Development of New Methods for The Synthesis of Pharmacologically Active Compounds. Synthesis of New Immobilized Homo- and Heterogeneous Catalysts for The Chemoselective Oxidation of Alcohols.

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vorgelegt von
Alexandru Gheorghe

aus
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Prüfungsausschluß:	Prof. Dr. Hartmut Krienke	(Vorsitzender)
	Prof. Dr. Oliver Reiser	(1. Gutachter)
	Prof. Dr. Burkhard König	(2. Gutachter)
	Prof. Dr. Sigurd Elz	(3. Prüfer)

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In Memory of my Mother

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Abbreviations

AIBN	azo-isobutyronitrile
Boc	*tert*-butoxycarbonyl
*n*BuLi	*n*-butyl lithium
nBu_3SnH	tributyltinhydride
CI	chemical ionisation
CSA	(+)-camphorsulfonic acid
m-CPBA	*m*-chloroperbenzoic acid
CNS	central nervous system
CuACC	copper catalyzed azide-alkyne cycloaddition
DBU	1,8-Diazabicyclo[5.4.0]-undec-7-ene
DCM	dichloromethane
Dec.	decomposition
DIPEA	di(isopropyl)ethylamine
DMF	dimethyl formamide
DMSO	dimethylsulfoxide
ee	enantiomeric excess
EI	electron impact (MS)
equiv.	equivalent
ES	electron spray (MS)
EtOAc	ethyl acetate
GABA	gamma-aminobutyric acid
GABA-T	gamma-aminobutyric acid transaminase
h	hours
HPLC	high pressure liquid chromatography
HRMS	high resolution mass spectrum
IR	infra red (spectrum)
J	coupling constant
K	Kelvin
LiHMDS	lithium hexamethyldisilazide
LMWG	low-molecular weight gelator
LRMS	low resolution mass spectrum

CH_3CN	acetonitrile
min	minutes
mp	melting point
MS	mass spectrum
NBS	N-bromosuccinimide
NMO	4-methyl morpholine N-oxide
NMR	nuclear magnetic resonance
Ph	Phenyl
PPh_3	tri-phenyl phosphine
rac	racemate
rt	room temperature
SAM	self-assembled monolayers
SEM	scanning electron micrograph
SMBC	simulated moving bed chromatography
tert	tertiary
TEMPO	2,2,6,6-tetramethylpiperidine-1-oxyl
THF	tetrahydrofuran
TMSCl	trimethylsilyl chloride
TPAP	tetra-n-propylammonium per-ruthenate
quant.	quantitative

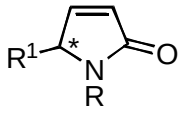
• *Chapter 1*

Synthesis of Functionalized Pyrrolidones and *S*-Vigabatrin from Pyrrole

1.1 Introduction

Five-membered aza-heterocycles are compounds of great biological and pharmacological interest. Several pyrrolidones are potent neuroactive compounds capable of interacting with pyroglutammate receptors,[1] and many hydroxylated pyrrolidines, pyrrolizidines and indolizidines are known for their glycosidase inhibitory activities.[2]

Chiral 5-substituted 3-pyrrolin-2-ones are ideally suited as versatile templates towards functionalized pyrrolidin-2-ones.



5-substituted 3-pyrrolin-2-ones

The combination of the chiral center being located adjacent to the β-center of the enone and the topology of the five-membered ring provides a high degree of regio- and stereocontrol for the functionalization of specific sites in the molecule. The α,β-unsaturated lactam moiety can be stereoselectively alkylated by conjugate addition of nucleophiles.[3] Alternatively, the double bond can be hydroxylated, leading to valuable pharmaceutical active intermediates.[4] Moreover, complex molecules can be synthesized by using the 3,4-didehydropyro-homoglutamate moiety as a dienophile in cycloaddition reactions.[5]

Consequently, a number of 5-substituted-3-pyrrolin-2-ones have been introduced as chiral building blocks, utilizing pyroglutamic acid (synthesis of **1**[6], **2**[3h] and **6**[7]), malic acid or enzymatic resolutions of lactams (synthesis of **3**[5c,8]), 2-siloxy substituted pyrroles (synthesis of **4**[9]), or chiral nitrones (synthesis of **5**[10]) as starting materials (Figure 1.1).

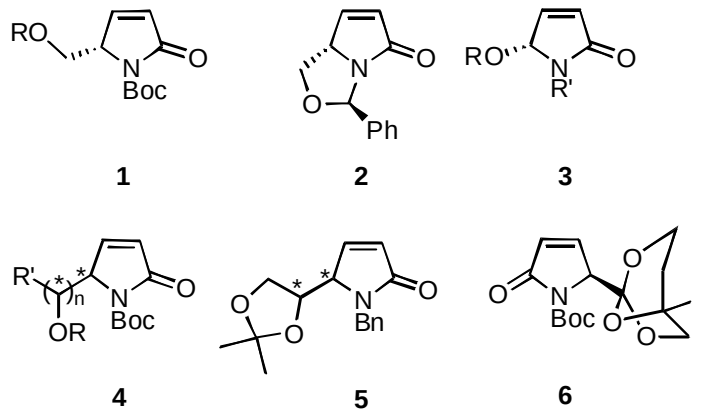
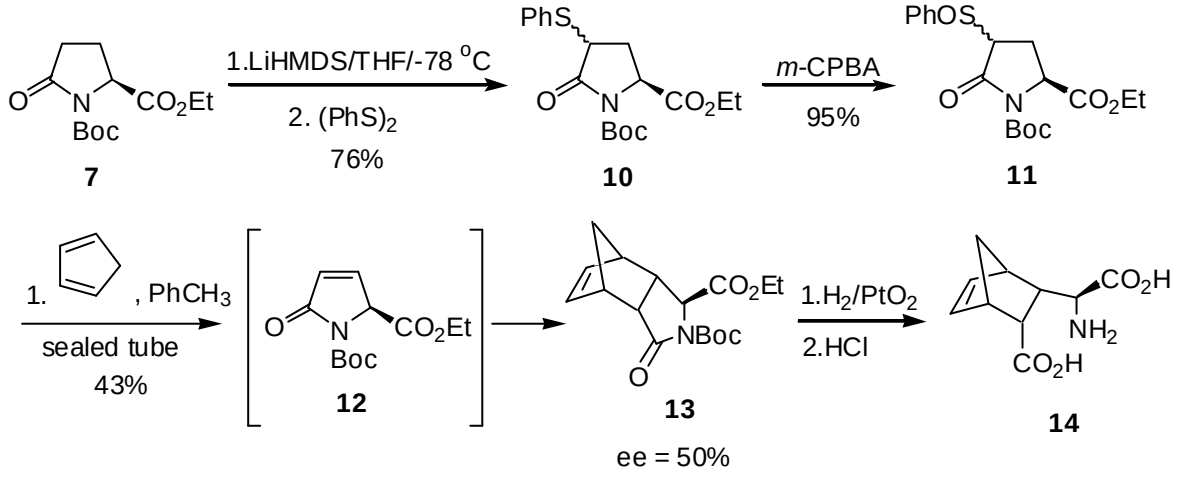


Figure 1.1. Chiral 5-substituted-3-pyrrolin-2-ones

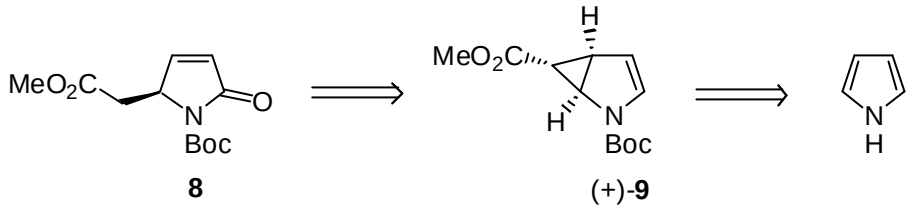
In contrast, the 3,4-didehydropyroglutamic ester **12**, being arguably the most readily accessible pyrrolin-2-one starting from pyroglutamic acid, cannot be used as a chiral building block due to its lability toward racemization and isomerization[11] and has so far only been trapped with cyclopentadiene in a Diels-Alder reaction in 50% *ee* (Scheme 1.1).[12]



Scheme 1.1. First trapping reaction of *N*-Boc ethyl 3,4-Dehydropyroglutamate **12**[12]

1.2 Aim of this work

In order to avoid racemization and isomerization related to the glutamic ester **12**, we envisioned that the corresponding homoglutamic ester **8** should be less prone to these unwanted side reactions (Scheme 1.2).

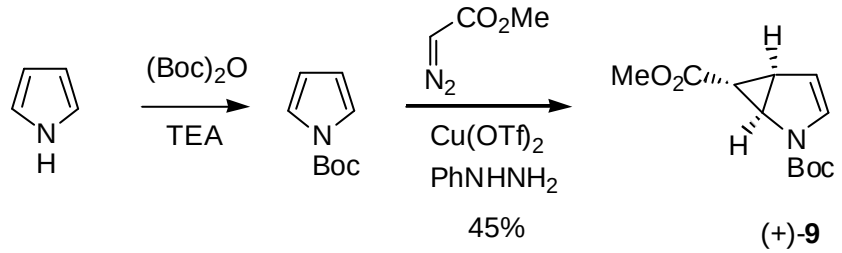


Scheme 1.2. Retrosynthesis of the chiral building block **8**

We will describe in this chapter an efficient access to this new building block in either enantiomeric form starting from **9**, which in turn can be readily synthesized from pyrrole on a multigram scale. We will also present its scope and limitation for the synthesis of functionalized pyrrolidones as well as a novel synthesis of (*S*)-Vigabatrin, an irreversible inhibitor for GABA-transaminase, which is used as adjunctive therapy in patients that suffer from epilepsy.

1.3 Synthesis and scope of homoglutamic ester 8

Based on our interest to develop asymmetric methodology towards chiral intermediates and natural products from inexpensive heteroarenes,[13] we have been able to synthesize as a starting point for ß-aminocyclopropanecarboxylic acids[14] the bicyclic adduct **9** enantiomerically pure in either form by cyclopropanation of *N*-Boc-pyrrole followed by enzymatic resolution (Scheme 1.3).[15]



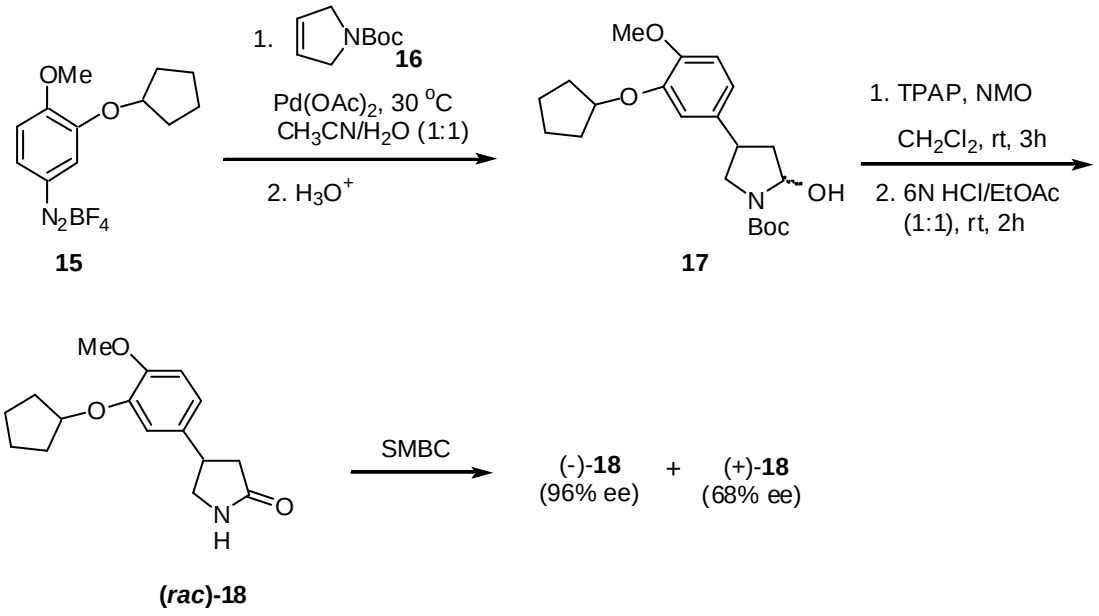
Scheme 1.3. Synthesis of bicyclic adduct **9**[15]

The latter step was not amenable to access optical pure **9** on large scale, making an alternative desirable. Unfortunately, we were not able to render the cyclopropanation of pyrrole with diazaoacetates asymmetric by employing a suitable chiral catalyst, in contrast to the use of furans as starting materials.[16]

However, we discovered that (*rac*)-**9** can be separated in its enantiomers by simulated moving bed chromatography (SMBC). The SMB chromatography is an automated, continuous, and

multicolumn chromatographic system, which has reduced solvent and time consumption, as well as purification costs. This technique simulates movement of the chromatographic packing material, or bed, against the liquid phase and allows a continuous recovery of the desired compound. In this process, the solvent and the binary mixture of compounds (racemate) to be resolved are injected into and withdrawn from a ring of chromatographic columns, at periodic and simultaneous switching points between the columns in the direction of the desorbent flow.

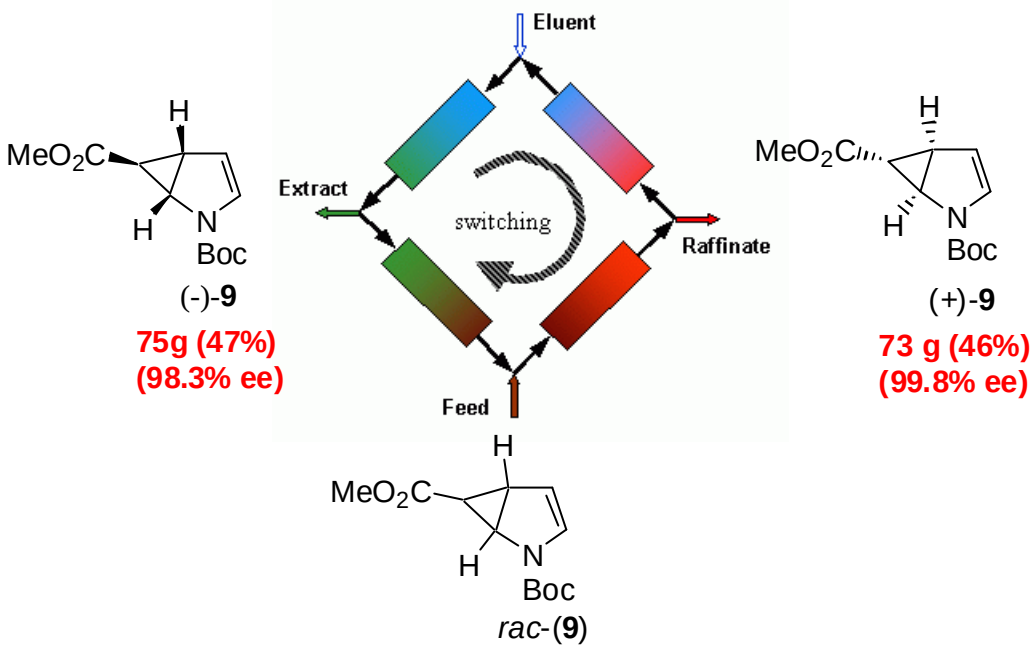
Recently, there has been increasing interest in the pharmaceutical sector in the synthesis of single enantiomers of chiral drugs.[17] Correia and co-workers reported a racemic synthesis of 4-aryl-2-pyrrolidones by a Heck arylation of 3-pyrrolines with arenediazonium tetrafluoroborates. These building blocks were used to synthesize on a multigram scale the phosphodiesterase inhibitor (±)-Rolipram, an expensive potential drug and pharmacological probe. The racemic Rolipram could successfully be resolved into its enantiomers using SMB chromatography (Scheme 1.4).



Scheme 1.4. *Correira's* synthesis of Rolipram[17a]

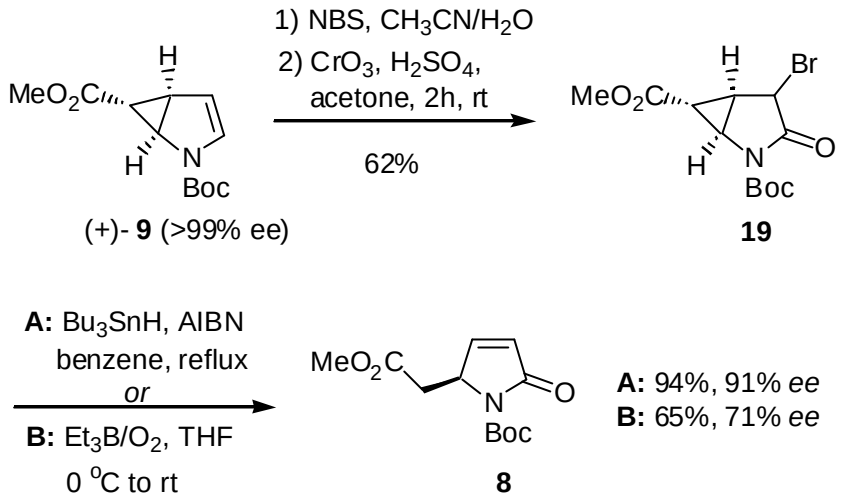
The separation of (*rac*)-**9** into its enantiomers succeeded by means of a semipreparative chiral simulated moving bed chromatographic unit having cellulose-tris-(3,5-dimethylphenylcarbamate) Chiralcel OC™(20 μm) as stationary phase with extraordinary productivity (separation of 1958 g (*rac*)-**9**/kg stationary phase and day). The SMBC was performed on a

160 g scale with ethanol as an eluent and with a feed concentration of 20 g/L to provide (+)-**9** (73 g, 99.8% *ee*) and (–)-**9** (75 g, 98.3% *ee*) along with 6 g of recovered (*rac*)-**9** (Scheme 1.5).



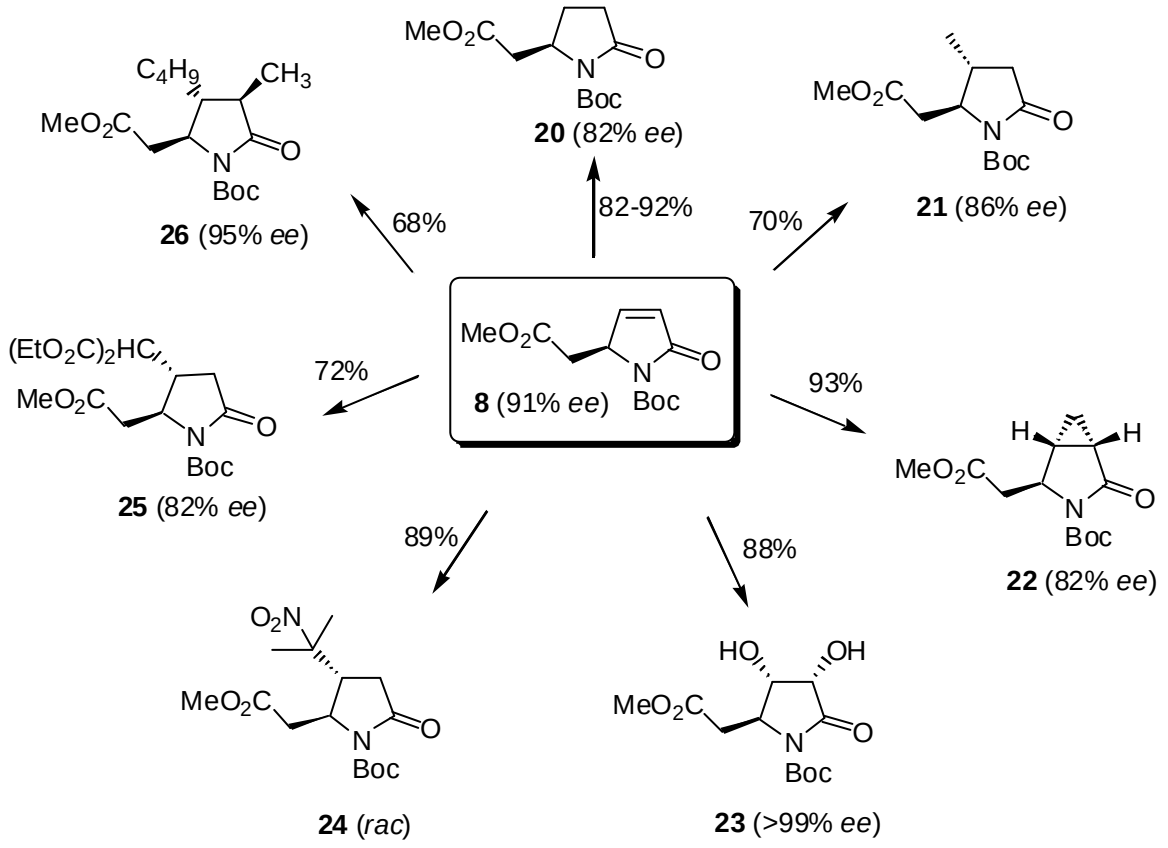
Scheme 1.5. SMB chromatography of racemic **9**

Having (+)-**9** in good quantities in hand, we next investigated its conversion to **8** (Scheme 1.6). Bromohydrine formation with NBS in water followed by oxidation smoothly gave rise to the α-bromo ketone **19** in 62% yield (2 steps). Utilizing the rapid ring opening of cyclopropylmethyl radicals, upon treatment of (+)-**9** with tributyltin hydride **8** was rapidly obtained in excellent yield (94%) by exclusive fission of the exocyclic cyclopropane bond. Unfortunately, the optical purity of **8** was somewhat reduced (91% *ee*) compared to the starting material. In the same way, (*ent*)-**8** is obtained from (–)-**9**. Alternatively, the transformation of **19** to **8** could also be achieved with Et_3B/O_2, but in this case the results were inferior (65% yield, 71% *ee*).



Scheme 1.6. Synthesis of **8**

Compound **8** appears to be considerable more stable compared to **12**: it can be stored at –20°C over months with no epimerzation or isomerization being observed, and even upon standing in solution (CH_2Cl_2) for several hours at room temperature no loss of optical purity is observed. A broad variety of functionalizations can be performed with **8** such as the conjugate addition of nucleophiles with or without the combination of trapping the resulting enolate with electrophiles, cycloadditions, hydrogenations or dihydroxylations (Scheme 1.7).



Scheme 1.7. Functionalizations of building block **8**

For all transformations, complete *anti*-selectivity was observed. However, reactions carried out with basic reagents gave rise to some erosion of stereochemistry, which could be remedied by recrystallization of some of the products. This complication was especially severe in the addition of 2-nitropropane in the presence of DBU, for which **24** was only obtained in racemic form.

1.4 Vigabatrin: Mode of action

1.4.1 Introduction

The central nervous system (CNS) contains uniquely high concentrations of certain amino acids, notably glutamate and gamma-aminobutyric acid (GABA). The dicarboxylic amino acids (e.g. glutamate, aspartate) mediate excitatory responses while the monocarboxylic acids (GABA, glycine) mediate inhibitory stimuli. Several therapeutic classes have, in recent years, been found to elicit their pharmacologic and therapeutic effects by modulating neurotransmission in the CNS of these amino acid neurotransmitters.

It is generally believed that the overall excitability of the CNS is modulated by balanced physiologic activity of two amino acid neurotransmitters, GABA - (*inhibitory*) and glutamic acid - (*excitatory*). Glycine, a second inhibitory amino acid neurotransmitter, is primarily localized in the brainstem and spinal cord. Hence, drugs that depress CNS excitability such as the sedative/hypnotics and anxiolytics may do so by enhancing GABA neurotransmission or by interfering with glutamate neurotransmission. Drug actions that could theoretically achieve a GABA mimetic response include stimulants of biosynthesis and/or release, GABA receptor agonists and inhibitors of GABA metabolism.

A. GABA biosynthesis, storage and release

- GABA is directly biosynthesized from L-glutamic acid by the action of glutamic acid decarboxylase (GAD) (Figure 1.2). L-glutamic acid is available from α-ketoglutarate, a product of glucose metabolism. Glucose is a normal nutrient supplied to the CNS via the blood via active transport.
- GABA is stored in synaptic vesicles and is released in a Ca^{2+}-dependent manner upon depolarization of the presynaptic membrane.

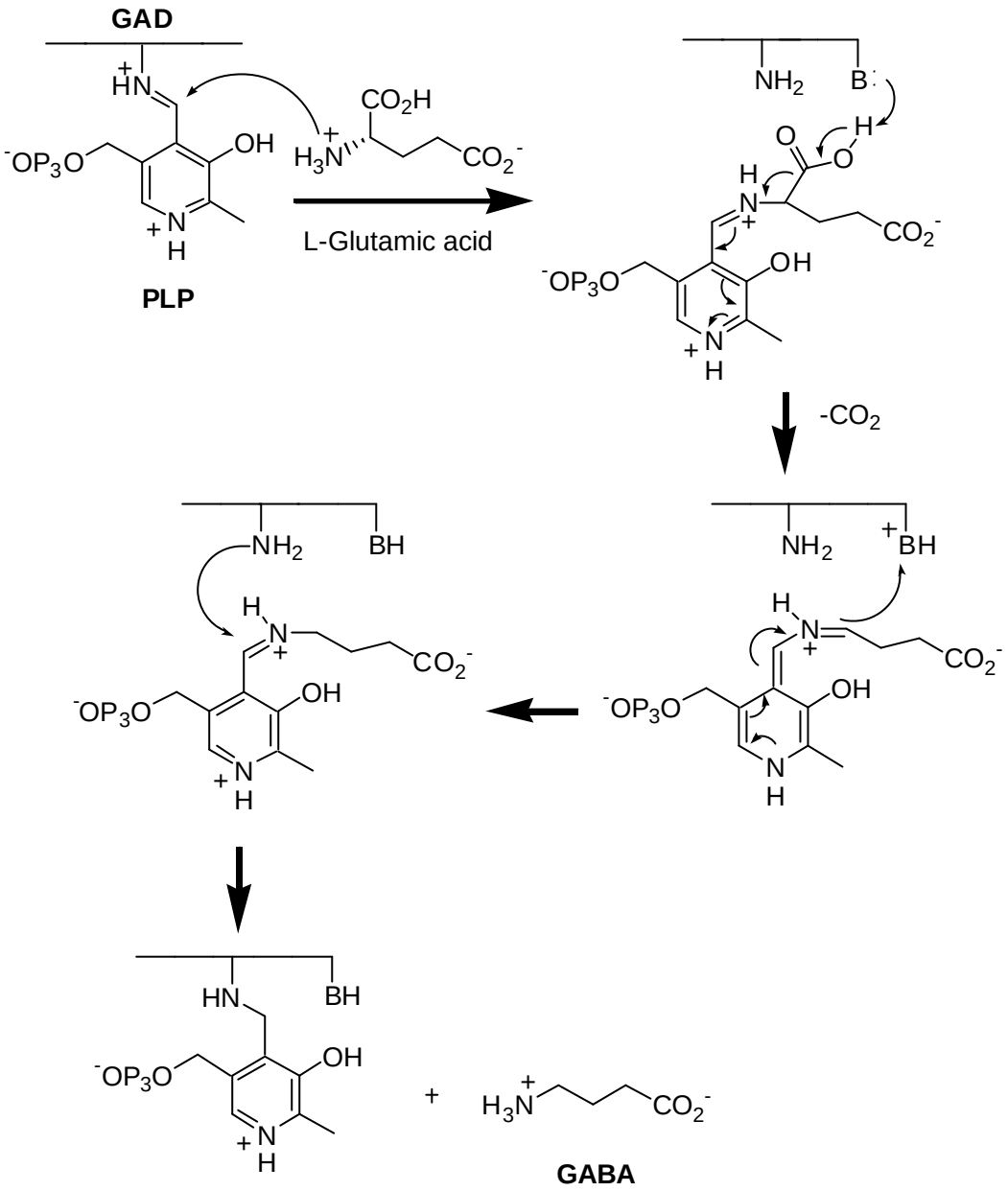


Figure 1.2. Mechanism of GABA biosynthesis

B. Termination of GABA neurotransmission

- Reuptake into presynaptic terminals and/or surrounding glial cells is the primary mechanism of termination.
- GABA catabolism by GABA-transaminase (aminotransferase, GABA-T) occurs once the neurotransmitter is taken up into tissues (Figure 1.3). The succinic semialdehyde formed from GABA can be oxidized to succinic acid which enters the Krebs cycle and is eventually utilized to synthesize additional GABA supplies.
- Neuronal uptake of GABA involves highly specific transmembrane transporters as is observed for other neurotransmitters.

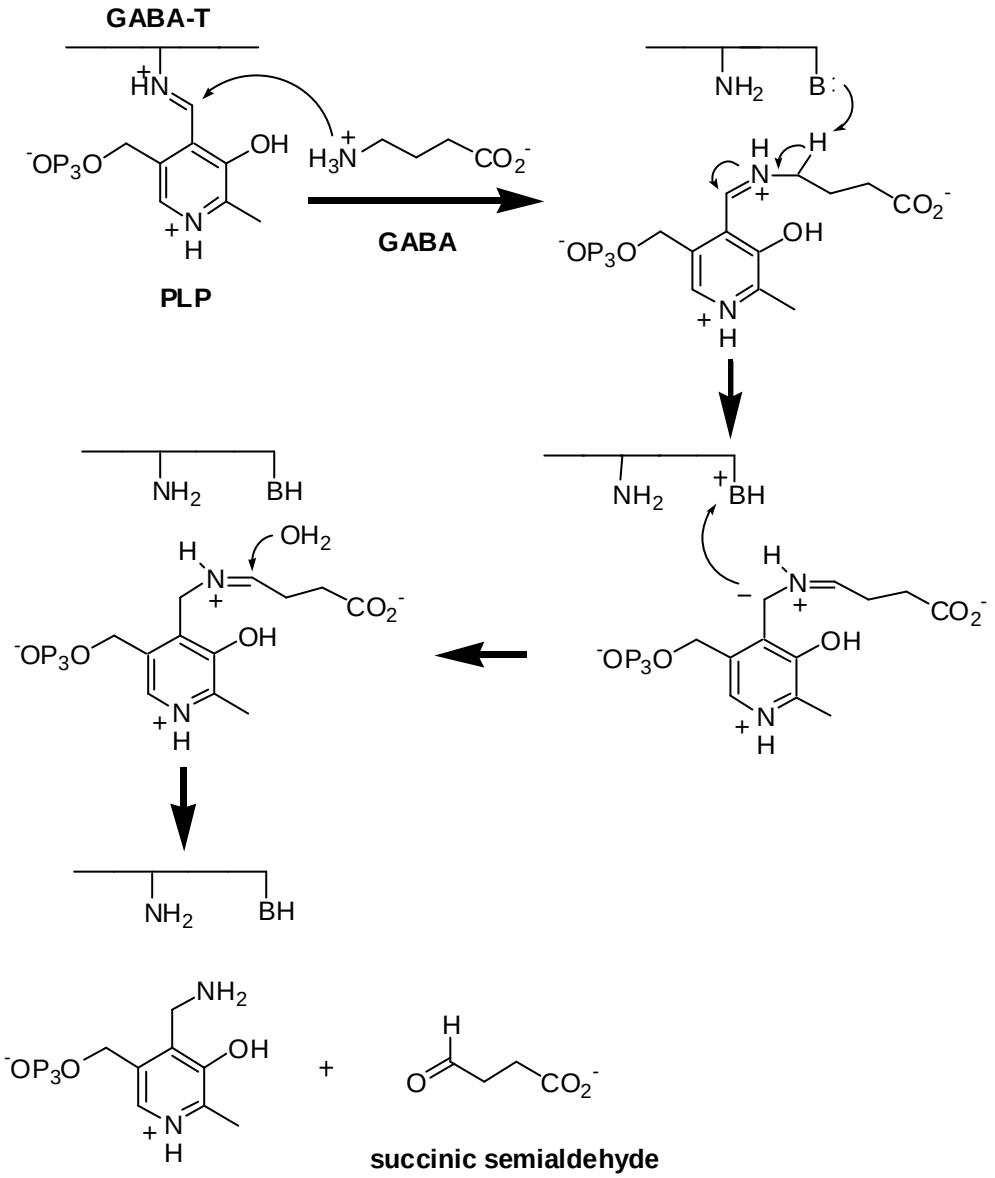


Figure 1.3. Mechanism of GABA transamination

Epilepsy is defined as any central nervous system disease characterized by recurring convulsive seizures, affecting approximately 50 million people worldwide. The biochemical mechanism leading to central nervous system electrical discharges and epilepsy are unknown, but there may be multiple mechanisms involved. However, it has been shown that convulsions arise when there is an imbalance in the two principal neurotransmitters in the brain, L-glutamic acid and GABA. The concentrations of these two amino acids are regulated by two pyridoxyl phosphate (PLP)-dependent enzymes, L-glutamic acid decarboxylase (GAD) which converts glutamate to GABA and GABA aminotransferase (GABA-T), which degrades GABA to succinic semialdehyde (Figure 1.2 and 1.3).[18]

Vigabatrin is a second generation antiepileptic which exerts its mechanism of action by increasing brain GABA levels by inhibition of GABA-transaminase-mediated metabolism via suicide inhibition (mechanism-based inhibition).

Vigabatrin is a GABA analogue containing an alpha-vinyl group that is critical for expression of activity. Due to its structural similarity to the normal substrate, vigabatrin is recognized at the active site of GABA-T which initiates the transamination reaction. During this reaction a reactive unsaturated iminium species forms which can alkylate the enzyme as shown in the Figure 1.4.

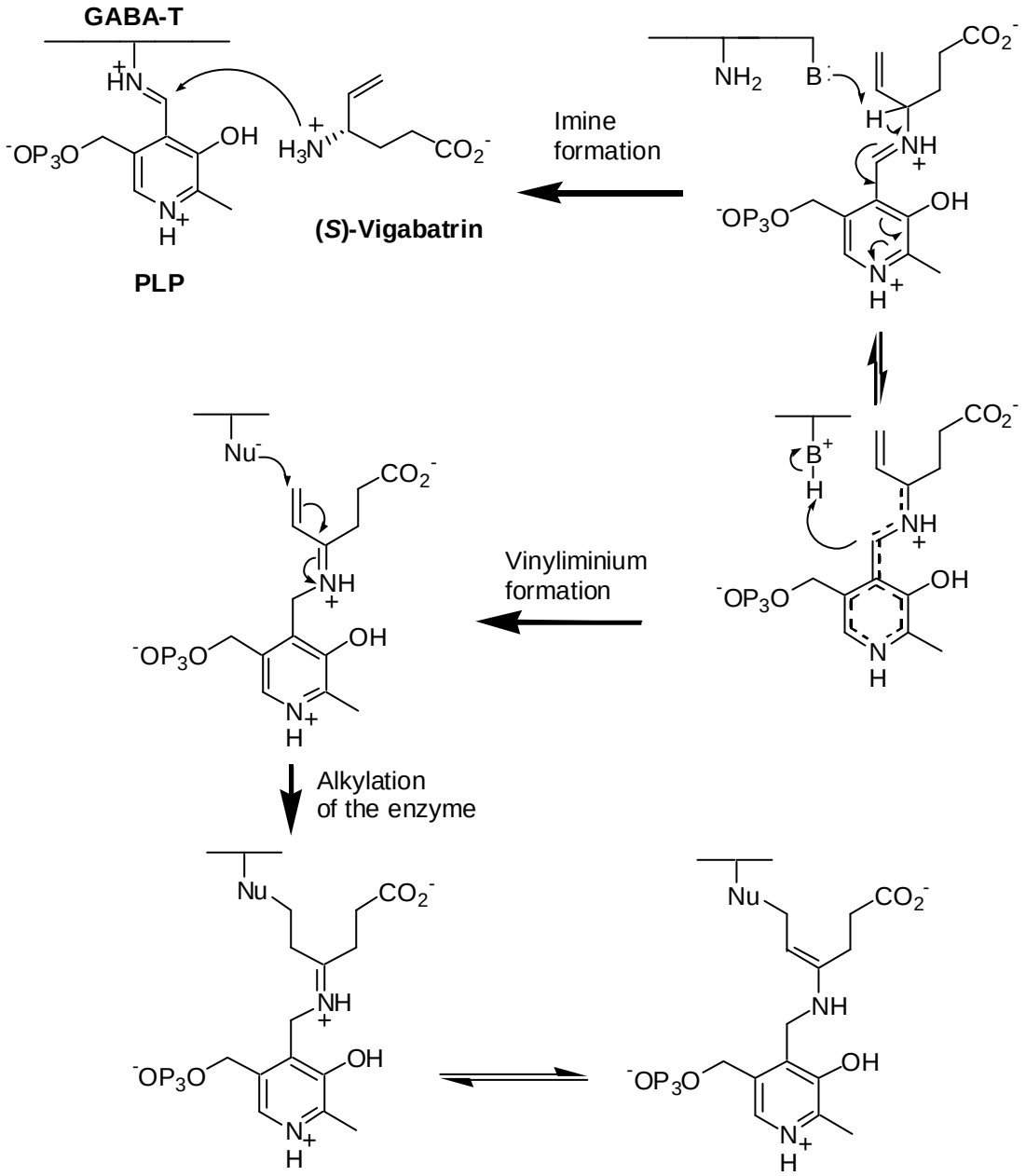
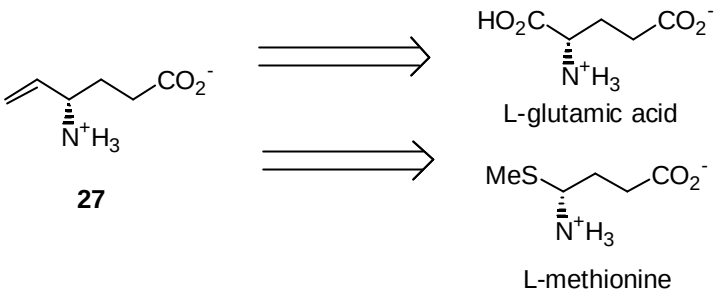


Figure 1.4. Mechanism of Vigabatrin

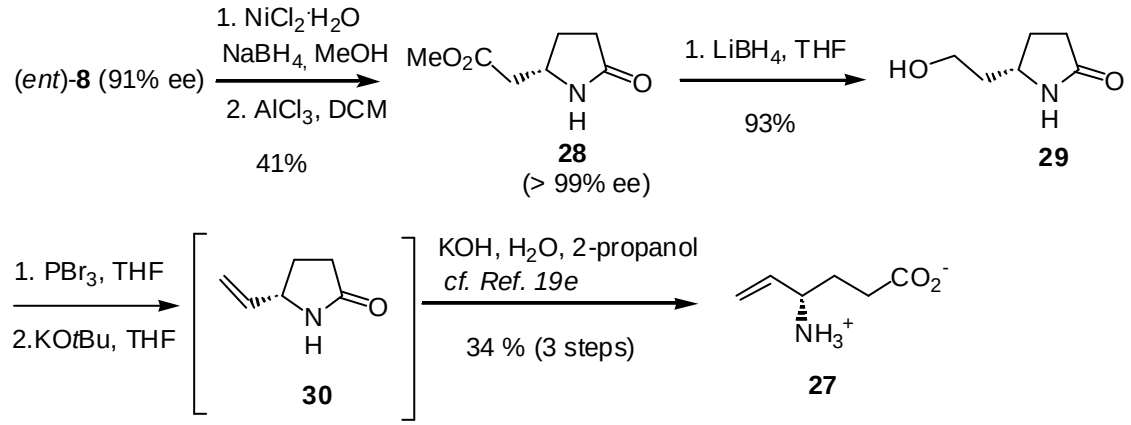
1.4.2 Synthesis of (*S*)-Vigabatrin

To date, a number of enantioselective synthesis of (*S*)-γ-vinyl GABA **27** have been developed. These procedures mostly employ L-glutamic acid or L-methionine as starting materials.[19]



Scheme 1.8.

We developed a novel synthetic route, which allows the transformation of (*ent*)-**8**, previously obtained from pyrrole, into the pharmacologically active (+)-(*S*)-enantiomer[20] of vigabatrin (Scheme 1.9), which is being commercialized as Sabril in racemic form for the treatment of epilepsy.[21]



Scheme 1.9. Synthesis of (*S*)-Vigabatrin

Conjugate reduction of the enone (*ent*)-**8** followed by *N*-Boc deprotection afforded **28**,[22] which could be recrystallized to enantiopurity. Subsequent reduction of the methyl ester to the alcohol **29** could be achieved with $LiBH_4$ in high yield. Final transformation of **29** to (*S*)-Vigabatrin (**27**) was best carried out by a three-step protocol, forming first the bromide with

PBr_3, followed by dehydrobromination with KO*t*-Bu, and finally hydrolysis of the vinylpyrrolidinone **30** with KOH, as previously described by Knaus and Wey.[19e]

In conclusion, starting from inexpensive pyrrole, we could develop a 4-step synthesis of the new 5-substituted 3-pyrrolinone **8** and (*ent*)-**8** in 91% ee and demonstrate its scope and limitation for the synthesis of functionalized pyrrolidinones and (*S*)-Vigabatrin.

1.5 LITERATURE

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• *Chapter 2*

Synthesis of the Hydroxyamino Acid Moiety of AI-77-B

2.1 Introduction

Polyhydroxylated aza-sugars are monosaccharide analogues and potent glycosidase inhibitors.[1] The aza-sugars have a nitrogen atom instead of ring oxygen atom and may mimic, after protonation, the structure of the oxycarbenium ion liberated during the enzyme catalyzed hydrolytical process (e.g. inhibition of α-mannosidase Figure 2.1).[2]

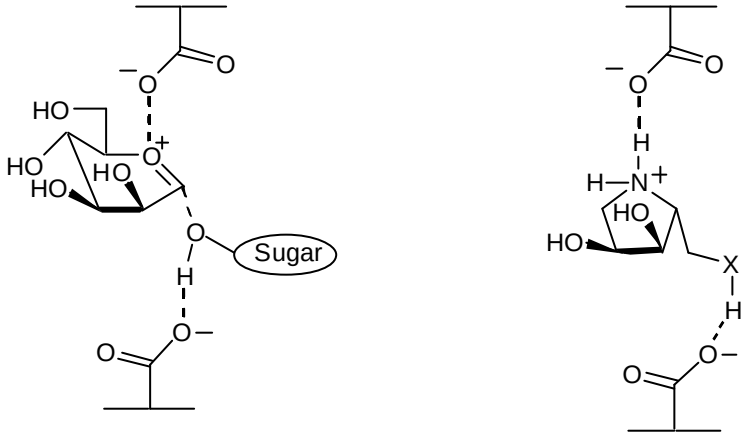
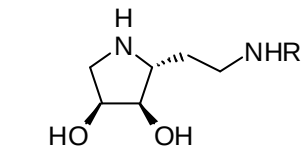


Figure 2.1. Inhibition of α-mannosidase by a dihydroxylated pyrrolidine[2b]

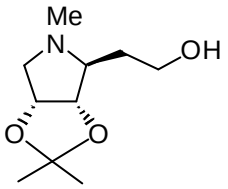
The glycosidase cleavage is a biologically widespread process, therefore the glycosidase inhibitors can be used to treat several diseases: viral infections, fungal infections, cancer, diabetes, tuberculosis, parasitic protozoa and xenotransplant rejection.[3] They are also useful tools in the study of the mecanism of action of enzymes.

The aza-sugars constitute an interesting target for organic and medicinal chemists due to their high therapeutic potential and versatility. Over the last 30 years many synthetic routes to different pyrrolidine and piperidine aza-sugars have been reported.[4] A few examples of interesting five-membered ring aza-sugars are depicted in Figure 2.2.[5]



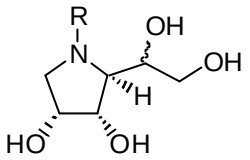
β-glucosidase inhibitors

31



building block for antihyperglycemic compounds

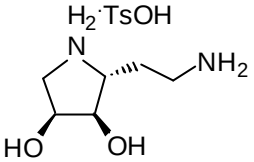
32



R=H, Me, -CH_2Ph

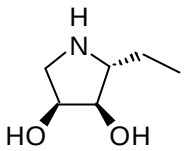
glycosidase inhibitors

33



moderate inhibitor of fucosidase

34

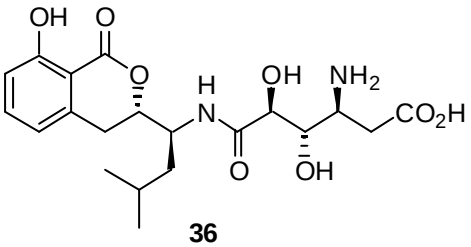


galactosidase and fucosidase inhibitor (K_i=1.43 and 9 μM)

35

Figure 2.2. Various five-membered ring aza-sugars inhibitors[5]

Another class of biologically active compounds are the 3,4-dihydroisocoumarin derivatives containing an open chain aza-sugar moiety, which are common structural features of numerous natural products and exhibit a wide range of important biological properties.[6,7] AI-77-B (**36**) is a novel pseudopeptide, which contains a 3,4-dihydroisocoumarin linked to a dihydroxy ß-amino acid side chain. AI-77-B (**36**) has been isolated from the culture broth of *Bacillus pumilus* and it has been found to exhibit potent gastroprotective activity without anticholinergic, antihistaminergic or central suppressive effects.[8]



36

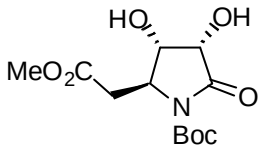
Figure 2.3. Structure of AI-77-B

The therapeutic potential of AI-77-B is, however, limited by its poor oral absorption properties. Due to its interesting biological properties, there has been significant interest in the synthesis and structural modification of AI-77-B. To date, a number of orally active prodrug analogues possessing both antiinflammatory and antiulcer activities have been reported.[9,10] Several total syntheses of AI-77-B have been also reported, as well as synthetic approaches to either the dihydroisocoumarin or the hydroxy amino acid fragment.[11-27] The

majority of these previously described syntheses utilised chirality derived from D-ribose,[11] L-leucine,[12-18,19] L-aspartic acid [12,13,15,16] or D-glutamic acid.[17,18]

2.2 Aim of this work

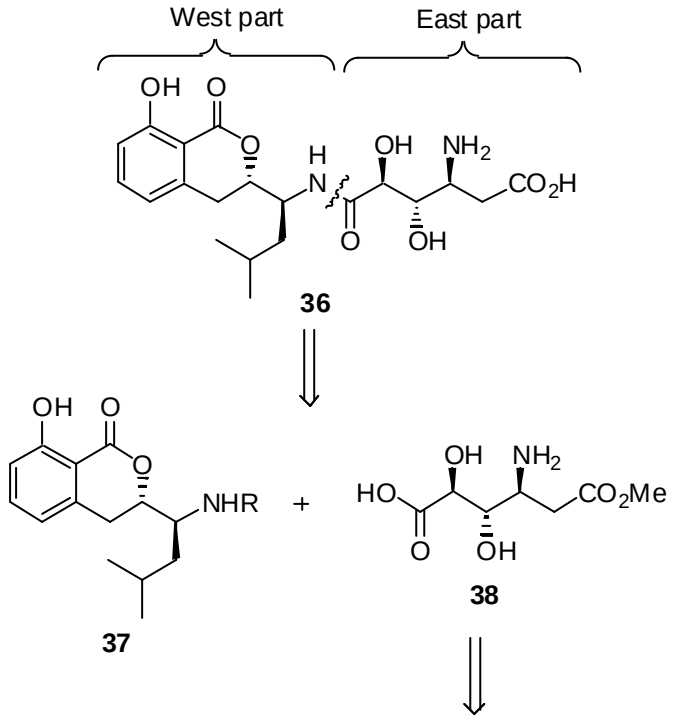
We have introduced in Chapter 1 a novel methodology to produce chiral 5-substituted 3-pyrrolin-2-ones, which gave access to various substituted pyrrolidones, including the dihydroxylated pyrrolidone **23**. Compound **23** can be a useful building block for the synthesis of aforementioned glycosidase inhibitors **31-35**, as well as for the synthesis of the dihydroxyamino acid moiety of the gastroprotective drug AI-77-B.



23

2.3 Synthesis of the dihydroxyamino acid moiety

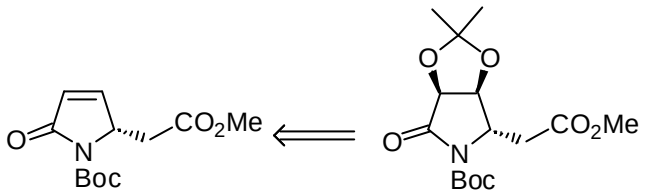
We planed to synthesize the dihydroxyamino acid moiety using our previously developed methodology to produce chiral 5-substituted 3-pyrrolin-2-ones. As outlined in Scheme 2.1, the east part of AI-77-B, the hydroxyamino acid fragment **38**, would be constructed by means of a chemoselective hydrolysis of the lactame **39**. The tri-substituted pyrrolidone **39** should be accessible from our building block **8** through dihydroxylation of the conjugated double bond followed by protection of the subsequent diol.



36

37

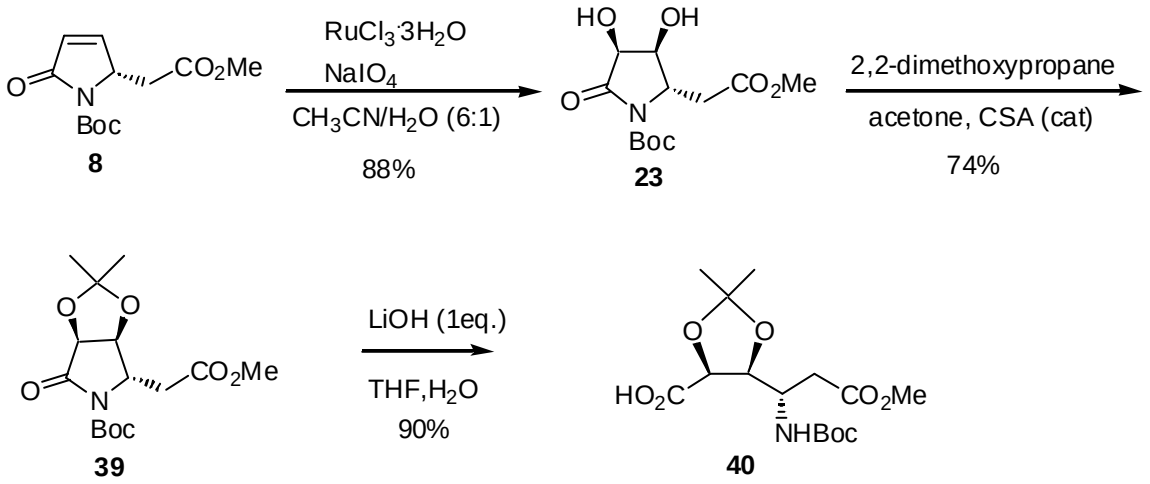
38



8 **39**

Scheme 2.1. Retrosynthesis of the dihydroxyamino acid moiety of AI-77-B

The synthesis of the dihydroxyamino acid fragment started with the flash dihydroxylation of **8** using RuO_4 generated *in situ* from $RuCl_3$ and $NaIO_4$ in CH_3CN/H_2O (6:1) at 0-5 ^oC for 3 minutes to provide the diol **23** in 88% yield (Scheme 2.2). Subsequent protection of the diol with 2,2-dimethoxypropane and catalytic amount of CSA at room temperature for 20 h, afforded the cyclic aza-compound **39** in good yield. In order to hydrolyze selectively the lactame and to let untouched the methylester group we used one equivalent of LiOH in THF/H_2O at 0 ^oC for 30 minutes, to provide the hydroxyamino acid fragment **40** in 90% yield. The lactame could be selectively cleaved due to the activation of the vicinal Boc group, which rends the amide more electrophilic.



Scheme 2.2. Synthesis of the dihydroxyamino acid moiety of AI-77-B

One can assemble the novel β-amino acid fragment **40** to the dihydroisocoumarin **37** through a normal peptide coupling between the amino group of **37** and the carboxylic acid of **40**. The last step of the synthesis of AI-77-B **36** would be the known deprotection of the acetonide and *N*-Boc function under mildly acidic conditions.[11]

In conclusion, we synthesized a new hydroxyamino acid moiety of AI-77-B in a straightforward three-step procedure from **8** using the simplicity of our methodology to produce chiral pyrrolidones from pyrrole. Moreover, the dihydroxylated pyrrolidone **23** can be a very usefull buiding block for the synthesis of various glycosidase inhibitors.

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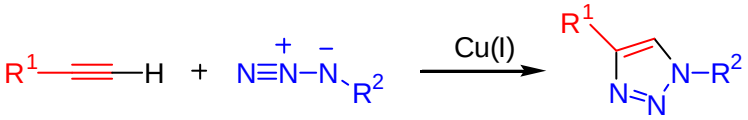
• *Chapter 3*

Expedient Immobilization of TEMPO by Copper-Catalyzed Azide-Alkyne [3+2]-Cycloaddition onto Polystyrene Resin

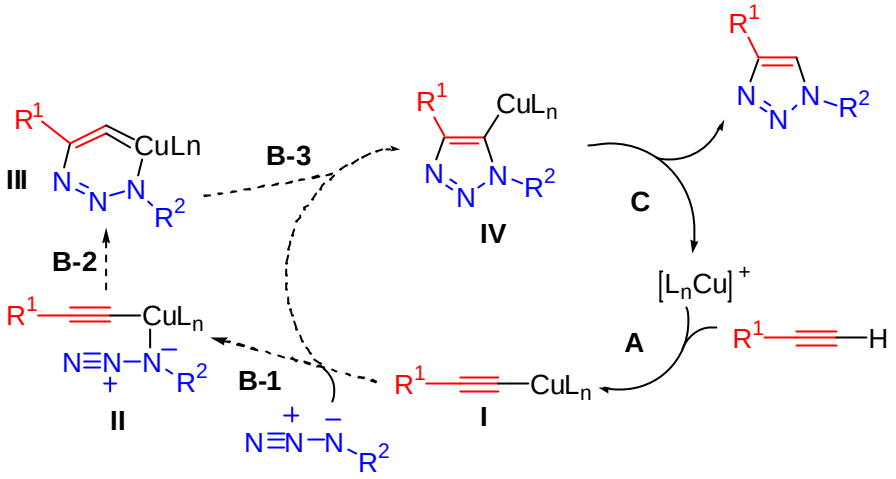
3.1 Introduction

The copper(I)-catalyzed[1] azide-alkyne cycloaddition[2] (CuAAC) reaction, coined as a click reaction,[3] has proven to be most powerful for ligating functional molecules to supporting scaffolds or to each other.[4] Since its introduction by Sharpless in 2001, the CuAAC proved to be the "cream of the crop" among all click reactions, due to the simplicity with which azides and alkynes functionalities can be introduced into a molecule and their high chemical stability towards water and oxygen. The "click reaction" occurs smoothly, in the presence of a catalytic amount of Cu(I)-, Cu(II)-salts or even Cu metal in most of the known solvents, including water, giving access to regiospecific 1,4-disubstituted 1,2,3-triazoles with 100% atom economy and without additional purification (Scheme 3.1).



Scheme 3.1. Copper(I)-catalyzed synthesis of 1,4-disubstituted 1,2,3-triazoles

In 2002, Sharpless proposed a mechanism for the copper(I)-catalyzed azide-alkyne 1,3-dipolar cycloaddition reaction.[1a] The catalytic cycle begins undoubtful with formation of the monomeric copper-acetylide **I** (Scheme 3.2). Previous experiments showed that internal alkynes have no activity in this reaction.[1b] The concerted cycloaddition of a copper–acetylene π complex with the appropriate azide (route B) would need an activation energy of 23.7 kcal/mol,[5] too high to be responsible for significant rate effect of CuI catalysis. Stepwise cycloaddition catalyzed by a monomeric CuI species would lower the activation barrier relative to the uncatalyzed process by as much as 11 kcal/mol, which is sufficient to explain the incredible rate enhancement observed under CuI catalysis. Therefore, the mechanism should occur via a stepwise, annealing sequence (B-1,B-2,B-3) through the intermediates **II** and **III**.



Scheme 3.2. Proposed mechanism for the copper(I)-catalyzed azide-alkyne 1,3-dipolar cycloaddition reaction[1]

The irreversible formed triazole is not only a rigid and almost chemically inert linkage but can also associate through hydrogen bonding and dipole interactions to biological targets and can be useful in organic catalysis.[6]

Following the seminal contributions of Gmeiner and co-workers,[7] there is a growing awareness that this reaction can also be used for the synthesis of functional polymers and dendrimers.[8] In addition, the CuAAC, offering wide tolerance for reactive or sensitive groups, should have great potential for the synthesis of heterogeneously immobilized catalysts and reagents.

