Photoaffinity Based Immobilization and Target Fishing of Atorvastatin Lactone and Synthesis of the C1-C13 Fragment of Biselyngbyaside

Photoaffinitäts-basierte Immobilisierung und Target Fishing von Atorvastatin-Lacton sowie Synthese des C1-C13 Fragments von Biselyngbyasid

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Publications:

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Abstract

Wir beschreiben eine neue Strategie zum Atorvastatin-Lacton mit einer Paal-Knorr Pyrrolsynthese über die Kondensation eines 1,4-Diketons mit einem Amin, welches bereits einen Großteil der Seitenkette aufweist. Das Amin beinhaltet eine *syn*-1,3-Diol Untereinheit und eine Benzylether-Funktion am Ende der Kette. Die C4-Position am Pyrrol erlaubt Funktionalisierungen über Iodierung, Li-X Austausch und Carboxylierung. Die 4-H Pyrrolsäure konnte schließlich über Amid-Bildung, Debenzylierung Oxidation und im letzten Schritt Lactonisierung in das Atorvastatin-Lacton überführt werden. Das Hauptfragment 2-((4*R*,6*S*)-6-(2-(Benzyloxy)ethyl)-2,2-dimethyl-1,3-dioxan-4-yl)ethanamin wurde über zwei sequentielle asymmetrische Transfer-Hydrier-Carbonyl-Allylierungs-Schritte nach Krische *et al.* erhalten. Um mit einem Linker verbundene Atorvastatin-Derivate zu erhalten, wurde die Pyrrol-4-Carbonsäure mir einem Triethylenglykol mit Anillin-Terminus kondensiert, um das entsprechende Amid zu erhalten. Nach Immobilisierung auf Toyopearl-Beads wurde klassische Affinitätschromatographie durchgeführt.

Als Alternative zur mühsamen Affinitätschromatographie beschreiben wir die Kombination der Osada-Strategie der Carben-basierten Immobilisierung kleiner Moleküle auf Affinitäts-Harzen und der Massenspektrometrie-basierten Markierung von Aminosäuren mit stabilen Isotopen in Zellkulturen (*SILAC*) für affinitätsbasierte Suche und Identifikation der biologischen Targets. Um dieses Konzept zu beweisen, verwendeten wir erfolgreich ein klassisches Beispiel, in dem wir Cyclophilin als bekanntes biologisches Target von Cyclosporin A identifzieren konnten. Des Weiteren wurde diese Strategie verwendet um biologische Off-Targets des Atovastatin Lactons und unbekannte Targets von Englerin A zu finden. Hierzu synthetisierten wir einen Diazirin-basierten Triethylenglycol-Linker mit Carboxyl-Terminus, der auf Toyopearl AF 650 Amino Beads immobilisiert wurde. Die so hergestellten Beads wurden unter Verwendung der Osada-Methode mit den kleinen Molekülen beladen, in dem man die kleinen Moleküle bestrahlte (Englerin A beziehungsweise Atorvastatin Lacton unter UV-Licht, 365 nm, 4 $J \cdot cm^{-2}$, 8 W). Das Fischen der Arzneimittel Targets wurde (von der Projektkollegin Yvonne Etzel) mit Zelllysat von HEK293T Zelllinien (Nierenzellen) durchgeführt. Die Experimente wurden sowohl mit Bead Kontrolle als auch mit löslichem Kompetitor durchgeführt. Die Analyse der gefischten Proteine wurde mit der SILAC-Technik durchgeführt. Erste Experimente ließen in der Tat einige

potentielle Protein-Targets erkennen. Dieser kombinierte Weg könnte hilfreich für die Identifizierung von unbekannten biologischen Targets von unterschiedlichen kleinen Molekülen sein. Hinblick auf die Totalsynthese eines Naturstoffes entwickelten wir eine kurze Syntheseroute zu einem Schlüsselfragment von Biselyngbyasid. Dieses neue Makrolacton wurde aus einem marinen Cyanobakterium *Lyngbya sp*. aus der Präfektur Okinawa isoliert. Es zeigt Zytotoxizität gegenüber HeLa S3 Zellen mit einem IC_{50} von 0.1 $mg \cdot mL^{-1}$. Die mittlere Wachstumshemmung (GI) lag bei 0.6 mM in einer Auswahl aus 39 Zelllinien. Ein anspruchsvolles Zwischenfragment C1–C13 von Biselingbyaside mit Vinyliodid an einem Ende wurde über eine Kreuzmetathesereaktion zwischen einem Vinylalkohol und Homoallylbausteinen hergestellt. Das Allylalkoholfragment wurde über eine Amano PS Lipase unterstützte hydrolytische kinetische Resolution von racemischer 3-Hydroxy-4-pentencarbonsäure synthetisiert, gefolgt von weiteren Modifizierungen. Das letzte Fragment, das zwei Stereozentren enthält, wurde unter Verwendung einer asymmetrischen Alkylierung, einer Wittig-Reaktion, einer Hydrozirconierung und einer Brown-Allylierung als Schlüsselschritte erhalten.

Table of Contents

Abbreviations

Ac	Acetyl
aq	aqueous
AIDS	Acquired Immunodeficiency Syndrome
ap.	apparent
Ar	Aromatic
Arg	Arginine
ATP	Adenosine triphosphate
ATV	Atorvastatin lactone
BASMs	Bioactive small molecules
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
(*R*)-(+)-Cl,MeO-BIPHEP	(*R*)-(+)-5,5'-Dichloro-6,6'-dimethoxy-2,2'-bis(diphenylphosphino)-1,1'-biphenyl
Bn	Benzyl
BOP	Benzotriazole-1-yl-oxy-tris-(dimethylamino)-phosphonium hexafluorophosphate
br	broad (NMR)
n-BuLi	*n*-Butyl lithium
t-BuLi	*tert*-Butyl lithium
n-Bu	*n*-Butyl
Bz	Benzoyl
c	concentration
CDI	*N*,*N*-carbodiimidazole
CHD	Coronary heart diseases
COD	1,5-Cyclooctadiene
m-CPBA	*meta*-Chloroperoxybenzoic acid
cp	Cyclopentadienyl

CRP	C-reactive protein
CSA	Camphorsulphonic acid
CsA	Cyclosporin A
Ctrl	Control
DCC	*N*,*N*'-Dicyclohexylcarbodiimide
DERA	2-deoxyribose-5-phosphate aldolase
DIBAL-H	Diisobutylaluminium hydride
DIC	*N*,*N*'-Diisopropylcarbodiimide
DIPEA	*N*,*N*-Diisopropylethylamine
DMAP	4-Dimethylaminopyridine
DMF	*N*,*N*-Dimethylformamide
DMPP	Dimethylallyl pyrophosphate
DMP	Dess-Martin periodinane
DMPU	1,3-Dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone
DMSO	Dimethylsulfoxide
de	Diastereomeric excess
ee	Enantiomeric excess
E	trans (entgegen)
ent	enantiomeric
ESI	electrospray ionization
Et_2O	Diethyl ether
EtOAc	Ethyl acetate
FPP	Farnesyl pyrophosphate
g	Gram
GC	Gas chromatography
GI	Growth Inhibition
GPP	Geranyl-pyrophosphate

Grubb's 2nd	(1,3-Bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene)dichloro(phenylmethylene)(tricyclohexylphosphine)ruthenium
h	hour(s)
HATU	O-(7-Azabenzotriazol-1-yl)-N,N,N′,N′-tetramethyluronium hexafluorophosphate
HBTU	2-(1*H*-Benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HDL	High density lipoprotein
HEK	Human embryonic kidney
HIV	Human immunodeficiency virus
HMG-CoA	Hexamethyl glutaryl co-enzyme
HOAt	1-Hydroxy-7-azabenzotriazole
Hoveyda-Grubbs 2nd	(1,3-Bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidene)dichloro(o-isopropoxyphenylmethylene)ruthenium
HRMS	High resolution mass spectrometry
Hz	Hertz
Im-H	imidazole
Ipc	Isopinocamphenyl borane
IPP	Isopentenyl pyrophosphate
J	Coupling constant
kDa	Kilo Dalton
LC	Liquid chromatography
LC-MS	Liquid chromatography-mass spectrometry
LDL	Low density lipoprotein
LDA	Lithium diisopropyl amide
LFA-1	Leukocyte function antigen-1
Ln	Ligand
lys	Lysine

m	Multiplet (NMR)
MALDI-MS	Matrix-assisted laser desorption/ionization-mass spectrometry
Me	Methyl
Mes	Mesityl
MHz	Megahertz
mL	milliliter
μL	microliter
mol	mole
mmol	millimole
m.p.	Melting point
NaHMDS	Sodium bis(trimethylsilyl)amide
NADPH	Nicotinamide adenine dinucleotide phosphate
NBS	N-Bromosuccinimide
NCI	National cancer institute
NIS	*N*-Iodosuccinimide
NMM	*N*-Methylmorpholine
NMR	Nuclear magnetic resonance
OXB	Oxazaborolidinone
P	Protecting group
PALC	Photoaffinity-linker-coated
Ph	Phenyl
Piv	Pivaloyl
PMB	*para*-Methoxybenzyl
ppm	Parts per million
PROVE-IT	Pravastatin or Atorvastatin Evaluation and Infection Trial
*i*Pr	*iso*-Propyl
PyBOP	(Benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate

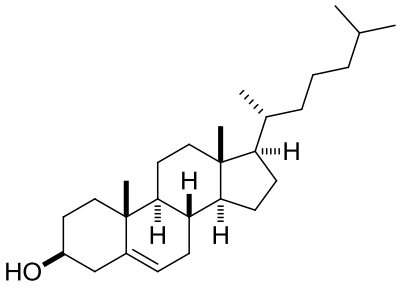
PyBrOP	Bromo-tris-pyrrolidino phosphoniumhexafluorophosphate
rac	racemic
RANKL	Receptor activator nuclear factor κB ligand
R_f	Retention factor (TLC)
RT	Room temperature (ca. 23 °C)
s	Singlet (NMR)
SDS-PAGE	Sodium dodecyl sulfate polyacrylamide gel electrophoresis
sept	septet
SILAC	Stable isotope labeling by amino acids in cell culture
t	triplet (NMR)
TBAF	Tetra-*n*-butylammonium fluoride trihydrate
TBAHS	Tetra-*n*-butylammoniumhydrogen sulphate
TBDPS	*tert*-Butyldiphenylsilyl
TBS	*tert*-Butyldimethylsilyl
TEG	Triethylene glycol
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic acid anhydride
THF	Tetrahydrofuran
THP	Tetrahydropyranyl
TIMI	Thrombolysis In Mayocardial Infarction
TLC	Thin layer chromatography
TMS	Trimethylsilyl
Ts	*para*-Toluenesulphonyl
p-TSA	*para*-Toluenesulphonic acid
UV	Ultraviolet
VMAR	vinylogous Mukaiyama aldol reaction

Chapter I

Synthesis of Atorvastatin Lactone and Analogues for Off-Target Fishing

1 Introduction

Statins are a well known class of drugs used for lowering the blood cholesterol level by interrupting cholesterol synthesis in the liver.[1] They efficiently reduce the plasma cholesterol levels by lowering the synthesis of low density lipoprotein (LDL) at the same time increasing the concentration of high density lipoprotein (HDL) which leads to improved HDL to LDL ratio for good health. Cholesterol is a useful waxy steroid present in all mammals and is the essential component of cell membranes and is used to produce bile acids and steroid hormones like estrogen, testosterone, progesterone, cortisol and aldosterone.[2,3] However, presence of high level of cholesterol is due to the abnormal increase in lipoprotein which is the carrier of cholesterol in the blood stream. The elevated cholesterol level in the blood is called hypercholesterolemia[4] which is the major reason for high risk of coronary heart disease (CHD),[5] atherosclerosis[6] and stroke.[7] Hypercholesterolemia is a major human body disorder specifically due to the very high LDL level which promotes cardiovascular diseases.



Cholesterol **1-1**

Figure 1. Chemical structure of cholesterol **1-1**.

Today, heart failure due to the elevated blood cholesterol level is the leading cause of mortality in developed countries like United States and some of the European countries.[8] CHD causes one third of the total deaths (mortality) majorly in these countries. One third of all deaths worldwide, approximately 17 million are due to the increase in blood cholesterol level and more than one third of these occur in middle aged adults. In this regard, statin therapy emerged as promising treatment in patients having a high risk of coronary artery diseases with an increase in serum cholesterol level.

Lovastatin **1-2**, which is a fungal metabolite was the first approved 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inihibitor accepted as a drug.[9] Since then, several highly potent statins either from natural sources or chemically synthesized became commercially available in the market being served for treatment of regulation of cholesterol levels. Today, statins are among the most selling drugs in the world. Some of the statins available in the market as pharmaceutical drugs are lovastatin **1-2** (mevacor),[9b] simvastatin **1-3** (zocor),[10] pravastatin **1-4** (pravacol),[11] fluvastatin **1-5** (lescol),[12] atorvastatin **1-6** (lipitor),[13] rosuvastatin **1-7** (crestor),[14] and pitavastatin **1-8**[15] (livalo) (**Figure 2 & 3**).

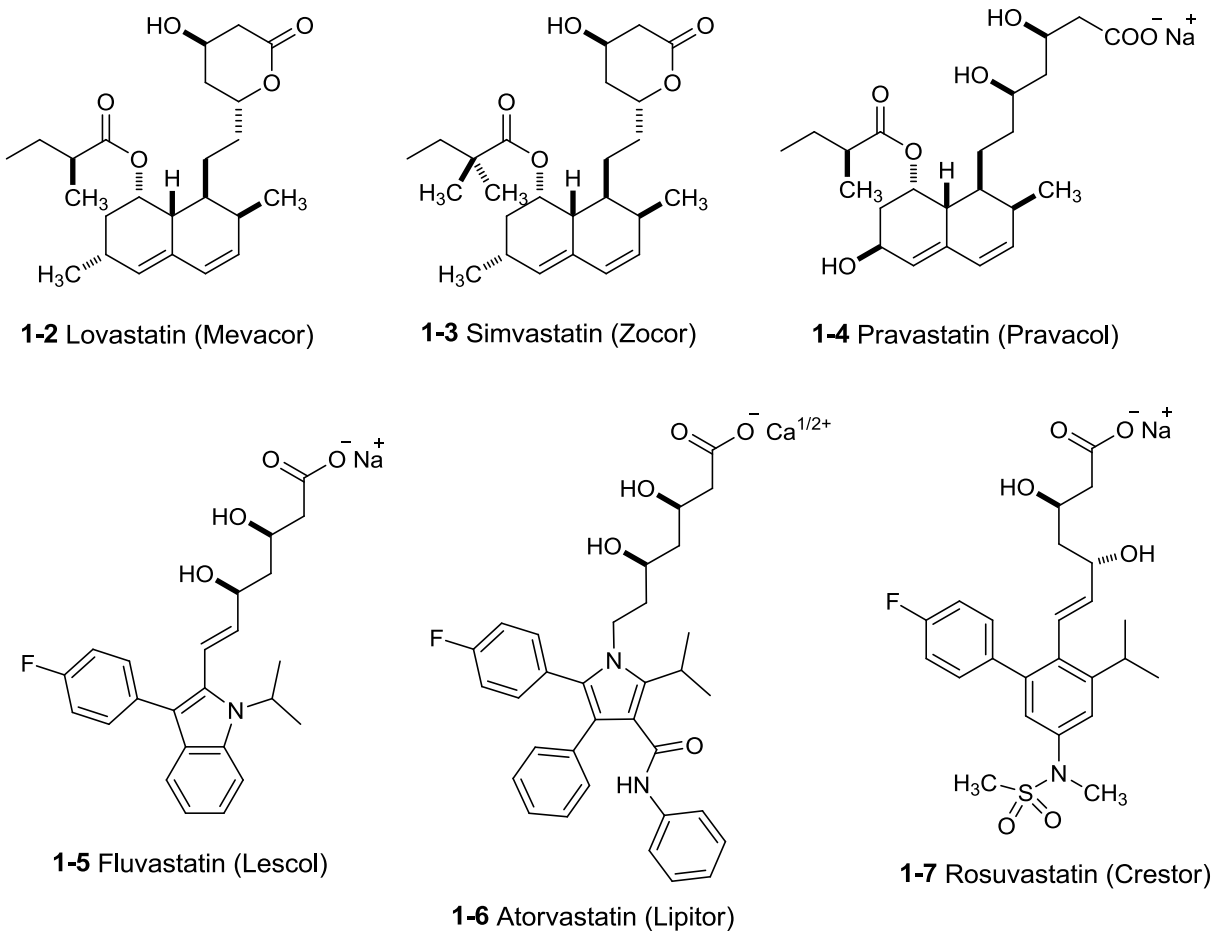
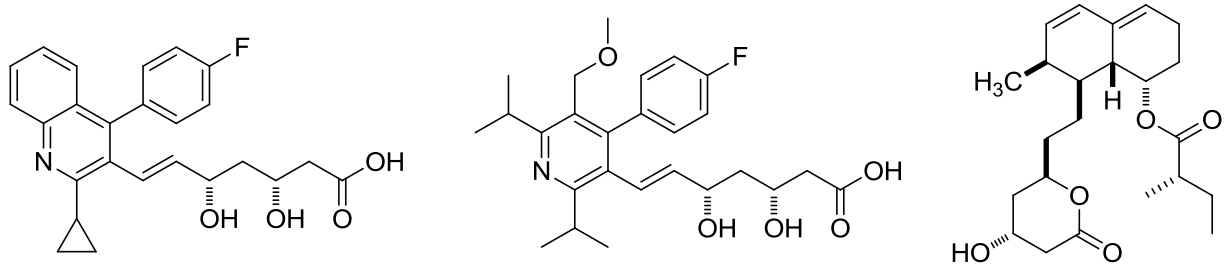


Figure 2. Statin drugs available in the market as cholesterol lowering agents.

Other examples of statin molecules are compactin **1-10,**[16] cerivastatin **1-9**[17] etc. (see **Figure 3**). Compactin **1-10** is isolated from the mold *Penicillium citrinum* by A. Endo et al.,[16] while lovastatin **1-2** is from the fermentation broth of *Aspergillus terreus*.[9] Pravastatin **1-4** is derived

from compactin **1-10** by biotransformation while simvastatin **1-3** is a semisynthetic form of lovastatin **1-2**. Other statins including fluvastatin **1-5**, atorvastatin **1-6**, rosuvastatin **1-7** and pitavastatin **1-8** are chemically synthesized in the laboratory.[18]



1-8 Pitavastatin **1-9** Cerivastatin **1-10** Compactin

Figure 3. Some other examples of statins.

Among all statins, atorvastatin **1-6** and rosuvastatin **1-7** are highly potent while fluvastatin is the least potent.[1] According to the annual report of Pfizer pharmaceuticals (2008), atorvastatin **1-6** remained the largest selling drug in the world.[19] Statins show minimal adverse effects like cognitive loss, raised liver enzymes, pancreatic and hepatic dysfunction and muscle problem. In contrast to this, in 2001 cerivastatin **1-9** was withdrawn from the market due to severe adverse effects of rhabdomyolysis in the patients.[20] The development of compactin **1-10** was as well discontinued from the preclinical trial in 1980 because of its toxicity in an animal model.[18]

Though the statin drugs are used extensively for lowering the LDL and triglycerides, some studies over several years also revealed a range of additional, mostly positive side effects. These are independent of their cholesterol lowering ability and referred as pleiotropic effects. These beneficial effects include antioxidant properties, increased nitric oxide bioavailability, and particularly anti-inflammatory effects which are key contributor to atherosclerosis.[21] Clinical and experimental observations strongly suggest that inhibition of inflammation contributes to the beneficial effect of statins.[22] The study by Ridker et al. provided evidence that aggressive statin therapy achieves the target levels of LDL, independent of C-reactive protein (CRP) in patients having risks of myocardial infarction, and patients having acute coronary syndromes[23] where CRP is known as the clinical marker of inflammation.[24] There is no evidence seen yet for the relationship between lowering CRP levels and the lipid lowering ability of statins. For lovastatin **1-2** and other decalin ring statins, it was shown that they suppress the inflammatory response in

an animal model of peritonitis by binding to the β2 integrin leukocyte function antigen-1 (LFA-1).[25] But, this elucidation given by the author seems to be limited only for the statins with a decalin system and remained unanswered for other statins like atorvastatin **1-6**. A clinical trial with aggressive doses (up to 80 mg/day) of atorvastatin **1-6** with patients having elevated lipid levels and high risk of heart diseases led to a significant improvement in inflammatory, thrombogenic states and as well as improvement in lipid profile.[26] This is in agreement with the analysis of Pravastatin or Atorvastatin Evaluation and Infection Trial (PROVE-IT), Thrombolysis In Myocardial Infarction (TIMI)-22 study by Ridker et al.[22,27]

These reports highlight the beneficial effects of atorvastatin and other statins in lowering inflammation which provides a new sight of clinical research. This means that in order to detect other cellular targets than HMG-CoA reductase (HMGR) enzyme, statins like atorvastatin as affinity probe might be useful.

2 Goal of the research

The pharmacological therapy of different diseases with the help of numerous drug molecules is a cornerstone of medicine. However, the molecular mode of action of several drug molecules is often unclear and the cellular targets are not yet completely known. Besides, pharmacological and pharmacokinetic interactions of some drug molecules are very often different than their postulated targets. In 95% of cases, targets of drug molecules are proteins whose functions are primarily enzyme, receptor, ion channel, or transport proteins in cellular systems. In case of anti-inflammatory drugs partially effective targets are glucocorticoid receptor,[28] cyclooxygenases,[29] 5-lipoxygenase,[30] tumor necrosis factor alpha (TNF-α) and interleukin-1 (IL-1).[31] In particular, inflammatory diseases like rheumatoid arthritis are very common chronic diseases among the Western nations. Despite the wealth of available drugs used in the therapy of inflammatory diseases there is still a lack of understanding of the molecular basis of the mechanism of action. A number of different pharmacological approaches are pursued in "Pain-fever-inflammation", however the exact effects of the drugs and in particular the origins of the side effects are often unclear. Some examples of well served anti-inflammatory drugs metamizol **1-11**,[32] celecoxib **1-12**,[33] paracetamol **1-13**,[34] aspirin **1-14**[35] and clofibrate **1-15**[36] (**Figure 4**) and anti-cholesterol drugs like lovastatin **1-2**, atorvastatin **1-6** (**Figure 2**) having considerable positive anti-inflammatory side effects which could be part of proposed research program. The primary biological targets of these ligands are known, but their molecular mode of action as well as origin of side effects is not yet fully understood. One further example of a positive side effect of statin drugs could be given as their association with decreased prevalence of Alzheimer's disease.[37]

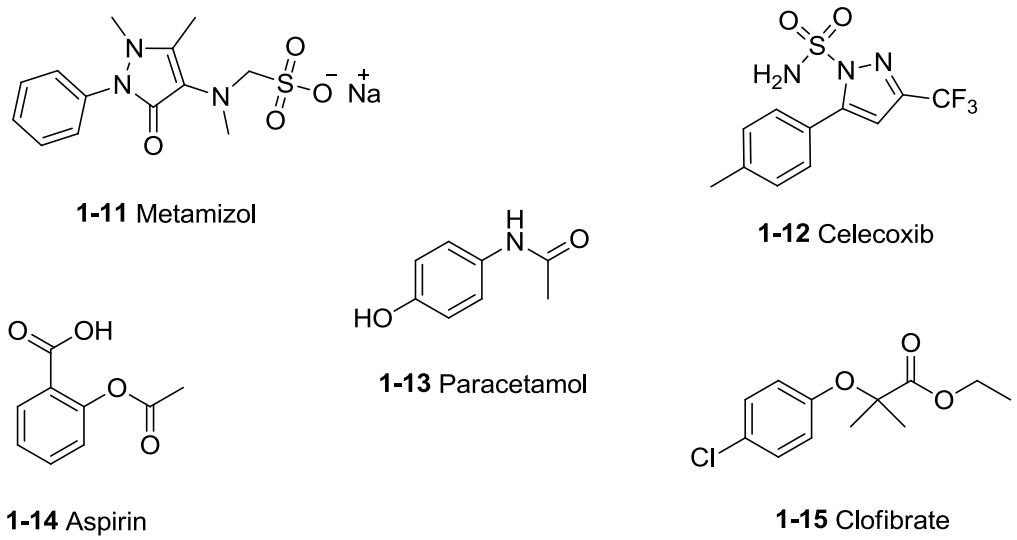


Figure 4. Some commonly used anti-inflammatory drugs.

The main objective of the research program was the identification of the relevant pharmacological targets and to contribute to the understanding of the mechanism of action of the above mentioned anti-inflammatory drugs. The research program aimed to develop chemical methods to synthesize the proposed drugs or their modified analogues attached to some suitable linkers for immobilization on affinity resins, fishing the drug targets from the cell lysate using affinity based method and their identification using suitable methods like MALDI-MS and other bio-analytical methods. The functionality of the drug-target interaction will be eventually characterized and validated. To explore the whole concept, we succeeded with an interdisciplinary group of scientists and graduate students to work on the various issues during the course. Being a part of this research program, our goal was to synthesize atorvastatin lactone and their derivatives coupled to a suitable linker system without affecting the hydroxy lactone region, which in its open form is crucial for the HMG-CoA reductase inhibition.

3 Literature Review

3.1 Mevalonate pathway of cholesterol biosynthesis[2]

Isoprenoids, derived from the mevalonate pathway are essential components of cells to maintain membrane fluidity and to assist in cell proliferation in all plants, fungi and mammals.[38] Mevalonate is formed from acetyl co-enzyme A via intermediate HMG-CoA. The 4-electron reduction of HMG-CoA to mevalonate is an early key step in the biosynthetic pathway. The reaction is catalyzed by HMG-CoA reductase (HMGR) and proceeds as follows.[1]

$$(S)\text{-HMG-CoA} + 2\ \text{NADPH} + 2\text{H}^+ \longrightarrow (R)\text{-mevalonate} + 2\ \text{NADP}^+ + \text{CoASH}$$

Where NADPH is nicotinamide adenine dinucleotide phosphate and $NADP^+$ is the oxidized form of NADPH.

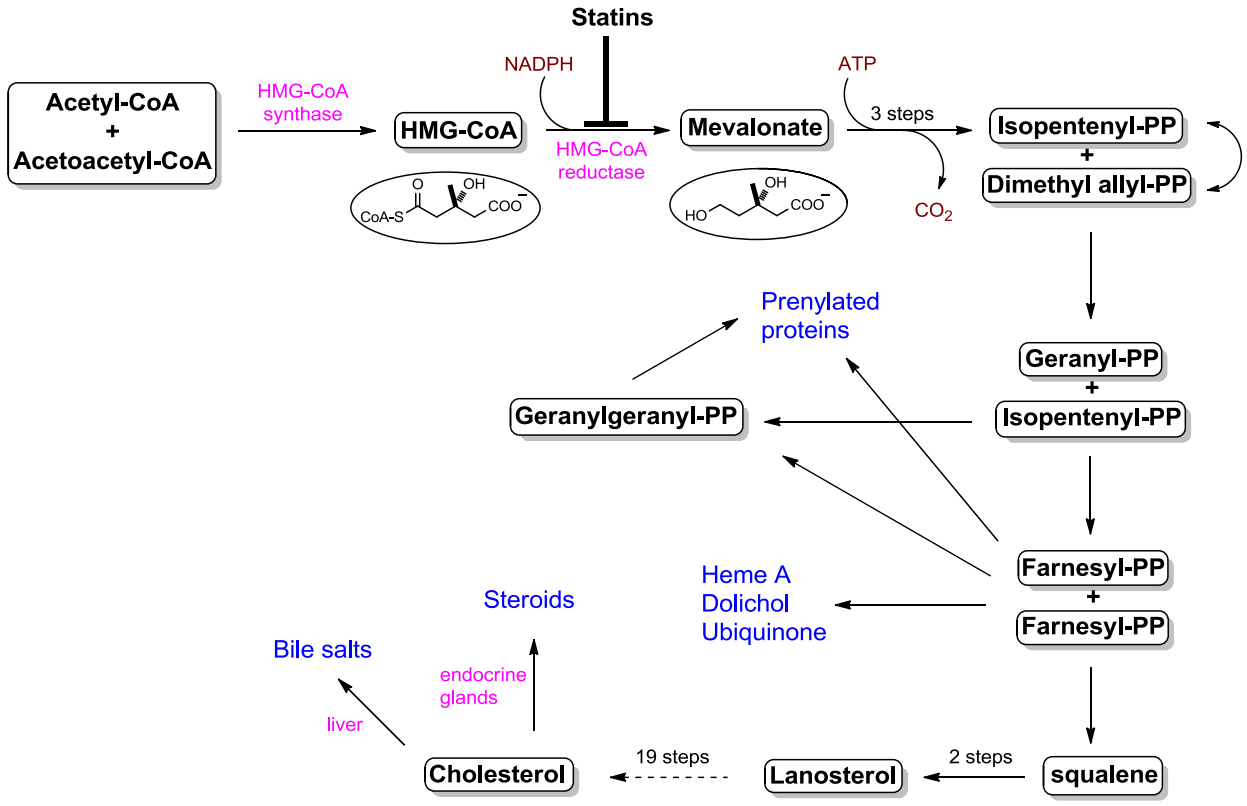


Figure 5. Mevalonate pathway in animal cells.

Mevalonate is converted into isoprene based molecules named as isopentenyl pyrophosphate (IPP) and dimethyl allyl pyrophosphate (DMPP) with adenosine triphosphate (ATP) dependent CO_2 loss. Here IPP remains in equilibrium with DMPP by isomerization of the double bond.[2] Synthesis continues with the formation of geranyl-pyrophosphate (GPP) by condensation of one molecule of IPP with one molecule of DMPP. GPP then enters into the synthesis of squalene via farnesyl pyrophosphate (FPP) as an intermediate which is formed by combination of one GPP and one IPP. Squalene is then converted to cholesterol after 21 intermediate steps.[2] Isoprenoid intermediates (FPP) are also diverted to the synthesis of other biological important compounds like heme A, dolichol and ubiquinone (**Figure 5**).

3.2 Binding mechanism of atorvastatin in cholesterol metabolism

All statins are competitive inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMGR). As discussed above, a crucial step in the cholesterol biosynthesis is the conversion of HMG-CoA to mevalonate which is blocked by the so called statins. They all share a HMG-like moiety in the structure as either active hydroxy acid form or as inactive lactone form which is enzymatically hydrolyzed to the active form in vivo.[1,39]

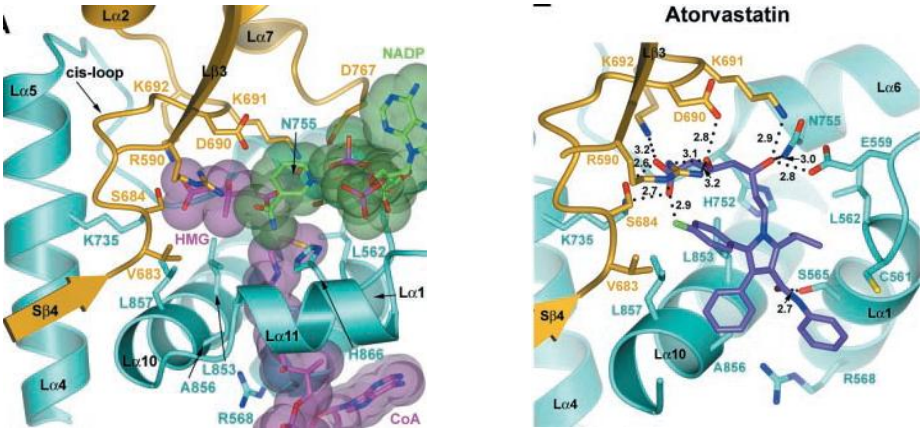


Figure 6. (A) Active site of human HMGR in complex with HMG, CoA, and NADP; **(B)** Mode of binding of atorvastatin (**1-6**) with HMGR.[1]

The structural similarity of the statin's heptanoic acid functional group to HMG suggests that these agents interfere with HMG-CoA binding to the HMGR enzyme. Indeed, all statins are competitive inhibitors of HMGR with respect to binding of HMG-CoA, but not with respect to binding of NADP(H).[1] In particular, an X-ray structure revealed that the HMG like moiety of atorvastatin occupies the active site (*cis* loop of residues 682-694) of HMGR enzyme while the bulky hydrophobic part of the statins is located in a shallow groove that is formed after rearrangement of the C-terminal residues of the enzyme (**Figure 6**).[1] As a result, there is no access for the substrate HMG-CoA to HMGR enzyme which is blocked after binding of a statin. The surface complementarity between HMGR and the hydrophobic part of atorvastatin is present in the statin-enzyme complex which is possible because atorvastatin adopts a conformation that allows its hydrophobic group to maximize contact with the hydrophobic region of the protein.[39]

Comparing the substrate-bound HMGR structures with the inhibitor-bound structures (**Figure 6**) illustrates that a rearrangement of the active site is required to accommodate the statin. Interactions that distinguish atorvastatin from decalin ring containing statins are hydrogen bonding between Ser^{565} OH group of the protein and either carbonyl oxygen or *O*-5 hydroxyl of atorvastatin. Also, the fluorophenyl group of atorvastatin stacks on the guanidinium group of Arg^{590} where polar interactions between guanidine nitrogens and fluorine atom are observed. The tight binding of atorvastatin is probably due to the large number of van der Waal interactions between atorvastatin and HMGR.

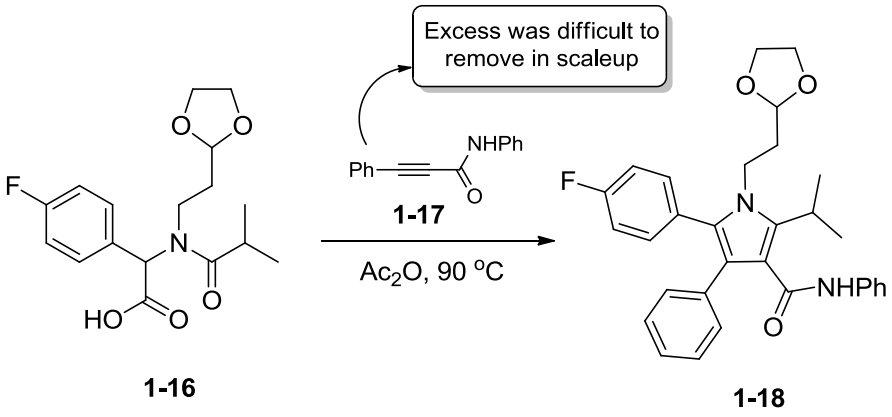
3.3 Development of atorvastatin calcium by Bruce Roth

Atorvastatin, a completely synthetic drug was first prepared by Bruce Roth in 1985 while working as medicinal chemist at Parke-Davis Warner-Lambert Company (now Pfizer pharmaceuticals). It is a penta-substituted pyrrole having a 3-hydroxy-3-methylglutaryl (HMG) like moiety on the terminus of the amine side chain. The design of atorvastatin was partly based on molecular modeling comparisons of the structures of fungal metabolites and other synthetically derived analogues.[40] For the design and discovery of this highly potent drug, Roth and coworkers had screened 30 pyrrole analogues out of which only the analogue with a 4-fluorophenyl at the 2-position and an isopropyl substituted at the 5-position of the pyrrole ring

led to good potency. Furthermore they screened about 20 analogues having different substituents at the 3 and 4-positions of the ring where they settled with a phenyl ring and phenyl amide group at the respective positions. With these substituents they found the best potency (IC_{50} = *0.007*μM) among all other analogues.[40]

3.3.1 Enantioselective linear synthesis of atorvastatin lactone

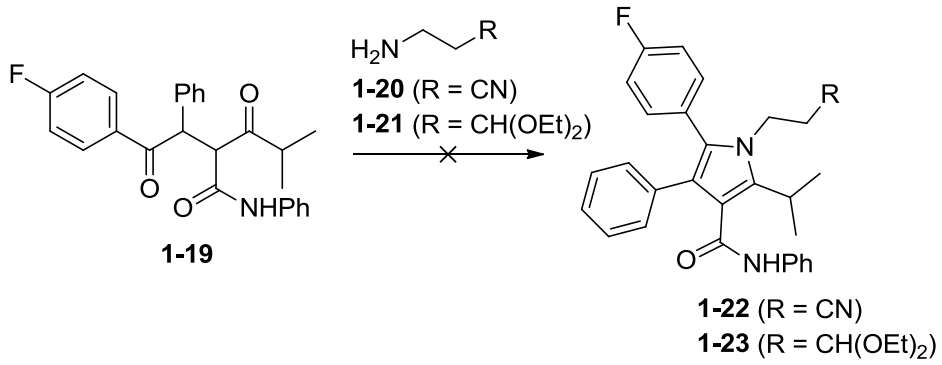
One of the two subgroups working under the supervision of Bruce Roth explored a synthesis that would achieve the fully functionalized pyrrole ring. Thus, treatment of acylated amino acid **1-16** with Ac_2O generated an intermediate that reacted with acetylene **1-17**, containing the carboxamide group, in a [3+2] cycloaddition manner and led to the penta-substituted pyrrole **1-18**. The reaction was found to be highly regioselective with regard to the orientation of the substituents and high yielding.



Scheme 1. [3+2] cycloaddition of azalactone **1-16** and phenyl acetylene **1-17**.

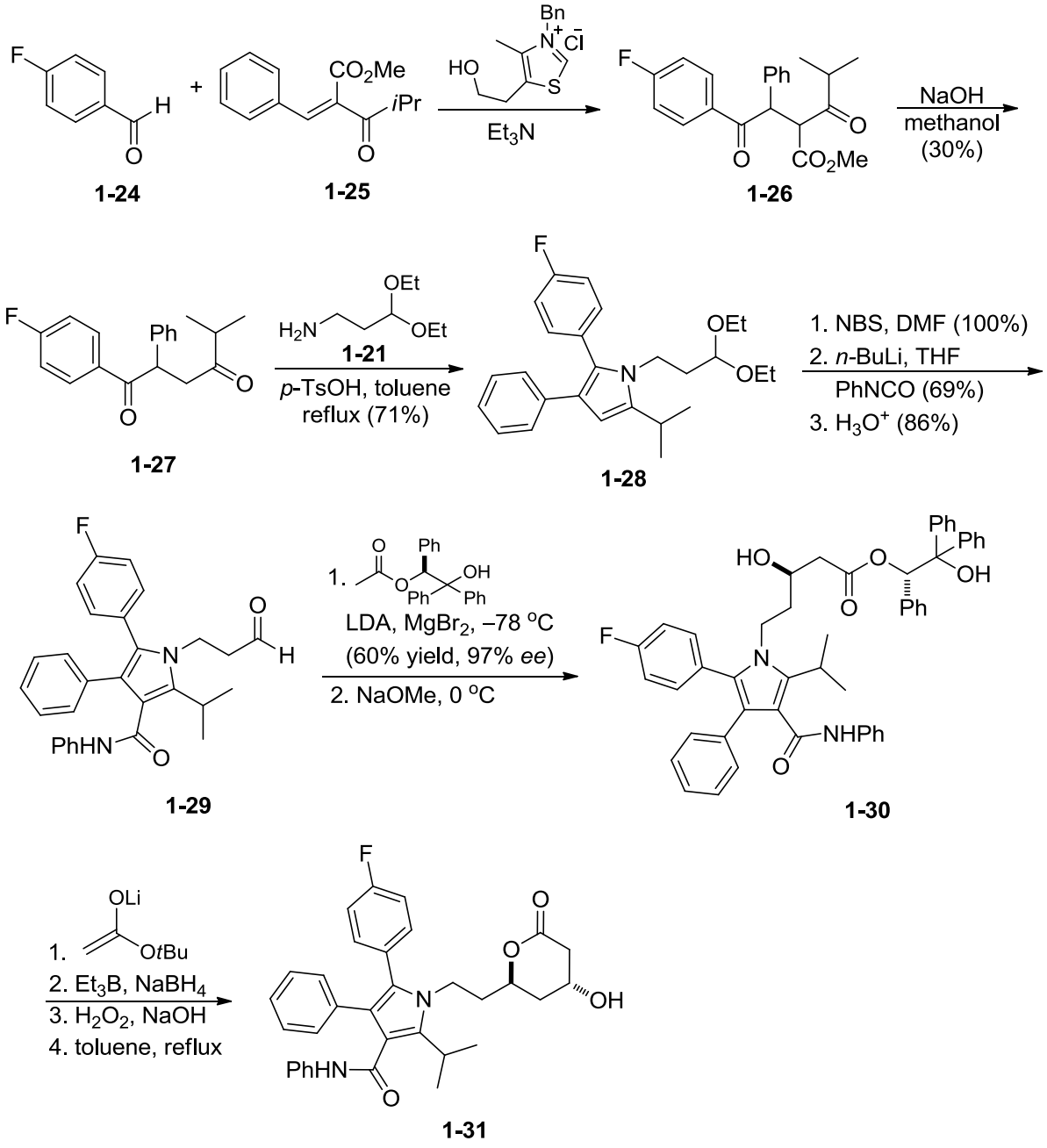
To improve the yield of the reaction, an excess of **1-17** was required but its removal in the workup was difficult in the large scale synthesis. This experience made them to look for other options like Paal-Knorr cyclodehydration using diketone **1-19** and various amines to generate the penta-substituted ring. But the reaction failed to give the corresponding cyclodehydration products (**Scheme 2**) under a variety of conditions.

An alternative option was to a make pyrrole ring with a tetra-substituted ring without the carboxamide group and to install it in later stage of synthesis.



Scheme 2. Attempts for the synthesis of pyrrole bearing phenyl carboxamide.

The precursor for the Paal-Knorr cyclodehydration was prepared by heating a mixture of 4-fluorobenzaldehyde **1-24** and unsaturated ester **1-25** under Stetter conditions followed by saponification and decarboxylation of ketoester **1-26** to afford 1,4-diketone **1-27**. Paal-Knorr cyclization of 1,4-diketone **1-27** with amine **1-21** proceeded smoothly to furnish pyrrole **1-28**.[41] The *N*-phenyl carboxamide was introduced by bromination at the 4-position of pyrrole **1-28** followed by subsequent Li–Br exchange and treatment with phenyl isocyanate. Hydrolysis of the diethylacetal provided aldehyde **1-29** which after a diastereoselective aldol condensation with the dianion of (*S*)-(+)-2-acetoxy-1,1,2-triphenylethanol resulted in the diastereomeric mixture of an intermediate (60% yield and 97% *ee*) which upon treatment with NaOMe at 0 °C gave ester **1-30** in 68% yield. Reaction of ester **1-30** with the lithium enolate of *tert*-butyl acetate followed by reduction with Et_3B-$NaBH_4$ mixture yielded intermediate *syn*-dihydroxyester enantioselectively. Base hydrolysis using NaOH followed by reflux in toluene and then purification by recrystallization from EtOAc/hexane afforded final lactone (+)-**1-31** (**Scheme 3**) as 100% enantiomerically pure.[40,41]

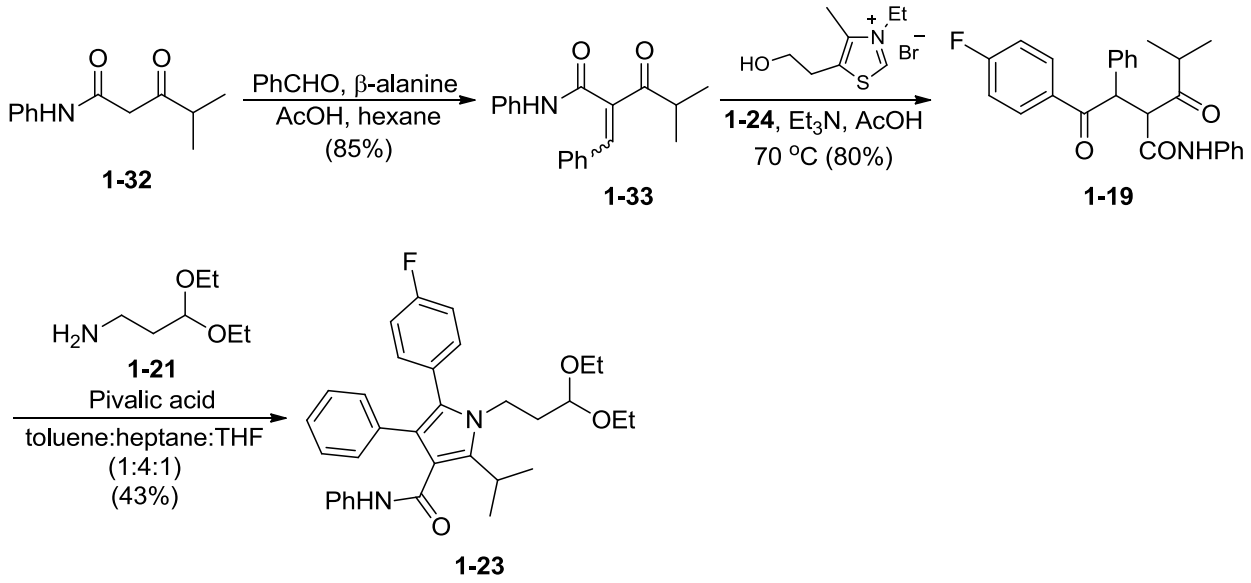


Scheme 3. Synthesis of atorvastatin lactone by subgroup of Roth et al.

Despite the successful isolation of highly enantiomerically pure (+)-**1**-**31** on gram scale, the reaction scheme involved several low temperature reactions, low yielding steps particularly in the final stage and a final recrystallization making this synthesis less efficient for kilogram scale synthesis. This made Roth and coworkers to think for a more economical and more efficient route.

3.3.2 Convergent route towards the synthesis of atorvastatin calcium[40]

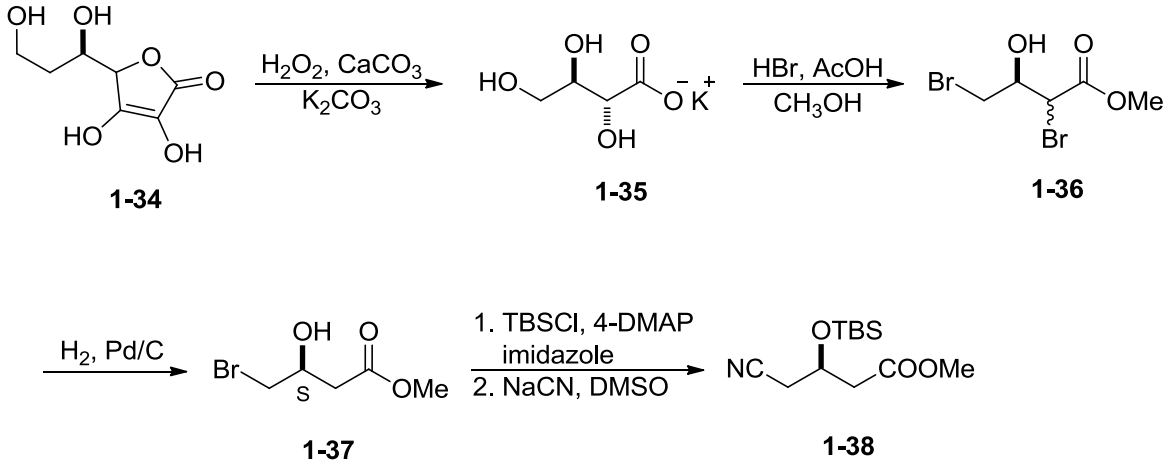
Therefore, the Paal-Knorr route was reinvestigated and the Roth subgroup from the chemical development eventually found suitable conditions for this transformation. The required diketone **1-19** was prepared by condensation of commercially available isobutyrylacetanilide **1-32** with benzaldehyde in presence of *β*-alanine and acetic acid to afford enone system **1-33** in 85% yield.[42] Reaction of 4-fluorobenzaldehyde **1-24** with **1-33** under Stetter conditions using an *N*-ethylthiazolium catalyst (**Scheme 4**) furnished substituted 1,4-diketone **1-19** in 80% yield. After extensive investigation of the classical Paal-Knorr condensation, success in the cyclodehydration was achieved by refluxing diketone **1-19** and acetal protected propanal amine **1-21** in presence of a full equivalent of pivalic acid in a ternary mixture (1:4:1) of the solvents toluene/THF/heptane providing fully functionalized pyrrole **1-23** in 43% yield.



Scheme 4. Synthesis of pyrrole ring bearing phenyl carboxamide group.

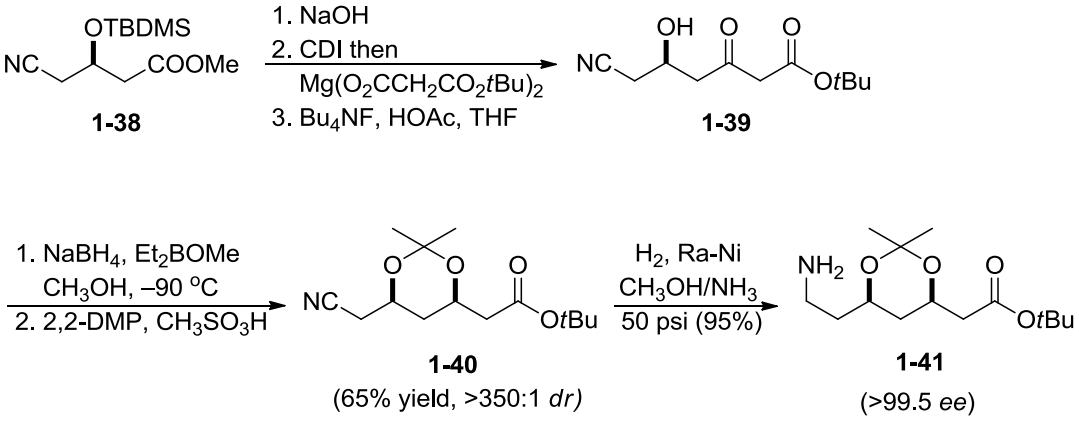
Now, a route could be foreseen in which the amine side chain having the complete functionality required for the synthesis could be condensed with diketone **1-19** to access the complete molecule in one step. To this end, a versatile intermediate (*S*)-methyl-4-bromo-hydroxybutyrate **1-37**[43] which is known from the synthesis of other HMG reductase inhibitors was converted to amine building block **1-41**.

This intermediate was efficiently synthesized from isoascorbic acid **1-34** by treating it with H_2O_2 in presence of $CaCO_3$ and K_2CO_3 to afford the salt of trihydroxy acid **1-35** which on further bromination and then esterification led to α-bromoester **1-36** using HBr, AcOH and methanol. Further catalytic hydrogenation of α-bromoester **1-36** using Pd/C yielded versatile intermediate **1-37**.[44] Protection of the hydroxyl group followed by substitution of the bromide with cyanide provided **1-38** (**Scheme 5**) as an advanced precursor.



Scheme 5. Synthesis of an advanced intermediate **1-38**.

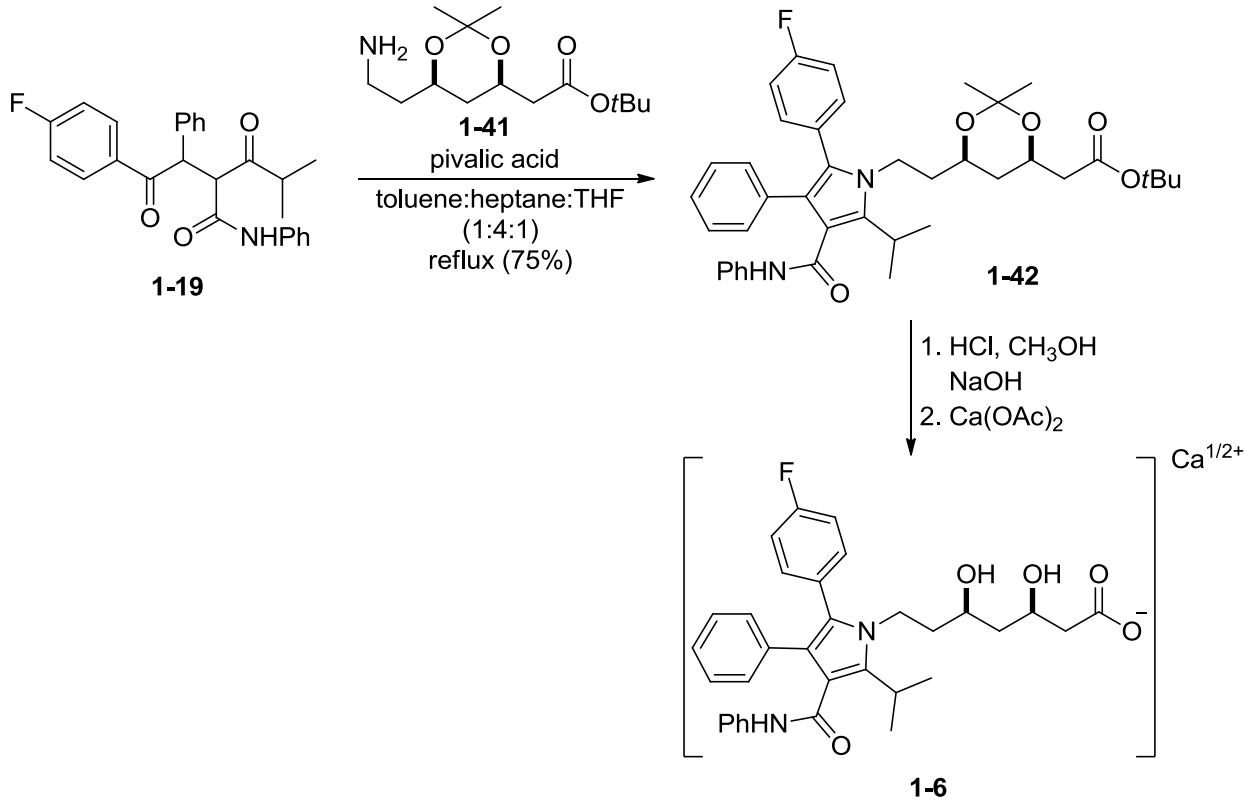
Afterwards, hydrolysis of methyl ester **1-38** and its subsequent activation using *N*,*N*-carbodiimidazole (CDI) followed by treatment with the magnesium salt of *t*-butyl malonate and removal of silyl ether using buffered fluoride afforded δ-hydroxy-β-ketoester **1-39**.



Scheme 6. Synthesis of functionalized amine side chain **1-41**.

Stereoselective reduction of the keto group using $NaBH_4$ and Et_2BOMe at low temperature (−90 °C) led to *syn*-1,3-diol;[45] then acetonide protection of the resulting diol using acetone dimethyl acetal produced **1-40** in 65% yield as crystalline solid and excellent diastereoselectivity (100:1) which was improved to 350:1 after recrystallization.[46] Catalytic reduction using molybdenum doped Raney nickel catalyst under 50 psi hydrogen pressure of nitrile **1-40** delivered amine **1-41** (**Scheme 6**) with outstanding enantiomeric excess (*ee*) value (>99.5).[47]

Cyclodehydration of the functionalized and enantioenriched amine side chain **1-41** with fully substituted 1,4-diketone **1-19** was carried out under carefully derived conditions (1 equiv pivalic acid and 1:4:1 mixture of toluene/heptane/THF) which yielded 75% of the desired pyrrole **1-42**. Further deprotection of the acetonide ester and treatment with $Ca(OH)_2$ provided stereochemically pure calcium salt of atorvastatin **1-6** (**Scheme 7**). This convergent route is high yielding and commercially viable for the large scale synthesis of the molecule.



Scheme 7. Synthesis of atorvastatin calcium from functionalized precursors.

4 Retrosynthesis

Since atorvastatin in its lactone form is easier to prepare and is a precursor for its dihydroxy carboxylate as active form, our proposed synthesis aimed at atorvastatin lactone with the possibility to attach a ethylene glycol linker to the aniline ring of carboxamide group. Retrosynthetic analysis of atorvastatin lactone (**1-31** or **1-43**) suggests a first retrosynthetic cut at lactone C–O bond which directs acetonide acid (**1-44** or **1-45**) as synthetic equivalent which could be functionalized by oxidation of primary alcohol. Amide function on the pyrrole ring **1-44** or **1-45** can be developed by insertion of the carboxyl group at 4-position on the ring of pyrrole **1-46** followed by coupling with simple amine **1-47** or derived amine **1-48** (**Figure 7**).

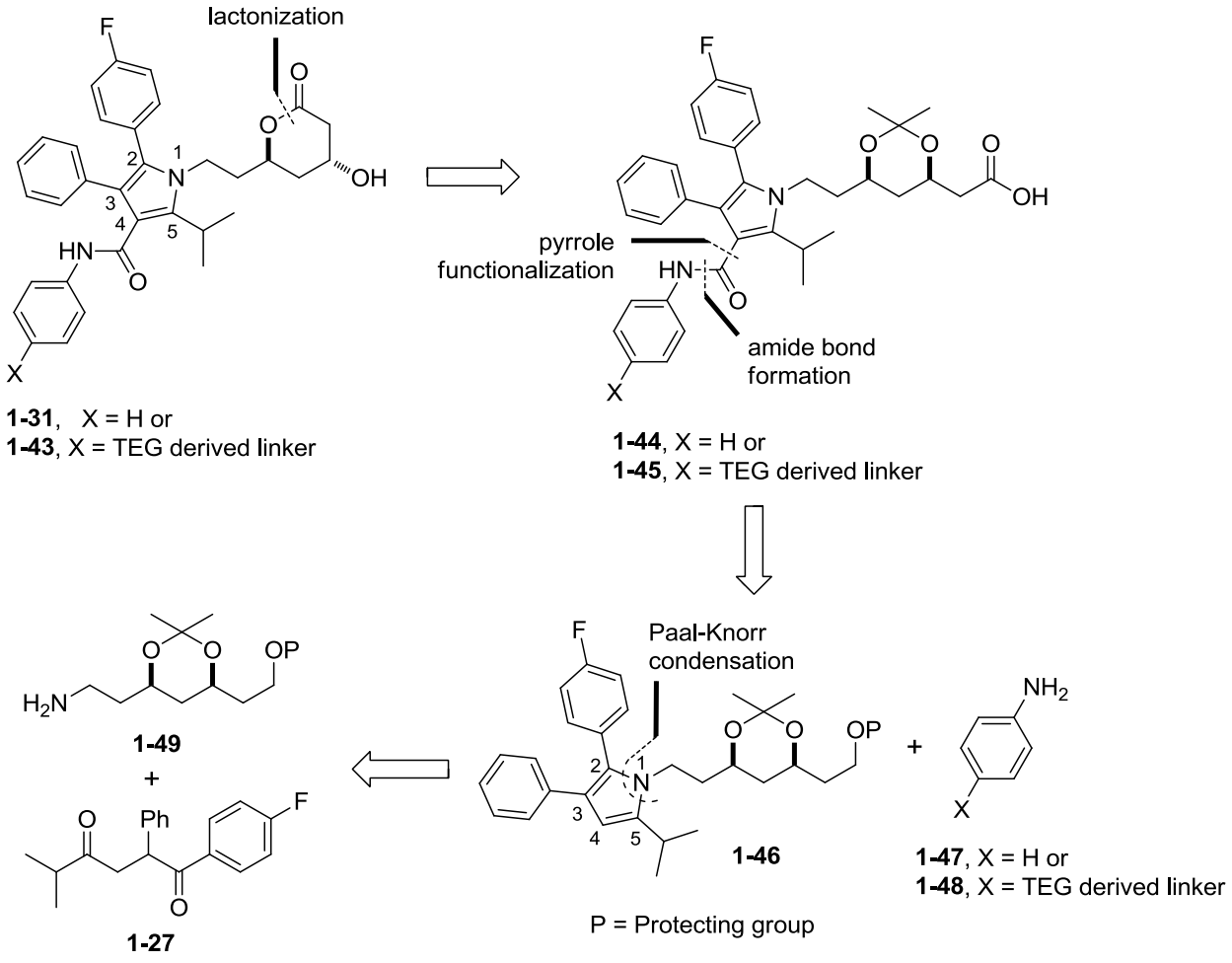


Figure 7. Retrosynthetic analysis of atorvastatin lactone and derived analogues.

Here, to build a polyethylene glycol derived linker system to the phenyl ring of the carboxamide part of the molecule might be suitable to provide flexibility to the resulting derivative in target fishing experiments. A fundamental building block, pyrrole **1-46** could be obtained from diketone **1-27** and functionalized amine side chain **1-49** using an acid catalyzed classical Paal-Knorr cyclization. Diketone **1-27** is a known starting material which might be synthesized easily according to the literature procedures.

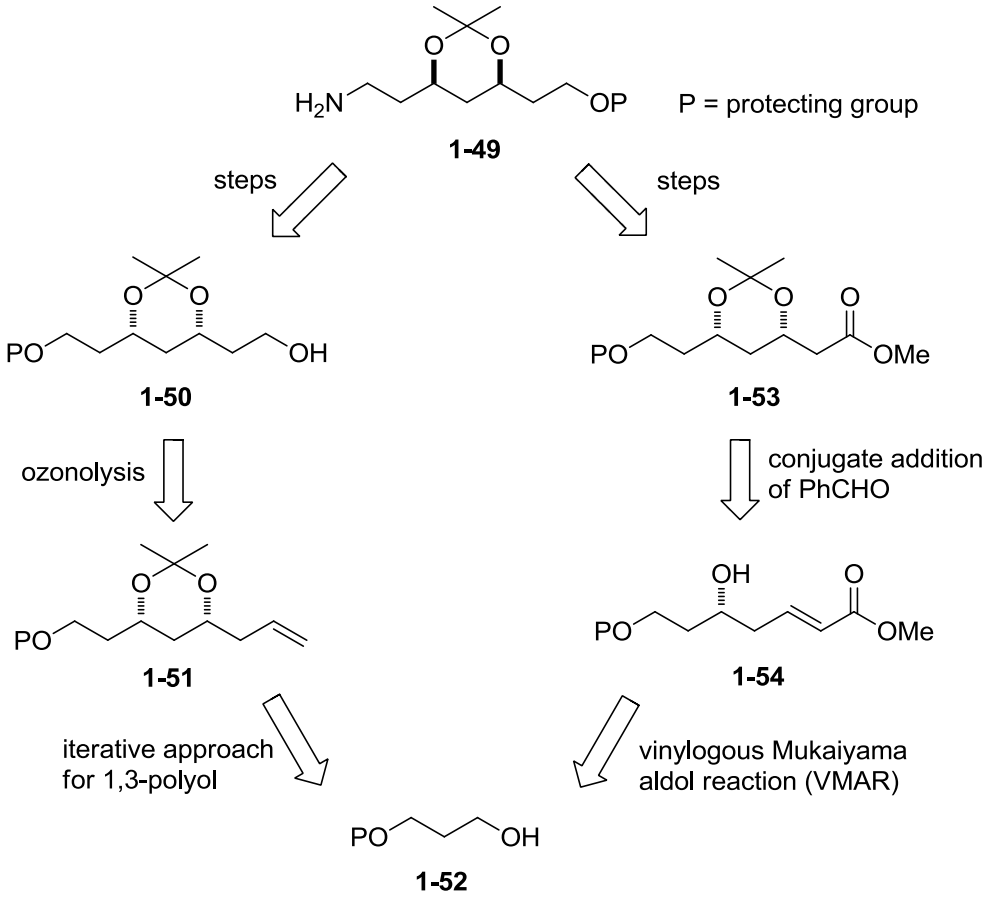


Figure 8. Retrosynthetic consideration for amine side chain **1-49**.

