has been prepared by conversion of racemic phenylalaninol **5** to the corresponding phthalimide with phthalic anhydride[62] or more efficiently with N-carbethoxyphthalimide (Nefkens-reagent)[63] in a yield of 65.5%. Compound **15** was then transformed analogous to literature[64] to the iodo compound **16**[62] under Mitsunobu conditions with triphenylphosphine/imidazole/I_2 in DCM in a yield of 67.3%.

Mesylate **17** was prepared using standard conditions[42] for the mesylation of hydroxyl groups from alcohol **3** in 94.0 % yield. This approach was just started towards the end of the diploma thesis and by now no successful results for this approach can be reported.

2.6 Oxidation of Alcohol 4 to the Corresponding Ketone 19



Scheme 34

In the PhD Thesis of D. Niepel it is reported that it should in principle be possible to obtain ketone **18** by oxidation of alcohol **4** with Dess-Martin periodinane. Due to the very high price of Dess-Martin reagent and the rather delicate conditions[65,66] for its preparation in laboratory scale - involving an explosive intermediate – another more suitable oxidant was searched for.

It can be reported that oxidation of the shorter alcohol **3** with PCC, PDC and Dess-Martin Reagent[67] all in DMC worked smoothly under standard conditions. Corresponding ketone **18** was obtained in yields of around 70 % at first attempt. However a variant where PCC was adsorbed on silica gel, which simplifies work-up was chosen and applied to compound **4**. In

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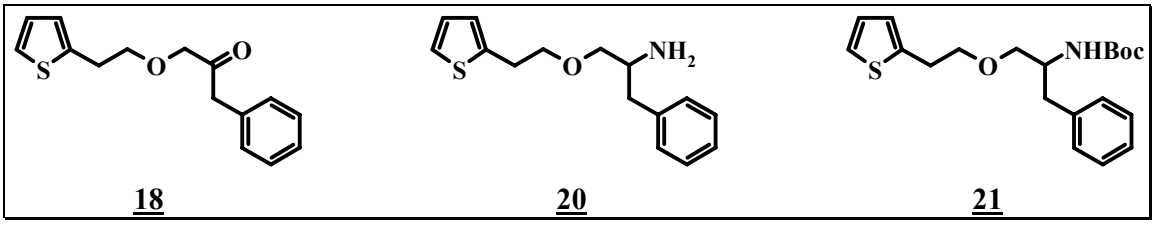
[62] Carocci, A.; Catalano, A.; Corbo, F.; Duranti, A.; Amoroso, R.; Franchini, C.; Lentini, G.; Tortorella, V. *Tetrahedron: Assymetry* **2000**, *11*, 3619-3636
[63] analogous to: Grote, C.W.; Kim, D.J.; Rapoport, H. *J. Org. Chem.* **1995**, *60*, 6987-6997
[64] Quagliato, D.A.; Andrae, P.M.; Matelan, E.M. *J. Org. Chem.* **2000**, *65*, 5037-5042
[65] Dess, D.B.; Martin, J.C. *J. Org. Chem.* **1983**, *48*, 4155-4156
[66] Ireland, R.E.; Liu, L. *J. Org. Chem.* **1993**, *58*, 2899
[67] Bach, T.; Kirsch, St. *Synlett* **2001**, *12*, 1974-1976

contrast to the oxidation with Dess-Martin reagent, always traces of alcohol remained in the reaction mixture although an excess of up to three equivalents of PCC was added in several portions and the reaction was stirred for two days. However, these traces of starting material can be separated easily by means of flash column chromatography or bulb to bulb distillation.

2.6.1 Smaller Analogues of Ketone 19 and Amine 22

As mentioned above, the screening for an appropriate oxidant for alcohol **4** as well as the first attempt towards the reductive amination and protection of the corresponding amine were performed with the shorter alcohol **3.**



18 **20** **21**

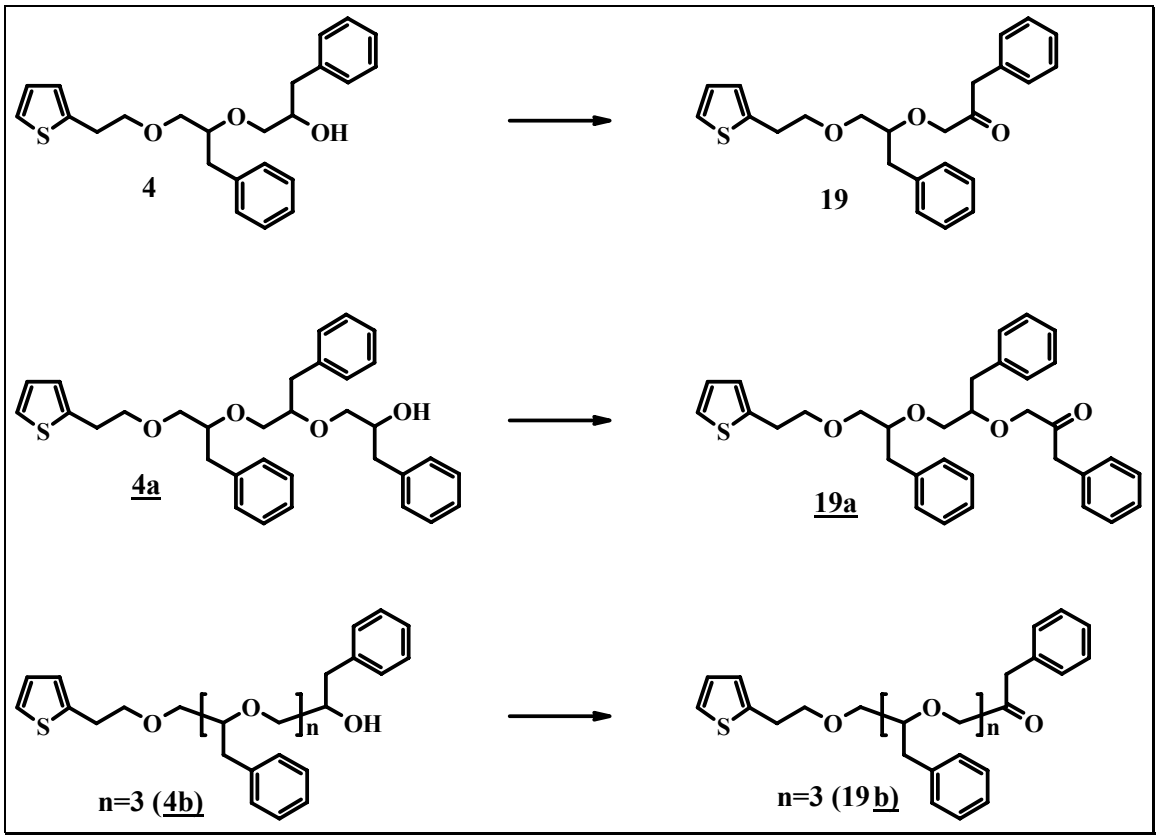
Scheme 35: Analogous compounds of lower complexity

Establishing the subsequent steps for the total synthesis of **1**, small molecule analogues were used to optimize the reaction conditions. Furthermore, due to the high structural similarity the availability of NMR spectra for compounds **18**, **20** and **21** facilitated the interpretation of the NMR spectra of the actual intermediates a lot.

Synthesis and analysis of the shorter compounds **18, 20** and **21** are included in the Experimental Part but in general the discussion is focused on the main route containing the structures with two benzyl groups.

Separation of Longer Oligo Ether Impurities

As discussed above, alcohol **4** could in general only be obtained contaminated with tri and traces of higher oligoether derivatives (Scheme 36) and therefore the oxidation was performed with these mixtures. *Kugelrohr* distillation turned out to be a facile and efficient tool for obtaining pure samples.

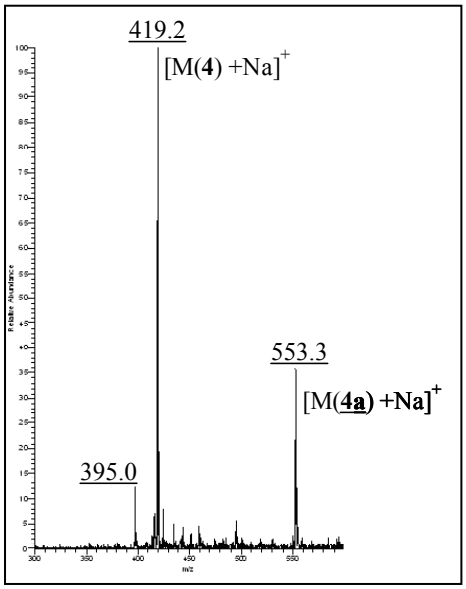


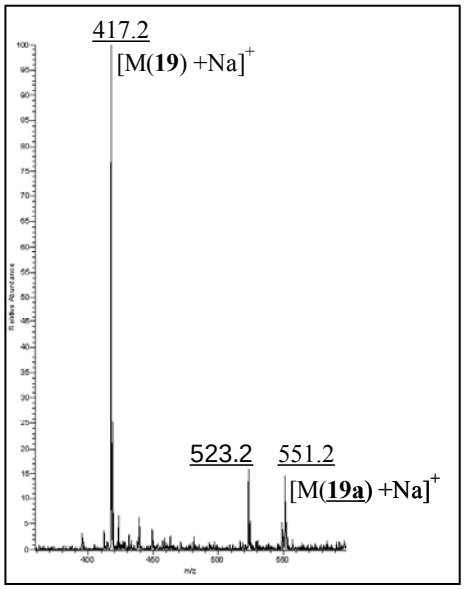
Scheme 36: Oxidation of mixtures

On the alcohol step no prominent signals in the ^{1}H-NMR can be found to differentiate between compound **4** and compounds containing more than 2 benzyl groups (**4a, 4b**…). The only possibility to estimate the degree of purity with NMR is the ratio of the integrals of two prominent thiophene signals related to the sum of the other aromatic signals in the ^{1}H spectrum. In the ^{13}C-NMR smaller amounts of triether **4a** – obtained as a mixture of 2 diastereomers – or of longer ones with even more diastereomers can not be detected. The composition of the material can easier be estimated by mass spectroscopy.

Material consisting mostly of alcohol **4** (395: M+H; 419.2: M+Na) (left spectrum) was obtained as a 250°C fraction of a bulb to bulb distillation. It was contaminated according to

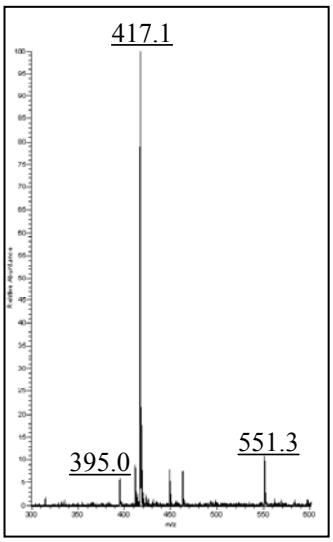
MS by *ca.* 30% of triether **4a** (553.3: M+Na). This mixture was oxidized to obtain a crude product **19** (417.2: M+Na) in which the longer triether **19a** (551.1: M+Na) can still be identified in the MS spectrum (right spectrum).

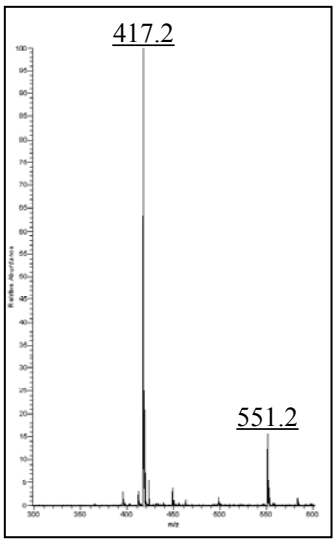


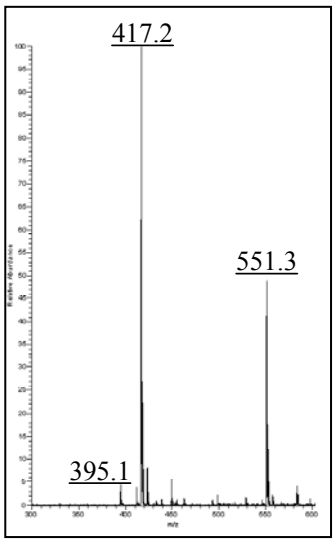


As a first attempt it was tried to purify this crude product by column chromatography. All obtained fractions containing any ketone species were collected into 5 different portions beginning from the first to the last ketone containing fractions. From all of these portions MS-spectra were recorded.

First fractions **Middle fractions** **Last fractions**

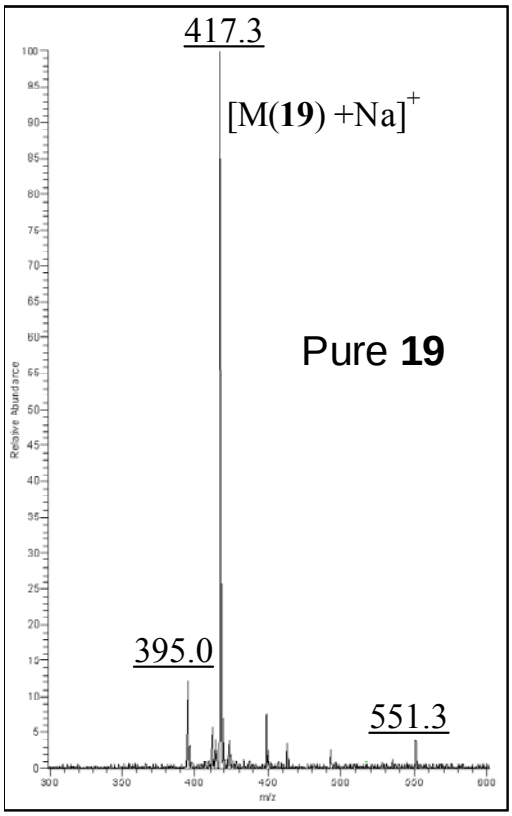


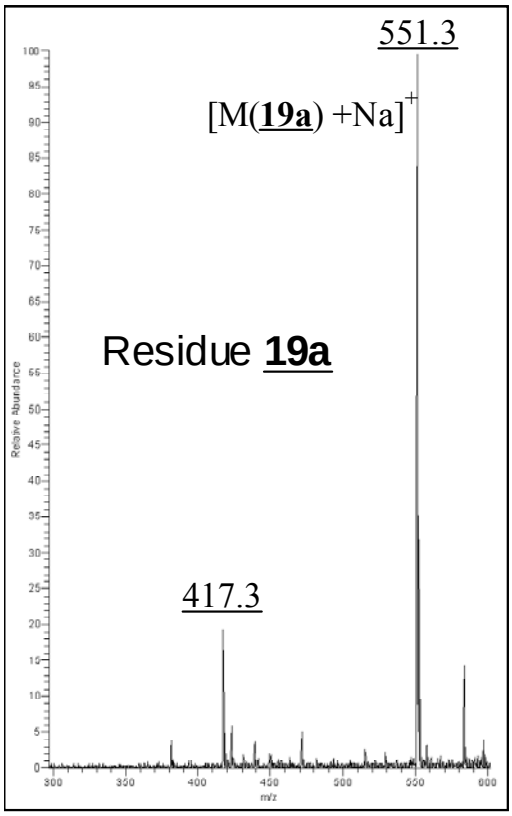




It was obvious that the triether **19a** is enriched in the latest of the ketone fractions. However, no real purification effect can be achieved *via* this way. All fractions containing ketone **19** were combined and submitted to *Kugelrohr* distillation. At 225°C (0.1mbar) a main fraction

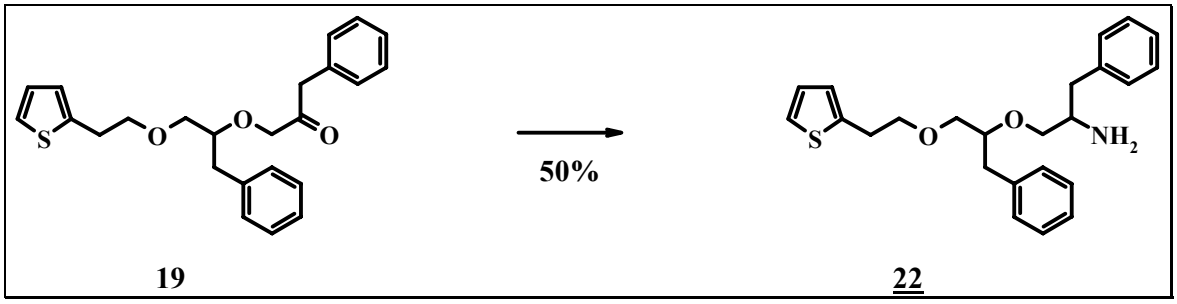
was obtained containing target compound ketone **19** according to MS and also ^{1}H-NMR with almost no (<5% in MS) triether ketone **19a**.





The residue of the distillation was almost pure **19a** according to MS which was confirmed by ^{1}H- and ^{13}C-NMR. Based on these results in general no column chromatography was performed. The traces of starting material alcohol **4** remained in the residue of the bulb to bulb distillation together with the by-products, ketones **19a**, **19b.** For the subsequent reaction steps certainly material of this quality (around 5% impurities) had to be accepted. During the column chromatographic purifications a "pure impurity" was never isolated therefore it never was completely separated. Although in all the subsequent reaction steps of the synthesis pure ^{13}C-NMR spectra (3000-5000 scans) of the intermediate compounds were obtained it was not achieved to obtain material that passed the tight ranges of combustion analysis.

2.7 Reductive Amination of Ketone 19



Scheme 37

The most usual methods for the conversion of a ketone to a primary amino group are catalytic reductive amination, Leuckart-Wallach procedures or reductive amination with $NH_4OAc/NaCNBH_3$ in alcohols[68]. Since catalytic reduction is in general not compatible with thiophenes and the Leukart-Wallach procedures for affording primary amines are reported under rather harsh conditions (elevated temperature/concentrated formic acid with or without formamide)[69,70] the reductive amination is reported under very mild conditions (0°C to rt in alcohols). Therefore, the latter method was applied to the current problem at first.

In analogy to a literature protocol[71], $NaCNBH_3$ was added to a cooled solution of ketone **19** and an excess of NH_4OAc in dry *i*-PrOH with molecular sieve (4Å). The yields were low and it was obvious that only very little NH_4OAc was soluble at this temperature. Therefore the reaction was performed in dry MeOH (molecular sieve 3Å). The reaction was fast and after two hours no starting material was detectable *via* TLC and a very promising crude product was obtained. Sometimes the crude product still contained a lot of boron species indicated by signals in the range of 1.0-1.5 ppm. Decomposition and liberation of the free amine species was accomplished by stirring in MeOH / 2N HCl and analogous work up like above.

The purification was performed by flash column chromatography which gave pure target compound **22** (diastereomers 1:1) in only about 50% yield and a mixture of several apolar by-products (TLC).

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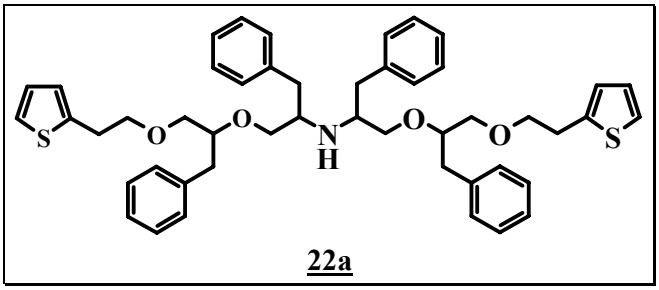
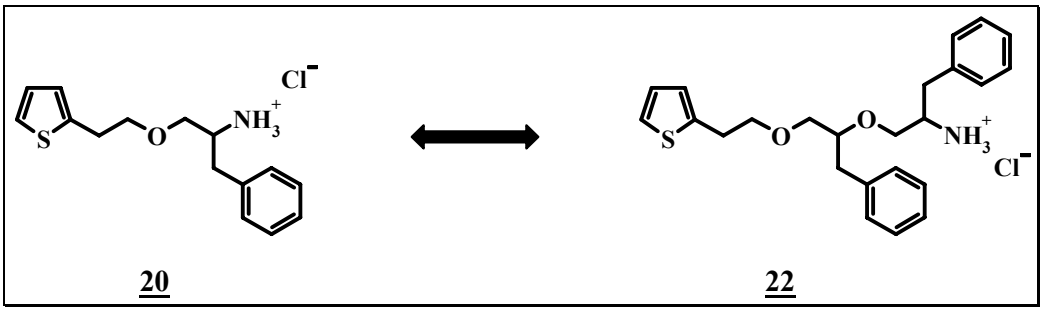
[68] e.g. Autorenkollektiv *Organikum*, Wiley-VCH, Weinheim, **2000**
[69] Burger, A.; Walter, R.C.Jr. *J. Am. Chem. Soc.* **1950**, *72*, 1988-1990
[70] Rohrmann, E.; Shonle, H.A. *J. Am. Chem. Soc.* **1944**, *66*, 1516-1520
[71] Jeong, E.J.; Sung, L.T.; Hong, S.K.; Lee, E. *J. Am. Chem. Soc.* **2002**, *124*, 14655-14662



22a

Scheme 38: By-product of the reductive amination

In the mixture the corresponding secondary amine was indicated in the MS by a predominant signal at m/z 774 $[M+H]^+$. It turned out to be crucial to separate the by-products to enable success in the following reaction steps.



20 **22**

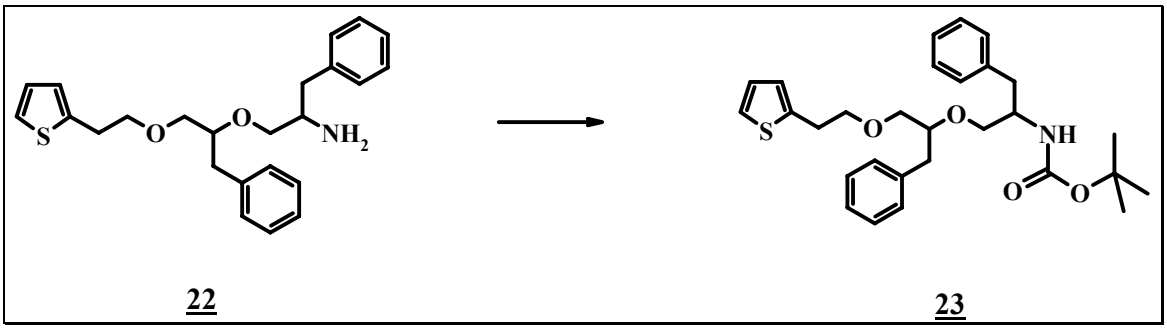
Scheme 39: Interesting differences in the solubility

An interesting difference between the smaller amine **20** and the larger amine **22** was that the extraction of the amine as hydrochloride worked very well in case of the shorter amine **20** but did totally fail in case of target compound **22**. The hydrochloride stayed dissolved in Et_2O and could not be extracted with 2N HCl.

Conclusion:

Although the results of the introduction of the amino moiety are not really satisfactory *via* this reductive amination protocol, it is at least possible in moderate yields of around 50%. In order to fulfill the synthetic goal in appropriate time further optimization of conditions or attempts with other methods like Leuckart-Wallach protocols or other reducing agents were not undertaken.

2.8 Boc-Protection of Amine 22

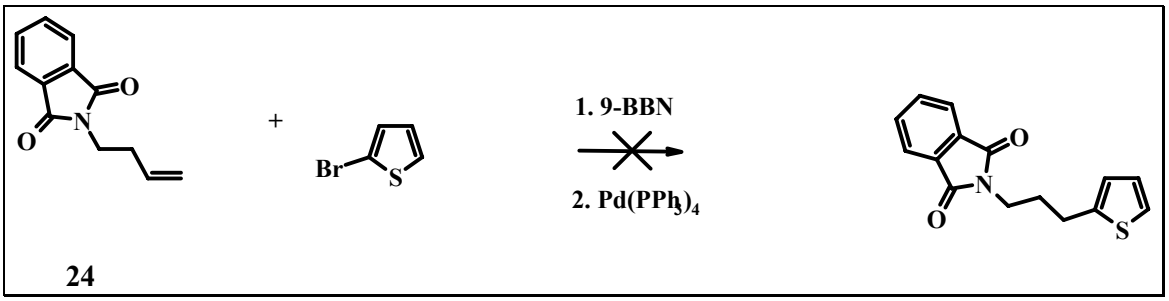


22 23

Scheme 40

It was shortly investigated, whether the left chain could be introduced *via* Suzuki coupling or by lithiation into 5-positon of the thiophene and Wurtz-type coupling, to save steps in the reaction sequence. The basic conditions of these methods made the Boc-amine **23** a reasonable intermediate. It was prepared in analogy to a literature procedure[64] with $(Boc)_2O$ in DCM and TEA from the pure or the crude amine **22**.

The first experiment related to this approach was an unsuccessful attempt to attach N-phthalyl protected 3-buten-1-amine **24**, prepared from 4-bromo-1-buteneamine and potassium phthalimide[72](45%), to 2-bromothiophene. A protocol with initial hydroboration using 9-BBN and subsequent $Pd(PPh_3)_4$ catalyzed Suzuki coupling according to literature conditions[73] was used, but only decomposition of the phthalyl group and multiple by-product formation was observed.