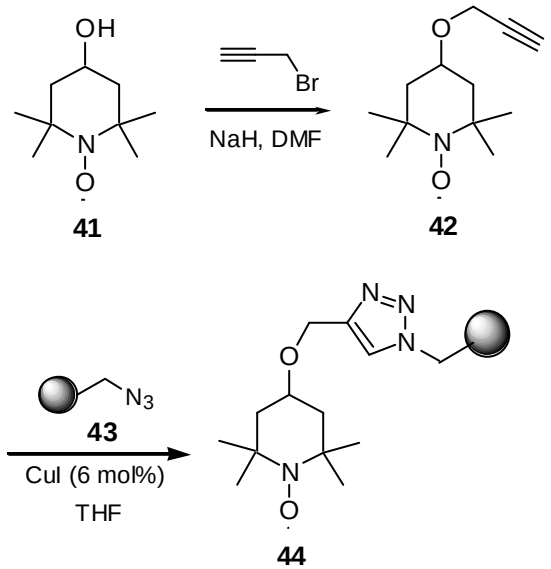
Oxidation of alcohols using catalytic amounts of the stable nitroxyl radical 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) in combination with safe and easy to handle primary oxidants has received significant attention due to the low toxicity of the reagent and the good chemoselectivity achieved.[9] The demands for inexpensive, environmentally friendly and renewable polymer-supported (PS) catalysts have led to the synthesis of several immobilized TEMPO moieties,[10] including silica-supported TEMPO,[10a,b] MCM-41-supported TEMPO,[10c] sol-gel TEMPO,[10d,e] PEG-TEMPO,[10f-h] polynorbornene-derived TEMPO,[10i] fluorous-tagged TEMPO,[10j,k] acid functionalized Fibre-Cat^{TM},[10l] polyamine TEMPO (PIPO)[10m] and polymersupported oxammonium salts.[10n] These catalysts have shown good efficiency for the selective oxidation of primary and secondary alcohols to the corresponding aldehydes and ketones. Alternatively, polymer bound co-oxidants have been proposed to overcome limitations associated with the necessity to employ stoichiometric amounts of the co-oxidant in solution, requiring additional purification steps.[11]

3.2 Aim of this work

We report in this chapter the simple and efficient preparation of a new polystyrene-supported TEMPO (PS-CLICK-TEMPO) by using click chemistry as a practical tagging method and demonstrate its high activity for the oxidation of alcohols using bleach or molecular oxygen as a co-oxidant.

3.3 Synthesis of polystyrene-supported TEMPO

The catalyst could be prepared in an easy two-step sequence starting from commercially available 4-hydroxy-TEMPO **41** and polystyrene-supported azide **43** (Scheme 3.3).[12] Propargylation of **41** was straight-forward giving rise to **42**, which set the stage for the subsequent copper(I)-catalyzed cycloaddition: following a protocol developed by Gmeiner and co-workers[7a] 6 mol% Cu(I) iodide were found to be optimal to achieve the smooth formation of **44** as judged by the complete disappearance of the typical IR absorption of the azide group (2095 cm^{-1}).



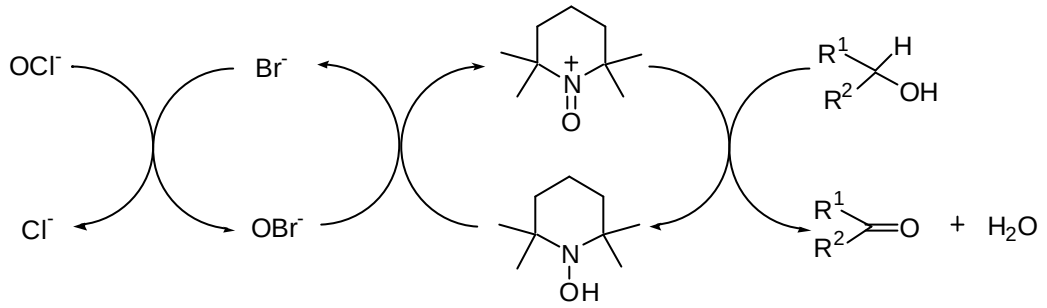
Scheme 3.3. Synthesis of PS-CLICK-TEMPO **44**

No co-reductant had to be added, indicating that no oxidation of Cu(I) by TEMPO had occurred. The estimated catalyst loading based on elemental analysis and recovered **42** was approx. 4.0 $mmolg^{-1}$ of nitroxyl radical. This value is very close to that of the original Merrifield resin (*ca.* 4.3 $mmolg^{-1}$) showing the high efficiency of this tagging method. When

3 mol% CuI were employed, only 50% conversion was achieved, resulting in a resin **44** with a catalyst loading of 2 $mmolg^{-1}$ of nitroxyl radical.

3.4 PS-CLICK-TEMPO oxidation of alcohols using bleach

The new heterogeneous "PS-CLICK-TEMPO" **44** was first tested in the selective oxidation of aliphatic and benzylic alcohols under Anelli's conditions[9b], using sodium hypochlorite as terminal oxidant and KBr as co-catalyst (Scheme 3.4).



Scheme 3.4. TEMPO-catalyzed bleach-oxidation of alcohols using bromide as cocatalyst

The active oxidant in this system is the corresponding oxoammonium cation. Oxidation of the alcohol affords the corresponding carbonyl compound and the reduced form of TEMPO, the hydroxylamine, TEMPOH. The latter is then reoxidized by NaOCl to regenerate the oxoammonium cation. In the general, catalytic amount of sodium bromide is used as a cocatalyst, as the reoxidation step is more favorable with hypobromite and the sodium bromide produced is readily reoxidized by hypochlorite.

In all cases 2.5 mol% of PS-CLICK-TEMPO **44** was used, allowing complete conversion of the substrates generally in 30 minutes (Table 3.1). Primary benzylic alcohols (entries 1–5) gave the corresponding aldehydes with high yields and complete chemoselectivity, no overoxidation to the respective carboxylic acids was observed. Moreover, **44** was also effective for the oxidation of the more challenging aliphatic alcohols (entries 6–10). Formation of the aldehydes from primary alcohols (entries 6–8) was accompanied by minute amounts (<5%) of carboxylic acids, while oxidation of more demanding secondary alcohols (entries 9 and 10) required somewhat longer reaction times (1–5 h) to achieve complete conversion. In all cases, the purity of the isolated aldehydes was >95% without the need for purification by column chromatography.

Table 3.1. PS-CLICK-TEMPO mediated oxidation of alcohols to carbonyl derivatives[a]

Entry	Alcohol	Conversion [%][b]	Yield [%][c]	Purity [%][b]
1	benzyl alcohol	>98	99	>98
2	4-bromobenzyl alcohol	>98	93	>98
3	4-methylbenzyl alcohol	>98	98	>98
4	4-methoxybenzyl alcohol	>98	92	>98
5	2-phenylethanol	>98	95	>98
6	1-octanol	>98	95	95
7	1-decanol	>98	96	95
8	1-dodecanol	>98	99	96
9	3-nonanol[d]	>98	99	>98
10	cyclohexanol[e]	>98	98	>98

[a] Alcohol (1 mmol) in CH_2Cl_2 (2 ml), KBr (0.3 mmol), PS-TEMPO (2.5 mol %), NaOCl (1.3 mmol), $NaHCO_3$ (0.2 mmol), 0 °C. Reaction time = 30 min.
[b] Determined by ^{1}H- and ^{13}C-NMR.
[c] Isolated yields. [d] Reaction time = 5h.
[e] Reaction time = 1h.

We next examined the recyclability of our catalyst (Table 3.2). PS-CLICK-TEMPO **44** was easily recovered by filtration and re-used for the next cycle without further activation in five subsequent runs employing 4-methylbenzyl alcohol as substrate. Virtually no loss of activity was observed, and also the chemoselectivity for the formation of the aldehyde remained very high in all cases. Only traces of carboxylic acid, being easily removed by washing the organic phase with sodium bicarbonate solution, were observed.

Table 3.2. Recycling of PS-CLICK TEMPO in the oxidation of 4-methylbenzyl alcohol.

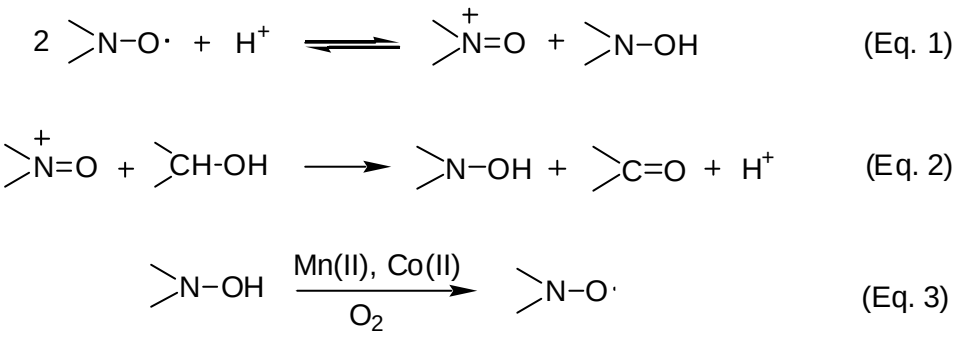
Run	Conversion [%][a]	Yield [%][b]	Purity [%][a]
1	>98	95	>98
2	>98	94	>98
3	>98	93	>98
4	>98	95	>98
5	>98	92	>98

[a] Determined by ^{1}H- and ^{13}C-NMR; >98% indicates that no starting material or by-products could be detected.
[b] Isolated yields.

3.5 Mn–Co–TEMPO-catalysed oxidation of alcohols by oxygen

In 1984, Semmelhack reported that TEMPO/CuCl can oxidize allylic and benzylic alcohols to aldehydes using molecular oxygen.[9a] This method was recently improved with the discovery of several variations of the original Cu/TEMPO catalytic systems.[13,15b] Minisci et al. showed that the aerobic oxidation of both activated and unactivated alcohols can be performed under mild conditions using Mn(II)-Co(II) or Mn(II)-Cu(II) nitrates in acetic acid under ambient pressure and temperature.[14]

The mechanism of this transformation is depicted in the Scheme 3.5. Am acidic medium is necessary to make the catalytic system effective; the oxidation takes place selectively in acetic acid solution, but no substantial oxidation occurs in acetonitrile solution under the same conditions. The actual oxidant is the oxoammonium salt, which is generated by disproportionation of TEMPO radical catalysed by the acidic medium (Eq. 1). Then, the oxoammonium salt oxidizes the alcohol to the carbonilic derivative (Eq. 2) and the TEMPO radical is regenerated by oxygen and the metal salt catalytic system (Eq. 3).



Scheme 3.5. Mn–Co–TEMPO-catalysed oxidation of alcohols by oxygen

Although numerous immobilized TEMPO variants on both organic and inorganic supports were synthesized, only few examples are known where molecular oxygen is used as terminal oxidant.[10c,h,l,15] We decided to investigate the catalytic properties of PS-CLICK-TEMPO **44** under the conditions developed by Minisci, being especially attractive for industrial processes since non-chlorinated solvents and oxygen as the terminal oxidant are used.

PS-CLICK-TEMPO **44** showed outstanding activity in all experiments with generally employing only 5 mol% of catalyst loading (Table 3.3) at reaction times of 3–6 h. Only

cinnamyl alcohol, which is known to be less reactive,[10h] was cleanly oxidized within 24 h in the presence of 10 mol% catalyst.

Table 3.3. Aerobic oxidation of alcohols to carbonyl compounds by PS-CLICK-TEMPO[a]

Entry	Alcohol	Time [h]	Conversion [%][b]	Yield [%][c]	Purity [%][b]
1	benzyl alcohol	3	>98	98	>98
2	4-bromobenzyl alcohol	3	>98	95	>98
3	4-methylbenzyl alcohol	3	>98	98	>98
4	1-octanol	6	>98	97	95
5	1-decanol	6	>98	96	95
6	cinnamyl alcohol[d]	24	>98	96	>98

[a] Alcohol (1 mmol) in AcOH (1 ml), $Mn(NO_3)_2 \cdot 4H_2O$ (0.2 mmol), $Co(NO_3)_3 \cdot 6H_2O$ (0.2 mmol), PS-TEMPO (2.0 mmol/g 25 mg, 5 mol%) 40 °C.
[b] Determined by ^{1}H- and ^{13}C-NMR; >98% indicates that no starting material or by-products could be detected.
[c] Isolated yields.
[d] PS-TEMPO (10 mol %).

Also under these conditions PS-CLICK-TEMPO **44** could be recycled efficiently. In five consecutive runs using 4-bromobenzyl alcohol as the substrate the catalyst was recovered by simple filtration and re-used as such giving high yields of aldehyde in all cases (Table 3.4).

Table 3.4. Aerobic oxidation of 4-bromobenzyl alcohol by PS-CLICK-TEMPO. Recycling experiment

Run	Conversion [%][a]	Yield [%][b]	Purity [%][a]
1	>98	94	>98
2	>98	95	>98
3	>98	93	>98
4	>98	91	>98
5	>96	93	96

[a] Determined by ^{1}H- and ^{13}C-NMR; >98% indicates that no starting material or by-products could be detected.
[b] Isolated yields.

In conclusion, we have developed an extremely simple and practical protocol for grafting TEMPO onto polystyrene resin from readily available and inexpensive starting materials using the copper(I)-catalyzed alkyne-azide cycloaddition as the ligation method. The resulting

PS-CLICK-TEMPO **44** proved to be highly effective in the chemoselective oxidation of alcohols with both bleach and molecular oxygen under mild conditions. Moreover, it can be easily recovered and recycled without any loss of catalytic activity.

3.6 LITERATURE

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• *Chapter 4*

A Facile Strategy to a New Fluorous-Tagged Immobilized TEMPO Catalyst Using a Click Reaction and its Catalytic Activity

4.1 Introduction

Fluorous catalysis emerged in 1994[1] with the publication by Horváth and Rábai of the Fluorous Biphasic Catalysis (FBC) concept first applied to the rhodium(I) catalyzed hydroformylation of alkenes. Since then, the use of fluorous biphasic separations has increased as a consequence that these technologies combine simplicity of operation, scaling up and high selectivity to separate exclusively a perfluorinated-tagged compound from a complex reaction mixture.[2]

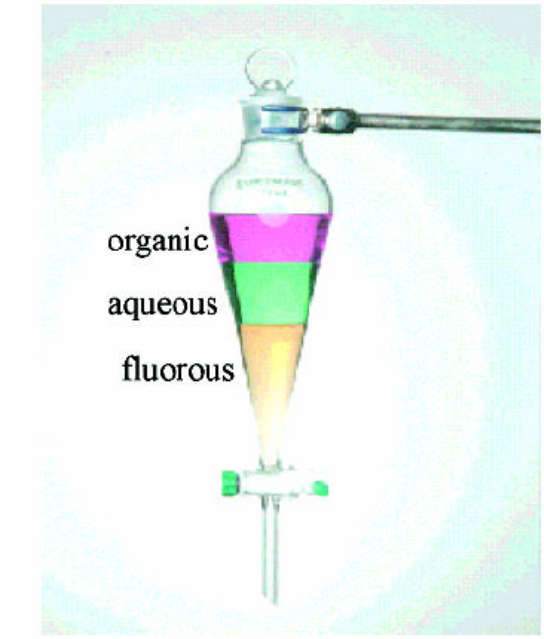


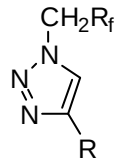
Figure 4.1. Fluorous liquid-liquid extraction (reproduced from ref. 2a)

This last property has provided an attractive method for catalyst recovery and recycling. Thus, perfluorinated tags were attached to several metal-based catalysts[3] and organocatalysts.[4] However, an inherent problem in this kind of compounds is that fluorous chains confer a highly hydrophobic character to the rest of the molecule, so that handling and

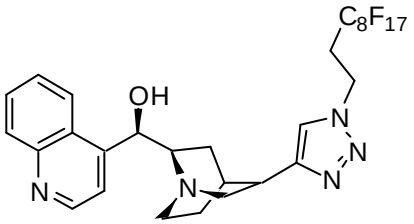
purification of the reaction products is complicated, and sometimes low yields are reported in these processes. This factor is relevant if the high perfluoroalkyl reagents costs are considered. For this reason, ideal synthetic routes should be those that attach the flourous tag in the final step,[5] ideally in a high yielding reaction, which also often turns out to be problematic due to the low reactivity of many perfluorinated precursors used for this purpose.

The copper catalyzed azide-alkyne cycloaddition (CuAAC) represents a simple method for the regioselective synthesis of 1,4 substituted 1,2,3-triazoles in almost quantitative yields and high efficiency in terms of atom economy. This process allows the formation of a thermally and hydrolytically stable linkage between two different molecules. As described in Chapter 3, the CuAAC has been demonstrated to be a powerful tool in preparing building blocks and dendrimers, as well as supporting functionalized molecules and diverse scaffolds. In this regard, our group has reported the successful ligation of azabis(oxazoline)[6] and TEMPO[7] catalysts to polymeric supports using the CuAAC approach.

Although a strong synergy in both fluorous and click chemistry is perceived, surprisingly there are few examples which report a convergence between these two fields. Wu and co-workers[8] reported the selective copper catalyzed cycloaddition of fluorinated azides to triple bonds to afford fluoroalkylated [1,2,3]-triazoles **45**, whereas the Soos group has described the preparation of a pefluorinated cinchona alkaloid **46** through the CuAAC (Figure 4.2).[9]



45



46

R: Ph, C_4H_9, C_6H_{13}, CH_2OTHP, CH_2OAc
R_f: CF_3, HCF_2CF_2, C_6F_{13}

Figure 4.2.

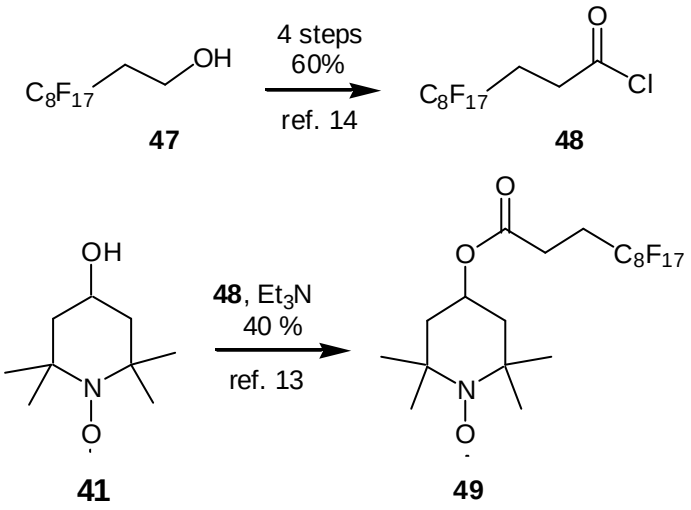
4.2 Aim of this work

With this precedence, we believed that it would be possible to take the advantages offered by fluorous and click chemistry in the synthesis of building blocks for catalysis. Specifically, we focused on developing novel perfluorinated building blocks for TEMPO, a metal-free catalyst for selective oxidation of alcohols to aldehydes under mild conditions. Initially, Montanari

and co-workers[10] introduced a versatile catalytic oxidation procedure based on TEMPO in which buffered bleach as terminal oxidant and bromide ion as co-catalyst is employed. Inspired by Montanari's work, various other groups introduced organic and inorganic terminal oxidants.[11] However, whichever oxidant is used, separation of TEMPO from the reaction mixture requires lengthy work up especially when reactions are run on large scale.[12] Therefore, the search for an efficient method for preparation, recovery and recycling of TEMPO catalysts is continuously ongoing (see Chapter 3).

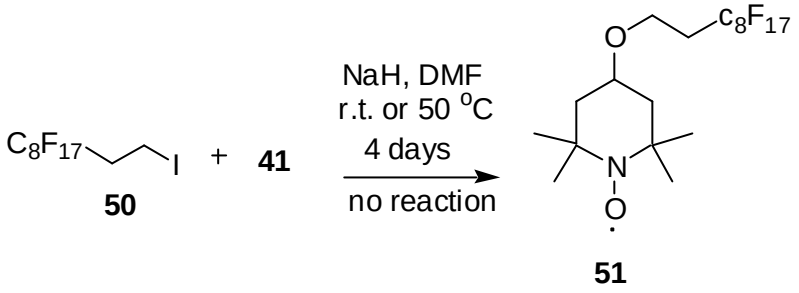
4.3 Synthesis of the novel fluorous-tagged TEMPO catalyst

Recently, Pozzi and co-workers[13] described the synthesis and catalytic activity of novel fluorous-tagged TEMPOs such as **49**, which in turn were separated from oxidation products by both liquid-liquid or solid-phase extraction. However, only moderate to unsatisfactory success in catalyst recycling with such "light fluorous catalysts" was achieved and moreover, low yields in the synthesis of fluorous precursors were encountered (Scheme 4.1).[13,14]



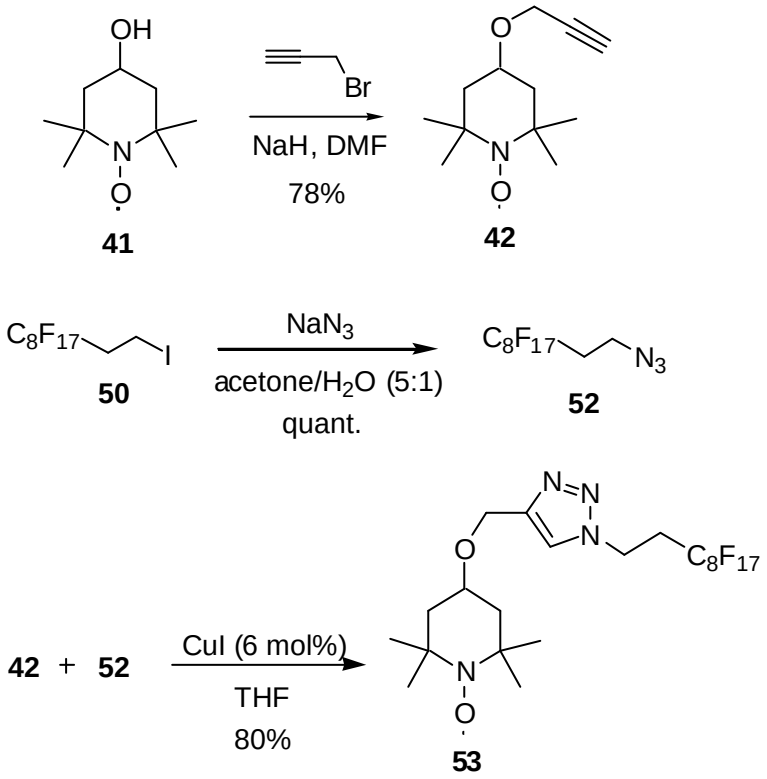
Scheme 4.1. Synthesis of "light"-fluorinated TEMPO by *Pozzi et al.*[13]

Our own attempts to achieve the direct attachment of the perfluorinated moiety **50** to 4-hydroxy-TEMPO **41** using NaH were not successful – even at long reaction times and elevated temperatures (Scheme 4.2). The low reactivity of **50** for nucleophilic substitution reaction has been noted before, calling for perfluorinated alkyl iodides with an additional methylene group of type $R_f(CH_2)_3I$, which are, however, considerably more expensive compared to building blocks of type $R_f(CH_2)_2I$.[2a]



Scheme 4.2.

However, the new fluorous catalyst **53** could be prepared in a three-step sequence starting from **41** and 1-iodoperfluorodecane **50** using the CuACC as the key step (Scheme 4.3). The 4-propargylated TEMPO **42**[7] was smoothly ligated with 1-azido-perfluorodecane **52**[15], accessible in quantitative yield from **50** by substitution with sodium azide. The F_{17}-CLICK-TEMPO **53** was obtained in 80% yield upon reacting **42** and **52** in the presence of catalytic amounts of CuI, proving the high efficiency of this ligation method.



Scheme 4.3. Synthesis of F_{17}-CLICK-TEMPO **53**

4.4 Catalytic activity and recovery of F_{17}-CLICK-TEMPO 53

The catalytic activity of **53** was tested in the chemoselective oxidation of aliphatic and benzylic alcohols using sodium hypochlorite as the terminal oxidant and KBr as a co-catalyst. The good solubility of **53** in dichloromethane at 0 °C makes it a very effective catalyst. In all cases complete conversion, high yield and excellent selectivity were observed (Table 4.1).

Table 4.1. Fluorous CLICK-TEMPO oxidation of alcohols to carbonyl derivatives[a]

Entry	Alcohol	Conversion [%][b]	Yield [%][c]	Purity [%][b]
1	benzyl alcohol[d]	>98	99	>98
2	4-bromobenzyl alcohol	>98	95	>98
3	4-methylbenzyl alcohol	>98	99	>98
4	4-chlorobenzyl alcohol	>98	99	>98
5	2-phenylethanol	>98	97	>96
6	1-octanol	>98	86	>96
7	1-decanol	>98	95	>98
8	1-dodecanol	>98	96	>98
9	cyclohexanol[d]	>98	92	>98
10	hexadecanol[e]	>98	96	>95

[a] Alcohol (1 mmol) in CH_2Cl_2 (2 mL), KBr (0.2 mmol), F_{17}-CLICK-TEMPO **53** (1.0 mol %), NaOCl (0.8 ml, 1.3 mmol), $NaHCO_3$ (40 mg, 50 mgmL^{-1} bleach), 0 °C. Reaction time = 15 min.
[b] Determined by ^1H- and ^{13}C-NMR.
[c] Isolated yields.
[d] Reaction time = 30 min.
[e] Reaction temperature = from 0 °C to rt

We tried to recover the F_{17}-CLICK-TEMPO **53** using fluorous silica gel prepared according the procedure of Bannwarth and co-workers.[16] However, we were not able to get good separation of the F_{17}-CLICK-TEMPO **53** from the oxidation products on this stationary phase. In addition, the catalyst **53** is only slightly soluble in perfluoromethyl cyclohexane and perfluoro-1,3-dimethylcyclohexane at room temperature, preventing liquid–liquid phase separation. This behaviour can be attributed to the relatively low fluorine content (F = 46%), but also to the presence of a polar linker in the molecule, namely the triazole ring. In this respect, other authors[17,18] have also reported discrepancies between the fluorine content of a compound and its solubility in fluorinated solvents. In general, it is assumed that a high fluorine percentage is needed to gain differential solubility in fluorous solvents, but there is

no clear correlation between polarity and molecular weight of a compound and its absolute solubility.[2b]

However, the triazole moiety present in catalyst **53**, beyond its chemical stability, could shift the overall polarity of the molecule and therefore, allow a better separation from the reaction mixture through other techniques. We were pleased to discover that silica gel 60 provides an easier and less expensive solution. Thus, the crude product was placed on a short bed of silica and eluted with dichloromethane in order to obtain the pure oxidation product with complete retention of **53** on silica (*Rf* = 0.1). The catalyst **53** (initial loading 75 mg, 1 mol%) was subsequently recovered from the column by elution with diethyl ether (*Rf* = 0.53) and re-used in a total of four cycles, each time oxidizing two grams of 4-bromobenzyl alcohol, without loss of activity and selectivity (Table 4.2). Specifically, the catalyst **53** was re-isolated with no observable degradation, emphasizing the stable linkage created through the triazole moiety.

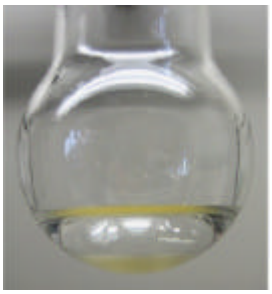
Table 4.2. Fluorous CLICK-TEMPO oxidation of 4-bromobenzyl alcohol. Recovery and recycling experiment[a]

Run	Conversion [%][b]	Yield [%][c]	Purity [%][b]	Recovery of catalyst **53** (mmol)
1	>98	94	>98	0.104
2	>98	94	>98	0.078
3	>98	92	>98	0.058
4	>98	90	>98	0.030

[a] Alcohol (10.7 mmol) in CH_2Cl_2 (20 ml), KBr (2.16 mmol), F_{17}-CLICK-TEMPO **53** (1.0 mol %, 0.107 mmol), NaOCl (8.6 ml,14 mmol), $NaHCO_3$ (430 mg, 50 $mgmL^{-1}$ bleach), 0 °C. Reaction time = 15 min.
[b] Determined by ^1H- and ^{13}C-NMR.
[c] Isolated yields.

The good solubility of **53** in dichloromethane and at the same time its high affinity to silica is striking. For example, 25 mg of **53** readily dissolve in 10 mL of dichloromethane. Upon addition of 1 g of silica, **53** was completely adsorbed in less than one minute, analysis of the decanted solvent showed only trace amounts of **53** still present (Figure 4.3).

a) 25 mg F_{17}-CLICK-TEMPO in 10 ml DCM



b) Addition of 1g of Silica gel 60 after 1 min**, note the yellow silica.**

c) Addition of 10 ml of EtOAc to the silica after the decantataion of DCM**,** 1 minute shaking, **note the white silica.**

Figure 4.3.

Upon subsequent addition of 10 mL of ethyl acetate (*Rf* = 0.85) to the silica, and stirring for 1 min catalyst **53** (19 mg) could be recovered from the solvent after decantation and concentration.

In contrast, in an analogous experiment with fluorous silica[16] most of **53** (>80%) could be recovered from the decanted dichloromethane phase.

In conclusion, we have developed a facile strategy for the synthesis of a new fluorous tagged, immobilized TEMPO catalyst from commercially readily available materials in high yield using the simplicity of the copper-catalyzed azide-alkyne cycloaddition. The new perfluorinated F_{17}-CLICK-TEMPO **53** proved to be very stable, highly effective in the chemoselective oxidation of alcohols with bleach, and after recovery it was re-used in four consecutive cycles without loss of catalytic activity.

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• *Chapter 5*

Synthesis of Novel Thermoresponsive Perfluorinated Building Blocks by "Click Chemistry"

5.1 Introduction

The use of organic templates for the synthesis of functional materials has received much attention over the last years as a consequence of their broad application in industrial, military, medical, automotive and aerospace fields. These materials can respond actively to changes in their environment such as temperature, pH, optical wavelength, electric and magnetic field and pressure.

One class of intelligent materials is represented by the thermomorphic perfluorinated molecules, which have recently attracted an increased interest due to their application in organic catalysis.[1] A thermomorphic system is characterized by solvent pairs (a perfluorinated and an organic solvent) that reversibly change from being biphasic to monophasic as a function of temperature. This characteristic is very useful for homogeneous catalysis because the reaction can be performed at an elevated temperature where the mixture becomes one-phase, overcoming any rate limitations due to mass transfer. By cooling down the reaction mixture, the products and catalyst can be easily separated under biphasic conditions (Figure 5.1).

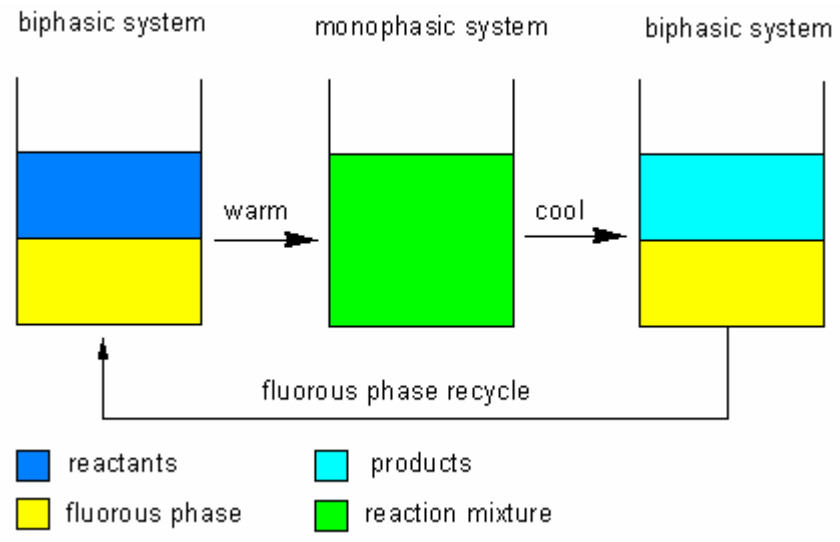


Figure 5.1. Fluorous biphasic reaction system

However, the relatively high cost and environmental persistence of the perfluorinated solvents rends this system less attractive for industrial application. These problems can be eliminated by using a fluorous solvent-free system in which the purification can be performed by fluorous solid-phase extraction (F-SPE) or fluorous flash chromatography (F-FC) for parallel synthesis and by fluorous HPLC (F-HPLC) for mixture synthesis (Figure 5.2).[2]

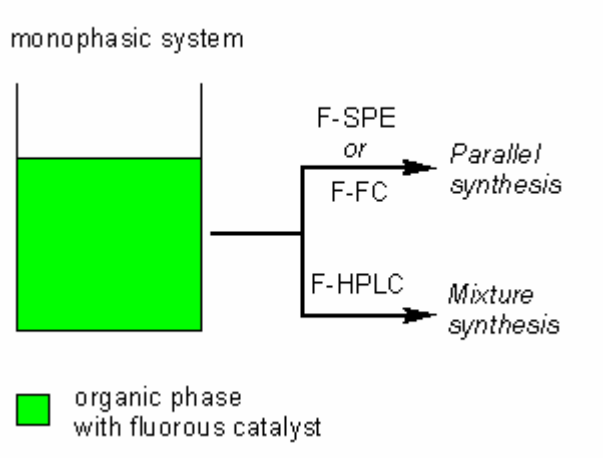


Figure 5.2. Fluorous solvent-free synthesis and separation

Recently, Gladysz[1f] and co-workers used the fluorous phosphane $P(CH_2CH_2C_8F_{17})_3$ as catalyst for the addition of alcohols to the triple bond of methyl propiolate. The reaction was performed in octane at 65 ^oC in order to dissolve the perfluorinated catalyst. Subsequently, the reaction mixture was cooled down to -30 ^oC and the catalyst was precipitated and separated by decantation without using fluorous solvent. The recovered catalyst was used for four further cycles without deterioration in yield.

In 2001, Gladysz introduced the term "ideal catalyst".[3] He proposed that an ideal catalyst should be one that:

1. *produces an infinite amount of product from a single catalyst molecule (or heterogeneous equivalent), a criterion that implies no deactivation under reaction conditions and no poisoning under reaction conditions;*
2. *effects a rapid reaction (high turnover frequency or TOF) without the need for external cooling or heating;*
3. *effects a rapid reaction under atmospheric pressures of gaseous reactants;*
4. *has no intrinsic inert atmosphere requirement;*
5. *is insensitive to reactant impurities;*

6. *gives a product yield of 100%;*
7. *is readily available and inexpensive;*
8. *is nontoxic and nonhazardous;*
9. *requires no activation or initiation step.*

He also mentioned that an *"ideal recoverable catalyst" is one that can be recovered quantitatively (e.g., every molecule for a homogeneous species), either as the catalyst precursor or a functionally equivalent rest state.*

Gladysz tried to put these ideas in practice by introducing a new recycling concept for fluorous catalysts. Thus, he discovered that Teflon tape can play the role of the fluorous support providing an intelligent and efficient method to recycle catalysts.[1h] Gladysz and co-workers tested their system by carrying out a ketone hydrosilation reaction using a phosphine-Rh complex as catalyst to which fluorine-containing ponytails had been incorporated. The catalyst is insoluble in dibutyl ether at room temperature, but dissolves at 55 ^{o}C. When the temperature was reduced to -30 ^{o}C the catalyst precipitated from the reaction mixture and was adsorbed onto the Teflon tape. The recovered catalyst could be re-used with the same protocol for three consecutive runs with no decrease in catalytic activity (> 96 % yield and similar TONs) showing that no deactivation and minor metal loss had occurred under these conditions.

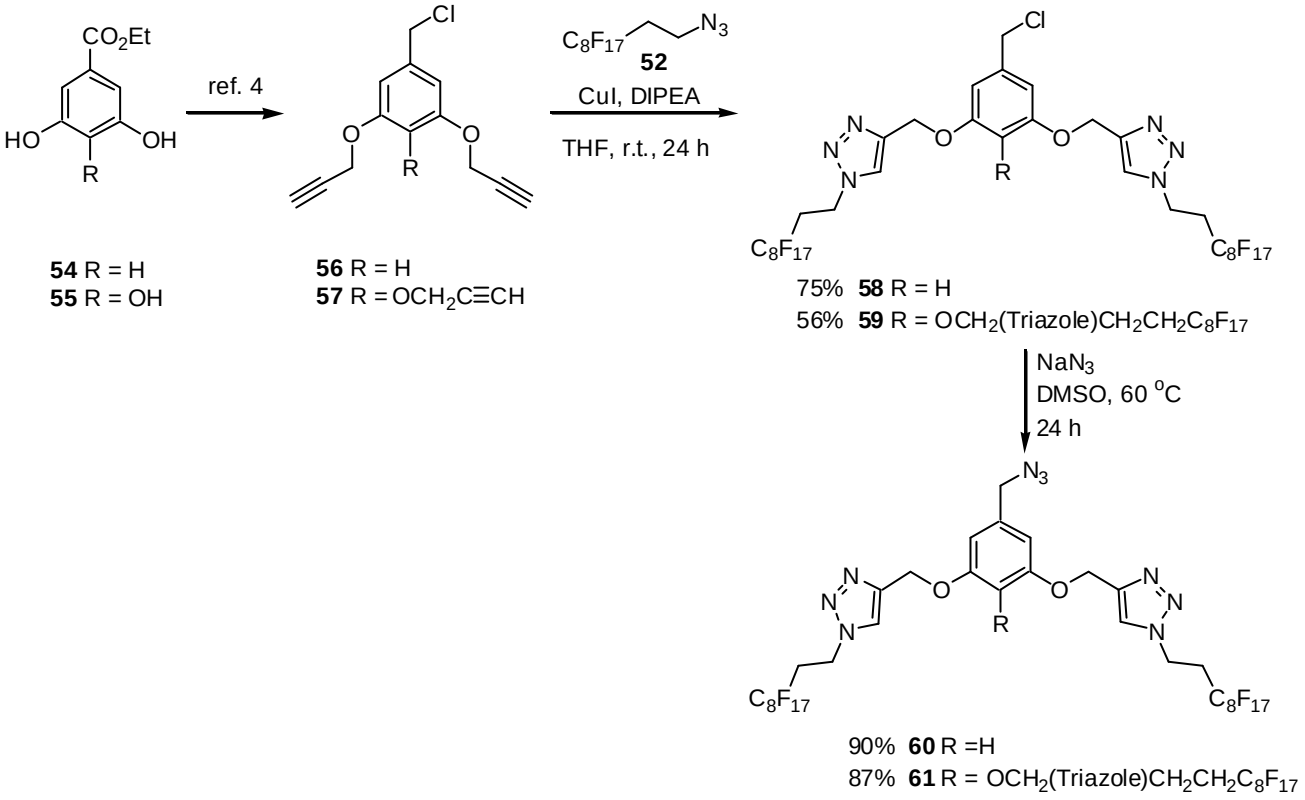
In the previous Chapter, we introduced a new "light fluorous" TEMPO **53** using the simplicity of the CuAAC as ligation method. This new perfluorinated CLICK-TEMPO proved to be highly effective in the chemoselective oxidation of alcohols with bleach and very stable after recovering and recycling without loss of catalytic activity. However, one limitation of the procedure is that a chromatographic separation was required to recover the catalyst.

5.2 Aim of this work

To circumvent this drawback we chose to attach more perfluorinated ponytails into the molecule by modifying the building block's core in order to increase the fluorine content of the catalyst.

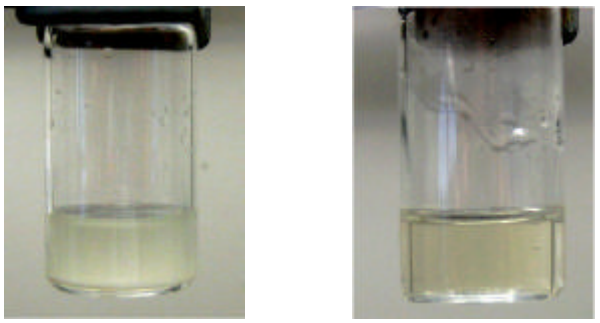
5.3 Synthesis of building blocks

Sharpless and co-workers reported the preparation of triazole dendrimers from 3,5-dihydroxylbenzyl derivatives as primary building blocks via a click reaction.[4] Inspired by their work, we prepared the propargyloxybenzyl chlorides **56** and **57** in a three-step procedure starting from the commercially available polyhydroxybenzoic esters **54** and **55** (Scheme 5.1). Then, the chlorides were smoothly clicked with 1-azido-perfluorodecane **52** to give the corresponding clicked-chlorides **58** and **59** in moderate to good yields. The next step was the introduction of azide functionality; the azides **60** and **61** were obtained in high yields by a nucleophilic substitution using sodium azide in warm DMSO.



Scheme 5.1. The synthesis of 2- and 3-ponytails perfluorinated azide **60** and **61**

The perfluorinated clicked-chlorides **58, 59**, as well as azides **60, 61** are not soluble in perfluorinated solvents (perfluoro-1,3-dimethylcyclohexane, perfluoromethyl cyclohexane) neither at room temperature nor at boiling temperature because of the triazoles polar character. However, they formed homogeneous solutions in polar organic solvents by heating the mixture at ≥70 °C (e.g. CH_2Cl_2, $CHCl_3$, THF, EtOAc, DMF, DMSO, CH_3CN, acetone) (Figure 5.3).



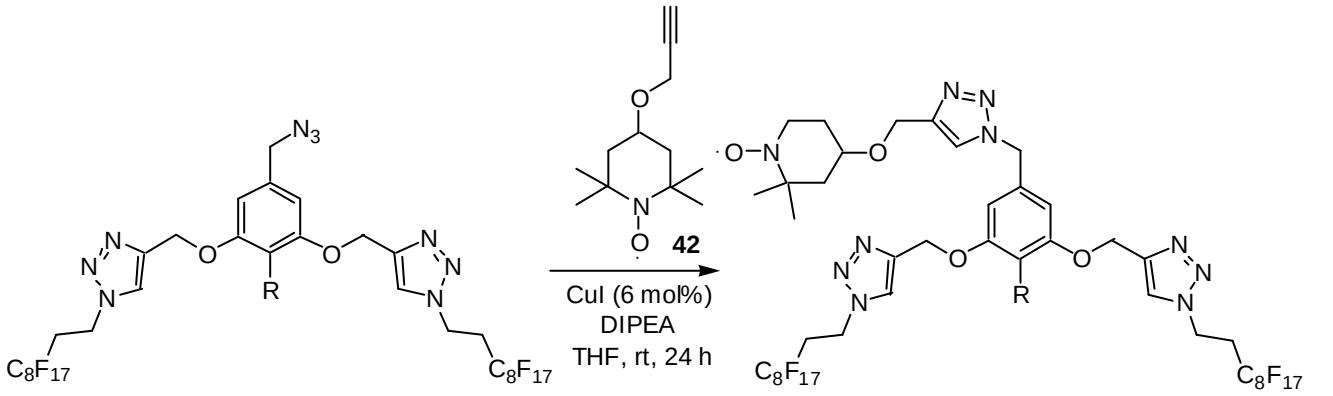
a) 20 mg of **60** in 2 ml EtOAc at rt. **Note the turbid mixture.**

b) 20 mg of **60** in 2 ml EtOAc after heating at 70 ^{o}C. **Note the clear solution.**

Figure 5.3. Thermomorphic property of azide **60**

5.4 Synthesis of perfluorinated TEMPOs

The fluorous-tagged TEMPOs **62** and **63** were synthesized by clicking the azides **60** and **61** with propargyloxy TEMPO radical **42** using 6 mol % of CuI and an excess of DIPEA in THF at room temperature (Scheme 5.2).



Scheme 5.2. The synthesis of 2- and 3-ponytails TEMPOs **62**, **63**

5.5 Catalytic activity of TEMPOs 62 and 63

We tested the catalytic activity of fluorous TEMPOs **62** and **63** in the chemoselective oxidation of aliphatic and benzylic alcohols using sodium hypochlorite as terminal oxidant and KBr as co-catalyst (Table 5.1 and 5.2).[5]

Table 5.1. Oxidation of alcohols to carbonyl derivatives using TEMPO **62**[a]

Entry	Alcohol	Conversion [%][b]	Yield [%][c]	Purity [%][b]
1	4-bromobenzyl alcohol	>98	95	>98
2	4-methylbenzyl alcohol	>98	98	>98
3	1-octanol	>98	95	>97
4	1-decanol	>98	98	>96
5	Cyclohexanol[d]	>98	92	>98

[a] Alcohol (1.0 mmol) in CH_2Cl_2 (2 ml), KBr (0.2 mmol), TEMPO **62** (1.0 mol %), NaOCl (0.8 ml, 1.3 mmol), $NaHCO_3$ (40 mg, 50 mgmL^{-1} bleach), 0 °C. Reaction time = 15 min.
[b] Determined by ^{1}H- and ^{13}C-NMR.
[c] Isolated yields.
[d] Reaction time = 1 h.

Table 5.2. Oxidation of alcohols to carbonyl derivatives using TEMPO **63**[a]

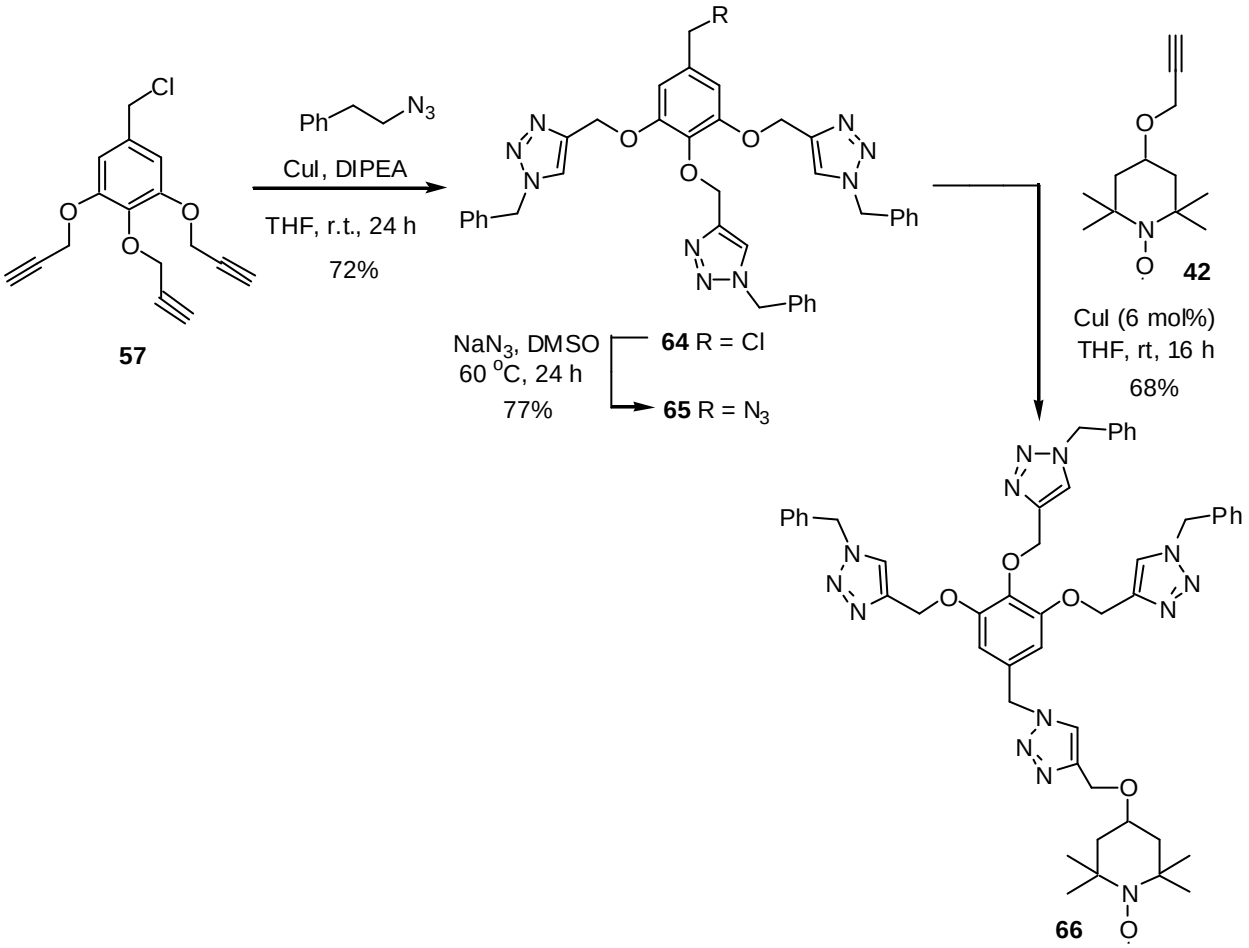
Entry	Alcohol	Conversion [%][b]	Yield [%][c]	Purity [%][b]
1	4-bromobenzyl alcohol	>98	95	>98
2	4-methylbenzyl alcohol	>98	98	>98
3	1-octanol	>98	96	>96
4	1-decanol	>98	92	>95
5	cyclohexanol[d]	>98	91	>98

[a] Alcohol (1.0 mmol) in CH_2Cl_2 (2 ml), KBr (0.2 mmol), TEMPO **63** (1.0 mol %), NaOCl (0.8 ml, 1.3 mmol), $NaHCO_3$ (40 mg, 50 mgmL^{-1} bleach), 0 °C. Reaction time = 15 min.
[b] Determined by ^{1}H- and ^{13}C-NMR.
[c] Isolated yields.
[d] Reaction time = 1 h.

The fluorous catalysts **62** and **63** behaved quite similarly in the presence of bleach, affording fast and selective oxidation of primary, secondary and benzylic alcohols to their corresponding carbonyl derivatives. All reactions were carried out at 0 °C in the presence of 1 mol % of catalyst and 1.3 mol% of terminal oxidant with respect to the substrate. Under these conditions, most alcohols were quantitatively oxidized within 15 min, excepting the more challenging cyclohexanol, which was smoothly oxidized within 1 h. In all cases, the purity of the isolated carbonyl derivatives was >95%.

Despite the fact that catalyst **63** is almost insoluble in dichloromethane at 0-5 °C, similar activity (TON and TOF) and selectivity compared to the homogeneous TEMPOs **53** and **66**

(Scheme 5.3) were observed when 1.0 mol%, respectively 0.2 mol% of catalyst were used in the oxidation of 4-methylbenzylic alcohol (Table 5.3).



Scheme 5.3. The synthesis of TEMPO **66**

It is noteworthy that the catalyst **63** is more active than the heterogeneous Merrifield-supported TEMPO **44**[6]: when 0.2 mol% of catalysts **63** and **44** were used in the oxidation of 25 mmol of 4-methylbenzylic alcohol, total conversion was observed after 40 min in the case of perfluorinated TEMPO **63** and only 60 % in the case of Merrifield-supported TEMPO **44**.

Moreover, **63** was showed higher TONs and TOFs than the heterogeneous polymer-supported TEMPOs **67**[7] and **68**.[8] Thus, the FibreCat-supported TEMPO **67** had a TON of 60 and a TOF of 360 h^{-1} in the oxidation of benzyl alcohol, when 1.67 mol% were used after 10 min, while TEMPO **63** (0.2 mol% catalyst with respect to the substrate) presented a eight times higher TON (500) and a double TOF (750 h^{-1}) within 40 min. **63** was also superior to the silica-supported TEMPO **68**, the latter catalyst showed lower TON (174) and TOF (174 h^{-1}) in the oxidation of benzyl alcohol after 60 min.

Table 5.3. Activity comparison of TEMPO catalysts **44**, **53**, **63, 66-68** in the Anelli oxidation of alcohols[a]

Catalyst	Catalyst loading	Alcohol	Reaction time [min]	Conversion [%][b]	Yield [%][c]	Purity [%][b]	TON	TOF [h^{-1}]
63	1.0 mol%	4-methylbenzyl alcohol	15	>98	98	>98	100	400
63	0.2 mol%[d]	4-methylbenzyl alcohol	40	>98	97	>98	500	750
44	2.5 mol%	4-methylbenzyl alcohol	15	73	68	>98	29	117
44	2.5 mol%	4-methylbenzyl alcohol	30	>98	98	>98	40	80
44	0.2 mol%	4-methylbenzyl alcohol	40	60	58	>98	300	450
53	1.0 mol%	4-methylbenzyl alcohol	15	>98	99	>98	100	400
53	0.2 mol%	4-methylbenzyl alcohol	40	>98	98	>98	500	750
66	1.0 mol%	4-methylbenzyl alcohol	15	>98	98	>98	100	400
66	0.2 mol%	4-methylbenzyl alcohol	40	>98	96	>98	500	750
67[7]	1.67 mol%	benzyl alcohol[e]	10	99[f]	n.a.	99[f]	60	360
68[8]	0.575 mol%	benzyl alcohol[g]	60	100[f]	92[f] 75	n.a.	174	174

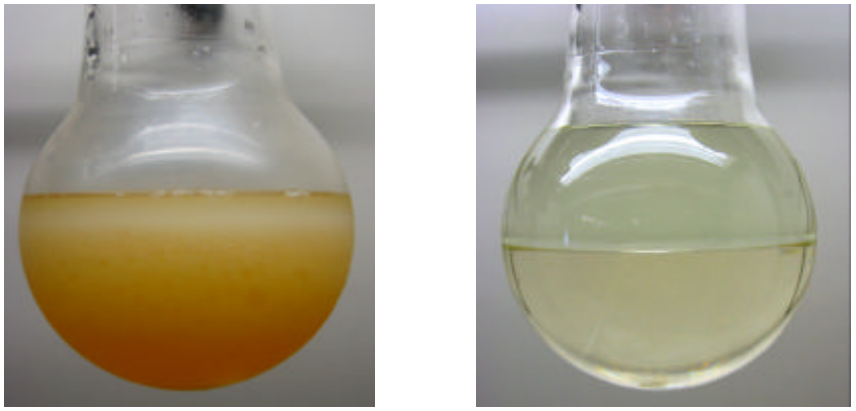
[a] Alcohol (25 mmol, 1.0 equiv.) in CH_2Cl_2, KBr (0.1 equiv.), TEMPO catalyst, NaOCl (1.3 equiv.), $NaHCO_3$ (50 $mgmL^{-1}$ bleach), 0 °C.
[b] Determined by ^1H- and ^{13}C-NMR.
[c] Isolated yields.
[d] 72 mg out of 100 mg recovered by filtration.
[e] 24 mmol.
[f] Determined by GC analysis.
[g] 4 mmol.

FibreCat-supported TEMPO **67**

Silica-supported TEMPO **68**

Figure 5.4. Heterogeneous polymer-supported TEMPOs **67**, **68**[7,8]

The enhancement in activity of the heterogeneous TEMPO **63** is intrinsically related to the formation of micelles at the boundaries of a two-phase system (CH_2Cl_2/aqueous bleach) (Figure 5.5). By contrast, the homogeneous TEMPO catalyst **66**, which has benzyl ponytails, does not form micelles in the reaction mixture.



a) Catalyst **63** in CH_2Cl_2/H_2O system. **Note the white micelles**

b) Catalyst **66** in CH_2Cl_2/H_2O system. **Note the phase-separation. No micelles were formed**

Figure 5.5.

It is known that amphiphilic compounds (molecules consisting of a hydrophilic head group and a hydrophobic tail) can increase the reaction rate by concentrating the reactants inside a micelle and cause also selective effects.[9] Micelles are especially simple spherical supramolecules, which are formed by amphiphiles in water or media similar to water. A micellar system appears to be homogeneous since these aggregates are of colloidal size; however, in reality the absorbed reactants are in a micro heterogeneous two-phase system. For organocatalysis, emulsions may be a "greener" alternative to perform organic reactions in water or aqueous organic solvents.[10]

The TEMPO catalyst **63** behaves in the reaction medium like a surfactant, the oxoammonium cation is the hydrophilic head group and the perfluorinated alkyl chains constitute the hydrophobic tail, reducing the surface tension of the water (Figure 5.6). Thus, the heterogeneous TEMPO catalyst **63** can accelerate the oxidation reaction due to its property to form emulsion, property that lacks in the case of the heterogeneous polystyrene-supported TEMPO **44**.

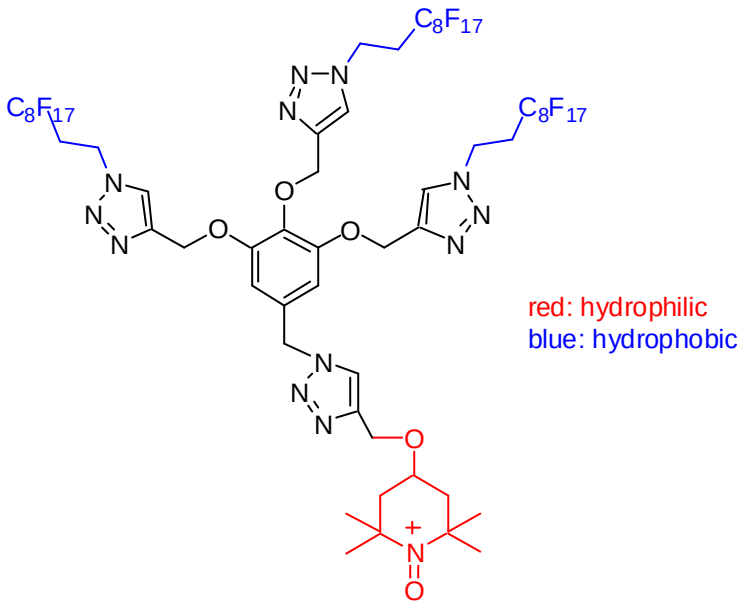


Figure 5.6.