The synthesis of the functionalized amine side chain **1-49** containing a *syn*-1,3-diol could be achieved in different ways. Here we proposed two different routes to prepare it from simple mono protected propanediol **1-52** as its earliest precursor (**Figure 8**). The first proposed strategy is based on Krische's approach[48] of iterative enantioselective carbonyl allylations to build the *syn*-1,3-polyol subunit by using iridium catalysis. This strategy involves two fold asymmetric

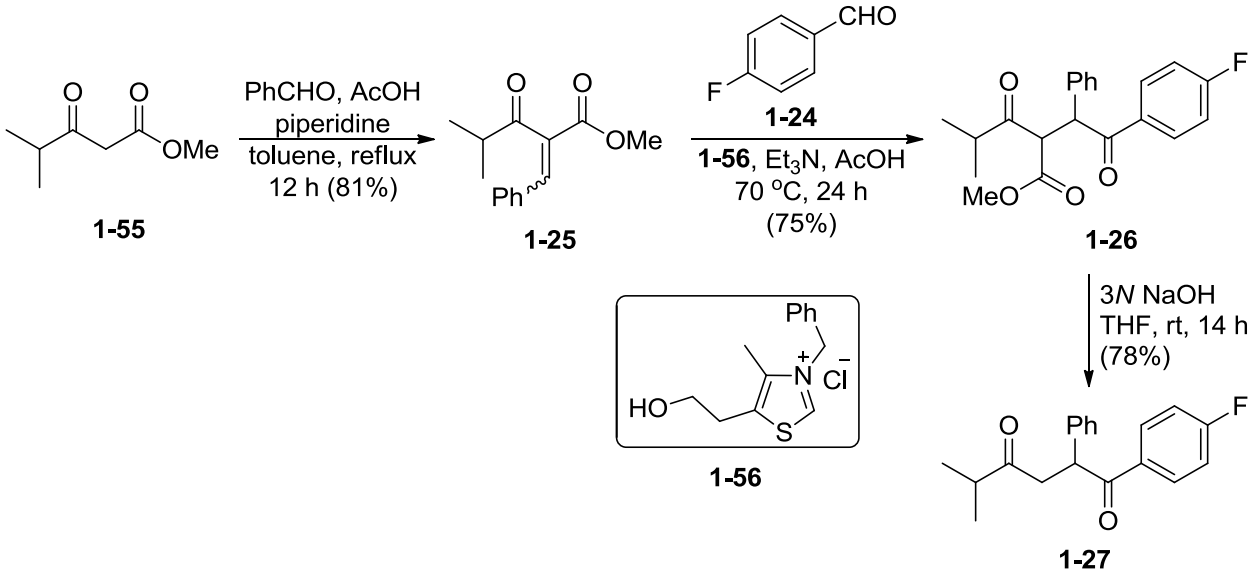
allylation followed by ozonolysis to provide tetraol derivative **1-50** as an advanced precursor which can be modified to amine **1-49** via simple functional group interconversions.

An alternative approach is based on a vinylogous Mukaiyama aldol reaction (VMAR)[49] of aldehyde prepared from alcohol **1-52** leading towards δ-hydroxy-α,β-unsaturated ester **1-54** as key intermediate (**Figure 8**) which introduces one asymmetric center in the molecule. The second asymmetric center can be brought in via base catalyzed intramolecular conjugate addition of hemiacetal derived alkoxide of benzaldehyde to δ-hydroxy enoate **1-54** followed by protection-deprotection steps to fashion *syn*-dihydroxy ester **1-53**. Towards the end of the side chain synthesis the methyl ester function can be transformed to amine **1-49** via its conversion to intermediate amide.

5 Results and Discussion

5.1 Initial attempts of synthesis and functionalization of the pyrrole ring

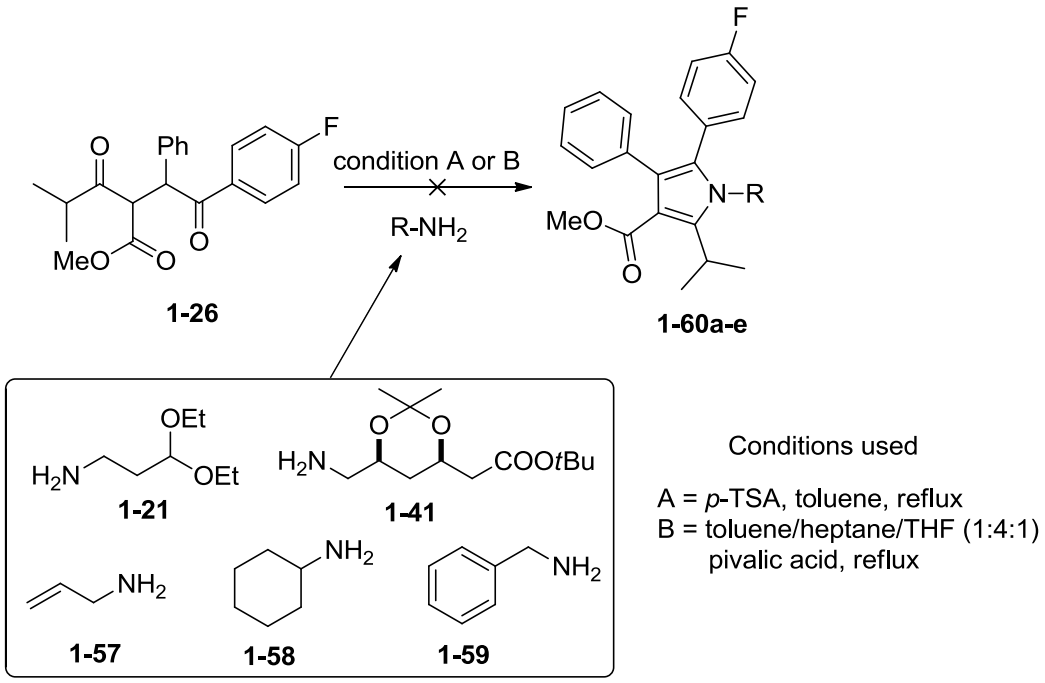
We decided first to synthesize achiral 1,4-diketone **1-26** containing a methyl ester for further manipulation towards the corresponding carboxamide. According to the literature procedure,[41] commercially available 4-methyl-3-oxopentanoate **1-55** was condensed with benzaldehyde in toluene under reflux condition whereby water was removed azeotropically yielding enone **1-25** as shown in **Scheme 8**. Under Stetter reaction conditions, using thiazolium salt **1-56** as catalyst, enone **1-25** was converted to 1,4-diketone **1-26** and further to **1-27** by base hydrolysis.



Scheme 8. Synthesis of 1,4-diketone **1-27**.

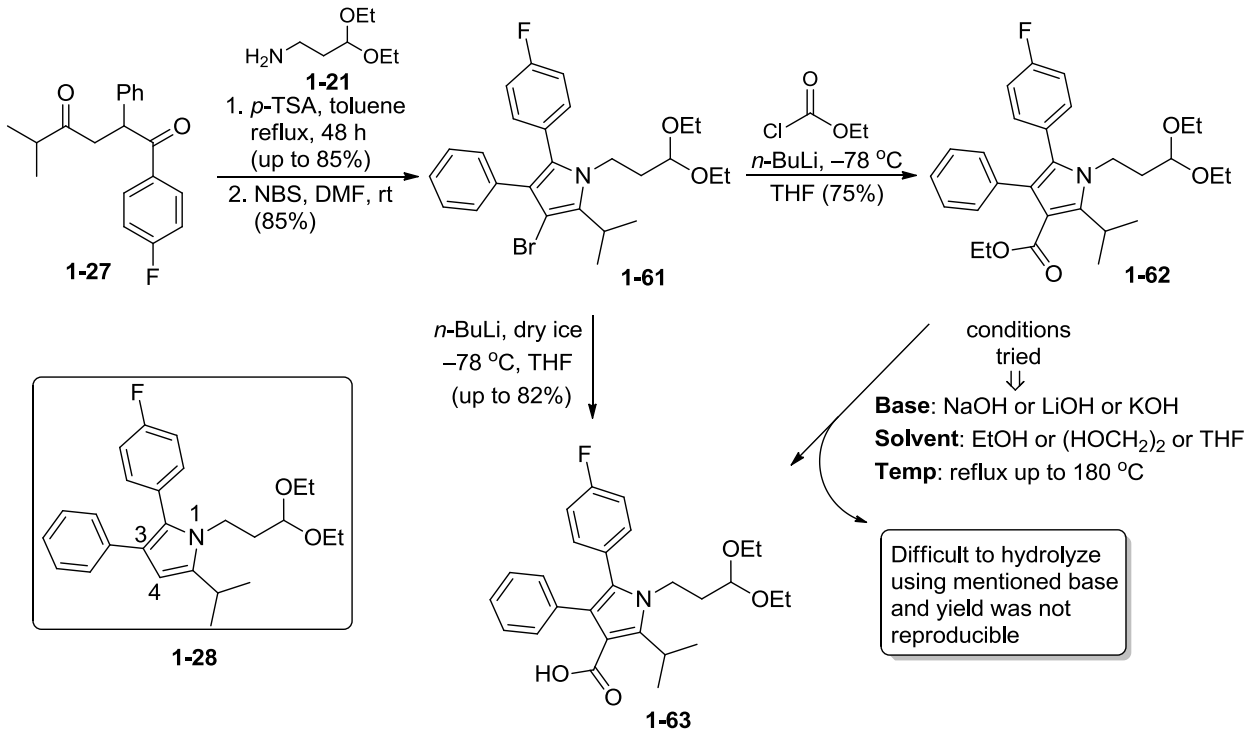
As initial approach, we planned to try cyclodehydration of diketone **1-26** with the amine **1-21** to check the feasibility of the reaction in presence of a methyl ester group present in **1-21**, and if it would be successful then we could modify the synthesis towards our goal. Accordingly, we attempted the condensation of diketone **1-26** with acetal protected 1-amino-3-propanal **1-21**, using *p*-TSA•H_2O as catalyst in a Dean-Stark apparatus for azeotropic removal of water but no desired conversion to the corresponding pyrrole has been observed (TLC). Repeated attempts provided the same result. Similar results were obtained when we used various amines under

different conditions[41,50] as shown in **Scheme 9** and prolonged heating. TLC always showed a series of spots as well as in LC-MS we did not observe the target compounds (**1-60a-e**).



Scheme 9. Screening of different conditions for synthesis of methyl ester functionalized pyrrole.

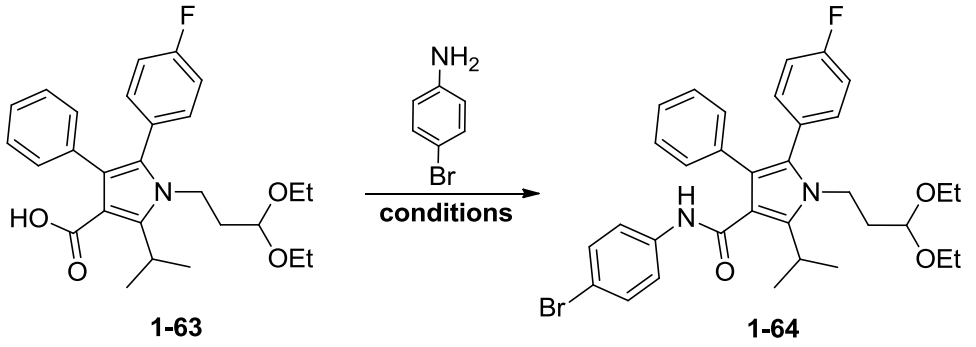
Consequently, we proposed to make a pyrrole without a methyl ester function with the speculation that it could be functionalized after pyrrole formation. Therefore, methyl ester **1-26** was converted to analogous diketone **1-27** by using 3N NaOH while vigorously stirring the mixture at room temperature (as shown in **Scheme 8**). Then, diketone **1-27** was refluxed with amine **1-21** under acidic conditions in toluene over 48 h. The reaction completed successfully and delivered pyrrole in 85% yield. Next task was to establish a carboxylic group at the C-3 position of the pyrrole ring. As proposed, the C-4 position of pyrrole **1-28** was brominated using NBS at room temperature in good yield.[51] Bromopyrrole **1-61** was subjected to lithium-bromine exchange using *n*-BuLi at −78 °C. The resulting organo-lithium species was quenched with ethyl chloroformate to furnish pyrrole ester **1-62** in 83% yield.



Scheme 10. Synthesis of pyrrole with carboxyl acid **1-63**.

In the next step, hydrolysis of the ethyl ester **1-62** was attempted using various bases and solvents (**Scheme 10**). However, very harsh conditions like repeated addition of base and high reflux temperature were required; despite this high yields could not be obtained in a reproducible way. This problem was resolved later successfully by the use of solid CO_2 as an electrophile to deliver acid **1-63** directly in a single step. Treatment of bromopyrrole **1-61** with *t*-BuLi followed by addition of excess of dry ice provided acid **1-63** in 82% yield in one step. Here, we used *t*-BuLi as base rather than *n*-BuLi followed by immediate quenching of the metalated species with hope to minimize the formation of 10–15% of pyrrole **1-28** as side product but only little improvement in the yield of the reaction was observed. Most probably the formation of pyrrole **1-28** as a side product is due to the moisture associated with the addition of solid dry ice.

With enough amount of acid **1-63** in hand, we were set to carry out a reaction with 4-bromoaniline for amide bond formation. We screened a variety of coupling agents under different conditions as stated in **Scheme 11** but only the reaction using PyBrOP and DIPEA was completed successfully to yield amide **1-64** in excellent yield.



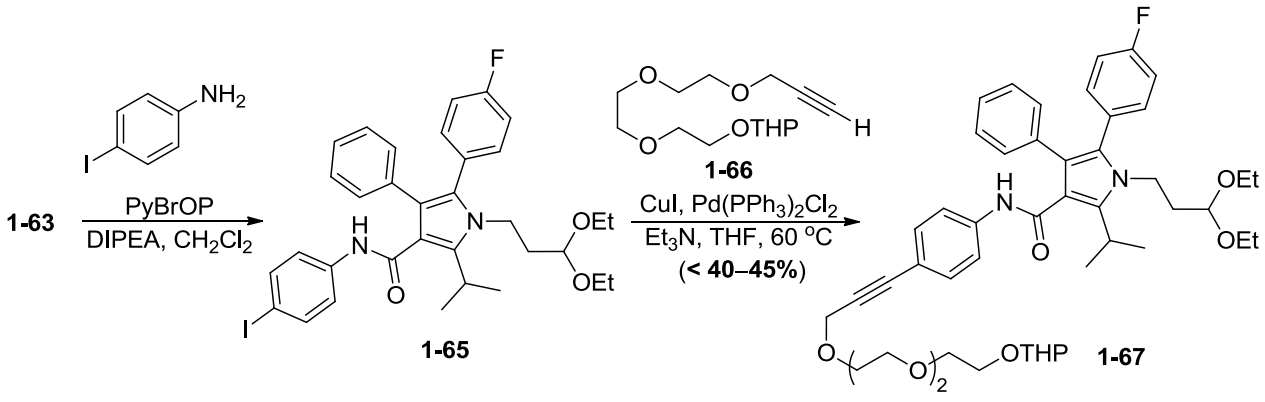
1-63 **1-64**

Reagents & conditions	Results
DCC, DMF/CH_2Cl_2 (1:3) or $CHCl_3$ 0 ^oC to rt, 24 h	partial conversion
CDI, DMF, 50 ^oC, 30 h	very slow to form activated ester
PivCl, CH_2Cl_2, 0 ^oC, 30 h	no conversion
BOP, NMM, THF, 0 ^oC to rt, 50 h	partial conversion
HOBt, NMM, HBTU, THF, 0 ^oC to rt, 120 h	only till intermediate activated ester
HATU, HOAt, DIPEA, CH_2Cl_2, 0 ^oC to rt, 44 h	moderate conversion
PyBOP, DIPEA, CH_2Cl_2, 0 ^oC to rt, 96 h	moderate conversion
PyBrOP, DIPEA, CH_2Cl_2, 0 ^oC to rt, 16 h	**complete conversion (94% yield)**

Scheme 11. Attempts made for synthesis of amide **1-64** using suitable coupling conditions.

For further extension, we treated amide **1-64** with THP protected and propargyl derived TEG linker **1-66** (received from M. Golkowski) under Sonogashira conditions[52] ($Pd(PPh_3)_2Cl_2$, CuI, Et_3N in THF) at room temperature but no conversion to the desired product has been observed. Repeated attempts of the reaction as well as solvent change to CH_3CN with longer stirring and heating to reflux did not produce linker coupled product **1-67** (**Scheme 12**). However, replacing the bromo derivative **1-64** with iodo derivative **1-65** which is prepared by using 4-iodo aniline, then heating the mixture in THF together with **1-66** at 60 °C, provided coupling product **1-67** in 45% yield. But, this reaction always remained low yielding in the poor range of 40–45% which was insufficient to carry out further transformations in order to reach atorvastatin lactone connected to a linker.

Therefore, we skipped this route and planned to design a better route towards atorvastatin lactone and derived analogues.

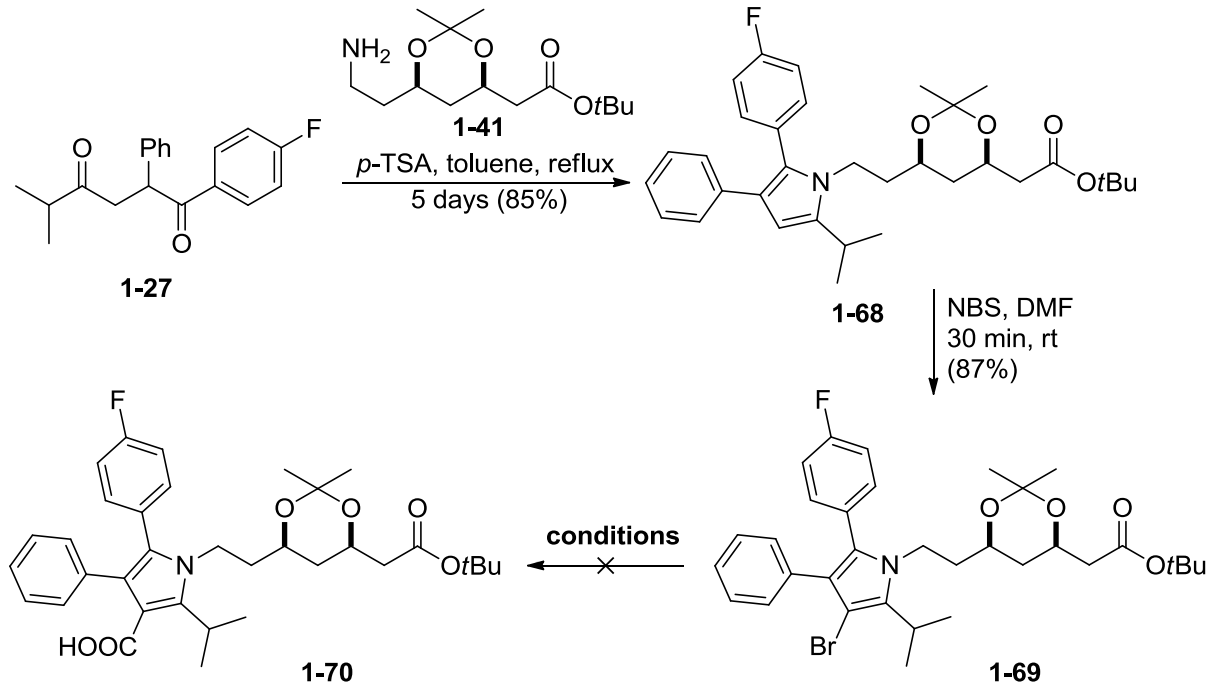


Scheme 12. Synthesis of pyrrole amide **1-67** under Sonogashira conditions.

We proposed to synthesize the pyrrole without ester function using diketone **1-27** and commercially available amine **1-41**, then introduction of amide on pyrrole ring would be followed by functionalization of the lactone in the subsequent steps. As well as, after disappointing results with the Sonogashira coupling, we proposed to synthesize linker derived aniline(s) which could be coupled via amide bond formation with the carboxyl derived pyrrole.

5.2 Atorvastatin lactone synthesis using commercially available side chain

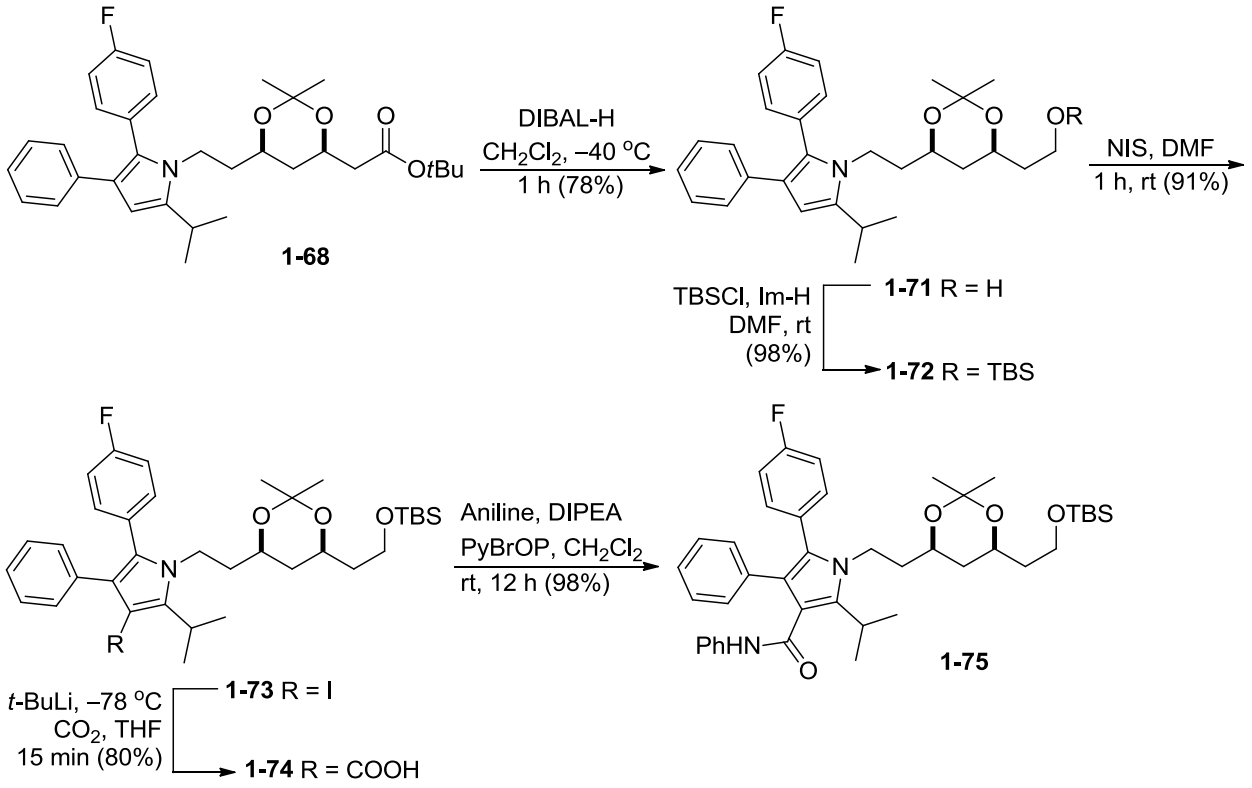
Accordingly, diketone **1-27** and amine **1-41** were refluxed in toluene to remove water as azeotrope under acidic condition using catalytic *p*-TSA•H_2O to afford pyrrole **1-68**. Subsequent bromination was completed within 30 min using NBS in DMF yielding bromopyrrole **1-69** in 74% yield over two steps. The next step was challenging since we had to carry out metal-halogen exchange selectively in presence of the sensitive *t*-butyl ester group. Obviously, *n*-BuLi and *t*-BuLi would not be useful under these circumstances for selective metal-halogen exchange while keeping an ester group intact. We tried some other selective reagents like mesityl lithium,[53] Zn•LiCl/CuCN•2LiCl,[54] and *i*-PrMgCl•LiCl[55] (**Scheme 13**) but we did not observe metal-halogen exchange; also TLC supported this observation.



Reagents & conditions	Results
Zn∗LiCl, CuCN∗2LiCl, –15 °C to rt	no reaction
*i*PrMgCl∗LiCl, –78 °C,	no reaction
mesityl lithium, –78 °C to rt	no reaction

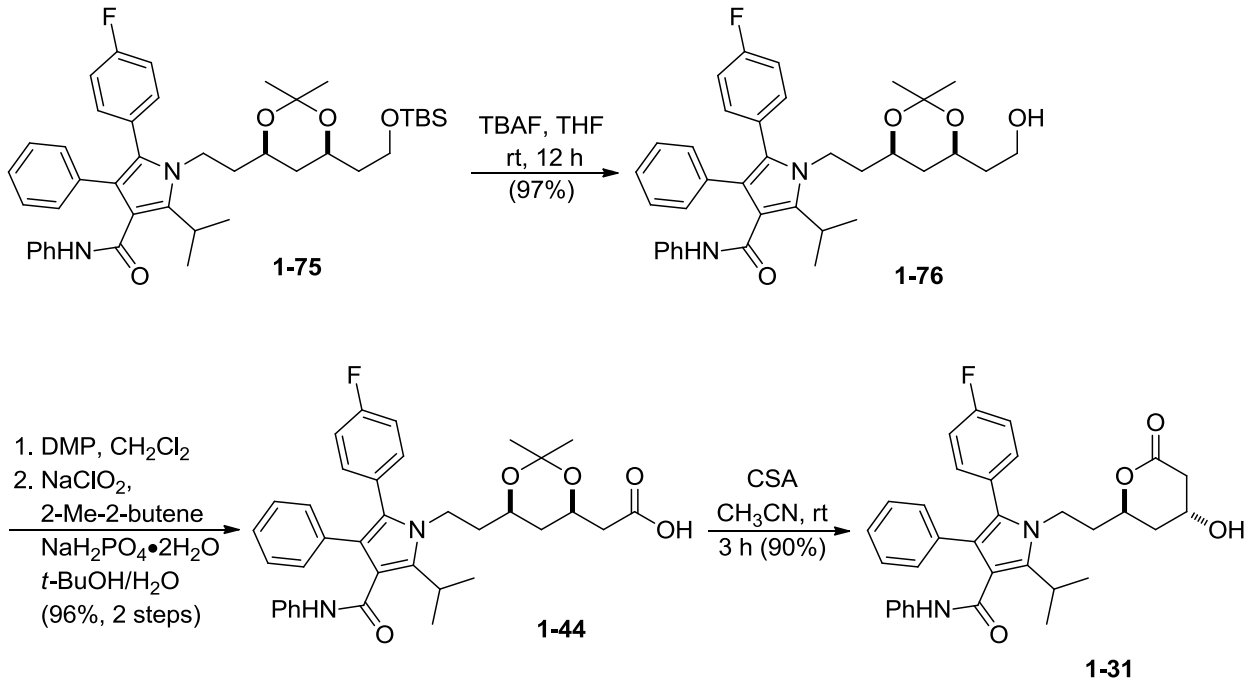
Scheme 13. Attempts towards the chemoselective Li–Br exchange on bromide **1-69** with various reagents.

The alternative solution for this issue was to change the *t*-butyl ester group to another functional group and then to carry out the metal-halogen exchange reaction. As a consequence, the *t*-butyl ester group of **1-68** (**Scheme 13**) was first reduced using DiBAL-H at −40 °C and protected as TBS ether **1-72** quantitatively using *t*-butyldimethylsilyl chloride and imidazole. Iodination at C-3 position using NIS in DMF at room temperature provided intermediate iodo analogue **1-73** quantitatively. Here, we used NIS as mild agent rather than NBS to avoid possible TBS group removal which we noticed while carrying out bromination of analogous TES ether of **1-72** using NBS at room temperature.



Scheme 14. Synthesis of intermediate **1-75** from amine side chain **1-41**.

Li–I exchange using *t*-BuLi at −78 °C followed by addition of excess of solid CO_2 furnished acid **1-73** in 80% yield. Aniline was coupled to **1-74** under predeveloped coupling conditions as shown in **Scheme 11**. Now turning to the side chain part, the TBS group was removed using TBAF•$3H_2O$ as 0.2M solution in THF which led to alcohol **1-76**. Oxidation using Dess-Martin periodinane in CH_2Cl_2 followed by subsequent oxidation of the resulting aldehyde with buffered $NaClO_2$,[56] in aq *t*-BuOH provided corresponding acid **1-44** in 96% yield. To complete the synthesis, acetonide acid **1-44** was treated with catalytic amount of camphorsulphonic acid in various solvents including CH_3CN, THF and methanol at room temperature. Among these, reaction in CH_3CN provided higher yield than in the other two solvents and we were able to isolate pure atorvastatin lactone **1-31** (**Scheme 15**) in 90% yield. Recrystallization from petroleum ether and ethyl acetate provided **1-31** as a white solid powder. Spectroscopic data of this final lactone were almost identical with the reported one.[57] Optical rotation of **1-31** was determined to be +25.5 (*c* 0.2, $CHCl_3$; Lit.[47] value +26.05).



Scheme 15. Synthesis of atorvastatin lactone **1-31**.

The only drawback of this synthesis was that the amine side chain **1-41** was quite expensive to purchase. And it was necessary to have gram scale intermediates in hand to synthesize TEG derived analogues of atorvastatin lactone. Therefore, we decided to synthesize the amine side chain by a novel route which would provide it on gram scale for further modifications.

5.3 Synthesis of functionalized amine side chain

As described in literature, amine **1-41** is generally prepared from *tert*-butyl-2-[(4*R*,6*S*)-6-(hydroxymethyl)-2,2-dimethyl-1,3-dioxan-4-yl]acetate **1-77** (**Figure 9**) via chain extension.[58] Several examples about synthesis of the side chain have been reported.[59] Some biocatalytic methods have been used to reduce prochiral precursors like 4-chloro/4-bromo-3-oxobutyrate **1-80** or 3,5-dioxy-6-benzyloxyhexanoate **1-86**.[60] Also, there are reports about an efficient, scalable enzyme catalyzed synthesis towards 3-hydroxyglutaronitrile **1-85**[61] or from 3-hydroxyglutaric acid ethyl ester **1-84**.[62]

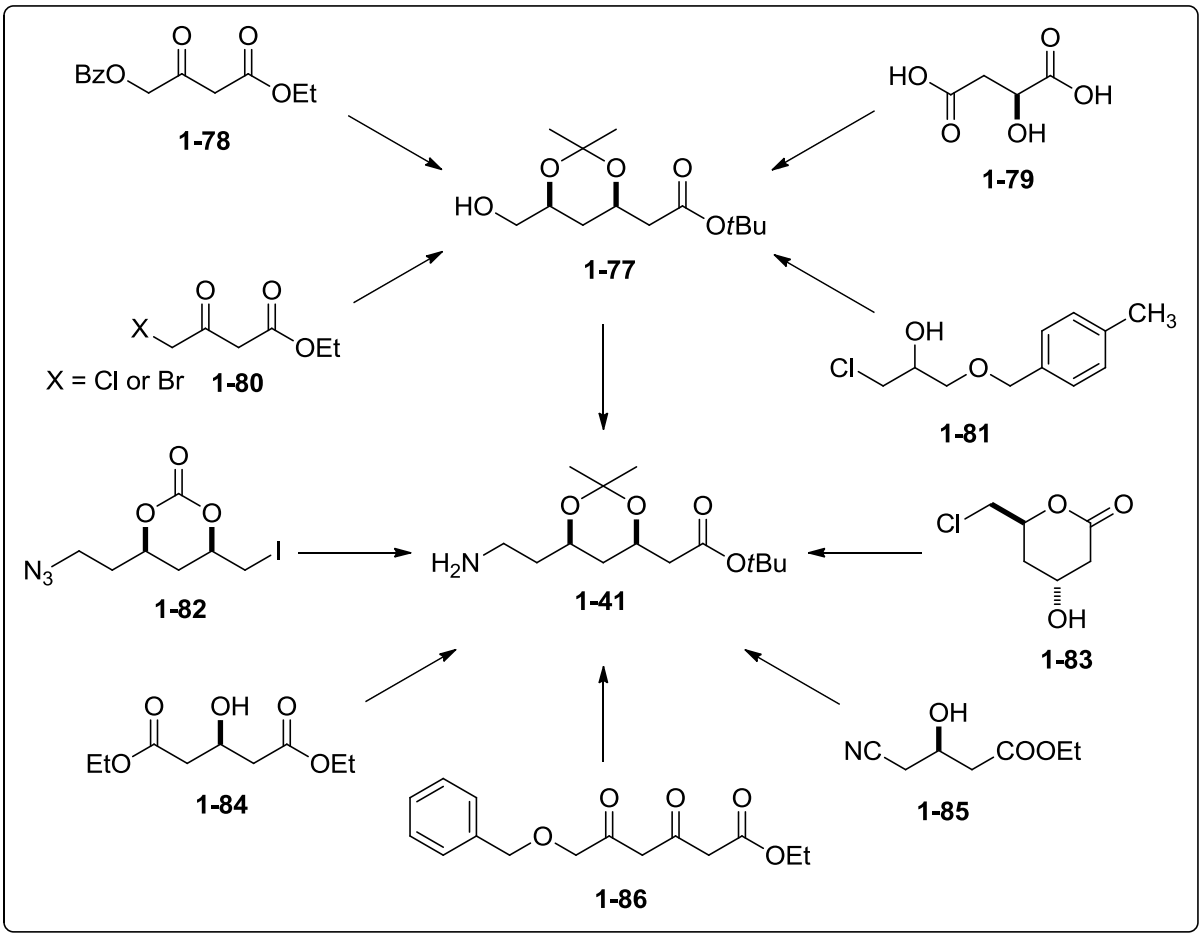


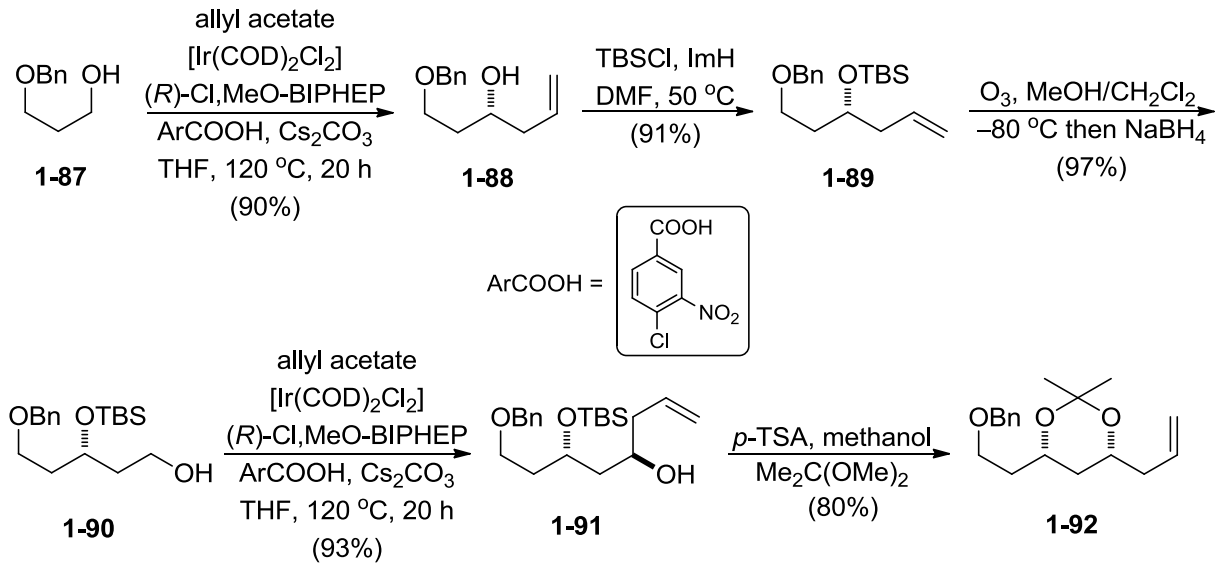
Figure 9. Various routes from the literature towards the synthesis of amine **1-41**.

Other publications have described the synthesis of versatile intermediate **1-77** from 1-chloro-3-(*p*-methylbenzyloxy)-2-propanol **1-81** derived from racemic epichlorohydrin,[63] (4*R*,6*S*)-6-(chloromethyl)-4-hydroxytetrahydro-2*H*-pyran-2-one **1-83** by sequential aldol reaction of azidoaldehyde and acetaldehyde catalyzed by Schiff's base 2-deoxyribose-5-phosphate aldose (DERA)[64] and other one starting from *L*-malic acid **1-79**.[65] Among all, a highly practical route to the precursor **1-77** includes Noyori type hydrogenation of ethyl-4-benzyloxy acetoacetate **1-78** followed by Claisen condensation and syn reduction of the hydroxy ketone.[66]

5.3.1 Amine side chain by Krische's iterative approach

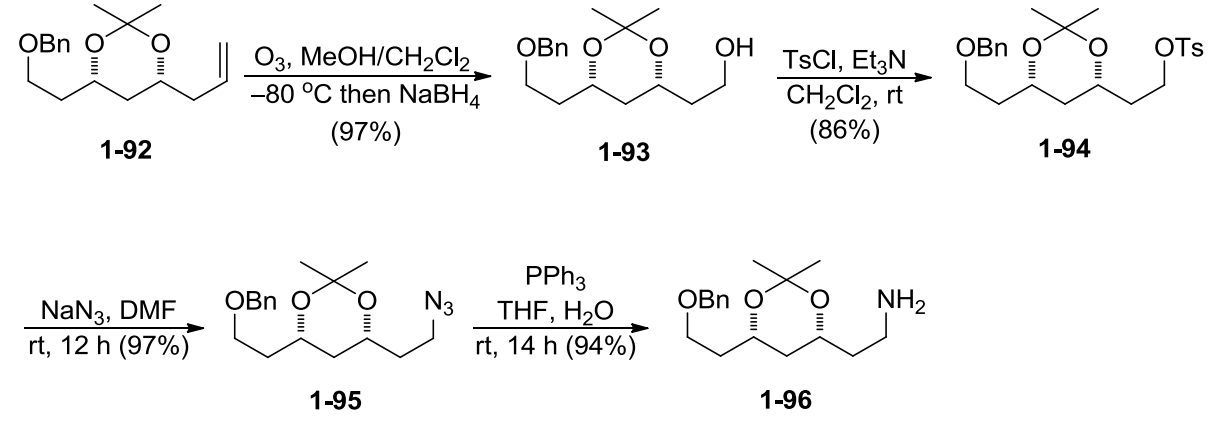
Recently Krische et al.[48] published an approach for the synthesis of *syn* or *anti*-1,3-polyols by iterative asymmetric transfer hydrogenative carbonyl allylation. In their work, they also reported an efficient synthesis of a possible precursor for the side chain namely *syn*-1,3-diol subunit **1-93** (see **Scheme 17**). This intermediate would be a useful starting point towards the synthesis of an amine side chain with a benzyl protected alcohol which could be functionalized to the lactone ring in the final steps of the synthesis as described above (**Scheme 15**).

The *syn*-1,3-diol subunit **1-93** was fashioned from 3-benzyloxy-1-propanol (**1-87**)[67] by two iterative asymmetric transfer hydrogenative carbonyl allylation reactions. Thus, reaction of alcohol **1-87** with allyl acetate in presence of a catalyst generated in situ from $[Ir(COD)_2Cl_2]$, (*R*)-(+)-Cl,MeO-BIPHEP, and 4-chloro-3-nitro-benzoic acid in THF at 120 °C yielded homoallyl alcohol **1-88** in 90% yield. As shown below, the iridium catalyst performs a redox reaction converting the alcohol to an aldehyde and using hydride ion to generate an allyl anion equivalent. The enantiomeric excess of homoallyl alcohol **1-88** was determined to be 92% by chiral GC analysis. Next, alcohol **1-88** was protected to the corresponding TBS ether **1-89** which was then subjected to ozonolysis employing Sudan III (2-3 drops, 1% in methanol) as an indicator. The completion of reaction was indicated by a change in color of the solution from pink to colorless. The reaction mixture upon in situ reduction using excess of $NaBH_4$ delivered an alcohol **1-90** in 97% yield (**Scheme 16**). Alcohol **1-90** under similar allylation conditions furnished *syn*-diol **1-91** in 93% yield which was then subjected to in situ deprotection of the silyl ether and protection of the diol as acetonide function to deliver the corresponding derivative **1-92** in 80% yield. Some alternative routes for the synthesis of intermediate **1-92** are reported in the literature.[68]



Scheme 16. Synthesis of an intermediate acetonide **1-92** using Krische's iterative approach.

Building block **1-92** was converted under ozonolysis conditions in a binary mixture of methanol/CH_2Cl_2 to acetonide alcohol **1-93**. Transformation of alcohol **1-93** to azide **1-95** was completed in two steps via intermediate tosylate **1-94** followed by treatment with NaN_3 in DMF in high yield (83%, over 2 steps). Reduction of azide **1-95** with PPh_3[69] in a water/THF mixture (1:9) for overnight provided the targeted amine side chain **1-96** (**Scheme 17**) in excellent yield.



Scheme 17. Synthesis of amine chain **1-96** from intermediate **1-92**.

5.3.2 Proposed mechanistic pathway for Krische's transfer hydrogenative carbonyl allylation

A plausible mechanism[70] for the iridium catalyzed hydrogenative carbonyl allylation reveals the association of chelating phosphine ligand and 4-Cl-3-NO_2-BzOH with [Ir(COD)$_2$Cl$_2$] to give iridium carboxylate **II** which shows equilibrium with *ortho*-cyclometalated complex **I**. Here, oxidative addition of allyl acetate to complex **II** should deliver an iridium carboxylate, which should be predisposed to acetate-assisted *ortho*-metalation through six membered transition state **III** to furnish the σ-allyl *C,O*-benzoate complex **IV**. The complex **IV** remains in rapid equilibrium with π-allyl haptomer **V** which could be characterized by single crystal X-ray diffraction analysis (where Ln = (*R*)-BINAP).[70]

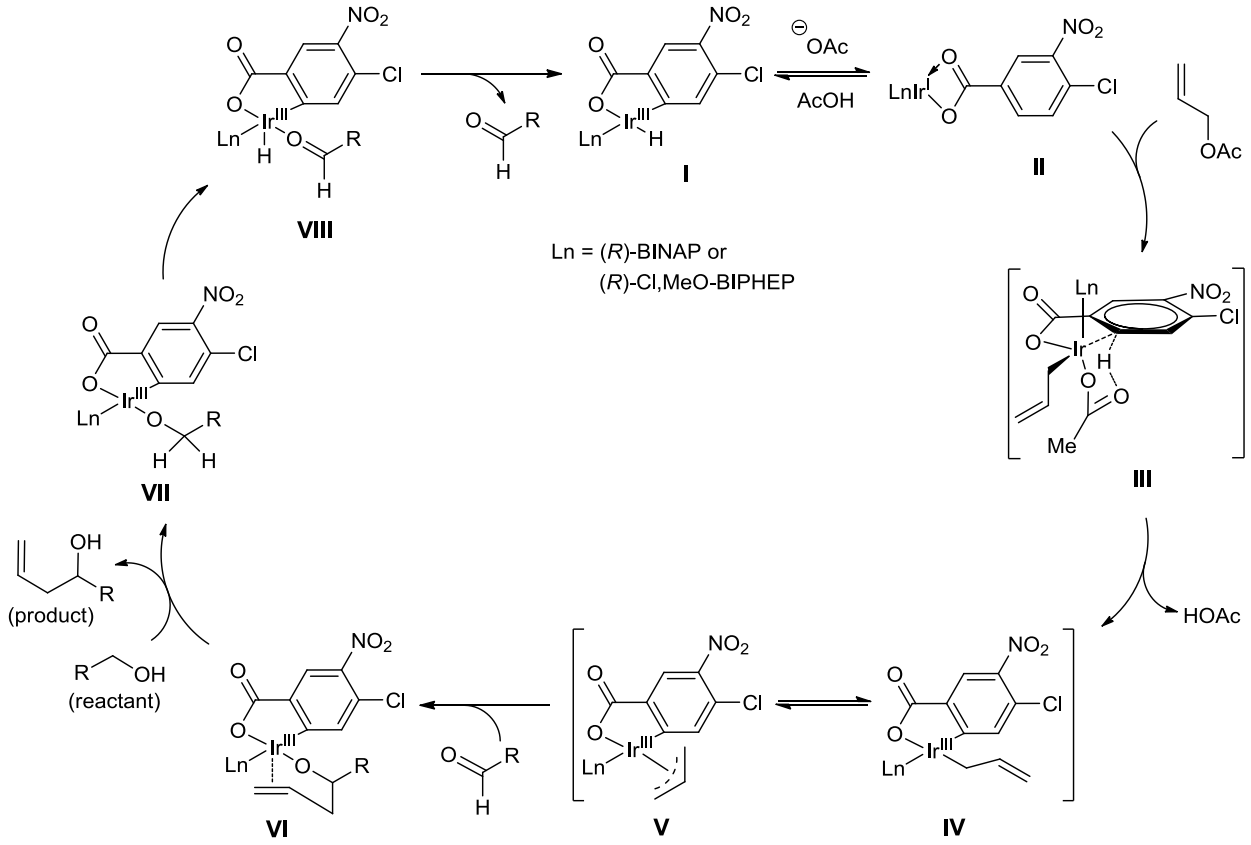


Figure 10. Postulated catalytic mechanisms for the iridium catalyzed transfer hydrogenative coupling from the alcohol or aldehyde oxidation level.[70]

Participation of an aldehyde in this cycle generates a new homoallyl oxy-iridium complex **VI** which is formed by the allylic transfer to the aldehyde through a chair like transition structure.[70] Configurational stability of the resulting homoallyl alcohol is most probably due to the co-ordination of iridium (III) with the olefin moiety of the homoallylic alcohol which in turn disables β-hydride elimination pathways. At this stage, exchange of the resulting homoallyl alcohol by the reactant alcohol ensue the conversion of **VI** to **VII**, a free co-ordination site becomes available and β-hydride elimination delivers complex **VIII**. Dissociation of the aldehyde regenerates back the *ortho*-cyclometallated complex **I** (**Figure 10**).

A stereochemical model accounting for the observed sense of absolute stereoinduction is based on the coordination mode as evident in the crystal structure of complex **V**. Complexation of the aldehyde with σ-allyl haptomer **IV** is postulated to occur at the indicated position adjacent to the *C,O*-benzoate. In this way, the sterically less demanding allyl moiety is placed between the napthyl and phenyl moieties of the ligand, allowing the aldehyde to reside in a more open environment. In the favored mode of addition, the aldehyde is bound in such a way that the aldehyde C−H bond projects into the π-face of a phenyl moiety of the ligand, giving rise to a weakly attractive aldehyde C−H π-interaction. In the disfavored mode of action, the aldehyde is bound such that the aldehyde "R group" projects into the π-face of a phenyl moiety of the ligand, giving rise to a severe non-bonded interaction (**Figure 11**).[70]

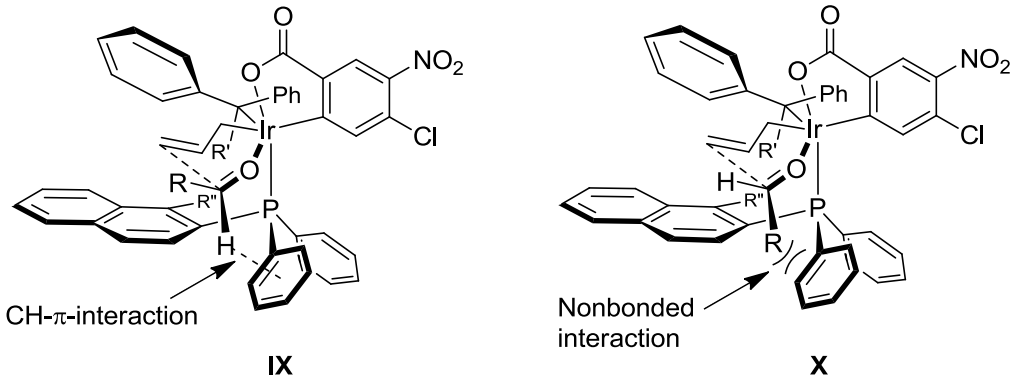
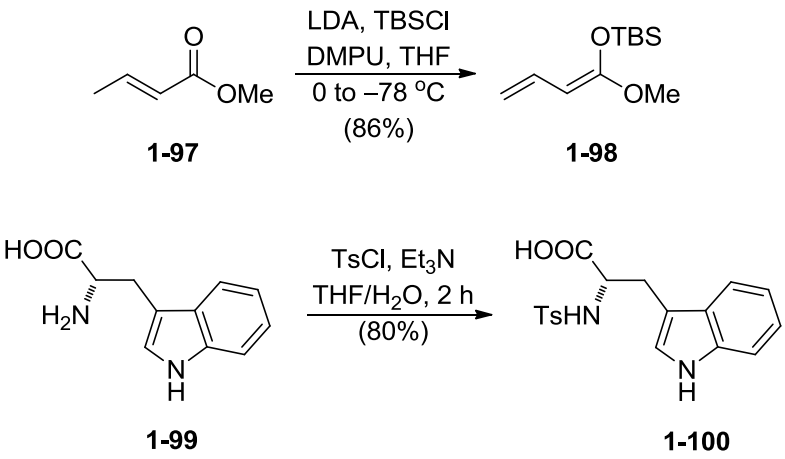


Figure 11. Study of stereochemical model accounting for the observed sense of absolute stereoinduction using (*R*)-BINAP ligand.[70]

5.3.3 Synthesis via vinylogous Mukaiyama aldol reaction (VMAR)

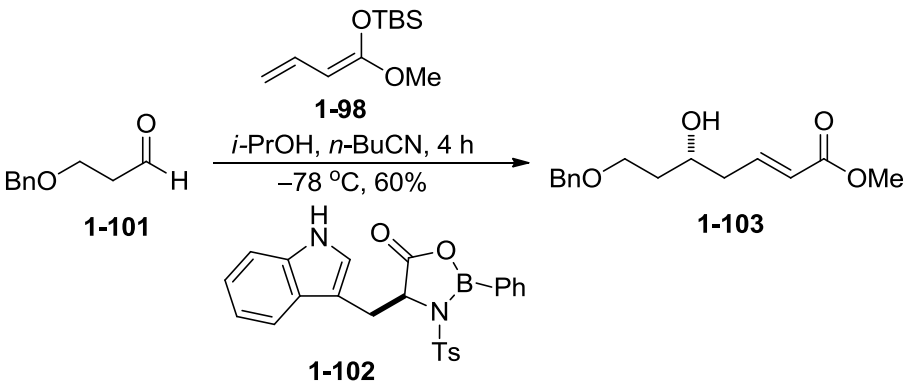
As an alternative for the synthesis of an amine side chain, we developed a new route by using a method published by Kalesse et al.[49] Recently he reported an oxazaborolidinone mediated synthesis of δ-hydroxy α,β-unsaturated esters with high enantioselectivity. This strategy has been proven to be very useful to build intermediates in the synthesis of natural products.[71] Kalesse and coworkers accomplished the synthesis of described intermediates from corresponding aldehydes using a tryptophan derived *B*-phenyloxazaborolidinone complex and freshly prepared *O,O*-silyl ketene acetal **1-98**. This methodology was found to be quite useful in our case to provide an alternative approach for the synthesis of the amine side chain.

Starting compound benzyloxy propanal **1-101** was prepared from **1-87** according to the literature procedure for Swern oxidation.[72] The other required reagents *O,O*-silyl ketene acetal **1-98** and *N*-Ts-(*L*)-tryptophan **1-100** were synthesized from *trans*-methyl crotonate **1-97** and *L*-tryptophan **1-99** respectively (**Scheme 18**) according to the literature procedure.[49]



Scheme 18. Synthesis of reagents **1-98** and **1-100** required for VMAR.

With these reagents in hand, we initiated the synthesis by treating suspensions of tryptophan **1-100** with dichlorophenyl borane under N_2 atmosphere. The resulting boron complex was then exposed under nitrogen with a mixture of aldehyde **1-101**, *O,O*-silyl ketene acetal **1-98** and 2-propanol in stoichiometric amounts in *n*-butyronitrile at −78 °C for 4 h and consequently produced hydroxy enoate **1-103** in 60% yield (**Scheme 19**).



Scheme 19. Synthesis of intermediate hydroxy enoate **1-103** by VMAR from aldehyde **1-101**.

The enantiomeric excess of alcohol **1-103** was determined to be 88% by Mosher ester analysis (**Figure 12**). Significant shift differences were seen for 2-H and 3-H.

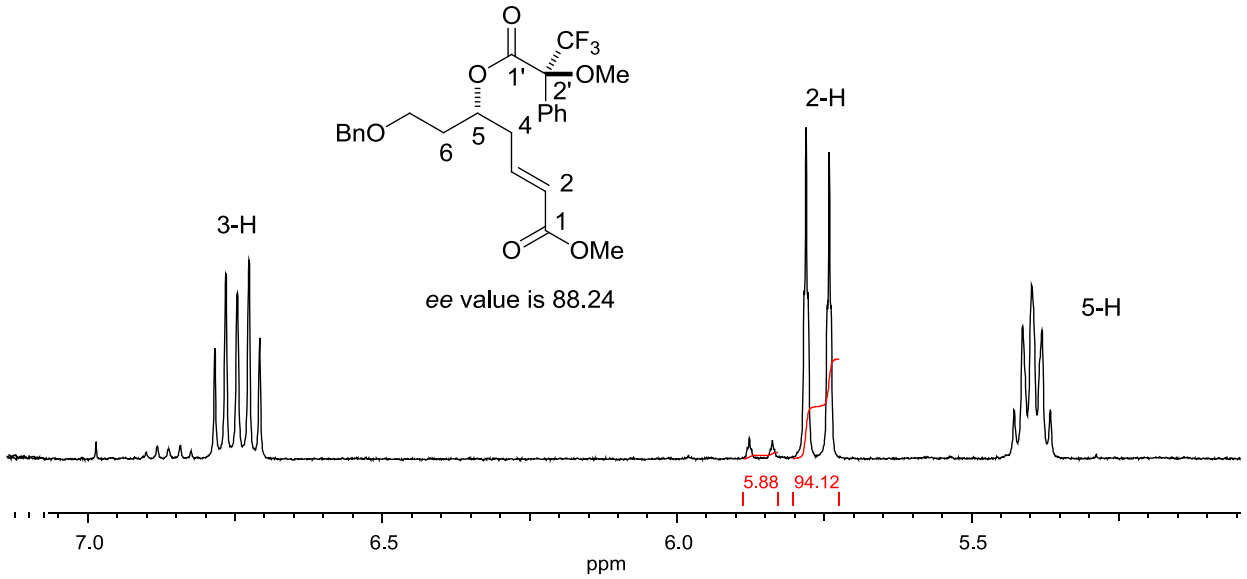


Figure 12. Mosher ester analysis of alcohol **1-103** using ^{1}H NMR spectrum.

As mentioned, the *B*-phenyloxazaborolidinone (OXB) **1-102** was prepared from phenyldichloroborane and *N*-Ts-(*L*)-tryptophan **1-100**. The proposed transition state[73,74] of the OXB-catalyzed aldol reaction involves the shielding of aldehyde's *si*-face through the indole moiety (see, **Figure 13**). As a result, nucleophilic attack of the *O,O*-silyl ketene is favored from the *re*-face of aldehyde to provide high enantioselectivity of the corresponding alcohol. Isopropyl alcohol in the reaction serves as an additive which suppresses the racemic TBS catalyzed pathway and enhances the enantioselectivity of the reaction.

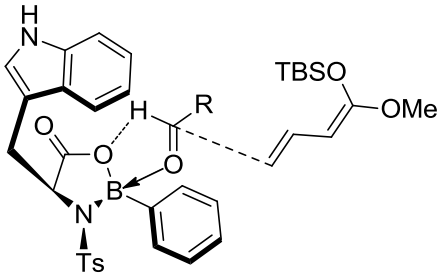


Figure 13. Proposed transition state of VMAR.

For the insertion of the second hydroxyl function, hydroxy enoate **1-103** was subjected to the conjugate addition of hemiacetal derived benzyloxy anion generated by PhCHO and *t*-BuOK at 0 °C[75] which afforded benzylidene acetal protected *syn*-dihydroxyl ester **1-104** as shown in **Scheme 20**. This oxy-Michael addition reaction proceeds via the intermediate hemiacetal alkoxide anion. Afterwards, deprotection of the benzylidene group followed by acetonide protection of resulting diol was achieved via a one pot synthesis in good yield. This transformation was completed successfully by heating benzylidene acetal **1-104** in a 1:1 mixture of 2,2-dimethoxypropane in CH_2Cl_2 in presence of catalytic *p*-TSA•H_2O within 24 h and led to a 95% of acetonide ester **1-105**. Here, δ values of acetonide methyl groups are at 19.7 and 30.0 ppm while the quaternary carbon resonates at 98.8 in ^{13}C NMR indicating the formation of the 1,3-diol in *syn* fashion (**Figure 14**).[76]

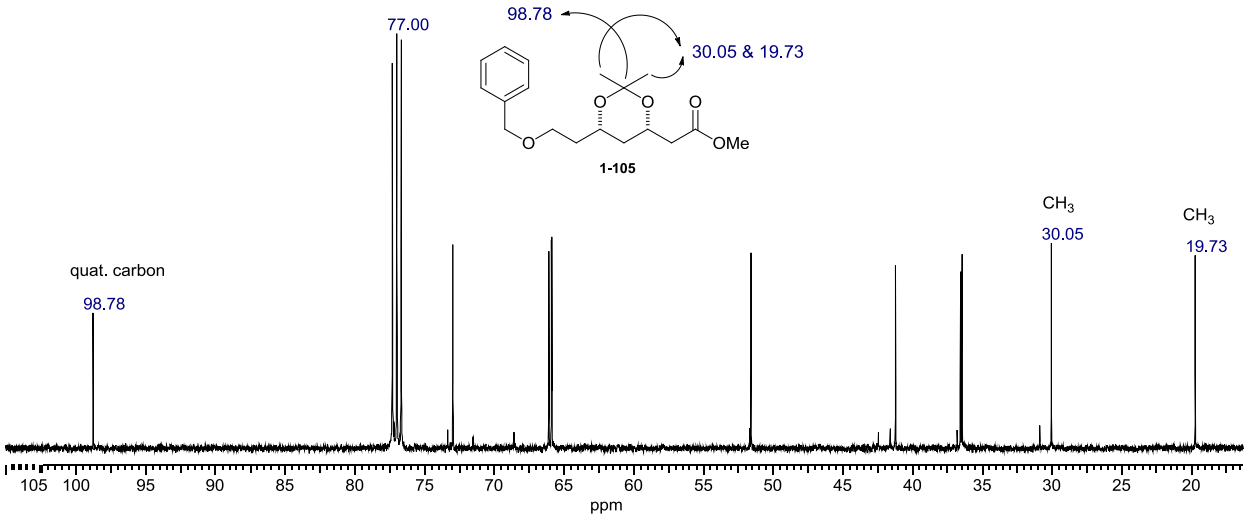
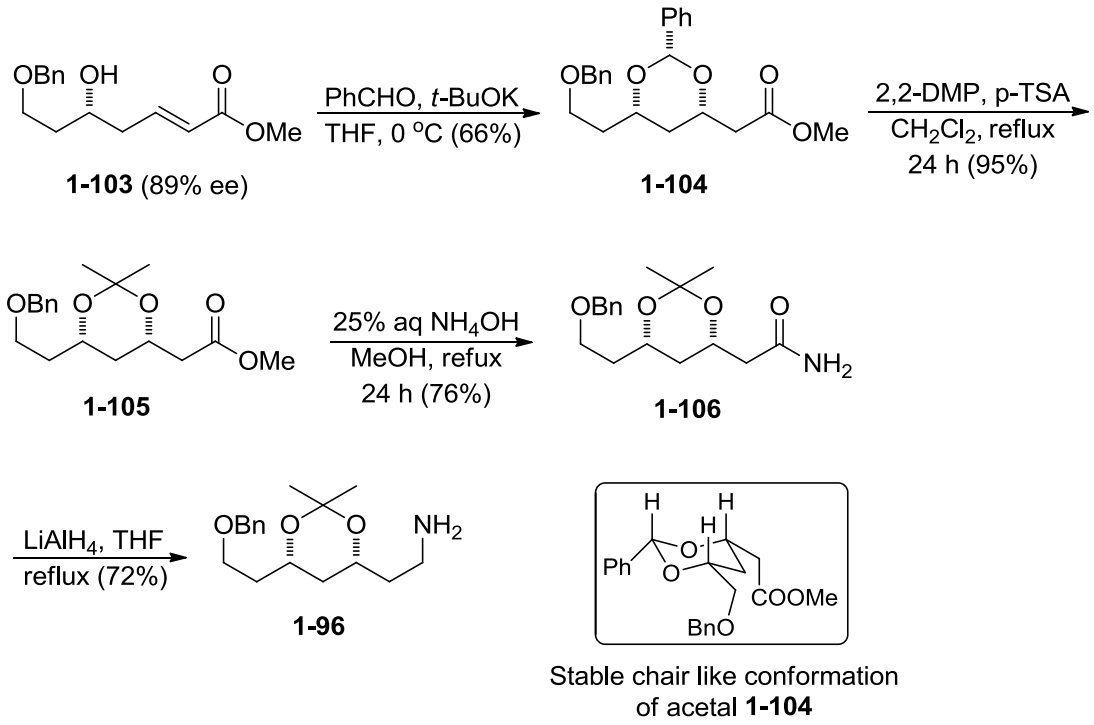


Figure 14. Confirmation of *syn* 1,3-diol formation by ^{13}C NMR of acetal **1-105**.