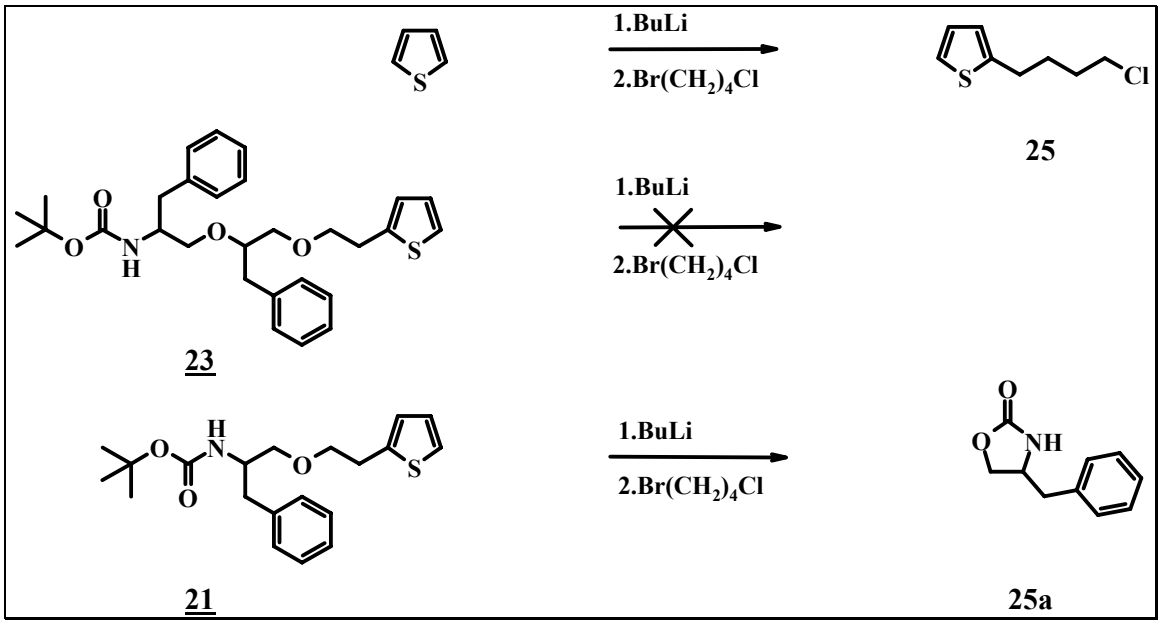
24

Scheme 41: Test reaction for Suzuki-Coupling approaches

[72] Vermeulen, M.; Zwanenburg, B.; Chittenden, G.J.F.; Verhagen, H. *Europ. J. Med. Chem.* **2003**, *38*, 729-737

[73] Miyaura, N.; Ishiiyama, T.; Sasaki, H.; Ishikawa, M.; Satoh, M.; Suzuki, A. *J. Am. Chem. Soc.* **1989**, *111*, 314-321

In a second approach it was tried to lithiate the Boc-amines **21** and **23** as well as unsubstituted thiophene in the 5 position and react it with 1-bromo-4-chlorobutane in a Wurtz-type coupling reaction. This strategy requires subsequent exchange of chloride by nitrogen.



Scheme 42: Lithiation and Wurtz-type coupling approach

In the test reaction the alkylation[74] was successfully performed with the unsubstituted thiophene (**25**[75]**,** 43% yield). An attempt to alkylate thiophene **23** giving no identified products and the isolation of unexpected oxazolidinone **25a**[76] - indicating elimination – as only identified product in the analogous alkylation of Boc-amine **21** made this strategy little promising.

The negative results of alternative strategies turned the attention back to the synthetic strategy established by former members of the group.

[74] Fillion, E.; Beingessner, R.L. *J. Org. Chem.* **2003**, *68*, 9485-9488
[75] Blicke, F.F.; Leonard, F. *J. Amer. Chem. Soc.* **1952**, *74*, 5105-5107
[76] Manas, M.M.; Padros, I. *J. Heterocycl. Chem.* **1993**, *30*, 1235-1239

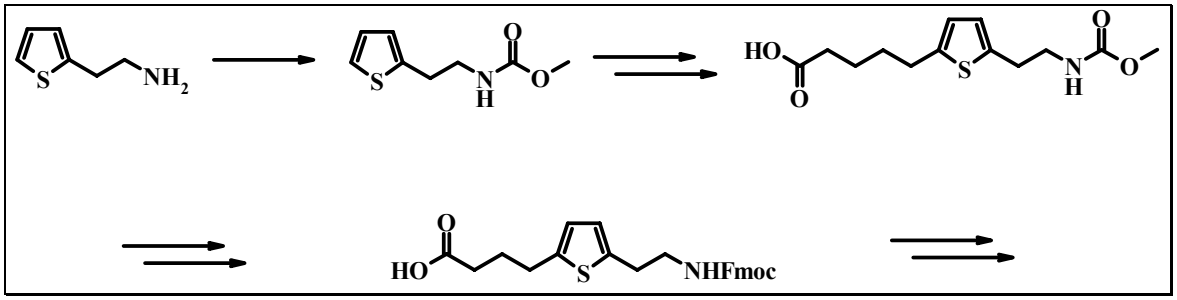
2.9 Fmoc-Protection of Amine 22

The well approved method for the introduction of the left side chain is based on a synthetic strategy worked out by Clemens Schödl and Oliver Schadt. It is based on Friedel-Crafts acylation and acidic deoxygenation in trifluoroacetic acid/Et_3SiH. These strong acid conditions make the acid labile Boc-group not applicable. Right on the contrary, a protection group was searched for, which must be very stable under acidic and Lewis acidic conditions.

Requirements for a suitable PG were stability towards Lewis acidic conditions and hot trifluoroacetic acid. Further more it has to be cleavable under conditions leaving the other moieties of the molecule unaffected[51,77]. Beside of more exotic PG the Fmoc group, methyl carbamate and 4,5-diphenyl-3-oxazolin-2-one were taken into consideration.

Preliminary Experience

Thomas Pöhler[41] has protected thiophene-2-ethanamine as methyl carbamate in a Friedel-Crafts acylation followed by acidic deoxygenation.



Scheme 43: Synthetic strategy reported by Thomas Pöhler

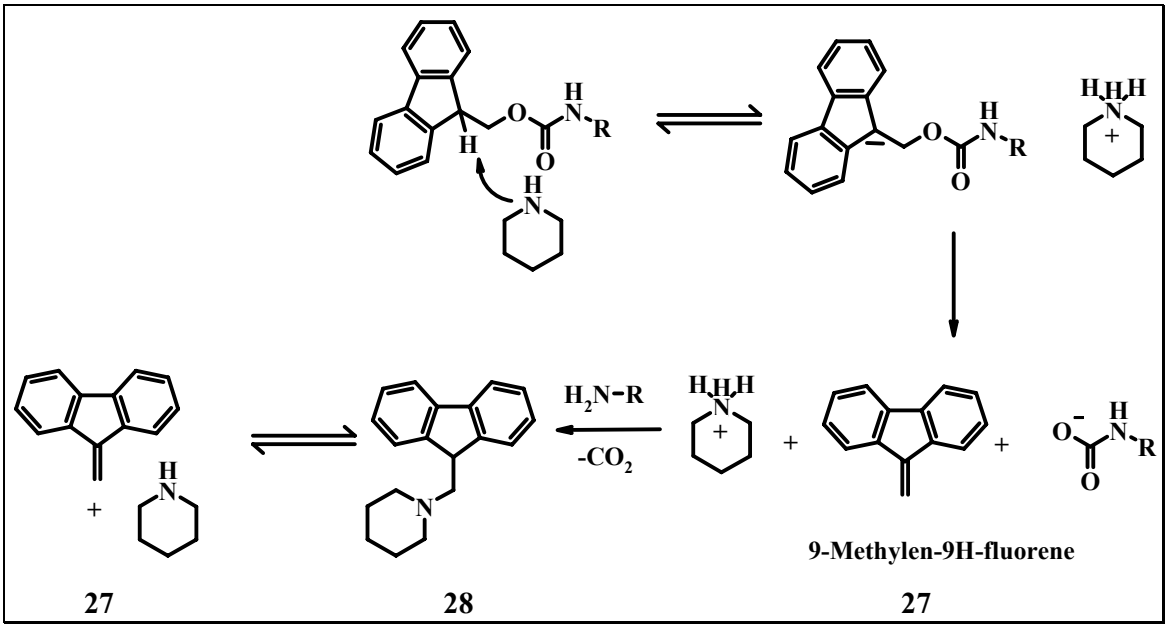
Afterwards he cleaved the methyl carbamate group under Huang-Minlon reduction conditions and protected the amine moiety *in situ* as Fmoc-group for further transformations. Due to the very harsh Huang-Minlon conditions that were supposed to be incompatible with the homobenzylic ether functions and because of the low yield of the PG-exchange (43%) it was decided not to repeat this strategy. Instead, the Fmoc group was envisioned to be introduced at the beginning. Thus, examination of the stability of the Fmoc group under conditions of Friedel-Crafts acylation and acidic deoxygenation is required.

---

[77] Greene, T.W.; Wuts, P.G.M. *Protective Groups in Organic Synthesis,* John Wiley&Sons, New York, **1980**

The Fmoc Group

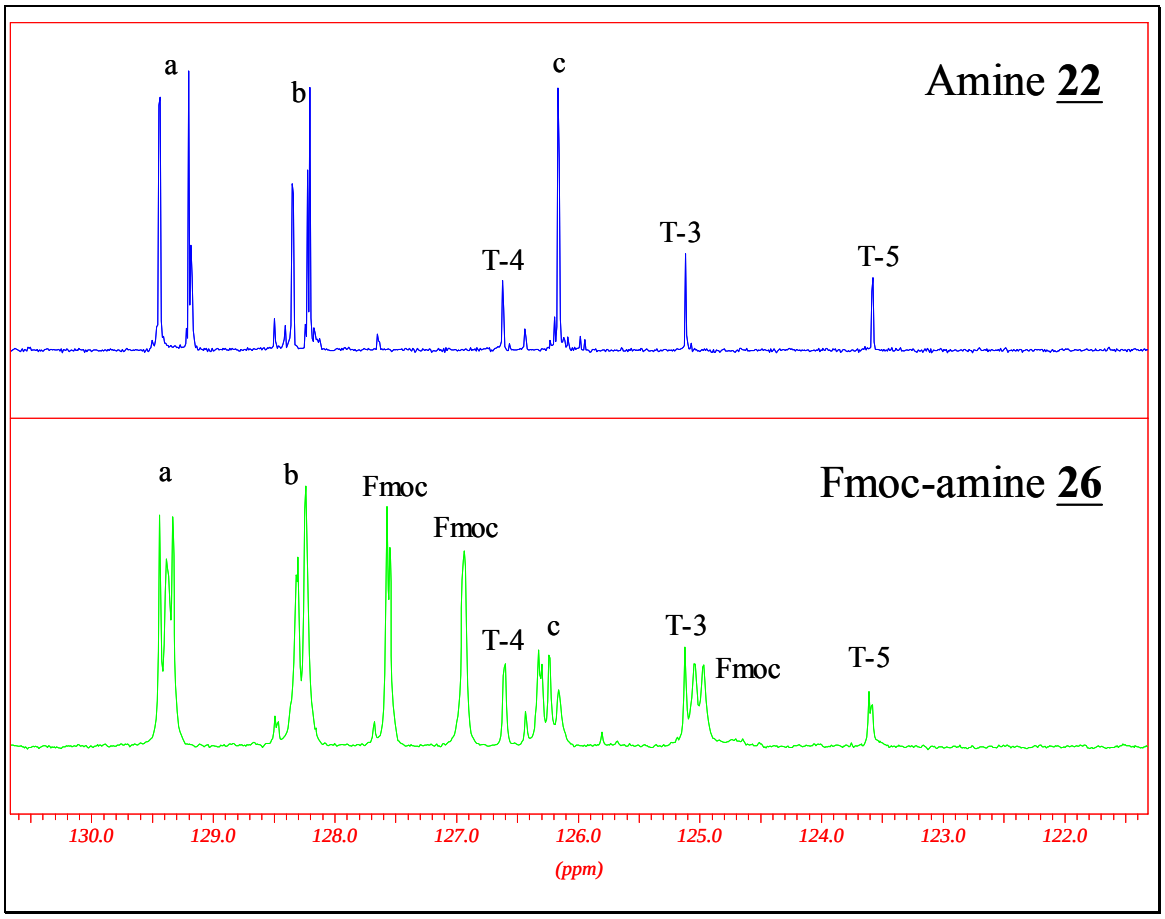
The most outstanding property of the Fmoc group is its high stability to acidic conditions; e.g. it is reported that the formation of acid chlorides can be performed without any deprotection.[51] Furthermore it can efficiently be removed with different secondary amines – normally piperidine is used. The only disadvantage is that the side products **27** and **28**, which are formed during the deprotection, can only be separated by column chromatography.



Scheme 44: Mechanism of the cleavage of the Fmoc-group

In the present case, the introduction of the Fmoc group especially complicated the NMR spectra of the following steps which is underlined by the comparison of the ^{13}C-spectra of the protected **26** *versus* the unprotected amine **22**. The relevant signals are assigned as follows:

Fmoc, T…thiophene, **a**…Ph-2/6 & Ph'-2/6, **b**…Ph-3/5 & Ph'-3/5, **c**…Ph-4 & Ph'-4



Scheme 45: Complexity derived from the Fmoc introduction

1) The introduction of the Fmoc-group leads in general to several new, partly overlapping signals in the aromatic region (**Fmoc** signals and **T-3** signal).

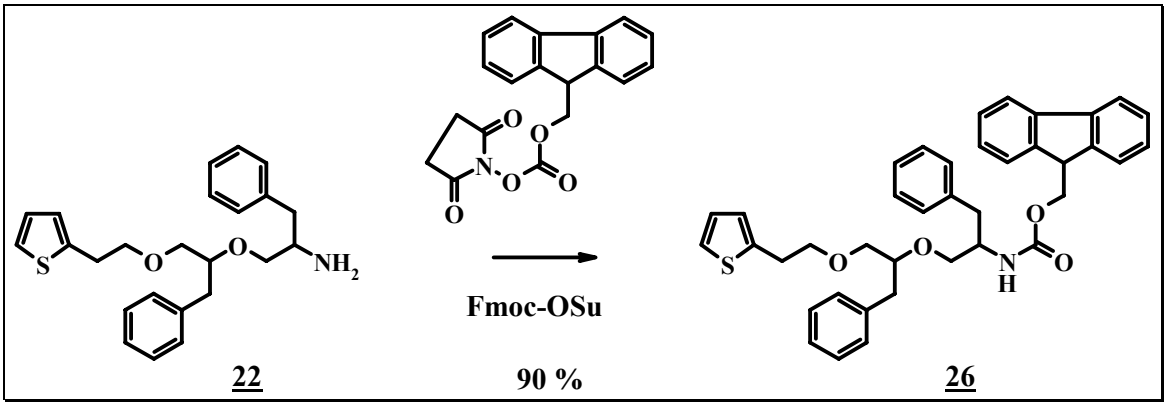
2) Many signals refer to diastereotopic positions and occur therefore in the asymmetric surrounding as two signals instead of one (refers to the aliphatic position).

3) Due to bulky ring system of the Fmoc group, the rotation of the NH-CO bond was restricted causing line broadening (**a** and **b**) and additional splitting of various signals (especially **c** and **Fmoc** signal at 125ppm**)**.

As a consequence, long-time detection and 2D-NMR experiments was necessary for the assignment of the signals for almost all following steps.

Introduction of the Fmoc group:

The Fmoc group was introduced according to a literature procedure[78] using N-(9-fluorenylmethoxycarbonyloxy)-succinimide (Fmoc-OSu) in DCM/THF 1:9 with excellent yields up to 90% after purification.



Scheme 46

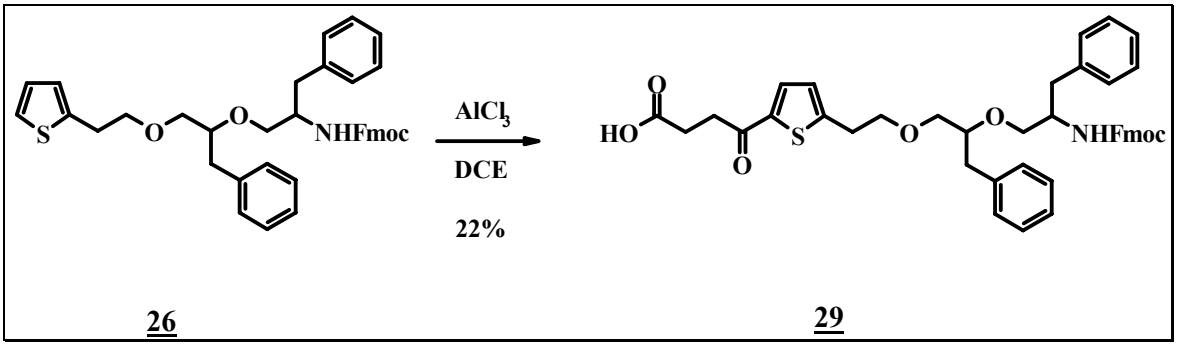
The always observed formation of fluorene derivative **27** makes fast chromatographic purification reasonable to obtain pure products.

It was once tried to directly use the crude product **22** of the reductive amination to save the chromatographic purification of the amine but under these conditions no product was formed. The reason for that might be the presence of secondary amines (see Chapter 2.7) in the crude material, which are excellent promoters for the decomposition of Fmoc-carbamates, as mentioned above.

[78] Myers, A.G.; Kung, D.W.; Zhong, B.; Movassaghi, M.; Kwon, S. *J. Am. Chem. Soc.* **1999**, *121*, 8401-8402

2.10 Friedel Crafts Acylation

2.10.1 Preparation of Acid 29

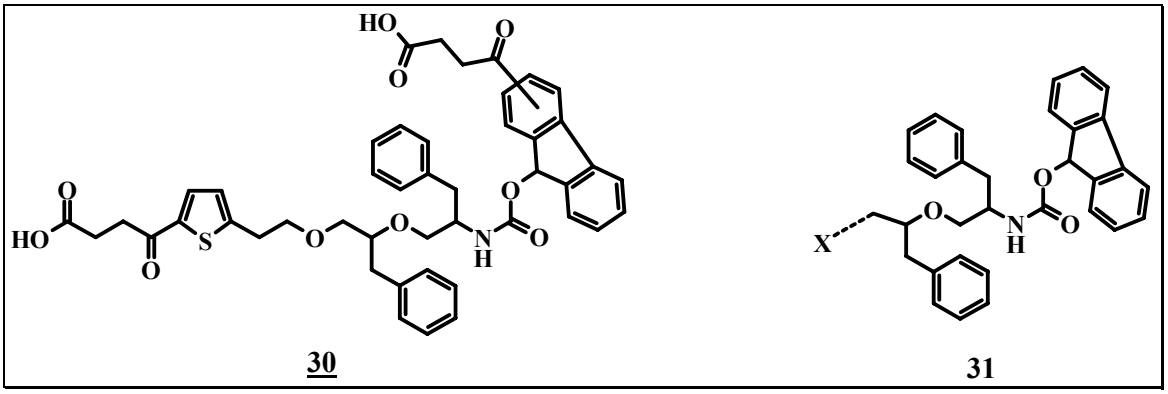


Scheme 47

Keeping in mind the acidic deoxygenation in the subsequent step the carboxylic acid **29** was the next essential key intermediate. It was prepared analogous to established procedures of our group[41] with succinic anhydride in dry DCE with 3.2 equiv. of $AlCl_3$ as catalyst. The first experiments already afforded the target compound **29**, isolated in a pure form after column chromatography although only in low yields of about 20%. A lot of material was lost due to the formation of a polar by-product **30** which was isolated in a pure form as well. The ^{13}C-NMR spectrum and MS (840m/z, $[M+Na]^+$) of **30** indicated a diacylated species. In addition to the expected carbonyl signal (references from analogous compounds) at 190.7ppm in the ^{13}C-NMR a second carbonyl signal was observed at 197.7ppm, typical for phenyl alkyl ketones[79]. This signal and the fact that various signals belonging to the Fmoc group were significantly shifted were the strongest indications that the ring system of the Fmoc group has been acylated. The suspicion was further supported by 2D-NMR experiments.

A second by-product **(31)** was a compound containing no thiophene-related signals and no carbonyl signals in the ^{13}C-NMR but seemed to have still the intact Fmoc-carbamate in its structure. Its exact structure was not determined.

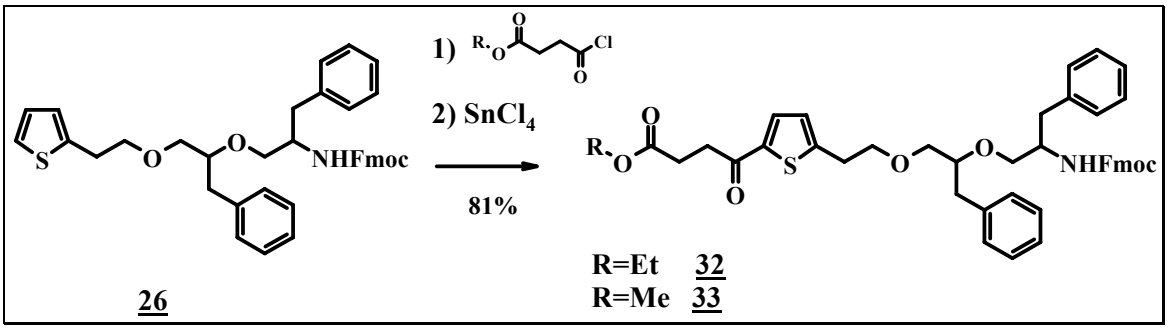
[79] Kalinowski, H.O.; Berger, St.; Braun, S. *^{13}C-NMR-Spektroskopie*, Georg Thieme Verlag, Stuttgart, **1984**



Scheme 48: By-products in $AlCl_3$ catalysis

2.10.2 Preparation of Esters 32 and 33

After variation of the reaction conditions the approach using $AlCl_3$ and succinic anhydride was abandoned and the Friedel-Crafts acylation was attempted with succinic acid mono ester mono chlorides (**35**, **37**). Initial experiments were carried out with $AlCl_3$ and gave analogous results as above. $SnCl_4$ is a much milder Friedel crafts catalyst and it is mainly applied to reactions of thiophenes and acid chlorides[80,81]. The acylation should therefore be highly selective for the 5-position of the thiophene.



Scheme 49

Both the thiophene and the acid chloride were dissolved in dry DCM and the catalyst (2.5 equiv.) was added as solution in dry DCM[81]. The mixture was stirred at temperatures below 10°C for several hours and after acidic workup the esters **32** and **33** were isolated in comparably good yields of 75% (**32**) and 81% (**33**) after column chromatography. Only little ether cleavage and no double acylation were observed. The yields are in the same range as

[80] Raposo, M.M.M; Kirsch, G. *Heterocycles* **2001**, *55*, 1487-1498
[81] Goodman, M.M.; Knapp, F.F. Jr. *J. Org. Chem.* **1984**, *49*, 2322-2325

previous $AlCl_3$ acylations described in the synthesis of other N-4-T-8-N derivatives. For the following ester hydrolysis, the methyl ester was preferred mostly because its cleavage can be monitored more easily *via* ^{1}H-NMR.

2.10.3 Preparation of the Mono Ester Mono Chlorides

Keeping in mind alternative reaction strategies for the final formation of the primary amine in the shorter chain using degradation reactions of thiophenepentanoic acid derivatives not only the already mentioned succinic acid derivatives but also glutaric acid monoethyl ester mono chloride **39** was prepared. All acid chlorides were prepared according or analogous to literature[82] starting from cyclic anhydrides *via* the corresponding succinic or glutaric acid mono ester.

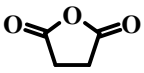
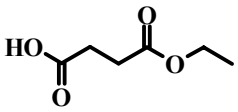
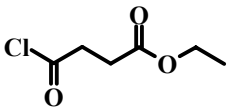
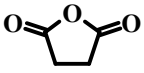
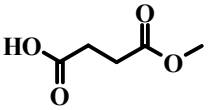
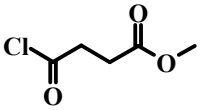
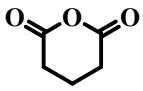
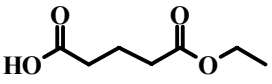
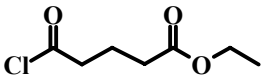
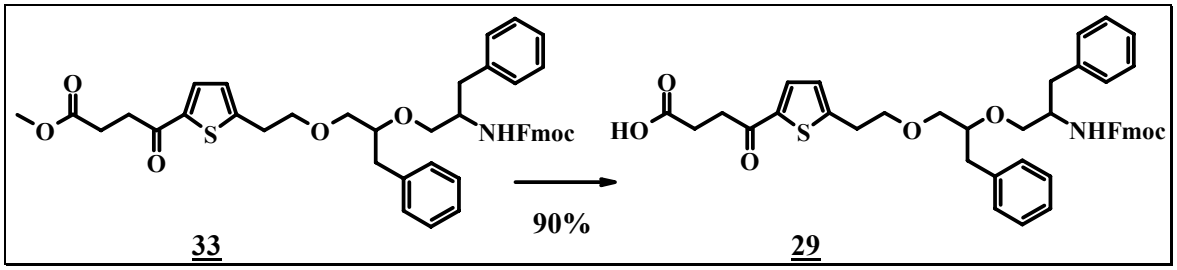
anhydride	alcohol	monoester	acid chloride
	**EtOH**	 **34**	 **35**
	**MeOH**	 **36**	 **37**
	**EtOH**	 **38**	 **39**

Table 5: Preparation of different diacid mono ester mono chlorides

The cyclic anhydride was refluxed in dry alcohol (~2 equiv.) for 4 to 5 hours. After evaporation of the excess of alcohol the monoester was distilled *in vacuo.* The chlorides were subsequently formed by refluxing the monoester in $SOCl_2$ for two hours and purified by vacuum distillation. To avoid the formation of diacid dichloride during the reaction with $SOCl_2$ the distillation of mono acid can be crucial for obtaining pure products.