5.6 Recovery of TEMPOs 62 and 63

The catalyst **63** could be recovered by filtering the reaction mixture using a sintered glass funnel (P40, 16-40 µm pore size). The catalyst was washed with water and CH_2Cl_2, then dried *in vacuo* and re-used, without further purification, in four-subsequent oxidation cycles without any loss in activity and selectivity (Table 5.4).

Table 5.4. TEMPO **63** oxidation of 4-methylbenzyl alcohol. Recovery and recycling experiment[a]

Run	Conversion [%][b]	Yield [%][c]	Purity [%][b]	Recovery of catalyst **59** (mmol)	Recovery of catalyst **59** (mg)
1	>98	98	>98	0.024	49
2	>98	99	>98	0.023	47
3	>98	97	>98	0.020	40
4	>98	92	>98	0.017	35

[a] Alcohol (2.5 mmol) in CH_2Cl_2 (5 ml), KBr (0.6 mmol), TEMPO **63** (1.0 mol %, 50 mg), NaOCl (2.0 ml, 1.3 mmol), $NaHCO_3$ (100 mg, 50 mg·mL^{-1} bleach), 0 °C. Reaction time = 15 min.
[b] Determined by ^{1}H- and ^{13}C-NMR.
[c] Isolated yields.

The effectiveness of the recycling is very high, almost 70% of the initial catalyst amount could be recovered after the fourth cycle emphasizing the chemical stability of the catalyst **63** and its potential scale-up for an industrial application.

In contrast, the catalyst **62** could not be recovered by filtration using the sintered glass funnel P40 (16-40 µm pore size). It seems that **62**, with only two perfluorinated ponytails, has a smaller particles size than the TEMPO **63** and thus, the filtration is not effective. However, **62** could be recovered taking advantage of its high polarity owing to the three triazole rings. Thus, the crude reaction mixture was placed on the top of a short bed of silica (5 g) and eluted with dichloromethane in order to obtain 4-methylbenzaldehyde. The silica was washed with 1,2,3-trifluoroethanol to recover the catalyst, which was re-used in four cycles without further purification (Table 5.5).

Table 5.5. TEMPO **62** oxidation of 4-methylbenzyl alcohol. Recovery and recycling experiment[a]

Run	Conversion [%][b]	Yield [%][c]	Purity [%][b]	Recovery of catalyst **62** (mmol)	Recovery of catalyst **62** (mg)
1	>98	98	>98	0.009	14
2	>98	97	>98	0.008	12
3	>98	92	>98	0.007	10
4	>98	95	>98	0.005	8

[a] Alcohol (1.0 mmol) in CH_2Cl_2 (2 ml), KBr (0.2 mmol), TEMPO **62** (1.0 mol %, 15 mg), NaOCl (0.8 ml, 1.3 mmol), $NaHCO_3$ (40 mg, 50 mg·mL^{-1} bleach), 0 °C. Reaction time = 15 min.
[b] Determined by ^{1}H- and ^{13}C-NMR.
[c] Isolated yields.

Although some catalyst was lost during the recovery process, high yields and excellent selectivity were obtained after the fourth cycle rendering **62** an efficient fluorinated tagged-TEMPO.

It is noteworthy that the homogeneous TEMPO catalyst **66** could not be recover neither by liquid- nor by solid-phase separation because of its high polarity and hydrophilicity.

In summary, we synthesized two novel perfluorinated building blocks with thermomorphic properties. Azides **60** and **61** were easily clicked with propargyloxy TEMPO radical and the obtained heterogeneous TEMPO catalysts were very effective in the oxidation of alcohols as

a consequence of their property to form microemulsion. Moreover, **63** could successfully be recovered by filtration and re-used in four catalytic cycles without any diminution of activity. The potential of the smart building blocks **60** and **61** is far away from being totally explored; we envisage attaching them to other homogeneous reagents in order to obtain efficient and easy to recycle surfactant-type catalytic systems. Current studies are performed in our laboratories and further results will be reported in due course.

5.7 LITERATURE

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• *Chapter 6*

Synthesis of Novel Perfluorinated Organogelators by "Click Chemistry"

6.1 Introduction

The study of molecules with gelation properties has recently received a special interest because of their diverse applications in cosmetics industry, drug delivery, biocatalysis and materials science.[1,2] There are two types of gelators, organo- and water (hydro)-gelators, depending on the solvent trapped inside the gel network.

Organogels can be defined as thermally reversible viscoelastic liquidlike or solidlike materials comprised of an organic liquid and low concentrations (typically <5 wt%) of relatively low-molecular weight gelators (LMWG).[1a] An organogel is formed by heating a mixture of a gelator and solvent until total dissolution of the solvent, then upon cooling, the solution thickens to form a gel. There exist two types of organogels, depending upon the nature of their networks, so called "strong" gels, with permanent solidlike networks, and "weak" gels in which the networks lose their elasticity over a period of time.

There are also gels formed by polymeric gelators, but their three-dimensional structures arise from the entanglement and interaction of covalently bonded chains, whereas in gels formed by LMWGs, the networks are held together by multiple noncovalent interactions, such as dipole-dipole, van der Waals and hydrogen bonding.[3]

6.2 Aim of this work

Recently, Shinkai[4] and Langford[2a] have introduced a new class of organogelators based on crown-ethers (Figure 6.1). The crown-appended cholesterol-based gelators **69** and their derivatives were able to gel a broad number of organic solvents at concentration of less than 1 wt%, whereas **70** and **71** were more selective and gelated only in chlorinated solvents (chloroform, 1,2-dichloroethane and 2-chloroethanol) at a concentration of 3 wt%.

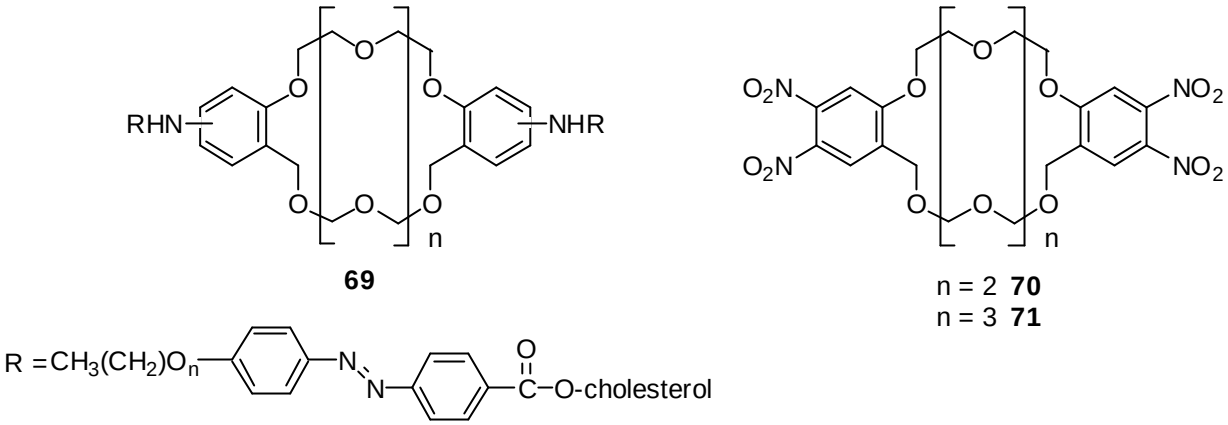
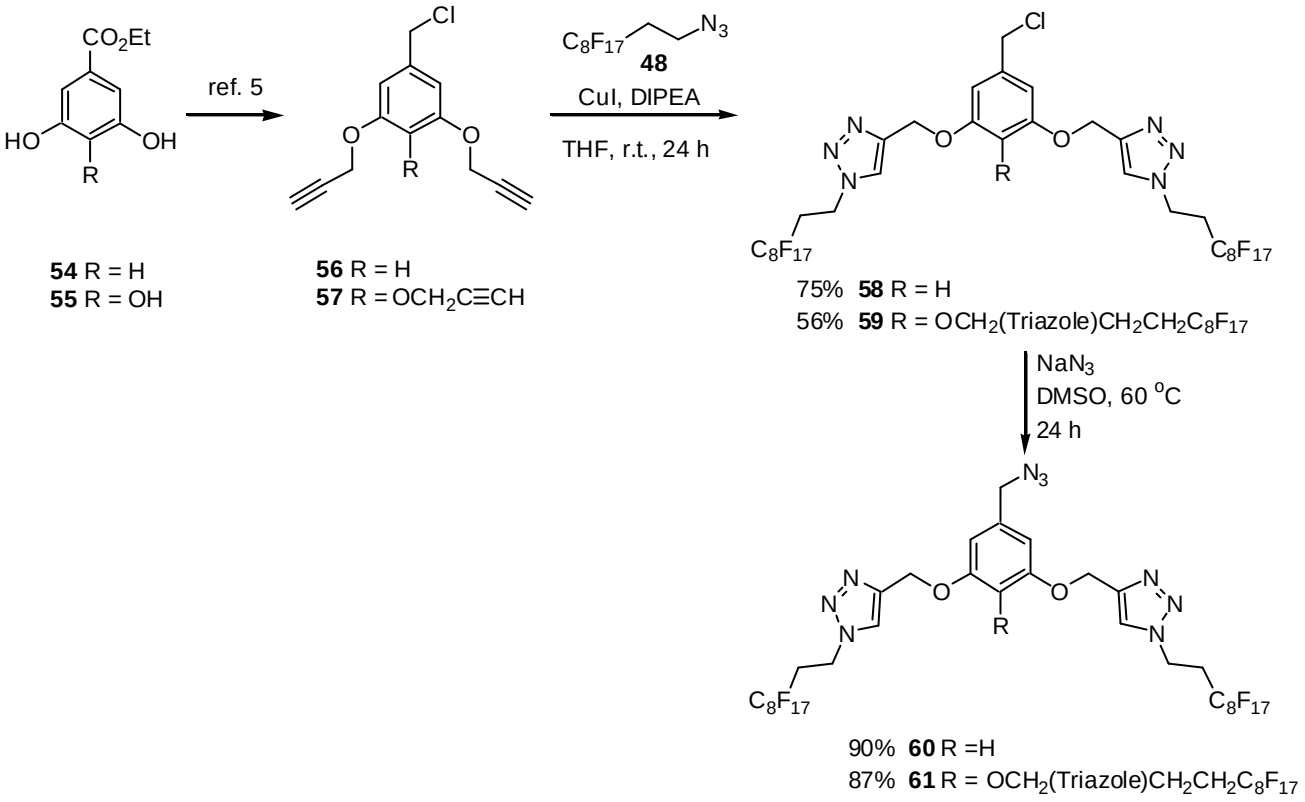


Figure 6.1. Novel organogelators[2a,4]

During our synthesis of the new thermomorphic perfluorinated azides **60**, **61** (see Chapter 5), we observed that these molecules are able to form organogels with most of the common organic solvents. Moreover, their chlorinated precursors, **58** and **59**, formed gels with some organic solvents. We decided to study more deeply these observations and to try to understand their behaviour. In this chapter, we will present our results and conclusions of this research.

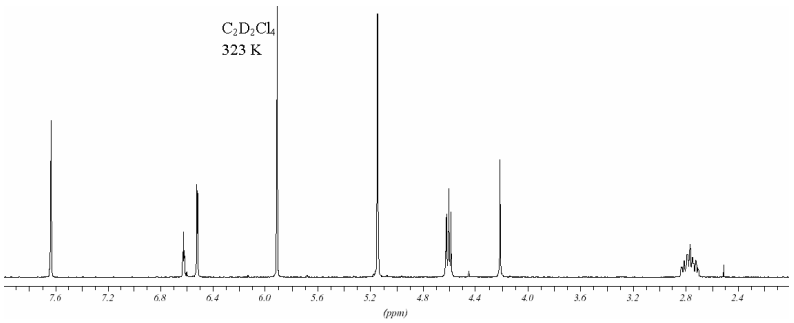
6.3 Synthesis of organogelators

The synthesis of organogelators **58-61** started from the commercially available polyhydroxybenzoic esters **54** and **55**. Using the three-step procedure developed by Sharpless, we obtained the chloromethyl-propynyloxy-benzene derivatives **56** and **57**.[5] Then, we attached the perfluorinated alkyl chains taking advantage of the CuACC approach. The coupling reaction was performed using an excess of DIPEA, 6 mol% Cu(I) iodide in THF strirring the reaction mixture at room temperature for 24 h. The azides **60** and **61** were obtained in high yields by nucleophilic substitution of the corresponding benzyl chlorides **58-59** using an excces of sodium azide in DMSO at 60 ^{o}C for 24 h (Scheme 6.1).



Scheme 6.1. The synthesis of organogelators **58**-**61**

The perfluorinated clicked-chlorides **58**, **59**, as well as azides **60**, **61**, are not soluble in perfluorinated solvents (perfluoro-1,3-dimethylcyclohexane or perfluoromethylcyclohexane) and only slightly soluble in most organic solvents at rt. In order to record satisfactory ^{1}H- and ^{13}C-NMR we had to perform the spectroscopic experiments in deuterated tetrachloroethane at high temperatures. The azide **60** showed at 300 K only broad signals which became sharp when recording the spectra at 323 K (Figure 6.2).



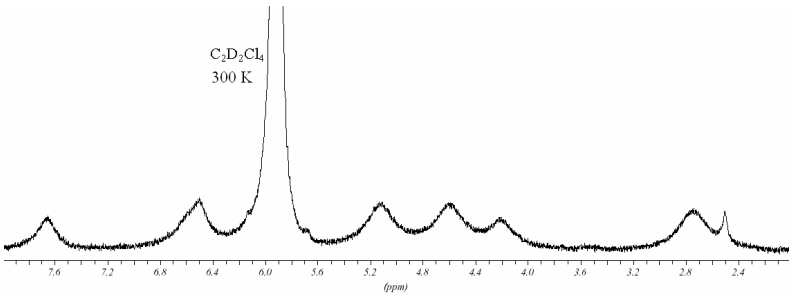
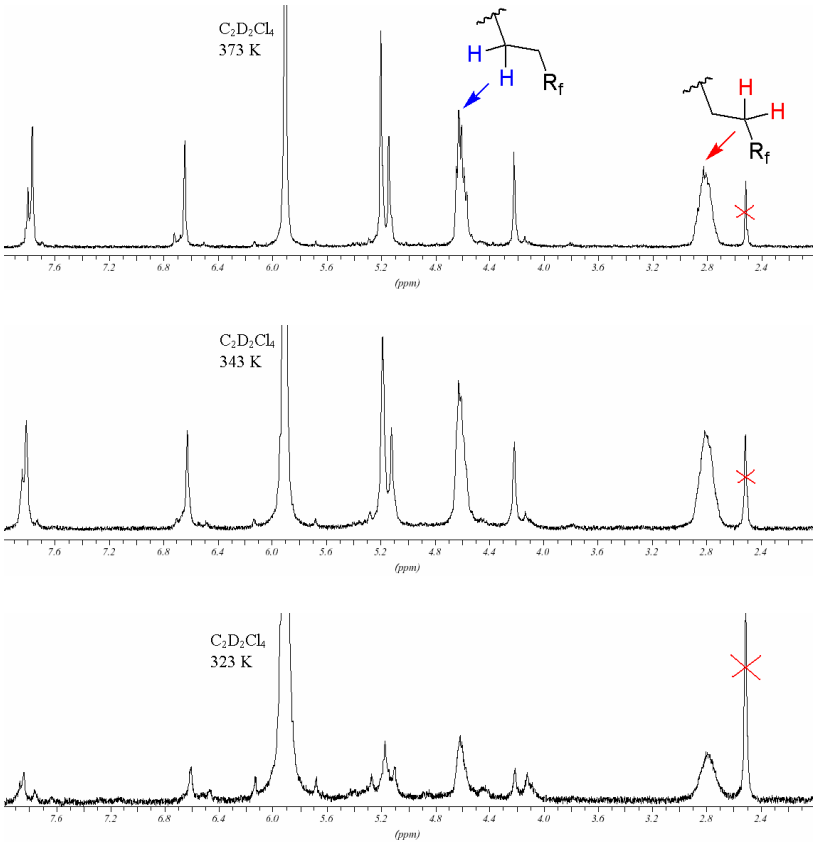


Figure 6.2. ^{1}H NMR spectra of **60** (20 mg in 0.8 ml $C_2D_2Cl_4$) at 300 K and 323 K

The azide **61** needed a higher temperature in order to give sharp signals. At 323 K the peaks are still broad, at 343 K the peaks were resoluted and at 373 K the coupling constants between the methylene protons from R_f-CH_2-CH_2 groups could be detected (Figure 6.3). The chlorides **58**, **59** showed a similar behaviour with their corresponding azides.



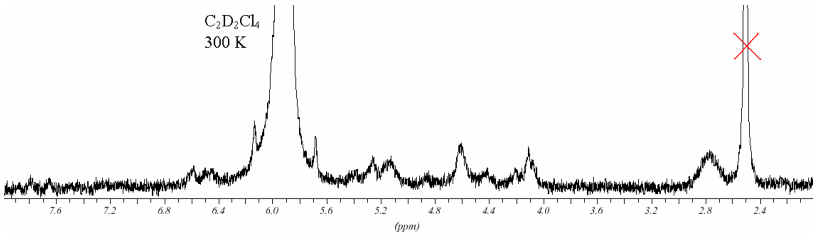


Figure 6.3. ^{1}H NMR spectra of **61** (20 mg in 0.8 ml $C_2D_2Cl_4$) at 300 K, 323 K, 343 K and 373 K

Then, we tested the solubility of these compounds in several frequently used organic solvents at ≥70 °C. We observed that by cooling down, compounds **58-61** formed stable gels with 1 mol% loading at 0 °C or room temperature in most of the polar organic solvents (Table 6.1).

Table 6.1. Gelation Ability of Building Blocks **58-61** at 1.0 w/v %[a]

Solvent	**58**	**59**	**60**	**61**	**61**[c]
ethyl acetate	L	G	G[b]	G	G[b]
chloroform	PS	PS	G	PS	PS
dichloromethane	G	PS	PG	PS	PS
acetone	L	P	L	PG	G[b]
toluene	G	P	G	P	P
acetonitrile	G	P	G	PG	G[b]
methanol	P	P	P	P	P
ethanol	PG	P	PG	P	P
tetrahydrofuran	PG	PG	L	G	G[b]
dimethylsulfoxide[b]	PS	P	G	PS	PS
dimethylformamide	G	L	G	L	L

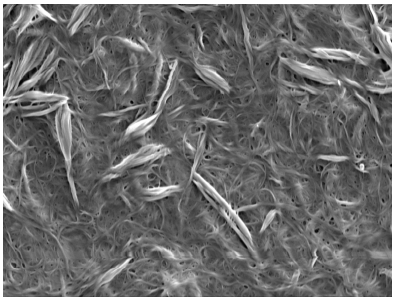
[a] Gelation was assigned after heating the organogelators in the respective solvents and cooling at 0 °C. G = gel, PG = partial gelation, P = precipitate, I = insoluble, PS = partially soluble. L = liquid.
[b] Cooling at rt.
[c] 2.0 m/w%.

At 0 °C, azide **60** formed stable gels (more than one day) with most of the tested organic solvents. It is noteworthy that **60** was able to form organogels with the very polar solvents like DMSO and DMF, but failed to totally gelate in THF, MeOH, EtOH or acetone. Moreover, **60** formed stable gel in toluene. On the other hand, the azide **61** proved to be more

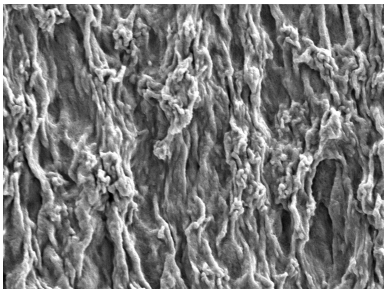
selective, only aggregating in EtOAc and THF, at 1.0 w/v % and also in acetone and CH_3CN at 2 w/v %. Again, the chlorides **58**, **59** showed quite similar behaviour with the corresponding azides. This striking discrepancy in gelation property between the 2- and 3-perfluorinated ponytails compounds could be best explained by a difference in the nature of interaction with the solvent.

Indeed, when analyzing by scanning electron micrograph (SEM) the dried gel formed by azides **60, 61** in EtOAc, we observed a fibrous ordered-network presenting some cavities, in the case of compound **61** and a more dense and irregular fibrous-network in the case of azide **60** (Figure 6.4).[6] This difference in network structures can explain the distinct behaviour of the two organogelators.

a) Gel formed by azide **60** in EtOAc (1 w/t%)



b) SEM image of dried gel from **60** in EtOAc (1 w/t%)



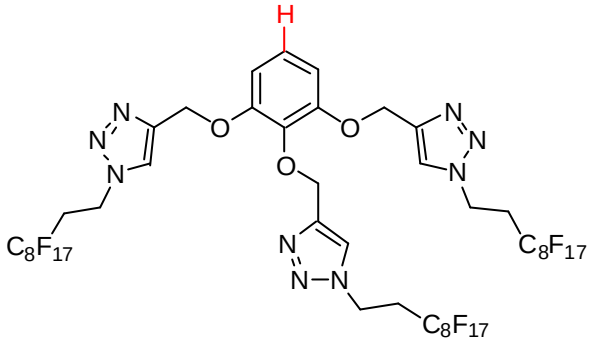
c) SEM image of dried gel from **61** in EtOAc (2 w/t%)

Figure 6.4.

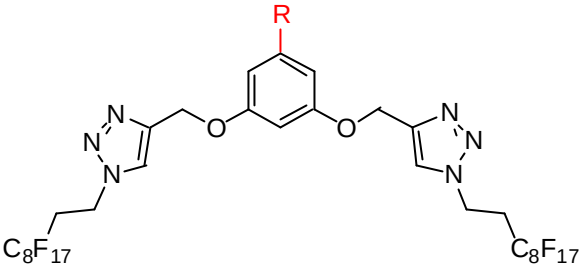
To our knowledge, this is the first example of organogelators having this structure, but is not surprising since self-assembled monolayers (SAMs) were obtained from polymeric perfluorinated-benzyl derivatives.[7]

The organogelators **58-61** are more attractive than their polymeric counterparts due to the thermoreversibility owing to the noncovalent nature of the gels. We think that the unique combination of both perfluorinated ponytails and the triazole rings is necessary to form a gel; the compounds **64**, **65** (see Chapter 5), which lack the perfluorinated chains do not present gelation properties. Moreover, Finn and co-workers reported recently the stabilization of organogels due to the formation of triazole rings by CuAAC.[8]

In order to study the influence of the head-group upon gelation we prepared some structural analogues of azides **60**, **61** (Figure 6.5) and tested their gelation power.



72



73 R = CO_2Et
74 R = CH_2OH

Figure 6.5.

We observed that only the benzylic alcohol derivative **74** preserved the gelation property of its structural analogues, indicating that the flexible methylene group plays an important role in forming the three-dimensional network with solvents (Table 6.2).

Table 6.2. Gelation Ability of Building Blocks **72**-**74** at 1.0 w/v %[a]

Solvent	**72**	**73**	**74**
ethyl acetate	P	P	PG
chloroform	PS	PS	P
dichloromethane	P	PS	P
acetone	PG	P	G
toluene	P	P	P
acetonitrile	P	P	G
methanol	P	I	G
ethanol	P	PS	G[c]
tetrahydrofuran	PS	PS	G[c]
dimethylsulfoxide[b]	PS	PS	P
dimethylformamide	G[b]	PS	PG

[a] Gelation was assigned after heating the organogelators in the respective solvents and cooling at 0 °C. G = gel, PG = partial gelation, P = precipitate, I = insoluble, PS = partially soluble. L = liquid.
[b] Cooling at rt.
[c] Gel for short time (less than 1 day).

Strange enough is the ability of **72** to form stable aggregates in DMF at rt, although it is the least polar compound among all the tested perfluorinated organogelators, and, moreover, **72** lacks the methylene group. We were unable to find a plausible explanation for this unexpected result, probably there are other factors that influence the ability of this molecule to form gels.

Based on the structure-activity relationship study, we depicted in Figure 6.6, the necessary elements for a compound of this class to form gels. We believe that there is a strong connection between the head-group, triazole rings and perfluorinated alkyl chains and the gelation property of a molecule.

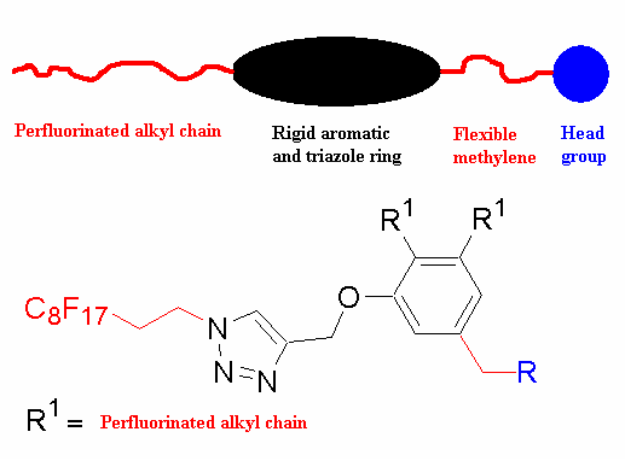


Figure 6.6. General structure of an organogelator

In conclusion, we synthesized a novel class of modular perfluorinated organogelators using the copper(I)-catalyzed azide-alkyne cycloaddition as ligation method. These compounds presented unique gelation properties with different organic solvents. Moreover, we observed a strong interaction between the structure and gelation power of these molecules.

As possible application of these compounds we envisage to use them as intelligent trapping-releasers molecules for different solvents, in order to create efficient recycling systems.[9] They can be also used as thermosensors in packaging applications. Current studies are performed in our laboratories in order to better understand the physical properties of this novel class of organogelators and to find more practical applications.

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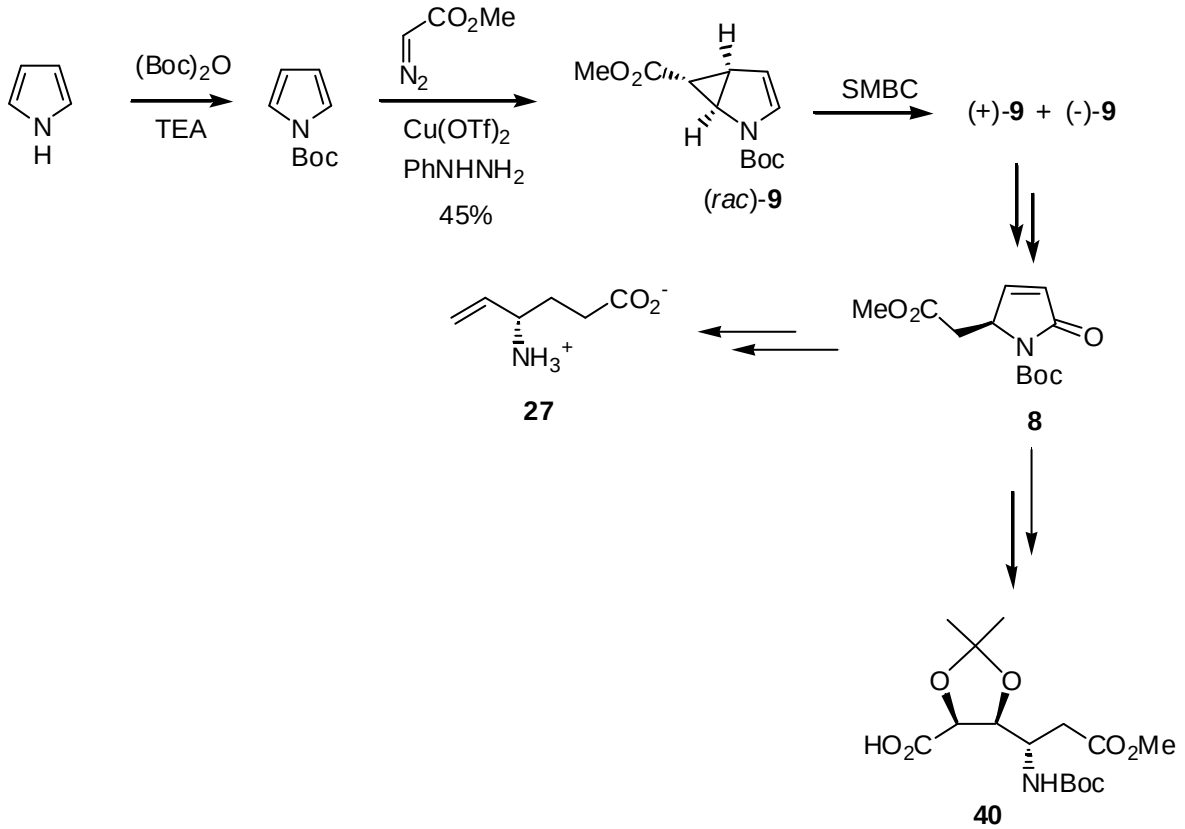
• *Chapter 7*

Summary

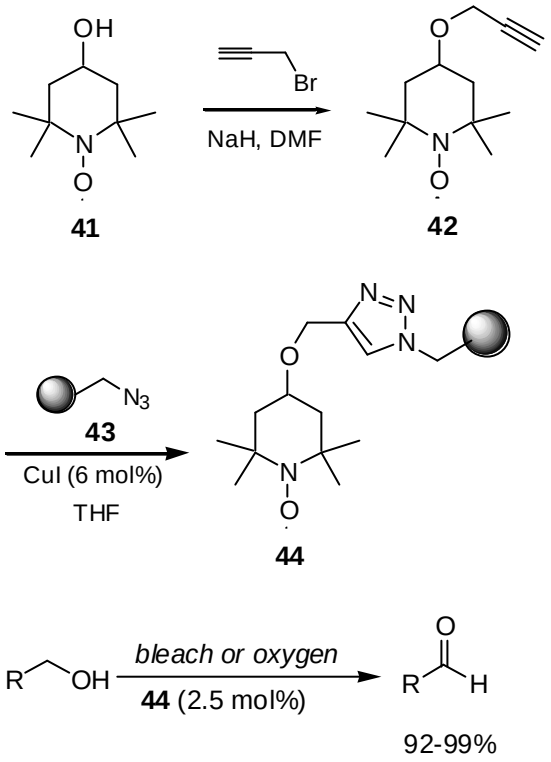
During this Ph.D. thesis, the following results were obtained:

1. We developed an efficient access to the novel 3,4-didehydropyrohomoglutamate **8** in either enantiomeric form starting from **9**, which in turn can be readily synthesized from pyrrole on a multigram scale. The racemic resolution of (*rac*)-**9** was done by simulated moving bed chromatography (SMBC) with very high productivity (separation of 1958 g (*rac*)-**9**/kg stationary phase and day).

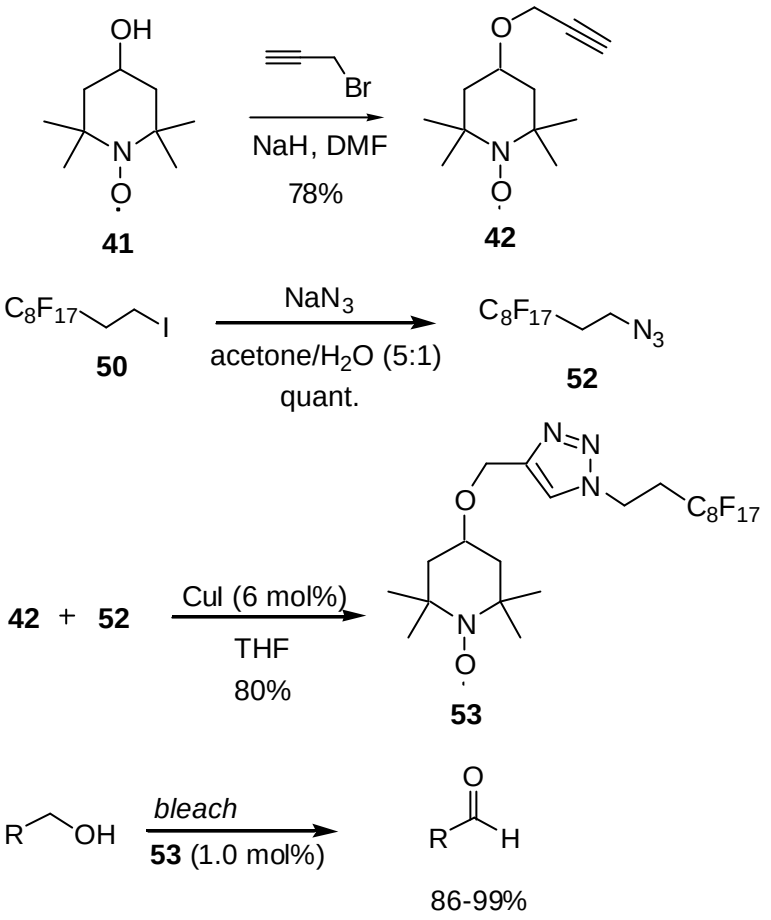
   We also presented the scope and limitation of **8** for the synthesis of functionalized pyrrolidones as well as a novel synthesis of (*S*)-Vigabatrin (**27**) (an antiepileptic drug) and a new hydroxyamino acid fragment (**40**) of AI-77-B (an anti-ulcer drug).



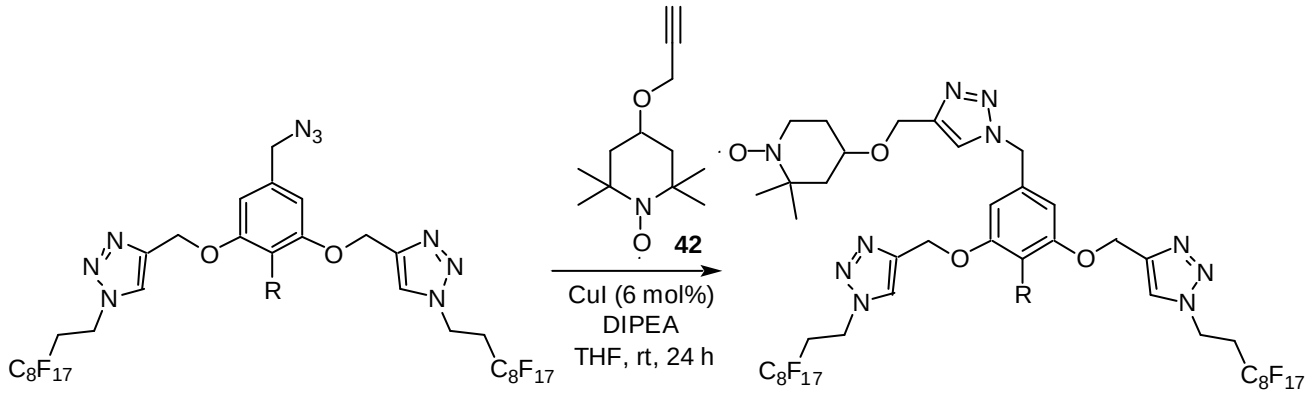
2. We developed an extremely simple and practical protocol for grafting TEMPO onto polystyrene resin from readily available and inexpensive starting materials using the copper(I)-catalyzed alkyne-azide cycloaddition as the ligation method. The resulting PS-CLICK-TEMPO **44** proved to be highly effective in the chemoselective oxidation of alcohols with both bleach and molecular oxygen under mild conditions. Moreover, it can be easily recovered and recycled without any loss of catalytic activity.



3. We synthesized a novel “light” fluorous-tagged TEMPO catalyst from commercially readily available materials in high yield using the simplicity of the copper-catalyzed azide-alkyne cycloaddition. The new perfluorinated F_{17}-CLICK-TEMPO **53** proved to be very stable, highly effective in the chemoselective oxidation of alcohols with bleach, and after recovery it was re-used in four consecutive cycles without loss of catalytic activity.

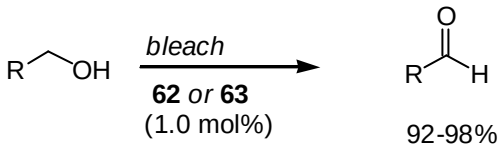


4. We synthesized two novel perfluorinated building blocks with thermomorphic properties. Azides **60** and **61** were easily clicked with propargyloxy TEMPO radical and the obtained heterogeneous TEMPO catalysts were very effective in the oxidation of alcohols as a consequence of their property to form microemulsion. Moreover, **63** could successfully be recovered by filtration and re-used in four catalytic cycles without any diminution of activity.

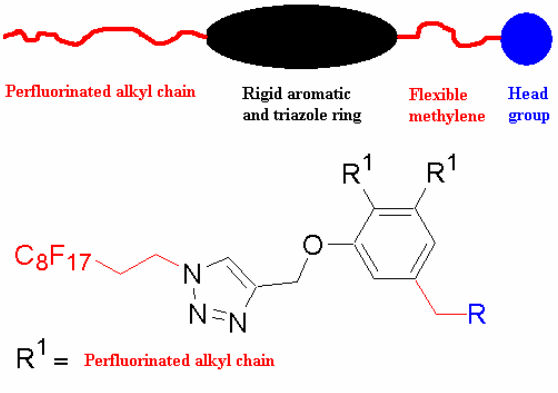


60 R = H
61 R = $OCH_2TrCH_2CH_2C_8F_{17}$

62 R = H
63 R = $OCH_2TrCH_2CH_2C_8F_{17}$



5. We prepared a novel class of modular perfluorinated organogelators using the copper(I)-catalyzed azide-alkyne cycloaddition as ligation method. These compounds presented unique gelation properties with different organic solvents.



• *Chapter 8*

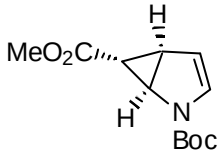
Experimental Section

8.1 General

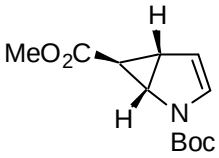
^{1}H NMR spectra were taken on BRUKER Avance 300 (300 MHz) and Buker Avance 400 (400 MHz) in the indicated solvent and are reported as follows: chemical shifts [multiplicity (s = singlet, d = doublet, dd = doublet of doublets, ddd = doublets of doublets of doublet, dt = doublet of triplets, t = triplet, q = quartet, qt = quintet, dq = doublet of quintets, m = multiplet, br = broadened), coupling constants in hertz, integration]. ^{13}C NMR spectra were taken on BRUKER ARX 300 (75Mhz) Buker Avance 400 (100 MHz) in the indicated solvent and are reported as follows: chemical shift (multiplicity detected by DEPT). IR-spectra were recorded with an ATI Mattson Genesis Series FT-IR. Elemental analysis (Heraeus elementar vario EL III) and mass spectrometry (Finnigan ThermoQuest TSQ 7000) were done by the Central Analytical Laboratory (University of Regensburg). HPLC analyses were performed on a “Daicel Chiracel OD-H” column (250 mm, 5 µm, flow: 0.5 ml/min, 25 °C) with 20% 2-propanol/hexane and a UV detector at 254 nm. Thin layer chromatography (TLC) was performed on alumina plates coated with silicagel (Merck silica gel 60 F 254, layer thickness 0.2 mm). Column chromatography was performed on silica gel Geduran SI 60 (0.063-0.200 mm) purchased from Merck and flash chromatography on flash-silica gel 60 (0.040-0.063 mm) purchased from Merck. Solvents were purified according to standard laboratory methods. THF, diethyl ether and benzene were distilled over sodium/benzophenone before use. Dichloromethane and acetonitrile were distilled over calcium hydride. Methanol was refluxed 2h over magnesium, distilled and stored under nitrogen over 4Å molecular sieves. All solvents were distilled before use. All reactions with oxygen or moisture sensitive reactants were performed under nitrogen atmosphere. All commercially available compounds were used as received.

8.2 Experimental details

(1*R*,5*R*,6*R*)-2-*tert*-butyl 6-methyl 2-azabicyclo[3.1.0]hex-3-ene-2,6-dicarboxylate (+)-9, (1*S*,5*S*,6*S*)-2-*tert*-butyl 6-methyl 2-azabicyclo[3.1.0]hex-3-ene-2,6-dicarboxylate (–)-9



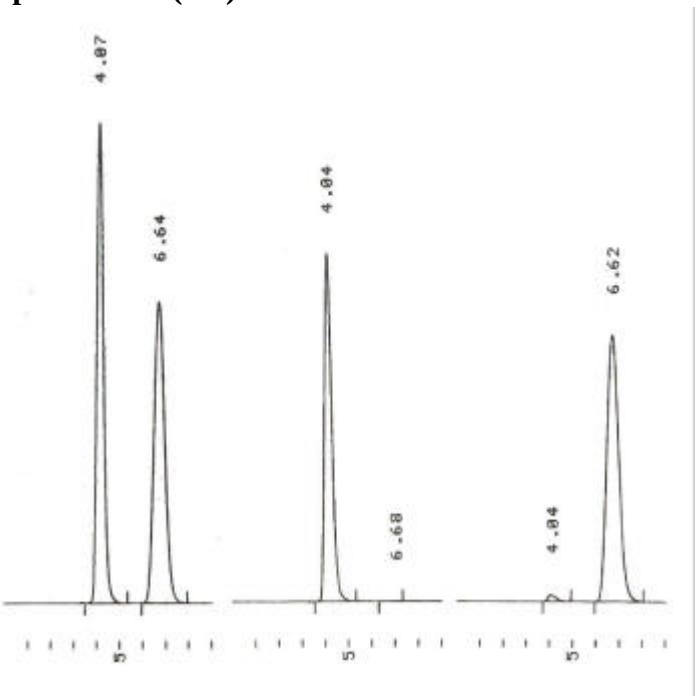
(+)- **9**



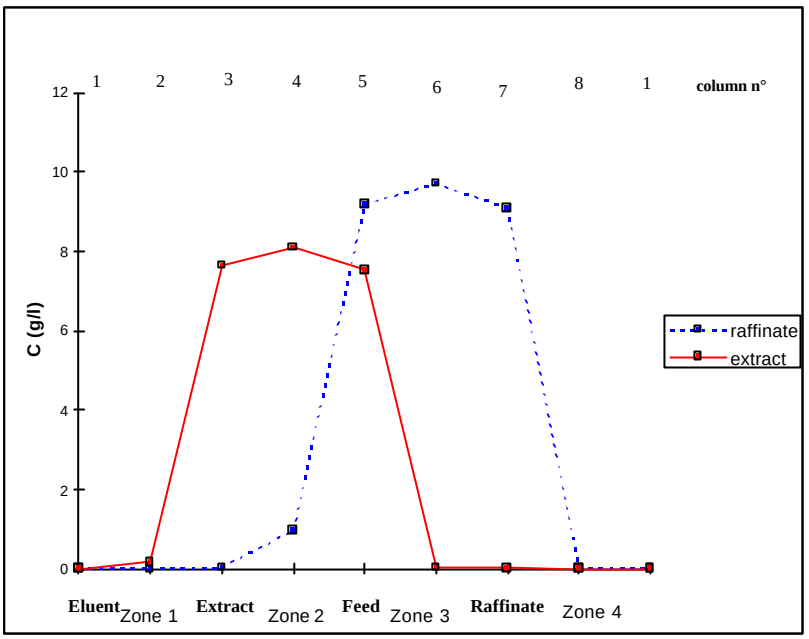
(-)- **9**

(*rac*)-**9** was separated into its constituent enantiomers using a preparative Chiral Simulated Moving Bed Chromatographic unit (Licosep Lab) composed of a set of eight columns (2.5 cm x 10 cm) interconnected in series and packed with Chiralcel OC, 20 µm. The mobile phase was ethanol at room temperature. Feed concentration = 20.0 g/L, feed rate = 16.0 ml/min. (+)-**9**: t_R 4.07 min (analytical HPLC, Chiralcel OC, 20 µm); 73g (46%; theoretical maximum 50%) 99.8% *ee*; $[a]_D^{20}$ = 260.9 (c = 1, CH_2Cl_2). (–)-**9**: t_R 6.64 min (analytical HPLC, Chiralcel OC, 20 µm); 75g (47%; theoretical maximum 50%) 98.3% *ee*; $[a]_D^{20}$ = -254.2 (c = 1, CH_2Cl_2).

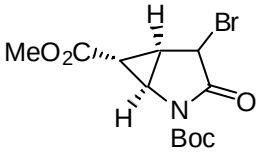
HPLC data SMB separation of (*rac*)-9



(*rac*)-**9** Raffinat: (+)-**9** (99.8% *ee*) Extract: (–)-**9** (98.3% *ee*)



(1*R*, 5*R*, 6*R*)-4-Bromo-3-oxo-2-aza-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid 2-tert-butyl ester 6-methyl ester (19)

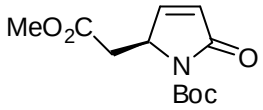


19

To a solution of olefin (+)-**9** (2.50 g, 10.46 mmol), in acetonitrile (10 mL) and water (20 mL) was added NBS (1.86 g, 10.46 mmol) in small portions at 5 ^{o}C. After stirring 5 min at the same temperature, the reaction mixture was extracted with CH_2Cl_2 (3x25 mL), and the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* at rt to afford 2.94 g of bromohydrine (84% crude yield). The bromohydrine was unstable at rt and purification by column chromatography failed. The crude bromohydrine (2.94 g, 8.78 mmol) was dissolved in acetone (40 mL) and Jones reagent was added (17.5 mmol). The reaction mixture was stirred at rt under N_2 for 2 h. The reaction was quenched by addition of saturated solution of $NaHCO_3$ (50 mL). CH_2Cl_2 (50 mL) was added to the mixture and the organic phase was separated. The organic layer was washed with brine (2x25 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude ketone was purified by flash column chromatography (silica gel, 20% EtOAc in hexanes) to afford **19** as a yellowish solid, mp 103-105 ^{o}C (2.16 g, 62% from olefin (+)-**9**). R_f= 0.6 (silica gel, hexanes/ethyl acetate, 3:2). $[a]_D^{20}$= -122 (c = 0.20, CH_2Cl_2). ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.54 (s, 9H), 1.76 (dd, *J* = 1.6, 4.1 Hz, 1H), 2.54 (dd, *J* = 4.1, 7.2 Hz, 1H), 3.71 (s, 3H), 4.17 (dt, *J* = 1.2, 7.9 Hz, 1H), 4.45 (d, *J* = 0.9 Hz, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 23.5, 27.9, 31.1, 41.2, 41.8, 52.5, 84.9, 149.2, 167.8, 168.6.

IR (KBr): 3074, 2982, 1796, 1443, 1410, 1368, 1302, 1150, 1041, 1012, 952, 914, 889, 839, 773 cm^{-1}. LRMS (CI, M+NH_4^+): 351/353. Anal. calcd for $C_{12}H_{16}BrNO_5$: C, 43.13; H, 4.83; N, 4.19. Found: C, 43.16; H, 4.93; N, 4.14.

(2*R*)-2-Methoxycarbonylmethyl-5-oxo-2,5-dihydro-pyrrole-1-carboxylic acid tert-butyl ester (8)

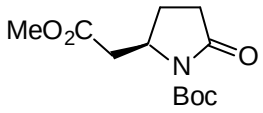


8

METHOD A: To a stirred solution of **19** (2.0 g, 6.0 mmol) in dry benzene (25 mL) at reflux tributyltin hydride (1.58 mL, 6.0 mmol) and AIBN (98 mg, 0.6 mmol) were added. The reaction mixture was stirred for 5 min, and then the solvent was evaporated. The crude mixture was dissolved in EtOAc (50 mL) and a saturated solution of KF (50 mL) was added. The mixture was stirred at rt for 18h. The white precipitate was removed by filtration and the organic phase was concentrated *in vacuo*. Flash column chromatography (silica gel, 30% EtOAc in hexanes) afforded **8** as a yellowish oil (1.44 g, 94% yield). $[a]_D^{20}$ = +176.4 (c = 0.81, CH_2Cl_2) with 91% *ee*: 20.67 min for minor (*S*) and 25.53 min for major (*R*). R_f= 0.26 (silica gel, hexanes/ethyl acetate, 3:2). ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.56 (s, 9H), 2.43 (dd, *J* = 10.0, 16.1 Hz, 1H), 3.33 (dd, *J* = 4.0, 16.1 Hz, 1H), 3.71 (s, 3H), 4.88 (ddd, *J* = 1.9, 3.8, 10.0 Hz, 1H), 6.12 (dd, *J* = 1.6, 6.1 Hz, 1H), 7.34 (dd, *J* = 2.0, 6.1 Hz, 1H).^{13}C-NMR (75 MHz, $CDCl_3$): δ = 28.1, 36.5, 52.1, 58.7, 83.6, 127.0, 149.3, 149.9, 168.6, 170.4. IR (*neat*): 3097, 2981, 1782, 1741, 1439, 1363, 1323, 1257, 1161, 1105, 1049, 988, 918, 820, 744 cm^{-1}. LRMS (CI, M+NH_4^+): 273. Anal. calcd for $C_{12}H_{17}NO_5$: C, 56.46; H, 6.71; N, 5.49. Found: C, 56.32; H, 6.61; N, 5.40.

METHOD B: To a solution of **19** (90 mg, 0.27 mmol) in dry THF (4 mL), Et_3B (1 M in THF) was added (0.54 mL, 0.54 mmol) under nitrogen, at 0 ^oC. Then dry air (10 mL) was introduced with a syringe. The reaction mixture was stirred for 30 min and allowed to warm up to rt. The reaction was quenched with a saturated solution of $Na_2S_2O_4$ (10 mL) and extracted with EtOAc (3x15 mL). The combined organic phases were concentrated *in vacuo*. Flash column chromatography (silica gel, 30% EtOAc in hexanes) afforded **8** (45 mg, 65% yield). $[a]_D^{20}$ = +137.5 (c = 0.25, CH_2Cl_2) with 71% *ee*.

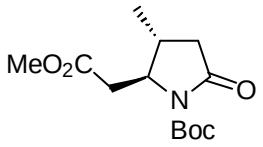
(2*R*)-2-Methoxycarbonylmethyl-5-oxo-pyrrolidine-1-carboxylic acid tert-butyl ester (20)



20

A solution of **8** (345 mg, 1.35 mmol) in methanol (3 mL) was cooled to 0 °C and treated with $NiCl_2 \cdot 6H_2O$ (239 mg, 1.01 mmol). The resulting mixture was stirred at the same temperature for 15 min before the addition of $NaBH_4$ (26 mg, 0.68 mmol). After 30 min, further portion of $NaBH_4$ (26 mg, 0.68 mmol) was added, and the reaction was allowed to stir for additional 10 min at rt. The reaction was quenched with a saturated solution of NH_4Cl (25 mL) and extracted with CH_2Cl_2 (3x25 mL). The combined extracts were dried ($MgSO_4$) and concentrated under vacuum. Flash column chromatography (silica gel, 30% EtOAc in hexanes) afforded **20** as a colourless oil (285 mg, 82% yield). R_f= 0.3 (silica gel, hexanes/ethyl acetate, 3:2). $[\alpha]_D^{20}$ = +57 (c = 0.63, CH_2Cl_2) with 82% *ee*: 21.93 min for major (*R*) and 30.0 min for minor (*S*). ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.53 (s, 9H), 1.81-1.93 (m, 1H), 2.17-2.30 (m, 1H), 2.40-2.66 (m, 3H), 2.90 (dd, *J* = 3.3, 15.5 Hz, 1H), 3.70 (s, 3H), 4.46-4.54 (m, 1H).^{13}C-NMR (75 MHz, $CDCl_3$): δ = 23.0, 28.0, 30.9, 38.0, 51.9, 54.6, 83.3, 149.3, 170.9, 173.8. IR (*neat*): 2980, 1786, 1739, 1438, 1364, 1310, 1256, 1196, 1154, 1020, 910, 847, 779 cm^{-1}. LRMS (CI, M+NH_4^+): 275. Anal. calcd for $C_{12}H_{19}NO_5$: C, 56.02; H, 7.44; N, 5.44. Found: C, 55.97; H, 7.74; N, 5.25.

(2*R*,3*S*)-2-Methoxycarbonylmethyl-3-methyl-5-oxo-pyrrolidine-1-carboxylic acid tert-butyl ester (21)

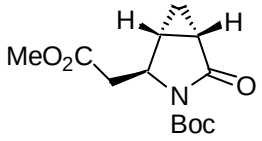


21

To a suspension of CuI (191 mg, 1.0 mmol) in dry THF (2 mL) was added at -20 °C 1.25 mL of a solution of MeLi (1.6 M in diethyl ether, 2.0 mmol). After 15 min, the reaction was cooled to -78 °C and a solution of **8** (51 mg, 0.2 mmol) and 0.5 mL of TMSCl (0.4 mmol) in THF (2 mL) was added. The mixture was stirred 1 h at the same temperature and then, allowed to warm to rt, quenched with a saturated solution of NH_4Cl (5 mL), diluted with ether (20 mL) and the organic layer was washed with brine and water. After drying ($MgSO_4$) and evaporation of solvent, **21** was obtained by column chromatography (silica gel, 20% EtOAc in hexanes) as a yellowish oil (38 mg, 70% yield). R_f= 0.3 (silica gel, hexanes/ethyl acetate, 3:2). $[\alpha]_D^{20}$ = + 38.3 (c = 0.1, CH_2Cl_2) with 86% *ee*: 38.28 min for major and 44.55 min for

minor. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.16 (d, *J* = 7.0 Hz, 3H), 1.53 (s, 9H), 2.10 (dd, *J* = 1.7, 17.6 Hz, 1H), 2.18 (m, 1H), 2.52 (dd, *J* = 9.8, 15.7 Hz, 1H), 2.78 (dd, *J* = 8.3, 17.7 Hz, 1H), 2.86 (dd, *J* = 3.3, 15.7 Hz, 1H), 3.70 (s, 3 H), 4.08 (ddd, *J* = 1.3, 3.2, 9.7 Hz, 1H).^{13}C-NMR (75 MHz, $CDCl_3$): δ = 20.7, 28.0, 30.37, 37.9, 38.9, 51.9, 61.7, 83.4, 150.0, 171.0, 173.3. IR (*neat*): 2972, 1786, 1739, 1439, 1366, 1309, 1256, 1154, 1020, 849, 777 cm^{-1}. LRMS (EI, M^+): 272. Anal. calcd for $C_{13}H_{21}NO_5$: C, 57.55; H, 7.80; N, 5.16. Found: C, 57.64; H, 7.93; N, 4.95.

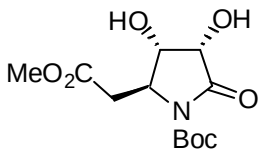
(1*S*,2*R*,3*S*)-2-Methoxycarbonylmethyl-4-oxo-3-aza-bicyclo[3.1.0]hexane-3-carboxylic acid tert-butyl ester (22)



22

To a solution of $Pd(OAc)_2$ (5 mg, 0.02 mmol) and **8** (51 mg, 0.02 mmol) in Et_2O (5 mL) was added slowly a solution of CH_2N_2 in EtO_2 (25 mL) at rt. The reaction mixture was stirred for 1 h and then filtered. The filtrate was concentrated *in vacuo* to give an oily residue. This was purified by column chromatography (silica gel, 30% EtOAc in hexanes) to give **22** as a yellowish oil (51 mg, 93% yield). R_f= 0.27 (silica gel, hexanes/ethyl acetate, 3:2). $[\alpha]_D^{20}$ = 60.3 (c = 0.31, CH_2Cl_2), with 82% *ee*: 22.84 min for major and 24.64 min for minor. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.77-0.84 (m, 1H), 1.17-1.25 (m, 1H), 1.50 (s, 9H), 1.83-1.89 (m, 1H), 1.96-2.02 (m, 1H), 2.60 (dd, *J* = 9.2, 15.5 Hz, 1H), 3.00 (dd, *J* = 3.2, 15.5 Hz, 1 H), 3.72 (s, 3H), 4.35 (ddd, *J* = 1.4, 3.0, 9.2 Hz, 1H), ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 12.5, 16.7, 20.8, 28.0, 39.1, 51.9, 55.9, 83.2, 150.1, 170.6, 173.3. IR (*neat*): 2981, 1785, 1711, 1439, 1361, 1315, 1256, 1158, 1109, 990, 953, 851, 820, 779 cm^{-1}. LRMS (CI, M+NH_4^+): 270. Anal. calcd for $C_{13}H_{19}NO_5$: C, 57.98; H, 7.11; N, 5.20. Found: C, 57.69; H, 7.35; N, 5.02.