Thereafter, ester **1-105** was converted to corresponding amide **1-106** which worked successfully in 24 h by refluxing the ester **1-105** in a mixture (1:2) of 25% aq NH_3 and methanol providing the amide in 76% yield. The outcome of this conversion was better than that in THF. In the end of the sequence, amide **1-106** was reduced using $LiAlH_4$ under reflux conditions in THF which yielded amine **1-96** (**Scheme 20**) in about 72% yield.

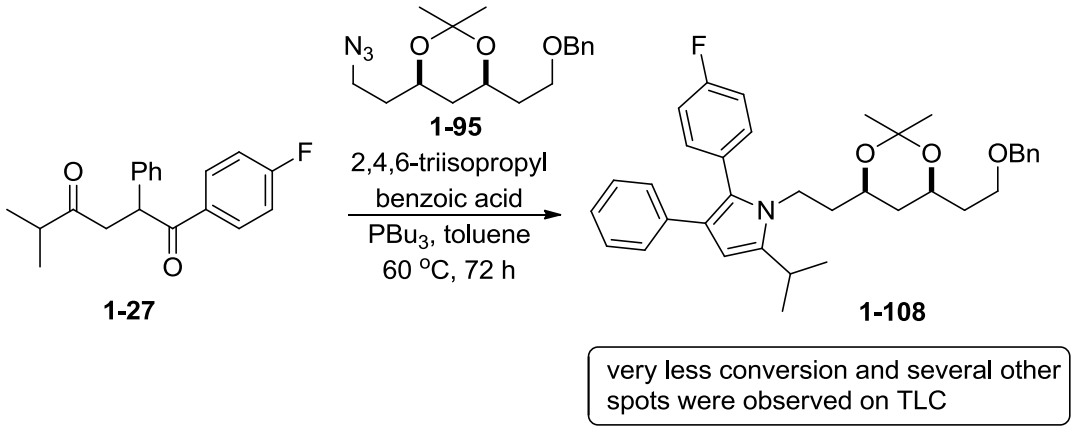


Scheme 20. Preparation of amine side chain **1-96** from 5-hydroxy enoate **1-103**.

Prior to the synthesis of benzyl protected amine side chain **1-96** using the above mentioned route, we attempted the same route to synthesize PMB protected analogous amine of **1-96** from *p*-methoxybenzyl protected analogue of hydroxy enoate **1-103** by following the same path (**Scheme 20**). Unwillingly, in the next step of pyrrole synthesis the PMB ether did not survive under reflux conditions using xylene in presence of catalytic *p*-TSA•H_2O. Removal of the PMB group was observed (LC-MS) during the reaction. Accordingly, we relied on the benzyl protecting group for the transformations indicated in the **Scheme 20**.

5.4 Atorvastatin lactone using benzyl protected amine side chain

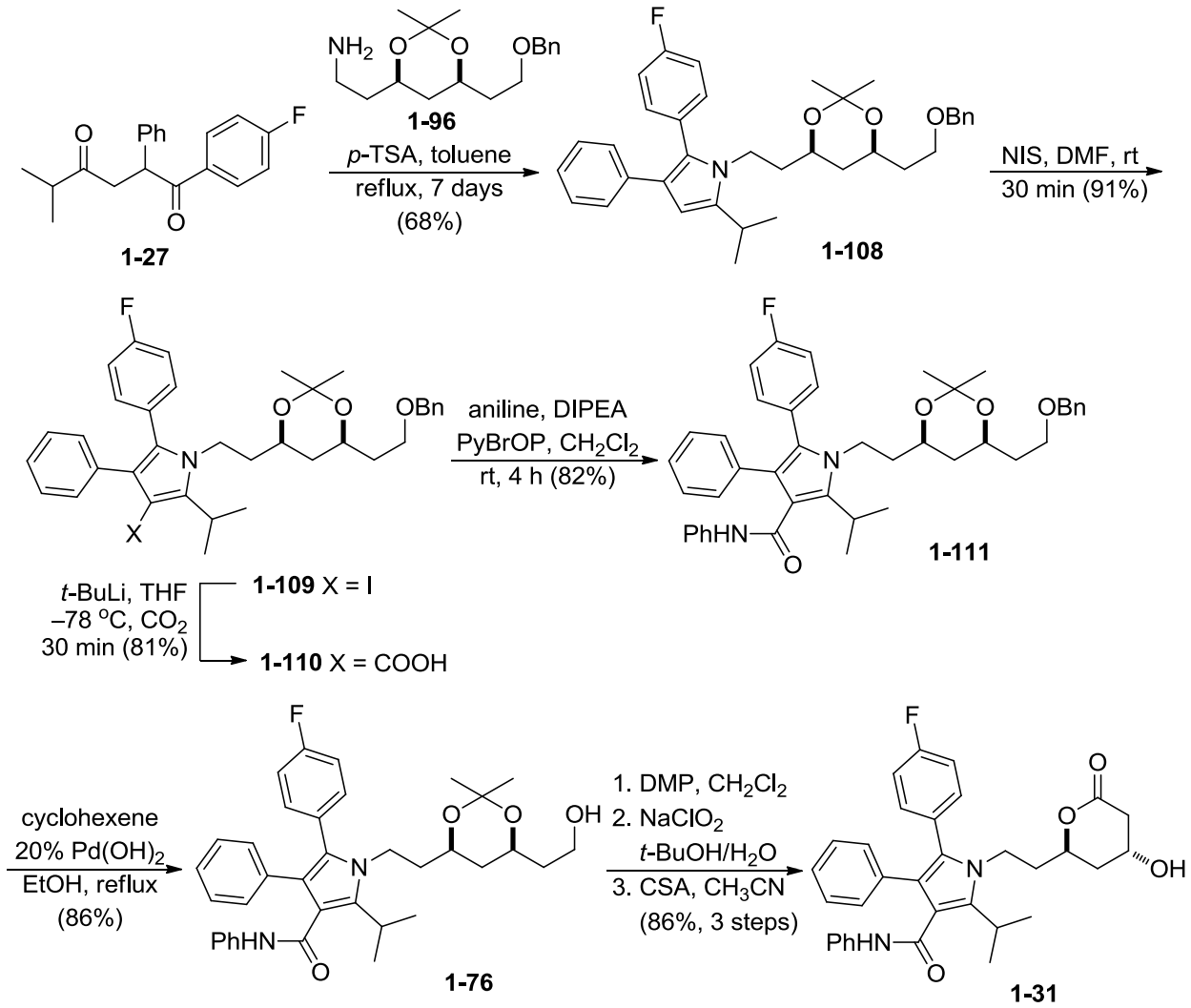
In 2003, Öhrlein et al. published the synthesis of full functionalized pyrrole from side chain containing azide substituent and functionalized diketone **1-19** (see **Scheme 7**) by aza-Wittig reaction.[62] The reaction proceeds via an imine intermediate promoted by a tri *n*-butyl phosphine and triisopropyl benzoic acid as a weak, sterically hindered acid. Using this reaction pyrrole can be obtained directly from azide containing side chain. Therefore we treated azide **1-95** with PBu_3 in dry toluene at room temperature then resulting imine intermediate was heated (60 °C) with 2,4,6-triisopropyl benzoic acid and diketone **1-27** for nearly 72 h. TLC showed very little conversion to the desired pyrrole **1-108** along with some other side products.



Scheme 21. Attempt for the synthesis of pyrrole **1-108** by aza-Wittig reaction.

Therefore we skipped this reaction and the substrates, diketone **1-27** and amine **1-96** were in hand subjected to Paal-Knorr condensation under the described conditions (*p*-TSA•H_2O, toluene, reflux) where it was expected to complete a synthesis smoothly as we did before (see, **Scheme 13**). But surprisingly, progress of the reaction was very slow and the reaction did not complete even after 10 days. Addition of excess of catalyst was risky because of possible acetonide deprotection as well as there was a possibility to form a furan ring from diketone **1-27**. Therefore, we refluxed the reaction at elevated temperature by changing the solvent to xylene. This amendment brought a better change in the progress of reaction. TLC showed nearly completion of the reaction within 6–7 days. After flash chromatographic purification, the isolated yield of the resulting pyrrole **1-108** was 68%. Interestingly, the acetonide group was found to be incredibly stable under the stated conditions.

Next, pyrrole **1-108** was treated with NIS to yield 91% of iodo pyrrole **1-109** which was further metallated using *t*-BuLi and quenched subsequently with excess of dry ice at −78 °C to furnish carboxyl derived pyrrole acid **1-110** in 81% yield. Modification to amide **1-111** using PyBrOP and debenzylation of the side chain from **1-111** by transfer hydrogenation using 20% of $Pd(OH)_2$ on carbon and cyclohexene yielded corresponding alcohol **1-76**.[77,78] Further oxidation using Dess-Martin periodinane and subsequently buffered $NaClO_2$ to acid **1-76** followed by CSA catalyzed lactone ring formation (as described in **Scheme 15**) delivered atorvastatin lactone **1-31** (**Scheme 22**) in high yield.



Scheme 22. Synthesis of atorvastatin lactone using side chain **1-96**.

A characteristic peak in the ^{1}H NMR spectrum of **1-31** indicating lactone ring formation is the 3-H proton at δ value ranging between 4.43–4.56 ppm (**Figure 15**). All carbon peaks from the molecule were in accordance with the literature data. Our synthesis provides a new approach for the highly enantioselective synthesis of atorvastatin lactone. The key feature of the synthesis includes the development of the amide function on the pyrrole ring via the corresponding carboxylic acid. The developed strategy opens the way to new amide derivatives of atorvastatin and allows attachment of a linker to the pyrrole carboxylic group.

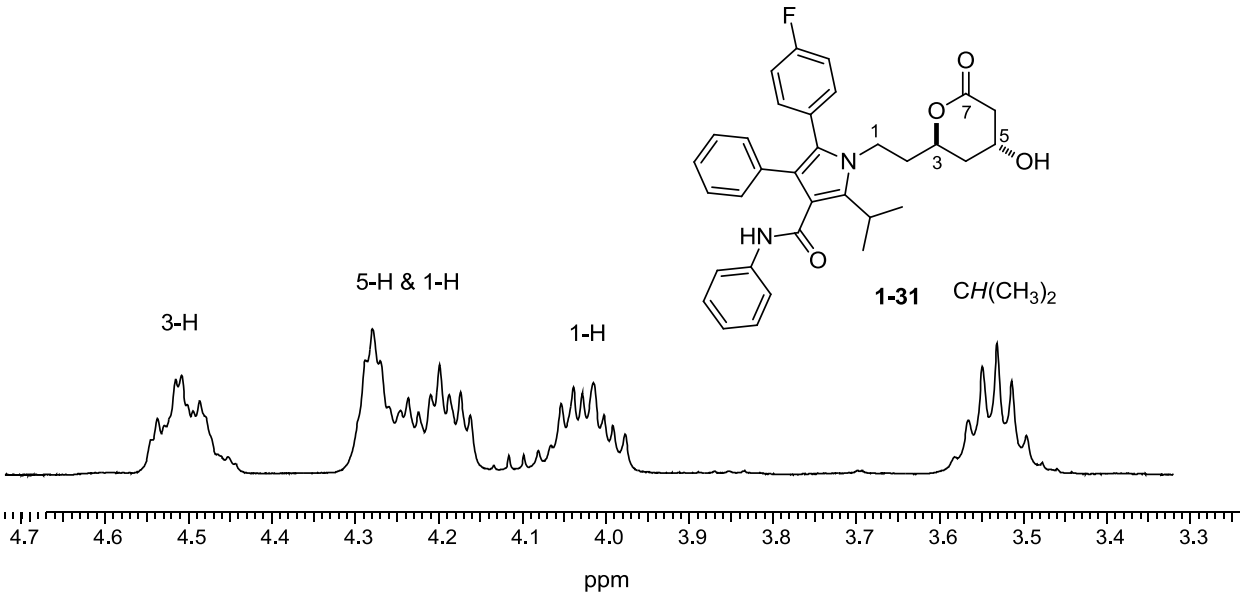


Figure 15. Fragment of the ^{1}H NMR spectrum of final atorvastatin lactone **1-31**.

5.5 Synthesis of triethylene glycol derived atorvastatin lactone for application in pull-down experiments

According to our revised synthesis plan, one alternative for obtaining an aniline based linker was to combine a nitro styrene with an allyl ether containing the remaining linker atoms via cross metathesis. For example, this could be achieved from cross metathesis reaction between *p*-nitro styrene **1-114** and the corresponding hydroxyl and acid derived *O*-allyl linkers. The resulting system would be reduced to the desired aromatic amines **1-112** and could be coupled to the intermediate acid **1-110**.

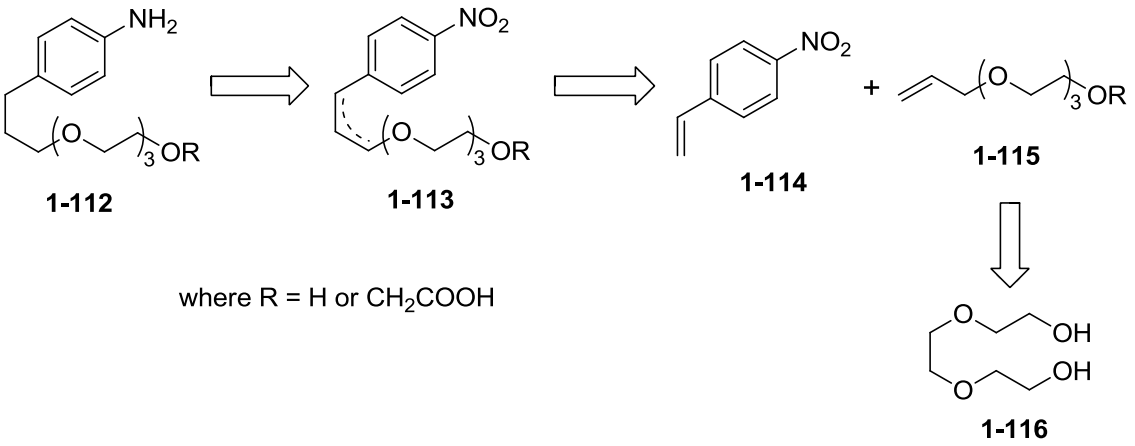
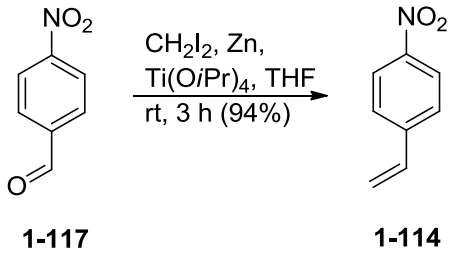


Figure 16. Retrosynthesis of functionalized TEG coupled aniline derivatives.

Therefore, we intended the synthesis of *p*-nitro styrene **1-114** from *p*-nitro benzaldehyde **1-117** under Wittig conditions at −40 °C for 3 h using the salt prepared from CH_3Br and PPh_3. However, the resulting less polar crude product containing small impurity turned out to be difficult to separate from the product using flash chromatography.

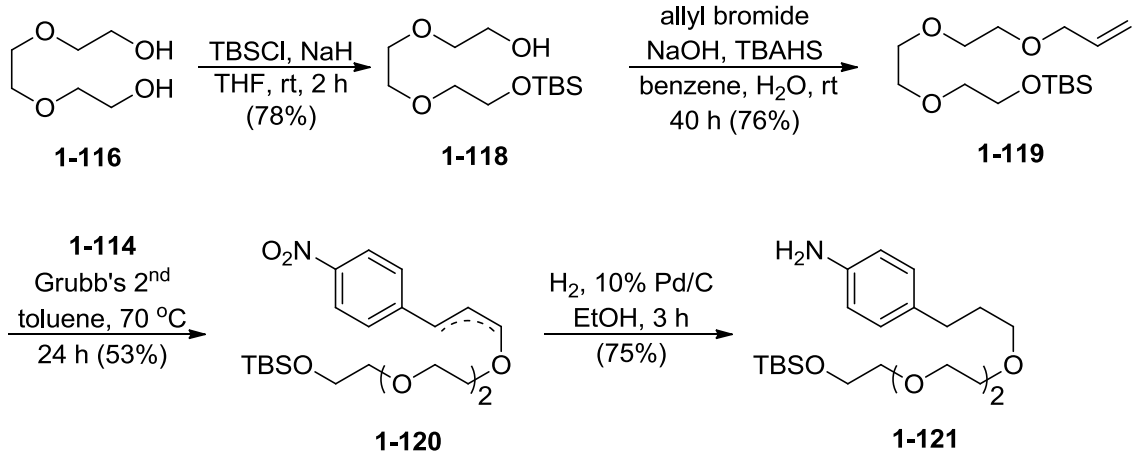


Scheme 23. Synthesis of 4-nitrostyrene **1-114**.

Alternatively, *p*-nitro styrene **1-114** with high purity and higher yield was obtained by Takai-Nozaki olefination using CH_2I_2 as the methylene source in combination with $Ti(OiPr)_4$ and activated zinc dust (**Scheme 23**).[79] Under these conditions, styrene **1-114** was obtained in 94% isolated yield.

5.5.1 Synthesis of a TEG linker with a hydroxyl function

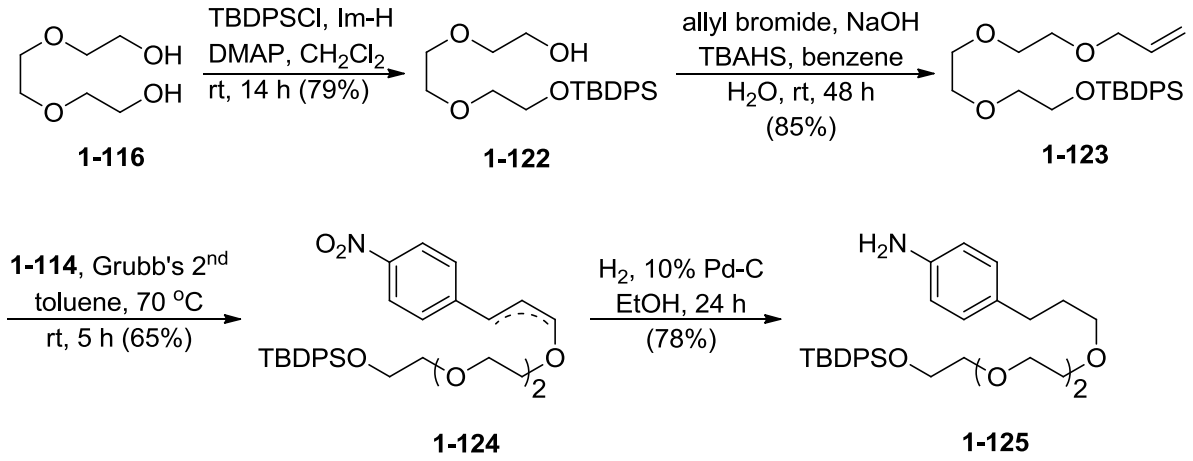
Triethylene glycol **1-116** was first protected with *t*-butyldimethylsilyl chloride using NaH as base in THF to yield mono protected TEG **1-118**. Allylation of the remaining hydroxyl group was carried out using tetra *n*-butyl ammonium hydrogen sulfate (TBAHS) as phase transfer catalyst and NaOH in a biphasic mixture of benzene and H_2O to furnish *O*-allyl TEG **1-119** in 76% yield.[80] Next, *O*-allyl TEG **1-119** and *p*-nitro styrene **1-114** were subjected to the olefin cross metathesis[81] in dry and degassed toluene at 70 °C. The cross metathesis product was isolated as a mixture of isomers (trans/vinylic trans/vinylic cis) in 53% yield. Subsequently the mixture of cross metathesis products was reduced using 10% Pd/C furnished 75% of pure amine **1-121** (**Scheme 24**).



Scheme 24. Synthesis of *t*-butyldimethylsilyl protected linker **1-121**.

Similarly, TEG **1-116** was protected with *t*-butyldiphenylsilyl chloride to afford TBDPS protected TEG **1-122**. This was followed by allylation using allyl bromide under basic condition providing the corresponding allyl ether derivative **1-123**.

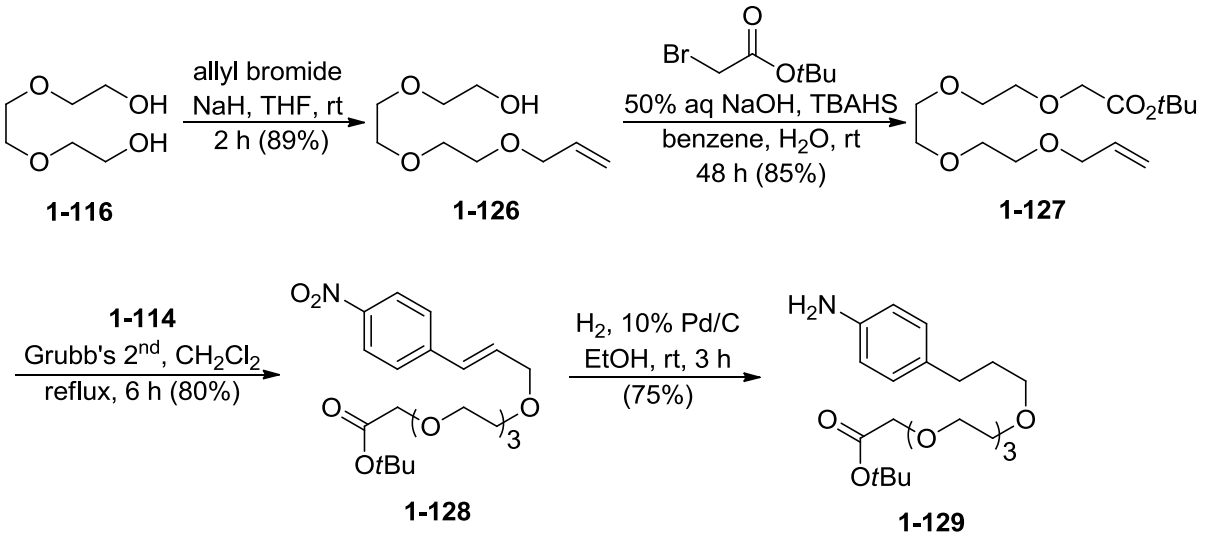
Further extension was fashioned using a cross metathesis reaction[81] under the same conditions to yield a mixture (trans/vinylic trans/vinylic cis) of cross metathesis products **1-124** which were further reduced to amine **1-125** as shown in **Scheme 25**.



Scheme 25. Synthesis of TBS protected TEG linker derived amine **1-125**.

5.5.2 Synthesis of TEG linker having carboxylic acid terminus

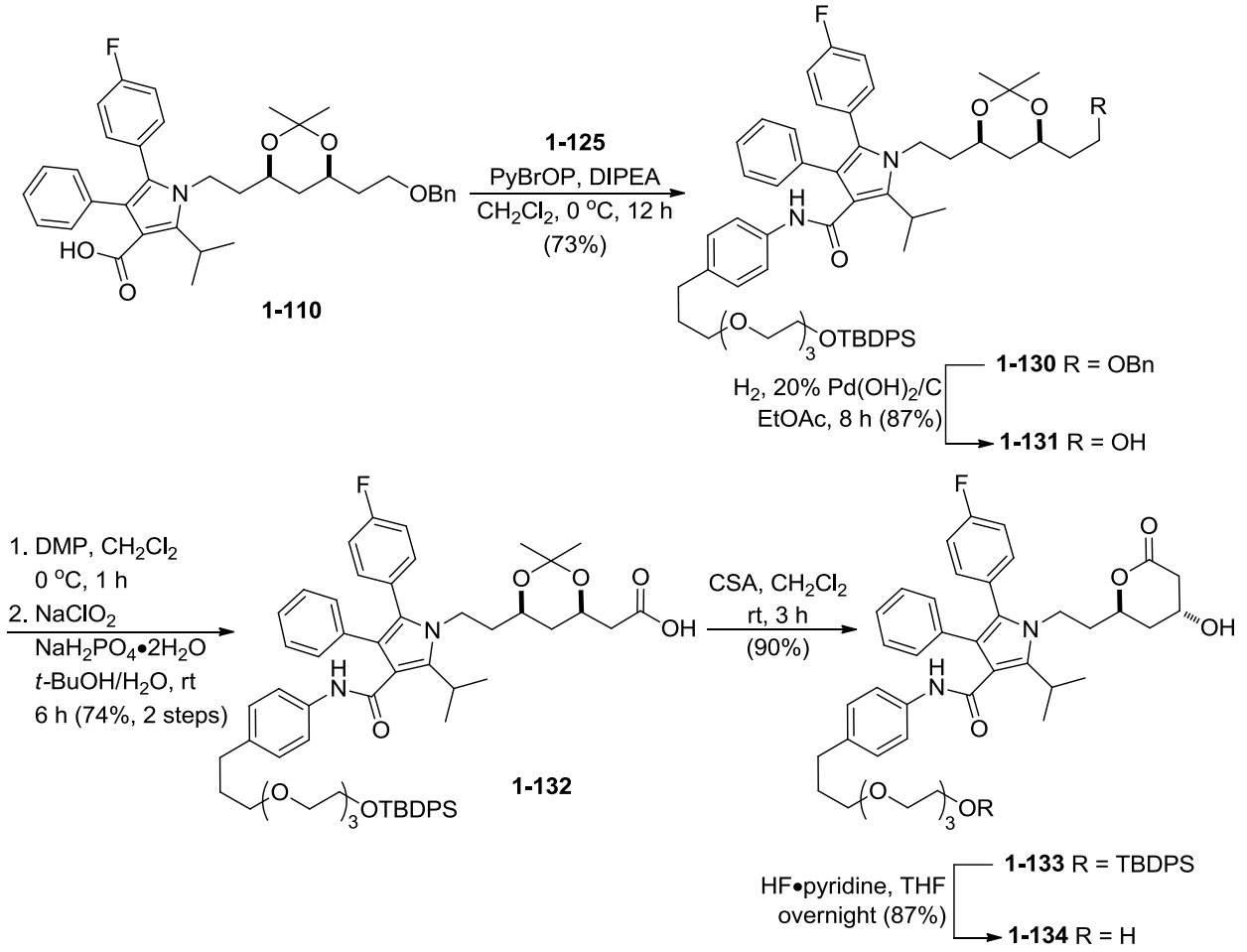
For the synthesis of amine **1-129** (**Scheme 26**), TEG was modified to mono *O*-allyl TEG **1-126** using allyl bromide and NaH at room temperature in 89% yield. Subsequent alkylation of **1-126** was completed by treating it with *t*-butyl bromoacetate in a biphasic mixture of 50% aq NaOH and benzene using catalytic TBASH as a phase transfer catalyst to furnish 85% of **1-127**. Cross metathesis[81] of styrene **1-114** and modified TEG **1-127** using 5 mol% of Grubb's 2nd catalyst in CH_2Cl_2 under reflux condition yielded 80% of metathesis product **1-128** with very high *E*-selectivity. Hydrogenation using catalytic 10% Pd/C in methanol under hydrogen balloon pressure provided carboxyl functionalized **1-129** in 75% yield.



Scheme 26. Synthesis of *t*-butyl ester derived linker **1-129**.

5.5.3 Synthesis of atorvastatin lactone containing TEG linker with hydroxyl function

With functionalized aniline **1-125** and pyrrole acid **1-110** in hand, we accomplished their coupling through the formation of a peptide bond to yield **1-130** using PyBrOP and DIPEA in CH_2Cl_2 at room temperature. Thereafter, the benzyl ether present on side chain was removed by hydrogenation using 20% $Pd(OH)_2/C$ in EtOAc under balloon pressure in 8 h to give alcohol **1-131**. Oxidation to acid **1-132** was completed quantitatively in two steps using Dess-Martin's reagent followed by buffered $NaClO_2$ in 50% aq *t*-butanol in 74% yield. Then, the acetonide acid **1-132** was cyclized to lactone **1-133** using CSA in very good yield. Finally, silyl group was removed using a mixture of 70% HF•pyridine at 0 °C to afford the TEG alcohol of atorvastatin lactone **1-134** (**Scheme 27**).

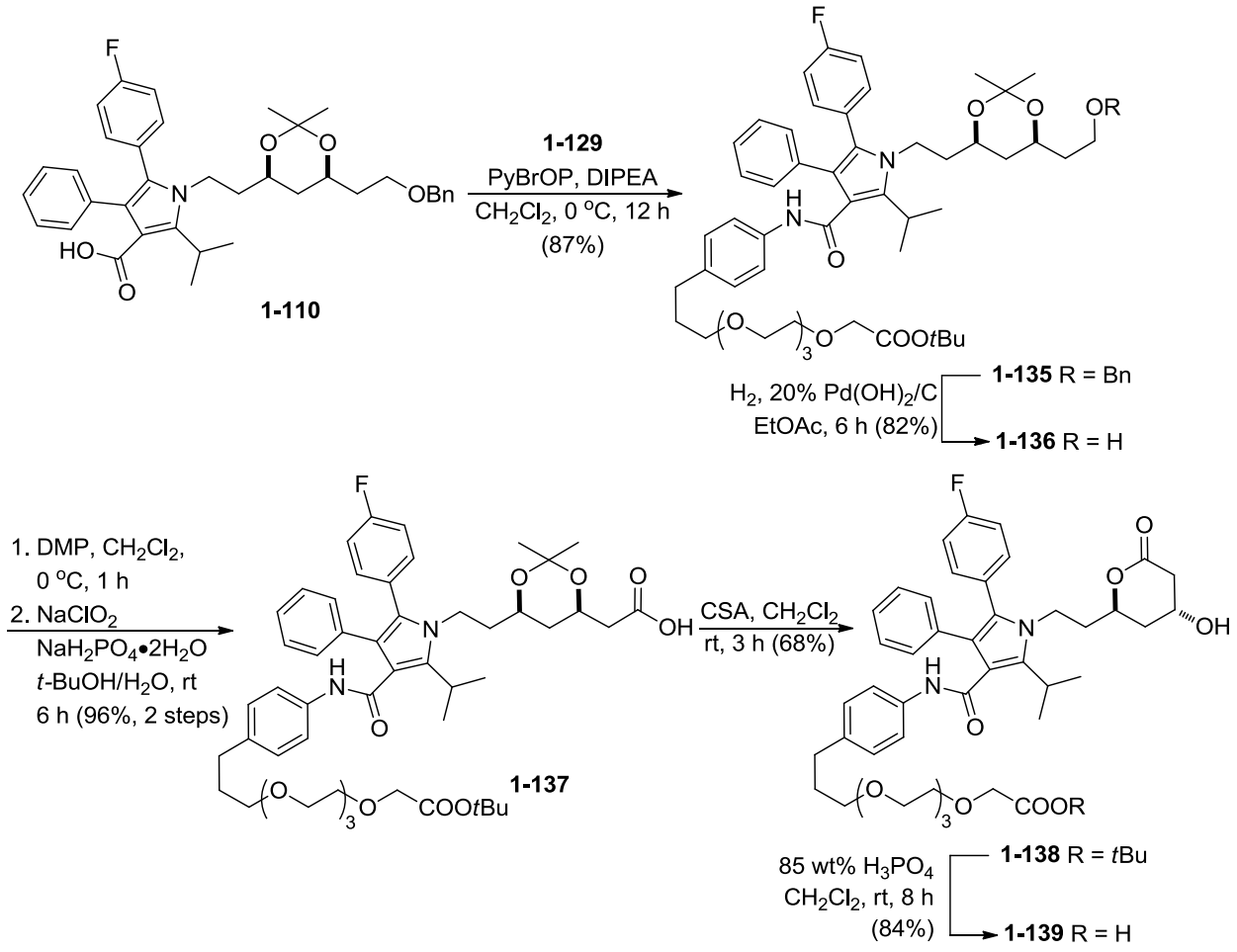


Scheme 27. Synthesis of hydroxyl TEG derived atorvastatin lactone **1-134**.

5.5.4 Synthesis of atorvastatin lactone coupled with the carboxyl derived TEG linker

To synthesize the carboxyl derived atorvastatin analogue, acid **1-110** and aniline **1-129** were coupled under similar conditions (PyBrOP, DIPEA, CH_2Cl_2, and rt) to afford the corresponding amide **1-135.** Subsequent debenzylation by hydrogenation on the surface of catalytic 20% of $Pd(OH)_2$ in EtOH on carbon under hydrogen balloon pressure afforded alcohol **1-136**. Oxidation to acetonide acid **1-137** was completed in two steps (**Scheme 28**). Then, lactone **1-138** was prepared using catalytic CSA in CH_2Cl_2 at room temperature followed by cleavage of the *t*-butyl ester from the linker part using a solution of 85 wt% aqueous phosphoric acid[82] which was delivered acid **1-139** in 75% yield over two steps.

In this case, *t*-butyl ester removal using TFA in CH_2Cl_2 at room temperature did not work well, while using mild acid (85 wt% H_3PO_4) at room temperature received the best result.

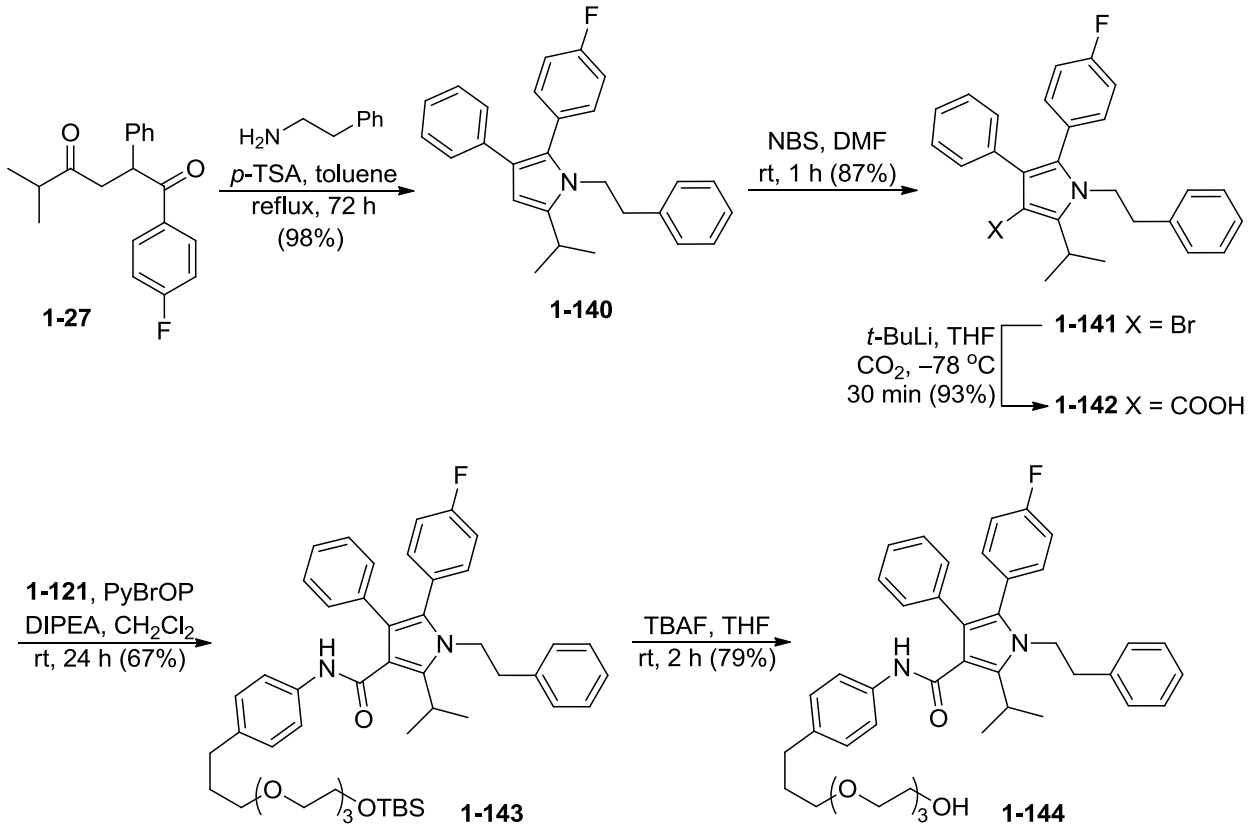


Scheme 28. Synthesis of carboxylic acid derived atorvastatin lactone analogue **1-139**.

5.5.5 Synthesis of TEG linker coupled pyrrole from 2-phenyl ethylamine

Since target fishing approaches either require beads with a control lacking the crucial target molecule or are performed with soluble controls, we decided to prepare the pyrrole **1-144** (**Scheme 29**) lacking the lactone. Accordingly, 1,4-diketone **1-27** and 2-phenylethyl amine were refluxed in presence of catalyst *p*-TSA in toluene in a Dean-Stark apparatus for 72 h to afford pyrrole **1-140** in 98% yield. Bromination to **1-141** using NBS in DMF at room temperature and subsequent Li–Br exchange using *t*-BuLi at −78 °C followed by addition of excess of solid CO_2

produced analogous acid **1-142** in 93% yield. Coupling of linker amine **1-121** with carboxylic acid **1-142** using PyBrOP in CH_2Cl_2 at room temperature provided corresponding amide **1-143** in 67% yield. Subsequent silyl removal using TBAF•$3H_2O$ in THF afforded final penta-substituted pyrrole **1-144** coupled with a linker (**Scheme 29**) in high yield.



Scheme 29. Synthesis of TEG derived simple penta-substituted pyrrole **1-144**.

We submitted these three modified analogues **1-134**, **1-139** and **1-144** samples to our project colleagues (Yvonne Etzel, Felix Behnke) for immobilization on suitable affinity beads and further target fishing experiments. We used here **1-134** and **1-139** analogues as hit compound while **1-144** was used as control for the analogue **1-134**.

5.6 Results of affinity based target fishing experiments with atorvastatin lactone derived analogues

First, hydroxyl derived analogue **1-134** and **1-144** were immobilized on Toyopearl AF epoxy 650 beads while acid derived analogue **1-139** was immobilized on Toyopearl AF amino 650 beads. The hydroxyl derived analogue **1-134** was tested against A549 lung cell lines whereas carboxylic acid analogue **1-139** was tested against HEK239T cell lines (Human Embryonic Kidney 293 cells) for which AcOH blocked amino beads were used as a control in the experiment.

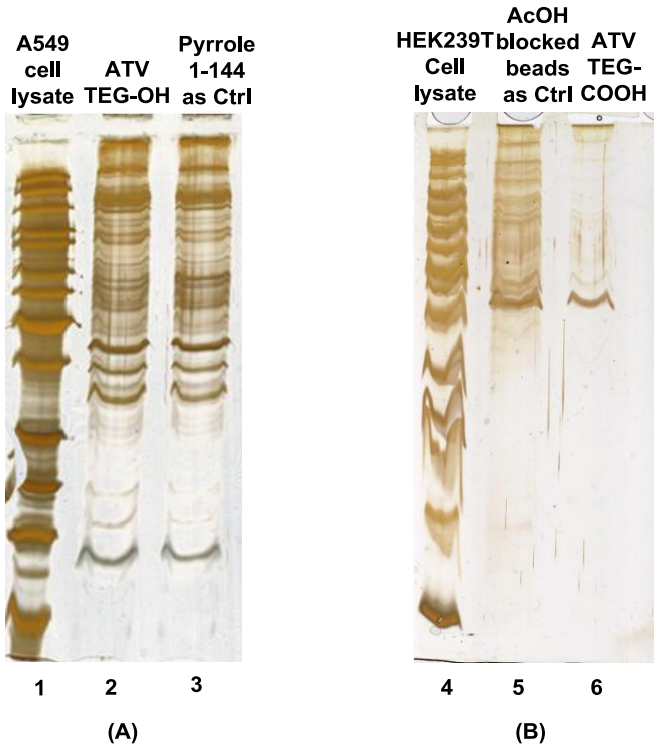


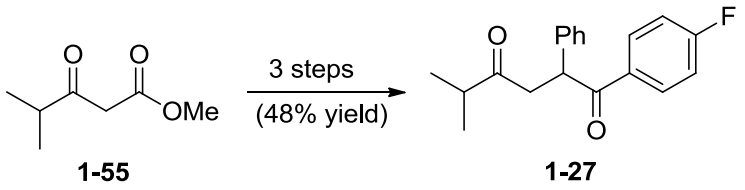
Figure 17. Detection of binding proteins for TEG hydroxyl functionalized atorvastatin lactone **1-134** (**A**) and TEG acid functionalized atorvastatin lactone **1-139** (**B**). In picture **A**, Lane 1: A549 cell lysate; Lane 2: Immobilized atorvastatin lactone analogue **1-134** in A549 cell lysate; Lane 3: penta-substituted pyrrole **1-144** as control in A549 cell lysate. In picture **B**, Lane 4: HEK239T cell lysate; Lane 5: AcOH blocked control beads with HEK239T cell lysate; Lane 6: Immobilized atorvastatin lactone analogue **1-139** in HEK239T cell lysate.

From the data of biological testing received from the colleagues responsible for biological experiments it was seen (**Figure 17**) that there are no distinguishing protein bands observed for

the analyzed molecule which were different from the control experiments in both cases of hydroxyl and acid derived analogues. However lane 6 indicates a more selective binding of proteins as compared to the control (lane 5). The probable reason for these disappointing results could be that the position where linker is connected on the molecule might not be suitable to preserve the biological activity of the molecule or the target proteins are of low abundance. Also the fact was that HMG-CoA reductase (98 or 19 kDa) was not found either. It can be explained by the absence of the dihydroxy carboxylate form of atorvastatin lactone.

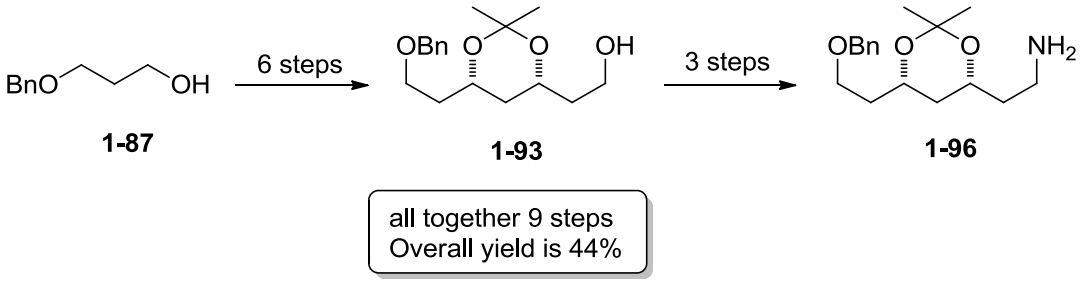
6 Conclusion I

In summary, we have developed a novel and efficient route towards the synthesis of atorvastatin lactone from 1,4-diktone **1-27** and the newly developed amine side chain **1-96** derived from simple 1,3-propanediol. The achiral part of the molecule, 1,4-diketone **1-27** was easily prepared from methyl-4-methyl-3-oxopentanoate **1-55** within 3 steps in overall 48% yield according to the literature procedure (**Scheme 30**).



Scheme 30. Synthesis of 1,4-diketone **1-27**.

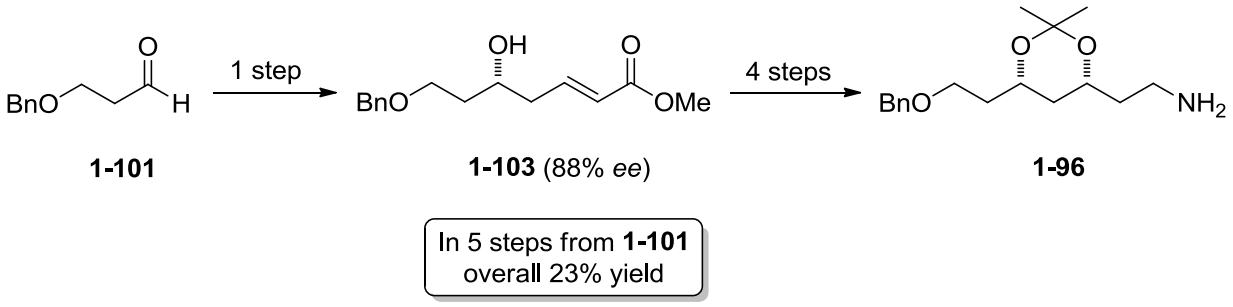
The asymmetric part of the molecule, aliphatic amine side chain **1-96** has been efficiently synthesized using two alternative routes. The first route involves as key steps of the synthesis, two Krische allylation reactions followed by ozonolysis associated with in situ $NaBH_4$ reduction to introduce the *syn*-1,3-diol subunit. Amine **1-96** was synthesized in 9 steps with overall 44% yield starting from alcohol **1-87** (**Scheme 31**).



Scheme 31. Amine side chain by Krische's iterative allylation approach.

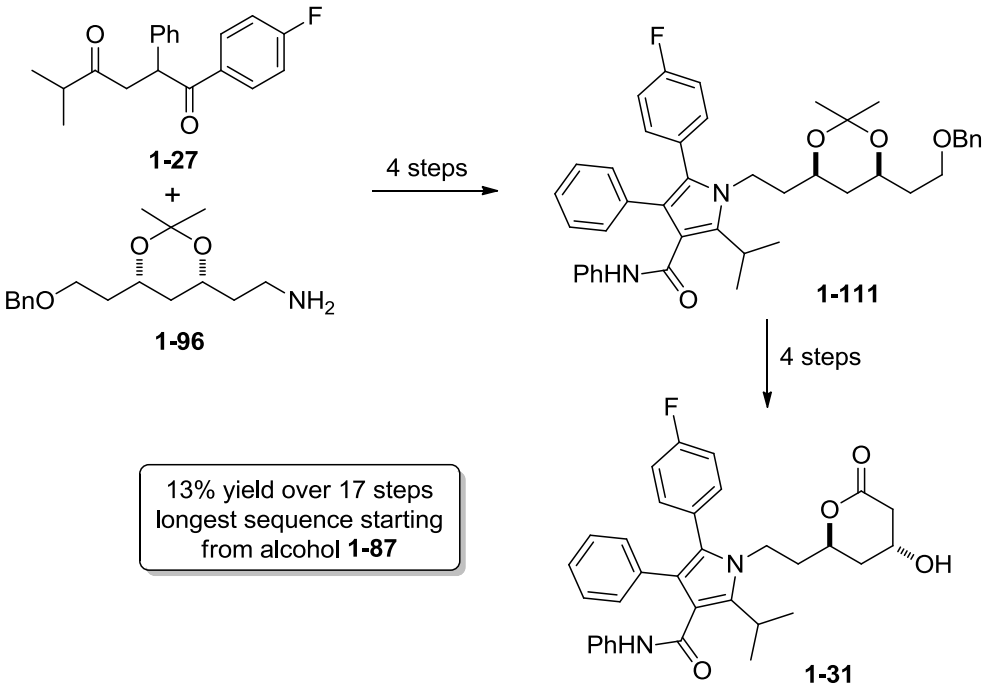
Alternatively, amine side chain **1-96** was prepared by using a vinylogous Mukaiyama aldol reaction (VMAR) in a comparatively shorter route than Krische's iterative approach. This route provided amine **1-96** in 5 steps from aldehyde **1-101** (**Scheme 32**). The overall yield of the sequence was 23% and included a single step deprotection of the benzylidene acetal and diol protection as acetonide.

Aqueous NH_3 mediated conversion of the ester to amide was used to establish the primary amine. This route provides the aliphatic side chain in fewer steps than Krische's iterative approach but isolated yields of various steps are in the range of moderate to high yield as well as enantioselectivity at VMAR step is somewhat less (< 88%).



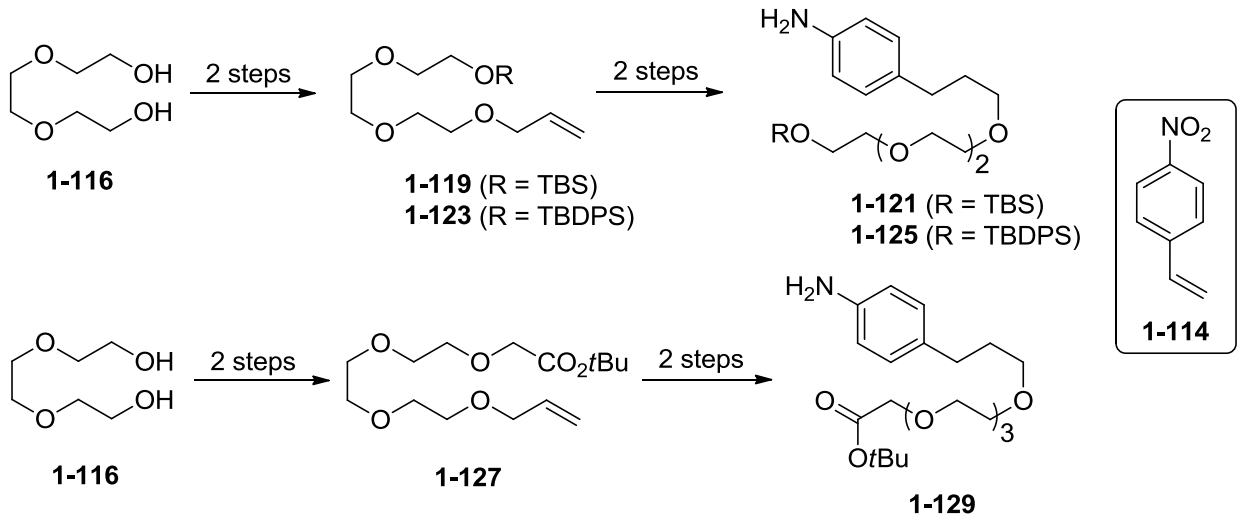
Scheme 32. Synthesis of the amine side chain **1-96** using a vinylogous Mukaiyama aldol reaction.

After the synthesis of the amine side chain, atorvastatin lactone **1-31** was obtained successfully over 8 steps from diketone **1-27** and amine **1-96** (**Scheme 33**). Crucial intermediate steps involved carboxyl insertion at the C-3' position of the pyrrole via metalation and trapping of the anion with CO_2 followed by coupling with aniline. Thereafter, the benzyl ether in the aliphatic side chain was converted to the desired lactone over 4 steps. Overall yield of the total synthesis in the longest chain sequence (17 steps) is 13% starting from alcohol **1-87** via Krische's approach.



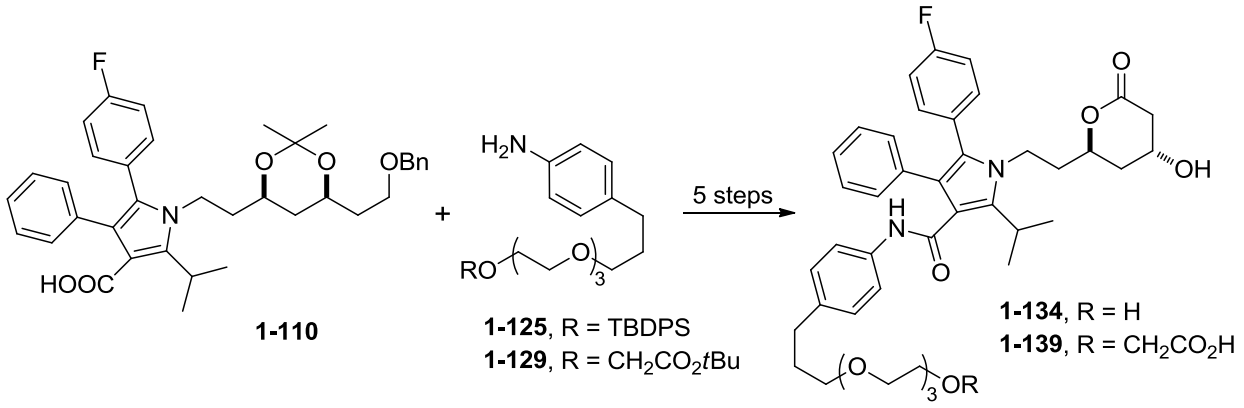
Scheme 33. Synthesis of atorvastatin lactone **1-31** from functionalized amine side chain **1-96**.

Aniline derived TEG linkers **1-121**, **1-125** and **1-129** were synthesized from *p*-nitro styrene **1-114** and hydroxyl as well as carboxyl functionalized TEG **1-119**, **1-123** and **1-127** respectively (**Scheme 34**). These linkers were synthesized in four steps for each.



Scheme 34. Synthesis of aniline derived triethylene glycol linkers.

Using these linkers **1-125** and **1-129** respective atorvastatin analogues **1-134** and **1-139** were obtained efficiently from acid **1-110** by following the above mentioned route to establish the corresponding lactone. Deprotection of protective groups under suitable conditions led to the corresponding analogues (**Scheme 35**). Our strategy provides efficient approaches towards linker derived analogues of atorvastatin useful for affinity based target fishing.



Scheme 35. Synthesis of triethylene glycol derived atorvastatin analogues.

In summary, the atorvastatin lactone analogues **1-134** and **1-139** were successfully immobilized on Toyopearl AF epoxy and amino beads, respectively. The choice of the Toyopearl beads was based on the positive experience of the co-workers from the biology section in other pull downs. Unfortunately, after incubation of the cell extracts with the loaded and control beads, the SDS-PAGE did not reveal a significant fishing. There were no distinct bands that differed between control and probe lanes. One might conclude that the linked analogues were either not biologically active, meaning the point of attachment interfered with protein binding or the concentration of the fished proteins was too low to be detected by SDS-PAGE. Accordingly, we were looking into a strategy that would allow for a simplified immobilization of small molecules and more sensitive detection methods.

Chapter II

A New Strategy for Photoaffinity based Identification and Evaluation of Biological Targets of Atorvastatin Lactone and Englerin A

7 Introduction

Bioactive small molecules (BASMs) are useful as affinity probes for the identification of their target proteins and other biological studies.[83] Their ability to induce phenotypic changes in a cellular system by modulating protein function has made them valuable as tools for the study of complex cellular processes and consequently as pharmaceutical drugs. Small molecules typically bind non-covalently to their biological targets which deserves high importance in the study of complex cellular processes. Cellular targets and the mode of action of many potent BASMs and drugs available today are known but at the same time the targets of several other BASMs are still unknown.[83,84]

Thus, determination of the protein-target interactions of BASMs is a focal challenge towards the increasing diversity of drug targets. Several methods of affinity purification of protein targets for biologically active small molecules have been developed in the context of chemical genetic studies.[85,86] Despite several target identification techniques available, affinity based chromatography still remains a widely used method. The target identification process basically involves relevant modification of the molecule of interest, coupling of the molecule to a biotinylated system or an affinity matrix via a suitable linker system. Then, the whole system is incubated with cell lysate of the desired body organ or cell lines. After washing procedures tightly bound proteins are eluted with excess of free drug or using highly denaturing conditions. Thereafter, the eluted proteins are analyzed by SDS-PAGE and protein bands isolated are identified by mass spectrometry (**Figure 18**).[87] As a classical example, Schreiber and co-workers reported that the immunosuppressant FK-506 (**2-1**) (see **Figure 20**) immobilized on agarose beads and incubated with cell lysate, bound to a protein called FKBP-12.[87d] The major protein target (FKBP-12) turned out to be a *cis-trans* prolyl isomerase with a moleculer weight of around 12 kDa. The strong binding of FK-506 (**2-1**) to FKBP-12 could be proven in separate binding experiments and by X-ray crystallography.

Although affinity chromatography has been used widely, it has some certain drawbacks. The ideal point of attachment of the small molecule to the linker must be developed according to the structure-activity relationships (SAR) which is time consuming. Even when available, many small molecules modified with a linker could affect the bioactivity of the small molecule.

However, an advantage of these affinity based methods is that they rely solely on binding of the drug to its target proteins.[88] Another big problem in affinity based methods is a non-specific binding of proteins to the linker part. Nowadays, small molecules are usually immobilized via polyethylene glycol linkers. The hydrophilic nature of these linkers reduces non-specific binding of proteins to the affinity matrices.

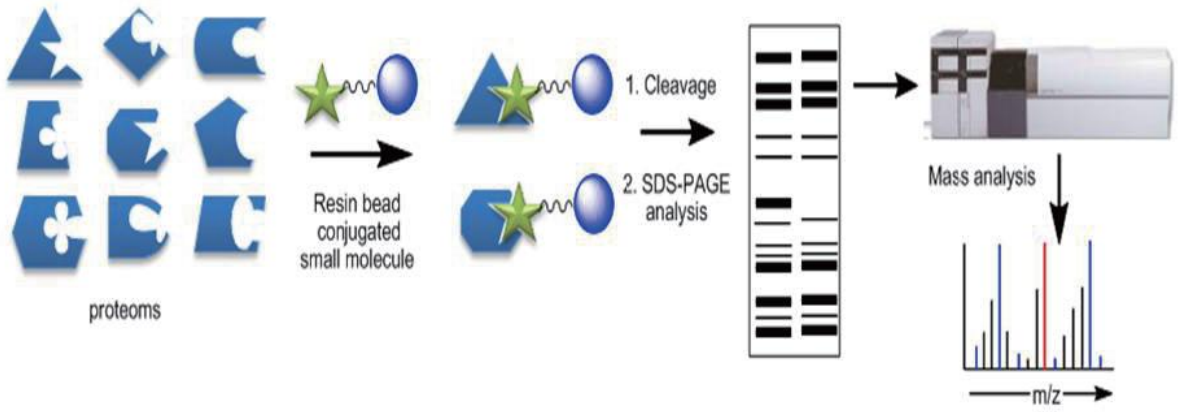


Figure 18. Schematic representation of the affinity matrix strategy for target identification.[86c]

To avoid the lengthy and cumbersome process of small molecule modification, recently a new method was introduced to immobilize small molecules on glass solid supports coated with a functionalized diazirine based photoaffinity linker.[89] A thought was to apply a solution of a small molecule to these glass slides and after UV exposure of the dried plates, the resulting reactive carbene would insert in a functional group independent manner in a C–H or X–H bond.[89] This approach provided a rapid access towards the development of small molecules immobilized on affinity matrices and the application of these conjugates in the field of proteome research. Taking an advantage of this approach, Sugawara et al.[90] and Osada et al.[91] successfully extended this technique to immobilize small molecules on photoaffinity linked beads as shown in **Figure 19**.

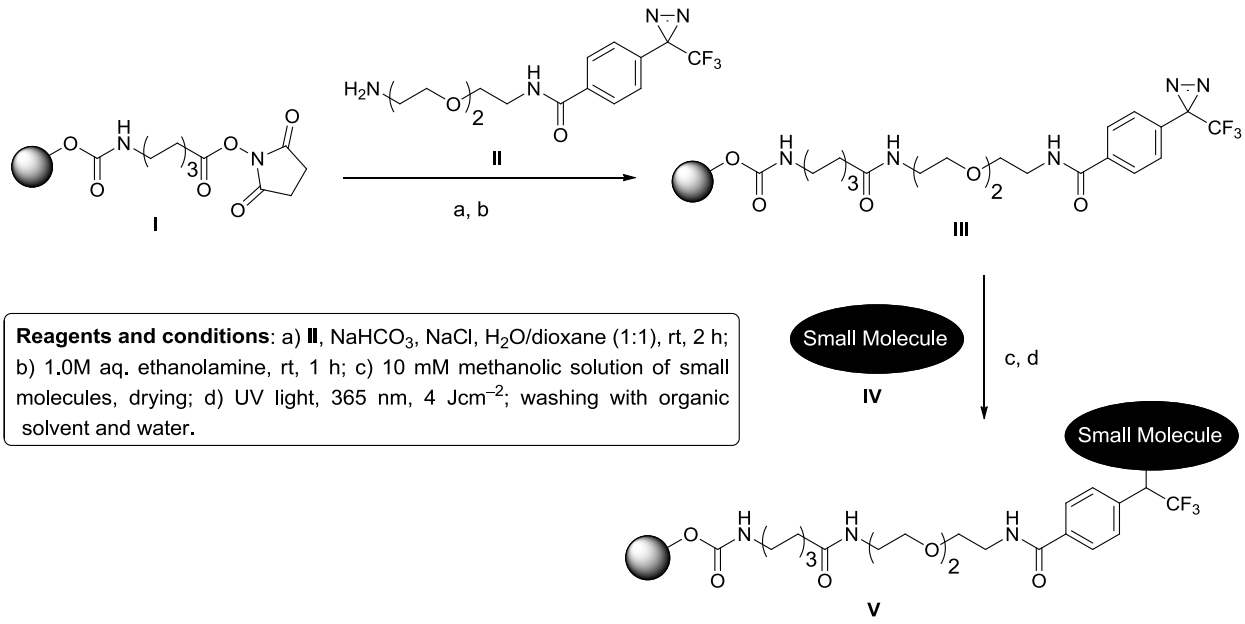


Figure 19. Preparation of PALC agarose beads and photo cross-linking of a small molecule.[91]

This strategy was quite successful for the identification and purification of target proteins of the small molecule cyclosporin A (**2-2**) and other agents.[91] Even though this strategy cannot be practical to those molecules that degrade upon UV irradiation, it should be advantageous to a wide range of small molecules and to facilitate the identification of the cellular targets of these small molecules.

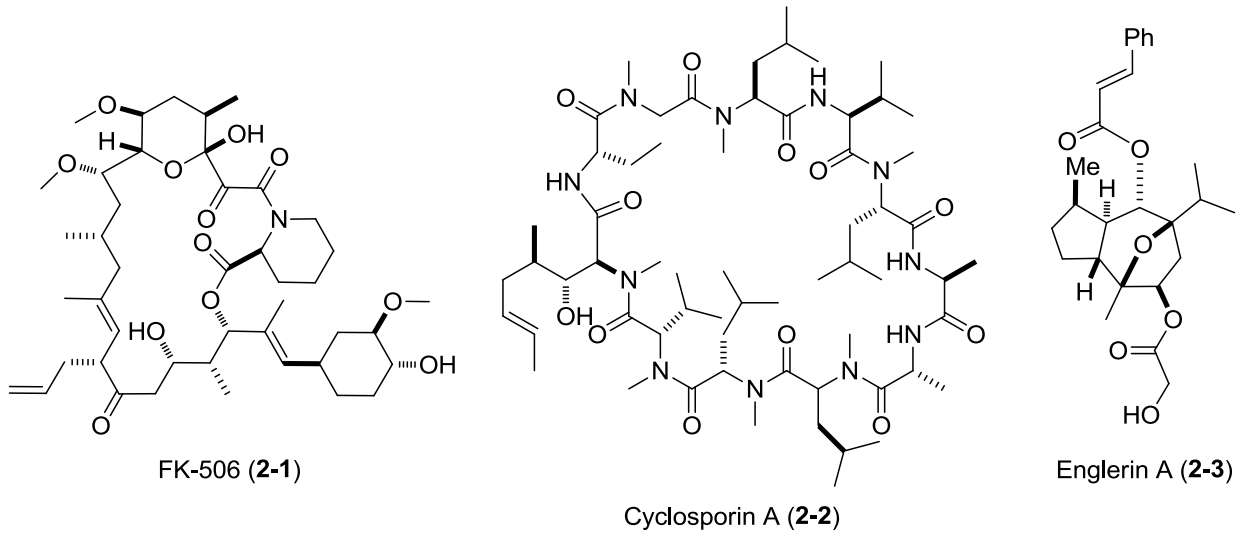


Figure 20. Structures of FK-506 (**2-1**), cyclosporin A (**2-2**) and englerin A (**2-3**).