[82] Riegel, B.; Lilienfeld, W.M. *J. Am. Chem. Soc.* **1945**, *67*, 1273-1275

2.11 Hydrolysis of Methyl Ester 33



Scheme 50

To end up with acid **29** in the "acid chloride approach" it was necessary to hydrolyze the ester moiety after the successful Friedel-Crafts acylation. Mostly[23,40,41,42] this transformation was done under basic conditions like LiOH/THF in an efficient way. In the present case the Fmoc-group required the hydrolysis to be performed under acidic condition which is in fact rather unusual.

The problem of ester cleavage parallel to an unaffected Fmoc group is frequently solved by using allylic esters which can be cleaved by isomerisation to vinylic esters under Pd catalysis and cleavage of these more labile esters[77]. In the present case it would have been necessary to prove the stability of the allylic ester under Friedel-Crafts acylation conditions which was decided not to be done.

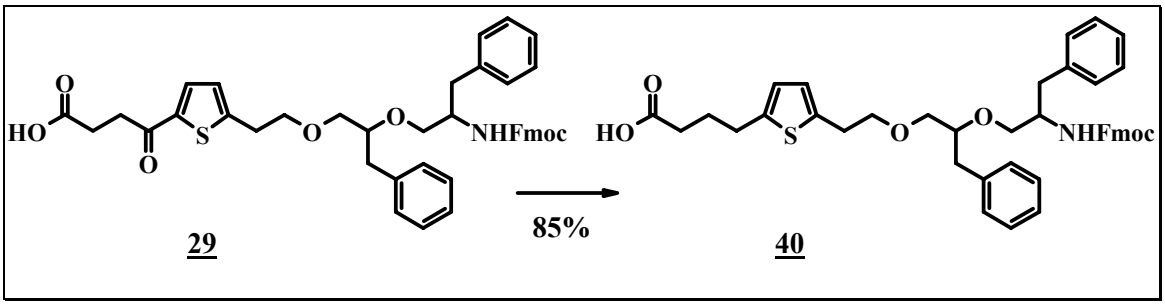
The mechanism of acidic ester formation and cleavage is an equilibrium reaction and therefore in principle only an excess of water is necessary for the cleavage. Still it is reported that it normally needs elevated temperatures and rather high concentration of strong acids to achieve good yields. Another possibility to promote the cleavage is to allow transesterification by addition of for example formic acid.

After less successful attempts in refluxing 2N HCl/THF another possibility was looked for. Fortunately, my colleague Muhamed Jasic was faced with a similar problem several years ago and - special thanks to him – did still remember a long process of optimization affording a very efficient "cleavage cocktail".

An aromatic methyl ester had to be cleaved in presence of an Fmoc-protected aniline moiety.[83] Based on transesterification with formic acid (80:20 with water) he had optimized the reaction conditions and identified p-toluenesulfonic acid (2 equiv.) as the best catalyst for it.

Despite of the obvious structural difference of the present molecule the conditions could be most efficiently applied. After refluxing for less than 1 hour the ester **33** was completely cleaved to the corresponding acid **29** without any traces of fluorene derivative **27**, which would have indicated the cleavage of the Fmoc group. After aqueous workup and extraction with EtOAc the crude product was obtained in good purity and without any identified by-products. For removing color and traces of p-toluenesulfonic acid and formic acid it can be purified by a short column chromatography to yield pure acid **29** in 90% yield. Acid **29** was isolated as white solid foam. Actually, it was the only time in this reaction series that anything else but more or less viscous oil was obtained.

2.12 Acidic Deoxygenation of Keto Acid 29



Scheme 51

In the synthesis of lead structure N-4-T-8-N and its derivatives many different conditions for the deoxygenation were applied depending on the structural features of the molecule. If possible the acidic deoxygenation with trifluoroacetic acid and triethylsilane[41] was favored due to reproducible high yields and a broad applicability.

The acidic conditions should not affect the Fmoc-group and the method was successfully applied to the current molecule. Starting material **29** was dissolved in trifluoroacetic acid to

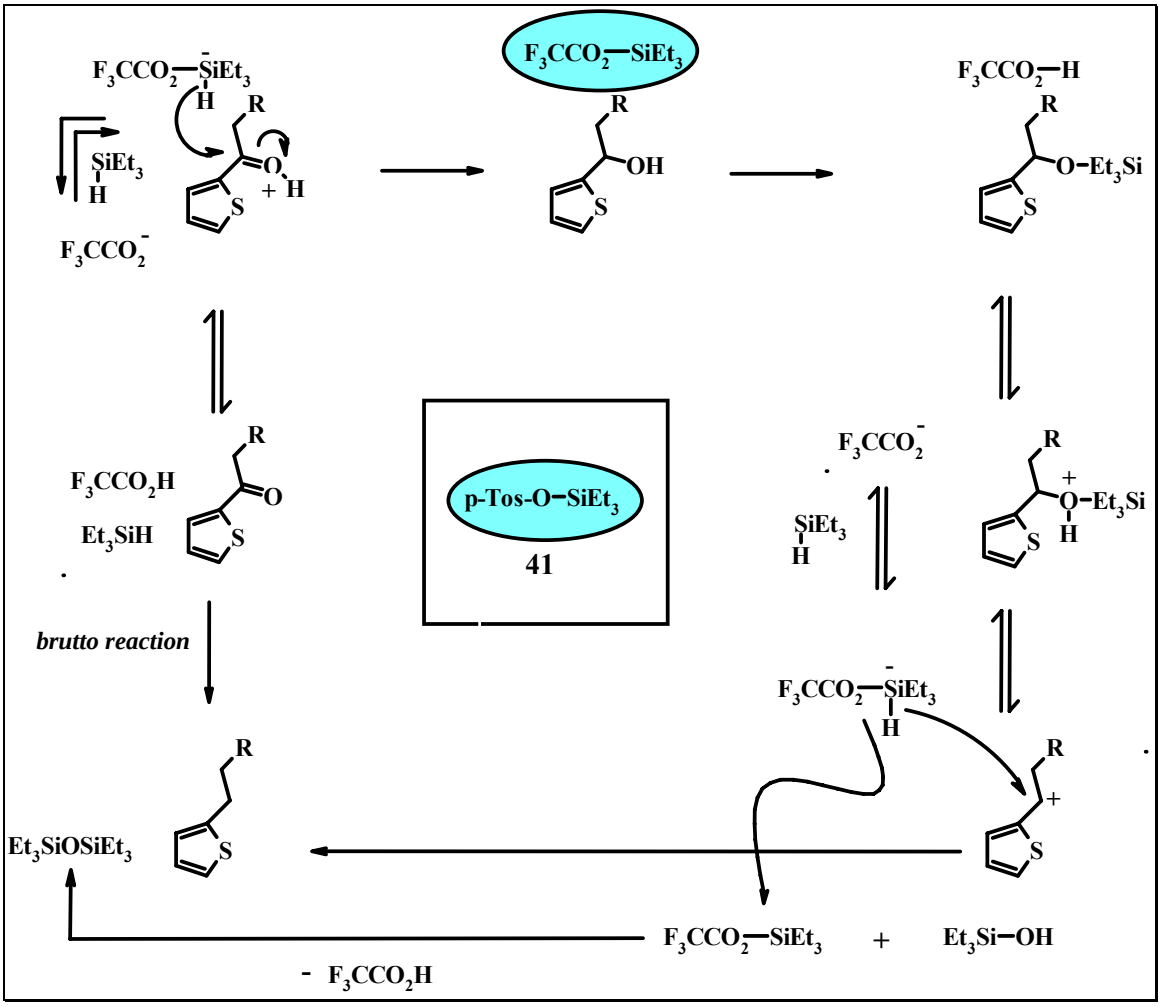
[83] Jasic M., *private communication*

give a violet solution and after addition of triethylsilane (ratio of CF_3COOH/Et_3SiH normally 3:5) the mixture was stirred at 60°C overnight. The reaction mixture was quenched with water, acidified with 1M $KHSO_4$ and extracted with EtOAc. Drying and evaporation gave a crude product that had to be purified by column chromatography.

Although excellent yields of up to 85% were obtained after purification, a full conversion of starting material was never observed which is consistent with former experiences in the group. Starting material **29** (8-9 %) was recovered in mixture with product and was again submitted to the same conditions. Similar yields and no additional by-products were observed in repeated deoxygenation experiments. It was unexpected that these two similar acids **29** and **40** could be purified by column chromatography so nicely with really little mixed fractions despite similar R_f values.

Mechanism and Limitation of the Acidic Deoxygenation

Once it was tried to submit a crude acid **29** - containing a lot of p-toluenesulfonic acid - directly from the ester hydrolysis to the acidic deoxygenation. Under the same conditions described above, in this case total decomposition of the starting material and various unidentified by-products were obtained.



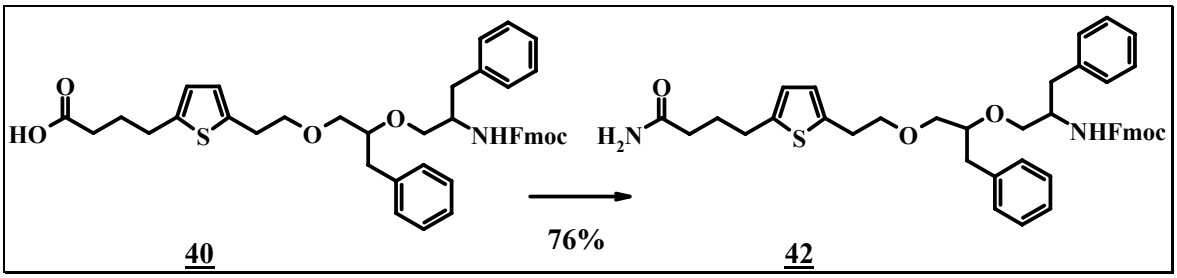
Scheme 52: Mechanism of the acidic deoxygenation

Considering the reason for this unexpected outcome the mechanism[84] of the acidic deoxigenation was studied. In the literature[85] several trialkylsilyl tosylates (most prominent is trimethylsilyl tosylate) are described as stable compounds. As a consequence it was supposed that the formation of intermediate **41** from triethylsilane and p-toluenesulfonic acid analogous to the one reported with trifluoroacetic acid might have caused the disaster that was observed.

[84] Brückner, R. *Reaktionsmechanismen: organische Reaktionen, Stereochemie, moderne Synthesemethoden*, Spektrum Akademischer Verlag, Heidelberg, **1996**

[85] Wang, M.C.; Yong, J.; Wang, D. *Heteroat. Chem.* **2001**, *12*, 534-538

2.13 Formation of Amide 42 *via* the Acid Chloride

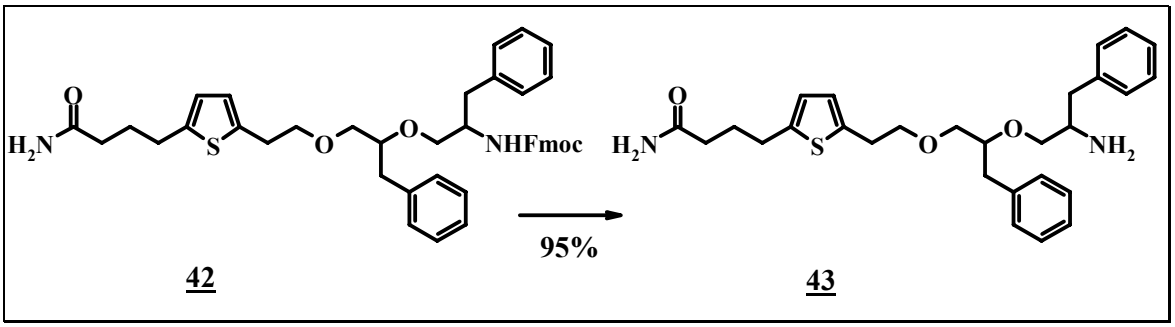


Scheme 53

The primary amide **42** was synthesized *via* the corresponding acid chloride according to a standard procedure[41]. The acid was transformed into the acid chloride by applying a small excess of oxalyl chloride and catalytic amounts of pyridine in THF at reflux temperature. The reaction was monitored *via* TLC by quenching the reaction mixture with MeOH and detecting the acid chloride as methyl ester. After around 90 minutes at reflux temperature the red-orange mixture was cooled to 0°C and NH_3 gas was bubbled through the solution changing the color to light yellow. After 30 minutes the reaction mixture was quenched with 0.5N HCl. Extraction with EtOAc and washing with water and brine gave amide **42** in good purity. An interesting detail is that despite the low temperature and short reaction time traces of the Fmoc group (<5%) were cleaved by the NH_3 gas, forming fluorene derivative **27**, detectable as apolar spot on the TLC plate and by its significant vinylic signal in the ^{1}H-NMR.

Another interesting detail of this reaction that required special attention, was the fact that the R_f values of amide **42** and acid **40** in different eluents were so similar that it was not possible to differentiate between the two species *via* TLC. By addition of a small amount of TEA to the sample, thus transforming the acid **40** into its triethylammonium salt with a very low R_f value it became possible to differentiate between acid **40** and amide **42**. With this trick also small amounts of acid were detectable and more important easily separable by just adding around 0.1% of TEA to the eluent of the column chromatography. The acid was recoverable by addition of little acetic acid to the eluent instead of TEA.

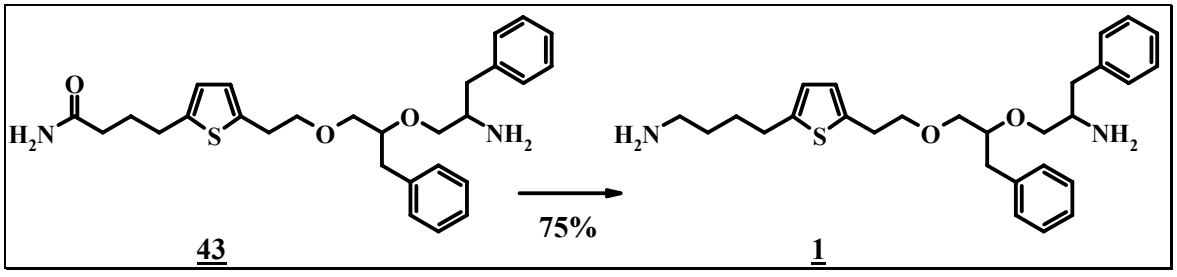
2.14 Deprotection of Fmoc Amine 42



Scheme 54

The deprotection of the amine moiety was performed by stirring carbamate **42** for half an hour in piperidine/DMF 4:1, a mixture in which the half life time of Fmoc-derivatives is only a few seconds[77]. Actually after 15 minutes at room temperature the reaction was "spot to spot". The side-product **28** of the cleavage (see mechanism in Chapter 2.9) was separated by a short column to yield pure product **43** in almost quantitative yield. However, at least in this case the equilibrium in Scheme 44 is totally on the side of compound **28**, almost no free fluorene **27** was observed on TLC or in ^{1}H-NMR.

2.15 Reduction of the Amide 43 to the Target Compound 1



Scheme 55

The reduction of the amide **43** was performed with 2.5 equivalents of $LiAlH_4$ in dry THF by refluxing overnight. Work up with sodium potassium tartrate solution, filtration through a short bed of Celite™ and extraction with DCM gave almost pure product that can be further purified by column chromatography to yield the target compound **1** in a yield of 75%.

2.16 Summary and Outlook

2.16.1 Pharmacological Result of Target Compound 1

After successful synthesis of target compound **1** it has already been begun to examine its pharmacological properties in the [^{3}H]-MK-801 binding essay. The test was performed under the guidance of Dr. Berger at the Center for Brain Research - Division of Biochemistry and Molecular Biology (Molecular Pharmacology). Under saturating concentrations of glycine and glutamate, the dependency of [^{3}H]-MK-801 specific binding (5nM) to NMDA-receptor containing membrane material (hippocampus of male rats) on the concentration of test compound was examined. 300 µM, 30 µM, 3 µM, and 0.3µM solutions of substrate were applied in the essay. The experiments were carried out in a total volume of 500µL Tris(50nM) buffer (pH=7.00). The specific binding was determined *via* measuring the total radioactivity on the filtrated and washed membrane material. Non linear approximation to the curve of the Hill equation (Hill factor = 1) gave an IC_{50} value of around 20µM.

$$BL(I) = [BL_0] \cdot \frac{IC_{50}}{IC_{50} + [I]} + NB \qquad \textit{Hill equation}$$

[BL] *concentration of the ligand binding complex*

[Bl$_0$] *concentration of the ligand binding complex in the absence of the inhibitor*

[I] *inhibitor concentration*

IC$_{50}$ *inhibitory concentration causing 50% displacement of specific binding*

NB *non specific binding evaluated in a parallel experiment*

The pharmacological examination could just be started in the very last days and there for the obtained result is evaluated from only one experiment. Repeated experiments together with the other relevant compounds like **TP-133**, **DN-25** and **N-4-T-8-N** have to be carried out. Furthermore, experiments in presence of spermine are necessary to define the selectivity of the ligand. Nevertheless, the obtained result makes clear that the combination of structural elements of **TP-133** and **DN-25** did not cause further increase in affinity.

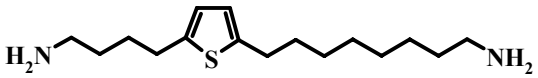
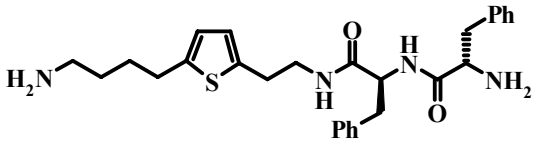
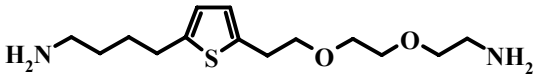
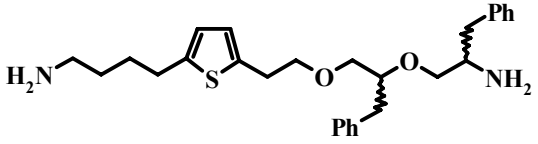
structure	IC_{50} [μM]	$\frac{IC_{50}\text{ (Spn) [μM]}}{IC_{50}\text{[μM]}}$
 **N-4-T-8-N**	0.4	9
 **TP-133**	28	7.9
 **DN-25**	5.0	16.1
 **CS-01**	20	waiting for result

Table 6

Table 6 makes a comparison of the structural motifs and the target compound of this thesis easier. It has to be stated once more that the result for compound **1** can not be directly compared to the results obtained for the other compounds in repeated experiments and under slightly different conditions (other Tris concentration). The accuracy for this result is not in the range of the results for the other compounds, but still it can be supposed that the affinity lies in the range of DN-26 and TP-133 and will therefore be two orders of magnitude higher compared with lead compound N-4-T-8-N. Compound **1** will most probably not be recommended as radio-ligand for the polyamine binding site of the NMDA receptor.

2.16.2 Synthetic Achievements

Within this thesis the synthesis of target compound **1** was successfully completed. All of the 11 steps leading to the target compound were either established or have been significantly improved in yield or understanding. It can be supposed that the reported synthetic strategy

will be applicable to the preparation of analogous compounds. In all steps but two the yields could be optimized to 75 to 95%, thus making further optimization not necessary.
What was achieved in methodological concerns is that the Fmoc group is a good choice for the protection of amine moieties during the whole introduction of a second alkyl chain in combination with the mild Friedel-Crafts catalyst $SnCl_4$ and the acidic ester cleavage protocol used in this thesis. The synthetic strategy used for the introduction of the second aminoalkyl chain is a nice variant for approaches towards derivatives of N-4-T-8-N.

2.16.3 Future Optimizations

Challenging potential can still be considered in the introduction of the primary amine moiety (**22**) *via* the reductive amination protocol, which could not be improved to more than 50% yield within this thesis. Fortunately, there are different possibilities to vary either the conditions or the reducing agent. Moreover, alternative methodologies of reductive amination such as the Leuckart-Wallach protocol do exist. There is certainly enough room for further efforts. Besides it can be suggested that the reason for the reported difficulties[42] in introducing the amine moiety *via* nucleophilic substitution (see Chapter 2.1) can be located in the steric hindrance of the present molecule. Thus, it can be assumed that analogous compounds with different residues and different steric demand will hopefully be accessible *via* this approach as well.

The formation of the second ether (**4**) on the other hand can - to the present knowledge - not easily be significantly improved, since the reason for the formation of the described oligoethers lies inherent in the mechanism of the addition reaction. It therefore has to be expected that the same side reaction will affect the preparation of analogous compounds in a similar manner. As it was presented in Chapters 2.3 and 2.5 several approaches to examine alternative formation of the ether bond have already been started within this thesis. Among them it was especially the aziridine approach which had already been brought to some early success and as reported would shorten the synthetic route tremendously. It also has the largest potential towards combinatorial synthesis, since many aziridines are easily obtainable from natural amino acids in two steps[44] and therefore even in enantiomerically pure form.

3 Experimental Part

3.1 General

3.1.1 Methods

Melting points (m.p.):

Melting points were determined using a Kofler-type Leica Galen III micro hot stage microscope and are uncorrected.

Nuclear magnetic resonance spectra (NMR):

NMR-spectra were recorded from $CDCl_3$ solutions on a Bruker Spectrospin for 200 MHz ^{1}H-NMR and 50 MHz ^{13}C-NMR or Varian Unity spectrometer for 500 MHz ^{1}H-NMR and 125 MHz ^{13}C-NMR at room temperature. Coupling constants are reported in Hz, chemical shifts (δ) in ppm using TMS as internal standard.
The spectra were calibrated to the solvent peak of $CDCl_3$ (^{1}H: 7.26ppm, ^{13}C: 77.0ppm).

Mass spectra (MS):

The mass spectra were recorded on a Finnigan LC Q DUO spectrometer with ESI ionization. 0.1% methanolic solutions were injected with a P/ACE MDQ autosampler with pressure.

Combustion Analysis

The element-analysis was performed at the micro analytical laboratory at the Institute of Physical Chemistry (Mag. Johannes Theiner), University of Vienna. The used equipment was a "EA 1108 CHNS-O" from Carlo Erba.

Chromatography:

For TLC pre-coated TLC plates silica gel 60 F_{254} from Merck were used. The substances were detected by ultraviolet light (254 nm) or with two various spray-reagents, followed by heating:

- solution of ninhydrine (0.5g ninhydrine in 100ml ethanol)
- phosphomolybdic acid (4g reagent in 100mL ethanol)

Flash column chromatography was performed on silica gel 60 from Merck (40-63μm).

3.1.2 Reagents and Solvents

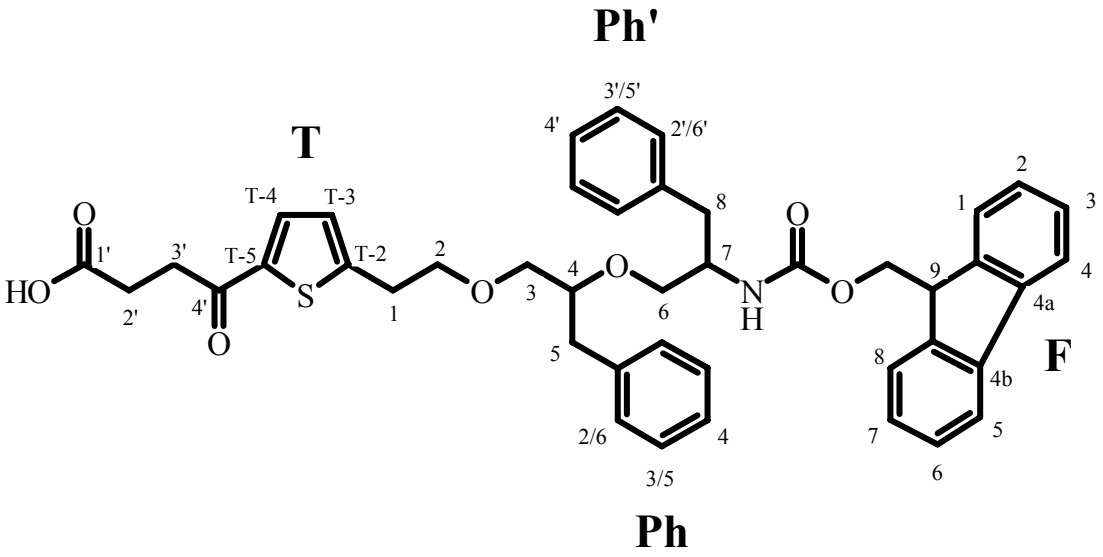
Unless otherwise noted, chemicals were purchased from commercial suppliers and used without further purification. Water free solvents were distilled from an adequate desiccant and stored under Ar. Diethyl ether, THF and dioxane were distilled from sodium/benzophenone, dichloromethane and 1,2-dichloroethane were distilled from phosphor pentoxide prior to use. Other solvents were stored over molecular sieve for at least one day.