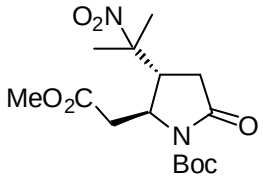
(2*S*,3*S*,4*S*)-3,4-Dihydroxy-2-methoxycarbonylmethyl-5-oxo-pyrrolidine-1-carboxylic acid tert-butyl ester (23)



23

To a vigorously stirred solution of **8** (51 mg, 0.2 mmol) in CH_3CN (1.2 mL) at 0-5 ^oC was added a solution of $RuCl_3 \cdot 3H_2O$ (3.66 mg, 0.014 mmol) and $NaIO_4$ (64 mg, 0.3 mmol) in distilled water (0.2 mL). The mixture was stirred for 3 min and then the suspension was filtered through a thin pad of silica gel, which was washed with EtOAc (20 mL). Concentration of the filtrate by flash chromatography (100% EtOAc) gave the diol **23**, which was recrystallized from CH_2Cl_2/ether to give a white solid, (51 mg, 88% yield). R_f= 0.20 (silica gel, hexanes/ethyl acetate, 2:3); mp 113-116 ^oC; $[\alpha]_D^{20}$ = -13.75 (c = 0.08, CH_2Cl_2), with >99% *ee*: 26.98 min. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.52 (s, 9H), 2.54 (dd, *J* = 10.0, 15.9 Hz, 1H), 2.85 (dd, *J* = 3.8, 15.8 Hz, 1H), 3.09-3-47 (br, 2H), 3.72 (s, 3 H), 4.29 (d, *J* = 4.7 Hz, 1H), 4.42 (dd, *J* = 3.8, 10.0 Hz, 1H), 4.46 (d, *J* = 4.7 Hz, 1H).^{13}C-NMR (75 MHz, $CDCl_3$): δ = 28.0, 35.5, 52.2, 59.4, 69.3, 70.8, 84.3, 149.4, 170.3, 172.8. IR (KBr): 3421, 2981, 1792, 1730, 1634, 1440, 1370, 1302, 1093, 971, 846, 777 cm^{-1}. LRMS (EI, M^+): 290. HRMS calc. for $C_{12}H_{20}NO_7$ [MH^+]: 290.1240, found 290.1239.

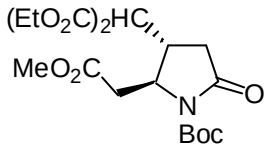
(*rac*)-2-Methoxycarbonylmethyl-3-(1'-methyl-1'-nitroethyl)-5-oxo-pyrrolidine-1-carboxylic acid tert-butyl ester (24)



24 (*rac*)

DBU (3 µl, 0.02 mmol) was added to a solution of **8** (51 mg, 0.2 mmol) and 2-nitropropane (27 µl, 0.3 mmol) in methylene chloride (1 mL). The solution was stirred at rt for 3 h and was then subjected to flash chromatography (30 % EtOAc in hexanes) to afford nitroalkane **24** as a yellowish oil (61 mg, 89% yield). R_f= 0.16 (silica gel, hexanes/ethyl acetate, 2:1). ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.52 (s, 9H), 1.53 (s, 3H), 1.58 (s, 3H), 2.18-2.28 (m, 1H), 2.67-2.85 (m, 2H), 2.95-3.00 (m, 2 H), 3.70 (s, 3 H), 4.22 (dd, *J* = 3.4, 8.1 Hz, 1H).^{13}C-NMR (75 MHz, $CDCl_3$): δ = 22.6, 23.0, 28.0, 33.95, 38.6, 42.8, 52.1, 56.2, 84.2, 90.3, 149.2, 170.2, 171.3. IR (*neat*): 2984, 2953, 1790, 1634, 1539, 1457, 1439, 1370, 1308, 1258, 1154, 1048, 1027, 987, 913, 849, 777, 746 cm^{-1}. LRMS (ES, M+NH_4^+): 362. HRMS calc. for $C_{15}H_{25}N_2O_7$ [MH^+]: 345.1662, found 345.1667.

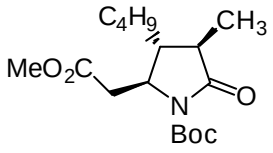
(2*R*,3*R*)-(1-tert-Butoxycarbonyl-2-methoxycarbonylmethyl-5-oxo-pyrrolidin-3-yl)-malonic acid diethyl ester (25)



25

To a suspension of NaH (40 mg, 1.0 mmol) in dry THF (1 mL) at 0 °C diethylmalonate (0.152 mL, 1.0 mmol) was added. The mixture was stirred 30 min and a solution of **8** (51 mg, 0.2 mmol) and TMSCl (75 µl, 0.6 mmol) in THF (2 mL) was added. The reaction mixture was stirred for 30 min at rt and quenched with a saturated solution of NH_4Cl (5 mL) and extracted with EtOAc (3x15 mL). After drying ($MgSO_4$) and evaporation of solvent, **25** was obtained by column chromatography (silica gel, 30% EtOAc in hexanes) as a white solid (72 mg, 87% yield); R_f= 0.26 (silica gel, hexanes/ethyl acetate, 3:2); mp 51-54 °C; $[\alpha]_D^{20}$ = + 23.3 (c = 0.275, CH_2Cl_2) with 83% *ee*: 27.39 min for minor and 36.39 min for major. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.23-1.29 (m, 6H), 1.52 (s, 9H), 2.45 (dd, *J* = 0.7, 17.6 Hz, 1H), 2.69 (dd, *J* = 8.6, 15.5 Hz, 1H), 2.80-2.97 (m, 3H), 3.54 (d, *J* = 7.2 Hz, 1H), 3.70 (s, 3 H), 4.15-4.24 (m, 4 H). 4.34-4.37 (ddd, *J* = 1.1, 3.2, 8.5 Hz, 1H).^{13}C-NMR (75 MHz, $CDCl_3$): δ = 14.00, 28.0, 34.8, 35.4, 38.28, 52.0, 55.1, 57.9, 62.0, 62.1, 83.6, 149.5, 167.6, 167.7, 170.6, 172.2. IR (KBr): 2982, 1788, 1738, 1440, 1369, 1310, 1254, 1156, 1098, 1030, 847, 778 cm^{-1}. LRMS (EI, M^+): 416. HRMS calc. for $C_{19}H_{30}NO_9$ [MH^+]: 416.1921, found 416.1925.

(2*R*,3*S*,4*R*)-3-Butyl-2-methoxycarbonylmethyl-4-methyl-5-oxo-pyrrolidine-1-carboxylic acid tert-butyl ester (26)

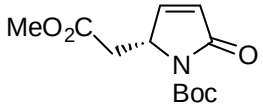


26

To a suspension of CuI (191 mg, 1.0 mmol) in dry THF (2 mL) was added at -20 °C 1.23 mL of a solution of nBuLi (15 % in hexane, 13.33 mmol). After 15 min, the reaction was cooled to -78 °C and a solution of **8** (51 mg, 0.2 mmol) in THF (2 mL) was added. The mixture was stirred 1 h at the same temperature and then, methyl iodide (0.25 mL, 4 mmol) was added. The reaction mixture was allowed to warm to rt, quenched with a saturated solution of NH_4Cl (5 mL), diluted with ether (20 mL) and the organic layer was washed with brine and water. After drying ($MgSO_4$) and evaporation of solvent, **26** was obtained by column chromatography (silica gel, 15% EtOAc in hexanes) as a yellowish oil (44 mg, 68% yield). R_f= 0.5 (silica gel, hexanes/ethyl acetate, 7:3). $[\alpha]_D^{20}$ = + 40 (c = 0.14, CH_2Cl_2) with 95% *ee*:

9.67 min for minor and 10.96 min for major. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.88-0.92 (m, 3H), 1.23-1.47 (m, 9H), 1.53 (s, 9H), 1.67-1.75 (m, 1H), 2.26 (ddd, *J* = 5.7, 7.4, 14.9 Hz, 1H), 2.65 (dd, *J* = 8.2, 15.4 Hz, 1H), 2.88 (dd, *J* = 3.5, 15.4 Hz, 1H), 3.69 (s, 3 H), 4.03 (qt, *J* = 3.8, 8.0 Hz, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 14.0, 17.5, 22.7, 28.0, 28.8, 34.6, 39.8, 43.5, 44.0, 51.8, 58.8, 83.4, 150.2, 170.9, 176.5. IR (*neat*): 2932, 2860, 1786, 1743, 1458, 1369, 1308, 1254, 1154 cm^{-1}. LRMS (EI, M^+): 328. Anal. calcd for $C_{17}H_{29}NO_5$: C, 62.36; H, 8.93; N, 4.28. Found: C, 62.14; H, 8.76; N, 4.06.

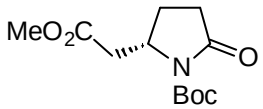
(2*S*)-2-Methoxycarbonylmethyl-5-oxo-2,5-dihydro-pyrrole-1-carboxylic acid tert-butyl ester (*ent*-8)



(*ent*)-**8**

Hydrobromination of (-)-**9** (3.0 g, 12.55 mmol) followed by Jones oxidation and ring opening with nBu_3SnH/AIBN afforded *ent*-**8** (1.53 g, 48 % over 3 steps) as a yellowish oil. $[\alpha]_D^{20}$ = – 182.4 (c = 0.63, CH_2Cl_2), with 91% *ee*: 20.67 min for minor (*R*) and 24.33 for major (*S*). This product showed NMR and IR spectra identical to those of its enantiomer **8** (*vide supra*).

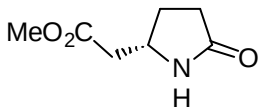
(2*S*)-2-Methoxycarbonylmethyl-5-oxo-pyrrolidine-1-carboxylic acid tert-butyl ester (*ent*-20)



(*ent*)-**20**

Following the reduction procedure starting from *ent*-**8** (1.50 g, 5.88 mmol) in MeOH (20 mL) and $NiCl_2 \cdot 6H_2O$ (1.05 g, 4.41 mmol) and $NaBH_4$ (223 mg, 5.88 mmol). *Ent*-**20** was obtained (1.16 g, 77%) as a colorless oil. This product showed NMR and IR spectra identical to those of its enantiomer **20** (*vide supra*).

(5*S*)-(Oxo-pyrrolidin-2-yl)-acetic acid methyl ester (28)

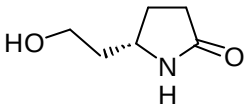


28

To a solution of *ent*-**20** (1.10 g, 4.28 mmol) in dry CH_2Cl_2 (15 mL) stirred under nitrogen atmosphere, was added $AlCl_3$ (171 mg, 1.28 mmol) at 0 °C. The reaction mixture was stirred

for 0.5 h at rt. Then, it was neutralized with aqueous $NaHCO_3$ solution (15 mL) and the product was extracted with CH_2Cl_2 (3x25 mL). The combined organic phases were dried ($MgSO_4$), and the solvent was removed *in vacuo* to give an oil, which was purified by flash chromatography (silica gel, 10% MeOH in EtOAc) to afford **28**. It was recrystallized from ether to give a white solid, (356 mg, 53% yield). R_f= 0.26 (silica gel, hexanes/ethyl acetate, 3:7); mp 63-65°C; $[\alpha]_D^{20}$ = + 21.5 (c = 0.63, EtOH) [lit.[1] $[\alpha]_D^{20}$ = +21.1], with > 99% *ee*: 25.04 min. ^{1}H-NMR and ^{13}C-NMR spectra were identical to the ones previously reported.[1]

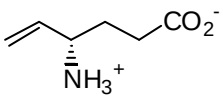
5(*S*)-(2-Hydroxyethyl)-pyrrolidin-2-one (29)



29

To a solution of ester **28** (196 mg, 1.25 mmol), in dry THF (6 mL) was added 1.25 mL of a 2 M solution of $LiBH_4$ in THF (2.5 mmol) at 4 °C. After stirring 15 min at the same temperature, the reaction mixture was allowed to stir at rt for 3 h. The reaction was quenched with a saturated solution of NH_4Cl (30 mL) and concentrated under vacuum. The residue was purified by column chromatography (silica gel, 10 % MeOH in EtOAc) to afford the corresponding alcohol as a white solid (150 mg, 93% yield). R_f= 0.22 (silica gel, MeOH/ethyl acetate, 1:4); mp 43-46 °C; $[\alpha]_D^{20}$ = +21.5 (c = 0.30, EtOH). ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.68-1.77 (m, 3H), 2.25-2.35 (m, 3H), 2.45 (br, 1H), 3.69-3.89 (m, 3H), 6.60 (br, 1H).^{13}C-NMR (75 MHz, $CDCl_3$): δ = 27.9, 30.2, 38.8, 53.8, 60.5, 178.6. IR (KBr): 3348, 3237, 2949, 1655, 1462, 1050 cm^{-1}. LRMS (CI, M^+): 129. HRMS calc. for $C_6H_{11}NO_2$ [MH^+]: 129.0790, found 129.0791.

(*S*)-Vigabatrin (27)

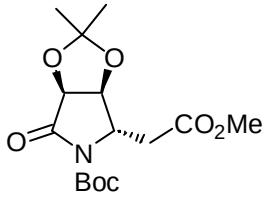


27

The alcohol **29** (150 mg, 1.16 mmol) was dissolved in dry THF (4 mL) and PBr_3 (0.164 mL, 1.74 mmol) was added at -20 °C under nitrogen. The reaction mixture was stirred for 2 h at rt. It was then diluted with chloroform (5 mL), washed with brine, aqueous solution of $NaHCO_3$ and again brine until neutral pH and dried over $MgSO_4$. After evaporation of solvent the 5(*S*)-(2-Bromo-ethyl)-pyrrolidin-2-one **75** was purified by column chromatography (silica gel, 5% MeOH in EtOAc) affording a white solid (125 mg, 56% yield). R_f= 0.3 (silica gel, ethyl

acetate,); mp 162-165 °C; $[\alpha]_D^{20}$ = +21.6 (c = 0.23, EtOH). ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.69-1.79 (m, 1H), 2.02-2.09 (m, 2H), 2.29-2.39 (m, 3H), 3.45 (t, *J* = 6.5, 6.8 Hz, 2H), 3.80-3.89 (m, 1H), 6.92 (br, 1 H).^{13}C-NMR (75 MHz, $CDCl_3$): δ = 27.0, 29.4, 29.9, 39.2, 53.0, 178.4. IR (KBr): 2959, 2363, 1690, 1425, 1387, 1319, 1268, 1163 cm^{-1}. LRMS (CI, $M+NH_4^+$): 209/211. To a solution of **75** (80 mg, 0.42 mmol) in dry THF (3 mL), was added potassium *tert*-butoxide (94 mg, 0.84 mmol). The reaction mixture was refluxed for 15 min and then quenched with brine (10 mL). The product was extracted with EtOAc (3x15 mL). The combined organic phases were dried ($MgSO_4$), and the solvent was removed *in vacuo* affording 37 mg (80% crude yield) of (5*S*)-5-vinyl-2-pyrrolidone (**30)**, which was used for the next step without further purification. A mixture of (5*S*)-5-vinyl-2-pyrrolidone (**30)** (37 mg, 0.33 mmol), KOH (40 mg, 0.71 mmol), water (0.2 mL), and isopropanol (2 mL) was refluxed for 24 h. After cooling at 0°C, the reaction mixture was neutralized with HCl (20 mg), and the solvent was removed *in vacuo* to give a residue, which was dissolved in water (3 mL) and this solution was applied to the top of a Amberlite IR-120 (H^+ form, 16-45 mesh) column. The column was eluted with water until the eluant was neutral, and then with 1N aqueous solution of NH_4OH. Ninhydrin-positive fractions were collected and concentrated *in vacuo* affording 32 mg (60% over 2 steps) Vigabatrin **27**, white solid. $[\alpha]_D^{20}$ = +12.2 (c = 0.45, H_2O) [lit.[2] $[\alpha]_D^{20}$ = +12.4]. ^{1}H-NMR and ^{13}C-NMR spectra were identical to the ones previously reported.[2]

4-Methoxycarbonylmethyl-2,2-dimethyl-6-oxo-tetrahydro-[1,3]dioxolo[4,5-c]pyrrole-5-carboxylic acid tert-butyl ester (39)

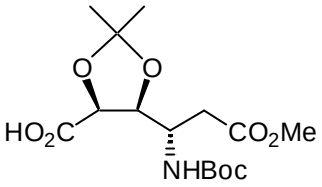


39

To a stirred solution of **23** (150 mg, 0.52 mmol) in acetone (10 mL), 2,2-dimethoxypropane (1.0 mL) and CSA (12 mg, 0.052 mmol) were added. The reaction mixture was stirred at rt for 20 h, neutralized with a saturated solution of $NaHCO_3$ (5 mL) and extracted with EtOAc (2x25 mL). The combined extracts were dried ($MgSO_4$) and concentrated under vacuum. Column chromatography (silica gel, 50% EtOAc in hexanes) afforded **39** as a white solid (125 mg, 74% yield); mp 85-88 °C; $[\alpha]_D^{20}$ = +59 (c = 0.4, CH_2Cl_2). ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.36 (s, 3H), 1.46 (s, 3H), 1.53 (s, 9H), 2.77-2.94 (m, 2H), 3.68 (s, 3H), 4.38 (dd, *J* = 3.92, 6.17 Hz, 1H), 4.55 (d, *J* = 5.71, 1H), 4.87 (d, *J* = 5.70 Hz, 1H).^{13}C-NMR (75 MHz,

$CDCl_3$): δ = 25.5, 26.9, 28.0, 35.7, 52.1, 57.7, 84.1, 112.6, 149.7, 170.5, 170.5. IR (*neat*): 2985, 1800, 1443, 1371, 1303, 1222, 1149, 1099, 1047, 989, 949, 844 cm^{-1}. LRMS (EI, M^+): 329. HRMS calc. for $C_{15}H_{23}NO_7$ [MH^+]: 329.1470, found 329.1470.

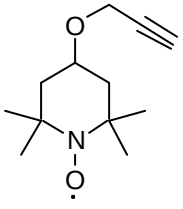
5-(1-tert-Butoxycarbonylamino-2-methoxycarbonyl-ethyl)-2,2-dimethyl-1,3]dioxolane-4-carboxylic acid (40)



40

To a stirred solution of **39** (100 mg, 0.3 mmol) in THF (6 mL) LiOH (7.2 mg, 0.3 mmol) in water (0.6 mL) was added. The reaction mixture was stirred at 0 °C for 30 min. The solvent was concentrated *in vacuo* and the remained solution was acidified with acetic acid to pH = 4 and extracted with EtOAc (2x10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under vacuum to afford **40** as a white solid (95 mg, 90% yield); mp 65-68 °C; $[\alpha]_D^{20}$ = +3.3 (c = 0.3, CH_2Cl_2). ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.29 (s, 3H), 1.35-1.40 (m, 9H), 1.53-1.55 (m, 3H), 2.65 (br, 2H), 3.69 (s, 3H), 3.78-4.01 (m, 1H), 4.59-4.65 (m, 2H), 5.41-5.50 (m, 0.5H), 6.65-6.72 (m, 0.5H), 10.43-10.49 (br, 1H).^{13}C-NMR (75 MHz, $CDCl_3$): δ = 25.2, 25.4, 26.5, 26.9, 27.5, 27.9, 35.5, 36.4, 47.9, 49.2, 51.84, 52.17, 57.7, 80.3, 84.2, 110.5, 110.9, 112.6, 149.7, 155.3, 157.1, 170.5, 170.8, 172.4, 172.9. IR (*neat*): 3353, 3210, 2986, 2938, 2623, 2361, 1683, 1531, 1447, 1370, 1316, 1253, 1171, 1073, 1060, 1016 cm^{-1}. LRMS (EI, MH^+): 348. HRMS calc. for $C_{15}H_{25}NO_8$ [MH^+]: 348.1658, found 348.1664.

Propargyl ether TEMPO (42)

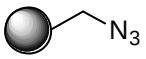


42

To a stirring suspension of NaH (60 % in mineral oil, 850 mg, 22.0 mmol) in dry DMF (100 mL) 4-hydroxy TEMPO **41** (3.0 g, 17.44 mmol) was added portionwise at 0 °C and stirred at rt for 30 min. Propargyl bromide (2.0 mL, 22.0 mmol) was added dropwise at 0 °C. The resulting mixture was stirred for 3 h at rt. Water (100 mL) was added and the solution was extracted with EtOAc (5x50 mL). The combined organics were washed with water (10x50

mL) and dried over $MgSO_4$, filtered and evaporated under reduced pressure and purified by column chromatography (silica gel, 10% EtOAc in hexanes) to give the title compound **42** (2.47 g, 78 %) as an orange solid. m.p. 58-59 ^oC; MS (PI-EIMS 70 eV) *m/z* 210.2 (M^+); Anal. calcd for $C_{12}H_{20}NO_2$: C, 68.54; H, 9.59; N, 6.66. Found: C, 68.21; H, 9.89; N, 6.33.

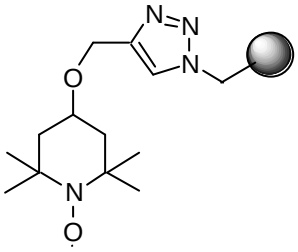
Azidomethyl polystyrene (43)



43

Merrifield resin (2.5 g, 4.3 mmol/g) in 25 mL DMSO was shaken at 50 ^oC with NaN_3 (2.45 g, 37.63 mmol) for 2 days. After being cooled to room temp., the suspension was filtrated and the resin was washed with MeOH (5x15 mL) and CH_2Cl_2 (5x15 mL) to give 2.4 g of resin **43**. IR (KBr): 2095 cm^{-1}.

PS-CLICK-TEMPO (44)



44

Method A: To a suspension of Merrifield supported azide **43**(estimated loading 4.3 mmol/g of azide, 1.10 g, 4.76 mmol) in degassed DCM (100 mL), 4-propargyloxy-TEMPO 38 (1.87 g, 8.58 mmol) and CuI (27 mg, 3 mol%) were added. The resulting mixture was shaken at room temperature for 3 days. The resin was filtered and washed with CH_2Cl_2 (5x50 mL) and dried under vacuum to afford PS-CLICK-TEMPO **44** with an estimated TEMPO loading of 2.0 mmol/g; yield: 1.40 g. The loading was determined by measurement the quantity of unreacted propargyl ether TEMPO **42**, elemental analysis and IR.

Method B: To a suspension of Merrifield supported azide **43** (estimated loading 4.3 mmol/g of azide, 570 mg, 2.43 mmol) in degassed THF (50 mL), 4-propargyloxy-TEMPO **42** (960 mg, 4.57 mmol) and CuI (27 mg, 6 mol%) were added. The resulting mixture was shaken at room temperature for 5 days. The resin was filtered and washed with CH_2Cl_2 (5x50 mL) and dried under vacuum to afford PS-CLICK-TEMPO **44** with an estimated TEMPO loading of 4.0 mmol/g; yield: 1.05 g. The loading was determined by measurement the quantity of unreacted propargyl ether TEMPO **42**, elemental analysis and IR.

General procedure for the oxidation of alcohols by PS-CLICK-TEMPO 44\bleach

Alcohol (1.0 mmol) in 2 mL CH_2Cl_2, KBr (40 mg, 0.3 mmol) and PS-CLICK-TEMPO **44** (2.0 mmol/g loading, 13 mg, 2.5 mol%) were added to a round-bottom flask. The reaction mixture was stirred at 0 ^oC before addition of 0.8 mL NaOCl (10%) and $NaHCO_3$ (40 mg, 50 mg/mL bleach). The resulting suspension was stirred at 0 ^oC for 30 min. The reaction mixture was filtered, washed with CH_2Cl_2, dried over $MgSO_4$ and concentrated *in vacuo* to afford the corresponding aldehyde.

Oxidation of 4-methylbenzyl alcohol by PS-CLICK-TEMPO 44\bleach; Recycling experiments

4-Methylbenzyl alcohol (366 mg, 3.0 mmol) in 6 mL CH_2Cl_2, KBr (120mg 1.0 mmol) and PS-CLICK-TEMPO **44** (4.0 mmol/ loading, 23 mg, 3.0 mol%) were added to a round-bottom flask. The reaction mixture was stirred at 0 ^oC before addition of 2.4 mL NaOCl (10%) and $NaHCO_3$ (120 mg, 50 mg/mL bleach). The resulting suspension was shaken at 0 ^oC for 1 h. Then the reaction mixture was filtered, extracted with CH_2Cl_2 (2x10 mL), washed with a saturated $NaHCO_3$ solution (5 mL) and concentrated *in vacuo* to afford 4-methylbenzaldehyde. PS-TEMPO **44** was washed with water and CH_2Cl_2 and re-used without further purification.

General procedure for the aerobic oxidation of alcohols to carbonyl compounds by PS-CLICK-TEMPO 44

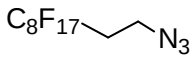
Alcohol (1.0 mmol), $Mn(NO_3)_2{\cdot}4H_2O$ (0.2 mmol), $Co(NO_3)_3{\cdot}6H_2O$ (0.2 mmol), PS-TEMPO **44** (2.0 mmol/g loading, 25 mg, 5 mol%) and glacial acetic acid (1 mL) were added to a Schlenk flask and heated at 40 ^oC under an oxygen atmosphere until completion. Then, the reaction mixture was filtered, washed with water and CH_2Cl_2. The organic layer was washed with water (2x10 mL), dried over $MgSO_4$ and concentrated *in vacuo* to afford the corresponding carbonyl derivative.

Aerobic oxidation of 4-bromobenzyl alcohol by PS-CLICK-TEMPO 44; recycling experiments

4-bromobenzyl alcohol (561 mg, 3 mmol), $Mn(NO_3)_2{\cdot}4H_2O$ (15 mg, 0.6 mmol), $Co(NO_3)_3{\cdot}6H_2O$ (18 mg, 0.6 mmol), PS-TEMPO **44** (4.0 mmol/ loading, 38 mg, 5 mol%) and glacial acetic acid (3 mL) were added to a Schlenk flask and heated at 40 ^oC under an oxygen

atmosphere. After 4 hours the reaction mixture was filtered, washed with water and CH_2Cl_2. The organic layer was washed with water (2x10 mL), dried over $MgSO_4$ and concentrated *in vacuo* to afford the 4-bromobenzaldehyde. PS-TEMPO was washed with water and CH_2Cl_2 and re-used without further purification. Fresh $Mn(NO_3)_2 \cdot 4H_2O$ (15 mg, 0.6 mmol) and $Co(NO_3)_3 \cdot 6H_2O$ (18 mg, 0.6 mmol) were added to each run.

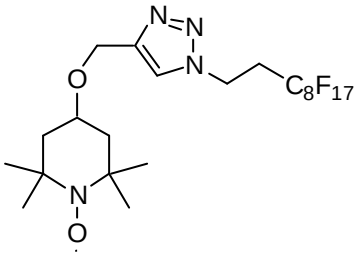
1-Azido-perfluorodecane (52)



52

2-(n-perfluorooctyl) ethyl iodide **50** was reacted with sodium azide in acetone: water (5:1) under reflux conditions for 7 h, resulted 2-(n-perfluorooctyl) ethyl azide **52** in quantitative yield. ^{1}H-NMR and ^{13}C-NMR spectra were identical to the ones previously reported.[3]

F_{17}-CLICK-TEMPO (53)



53

To a stirred mixture of 1-azidoperfluorodecane **52** (1.19 g, 2.43 mmol) and propargyl ether TEMPO **42** (0.95 g, 4.54 mmol) in degassed THF (15 mL), CuI (27 mg, 6 mol%) was added. The resulting mixture was stirred under nitrogen atmosphere at rt for 1 day. Then, the solvent was removed *in vacuo* and the residue was purified by column chromatography (silica, from 20% to 50% EtOAc in hexanes) to give the recovered **42** (0.4 g, 42%) and the title compound **53** (1.35g, 80%) as a light orange solid. Mp. 105-107 ^{o}C; IR (KBr): 2984, 1468, 1371, 1410, 1177, 1142, 1084, 1045, 989, 957, 661 cm^{-1}. MS (PI-EIMS 70 eV) *m/z* 699 (M^+); HRMS calc. for $C_{22}H_{24}F_{17}N_4O_2$ [MH^+]: 699.1628, found 699.1620.

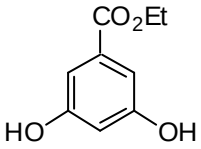
General procedure for the oxidation of alcohols by F_{17}-CLICK-TEMPO 53/bleach: In a typical reaction the alcohol (1.0 mmol) in 2 mL CH_2Cl_2, KBr (24 mg, 0.2 mmol) in water (2 mL) and F_{17}-CLICK-TEMPO **53** (7 mg, 1 mol%) were added to a round-bottom flask. The reaction mixture was stirred at 0 ^{o}C before addition of 0.8 mL NaOCl (10%) and $NaHCO_3$ (40 mg, 50mgmL^{-1} bleach). The resulting mixture was stirred at 0 ^{o}C for 15 min. Reaction was quenched by addition of water (5 mL) and the organic layer was extracted with

dichloromethane (2x5 mL). Combined organic layers were dried over anhydrous sodium sulphate and concentrated to give crude product, which was placed on a short bed of silica and eluted with dichloromethane in order to obtain pure carbonyl derivative.

Aerobic oxidation of 4-bromobenzyl alcohol by F_{17}-CLICK-TEMPO 53; recycling experiments

4-Bromobenzyl alcohol (2.0 g, 10.7 mmol) in dichloromethane (20 mL), KBr (257 mg, 2.16 mmol) in water (2 mL) and fluorous F_{17}-CLICK-TEMPO **53** (75 mg, 1 mol%) were added to a round-bottom flask. The reaction mixture was stirred at 0 ^{o}C before addition of NaOCl (8.6 mL, 14 mmol), $NaHCO_3$ (430 mg, 50 $mgmL^{-1}$ bleach). The resulting mixture was stirred at 0 ^{o}C for 15 min. Reaction was quenched by addition of water (10 mL) and the organic layer was extracted with dichloromethane (2x10 mL). Combined organic layers were dried over anhydrous sodium sulphate and concentrated to give crude product, which was place on a short bed of silica (5 g) and eluted with dichloromethane in order to obtain 4-bromobenzylaldehyde. The catalyst was recovered from the column by elution with diethyl ether and used for the next cycle.

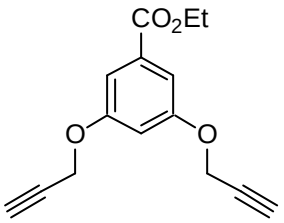
3,5-Dihydroxy-benzoic acid ethyl ester (**54**)



54

A solution of 3,5-dihydroxy-benzoic acid (20.0 g, 129.90 mmol) in dry ethanol (100 mL) and H_2SO_4 (1.0 mL) was refluxed for 20 h. The solvent was removed *in vacuo* and the residue was dissolved in EtOAc (100 mL) and washed with aqueous $NaHCO_3$ solution, water and brine. The organic phase was dried (Na_2SO_4) and evaporated to dryness. The crude material was crystallized in CH_2Cl_2 to give the ester **54** (20.25 g, 86 %) as a white solid. ^{1}H-NMR (300 MHz, [D_4] MeOH): δ = 1.35 (t, *J* = 7.11, 3H), 4.28 (q, *J* = 7.13, 2H), 4.97 (br, 1H), 6.47 (t, *J* = 2.25, 1H), 6.92 (d, *J* = 2.32, 2H). ^{13}C-NMR (75 MHz, [D_4] MeOH): δ = 14.00, 60.39, 106.95, 106.99, 131.48, 158.41, 165.63.

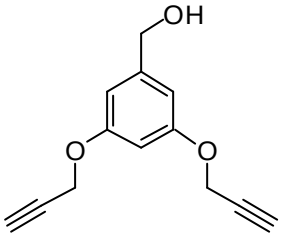
3,5-Bis-prop-2-ynyloxy-benzoic acid ethyl ester (76)



76

To a stirred solution of **54** (1.82 g, 10.0 mmol) and propargyl bromide (80% wt, 2.37 mL, 27.5 mmol) in acetone (30 mL) were added K_2CO_3 (1.52 g, 11.0 mmol) and 18-crown-6 (11 mg, 0.04 mmol). The reaction mixture was refluxed for 24 h, filtered and evaporated to dryness. The crude product was crystallized in MeOH to afford the title compound **76** (2.20 g, 85 %) as a pale yellow solid. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.39 (t, *J* = 7.11, 3H), 2.55 (t, *J* = 2.41, 2H), 4.36 (q, *J* = 7.13, 2H), 4.41 (d, *J* = 2.72, 4H), 6.80 (t, *J* = 2.36, 1H), 7.29 (d, *J* = 2.35, 2H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 14.30, 56.14, 61.28, 107.26, 108.92, 132.56, 158.49, 165.96.

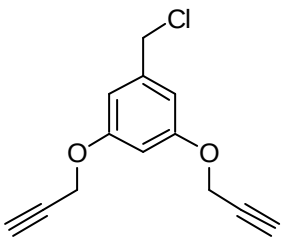
3,5-Bis-(propargyloxy)benzyl alcohol (77)



77

To a stirred solution of ester **76** (2.00 g, 7.75 mmol) in dry THF (20 mL) $LiAlH_4$ (367 mg, 9.69 mmol) was added in small fractions. The reaction mixture was quenched with NH_4Cl saturated aqueous solution (100 mL) and extracted with CH_2Cl_2 (5x100 mL). Evaporation of the solvent afforded the title compound **77** (1.35 g, 81 %) as white solid. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.98 (br, 1H), 2.56 (t, *J* = 2.40, 2H), 4.45 (d, *J* = 2.40, 4H), 6.46 (s, 1H), 6.56 (s, 2H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 55.92, 65.08, 73.73, 78.38, 101.50, 106.24, 143.57, 158.96.

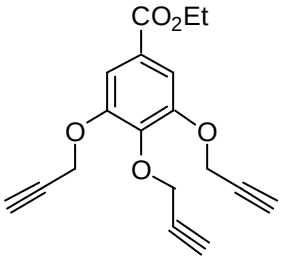
3,5-Bis-(propargyloxy)benzyl chloride (56)



56

A mixture of PhP_3 (3.73 g, 14.22 mmol), CCl_4 (12.0 mL) in dry THF (80 mL) was stirred at reflux for 30 min. The reaction mixture was cooled down to rt and alcohol **77** (2.56 g, 11.85 mmol) was then added. The resulting mixture was refluxed for 48 h. The solvent was evaporated *in vacuo* and the crude product was purified by column chromatography (silica gel, 20% EtOAc in hexanes) to afford the chloride **56** (1.82 g, 66%) as a white solid. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 2.54 (t, *J* = 2.37, 2H), 4.52 (s, 2H), 4.68 (d, *J* = 2.42, 4H), 6.58 (t, *J* = 2.26, 2H), 6.65 (d, *J* = 2.25, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 44.98, 55.98, 75.83, 78.20, 102.04, 108.20, 139.70, 158.79.

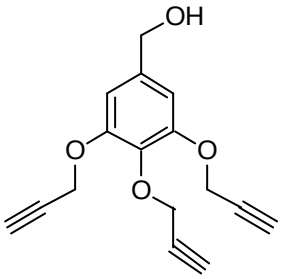
3,4, 5-Tris-prop-2-ynyloxy-benzoic acid ethyl ester (78)



78

To a stirred solution of 3,5-dihydroxy-benzoic acid ethyl ester **55** (5.0 g, 25.25 mmol) and propargyl bromide (80% wt, 8.43 mL, 78.28 mmol) in acetone (75 mL) were added K_2CO_3 (10.8 g, 11.0 mmol) and 18-crown-6 (26 mg, 0.10 mmol). The reaction mixture was refluxed for 24 h, filtered and evaporated to dryness. Water (50 mL) was added and the mixture was extracted with CH_2Cl_2 (3x30 mL). The organic phases were joined, dried over Na_2SO_4 and the solvent was evaporated *in vacuo*. The crude product was crystallized in CH_2Cl_2-hexane to afford the title compound **78** (7.87 g, 83 %) as a white solid, mp 64-65 ^{o}C. ^{1}H-NMR (300 MHz, [D_4] MeOH): δ = 1.38 (t, *J* = 7.11, 3H), 2.86 (t, *J* = 2.44, 1H), 3.00 (t, *J* = 2.39, 2H), 4.34 (q, *J* = 7.12, 2H), 4.77 (d, *J* = 2.49, 2H), 4.82-4.85 (m, 4H), 7.46 (s, 2H). ^{13}C-NMR (75 MHz, [D_4] MeOH): δ = 14.70, 58.08, 61.11, 62.48, 77.06, 77.61, 79.34, 79.75, 110.99, 127.21, 142.50, 152.82, 167.30. IR (KBr): 2997, 2125, 1701, 1588 cm^{-1}. LRMS (CI, MH^+): 313. HRMS calc. for $C_8H_{16}O_5$ [MH^+]: 312.0998, found 312.0994.

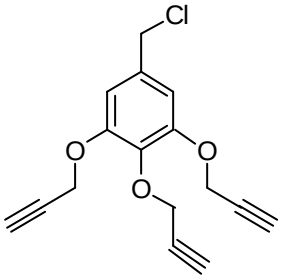
3,4,5-Tris-(propargyloxy)benzyl alcohol (79)



79

To a stirred solution of ester **78** (6.59 g, 21.12 mmol) in dry THF (63 mL) $LiAlH_4$ (0.99 g, 26.19 mmol) was added in small fractions. The reaction mixture was cooled to 0 °C and quenched with NH_4Cl saturated aqueous solution (50 mL). The mixture was acidified with 10 % HCl to pH= 2 and concentrated *in vacuo*. The mixture was extracted with CH_2Cl_2 (5x20 mL). The organic phases were joined, dried over Na_2SO_4 and the solvent was evaporated *in vacuo* to afford the title compound **79** (1.35 g, 81 %) as a white solid, mp 99-100 ^oC. ^1H-NMR (300 MHz, [D_4] MeOH): δ = 2.82 (t, *J* = 2.44, 1H), 2.95 (t, *J* = 2.39, 2H) 4.54 (s, 2H), 4.66 (d, *J* = 2.39, 2H), 4.77 (d, *J* = 2.20, 4H), 4.86 (s, 2H), 6.80 (s, 2H). ^{13}C-NMR (75 MHz, [D_4] MeOH): δ = 57.95, 61.07, 65.05, 76.58, 77.15, 79.78, 80.19, 108.14, 137.30, 139.39, 153.01. IR (KBr): 3539, 3289, 2928, 2119, 1595 cm^{-1}. LRMS (CI, M^+): 270. HRMS calc. for $C_{16}H_{14}O_4$ [MH^+]: 270.0892, found 270.0898.

3,4,5-Tris-(propargyloxy)benzyl chloride (57)

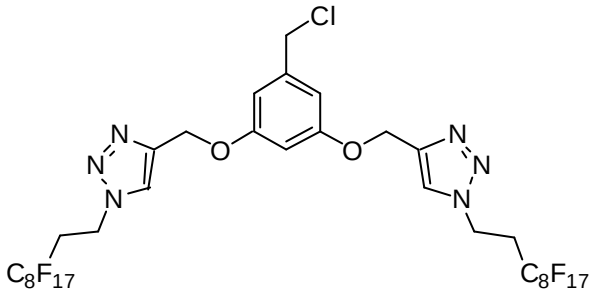


57

A mixture of PPh_3 (5.97 g, 22.82 mmol), CCl_4 (19.0 mL) in dry THF (100 mL) was stirred at reflux for 30 min. The reaction mixture was cooled down to rt and alcohol **79** (5.13 g, 19.05 mmol) was then added. The resulting mixture was refluxed for 24 h. The solvent was evaporated *in vacuo* and the crude product was purified by column chromatography (silica gel, 20% EtOAc in hexanes) to afford the chloride **57** (2.84 g, 52%) as a white solid, mp 61 ^oC. ^1H-NMR (300 MHz, $CDCl_3$): δ = 2.47 (t, *J* = 2.44, 1H), 2.53 (t, *J* = 2.38, 2H), 4.54 (s, 2H), 4.72 (d, *J* = 2.45, 2H), 4.76 (d, *J* = 2.42, 4H), 6.79 (s, 2H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 46.36, 57.10, 60.36, 75.37, 76.10, 78.27, 79.06, 109.02, 133.49, 137.21, 151.65. IR

(KBr): 2945, 2122, 1580 cm-1. LRMS (CI, M^+): 288. HRMS calc. for $C_{16}H_{13}ClO_3$ [MH^+]: 288.0553, found 288.0553.

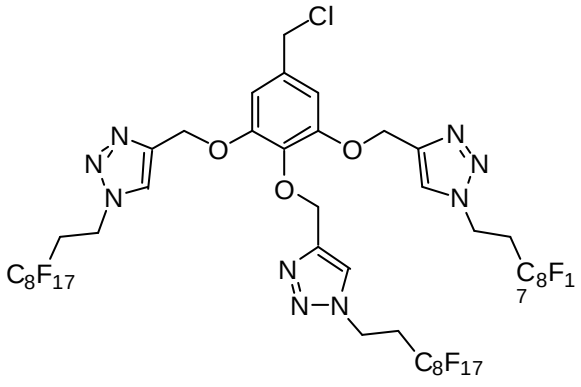
2-Ponytails perfluorinated chloride (58)



58

To a stirred solution of **56** (400 mg, 1.70 mmol) in dry THF (85 mL), 1-azido-perfluorodecane **52** (3.33 g, 6.80 mmol), CuI (39 mg, 0.204 mmol) and DIPEA (8.5 mL) were added and the reaction mixture was stirred at rt (26-27 ^oC) for 24 h. The reaction was quenched with a saturated aqueous solution of NH_4Cl (100 mL) and extracted with warm EtOAc (200 mL). The solvent was evaporated *in vacuo* and the residue crystallized in ether to afford the title compound **58** as a white solid (1.55 g, 75%), mp 198-200 ^oC (Dec.). ^{1}H-NMR (400 MHz, $C_2D_2Cl_4$, 100 ^oC): δ = 2.76-2.93 (m, 4H), 4.50 (s, 2H), 4.69 (t, J = 7.35, 4H), 5.20 (s, 4H), 6.62-6.65 (m, 3H), 7.71 (s, 2H). ^{13}C-NMR (100 MHz, $C_2D_2Cl_4$, 100 ^oC): δ = 32.12, 32.33, 32.55, 42.64, 46.13, 62.78, 103.04, 109.09, 123.22, 140.21, 144.72, 160.00. IR (KBr): 3146, 2964, 2200, 1595, 1467, 1396, 1335, 1201, 1147, 1047 cm^{-1}. LRMS (ES, MH^+): 1213. Anal. calcd for $C_{33}H_{19}ClF_{34}N_6O_2$: C, 32.68; H, 1.58; N, 6.93. Found: C, 32.43; H, 1.69; N, 7.09.

3-Ponytails perfluorinated chloride (59)

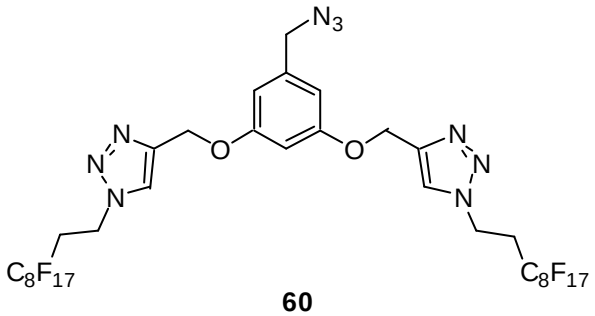


59

To a stirred solution of **57** (144 mg, 0.5 mmol) in dry THF (25 mL), 1-azido-perfluorodecane **52** (1.46 g, 3.00 mmol), CuI (17 mg, 0.09 mmol) and DIPEA (1.25 mL) were added and the

reaction mixture was stirred at rt (26-27 °C) for 24 h. The reaction was quenched with a saturated aqueous solution of NH_4Cl (50 mL) and the solvent was evaporated *in vacuo*. The suspension was filtrated and the residue was washed with ether (5x15 mL), CH_2Cl_2 (5x15 mL) and water (5x15 mL). Drying of the residue in vacuum afforded the title compound **59** as a white solid (492 mg, 56%), mp 165-166 °C (Dec.). ^{1}H-NMR (400 MHz, $C_2D_2Cl_4$, 100 °C): δ = 2.75-2.89 (m, 6H), 4.46 (s, 2H), 4.63 (m, 6H), 5.12 (s, 2H), 5.19 (s, 4H), 6.73 (s, 2H), 7.77 (s, 2H), 7.81 (s, 1H). ^{13}C-NMR (100 MHz, $C_2D_2Cl_4$, 100 °C): δ = 32.02, 32.24, 32.47, 42.64, 46.28, 64.12, 66.63, 110.24, 123.61, 124.26, 133.89, 139.35, 144.55, 145.16, 152.68. IR (KBr): 2963, 1598, 1442, 1203, 1147 cm^{-1}. LRMS (ES, MH^+): 1756.

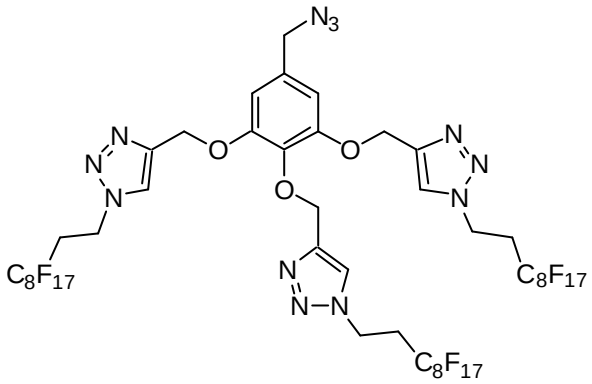
2-Ponytails perfluorinated azide (60)



60

To a suspension of chloride **58** (975 mg, 0.805 mmol), in DMSO (20 mL), NaN_3 (523 mg, 8.05 mmol) was added and the reaction mixture was heated at 60 °C for 24 h. Then, the solution was cooled to rt and water (20 mL) was added. The precipitate was filtered and washed with water and cold ether and dried *in vacuo* to afford the azide **60** (883 mg, 90%) as a white solid, mp 177-180 °C (Dec.). ^{1}H-NMR (400 MHz, $C_2D_2Cl_4$): δ = 2.76-2.93 (m, 4H), 4.26 (s, 2H), 4.70 (t, *J* = 7.40, 4H), 5.22 (s, 4H), 6.56 (d, *J* = 2.13, 1H), 6.64 (t, *J* = 2.16, 2H), 7.70 (s, 2H). ^{13}C-NMR (100 MHz, $C_2D_2Cl_4$, 100 °C): δ = 32,09, 32.31, 32.52, 42.63, 55.05, 62.79, 102.97, 108.65, 123.22, 138.35, 144.72, 160.18. IR (KBr): 3140, 2106, 1599, 1335, 1292, 1203, 1148, 1113, 1049, 1026 cm^{-1}. LRMS (ES, MH^+): 1220. Anal. calcd for $C_{33}H_{19}F_{34}N_9O_2$: C, 32.50; H, 1.57; N, 10.34. Found: C, 32.36; H, 1.86; N, 10.32.

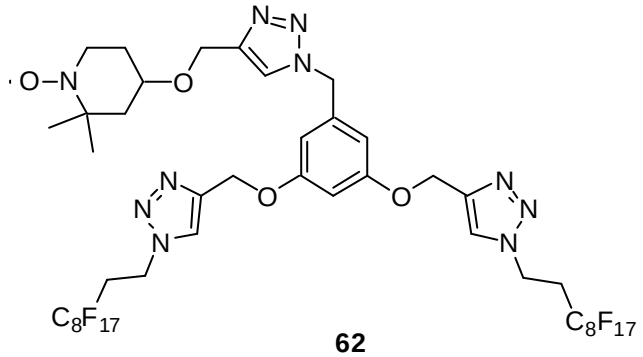
3-Ponytails perfluorinated azide (61)



61

To a suspension of chloride **59** (490 mg, 0.280 mmol) in DMSO (7.7 mL) was added NaN_3 (182 mg, 2.80 mmol) and the reaction mixture was heated at 60 ^oC for 24 h. Then, the solution was cooled to rt and water (20 mL) was added. The precipitate was filtered and washed with water and cold ether and dried *in vacuo* to afford the azide **61** (432 mg, 87%) as a white solid, mp 167-169 ^oC (Dec.). ^{1}H-NMR (400 MHz, $C_2D_2Cl_4$, 100 °C): δ = 2.73-2.89 (m, 6H), 4.22 (s, 2H), 4.64 (m, 6H), 5.14 (s, 2H), 5.20 (s, 4H), 6.64 (s, 2H), 7.77 (s, 2H), 7.81 (s, 1H). ^{13}C-NMR (100 MHz, $C_2D_2Cl_4$, 100 °C): δ = 32.00, 32.22, 32.44, 42.65, 55.03, 64.09, 66.55, 109.79, 123.61, 124.28, 131.90, 139.17, 144.54, 145.16, 152.85. IR (KBr): 2105, 1597, 1203, 1148, cm^{-1}. LRMS (ES, MH^+): 1763. Anal. calcd for $C_{46}H_{25}F_{51}N_{12}O_3$: C, 31.34; H, 1.43; N, 9.54. Found: C, 31.63; H, 1.77; N, 9.37.

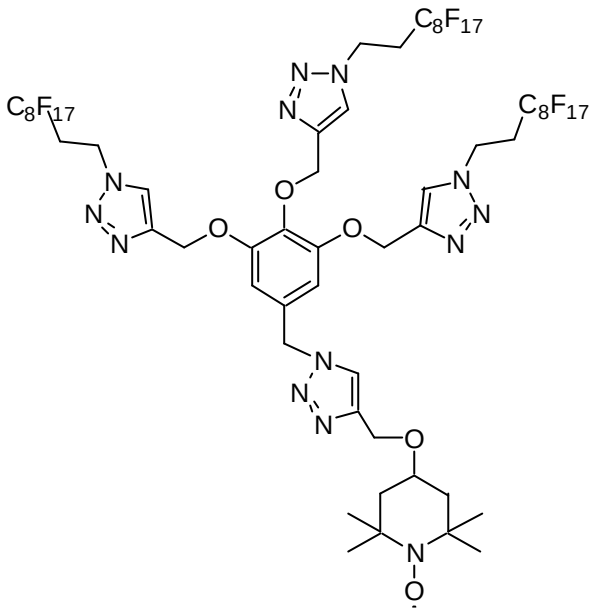
2-Ponytails perfluorinated TEMPO (62)



62

To a stirred mixture of azide **60** (200 mg, 0.165 mmol) and propargyl ether TEMPO **42** (65 mg, 0.31 mmol) in degassed THF (15 mL), CuI (2 mg, 6 mol%) was added. The resulting mixture was stirred under nitrogen atmosphere at rt (26-27 ^oC) for 24 h and then quenched with water (5 mL). The precipitate was filtered and washed with water and cold ether and dried *in vacuo* to afford the TEMPO **62** (170 mg, 73%) as a pale orange solid, mp 175-178 ^oC (Dec.). IR (KBr): 3138, 2977, 2940, 1598, 1464, 1333, 1203, 1148, 1051 cm^{-1}. LRMS (ES, MH^+): 1430.

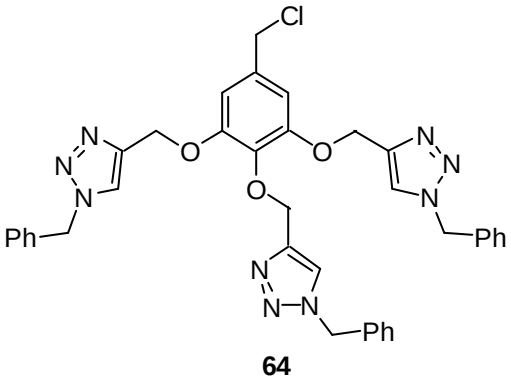
3-Ponytails perfluorinated TEMPO (63)



63

To a stirred mixture of azide **61** (250 mg, 0.141 mmol) and propargyl ether TEMPO **42** (56 mg, 0.26 mmol) in THF (2.5 mL), DIPEA (0.25 mL) and CuI (2 mg, 6 mol%) were added. The resulting mixture was stirred under nitrogen atmosphere at rt (26-27 ^{o}C) for 72 h and then quenched with a saturated aqueous solution of NH_4Cl (5 mL). The precipitate was filtered and washed with water and cold ether and dried *in vacuo* to afford the TEMPO **63** (236 mg, 84%) as a pale yellow solid, mp 198 ^{o}C (Dec.). IR (KBr): 3138, 2982, 1600, 1202, 1148 cm^{-1}. LRMS (ES, MH^{+}): 1973.

3-Benzyl tailed chloride (64)

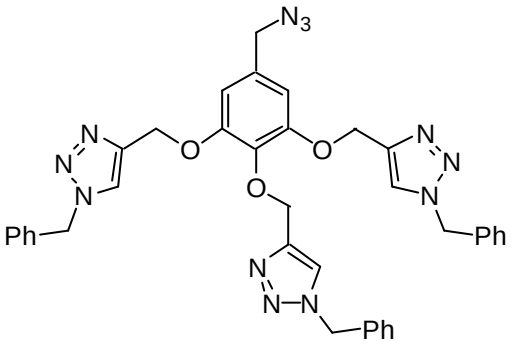


64

To a stirred solution of **57** (408 mg, 1.41 mmol) in dry THF (17.6 mL), benzyl azide (1.0 g, 6.37 mmol), CuI (48 mg, 0.25 mmol) and DIPEA (1.76 mL) were added and the reaction mixture was stirred at rt (26-27 ^{o}C) for 24 h. The reaction was quenched with a saturated aqueous solution of NH_4Cl (50 mL) and the solvent was evaporated *in vacuo*. The aqueous suspension was extracted with CH_2Cl_2 (3x20 mL). The organic phases were joined, dried

over Na_2SO_4 and the solvent was evaporated *in vacuo*. The crude product was crystallized in CH_2Cl_2-ether to afford the title compound **64** (702 mg, 72 %) as a white solid, mp 138-139 °C (Dec.). ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 4.44 (s, 2H), 5.10 (s, 6H), 5.43 (s, 2H), 5.48 (s, 4H), 6.67 (s, 2H), 7.10-7.77 (m, 17H), 7.81 (s, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 46.39, 53.92, 54.21, 63.15, 66.24, 108.24, 123.25, 123.86, 127.99, 128.17, 128.76, 128.87, 129.02, 129.12, 133.42, 134.58, 134.95, 137.38, 144.07, 144.68, 152.15. IR (KBr): 3138, 2941, 1595, 1439, 1112 cm^{-1}. LRMS (ES, MH^+): 688. Anal. calcd for $C_{37}H_{34}ClN_9O_3$: C, 64.58; H, 4.98; N, 18.32. Found: C, 64.17; H, 4.98; N, 18.38.

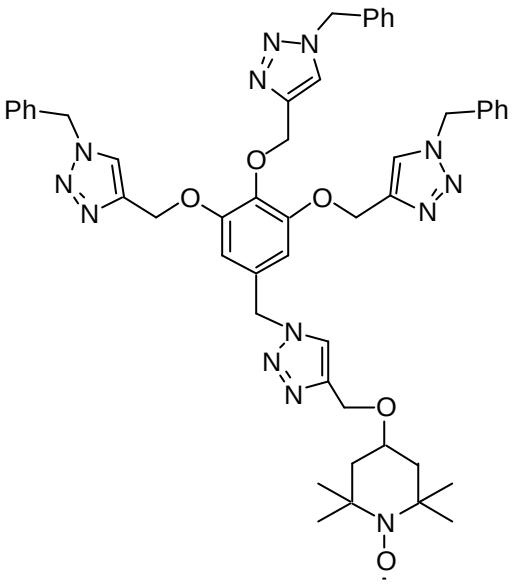
3-Benzyl tailed azide (65)



65

To a solution of chloride **64** (144 mg, 0.209 mmol) in DMSO (5 mL), was added NaN_3 (136 mg, 2.09 mmol) and the reaction mixture was heated at 60 °C for 24 h. Then, the solution was cooled to rt, a saturated aqueous solution of NaCl (20 mL) was added and the product was extracted with CH_2Cl_2 (3x20 mL). The organic phases were joined, dried over Na_2SO_4 and the solvent was evaporated *in vacuo*. The final product was purified by column chromatography (silica gel, 100 % EtOAc) to afford the azide **65** (113 mg, 77%) as a white solid, mp 128-129 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 4.10 (s, 2H), 5.10 (s, 6H), 5.40 (s, 2H), 5.50 (s, 4H), 6.67 (s, 2H), 7.10-7.77 (m, 17H), 7.81 (s, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 53.94, 54.22, 54.70, 63.21, 66.21, 107.98, 123.22, 128.00, 128.18, 128.59, 128.76, 129.00, 129.11, 131.40, 134.58, 134.93, 137.30, 144.07, 144.68, 152.34. IR (KBr): 2097, 1596, 1109, cm^{-1}. LRMS (ES, MH^+): 695.

3-Benzyl tailed TEMPO (66)



66

To a stirred mixture of azide **65** (50 mg, 0.072 mmol) and propargyl ether TEMPO **42** (28 mg, 0.13 mmol) in THF (1 mL) CuI (1 mg, 6 mol%) was added. The resulting mixture was stirred under nitrogen atmosphere at rt (26-27 ^{o}C) overnight and then quenched with a saturated aqueous solution of NH_4Cl (5 mL), the solvent was evaporated *in vacuo*, and the product was extracted with CH_2Cl_2 (3x10 mL). The organic phases were joined, dried over Na_2SO_4 and the solvent was evaporated *in vacuo.* The final product was purified by column chromatography (silica gel, 5% MeOH in CH_2Cl_2) to afford the TEMPO **66** (44 mg, 68%) as an orange solid, mp 157 ^{o}C. IR (KBr): 2934, 1597, 1114 cm^{-1}. LRMS (ES, MH^+): 905.