As discussed in **Chapter I** (**Section 5.6**), we were not fortunate to find off-targets of triethylene glycol linker modified atorvastatin lactone using the classical affinity based method of immobilization on beads. It appeared to us that this photoaffinity based method for immobilization of small molecules might be useful for atorvastatin lactone and several other small molecules. So we changed our strategy to the carbene based immobilization of small molecules as an alternative approach with the hope that this would give us a promising outcome. Besides atorvastatin lactone we planned to study a recently isolated new antitumor molecule, englerin A (**2-3**).[92] Its core structure has been lately synthesized in our group.[93] Englerin A (**2-3**) shows antitumor activity against renal cancer cell lines in the NCI 60 cell panel[94] with GI_{50} values from 1–87 nM. A COMPARE analysis[133] of the englerin A 60 cell panel data against NCI standard agents did not suggest a known mechanism of action. All this information increased our interest to find out its protein target and binding properties.

Since the previous fishing experiments indicated that proteins bound to atorvastatin lactone are of low abundance, we furthermore planned to combine the Osada method with a highly sensitive mass spectrometry based technique called *SILAC* (vide infra).

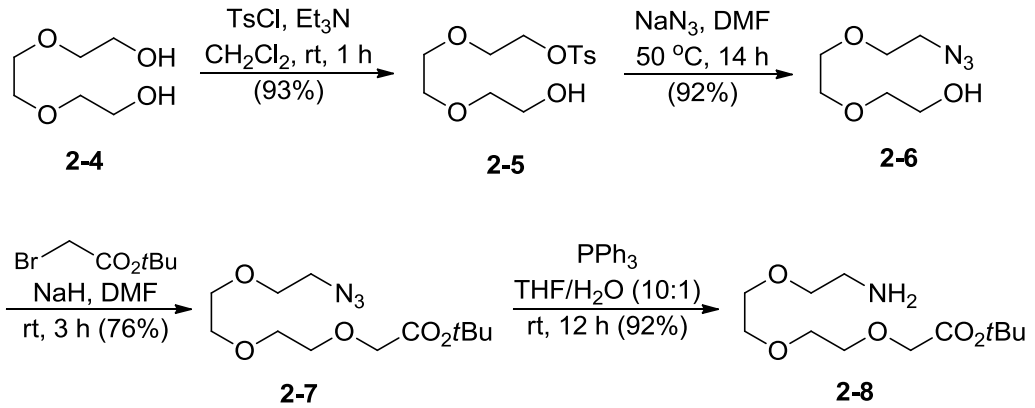
8 Results and Discussion

8.1 Synthesis of photoaffinity based TEG derived linker

For fishing experiments, the initial task was to synthesize a suitable linker to immobilize it on the surface of amino functionalized Toyopearl-AF-Amino-650 beads. In that case, a carboxylic acid derived triethylene glycol linker system which is coupled to 3-trifluoromethyl-3-phenyl diazirine[95] appeared as a best option.

8.1.1 Synthesis of carboxyl functionalized triethylene glycol linker 2-8

According to the proposed plan, we initiated with the synthesis of amine and *t*-butyl ester functionalized TEG linker **2-8** from triethylene glycol **2-4**. TEG was first mono tosylated to **2-5** by *p*-toluenesulphonyl chloride and Et_3N in CH_2Cl_2 followed by its subsequent modification to azide **2-6**[96] using NaN_3 in 85% yield over two steps (**Scheme 36**). Now, the free hydroxyl function of **2-6** was alkylated using *tert*-butyl bromoacetate and NaH in DMF which delivered **2-7** in 76% yield. Further reduction of azide of **2-7** under mild conditions using PPh_3[69] in a THF/H_2O (10:1) mixture provided TEG derived amine *t*-butyl ester **2-8** ready for coupling with the photoaffinity tag.

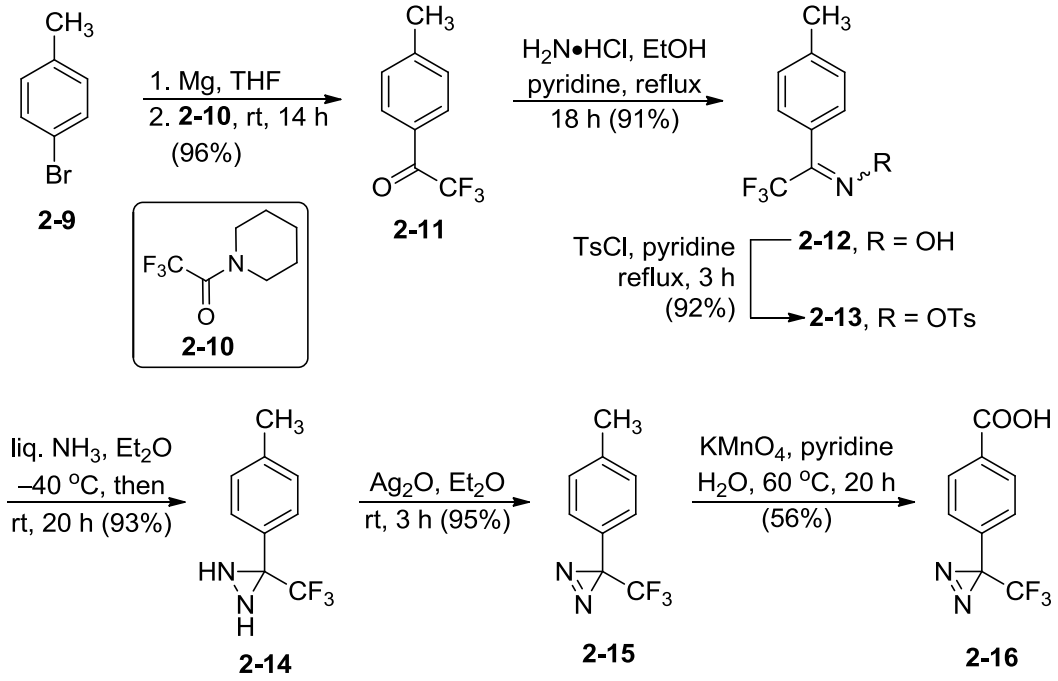


Scheme 36. Synthesis of functionalized TEG linker **2-8**.

8.1.2 Synthesis of 4-(3-(trifluoromethyl)-3*H*-diazirin-3-yl)benzoic acid 2-16.

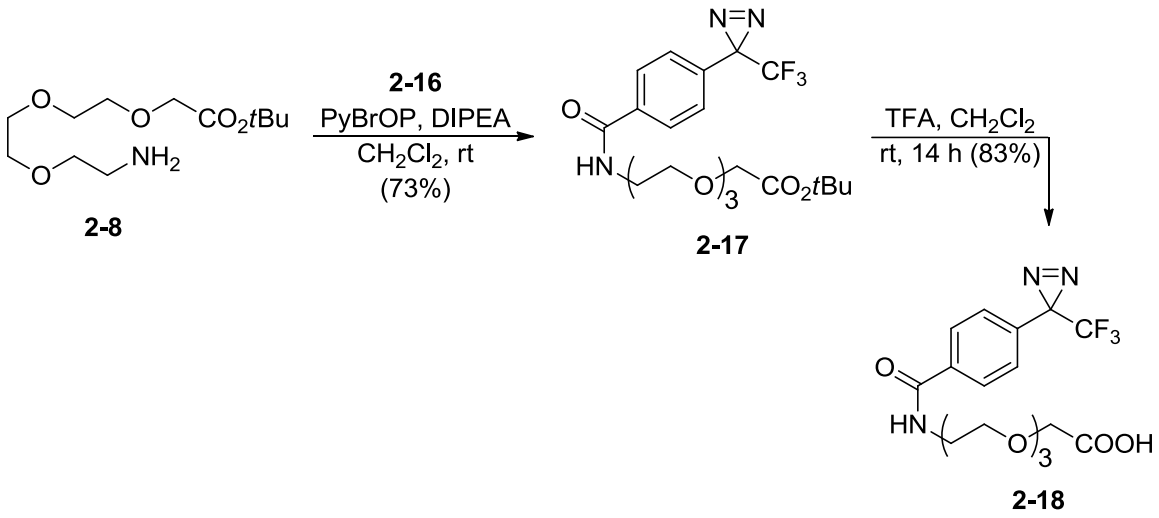
Phenyl diazirine is widely used in the field of chemical biology for photoaffinity labeling. Several reports are available about its application in affinity based target fishing.[86a,91,97] As consequence, their synthesis in various applications have been studied.[98] Using some of these efficient literature procedures we synthesized desired diazirine **2-16** in high overall yield.

In the beginning, ketone **2-11** was prepared by a Grignard reaction using 4-bromotoluene **2-9** derived Grignard reagent and the amide **2-10**[98a] as electrophile. Ketone **2-11** on treatment with NH_2OH•HCl in a mixture of pyridine and ethanol[98c] followed by subsequent modification using tosyl chloride delivered tosyl oxime **2-13** in 83% yield over 2 steps. The tosylated oxime **2-13** was then treated with liq NH_3[98a] in a closed flask to furnish a 93% yield of diaziridine **2-14**. In presence of freshly prepared Ag_2O, diaziridine **2-14** was readily converted to the required diazirine **2-15** in excellent yield.[98c] In the final step, the methyl group of toluene derivative **2-15** was oxidized using $KMnO_4$ in aq pyridine at room temperature to provide target acid **2-16**[98a] in 56% yield ready for coupling with the TEG derived linker (**Scheme 37**).



Scheme 37. Synthesis of carboxyl derived phenyl diazirine **2-16**.

Thereafter, phenyl diazirine **2-16** and amine **2-8** were coupled together using PyBrOP which yielded amide **2-17**. Deprotection of *t*-butyl ester using a mixture (1:3) of TFA in CH_2Cl_2 provided photo labeled cross linker **2-18** (**Scheme 38**) ready for immobilization on affinity beads. As a precaution, diazirine containing compounds were protected from light.

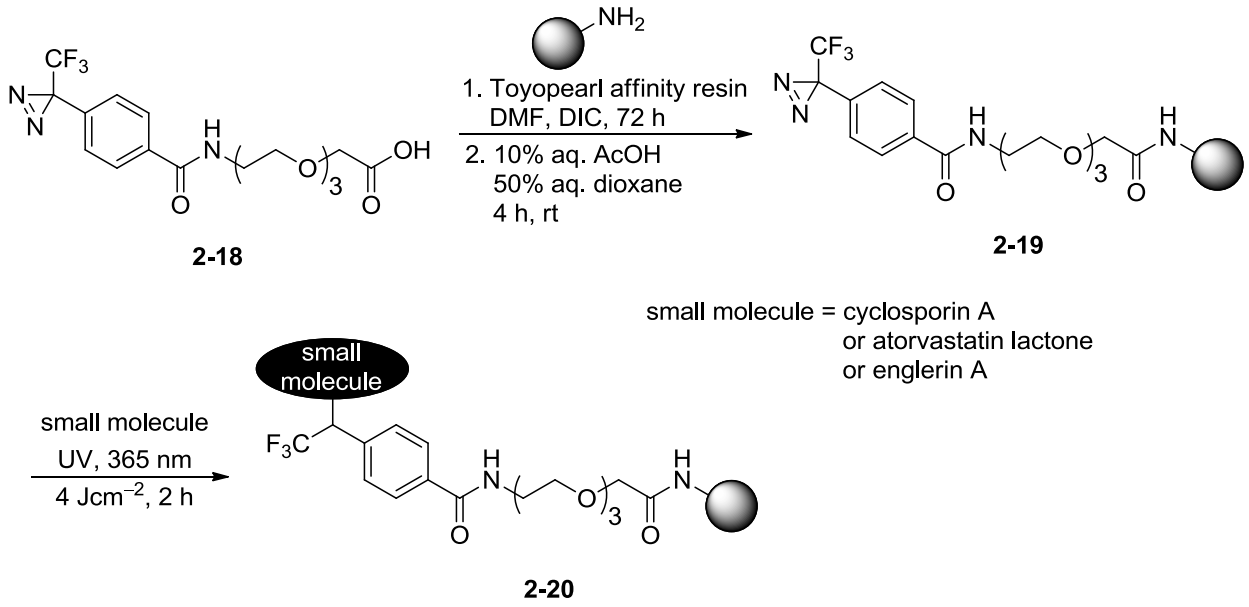


Scheme 38. Synthesis of linker **2-18** from diazirine **2-16** and TEG derived amine **2-8**.

8.1.3 Preparation of small molecule immobilized affinity beads

To obtain the affinity beads with a photo label at the terminus, we immobilized the diazirine coupled linker system **2-18** on amino functionalized Toyopearl AF 650 Amino beads (Tosoh Bioscience) using the standard protocol recommended for the immobilization of ligand or linker systems on these beads. According to the standard protocol, in the immobilization process for 1 mL of a 10% aq ethanol suspension of Toyopearl affinity beads, 330 μmol of linker (or ligand) and 233 μL of DIC were used. Here, we preferred DMF as a solvent rather than DMSO to avoid possible oxidation[99] of secondary hydroxyl groups present on Toyopearl beads. Carboxyl functionalized photo cross linker **2-18** and amino functionalized beads were gently shaken in absence of light at room temperature using DIC as a coupling agent for 72 h at room temperature. Then, the remaining free amino groups still present on the resulting beads **2-19** were blocked with 10% aq AcOH by gentle shaking on shaker instrument in presence of the condensing agent for 4 h (**Scheme 39**). After washing with appropriate solvents like 50% aq

dioxane, washing buffers (pH ~4 and pH ~8), dd H_2O and 20% aq ethanol, the resulting dry beads **2-19** were stored at 2–3 °C as suspensions in 20% aq ethanol and the total volume of the bead suspensions were recorded to consider its molar concentration. According to the concentration of these bead suspensions in 20% ethanolic solution, in the subsequent immobilization process for 1 equiv of photo labeled beads **2-19** from the suspensions, about 1 equiv of small molecule were used for UV irradiation. The whole process was carried out carefully to maintain the concentration of used beads. After UV irradiation of the mixture, we estimated that at least 10% loading of small molecule on the beads was achieved.



Scheme 39. Immobilization of the linker **2-18** on Toyopearl affinity beads and photo cross linking of the small molecules.

In a proof of concept study we decided to apply this target fishing approach to a small molecule with a known target. Thus, cyclosporin A (**2-2**) appeared as the best example in our eye to find its known cellular target cyclophilin.[100] Also, Osada and coworkers had used successfully the same example to prove their approach on Affigel loaded beads. To carry out this model experiment, cyclosporin A (**2-2**) immobilized on photoaffinity labeled Toyopearl beads was prepared. For this, an ethanolic solution of cyclosporin A **2-2** (~ 1 equiv) was added to the dry beads. Then the suspension was concentrated and dried under vacuum. These dry beads were then irradiated under a UV lamp (365 nm, 4 J cm^{-2}, 4 watts) for 2 h, washed with ethanol, water

and 50% aq ethanol in a sintered glass funnel. The resulting dry beads were diluted with 20% aq ethanol (200 μL) and handed over to the project colleague (Yvonne Etzel) responsible for performing the pull down experiments. As outcome of the target fishing approach using lung cells and further mass spectrometry analysis, cyclophilin was identified in abundance as a target protein with the mass of 18 kDa. For this fishing experiment lung cells (A549 cells) were used. In the SDS-PAGE a strong and distinct band with a molecular weight of 18 kDa could be seen (**Figure 21**). This band was further analyzed by mass spectrometry and Mascot analysis, which proved it to be cyclophilin.

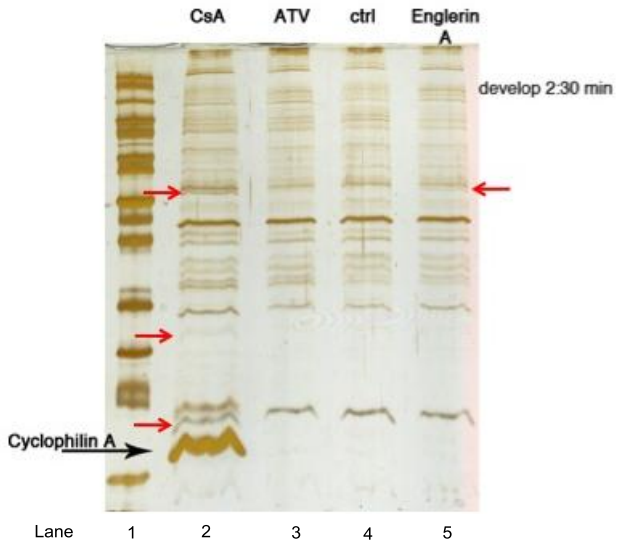


Figure 21. Detection of the binding proteins for cyclosporin A **2-2** immobilized beads. Lane 1: A549 cell lysate; Lane 2: A549 cell lysate with cyclosporin immobilized beads; Lane 3: cell lysate with atorvastatin **1-31** immobilized beads; Lane 4: **2-19** as control beads with cell lysate; Lane 5: cell lysate with englerin A **2-3** immobilized beads.

Inspired by the results of model experiment, we prepared three different sets of photoaffinity linker immobilized beads and irradiated them in presence of atorvastatin lactone (**1-31**), cyclosporin A (**2-2**) and englerin A (**2-3**) respectively as mentioned above. After washing with the solvents, the resulting bead samples and an additional sample of photoaffinity linker immobilized beads without irradiation as a control were provided to the colleague (Yvonne Etzel) to validate the binding ability of these small molecules. The results of the SDS-PAGE analysis showed again a band for the cyclosporin A binding protein (cyclophilin). But in case of

atorvastatin lactone (**1-31**) and englerin A (**2-3**) the resulting gel pattern was looking similar like the lane from the control beads. The exact reason here could be substantial non-specific binding of proteins and low abundance of target proteins. To find out the specifically or non-specifically bound protein targets of these molecules stable isotope labeling by amino acids, *SILAC*[101]appeared as the ideal better option. In this situation, we decided to carry out *SILAC* experiments to encounter the specifically bound proteins. For this, to perform *SILAC* experiment with solubility control as well as bead control might provide comparative information about binding proteins.[102] Since we were also interested in finding the putative targets of englerin A which shows selectivity towards renal cell lines, the HEK239T cells were chosen for the pull down experiments with the three samples. Consequently, we provided samples of small molecules (englerin A and atorvastatin lactone) immobilized bead samples as well as affinity labeled bead sample for bead control experiment together with solutions of the small molecules (1.53 mM solution of atorvastatin lactone and 1.14 mM of englerin A in 50 µL each of EtOH) for the solubility control experiments.

8.2 Stable isotope labeling by amino acids, *SILAC*

SILAC is a metabolic labeling technique for mass spectrometry (MS) based quantitative proteomics. In this technique, cells are cultivated in cell culture. One group of cells is fed with growth medium containing normal particular amino acids (light) while another set is fed with growth medium containing non-radioactive stable isotopes (heavy) of amino acids (generally leucine, or lysine or arginine). Consequently, heavy and light amino acids are incorporated into all proteins after several rounds of cell divisions. There is a hardly difference between heavy and light cells after incorporation, except the difference in mass of comparable proteins.

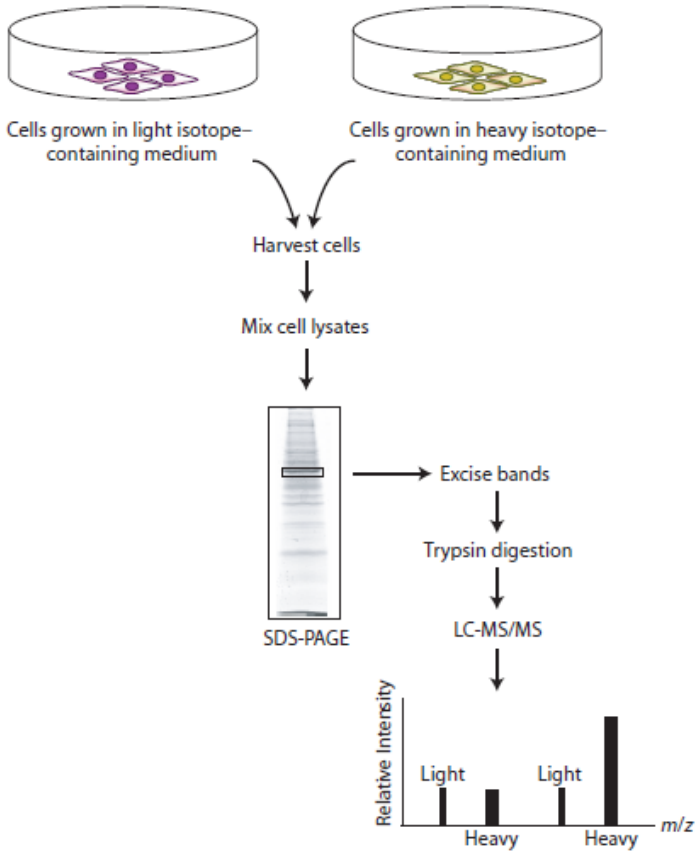


Figure 22. Schematic work flow of the *SILAC* technique.[103]

In the target fishing approach the heavy and light cells are individually lysed. One population of the cell lysate serves as the control and is either treated with control beads or with loaded beads in presence of small molecule competitor. Here one has to take care that the lysed cells are treated similarly in order to avoid errors. After the pull downs the cell extracts were combined heavy/light or heavy/medium respectively and subjected to the *SILAC* analysis. Typically SDS-PAGE gels are cut into 10 pieces, extracted and each of these portions is analyzed by LC coupled to an orbitrap mass detector. High ratios (high $\log_2$ values) indicate potential hits. Pairs of chemically identical peptides of different stable-isotope composition can be differentiated and assigned in a mass spectrometer owing to their mass difference. The ratio of peak intensities in the mass spectrum for such peptide pairs reflects the abundance ratio for the two proteins. Potential hits are those proteins where the peptide pairs have high $\log_2$ values in the intensity ratios, of course later then needs to be confirmed by separate biological experiments.

8.3 Outcome of *SILAC* experiment

In the *SILAC* experiments, for SDS-PAGE analysis 50 μL each of dry, loaded beads and control beads each with 2 mg of labeled HEK239T cells or lysate respectively were used. The cells were fed with heavy, medium and light labeled lysine and arginine using to the standard protocol which was performed by project colleague (Yvonne Etzel). The labeling of the amino acids lysine and arginine in cell lysate was as shown in **Table 1**. The loaded beads (small molecule immobilized) are mixed with heavy (H) labeled cells. The loaded beads and the small molecule solution (as soluble competitor) were mixed with medium (M) labeled cells and the unloaded beads (**2-19**) were mixed with light (L) labeled cells.

Table 1. Distribution of labeled amino acids in cell lysates.

Labels	**Lysine**	**Arginine**
Light	Lys 0	Arg 0
Medium	Lys 4	Arg 6
Heavy	Lys 8	Arg 10

Here for example, in medium (M) label Lys 4 refers to Lysine with $^{2}H_4$ labeling and Arg 6 means $^{13}C_6$-arginine. The heavy (H) label contains $^{15}N_2$ $^{13}C_6$ labeled lysine and $^{15}N_4$ $^{13}C_6$-arginine as supplement. Light (L) label contains Lys 0 and Arg 0 without labeled atoms. After the pull downs which were performed by Yvonne Etzel, the further steps (digestion with trypsin) and quantification by LC-HRMS were done in the Proteome Zentrum, Tübingen headed by Prof. Dr. Boris Macek. The results from the analysis were presented to us as an excel table containing various columns including protein ID numbers, Gene names and in particular the H/L and H/M ratios for each protein as determined from their respective fragments. The ratios are listed in unnormalized ratios and normalized form. For generation of graphs in **Figure 23** we used the unnormalized ratios.

In graph A and C the H/M ratios were converted to their $\log_2$ values and then sorted in descending order. The protein index is just an integer number with the lowest index being the highest ratio. Our coworkers recommended two ways of identifying interacting hits. In method one, a ruler is aligned to the almost linear line in the middle section. Proteins with the ratio above this line are likely binding to the immobilized small molecule. The right panel reflects procedure two. In principle the bead control experiment (H/L) and the soluble competitor experiment (H/M) should identify similar proteins. Thus, the cross-sectional graph would show interacting proteins if they have high ratios in both experiments. The loaded beads were mixed with heavy (H) labeled cells. The loaded beads containing small molecule and the small molecule solution (soluble competitor) were mixed with medium (M) labeled cells and the unloaded beads (**2-19**) were treated with light (L) labeled cells.

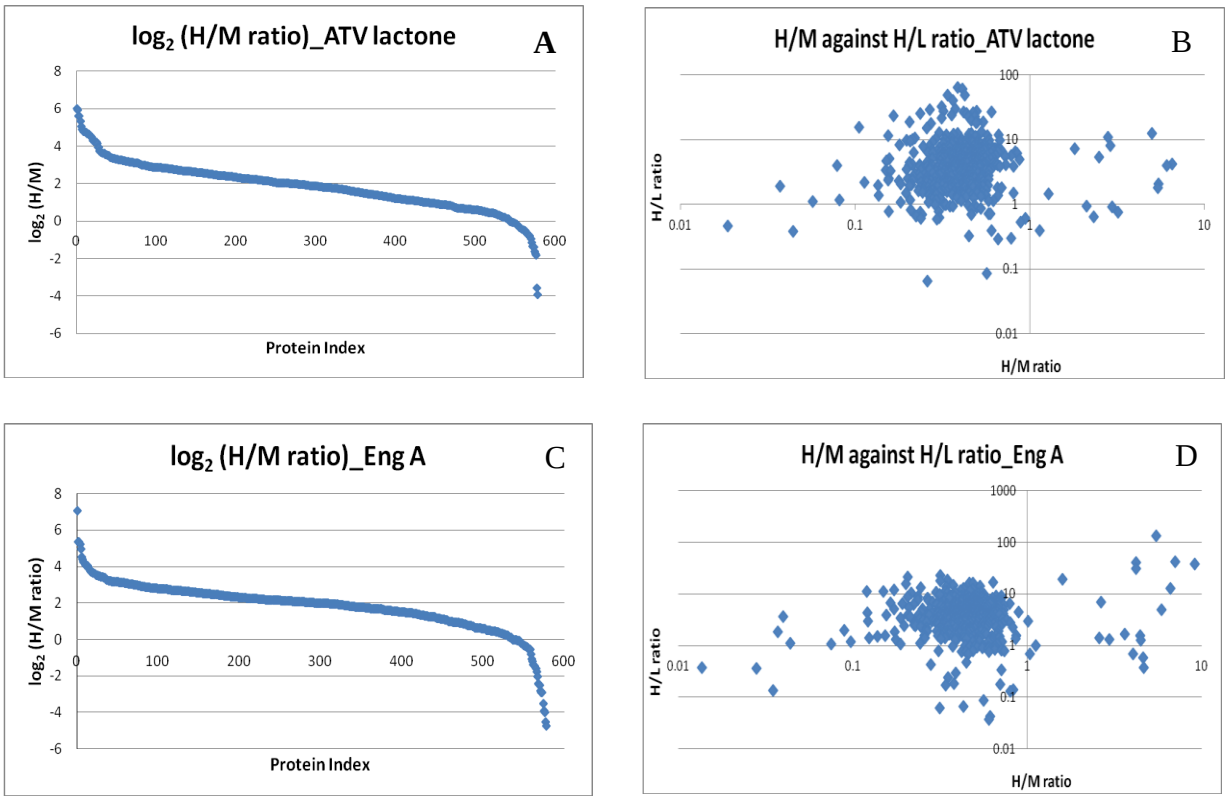


Figure 23. a) Plots of $\log_2$ *SILAC* ratios against proteins sorted by their ratios in descending order (A and C); b) logarithmic cross-sectional graphs of H/M ratio against H/L ratio (B and D).

According to the graphs A and C (**Figure 23**), proteins having higher $\log_2$ numbers can be possible target proteins while cross-sectional graphs B and D of H/M ratio against H/L ratio

provides distribution of bound proteins. The proteins from the (upper right) of graphs B and D (**Figure 23**) could be possible binding targets of atorvastatin lactone and englerin A. The proteins from graphs B and D are shortlisted in the following **Table 2** (for atorvastatin lactone) and **Table 3** (for englerin A) as probable binding targets of these molecules.

For atorvastatin lactone, top ten possible binding targets are listed while for englerin A top fourteen binding targets are listed. Certainly some of the possible listed candidates will be non-specific binding partners. There are some candidates in both lists which are common. If we cancel these commonly found protein candidates from both experiments then from **Table 2**, acylglycerol kinase (AGK) is the only candidate that remains for atorvastatin lactone. For englerin A, RNA-binding protein 39 (RBM39), DnaJ homolog subfamily C member 9 (DNAJC9), Coiled-coil-helix-coiled-coil-helix domain-containing protein 3 (CHCHD3), Complement component 1 Q subcomponent-binding protein (C1QBP), ATP synthase subunit gamma (ATP5C1) and Stomatin-like protein 2 (STOML2) are the remaining candidates for further validation. There is some literature available for non-specific binding partners of the sepharose beads where some candidates like prohibitin, voltage dependent anion channel-2 and 3, transitional endoplasmic reticulum ATPase are reported as non-specific binders.[104] Therefore, it is not clear to us weather these proteins bind similarly with Toyopearl beads.

It is reported that acylglycerol kinase may regulate lysophosphatidic acid (LPA) induced pro- and anti inflammatory signals which regulate innate immunity in the airway epithelium.[105] This could be a hot binding target for atorvastatin lactone. The analysis for englerin A points to a mode of action which interferes with electron transport. Thus, ATP synthase subunit gamma which provides energy to a cell could be one of the possible targets for englerin A. Also, among all possible targets listed in **Table 3** for englerin A, prohibitin is a known tumor suppressor protein which could be a major binding target. It is known to interact with histone deacetylase 1 (HDAC1),[106] Ratinoblastoma protein,[107] Ratinoblastoma like protein-1 and 2,[107] Akt (protein kinase B).[108] But in this case we are not sure if prohibitin binds specifically or non-specifically. Therefore, further analysis would now be required to validate these findings. In any way one can say that this strategy appears promising in narrowing down potential protein targets of small molecules.

Table 2. List of top 10 possible binding targets of atorvastatin lactone from *SILAC* experiment.[a]

ID	Protein Names	Gene Names	Uniprot ID	Ratio H/M R04_ATV
365	Prohibitin-2	PHB2	Q99623, Q9BXV3	12.623
417	Voltage-dependent anion-selective channel protein 3	VDAC3	Q9Y277-2, Q9Y277	10.79
323	Voltage-dependent anion-selective channel protein 2	VDAC2	P45880-1, P45880	8.1318
307	Transitional endoplasmic reticulum ATPase	VCP	P55072, Q0IIN5	7.2552
151	Sideroflexin-1	SFXN1	Q9H9B4, D6RFI0	5.3494
253	Prohibitin	PHB	P35232, A8K401	4.2044
556	Voltage-dependent anion-selective channel protein 1	VDAC1	P21796, B3KTS5	3.9563
470	Rab-like protein 3	RABL3	Q5HYI8, C9JXM3	2.067
385	KIAA1715 protein	KIAA1715	B7ZLA8, B7Z829	1.8009
269	Acylglycerol kinase	AGK	Q53H12-1, Q53H12	1.4674

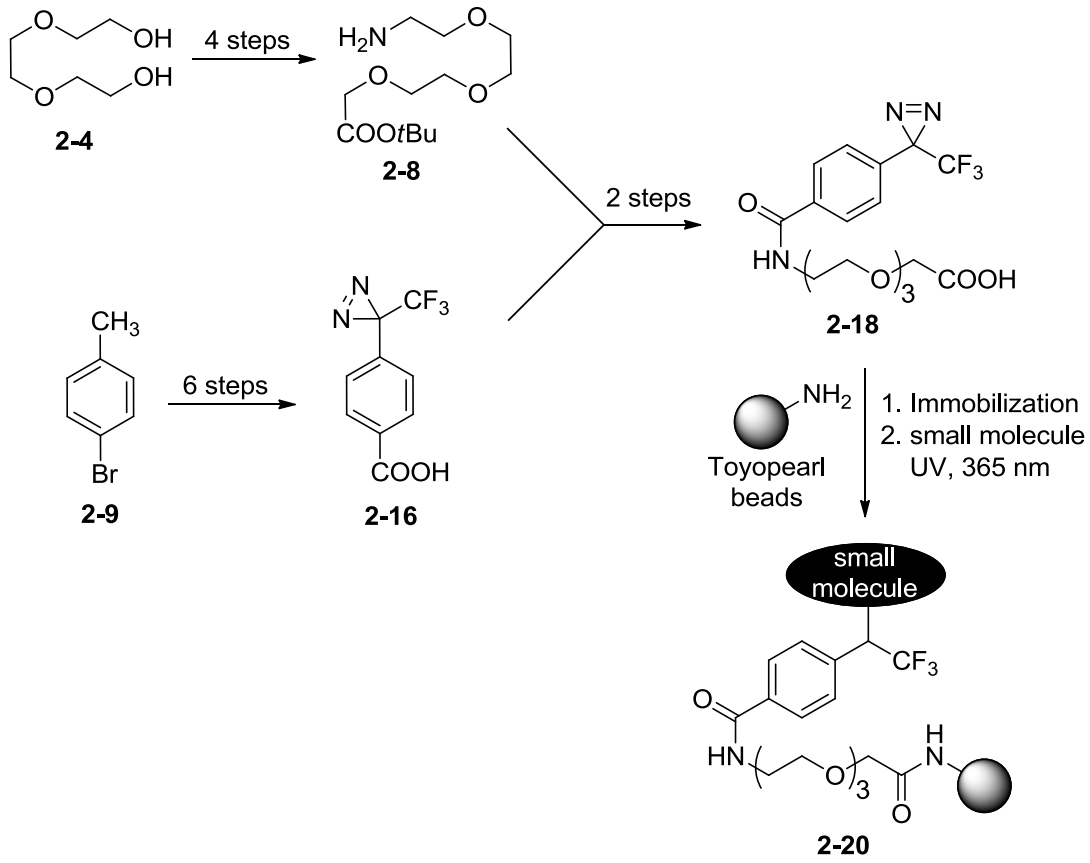
[a] Only two Uniprot IDs are listed.

Table 3. List of top 15 possible binding targets of englerin A from *SILAC* experiment.

ID	Protein Names	Gene Names	Uniprot ID	Ratio H/M R05_Eng A
365	Prohibitin-2	PHB2	Q99623, Q9BXV3	134.6
253	Prohibitin	PHB	P35232, A8K401	41.52
417	Voltage-dependent anion-selective channel protein 3	VDAC3	Q9Y277, Q9Y277-2	40.616
556	Voltage-dependent anion-selective channel protein 1	VDAC1	P21796, B3KTS5	37.787
323	Voltage-dependent anion-selective channel protein 2	VDAC2	P45880-1, P45880	31.453
492	RNA-binding protein 39	RBM39	Q14498-1, Q14498	19.222
470	Rab-like protein 3	RABL3	Q5HYI8, C9JXM3	12.854
307	Transitional endoplasmic reticulum ATPase	VCP	P55072,Q0IIN5	6.8867
385	KIAA1715 protein	KIAA1715	B7ZLA8, B7Z829	4.9266
488	DnaJ homolog subfamily C member 9	DNAJC9	Q8WXX5, B2RMW6	3.0186
234	Coiled-coil-helix-coiled-coil-helix domain-containing protein 3	CHCHD3	C9JRZ6, Q9NX63	1.6941
151	Sideroflexin-1	SFXN1	Q9H9B4, D6RFI0	1.552
226	Complement component 1 Q subcomponent-binding protein	C1QBP	Q07021, A8K651	1.4169
765	ATP synthase subunit gamma	ATP5C1	P36542-1, P36542	1.3018
739	Stomatin-like protein 2	STOML2	Q9UJZ1, B4E1K7	1.2746

9 Conclusion II

As a summary, we used the Osada method of photo-immobilization of small molecules on the surface of photo labeled affinity beads and *SILAC* based proteomics for the identification of biological targets. These strategies as a combined approach could be quite useful to identify the target proteins out of the non-specific binding proteins. For this we prepared a diazirine coupled suitable linker system containing a carboxyl group at the terminus (**2-18)** which is suitable to immobilize it on the Toyopearl affinity beads (**Scheme 40**). The small molecule immobilized affinity beads were prepared according to the Osada protocol.



Scheme 40. Preparation of small molecule immobilized affinity beads using UV irradiation.

We successfully proved this as a combined approach by the fishing of cyclophilin (18 kDa) as a binding target of cyclosporin A from A549 cell lysate. With the same approach we were able to fish some possible binding targets of atorvastatin lactone (Off-targets) and englerin A as shown in **Table 2** and **3**. In general we could say that this combined approach can be quite useful for the

fishing of biological targets of small molecules without any structural modification prior to the pull down experiments. In particular this strategy appears advantageous for protein targets of low abundance and small affinity.

Chapter III

Synthesis of the C1-C13 Fragment of Biselyngbyaside

10 Introduction

Natural products, especially those from terrestrial plants and microbes, have long been a traditional source of drug molecules. Indeed, pharmacologically active compounds from plants and microbes represent an important pipeline for new investigational drugs.[109] Around half of the pharmaceutical drugs currently available in the market are of natural product origin.[110] Marine organisms are relatively new sources of medicines for the treatment of human disorders in comparison with the terrestrial organisms. About 70% of the area of earth is covered by wide spread ocean. Over the last few decades, marine sources have attracted much attention of biologists and chemists in the world due to their diverse biologically potent activity and ability of treating human diseases like malaria, cancer, AIDS, etc.[111]

The collection and extraction of marine species like sponges, fish, coral, bryozoans, tunicates, algae and other microorganisms has led to a wealth of novel bioactive drugs with anti-inflammatory, antiviral, antitumor activity and many more.[112] Basic scientific research in the field of chemistry and pharmacology of marine natural products and its directed efforts in the drug development delivered a fruit for marine based drug discovery. Ziconotide (**3-1**), a synthetic form of ω-conotoxin MVIIA[113] (isolated from the marine cone snails) became a first marine derived natural product approved as a medicine for the treatment of chronic pain.[114] Several other structurally unique isolated secondary metabolites from marine organisms and their structurally derived analogues have reached preclinical and phase I–III clinical trials.[115] Discodermolide (**3-2**),[116] E-7369 (**3-3**, halichondrin analogue),[117] halichondrin B (**3-4**),[118] bryostatin 1 (**3-5**),[119] kahalalide F (**3-6**)[120] and dolastatin 10 (**3-8**)[121] (**Figure 24** and **Figure 25**) are a few examples being tested as such or their synthetic analogues in different phases of clinical trials.[122]

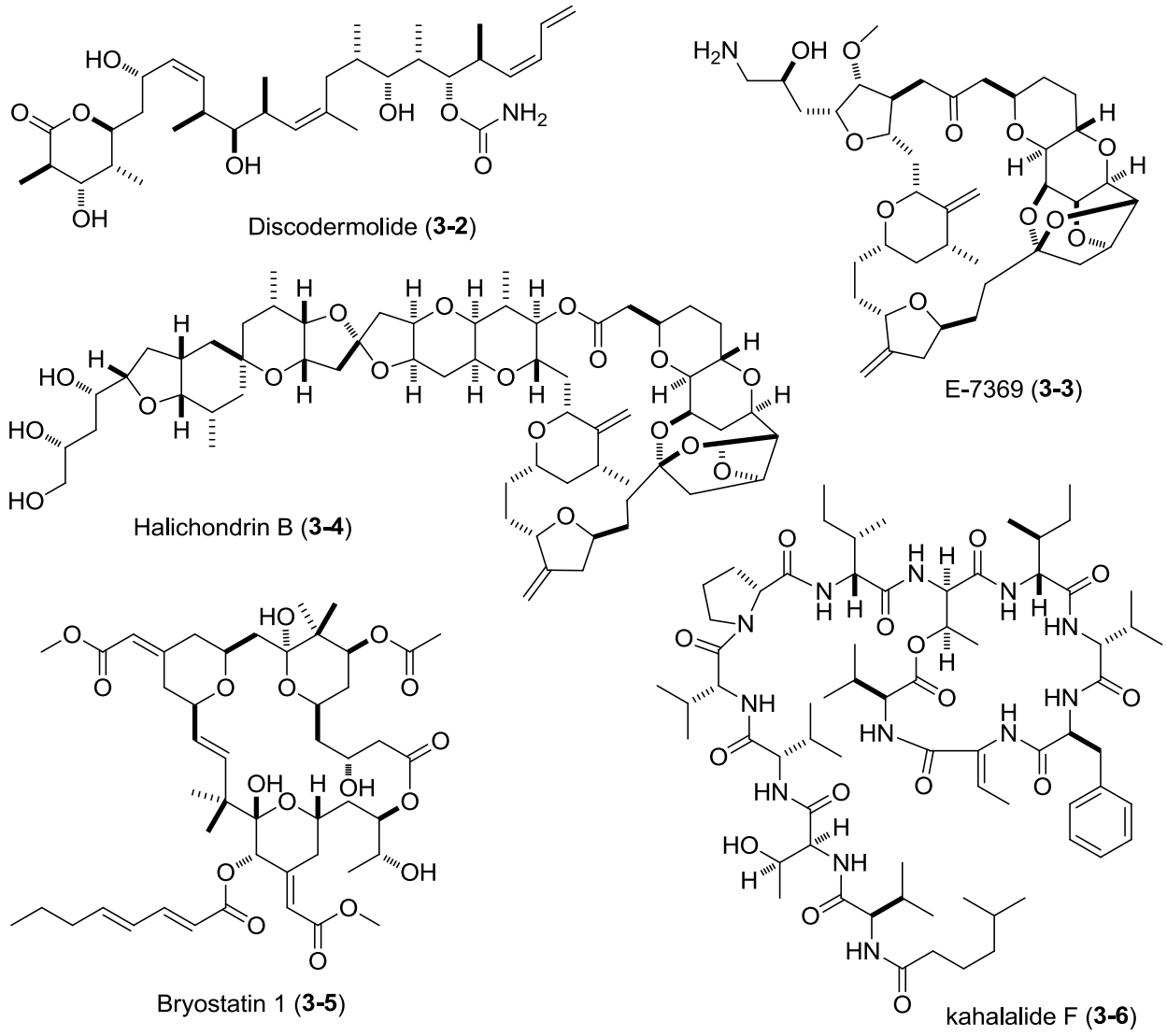


Figure 24. Examples of marine metabolites in clinical different clinical trials.

Among all marine sources, cyanobacterium (blue green algae) is one of the widespread marine species having the ability of producing biologically active chemicals as their secondary metabolites which show powerful anti-tubulin and anti-actin properties.[123] Cyanobacteria is a phylum of bacteria which live in water and can manufacture their own food through photosynthesis. It is one of the richest sources of leading therapeutic agents and their synthetic analogues for the treatment of cancer. Curacin A (**3-7**),[124] dolastatin 10 (**3-8**),[121] symplostatin 1 (**3-9**),[125] dolastatin 15 (**3-10**)[126] and apratoxin A (**3-11**)[127] are few examples (**Figure 25**) of the antitumor substances isolated from different marine cyanobacteria.[128]

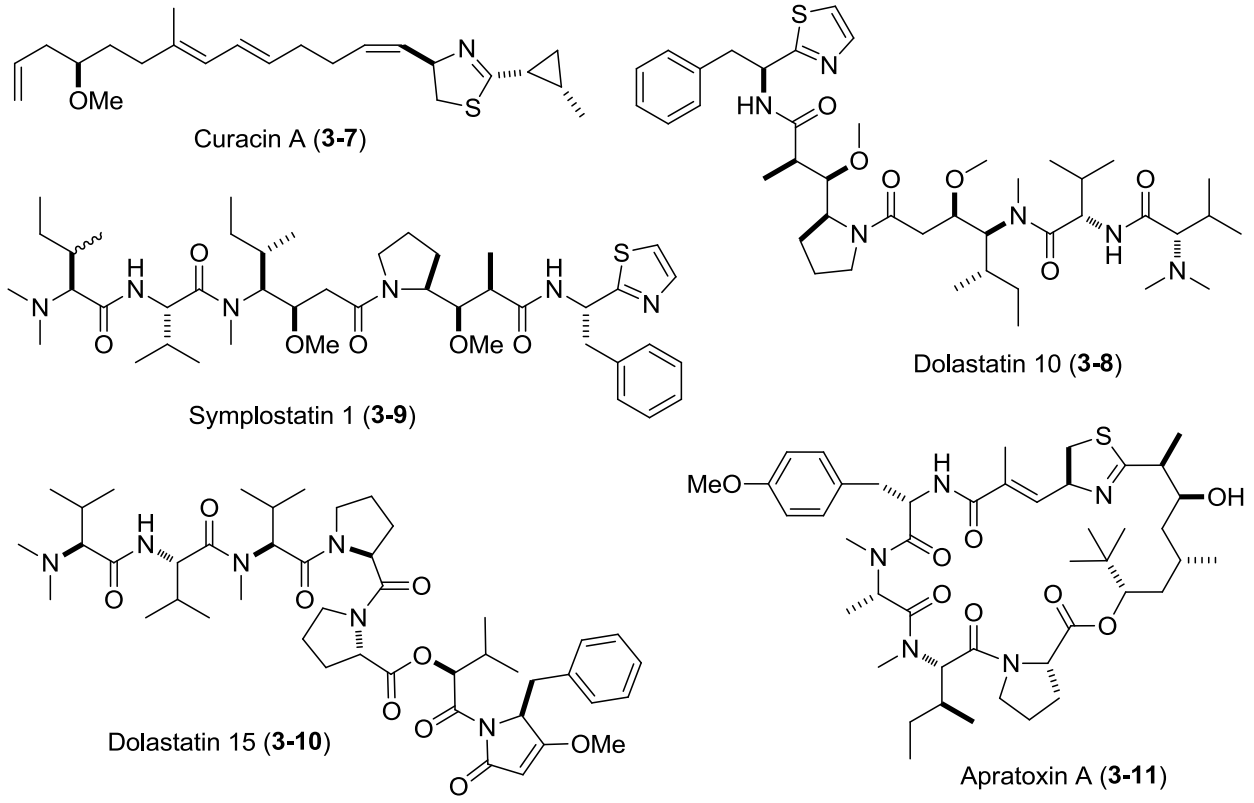


Figure 25. Antitumor substances isolated from marine cyanobacteria.

Today, cancer accounts for one in every eight deaths worldwide; more than HIV/AIDS, tuberculosis, and malaria combined. According to an estimate of the American Cancer Society (2008), out of 12.7 million cases of cancer diagnosed, 7.6 million people died due to cancer around the world.[129] Despite of the availability of several anticancer drugs in the market, there is an urgent need of new potent anticancer drugs. It is observed that tumor cells are developing resistance against presently available drugs like vinca alkaloids and taxanes etc. which is becoming a major cause of failure in the chemotherapeutic treatment of cancer.[130] As a result, treatment of cancer still remains as a challenge for worldwide researchers to find a better solution.

Figure 26. Marine cyanobacterium *Lyngbya sp.* and structure of biselyngbyaside.

In this context, biselyngbyaside is a new promising macrolide isolated from the marine cyanobacterium *Lyngbya sp.* (**Figure 26**) at Okinawa prefecture.[131] Biselyngbyaside **3-12** was isolated from the polar methanol extract. The polarity of the compound is likely due to the sugar moiety attached to the molecule which itself is somewhat unusual because it contains methoxy group at 3-position. Preliminary assays of biselyngbyaside **3-12** displayed cytotoxicity against HeLa cell lines with an IC_{50} value of 0.1 μg mL^{-1}. In addition, average growth inhibition (GI) value across 39 human cancer cell lines was 0.6 μM and with differential cytotoxicities. The central nervous system cancer SNB-78 (GI_{50} 0.036 μM) and lung cancer NCI H522 (GI_{50} 0.067 μM) cell line were especially sensitive.[132] Negative results of COMPARE analysis[133] of biselyngbyaside indicated that it likely inhibits cancer cell proliferation through a novel mechanism.[134]

Recently Woo et al. reported that biselyngbyaside **3-12** inhibits receptor activator nuclear factor κB ligand (RANKL) induced osteoclastogenesis in mouse monocytic RAW264 cells and primary bone marrow-derived macrophages at a low concentration.[135] Bone remodeling occurs continuously to maintain the bone mass during life, and is comprised of opposing processes involving bone resorption by osteoclasts and bone formation by osteoblasts. Osteoclasts are differentiated from hematopoietic cells of the monocyte/macrophage lineage, and the bone lytic function of osteoclasts is involved in many bone-destructive diseases, such as osteoporosis, hypercalcemia, rheumatoid arthritis, bone tumor metastasis, periodontitis and Paget's disease.[135] Therefore, suppression of osteoclastogenesis with drug is a major therapeutic target for these diseases. Biselyngbyaside **3-12** suppresses bone resorption via inhibition of osteoclastogenesis

and induction of apoptosis. Thus, biselyngbyaside **3-12** may also be useful for the prevention of bone lytic diseases.[135] Quite recently a related molecule called biselyngbyolide was described in the literature.[136] It is devoid of the sugar part and instead of the C4-C5 double bond there is a hydroxyl function at C5.

11 Retrosynthesis

Biselyngbyaside **3-12** is a 18 membered macrolactone consisting of six carbon-carbon double bonds and four asymmetric centers and a 3'-methoxyglucose moiety at C3-position. From a structural point of view, the presence of one isolated double bond, one conjugated double bond and four allylic alcohols make this macrolide very challenging for a chemical synthesis.

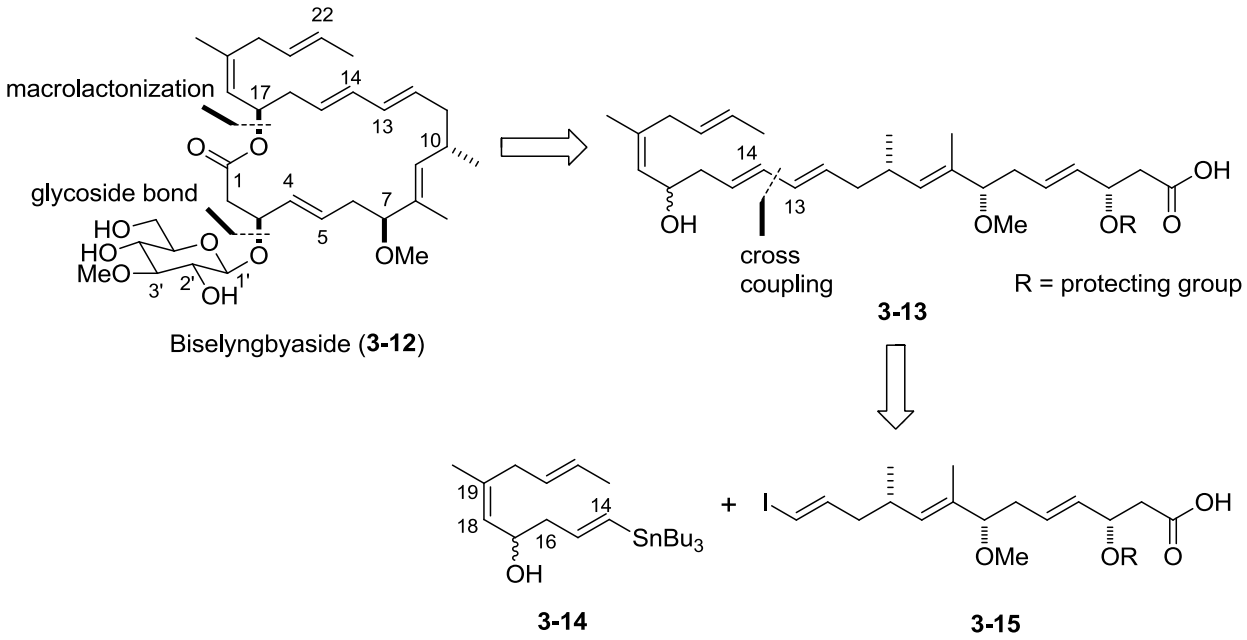


Figure 27. Retrosynthetic analysis of biselyngbyaside (**3-12**).

An initial option would be the formation of the macrolactone ring at C4 and C5 carbons via ring closing metathesis before glycoside bond construction. But the presence of many double bonds in the molecule could make this strategy impractical. In that case, the most favorable option for ring closing appears to be macrolactonization via classical reactions like Yamaguchi esterification[137] or Mitsonobu esterification[138] from seco acid **3-13** (**Figure 27**) as an advanced precursor. Disconnection at the C13-C14 bond would suggest formation of fragment **3-15** and vinyl stannane **3-14**. In this case, side chain C18-C23 will be established after macrolactone formation.

Synthesis of fragment **3-15** (**Figure 28**) bearing three asymmetric centers should be possible by cross metathesis reaction between homoallyl fragment **3-16** and allyl alcohol **3-17**.

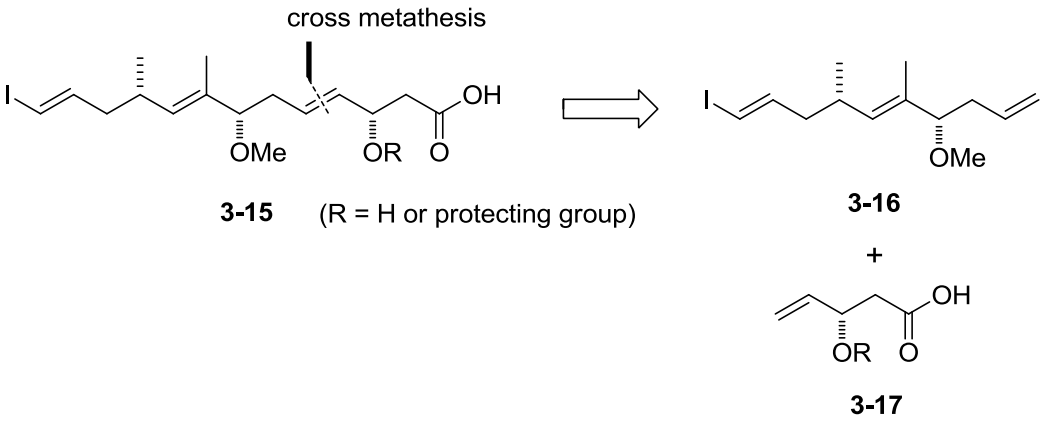


Figure 28. Retrosynthetic analysis for seco acid **3-15.**

Further retrosynthetic simplification suggest that the C5-C13 fragment **3-16** (**Figure 29**) can be synthesized using a Wittig reaction of aldehyde **3-19** providing advanced aldehyde **3-18**, which could be modified to fragment **3-16** using hydrozirconation/iodination and asymmetric allylation as intermediate steps in the synthetic pathway. Aldehyde **3-19** could possibly be synthesized by stereocontrolled alkylation of a chiral propionate derivative.

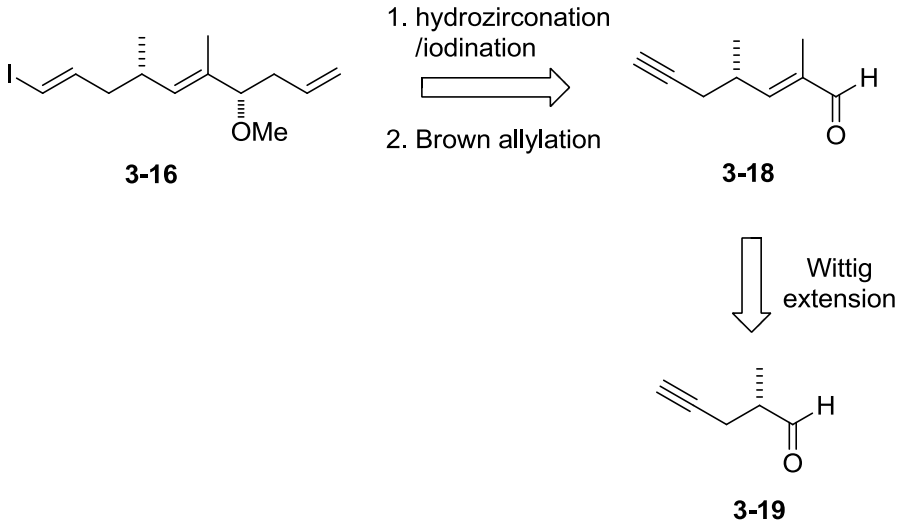


Figure 29. Retrosynthetic consideration for fragment **3-16**.

The C1-C4 fragment **3-17** can be synthesized from its racemic precursor **3-20** by enzymatic kinetic resolution. In this case racemic **3-20** can be prepared from commercially available acrolein **3-21** and *tert*-butyl acetate (**Figure 30**).

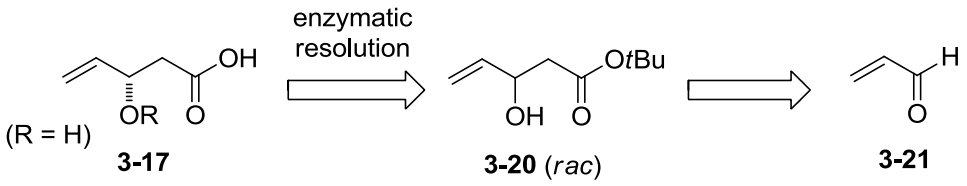


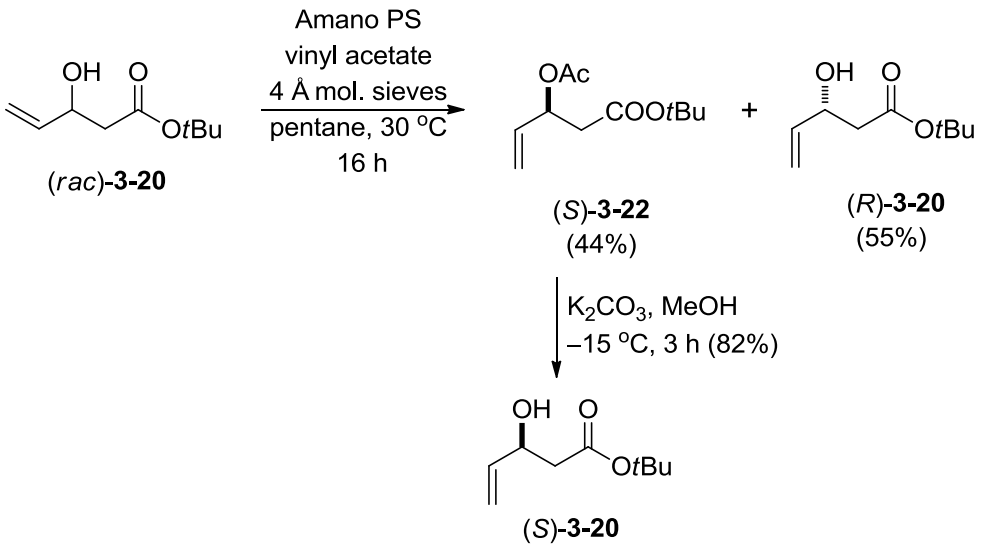
Figure 30. Retrosynthetic analysis of fragment **3-17**.

12 Results and Discussion

12.1 Synthesis of fragment C1-C13

12.1.1 Synthesis of fragment C1-C4 by enzymatic resolution

As discussed in the retrosynthetic section, preparation of fragment **3-17** could be possible by enzyme catalyzed kinetic resolution of racemic *tert*-butyl 3-hydroxypent-4-enoate **3-20**. Initially (*rac*)-**3-20** was prepared according to the literature procedure from commercially available acrolein and *tert*-butyl acetate in presence of LDA.[139] Alcohol (*rac*)-**3-20** was subjected to resolution using Amano PS lipase enzyme (Sigma-Aldrich Co.), vinyl acetate, and powdered 4 Å molecular sieves in dry pentane at 30 °C for 16 h.[140] The progress of reaction was followed by ^{1}H NMR. After about 16 h, a 50% conversion could be observed. The mixture was separated by flash chromatography to (*S*)-acetate **3-22** and alcohol (*R*)-**3-20** (**Scheme 41**).



Scheme 41. Enzymatic kinetic resolution of (*rac*)-**3-20** by Amano PS lipase enzyme.

Thereafter, (*S*)-acetate **3-22** was treated with anhydrous K_2CO_3 in methanol at −10 °C under controlled condition (TLC) to avoid hydrolysis of the ester function yielding (*S*)-**3-20** in 82% yield. Enantiomeric excess (*ee*) of resulting allyl alcohol (*S*)-**3-20** was determined by chiral gas chromatography which was found to be 98.5% as shown in **Figure 31**.