3.1.3 Abbreviations

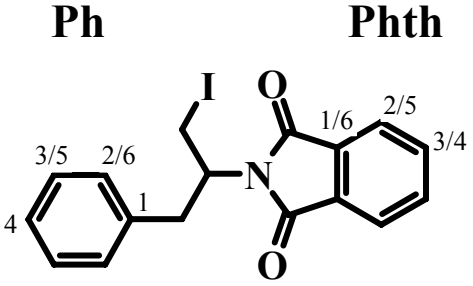
b.p.	boiling point
m-CPBA	*meta*-chloroperbenzoic acid
DCE	1,2-dichloroethane
DCM	dichloromethane
DEAD	diethyl azo dicarboxylate
DIPE	diisopropyl ether
DMAP	4-dimethylaminopyridine
DMF	N,N-dimethylformamide
EtOAc	ethyl acetate
Et_2O	diethyl ether
EtOH	ethanol
Fmoc-OSu	9-fluorenylmethoxycarbonyloxysuccinimide
KRD	*Kugelrohr* distillation
LP	light petroleum (b.p. 40-60°C)
MeOH	methanol
MTBE	methyl *t*-butyl ether
m.p.	melting point
PCC	pyridinium chloro chromate
PDC	pyridinium dichromate
rt	room temperature
THF	tetrahydrofuran
TLC	thin layer chromatography
TEA	triethylamine

3.1.4 Nomenclature for NMR:

In case that the position in the molecule related to a certain signal could not clearly be referred to, the abbreviations **Ph** (phenyl), **F** (ring system of the Fmoc group), **T** (thiophene), **Phth** (phthalyl) were used to differentiate between different aromatic systems. To allow uniform description of the corresponding positions in all compounds during the course of the synthesis the positions were not labelled according to IUPAC nomenclature but analogous to the following two examples.

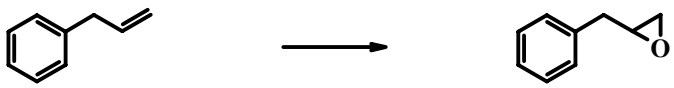


Ph



3.2 Synthetic Procedures and Analytical Data

3.2.1 (R/S)-Benzyloxirane (2)



2

Procedure: Epoxidation with m-CPBA

To a solution of allylbenzene (34.14g, 288.9mmol, 1.00equiv.) in DCM (190mL) a solution of m-CPBA (60%) (99.70g, 346.7mmol, 1.2equiv) in DCM (350mL) was added at rt within 10 to 15 minutes. The reaction was stirred overnight. In the morning the white suspension was filtered and washed with DCM twice before the collected filtrate was washed with 20% $Na_2S_2O_3$ twice (100mL each, first time stirring for 15 minutes) and twice with satd. $NaHCO_3$ (100mL each, first time stirring for 15 minutes). The combined aqueous layers were extracted with DCM (100mL) twice and the collected organic layers were washed with brine, dried over Na_2SO_4 and evaporated to give an almost colorless liquid that was purified by vacuum distillation to give 33.51g of pure target compound **2**.

Yield: 33.51g (86.5%) as colorless liquid

Physical Properties

$C_9H_{10}O$ (134.18)

b.p.: 84°C/12mbar (Lit.[86] 95°C/12Torr)

TLC: (LP/MTBE = 3:1) $R_f = 0.88$ (LP/Et_2O = 19:1) $R_f = 0.31$

[86] Kropf, H.; Yazanbakhch, M.R. *Synthesis* **1977**, 711

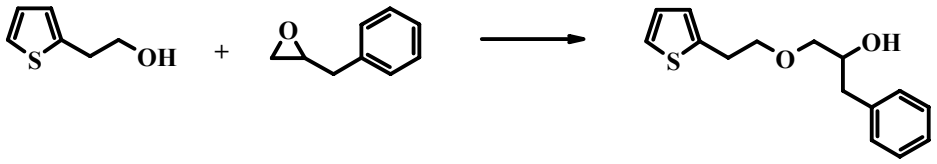
^{1}H-NMR ($CDCl_3$)[87]

δ 2.53 (d, J=4.9Hz, J=2.7Hz, 1H, Ph-C**H**H), 2.75 –2.96 (m, 3H, Ph-CH**H**, OCH_2), 3.10-3.18 (m, 1H, O-CH), 7.18-7.35 (m, 5H, 5×Ph-H)

^{13}C-NMR ($CDCl_3$)

δ 38.7 (t, Ph-CH_2), 46.8 (t, O-CH_2), 52.3 (d, O-CH), 126.6 (d, Ph-C-4), 128.4, 128.9 (2×d, Ph-C-3/5, Ph-C-2/6), 137.1 (s, Ph-C-1)

3.2.2 (R/S)-α-[2-(2-Thienyl)ethoxymethyl]benzeneethanol (3)



2 **3**

Procedure: Nucleophilic Ring Opening of Benzyloxirane 2

NaH (0.240g, 9.98mmol, 0.27equiv.) was added in one shot to thiophene-2-ethanol (7.11g, 55.5mmol, 1.50 equiv.) under an argon atmosphere. A lot of heat and gas was formed and a white precipitate formed. The mixture was stirred at temperatures below 50°C until it became a solution. Then it was allowed to cool to rt and benzyloxirane **2** (4.96g, 37.0mmol, 1.00equiv.) was added and the mixture was heated to 65°C and was stirred overnight. The dark solution was diluted with MTBE (10mL) and poured on MTBE (20mL) and 0.5N HCl (10mL). After stirring for several minutes the aqueous layer was diluted with satd. $NaHCO_3$ (5mL) and the phases were separated. The aqueous layer was extracted with MTBE two times and the combined organic layers were washed with brine once, dried over Na_2SO_4 and evaporated. The crude product was purified by KRD.

125°C (0.1mbar) 3.07g (0.65 equiv.) thiophene-2-ethanol
225°C (0.1mbar) 6.970g (71.7%) compound **3** as yellow liquid

[87] Yudin, A.K.; Chiang, J.P.; Adolfsson, H.; Coperet, C. *J.Org.Chem.* **2001**, *66*, 4713-4718

Yield: 6,970g (71.7%) as yellow liquid (Lit.[42] 40%)

Physical Properties

$C_{15}H_{18}O_2S$ (262.37)

TLC: (LP/MTBE = 3:1) $R_f = 0.17$ (LP/MTBE = 3:2) $R_f = 0.21$

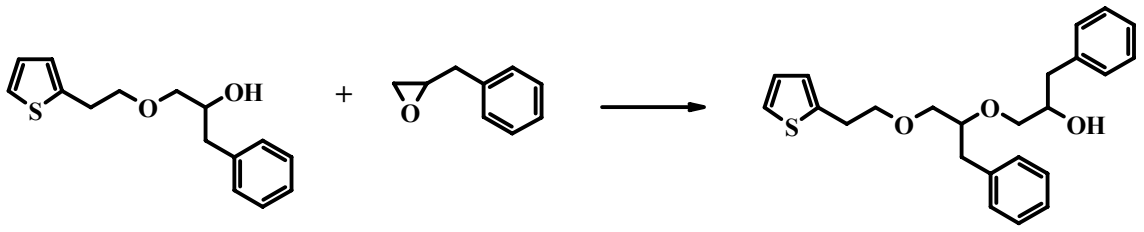
^{1}H-NMR ($CDCl_3$)[42]

δ 2.42 (d, ^{3}J=2.7Hz, 1H, OH), 2.73-2.80 (m, 1H, H-5), 2.83-2.91 (m, 1H, H-5), 3.12 (t, ^{3}J=6.5Hz 1H, H-1) 3.37 (dd, ^{2}J=14.0Hz ^{3}J=6.9Hz, 1H; H-3), 3.51 (dd, ^{2}J=13.8Hz ^{3}J=3.3Hz, 1H; H-3) 3.62-3.80 (m, 2H, H-2), 3.95-4.10 (m, 1H, H-4) 6.86 (dd, ^{3}J=3.2Hz ^{4}J=0.6Hz, 1H, Th-H-3), 6.95 (dd, ^{3}J=5.1Hz ^{3}J=3.5Hz, 1H, Th-H-4) 7.16 (dd, ^{3}J=5.2Hz ^{4}J=0.9Hz, 1H, Th-H-5) 7.17-7.36 (m, 5H, 5× Ph-H)

^{13}C-NMR ($CDCl_3$)

δ 30.4 (t, C-1), 39.8 (t, C-5), 71.2 (d, C-4), 71.7 (t, C-2), 74.0 (t, C-3), 123.7 (d, T-C-5), 125.1 (d, T-C-3), 126.3 (d, Ph-C-4), 126.6 (d, T-C-4), 128.4 (d, Ph-C-3/5), 129.3 (d, Ph-C-2/6), 137.9 (s, Ph-C-1), 141.11 (s, T-C-1)

3.2.3 α-{1-Benzyl-2-[2-(2-thienyl)ethoxy]ethoxymethyl}benzeneethanol (4)



3 **2** **4**

Procedure: Nucleophilic Ring Opening of Benzyloxirane 2

NaH (0.983g, 40.98mmol, 0.36equiv.) was added in one shot to alcohol **3** (43.0g, 163.891mmol, 1.43 equiv.) under an argon atmosphere when a lot of heat and gas was formed and a white precipitate formed. The mixture was stirred at temperatures below 50°C until it became a solution. Then it was allowed to cool to 40°C, benzyloxirane **2** (15.39g, 114.7mmol, 1.00equiv.) was added and the mixture was stirred at 65°C overnight. The dark solution was diluted with MTBE (100mL) and poured on MTBE (200mL) and 0.5N HCl (80mL). The phases were separated, the aqueous layer extracted with MTBE (2x50mL) and the combined organic layers were washed with $NaHCO_3$, brine, dried over Na_2SO_4 and evaporated. The crude product was purified by KRD. After 30 minutes at 150°C and 205°C (0.15mbar) the target compound was distilled off at 250°C (0.075mbar) to yield 15.8 g compound 4 as a mixture of diastereomers (1:1 according to ^{13}C-NMR).

Yield: 15.8g (34.4%) as viscous yellow liquid (Lit.[42] 22.0%)

Physical Properties

$C_{24}H_{28}O_3S$ (396.55)

TLC: (LP/MTBE = 3:1) $R_f = 0.15$ (LP/MTBE = 3:2) $R_f = 0.21$

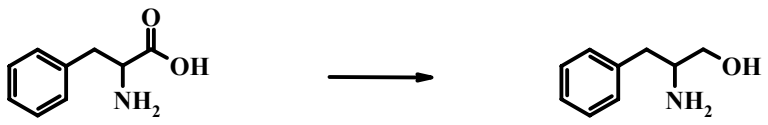
^{1}H-NMR ($CDCl_3$)[42]

δ 2.56-2.83(m, 4H, H-5, H-8), 3.08 (t, ^{3}J=6.8Hz, 2H, H-1), 3.23-3.29 (m, 1H, H-6), 3.42-3.50 (m, 3H, H-6, H-3) 3.57-3.78 (m, 1H, H-4), 3.64-3.67 (m, 2H; H-2), 3.83-3.90 (m, 1H; H-7) 6.81-6.84, (m, 1H, T-H-3) 6.90 (dd, ^{3}J=5.0Hz ^{3}J=3.5Hz, 1H, T-H-4) 7.11 (dd, ^{3}J=5.0Hz, ^{4}J=1.3Hz, 1H, Th-5) 7.10-7.28 (m, 10H, 10× Ph-H)

^{13}C-NMR ($CDCl_3$)

δ 30.3, 30.33 (2×t, C-1), 38.4, 38.5 (2×t, C-5), 39.4, 39.5 (2×t, C-8), 71.3, 71.7 (2×d, C-7), 72.0 (t, C-2), 72.8, 72.9 (2×t, C-6), 73.6, 74.2 (2×t, C-3), 80.5, 81.1 (2×d, C-4) 123.6 (d, T-C-5), 125.2 (d, T-C-3), 126.2, 126.3 (2×d, Ph-C-4, Ph-C-4'), 126.6 (d, T-C-4), 128.27, 128.3, 128.4 (3×d, Ph-C-3/5, Ph-C-3'/5'), 129.2, 129.3, 129.33 (3×d, Ph-C-2/6, Ph-C-2'/6'), 138.1-138.2 (4×s, Ph-C-1, Ph-C-1'), 140.9, 141.0 (2×s, T-C-2)

3.2.4 (R/S)-Phenylalaninol (5)



5

Procedure A: Reduction with Sodiumborohydride/Iodine

To a solution of (R/S)-phenylalanine (8.26g 50.0mmol, 1.0equiv) in dry THF (40mL) $NaBH_4$ (3.41g, 90.0mmol, 1.8equiv) was added in one shot before a solution of I_2 (11.42g, 45.0mmol, 0.9equiv) in dry THF (20mL) was added at external water bath cooling. The reaction mixture was stirred at rt overnight. The next morning MeOH (10mL) was added and the reaction mixture heated. The formation of a lot of gas could be observed. The clear solution was allowed to cool to rt before 10% NaOH (50mL) was added. The reaction mixture was kept at 60°C for 1h before most of the solvent was evaporated and the aqueous layer was extracted with EtOAc, dried over Na_2SO_4 and evaporated. The solid residue was dissolved in EtOAc and extracted with 2N HCl four times. The combined aqueous layers were adjusted to basic pH with 6N NaOH and extracted with EtOAc four times. The organic layers were washed with water once, once with brine dried over Na_2SO_4 and evaporated to give white solid, NMR pure.

Yield: 5.6g (74.1 %) as white solid

Procedure B: Reduction with Lithiumaluminiumhydride

Phenylalanine (3.89g, 23.54mmol, 1.0equiv.) was carefully added to a stirred suspension of $LiAlH_4$ (1.79g, 47.15mmol, 2.0 equiv.) in dry THF (250mL) at 0°C within 15 minutes. The reaction mixture was allowed to come to rt and stirred overnight at reflux temperature. Then the reaction mixture was cooled to 0°C and the excess of $LiAlH_4$ was hydrolyzed with 2N NaOH (25mL) and water (25mL). The immediately formed white suspension was filtered over a bed of Celite™ and washed with THF excessively. Most of the THF was removed *in vacuo*. It was extracted with DCM. The combined organic layers were washed once with

water, once with brine, dried over Na_2SO_4 and evaporated to yield a yellow solid - NMR pure compound **5** - that was used without further purification.

Yield: 3.1g (86.8 %) as yellow solid (Lit.[46] 100%)

Physical Properties

$C_9H_{13}NO$ (151.21)

m.p.: 59-61°C (Lit.[88] 64-65°C (Et_2O))

TLC: (DCM/MeOH 5:1) $R_f = 0.09$ (DCM/MeOH/TEA 3:1+1%) $R_f = 0.24$

^{1}H-NMR ($CDCl_3$)[89]

δ 2.08 (bs, 3H, NH_2, OH), 2.51 (dd, 2J=13.5Hz, 3J=8.7Hz, 1H, Ph-CHH), 2.80 (dd, 2J=13.5Hz, 3J=5.1Hz, 1H, Ph-CHH), 3.06-3.18 (m, 1H, N-CH), 3.39 (dd, 2J=10.7Hz, 3J=7.1Hz, 1H, O-CHH), 3.63 (dd, 2J=10.6Hz, J=3.9Hz, 1H, O-CHH), 7.17-7.35 (m, 5H, Ph-H)

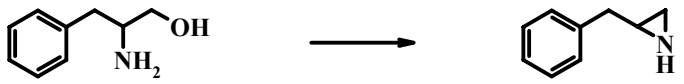
^{13}C-NMR ($CDCl_3$)

δ 40.9 (t, Ph-CH_2), 54.1 (d, N-CH), 66.4 (t, O-CH_2), 126.4 (d, C-4'), 128.6, 129.2 (2×d, C-2'/6', C-3'/5'), 138.6 (s, C-1')

[88] Iwai, I. *Chem. Pharm. Bull.* **1965**, *13*, 118-129

[89] Grunewald, G.L.; Caldwell, T.M.; Li, Q.; Dahanukar, V.H.; McNeil, B.; Criscione K.R. *J. Med. Chem.* **1999**, *42*, 4351-4361

3.2.5 (R/S)-2-Benzylaziridine (6)



5 **6**

Procedure: Ring Closure *via* Mitsunobu Type Reaction

To a solution of triphenylphosphine (4.68g, 17.9mmol, 1.05equiv.) and DEAD (3.11g, 17.9mmol, 1.05equiv.), in toluene (40mL) a solution of phenylalaninol **5** (2.57g, 17.0mmol, 1.0equiv.) in toluene (80mL) was added at external water bath cooling. The solution was stirred at reflux temperature overnight before it was poured on water (60mL) and diluted with Et_2O (60mL). The phases were separated, the aqueous layer was extracted with Et_2O, the organic layers washed with brine dried over Na_2SO_4 and evaporated. Et_2O (15mL) was added and the mixture was left in the freezer overnight. The precipitated triphenylphosphine oxide was filtered, washed once with cold Et_2O and the filtrate evaporated. The resulting residue was purified by flash column chromatography (90g SiO_2, THF/TEA 100:1) to give pure target compound **6**.

Yield: 817mg (36.1%) as yellow oil (Lit.[48] 85% enantiopure)

Physical Properties

$C_9H_{11}N$ (133.19)

TLC: (DCM/MeOH/TEA 10:1 + 1%) $R_f = 0.20$

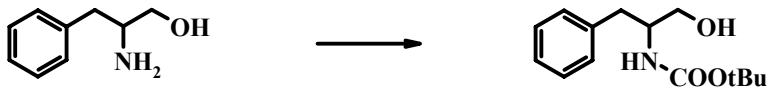
^{1}H-NMR ($CDCl_3$)[52]

δ 1.39 (d, ^{3}J=3.5Hz, 1H, N-CH**H**), 1.75 (d, ^{3}J=5.7Hz, 1H, N-C**H**H), 2.10-2.21 (m, 1H, N-CH), 2.59 (dd, ^{2}J=14.4Hz, ^{3}J=5.8Hz, 1H, Ph-C**H**H), 2.75 (dd, ^{2}J=14.4Hz, ^{3}J=6.1Hz, 1H, Ph-CH**H**), 7.15-7.24 (m, 5H, Ph-H)

^{13}C-NMR ($CDCl_3$)

δ 24.8 (t, N-CH_2), 30.9 (d, N-CH), 40.0 (t, Ph-CH_2), 126.4 (d, C-4'), 128.4,128.8 (2×d, C-2'/6', C-3'/5'), 139.1(s, C-1')

3.2.6 (R/S)-N-Boc-phenylalaninol (7)



5 **7**

Procedure: N-Boc Protection of Phenylalaninol 5

To a solution of phenylalaninol **5** (1.06g, 7.00mmol, 1.00equiv.) in chloroform (18mL) solid $(Boc)_2O$ (1.53g, 7.00mmol, 1.00equiv.) was added at 0°C. The solution was allowed to come to rt and stirred overnight. Phosphoric acid (20%, 10mL) was added and after stirring for 5 min the phases were separated. The organic layer was washed with satd. $NaHCO_3$ and brine, dried over Na_2SO_4 and evaporated to give a yellow solid that was purified by trituration with LP/MTBE = 10:1 to give colorless crystals of compound **7**.

Yield: 1.37g (77.9%) as colorless crystals (Lit.[64] 88.0%)

Physical Properties

$C_{14}H_{21}NO_3$ (251.33)

m.p.: 94.5-96°C (Lit.[90] 93-94°C°C)

TLC: (LP/EtOAc = 2:1) R_f =0.36

[90] Yankeelov, J.A. Fok, K.-F.; Louisvill, K. *DE: 2900926*, **1979**

^{1}H-NMR ($CDCl_3$)[91]

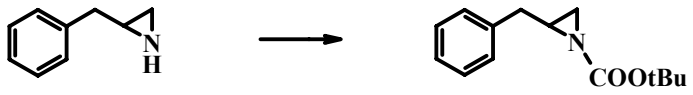
δ 1.41 (s. 9H, $C(CH_3)_3$), 2.84 (d, ^{3}J=7.1Hz, 2H, Ph-CH_2), 3.54 (dd, ^{2}J=11.0Hz, ^{3}J=5.2Hz, 1H, O-CH**H**), 3.66 (dd, ^{2}J=11.1Hz, ^{3}J=3.5Hz, 1H, O-C**H**H), 3.78-3.94 (m, 1H, N-CH), 4.76 (bs, 1H, NH), 7.19-7.35 (m, 5H, Ph-H)

^{13}C-NMR ($CDCl_3$)

δ 28.3 (q, ($\mathbf{C}H_3)_3$C), 37.4 (t, Ph-CH_2), 53.6 (d, N-CH), 64.1 (t, O-CH_2), 79.6(s, $(CH_3)_3\mathbf{C}$), 126.4 (d, C-4'), 128.5,129.3 (2×d, C-2'/6', C-3'/5'), 137.8 (s, C-1'), 156.1 (s, C=O)

3.2.7 (R/S)-2-Benzylaziridine-1-carboxylic acid *t*-butyl ester (8)

(Route A)



6 **8**

Procedure A: N-Boc-Protection of Aziridine 6

To a solution of aziridine **6** (176mg, 1.32mmol, 1.00 equiv.) in dioxane (4.5mL) 2N NaOH (2.2mL) was added at 0°C before a solution of $(Boc)_2O$ (739mg, 3.39mmol, 2.57equiv.) in dioxane (2.5mL) was added slowly. The reaction mixture was stirred at rt for 3 hours. Then it was diluted with Et_2O and water, the phases were separated, the aqueous layer extracted twice with Et_2O, the organic layers were washed with water and brine, dried over Na_2SO_4 and evaporated. The crude product was purified by flash column chromatography (9g SiO_2, LP/Et_2O = 7:1) to give pure target compound **8**.

Yield: 200mg (64.9%) as colorless liquid

Procedure B: N-Boc-Protection of Aziridine 9

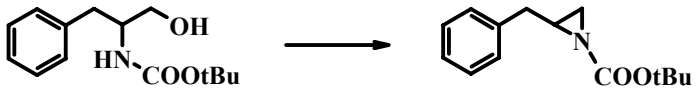
To a solution of $(Boc)_2O$ (1.96g, 9.00 mmol, 3.00 equiv.) and aziridine **6** (0.40g, 3.00 mmol, 1.00 equiv.) in DCM (16mL) solid DMAP (0.122g, 1.00 mmol, 0.33 equiv.) was added within

[91] Moree, W.J.; van der Marel, G.A.; Liskamp, R.J. *J. Org. Chem.* **1995**, *60*, 5157-5169

5 minutes at rt and the reaction mixture was stirred for 5 h. Then the reaction mixture was washed with water twice, dried over Na_2SO_4 and evaporated. The residue was purified by column chromatography (18g SiO_2, LP/Et_2O = 7:1) to give pure target compound **8**.

Yield: 430mg (61.4%) as colorless liquid

(Route B)



7 **8**

Procedure: Ring Closure by Mitsunobu Type Reaction

To a chilled solution of **7** (1.01g, 4.00mmol, 1.00equiv.) in dry THF (48mL) first triphenylphosphine (1.57g, 6.00mmol, 1.50equiv) was added in one portion and then DEAD (1.39g, 8.00 mmol, 2.00 equiv.) added dropwise. After 30 minutes the solution turned orange and was stirred for 4 more hours. The solvent was removed *in vacuo* and the crude product purified by flash column chromatography (60g SiO_2, LP/Et_2O = 6:1) to yield the pure target compound **8**.