Oxidation of alcohols by 2-ponytails perfluorinated TEMPO 62\bleach

Alcohol (1.0 mmol) in 2 mL CH_2Cl_2, KBr (24 mg, 0.2 mmol) and TEMPO **62** (15 mg, 1.0 mol%) were added to a round-bottom flask. The reaction mixture was stirred at 0 ^{o}C before addition of 0.8 mL NaOCl (10%) and $NaHCO_3$ (40 mg, 50 mg/mL bleach). The resulting suspension was stirred at 0 ^{o}C for 15 min. The reaction was quenched by addition of water (5 mL) and the organic layer was extracted with dichloromethane (2x5 mL). Combined organic layers were dried over anhydrous sodium sulphate and concentrated to give crude product, which was placed on a short bed of silica (5 g) and eluted with dichloromethane in order to obtain pure carbonyl compound.

Oxidation of 4-methylbenzyl alcohol 2-ponytails perfluorinated TEMPO 62\bleach; recycling experiments

4-methylbenzyl alcohol (122 mg, 1 mmol) in 2 mL CH_2Cl_2, KBr (24 mg 0.2 mmol) and TEMPO **62** (15 mg, 0.01 mmol) were added to a round-bottom flask. The reaction mixture

was stirred at 0 ^{o}C before addition of 0.8 mL NaOCl (10%) and $NaHCO_3$ (40 mg, 50 mg/mL bleach). The resulting suspension was stirred at 0 ^{o}C for 15 min. The reaction was quenched by addition of water (5 mL) and the organic layer was extracted with dichloromethane (2x5 mL). Combined organic layers were dried over anhydrous sodium sulphate and concentrated to give crude product, which was placed on a short bed of silica (5 g) and eluted with dichloromethane in order to obtain 4-methylbenzaldehyde. The silica was washed with trifluoroethanol to recover the catalyst, which was re-used without further purification.

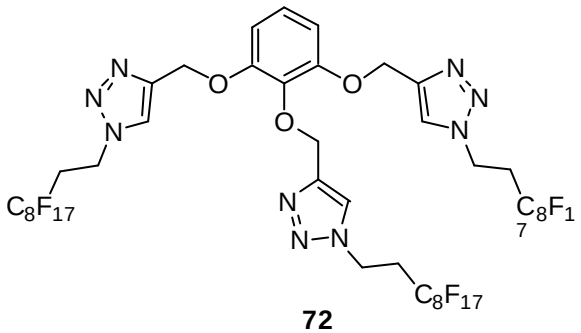
Oxidation of alcohols by 3-ponytails perfluorinated TEMPO 63\bleach

Alcohol (1.0 mmol) in 2 mL CH_2Cl_2, KBr (24 mg, 0.2 mmol) and TEMPO **63** (20 mg, 1.0 mol%) were added to a round-bottom flask. The reaction mixture was stirred at 0 ^{o}C before addition of 0.8 mL NaOCl (10%) and $NaHCO_3$ (40 mg, 50 mg/mL bleach). The resulting suspension was stirred at 0 ^{o}C for 15 min. The reaction mixture was filtered off using a sintered glass funnel (P40, 16-40 µm pore size) and the solid washed with water (5 mL) and CH_2Cl_2 (2x5 mL). The organic phase was separated and the aqueous layer was extracted with CH_2Cl_2 (3x5 mL). Combined organic layers were dried over anhydrous sodium sulphate and concentrated to give pure carbonyl compound.

Oxidation of 4-methylbenzyl alcohol by -ponytails perfluorinated TEMPO 63\bleach; recycling experiments

4-methylbenzyl alcohol (305 mg, 2.50 mmol) in 5 mL CH_2Cl_2, KBr (60 mg, 0.50 mmol) and TEMPO **63** (50 mg, 0.025 mmol) were added to a round-bottom flask. The reaction mixture was stirred at 0 ^{o}C before addition of 2.0 mL NaOCl (10%) and $NaHCO_3$ (100 mg, 50 mg/mL bleach). The resulting suspension was stirred at 0 ^{o}C for 15 min. The reaction mixture was filtered off using a sintered glass funnel (P40, 16-40 pore size) and the solid washed with water (5 mL) and CH_2Cl_2 (2x5 mL), dried *in vacuo* and re-used without further purification. The organic phase was separated and the aqueous layer was extracted with CH_2Cl_2 (3x5 mL). Combined organic layers were dried over anhydrous sodium sulphate and concentrated to give 4-methylbenzaldehyde. .

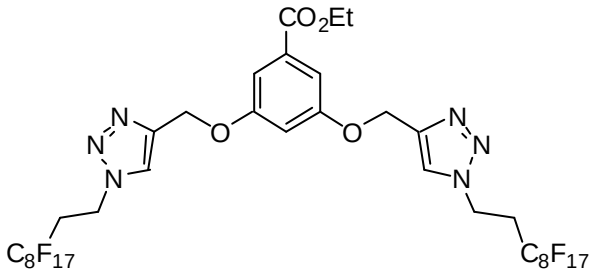
3-perfluorinated tailed benzene (72)



72

To a stirred solution of 3,4,5-tris-(propargyloxy)benzene **80**[4] (100 mg, 0.42 mmol) in dry THF (10 mL), 1-azido-perfluorodecane **52** (819 mg, 1.66 mmol), CuI (14 mg, 0.075 mmol) and DIPEA (0.5 mL) were added and the reaction mixture was stirred at rt (26-27 ^{o}C) for 24 h. The reaction was quenched with a saturated aqueous solution of NH_4Cl (10 mL) and extracted with warm EtOAc (50 mL). The solvent was evaporated *in vacuo* and the residue crystallized in ether to afford the title compound **72** as a yellowish solid (652 mg, 91%), mp 183-185 ^{o}C (Dec.).^{1}H-NMR (400 MHz, $C_2D_2Cl_4$, 100 °C): δ = 2.73-2.89 (m, 6H), 4.56-4.65 (m, 6H), 5.14 (s, 2H), 5.18 (s, 2H), 5.19 (s, 4H), 6.70 (d, *J* = 8.32, 2H), 6.95 (t, *J* = 8.24, 1H), 7.77 (s, 2H), 7.81 (s, 1H). ^{13}C-NMR (100 MHz, $C_2D_2Cl_4$, 100 °C): δ = 32.04, 32.26, 42.64, 64.04, 66.55, 110.02, 123.55, 124.26, 139.44, 144.85, 145.37, 152.90. IR (KBr): 1600, 1472, 1336, 1204, 1149, 1049 cm^{-1}. LRMS (ES, MH^+): 1708.

2-Ponytails perfluorinated benzyl ethylester (73)

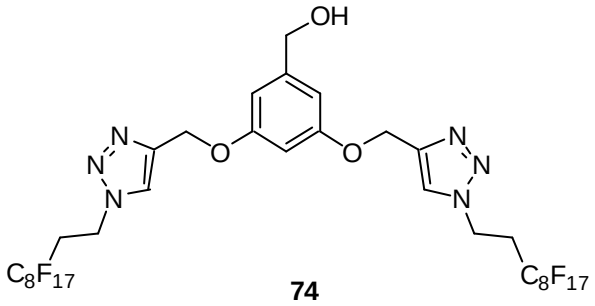


73

To a stirred solution of **67** (100 mg, 0.387 mmol) in dry THF (10 mL), 1-azido-perfluorodecane **48** (758 mg, 1.55 mmol), CuI (9 mg, 0.046 mmol) and DIPEA (0.5 mL) were added and the reaction mixture was stirred at rt (26-27 ^{o}C) for 24 h. The reaction was quenched with a saturated aqueous solution of NH_4Cl (10 mL) and extracted with warm EtOAc (50 mL). The solvent was evaporated *in vacuo* and the residue crystallized in ether to afford the title compound **64** as a white solid (430 mg, 90%), mp 168-171 ^{o}C (Dec.). ^{1}H-NMR (400 MHz, $C_2D_2Cl_4$, 100 ^{o}C): δ = 1.37 (t, *J* = 7.07, 3H), 2.75-2.87 (m, 4H), 4.32 (t, *J* = 7.07, 2H), 4.63 (t, *J* = 7.12, 4H), 5.20 (s, 4H), 6.87 (s, 1H), 7.29 (d, *J* = 2.04, 2H), 7.60 (s, 2H). ^{13}C-NMR (100 MHz, $C_2D_2Cl_4$, 100 ^{o}C): δ = 14.40, 32.10, 32.33, 32.55, 42.66, 46.13,

61.37, 62.90, 107.70, 110.02, 123.26, 133.40, 144.55, 159.61, 166.03. IR (KBr): 3146, 1719, 1602, 1450, 1370, 1341, 1296, 1204, 1148 cm^{-1}. LRMS (ES, MH^+): 1237.

2-Ponytails perfluorinated benzyl alcohol (74)



74

To a stirred solution of 3,5-bis-(propargyloxy)benzyl alcohol **77** (100 mg, 0.463 mmol) in dry THF (10 mL), 1-azido-perfluorodecane **52** (905 mg, 1.85 mmol), CuI (11 mg, 0.055 mmol) and DIPEA (0.5 mL) were added and the reaction mixture was stirred at rt (26-27 ^oC) for 24 h. The reaction was quenched with a saturated aqueous solution of NH_4Cl (10 mL) and the solvent was evaporated *in vacuo.* The suspension was filtrated and the residue was washed with ether (5x15 mL), CH_2Cl_2 (5x15 mL) and water (5x15 mL). Drying of the residue in vacuum afforded the title compound **74** as a white solid (512 mg, 93%), mp 210-213 ^oC (Dec.). ^{1}H-NMR (400 MHz, $C_2D_2Cl_4$, 100 ^oC): δ = 1.57 (br, 1H), 2.75-2.87 (m, 4H), 4.58-4.63 (m, 6H), 5.17 (s, 4H), 6.59-6.61 (m, 3H), 7.60 (s, 2H). ^{13}C-NMR (100 MHz, $C_2D_2Cl_4$, 100 ^oC): δ = 32.10, 32.32, 32.53, 42.64, 62.70, 65.20, 102.25, 107.28, 123.22, 144.16, 144.98, 166.06. IR (KBr): 1600, 1463, 1337, 1194, 1144, 1047, 1028 cm^{-1}. LRMS (ES, MH^+): 1195.

1. Nagao, Y.; Dai, W.-M; Tsukagoshi, S.; Fujita, E. *J. Org. Chem*. **1990**, *55*, 1148.
2. (a) Wey, Z. Y.; Knaus, E. E. *Synlett* **1994**, 345. (b) Kwon, T. W.; Keusenkothen, P. F.; Smith, M. B. *J. Org. Chem.* **1992**, *57*, 6169.
3. Szonyi, F.; Cambon, A. *J. Fluorine Chem.* **1989**, *42*, 59.
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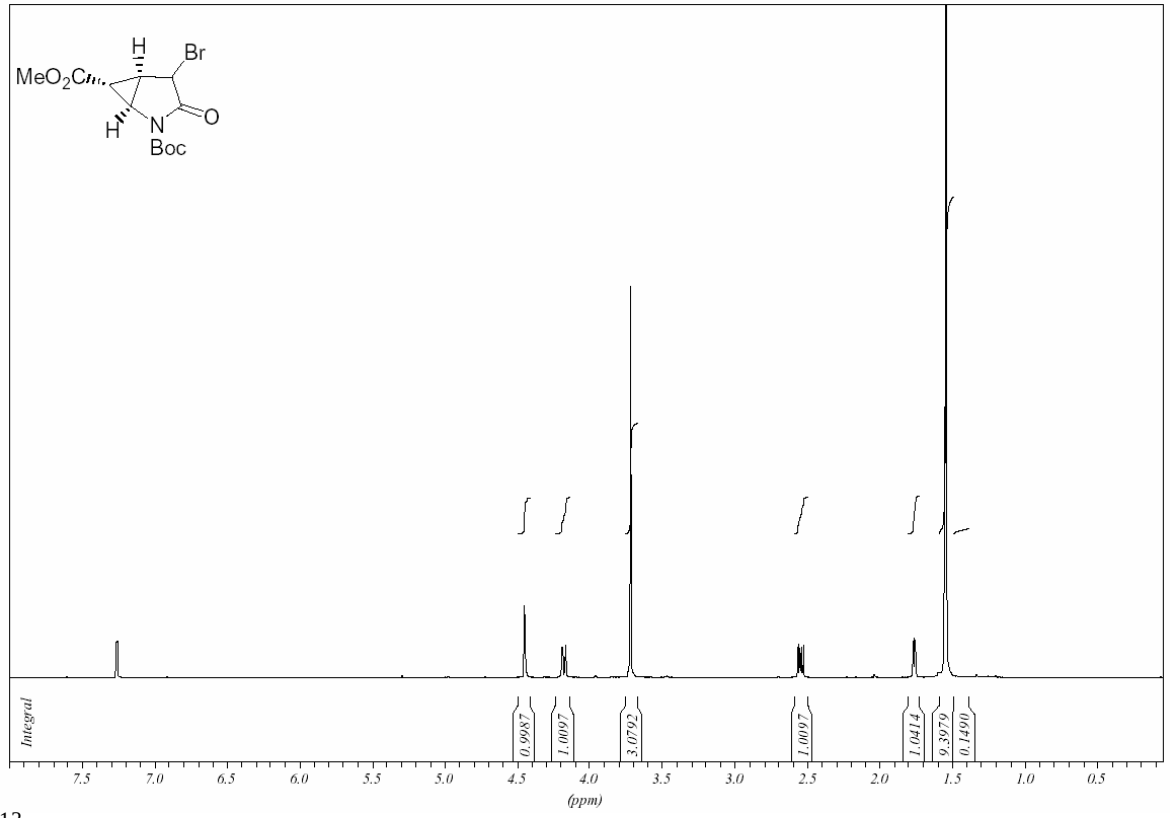
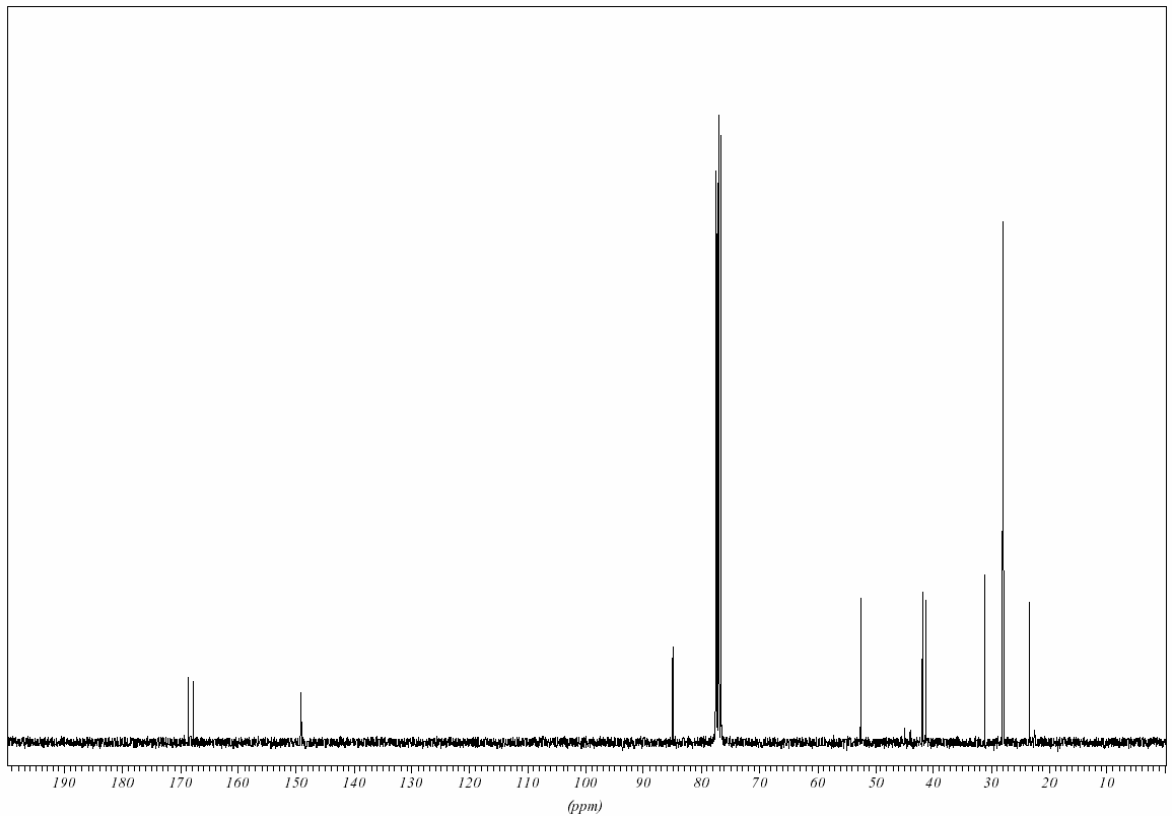
8.3 NMR-Spectra

(1*R*, 5*R*, 6*R*)-4-Bromo-3-oxo-2-aza-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid 2-tert-butyl ester 6-methyl ester (19)

^{1}H-NMR (300 MHz, $CDCl_3$)

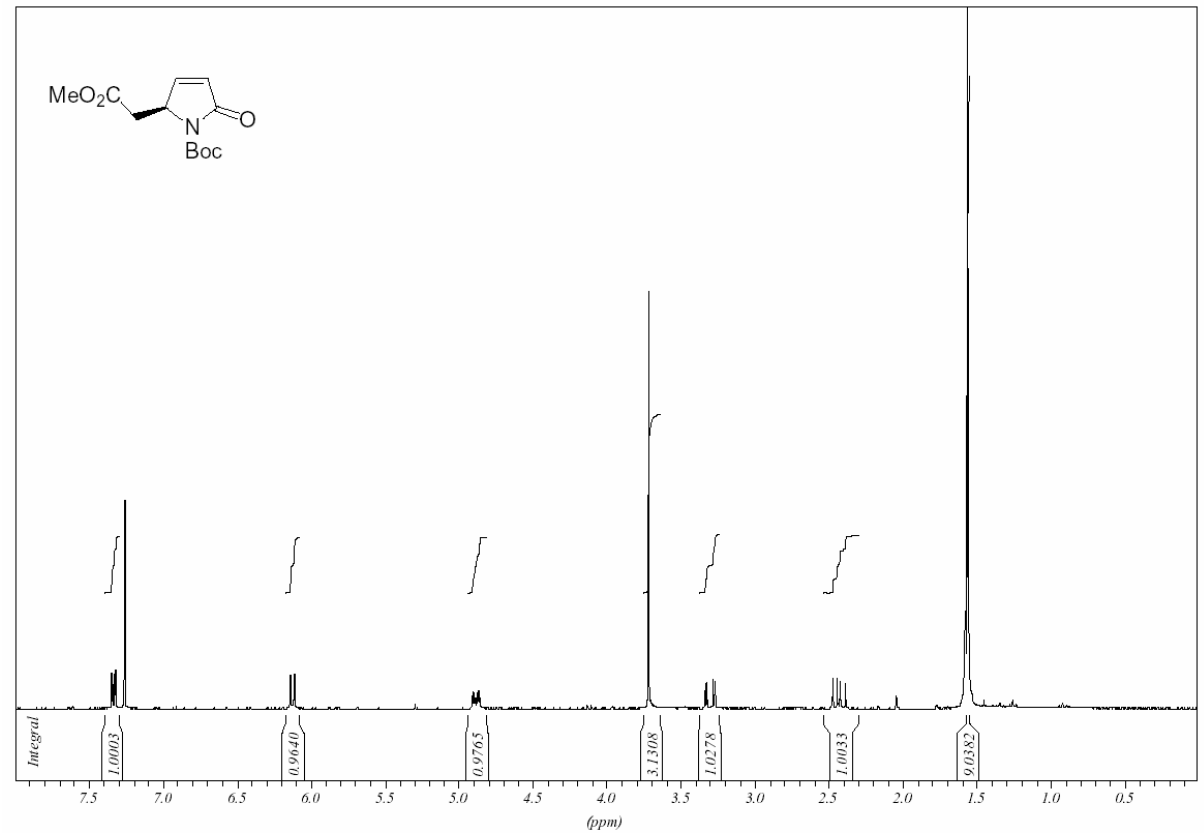


^{13}C-NMR (75 MHz, $CDCl_3$)

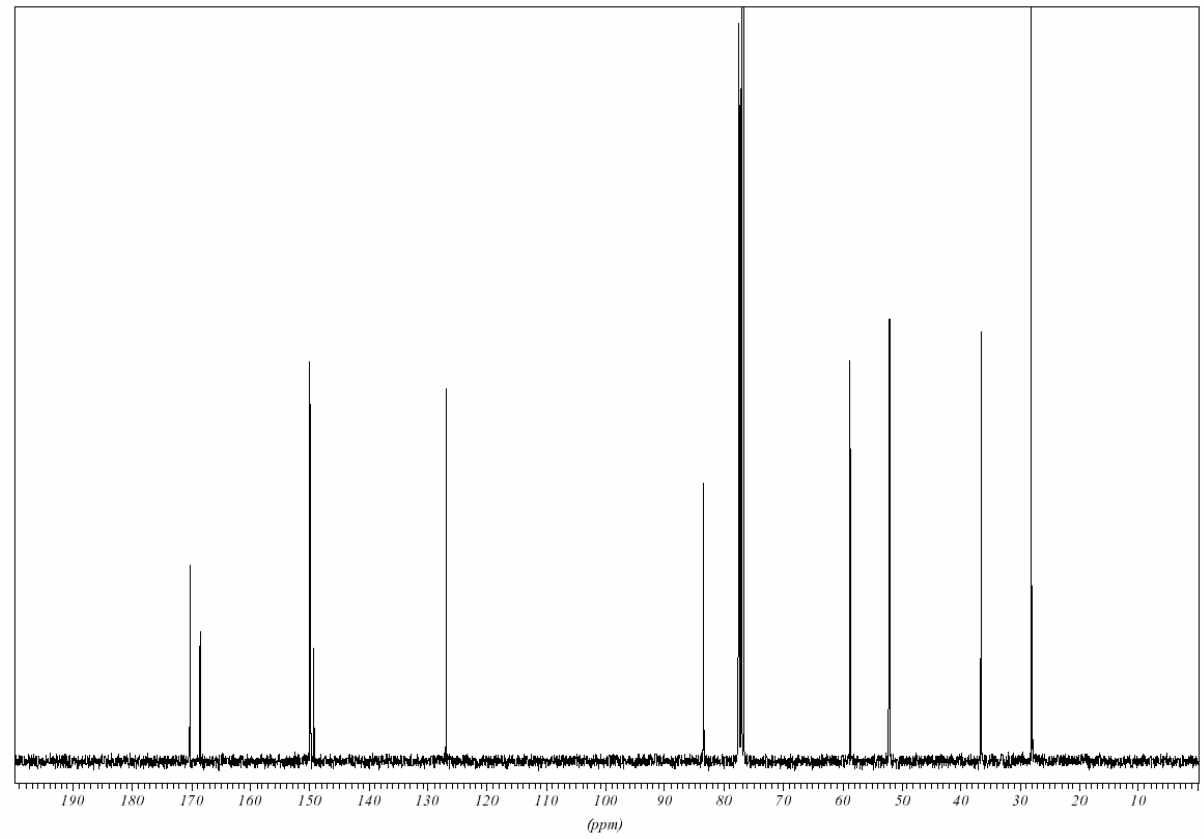


(2*R*)-2-Methoxycarbonylmethyl-5-oxo-2,5-dihydro-pyrrole-1-carboxylic acid tert-butyl ester (8)

^{1}H-NMR (300 MHz, $CDCl_3$)

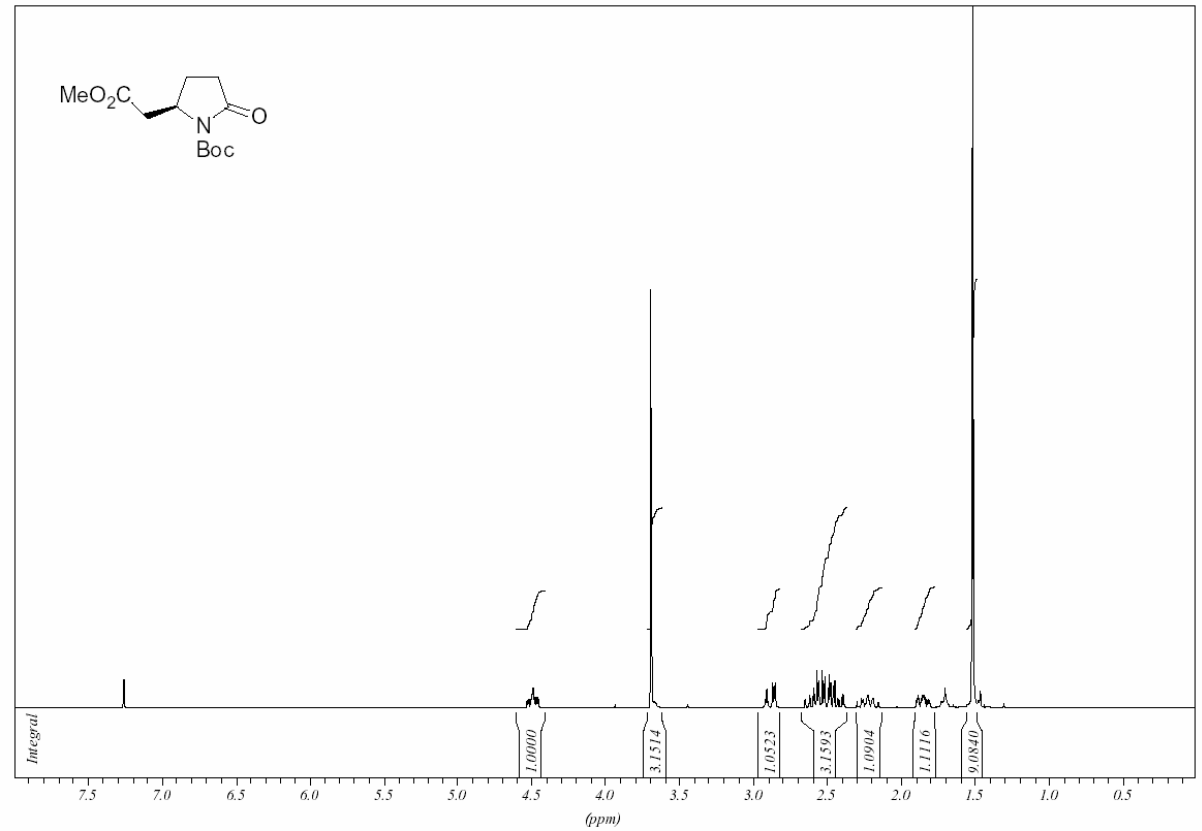


^{13}C-NMR (75 MHz, $CDCl_3$)

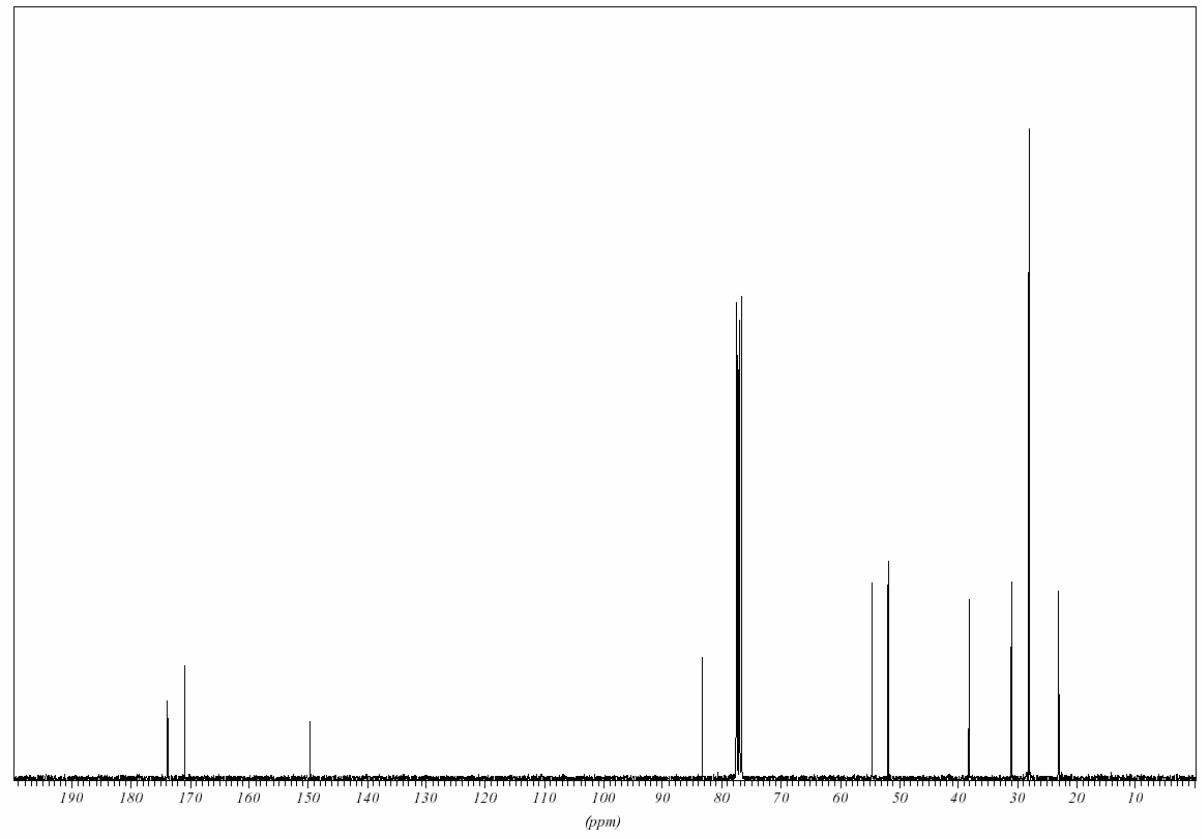


(2*R*)-2-Methoxycarbonylmethyl-5-oxo-pyrrolidine-1-carboxylic acid tert-butyl ester (20)

^{1}H-NMR (300 MHz, $CDCl_3$)

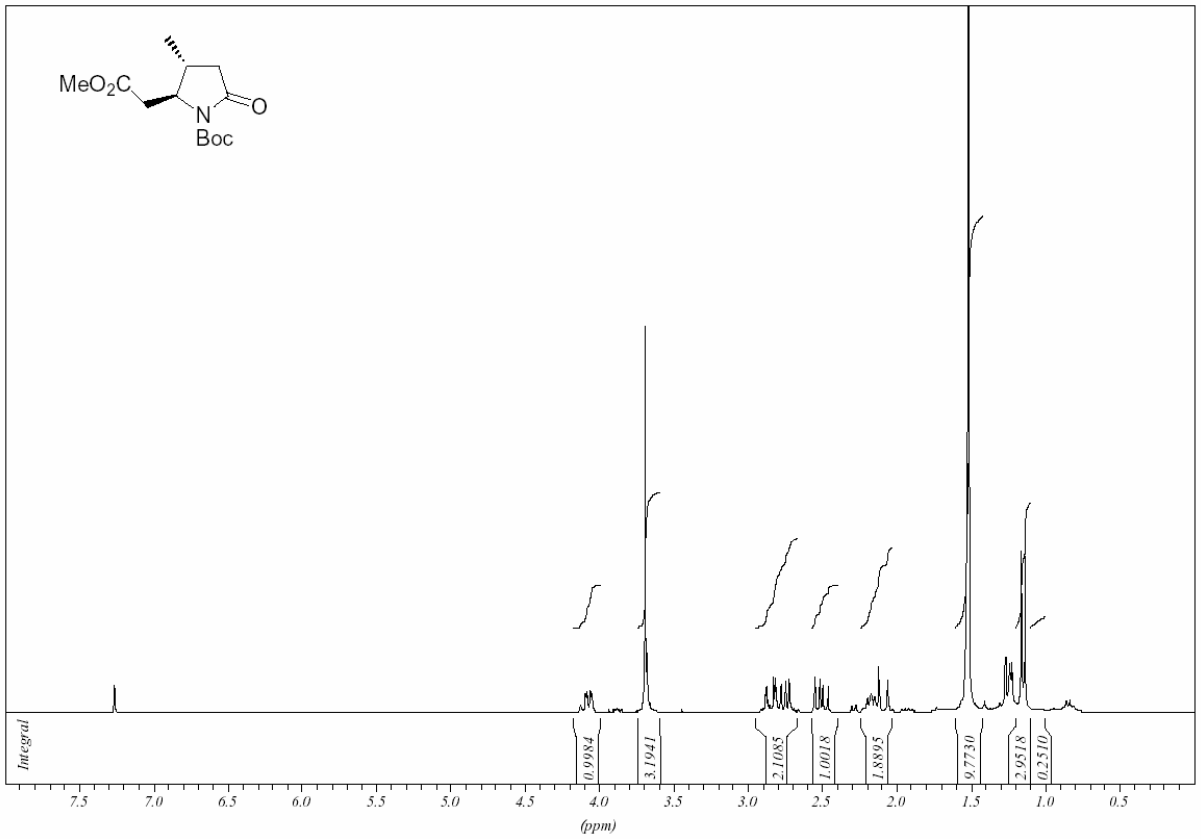


^{13}C-NMR (75 MHz, $CDCl_3$)

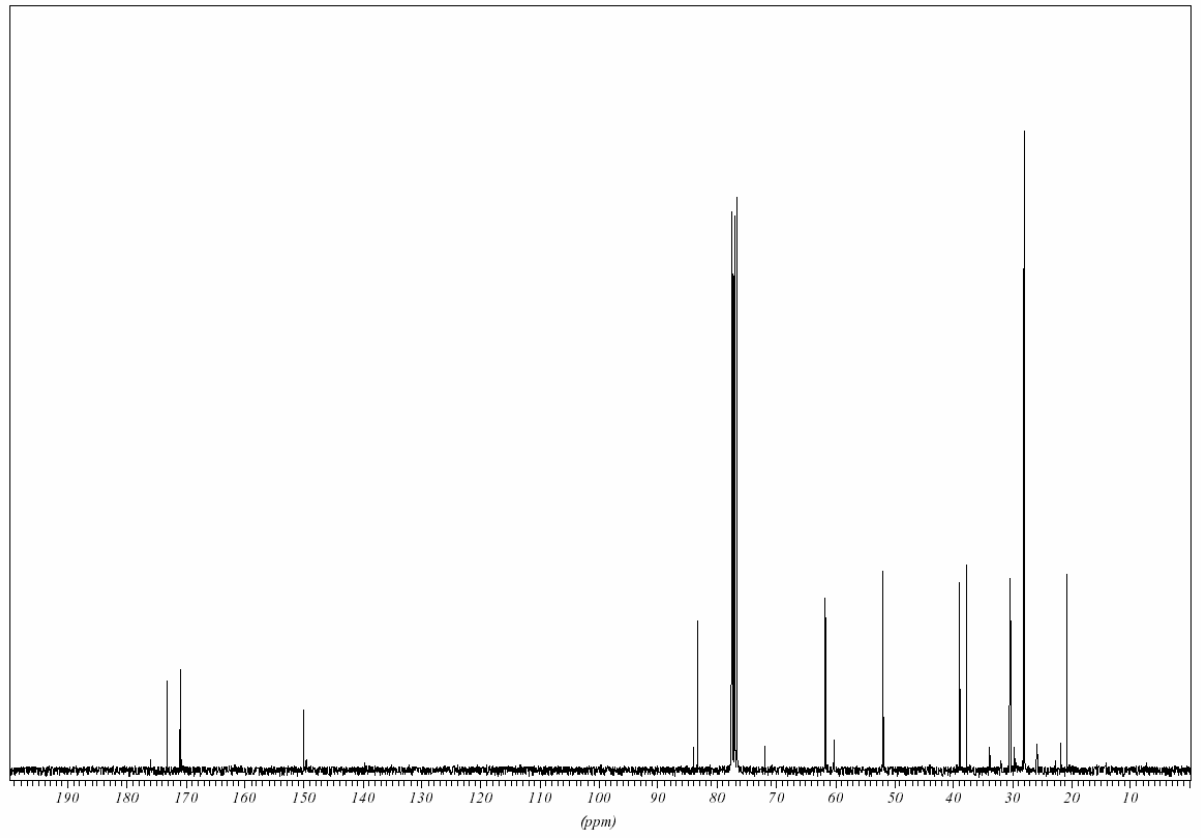


(2*R*,3*S*)-2-Methoxycarbonylmethyl-3-methyl-5-oxo-pyrrolidine-1-carboxylic acid tert-butyl ester (21)

^{1}H-NMR (300 MHz, $CDCl_3$)

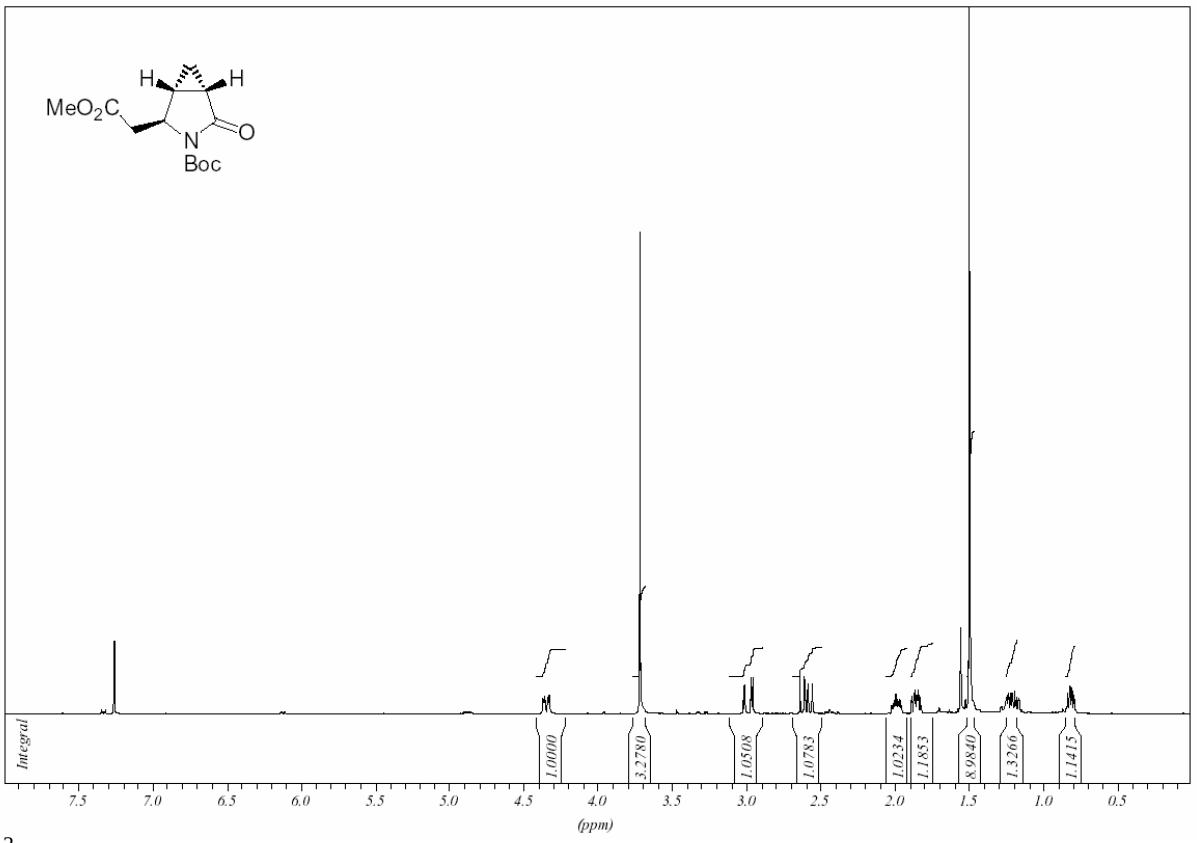


^{13}C-NMR (75 MHz, $CDCl_3$)

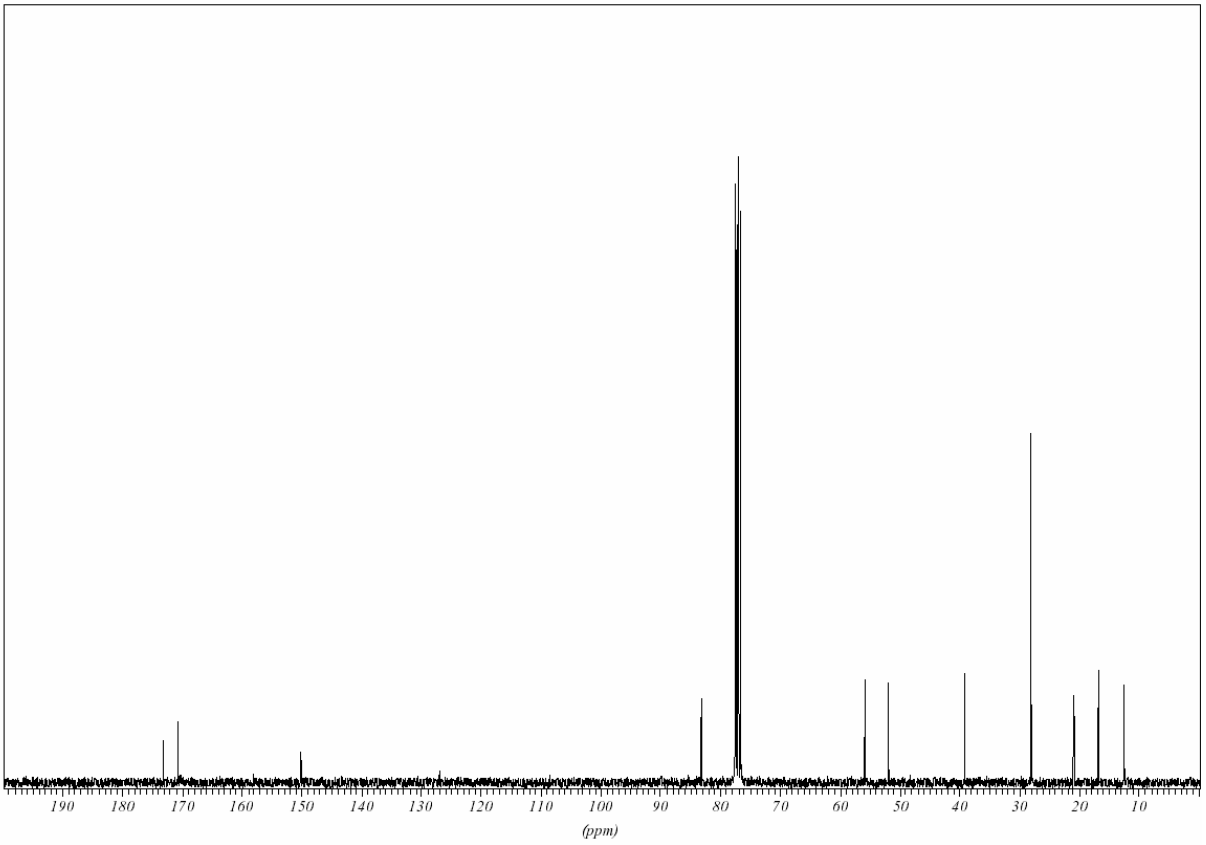


(1*S*,2*R*,3*S*)-2-Methoxycarbonylmethyl-4-oxo-3-aza-bicyclo[3.1.0]hexane-3-carboxylic acid tert-butyl ester (22)

^{1}H-NMR (300 MHz, $CDCl_3$)

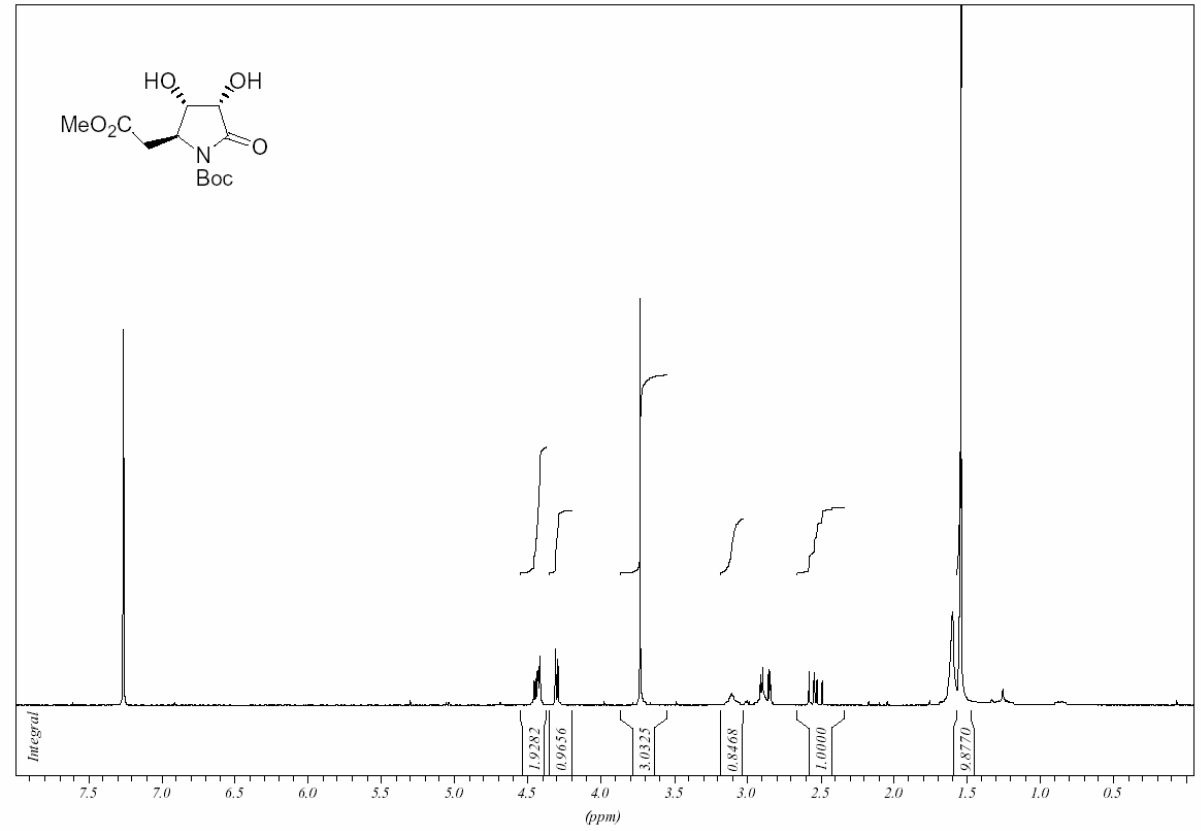


^{13}C-NMR (75 MHz, $CDCl_3$)

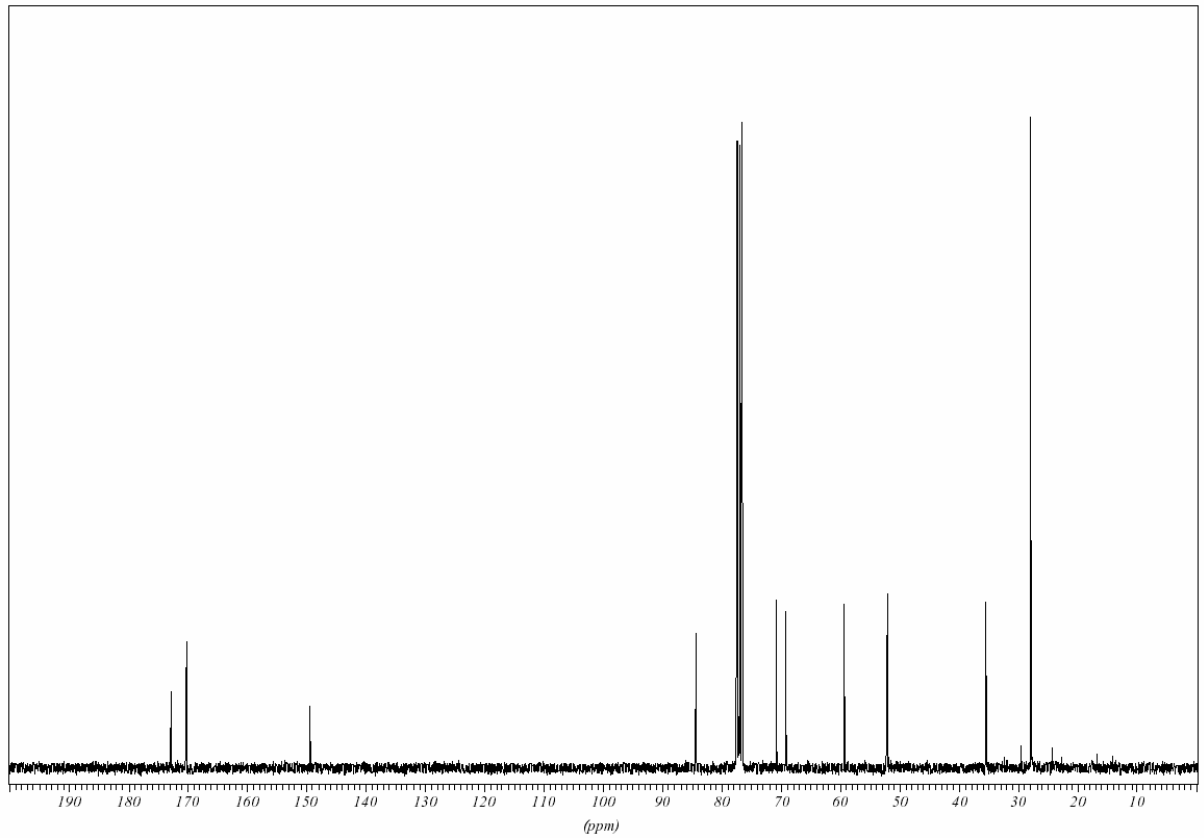


(2*R*,3*S*,4*S*)-3,4-Dihydroxy-2-methoxycarbonylmethyl-5-oxo-pyrrolidine-1-carboxylic acid tert-butyl ester (23)

^{1}H-NMR (300 MHz, $CDCl_3$)

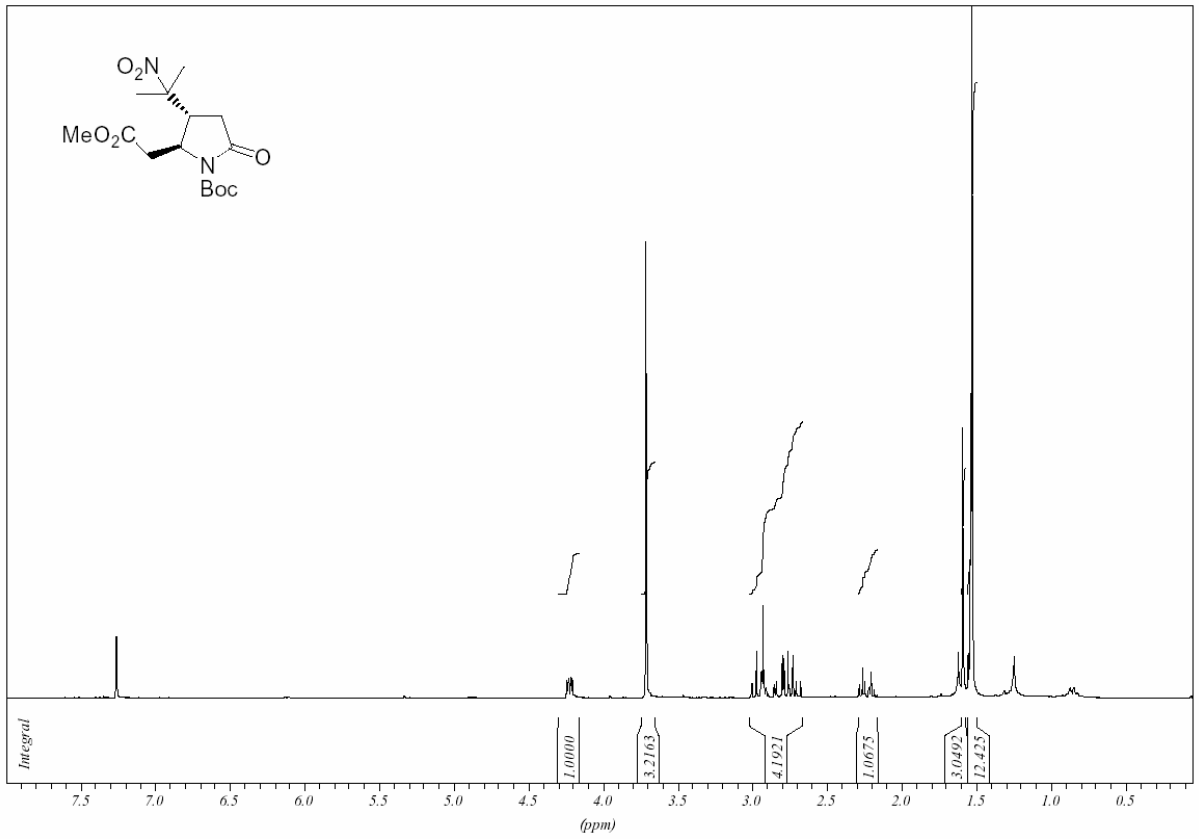


^{13}C-NMR (75 MHz, $CDCl_3$)

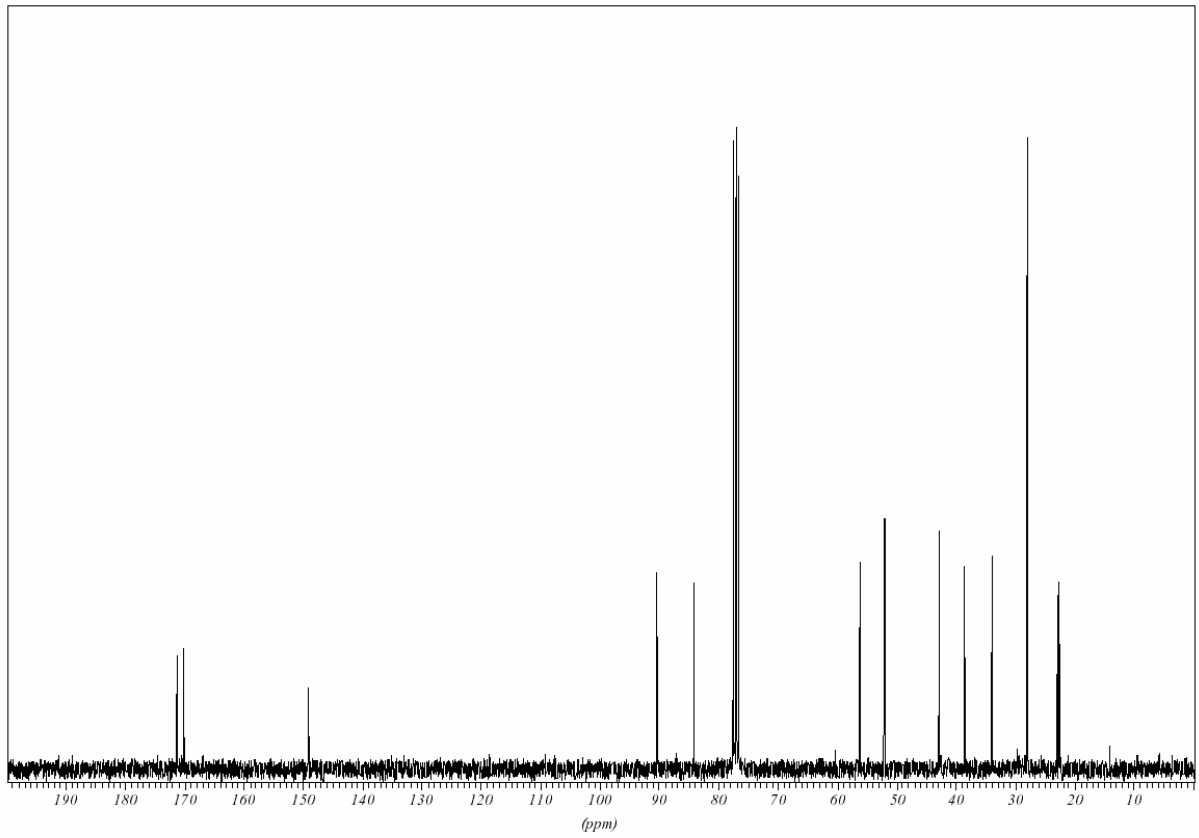


(*rac*)-2-Methoxycarbonylmethyl-3-(1'-methyl-1'-nitroethyl)-5-oxo-pyrrolidine-1-carboxylic acid tert-butyl ester (24)

^{1}H-NMR (300 MHz, $CDCl_3$)