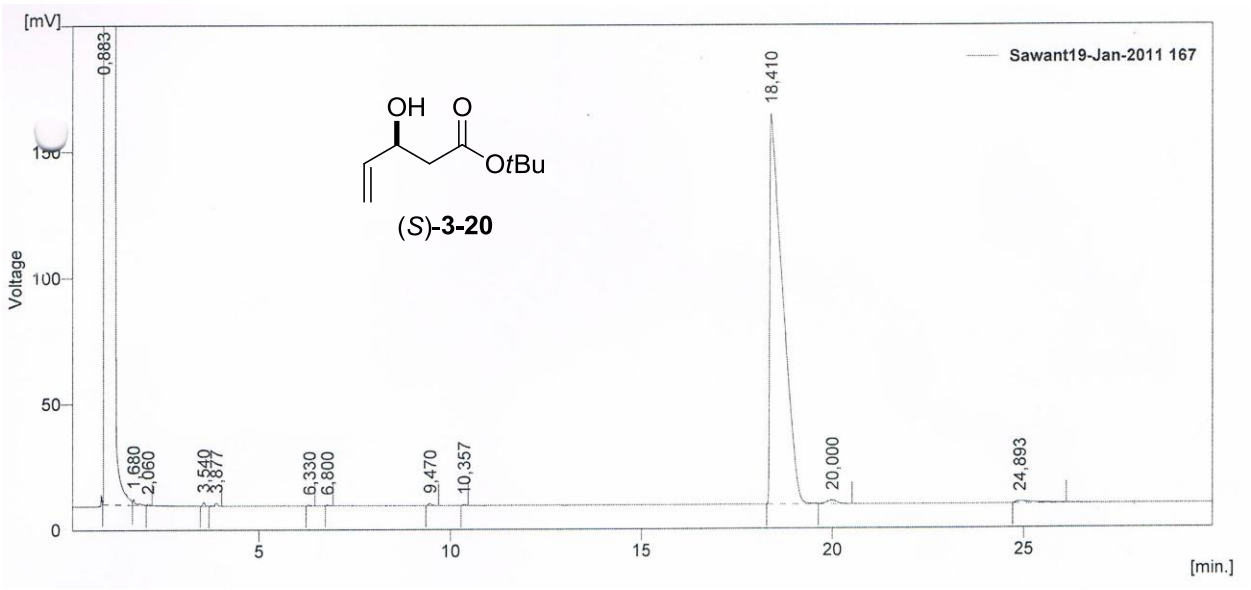
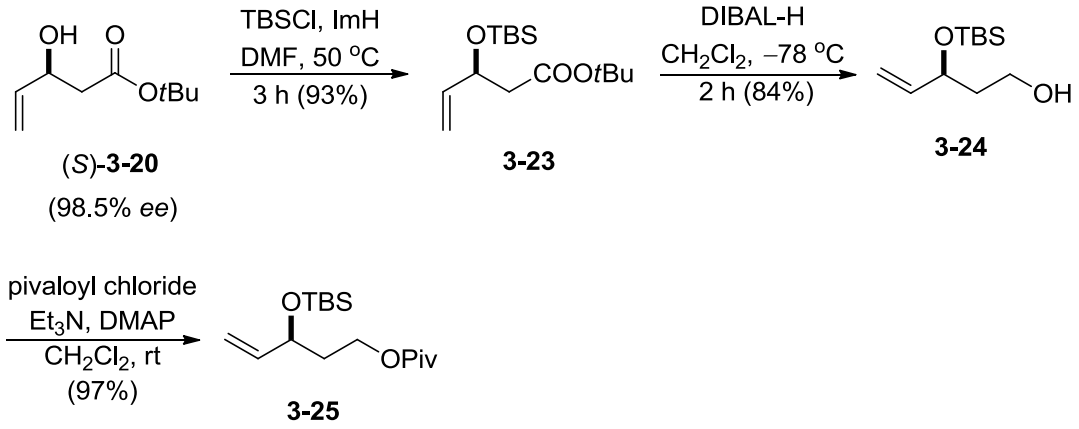


Figure 31. Chiral GC analysis of (*S*)-3-23; conditions: (column: 6-*tert*-butyl-2,3-di-*O*-ethyl-β-cyclodextrin, mobile phase: H_2, detection: FID, temperature: 70 °C, pressure: 75 kPa.

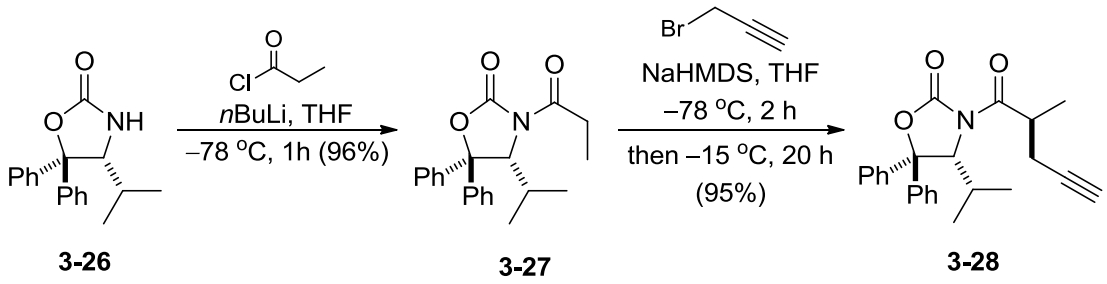
Thereafter, alcohol **3-20** was protected as silyl ether **3-23** using *t*-butyldimethylsilyl chloride and the carboxylic group was reduced to alcohol **3-24** using DIBAL-H (1M in hexane) in CH_2Cl_2 at −78 °C. Protection of the primary alcohol **3-24** was performed at room temperature using pivaloyl chloride in presence of Et_3N to provide fragment **3-25** quantitatively (**Scheme 42**).



Scheme 42. Synthesis of advanced fragment **3-25**.

12.1.2 Synthesis of fragment C5-C13

In fragment **3-15** besides C3, there are two more stereocenters at C7 and C10. Those could be introduced accordingly at C7 by asymmetric Brown allylation and at C10 by stereocontrolled alkylation of propionyl chloride derivative **3-27** derived from the Seebach auxiliary **3-26**.[141]



Scheme 43. Stereocontrolled propargylation of Seebach auxiliary **3-27** to **3-28**.

Therefore, chiral oxazolidinone **3-26** on treatment with *n*-BuLi (2.5M in hexane) followed by addition of freshly distilled propionyl chloride at 0 °C delivered propionyl oxazolidinone **3-27**[142] (**Scheme 43**) quantitatively. Asymmetric alkylation[143] of **3-27** using NaHMDS (2.0M in THF) and propargyl bromide within the temperature range of −78 °C to −15 °C over 20 h permitted propargyl analogue **3-28** in 95% yield. The diastereoselectivity of **3-28** was found to be 23:1, from ^{1}H NMR spectrum as shown in **Figure 32**.

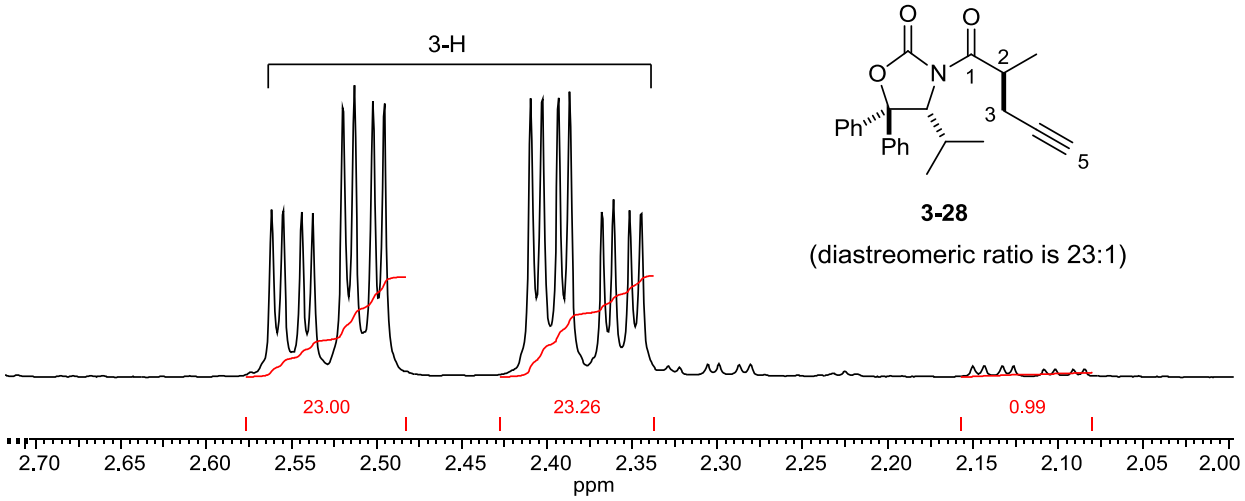
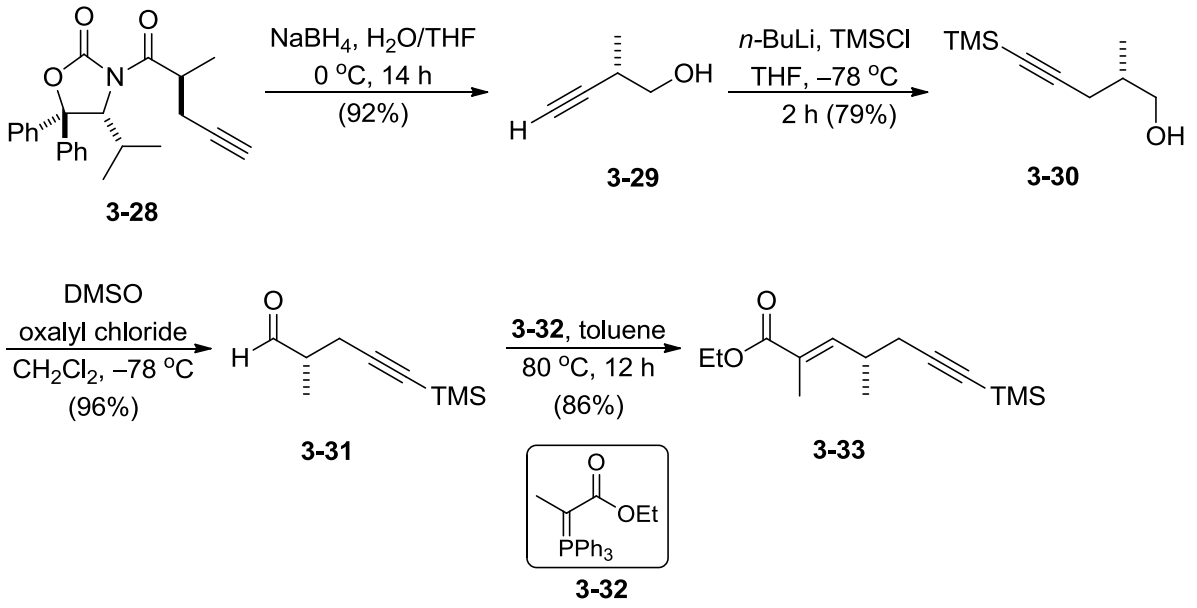


Figure 32. Diastereoselectivity ratio determination of **3-28** from ^{1}H NMR spectra.

Reductive cleavage of the auxiliary from **3-28** by $NaBH_4$ in a mixture (4:1) of THF and water led to alcohol **3-29**[144] as volatile liquid and roughly 70% of the auxiliary. Here, loss of **3-29** was observed under high vacuum because of its low molecular weight. Therefore, alcohol **3-29** was isolated from the solution under vacuum not less than 300 mbar.

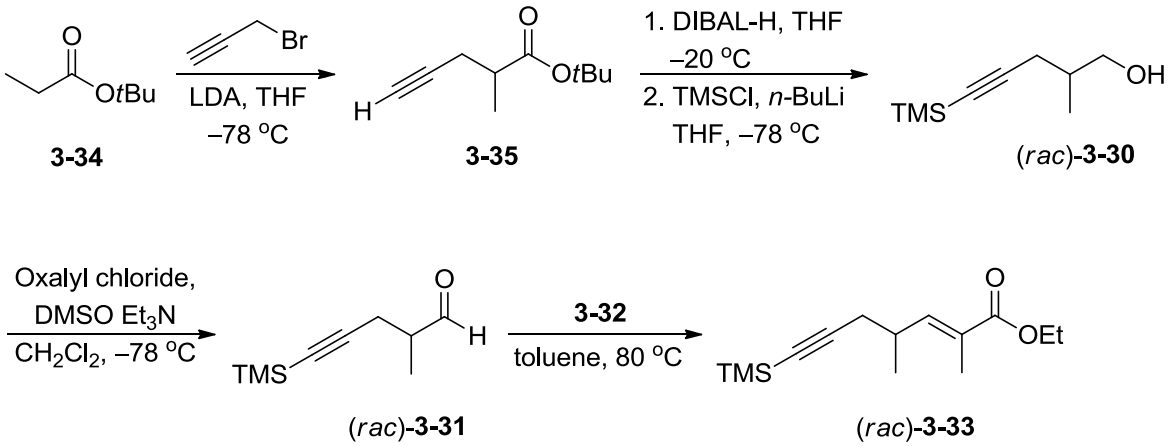
To reduce the volatile nature of alcohol **3-29** and further analogues, the acetylene proton was protected using TMSCl and *n*-BuLi (2.5M in hexane) to yield TMS acetylene **3-30**[145] which was further converted to the aldehyde **3-31** by using Swern oxidation[72] in very good yield. Aldehyde **3-31** was extended to enoate **3-33** by Wittig reaction with stabilized ylide **3-32** in toluene at 80 °C with high *E*-selectivity. Here, the stabilized ylide **3-32** (**Scheme 44**) for the Wittig extension was prepared according to the literature procedure[146] by heating PPh_3 and ethyl-2-bromopropionate without solvent followed by proton abstraction with the use of aqueous solution of NaOH (only 1 equiv) to avoid possible racemization in the Wittig reaction. Keeping this in mind, we tested the enantioselectivity of enoate **3-33** after Wittig reaction to check sensitivity of the chiral center substituent towards racemization.



Scheme 44. Synthesis of fragment **3-33** by Wittig reaction using stabilized ylide **3-32**.

Racemic adduct (*rac*)-**3-33** was easily prepared in a 5 step sequence (see **Scheme 45**) from *tert*-butyl propionate **3-34** by propargylation to have ester **3-35** which was then reduced to corresponding alcohol using DIBAL-H (1M in THF) and acetylene group was subsequently

protected by TMS chloride yielding (*rac*)-**3-30**. Swern oxidation of (*rac*)-**3-30** provided aldehyde (*rac*)-**3-31** in quantitative yield which on Wittig extension using stabilized ylide **3-32** furnished enoate (*rac*)-**3-33**.



Scheme 45. Synthesis of *rac*-**3-34** for enantiomeric excess determination.

Optical purity of (*ent*)-**3-33** by chiral gas chromatography analysis was found to be 89.8% as shown in F**igure 33**.

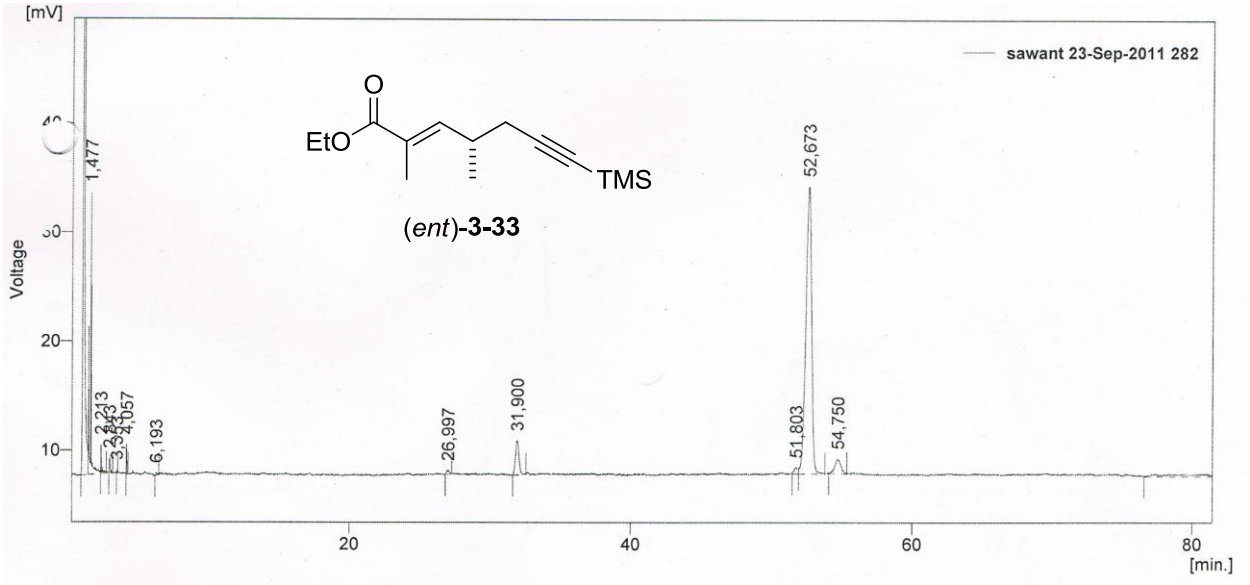
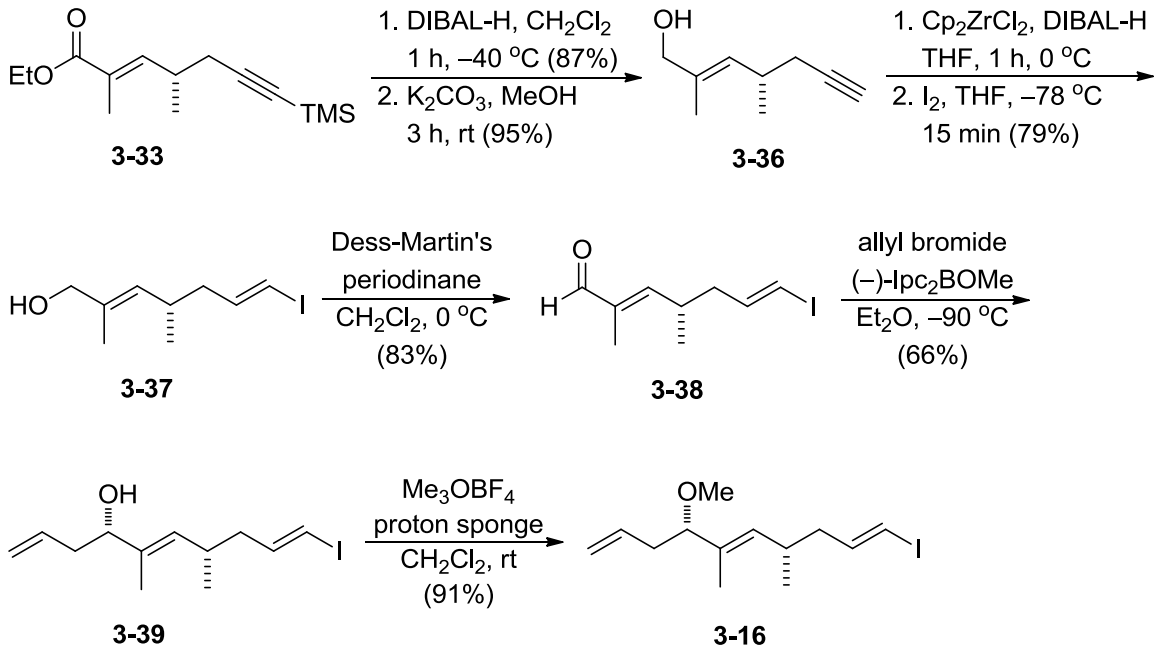


Figure 33. Chiral GC of Wittig product **3-33**; major isomer. t_R = 52.67, minor isomer t_R = 54.75; resolution was done using chiral column: AKS50 6-*tert*-butyl-2,3-di-*O*-ethyl-β-cyclodextrin, mobile phase: H_2, detection: FID, temperature: 100 isotherm, pressure: 75 kPa.

In the next step, enone **3-33** was reduced to corresponding alcohol using DIBAL-H (1.0M in hexane) followed by removal of the TMS group using K_2CO_3 in methanol at room temperature which provided modified alcohol **3-36**. The subsequent hydrozirconation[147,148] of alcohol **3-36** was done on the di-isobutylalkoxy derivative of alcohol **3-36**, it was generated by combination of **3-36** and DIBAL-H (1.0 equiv) at 0 °C. This solution was then added to the suspension of in situ generated Cp_2ZrHCl (Schwartz's reagent)[149] from Cp_2ZrCl_2 and DIBAL-H (1.0M in hexane). The resulting vinyl metal species was quenched by addition of molecular iodine as a THF solution at low temperature (−78 °C) to yield vinyl iodide **3-37** in 79% yield (**Scheme 46**). At this stage, the hydroxyl group of **3-37** was oxidized to aldehyde **3-38** using Dess-Martin periodinane. This aldehyde was then subjected to the Brown allylation reaction.[150] (+)-$Ipc_2Ballyl$ was generated in situ by treatment of (−)-Ipc_2BOMe with allyl magnesium bromide at −78 °C followed by dropwise addition of aldehyde **3-38** in THF into the boron complex solution at −90 °C. The resulting complex was quenched with H_2O_2/NaOH providing homoallyl alcohol **3-39** as a mixture of distereoisomers in 66% yield. Extending the synthesis, secondary alcohol function of **3-39** was methylated using Meerwein's reagent (Me_3OBF_4)[151,152,153] and proton sponge to have building block **3-16** ready for cross metathesis reaction (**Scheme 46**).



Scheme 46. Synthesis of fragment **3-16** from Wittig product **3-33**.

The diastereomeric ratio of homoallyl alcohol **3-39** was found to be 18:1, determined from the ^{1}H NMR spectrum considering integration of the 7-CH_3 group (**Figure 34**). This result indicated independently that the racemization of an aldehyde **3-31** during the Wittig reaction to yield **3-33** was minimal.

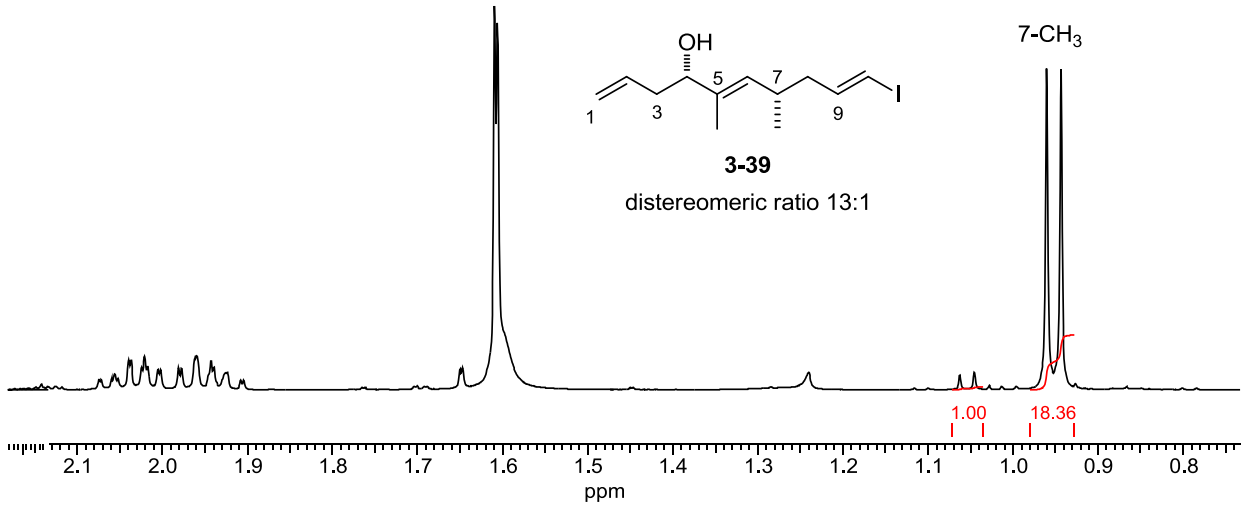


Figure 34. Determination of diastereoisomeric ratio of alcohol **3-39** after Brown allylation from ^{1}H NMR spectra.

12.1.3 Mechanistic pathway of Brown allylation

According to the well accepted model, the Brown allylation proceeds through a six membered chair like transition state (**Figure 35**). The large substituent R of the aldehyde occupies an equatorial position and the aldehyde facial selectivity derives from minimization of steric interactions between the Ipc ligand and the approaching aldehyde.[154] Boron as Lewis acid helps to activate the aldehyde and coordinates to the oxygen atom in the transition state.

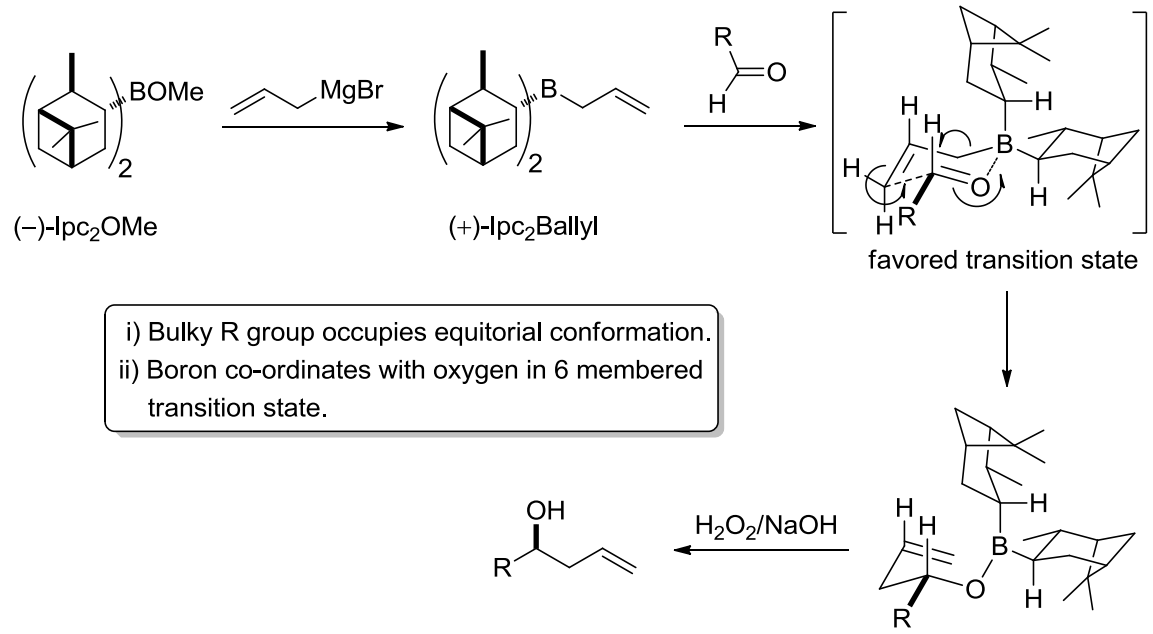
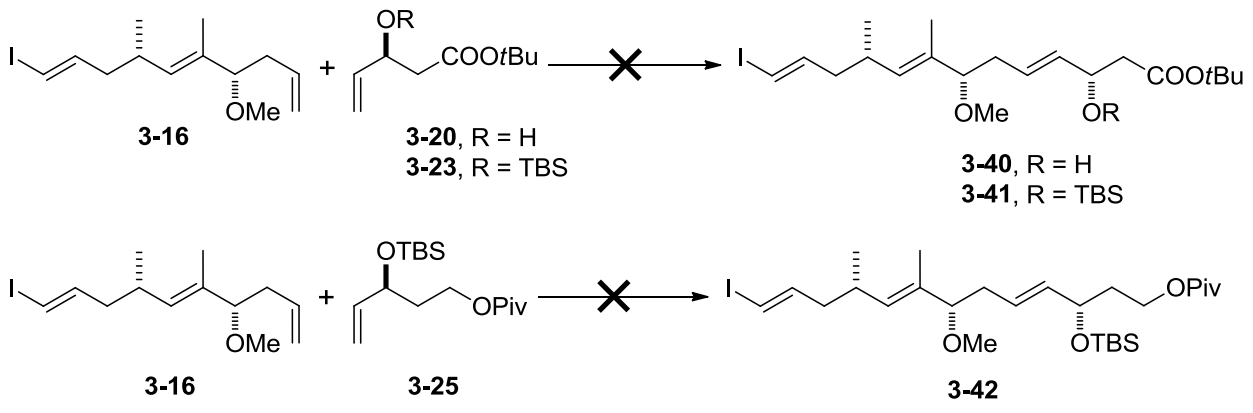
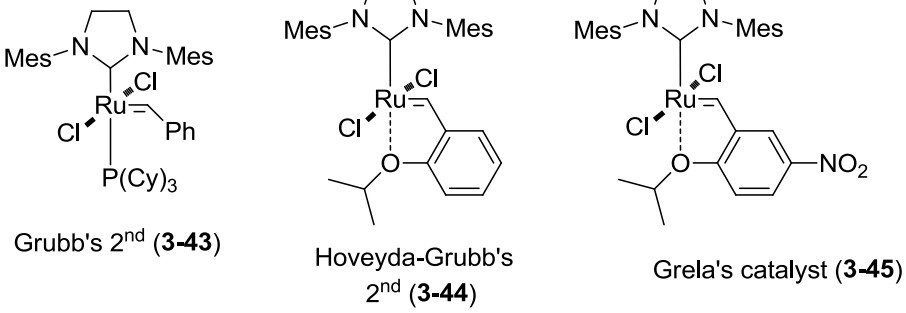


Figure 35. Mechanistic pathway for Brown allylation via six membered transition state.

12.2 Cross metathesis approach for the synthesis of fragment C1-C13

Recently, Oishi et al. demonstrated that a highly chemoselective cross metathesis reaction[81] between allyl alcohols can be successfully achieved in presence of an iodo-olefin.[155] They found that the vinyl iodide remains intact in the course of the cross metathesis reaction. Taking an advantage of this strategy, protected allyl alcohol **3-23** and homoallyl alcohol **3-16** were subjected to the cross metathesis reaction in dry and degassed CH_2Cl_2 as well as toluene simultaneously under various conditions (**Scheme 47**) but none of the Grubb's 2nd **3-43**,[156] Hoveyda-Grubb's 2nd **3-44**,[157] or Grela catalyst **3-45**[158] offered the successful transformation. This was in agreement with the result reported by Yamamoto et al. during their stereocontrolled synthesis of the AB ring segment of ciguatoxin.[159] In this regard, they had better success after the deprotection of the homoallylic alcohol. In addition to this report, some other successful examples of cross metathesis between unprotected allyl alcohols and its metathesis partners have been reported.[160]



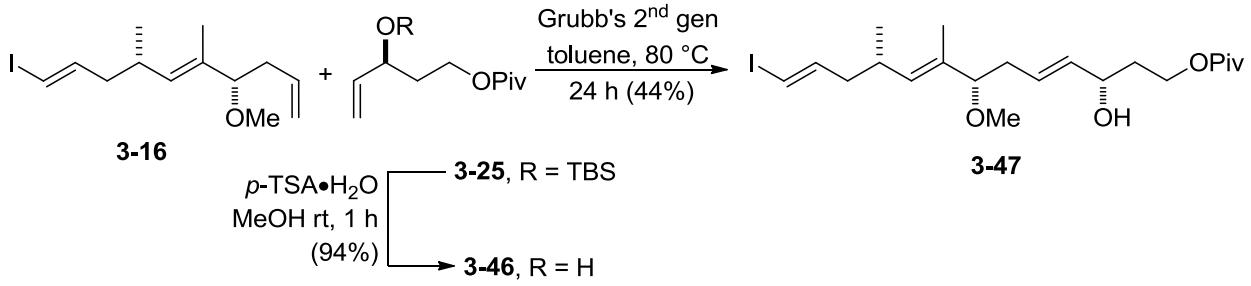


catalyst	conditions	result
3-43	CH_2Cl_2, rt to reflux	no reaction
	toluene, rt to 80 °C	
3-44	CH_2Cl_2, rt to reflux	no reaction
	toluene, rt to 80 °C	
3-45	CH_2Cl_2, rt to reflux	no reaction
	toluene, rt to 80 °C	

Scheme 47. Attempts made for cross metathesis reaction.

Accordingly, we altered silyl ether **3-25** to the free hydroxyl analogue **3-46** using *p*-TSA•H_2O in methanol in 94% yield. Modified analogue **3-46** and fragment **3-16** were then subjected to the cross metathesis reaction with Grubb's 2nd catalyst in CH_2Cl_2 at room temperature but no progress in the reaction was observed while after refluxing the reaction mixture for longer period (~ 24 h), only slow conversion was experienced. After changing the solvent to toluene and upon heating (80 °C), TLC showed conversion to a new spot and LC-MS confirmed the desired cross metathesis product **3-47**. After 24 h, nearly complete consumption of **3-16** was observed on TLC without formation of notable side products. Purification by flash chromatography provided

metathesis product **3-47** (**Scheme 48**) in 44% yield as colorless oil. After this successful reaction between free allyl alcohol **3-16** and homoallyl alcohol **3-46**, we attempted cross metathesis between free hydroxyl ester **3-20** with homoallyl alcohol **3-16** in presence of Grubb's 2nd catalyst but surprisingly the allylic alcohol **3-20** did not engage in the cross metathesis reaction with **3-16** (**Scheme 47**). Only the cross metathesis reaction between **3-16** and pivaloyl analogue **3-46** worked best in this case.



Scheme 48. Synthesis of a fragment **3-47** by cross metathesis reaction.

The exact mass of the building block **3-47** was determined by high resolution mass spectroscopy (HRMS). The optical rotation of the final building block was measured as $[\alpha]_D^{22}$ = +11.72 in $CHCl_3$ (*c* 1.0). ^{1}H NMR, ^{13}C NMR, H–H and C–H correlation spectra confirmed the structure of the building block **3-47**. **Figure 36** confirms the formation of the C4-C5 double bond in addition to the presence of double bonds at C12-C13 and C8-C9.

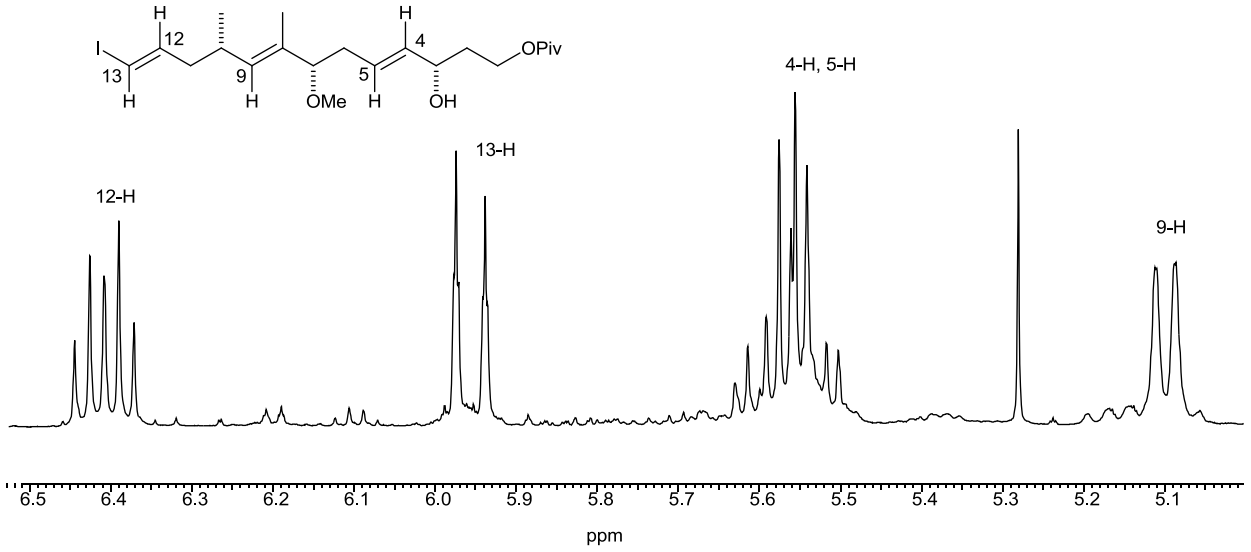
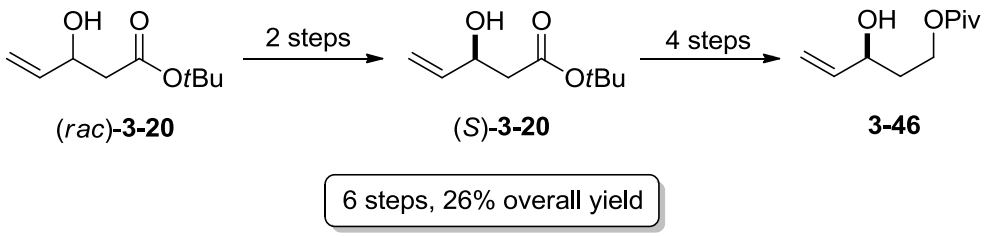


Figure 36. Down field region of fragment **3-47** in the ^{1}H NMR spectrum.

After the successful and efficient synthesis of fragment **3-47**, further research towards the total synthesis of biselyngbyaside is under progress in our group.

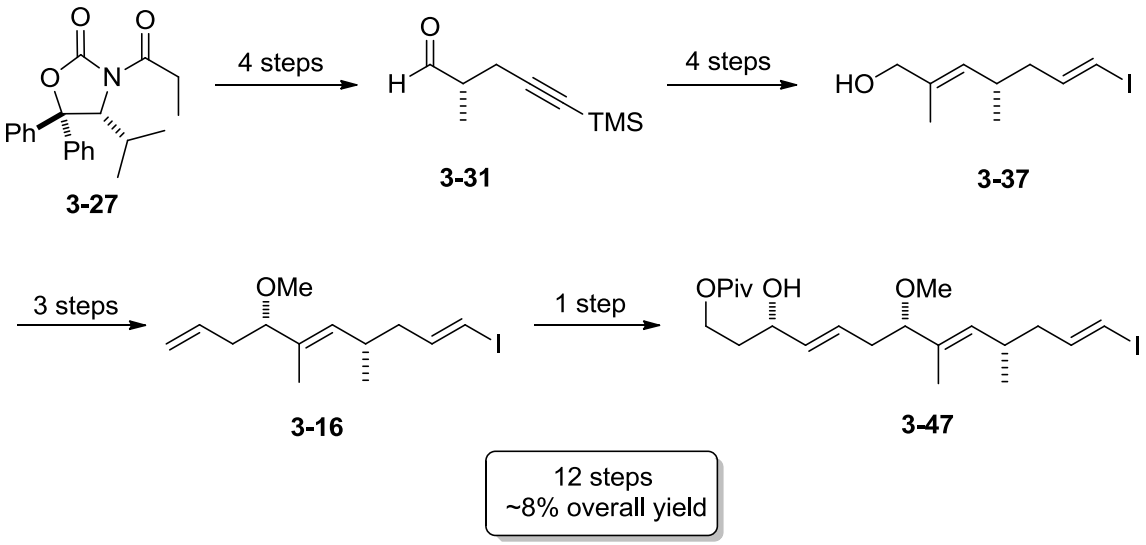
13 Conclusion III

In conclusion, we have developed a practical route for the synthesis of fragment **3-47** towards the total synthesis of the novel macrolide biselyngbyaside. The key features of this strategy include synthesis of fragment **3-46** (**Scheme 49**) via a very efficient and highly enantioselective enzyme catalyzed resolution in overall 26% yield over 6 steps starting from racemic alcohol (*rac*)-**3-20**.



Scheme 49. Summary of the synthesis of fragment **3-46**.

Fragment **3-32** was synthesized from *N*-propionyl derivative of Seebach auxiliary **3-26** including a stereoselective propargylation, reductive cleavage to the corresponding alcohol and Swern oxidation as key intermediate steps. Further chain extension was achieved by Wittig reaction using a stabilized Wittig ylide followed by DIBAL-H mediated reduction of corresponding ethyl ester. Hydrozirconation of the triple bond using in situ generated Schwartz reagent followed by iodination provided alcohol **3-37** as advanced precursor. Further, Dess-Martin oxidation, allylation using Brown conditions, and afterward methylation by Me_3OBF_4 and proton sponge of this hydroxyl group produced intermediate **3-16** as a precursor for cross metathesis reaction. After the crucial cross metathesis reaction, the longest chain yielded fragment **3-47** in around 8% overall yield (**Scheme 50**).



3-27 **3-31** **3-37** **3-16** **3-47**

Scheme 50. Summary of the synthesis of final fragment **3-47**.

14 Experimental Section

14.1 General Remarks

14.1.1 Chemicals and working techniques

The chemicals were purchased from the firms Acros, Aldrich, Applichem, Fluka, Lancaster, Merck, STREM and TCI. All reagents were obtained from commercial suppliers, and were used without further purification unless otherwise stated. All solvents were distilled and/or dried prior to use by standard methodology except for those, which were reagent grade. The applied petroleum ether fraction had a boiling point of 40–60 °C. Anhydrous solvents were obtained as follows: THF, diethyl ether and toluene by distillation from sodium and benzophenone; dichloromethane and chloroform by distillation from calcium hydride; acetone by distillation from phosphorous pentoxide. Absolute triethylamine and pyridine and diisopropylethylamine were distilled over calcium hydride prior to use. Unless and otherwise mentioned, all the reactions were carried out under a nitrogen atmosphere and the reaction flasks were pre-dried with a heat gun under high vacuum. All the chemicals, which were air or water sensitive, were stored under inert atmosphere. Compounds that are not described in the experimental part were synthesized according to the literature.

14.1.2 NMR-spectroscopy

All the spectra were measured on a Bruker Avance 400 spectrometer, which operates at 400 MHz for ^{1}H and 100 MHz for ^{13}C nuclei, respectively. ^{1}H (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded at 295 K either in $CDCl_3$ or CD_3OD; chemical shifts are calibrated to the residual proton and carbon resonance of the solvent: $CDCl_3$ (δ_H = 7.25 ppm, δ_C = 77.0 ppm), CD_3OD (δ_H = 3.30 ppm, δ_C = 49.0 ppm). Data are reported as follows: chemical shift (multiplicity: s = singlet, d = doublet, t = triplet, ap. sept = apperent septet, dd = doublet of doublet, ddd = doublet of doublet of doublet, dddd = doublet of doublet of doublet of doublet, m

= multiplet, br = broadened, J = coupling constant (Hz), integration, peak assignment in italic form).

14.1.3 Mass Spectrometry

Mass spectra were recorded on a Finnigan Triple-Stage-Quadrupol Spectrometer (TSQ-70) from Finnigan-Mat. High-resolution mass spectra were measured on a modified AMD Intectra MAT 711 A from the same company. The used mass spectrometric ionization methods were electron-impact (EI), fast-atom bombardment (FAB) or field desorption (FD). HR-FT-ICR mass spectra were measured on an APEX 2 spectrometer from Bruker Daltonic with electrospray ionization method (ESI). Analytical HPLC-MS: HP 1100 Series connected with an ESI MS detector Agilent G1946C, positive mode with fragmentor voltage of 40 eV, column: Nucleosil 100–5, C-18 HD, 5 mm, 70 × 3 mm Machery Nagel, eluent: NaCl solution (5 mM)/acetonitrile, gradient: 0/10/15/17/20 min with 20/80/80/99/99% acetonitrile, flow: 0.6 mL min^{-1}. High resolution mass (HRMS) are reported as follows: (ESI): calcd mass for the related compound followed by found mass.

14.1.4 Polarimetry

Optical rotations were measured on a Perkin-Elmer Polarimeter Model 341. They are reported as follows: $[\alpha]^{temperature}$ D (concentration, solvent). The unit of *c* is g/100 mL. Anhydrous CH_2Cl_2, $CHCl_3$ or MeOH was used as a solvent. For the measurement the sodium D line = 589 nm was used.

14.1.5 Melting Points

Melting points were determined with a Büchi Melting point B-540 apparatus and were not corrected.

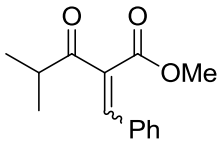
14.1.6 Chromatographic Methods

Flash chromatography was performed using flash silica gel (40-63 μm, 230-400 mesh ASTM) from Macherey-Nagel. Gas chromatography was performed on a CHROMPACK CP 9000 using a flame ionization detector, and carrier gas H_2. Chiral gas chromatographic analyses were carried out on 13.5 m × 0.25 mm column filled with deactivated fused silica with 30% 6-TBDMS-2,3-diacetyl-β-cyclodextrin in PS 086 (d_f = 0.13 μm) and carrier gas H_2 at 50 kPa and 30 °C. For GC-MS coupled chromatography, a GC-system series 6890 with an injector series 7683 and MS-detector series 5973 from Hewlett Packard was used, with EI method, and carrier gas He. Analytical HPLC was performed on a Hewlett Packard HP 1100 system. Analytical thin layer chromatography (TLC) was performed on precoated with silica gel 60 F_{254} plates (Merck) or Polygram Sil G/UV_{254} (Macherey Nagel). The compounds were visualized by UV_{254} light and the chromatography plates were developed with an aqueous solution of molybdophosphorous acid or an aqueous solution of potassium permanganate (heating with the hot gun). For preparation of the molybdate solution 20 g ammonium molybdate [$(NH_4)_6Mo_7O_{24}\cdot 4H_2O$] and 0.4 g $Ce(SO_4)_2\cdot 4H_2O$ were dissolved in 400 mL of 10% H_2SO_4. The potassium permanganate solution was prepared from 2.5 g $KMnO_4$ and 12.5 g Na_2CO_3 in 250 mL H_2O.

14.2 Experimental Procedures

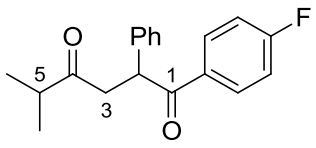
All the experimental procedures are arranged to reflect the synthetic sequences shown in the Schemes.

2-Benzylidene-4-methyl-3-oxo-pentanoic acid methyl ester (1-25)[41]



A solution of 4-methyl-3-oxo-pentanoic acid methyl ester **1-55** (10 g, 9.9 mL, 69.4 mmol), benzaldehyde (7.74 mL, 76.3 mmol), piperidine (0.4 mL) and acetic acid (1.2 mL) was refluxed in toluene (50 mL) to remove water as azeotrope. After 12 h, the reaction was cooled to room temperature, diluted with diethyl ether (150 mL) and washed with 1N HCl (70 mL) followed by saturated $NaHCO_3$ solution (70 mL) and saturated NaCl solution. The organic layer was separated, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude concentrate was purified by flash chromatography (EtOAc/petroleum ether, 1:9) to yield unsaturated ester **1-25** (13.1 g, 81%) as orange-red oil as mixture of two isomers. $\mathbf{R_f}$ = 0.28 (ethyl acetate/petrol ether, 1:9); **^{1}H NMR** (400 MHz, $CDCl_3$): *major isomer* δ = 1.07 (d, 6H, *J* = 6.8 Hz, $CH(CH_3)_2$), 2.55 (ap. septet, 1H, *J* = 6.8 Hz, $CH(CH_3)_2$), 3.72 (s, 3H, OCH_3), 7.31 (m, 5H, Ar), 7.48 (s, 1H, C=CHPh); *minor isomer* δ = 0.94 (d, 6H, *J* = 6.8 Hz, $CH(CH_3)_2$), 2.55 (sept, 1H, *J* = 6.8 Hz, $CH(CH_3)_2$), 3.71 (s, 3H, OCH_3), 7.29 (m, 5H, Ar), 7.69 (s, 1H, C=CHPh); **^{13}C NMR** (100 MHz, $CDCl_3$): *major isomer* δ = 17.9 ($CH(CH_3)_2$), 36.1 ($CH(CH_3)_2$), 52.4 (OCH_3), 128.8 (2CH, Ar), 129.7 (2CH, Ar), 130.4 (CH, Ar), 133.1 (C, Ar), 133.3 (*C*=CHPh), 141.5 (C=*C*HPh), 165.3 (C=O, ester), 209.2 (C=O, ketone); *minor isomer* δ = 18.9 ($CH(CH_3)_2$), 36.1 ($CH(CH_3)_2$), 52.5 (OCH_3), 128.8 (2CH, Ar), 129.4 (2CH, Ar), 130.6 (CH, Ar), 133.2 (*C*=CHPh), 140.9 (C=*C*HPh), 168.5 (C=O, ester), 201.0 (C=O, ketone).

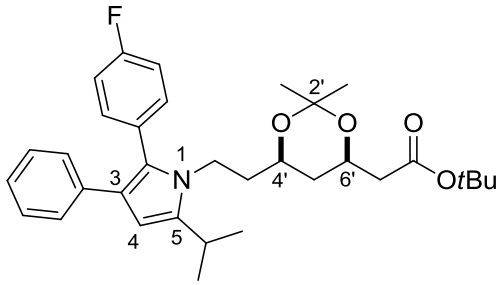
1-(4-Fluoro-phenyl)-5-methyl-2-phenyl-hexane-1,4-dione (1-27)[41]



A mixture of 2-benzylidene-4-methyl-3-oxo-pentanoic acid methyl ester **1-25** (13.1 g, 56.4 mmol), 4-fluorobenzaldehyde (6.35 mL, 59.2 mmol), thiazolium salt 3-benzyl-5-(2-

hydroxyethyl)-4-methyl-1,3-thiazolium chloride (2.42 g, 15 mol%) as catalyst and Et_3N (8 mL) was heated at 70 °C for 24 h. The reaction mixture was diluted with diethyl ether (100 mL), washed with water (100 mL), 1N HCl solution (75 mL) followed by saturated $NaHCO_3$ (75 mL) and saturated NaCl solution. The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was subjected for vigorous stirring in a mixture of THF (100 mL) and 3N NaOH (50 mL) solution. After 15 h, the reaction mixture was acidified with 2N HCl solution to pH~5, and extracted with diethyl ether (3 × 100 mL). The combined organic layers were washed with saturated $NaHCO_3$ solution and saturated NaCl solution, dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The crude product was purified by flash chromatography (EtOAc/petroleum ether, 1:9) to provide 1,4-diketone **1-27** (9.82 g, 59%, over 2 steps) as colorless thick oil. $\mathbf{R_f}$ = 0.32 (EtOAc/petroleum ether, 1:9); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.05 (d, *J* = 6.8 Hz, 3H, 6-H), 1.10 (d, *J* = 6.8 Hz, 3H, 5-CH_3), 2.62 (ap. septet, *J* = 6.8 Hz, 1H, 5-H), 2.78 (dd, *J* = 17.9, 3.8 Hz, 1H, 3-H), 3.62 (dd, *J* = 17.9, 10.1 Hz, 1H, 5-H), 5.06 (dd, *J* = 10.1, 3.8 Hz, 1H, 4-H), 7.01 (m, 2H, Ar-H), 7.15–7.31 (m, 5H, Ar-H), 7.98 (m, 2H, Ar-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 18.1 (5-CH_3, C-6), 40.7 (C-4), 45.1 (C-3), 48.5 (C-2), 115.5 (d, J_{CF} = 22.0 Hz, 2CH, Ar), 127.3 (CH, Ar), 128.0 (2CH, Ar), 129.2 (2CH, Ar), 131.4 (d, J_{CF} = 9.5 Hz, 2CH, Ar), 132.7 (d, J_{CF} = 2.9 Hz , 2CH, Ar), 138.4 (C, Ar), 165.5 (d, J_{CF} = 254.0 Hz, C, Ar), 197.4 (C-4), 212.7 (C-1).

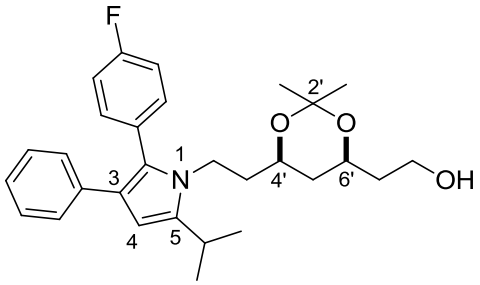
tert-Butyl 2-((4*R*,6*R*)-6-(2-(2-(4-fluorophenyl)-5-isopropyl-3-phenyl-1*H*-pyrrol-1-yl)ethyl)-2,2-dimethyl-1,3-dioxan-4-yl)acetate (1-68)



A mixture of 1,4-diketone **1-27** (800 mg, 2.9 mmol), amine **1-41** (873 mg, 2.9 mmol) and *p*-toluenesulphonic acid (111 mg, 20 mol%) as catalyst in toluene (10 mL) was refluxed for 5 days in a Dean-Stark apparatus to remove water as azeotrope. After completion of reaction the

mixture was cooled to room temperature and diluted with diethyl ether (20 mL) and washed with saturated $NaHCO_3$ (10 mL) solution followed by saturated NaCl solution. The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The crude mixture was purified by flash chromatography (diethyl ether/petroleum ether, 1:30) to afford pyrrole **1-68** (950 mg, 85%) as white solid, **m.p.** 45–55 °C. $\mathbf{R_f}$ = 0.35 (diethyl ether/petroleum ether, 1:20); $\mathbf{[\alpha]_D^{20}}$ = +10.5 (*c* 1, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 0.98 (dd *J* = 11.6, 11.9 Hz, 1H, 5'-H), 1.23–1.38 (m, 13H, 5'-H, $CH(CH_3)_2$, 2'-CH_3), 1.42 (s, 9H, $C(CH_3)_3$), 1.46–1.60 (m, 2H, NCH_2CH_2), 2.14–2.26 (m, 1H, CH_2CO_2tBu), 2.28–2.40 (m, 1H, CH_2CO_2tBu), 3.00 (ap. septet, *J* = 6.6 Hz, 1H, $CH(CH_3)_2$), 3.52–3.64 (m, 1H, 4'-H), 3.73–3.88 (m, 1H, NCH_2CH_2), 3.96 (ddd, *J* = 14.1, 9.1, 4.8 Hz, 1H, NCH_2CH_2), 4.05–4.18 (m, 1H, 6'-H), 6.18 (s, 1H, 4-H, pyrrole), 6.98–7.18 (m, 6H, Ar-H), 7.22–7.40 (m, 3H, Ar-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 19.6 (2'-CH_3), 23.3 ($CH(CH_3)_2$), 23.7 ($CH(CH_3)_2$), 25.5 ($CH(CH_3)_2$), 28.1 ($C(CH_3)_3$), 29.9 (2'-CH_3), 36.0 (C-5'), 37.8 (NCH_2CH_2), 39.7 (NCH_2CH_2), 42.5 (CH_2CO_2tBu), 65.9 (C-6'), 66.1 (C-4'), 80.6 ($C(CH_3)_3$), 98.6 (C-2'), 103.4 (C-4, pyrrole), 115.6 (d, J_{CF} = 21.2 Hz, 2CH, Ar), 122.1 (C, Ar), 124.6, 124.8 (CH, Ar), 127.3, 127.5 (2CH, Ar), 127.8 (C, Ar), 127.9, 127.9 (2CH, Ar), 128.5, 129.1, 129.8 (d, J_{CF} = 3.7 Hz, C, Ar), 131.2, 132.9 (d, J_{CF} = 8.0 Hz, 2CH, Ar), 133.9, 136.5 (C, Ar), 136.7, 140.3, 140.4 (C, Ar), 162.2 (d, J_{CF} = 247.4 Hz, C, Ar) 170.2 (CO_2tBu); **HRMS** (ESI): $[M+Na]^+$ calcd for $C_{33}H_{42}FNO_4Na$ 558.29901, found 558.299441.

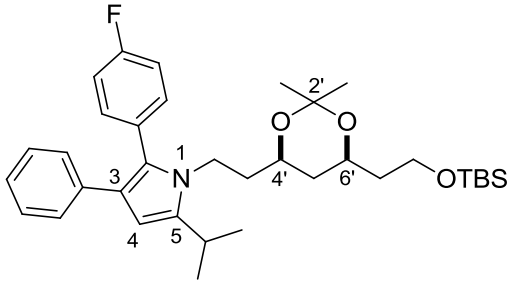
2-((4*S*,6*R*)-6-(2-(2-(4-Fluorophenyl)-5-isopropyl-3-phenyl-1*H*-pyrrol-1-yl)ethyl)-2,2-dimethyl-1,3-dioxan-4-yl)ethanol (1-71)



A solution of pyrrole **1-68** (1.07 g, 2.0 mmol) in absolute CH_2Cl_2 (15 mL) was cooled to −40 °C then DIBAL-H (6 mL, 6.0 mmol, 1M in hexane) was added dropwise slowly over 15 min using a syringe pump and the mixture stirred 10 min at same temperature. The reaction mixture was

allowed to stir at room temperature for overnight and the mixture was cooled to 0 °C, then methanol was added slowly followed by addition of saturated NH_4Cl solution. The mixture was stirred vigorously at room temperature for 1 h before it was extracted with CH_2Cl_2 (3 × 60 mL). The combined organic layers were washed with saturated NaCl solution, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (ethyl acetate/petroleum ether, 3:7) afforded corresponding alcohol **1-71** (723 mg, 78%) as white solid, **m.p.** 45–60 °C. $\mathbf{R_f}$ = 0.22 (EtOAc/petroleum ether, 3:7); $\mathbf{[\alpha]_D^{20}}$ = +0.6, (*c* 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, CD_3OD): δ = 0.89 (dd, *J* = 12.9, 11.6 Hz, 1H, 5'-H), 1.18 (dt, *J* = 12.9, 2.3 Hz, 1H, 5'-H), 1.26 (s, 3H, 2'-CH_3), 1.29 (d, *J* = 6.8 Hz, 3H, CH(C*H*$_3$)), 1.32 (d, *J* = 6.6 Hz, 3H, CH(C*H*$_3$)$_2$), 1.34 (s, 3H, 2'-CH_3), 1.41–1.63 (m, 4H, NCH_2CH_2, CH_2CH_2OH), 3.04 (ap. sept, *J* = 6.8 Hz, 1H, C*H*(CH$_3$)$_2$), 3.51–3.61 (m, 2H, CH_2CH_2OH), 3.63 (dddd, *J* = 11.8, 9.3, 5.0, 2.3 Hz, 1H, 4'-H), 3.80–4.04 (m, 3H, 6'-H, NCH_2CH_2), 6.11 (s, 1H, 4-H, pyrrole), 6.95–7.42 (m, 9H, Ar-H); **^{13}C NMR** (100 MHz, CD_3OD): δ = 20.1 (2'-CH_3), 23.7 (CH(*C*H$_3$)$_2$), 24.2 (CH(*C*H$_3$)$_2$), 26.7 (*C*H(CH$_3$)$_2$), 30.5 (2'-CH_3), 37.8 (C-5'), 39.0 (NCH_2CH_2), 40.1 (CH_2CH_2OH), 40.7 (NCH_2CH_2), 59.0 (CH_2CH_2OH), 67.3 (C-6'), 67.6 (C-4'), 99.7 (C-2'), 104.3 (C-4, pyrrole), 116.5 (d, J_{CF} = 21.9 Hz, CH, Ar), 123.5 (C, Ar), 125.6, 125.7 (CH, Ar), 128.5 (2CH, Ar), 128.9 (2CH, Ar), 129.2 (C, Ar), 129.7, 130.4 (C, Ar), 131.6 (d, J_{CF} = 3.7 Hz, C, Ar), 132.5, 134.4 (d, J_{CF} = 8.8 Hz, 2CH, Ar), 135.5, 138.3 (C, Ar), 138.4, 141.5, 141.6 (C, Ar), 163.7 (d, J_{CF} = 245.9 Hz, C, Ar); **HRMS** (ESI): $[M+Na]^+$ calcd for $C_{36}H_{41}FN_2O_4Na$ 488.25714, found 488.2569987.

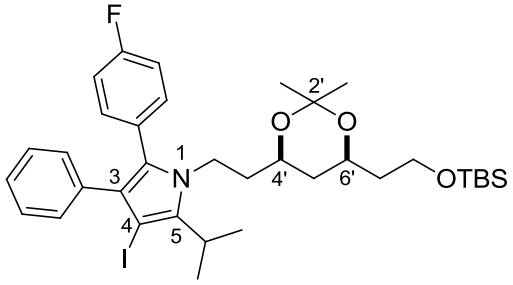
1-(2-((4*R*,6*S*)-6-(2-((*tert*-Butyldimethylsilyl)oxy)ethyl)-2,2-dimethyl-1,3-dioxan-4-yl)ethyl)-2-(4-fluorophenyl)-5-isopropyl-3-phenyl-1*H*-pyrrole (1-72)



To a stirred solution of alcohol **1-71** (640 mg, 1.3 mmol) in DMF (10 mL), at room temperature was added imidazole (187 mg, 2.7 mmol) followed by the addition of *tert*-butyldimethylsilyl

chloride (227 mg, 1.512 mmol) in one portion and the reaction mixture was allowed to stir at room temperature for 1 h. The reaction was diluted with diethyl ether (30 mL) and washed with saturated $NaHCO_3$ solution (10 mL), water (3 × 50 mL), and saturated NaCl solution. The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude residue was purified by flash chromatography (diethyl ether/petroleum ether, 1:10) to isolate protected alcohol **1-72** (781 mg, 98%) as pale yellow oil. $\mathbf{R_f}$ = 0.37 (diethyl ether/petroleum ether, 1:20); $\mathbf{[\alpha]_D^{20}}$ = +1.89, (*c* 1, $CHCl_3$); **^{1}H NMR** (400 MHz, CD_3OD): δ = 0.03 (s, 6H, 2 $Si(CH_3)_2$), 0.88 (s, 9H, $SiC(CH_3)_3$), 0.82–0.94 (m, 1H, 5'-H), 1.13–1.19 (m, 1H, 5'-H), 1.25 (s, 3H, 2'-CH_3), 1.27–1.32 (m, 6H, $CH(CH_3)_2$), 1.32 (s, 3H, 2'-CH_3), 1.40–1.55 (m, 4H, NCH_2CH_2, CH_2CH_2OTBS), 3.04 (m, 1H, $CH(CH_3)_2$), 3.52–3.71 (m, 3H, CH_2CH_2OTBS, 4'-H), 3.80–4.02 (m, 3H, NCH_2CH_2, 6'-H), 6.11 (s, 1H, 4-H, pyrrole), 6.93–7.13 (m, 6H, Ar-H), 7.21–7.39 (m, 3H, Ar-H); **^{13}C NMR** (100 MHz, CD_3OD): δ = −5.22 ($Si(CH_3)_2$), 19.1 ($SiC(CH_3)_3$), 20.2 (2'-CH_3), 23.7 ($CH(CH_3)_2$), 24.2 ($CH(CH_3)_2$), 26.4 ($C(CH_3)_3$), 26.7 ($CH(CH_3)_2$), 30.5 (2'-CH_3), 37.9 (C-5'), 39.0 (NCH_2CH_2), 40.4 (CH_2CH_2OTBS), 40.8 (NCH_2CH_2), 59.9 (CH_2CH_2OTBS), 66.8 (C-6'), 67.7 (C-4'), 99.7 (C-2'), 104.4 (C, Ar), 116.5 (d, J_{CF} = 21.2 Hz, 2CH, Ar), 123.3, 123.6 (C, Ar), 125.6, 125.8 (CH, Ar), 128.5, 128.6 (2CH, Ar), 128.9, 128.9 (2CH, Ar), 129.2 (C, Ar), 129.7, 130.5, 131.6 (d, J_{CF} = 3.7 Hz, C, Ar), 132.5, 134.4 (d, J_{CF} = 8.0 Hz, 2CH, Ar), 135.5, 138.3 (C, Ar), 138.4, 141.5, 141.6 (C, Ar), 163.7 (d, J_{CF} = 245.9 Hz, C, Ar); **HRMS** (ESI): $[M+Na]^+$ calcd for $C_{35}H_{50}FNO_3SiNa$ 602.34362, found 602.344059.