Yield: 0.648g (69.44%) as colorless liquid

Physical Properties

$C_{14}H_{19}NO_2$ (233.31)

TLC: (LP/MTBE = 3:1) R_f = 0.66 (LP/MTBE = 3:2) R_f = 0.81

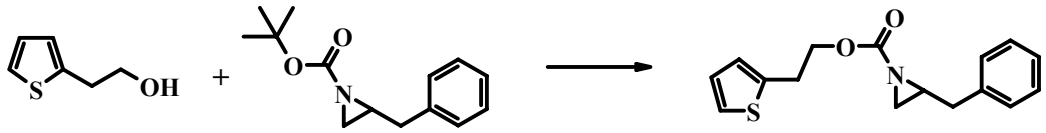
^{1}H-NMR (CDCl3)[92]

δ 1.44 (s, 9H, C(CH_3)$_3$), 2.03 (d, ^{3}J=3.4Hz, 1H, N-C**H**H), 2.31 (d, ^{3}J=5.8Hz, 1H, N-CH**H**), 2.57-2.63 (m, 1H, N-CH), 2.60-2.72 (m, 1H, Ph-CH**H**), 2.91-3.03 (m, 1H, Ph-C**H**H), 7.23-7.33 (m, 5H, 5×Ph-H)

^{13}C-NMR ($CDCl_3$)

δ 27.9 (q, C(**C**H_3)$_3$), 31.4 (t, N-CH_2), 38.3 (d, N-CH), 38.4 (t, Ph-CH_2), 81.1 (s, **C**(CH_3)$_3$) 126.5 (d, C-4'), 128.4,128.7 (2×d, Ph-C-2/6, Ph-C-3/5), 138.0 (s, Ph-C-1), 162.4 (s, C=O)

3.2.8 (R/S)-2-Benzylaziridine-1-carboxylic acid 2-(2-thienyl) ethyl ester (9)



8 **9**

Procedure: Nucleophilic Attack on BOC-group

Thiophene-2-ethanol (71mg, 0.55mmol, 1.1equiv) was added to a suspension of NaH (14mg, 0.6mmol, 1.2 equiv.) in dry toluene (1mL) at rt. The formation of gas was observed and the mixture was stirred for 10min. Then a solution of Boc-aziridine **8** (117mg, 0.50mmol, 1.00equiv.) in dry toluene (1mL) was added at rt and the mixture was stirred overnight. Little water was added, the phases were separated and the aqueous layer was extracted with DCM. The combined organic layers were dried over Na_2SO_4, evaporated and the crude product purified by column chromatography (60g SiO_2, LP/Et_2O/TEA 3:1:1%) to give compound **9.**

Yield: 23mg (16.0%) as oil

Physical Properties

[92] Christoffer, J. *Helv. Chim. Acta* **1998**, *81*, 845-852

$C_{16}H_{17}NO_2S$ (287.38)

TLC: (LP/MTBE = 3:1) $R_f = 0.45$ (LP/MTBE = 3:2) $R_f = 0.63$

^{1}H-NMR ($CDCl_3$)

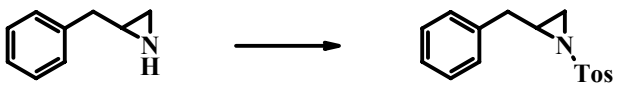
δ 2.08 (d, ^{3}J=3.41Hz, 1H, N-C**H**H), 2.36 (d, ^{3}J=5.7Hz, 1H, N-CH**H**), 2.60-2.73 (m, 2H, N-CH, Ph-CH**H**), 3.01 (dd, ^{2}J=16.2Hz, ^{3}J=7.8Hz, 1H, Ph-C**H**H), 3.15 (t, ^{3}J=6.6Hz, 2H, Th-CH_2), 4.31 (t, ^{3}J=6.6Hz, 2H, OCH_2), 6.82 (d, ^{3}J=3.4Hz, 1H, T-H-3), 6.93 (dd, ^{3}J=5.1Hz, ^{3}J=3.4Hz 1H, T-H-4), 7.15 (dd, ^{3}J=5.1, ^{4}J=1.07, 1H, T-H-5), 7.23-7.33 (m, 5H, Ph-H)

^{13}C-NMR ($CDCl_3$)

δ 29.3 (t, Th-CH_2), 31.5 (t, N-CH_2), 38.2 (t, Ph-CH_2), 38.4 (d, N-CH), 66.5 (t, O-CH_2), 124.0 (d, Th-C-5), 125.6 (d, Th-C-3), 126.6 (d, Ph-C-4), 126.8 (d, Ph-C-4), 128.5 (d, Ph-C-3/5,), 128.8 (d, Ph-C-2/6),137.6 (s, Ph-C-1), 139.6 (s, Th-C-2), 163.2 (s, N-C=O)

3.2.9 (R/S)-2-Benzyl-1-(4-methylbenzenesulfonyl)-aziridine (10)

(Route A)



6 **10**

Procedure: N-Tosylation of Aziridine 6

A solution of tosyl chloride (343mg, 1.80mmol, 0.90equiv) in DCM (4mL) was added to a solution of aziridine **6** (266mg, 2.00mmol, 1.00equiv.) and TEA (233mg, 2.30mmol, 1.15equiv.) in DCM (2mL) at 0°C. The reaction mixture was stirred for 3 hours before it was poured on water. The phases were separated the organic layer was washed with 2N HCl (3×), once with $NaHCO_3$ and once with brine, dried over Na_2SO_4 and evaporated. The crude product was crystallized from LP/Et_2O = 2:1 washed with cold LP/Et_2O = 2:1 once and with LP twice to yield in pure compound **10**.

Yield: 100mg (19.33%) as white crystals (Lit.[93] 70%)

(Route B)

5 **10**

Procedure: One Pot N-Tosylation and Ring Closure

To a suspension of phenylalaninol **5** (3.02g, 20.0mmol, 1.00 equiv.) in DCM/Pyridine 2:1 (15mL) tosyl chloride (11.44g, 60.00mmol, 3.00equiv.) was added in three portion within 10 minutes keeping the temperature between 5 and 15°C. The suspension turned to be a red solution and was stirred at rt overnight while a white precipitate was formed. The reaction mixture was diluted with DCM (70mL) and washed with 2N HCl (3×) and 2N NaOH (4×).

[93] Kolb, H.C.; Kanamarlapudi, R.C.; Richardson, P.F.; Khan, G. *US: 20030153771*, **2003**

All aqueous layers were re-extracted subsequently. The combined organic layers were washed once with water, once with brine, dried over Na_2SO_4 and evaporated. The crude product was purified by flash column chromatography (100g SiO_2, LP/Et_2O 2:1 to 1:1) to give 5.34 g of white solid that was triturated with LP/MTBE = 10mL : 0.5mL to yield in pure target compound **10**.

Yield: 4.95g (86.12%) as white crystals

Physical Properties

$C_{16}H_{17}NO_2S$ (287.38)

m.p.:70-73°C (EtOAc/LP) (Lit.[94] 79-80°C (EtOAc/Pentane)

TLC: (LP/MTBE = 3:1) $R_f = 0.32$ (LP/MTBE = 3:2) $R_f = 0.48$

^{1}H-NMR ($CDCl_3$)[93]

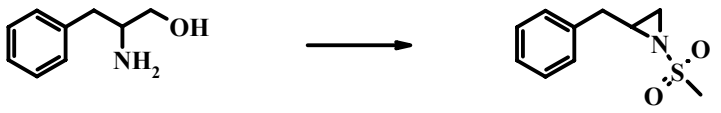
δ 2.16 (d, ^{3}J=4.0Hz, 1H, N-CH**H**), 2.42 (s, 3H, CH_3), 2.69 (dd, ^{2}J=14.5Hz, ^{3}J=7.0Hz, 1H, Ph-C**H**H), 2.71 (d, ^{3}J=6.5Hz, 1H, N-CH**H**), 2.81 (dd, ^{2}J=14.5Hz, ^{3}J=5.5Hz, 1H, Ph-CH**H**), 2.93-2.98 (m, 1H, N-CH), 7.03-7.06 (m, 2H, 2×Ph-H), 7.14-7.17 (m, 3H, 3×Ph-H), 7.21 (d, ^{3}J=8.0Hz, 2H, Tos-H-3/5), 7.69 (d, ^{3}J=8.0Hz, 2H, Tos-H-2/6)

^{13}C-NMR ($CDCl_3$)

δ 21.6 (q, CH_3), 32.8 (t, N-CH_2), 37.5 (t, Ph-CH_2), 41.1 (d, N-CH), 126.5 (d, Ph-C-4), 127.8 (d, Tos-C-2/6), 128.4, (d, Ph-C-3/5), 128.7 (d, Ph-C-2/6), 129.5 (d, Tos-C-3/5), 134.8 (s, Tos-C-1), 137.0 (s, Ph-C-1), 144.3 (s, Tos-C-4)

[94] Södergrenn M.J.; Alonso, D.A.; Bedekar, A.V.; Andersson, P.G. *Tetrahedron Lett.* **1997**, *38*, 6897-6900

3.2.10 (R/S)-2-Benzyl-1-methanesulfonyl-aziridine (11)



5 **11**

Procedure: One pot N-Mesylation and Ring Closure

To a suspension of phenylalaninol **5** (0.45g, 3.00mmol, 1.00 equiv.) in DCM/Pyridine 2:1 (2.5mL) mesyl chloride (1.03g, 9.00mmol, 3.00 equiv.) was added in one portion at 0°C. The suspension turned to be a red solution and was stirred at rt overnight. The resulting white suspension was diluted with DCM, washed with 2N HCl (3×) then with 2N NaOH (4×). All aqueous layers were re-extracted subsequently. The combined organic layers were washed once with water, once with brine, dried over Na_2SO_4 and evaporated. The crude product was purified by flash column chromatography (10g SiO_2, LP/EtOAc = 3:1) to give target compound **11**, NMR pure.

Yield: 450mg (71%) as colorless liquid

Physical Properties

$C_{10}H_{13}NO_2S$ (211.28)

calc.: C: 56.85 H: 6.20 N: 6.63 S: 15.18

found: C: 56.29 H: 6.36 N: 6.66 S: 14.18

TLC: (LP/MTBE = 3:1) $R_f = 0.13$ (LP/MTBE = 3:2) $R_f = 0.21$

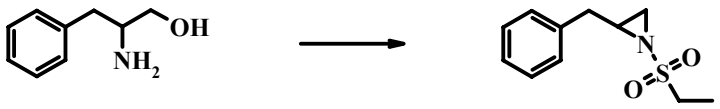
^{1}H-NMR ($CDCl_3$)

δ 2.22 (d, ^{3}J=4.7Hz, 1H, N-CH**H**), 2.69 (dd, ^{2}J=14.2Hz, ^{3}J=7.9Hz, 1H, Ph-C**H**H), 2.70 (d, ^{3}J=6.6Hz, 1H, N-C**H**H), 2.72 (s, 3H, CH_3), 2.88-2.93 (m, 1H, NCH), 2.99 (dd, ^{2}J=14.2Hz, ^{3}J=5.1Hz, 1H, Ph-CH**H**), 7.25-7.28 (m, 3H, H-2'/6', H-4'), 7.32-7.35 (m, 2H, H-3'/5')

^{13}C-NMR ($CDCl_3$)

δ 32.5 (t, N-CH_2), 37.5 (t, Ph-CH_2), 39.2 (q, CH_3), 41.3 (d, N-CH), 127.0 (d, Ph-C-4), 128.7(d, Ph-C-3/5), 128.9 (d, Ph-C-2/6), 137.2 (s, Ph-C-1)

3.2.11 (R/S)-2-Benzyl-1-ethanesulfonyl-aziridine (12)



5 **12**

Procedure: One Pot N-Ethanesulfonation and Ring Closure

To a suspension of phenylalaninol **5** (0.90g, 6.00mmol, 1.00 equiv.) in DCM/Pyridine 2:1 (6mL) ethanesulfonyl chloride (2.314g, 18mmol, 3.00 equiv.) was added in one portion at 0°C. The suspension dissolved and was stirred at rt over night. The reaction mixture was diluted with DCM washed three times with 2N HCl and four times with 2N NaOH. All aqueous layers were re-extracted subsequently. The combined organic layers were washed with brine twice, dried over Na_2SO_4 and evaporated. The crude product was purified by flash column chromatography (60g SiO_2, LP/EtOAc = 3:1) to give target compound **12** in pure form.

Yield: 692mg (51.2%) as colorless liquid

Physical Properties

$C_{11}H_{15}NO_2S$ (225.31)

calc.: C: 58.64 H: 6.71 N: 6.22 S: 14.23

found: C: 57.20 H: 6.73 N: 6.04 S: 13.68

TLC: (LP/MTBE = 3:1) R_f = 0.20 (LP/MTBE = 3:2) R_f = 0.31

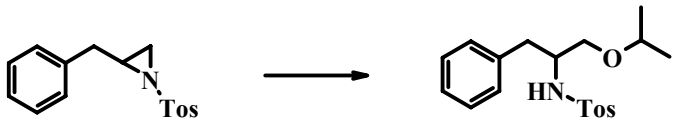
^{1}H-NMR ($CDCl_3$)

δ 1.31 (t, ^{3}J=7.3Hz, 3H, CH_3) 2.17 (d, ^{3}J=4.1Hz, 1H, N-CH**H**), 2.68 (d, ^{3}J=6.7Hz, 1H, N-C**H**H), 2.75 (dd, ^{2}J=15.8Hz, ^{3}J=8.8Hz, 1H, Ph-C**H**H), 2.88 (q, ^{3}J=7.6Hz, 2H, SO_2-CH_2), 2.91-2.96 (m, 2H, Ph-CH**H,** N-CH), 7.21-7.28 (m, 3H, H-2'/6'+H-4'), 7.29-7.34 (m, 2H, H-3'/5')

^{13}C-NMR ($CDCl_3$)

δ 7.6 (q, CH_3), 32.3 (t, N-CH_2), 37.5 (t, Ph-CH_2), 40.5 (d, N-CH), 127.0 (d, Ph-C-4), 128.6(d, Ph-C-3/5), 128.9 (d, Ph-C-2/6), 137.0 (s, Ph-C-1)

3.2.12 (R/S)-N-(1-Benzyl-2-isopropoxyethyl)-4-methyl benzenesulfonamide (14)



10 **14**

Procedure: Nucleophilic Ring Opening of Aziridine 10

Dry *i*-PrOH (0.870g, 14.5mmol, 3.00equiv.) was slowly added under argon atmosphere to a suspension of NaH in dry dioxane (18mL) keeping the temperature below 30°C. After complete addition the reaction mixture was stirred at rt until no more gas formation was observed and then for 30 minutes at 50°C. A predried (2d over molecular sieve 4Å) solution of **10** in dioxane (9mL) was then slowly added at 50°C within 25 minutes *via* syringe and septum. The reaction mixture was stirred at 50°C for 4 hours before a small sample was taken and analyzed by ^{1}H-NMR. The reaction mixture was worked up by pouring on ice water (30mL) and evaporation of most of the solvent. The aqueous layer was diluted with 10% NH_4Cl (15mL) and extracted with MTBE three times (100mL). The combined organic layers were washed once with brine, dried over Na_2SO_4 and evaporated to give 1.4g of dark liquid. The crude product was purified by flash column chromatography (50g SiO_2, PE:MTBE = 5:1) to yield pure compound **14**.

Yield: 720mg (42.9%) as colorless liquid

Physical Properties

$C_{19}H_{25}NO_3S$ (347.48)

calc.: C: 65.68 H: 7.25 N: 4.03 S: 9.23

found: C: 65.34 H: 7.32 N: 4.11 S: 8.76

TLC: (LP/MTBE = 3:1) $R_f = 0.34$ (LP/MTBE = 3:2) $R_f = 0.52$

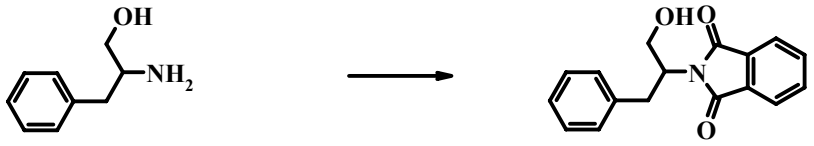
^{1}H-NMR ($CDCl_3$)

δ 1.06 (d, ^{3}J=6.3Hz, 3H, *i*-Pr-CH_3), 1.08 (d, ^{3}J=6.0Hz, 3H, *i*-Pr-CH_3), 2.40 (s, 3H, CH_3), 2.79 (d, ^{3}J=7.3Hz, 1H, Ph-CH_2), 3.13 (dd, ^{2}J=9.5Hz ^{3}J=4.8Hz, 1H, O-CH**H**), 3.22 (dd, ^{2}J=9.2Hz ^{3}J=3.4Hz, 1H, O-CH**H**), 3.41 (septet, ^{3}J=6.0Hz, 1H, *i*-Pr-CH) 3.47-3.53 (m, 1H, N-CH), 4.86 (d, 7.9Hz, 1H, NH) 7.05-7.06 (m, 2H, 2× Ph-H), 7.14-7.25 (m, 5H, 3× Ph-H+Tos-H-3/5) 7. 7.67 (d, ^{3}J=8.2Hz, 2H, Tos-H-2/6)

^{13}C-NMR ($CDCl_3$)

δ 21.5 (q, Tos-CH_3), 21.9, 22.0 (q, 2× *i*-Pr-CH_3), 38.2 (t, Ph-CH_2), 54.8 (d, N-CH), 67.6 (t, O-CH_2), 72.0 (d, O-CH) 126.5 (d, Ph-C-4), 127.0 (d, Tos-C-2/6), 128.4, (d, Ph-C-3/5), 129.4 (d, Ph-C-2/6), 129.5 (d, Tos-C-3/5), 137.5 (s, Ph-C-1), 137.8 (s, Tos-C-1), 143.1 (s,Tos-C-4)

3.2.13 (R/S)-N-(1-Benzyl-2-hydroxyethyl)phthalimide (15)



5 **15**

Procedure A: Condensation with Phthalic Anhydride

A suspension of phenylalaninol **5** (0.99g, 6.56mmol, 1.00equiv.) and phthalic anhydride (0.97g, 6.56mmol, 1.00equiv.) in TEA (664mg, 6.56mmol, 1.00 equiv.) and toluene (20mL) was heated to reflux in a 25mL flask fitted with a Dean-Stark tube. After 8 h the reaction mixture was evaporated and distributed between EtOAc and 2N HCl. The organic layer was washed twice with 2N HCl, once with $NaHCO_3$ and once with brine, dried over Na_2SO_4 and evaporated to yield in 460mg of a pure compound **15** that was crystallized from Et_2O and evaporated.

Yield: 460mg (24.4%) as white solid (Lit.[62] 77% enantiopure)

Procedure B: Condensation with "Nefkens" Reagent

To a solution of phenylalaninol **5** (1.06g, 7.00mmol, 1.00equiv.) in dry THF (28mL) N-carbethoxyphthalimide (1.69g, 7.70mmol, 1.10 equiv.) and Na_2CO_3 (0.82g, 7.70mmol, 1.10equiv) were added and the reaction mixture was stirred at rt for 18 h. Then the reaction mixture was filtered and the filtrate evaporated. The crude product was purified by flash column chromatography (30g SiO_2, LP/EtOAc = 3:2) to give target compound contaminated with ethyl carbamate that was removed on the *Kugelrohr* (30 minutes, 110°C, 0.3 mbar) to give pure target compound **15**.

Yield: 1.29g (65.5%) as white solid.

Physical Properties

$C_{17}H_{15}NO_3$ (381.31)

m.p.: 92-94 (Lit.[95] 97-98°C (benzene/hexane))

TLC: (LP/MTBE = 3:1) $R_f = 0.06$ (LP/MTBE = 3:2) $R_f = 0.15$

^{1}H-NMR ($CDCl_3$)[96]

δ 3.13 (d, ^{3}J=8.1Hz, 2H, Ph-CH_2), 3.85 (dd, ^{2}J=11.7Hz, ^{3}J=3.7Hz, 1H, O-C**H**H), 4.00 (dd, ^{2}J=11.9Hz, ^{3}J=7.1Hz, 1H, OCH**H**), 4.49-4.63 (m, 1H, NCH), 7.05-7.19 (m, 5H, 5×Ph-H), 7.58-7.72 (m, 4H, 4×Phth-H)

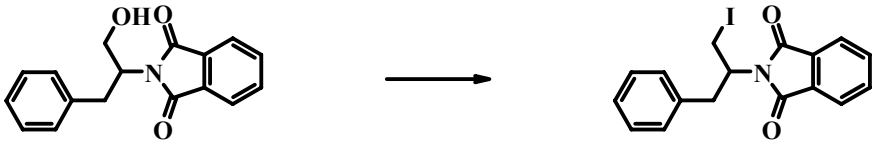
^{13}C-NMR ($CDCl_3$)

δ 34.7 (t, Ph-CH_2), 55.2 (d, N-CH), 62.7 (t, O-CH_2), 123.3 (d, Phth-C-3/4)126.6 (d, Ph-C-4), 128.5, 129.0 (2×d, Ph-C-2/6, Ph-C-3/5), 131.6 (s, Phth-C-1), 134.0 (d, Phth-C-2/5) 137.4 (s, Ph-C-1) 168.9 (s, NC=O)

[95] Yamada, S.; Matsuo, H.; Koga, K. *Chem. Pharm. Bull.* **1963**, *11*, 1140-1144.

[96] Neidlein, R.; Greulich, P.; Kramer, W. *Helv. Chim. Acta* **1993**, *76*, 2407-2417

3.2.14 (R/S)-N-(1-Benzyl-2-iodoethyl)phthalimide (16)



15 **16**

Procedure: Mitsunobu Type Reaction with I_2

To a chilled solution of triphenylphosphine (0.54g, 2.05mmol, 2.2equiv.) in dry DCM (8mL) first I_2 (520mg, 2.05mmol, 2.20equiv.) and then imidazole (0.152g, 2.23mmol, 2.40equiv.) were added in one portion each. At the addition of imidazole a white precipitate formed. The mixture was stirred for 30 minutes at rt before a solution of the alcohol **6** (0.262g, 0.93mmol, 1equiv.) in dry DCM (4mL) was added dropwise over a period of 20 minutes *via* syringe and septum. The reaction mixture was heated at reflux for 2h and was stirred at rt overnight. The suspension of white crystals in orange solution was washed twice with $Na_2S_2O_3$ (10%), once with water and once with brine. All aqueous layers were re-extracted and the combined organic layers were dried over Na_2SO_4 and evaporated. The crude product was purified by flash column chromatography (20g SiO_2, LP/EtOAc = 15:1) to give pure target compound **16** as white solid.

Yield: 245mg (67.3%) as white solid

Physical Properties

$C_{17}H_{14}INO_2$ (391.21)

m.p.: 112-116°C (Lit.[97] 138-140°C (R-enantiomer))

TLC: (LP/MTBE = 3:1) $R_f = 0.48$ (LP/MTBE = 3:2) $R_f = 0.49$

[97] Kato, T.; Zemlicka, J. *J. Org. Chem.* **1980**, *45*, 4006-4010

^{1}H-NMR ($CDCl_3$) [98]

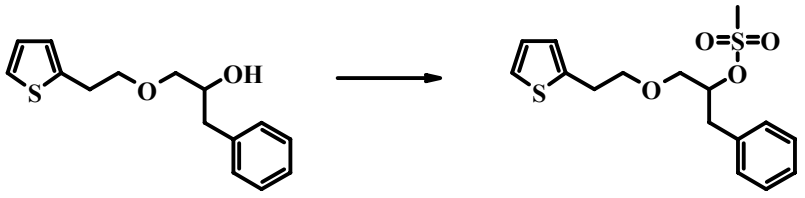
δ 3.30 (d, ^{3}J=7.9Hz, 2H, Ph-CH_2), 3.55 (dd, ^{2}J=10.2Hz, ^{3}J=4.,9Hz, 1H, I-C**H**H), 3.97 (t, J=10.5Hz, 1H, I-CH**H**), 4.66-4.81 (m, 1H, NCH), 7.11-7.21 (m, 5H, 5×Ph-H), 7.67-7.82 (m, 4H, 4×Phth-H)

^{13}C-NMR ($CDCl_3$)

δ 5.01 (t, I-CH_2), 38.3 (t, Ph-CH_2), 54.9 (d, N-CH), 123.3 (d, Phth-C-3/4), 126.9 (d, Ph-C-4), 128.6, 128.8 (2×d, Ph-C-2/6, Ph-C-3/5), 131.4 (s, Phth-C-1/6), 134.0 (d, Phth-C-2/5) 136.9 (s, Ph-C-1) 167.8 (s, N(**C**=O)$_2$)

[98] Rozwadowska, M.D. *Tetrahedron: Asymmetry* **1993**, *4*, 1619-1624

3.2.15 (R/S) α-[2-(2-Thienyl)ethoxymethyl]benzeneethanol methylsulfonate (17)



3 **17**

Procedure: Mesylation of Alcohol 3

Mesyl chloride (480mg, 4.20mmol, 1.40equiv.) was added dropwise to a chilled solution of alcohol **3** (0.79g, 3.00mmol, 1.00equiv.) and TEA (0.455g, 4.50mmol, 1.5equiv.) in dry DCM (4.5mL) keeping the temperature below 10°C. After complete addition the reaction mixture was stirred at rt for 2 hours before the reaction was quenched with 1N HCl. The phases were separated and the aqueous layer was washed with 1N HCl twice, followed by subsequent re-extraction with DCM. The combined organic layers were washed once with $NaHCO_3$, once with brine, dried over Na_2SO_4 and evaporated to give pure target compound **17**.