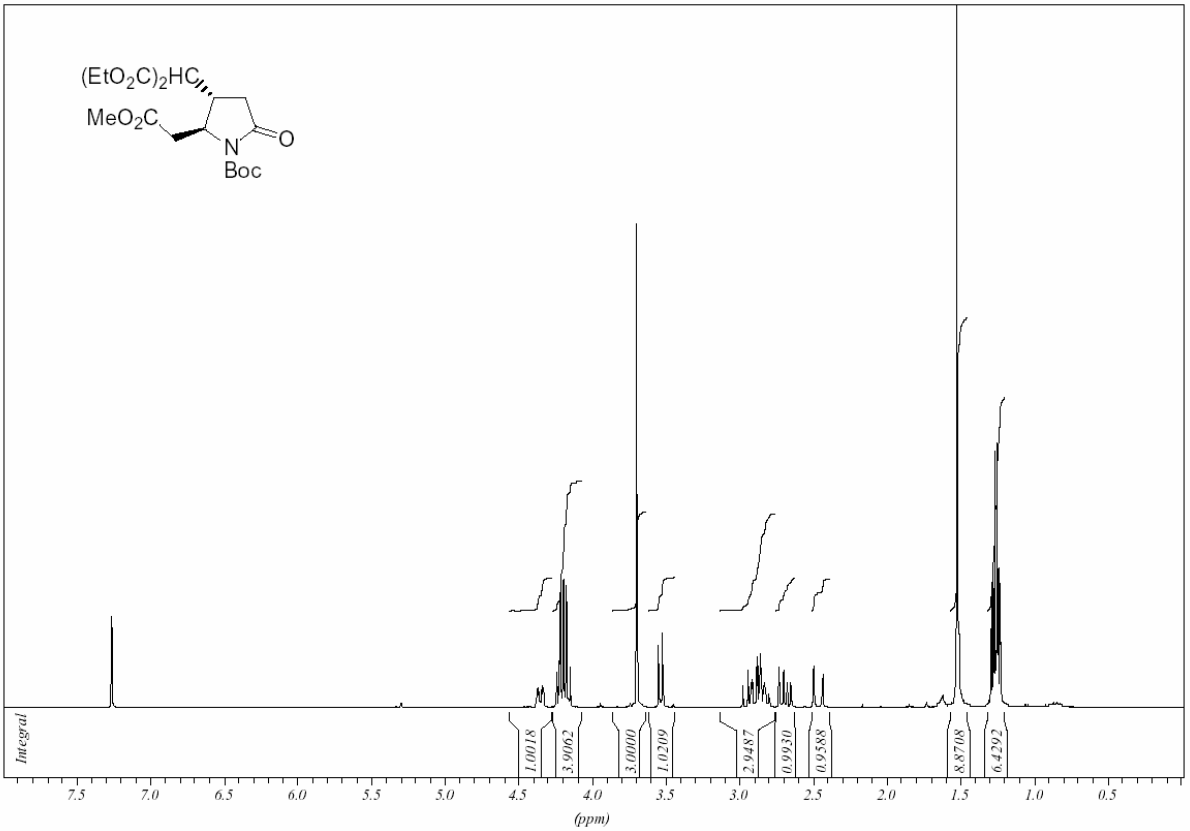


^{13}C-NMR (75 MHz, $CDCl_3$)

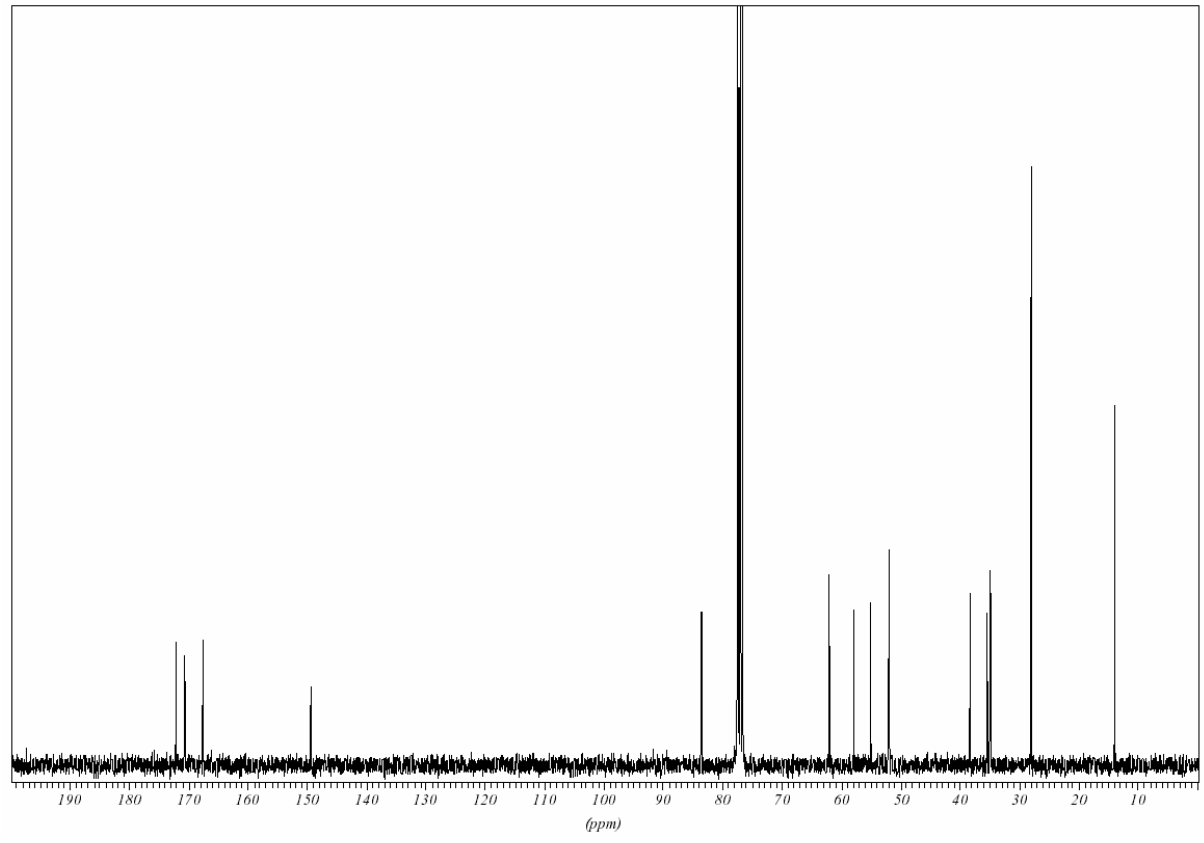


(2*R*,3*R*)-(1-tert-Butoxycarbonyl-2-methoxycarbonylmethyl-5-oxo-pyrrolidin-3-yl)-malonic acid diethyl ester (25)

^{1}H-NMR (300 MHz, $CDCl_3$)

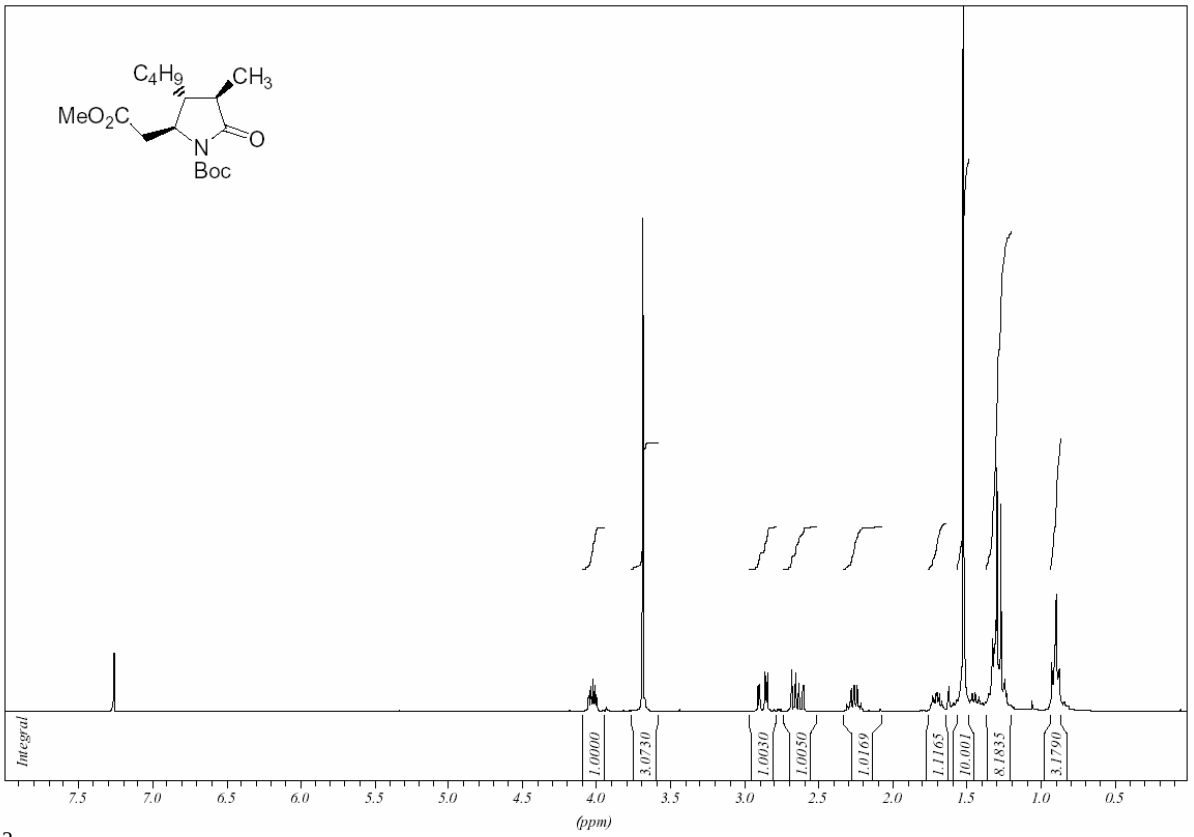


^{13}C-NMR (75 MHz, $CDCl_3$)

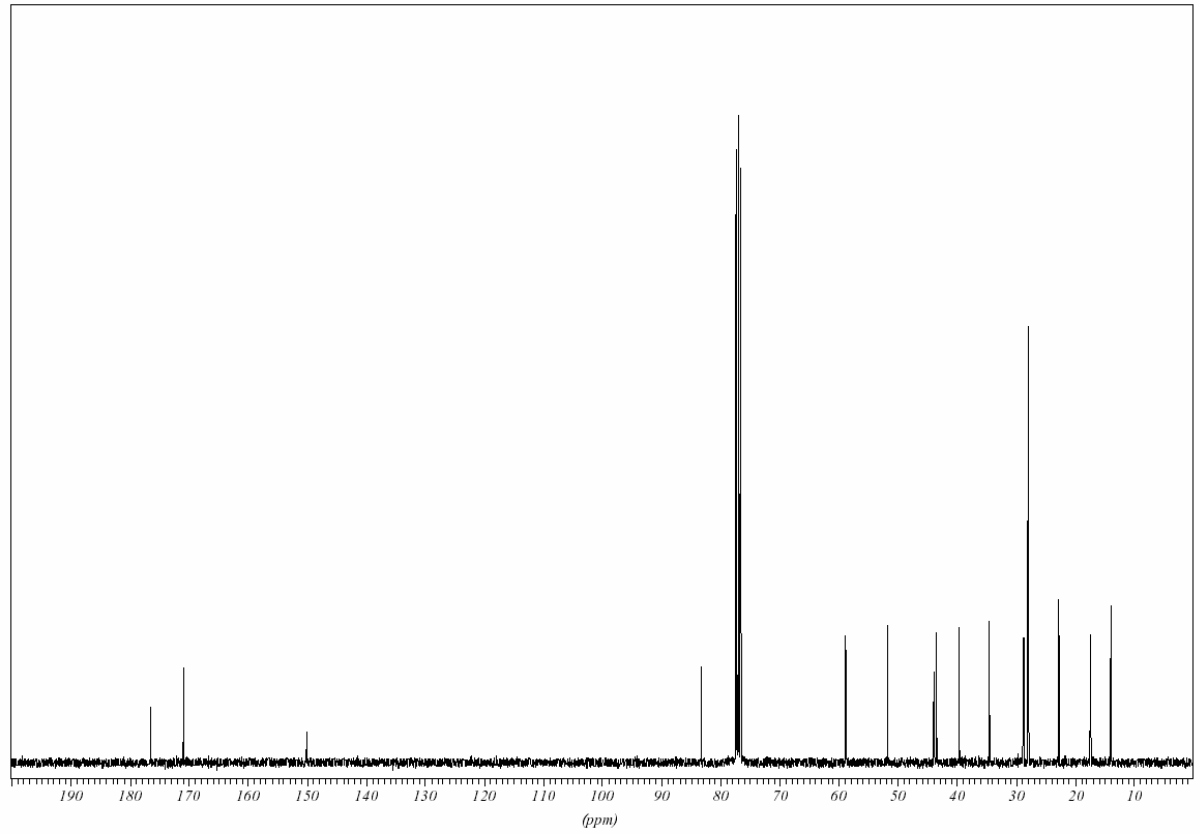


(2*R*,3*S*,4*R*)-3-Butyl-2-methoxycarbonylmethyl-4-methyl-5-oxo-pyrrolidine-1-carboxylic acid tert-butyl ester (26)

^{1}H-NMR (300 MHz, $CDCl_3$)

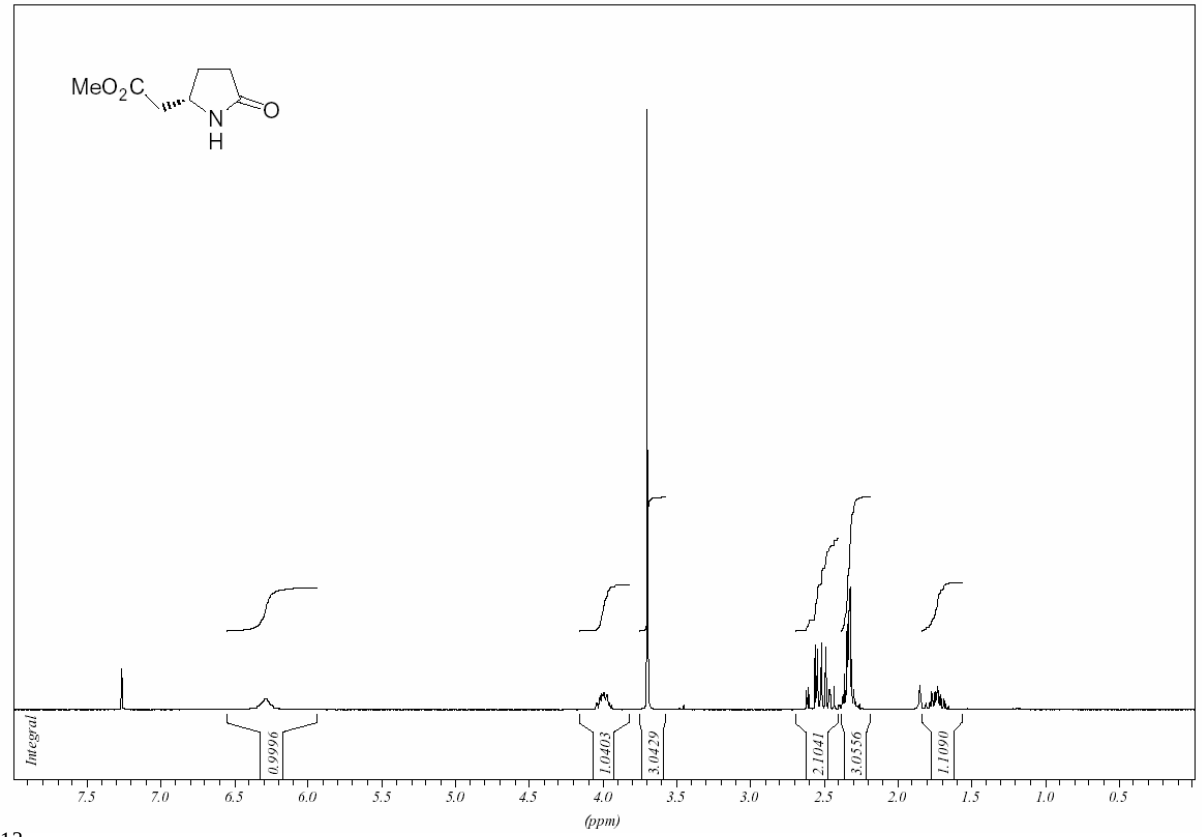


^{13}C-NMR (75 MHz, $CDCl_3$)

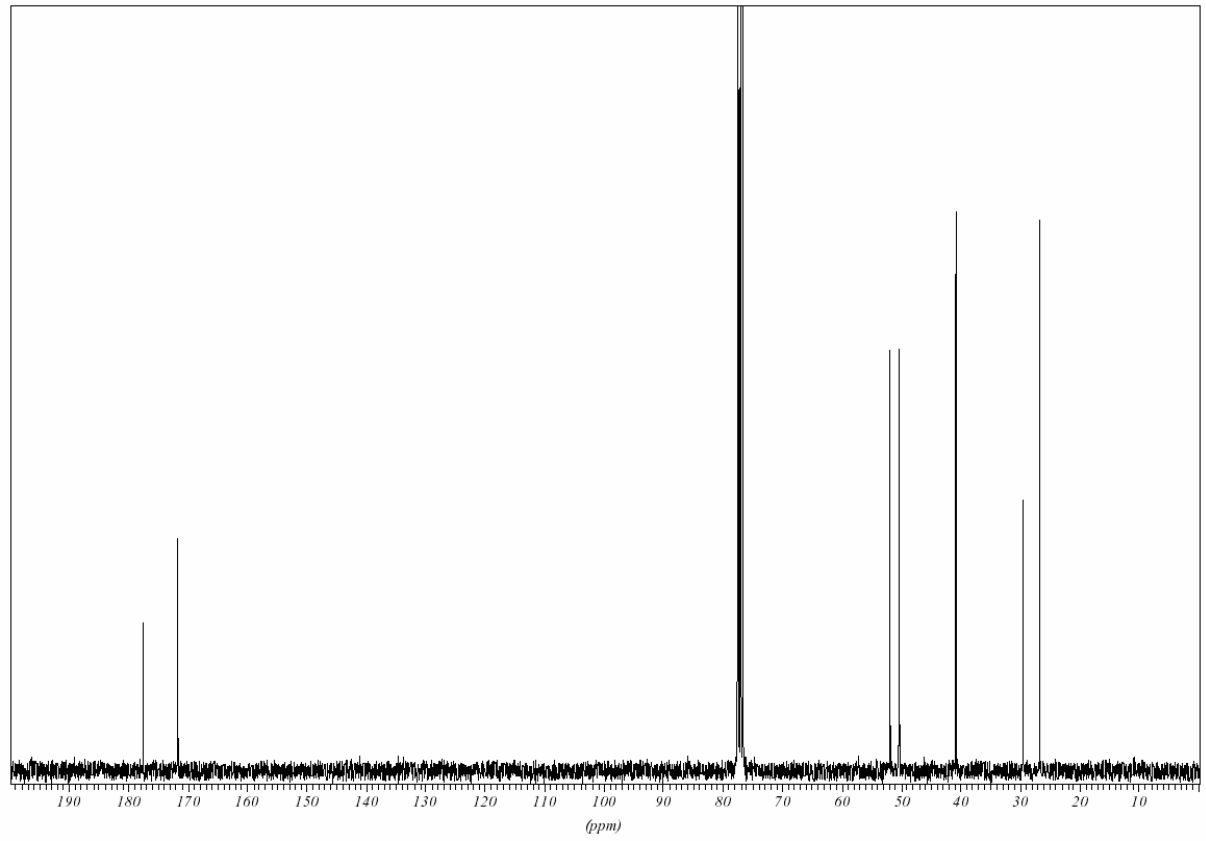


(5*S*)-(Oxo-pyrrolidin-2-yl)-acetic acid methyl ester (28)

^{1}H-NMR (300 MHz, $CDCl_3$)

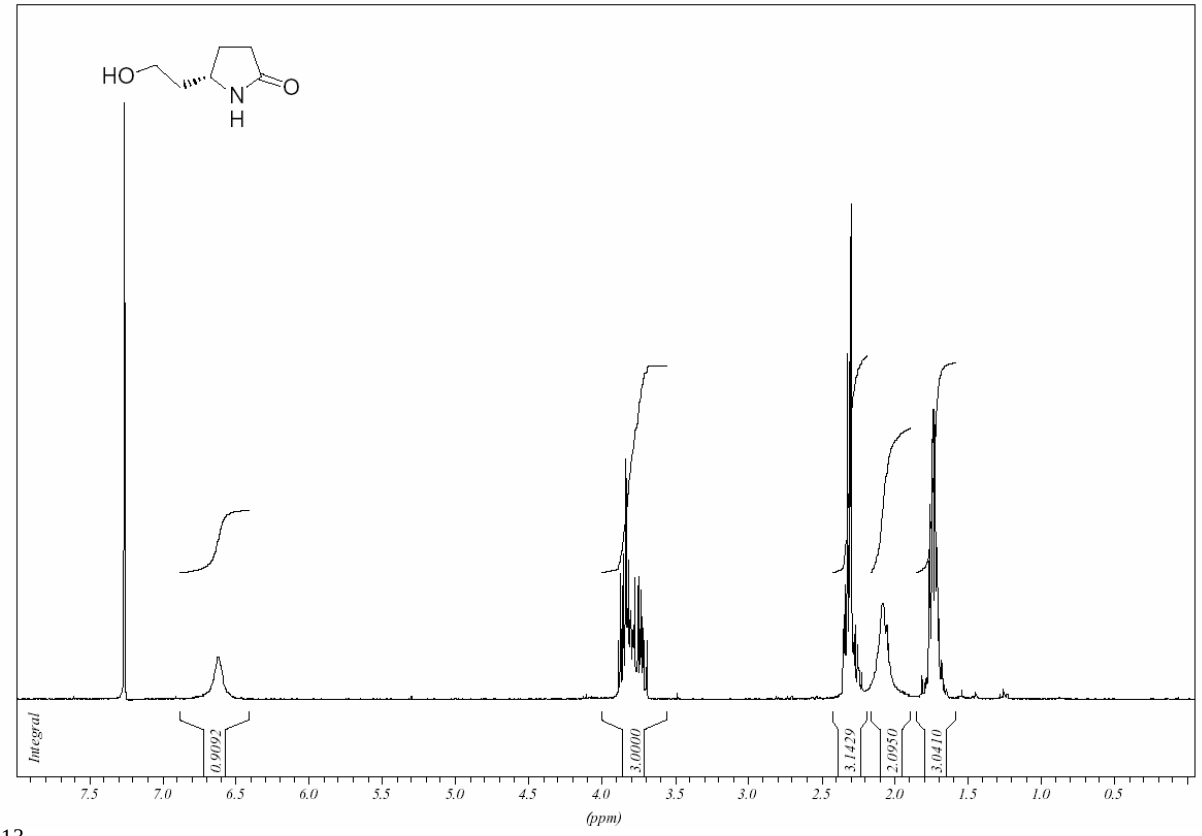


^{13}C-NMR (75 MHz, $CDCl_3$)

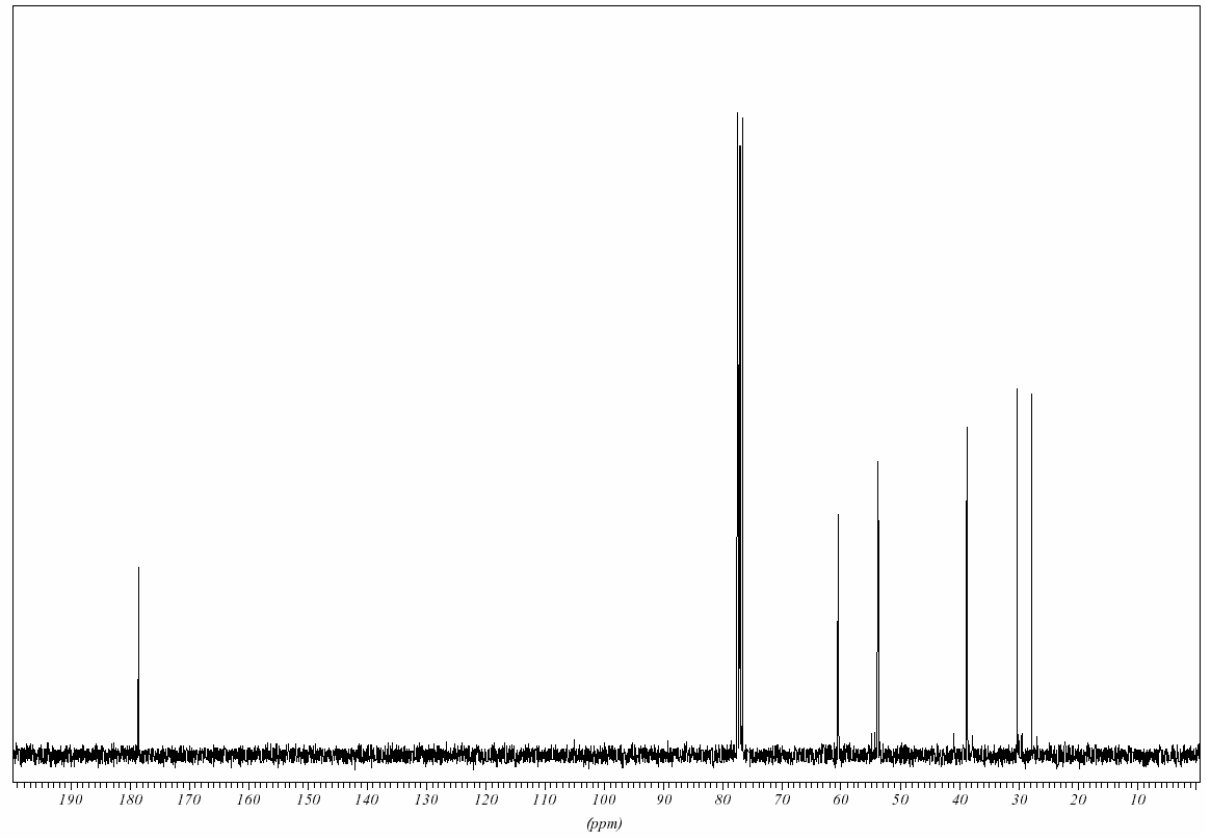


5(*S*)-(2-Hydroxyethyl)-pyrrolidin-2-one (29)

^{1}H-NMR (300 MHz, $CDCl_3$)

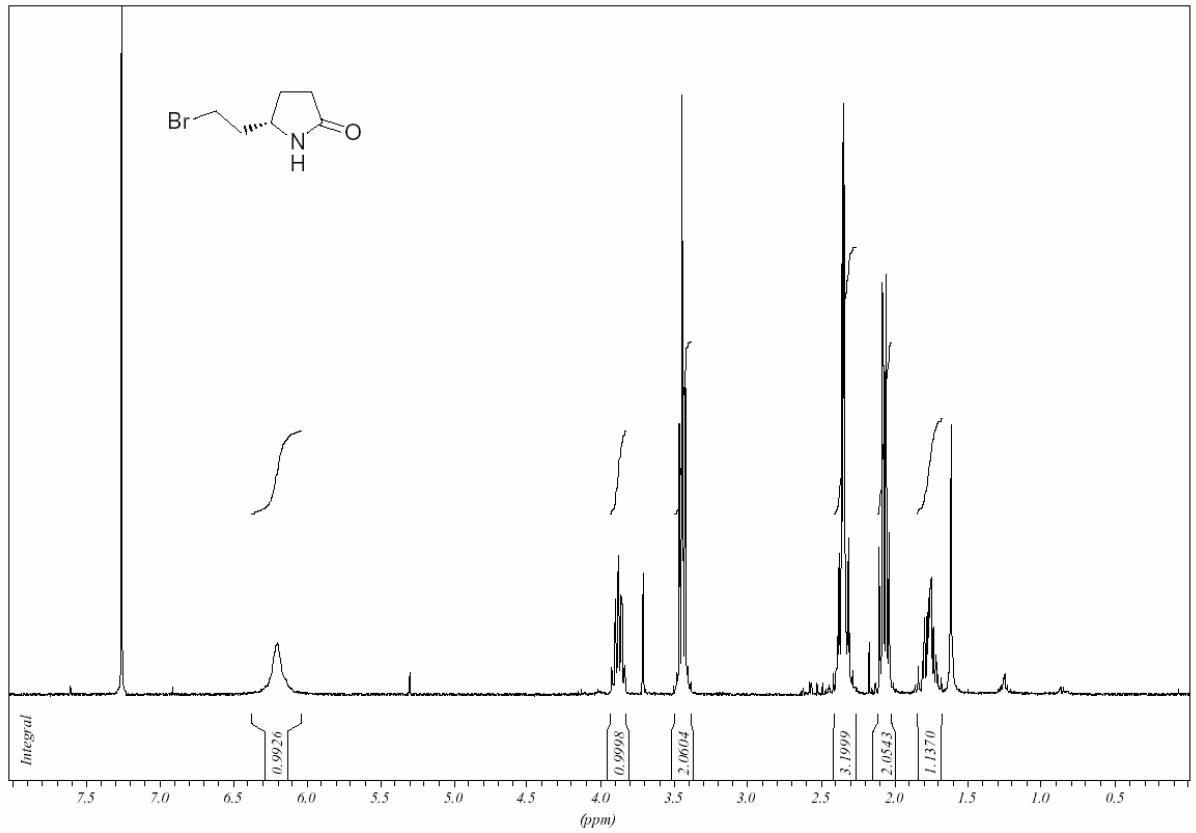


^{13}C-NMR (75 MHz, $CDCl_3$)

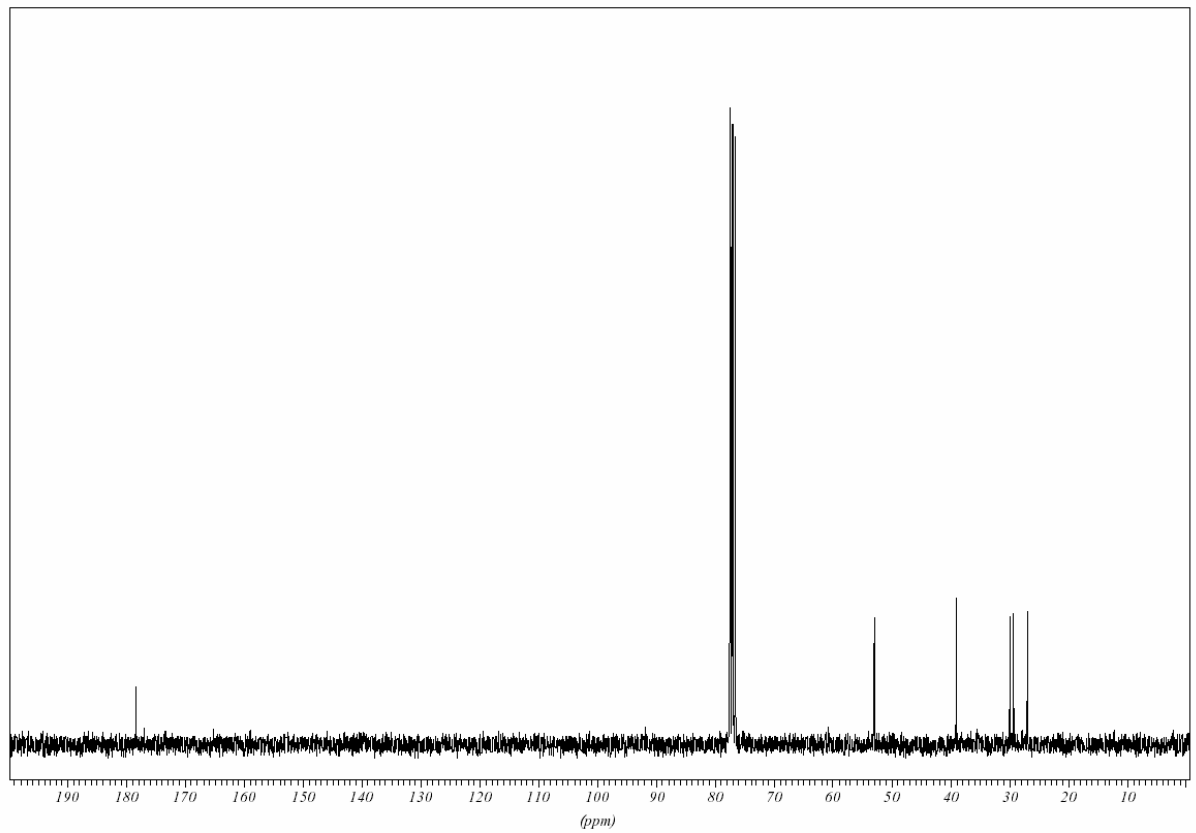


5(*S*)-(2-Bromo-ethyl)-pyrrolidin-2-one (75)

^{1}H-NMR (300 MHz, $CDCl_3$)

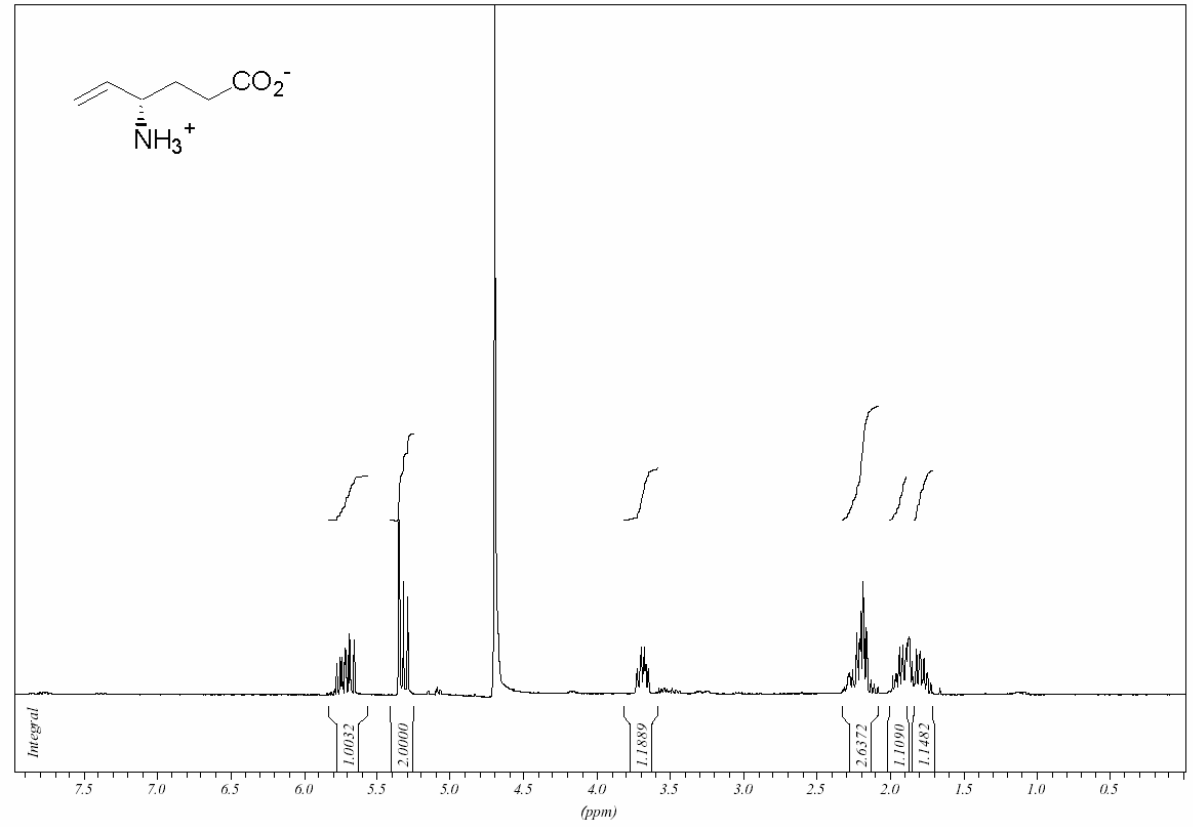


^{13}C-NMR (75 MHz, $CDCl_3$)

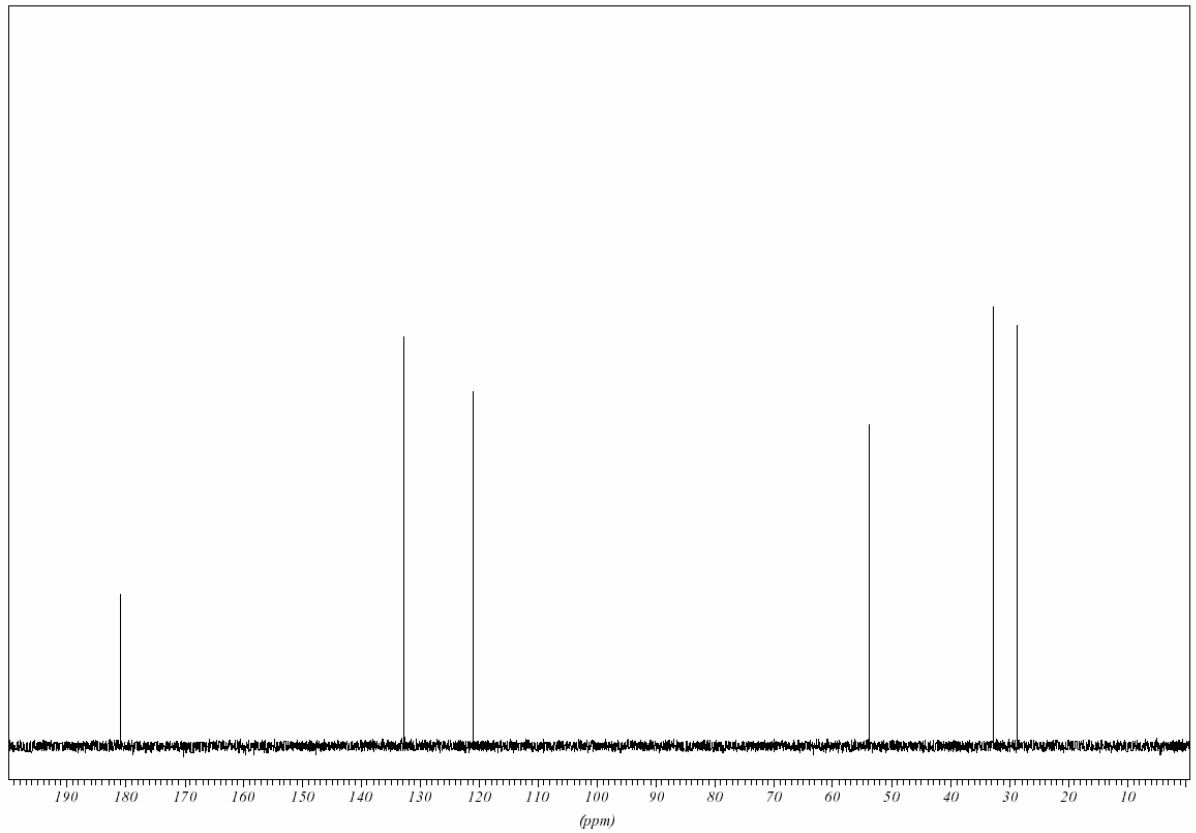


(*S*)-Vigabatrin (27)

^{1}H-NMR (300 MHz, D_2O)

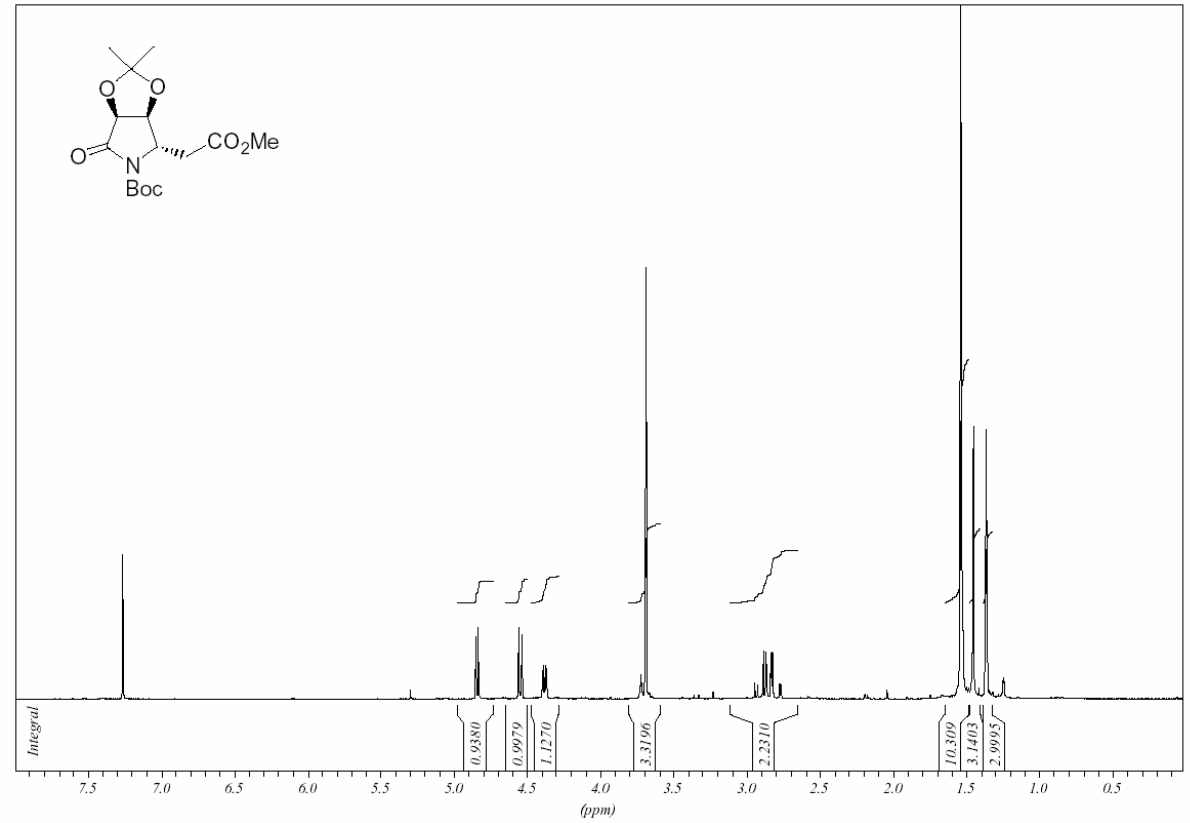


^{13}C-NMR (75 MHz, D_2O)

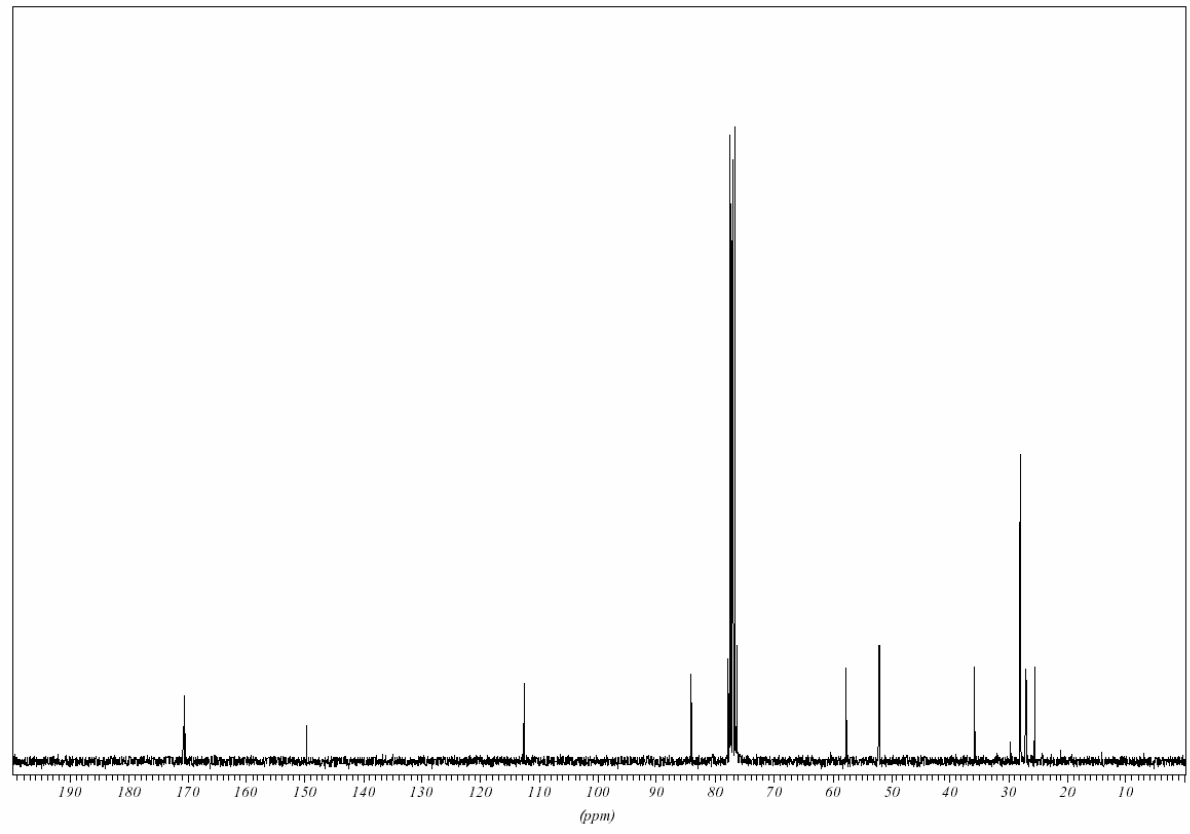


4-Methoxycarbonylmethyl-2,2-dimethyl-6-oxo-tetrahydro-[1,3]dioxolo[4,5-c]pyrrole-5-carboxylic acid tert-butyl ester (39)

^{1}H-NMR (300 MHz, $CDCl_3$)

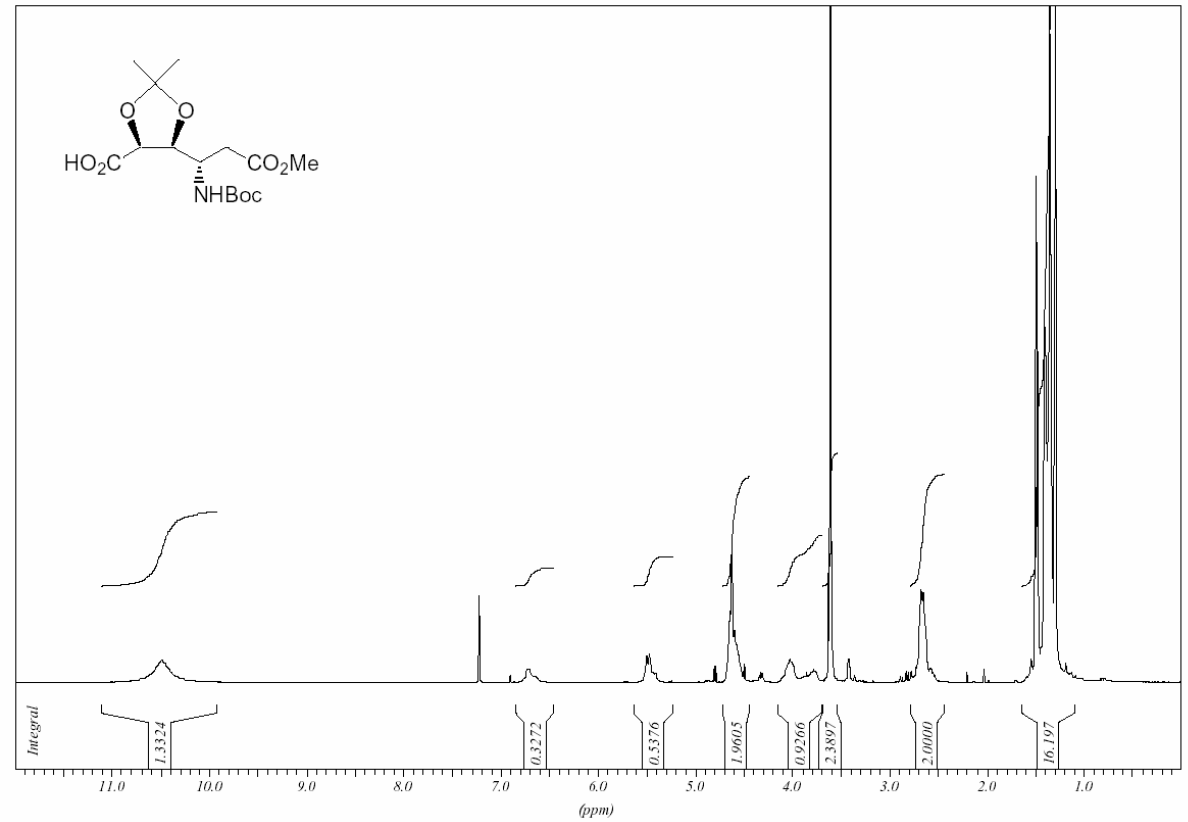


^{13}C-NMR (75 MHz, $CDCl_3$)

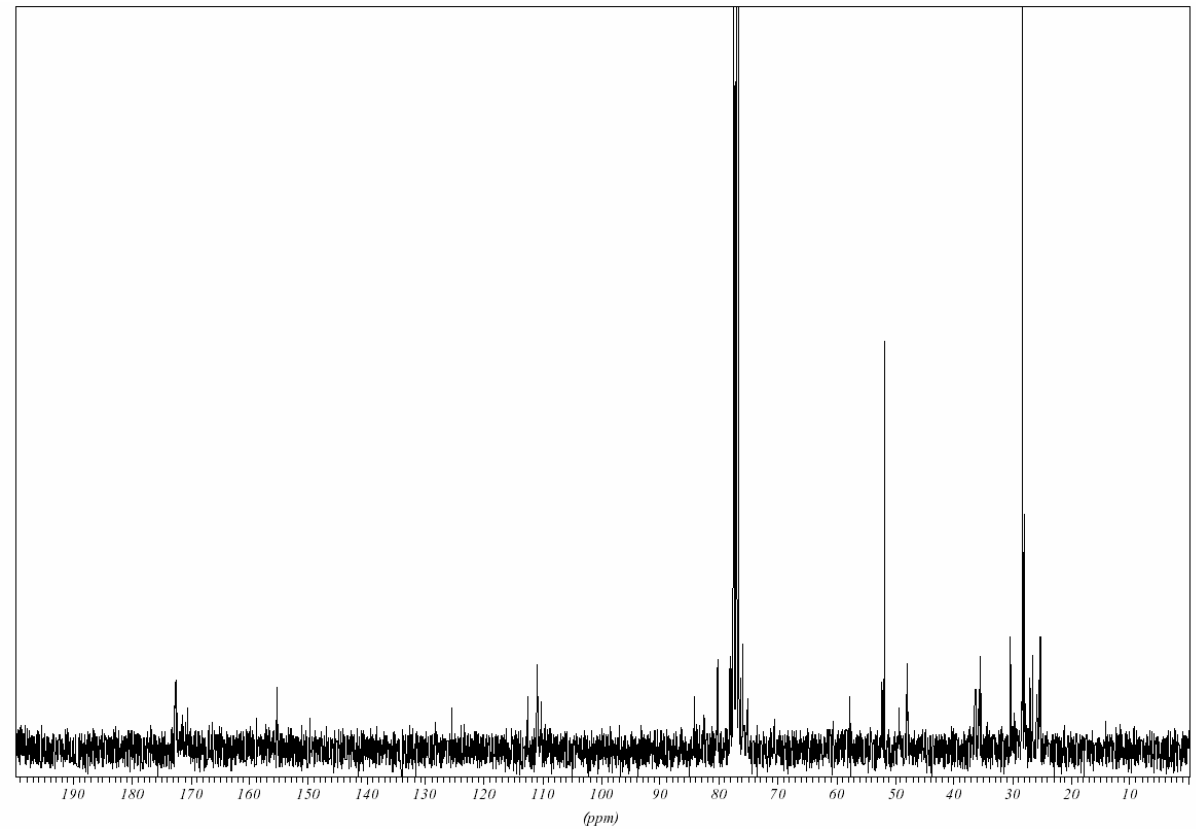


5-(1-tert-Butoxycarbonylamino-2-methoxycarbonyl-ethyl)-2,2-dimethyl-1,3]dioxolane-4-carboxylic acid (40)

^{1}H-NMR (300 MHz, $CDCl_3$)

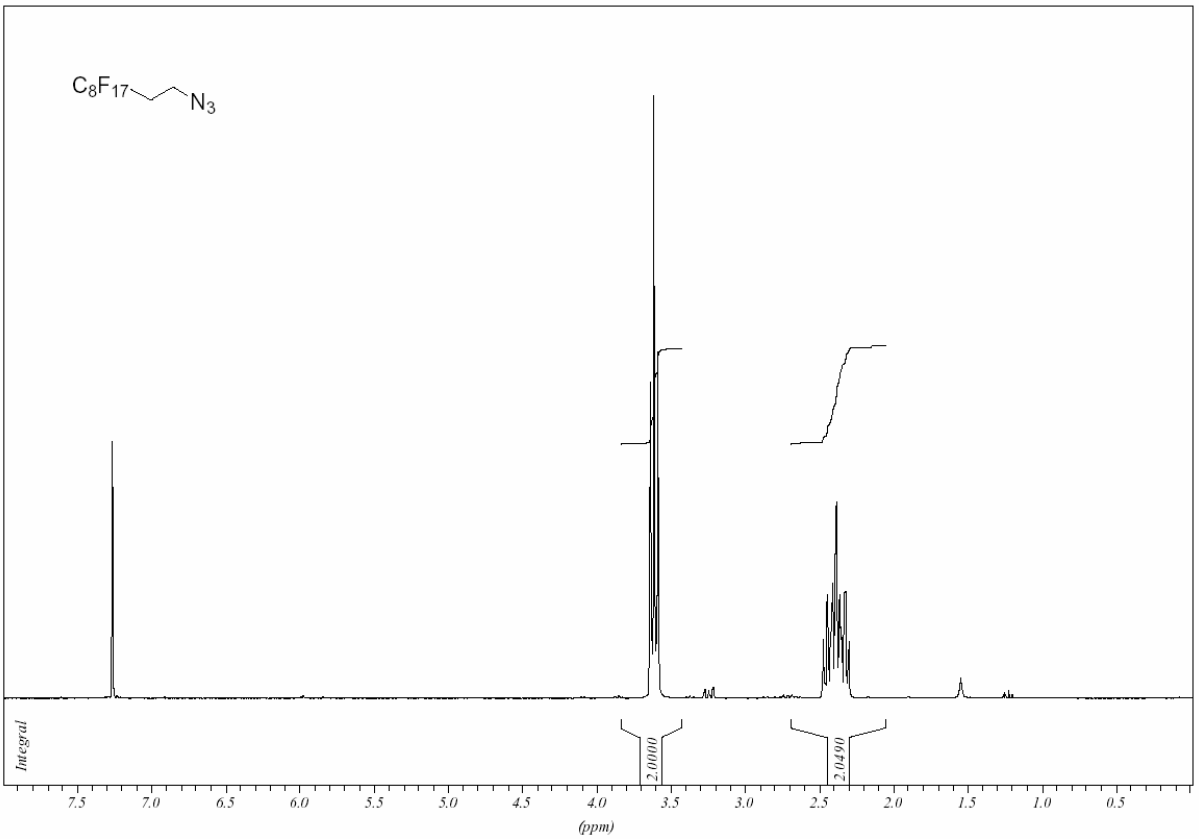


^{13}C-NMR (75 MHz, $CDCl_3$)

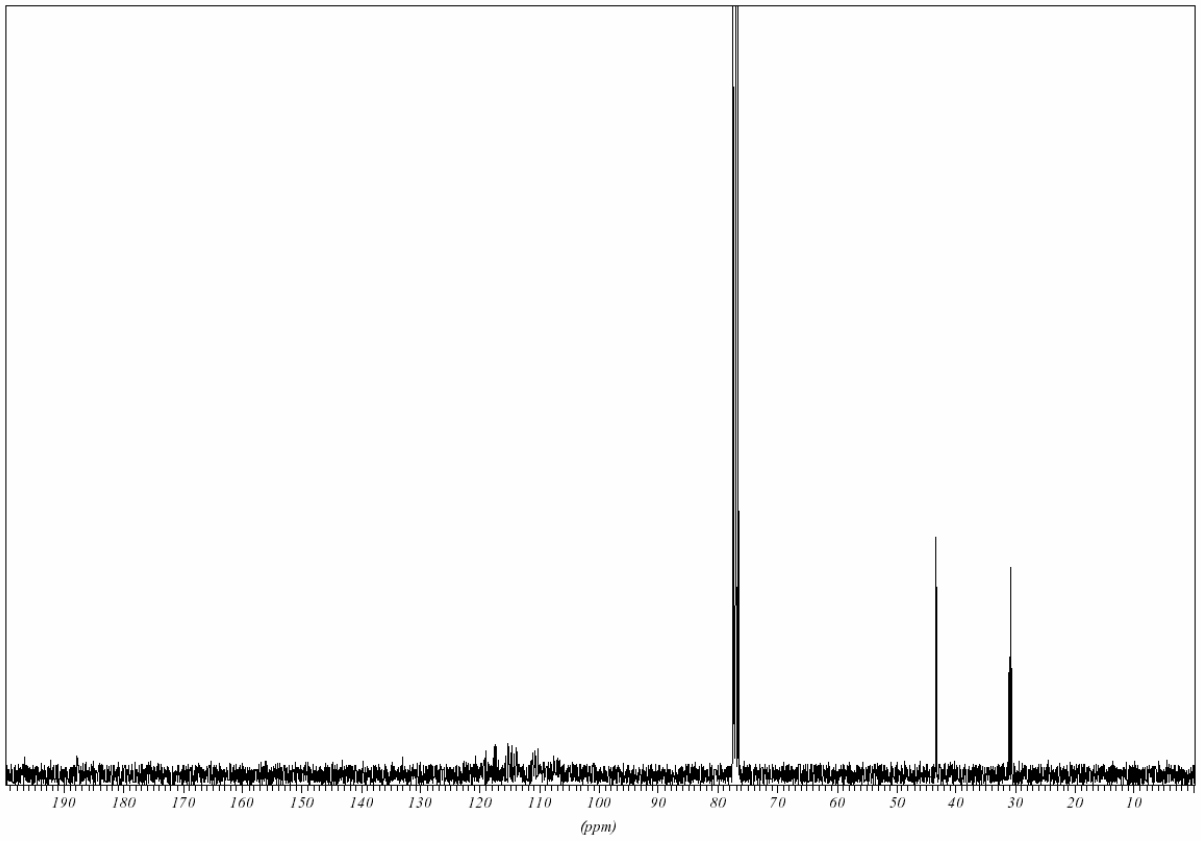


1-Azido-perfluorodecane (52)