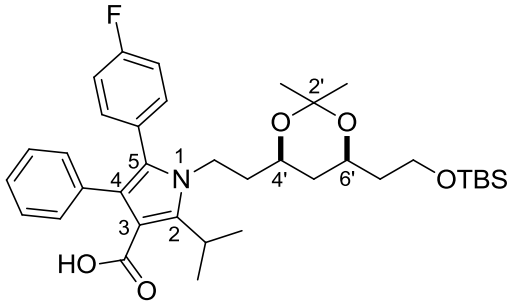
1-(2-((4*R*,6*S*)-6-(2-((*tert*-Butyldimethylsilyl)oxy)ethyl)-2,2-dimethyl-1,3-dioxan-4-yl)ethyl)-2-(4-fluorophenyl)-4-iodo-5-isopropyl-3-phenyl-1*H*-pyrrole (1-73)



N-iodosuccinimide (353 mg, 1.6 mmol) was added to a solution of pyrrole **1-72** (758 mg, 1.3 mmol) in DMF (8 mL) and the mixture was stirred at room temperature. After 1 h, the mixture

was diluted with diethyl ether, washed with saturated $NaHCO_3$ solution, water (3 × 15 mL), 10% aq $Na_2S_2O_3$ solution and saturated NaCl solution. The organic layer was dried over Na_2SO_4, filtered and concentrated under vacuum. Purification by flash chromatography (ethyl acetate/petroleum ether, 1:9) furnished iodopyrrole **1-73** (835 mg, 91%) as brown colored oil. $\mathbf{R_f}$ = 0.24 (petroleum ether/EtOAc, 1:9); $\mathbf{[\alpha]_D^{21}}$ = −2.96 (*c* 1, $CHCl_3$); **^{1}H NMR** (400 MHz, CD_3OD): δ = 0.04 (s, 6H, $Si(CH_3)_2$), 0.88 (s, 9H, $SiC(CH_3)_3$); 0.92 (ddd, *J* = 12.6, 11.6, 11.6 Hz, 1H, 5'-H), 1.20 (ddd, *J* = 12.9, 2.5, 2.3 Hz, 1H, 5'-H), 1.23 (s, 3H, 2'-CH_3), 1.32 (s, 3H, 2'-CH_3), 1.47 (d, *J* = 7.1 Hz, 3H, $CH(CH_3)_2$), 1.48 (d, *J* = 7.1 Hz, 3H, $CH(CH_3)_2$), 1.50–1.65 (m, 4H, NCH_2CH_2, CH_2CH_2OTBS), 3.37 (ap. septet, 1H, *J* = 7.1 Hz, $CH(CH_3)_2$), 3.57–3.72 (m, 3H, 4'-H, CH_2CH_2OTBS), 3.84–3.98 (m, 2H, NCH_2CH_2, 6'-H), 4.01–4.13 (m, 1H, NCH_2CH_2), 6.96–7.29 (m, 9H, Ar-H); **^{13}C NMR** (100 MHz, CD_3OD): δ = −5.2 ($Si(CH_3)_2$), 19.1 ($SiC(CH_3)_3$), 20.2 (2'-CH_3), 21.8 ($CH(CH_3)_2$), 26.4 ($CH(CH_3)_2$), 30.5 (2'-CH_3), 37.8 (C-5'), 39.5 (NCH_2CH_2), 40.4 (CH_2CH_2OTBS), 42.2 (NCH_2CH_2), 59.9 (CH_2CH_2OTBS), 64.0 (C-4, pyrrole), 66.7 (C-6'), 68.0 (C-4'), 99.7 (C-2'), 116.0 (d, J_{CF} = 22.0 Hz, 2CH, Ar), 126.9, 127.0 (CH, Ar), 128.2 (C, Ar), 128.4, 128.5 (2CH, Ar), 129.2, 130.4 (d, J_{CF} = 3.7 Hz, C, Ar), 131.2 (C, Ar), 132.1 (2CH, Ar), 132.2, 132.6, 134.5 (d, J_{CF} = 8.0 Hz, 2CH, Ar), 137.7 (C, Ar), 137.8, 138.1, 138.2 (C, Ar), 163.6 (d, J_{CF} = 245.9 Hz, C, Ar); **HRMS** (ESI): $[M+Na]^+$ calcd for $C_{35}H_{49}FINO_3SiNa$ 728.24026, found 728.240251.

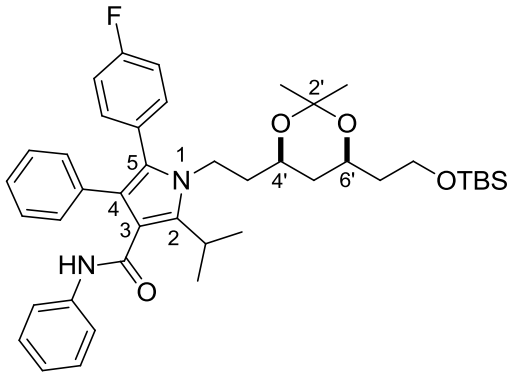
1-(2-((4*R*,6*S*)-6-(2-((*tert*-Butyldimethylsilyl)oxy)ethyl)-2,2-dimethyl-1,3-dioxan-4-yl)ethyl)-5-(4-fluorophenyl)-2-isopropyl-4-phenyl-1*H*-pyrrole-3-carboxylic acid (1-74)



To a cooled (−78 °C) solution of iodo pyrrole **1-73** (820 mg, 1.2 mmol) in THF (10 mL) *t*-BuLi (1.0 mL, 2.4 mmol, 1.6M in pentane) was added dropwise slowly. The resulting yellow colored

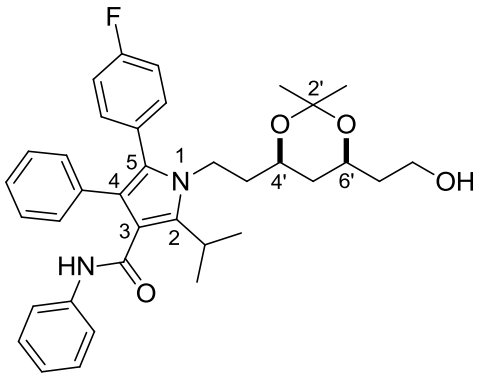
solution was stirred for additional 15 min and excess of solid CO_2 was added to the reaction mixture. After 10 min of stirring at −78 °C, the reaction was allowed to warm to the room temperature to evaporate excess of CO_2. The reaction was quenched by addition of saturated NH_4Cl solution and the mixture was extracted with ether (3 × 30 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, concentrated under vacuum and the residue was purified by flash chromatography (ethyl acetate/petroleum ether, 2:8) to afford acid **1-74** (580 mg, 80%) as white solid, **m.p.** 127–129 °C. $\mathbf{R_f}$ = 0.28 (EtOAc/petroleum ether, 1:4); **^{1}H NMR** (400 MHz, CD_3OD): δ = 0.04 (s, 6H, $Si(CH_3)_2$), 0.89 (s, 9H, $SiC(CH_3)_3$), 0.93 (dd, *J* = 12.6, 11.6, Hz, 1H, 5'-H), 1.20–1.27 (m, 1H, 5'-H), 1.24 (s, 3H, 2'-CH_3), 1.33 (s, 3H, 2'-CH_3), 1.46 (d, *J* = 7.1 Hz, 3H, $CH(CH_3)_2$), 1.47 (d. *J* = 7.3 Hz, 3H, $CH(CH_3)_2$), 1.49–1.56 (m, 2H, CH_2CH_2OTBS), 1.57–1.67 (m, 2H, NCH_2CH_2), 3.52–3.74 (m, 4H, $CH(CH_3)_2$, 4'-H, CH_2CH_2OTBS), 3.82–4.00 (m, 2H, NCH_2CH_2, 6'-H), 4.01–4.12 (m, 1H, NCH_2CH_2), 6.96–7.11 (m, 6H, Ar-H), 7.13–7.21 (m, 2H, Ar-H), 7.24–7.31 (m, 1H, Ar-H); **^{13}C NMR** (100 MHz, CD_3OD): δ = −5.2 ($Si(CH_3)_2$), 19.1 ($SiC(CH_3)_3$), 20.2 (2'-CH_3), 21.6 ($CH(CH_3)_2$), 21.7 ($CH(CH_3)_2$), 26.4 ($SiC(CH_3)_3$), 27.2 ($CH(CH_3)_2$), 30.5 (2'-CH_3), 37.8 (C-5'), 39.2 (NCH_2CH_2), 40.4 (CH_2CH_2OTBS), 41.9 (NCH_2CH_2), 59.9 (CH_2CH_2OTBS), 66.7 (C-6'), 67.9 (C-4'), 99.7 (C-2'), 112.6 (C-4, pyrrole), 116.0 (d, J_{CF} = 21.9 Hz, 2CH, Ar), 125.9 (C, Ar), 126.5, 126.6 (CH, Ar), 128.1, 128.2 (2CH, Ar), 128.7, 129.2, 130.0 (d, J_{CF} = 3.7 Hz, C, Ar), 130.8, 131.6 (2CH, Ar), 132.0 (C, Ar), 132.9, 133.9 (C, Ar), 134.9 (d, J_{CF} = 8.0 Hz, 2CH, Ar), 137.3 (C, Ar), 137.4, 143.3, 143.5 (C, Ar), 163.7 (d, J_{CF} = 246.6 Hz, C, Ar), 170.4 (COO).

1-(2-((4*R*,6*S*)-6-(2-((*tert*-Butyldimethylsilyl)oxy)ethyl)-2,2-dimethyl-1,3-dioxan-4-yl)ethyl)-5-(4-fluorophenyl)-2-isopropyl-*N*,4-diphenyl-1*H*-pyrrole-3-carboxamide (1-75)



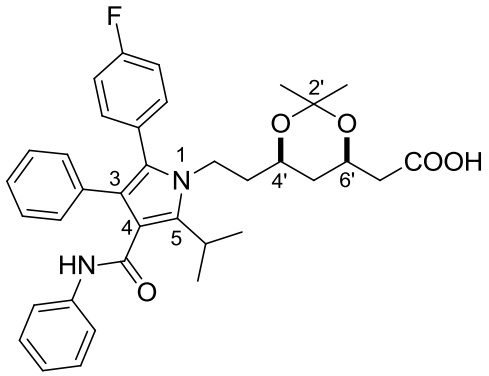
A solution of acid **1-74** (100 mg, 0.16 mmol) and aniline (16 μL, 0.18 mmol) in CH_2Cl_2 (5 mL) was cooled to 0 °C (salt-ice bath) then diisopropylethylamine (82 µL, 0.48 mmol) was added followed by subsequent addition of PyBrOP (112 mg, 0.24 mmol). The reaction mixture was allowed to stir at room temperature for overnight (~ 12 h). The reaction was diluted with CH_2Cl_2, washed with saturated $NaHCO_3$ solution (5 mL), water (5 mL), and saturated NaCl solution. The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. Purification by flash chromatography (ethyl acetate/petroleum ether, 1:9) provided amide **1-75** (110 mg, 98%) as yellow colored oil. $\mathbf{R_f}$ = 0.43 (EtOAc/petroleum ether, 1:4); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 0.02 (s, 6H, $Si(CH_3)_2$), 0.87 (s, 9H, $SiC(CH_3)_3$), 1.03 (ddd, *J* = 12.6, 11.6, 11.6 Hz, 1H, 5'-H), 1.26 (ddd, *J* = 12.6, 2.8, 2.0 Hz, 1H, 5'-H), 1.30 (s, 3H, 2'-CH_3), 1.34 (s, 3H, 2'-CH_3), 1.53 (d, *J* = 7.1 Hz, 6H, $CH(CH_3)_2$), 1.49–1.76 (m, 4H, NCH_2CH_2, CH_2CH_2OTBS), 3.52–3.73 (m, 4H, $CH(CH_3)_2$, 4'-H, CH_2CH_2OTBS), 3.76–3.98 (m, 2H, NCH_2CH_2, 6'-H), 4.03–4.12 (m, 1H, NCH_2CH_2), 6.85 (s, 1H, CONH), 6.93–7.32 (m, 14H, Ar-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = −5.4 ($Si(CH_3)_2$), 18.2 ($SiC(CH_3)_3$), 19.8 (2'-CH_3), 21.5 ($CH(CH_3)_2$), 21.7 ($CH(CH_3)_2$), 25.9 ($C(CH_3)_3$), 26.1 ($CH(CH_3)_2$), 30.1 (2'-CH_3), 36.6 (C-6'), 38.2 (NCH_2CH_2), 38.3 (CH_2CH_2OTBS), 40.9 (NCH_2CH_2), 58.7 (CH_2CH_2OTBS), 65.3 (C-6'), 66.6 (C-4'), 98.4 (C-2'), 115.3 (d, J_{CF} = 22.0 Hz, 2CH, Ar), 119.5, 121.7, 123.5, 126.4, 126.5, 127.6, 125.2 (d, J_{CF} = 3.7 Hz, C, Ar), 128.3, 128.6, 128.8, 130.5, 130.5, 132.3, 133.2 (d, J_{CF} = 8.0 Hz, CH, Ar), 134.6, 134.8, 138.4, 141.5, 162.2 (d, J_{CF} = 247.4 Hz, C, Ar); **HRMS** (ESI): $[M+Na]^+$ calcd for $C_{42}H_{55}FN_2O_4SiNa$ 721.38073, found 721.380841.

5-(4-Fluorophenyl)-1-(2-((4*R*,6*S*)-6-(2-hydroxyethyl)-2,2-dimethyl-1,3-dioxan-4-yl)ethyl)-2-isopropyl-*N*,4-diphenyl-1*H*-pyrrole-3-carboxamide (1-76)



Silyl ether **1-75** (180 mg, 0.26 mmol) was treated with 0.2M solution of tetra *n*-butyl ammonium fluoride in THF (5 mL) at room temperature for overnight (~12 h). The reaction was diluted with ethyl acetate, washed with water and saturated NaCl solution, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (petroleum ether/EtOAc, 7:3) to furnish alcohol **1-76** (150 mg, 97%) as white amorphous solid, **m.p.** 75–85 °C. $\mathbf{R_f}$ = 0.26 (EtOAc/petroleum ether, 1:1); $\mathbf{[\alpha]_D^{20}}$ = −6.0, (*c* 1, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.11 (ddd, *J* = 12.6, 11.4, 11.1 Hz, 1H, 5'-H), 1.21 (ddd, *J* = 12.6, 2.9, 2.3 Hz, 1H, 5'-H), 1.31(s, 3H, 2'-CH_3), 1.36 (s, 3H, 2'-CH_3), 1.52 (d, *J* = 7.1 Hz, 6H, CH(CH_3)$_2$), 1.52–1.65 (m, 4H, NCH_2CH_2, CH_2CH_2OH), 3.56 (ap. septet, *J* = 7.1 Hz, 1H, CH(CH_3)$_2$), 3.62–3.88 (m, 4H, NCH_2CH_2, 4'-H, CH_2CH_2OH), 3.96–4.13 (m, 2H, NCH_2CH_2, 6'-H), 6.85 (s, 1H, NH), 6.92–7.10 (m, 5H, Ar-H), 7.11–7.23 (m, 9H, Ar-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 19.9 (2'-CH_3), 21.6 (CH(CH_3)$_2$), 21.7 (CH(CH_3)$_2$), 26.1 (CH(CH_3)$_2$), 30.4 (2'-CH_3), 37.7 (5'-H), 39.4 (NCH_2CH_2), 40.1 (CH_2CH_2OH), 41.4 (NCH_2CH_2), 59.0 (CH_2CH_2OH), 67.3 (C-6'), 67.8 (C-4'), 99.8 (C-2'), 115.2 (d, J_{CF} = 22.0 Hz, CH, aryl), 115.3 (C, aryl), 119.5 (CH, aryl), 121.8 (C, aryl), 123.5 (CH, aryl), 126.5 (CH, aryl), 128.3 (d, J_{CF} = 3.7 Hz, C, aryl), 128.3 (CH, aryl), 128.7 (CH, aryl), 128.7 (C, aryl), 130.5 (CH, aryl), 133.2 (d, J_{CF} = 8.0 Hz, CH, aryl), 134.6 (C, aryl), 138.3 (C, aryl), 141.5 (C, aryl), 162.2 (d, J_{CF} = 248.1 Hz, C, aryl), 164.8 (CONH); **HRMS** (ESI): $[M+Na]^+$ calcd for $C_{36}H_{41}FN_2O_4Na$ 607.29426, found 607.294097.

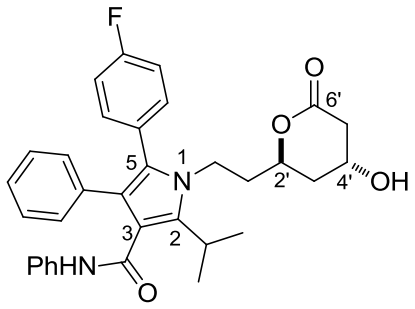
2-((4*R*,6*R*)-6-(2-(2-(4-Fluorophenyl)-5-isopropyl-3-phenyl-4-(phenylcarbamoyl)-1*H*-pyrrol-1-yl)ethyl)-2,2-dimethyl-1,3-dioxan-4-yl)acetic acid (1-44)



To a cooled (salt-ice bath) solution of alcohol **1-76** (147 mg, 0.25 mmol) in CH_2Cl_2 (10 mL) Dess-Martin periodinane (145 mg, 0.50 mmol) was added and the reaction mixture was stirred at room temperature for 1 h. Then a mixture (1:1) of saturated $NaHCO_3$ and 0.1M $Na_2S_2O_3$ solution (4 mL) was added into the reaction mixture and this mixture was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with saturated NaCl solution, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude aldehyde was dissolved in *t*-butanol (10 mL) and 2-methyl-2-butene (1.2 mL) was added. The mixture was cooled in an ice bath and a solution of $NaH_2PO_4 \bullet 2H_2O$ (224 mg, 1.4 mmol) and $NaClO_2$ (43 mg, 0.48 mmol) in H_2O (10 mL) was added dropwise and the reaction mixture was allowed to stir at room temperature for 6 h. The mixture was diluted with saturated NaCl solution (5 mL) and extracted with ethyl acetate (3 × 15 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, concentrated and purified by flash chromatography (CH_2Cl_2/methanol/AcOH, 25:1:0.1) to furnish acid **1-44** (144 mg, 96%). $\mathbf{R_f}$ = 0.33 (CH_2Cl_2/methanol/AcOH, 25:1:0.1); $\mathbf{[\alpha]_D^{20}}$ = +5.0 (*c* 1, $CHCl_3$); **^{1}H NMR** (400 MHz, CD_3OD): δ = 0.92–1.03 (m, 1H, 5'-H), 1.25 (s, 3H, 2'-CH_3), 1.28–1.35 (m, 1H, 5'-H), 1.37 (s, 3H, 2'-CH_3), 1.46 (d, *J* = 7.1 Hz, 3H, CH(CH_3)$_2$), 1.47 (d, *J* = 6.8 Hz, 3H, CH(CH_3)$_2$), 1.57–1.69 (m, 2H, NCH_2CH_2), 2.24–2.39 (m, 2H, CH_2COOH), 3.31–3.40 (m, 1H, CH(CH$_3$)$_2$), 3.70–3.82 (m, 1H, 4'-H), 3.85–3.94 (m, 1H, NCH_2CH_2), 4.03–4.12 (m, 1H, NCH_2CH_2), 4.16–4.26 (m, 1H, 6'-H), 7.00–7.36 (m, 14H, Ar-H); **^{13}C NMR** (100 MHz, CD_3OD): δ = 20.0 (2'-CH_3), 22.6 (CH(CH_3)$_2$), 22.8 (CH(CH_3)$_2$), 27.6 (CH(CH$_3$)$_2$), 30.3 (2'-CH_3), 37.1 (NCH_2CH_2), 39.4 (C-5'), 41.4 (CH_2COOH), 42.2 (NCH_2CH_2), 67.2 (C-6'), 67.7 (C-4'), 100.0 (C-2'), 116.3 (d, J_{CF} = 22.0 Hz, 2CH, Ar), 118.1 (C, Ar), 121.5

(2CH, Ar), 123.3 (C, Ar), 125.1 (CH, Ar), 126.9 (CH, Ar), 128.8, 128.9 (2CH, Ar), 129.0, 129.5, 129.6 (2CH, Ar), 129.6, 129.8 (d, J_{CF} = 2.9 Hz, C, Ar), 131.0 (2CH, Ar), 131.8, 132.8, 134.8 (d, J_{CF} = 8.0 Hz, 2CH, Ar), 136.3 (C, Ar), 139.0 (C, Ar), 139.8 (C, Ar), 163.8 (d, J_{CF} = 246.6 Hz, Ar-C), 169.5 (C=O, amide), 174.6 (C=O, acid); **HRMS** (ESI): $[M+Na]^+$ calcd for $C_{36}H_{39}FN_2O_5Na$ 621.27352, found 621.27359.

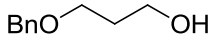
5-(4-Fluorophenyl)-1-(2-((2*R*,4*R*)-4-hydroxy-6-oxotetrahydro-2*H*-pyran-2-yl)ethyl)-2-isopropyl-*N*,4-diphenyl-1*H*-pyrrole-3-carboxamide (1-31)



A solution of acid **1-44** (52 mg, 0.08 mmol) and a catalytic amount of camphorsulphonic acid in THF (2 mL) was stirred at room temperature for 3 h. The mixture was concentrated and the residue purified by flash chromatography (diethyl ether/methanol, 50:1) to afford atorvastatin lactone **1-31** (38 mg, 90%) as white solid. It was recrystallized from petroleum ether/ethyl acetate to give an amorphous white solid, **m.p.** 150–155 °C {ref.[57] 160–162 °C}. $\mathbf{R_f}$ = 0.25 (diethyl ether/methanol, 50:1); $\mathbf{[\alpha]_D^{20}}$ = +25.5 (*c* 0.2, $CHCl_3$) {ref.[47] $[\alpha]_D$ +26.05 (*c* 1, $CHCl_3$), ref.[41] $[\alpha]_D^{23}$ +24.53 (0.53% in $CHCl_3$)}; **^{1}H NMR** (400 MHz, CD_3OD): δ = 1.50–1.53 (m, 6H, $CH(CH_3)_2$), 1.55–1.60 (m, 1H, 5'-H), 1.65–1.77 (m, 2H, NCH_2CH_2, 3'-H), 1.82–1.91 (m, 1H, NCH_2CH_2), 2.37 (s, 1H, OH), 2.49–2.66 (m, 2H, 5'-H), 3.48–3.58 (m, 1H, $CH(CH_3)_2$), 3.98–4.10 (m, 1H, NCH_2CH_2), 4.16–4.29 (m, 2H, NCH_2CH_2, 4'-H), 4.44–4.54 (m, 1H, 2'-H), 6.87 (s, 1H, NH, amide), 6.95–7.33 (m, 14H, Ar-H); **^{13}C NMR** (100 MHz, CD_3OD): δ = 21.7 ($CH(CH_3)_2$), 22.0 ($CH(CH_3)_2$), 26.1 ($CH(CH_3)_2$), 35.6 (C-3'), 37.0, 37.1 (NCH_2CH_2), 38.5 (C-5'), 40.7 (NCH_2CH_2), 62.4 (C-4'), 73.0 (C-2'), 73.1, 115.6 (d, J_{CF} = 22.0 Hz, 2CH, Ar), 115.6 (C-4, Ar), 119.7 (2CH, Ar), 122.1 (C, Ar), 123.7 (CH, Ar), 126.6 (CH, Ar), 128.0 (d, J_{CF} = 2.9 Hz, C, Ar), 128.3, 128.4 (2CH, Ar), 128.4, 128.7 (2CH, Ar), 128.7 (C, Ar), 130.4 (2CH, Ar),

131.3, 133.1 (d, J_{CF} = 8.1 Hz, 2CH, Ar), 134.4 (C, Ar), 138.2 (C, Ar), 141.3 (C, Ar), 162.3 (d, J_{CF} = 248.8 Hz, C, Ar), 164.9 (C=O, amide), 169.4 (C=O, lactone); **HRMS** (ESI): $[M+Na]^+$ calcd for $C_{33}H_{33}FN_2O_4Na$ 563.23166, found 563.23154.

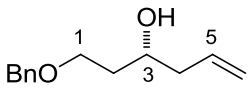
3-(Benzyloxy)propan-1-ol (1-87)[161]



1-87

A mixture of NaH (2.89 g, 72.3 mmol) in dry THF (300 mL) and DMSO (75 mL) was stirred for 30 min at room temperature. Then, 1,3-propanediol (5.0 g, 65.7 mmol) in THF (250 mL) was added dropwise over 30 min followed by slow dropwise addition of benzyl bromide (8.60 mL, 72.3 mmol) in THF (140 mL). Subsequently, tetra *n*-butylammonium iodide (12.1 g, 32.6 mmol) was added in one portion. The reaction mixture was stirred at 60 °C for ~12 h (overnight). After cooling, water (500 mL) was added to the reaction mixture which was then extracted with diethyl ether (3 × 150 mL). The combined organic layers were washed with saturated NaCl solution, dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 7:3) to give alcohol **1-87** (7.02 g, 64%) as pale yellow colored oil. $\mathbf{R_f}$ = 0.26 (petroleum ether/EtOAc, 7:3); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.86 (pentet, *J* = 5.8 Hz, 2H, $BnOCH_2CH_2$), 2.43 (s, 1H, CH_2OH), 3.65 (t, *J* = 5.8 Hz, 2H, CH_2CH_2OH), 3.77 (t, *J* = 5.8 Hz, 2H, $BnOCH_2$), 4.52 (s, 2H, OCH_2Ph), 7.26–7.37, (m, 5H, phenyl); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 32.0 (CH_2), 61.7 (CH_2OH), 69.3 ($BnOCH_2$), 73.2 ($PhCH_2$), 127.6 (2CH, phenyl), 127.7 (C, phenyl), 128.4 (2CH, phenyl), 136.0 (CH, phenyl).

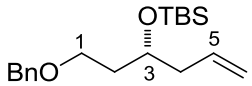
(*R*)-1-(Benzyloxy)hex-5-en-3-ol (1-88)



In an oven dried screw cap glass bottle, a mixture of alcohol **1-87** (4.0 g, 24.1 mmol), allyl acetate (5.24 mL, 48.1 mmol), $[Ir(cod)Cl]_2$, (404 mg, 2.5 mol%), (*R*)-(+)-Cl,MeO-BIPHEP, (784

mg, 5 mol%), 4-Cl-3-NO_2-benzoic acid (485 mg, 2.4 mmol), and Cs_2CO_3 (1.57 g, 4.8 mmol) in THF (130 mL) was heated at 120 °C under nitrogen for 20 h. The reaction mixture was adsorbed on silica gel and purified by flash chromatography (EtOAc/petroleum ether, 1:4) to furnish alcohol **1-88** (4.50 g, 90%, 92% *ee* by Mosher ester method) as colorless oil. $\mathbf{R_f}$ = 0.34 (EtOAc/petroleum ether, 1:4); $\mathbf{[\alpha]_D^{20}}$ = +2.7 (*c* 1.0, $CHCl_3$); (Ref.[162] +2.2, *c* 1.0, $CHCl_3$; Ref.[59b] +2.08, *c* 1.25, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.73–1.81 (m, 2H, 2-H), 2.21–2.28 (m, 2H, 4-H), 2.60 (s, br, 1H, OH), 3.61–3.67 (m, 1H, 1-H), 3.71 (ddd, *J* = 9.3, 5.3, 5.3 Hz, 1H, 1-H), 3.83–3.92 (m, 1H, 3-H), 4.52 (s, 2H, OC*H*$_2$Ph), 5.06–5.14 (m, 2H, Ar-H), 5.78–5.88 (dddd, *J* = 16.9, 10.1, 7.3, 7.1 Hz, 1H, 5-H), 7.26–7.36 (m, 5H, Ar-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 35.8 (C-2), 41.9 (C-4), 68.9 (C-1), 70.3 (C-3), 73.3 (O*C*H$_2$Ph), 117.5 (C-6), 127.6 (2CH, phenyl), 127.7 (CH, phenyl), 128.4 (2CH, phenyl), 134.8 (C-5), 137.9 (C, phenyl).

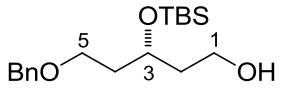
(*R*)-((1-(Benzyloxy)hex-5-en-3-yl)oxy)(*tert*-butyl)dimethylsilane (1-89)



A mixture of alcohol **1-88** (877 mg, 4.3 mmol), imidazole (723 mg, 10.6 mmol) and TBSCl (1.28 g, 8.5 mmol) in DMF (5 mL) was stirred overnight at 50 °C. Thereafter, water (10 mL) was added and the mixture extracted with diethyl ether (3 × 30 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (diethyl ether/petroleum ether, 1:50) to give silyl ether **1-89** (1.27 g, 91%) as colorless oil. $\mathbf{R_f}$ = 0.34 (petroleum ether/diethyl ether, 50:1); $\mathbf{[\alpha]_D^{20}}$ = −17.3 (*c* 1, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 0.03 (s, 3H, Si(CH_3)$_2$), 0.05 (s, 3H, Si(CH_3)$_2$), 0.87 (s, 9H, SiC(CH_3)$_3$), 1.69 (dddd, *J* = 13.9, 7.8, 6.1, 6.1 Hz, 1H, 2-H), 1.79 (dddd, *J* = 13.9, 7.1, 7.1, 4.5 Hz, 1H, 2-H), 2.16–2.29 (m, 2H, 4-H), 3.52–3.55 (m, 2H, 1-H), 3.85–3.93 (m, 1H, 3-H), 4.43 (d, *J* = 11.9 Hz, 1H, OC*H*$_2$Ph), 4.49 (d, *J* = 11.9 Hz, 1H, OC*H*$_2$Ph), 4.99–5.06 (m, 2H, 6-H), 5.80 (dddd, *J* = 17.7, 9.6, 7.3, 7.3 Hz, 1H, 5-H), 7.26–7.36 (m, 5H, Ar-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = −4.4 (Si(CH_3)$_2$), 18.1 (Si*C*(CH_3)$_3$), 25.8 (SiC(*C*H$_3$)$_3$), 36.7 (C-2), 42.3 (C-4), 67.0 (C-1), 68.9 (C-3), 72.9 (O*C*H$_2$Ph), 116.9 (C-6), 127.5 (CH, phenyl), 127.6 (2CH, phenyl), 128.3

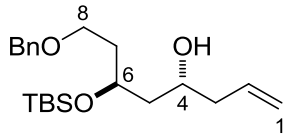
(2CH, phenyl), 134.9 (C-5), 138.5 (C, phenyl); **HRMS** (ESI): $[M+Na]^+$ calcd for $C_{19}H_{32}O_2SiNa$ 343.20638, found 343.206354.

(*R*)-5-(Benzyloxy)-3-((*tert*-butyldimethylsilyl)oxy)pentan-1-ol (1-90)



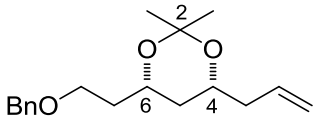
To a solution of alcohol **1-89** (5.61 g, 17.5 mmol) in methanol (74 mL, 0.15M), 2-3 drops of Sudan-III (1% in methanol) were added as an indicator resulting in a pink colored solution. The mixture was cooled to −80 °C and ozone gas was bubbled through the solution until it turned pink to colorless (about 50 min). Residual O_3 was removed by passing nitrogen through the reaction (about 5 min). Thereafter, $NaBH_4$ (6.62 g, 175 mmol) was added and the reaction mixture was slowly allowed to reach room temperature, with the flask kept in the cooling bath. Water (30 mL) was added and the mixture was concentrated to ~50 mL on a rotary evaporator before it was extracted with ethyl acetate (3 × 120 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 5:1) to provide alcohol **1-90** (5.52 g, 97%) as colorless oil. $\mathbf{R_f}$ = 0.24 (petroleum ether/EtOAc, 5:1); $\mathbf{[\alpha]_D^{20}}$ = +3.2 (*c* 1, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 0.07 (s, 3H, $Si(CH_3)_2$), 0.09 (s, 3H, $Si(CH_3)_2$), 0.88 (s, 9H, $SiC(CH_3)_3$), 1.61–1.70 (m, 1H, 4-H), 1.76–1.92 (m, 3H, 4-H, 2-H), 2.18 (br, s, 1H, OH), 3.52 (t, *J* = 6.3 Hz, 2H, 5-H), 3.67–3.73 (ddd, *J* = 11.1, 5.5, 5.3 Hz, 1H, 1-H), 3.78–3.84 (dddd, *J* = 8.3, 6.6, 4.5, 3.8 Hz, 1H, 3-H), 4.10 (ddd, *J* = 10.9, 5.8, 5.8 Hz, 2H, 1-H), 4.43 (d, *J* = 11.9 Hz, 1H, OCH_2Ph), 4.49 (d, *J* = 11.9 Hz, 1H, OCH_2Ph); 7.26–7.36 (m, 5H, Ar-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = −4.7 ($Si(CH_3)_2$), 17.9 ($SiC(CH_3)_3$), 25.8 ($SiC(CH_3)_3$), 36.7 (C-4), 38.3 (C-2), 60.0 (C-1), 66.8 (C-5), 69.0 (C-3), 73.0 ($PhCH_2O$), 127.6 (CH, phenyl), 127.7 (2CH, phenyl); 128.4 (2CH, phenyl), 138.3 (C, phenyl); **HRMS** (ESI): $[M+Na]^+$ calcd for $C_{18}H_{32}O_3SiNa$ 347.20129, found 347.201340.

(4*R*,6*S*)-8-(Benzyloxy)-6-((*tert*-butyldimethylsilyl)oxy)oct-1-en-4-ol (1-91)



An oven dried screw cap glass bottle was charged under nitrogen with alcohol **1-90** (5.90 g, 18.2 mmol), $[Ir(cod)Cl]_2$ (305 mg, 0.46 mmol), (*R*)-(+)-Cl,MeO-BIPHEP (592 mg, 0.9 mmol), Cs_2CO_3 (1.18 g, 1.2 mmol) and 4-Cl-3-NO_2-benzoic acid (366 mg, 1.8 mmol) in THF (100 mL) to which allyl acetate (3.64 g, 36.4 mmol) was added. The mixture was heated at 100 °C for 40 h. The mixture was cooled and then adsorbed on silica gel (about 40 g) and purified by flash chromatography (petroleum ether/EtOAc, 6:1) to afford homoallyl alcohol **1-91** (5.26 g, 93%) as colorless oil. $\mathbf{R_f}$ = 0.38 (petroleum ether/EtOAc, 6:1); $\mathbf{[\alpha]_D^{20}}$ = +14.2 (*c* 1, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 0.08 (s, 3H, $Si(CH_3)_2$), 0.10 (s, 3H, $Si(CH_3)_2$), 0.88 (s, 9H, $SiC(CH_3)_3$), 1.55 (ddd, *J* = 14.4, 8.6, 8.3 Hz, 1H, 5-H), 1.65 (ddd, *J* = 14.4, 5.1, 2.8 Hz, 1H, 5-H), 1.76–1.91 (m, 2H, 7-H), 2.18–2.22 (m, 2H, 3-H), 3.51 (dd, *J* = 6.6, 6.3 Hz, 2H, 8-H), 3.77–3.80 (dddd, *J* = 11.6, 6.1, 3.3, 2.8 Hz, 1H, 4-H), 4.04–4.10 (dddd, *J* = 11.6, 6.3, 3.5, 1.5 Hz, 1H, 6-H), 4.44 (d, *J* = 11.9 Hz, 1H, OCH_2Ph), 4.48 (d, *J* = 11.9 Hz, 1H, OCH_2Ph), 5.05–5.13 (m, 2H, 1-H), 5.80 (dddd, *J* =16.9, 10.6, 7.3, 7.1 Hz, 1H, 2-H), 7.26–7.35 (m, 5H, Ar-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = −4.6 ($Si(CH_3)_2$), −4.3 ($Si(CH_3)_2$), 17.9 ($SiC(CH_3)_3$), 25.8 ($SiC(CH_3)_3$), 37.7 (C-7), 42.2 (C-5), 42.8 (C-3), 66.6 (C-4), 69.7 (C-8), 70.2 (C-6), 73.0 (OCH_2Ph), 117.5 (C-1), 127.6 (CH, Ar), 127.6 (2CH, Ar), 128.4 (2CH, Ar), 134.8 (C-2), 138.3 (C, Ar); **HRMS** (ESI): $[M+Na]^+$ calcd for $C_{21}H_{37}O_3SiNa$ 387.23259, found 387.232566.

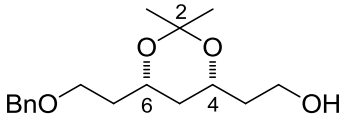
(4*R*,6*S*)-4-Allyl-6-(2-(benzyloxy)ethyl)-2,2-dimethyl-1,3-dioxane (1-92)



A mixture of *p*-toluenesulphonic acid monohydrate (268 mg, 1.51 mmol) and alcohol **1-91** (5.49 g, 15.1 mmol) in methanol (150 mL) was stirred at room temperature for 1 h to complete the

deprotection (TLC control). The reaction mixture was concentrated on the rotary evaporator to about 50 mL before it was diluted with 2,2-dimethoxypropane (150 mL, 602 mmol) and stirred for further 30 min at room temperature. The reaction mixture was concentrated in vacuo, the residue diluted with CH_2Cl_2 (500 mL), then washed with saturated $NaHCO_3$ solution (150 mL) and saturated NaCl solution (150 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 19:1) to yield acetal **1-92** (3.51 g, 80%) as colorless oil. $\mathbf{R_f}$ = 0.48 (petroleum ether/ethyl acetate, 17:3); $\mathbf{[\alpha]_D^{20}}$ = −9.0 (*c* 1, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.15 (ddd, *J* = 12.9, 11.6, 11.6 Hz, 1H, 5-H), 1.37 (s, 3H, 2-CH_3), 1.42 (s, 3H, 2-CH_3), 1.50 (ddd, *J* = 12.9, 2.5, 2.5 Hz, 1H, 5-H), 1.66–1.82 (m, 2H, BnOCH$_2$C*H*$_2$), 2.09–2.18 (m, 1H, C*H*$_2$CH=CH$_2$), 2.25–2.34 (m, 1H, CH$_2$C*H*=CH$_2$), 3.48–3.62 (m, 2H, BnOC*H*$_2$CH$_2$), 3.86 (dddd, *J* = 13.9, 6.3, 3.8, 2.5 Hz, 1H, 6-H), 4.02 (dddd, *J* = 11.6, 7.3, 5.1, 2.5 Hz, 1H, 4-H), 4.48 (d, *J* = 12.1 Hz, 1H, PhCH$_2$O), 4.52 (d, *J* = 12.1 Hz, 1H, PhCH$_2$O), 5.01–5.11 (m, 2H, CH$_2$CH=C*H*$_2$), 5.79 (dddd, *J* = 17.8, 10.4, 7.3, 6.6 Hz, 1H, CH$_2$CH=C*H*$_2$), 7.23–7.37 (m, 5H, Ar-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 19.8 (2-CH_3), 30.2 (2-CH_3), 36.5 (BnO*C*H$_2$CH$_2$), 36.6 (C-5), 40.8 (*C*H$_2$CH=CH$_2$), 66.0 (C-4), 66.2 (BnO*C*H$_2$CH$_2$), 68.6 (C-6), 73.0 (O*C*H$_2$Ph), 98.5 (C-2), 117.2 (CH$_2$CH=*C*H$_2$), 127.5 (CH, phenyl), 127.6 (2CH, phenyl), 128.3 (2CH, phenyl), 134.2 (CH$_2$*C*H=CH$_2$), 138.5 (C, phenyl); **HRMS** (ESI): $[M+Na]^+$ calcd for $C_{18}H_{26}O_3Na$ 313.17742, found 313.177541.

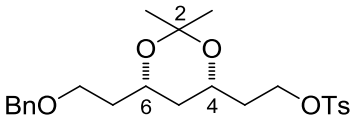
2-((4*R*,6*S*)-6-(2-(Benzyloxy)ethyl)-2,2-dimethyl-1,3-dioxan-4-yl)ethanol (1-93)



A solution of alkene **1-92** (2.69 g, 9.3 mmol) in methanol/CH_2Cl_2 (7:3, 100 mL), containing 4-5 drops of Sudan III (1% in methanol) was cooled to −80 °C followed by bubbling ozone through the solution for 1 h until it became colorless. Residual O_3 was removed by bubbling nitrogen through the solution. Thereafter, $NaBH_4$ (3.50 g, 92.6 mmol) was added and the reaction mixture allowed to reach room temperature with the flask kept in the cooling bath. Now, H_2O (40 mL) was added and the mixture concentrated to ~50 mL before it was extracted with ethyl acetate (3

× 60 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 1:1) to furnish primary alcohol **1-93** (2.60 g, 97%) as colorless oil. $\mathbf{R_f}$ = 0.2 (petroleum ether/ethyl acetate, 1:1); $\mathbf{[\alpha]_D^{20}}$ = −10.0 (*c* 1, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.28 (ddd, *J* = 12.9, 11.6, 11.6 Hz, 1H, 5-H), 1.36 (s, 3H, 2-CH_3), 1.44 (s, 3H, 2-CH_3), 1.45 (ddd, *J* = 12.9, 2.5, 2.5 Hz, 1H, 5-H), 1.64–1.80 (m, 4H, OBnCH_2CH_2, CH_2CH_2OH), 2.16 (s, 1H, OH), 3.49–3.67 (m, 2H, BnOCH_2CH_2), 3.71–3.84 (m, 2H, CH_2CH_2OH), 4.02–4.18 (m, 2H, 4-H, 6-H), 4.48 (d, *J* = 12.1 Hz, 1H, OCH_2Ph), 4.52 (d, *J* = 12.1 Hz, 1H, OCH_2Ph), 7.27–736 (m, 5H, Ar-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 19.9 (2-CH_3), 30.2 (2-CH_3), 36.4 (BnOCH_2CH_2), 36.7 (C-5), 38.0 (CH_2CH_2OH), 60.9 (OBnCH_2CH_2), 65.9 (C-4), 66.0 (CH_2CH_2OH), 69.4 (C-6), 73.0 (OCH_2Ph), 98.6 (C-2), 127.5 (CH, Ar), 127.6 (2CH, Ar), 128.3 (2CH, Ar), 138.5 (C, Ar); **HRMS** (ESI): $[M+Na]^+$ calcd for $C_{17}H_{26}O_4Na$ 317.17233, found 317.172357.

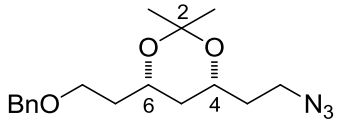
2-((4*R*,6*S*)-6-(2-(Benzyloxy)ethyl)-2,2-dimethyl-1,3-dioxan-4-yl)ethyl 4-methylbenzenesulfonate (1-94)[163]



To a mixture of alcohol **1-93** (2.60 g, 8.8 mmol), Et_3N (3.69 mL, 26.5 mmol), DMAP (323 mg, 2.7 mmol) in CH_2Cl_2 (50 mL), *p*-toluenesulphonyl chloride (3.37 g, 17.7 mmol) was added in one portion at 0 °C. The reaction mixture was allowed to stir overnight at room temperature before it was diluted with CH_2Cl_2 (70 mL), washed with saturated $NaHCO_3$ solution (50 mL) and saturated NaCl solution (50 mL) then dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 4:1) to afford tosylate **1-94** (3.42 g, 86%) as colorless oil. $\mathbf{R_f}$ = 0.28 (petroleum ether/EtOAc, 4:1); $\mathbf{[\alpha]_D^{20}}$ = −2.6 (*c* 1, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.09 (ddd, *J* = 12.6, 11.6, 11.6 Hz, 1H, 5-H), 1.27 (s, 3H, 2-CH_3), 1.31 (s, 3H, 2-CH_3), 1.39 (ddd, *J* = 12.6, 2.5, 2.5 Hz, 1H, 5-H), 1.63–1.81 (m, 4H, OBnCH_2CH_2, CH_2CH_2OTs), 2.43 (s, 3H, CH_3, tosyl), 3.46–3.59 (m, 2H, OBnCH_2CH_2), 3.90 (dddd, *J* = 11.4, 7.6, 4.8, 3.0 Hz, 1H, 4-H), 3.98 (dddd, *J* = 11.4, 7.6, 5.0, 2.8 Hz, 1H, 6-H), 4.07

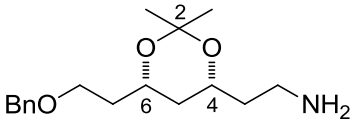
(ddd, *J* = 9.8, 5.3, 4.5 Hz, 1H, CH_2CH_2OTs), 4.11–4.20 (m, 1H, CH_2CH_2OTs), 4.44 (d, *J* = 12.1 Hz, 1H, OCH_2Ph), 4.47 (d, *J* = 12.1 Hz, 1H, OCH_2Ph), 7.23–7.37 (m, 7H, Ar-H), 7.78 (d, *J* = 8.3 Hz, 2H, Ar-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 19.7 (2-CH_3), 21.6 (CH_3, tosyl), 30.0 (2-CH_3), 35.5 (CH_2CH_2OTs), 36.5 (C-5), 36.8 ($OBnCH_2CH_2$), 64.9 (C-4), 65.9 (C-6), 66.1 ($OBnCH_2CH_2$), 66.8 (CH_2CH_2OTs), 73.0 (OCH_2Ph), 98.6 (C-2), 127.6 (CH, phenyl), 127.6 (2CH, phenyl), 127.9 (2CH, tosyl), 128.4 (2CH, phenyl), 129.8 (2CH, tosyl), 133.1 (C, tosyl), 138.5 (C, phenyl), 144.7 (C, tosyl); **HRMS** (ESI): $[M+Na]^+$ calcd for $C_{24}H_{32}O_6SNa$ 471.18118, found 471.181152.

(4*R*,6*S*)-4-(2-Azidoethyl)-6-(2-(benzyloxy)ethyl)-2,2-dimethyl-1,3-dioxane (1-95)[163]



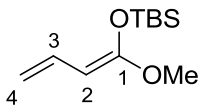
A mixture of tosylate **1-94** (3.41 g, 7.6 mmol) and NaN_3 (1.05 g, 15.2 mmol) in DMF (40 mL) was stirred for 12 h at room temperature. The reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (3 × 100 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude azide was purified by a simple filtration column (flash silica gel, petroleum ether/EtOAc, 4:1) yielding pure azide **1-95** (2.35 g, 97%) as colorless oil. $\mathbf{R_f}$ = 0.53 (petroleum ether/EtOAc, 4:1); $\mathbf{[\alpha]_D^{20}}$ = −3.0 (*c* 1, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.17 (ddd, *J* = 12.6, 11.6, 11.6 Hz, 1H, 5-H), 1.36 (s, 3H, 2-CH_3), 1.42 (s, 3H, 2-CH_3), 1.46 (ddd, *J* = 12.9, 2.5, 2.5 Hz, 1H, 5-H), 1.64–1.82 (m, 4H, $BnOCH_2CH_2$, $CH_2CH_2N_3$), 3.30–3.45 (m, 2H, $CH_2CH_2N_3$), 3.49–3.61 (m, 2H, $BnOCH_2CH_2$), 3.95 (dddd, *J* = 11.6, 7.3, 4.8, 2.8 Hz, 1H, 4-H), 4.01 (dddd, *J* = 11.4, 7.6, 5.0, 2.5 Hz 1H, 6-H), 4.46 (d, *J* = 12.1 Hz, 1H, OCH_2Ph), 4.49 (d, *J* = 12.1 Hz, 1H, OCH_2Ph), 7.24–7.38 (m, 5H, Ar-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 17.8 (2-CH_3), 28.1 (2-CH_3), 33.6 ($CH_2CH_2N_3$), 34.5 ($BnOCH_2CH_2$), 35.0 (C-6'), 45.5 ($CH_2CH_2N_3$), 63.9 (C-6), 64.0 (C-4), 64.1 ($BnOCH_2CH_2$), 73.0 ($PhCH_2O$), 98.7 (C-2), 127.6 (CH, phenyl), 127.6 (2CH, phenyl), 128.3 (2CH, phenyl), 138.5 (C, phenyl); **HRMS** (ESI): $[M+Na]^+$ calcd for $C_{17}H_{25}N_3O_3Na$ 342.17881, found 342.178839.

2-((4*R*,6*S*)-6-(2-(Benzyloxy)ethyl)-2,2-dimethyl-1,3-dioxan-4-yl)ethanamine (1-96)[163]



To a solution of azide **1-95** (2.55 g, 8.0 mmol) in a mixture of THF (50 mL) and H_2O (5 mL), PPh_3 (4.19 g, 16.0 mmol) was added and the mixture was stirred at room temperature for 10–12 h. The reaction mixture was concentrated to remove most of the THF. Benzene (100 mL) was added and the reaction mixture was concentrated to remove water as azeotrope. This manipulation was repeated once. The crude residue was purified by flash chromatography (CH_2Cl_2/MeOH/Et_3N, 9.5:0.4:0.1) to furnish amine **1-96** (2.2 g, 94%) as colorless oil. $\mathbf{R_f}$ = 0.29 (CH_2Cl_2/MeOH/Et_3N, 9.5:0.4:0.1); $\mathbf{[\alpha]_D^{20}}$ = −10.0 (*c* 1, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.19 (ddd, *J* = 12.6, 11.6, 11.6 Hz, 1H, 5-H), 1.35 (s, 3H, 2-CH_3), 1.41 (s, 3H, 2-CH_3), 1.44 (ddd, *J* = 12.6, 2.5, 2.3 Hz, 1H, 5-H), 1.53–1.80 (m, 4H, BnOCH_2CH_2, CH_2CH_2NH_2), 1.97 (br, s, 2H, NH_2), 2.80, (d, *J* = 6.8, 6.6 Hz, 2H, CH_2CH_2NH_2), 3.51 (ddd, *J* = 9.3, 5.8, 5.8 Hz, 1H, BnOCH_2CH_2), 3.54–3.61 (m, 1H, BnOCH_2CH_2), 3.94 (dddd, *J* = 11.4, 7.3, 4.8, 2.8 Hz, 1H, 4-H), 4.02 (dddd, *J* = 11.4, 7.6, 5.0, 2.5 Hz, 1H, 6-H), 4.45 (d, *J* = 11.9 Hz, 1H, OCH_2Ph), 4.49 (d, *J* = 11.9 Hz, 1H, OCH_2Ph), 7.26–7.35 (m, 5H, Ar-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 19.9 (2-CH_3), 30.2 (2-CH_3), 36.5 (BnOCH_2CH_2), 37.0 (C-5), 38.5 (CH_2CH_2NH_2), 39.4 (CH_2CH_2NH_2), 66.0 (C-4), 66.1 (BnOCH_2CH_2), 67.7 (C-6), 73.0 (OCH_2Ph), 127.5 (CH, phenyl), 127.6 (2CH, phenyl), 128.34 (2CH, phenyl), 138.49 (C, phenyl); **HRMS** (ESI): $[M+Na]^+$ calcd for $C_{17}H_{27}NO_3Na$ 294.20637, found 294.206401.

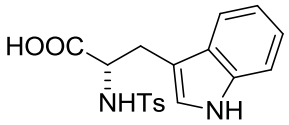
(*Z*)-*tert*-Butyl((1-methoxybuta-1,3-dien-1-yl)oxy)dimethylsilane (1-98)[49]



To a cooled (0 °C) solution of diisopropylamine (8.81 mL, 62.4 mmol) in THF (100 mL) was added dropwise *n*-BuLi (24.0 mL, 60 mmol, 2.5M in hexane) followed by stirring the mixture for 15 min. The mixture was cooled to −78 °C and subjected to the successive addition of DMPU

(9.06 mL, 74.9 mmol), *trans*-methylcrotonate **1-97** (5.0 g, 49.9 mmol) and a solution of *tert*-butyldimethylsilyl chloride (9.41 g, 62.4 mmol) in THF (10 mL) after a 15 min interval each. The reaction mixture was stirred for additional 45 min and allowed to stir for 2 h at room temperature, treated with saturated $NaHCO_3$ solution (50 mL) and extracted with *n*-hexane (3 × 100 mL). The combined organic layers were washed with saturated $NaHCO_3$ solution (4 × 50 mL) and saturated NaCl solution, dried over $MgSO_4$, filtered and concentrated on a rotary evaporator. The residue was distilled out under high vacuum (1 mbar, distillate temp. 60–70 ^oC) to yield ketene acetal **1-98** (9.2 g, 86%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 0.17 (s, 6H, $Si(CH_3)_2$), 0.94 (s, 9H, $SiC(CH_3)_3$), 3.56 (s, 3H, OCH_3), 4.46 (d, *J* = 10.4 Hz, 1H, 2-H), 4.59 (dd, *J* = 10.4, 2.0 Hz, 1H, 4-H), 4.83 (dd, *J* = 17.2, 2.0 Hz, 1H, 4-H), 6.51 (ddd, *J* = 17.2, 10.4, 10.4 Hz, 1H, 3-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = −4.3 ($2CH_3$, $Si(CH_3)_2$), 18.1 ($SiC(CH_3)_3$), 25.6 ($SiC(CH_3)_3$), 54.8 (OCH_3), 80.2 (C-2), 106.7 (C-4), 132.4 (C-3), 158.7 (C-1).

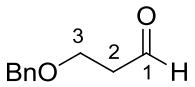
N-((4-Methylphenyl)sulfonyl)-(*L*)-tryptophan (1-100)[49]



(*L*)-Tryptophan **1-99** (5.0 g, 24.5 mmol) was dissolved in a mixture of THF/water (1:9, 30 mL) to which triethylamine (6.82 mL, 49.0 mmol) and *p*-toluenesulphonyl chloride (4.67g, 24.5 mmol) in THF (10 mL) were added subsequently using a dropping funnel. The mixture was stirred for 3 h and then extracted with diethyl ether (2 × 20 mL). The ether layers were discarded. Then 1N HCl was added to the aqueous phase which was extracted with ethyl acetate (3 ×30 mL). The combined organic layers were dried over $MgSO_4$, filtered, concentrated and the crude brownish residue was purified by flash chromatography (methanol/toluene, 1:8) to afford *N*-Ts-*L*-tryptophan **1-100** (7.01 g, 80%) as brownish solid. $\mathbf{R_f}$ = 0.2 (methanol/toluene, 1:8); $\mathbf{[\alpha]_D^{22}}$ = −39.5 (*c* 1, ethanol); **^{1}H NMR** (400 MHz, CD_3OD): δ = 2.29 (s, 3H, CH_3), 2.97 (dd, *J* = 14.4, 8.3 Hz, 1H, CH_2), 3.18 (dd, *J* = 14.4, 5.3 Hz, 1H, CH_2), 4.04 (dd, *J* = 8.3, 5.3 Hz, 1H, CH), 6.9 (ddd, *J* = 8.1, 7.1, 1.0 Hz, 1H, Ar-H, tryp), 6.98 (s, 1H, Ar-H, tryp), 7.02 (d, *J* = 7.83 Hz, 2H, Ar-H, tosyl), 7.04 (ddd, *J* = 7.8, 7.1, 1.0 Hz, Ar-H, tryp), 7.08–7.22 (m, 1H), 7.26 (d, *J* = 8.1 Hz, 1H,

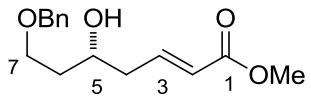
Ar-H, tryp), 7.36 (d, *J* = 7.8 Hz, 1H, Ar-H, tryp), 7.39 (d, *J* = 8.3 Hz, 2H, Ar-H, tosyl); **^{13}C NMR** (100 MHz, CD_3OD): δ = 21.5 (CH_3), 30.0 (CH_2), 57.9 (CH), 110.2 (C, Ar), 112.2 (CH, Ar), 119.6 (CH, Ar), 119.7 (CH, Ar), 122.2 (CH, Ar), 124.8 (CH, Ar), 127.7 (2CH, Ar), 128.4 (C, Ar), 130.2 (2CH, Ar), 138.0 (C, Ar), 138.6 (C, Ar), 144.2 (C, Ar), 175.3 (C=O).

3-(Benzyloxy)propanal (1-101)[164]



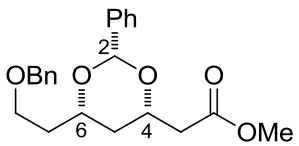
To a cooled solution (−78 °C) of oxalyl chloride (6.06 mL, 70.7 mmol) in CH_2Cl_2 (200 mL) in a three neck flask fitted with thermometer, rubber septum and pressure equalizer with N_2 inlet, was added DMSO (10.04 mL, 141.4 mmol) dropwise very slowly to maintain the temperature below −75 °C. After 40 min a solution of alcohol **1-87** (9.79 g, 58.9 mmol) in CH_2Cl_2 (50 mL) was added dropwise using a syringe pump over 20 min followed by addition of triethylamine (41.05 mL, 294.5 mmol) after 30 min. The reaction mixture was allowed to warm slowly to room temperature and stirred for 30 min before it was quenched with saturated NH_4Cl solution. The organic layer was separated and aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL) and the combined organic layers were washed with saturated $NaHCO_3$ solution (100 mL) and saturated NaCl solution. The organic layer was dried over Na_2SO_4, filtered, concentrated and purified by flash chromatography (EtOAc/petroleum ether, 1:3) to give aldehyde **1-101** (9.23 g, 95%) as colorless oil. $\mathbf{R_f}$ = 0.46 (EtOAc/petroleum ether, 1:3); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 2.69 (dt, *J* = 6.3, 2.0 Hz, 2H, 2-H), 3.81 (t, *J* = 6.1 Hz, 3H, 3-H), 4.53 (s, 2H, O*C*H_2Ph), 7.24-7.39 (5H, Ar-H), 9.79 (t, *J* = 1.8 Hz, 1-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 43.9 (C-2), 63.8 (C-3), 73.2 (O*C*H_2Ph), 127.7 (2CH, phenyl), 127.8 (CH, phenyl), 128.4 (2CH, phenyl), 137.8 (C, phenyl), 201.1 (C-1).

(*R*,*E*)-Methyl 7-(benzyloxy)-5-hydroxyhept-2-enoate (1-103)[49]



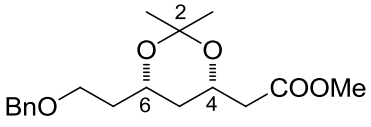
Dichlorophenylborane (1.61 g, 12.2 mmol) was added to a mixture of *N*-Ts-(*L*)-tryptophan **1-100** (4.39 g, 12.2 mmol) in CH_2Cl_2 (100 mL) dropwise at room temperature which led to persistent HCl gas evolution immediately. The resulting dark brown solution was stirred at room temperature for 1 h. The solvent was evaporated under reduced pressure and the dark brown foamy solid was dissolved in *n*-butyronitrile (44 mL). The solution was cooled to −78 °C and a mixture of aldehyde **1-101** (2.01 g, 12.2 mmol), 2-propanol (1.14 mL, 14.7 mmol) and ketene acetal **1-98** (3.15 g, 14.7 mmol) in *n*-butyronitrile (10 mL) was added dropwise using a syringe pump over 40 min. The reaction mixture was stirred for 4 h, quenched with saturated $NaHCO_3$ solution (30 mL), brought to the room temperature and extracted with diethyl ether (3 × 60 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under vacuum. Purification of the crude residue by flash chromatography (EtOAc/petroleum ether, 3:7) afforded *δ*-hydroxy-*α*,*β*-unsaturated ester **1-103** (1.95 g, 60%, 88% *ee* by Mosher ester method) as colorless oil. $\mathbf{R_f}$ = 0.4 (EtOAc/petroleum ether, 2:3); $\mathbf{[\alpha]_D^{22}}$ = +10.1 (*c* 1, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.68–1.83 (m, 2H, 6-H), 2.30–2.44 (m, 2H, 4-H), 3.64 (ddd, *J* = 9.3, 7.6, 5.0 Hz, 1H, 7-H), 3.68–3.74 (m, 1H, 7-H), 3.71 (s, 3H, OCH_3), 3.92–4.01 (m, 1H, 5-H), 4.51 (s, 2H, C*H*$_2$Ph), 5.88 (ddd, *J* = 15.7, 1.5, 1.3 Hz, 1H, 2-H), 6.98 (ddd, *J* = 15.7, 7.6, 7.3 Hz, 1H, 3-H), 7.25–7.37 (m, 5H, Ar-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 35.9 (C-6), 40.5 (C-4), 51.4 (OCH_3), 68.9 (C-7), 70.2 (C-5), 73.4 (*C*H_2Ph), 123.2 (C-2), 127.7 (2CH, phenyl), 127.8 (CH, phenyl), 128.5 (2CH, phenyl), 137.7 (C, phenyl), 145.5 (C-3), 166.7 (C-1); **HRMS** (ESI): $[M+Na]^+$ calcd for $C_{18}H_{26}O_5Na$ 287.12538, found 287.125232.

Methyl 2-((2*S*,4*S*,6*S*)-6-(2-(benzyloxy)ethyl)-2-phenyl-1,3-dioxan-4-yl)acetate (1-104)[165]



To a cooled (salt-ice bath) solution of enoate **1-103** (2.02 g, 7.6 mmol) in THF (40 mL) under N_2 atmosphere was added freshly distilled benzaldehyde (0.86 mL, 8.4 mmol), and potassium *tert*-butoxide (86 mg, 0.76 mmol). This manipulation was repeated three times in 15 min intervals. After additional 30 min of stirring, the reaction mixture was quenched by addition of pH 7 phosphate buffer solution (30 mL). The mixture was extracted using diethyl ether (3 × 70 mL), the combined organic layers were washed with saturated NaCl solution, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash chromatography (EtOAc/petroleum ether, 1:9 then 1:4) to yield acetal **1-104** (1.86 g, 66%) as colorless thick oil. $\mathbf{R_f}$ = 0.37 (EtOAc/petroleum ether, 2:3); $\mathbf{[\alpha]_D^{21}}$ = −27.3 (*c* 1, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.46 (ddd, *J* = 12.9, 11.4, 11.1 Hz, 1H, 5-H), 1.73 (ddd, *J* = 12.9, 2.3, 2.3 Hz, 1H, 5-H), 1.81–1.99 (m, 2H, $BnOCH_2CH_2$), 2.52 (dd, *J* = 15.7, 6.1 Hz, 1H, CH_2CO_2Me), 2.74 (dd, *J* = 15.7, 7.1 Hz, 1H, CH_2CO_2Me), 3.60 (ddd, *J* = 9.3, 5.6, 5.6 Hz, 1H, $BnOCH_2CH_2$), 3.66–3.76 (m, 1H, $BnOCH_2CH_2$), 3.70 (m, 3H, OCH_3), 4.08 (dddd, *J* = 10.6, 8.3, 4.5, 2.5 Hz, 1H, 6-H), 4.32 (dddd, *J* = 11.1, 8.8, 6.3, 2.3 Hz, 1H, 4-H), 4.50 (d, *J* = 11.9 Hz, 1H, OCH_2Ph), 4.54 (d, *J* = 11.9 Hz, 1H, OCH_2Ph), 5.56 (s, 1H, CHPh), 7.23–7.38 (m, 8H, Ar-H), 7.42–7.47 (m, 2H, Ar-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 36.0 ($BnOCH_2CH_2$), 36.6 (C-5), 40.3 (CH_2CO_2Me), 51.7 (OCH_3), 65.9 ($BnOCH_2CH_2$), 73.0 (OCH_2Ph), 73.1 (C-4), 73.6 (C-6), 100.5 (CHPh), 126.0 (2CH, Ar), 127.6 (CH, Ar), 127.6 (2CH, Ar), 128.1 (2CH, Ar), 128.4 (2CH, Ar), 128.6 (CH, Ar), 138.4 (2CH, Ar), 171.1 (CO_2Me); **HRMS** (ESI): $[M+Na]^+$ calcd for $C_{22}H_{26}O_5Na$ 393.16725, found 393.167621.