Yield: 0.96g (94.0%) as yellow oil

Physical Properties

$C_{16}H_{20}O_4S_2$ (340.46)

TLC: (LP/MTBE = 3:1) $R_f = 0.30$ (LP/MTBE = 3:2) $R_f = 0.52$

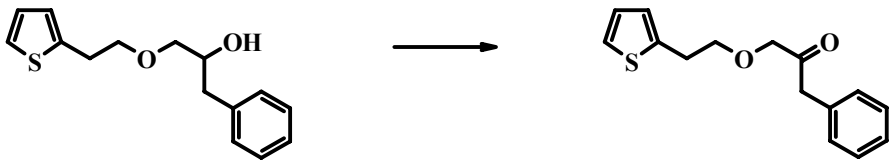
^{1}H-NMR ($CDCl_3$)

δ 2.62 (s, 3H, CH_3), 2.98-3.05(m, 2H, H-5), 3.09 (t, ^{3}J=6.7Hz 1H, H-1), 3.59 (d, ^{3}J=4.8Hz, 2H; H-3), 3.65-3.74 (m, 2H; H-2), 4.84-4.88 (m, 1H, H-4), 6.84 (dd, ^{3}J=3.5Hz, ^{4}J=1.3Hz, 1H, Th-H-3), 6.92 (dd, ^{3}J=5.1Hz, ^{3}J=3.5Hz, 1H, Th-H-4) 7.13 (dd, ^{3}J=5.0Hz ^{4}J=1.0Hz, 1H, Th-H-5) 7.20-7.32 (m, 5H, 5×Ph-H)

^{13}C-NMR ($CDCl_3$)

δ 30.3 (t, C-1), 37.7 (t, C-5), 38.2 (q, CH_3), 71.5, 71.9 (2×d, C-2, C-3), 82.6 (t, C-4), 123.7 (d, T-C-5), 125.2 (d, T-C-3), 126.7, 127.1 (2×d, Ph-C-4, T-C-4), 128.6, 129.6 (2×d, Ph-C-2/6, Ph-C-3/5), 136.1 (s, T-C-1), 141.0 (s, Ph-C-1)

3.2.16 (R/S)-1-Phenyl-3-[2-(2-thienyl)ethoxy]acetone (18)



3 **18**

Procedure: Oxidation with Dess-Martin Reagent

Dess-Martin periodinane (284mg, 0.67mmol, 1.34equiv.) was added to a solution of alcohol **3** (131mg, 0.50mmol, 1.00equiv.) in DCM (2.5mL) at rt and stirred for 90 minutes. According to TLC the reaction was "spot to spot". Therefore the reaction was diluted with Et_2O (15mL) and a white precipitate formed. Satd. $NaHCO_3$ (1.5mL) and 10% $Na_2S_2O_3$ (1.5mL) were added and the mixture was stirred for 20 minutes. The organic layer cleared, was separated, once washed with brine, dried over Na_2SO_4 and evaporated to give 100mg of colorless liquid, NMR-pure compound **18**.

Yield: 100mg (76.8%) as colorless liquid

Procedure: Oxidation with PDC

To a solution of alcohol **3** (525mg, 2.00mmol, 1.00equiv) in DCM (100mL) PDC (1.51g, 4.00mmol, 2.00equiv.) was added in one shot at rt and the reaction mixture was stirred at reflux for 5 hours. The reaction was cooled to rt, filtered over a bed of Na_2SO_4 and washed with DCM. After evaporation a dark residue was obtained, which was purified by column chromatography (20g SiO_2, LP/EtOAc 7:1) to give 325mg of target compound **18** in pure form as a colorless liquid.

Yield: 325 mg (62.4%) as colorless liquid

Procedure: Oxidation with PCC

To a solution of alcohol **3** (118mg, 0.45mmol, 1.0equiv) in DCM (5mL) PCC (116mg, 0.54mmol, 1.2equiv.) was added in one shot at rt and the reaction mixture stirred for 3h at rt. Then another 0.8equiv. PCC (78mg, 0.36mmol, 0.8equiv.) and 2mL of DCM were added and the mixture was stirred over night. In the morning 700mg of silica gel were added and all solid was scraped off the flask and the mixture was stirred for 30 minutes. Then it was filtered over a short bed of silica and washed with LP/EtOAc (120mL) and the filtrate evaporated to give 120mg of a crude product **18,** which was almost pure according to ^{1}H-NMR.

Physical Properties

$C_{15}H_{16}O_2S$ (260.36)

TLC: (LP/EtOAc = 7:1) $R_f = 0.38$

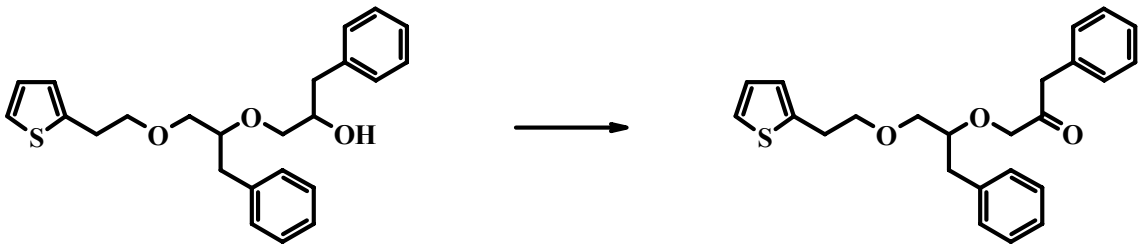
^{1}H-NMR ($CDCl_3$)

δ 3.13 (t, ^{3}J=6.6Hz 1H, H-1) 3.69 (t, ^{3}J=6.6Hz, 2H, H-2), 3.75(s, 2H, H-5), 4.09 (s, 2H, H-3), 6.85(dd, ^{3}J=3.4Hz ^{4}J=0.9Hz, 1H, T-H-3) 6.93 (dd, ^{3}J=5.1Hz ^{3}J=3.4Hz, 1H, Th-4) 7.12-7.35 (m, 6H, T-H-5, 5× Ph-H)

^{13}C-NMR ($CDCl_3$)

δ 30.3 (t, C-1), 46.1 (t, C-5), 72.1 (t, C-2), 75.5 (t, C-3), 123.7 (d, T-C-5), 125.3 (d, T-C-3), 126.7, 127.0 (2×d, Ph-C-4, T-C-4), 128.6 (d, Ph-C-3/5), 129.4 (d, Ph-C-2/6), 133.4 (s, Ph-C-1), 140.7 (s, T-C-1), 206.2(s, C=O)

3.2.17 (R/S)-1-{1-Benzyl-2-[2-(2-thienyl)ethoxy]ethoxy}-3-phenylacetone (19)



4 **19**

Procedure: Oxidation with PCC

To a solution of alcohol 4[99] (3.92g, 9.89mmol, 1.00equiv.) first SiO_2 (8g) and then PCC (4.26g, 19.8mmol, 2 equiv.) was added and the reaction mixture stirred at rt overnight. Then it was filtered over a short bed of SiO_2 and washed with DCM. The filtrate was evaporated to give 3.3 g of yellow oil. Purification with column chromatography (70g SiO_2, LP/MTBE = 7:1) gave target compound **19** in a pure form.

Yield: 2.78g (71.3%) as yellow liquid

Physical Properties

$C_{24}H_{28}O_3S$ (394.54)

TLC: (LP/MTBE = 3:1) $R_f = 0.34$ (LP/MTBE = 3:2) $R_f = 0.54$

[99] the material for this experiment was obtained as by-product in the preparation of **3** and in high purity

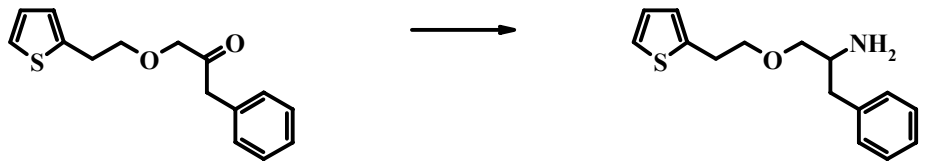
^{1}H-NMR ($CDCl_3$)[42]

δ 2.85(d, ^{3}J=6.6Hz, 2H, H-5), 3.05 (t, ^{3}J=6.6Hz, 2H, H-1), 3.45-3.51 (m, 2H, H-3), 3.60-3.63 (m, 2H, H-2) 3.65(d, ^{3}J=6.7Hz, 2H, H-8), 3.68-3.70 (m, 1H, H-4), 4.07(d, ^{2}J=17.1Hz, 1H, H-6), 4.18(d, ^{2}J=17.1Hz, 1H, H-6), 6.82 (dd, ^{3}J=4.5Hz ^{4}J=1.0Hz, 1H, Th-H-3) 6.91 (dd, ^{3}J=5.4Hz ^{3}J=3.45Hz, 1H, Th-H-4) 7.10-7.30 (m, 11H, 10× Ph-H, Th-H-5)

^{13}C-NMR ($CDCl_3$)

δ 30.4 (t, C-1), 38.1 (t, C-5), 45.9 (t, C-8), 71.9 (t, C-2), 72.8 (t, C-3), 75.2 (t, C-6), 80.9 (d, C-4) 123.6 (d, T-C-5), 125.1 (d, T-C-3), 126.3, 126.9 (2×d, Ph-C-4/Ph-C-4'), 126.6 (d, T-C-4), 128.3, 128.5, (2×d, Ph-C-3/5, Ph-C-3'/5'), 129.4, 129.5 (2×d, Ph-C-2/6, Ph-C-2'/6'), 133.6 (s, Ph-C-1'), 138.0 (s, Ph-C-1), 141.2 (s, T-C-2), 206.57 (s, C=O)

3.2.18 (R/S)-α-[2-(2-Thienyl)ethoxymethyl]benzeneethanamine (20)



18 20

Procedure: Reductive Amination of Ketone 18

Ketone **18** (1.345g, 5.17mmol, 1.00equiv.) was dissolved in dry MeOH and molecular sieve (3Å!) was added and the solution stirred at rt for 30 minutes. Then NH_4OAc (predried *in vacuo*) was added in one shot and the reaction mixture stirred at 0°C for 40 minutes before $NaCNBH_3$ was added in three portions within 60 minutes. After 2h at 0°C the reaction mixture was quenched with $NaHCO_3$ (10mL). MeOH was partly evaporated, little water was added and the aqueous layer extracted three times with MTBE. After evaporation the residue was dissolved in MTBE (30mL) and extracted with 2N HCl. The aqueous layer was adjusted to basic pH with Na_2CO_3 and extracted with MTBE. The combined organic layers were washed with brine, dried over Na_2SO_4 and evaporated to give compound **20**.

Yield: 400mg (29.6 %) as yellow oil

Physical Properties

$C_{15}H_{19}NOS$ (261.39)

TLC: (DCM/MeOH = 10:1) $R_f = 0.26$

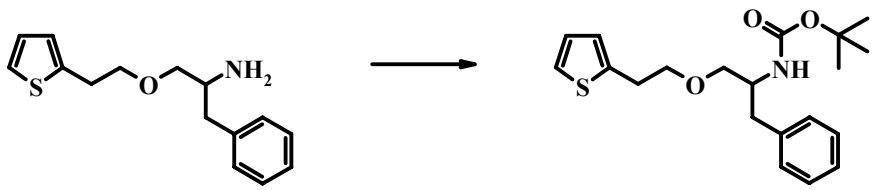
^{1}H-NMR ($CDCl_3$)

δ 1.80 (bs, 2H, NH_2), 2.59 (dd, ^{2}J=13.4Hz, ^{3}J=8.0Hz, 1H, Ph-C**H**H), 2.78 (dd, ^{2}J=13.4Hz, ^{3}J=5.5Hz, 1H, Ph-CH**H**), 3.10 (t, ^{3}J=6.5Hz, 2H, H-1), 3.22-3.26(m, 1H, C**H**-NH_2), 3.30 (dd, ^{2}J=9.1Hz, ^{3}J=6.9Hz, 1H, O-CH**H)** 3.46 (dd, ^{2}J=8.8Hz, ^{3}J=3.8Hz, 1H, O-C**H**H), 3.67 (q, 2H, ^{3}J=9.1Hz, 2H, H-2), 6.84(dd, ^{3}J=3.3Hz, ^{4}J=0.8Hz,1H, T-H-3), 6.92 (dd, ^{3}J=5.2Hz, ^{3}J=3.6Hz, 1H, T-H-4), 7.13 (dd, ^{3}J=5.0Hz, ^{4}J=0.9Hz,1H, T-H-5), 7.17-7.35 (m, 5H, 5×Ph-H)

^{13}C-NMR ($CDCl_3$)

δ 30.5 (t, C-1), 40.6 (t, C-5), 52.4 (d, C-4), 71.7 (t, C-2), 75.2 (t, C-3), 123.7 (d, T-C-5), 125.1 (d, T-C-3), 126.3 (d, Ph-C-4), 126.6 (d, T-C-4), 128.5 (d, Ph-C-3/5), 129.3 (d, Ph-C-2/6), 138.8 (s, Ph-C-1) 141.4 (s, T-C-2)

3.2.19 (R/S)-Preparation N-Boc-α-[2-(2-thienyl)ethoxymethyl] benzeneethanamine (21)



20 21

Procedure: Boc-Protection of Primary Amine 20

$(Boc)_2O$ (501mg, 2.29mmol, 1.50equiv.) was added to a solution of amine **20** (400mg, 1.53mmol, 1.00equiv.) in DCM and TEA (0.47g, 4.6mmol, 3.0 equiv.) and the reaction mixture stirred at rt under TLC monitoring. After 3 hours the solvent was evaporated to give 650mg of crude product. It was purified by column chromatography (10g SiO_2, LP/MTBE = 10:1) to give 290mg of target compound **21** that crystallized on storage.

Yield: 290mg (52.4 %) as white solid

Physical Properties

$C_{20}H_{27}NO_3S$ (361.51)

calc.: C: 66.45 H: 7.53 S: 8.87 N: 3.87

found: C: 65.90 H: 7.67 S: 8.52 N: 3.91

m.p.: 80-81.5°C (DIPE)

TLC: (LP/MTBE = 3:1) $R_f = 0.53$ (LP/MTBE = 3:2) $R_f = 0.71$

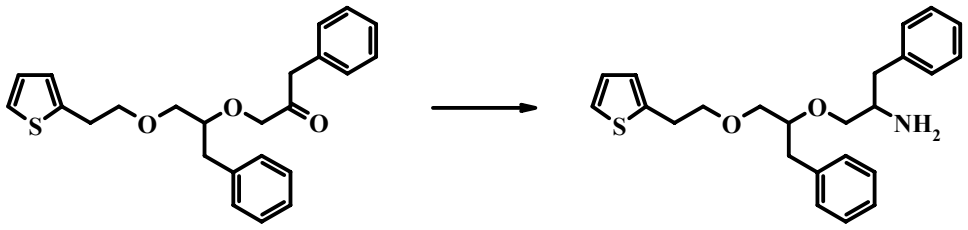
^{1}H-NMR ($CDCl_3$)

δ 1.42 (s, 9H, $C(CH_3)_3$), 2.83 (dd, ^{2}J=13.2Hz, ^{3}J=8.5Hz, 1H, Ph-C**H**H), 2.86-2.90 (bm, 1H, Ph-CH**H**), 3.10 (t, ^{3}J=6.3Hz, 2H, H-1), 3.33 (dd, ^{2}J=9.1Hz, ^{3}J=3.5Hz, 1H, O-CH**H)** 3.36 (dd, ^{2}J=9.3Hz, ^{3}J=3.9Hz, 1H, O-C**H**H), 3.63 (q, 2H, ^{3}J=6.6Hz, 2H, H-2), 3.91 (bs, 1H, H-4), 4.87(bs, 1H, NH), 6.86(dd, ^{3}J=3.5Hz, ^{4}J=0.9Hz,1H, T-H-3), 6.94 (dd, ^{3}J=5.2Hz, ^{3}J=3.3Hz, 1H, T-H-4), 7.14-7.37 (m, 6H, 5×Ph-H, Th-H-5)

^{13}C-NMR ($CDCl_3$)

δ 28.4 (q, 3×CH_3), 30.4 (t, C-1), 37.8 (t small, C-5), 51.6 (d small, C-5), 70.6 (t small, C-3), 71.7 (t, C-3), 79.2 (s, $C(CH_3)_3$), 123.7 (d, T-C-5), 125.2 (d, T-C-3), 126. 2(d, Ph-C-4), 126.7 (d, T-C-4), 128.3 (d, Ph-C-3/5), 129.4 (d, Ph-C-2/6), 138.3 (s, Ph-C-1) 141.4 (s, T-C-2), 155.3 (s, NC=O)

3.2.20 α-{1-Benzyl-2-[2-(2-thienyl)ethoxy]ethoxymethyl} benzeneethanamine (22)



19 **22**

Procedure: Reductive Amination of Ketone 19

Ketone **19** (4.27g, 10.8mmol, 1.00equiv.) was dissolved in MeOH (55mL), molecular sieve (3Å) added and the reaction mixture was stirred for 15 minutes. After addition of NH_4OAc (8.35g, 108mmol, 10equiv.) the reaction mixture was cooled to 0°C, $NaCNBH_3$ (0.477g, 7.58mmol, 0.7equiv.) was added and the reaction mixture stirred for two hours at rt. After another addition of $NaCNBH_3$ (0.204mg, 3.25mmol, 0.3equiv.) at 0°C the reaction mixture was stirred at rt overnight. The reaction mixture was cooled to 0°C, 2N HCl (15mL) was added and stirred for 15 minutes at rt. After neutralization with satd. $NaHCO_3$ (30mL) the aqueous layer (pH 8) was poured on 200mL of MTBE. The phases were separated and the aqueous layer was extracted twice with MTBE. The combined organic layers were evaporated and diluted with Et_2O. The two phases were separated and the organic layer was washed with brine, dried over Na_2SO_4 and evaporated to give 4.45g of yellow oil, which was purified by column chromatography (50g SiO_2, DCM/MEOH = 30:1to 10:1) to give pure target compound **22** as a mixture of diastereomers (1:1 according to ^{13}C-NMR).

Yield: 2.02g (47.1%) as yellow oil

Physical Properties

$C_{24}H_{29}NO_2S$ (395.57)

TLC: (DCM/MeOH = 20:1) $R_f = 0.10$ (DCM/MeOH = 10:1) $R_f = 0.37$

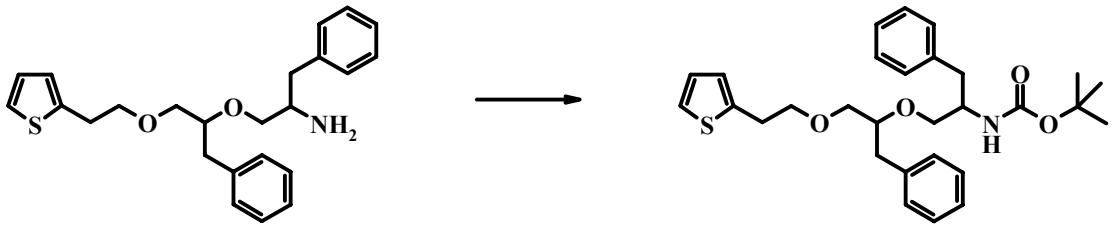
^{1}H-NMR ($CDCl_3$)

δ 1.63 (bs, 2H, NH_2), 2.44-2.49(m, 1H, H-8), 2.64-2.71(m, 1H, H-8), 2.79(dd, ^{2}J=13.9Hz, ^{3}J=7.3Hz, 1H, H-5), 2.87(dd, ^{2}J=14.3Hz, ^{3}J=5.5Hz, 1H, H-5), 3.05-3.14 (m, 3H, H-1, H-7), 3.18 (dd, J=9.2Hz, J=7.3Hz, 0.5H, H-6), 3.35 (dd, J=9.5Hz, J=7.0Hz, 0.5H, H-6) 3.40 (dd, J=9.5Hz, J=4.1Hz, 0.5H, H-6), 3.45-3.52 (m, 2H, H-3), 3.58 (dd, J=9.1Hz, J=3.5Hz, 0.5H, H-6), 3.64-3.71 (m, 3H, H-2, H-4), 6.84-6.85(m, 1H, T-H-3), 6.91-6.93 (m, 1H, T-H-4), 7.11-7.15 (m, 3H, T-H-5, 2×Ph-H), 7.17-7.30 (m, 8H, 8×Ph-H)

^{13}C-NMR ($CDCl_3$)

δ 30.4 (t, C-1), 2×38.3 (2×t, C-5), 2×40.3 (2×t, C-8), 52.5, 52.6 (2×d, C-7), 2×71.9 (2×t, C-2), 72.4, 72.5 (2×t, C-3), 74.5, 74.7 (2×t, C-6), 80.3, 80.4 (2×d, C-4), 123.6 (d, T-C-5), 125.1 (d, T-C-3), 126.2 (d, Ph-C-4, Ph-C-4'), 126.6 (d, T-C-4), 128.2-128.4 (3×d, Ph-C-3/5, Ph-C-3'/5'), 129.2-129.4 (3×d, Ph-C-2/6, Ph-C-2'/6'), 2×138.6 (2×s, Ph-C-1'), 138.8 (s, Ph-C-1), 141.3 (s, T-C-2)

3.2.21 N-Boc-α-{1-Benzyl-2-[2-(2-thienyl)ethoxy]ethoxymethyl} benzeneethanamine (23)



22 23

Procedure: Boc-Protection of Primary Amine 22

Solid $(Boc)_2O$ was added to a solution of crude amine **22** (185mg, 0.47mmol, 1.0 equiv.) in $CDCl_3$ (1mL) at 0°C. The solution was allowed to come to rt and stirred for three hours. According to ^{1}H-NMR total conversion from starting material was observed and the reaction was worked up. Phosphoric acid (15%, 1mL) was added and the mixture stirred for 5 minutes. The phases were separated, the aqueous layer was extracted twice with DCM, the combined organic layers were washed twice with satd. $NaHCO_3$, dried over Na_2SO_4 and evaporated. The crude product was purified by column chromatography (7g SiO_2, LP/Et_2O 5:1) to give pure compound **23**.

Yield: 85mg (36.6%) as oil

Physical Properties

$C_{29}H_{37}NO_4S$ (495.69)

calc.: C: 70.27 H: 7.52 N: 2.83 S: 6.47

found: C: 68.89 H: 7.56 N: 3.52 S: 6.62

TLC: (LP/EtOAc = 10:1) $R_f = 0.22$

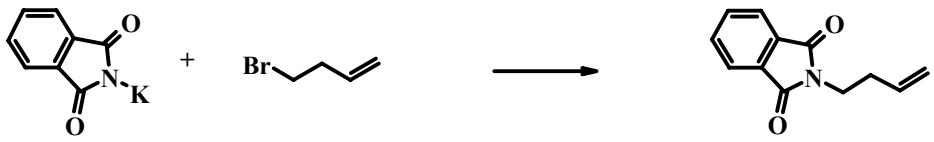
^{1}H-NMR ($CDCl_3$)

δ 1.41, 1.42 (2×s, 9H, $C(CH_3)_3$), 2.75-2.88(m, 4H, H-5, H-8), 3.08 (t, ^{3}J=6.8Hz, 1H, H-1), 3.11 (t, ^{3}J=6.8Hz, 1H, H-1), 3.22-3.50 (4×m, 2H, H-6), 3.44-3.48 (m, 2H, H-3), 3.54-3.66 (m, 2H, H-4), 3.64-3.69 (m, 2H, H-2), 3.74-3.80 (bs, 1H, H-7), 4.64 (bs, 0.5H, NH), 5.24 (bs, 0.5H, NH), 6.83-6.84(m, 1H, T-H-3), 6.90-6.92 (m, 1H, T-H-4), 7.11-7.13 (m, 1H, T-H-5) 7.13-7.32 (m, 10H, 10×Ph-H,)

^{13}C-NMR ($CDCl_3$)

δ 28.4 (q, $C(\mathbf{C}H_3)_3$), 2×30.5 (2×t, C-1), 37.7 (t small, C-8), 38.3, 38.6 (2×t, C-5), 52.0, 52.4 (2×d, C-7), 69.8 (t, C-6), 72.0 (t, C-2), 72.6 (t, C-3), 78.9 (s, $\mathbf{C}(CH_3)_3$)80.3, 80.9 (2×d, C-4), 123.6 (d, T-C-5), 125.2 (d, T-C-3), 126.0-126.3 (4×d, Ph-C-4, Ph-C-4'), 126.7 (d, T-C-4), 128.2-128.5 (3×d, Ph-C-3/5, Ph-C-3'/5'), 129.4-129.5 (3×d, Ph-C-2/6, Ph-C-2'/6'), 3×138.5 (3×s, Ph-C-1, Ph-C-1'), 141.2 (s, T-C-2), 155.3 (2×s, N-C=O)

3.2.22 N-(3-Butenyl)phthalimide (24)



24

Procedure: Gabriel Reaction

Potassium phthalimide (1.69g, 9.10mmol, 0.91 equiv.) was added to a solution of 4-bromo-1-butene (1.35g, 10mmol, 1.00 equiv.) in DMF and the mixture stirred for five hours at rt.
Most of the solvent was evaporated and the residue was dissolved in EtOAc/H_2O 1:1. The phases were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed once with water, once with brine, dried over Na_2SO_4 and evaporated. The crude product was dissolved in Et_2O and washed twice with 1N NaOH. The aqueous layers were re-extracted, the combined organic layers were washed once with water, once with brine dried over Na_2SO_4 and evaporated to give 900mg of pure target compound.