^{1}H-NMR (300 MHz, $CDCl_3$)

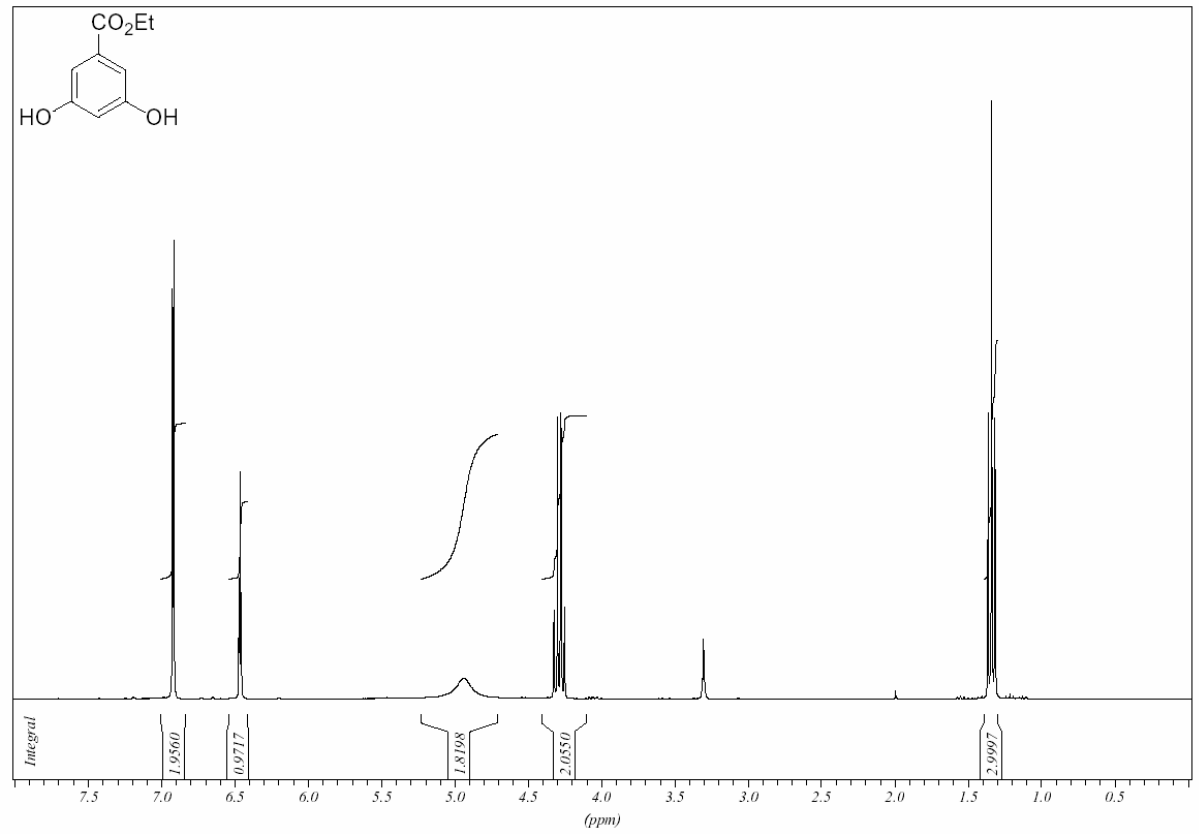


^{13}C-NMR (75 MHz, $CDCl_3$)

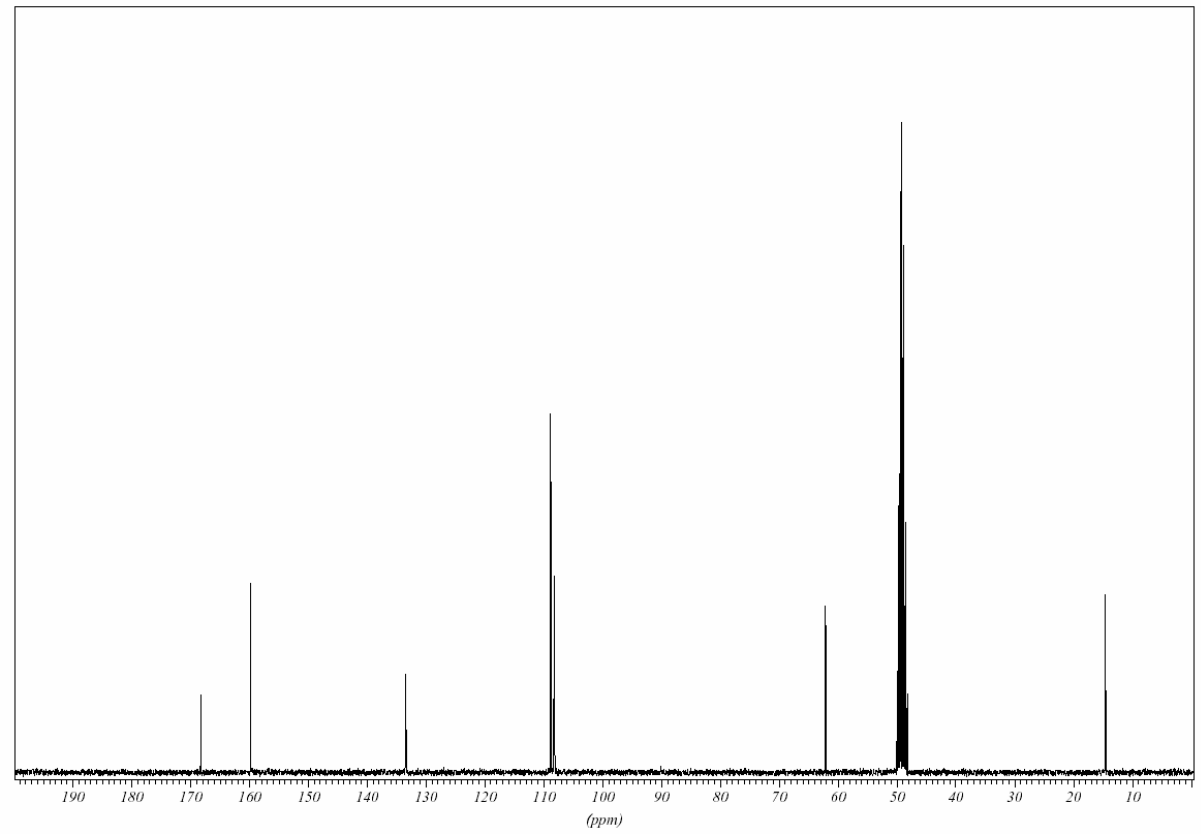


3,5-Dihydroxy-benzoic acid ethyl ester (**54**)

^{1}H-NMR (300 MHz, [D_4] MeOH)

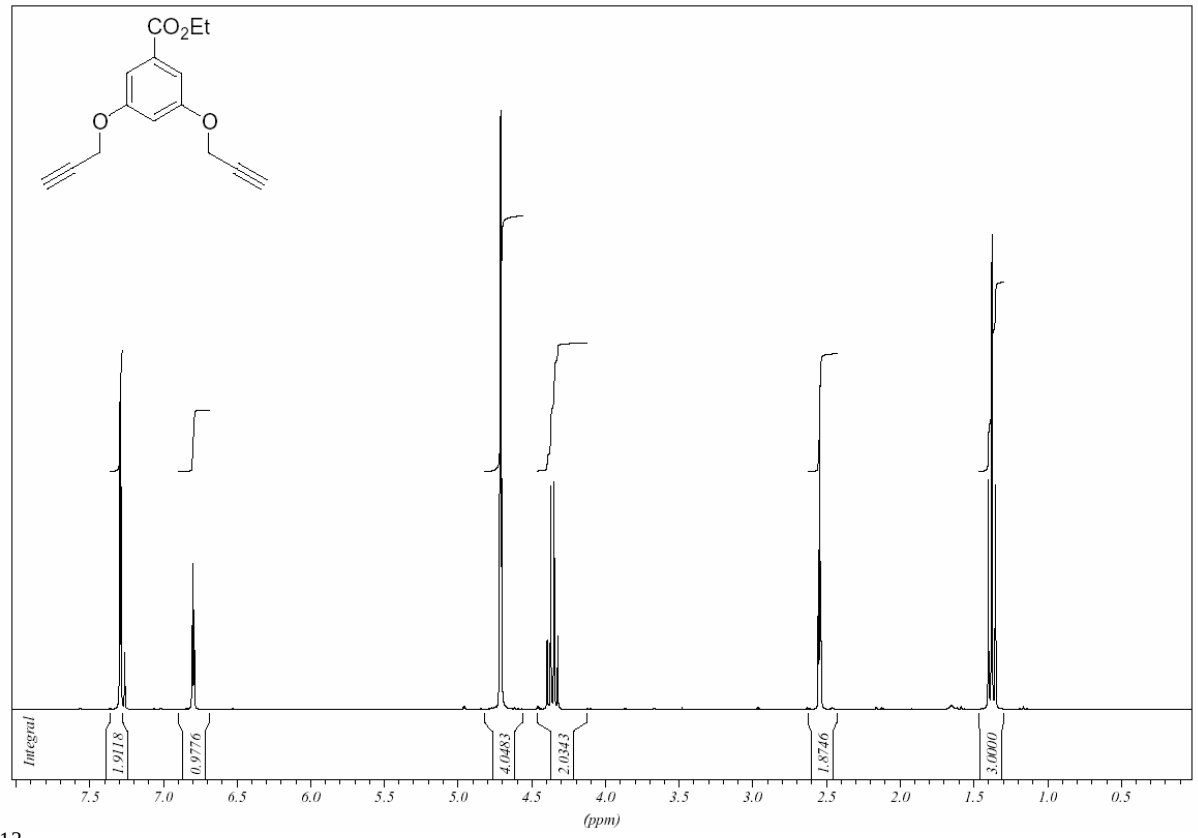


^{13}C-NMR (75 MHz, [D_4] MeOH)

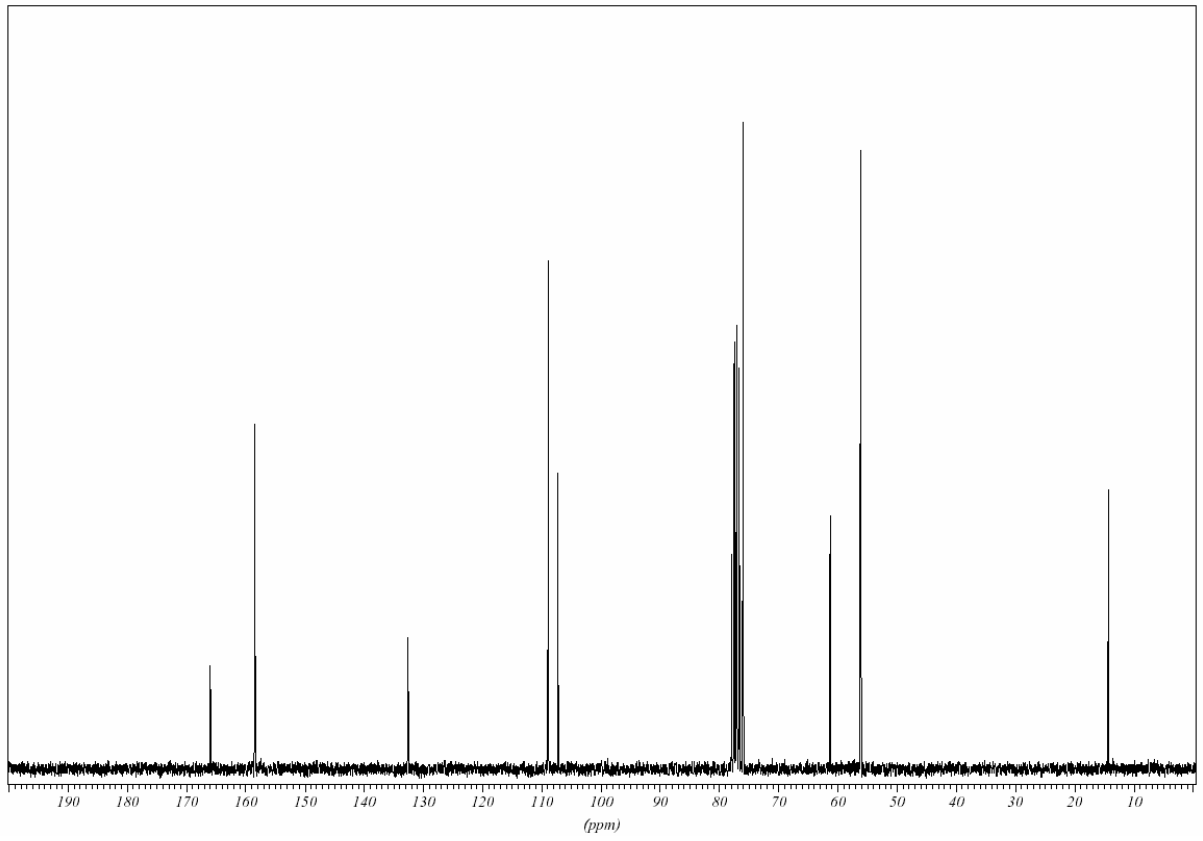


3,5-Bis-prop-2-ynyloxy-benzoic acid ethyl ester (76)

^{1}H-NMR (300 MHz, $CDCl_3$)

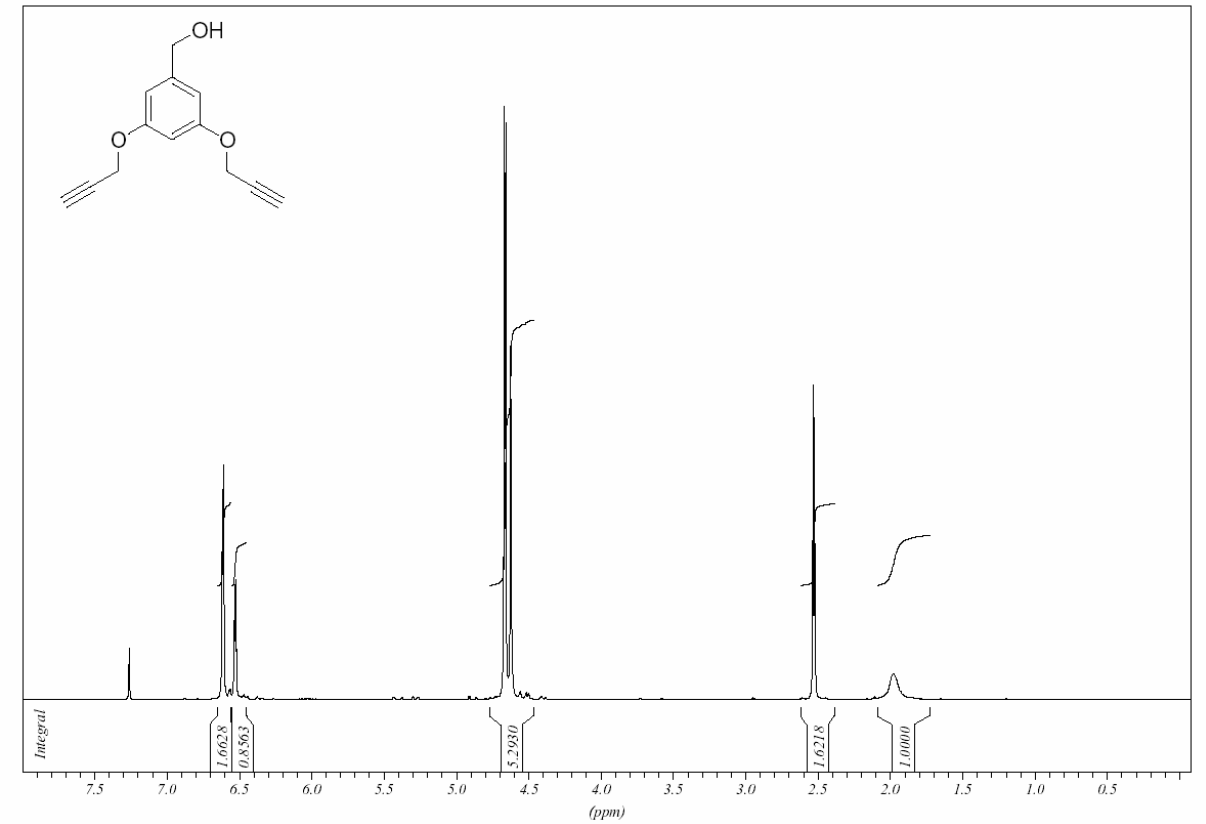


^{13}C-NMR (75 MHz, $CDCl_3$)

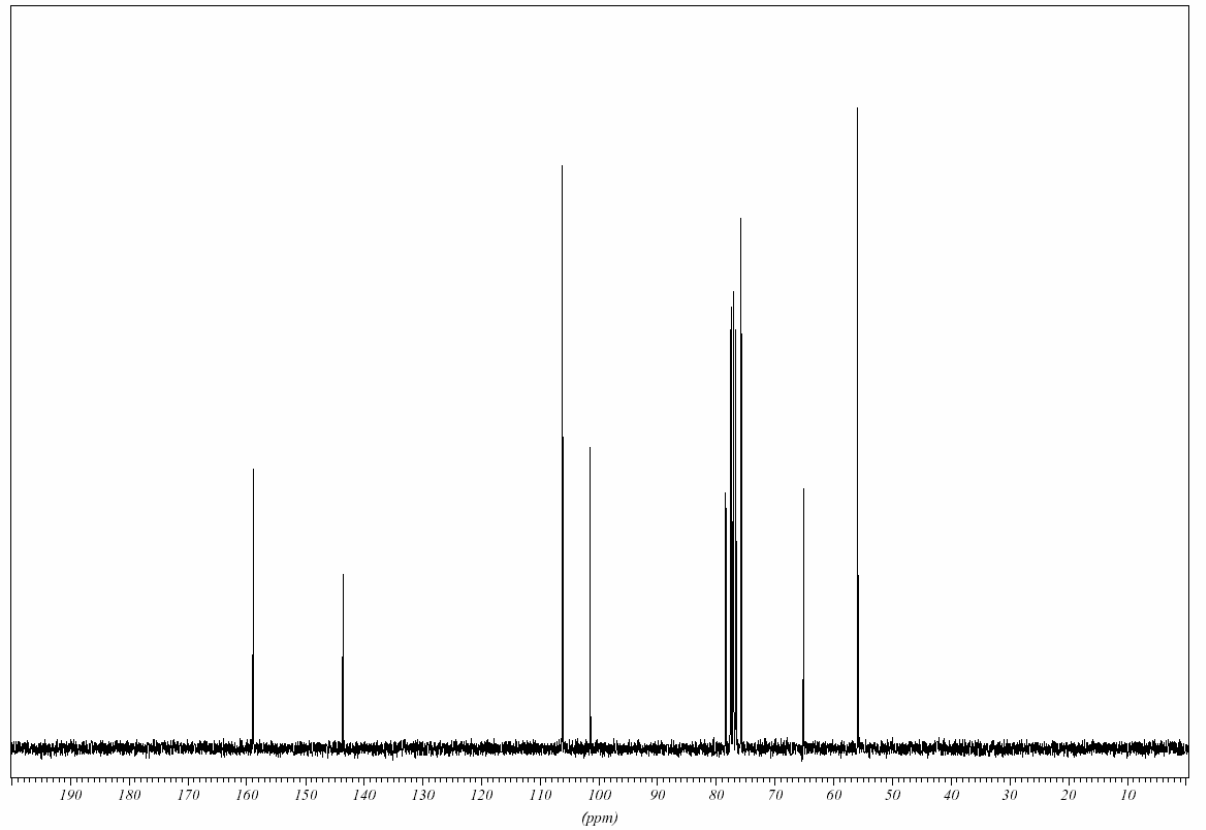


3,5-Bis-(propargyloxy)benzyl alcohol (77)

^{1}H-NMR (300 MHz, $CDCl_3$)

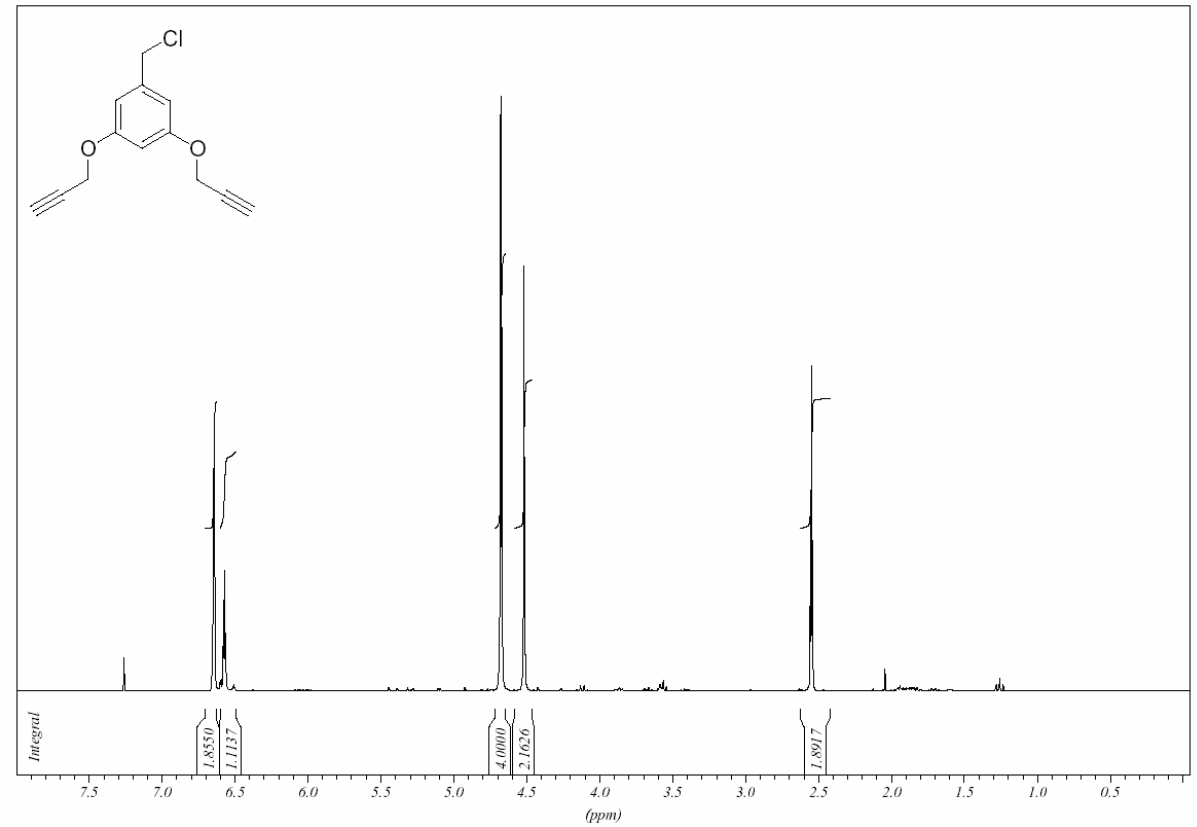


^{13}C-NMR (75 MHz, $CDCl_3$)

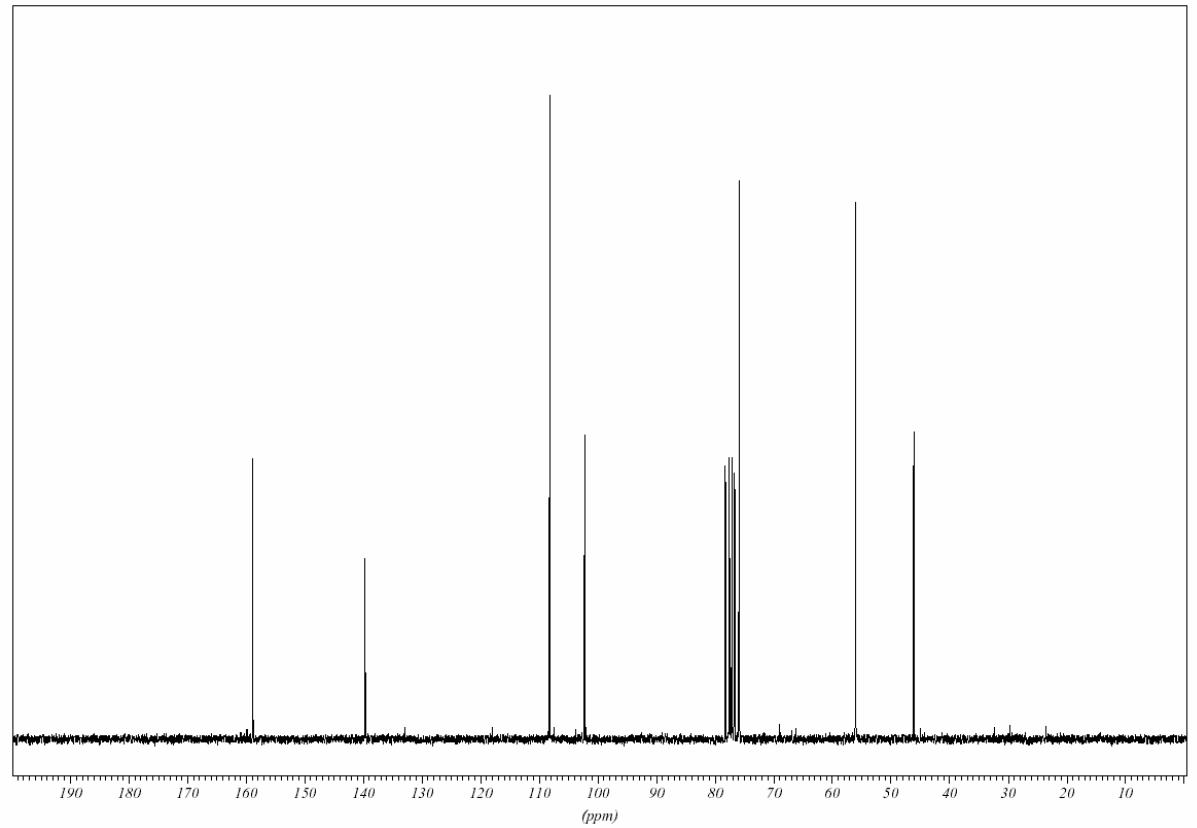


3,5-Bis-(propargyloxy)benzyl chloride (56)

^{1}H-NMR (300 MHz, $CDCl_3$)

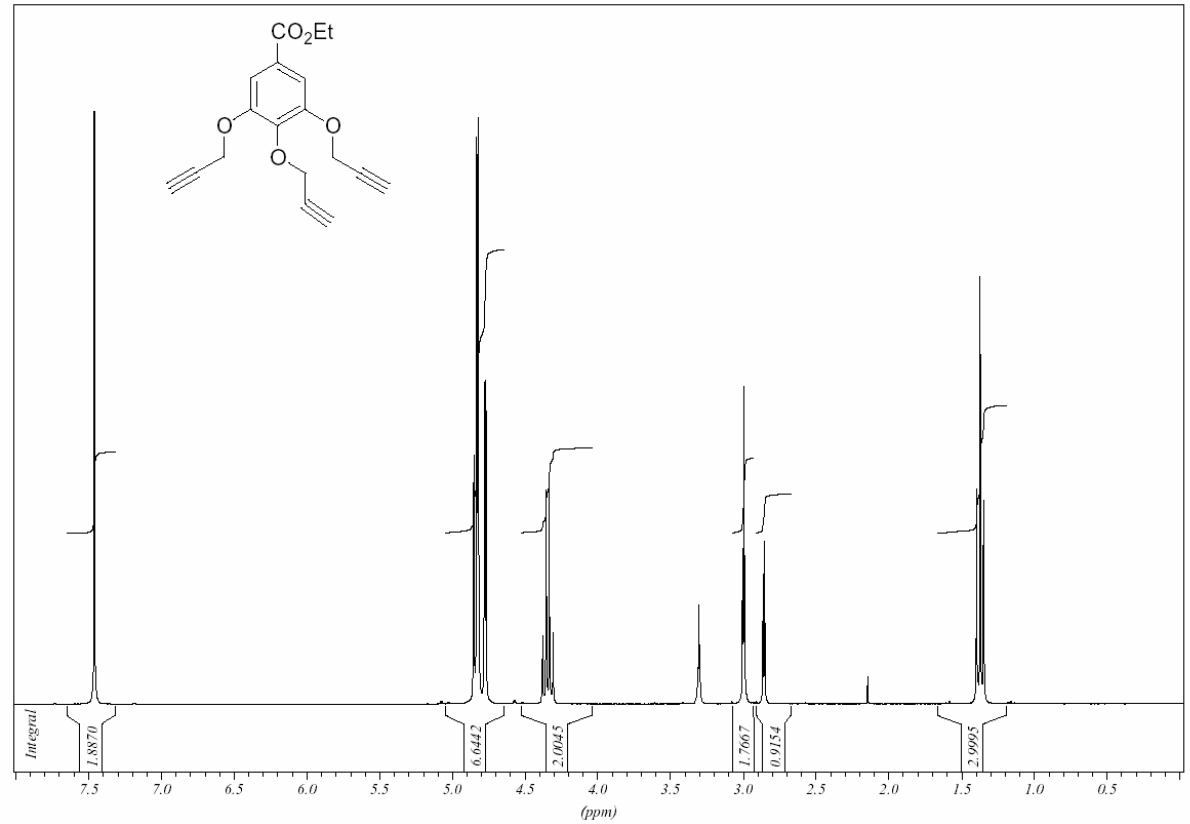


^{13}C-NMR (75 MHz, $CDCl_3$)

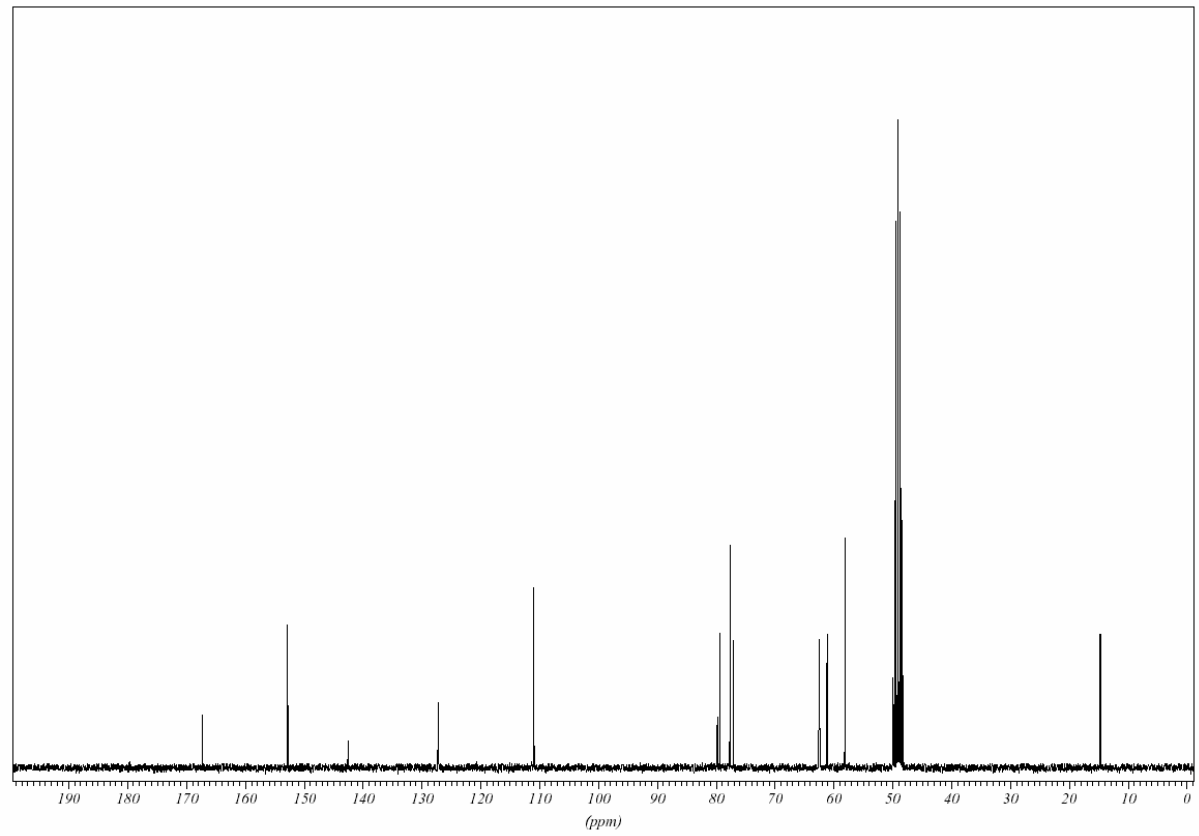


3,4, 5-Tris-prop-2-ynyloxy-benzoic acid ethyl ester (78)

^{1}H-NMR (300 MHz, [D_4] MeOH)

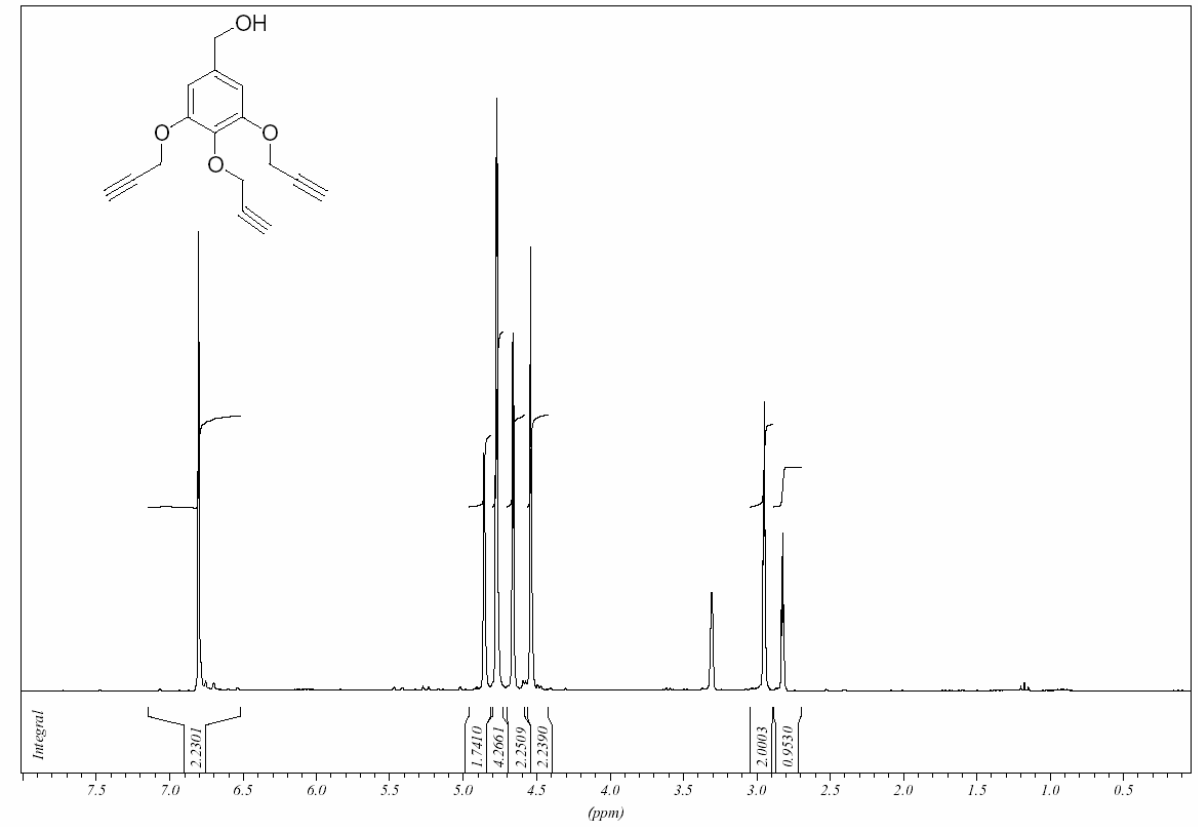


^{13}C-NMR (75 MHz, [D_4] MeOH)

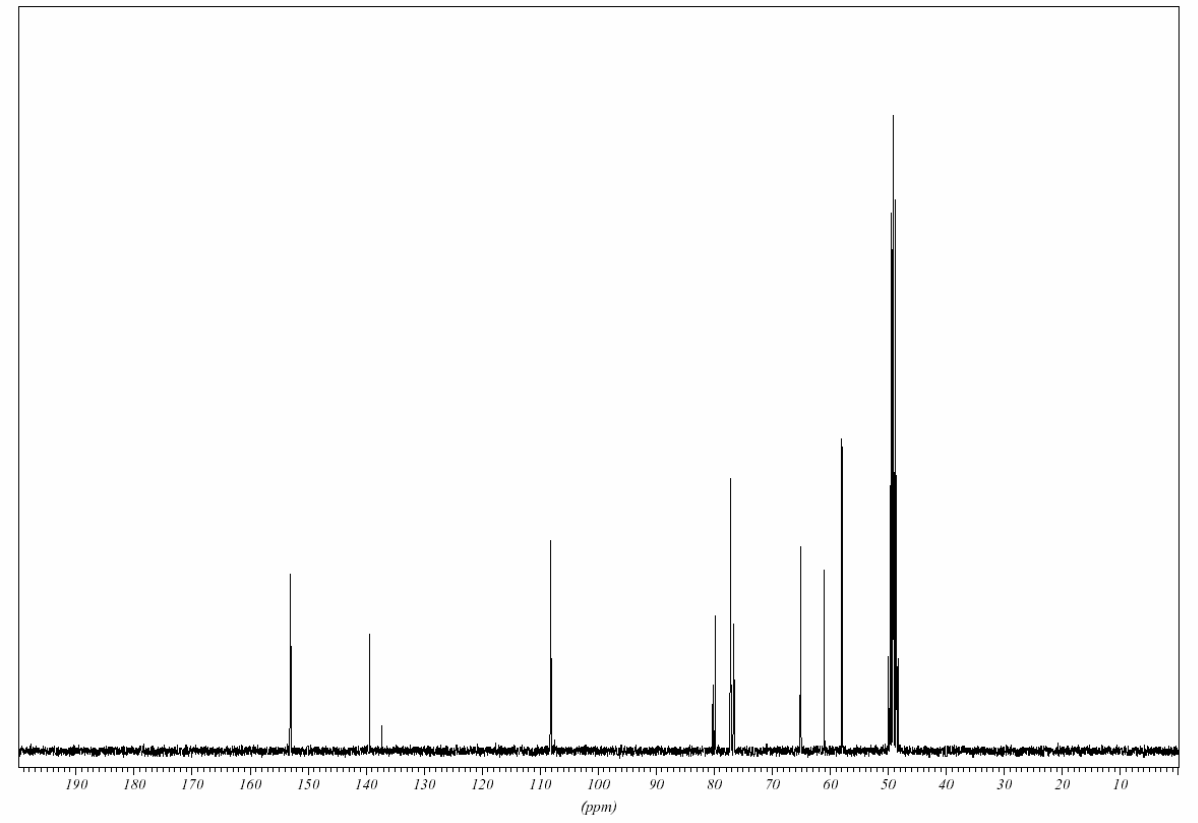


3,4,5-Tris-(propargyloxy)benzyl alcohol (79)

^{1}H-NMR (300 MHz, [D_4] MeOH)

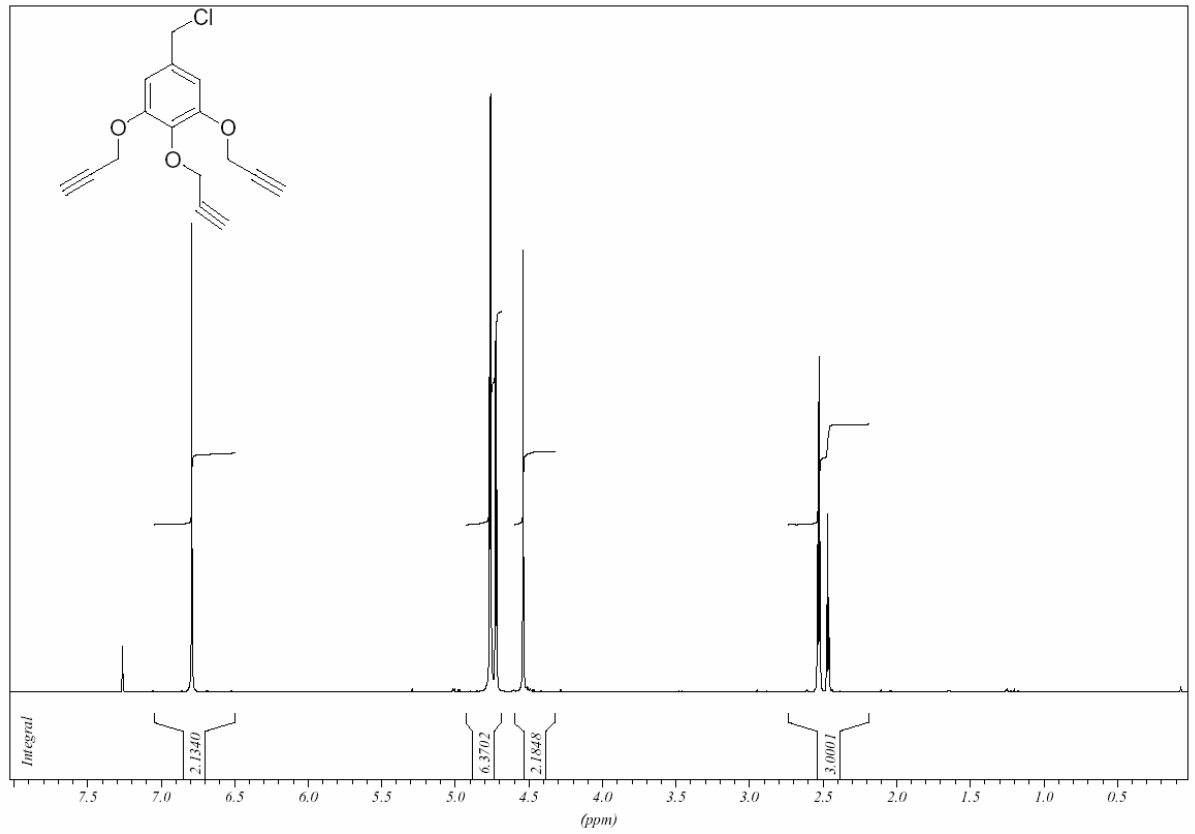


^{13}C-NMR (75 MHz, [D_4] MeOH)

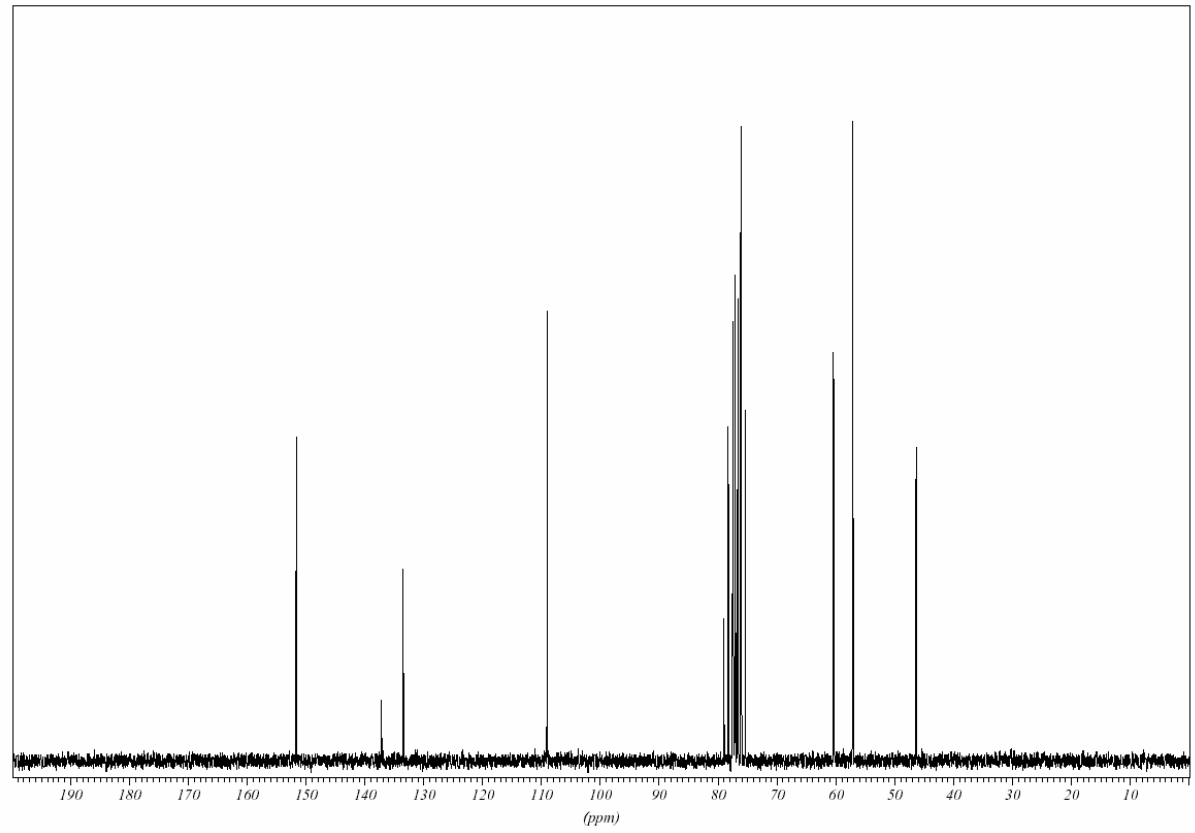


3,4,5-Tris-(propargyloxy)benzyl chloride (57)

^{1}H-NMR (300 MHz, $CDCl_3$)

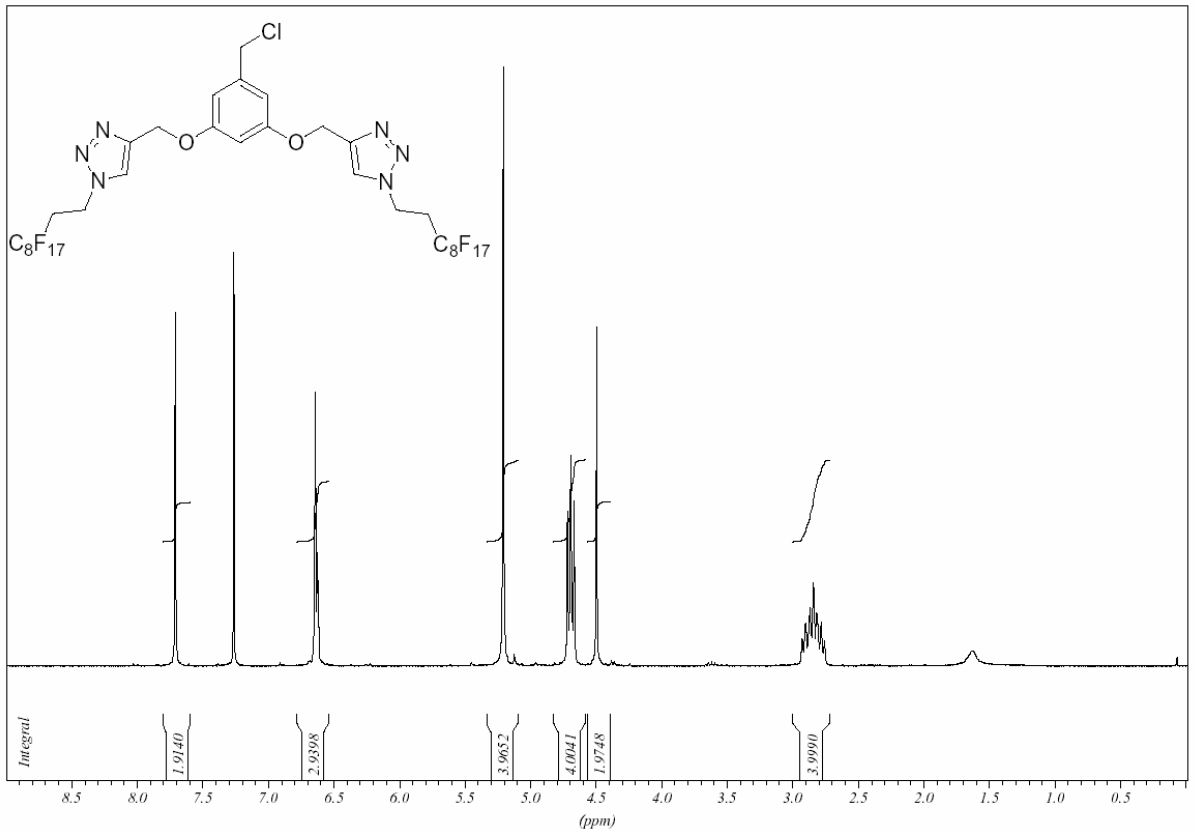


^{13}C-NMR (75 MHz, $CDCl_3$)

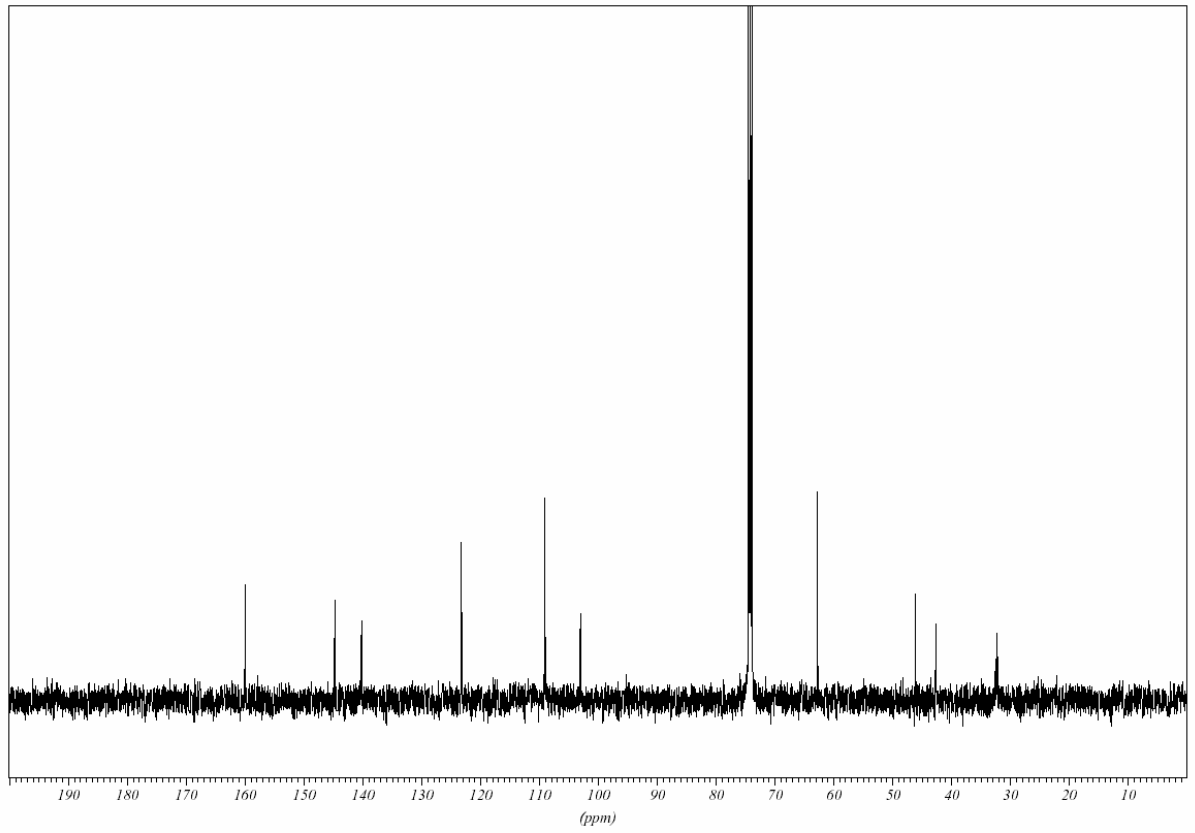


2-Ponytails perfluorinated chloride (58)

^{1}H-NMR (400 MHz, $C_2D_2Cl_4$)

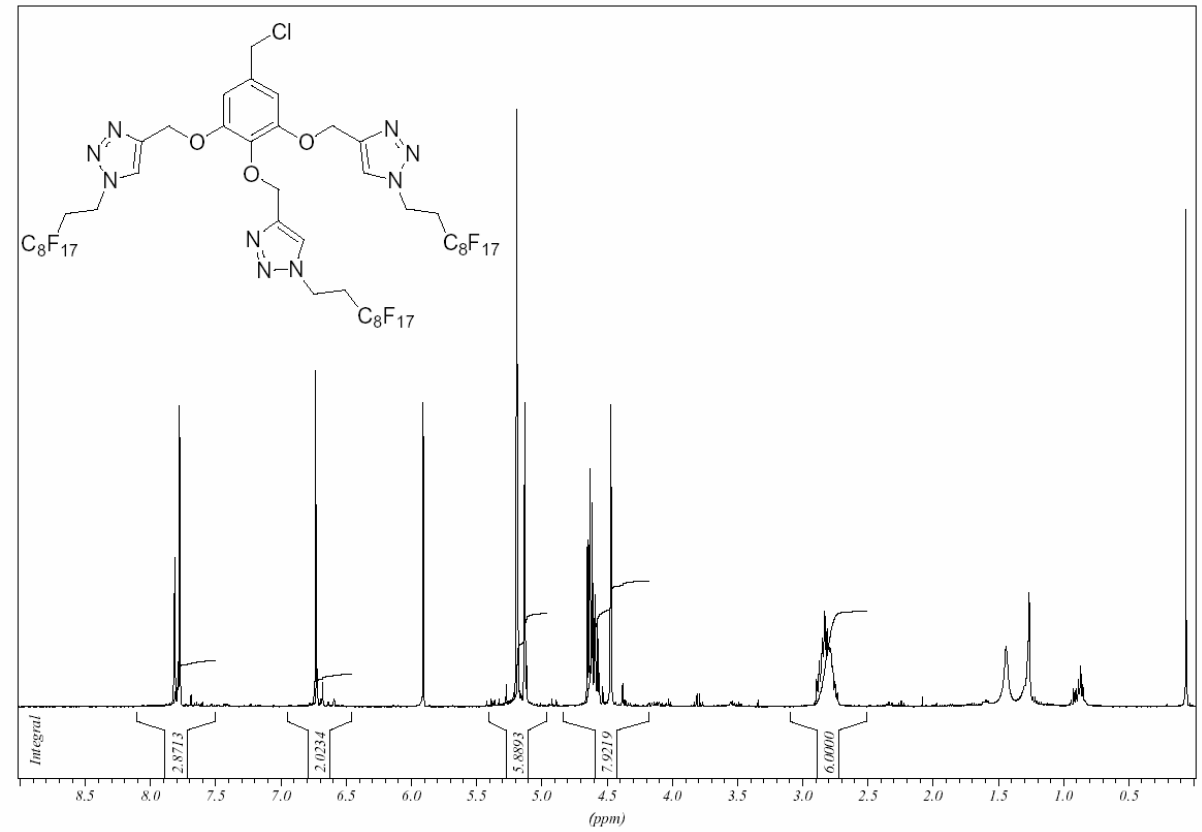


^{13}C-NMR (100 MHz, $C_2D_2Cl_4$)