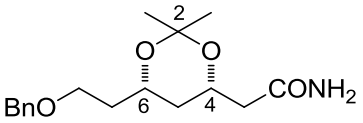
Methyl 2-((4*S*,6*S*)-6-(2-(benzyloxy)ethyl)-2,2-dimethyl-1,3-dioxan-4-yl)acetate (1-105)



Acetal **1-104** (3.04 g, 8.2 mmol) was dissolved in CH_2Cl_2 (30 mL) to which 2,2-dimethoxypropane (30 mL) and *p*-toluenesulphonic acid monohydrate (312 mg, 0.16 mmol) were added. The mixture was heated to reflux for 24 h and brought to room temperature. The volatiles were evaporated under vacuum and the residual mixture was diluted with CH_2Cl_2 (100

mL), washed with saturated $NaHCO_3$ solution (50 mL), saturated NaCl solution, dried over Na_2SO_4, filtered and concentrated in vacuo. Flash chromatography (EtOAc/petroleum ether, 1:9) furnished acetonide ester **1-105** (2.51 g, 95%) as colorless oil. $\mathbf{R_f}$ = 0.52 (EtOAc/petroleum ether, 1:4); $\mathbf{[\alpha]_D^{20}}$ = −18.34 (*c* 1, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.18 (ddd, *J* = 12.6, 12.6, 11.6 Hz, 1H, 5-H), 1.34 (s, 3H, 2-CH_3), 1.43 (m, 3H, 2-CH_3), 1.57 (ddd, *J* = 12.6, 2.5, 2.3 Hz, 1H, 5-H), 1.67–1.81 (m, 2H, BnOCH$_2$CH_2), 2.36 (dd, *J* = 15.4, 6.1 Hz, 1H, CH_2CO$_2$Me), 2.53 (dd, *J* = 15.4, 6.8 Hz, 1H, CH_2CO$_2$Me), 3.48–3.62 (m, 2H, BnOCH_2CH$_2$), 3.67 (s, 3H, OCH_3), 4.05 (dddd, *J* = 11.4, 6.8, 5.0, 2.8 Hz, 1H, 6-H), 4.29 (dddd, *J* = 11.4, 8.6, 4.8, 2.3 Hz, 1H, 4-H), 4.46 (d, *J* = 12.1 Hz, 1H, OCH_2Ph), 4.50 (d, *J* = 12.1 Hz, 1H, OCH_2Ph), 7.24–7.36 (m, 5H, Ar-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 20.2 (2-CH_3), 30.5 (2-CH_3), 36.9 (BnOCH$_2$*C*H$_2$), 37.0 (C-5), 41.7 (*C*H$_2$CO$_2$Me), 52.0 (OCH_3), 66.3 (C-4), 66.3 (C-6), 66.5 (BnO*C*H$_2$CH$_2$), 73.4 (O*C*H$_2$Ph), 99.2 (C-2), 128.0 (CH, phenyl), 128.0 (2CH, phenyl), 128.8 (2CH, phenyl), 138.9 (C, phenyl), 171.8 (CO_2Me); **HRMS** (ESI): $[M+Na]^+$ calcd for $C_{18}H_{26}O_5Na$ 345.16725, found 345.167000.

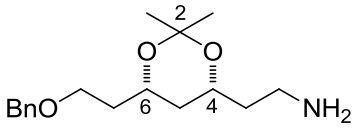
2-((4*S*,6*S*)-6-(2-(Benzyloxy)ethyl)-2,2-dimethyl-1,3-dioxan-4-yl)acetamide (1-106)[166]



Ester **1-105** (450 mg, 1.4 mmol) was heated in a screw cap bottle in a mixture of 25% aq NH_4OH solution (5 mL) and methanol (10 mL) for 48 h. The mixture was cooled to room temperature and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with saturated NaCl solution (5 mL), dried over anhydrous $MgSO_4$ and filtered. The filtrate was concentrated and purified by flash chromatography (methanol/CH_2Cl_2, 1:20) to yield amide **1-106** (327 mg, 76%) as yellow colored thick oil. $\mathbf{R_f}$ = 0.31 (methanol/CH_2Cl_2, 1:20); $\mathbf{[\alpha]_D^{20}}$ = −5.34 (*c* 1, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.24 (ddd, *J* = 12.6, 11.6, 11.6 Hz, 1H, 5-H), 1.37 (s, 3H, 2-CH_3), 1.43 (s, 3H, 2-CH_3), 1.52 (ddd, *J* = 12.9, 2.5, 2.3 Hz, 1H, 5-H), 1.65–1.80 (m, 2H, BnOCH$_2$CH_2), 2.32 (dd, *J* = 15.4, 4.0 Hz, 1H, CH_2CONH$_2$), 2.39 (dd, *J* = 15.1, 7.6 Hz, 1H, CH_2CONH$_2$), 3.46–3.62 (m, 2H, BnOCH_2CH$_2$), 4.05 (dddd, *J* = 11.9, 7.6, 5.0, 2.3 Hz,

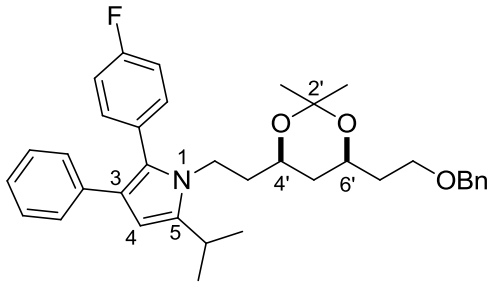
1H, 4-H), 4.21 (dddd, *J* = 11.4, 7.3, 4.3, 2.8 Hz, 1H, 6-H), 4.45 (d, *J* = 12.1 Hz, 1H, OC*H*$_2$Ph), 4.49 (d, *J* = 11.9 Hz, 1H, OC*H*$_2$Ph), 5.74 (s, 1H, CONH$_2$), 6.31 (s, 1H, CONH$_2$), 7.23–7.38 (m, 5H, Ar-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 19.8 (2-CH_3), 30.1 (2-CH_3), 36.2 (C-5), 36.3 (BnOCH$_2$*C*H$_2$), 42.8 (*C*H$_2$CO$_2$Me), 65.9 (BnO*C*H$_2$CH$_2$), 65.9 (C-4), 66.2 (C-6), 73.0 (O*C*H$_2$Ph), 98.9 (C-2), 127.5 (CH, phenyl), 127.6 (2CH, phenyl), 128.3 (2CH, phenyl), 138.4 (C, phenyl), 173.2 (C=O, amide); **HRMS** (ESI): $[M+Na]^+$ calcd for $C_{17}H_{25}NO_4Na$ 330.16758, found 330.167335.

2-((4*R*,6*S*)-6-(2-(Benzyloxy)ethyl)-2,2-dimethyl-1,3-dioxan-4-yl)ethanamine (1-96)



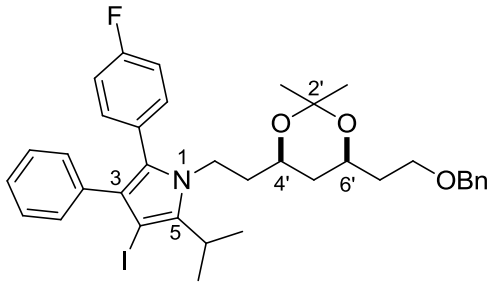
Amide **1-106** (350 mg, 0.14 mmol) in THF (1.5 mL) was added to a cooled (0 °C) solution of $LiAlH_4$ in THF (2 mL) dropwise under nitrogen atmosphere. The reaction mixture was heated to reflux for overnight (~12 h), cooled to room temperature and 3N KOH (2 mL) was added to the mixture. After 2 h of stirring, the mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo. Purification by flash chromatography ($MeOH/CH_2Cl_2$/25% NH_4OH, 1:9:0.005) afforded amine **1-96** (240 mg, 72%) as colorless oil. **$[\alpha]_D^{20}$** = −9.1 (*c* 1, $CHCl_3$). All spectral information is mentioned above.

1-(2-((4*R*,6*S*)-6-(2-(Benzyloxy)ethyl)-2,2-dimethyl-1,3-dioxan-4-yl)ethyl)-2-(4-fluorophenyl)-5-isopropyl-3-phenyl-1*H*-pyrrole (1-108)



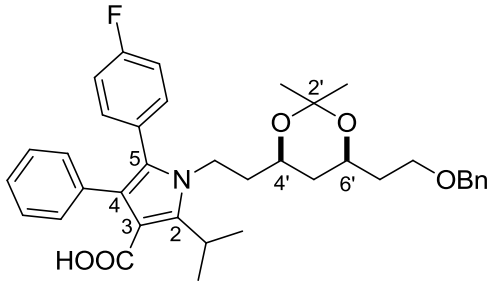
A mixture of 1,4-diketone **1-27** (500 mg, 1.7 mmol), amine **1-96** (516 mg, 1.8 mmol), and *p*-TSA•H_2O (64 mg, 0.33 mmol) in xylene (20 mL) was refluxed for 7 days using a Dean-Stark trap to remove water as an azeotropic mixture. The completion of the reaction was checked by TLC. The reaction mixture was diluted with diethyl ether (30 mL), washed with saturated $NaHCO_3$ (30 mL) and saturated NaCl solution (30 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude residue was purified by flash chromatography (petroleum ether/diethyl ether, 9:1) to afford pyrrole **1-108** (520 mg, 68%) as colorless sticky solid. $\mathbf{R_f}$ = 0.25 (petroleum ether/diethyl ether, 9:1); $\mathbf{[\alpha]^{20}_D}$ = +4.0 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 0.95 (ddd, *J* = 12.6, 11.6, 11.6 Hz, 1H, 5'-H), 1.15 (ddd, *J* = 12.6, 2.3, 2.3 Hz, 1H, 5'-H), 1.28–1.38 (m, 12H, 2'-CH_3, $CH(CH_3)_2$), 1.44–1.75 (m, 4H, NCH_2CH_2, CH_2CH_2OBn), 3.01 (ap. sept, *J* = 6.8 Hz, 1H, $CH(CH_3)_2$), 3.44–3.59 (m, 3H, 4'-H, CH_2CH_2OBn), 3.75–3.85 (m, 1H, NCH_2CH_2), 3.88–3.99 (m, 2H, NCH_2CH_2, 6'-H), 4.44 (d, *J* = 12.1 Hz, 1H, OCH_2Ph), 4.47 (d, *J* = 12.1 Hz, 1H, OCH_2Ph), 6.18 (s, 1H, 4-H, pyrrole), 7.00–7.17 (m, 7H, Ar-H), 7.23–7.37 (m, 7H, Ar-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 19.8 (2'-CH_3), 23.3 ($CH(CH_3)_2$), 23.7 ($CH(CH_3)_2$), 25.5 ($CH(CH_3)_2$), 30.1 (2'-CH_3), 36.4 (NCH_2CH_2), 36.5 (C-5'), 37.9 (CH_2CH_2OBn), 39.8 (NCH_2CH_2), 65.7 (C-6'), 66.0 (CH_2CH_2OBn), 66.3 (C-4'), 72.9 (OCH_2Ph), 98.4 (C-2'), 103.4 (C-4, pyrrole), 115.6 (d, J_{CF} = 21.2 Hz, CH, Ar), 122.0 (C, Ar), 124.8 (CH, Ar), 127.5 (CH, Ar), 127.5 (CH, Ar), 127.6 (CH, Ar), 127.8 (C, Ar), 128.0 (CH, Ar), 128.3 (CH, Ar), 129.8 (d, J_{CF} = 3.7 Hz, C, Ar), 132.9 (d, J_{CF} = 8.1 Hz, CH, Ar), 136.5 (C, Ar), 138.5 (C, Ar), 140.4 (C, Ar), 162.2 (d, J_{CF} = 246.6 Hz, C, Ar); **HRMS** (ESI): $[M+Na]^+$ calcd for $C_{36}H_{42}FNO_3Na$ 578.30409, found 578.304437.

1-(2-((4*R*,6*S*)-6-(2-(Benzyloxy)ethyl)-2,2-dimethyl-1,3-dioxan-4-yl)ethyl)-2-(4-fluorophenyl)-4-iodo-5-isopropyl-3-phenyl-1H-pyrrole (1-109)



To a solution of pyrrole **1-108** (206 mg, 0.37 mmol) in DMF (5 mL), *N*-iodosuccinimide (100 mg, 0.45 mmol) was added in one portion and the reaction mixture was stirred for 30 min at room temperature. The reaction mixture was diluted with diethyl ether (15 mL), washed with 10% $Na_2S_2O_3$ solution (5 mL), saturated $NaHCO_3$ solution (10 mL) and saturated NaCl solution (10 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The crude product was purified by flash chromatography (petroleum ether/EtOAc, 9:1) to give iodopyrrole **1-109** (230 mg, 91%) as colorless oil. $\mathbf{R_f}$ = 0.3 (petroleum ether/EtOAc, 9:1); $\mathbf{[\alpha]_D^{20}}$ = −2.0 (*c* 1, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 0.98 (ddd, *J* = 12.4, 11.6, 11.6 Hz, 1H, 5'-H), 1.20 (ddd, *J* = 12.9, 2.5, 2.3 Hz, 1H, 5'-H), 1.29 (s, 3H, 2'-CH_3), 1.32 (s, 3H, 2'-CH_3), 1.49 (d, *J* = 7.1 Hz, 3H, CH(CH_3)$_2$), 1.51 (d, *J* = 7.1 Hz, 3H, CH(CH_3)$_2$), 1.56–1.75 (m, 4H, NCH$_2$CH_2, CH_2CH$_2$OBn), 3.32 (ap. sept, *J* = 7.1 Hz, 1H, CH(CH$_3$)$_2$), 3.44–3.58 (m, 2H, CH$_2$CH_2OBn), 3.61 (dddd *J* = 11.1, 7.1, 4.3, 3.0 Hz, 1H, 4'-H), 3.80 (ddd, *J* = 15.7, 10.4, 5.6 Hz, 1H, NCH_2CH$_2$), 3.92 (dddd, *J* = 11.4, 7.3, 5.1, 2.5 Hz, 1H, 6'-H), 4.04 (ddd, *J* = 15.4, 10.3, 4.5 Hz, 1H, NCH_2CH$_2$), 4.44 (d, *J* = 12.1 Hz, 1H, OCH_2Ph), 4.48 (d, *J* = 12.1 Hz, 1H, OCH_2Ph), 6.89–7.00 (m, 2H, Ar-H), 7.06–7.38 (m, 7H, Ar-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 19.8 (2'-CH_3), 21.4 (CH(*C*H$_3$)$_2$), 21.5 (CH(*C*H$_3$)$_2$), 27.2 (*C*H(CH$_3$)$_2$), 30.0 (2'-CH_3), 36.4 (*C*H$_2$CH$_2$OBn), 36.5 (C-5'), 38.3 (NCH$_2$*C*H$_2$), 41.2 (N*C*H$_2$CH$_2$), 65.7 (C-6'), 66.0 (CH$_2$*C*H$_2$OBn), 66.5 (C-4'), 72.9 (O*C*H$_2$Ph), 98.5 (C-2'), 117.2 (d, J_{CF} = 21.2 Hz, 2CH, aryl), 126.0 (CH, aryl), 126.5 (C, aryl), 127.4 (CH, aryl), 127.5 (CH, aryl), 127.6 (CH, aryl), 128.3 (CH, aryl), 129.8 (d, J_{CF} = 3.7 Hz, C, aryl), 128.7 (C, aryl), 129.7 (C, aryl), 130.9 (2CH, aryl), 132.9 (C-1, J_{CF} = 8.1 Hz, 2CH, aryl), 135.9 (C, aryl), 137.1 (C, aryl), 138.5 (C, aryl), 162.1 (d, J_{CF} = 247.4 Hz, C, aryl); **HRMS** (ESI): $[M+Na]^+$ calcd for $C_{36}H_{41}FINO_3Na$ 704.20074, found 704.200369.

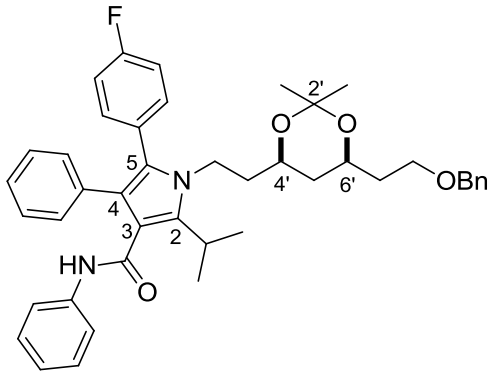
1-(2-((4*R*,6*S*)-6-(2-(Benzyloxy)ethyl)-2,2-dimethyl-1,3-dioxan-4-yl)ethyl)-5-(4-fluorophenyl)-2-isopropyl-4-phenyl-1*H*-pyrrole-3-carboxylic acid (1-110)



A solution of iodopyrrole **1-109** (201 mg, 0.29 mmol) in THF (10 mL) was cooled to −80 °C, then *t*-BuLi (0.387 mL, 0.62 mmol, 2.5M in hexane) was added dropwise. After 10 min, excess of CO_2 gas was bubbled through the reaction mixture with stirring for 15 min. Thereafter, the mixture was allowed to reach room temperature within 1 h. The progress of the reaction was checked by TLC. Saturated NH_4Cl solution (2 mL) was added and the mixture was extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with saturated NaCl solution, dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (petroleum ether/EtOAc, 8:2) to furnish acid **1-110** (144 mg, 81%) as white solid, **m.p.** 73–78 °C. $\mathbf{R_f}$ = 0.3 (petroleum ether/EtOAc, 7:3); $\mathbf{[\alpha]_D^{20}}$ = −1.7 (*c* 1, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 0.97 (ddd, *J* = 12.4, 11.9, 11.6 Hz, 1H, 5'-H), 1.19 (ddd, *J* = 13.1, 2.3, 2.3 Hz, 1H, 5'-H), 1.28 (s, 3H, 2'-CH_3), 1.31 (s, 3H, 2'-CH_3), 1.46 (d, *J* = 7.1 Hz, 3H, CH(C*H*$_3$)$_2$), 1.47 (d, *J* = 7.3 Hz, 3H, CH(C*H*$_3$)$_2$), 1.54–1.75 (m, 4H, NCH$_2$C*H*$_2$, C*H*$_2$CH$_2$OBn), 3.43–3.66 (m, 4H, 4'-H, CH$_2$C*H*$_2$OBn, C*H*(CH$_3$)$_2$), 3.77 (ddd, *J* = 14.9, 10.6, 5.8 Hz, 1H, NC*H*$_2$CH$_2$), 3.92 (dddd, *J* = 11.8, 7.3, 4.8, 2.3 Hz, 1H, 6'-H), 4.04 (ddd, *J* = 14.9, 9.3, 4.5 Hz 1H, NC*H*$_2$CH$_2$), 4.44 (d, *J* = 12.1 Hz, 1H, OC*H*$_2$Ph), 4.48 (d, *J* = 12.1 Hz, 1H, OC*H*$_2$Ph), 6.90–6.97 (m, 2H, Ar-H), 7.02–7.16 (m, 7H, Ar-H), 7.25–7.36 (m, 5H, Ar-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 19.8 (2'-CH_3), 20.8 (CH(*C*H$_3$)$_2$), 26.0 (*C*H(CH$_3$)$_2$), 30.0 (2'-CH_3), 36.4 (*C*H$_2$CH$_2$OBn), 36.4 (C-5'), 37.9 (NCH$_2$*C*H$_2$), 41.1 (N*C*H$_2$CH$_2$), 65.7 (C-6'), 66.0 (CH$_2$*C*H$_2$OBn), 66.5 (C-4'), 72.9 (O*C*H$_2$Ph), 98.5 (C-2'), 109.4 (C, aryl), 115.2 (d, J_{CF} = 21.2 Hz, CH, aryl), 125.8 (CH, aryl), 127.2 (CH, aryl), 127.6 (CH, aryl), 127.6 (CH, aryl), 128.1 (d, J_{CF} = 2.9 Hz, C, aryl), 128.3 (CH, aryl), 130.0 (C, aryl), 130.5 (CH, aryl), 133.2 (d, J_{CF} = 8.1 Hz, CH, aryl), 135.4 (C, aryl), 138.4 (C, aryl), 144.9 (C, aryl), 162.2 (d, J_{CF} = 248.1 Hz, C, aryl),

170.7 (C, aryl), 177.3 (COOH); **HRMS** (ESI): $[M+Na]^+$ calcd for $C_{37}H_{42}FNO_5Na$ 622.29392, found 622.293491.

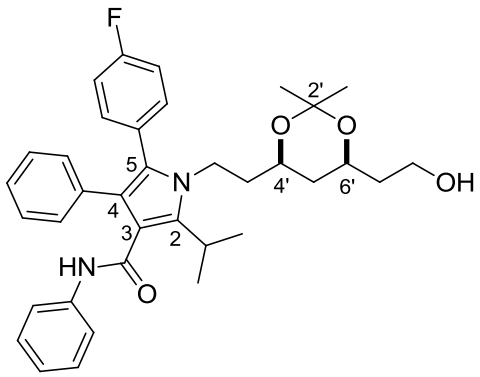
1-(2-((4*R*,6*S*)-6-(2-(Benzyloxy)ethyl)-2,2-dimethyl-1,3-dioxan-4-yl)ethyl)-5-(4-fluorophenyl)-2-isopropyl-*N*,4-diphenyl-1*H*-pyrrole-3-carboxamide (1-111)



To a solution of acid **1-110** (73 mg, 0.12 mmol) and aniline (13 μL, 0.15 mmol) in CH_2Cl_2 (5 mL), DIPEA (63 μL, 0.36 mmol) was added and the reaction mixture was cooled to 0 °C. PyBrOP (85 mg, 0.18 mmol) was then added and the mixture allowed to stir at room temperature for 4 h. Completion of the reaction was checked by TLC. The reaction mixture was diluted with CH_2Cl_2 (5 mL), washed with water (3 × 5 mL) and saturated NaCl solution. The organic layer was dried over Na_2SO_4, filtered and concentrated in vacuo. The crude residue was purified by flash chromatography (petroleum ether/EtOAc, 4:1) to afford amide **1-111** (65 mg, 82%) as white solid, **m.p.** 75–82 °C. $\mathbf{R_f}$ = 0.29 (petroleum ether/EtOAc, 4:1); $\mathbf{[\alpha]_D^{20}}$ = −1.5 (*c* 1, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.00 (ddd, *J* = 12.4, 11.6, 11.6 Hz, 1H, 5'-H), 1.14–1.26 (m, 1H, 5'-H), 1.29 (s, 3H, 2'-CH_3), 1.33 (s, 3H, 2'-CH_3), 1.52 (d, *J* = 7.1 Hz, 6H, CH(CH_3)$_2$), 1.58–1.77 (m, 4H, NCH$_2$CH_2, CH_2CH$_2$OBn), 3.42–3.70 (m, 4H, 4'-H, CH$_2$CH_2OBn, CH(CH$_3$)$_2$), 3.80 (ddd, *J* = 14.6, 9.8, 6.3 Hz, 1H, NCH_2CH$_2$), 3.89–3.99 (m, 1H, 6'-H), 4.06 (ddd, *J* = 14.9, 9.1, 4.5 Hz, 1H, NCH$_2$CH$_2$), 4.35 (d, *J* = 12.4 Hz, 1H, OCH_2Ph), 4.48 (d, *J* = 12.4 Hz, 1H, OCH_2Ph), 6.85 (s, 1H, NH), 6.92–7.02 (m, 3H, Ar-H), 7.03–7.10 (m, 2H, Ar-H), 7.11–7.23 (m, 9H, Ar-H), 7.24–7.40 (m, 5H, Ar-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 19.8 (2'-CH_3), 21.5 (CH(*C*H$_3$)$_2$), 21.7 (CH(*C*H$_3$)$_2$), 26.1 (*C*H(CH$_3$)$_2$), 30.0 (2'-CH_3), 36.4 (*C*H$_2$CH$_2$OBn), 36.4 (C-5'), 38.1 (NCH$_2$*C*H$_2$), 40.9 (N*C*H$_2$CH$_2$), 65.7 (C-6'), 66 0 (CH$_2$*C*H$_2$OBn), 66.5 (C-4'), 72.9 (O*C*H$_2$Ph),

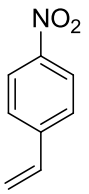
98.5 (C-2'), 115.2 (C, aryl), 115.3 (d, J_{CF} = 21.2 Hz, CH, aryl), 119.5 (CH, aryl), 121.7 (C, aryl), 123.5 (CH, aryl), 126.5 (CH, aryl), 127.6 (CH, aryl), 127.6 (CH, aryl), 128.2 (C, aryl), 128.3 (CH, aryl), 128.6 (CH, aryl), 128.7 (C, aryl), 130.5 (CH, aryl), 133.2 (d, J_{CF} = 8.1 Hz, C, aryl), 134.6 (C, aryl), 138.4 (d, J_{CF} = 7.3 Hz, CH, aryl), 141.5 (C, aryl), 149.9 (C, aryl), 141.5 (C, aryl), 162.2 (d, J_{CF} = 248.1 Hz, C, aryl), 164.8 (CONH); **HRMS** (ESI): $[M+Na]^+$ calcd for $C_{43}H_{47}FO_4Na$ 697.34121, found 697.341636.

5-(4-Fluorophenyl)-1-(2-((4*R*,6*S*)-6-(2-hydroxyethyl)-2,2-dimethyl-1,3-dioxan-4-yl)ethyl)-2-isopropyl-*N*,4-diphenyl-1*H*-pyrrole-3-carboxamide (1-76)



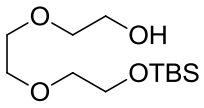
A solution of benzyl ether **1-108** (20 mg, 0.03 mmol) containing 20% $Pd(OH)_2$ on carbon (5 mg, 25 wt%), cyclohexene (1 mL) and ethanol (2 mL) was stirred for 4 h at 80 °C. After cooling, the catalyst was filtered off, and the filtrate concentrated in vacuo. The crude product was purified by flash chromatography (petroleum ether/EtOAc, 3:2) to afford alcohol **1-76** (15 mg, 86%) as white solid, **m.p.** 75–85 °C. $\mathbf{R_f}$ = 0.11 (petroleum ether/EtOAc, 6:4); $\mathbf{[\alpha]_D^{20}}$ = −6.0 (*c* 1, $CHCl_3$). Spectral details are reported above.

1-Nitro-4-vinylbenzene (1-114)[79]



In a well stirred mixture of zinc powder (19.57 g, 0.30 mol) in THF (300 mL) in an ice bath, CH_2I_2 (13.43 mL, 0.17 mol) was added dropwise carefully (sudden exotherm is possible after addition) using dropping funnel. The mixture was stirred for 30 min at room temperature, then $Ti(O\textit{i}Pr)_4$ (9.96 mL, 0.033 mol) was added over 20 min and stirring was continued for 30 min before 4-nitro benzaldehyde **1-117** (5.0 g, 0.033 mol) in THF (50 mL) was added to the reaction mixture. After being stirred for 3 h at room temperature excess of zinc was removed by filtration through celite and the filtrate was diluted with diethyl ether (100 mL). 1N HCl was added to the solution until a clear orange red color persisted. The organic layer was separated and the aqueous layer extracted with diethyl ether (3 × 40 mL). The combined organic layers were washed with saturated $NaHCO_3$ solution, saturated NaCl solution, dried over $MgSO_4$, and concentrated in vacuo. Purification by flash chromatography (petroleum ether/diethyl ether, 25:1) afforded styrene **1-114** (4.69 g, 94%) as yellow colored liquid which solidified at low temperature. $\mathbf{R_f}$ = 0.36 (petroleum ether/diethyl ether, 25:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 5.48 (d, *J* = 10.9 Hz, 1H, CH=C*H*$_2$), 5.92 (d, *J* = 17.4 Hz, 1H, CH=C*H*$_2$), 6.77 (dd, *J* = 10.9, 17.4 Hz, 1H, C*H*=CH$_2$), 7.52 (d, *J* = 8.6 Hz, 2H, Ar-H), 8.17 (d, *J* = 8.8 Hz, 2H, Ar-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 118.6 (CH=*C*H$_2$), 123.9 (2CH, aryl), 126.8 (2CH, aryl), 135.0 (*C*H=CH$_2$), 143.8 (C, aryl).

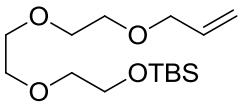
2-(2-(2-(*tert*-Butyl-dimethyl-silanyloxy)-ethoxy)-ethoxy)-ethanol (1-118)[167]



A solution of triethylene glycol **1-116** (3.0 g, 20.0 mmol) in THF (60 mL) was cooled in ice bath. NaH (0.8 g, 20.0 mmol) was added portionwise to the reaction mixture which was stirred at room temperature for 45 min before *tert*-butyldimethylsilyl chloride (3.01 g, 20.0 mmol) in THF (10 mL) was added dropwise at the same temperature and the resulting milky solution was allowed to stir at room temperature. After 2 h, the mixture was diluted with diethyl ether (50 mL), washed with 10% aq K_2CO_3 solution (30 mL) and saturated NaCl solution. The separated organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated under vacuum. The crude oil was purified by flash chromatography (petroleum ether/EtOAc, 3:7) to isolate

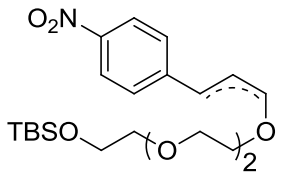
monoprotected alcohol **1-118** (4.10 g, 78%) as colorless oil. $\mathbf{R_f}$ = (petroleum ether/EtOAc, 3:7) 0.19; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 0.05 (s, 6H, $Si(CH_3)_2$), 0.87 (s, 9H, $SiC(CH_3)_3$), 2.38 (s, 1H, OH), 3.55 (d, *J* = 5.6, 5.0 Hz, 2H, OCH_2), 3.58−3.61 (m, 2H, OCH_2), 3.65 (s, 4H, OCH_2), 3.69–3.73 (m, 2H, OCH_2), 3.73–3.77 (dd, *J* = 5.6, 5.0 Hz, 2H, OCH_2); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = −5.3 ($Si(CH_3)_2$), 18.3 ($C(CH_3)_3$), 25.9 ($C(CH_3)_3$), 61.8 (OCH_2), 62.7 (OCH_2), 70.4 (OCH_2), 70.7 (OCH_2), 72.5 (OCH_2), 72.7 (OCH_2).

2,2,3,3-Tetramethyl-4,7,10,13-tetraoxa-3-silahexadec-15-ene (1-119)[80]



A solution of NaOH (1.40 g, 34.0 mmol), tetra *n*-butyl ammonium hydrogen sulphate (148 mg, 0.44 mmol) and alcohol **1-118** (2.31 g, 8.7 mmol) in a mixture of benzene (18 mL) and water (3 mL) was cooled to ~0 °C (ice bath). Allyl bromide (2.11 g, 17.4 mmol) was added dropwise to the mixture which was stirred vigorously at room temperature for 40 h (TLC). The reaction mixture was diluted with diethyl ether (30 mL) and washed with 10% HCl solution (20 ml) and saturated $NaHCO_3$ solution (20 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated in vacuo. The crude ether was purified by flash chromatography (petroleum ether/EtOAc, 1:4) to furnish *O*-allyl TEG **1-119** (2.01 g, 76%) as colorless liquid. $\mathbf{R_f}$ = 0.5 (petroleum ether/EtOAc, 1:4); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 0.05 (s, 6H, $Si(CH_3)_2$), 0.88 (s, 9H, $SiC(CH_3)_3$), 3.54 (dd, *J* = 5.5, 5.3 Hz, 2H, OCH_2), 3.57–3.61 (m, 2H, OCH_2), 3.63–3.66 (m, 6H, OCH_2), 3.75 (dd, *J* = 5.6 Hz, 2H, OCH_2), 4.01 (ddd, *J* = 5.6, 1.5, 1.3 Hz, 2H, $OCH_2CH{=}CH_2$), 5.16–5.18 (m, 1H, $CH{=}CH_2$), 5.25 (dddd, *J* = 17.2, 1.8, 1.5, 1.5 Hz, 1H, $CH{=}CH_2$), 5.90 (dddd, *J* = 17.2, 10.4, 5.8, 5.6 Hz, 1H, $CH{=}CH_2$); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = −5.3 ($Si(CH_3)_2$), 18.3 ($SiC(CH_3)_3$), 25.9 ($C(CH_3)_3$), 62.7 (OCH_2), 69.4 (OCH_2), 70.6 (OCH_2), 70.7 (2 OCH_2), 72.2 (OCH_2), 72.6 (OCH_2), 117.1 ($CH{=}CH_2$), 134.8 ($CH{=}CH_2$); **HRMS** (ESI): $[M + Na]^+$ calcd for $C_{15}H_{32}O_4SiNa$ 327.196188, found 327.19621.

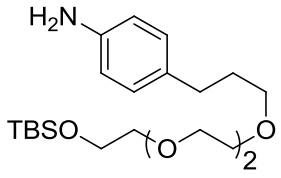
2,2,3,3-Tetramethyl-16-(4-nitrophenyl)-4,7,10,13-tetraoxa-3-silahexadec-15-ene (1-120)



To a solution of *O*-allyl TEG **1-119** (100 mg, 0.3 mmol) and *p*-nitro styrene **1-114** (195 mg, 1.3 mmol) in dry, degassed toluene (2 mL) Grubb´s 2nd catalyst (14 mg) in toluene (0.2 mL) was added dropwise and the reaction mixture was heated to 70 °C for 24 h. The reaction mixture was cooled to room temperature. The solvent was evaporated under vacuum and the crude compound was purified by flash chromatography (petroleum ether/EtOAc, 4:1) to afford an isomeric mixture of isomers (trans/vinlylic trans/vinylic cis) of metathesis products **1-120** (75 mg, 53%) as red yellow colored oil. $\mathbf{R_f}$ = (petroleum ether/EtOAc, 4:1) 0.11 (trans), 0.24 (vinylic trans), 0.29 (vinylic cis); **^{1}H NMR** (400 MHz, $CDCl_3$) (*vinylic cis*): δ = 0.04 (s, 6H, $Si(CH_3)_2$), 0.87 (s, 9H, $SiC(CH_3)_3$), 3.50 (d, *J* = 7.6 Hz, 2H, OCH_2), 3.55 (dd, *J* = 5.5, 5.3 Hz, 2H, OCH_2), 3.65 (s, 4H, OCH_2), 3.68−3.70 (m, 2H, OCH_2), 3.75 (dd, *J* = 5.6, 5.3 Hz, 2H, OCH_2), 3.93–395 (m, 2H, OCH_2), 4.53 (ddd, *J* = 7.6, 7.6, 6.1 Hz, 1H, OCH=C*H*CH_2), 6.16 (ddd, *J* = 6.3, 1.5, 1.3 Hz, 1H, OC*H*=$CHCH_2$), 7.36 (d, *J* = 8.6 Hz, 2H, Ar), 8.11 (d, *J* = 8.6 Hz, 2H, Ar); (*vinylic trans*): δ = 0.04 (s, 6H, $Si(CH_3)_2$), 0.87 (s, 9H, $SiC(CH_3)_3$), 3.34 (d, *J* = 7.6 Hz, 2H, OCH=CHCH_2), 3.54 (dd, *J* = 5.5, 5.3 Hz, 2H, OCH_2), 3.65 (s, 4H, OCH_2), 3.71−3.76 (m, 4H, OCH_2), 3.83−3.85 (m, 2H, OCH_2), 4.87 (ddd, *J* = 12.6, 7.3, 5.3 Hz, 1H, OCH=C*H*CH_2Ar), 6.42 (d, *J* = 12.6 Hz, 1H, OC*H*=$CHCH_2$Ar), 7.34 (d, *J* = 8.8 Hz, 2H, Ar-H), 8.12 (d, *J* = 8.8 Hz, 2H, Ar-H); (*trans isomer*): δ = 0.05 (s, 6H, $Si(CH_3)_2$), 0.87 (s, 9H, $SiC(CH_3)_3$), 3.55 (dd, *J* = 5.6, 5.3 Hz, 2H, OCH_2), 3.64–3.71 (m, 8H, OCH_2), 3.75 (dd, *J* = 5.6, 5.3 Hz, 2H, OCH_2), 4.23 (dd, *J* = 5.3, 1.5 Hz, 2H, OCH_2CH=CHAr), 6.46 (ddd, *J* = 15.9, 5.6, 5.6 Hz, 1H, OCH_2C*H*=CHAr), 6.68 (d, *J* = 16.2 Hz, 1H, OCH_2CH=C*H*Ar), 7.49 (d, *J* = 8.8 Hz, 2H, Ar-H), 8.16 (d, *J* = 8.8 Hz, 2H, Ar-H); **^{13}C NMR** (100 MHz, $CDCl_3$): (*vinylic cis*) δ = −5.3 ($Si(CH_3)_2$), 18.3 (Si*C*$(CH_3)_3$), 25.9 ($SiC(CH_3)_3$), 30.1 (Ar*C*H_2CH=CH), 62.7 (OCH_2), 70.4 (OCH_2), 70.8 (2 × OCH_2), 71.6 (OCH_2), 72.7 (OCH_2), 103.4 (CH_2*C*H=CHO), 123.5 (2CH, Ar), 129.1 (2CH, Ar), 146.2 (C, Ar), 146.8 (CH_2CH=*C*HO), 149.8 (C, Ar); (*vinylic trans*) δ = −5.3 ($Si(CH_3)_2$), 18.3 (Si*C*$(CH_3)_3$), 25.9 ($SiC(CH_3)_3$), 33.9 (OCH=CH*C*H_2Ar), 62.7 (OCH_2), 68.6 (OCH_2), 69.8 (OCH_2), 70.7 (OCH_2),

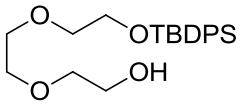
70.8 (OCH_2), 72.7 (OCH_2), 101.2 (OCH=*C*HCH$_2$Ar), 123.6 (2CH, Ar), 129.0 (2CH, Ar), 146.4 (C, Ar), 148.3 (O*C*H=CHCH$_2$), 149.3 (C, Ar); (*trans isomer*) δ = −5.3 ($Si(CH_3)_2$), 18.3 (Si*C*(CH_3)$_3$), 25.9 (SiC(*C*H$_3$)$_3$), 62.7 (OCH_2), 70.0 (OCH_2), 70.7 (OCH_2), 70.8 (2 × OCH_2), 71.2 (OCH_2), 72.7 (OCH_2), 124.0 (2CH, Ar), 126.9 (2CH, Ar), 129.5 (OCH_2CH=*C*H), 131.3 (OCH_2*C*H=CH), 143.4 (C, Ar), 146.9 (C, Ar); **HRMS** (ESI): $[M + Na]^+$ calcd for $C_{21}H_{35}NO_6SiNa$ 448.21259, found 450.22824.

4-(2,2,3,3-Tetramethyl-4,7,10,13-tetraoxa-3-silahexadecan-16-yl)aniline (1-121)



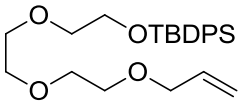
A solution of *p*-nitro styrene derivative **1-120** (570 mg, 1.3 mmol) in methanol (10 mL) was hydrogenated in presence of a catalytic amount of 10% Pd/C under hydrogen balloon pressure for 3 h. The catalyst was filtered off through a pad of celite and the filtrate was concentrated in vacuo. Residual oil was purified by flash chromatography (petroleum ether/EtOAc, 7:3) which furnished TEG coupled aniline **1-121** (400 mg, 75%) as reddish brown colored oil. $\mathbf{R_f}$ = 0.26 (petroleum ether/EtOAc, 7:3); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 0.05 (s, 6H, $Si(CH_3)_2$), 0.88 (s, 9H, SiC(CH_3)$_3$), 1.80–1.87 (m, 2H, OCH_2C*H*$_2CH_2$Ar), 2.57 (dd, *J* = 7.8, 7.6 Hz, 2H, OCH_2CH_2C*H*$_2$Ar), 3.44 (dd, *J* = 6.6, 6.6 Hz, 2H, OCH_2), 3.53–3.58 (m, 4H, OCH_2), 3.63–3.66 (m, 6H, OCH_2), 3.75 (dd, *J* = 5.6, 5.3 Hz, 2H, OCH_2), 6.68 (d, *J* = 8.3 Hz, 2H, Ar-H), 6.98 (d, *J* = 8.1 Hz, 2H, Ar-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = −5.3 ($Si(CH_3)_2$), 18.4 (Si*C*(CH_3)$_3$), 25.9 (SiC(*C*H$_3$)$_3$), 31.4 (CH_2), 31.4 (CH_2Ar), 62.7 (OCH_2), 70.1 (OCH_2), 70.5 (OCH_2), 70.6 (OCH_2), 70.7 (OCH_2), 70.8 (OCH_2), 72.7 (OCH_2), 115.9 (2CH, Ar), 129.3 (2CH, Ar), 133.0 (C, Ar), 142.7 (C, Ar); **HRMS** (ESI): $[M+H]^+$ calcd for $C_{21}H_{39}NO_4SiNa$ 398.27211, found 398.27244.

2-(2-(2-(*tert*-Butyl-diphenyl-silanyloxy)-ethoxy)-ethoxy)-ethanol (1-122)[168]



Imidazole (4.53 g, 66.6 mmol) and DMAP (813 mg, 6.7 mmol) were added to a solution of triethylene glycol **1-116** (5.02 g, 33.3 mmol) in dry CH_2Cl_2 (100 mL) and the mixture was stirred at room temperature for 10 min. Then *tert*-butyldiphenylsilyl chloride (4.12 g, 15.0 mmol) in CH_2Cl_2 (25 mL) was added and stirring was continued for 14 h at room temperature. The reaction mixture was washed with saturated $NaHCO_3$ solution (30 mL), water (30 mL) and saturated NaCl (30 mL) solution. The organic layer was dried over Na_2SO_4, filtered and concentrated in vacuo. The crude oil was purified by flash chromatography (petroleum ether/EtOAc, 3:7) to give alcohol **1-122** (4.59 g, 79%) as colorless oil. $\mathbf{R_f}$ = 0.36 (petroleum ether/EtOAc, 3:7); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.04 (s, 9H, $SiC(CH_3)_3$), 2.09 (s, 1H, OH), 3.59–3.62 (m, 4H, OCH_2), 3.63–3.67 (m, 4H, OCH_2), 3.70–3.72 (m, 2H, OCH_2), 3.81 (dd, *J* = 5.3, 5.3 Hz, 2H, OCH_2), 7.35–7.43 (m, 6H, Ar-H), 7.66–7.69 (m, 4H, Ar-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 19.2 ($SiC(CH_3)_3$), 26.8 ($SiC(CH_3)_3$), 61.8 (OCH_2), 63.4 (OCH_2), 70.5 (OCH_2), 70.8 (OCH_2), 72.4 (OCH_2), 72.5 (OCH_2), 127.6 (4CH, Ar), 129.6 (2CH, Ar), 133.6 (2C, Ar), 135.6 (4CH, Ar).

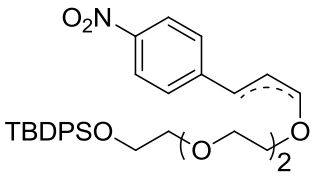
2,2-Dimethyl-3,3-diphenyl-4,7,10-trioxa-3-siladodecan-12-ol (1-123)[80]



A biphasic mixture of alcohol **1-122** (3.01 g, 7.7 mmol), NaOH pellets (1.23 g, 30.9 mmol) and tetra *n*-butyl ammonium hydrogen sulphate (131 mg, 0.3 mmol) in benzene (36 mL) and water (6 mL) was cooled in an ice bath. Allyl bromide (1.87 g, 15.4 mmol) was added to the reaction mixture which was allowed to stir at room temperature for 24 h. The reaction was found to be incomplete (TLC control), therefore excess of reagents NaOH (1 equiv) and allyl bromide (0.5 equiv) was added and the mixture was stirred for 24 h. The reaction mixture was diluted with

diethyl ether (20 mL) and water (20 mL). The organic layer was washed with 5% HCl solution (20 mL), water (2 × 20 mL), dried over Na_2SO_4, filtered and concentrated under vacuum. The crude oil was purified by flash chromatography (petroleum ether/EtOAc, 4:1) to furnish mono allyl TEG **1-123** (2.82 g, 85%) as colorless oil. $\mathbf{R_f}$ = 0.3 (petroleum ether/EtOAc, 5:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.04 (s, 9H, $SiC(CH_3)_3$), 3.57–3.67 (m, 10H, OCH_2), 3.80 (dd, *J* = 5.6, 5.3 Hz, 2H, $CH_2OTBDPS$), 4.01 (d, *J* = 5.8 Hz, 2H, $OCH_2CH{=}CH_2$), 5.15–5.18 (m, 1H, $CH{=}CH_2$), 5.24–5.28 (m, 1H, $CH{=}CH_2$), 5.86–5.95 (m, 1H, $CH{=}CH_2$), 7.35–7.43 (m, 6H, Ar-H), 7.67–7.69 (m, 4H, Ar-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 19.2 ($SiC(CH_3)_3$), 26.8 ($SiC(CH_3)_3$), 63.4 (OCH_2), 69.4 (OCH_2), 70.7 (2 × OCH_2), 70.8 (OCH_2), 72.2 (OCH_2), 72.4 (OCH_2), 117.1 ($CH{=}CH_2$), 127.6 (4CH, Ar), 129.6 (2CH, Ar), 133.7 (2C, Ar), 134.8 ($CH{=}CH_2$), 135.6 (4CH, Ar); **HRMS** (ESI): $[M + Na]^+$ calcd for $C_{25}H_{36}O_4SiNa$ 451.22751, found 451.227742.

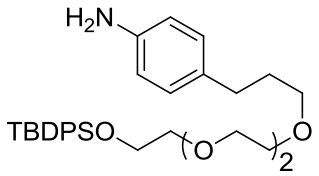
2,2-Dimethyl-16-(4-nitrophenyl)-3,3-diphenyl-4,7,10,13-tetraoxa-3-silahexadec-15-ene (1-124)



A solution of Grubb´s 2nd gen catalyst (198 mg, 5 mol%) in toluene (3 mL) was added at room temperature to a mixture of mono allyl TEG **1-123** (2.01 g, 4.7 mmol) and 4-nitro styrene **1-114** (2.1 g, 14.0 mmol) in dry and degassed toluene (20 mL). The reaction mixture was heated to 70 °C for 5 h before it was concentrated under vacuum. The crude product was purified by flash chromatography (petroleum ether/EtOAc, 17:3) to afford a mixture of isomers (trans/vinlylic trans/vinylic cis) of cross metathesis product **1-124** (1.67 g, 65 %) as yellow red oil. $\mathbf{R_f}$ = (petroleum ether/EtOAc, 4:1) 0.16 (trans), 0.29 (vinylic trans), 0.33 (vinylic cis); **^{1}H NMR** (400 MHz, $CDCl_3$): (vinylic cis) δ = 1.04 (s, 9H, $SiC(CH_3)_3$), 3.49 (d, *J* = 7.6 Hz, 2H, $CH{=}CHCH_2Ar$), 3.59–3.70 (m, 8H, OCH_2), 3.80 (dd, *J* = 5.6, 5.0 Hz, 2H, $CH_2OTBDPS$), 3.91–3.94 (m, 2H, CH_2), 4.51 (ddd, *J* = 7.6, 7.3, 6.3, Hz, 1H, $OCH{=}CHCH_2$), 6.15 (ddd, *J* = 6.1, 1.3,

1.3 Hz, 1H, OC*H*=CHCH$_2$), 7.33–7.42 (m, 8H, Ar-H), 7.66–7.68 (m, 4H, Ar-H), 8.10 (d, *J* = 8.6 Hz, 2H, Ar-H); (vinylic trans) δ = 1.03 (s, 9H, SiC(CH$_3$)$_3$), 3.33 (d, *J* = 7.3 Hz, 2H, CH=CHC*H*$_2$Ar), 3.60 (dd, *J* = 5.6, 5.0 Hz, 3H, OCH$_2$), 3.62–3.68 (m, 4H, OCH$_2$), 3.71–3.73 (m, 2H, OCH$_2$), 3.79–3.83 (m, 4H, OCH$_2$), 4.86 (ddd, *J* = 12.6, 7.6, 5.0 Hz, 1H, OCH=C*H*CH$_2$), 6.41 (d, *J* = 12.6 Hz, 1H, OC*H*=CH), 7.32–7.42 (m, 8H, Ar-H), 7.66–7.68 (m, 4H, Ar-H), 8.12 (d, *J* = 8.6 Hz, 2H, Ar-H); (allylic trans) δ = 1.03 (s, 9H, SiC(CH$_3$)$_3$), 3.58–3.71 (m, 10H, OCH$_2$), 3.80 (dd, *J* = 5.3, 5.3 Hz, 2H, OCH$_2$), 4.22 (dd, *J* = 5.6, 1.5 Hz, 2H, OC*H*$_2$CH=CH), 6.45 (ddd, *J* = 16.2, 5.6, 5.3 Hz, 1H, OCH$_2$C*H*=CH), 6.67 (d, *J* = 16.2 Hz, 1H, OCH$_2$CH=C*H*), 7.33–7.42 (m, 6H, Ar-H), 7.47 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.66–7.68 (m, 4H, Ar-H), 8.15 (d, *J* = 8.8 Hz, 2H, Ar-H); **^{13}C NMR** (100 MHz, CDCl$_3$): (vinylic cis) δ = 19.2 (Si*C*(CH$_3$)$_3$), 26.8 (SiC(*C*H$_3$)$_3$), 30.1 (*C*H$_2$Ar), 63.4 (OCH$_2$), 70.4 (OCH$_2$), 70.8 (OCH$_2$), 70.9 (OCH$_2$), 71.6 (OCH$_2$), 72.5 (OCH$_2$), 103.4 (OCH=*C*H), 123.5 (2CH, Ar), 127.6 (4CH, Ar), 129.0 (2CH, Ar), 129.6 (2CH, Ar), 133.6 (2C, Ar), 135.6 (4CH, Ar), 146.2 (C, Ar), 146.8 (O*C*H=CH), 149.8 (C, Ar); (vinylic trans) δ = 19.2 (Si*C*(CH$_3$)$_3$), 26.8 (SiC(*C*H$_3$)$_3$), 33.9 (*C*H$_2$Ar), 63.4 (OCH$_2$), 68.6 (OCH$_2$), 69.8 (OCH$_2$), 70.8 (2 × OCH$_2$), 72.5 (OCH$_2$), 101.1 (CH=*C*HCH$_2$), 123.6 (2CH, Ar), 127.6 (4CH, Ar), 129.0 (2CH, Ar), 129.6 (2CH, Ar), 133.7 (2C, Ar), 135.6 (4CH, Ar), 146.5 (C, Ar), 148.3 (*C*H=CHCH$_2$), 149.4 (C, Ar); (allylic trans) δ = 19.2 (Si*C*(CH$_3$)$_3$), 26.8 (SiC(*C*H$_3$)$_3$), 63.4 (OCH$_2$), 70.0 (OCH$_2$), 70.7 (OCH$_2$), 70.8 (2 × OCH$_2$), 71.2 (OCH$_2$), 72.5 (OCH$_2$), 124.0 (OCH$_2$CH=*C*H), 126.9 (2CH, Ar), 127.6 (4CH, Ar), 129.5 (C, Ar), 129.6 (2CH, Ar), 133.7 (2C, Ar), 135.6 (4CH, Ar), 143.3 (OCH$_2$*C*H=CH), 146.9 (C, Ar); **HRMS** (ESI): [M+Na]$^+$ calcd for $C_{31}H_{39}NO_6SiNa$ 572.24389, found 572.243999.

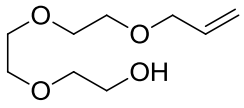
4-(2,2-Dimethyl-3,3-diphenyl-4,7,10,13-tetraoxa-3-silahexadecan-16-yl)aniline (1-125)



A mixture of metathesis products **1-124** (1.52 g, 2.8 mmol) in methanol (15 mL) was hydrogenated in presence of a catalytic amount of 10% Pd/C at room temperature under

hydrogen balloon pressure. After 24 h (TLC control), the reaction mixture was filtered through a pad of celite to remove the catalyst and the filtrate was concentrated under vacuum. The residue was purified by flash chromatography (petroleum ether/EtOAc, 3:2) to afford aniline **1-125** (1.14 g, 79%) as yellow red oil. $\mathbf{R_f}$ = 0.37 (petroleum ether/EtOAc, 3:2); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.04 (s, 9H, $SiC(CH_3)_3$), 1.78–1.88 (m, 2H, $OCH_2CH_2CH_2Ar$), 2.56 (dd, *J* = 7.8, 7.3 Hz, 2H, $OCH_2CH_2CH_2Ar$), 3.43 (dd, *J* = 6.6, 6.3 Hz, 2H, $OCH_2CH_2CH_2Ar$), 3.54–3.65 (m, 10H, OCH_2), 3.80 (dd, *J* = 5.6, 5.0 Hz, 2H, OCH_2), 6.68 (d, *J* = 8.3 Hz, 2H, Ar-H), 6.98 (d, *J* = 8.3 Hz, 2H, Ar-H), 7.34–7.43 (m, 6H, Ar-H), 7.66–7.69 (m, 4H, Ar-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 19.2 ($SiC(CH_3)_3$), 26.8 ($SiC(CH_3)_3$), 31.3 (2 × CH_2), 63.4 (OCH_2), 70.1 (OCH_2), 70.5 (OCH_2), 70.6 (OCH_2), 70.7 (OCH_2), 70.8 (OCH_2), 72.4 (OCH_2), 116.0 (2CH, Ar), 127.6 (4CH, Ar), 129.3 (2CH, Ar), 129.6 (2CH, Ar), 133.1 (C, Ar), 133.7 (2C, Ar), 135.6 (4CH, Ar), 142.5 (C, Ar); **HRMS** (ESI): $[M + Na]^+$ calcd for $C_{31}H_{43}NO_4SiNa$ 544.28536, found 544.285897.

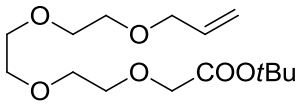
2-(2-(2-(Allyloxy)ethoxy)ethoxy)ethanol (1-126)[169]



To a solution of triethylene glycol **1-116** (22.34 g, 149 mmol) in dry THF (50 mL) under nitrogen, NaH (3.2 g, 79 mmol, 60% in mineral oil) was added portionwise at room temperature. The mixture was stirred for 15 min before allyl bromide (6.0 g, 50.0 mmol) was added. The reaction mixture was stirred further for 1 h at room temperature before the solvent was removed under vacuum. The residue was diluted with ethyl acetate (50 mL) and washed with saturated NaCl solution. The aqueous layer was extracted with EtOAc (2 × 15 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (EtOAc) to yield mono allyl TEG **1-126** (6.78 g, 89%) as colorless oil. $\mathbf{R_f}$ = 0.24 (EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 2.58 (s, 1H, OH), 3.57–3.60 (m, 4 H, OCH_2), 3.63–3.65 (m, 6H, OCH_2), 3.69–3.71 (m, 2H, CH_2OH), 4.00 (ddd, *J* = 5.8, 1.5, 1.3 Hz, 2H, $CH_2CH{=}CH_2$), 5.16 (dddd, *J* = 10.4, 1.5, 1.3, 1.3 Hz, 1H, $CH_2CH{=}CH_2$), 5.23–5.30 (m, 1H, $CH_2CH{=}CH_2$), 5.85–5.94 (m, 1H, $CH_2CH{=}CH_2$); **^{13}H NMR** (100 MHz,

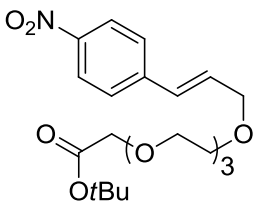
$CDCl_3$): δ = 61.7 (CH_2OH), 69.3 (OCH_2), 70.3 (OCH_2), 70.5 (OCH_2), 70.6 (OCH_2), 72.2 (OCH_2), 72.5 (OCH_2), 117.2 (CH=*C*H_2), 134.6 (*C*H=CH_2).

tert-Butyl 3,6,9,12-tetraoxapentadec-14-en-1-oate (1-127)[170]



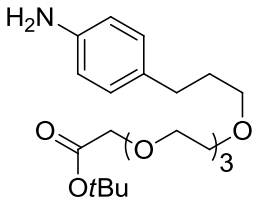
To a mixture of alcohol **1-126** (4.5 g, 23.6 mmol), *tert*-butyl bromoacetate (11.2 mL, 70.9 mmol) and tetra *n*-butyl ammonium hydrogen sulphate (2.0 g, 5.9 mmol) in benzene (23 mL) a 50% aq solution of NaOH (25 mL) was added slowly at room temperature. The reaction mixture was stirred at room temperature for 5 h (TLC control) before it was neutralized with a 1N HCl solution to pH ~5 and extracted with ethyl acetate (3 × 100 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under vacuum. The crude concentrate was purified by flash chromatography (petroleum ether/EtOAc, 1:1) to give *O*-alkylated compound **1-127** (6.95 g, 96%) as colorless oil. $\mathbf{R}_f$ = 0.3 (petroleum ether/EtOAc, 3:2); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.45 (s, 9H, $C(CH_3)_3$), 3.56–3.59 (m, 2H, OCH_2), 3.62–3.71 (m, 10H, OCH_2), 3.99–4.01 (m, 4H, O*C*H_2CH=CH_2, O*C*H_2CO), 5.14–5.17 (m, 1H, CH=CH_2), 5.25 (dddd, *J* = 17.2, 1.8, 1.5, 1.5 Hz, 1H, C*H*=CH_2), 5.84–5.94 (m, 1H, C*H*=CH_2); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 28.1 (C(*C*H_3)$_3$), 69.0 (O*C*H_2CO), 69.4 (OCH_2), 70.6 (4 OCH_2), 70.7 (OCH_2), 72.2 (O*C*H_2CH=CH_2), 81.5 (*C*(CH_3)$_3$), 117.0 (CH=*C*H_2), 134.7 (*C*H=CH_2), 169.6 (*C*O_2*t*Bu); **HRMS** (ESI): [M+Na]+ calcd for $C_{15}H_{28}O_6Na$ 327.17781, found 327.17765.

(*E*)-*tert*-Butyl 15-(4-nitrophenyl)-3,6,9,12-tetraoxapentadec-14-en-1-oate (1-128)



To a solution of *O*-allyl TEG **1-127** (2.2 g, 7.2 mmol) and 4-nitrostyrene **1-114** (3.23 g, 21.7 mmol) in CH_2Cl_2 (55 mL, dry and degassed) Grubb's 2nd catalyst (307 mg, 5 mol%) in CH_2Cl_2 (5 mL) was added dropwise over 10 min at room temperature and the reaction mixture was heated to reflux for 6 h. After complete conversion, the reaction mixture was concentrated under vacuum and the residue was purified by flash chromatography (petroleum ether/EtOAc, 1:1) to furnish *trans* isomer of metathesis product **1-128** (2.43 g, 80%) as reddish brown oil. $\mathbf{R_f}$ = 0.2 (petroleum ether/EtOAc, 1:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.43 (s, 9H, $C(CH_3)_3$), 3.63–3.69 (m, 12H, OCH_2), 3.98 (s, 2H, OCH_2CO_2tBu), 4.21 (dd, *J* = 5.6, 1.5 Hz, 2H, $ArCH{=}CHCH_2$), 6.44 (ddd, *J* = 15.9, 5.6, 5.5 Hz, 1H, $ArCH{=}CHCH_2$), 6.66 (d, *J* = 16.2 Hz, 1H, $ArCH{=}CHCH_2$), 7.47 (d, *J* = 8.6 Hz, 2H, Ar-H), 8.13 (d, *J* = 8.6 Hz, 2H, Ar-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 28.0 ($C(CH_3)_3$), 68.9 (OCH_2CO_2tBu), 69.9 (OCH_2), 70.5 (2 × OCH_2), 70.6 (2 × OCH_2), 71.1 (OCH_2), 81.4 ($C(CH_3)_3$), 123.9 (CH, Ar), 126.8 (CH, Ar), 129.4 ($ArCH{=}CHCH_2$), 131.3 ($ArCH{=}CHCH_2$), 143.2 (C, Ar), 146.8 (C, Ar), 169.5 (CH_2COO); **HRMS** (ESI): $[M + Na]^+$ calcd for $C_{21}H_{31}NO_8Na$ 448.19419, found 448.194519.

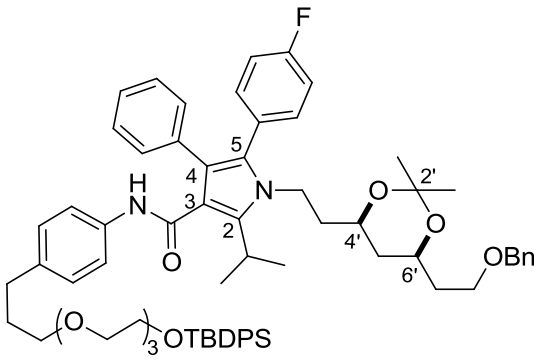
tert-Butyl-15-(4-aminophenyl)-3,6,9,12-tetraoxapentadecan-1-oate (1-129)



A solution of nitro compound **1-128** (2.55 g, 5.5 mmol) in dry EtOAc (40 mL) was hydrogenated under balloon pressure in presence of a catalytic amount of 10% Pd/C overnight (~14 h). The catalyst was filtered through a pad of celite and the filtrate was concentrated in vacuo. The crude oil was purified by flash chromatography (petroleum ether/EtOAc, 2:3) to furnish amine **1-129** (2.3 g, 96%) as slightly green oil. $\mathbf{R_f}$ = 0.2 (petroleum ether/EtOAc, 2:3); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.46 (s, 9H, $C(CH_3)_3$), 1.79–1.86 (m, 2H, CH_2CH_2Ar), 2.55 (dd, *J* = 7.8, 7.3 Hz, 2H, CH_2CH_2Ar), 3.43 (dd, *J* = 6.6, 6.6 Hz, 2H, $OCH_2CH_2CH_2Ar$), 3.55–3.58 (m, 4H, NH_2, OCH_2), 3.61–3.71 (m, 10H, OCH_2), 4.00 (m, 2H, OCH_2CO_2tBu), 6.60 (d, *J* = 8.3 Hz, 2H, Ar-H), 6.95 (d, *J* = 8.3 Hz, 2H, Ar-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 28.1 ($C(CH_3)_3$), 31.3 (CH_2), 31.4

(CH_2), 69.0 (O*C*H_2CO_2tBu), 70.1 (OCH_2), 70.5 (OCH_2), 70.6 (4 × OCH_2), 70.7 (OCH_2), 81.5 (*C*$(CH_3)_3$), 115.2 (2CH, Ar), 129.2 (2CH, Ar), 131.9 (C, Ar), 144.2 (C, Ar), 169.7 (OCH_2*C*O_2tBu); **HRMS** (ESI): $[M + Na]^+$ calcd for $C_{15}H_{35}NO_6Na$ 420.23566 found 420.235325.