Yield: 900mg (44.7 %) as yellow needles

Physical Properties

$C_{12}H_{11}NO_2$ (201.23)

m.p.: 51-53°C (Lit.[100] 51-52°C)

^{1}H-NMR ($CDCl_3$)[101]

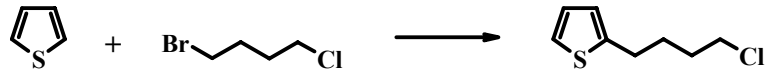
δ 2.44 (q, ^{3}J=7.0Hz, 2H, C**H$_2$**-C=C), 3.77 (t, ^{3}J =7.1Hz, 2H, N-CH_2), 4.98-5.10(m, 2H, **CH$_2$**=CH), 5.69-5.89(m, 1H, CH_2=**CH**), 7.68-7.86 (m, 4H, 4×Phth-H)

[100] Frank, W.C.; Kim, Y.C.; Heck, R.F. *J. Org. Chem.* **1978**, *43*, 2947-2949
[101] Jiranusornkul, S.; Sirithunyalug, B.; Nemoto, H.; Takahata, H. *Heterocycles*, **2002**, *56*, 487-496

^{13}C-NMR ($CDCl_3$)

δ 32.8 (t, CH_2), 37.3 (t, CH_2), 117.5 (t, **C**H_2-CH) 123.2 (d, Phth-C-3/4), 132.0 (s, Phth-C-1/6), 133.9 (d, Phth-C-2/5), 134.4 (d, **C**H=CH_2), 168.3 (s, NC=O)

3.2.23 2-(4-Chlorobutyl)thiophene (25)



25

Procedure: Lithiation and Wurtz-type Coupling

To a solution of thiophene (168mg, 2.00mmol, 1.00equiv.) 2.5M BuLi in THF (0.72mL, 1.8mmol, 0.90equiv.) was added at –78°C and the reaction mixture was stirred at this temperature for 1h. 1-Bromo-4-chlorobutane (514mg, 3.00mmol, 1.50equiv.) was dissolved in THF and added dropwise to the solution at –78°C. The mixture was allowed to come to rt and stirred overnight. The mixture was quenched with NH_4Cl (10%, 2mL) at –78°C and the aqueous layer was extracted with MTBE. The combined organic layers were washed with brine dried over Na_2SO_4 and evaporated (45°C/100 mbar). The crude product was purified by *Kugelrohr* distillation.

80°C/15mbar: 200mg, pure starting material
150°C/15mbar: 120mg, clear liquid, the target compound **25**

Yield: 120mg (42.8 %) as colorless liquid

Physical Properties

$C_8H_{11}ClS$ (174.69)

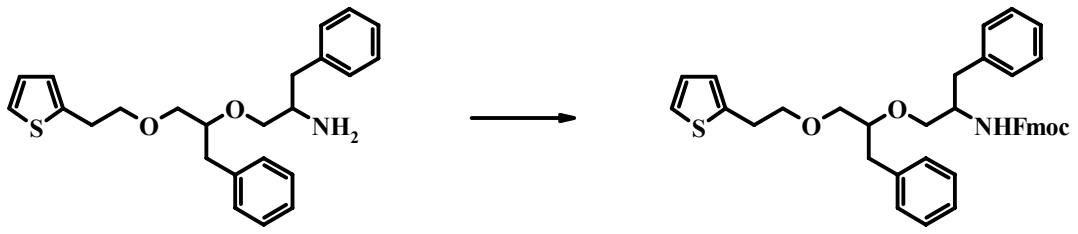
^{1}H-NMR ($CDCl_3$

δ 1.81-1.88 (m, 4H, 2×CH_2), 2.97 (t, ^{3}J=6.8Hz, 2H, Th-CH_2), 3.56 (t, ^{3}J=6.1Hz, 2H, Cl-CH_2), 6.79 (dd, ^{3}J=3.2Hz, ^{4}J=0.6Hz, 1H, T-H-3), 6.92 (dd, ^{3}J=5.2Hz, ^{3}J=3.4Hz, 1H, T-H-4), 7.12 (dd, ^{3}J=5.1Hz, ^{4}J=1.2Hz, 1H, T-H-5)

^{13}C-NMR ($CDCl_3$)

δ 28.9 (t, CH_2), 29.1 (t, Th-CH_2), 31.8 (t, CH_2), 44.7 (t, Cl-CH_2), 123.1 (d, T-C-5), 124.3 (d, T-C-3), 126.7 (d, T-C-4), 144.6 (s, T-C-2)

3.2.24 N-Fmoc-α-{1-Benzyl-2-[2-(2-thienyl)ethoxy]ethoxy methyl} benzeneethanamine (26)



22 26

Procedure: Fmoc-Protection of Amine 22

Fmoc-OSu (1.62g, 4.81mmol, 1.10equiv.) was added to a solution of amine **22** (1.73g, 4.37mmol, 1.00equiv.) and TEA (0.53g, 5.25mmol, 1.20equiv.) in THF/DCM 9:1 (30mL). The reaction mixture was stirred for 2 hours at rt before it was diluted with EtOAc (20mL), washed with half satd. NH_4Cl with halve satd. $NaHCO_3$, dried over Na_2SO_4 and evaporated. The crude product was purified by flash column chromatography (80g SiO_2, LP/Et_2O = 2:1) to yield pure target compound **26**.

Yield: 2.45g (90.7%) as highly viscous oil

Physical Properties

$C_{39}H_{39}NO_4S$ (617.81)

TLC: (LP/MTBE = 3:1) $R_f = 0.22$ (LP/MTBE = 3:2) $R_f = 0.46$

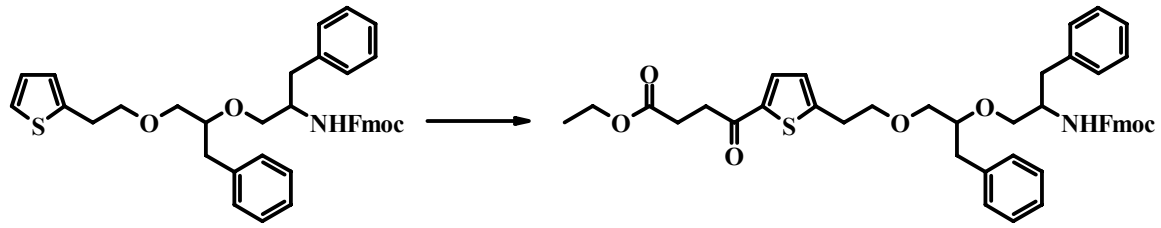
^{1}H-NMR ($CDCl_3$)

δ 2.69-2.89(m, 4H, H-5, H-8), 3.07 (t, ^{3}J=6.6Hz, 2H, H-1), 3.23-3.51 (4×m, 2H, H-6), 3.42-3.48 (m, 2H, H-3), 3.54-3.66 (m, 2H, H-4), 3.63-3.67 (m, 2H, H-2), 3.80-3.88 (m, 1H, H-7), 4.17-4.19 (m, 1H, F-H-9), 4.30-4.34(m, 1H, F-CH_2O), 4.40-4.44 (m, 1H, F-CH_2O), 4.81 (d, ^{3}J=8.5Hz, 0.5H, NH), 5.55 (d, ^{3}J=8.5Hz, 0.5H, NH), 6.76-6.80(m, 0.5H, T-H-3), 6.82 (dd, ^{3}J=3.2Hz, ^{4}J=0.9Hz, 0.5H, T-H-3), 6.86-6.89 (m, 0.5H, T-H-4), 6.90 (dd, ^{3}J=5.0Hz, ^{3}J=3.5Hz, 0.5H, T-H-4), 6.90 (dd, ^{3}J=5.0Hz, ^{4}J=1.3Hz, 1H, T-H-5) 7.03-7.33 (m, 12H, 10×Ph-H, F-H-2,7), 7.36-7.42 (m, 2H, F-H-3,6), 7.56-7.57 (m, 2H, F-H-1,8), 7.74-7.78(m, 2H, F-H-4,5)

^{13}C-NMR ($CDCl_3$)

δ 2×30.4 (2×t, C-1), 37.5 (t, C-8), 38.4, 38.6 (2×t, C-5), 47.3 (d, F-C-9), 52.6, 52.8 (2×d, C-7), 66.3 (t, Fmoc-CH_2), 69.9 (t, C-6), 72.0 (t, C-2), 2×72.8 (2×t, C-3), 80.4, 81.1 (2×d, C-4), 119.9 (d, F-C-4,5), 2×123.6 (2×d, T-C-5), 125.0,125.1 (2×d, F-C-1,8), 125.2 (d, T-C-3), 126.2-126.4 (4×d, Ph-C-4, Ph-C-4'), 126.6 (d, T-C-4), 127.0 (d, F-C-2,7) 2×127.6 (2×d, F-C-3,6), 128.3-128.4 (3×d, Ph-C-3/5, Ph-C-3'/5'), 129.4-129.5 (3×d, Ph-C-2/6, Ph-C-2'/6'), 2×138.2, 138.4,138.6 (4×s, Ph-C-1, Ph-C-1'), 141.2-141.3 (s, F-C-4a,4b, T-C-2), 2×144.0 (2×s, F-C-8a,9a) 155.8, 155.9 (2×s, N-C=O)

3.2.25 5-{2-[2-Benzyl-2-(2-Fmoc-amino-3-phenyl-propoxy)ethoxy]ethyl}-γ-oxo-thiophene-2-butyric acid ethylester (32)



26 **32**

Procedure: Friedel-Crafts Acylation with $SnCl_4$

A 1M solution of $SnCl_4$ in DCM (5.02mL, 5.02mmol, 2.5equiv.) was added to a chilled solution of thiophene **26** (1.24g, 2.01mmol, 1.00equiv.) and acid chloride **35** (0.40g, 2.41mmol, 1.20equiv.) in DCM (14mL) *via* syringe and septum within 10 minutes. The reaction was stirred at rt for two hours turning purple during addition of $SnCl_4$. The reaction was quenched with 2N HCl (8mL) to give an orange solution. The phases were separated and the aqueous layer was extracted two times with DCM. The combined organic layers were washed with $NaHCO_3$ and brine, dried over Na_2SO_4 and evaporated. Purification with flash column chromatography (50g SiO_2, LP/MTBE = 3:1 to 3:2) yielded pure target compound **32**.

Yield: 1.05g (70.1%) as slightly colored oil.

Physical Properties

$C_{45}H_{47}NO_7S$ (745.94)

TLC: (LP/MTBE = 3:2) $R_f = 0.10$

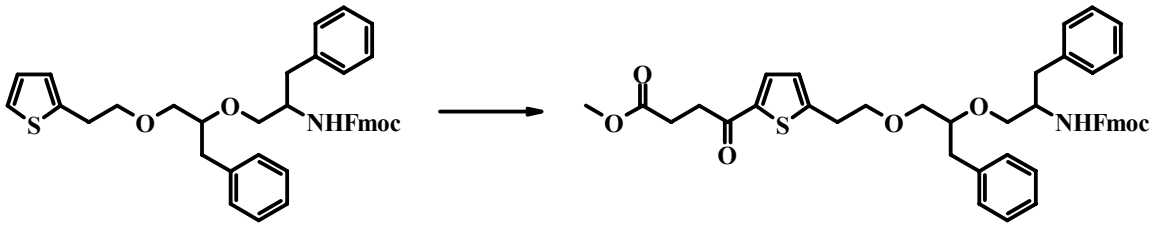
^{1}H-NMR ($CDCl_3$)

δ 2×1.24 (2×t, ^{3}J=7.3Hz, 3H, CH_3), 2.68-2.84(m, 4H, H-5, H-8), 2.71 (t, ^{3}J=6.6Hz, 2H, H-3'), 3.01-3.07 (m, 2H, H-1), 3.12-3.17 (m, 2H, H-2'), 3.24-3.51 (4×m, 2H, H-6), 3.42-3.51 (m, 2H, H-3), 3.55-3.70 (m, 2H, H-4), 3.60-3.70 (m, 2H, H-2), 3.80-3.90 (m, 1H, H-7), 4.11-4.15 (m, 2H, O-C**H$_2$**CH_3), 4.17-4.19 (m, 1H, F-H-9), 4.31-4.34(m, 1H, F-CH_2O), 4.38-4.47(m, 1H, F-CH_2O), 4.84 (d, ^{3}J=8.5Hz, 0.5H, NH), 5.51 (d, ^{3}J=8.5Hz, 0.5H, NH), 6.71-6.78 (m, 0.5H, T-H-3), 6.84 (d, ^{3}J=3.5Hz, 0.5H, T-H-3), 7.04-7.33 (m, 12H, 10×Ph-H, F-H-2,7), 7.34-7.44 (m, 2H, F-H-3,6), 7.48-7.61 (m, 3H, T-H-5, F-H-1,8), 7.74-7.78(m, 2H, F-H-4,5)

^{13}C-NMR ($CDCl_3$)

δ 14.1 (q, CH_3), 28.2 (t, C-3'), 31.0, 31.2 (2×t, C-1), 33.4 (t, C-2') 37.5, 37.6 (2×t, C-8), 38.3, 38.5 (2×t, C-5), 47.3 (d, F-C-9), 52.5, 52.8 (2×d, C-7), 60.6 (t, O-**C**H_2CH_3), 66.2, 66.3 (2×t, F-CH_2O), 69.9, 70.0 (2×t, C-6), 71.2 (t, C-2), 72.9 (t, C-3), 80.3, 80.9 (2×d, C-4), 119.9 (d, F-C-4,5), 124.9 ,125.1 (2×d, F-C-1,8), 126.2-126.4 (4×d, Ph-C-4, Ph-C-4'), 126.6 (d, T-C-3), 126.9 (d, F-C-2,7) 127.6 (d, F-C-3,6), 128.3-128.4 (3×d, Ph-C-3/5, Ph-C-3'/5'), 129.3-129.4 (3×d, Ph-C-2/6, Ph-C-2'/6'), 132.1(d, T-C-4), 138.1, 138.2, 138.4 (3×s, Ph-C-1, Ph-C-1'), 141.3 (s, F-C-4a,4b), 141.8, 141.9 (2×s, T-C-2), 143.9-144.0 (3×s, F-C-8a,9a) 151.0,151.1 (2×s, T-C-5), 2×155.8, (2×s, N-C=O), 172.7 ((s, COOEt), 190.7 (s, C=O)

3.2.26 5-{2-[2-Benzyl-2-(2-Fmoc-amino-3-phenyl-propoxy)ethoxy]ethyl}-γ-oxo-thiophene-2-butyric acid methylester (33)



26 **33**

Procedure: Friedel Crafts Acylation with $SnCl_4$

A 1M $SnCl_4$ solution in DCM (23.0mL, 23.0mmol, 2.5equiv.) was added to a chilled solution of thiophene **26** (5.70g, 9.23mmol, 1.00equiv.) and acid chloride **37** (1.67g, 11.1mmol, 1.20equiv.) in DCM (80mL) within 15 minutes, keeping the temperature below 5°C. The reaction mixture turned red and was stirred below 10°C for two and a half hours. The reaction was quenched by addition of 2N HCl (50mL) keeping the temperature below 5°C and stirring for 15 minutes at ice bath temperature to give a yellow solution. The phases were separated the aqueous layer extracted two times with DCM. The combined organic layers were washed with $NaHCO_3$ and brine, dried over Na_2SO_4 and evaporated to leave 7g of yellow oil. The crude product was purified by column chromatography (130g SiO_2, LP/MTBE = 2:1 to 1:1) to give 5.62g of pure target compound.**33**.

Yield: 5.62g (81.6%) as slightly colored oil.

Physical Properties

$C_{44}H_{45}NO_7S$ (731.92)

calc.: C: 72.46 H: 6.35 N: 1.88 S: 4.30

found: C: 70.95 H: 6.09 N: 2.00 S: 4.36

TLC: (LP/MTBE = 3:2) $R_f = 0.11$

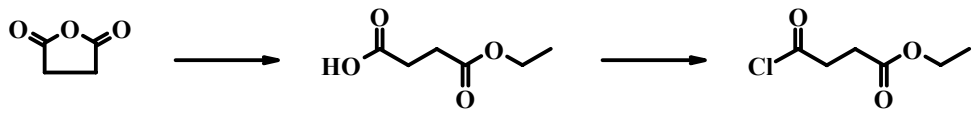
^{1}H-NMR ($CDCl_3$)

δ 2.68-2.85 (m, 4H, H-5, H-8), 2.73 (t, ^{3}J=6.8Hz, 2H, H-3'), 3.02-3.08 (m, 2H, H-1), 3.13-3.19 (m, 2H, H-2'), 3.25-3.51 (4×m, 2H, H-6), 3.44-3.51 (m, 2H, H-3), 3.58-3.66 (m, 2H, H-4), 3.64-3.67 (m, 2H, H-2), 3.68, 3.69 (2×s, 3H OCH_3), 3.80-3.86 (m, 1H, H-7), 4.19 (t, ^{3}J=6.8Hz, 1H, F-H-9), 4.31-4.34(m, 1H, F-CH_2O), 4.40-4.46 (m, 1H, F-CH_2O), 4.83 (d, ^{3}J=8.5Hz, 0.5H, NH), 5.50 (d, ^{3}J=8.2Hz, 0.5H, NH), 6.78 (d, ^{3}J=3.2Hz, 0.5H, T-H-3), 6.85 (d, ^{3}J=3.8Hz, 0.5H, T-H-3), 7.04-7.33 (m, 12H, 10×Ph-H, F-H-2,7), 7.35-7.43 (m, 2H, F-H-3,6), 7.52-7.57 (m, 3H, T-H-5, F-H-1,8), 7.75-7.79(m, 2H, F-H-4,5)

^{13}C-NMR ($CDCl_3$)

δ 27.9 (t, C-3'), 31.0, 31.1 (2×t, C-1), 33.4 (t, C-2') 37.4, 37.5 (2×t, C-8), 38.2, 38.5 (2×t, C-5), 47.2 (d, F-C-9), 51.7 (q, OCH_3), 52.5, 52.7 (2×d, C-7), 2×66.2 (2×t, F-CH_2O), 69.9, 70.0 (2×t, C-6), 71.1 (t, C-2), 72.8 (t, C-3), 80.2, 80.9 (2×d, C-4), 119.9 (d, F-C-4,5), 124.9-125.0 (3×d, F-C-1,8), 126.1-126.3 (4×d, Ph-C-4, Ph-C-4'), 126.6 (d, T-C-3), 126.9 (d, F-C-2,7) 127.5 (d, F-C-3,6), 128.2-128.3 (3×d, Ph-C-3/5, Ph-C-3'/5'), 129.3-129.4 (3×d, Ph-C-2/6, Ph-C-2'/6'), 132.1 (d, T-C-4), 138.1-138.4 (3×s, Ph-C-1, Ph-C-1'), 2×141.2 (2×s, F-C-4a,4b), 2×141.7 (2×s, T-C-2), 143.8-143.9 (3×s, F-C-8a,9a), 151.0, 151.1 (2×s, T-C-5), 2×155.7, (2×s, N-C=O), 173.1 ((s, **C**OOMe), 190.5 (s, C=O)

3.2.27 4-Chloro-4-oxo-butyric acid ethyl ester (35)



34 **35**

Procedure: Ethanolysis of Succinic Anhydride and Formation of Acid Chloride

A mixture of dry EtOH (23mL, 2 equiv.) and succinic anhydride (19.63g, 196.19mmol, 1.00 equiv.) was heated to 100°C for 3.5h. The excess of EtOH was evaporated (30 minutes, 7mbar, 70°C) and 27.6g of a crude product were obtained, the monoester according to ^{1}H and ^{13}C-NMR. $SOCl_2$ (23mL) was added at 0°C and the reaction mixture was stirred at 110 °C for two hours. It was allowed to cool to rt, the excess of $SOCl_2$ was evaporated and the product was distilled *in vacuo* (10-15mbar 83-89°C) to give pure target compound **35**.

Yield: 26.3g (81.4%) (Lit.[82] 94.0%) as colorless liquid

Physical Properties

$C_6H_9ClO_3$ (164.59)

b.p.: 83-89°C/10-15mbar (Lit.[82] 110-115°/30 Torr)

^{1}H-NMR ($CDCl_3$)[102]

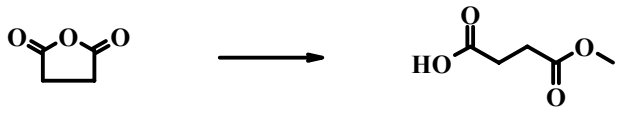
δ 1.26 (t, ^{3}J=7.1Hz, 3H, CH_3), 2.67 (t, ^{3}J =6.6Hz, 2H, EtOCO**CH_2**), 3.21 (t, ^{3}J =6.6Hz, 2H, ClCOC**H_2**), 4.17 (q, ^{3}J=7.2Hz, 2H, O-CH_2)

^{13}C-NMR ($CDCl_3$)

δ 14.1 (q, CH_3), 29.4 (t, EtOCO-**C**H_2), 41.7 (t, ClCO-**C**H_2), 61.2 (t, O-CH_2), 170.8 (s, C=O), 173.0 (s, C=O)

[102] Aldrich NMR Data Base

3.2.28 Succinic acid monomethyl ester (36)



36

Procedure: Methanolysis of Succinic Anhydride

A mixture of MeOH (41mL) and succinic anhydride (39.0g, 389.73mmol, 1.0 equiv.) was heated to 90°C for 5h. The excess of MeOH was evaporated and the crude product was purified by vacuum distillation. Since the product crystallized in the condenser the water cooling was changed to air cooling and 40.1g of pure product **36** were obtained as colorless crystals.

Yield: 40.1g (77.8%) as colorless crystals

Physical Properties

$C_5H_8O_4$ (132.12)

b.p.: 144°C/10-15mbar (Lit.[103] 151°C/20 Torr)

m.p.: 52-56°C (Lit.[103] 56-59°C)

^{1}H-NMR ($CDCl_3$)[102]

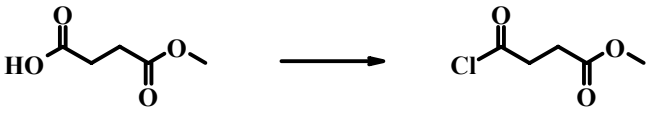
δ 2.58-2.74 (m, 4H, H-2, H-3), 3.70 (s, 3H, O-CH_3)

^{13}C-NMR ($CDCl_3$)

δ 28.6, 28.9 (2×t, 2×CO-**C**H_2), 52.0 (q, O-CH_3), 172.6, 178.2 (2×s, 2×C=O)

[103] Aldrich Catalog

3.2.29 4-Chloro-4-oxo-butyric acid methyl ester (37)



36 **37**

Procedure: Formation of Acid Chloride with $SOCl_2$

$SOCl_2$ (34.3mL, 470.24mmol, 1.6 equiv.) was added to mono acid **36** (38,8g, 294mmol, 1.00 equiv.) at external ice bath cooling and after complete addition the mixture was refluxed for three hours. Most of the $SOCl_2$ was evaporated and the crude product was distilled *in vacuo* (b.p.: 71°C (20mbar). Target compound **37** was obtained, slightly contaminated with dimethyl succinate.

Yield: 25.2g (50.4%) as colorless liquid

Physical Properties

$C_5H_8ClO_3$ (150.56)

b.p.: 71°C/20mbar (Lit.[103] 58-65°C/3 Torr)

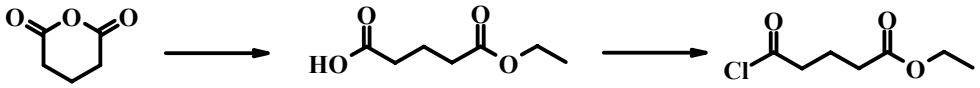
^{1}H-NMR ($CDCl_3$)[102]

δ 2.68 (t, ^{3}J=6.4Hz, 2H, CH_3OCO-C**H$_2$**), 3.22 (t, ^{3}J=6.4Hz, 2H, ClCO-C**H$_2$**) 3.71 (s, ^{3}H, O-CH_3)

^{13}C-NMR ($CDCl_3$)

δ 29.1 (t, CH_3OCO-**C**H_2), 41.7 (t, ClOCO-**C**H_2), 52.2 (q, O-CH_3), 171.3 (s, C=O), 173.0 (s, C=O)

3.2.30 5-Chloro-5-oxo-pentanoic acid ethyl ester (39)



38 **39**

Procedure: Ethanolysis of Glutaric Anhydride and Formation of Acid Chloride

A suspension of glutaric anhydride (18.61g, 163.1mmol, 1.00equiv.) in dry EtOH (20mL, 2equiv.) was stirred at 100°C bath temperature till a clear solution was obtained and the reflux decreased (3h). The excess of EtOH was evaporated at 8mbar and the crude product purified by vacuum distillation (155°C / 10-15mbar; Lit.[104] 140-143°C/6 Torr) to give a colorless liquid, compound **38**[105]**.** $SOCl_2$ (20mL) was added at external ice bath cooling and the mixture stirred at 80°C for 2 hours. Decrease of CO_2 evolution indicated total conversion and the excess of $SOCl_2$ was evaporated. Pure acid chloride **39** was obtained by vacuum distillation.