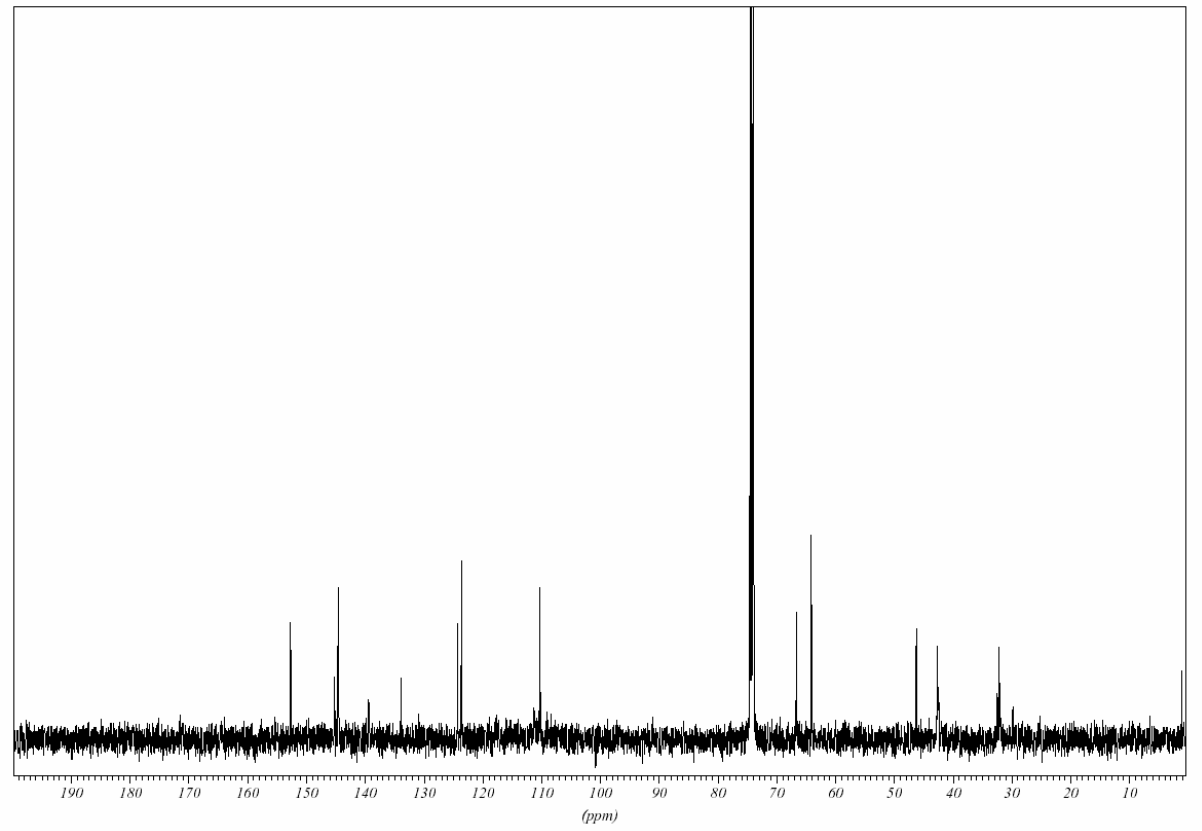


3-Ponytails perfluorinated chloride (59)

^{1}H-NMR (400 MHz, $C_2D_2Cl_4$)

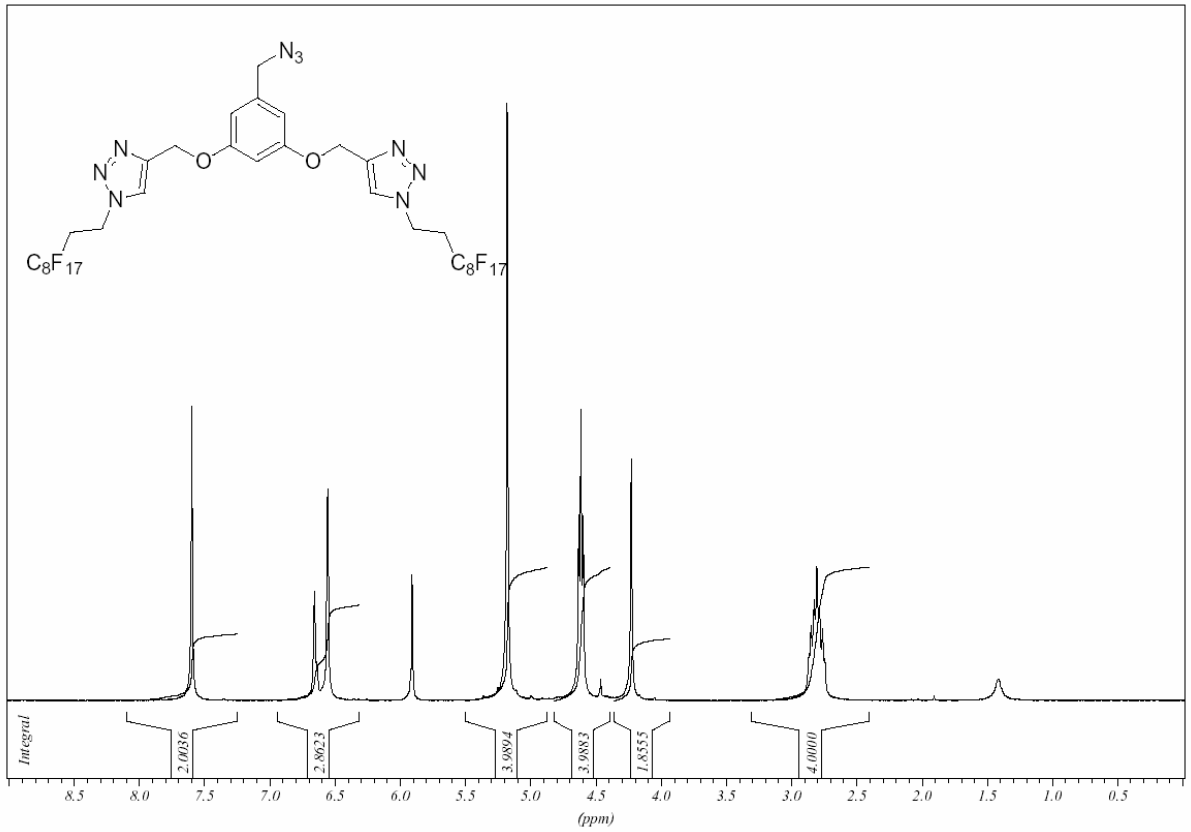


^{13}C-NMR (100 MHz, $C_2D_2Cl_4$)

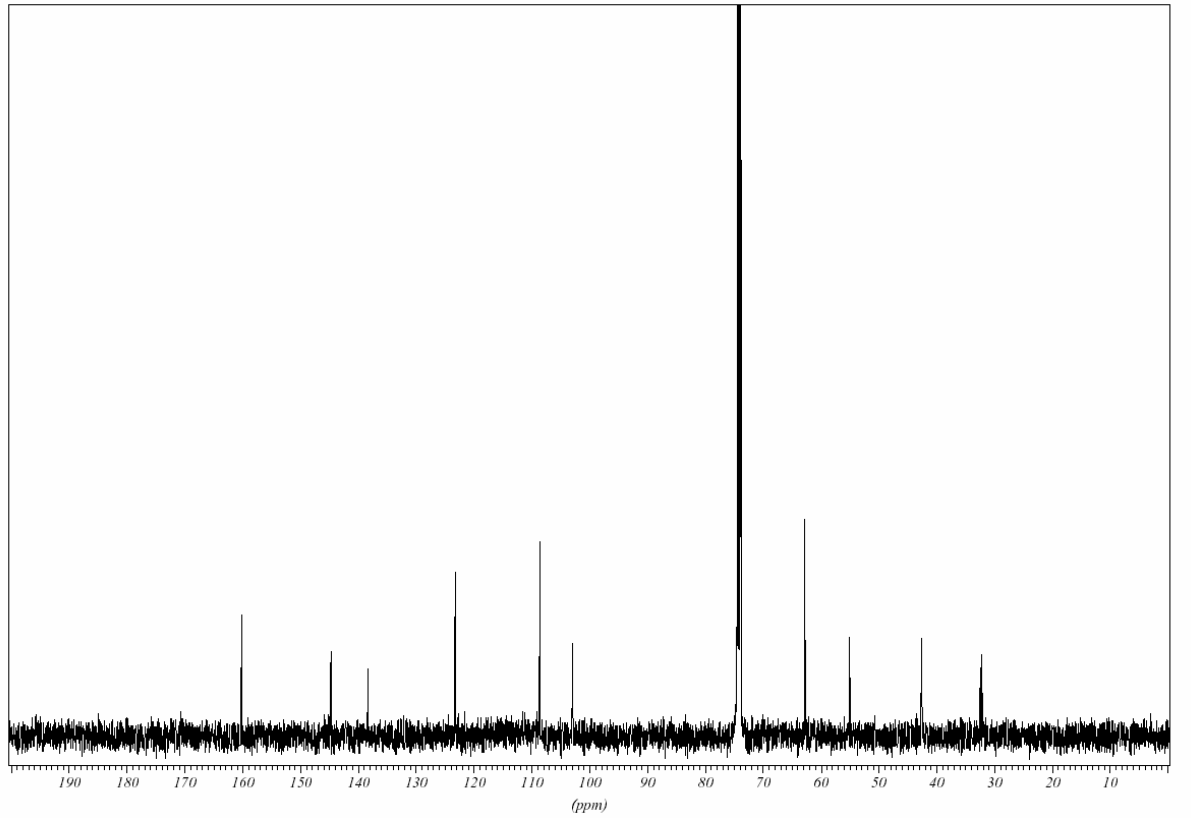


2-Ponytails perfluorinated azide (60)

^{1}H-NMR (400 MHz, $C_2D_2Cl_4$)

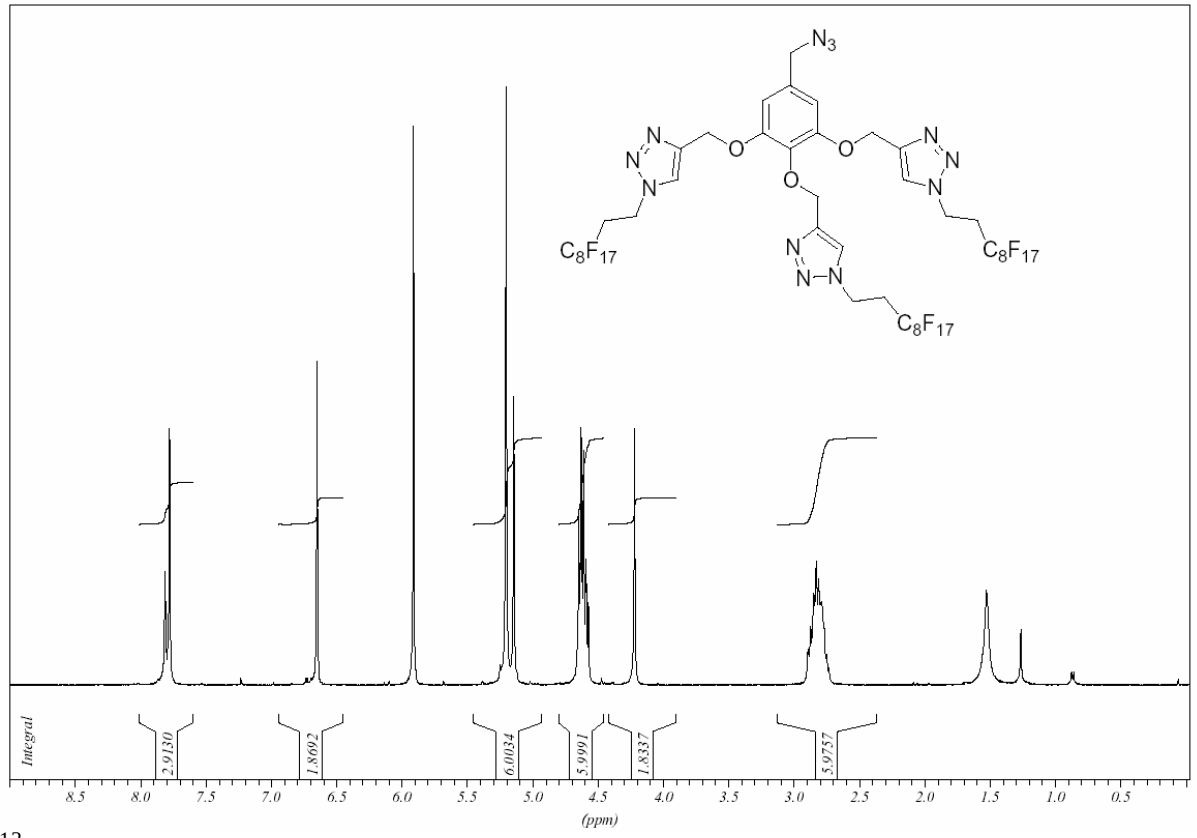


^{13}C-NMR (100 MHz, $C_2D_2Cl_4$)

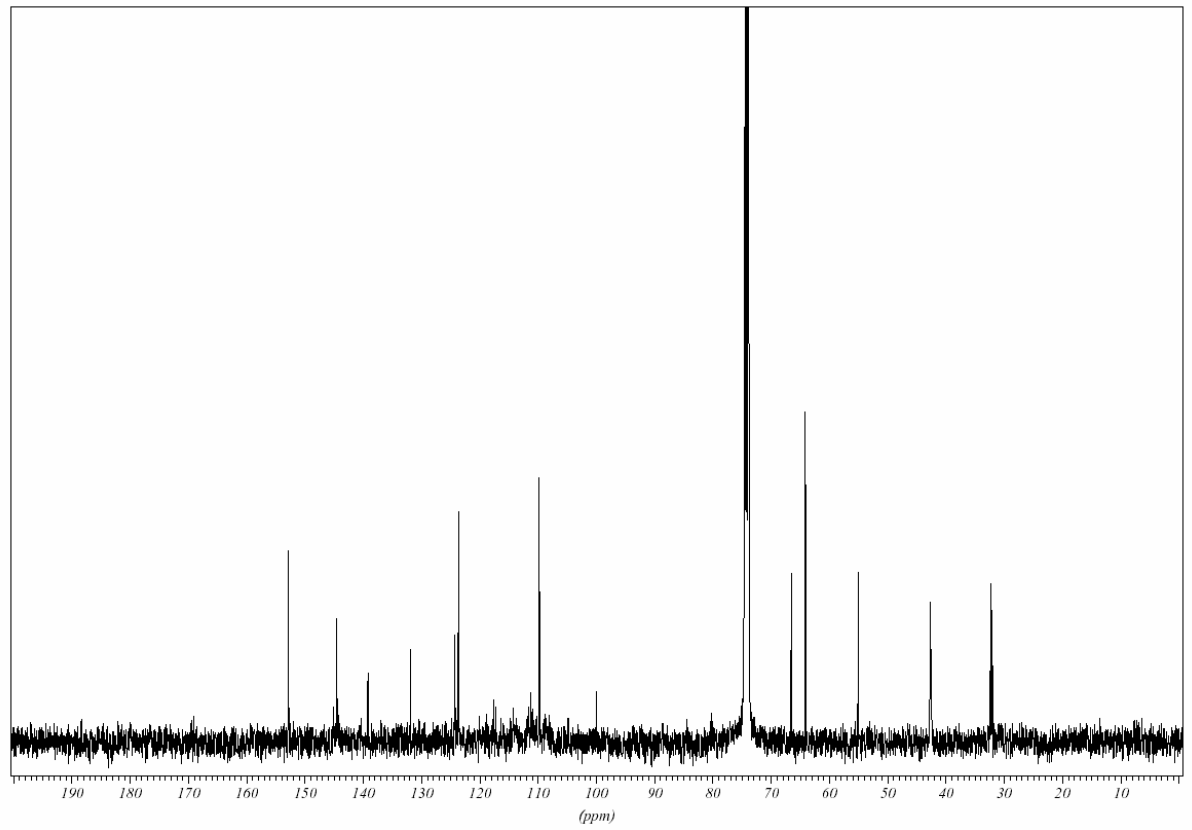


3-Ponytails perfluorinated azide (61)

^{1}H-NMR (400 MHz, $C_2D_2Cl_4$)

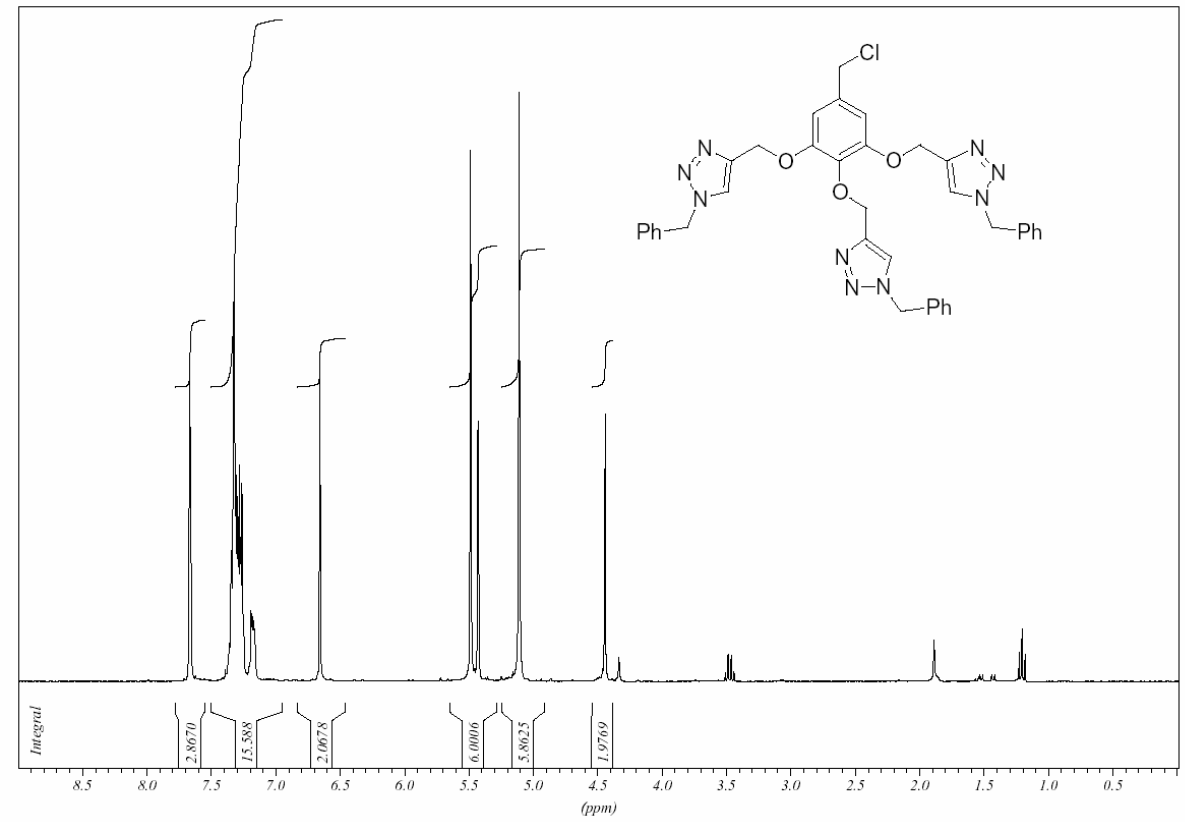


^{13}C-NMR (100 MHz, $C_2D_2Cl_4$)

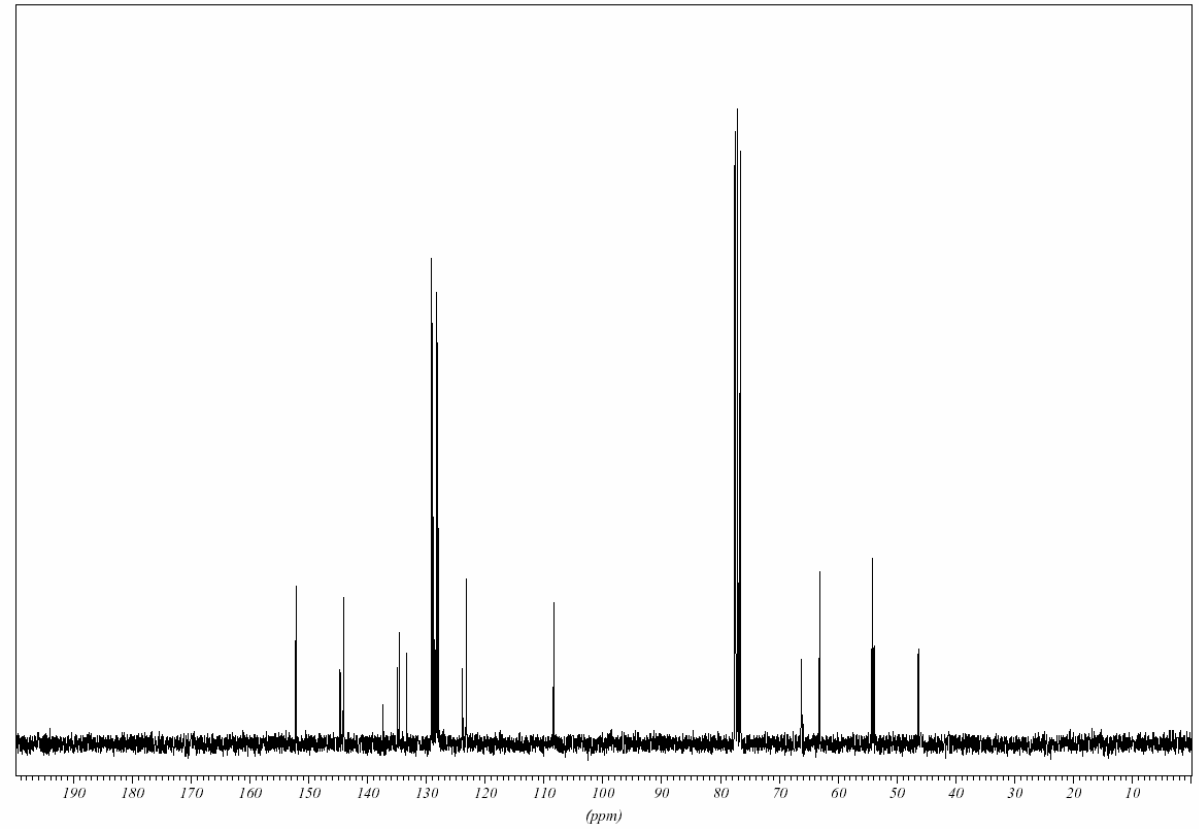


3-Benzyl tailed chloride (64)

^{1}H-NMR (300 MHz, $CDCl_3$)

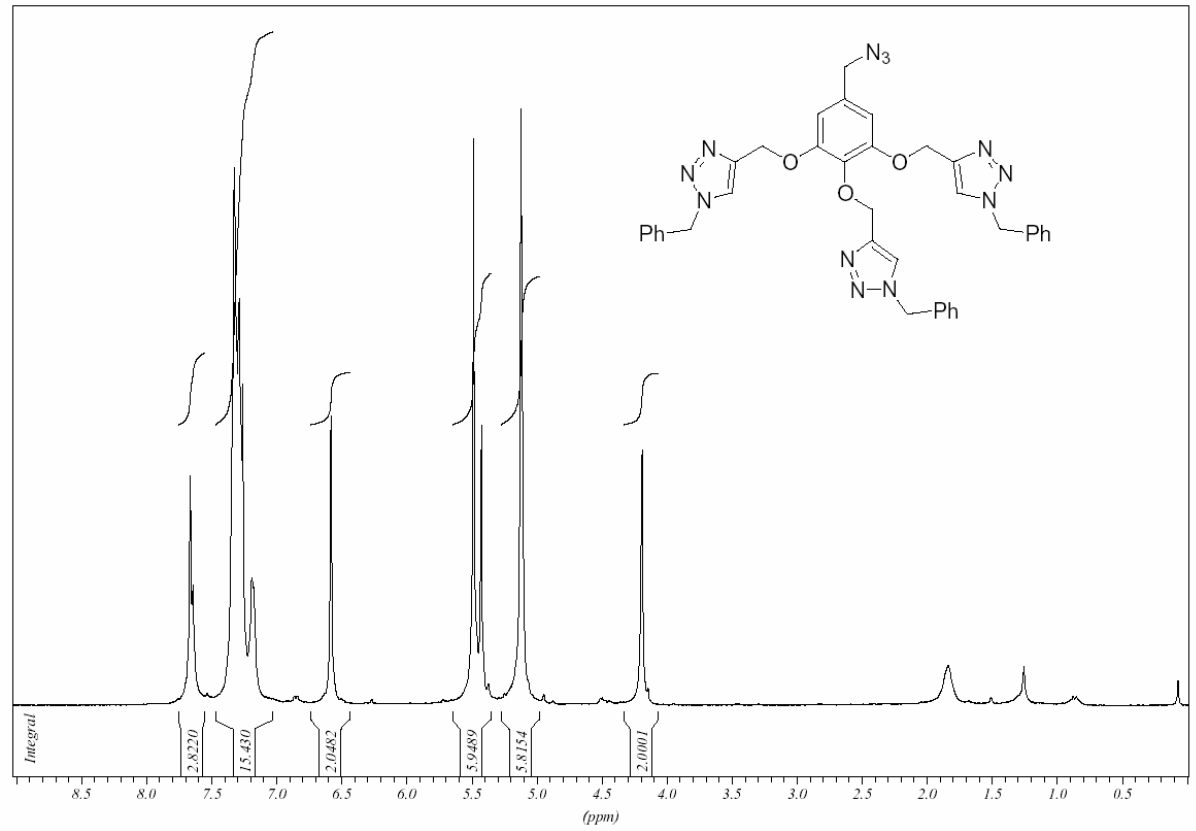


^{13}C-NMR (75 MHz, $CDCl_3$)

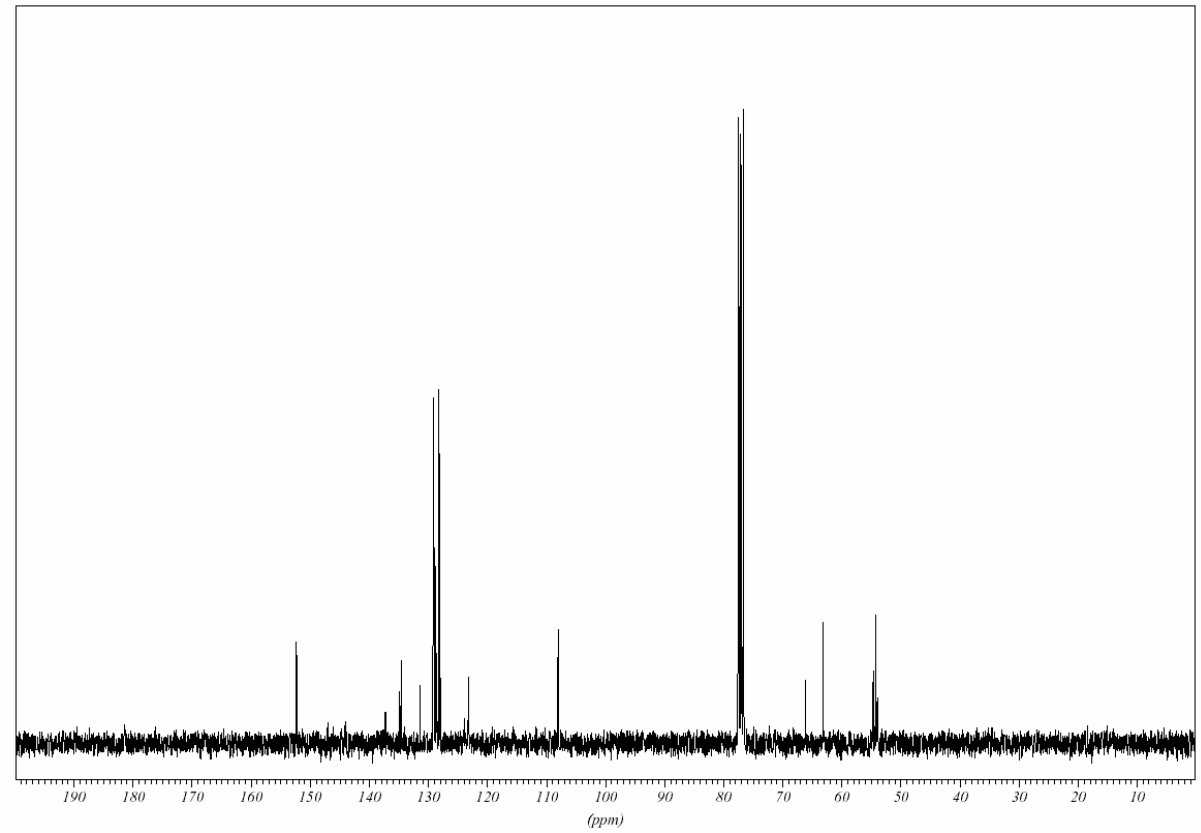


3-Benzyl tailed azide (65)

^{1}H-NMR (300 MHz, $CDCl_3$)

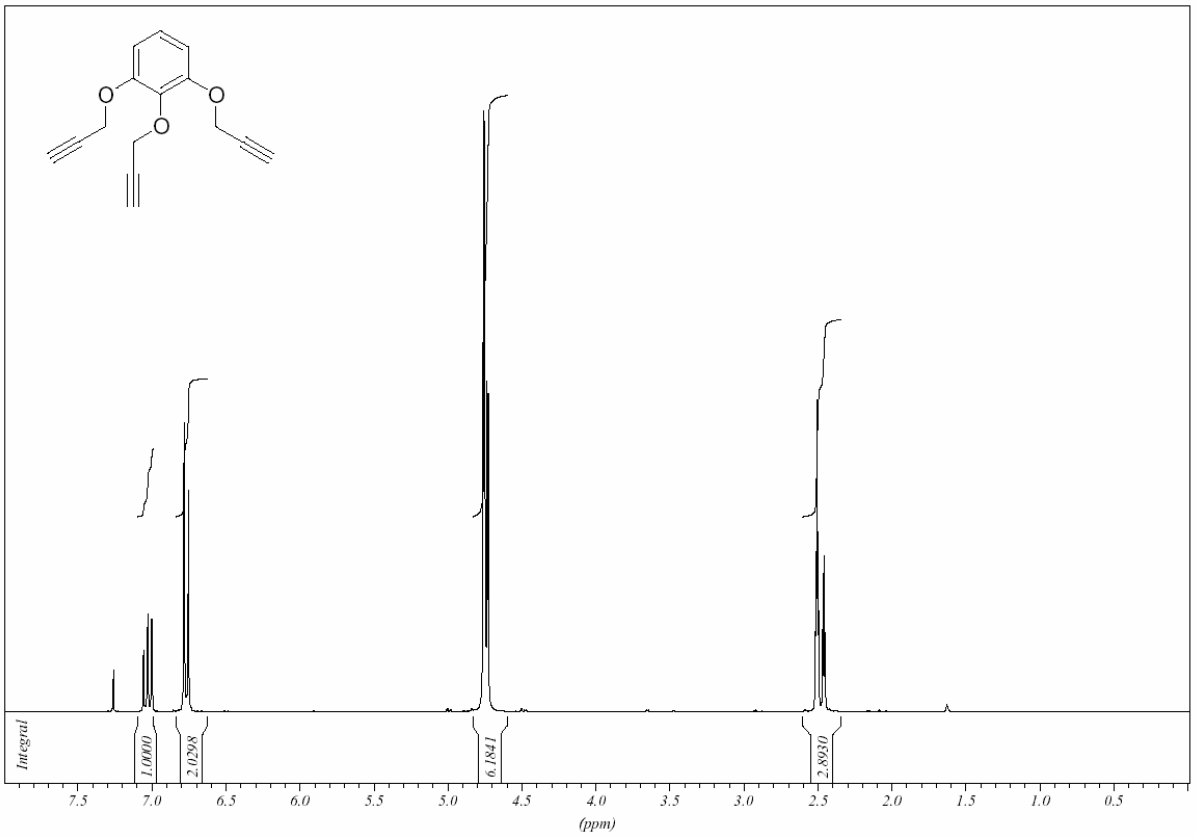


^{13}C-NMR (75 MHz, $CDCl_3$)

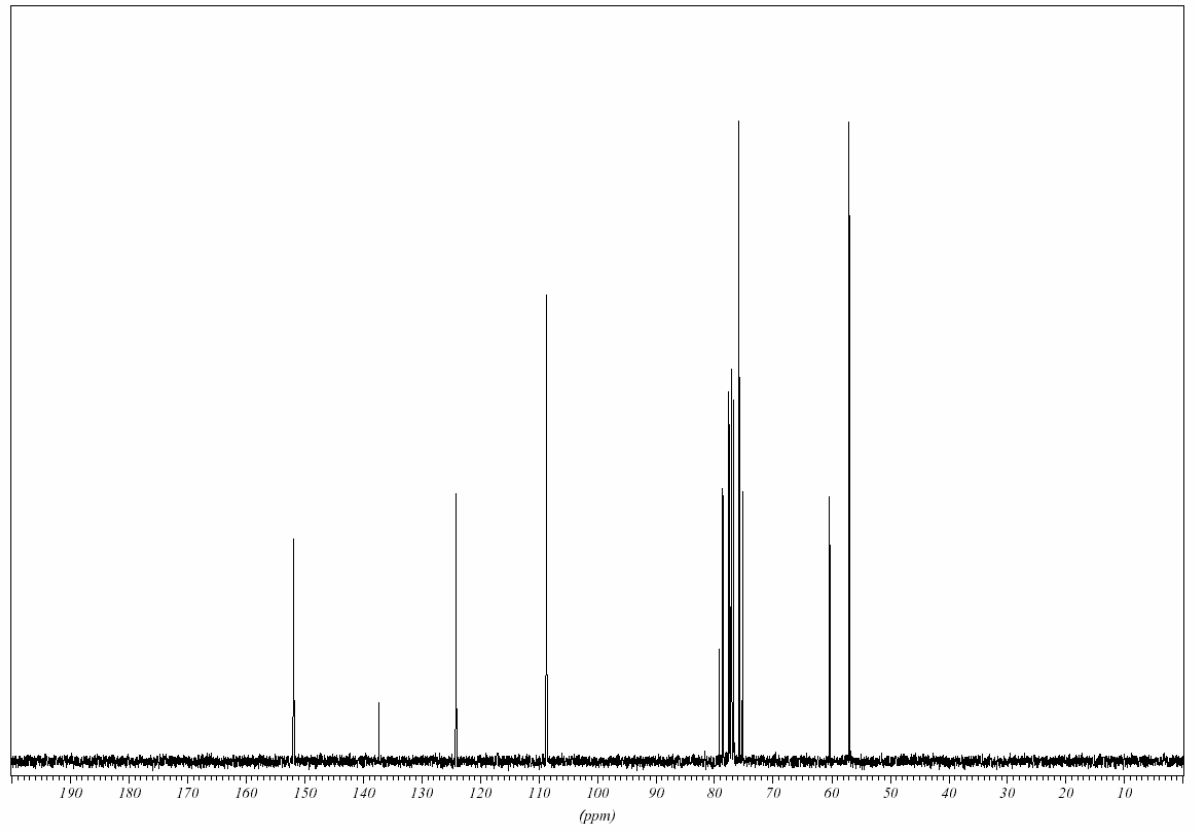


3,4,5-tris-(propargyloxy)benzene (80)

^{1}H-NMR (300 MHz, $CDCl_3$)

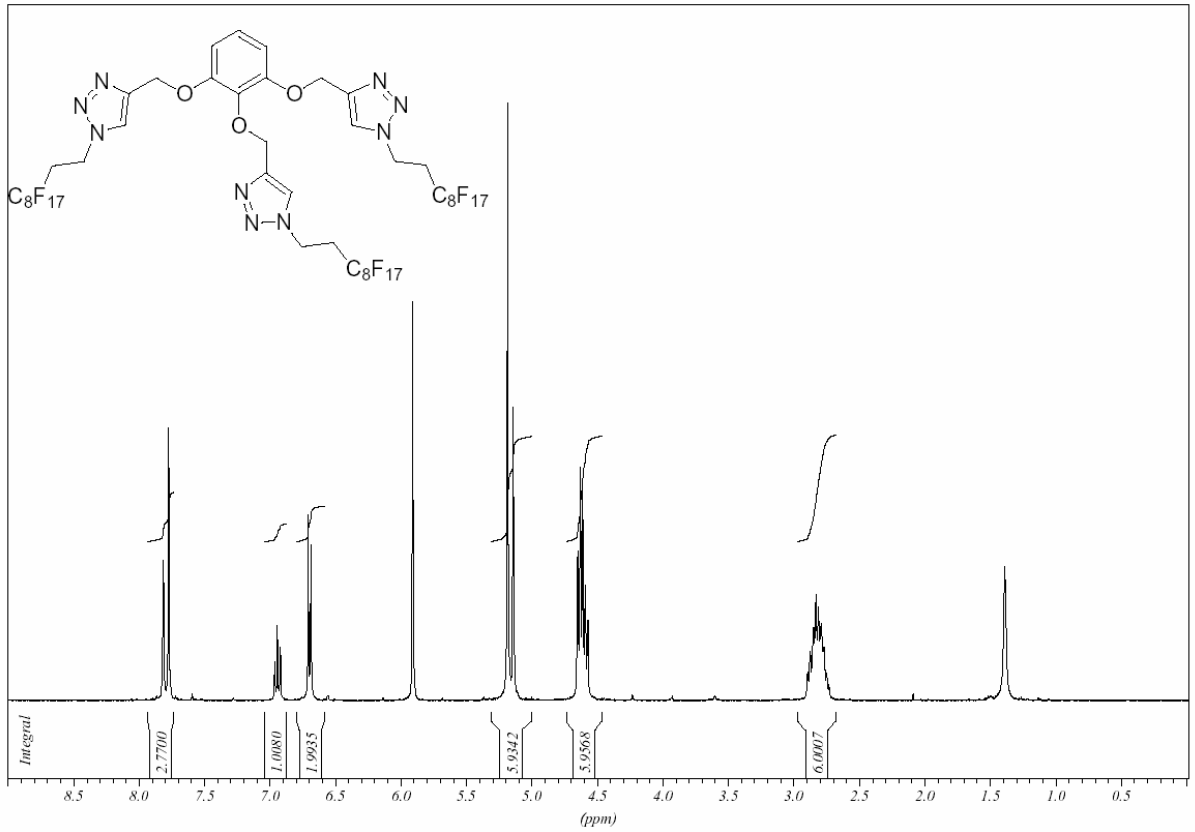


^{13}C-NMR (75 MHz, $CDCl_3$)

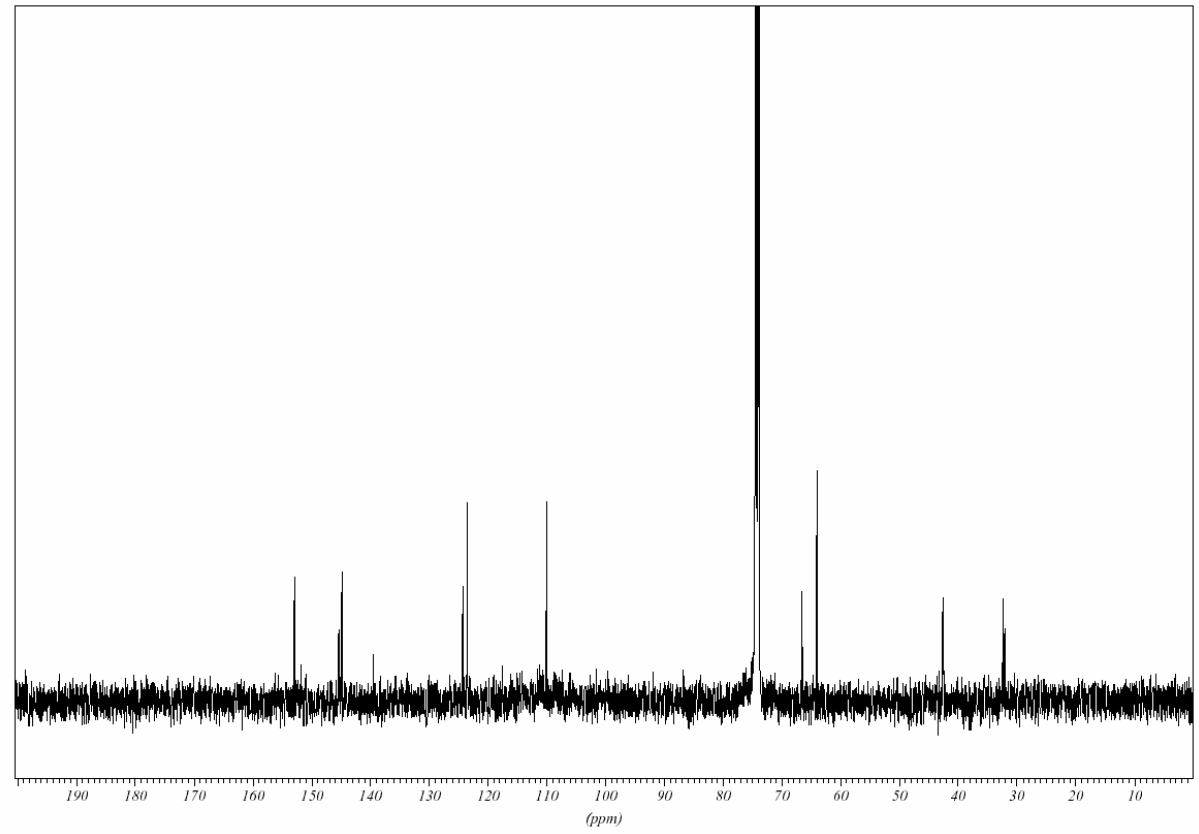


3-perfluorinated tailed benzene (72)

^{1}H-NMR (400 MHz, $C_2D_2Cl_4$)

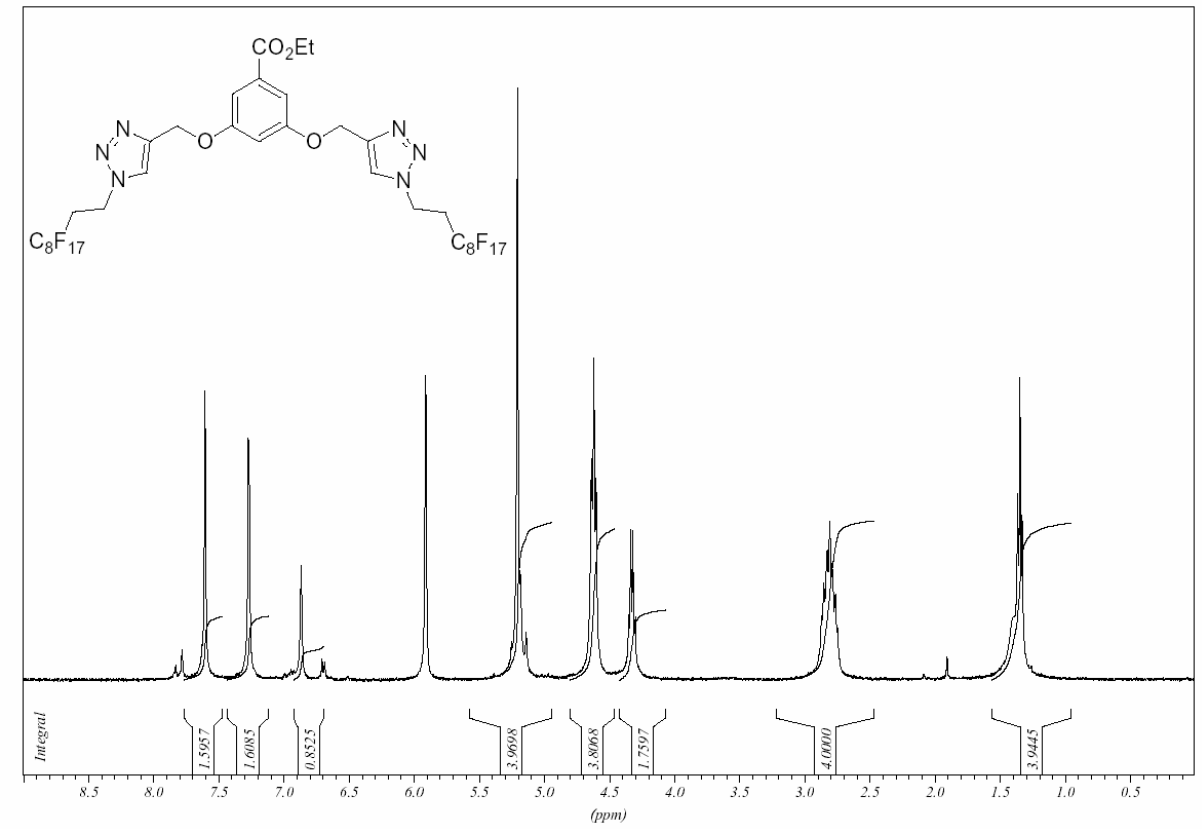


^{13}C-NMR (100 MHz, $C_2D_2Cl_4$)

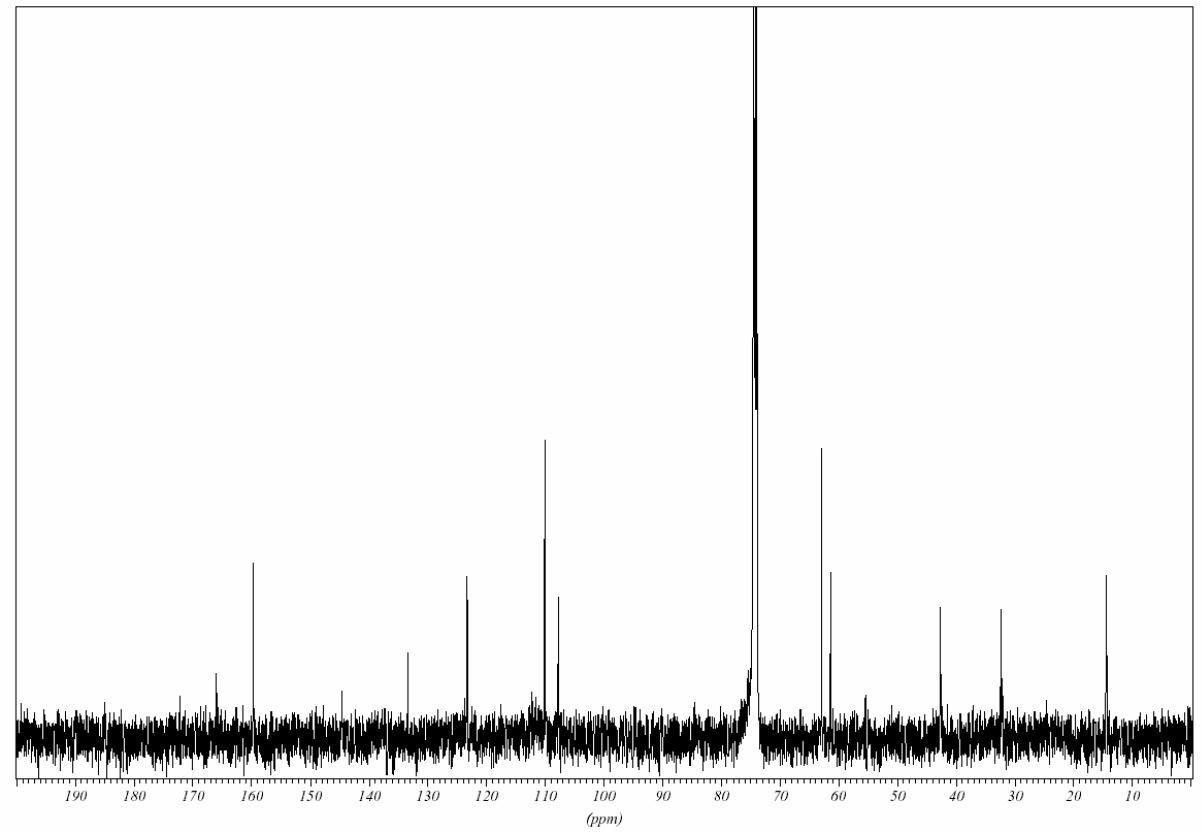


2-Ponytails perfluorinated benzyl ethylester (73)

^{1}H-NMR (400 MHz, $C_2D_2Cl_4$)

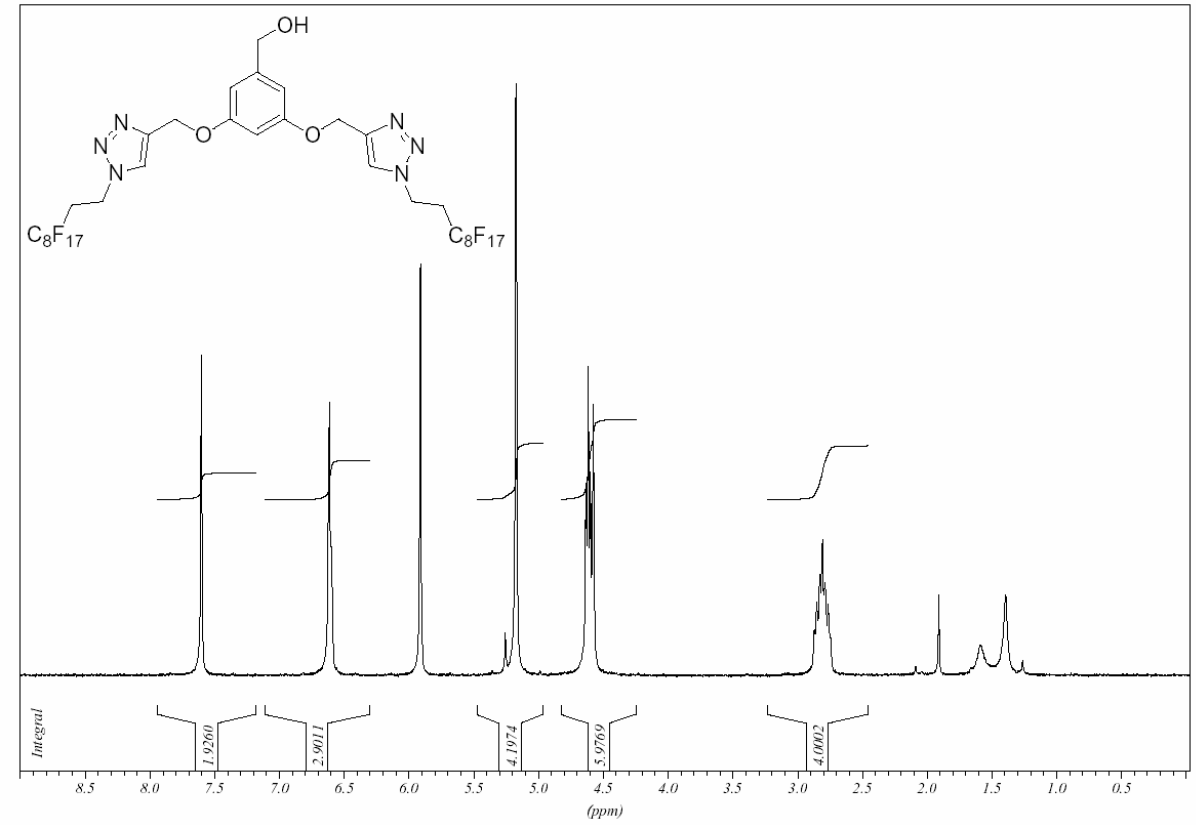


^{13}C-NMR (100 MHz, $C_2D_2Cl_4$)

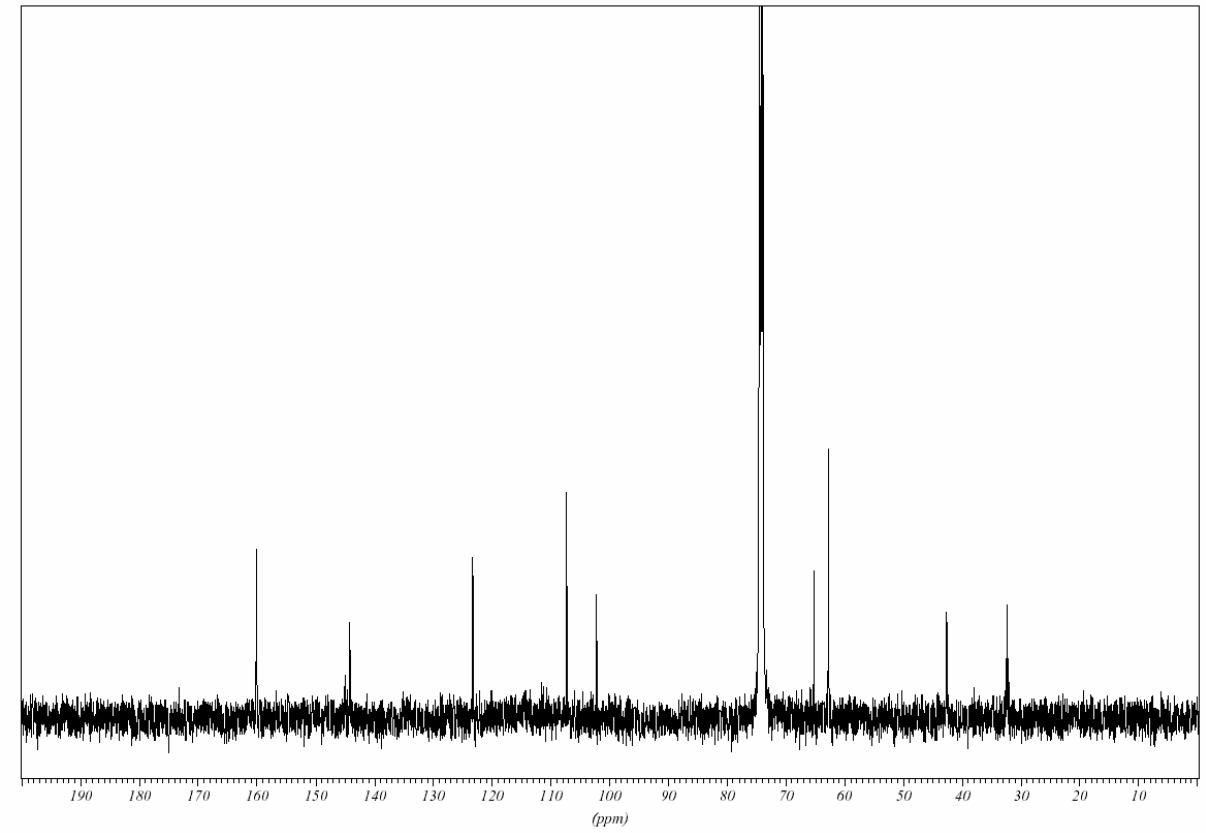


2-Ponytails perfluorinated benzyl alcohol (74)

^{1}H-NMR (400 MHz, $C_2D_2Cl_4$)



^{13}C-NMR (100 MHz, $C_2D_2Cl_4$)



CURRICULUM VITAE

Alexandru Gheorghe

Born on 18th Jan. 1980 in Bucharest, Romania

Education

Oct. 2003 - Oct. 2006	**Ph.D. in Organic Chemistry, University of Regensburg, Germany** Supervisor: Prof. Dr. Oliver Reiser
Sep. 2002 - Jun. 2003	**DEA Multinational de Chimie Moléculaire**, **École Polytechnique, Paris, France** - equivalent to a M.Sc. in Organic Chemistry Supervisor: Prof. Dr. Samir Zard Final average: 14.41 out of 20
Oct. 1998 - Sep. 2003	**B.Sc. in Organic Chemistry, "Politehnica" University, Bucharest, Romania** Department of Engineering Sciences, Chemistry Division, English Stream Final average: 10 out of 10
Oct. 2001 - Jul. 2002	**Visiting Student, École Polytechnique, Paris, France** Graduated with "High Honours"
Sep. 1999 - Jul. 2000	**Erasmus Student, "Universidad Autónoma de Madrid", Spain**

Scientific conferences and sommer courses

24th - 28th Sep. 2005	Summer School Medicinal Chemistry, SIOC, Shanghai, China
11th - 14th Sep. 2005	Annual meeting of the German Chemical Society (GDCh), Düsseldorf, Germany
17th - 30th Jul. 2005	109th International Summer Course at BASF, Ludwigshafen, Germany

Awards

Jul. 2004 - Mar. 2005	Scholarship granted by the **International Quality Network - Medicinal Chemistry**, Germany
Sep. 2002 - Aug. 2003	Scholarship granted by **EGIDE**, France
Oct. 2001 - Jul. 2002	Scholarship granted by the **Foundation of the Ecole Pdytechnique**, Paris, France
Oct. 1999 - Jul. 2000	**Erasmus/Socrates** scholarship
Oct. 1998 - Jul. 2001	Scholarship granted by the Ministry of Education and Research, Romania

Publications List

1. Alexandru Gheorghe, Erick Cuevas-Yañez, Joachim Horn, Willi Bannwarth, Banda Narsaiah and Oliver Reiser, *Synlett* **2006**, *17*, 2767-2770.
   A Facile Strategy to a New Fluorous-Tagged, Immobilized TEMPO Catalyst Using a Click Reaction, and its Catalytic Activity.

2. Alexandru Gheorghe, Michael Schulte and Oliver Reiser, *J. Org. Chem.* **2006**, *71*, 2173-2176.
   Synthesis of Functionalized Pyrrolidin-2-ones and (*S*)-Vigabatrin from Pyrrole.

3. Alexandru Gheorghe, Ai Matsuno and Oliver Reiser, *Adv. Synth. Catal.* **2006**, *348*, 1016-1020.
   Expedient Immobilization of TEMPO by Copper-Catalyzed Azide-Alkyne [3+2]-Cycloaddition onto Polystyrene Resin

4. Alexandru Gheorghe, Béatrice Quiclet-Sire, Xavier Vila and Samir Z. Zard, *Org. Lett.* **2005**, *7*, 1653-1656.
   Synthesis of 3-Arylpiperidines by a Radical 1,4-Aryl Migration.

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