Yield: 16.6g (57.0 %) as colorless liquid

Physical Properties

$C_7H_{11}ClO_3$ (178.62)

b.p.: 101°C/10-15mbar (Lit.[106] 104-106°C/15Torr)

^{1}H-NMR ($CDCl_3$)

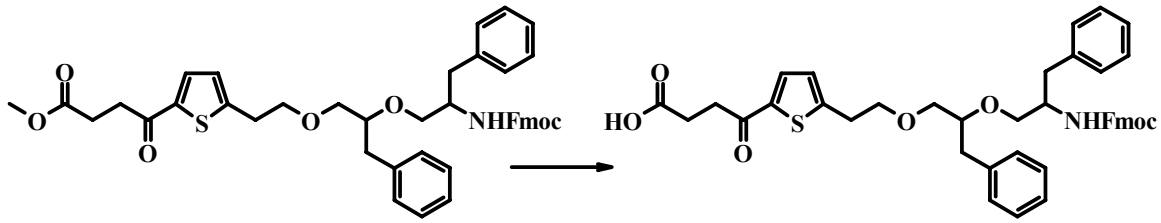
δ 1.36 (t, ^{3}J=7.2Hz, 3H, CH_3), 2.1 (q, ^{3}J =7.1Hz, 2H, H-3), 2.49 (t, ^{3}J =7.1Hz, 2H, EtOCOC**H$_2$**), 3.10 (t, ^{3}J =7.1Hz, 2H, ClCOC**H$_2$**), 4.25 (q, ^{3}J=7.1Hz, 2H, Et-CH_2)

^{13}C-NMR ($CDCl_3$)

δ 14.2 (q, CH_3), 20.2 (t, C-3), 32.3 (t, EtOCO-**C**H_2), 46.0 (t, ClCO-**C**H_2), 60.6 (t, O-CH_2), 172.3, 173.4 (2×s, 2×C=O)

[104] Meyer, R.B.; Hauser, C.R.; *J. Org. Chem.* **1961**, *26*, 3183-3186
[105] Sugiyama, T.; Yamakoshi, H.; Nojima, M. *J. Org. Chem.* **1993**, *58*, 4211-4218
[106] Lartillot, S.; Baron, C. *Bull. Soc. Chim.* Fr. **1964**, 783-786

3.2.31 5-{2-[2-Benzyl-2-(2-Fmoc-amino-3-phenyl-propoxy)ethoxy]ethyl}-γ-oxo-thiophene-2-butyric acid (29)



33 29

Procedure: Acidic Ester Hydrolysis with Formic Acid and p-Toluenesulfonic Acid

4-Toluenesulfonic acid (2.42g, 12.7mmol, 2.0 equiv.) was added to a suspension of ester **33** (4.75g, 6.37mmol, 1.00equiv) in formic acid :water 80:20 (95mL) at 40°C and the reaction mixture heated to reflux temperature getting homogenous below 70°C. After 70 minutes the reaction was worked up by evaporation of most of the solvent and taking up in water/EtOAc (50mL/100mL). The aqueous layer was extracted two times with EtOAc (50mL), the combined organic layers were washed with brine, dried over Na_2SO_4 and evaporated to give 4.7g of dark oil. Purification by flash column chromatography (100g SiO_2, DCM/MeOH = 40:1) gave 4.15g of pure product **29,** which was obtained as white solid foam. The foam was dried *in vacuo* and ground in a mortar to give a white solid.

Yield: 4.15g (90.8%) as solid white foam

Physical Properties

$C_{43}H_{43}NO_7S$ (717.89)

calc.: C: 71.94 H: 6.04 N: 1.95 S: 4.47

found: C: 71.26 H: 6.23 N: 2.11 S: 4.47

"m.p.": 50-60°C (softening range)

TLC: (DCM/MeOH = 20:1) $R_f = 0.10$ (DCM/MeOH = 10:1) $R_f = 0.41$

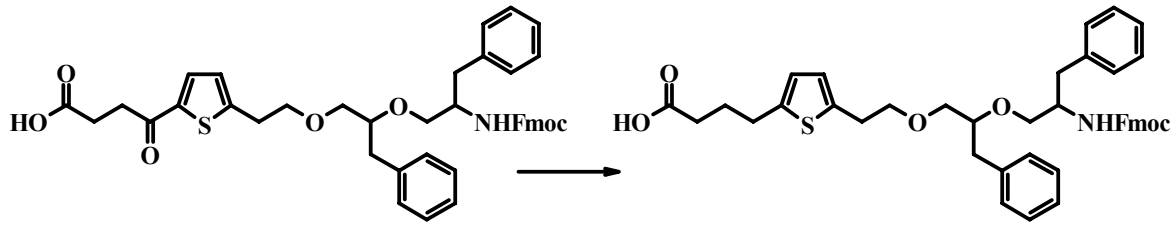
^{1}H-NMR ($CDCl_3$)

δ 2.63-2.85 (m, 6H, H-5, H-8, H-3'), 2.98-3.07 (m, 2H, H-1), 3.09-3.17 (m, 2H, H-2'), 3.25-3.51 (4×m, 2H, H-6), 3.41-3.48 (m, 2H, H-3), 3.57-3.69 (m, 4H, H-4, H-2) 3.75-3.86 (m, 1H, H-7), 4.10-420 (m, 1H, F-H-9), 4.29-4.33(m, 1H, F-CH_2O), 4.39-4.45 (m, 1H, F-CH_2O), 4.82 (d, ^{3}J=8.5Hz, 0.5H, NH), 5.50 (d, ^{3}J=8.2Hz, 0.5H, NH), 6.77 (d, ^{3}J=3.2Hz, 0.5H, T-H-3), 6.81 (d, ^{3}J=3.8Hz, 0.5H, T-H-3), 7.12-7.33 (m, 12H, 10×Ph-H, F-H-2,7), 7.36-7.42 (m, 2H, F-H-3,6), 7.49-7.57 (m, 3H, T-H-5, F-H-1,8), 7.74-7.78(m, 2H, F-H-4,5)

^{13}C-NMR ($CDCl_3$)

δ 28.0 (t, C-3'), 31.0, 31.2 (2×t, C-1), 33.2 (t, C-2') 37.5, 37.6 (2×t, C-8), 38.3, 38.5 (2×t, C-5), 47.3 (d, F-C-9), 52.5, 52.8 (2×d, C-7), 66.3 (t, F-CH_2O), 69.9, 70.0 (2×t, C-6), 71.1, 71.2 (2×t, C-2), 73.0, 73.2 (2×t, C-3), 80.3, 80.9 (2×d, C-4), 119.9 (d, F-C-4,5), 125.0-125.1 (3×d, F-C-1,8), 126.2-126.4 (3×d, Ph-C-4, Ph-C-4'), 126.7 (d, T-C-3), 127.0 (d, F-C-2,7) 127.6 (d, F-C-3,6), 128.3,128.4 (2×d, Ph-C-3/5, Ph-C-3'/5'), 129.3-129.5 (3×d, Ph-C-2/6, Ph-C-2'/6'), 132.3 (d, T-C-4), 138.1-138.4 (3×s, Ph-C-1, Ph-C-1'), 141.3 (s, F-C-4a,4b), 141.6, 141.7 (2×s, T-C-2), 143.9-144.0 (3×s, F-C-8a,9a), 151.3, 151.4 (2×s, T-C-5), 155.7 (s, N-C=O), 176.9, 177.0 (2×s, COOH), 190.5 (s, C=O)

3.2.32 5-{2-[2-Benzyl-2-(2-Fmoc-amino-3-phenyl-propoxy)ethoxy]ethyl}-thiophene-2-butyric acid (40)



29 **40**

Procedure: Acidic Deoxygenation with Trifluoroacetic acid / Triethylsilane

Ketone **29** (2.28g, 3.18mal, 1.0 equiv.) was dissolved in trifluoroacetic acid (5.43g, 47.6mmol, 15.0equiv.) at rt. Triethylsilane (3.32g, 28.6mmol, 9.00equiv.) was added to the violet solution at rt and the mixture stirred at 60°C for 18hours. Then it was quenched by addition of water (10mL) and extracted three times with EtOAc. The combined organic layers were washed once with brine, dried over Na_2SO_4 and evaporated to give a crude product of 3.20 g, which was purified by column chromatography (120g SiO_2, DCM/MeOH = 40:1 to 20:1) to give 1.93g of pure target compound **40** as highly viscous oil and 180mg (7.9%) of starting material with little target compound.

Yield: 1.93g (86.33%) as viscous yellow oil

Physical Properties

$C_{43}H_{45}NO_6S$ (703.91)

calc.: C: 73.37 H: 6.44 N: 1.99 S: 4.56

found: C: 72.35 H: 6.54 N: 2.01 S: 4.23

TLC: (DCM/MeOH = 20:1) $R_f = 0.18$ (DCM/MeOH = 10:1) $R_f = 0.46$

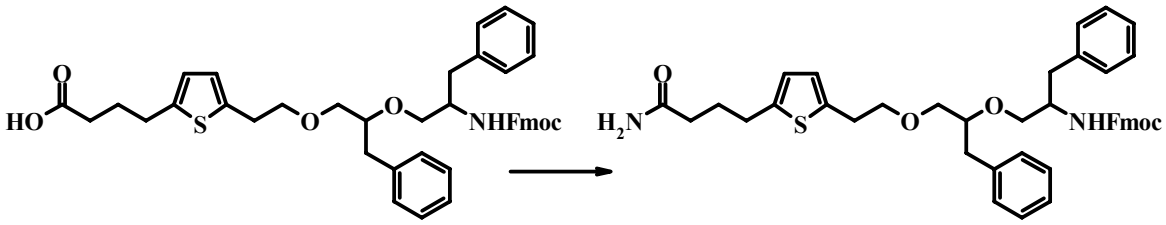
^{1}H-NMR ($CDCl_3$)

δ 1.91-1.97 (m, 2H, H-3'), 2.34-2.38 (m, 2H, H-2'), 2.69-2.87(m, 5H, H-8, H-5, H-4'), 2.94-3.04(m, 2H, H-1), 3.24-3.27 (m, 0.5H, H-6), 3.30-3.33 (m, 0.5H, H-6), 3.39-3.42 (m, 0.5H, H-6), 3.43-3.54 (m, 2.5H, H-3, H-6), 3.54-3.68 (m, 3H, H-2, H-4), 3.79-3.88 (m, 1H, H-7), 4.12-4.22 (m, 1H, F-H-9), 4.28-4.34(m, 1H, F-CH2O), 4.37-4.45 (m, 1H, F-CH2O), 4.85 (d, 3J=8.6Hz, 0.5H, NH), 5.61 (d, 3J=8.2Hz, 0.5H, NH), 6.54-6.61 (2×m, 2H, T-H-4, T-H-3), 7.03-7.32 (m, 12H, 10×Ph-H, F-H-2,7), 7.36-7.41 (m, 2H, F-H-3,6), 7.53-7.57 (m, 2H, F-H-1,8), 7.73-7.77 (m, 2H, F-H-4,5)

^{13}C-NMR ($CDCl_3$)

δ 26.4 (t, C-3'), 29.2 (t, C-2'), 30.6, 30.7 (2×t, C-1), 32.9 (t, C-3'), 2×37.6, (2×t, C-8), 38.4, 38.6 (2×t, C-5), 47.3 (d, F-C-9), 52.6, 52.9 (2×d, C-7), 66.4, 66.5 (2×t, F-CH_2O), 69.9, 70.0 (2×t, C-6), 72.1 (t, C-2), 72.8 (2×t, C-3), 80.4, 81.1 (2×d, C-4), 119.9 (d, F-C-4,5), 124.1 (d, T-C-4), 124.8 (d, T-C-3), 125.0, 125.1(2×d, F-C-1,8), 126.2-126.3 (3×d, Ph-C-4, Ph-C-4'), 127.0 (d, F-C-2,7) 127.6 (d, F-C-3,6), 128.3-128.4 (2×d, Ph-C-3/5, Ph-C-3'/5'), 129.2-129.5 (3×d, Ph-C-2/6, Ph-C-2'/6'), 138.1-138.6 (4×s, Ph-C-1, Ph-C-1'), 139.0, 139.1 (2×s, T-C-2), 141.3 (2×s, F-C-4a,4b), 142.1, 142.2 (2×s, T-C-5), 143.9-144.0 (3×s, F-C-8a,9a), 2×155.9 (2×s, N-C=O), 178.7 (s, COOH)

3.2.33 5-{2-[2-Benzyl-2-(2-Fmoc-amino-3-phenyl-propoxy)ethoxy]ethyl}-thiophene-2-butanamide (42)



40 **42**

Procedure: Amide Formation *via* Acid Chloride

Freshly distilled oxalyl chloride (625mg, 5.48 mmol, 1.40equiv.) in dry THF (6mL) was added to a solution of acid **40** (2.75g, 3.91mmol, 1.0 equiv.) in dry THF (30mL) and the reaction stirred at rt for 5 minutes. Then 7 drops of dry pyridine were added and a white precipitate was formed. The mixture was stirred at rt for 30 minutes and 30 minutes at reflux temperature changing color from yellow to orange to deep red. The reaction mixture was cooled to 5°C and NH_3 (g) was bubbled through at ice bath temperature for 20 minutes while the reaction mixture lost its red color. The reaction was worked up by addition of 0.5M HCl (20mL) and extraction with EtOAc. The combined organic layers were washed with water and brine, dried over Na_2SO_4 and evaporated to give 3.3g of crude product which was purified by column chromatography (100g SiO_2, DCM/MeOH/TEA 100:1.5:0.1%) to give pure compound **42**.

Yield: 2.10g (76.1%) as viscous oil

Physical Properties

$C_{43}H_{46}N_2O_5S$ (702.92)

calc.: C: 73.48 H: 6.60 N: 3.99 S: 4.56

found: C: 71.87 H: 6.79 N: 4.39 S: 4.54

TLC: (DCM/MeOH = 20:1) $R_f = 0.18$ (DCM/MeOH = 10:1) $R_f = 0.48$

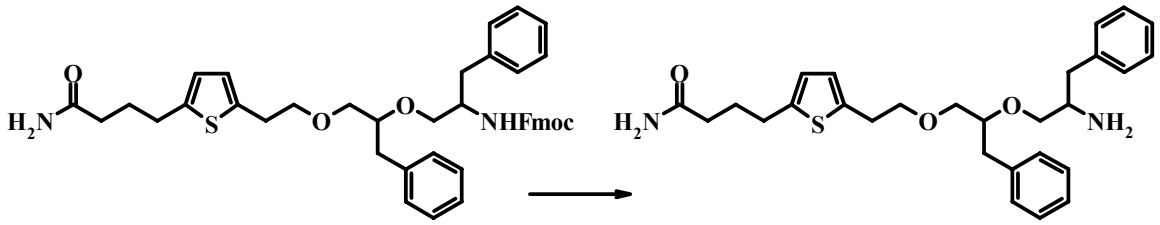
^{1}H-NMR ($CDCl_3$)

δ 1.92-1.99 (m, 2H, H-3'), 2.17-2.23 (m, 2H, H-2'), 2.68-2.89(m, 5H, H-8, H-5, H-4'), 3.01(t, 3J=6.6Hz, 2H, H-1), 3.24-3.27 (m, 0.5H, H-6), 3.31-3.34 (m, 0.5H, H-6), 3.39-3.42 (m, 0.5H, H-6), 3.43-3.54 (m, 2.5H, H-3, H-6), 3.57-3.69 (m, 3H, H-2, H-4), 3.78-3.87 (m, 1H, H-7), 4.14-4.23 (m, 1H, F-H-9), 4.29-4.36(m, 1H, F-CH2O), 4.38-4.46 (m, 1H, F-CH_2O), 4.85 (d, 3J=8.6Hz, 0.5H, NH), 5.45 (bs, 2H, $CONH_2$), 5.63 (d, 3J=8.5Hz, 0.5H, NH), 6.53-6.62(3×m, 2H, T-H-4, T-H-3), 7.04-7.34 (m, 12H, 10×Ph-H, F-H-2,7), 7.38-7.43 (m, 2H, F-H-3,6), 7.54-7.59 (m, 2H, F-H-1,8), 7.76-7.79 (m, 2H, F-H-4,5)

^{13}C-NMR ($CDCl_3$)

δ 27.0 (t, C-3'), 29.2 (t, C-4'), 30.5, 30.7 (2×t, C-1), 2×34.5 (2×t, C-2'), 37.5,37.6 (2×t, C-8), 38.3, 38.6 (2×t, C-5), 47.3 (d, F-C-9), 52.6, 52.9 (2×d, C-7), 66.3, 66.4 (2×t, F-CH2O), 69.9, 70.0 (2×t, C-6), 72.0 (t, C-2), 2×72.8 (2×t, C-3), 80.4, 81.1 (2×d, C-4), 119.9 (d, F-C-4,5), 124.1 (d, T-C-4), 2×124.8 (d, T-C-3), 125.0, 125.1 (2×d, F-C-1,8), 126.2-126.4 (3×d, Ph-C-4, Ph-C-4'), 127.0 (d, F-C-2,7) 127.6 (d, F-C-3,6), 128.3, 128.4 (2×d, Ph-C-3/5, Ph-C-3'/5'), 129.4-129.5 (3×d, Ph-C-2/6, Ph-C-2'/6'), 138.2-138.6 (4×s, Ph-C-1, Ph-C-1'), 139.0, 139.1 (2×s, T-C-2), 2×141.3 (2×s, F-C-4a,4b), 2×142.4, (2×s, T-C-5), 143.9, 144.0 (2×s, F-C-8a,9a), 155.8, 155.9 (2×s, N-C=O), 174.8 (s, $CONH_2$)

3.2.34 5-{2-[2-Benzyl-2-(2-Fmoc-amino-3-phenyl-propoxy)ethoxy]ethyl}-thiophene-2-butanamide(43)



42 43

Procedure: Fmoc-Deprotection in DMF/Piperidine

Fmoc-amine **42** was dissolved in a mixture of DMF/piperidine (16mL:4mL) and was stirred at rt for 20 minutes. The reaction mixture was evaporated to give a mixture of white crystals and yellow oil. The crude product (2.2.g) was purified by column chromatography (60g SiO_2, DCM/MeOH 30:1 to 10:1) to give 1.28 g of pure target compound **43**.

Yield: 1.28g (94.8%) of colorless liquid

Physical Properties

$C_{28}H_{36}N_2O_3S$ (480.67)

calc.: C: 69.97 H: 7.55 N: 5.83 S: 6.67

found: C: 68.06 H: 7.80 N: 5.80 S: 6.31

TLC: (DCM/MeOH = 10:1) $R_f = 0.13$ (DCM/MeOH = 5:1) $R_f = 0.37$

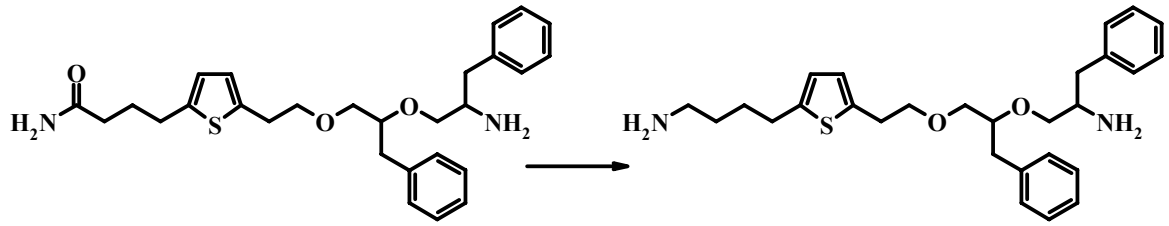
^{1}H-NMR ($CDCl_3$)

δ 1.69 (bs, 2H, NH_2), 1.92-1.97 (m, 2H, H-3'), 2.19 (t, 3J=7.4Hz, 2H, H-2'), 2.42-2.47(m, 1H, H-8), 2.62-2.69(m, 1H, H-8), 2.75-2.86(m, 2H, H-5), 2.79 (t, ^{3}J=7.3Hz, 2H, H-4'), 3.00 (t, ^{3}J=5.8Hz, 2H, H-1), 3.03-3.13 (m, 1H, H-7), 3.18 (dd, J=9.3Hz, J=7.1Hz, 0.5H, H-6), 3.32 (dd, J=9.3Hz, J=7.1Hz, 0.5H, H-6) 3.39 (dd, J=9.9Hz, J=4.5Hz, 0.5H, H-6), 3.42-3.49 (m, 2H, H-3), 3.54 (dd, J=9.3Hz, J=3.6Hz, 0.5H, H-6), 3.58-3.69 (m, 3H, H-2, H-4), 6.55-6.58(m, 1H, T-H-4), 6.61-6.62 (m, 1H, T-H-3), 7.08-7.13 (m, 2H, 2Ph-H), 7.17-7.21 (m, 4H, 4Ph-H), 7.24-7.29 (m, 4H, 4Ph-H)

^{13}C-NMR ($CDCl_3$)

δ 26.9 (t, C-3'), 29.1 (t, C-4'), 30.6 (t, C-1), 34.4 (t, C-2'), 2× 38.2 (2×t, C-5), 40.0, 40.1 (2×t, C-8), 2×52.5 (d, C-7), 71.8 (t, C-2), 72.3, 72.5 (2×t, C-3), 74.4,74.5 (2×t, C-6), 80.2, 80.3 (2×d, C-4), 124.0 (d, T-C-4), 124.7 (d, T-C-3), 126.1 (d, Ph-C-4, Ph-C-4'), 128.2-128.3 (3×d, Ph-C-3/5, Ph-C-3'/5'), 129.1, 129.4 (2×d, Ph-C-2/6, Ph-C-2'/6'), 138.4, 138.7, 139.2 (3×s, Ph-C-1', Ph-C-1, T-C-2) 142.4 (s, T-C-5), 2×175.1 (2×s, $CONH_2$)

3.2.35 5-{2-[2-Benzyl-2-(2-amino-3-phenyl-propoxy)ethoxy]ethyl}-thiophene-2-butanamine (1)



43 **1**

Procedure: Amide Reduction with Lithiumaluminiumhydride

To a suspension of $LiAlH_4$ (60mg, 1.59mmol, 2.5 equiv.) in 3mL of dry THF amide **43** (305mg, 0.635mmol, 1.0 equiv.) in dry THF (1mL) was added and the reaction stirred at reflux temperature overnight (11hours). The reaction mixture was cooled to 0°C and quenched with a 10% solution of potassium sodium tartrate (3mL) and extracted with DCM. The phases were separated and the aqueous layer was extracted with DCM. The organic layer was washed with water and brine dried over Na_2SO_4 and evaporated to give a 260mg of crude product, which was purified by column chromatography (10g SiO_2, DCM/MeOH/TEA 100:10:1) to give 230mg of pure target compound **1**.

Yield: 230mg (77.8%) as colorless liquid

Physical Properties

$C_{28}H_{38}N_2O_2S$ (466.69)

calc.: C: 72.06 H: 8.21 N: 6.00 S: 6.87

found: C: 67.94 H: 8.28 N: 5.70 S: 6.90

TLC: (DCM/MeOH = 5:1) $R_f = 0.02$

^{1}H-NMR ($CDCl_3$)

δ 1.44 (bs, 4H, 2×NH_2), 1.44-1.52 (m, 2H, H-2'), 1.62-1.69(m, 2H, H-3'), 2.42-2.47(m, 1H, H-8), 2.64-2.70(m, 1H, H-8), 2.68(t, ^{2}J=7.1Hz, 2H, H-1'), 2.75 (t, ^{3}J=7.6Hz, 2H, H-4'), 2.78(dd, ^{2}J=13.1Hz, ^{3}J=6.8Hz, 1H, H-5), 2.86(dd, ^{2}J=13.7Hz, ^{3}J=5.5Hz, 1H, H-5), 3.00(t, ^{3}J=6.6Hz, 2H, H-1), 3.04-3.13 (m, 1H, H-7), 3.17 (dd, J=9.1Hz, J=7.3Hz, 0.5H, H-6), 3.34 (dd, J=9.5Hz, J=6.9Hz, 0.5H, H-6) 3.39 (dd, J=9.5Hz, J=4.1Hz, 0.5H, H-6), 3.45-3.47 (m, 2H, H-3), 3.58 (dd, J=9.1Hz, J=3.5Hz, 0.5H, H-6), 3.60-3.69 (m, 3H, H-2, H-4), 6.57(d, J=3.5Hz, 1H, T-H-4), 6.61-6.62 (m, 1H, T-H-3), 7.10-7.14 (m, 2H, Ph-H-2/6 or Ph-H-2'/6'), 7.17-7.21 (m, 4H, Ph-H-2/6 or Ph-H-2'/6', Ph-H-4, Ph-H-4'), 7.25-7.29 (m, 4H, Ph-H-3/5, Ph-H-3'/5')

^{13}C-NMR ($CDCl_3$)

δ 28.9 (t, C-3'), 29.9 (t, C-4'), 30.6 (t, C-1), 33.0 (t, C-2'), 2×38.3 (2×t, C-5), 40.4, 40.5 (2×t, C-8), 41.8 (t, C-1') 52.5, 52.6 (2×d, C-7), 72.0 (t, C-2), 72.3, 72.4 (2×t, C-3), 74.6, 74.8 (2×t, C-6), 2×80.3 (2×d, C-4), 123.5 (d, T-C-4), 124.6 (d, T-C-3), 2×126.1 (d, Ph-C-4, Ph-C-4'), 128.2-128.3 (3×d, Ph-C-3/5, Ph-C-3'/5'), 129.2-129.4 (3×d, Ph-C-2/6, Ph-C-2'/6'), 2×138.6, 138.7 (3×s, Ph-C-1', T-C-2), (s, Ph-C-1, Ph-C-1'), 138.9 (s, Ph-C-1), 143.6 (s, T-C-5)

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