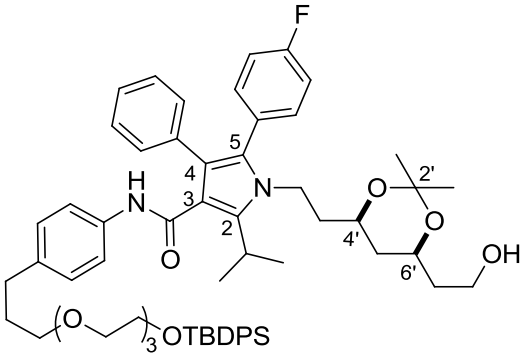
1-(2-((4*R*,6*S*)-6-(2-(Benzyloxy)ethyl)-2,2-dimethyl-1,3-dioxan-4-yl)ethyl)-*N*-(4-(2,2-dimethyl-3,3-diphenyl-4,7,10,13-tetraoxa-3-silahexadecan-16-yl)phenyl)-5-(4-fluorophenyl)-2-isopropyl-4-phenyl-1*H*-pyrrole-3-carboxamide (1-130)



To a cooled solution of acid **1-110** (440 mg, 0.73 mmol) and amine **1-125** (382 mg, 0.73 mmol) in CH_2Cl_2 (10 mL) at 0 °C were added diisopropylethylamine (376 μL, 2.2 mmol) and PyBrOP (410 mg, 0.88 mmol) successively. The mixture was stirred at room temperature for 12 h then diluted with CH_2Cl_2 (10 mL), washed with saturated $NaHCO_3$ solution (10 mL) and saturated NaCl solution. The organic layer was dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography to afford amide **1-130** (540 mg 73%) as yellow colored sticky oil. $\mathbf{R_f}$ = 0.32 (EtOAc/petroleum ether, 3:7); $\mathbf{[\alpha]_D^{20}}$ = −0.6 (*c* 1, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 0.95–1.07 (m, 1H, 5'-H), 1.04 (s, 9H, $SiC(CH_3)_3$), 1.22 (ddd, *J* = 12.9, 2.5, 2.3 Hz, 1H, 5'-H), 1.29 (s, 3H, 2'-CH_3), 1.33 (s, 3H, 2'-CH_3), 1.52 (d, *J* = 7.1 Hz, 6H, $CH(CH_3)_2$), 1.60–1.74 (m, 4H, CH_2, NCH_2CH_2, CH_2CH_2OBn), 1.77–1.87 (m, 2H, $OCH_2CH_2CH_2Ar$), 2.56 (dd, *J* = 8.1, 7.3 Hz, 2H, $OCH_2CH_2CH_2Ar$), 3.41 (dd, *J* = 6.6, 6.3 Hz, 2H, $OCH_2CH_2CH_2Ar$), 3.44–3.68 (m, 14H, 4'-H, $CH(CH_3)_2$, OCH_2), 3.75–3.85 (m, 1H, NCH_2CH_2), 3.80 (dd, *J* = 5.6, 5.3 Hz, 2H, CH_2CH_2OBn), 3.93 (dddd, *J* = 11.6, 7.3, 5.0, 2.3 Hz, 1H, 6'-H), 3.99–4.11 (m, 1H, NCH_2CH_2), 4.45 (d, *J* = 12.1 Hz, 1H, OCH_2Ph), 4.48 (d, *J* = 12.1 Hz, 1H, OCH_2Ph), 6.80 (br, s, 1H, NH), 6.92–7.03 (m, 6H, Ar-H), 7.09–7.21 (m, 7H, Ar-H),

7.26–7.43 (m, 11H, Ar-H), 7.64–7.71 (m, 4H, Ar-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 19.2 (Si*C*$(CH_3)_3$), 19.8 (2'-CH_3), 21.6 (CH(*C*$H_3)_2$), 21.7 (CH(*C*$H_3)_2$), 26.1 (*C*H$(CH_3)_2$), 26.8 (SiC(*C*$H_3)_3$), 30.0 (2'-CH_3), 31.2 (OCH_2*C*H_2CH_2Ar), 31.6 (OCH_2CH_2*C*H_2Ar), 36.4 (C-5'), 36.5 (NCH_2*C*H_2), 38.1 (*C*H_2CH_2OBn), 40.8 (NCH_2*C*H_2), 63.4 (CH_2*C*H_2OBn), 65.7 (C-6'), 66.0 (OCH_2), 66.5 (C-4'), 70.1 (OCH_2), 70.4 (OCH_2), 70.6 (OCH_2), 70.7 (OCH_2), 70.8 (OCH_2), 72.4 (OCH_2), 72.9 (O*C*H_2Ph), 98.5 (C-2'), 115.3 (d, J_{CF} = 22.0 Hz, 2CH, Ar), 115.4 (C, Ar), 119.7 (2CH, Ar), 121.7 (C, Ar), 126.5 (CH, Ar), 127.6 (7CH, Ar), 128.3 (C, Ar), 128.3 (4CH, Ar), 128.6 (2CH, Ar), 128.7 (C, Ar), 129.6 (2CH, Ar), 130.5 (2CH, Ar), 133.2 (d, J_{CF} = 8.0 Hz, 2CH, Ar), 133.7 (C, Ar), 134.7 (C, Ar), 135.6 (4CH, Ar), 136.1 (C, Ar), 137.2 (C, Ar), 138.5 (2C, Ar), 141.3 (C, Ar), 162.9 (d, J_{CF} = 377.6 Hz, C, Ar), 163.5 (C=O, amide); **HRMS** (ESI): $[M+Na]^+$ calcd for $C_{68}H_{83}FN_2O_8SiNa$ 1125.579493, found 1125.579667.

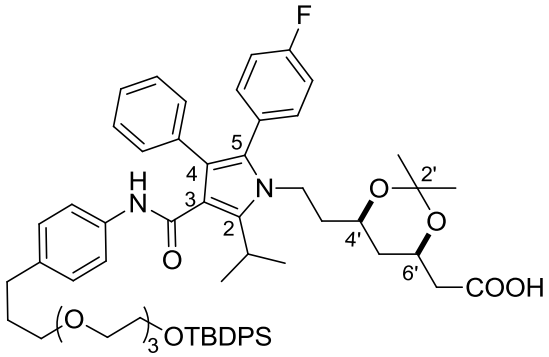
_N_-(4-(2,2-Dimethyl-3,3-diphenyl-4,7,10,13-tetraoxa-3-silahexadecan-16-yl)phenyl)-5-(4-fluorophenyl)-1-(2-((4_R_,6_S_)-6-(2-hydroxyethyl)-2,2-dimethyl-1,3-dioxan-4-yl)ethyl)-2-isopropyl-4-phenyl-1_H_-pyrrole-3-carboxamide (1-131)



A solution of benzyl ether **1-130** (550 mg, 0.50 mmol) in dry ethyl acetate (15 mL) was hydrogenated under balloon pressure in presence of 20% $Pd(OH)_2$ on carbon (110 mg, 20 wt%) for 8 h. The mixture was filtered through a pad of celite, the filtrate was concentrated under reduced pressure and purified by short filtration column (EtOAc/petroleum ether, 1:1) to afford alcohol **1-131** (438 mg, 87%) as yellow colored thick oil. $\mathbf{R_f}$ = 0.27 (EtOAc/petroleum ether, 1:1); $\mathbf{[\alpha]_D^{20}}$ = −0.6 (*c* 1, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.03 (s, 9H, SiC$(CH_3)_3$), 1.12 (ddd, *J* = 12.9, 11.4, 11.1 Hz, 1H, 5'-H), 1.21 (ddd, *J* = 12.9, 2.8, 2.5 Hz, 1H, 5'-H), 1.25 (s, 1H,

OH), 1.31 (s, 3H, 2'-CH_3), 1.36 (s, 3H, 2'-CH_3), 1.52 (d, J = 7.1 Hz, 6H, CH(CH_3)$_2$), 1.58–1.71 (m, 4H, NCH$_2$CH_2, CH_2CH$_2$OH), 1.76–1.87 (m, 2H, OCH$_2$CH_2CH$_2$Ar), 2.56 (dd, J = 8.1, 7.3 Hz, 2H, OCH$_2$CH$_2$CH_2Ar), 3.41 (dd, J = 6.6, 6.3 Hz, 2H, OCH_2CH$_2$CH$_2$Ar), 3.51–3.76 (m, 14H, 4'-H, CH$_2$CH_2OH, CH(CH$_3$)$_2$, OCH$_2$), 3.79 (dd, J = 5.5, 5.3 Hz, 2H, OCH$_2$), 3.78–3.87 (m, 1H, NCH_2CH$_2$), 3.95–4.12 (m, 2H, NCH_2CH$_2$, 6'-H), 6.81 (s, 1H, CONH), 5.92–7.04 (m, 6H, Ar-H), 7.10–7.21 (m, 7H, Ar-H), 7.32–7.44 (m, 6H, Ar-H), 7.64–7.70 (m, 4H, Ar-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 19.2 (SiC(CH$_3$)$_3$), 19.8(2'-CH_3), 21.6 (CH(CH$_3$)$_2$), 21.8 (CH(CH$_3$)$_2$), 26.1 (CH(CH$_3$)$_2$), 26.8 (SiC(CH$_3$)$_3$), 30.0 (2'-CH_3), 31.2 (OCH$_2$CH_2CH$_2$Ar), 31.6 (OCH$_2$CH$_2$CH_2Ar), 36.1 (C-5'), 38.0 (NCH$_2$$CH_2$), 38.0 ($CH_2CH_2$OH), 40.8 (N$CH_2CH_2$), 60.6 (CH$_2$$CH_2$OH), 63.4 (OCH$_2$), 66.5 (C-4'), 68.8 (C-6'), 70.1 (OCH$_2$), 70.4 (OCH$_2$), 70.6 (OCH$_2$), 70.7 (2OCH$_2$), 72.4 (OCH$_2$), 98.6 (C-2'), 115.3 (d, J_{CF} = 21.2 Hz, 2CH, Ar), 119.7 (2CH, Ar), 121.7 (C, Ar), 126.5 (CH, Ar), 127.6 (4CH, Ar), 128.4 (d, J_{CF} = 3.7 Hz, C, Ar), 128.3 (C, Ar), 128.3 (2CH, Ar), 128.6 (2CH, Ar), 128.7 (C, Ar), 129.6 (2CH, Ar), 130.4 (2CH, Ar), 133.2 (d, J_{CF} = 8.0 Hz, 2CH, Ar), 133.7 (C, Ar), 134.6 (C, Ar), 135.6 (4CH, Ar), 136.1 (C, Ar), 137.2 (C, Ar), 141.2 (C, Ar), 162.9 (d, J_{CF} = 376.9 Hz, C, Ar), 163.5 (CONH); **HRMS** (ESI): $[M+Na]^+$ calcd for $C_{51}H_{77}FN_2O_8SiNa$ 1035.53254, found 1035.532117.

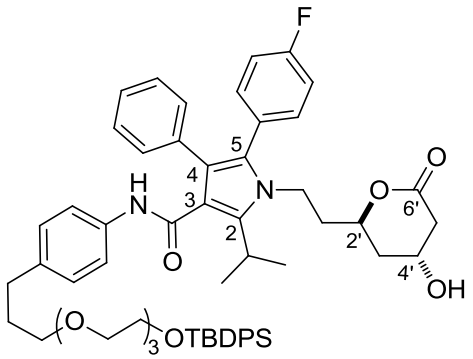
2-((4*R*,6*R*)-6-(2-(3-((4-(2,2-Dimethyl-3,3-diphenyl-4,7,10,13-tetraoxa-3-silahexadecan-16-yl)phenyl)carbamoyl)-5-(4-fluorophenyl)-2-isopropyl-4-phenyl-1*H*-pyrrol-1-yl)ethyl)-2,2-dimethyl-1,3-dioxan-4-yl)acetic acid (1-132)



Dess-Martin periodinane (69 mg, 0.16 mmol) was added in one portion to a solution of alcohol **1-131** (138 mg, 0.14 mmol) in CH_2Cl_2 (3 mL) at 0 °C. The mixture was stirred for 1 h at room

temperature, diluted with CH_2Cl_2 (5 mL), washed successively with saturated $NaHCO_3$ (5 mL), 1M $Na_2S_2O_3$ (5 mL), and saturated NaCl solution. The organic layer was filtered, dried over Na_2SO_4, filtered and purified through a short silica plug by flash chromatography to yield pure aldehyde (105 mg, 0.10 mmol) which was dissolved in *t*-butanol (6 mL) and 2-methyl-2-butene (0.6 mL) was added. Then a mixture of $NaClO_2$ (19 mg, 0.21 mmol) and $NaH_2PO_4 \bullet 2H_2O$ (97 mg, 0.62 mmol) in water (6 mL) was added dropwise to the reaction mixture at room temperature and the resultant biphasic reaction mixture was stirred for 6 h. The organic layer was separated and the aqueous layer extracted with ethyl acetate (3 × 10 mL), dried over $MgSO_4$, filtered, and concentrated under vacuum. The residue on purification by flash chromatography (EtOAc/petroleum ether/AcOH, 1:1:0.001) provided acid **1-132** (104 mg, 74%, two steps) as yellowish sticky solid. $\mathbf{R_f}$ = (EtOAc/petroleum ether/AcOH, 1:1:0.001) 0.29; $\mathbf{[\alpha]_D^{20}}$ = +1.8 (*c* 1, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.00–1.11 (m, 1H, 5'-H), 1.03 (s, 9H, $SiC(CH_3)_3$), 1.29–1.39 (m, 1H, 5'-H), 1.31 (s, 3H, 2'-CH_3), 1.36 (s, 3H, 2'-CH_3), 1.51 (d, *J* = 7.1 Hz, 6H, $CH(CH_3)_2$), 1.59–1.73 (m, 2H, NCH_2CH_2), 1.76–1.86 (m, 2H, $OCH_2CH_2CH_2Ar$), 2.38 (dd, *J* = 15.9, 5.8 Hz, 1H, CH_2COOH), 2.52 (dd, *J* = 15.9, 6.8 Hz, 1H, CH_2COOH), 2.56 (dd, *J* = 8.1, 7.3 Hz, 2H, $OCH_2CH_2CH_2Ar$), 3.41 (dd, *J* = 6.6, 6.6 Hz, 2H, $OCH_2CH_2CH_2Ar$), 3.48–3.73 (m, 12H, 4'-H, $CH(CH_3)_2$, OCH_2), 3.79 (dd, *J* = 5.6, 5.0 Hz, 2H, OCH_2), 3.83 (ddd, *J* = 15.9, 9.6, 6.3 Hz, 1H, NCH_2CH_2), 4.07 (ddd, *J* = 14.9, 9.8, 5.6 Hz, 1H, NCH_2CH_2), 4.14–4.24 (m, 1H, 6'-H), 6.81 (s, 1H, CONH), 6.92–7.04 (m, 6H, Ar-H), 7.10–7.21 (m, 7H, Ar-H), 7.31–7.43 (m, 6H, Ar-H), 7.62–7.71 (m, 4H, Ar-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 19.2 ($SiC(CH_3)_3$), 19.6 (2'-CH_3), 21.6 ($CH(CH_3)_2$), 21.8 ($CH(CH_3)_2$), 26.1 ($CH(CH_3)_2$), 26.8 ($SiC(CH_3)_3$), 29.8 (2'-CH_3), 31.2 ($OCH_2CH_2CH_2Ar$), 31.6 ($OCH_2CH_2CH_2Ar$), 35.7 (NCH_2CH_2), 37.8 (C-5') 40.7 (NCH_2CH_2, CH_2COOH), 63.4 (OCH_2), 65.5 (C-6'), 66.4 (C-4'), 70.1 (OCH_2), 70.4 (OCH_2), 70.6 (OCH_2), 70.7 (2 × OCH_2), 70.7 (OCH_2), 72.4 (OCH_2), 99.0 (C-2'), 115.4 (d, J_{CF} = 21.2 Hz, 2CH, Ar), 115.5 (C, Ar), 119.8 (2CH, Ar), 121.8 (C, Ar), 126.5 (CH, Ar), 127.6 (4CH, Ar), 128.1 (d, J_{CF} = 3.7 Hz, C, Ar), 128.3 (C, Ar), 128.3 (2CH, Ar), 128.6 (2CH, Ar), 128.7 (C, Ar), 129.6 (2CH, Ar), 130.4 (2CH, Ar), 133.1 (d, J_{CF} = 8.0 Hz, 2CH, Ar), 133.7 (C, Ar), 134.5 (C, Ar), 135.6 (4CH, Ar), 136.0 (C, Ar), 137.3 (C, Ar), 141.1 (C, Ar), 163.0 (d, J_{CF} = 393.0 Hz, C, Ar), 163.5 (CONH); **HRMS** (ESI): $[M+Na]^+$ calcd for $C_{61}H_{75}FN_2O_9Na$ 1049.51181, found 1049.511774.

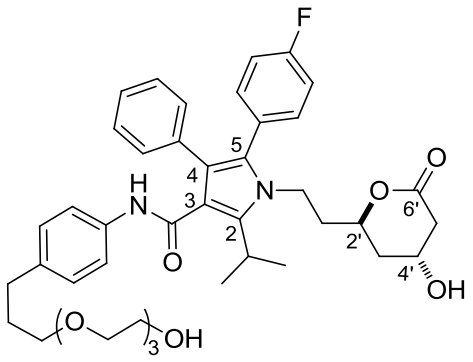
_N_-(4-(2,2-Dimethyl-3,3-diphenyl-4,7,10,13-tetraoxa-3-silahexadecan-16-yl)phenyl)-5-(4-fluorophenyl)-1-(2-((2*R*,4*R*)-4-hydroxy-6-oxotetrahydro-2*H*-pyran-2-yl)ethyl)-2-isopropyl-4-phenyl-1*H*-pyrrole-3-carboxamide (1-133)



A mixture of acetonide acid **1-132** (126 mg, 0.12 mmol) and camphorsulphonic acid (57 mg, 0.24 mmol) in CH_2Cl_2 (4 mL) was stirred at room temperature for 3 h. The mixture was diluted with CH_2Cl_2 (10 mL), washed with water (3 × 10 mL), saturated NaCl solution (10 mL), dried over Na_2SO_4, filtered and concentrated. The crude residue was purified by flash chromatography to afford pure lactone **1-133** (105 mg, 90%) as yellow colored sticky solid. $\mathbf{R_f}$ = 0.22 (EtOAc/petroleum ether, 7:3); $\mathbf{[\alpha]_D^{20}}$ = +13.2 (*c* 1, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.03 (s, 9H, $SiC(CH_3)_3$), 1.50 (d, *J* = 6.6 Hz, 3H, $CH(CH_3)_2$), 1.52 (d, *J* = 6.8 Hz, 3H, $CH(CH_3)_2$), 1.55–1.61 (m, 1H, 3'-H), 1.67–1.92 (m, 6H, NCH_2CH_2, 3'-H, $OCH_2CH_2CH_2Ar$, OH), 2.48–2.60 (m, 3H, 5'-H, $OCH_2CH_2CH_2Ar$), 2.64 (dd, *J* = 17.7, 4.8 Hz, 1H, 5'-H), 3.40 (dd, *J* = 6.6, 6.6 Hz, 2H, $OCH_2CH_2CH_2Ar$), 3.46–3.68 (m, 11H, $CH(CH_3)_2$, OCH_2), 3.79 (dd, *J* = 5.3, 5.3 Hz, 2H, OCH_2), 4.01 (ddd, *J* = 14.9, 9.1, 4.8 Hz, 1H, 1-H), 4.20 (ddd, *J* = 14.9, 9.8, 4.5 Hz, 1H, 1-H), 4.26–4.32 (m, 1H, 4'-H), 4.51 (dddd, *J* = 11.4, 8.6, 3.3, 3.0 Hz, 1H, 2'-H), 6.82 (s, 1H, CONH), 6.92–7.04 (m, 6H, Ar-H), 7.09–7.22 (m, 7H, Ar-H), 7.31–7.43 (m, 6H, Ar-H), 7.62–7.70 (m, 4H, Ar-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 19.2 ($SiC(CH_3)_3$), 21.7 ($CH(CH_3)_2$), 22.0 ($CH(CH_3)_2$), 26.2 ($CH(CH_3)_2$), 26.8 ($SiC(CH_3)_3$), 31.2 ($OCH_2CH_2CH_2Ar$), 31.6 ($OCH_2CH_2CH_2Ar$), 35.6 (C-3'), 37.1 (NCH_2CH_2), 38.5 (C-5'), 40.7 (NCH_2CH_2), 62.5 (C-4'), 63.4 (OCH_2), 70.1 (OCH_2), 70.4 (OCH_2), 70.6 (OCH_2), 70.7 (2 × OCH_2), 72.4 (OCH_2), 73.0 (C-2'), 115.6 (d, J_{CF} = 22.0 Hz, 2CH, Ar), 115.8 (C, Ar), 119.8 (2CH, Ar), 122.0 (C, Ar), 126.6 (CH, Ar), 127.6 (4CH, Ar), 128.0 (d, J_{CF} = 3.7 Hz, C, Ar), 128.3 (2CH, Ar), 128.6 (2CH, Ar), 129.6 (2CH, Ar), 130.3 (2CH, Ar), 133.1 (d, J_{CF} = 133.1 Hz, 2CH, Ar), 133.1 (2C, Ar), 134.4 (C,

Ar), 135.6 (4CH, Ar), 136.0 (C, Ar), 137.4 (C, Ar), 141.2 (C, Ar), 162.9 (d, J_{CF} = 374.0 Hz, C, Ar), 163.5 (CONH), 169.4 (C=O, lactone); **HRMS** (ESI): $[M+Na]^+$ calcd for $C_{58}H_{69}FN_2O_8SiNa$ 991.46994, found 991.469476.

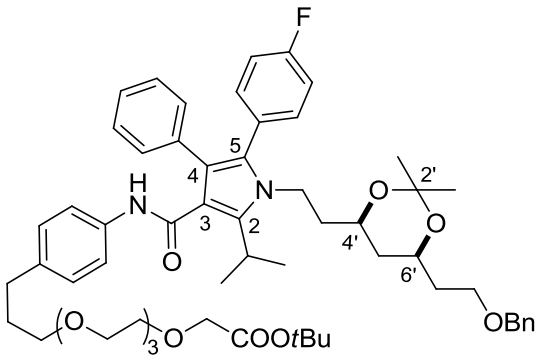
5-(4-Fluorophenyl)-1-(2-((2*R*,4*R*)-4-hydroxy-6-oxotetrahydro-2*H*-pyran-2-yl)ethyl)-*N*-(4-(3-(2-(2-(2-hydroxyethoxy)ethoxy)ethoxy)propyl)phenyl)-2-isopropyl-4-phenyl-1*H*-pyrrole-3-carboxamide (1-134)



HF•pyridine complex (53 μL, 1.86 mmol, 70%) was added to a cooled (0 ^{o}C) solution of silyl ether **1-133** (120 mg, 0.125 mmol) in THF (3 mL) in a plastic tube and the mixture was allowed to stir overnight. The mixture was diluted with ethyl acetate (10 mL), washed with the saturated $NaHCO_3$ solution (5 mL), 10% $CuSO_4$ solution (2 × 5 mL) followed by washing with saturated NaCl solution. The organic layer was dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash chromatography (methanol/CH_2Cl_2, 1:20) to afford lactone **1-134** (78 mg, 87%) as colorless sticky solid. $\mathbf{R_f}$ = 0.21 (methanol/CH_2Cl_2, 1:20); $\mathbf{[\alpha]_D^{20}}$ = +14.4 (*c* 1, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.50 (d, *J* = 6.8 Hz, 3H, CH(C*H*$_3$)$_2$), 1.51 (d. *J* = 6.6 Hz, 3H, CH(C*H*$_3$)$_2$), 1.54–1.61 (m, 1H, 3'-H), 1.64–1.96 (m, 6H, NCH$_2$C*H*$_2$, 3'-H, OCH$_2$C*H*$_2$CH$_2$Ar, OH), 2.48–2.60 (m, 3H, 5'-H, OCH$_2$CH$_2$C*H*$_2$Ar), 2.62 (dd, *J* = 17.9, 4.8 Hz, 1H, 5'-H), 3.41 (dd, *J* = 6.6, 6.3 Hz, 2H, OC*H*$_2$CH$_2$CH$_2$Ar), 3.46–3.74 (m, 13H, C*H*(CH$_3$)$_2$, OCH$_2$), 4.00 (ddd, *J* = 15.2, 10.1, 5.8 Hz, 1H, NC*H*$_2$CH$_2$), 4.19 (ddd, *J* = 14.9, 10.4, 4.8 Hz, 1H, NC*H*$_2$CH$_2$), 4.27 (m, 1H, 4'-H), 4.50 (dddd, *J* = 11.4, 8.6, 3.3, 3.0 Hz, 1H, 2'-H), 6.84 (s, 1H, CONH), 6.92–7.05 (m, 6H, Ar-H), 7.07–7.22 (m, 7H, Ar-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 21.7 (CH(*C*H$_3$)$_2$), 22.0 (CH(*C*H$_3$)$_2$), 26.1 (*C*H(CH$_3$)$_2$), 31.1 (OCH$_2$*C*H$_2$CH$_2$Ar), 31.5

($OCH_2CH_2CH_2Ar$), 35.6 (C-3'), 37.1 (NCH_2CH_2), 38.5 (C-5'), 40.7 (NCH_2CH_2), 61.7 (OCH_2), 62.4 (C-4'), 70.0 (OCH_2), 70.3 ($OCH_2CH_2CH_2Ar$), 70.4 (OCH_2), 70.5 (OCH_2), 70.6 (OCH_2), 72.5 (OCH_2), 73.0 (C-3), 115.6 (d, J_{CF} = 21.2 Hz, 2CH, Ar), 115.7 (C, Ar), 119.8 (2CH, Ar), 122.0 (C, Ar), 126.6 (CH, Ar), 128.0 (d, J_{CF} = 2.9 Hz, C, Ar), 128.3 (2CH, Ar), 128.6 (2CH, Ar), 130.3 (2CH, Ar), 133.1 (d, J_{CF} = 8.0 Hz, 2CH, Ar), 134.4 (C, Ar), 136.0 (C, Ar), 137.4 (C, Ar), 141.1 (C, Ar), 162.9 (d. J_{CF} = 378.4 Hz, C, Ar), 163.5 (CONH), 169.5 (C=O, lactone); **HRMS** (ESI): $[M+Na]^+$ calcd for $C_{42}H_{51}FN_2O_8Na$ 753.35217, found 753.352783.

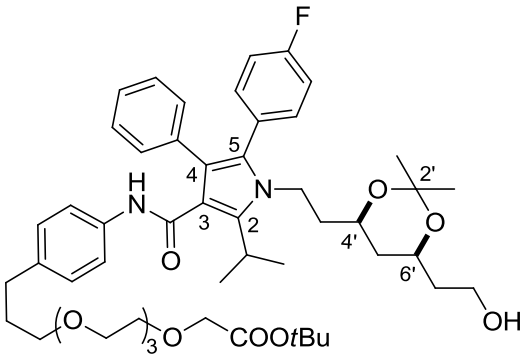
tert-Butyl 2-(2-(2-(3-(4-(1-(2-((4*R*,6*S*)-6-(2-(benzyloxy)ethyl)-2,2-dimethyl-1,3-dioxan-4-yl)ethyl)-5-(4-fluorophenyl)-2-isopropyl-4-phenyl-1*H*-pyrrole-3-carboxamido)phenyl)propoxy)ethoxy)ethoxy)acetate (1-135)



A mixture of acid **1-110** (520 mg, 0.87 mmol) and amine **1-129** (306 mg, 0.87 mmol) in CH_2Cl_2 (15 mL) was cooled to 0 °C followed by the addition of DIPEA (0.44 mL, 2.6 mmol) and PyBrOP (606 mg, 1.3 mmol). The mixture was stirred at room temperature for overnight before it was diluted with CH_2Cl_2 (10 mL), washed with saturated $NaHCO_3$ solution (10 mL), water (2 × 10 mL) and saturated NaCl solution. The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. Purification by flash chromatography (EtOAc/petroleum ether, 2:3) provided amide **1-135** (705 mg, 87%) as colorless sticky solid. $\mathbf{R_f}$ = 0.38 (EtOAc/petroleum ether, 3:2); $\mathbf{[\alpha]_D^{20}}$ = −0.6 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 0.99 (ddd, *J* = 12.4, 11.9, 11.6 Hz, 1H, 5'-H), 1.22 (ddd, *J* = 12.9, 2.5, 2.3 Hz, 1H. 5'-H), 1.29 (s, 3H, 2'-CH_3), 1.32 (s, 3H, 2'-CH_3), 1.46 (s, 9H, $C(CH_3)_3$), 1.51 (d, *J* = 7.3 Hz, 6H, $CH(CH_3)_2$), 1.56–1.76 (m, 4H, NCH_2CH_2, CH_2CH_2OBn), 1.77–1.87 (m, 2H, $OCH_2CH_2CH_2Ar$),

2.57 (dd, *J* = 8.1, 7.3 Hz, 2H, $OCH_2CH_2CH_2Ar$), 3.41 (dd, *J* = 6.6, 6.6 Hz, 2H, $OCH_2CH_2CH_2Ar$), 3.44–3.59 (m, 5H, CH_2CH_2OBn, $CH(CH_3)_2$, OCH_2), 3.59–3.73 (m, 11H, 4'-H, OCH_2), 3.79 (ddd, *J* = 14.9, 10.1, 6.3 Hz, 1H, NCH_2CH_2), 3.93 (dddd, *J* = 11.6, 7.3, 4.8, 2.3 Hz, 1H, 6'-H), 4.00 (s, 2H, OCH_2CO_2tBu), 4.05 (ddd, *J* = 14.9, 9.1, 4.8 Hz, 1H, NCH_2CH_2), 4.46 (d, *J* = 12.1 Hz, 1H, OCH_2Ph), 4.47 (d, *J* = 12.4 Hz, 1H, OCH_2Ph), 6.80 (s, 1H, CONH), 6.93–7.02 (m, 5H, Ar-H), 7.10–7.21 (m, 7H, Ar-H), 7.23–7.35 (m, 6H, Ar-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 19.8 (2'-CH_3), 21.6 ($CH(CH_3)_2$), 21.7 ($CH(CH_3)_2$), 26.1 ($CH(CH_3)_2$), 28.1 ($C(CH_3)_3$), 30.0 (2'-CH_3), 31.1 ($OCH_2CH_2CH_2Ar$), 31.6 ($OCH_2CH_2CH_2Ar$), 36.4 (C-5'), 36.4 (NCH_2CH_2), 38.1 (CH_2CH_2OBn), 40.8 (NCH_2CH_2), 65.7 (C-6'), 66.0 (OCH_2), 66.5 (C-3), 69.0 (C-7), 70.1 (OCH_2CO_2tBu), 70.4 (OCH_2), 70.6 (OCH_2), 70.6 (3 × OCH_2), 70.7 (OCH_2), 72.9 (OCH_2), 81.5 ($C(CH_3)_3$), 98.5 (C-2'), 115.3 (d, J_{CF} = 21.2 Hz, 2CH, Ar), 115.4 (C, Ar), 119.7 (2CH, Ar), 121.7 (C, Ar), 126.5 (CH, Ar), 127.6 (4CH, Ar), 128.2 (C, Ar), 128.3 (3CH, Ar), 128.6 (2CH, Ar), 128.7 (C, Ar), 130.4 (2CH, Ar), 133.2 (d, J_{CF} = 8.0 Hz, 2CH, Ar), 134.7 (C, Ar); 136.1 (C, Ar), 137.2 (C, Ar), 138.5 (C, Ar), 141.3 (C, Ar), 162.9 (d, J_{CF} = 379.8 Hz, C, Ar), 163.5 (CONH), 169.7 (CO_2tBu); **HRMS** (ESI): $[M+Na]^+$ calcd for $C_{58}H_{75}FN_2O_{10}Na$ 1001.52980, found 1001.530129.

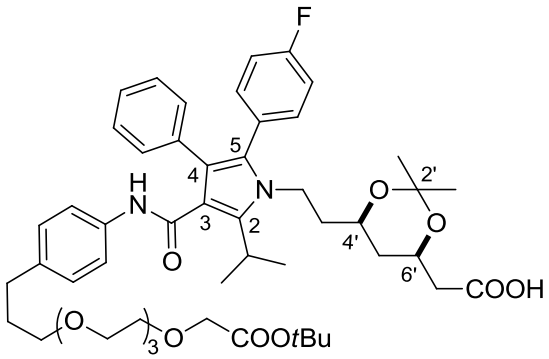
tert-Butyl 2-(2-(2-(3-(4-(5-(4-fluorophenyl)-1-(2-((4*R*,6*S*)-6-(2-hydroxyethyl)-2,2-dimethyl-1,3-dioxan-4-yl)ethyl)-2-isopropyl-4-phenyl-1*H*-pyrrole-3-carboxamido)phenyl)propoxy)ethoxy)ethoxy)acetate (1-136)



A solution of benzyl ether **1-135** (650 mg, 0.07 mmol) in dry ethyl acetate (7 mL) was hydrogenated for 6 h under balloon pressure in presence of a catalytic amount of 20% $Pd(OH)_2$

on carbon. The mixture was filtered through a pad of celite and the filtrate was concentrated in vacuo. The residue was purified by flash chromatography (ethyl acetate only) to afford alcohol **1-136** (540 mg, 82%) as colorless oil. $\mathbf{R_f}$ = 0.25 (EtOAc/petroleum ether, 7:3); $\mathbf{[\alpha]_D^{20}}$ = −2.8 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.12 (ddd, *J* = 12.9, 11.9, 11.1 Hz, 1H, 5'-H), 1.21 (ddd, *J* = 12.9, 2.8, 2.5 Hz, 1H, 5'-H), 1.30 (s, 3H, 2'-CH_3), 1.35 (s, 3H, 2'-CH_3), 1.45 (s, 9H, $C(CH_3)_3$), 1.51 (d, *J* = 7.1 Hz, 6H, $CH(CH_3)_2$), 1.57–1.73 (m, 4H, NCH_2CH_2, CH_2CH_2OH), 1.76–1.87 (m, 2H, $OCH_2CH_2CH_2Ar$), 2.39 (s, br, 1H, OH), 2.56 (dd, *J* = 7.8, 7.3 Hz, 2H, $OCH_2CH_2CH_2Ar$), 3.41 (dd, *J* = 6.6, 6.3 Hz, 2H, $OCH_2CH_2CH_2Ar$), 3.49–3.58 (m, 3H, $CH(CH_3)_2$, CH_2CH_2OH), 3.59–3.76 (m, 11H, 4'-H, OCH_2), 3.81 (ddd, *J* = 14.9, 10.1, 6.3 Hz, 1H, NCH_2CH_2), 3.94–4.02 (m, 1H, 6'-H), 4.00 (s, 2H, OCH_2CO_2tBu), 4.06 (ddd, *J* = 14.9, 10.1, 4.8 Hz, 1H, NCH_2CH_2), 6.81 (s, 1H, CONH), 6.92–7.02 (m, 6H, Ar-H), 7.09–7.22 (m, 7H, Ar-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 19.7 (2'-CH_3), 21.6 ($CH(CH_3)_2$), 21.7 ($CH(CH_3)_2$), 26.1 ($CH(CH_3)_2$), 28.1 ($C(CH_3)_3$), 30.0 (2'-CH_3), 31.1 ($OCH_2CH_2CH_2Ar$), 31.6 ($OCH_2CH_2CH_2Ar$), 36.1 (C-5'), 38.0 (NCH_2CH_2), 38.0 (CH_2CH_2OH), 40.8 (NCH_2CH_2), 60.6 (OCH_2), 66.5 (C-4'), 68.8 (C-6'), 69.0 (OCH_2CO_2tBu), 70.1 (CH_2CH_2OH), 70.4 ($OCH_2CH_2CH_2Ar$), 70.5 (2 × OCH_2), 70.6 (2 × OCH_2), 70.7 (OCH_2), 81.5 ($C(CH_3)_3$), 98.6 (C-2'), 115.3 (d, J_{CF} = 21.2 Hz, 2CH, Ar). 115.4 (C, Ar), 119.7 (2CH, Ar), 121.7 (C, Ar), 126.5 (CH, Ar), 128.3 (2CH, Ar), 128.3 (C, Ar), 128.6 (2CH, Ar), 128.7 (C, Ar), 128.4 (d, J_{CF} = 3.7 Hz, C, Ar), 130.4 (2CH, Ar), 133.1 (d, J_{CF} = 8.0 Hz, 2CH, Ar), 134.6 (C, Ar), 136.1 (C, Ar), 137.2 (C, Ar), 162.9 (d, J_{CF} = 378.4 Hz, C, Ar), 163.4 (CONH), 169.7 (CO_2tBu); **HRMS** (ESI): $[M+Na]^+$ calcd for $C_{51}H_{69}FN_2O_{10}Na$ 911.48285, found 911.483546.

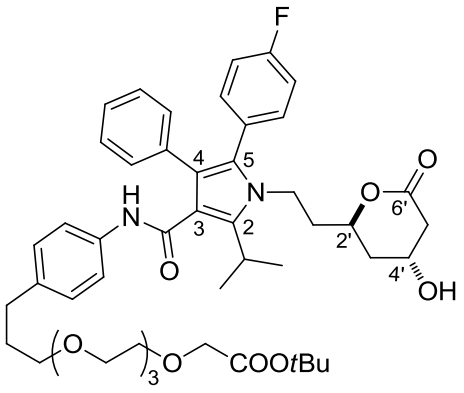
2-((4*R*,6*R*)-6-(2-(3-((4-(2,2-Dimethyl-4-oxo-3,6,9,12-tetraoxapentadecan-15-yl)phenyl)carbamoyl)-5-(4-fluorophenyl)-2-isopropyl-4-phenyl-1*H*-pyrrol-1-yl)ethyl)-2,2-dimethyl-1,3-dioxan-4-yl)acetic acid (1-137)



To a cooled solution (ice/water bath) of alcohol **1-136** (540 mg, 0.60 mmol) in CH_2Cl_2 (20 mL) was added Dess-Martin periodinane (335 mg, 0.78 mmol) in one portion. The mixture was stirred for 1 h at room temperature, washed with saturated $NaHCO_3$ (10 mL), 1M $Na_2S_2O_3$ (10 mL), and saturated NaCl solution. The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under vacuum. The residue was purified by passing it through a short silica gel column (EtOAc/petroleum ether, 3:2) to afford intermediate aldehyde (400 mg, 0.45 mmol) which was dissolved in *t*-butanol (15 mL). 2-Methyl-2-butene (2 mL) was added followed by the addition of an aqueous solution (15 mL) of NaH_2PO_4•$2H_2O$ (422 mg, 2.7 mmol) and $NaClO_2$ (81 mg, 0.90 mmol). The mixture was stirred for 6 h at room temperature and then extracted with ethyl acetate (3 × 15 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated under vacuum. The residue was purified by flash chromatography (methanol/CH_2Cl_2/AcOH, 1:20:0.001) to furnish acid **1-137** (390 mg, 96%) as yellow colored sticky oil. $\mathbf{R_f}$ = 0.11 (methanol/CH_2Cl_2/AcOH, 1:20:0.001); $\mathbf{[\alpha]_D^{20}}$ = 3.8 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.05 (dd, *J* = 12.4, 11.9 Hz, 1H, 5'-H), 1.30 (s, 3H, 2'-CH_3), 1.30–1.36 (m, 1H, 5'-H), 1.36 (s, 3H, 2'-CH_3), 1.45 (s, 9H, $C(CH_3)_3$), 1.51 (d, *J* = 7.1 Hz, 6H, $CH(CH_3)_2$), 1.57–1.72 (m, 2H, NCH_2CH_2), 1.76–1.90 (m, 2H, $OCH_2CH_2CH_2Ar$), 2.37 (dd, *J* = 15.9, 5.8 Hz, 1H, CH_2COOH), 2.52 (dd, *J* = 15.9, 6.8 Hz, 1H, CH_2COOH), 2.57 (dd, *J* = 8.1, 7.3 Hz, 2H, $OCH_2CH_2CH_2Ar$), 3.41 (dd, *J* = 6.6, 6.6 Hz, 2H, $OCH_2CH_2CH_2Ar$), 3.47–3.59 (m, 3H, $CH(CH_3)_2$, OCH_2), 3.59–3.74 (m, 11H, 4'-H, OCH_2), 3.82 (ddd, *J* = 14.9, 9.6, 6.1 Hz, 1H, NCH_2CH_2), 4.00 (s, 2H, OCH_2CO_2tBu), 4.07 (ddd, *J* = 14.9, 9.3, 5.0 Hz, 1H, NCH_2CH_2), 4.18

(dddd, J = 11.9, 9.6, 5.3, 3.3 Hz, 1H, 6'-H), 6.82 (s, 1H, CONH), 6.91–7.05 (m, 6H, Ar-H), 7.09–7.21 (m, 7H, Ar-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 19.6 (2'-CH_3), 21.6 (CH(CH_3)$_2$), 21.8 (CH(CH_3)$_2$), 26.1 ($CH(CH_3)_2$), 29.8 (2'-CH_3), 31.1 ($OCH_2CH_2CH_2Ar$), 31.6 ($OCH_2CH_2CH_2Ar$), 35.7 (C-5'), 37.8 (NCH_2CH_2), 40.8 (NCH_2CH_2), 40.8 (CH_2COOH), 65.5 (C-6'), 66.4 (C-4'), 69.0 (OCH_2CO_2tBu), 70.1 (OCH_2), 70.4(OCH_2), 70.5 (2 OCH_2), 70.6 (2 OCH_2), 70.6 ($OCH_2CH_2CH_2Ar$), 70.7 (OCH_2), 81.5 ($C(CH_3)_3$), 99.0 (C-2'), 115.4 (d, J_{CF} = 21.9 Hz, 2CH, Ar), 115.5 (C, Ar), 119.8 (2CH, Ar), 121.8 (C, Ar), 126.5 (CH, Ar), 128.3 (C, Ar), 128.3 (2CH, Ar), 128.6 (2CH, Ar), 128.7 (C, Ar), 130.4 (2CH, Ar), 133.1 (d, J_{CF} = 8.0 Hz, 2CH, Ar), 134.5 (C, Ar), 136.0 (C, Ar), 137.3 (C, Ar), 141.1 (C, Ar), 162.9 (d, J_{CF} = 393.7 Hz, C, Ar), 163.5 (CONH), 169.7 (CO_2tBu); **HRMS** (ESI): $[M+Na]^+$ calcd for $C_{51}H_{67}FN_2O_{11}Na$ 925.46211, found 925.462059.

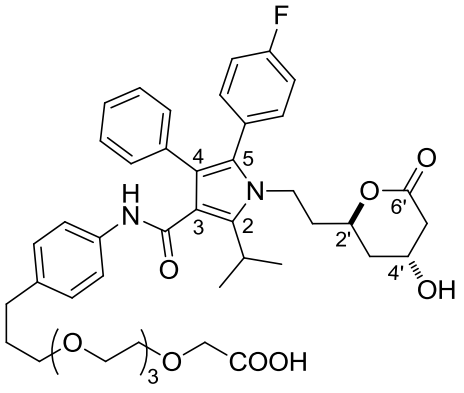
tert-Butyl 2-(2-(2-(3-(4-(5-(4-fluorophenyl)-1-(2-((2*R*,4*R*)-4-hydroxy-6-oxotetrahydro-2*H*-pyran-2-yl)ethyl)-2-isopropyl-4-phenyl-1*H*-pyrrole-3-carboxamido)phenyl)propoxy)ethoxy)ethoxy)acetate (1-138)



Camphorsulphonic acid (195 mg, 0.84 mmol) was added to a solution of acetonide acid **1-137** (380 mg, 0.42 mmol) in CH_2Cl_2 (5 mL). The reaction was completed within 3 h (TLC control). The solution was washed with saturated $NaHCO_3$ solution (5 mL), water (5 mL), and saturated NaCl solution. The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. Purification by flash chromatography (methanol/CH_2Cl_2/AcOH, 3:97: 0.001) provided lactone **1-138** (240 mg, 68%) as colorless sticky solid. $\mathbf{R}_f$ = 0.33 (methanol/CH_2Cl_2/AcOH, 3:97: 0.001); $\mathbf{[\alpha]_D^{20}}$ = +17.5 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.45 (s, 9H, C(CH_3)$_3$),

1.50 (d, *J* = 6.8 Hz, 3H, CH(C*H*$_3$)$_2$), 1.51 (d, *J* = 6.6 Hz, 3H, CH(C*H*$_3$)$_2$), 1.54–1.61 (m, 1H, 3'-H), 1.66–1.91 (m, 6H, NCH$_2$C*H*$_2$, 3'-H, OCH$_2$C*H*$_2$CH$_2$Ar, OH), 2.50–2.59 (m, 3H, 5'-H, OCH$_2$CH$_2$C*H*$_2$Ar), 2.62 (dd, *J* = 17.9, 4.8 Hz, 1H, 5'-H), 3.41 (dd, *J* = 6.6, 6.6 Hz, OC*H*$_2$CH$_2$CH$_2$Ar), 3.47–3.57 (m, 3H, C*H*(CH$_3$)$_2$, OCH$_2$), 3.59–3.72 (m, 10H, OCH$_2$), 3.95–4.06 (m, 1H, NC*H*$_2$CH$_2$), 4.00 (s, 2H, OCH$_2$CO$_2$*t*Bu), 4.19 (ddd, *J* = 14.9, 10.1, 4.8 Hz, 1H, NC*H*$_2$CH$_2$), 4.24–4.31 (m, 1H, 4'-H), 4.50 (dddd, *J* = 11.4, 8.6, 3.3, 3.0 Hz, 1H, 2'-H), 6.83 (s, 1H, CONH), 6.91–7.04 (m, 6H, Ar-H), 7.08–7.22 (m, 7H, Ar-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 21.7 (CH(*C*H$_3$)$_2$), 22.0 (CH(*C*H$_3$)$_2$), 26.1 (*C*H(CH$_3$)$_2$), 28.1 (C(*C*H$_3$)$_3$), 31.1 (OCH$_2$*C*H$_2$CH$_2$Ar), 31.6 (OCH$_2$CH$_2$*C*H$_2$Ar), 35.6 (C-3'), 37.1 (NCH$_2$*C*H$_2$), 38.5 (C-5'), 40.7 (N*C*H$_2$CH$_2$), 62.3 (C-4'), 69.0 (O*C*H$_2$CO*t*Bu), 70.1 (OCH$_2$), 70.4 (O*C*H$_2$CH$_2$CH$_2$Ar), 70.5 (3 OCH$_2$), 70.6 (OCH$_2$), 70.7 (OCH$_2$), 73.0 (C-3), 81.5 (*C*(CH$_3$)$_3$), 115.6 (d, J_{CF} = 21.9 Hz, 2CH, Ar), 115.7 (C, Ar), 119.8 (2CH, Ar), 122.0 (C, Ar), 126.6 (CH, Ar), 128.0 (d, J_{CF} = 3.7 Hz, C, Ar), 128.3 (2CH, Ar), 128.6 (2CH, Ar), 130.3 (2CH, Ar), 133.0 (d, J_{CF} = 8.0 Hz, 2CH, Ar), 134.4 (C, Ar), 135.9 (C, Ar), 137.4 (C, Ar), 141.1 (C, Ar), 162.9 (d, J_{CF} = 377.6 Hz, C, Ar), 163.5 (CONH), 169.5 (C=O, lactone), 169.7 (C=O, ester); **HRMS** (ESI): $[M+Na]^+$ calcd for $C_{48}H_{61}FN_2O_{10}Na$ 867.42025, found 867.420241.

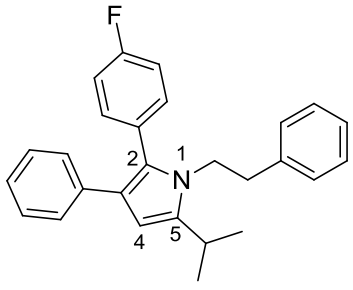
2-(2-(2-(3-(4-(5-(4-Fluorophenyl)-1-(2-((2*R*,4*R*)-4-hydroxy-6-oxotetrahydro-2*H*-pyran-2-yl)ethyl)-2-isopropyl-4-phenyl-1*H*-pyrrole-3-carboxamido)phenyl)propoxy)ethoxy)ethoxy)acetic acid (1-139)[82]



Aqueous phosphoric acid (58 μL, 0.5 mmol, 85 wt%) was added to a solution of ester **1-138** (85 mg, 0.1 mmol) in CH_2Cl_2 (2 mL). The reaction mixture was stirred about 7 h at room

temperature. After completion, the reaction mixture was diluted with water (2 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by flash chromatography (acetone/CH_2Cl_2/AcOH, 1:1:0.01) to afford atorvastatin lactone TEG acid **1-139** (45 mg, 84%) as sticky oil. $\mathbf{R_f}$ = 0.40 (acetone/CH_2Cl_2/AcOH, 3:7:0.01); $\mathbf{[\alpha]_D^{20}}$ = 15.5 (*c* 0.5, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.50 (d, *J* = 6.8 Hz, 6H, $CH(CH_3)_2$), 1.53–1.62 (m, 1H, 3'-H), 1.67–1.91 (m, 5H, NCH_2CH_2, 3'-H, $OCH_2CH_2CH_2Ar$), 2.48–2.59 (m, 3H, 5'-H, $OCH_2CH_2CH_2Ar$), 2.62 (dd, *J* = 17.7, 4.8 Hz, 1H, 5'-H), 3.42 (dd, *J* = 6.6, 6.6 Hz, 2H, $OCH_2CH_2CH_2Ar$), 3.46–3.74 (m, 13H, $CH(CH_3)_2$, OCH_2), 4.01 (ddd, *J* = 14.9, 8.8, 5.0 Hz, 1H, NCH_2CH_2), 4.10 (s, 2H, OCH_2CO_2tBu), 4.18 (ddd, *J* = 14.9, 9.9, 4.8 Hz, 1H, NCH_2CH_2), 4.24–4.30 (m, 1H, 4'-H), 4.45–4.55 (m, 1H, 2'-H), 6.86 (s, 1H, CONH), 6.92–7.04 (m, 6H, Ar-H), 7.07–7.23 (m, 8H, Ar-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 21.7 ($CH(CH_3)_2$), 22.0 ($CH(CH_3)_2$), 26.1 ($CH(CH_3)_2$), 30.8 ($OCH_2CH_2CH_2Ar$), 31.4 ($OCH_2CH_2CH_2Ar$), 35.6 (C-3'), 37.1 (NCH_2CH_2), 38.4 (C-5'), 40.7 (NCH_2CH_2), 62.3 (C-4'), 69.2 (OCH_2CO_2tBu), 70.0 (OCH_2), 70.2 (2 OCH_2), 70.3 (OCH_2), 70.4 (OCH_2), 70.5 (OCH_2), 71.1 (OCH_2), 73.0 (C-2'), 115.6 (d, J_{CF} = 22.0 Hz, 2CH, Ar), 115.7 (C, Ar), 120.0 (2CH, Ar), 122.0 (C, Ar), 126.6 (CH, Ar), 128.0 (d, J_{CF} = 3.7 Hz, C, Ar), 128.3 (2CH, Ar), 128.7 (2CH, Ar), 128.7 (C, Ar), 130.3 (2CH, Ar), 133.1 (d, J_{CF} = 8.0 Hz, 2CH, Ar), 134.4 (C, Ar), 135.9 (C, Ar), 137.3 (C, Ar), 141.0 (C, Ar), 163.0 (d, J_{CF} = 395.9 Hz, C, Ar), 163.5 (C=O, amide), 163.8 (C=O, lactone), 169.6 (C=O, acid); **HRMS** (ESI): $[M+Na]^+$ calcd for $C_{44}H_{53}FN_2O_{10}Na$ 787.36115, found 787.361297.

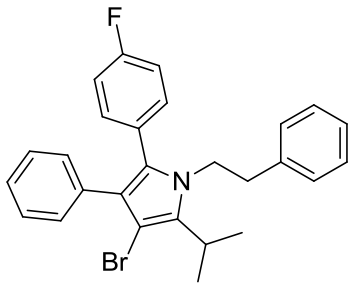
2-(4-Fluorophenyl)-5-isopropyl-1-phenethyl-3-phenyl-1*H*-pyrrole (1-140)



A mixture of diketone **1-27** (0.502 g, 1.7 mmol) and 2-phenylethyl amine (0.317 mL, 2.5 mmol) was refluxed in toluene (10 mL) in presence of *p*-TSA•H_2O (96 mg, 0.5 mmol) for 72 h. The

reaction mixture was cooled to the room temperature and diluted with diethyl ether (10 mL). The mixture was washed with saturated $NaHCO_3$ solution (5 mL), water (5 mL) and saturated NaCl solution. The organic layer was dried over $MgSO_4$, filtered and concentrated in vacuo. Purification of the crude residue by flash chromatography (diethyl ether/petroleum ether, 1:50) afforded pyrrole **1-140** (0.620 g, 98%) as white solid, **m.p.** 99–101 °C. $\mathbf{R_f}$ = 0.43 (EtOAc/petroleum ether, 1:25); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.33 (d, *J* = 6.6 Hz, 6H, $CH(CH_3)_2$), 2.67 (dd, *J* = 8.1, 7.8 Hz, 2H, NCH_2CH_2Ph), 2.91 (app septet, *J* = 6.6 Hz, 1H, $CH(CH_3)_2$), 3.98 (dd, *J* = 8.1, 7.8 Hz, 2H, NCH_2CH_2Ph), 6.22 (s, 1H, 4-H, pyrrole), 6.84 (d, *J* = 7.1 Hz, 2H, Ar-H), 7.01–7.32 (m, 12H, Ar-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 23.6 ($CH(CH_3)_2$), 25.9 ($CH(CH_3)_2$), 37.9 (NCH_2CH_2Ph), 45.4 (NCH_2CH_2Ph), 103.5 (CH, Ar), 115.6 (d, J_{CF} = 21.2 Hz, 2CH, Ar), 122.2 (C, Ar), 124.8 (CH, Ar), 126.5 (CH, Ar), 127.5 (2CH, Ar), 127.9 (C, Ar), 128.0 (2CH, Ar), 128.5 (4CH, Ar), 129.8 (d, J_{CF} = 3.7 Hz, C, Ar), 133.8 (d, J_{CF} = 7.3 Hz, 2CH, Ar), 136.5 (C, Ar), 138.1 (C, Ar), 140.2 (C, Ar), 162.3 (d, J_{CF} = 247.4 Hz, C, Ar); **HRMS** (ESI): $[M+H]^+$ calcd for $C_{27}H_{27}FN$ 384.212204, found 384.212478.

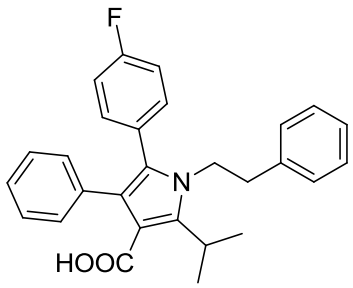
3-Bromo-5-(4-fluorophenyl)-2-isopropyl-1-phenethyl-4-phenyl-1*H*-pyrrole (1-141)



NBS (333 mg, 1.9 mmol) was added to a solution of pyrrole **1-140** (598 mg, 1.6 mmol) in DMF (12 mL) at room temperature and the mixture was stirred for 90 min (TLC control). The mixture was diluted with diethyl ether (15 mL), washed with saturated $NaHCO_3$ solution (10 mL), water (10 mL) and saturated NaCl solution. The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated under vacuum. Purification of the residue by passing it through a short plug of silica gel (EtOAc/petroleum ether, 1:20) yielded bromopyrrole **1-141** (629 mg, 87%) as pale yellow colored sticky oil. $\mathbf{R_f}$ = 0.33 (EtOAc/petroleum ether, 1:20); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.50 (d, *J* = 7.1 Hz, 6H, $CH(CH_3)_2$), 2.72 (dd, *J* = 7.8, 7.8 Hz, 2H, NCH_2CH_2Ph),

3.27 (app septet, J = 7.1 Hz, 1H, C*H*$(CH_3)_2$), 3.99 (dd, J = 7.8, 7.8 Hz, 2H, NC*H*$_2$CH$_2$Ph), 6.81 (d, J = 7.3 Hz, 2H, Ar-H), 6.89–7.05 (m, 4H, Ar-H), 7.06–7.23 (m, 8H, Ar-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 21.2 (CH(*C*H$_3$)$_2$), 26.5 (*C*H(CH$_3$)$_2$), 38.1 (NCH$_2$*C*H$_2$Ph), 46.2 (N*C*H$_2$CH$_2$Ph), 94.7 (C, Ar), 115.2 (d, J_{CF} = 21.2 Hz, 2CH, Ar), 123.1 (C, Ar), 125.9 (CH, Ar), 126.7 (CH, Ar), 127.5 (C, Ar), 127.5 (2CH, Ar), 128.2 (C, Ar), 128.5 (2CH, Ar), 128.6 (2CH, Ar), 128.9 (C, Ar), 130.5 (2CH, Ar), 133.0 (d, J_{CF} = 8.0 Hz, 2CH, Ar), 134.1 (C, Ar), 134.3 (C, Ar), 137.7 (C, Ar), 162.1 (d, J_{CF} = 247.4 Hz, C, Ar).

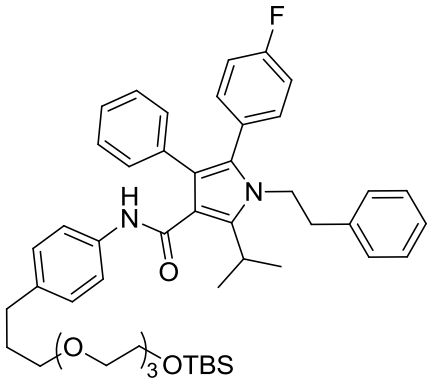
5-(4-Fluorophenyl)-2-isopropyl-1-phenethyl-4-phenyl-1*H*-pyrrole-3-carboxylic acid (1-142)



To a cooled (−78 °C) solution of bromopyrrole **1-141** (199 mg, 0.43 mmol) in THF (5 mL) was added slowly *n*-BuLi (0.361 mL, 0.90 mmol, 2.5M in hexane). After 5 min, excess of solid CO_2 was added to the mixture; the flask was removed from the cooling bath and allowed to warm to room temperature. After evolution of excess of CO_2 gas the mixture was quenched with saturated NH_4Cl solution and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated. Purification by flash chromatography (EtOAc/petroleum ether, 1:4) of the solid residue provided acid **1-142** (171 mg, 93%) as white solid. **R_f** = 0.27 (EtOAc/petroleum ether, 1:4); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.50 (d, J = 7.3 Hz, 6H, CH(C*H*$_3$)$_2$), 2.16 (acetone), 2.73 (dd, J = 8.3, 7.6 Hz, 2H, NCH$_2$C*H*$_2$Ph), 3.71 (app septet, J = 7.1 Hz, C*H*(CH$_3$)$_2$), 4.04 (dd, J = 8.1, 7.8 Hz, NC*H*$_2$CH$_2$Ph), 6.81 (d, J = 7.3 Hz, 2H, Ar-H), 6.93–7.30 (m, 12H, Ar-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 21.1 (CH(*C*H$_3$)$_2$), 26.1 (*C*H(CH$_3$)$_2$), 30.9 (CH(*C*H$_3$)$_2$), 37.7 (*C*H$_2$Ph), 46.4 (NCH$_2$), 115.2 (d, J = 21.2 Hz, 2CH, Ar), 124.9 (d, J_{CF} = 3.7 Hz, C, Ar), 125.9 (CH, Ar), 126.8 (CH, Ar), 127.3 (2CH, Ar), 128.5 (2CH, Ar), 128.7 (2CH, Ar), 130.1 (C, Ar), 130.5 (2CH, Ar), 133.3 (d, J = 8.0 Hz, 2CH, Ar), 135.3 (C,

Ar), 137.5 (C, Ar), 144.3 (C, Ar), 162.2 (d, J_{CF} = 248.8 Hz, C, Ar), 169.0 (COOH); **HRMS** (ESI): $[M+Na]^+$ calcd for $C_{28}H_{26}FNO_2Na$ 450.183978, found 450.183914.

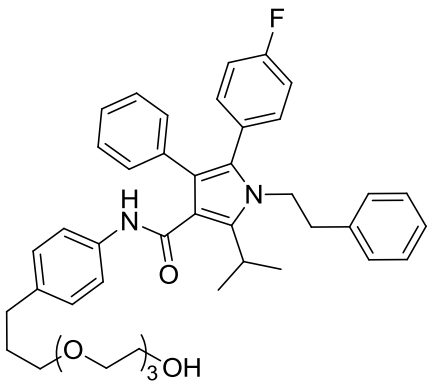
5-(4-Fluorophenyl)-*N*-(4-(3-(2-(2-(2-hydroxyethoxy)ethoxy)ethoxy)propyl)phenyl)-2-isopropyl-1-phenethyl-4-phenyl-1*H*-pyrrole-3-carboxamide (1-143)



To a cooled (~ 0 °C) solution of acid **1-142** (255 mg, 0.64 mmol) and amine **1-121** (275 mg, 0.64 mmol) in CH_2Cl_2 (10 mL) was added DIPEA (0.34 mL, 0.77 mmol) and PyBrOP (1.93 mmol). The mixture was allowed to stir at room temperature for completion (TLC control). After 24 h, the mixture was diluted with CH_2Cl_2 (10 mL), washed with water (5 × 20 mL) and saturated NaCl solution. The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum and the residue purified by flash chromatography (EtOAc/petroleum ether, 3:7) to yield amide **1-143** (350 mg, 67%) as reddish yellow oil. $\mathbf{R_f}$ = 0.34 (EtOAc/petroleum ether, 3:7); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 0.05 (s, 6H, $Si(CH_3)_2$), 0.88 (s, 9H, $SiC(CH_3)_3$), 1.56 (d, *J* = 7.1 Hz, 6H, $CH(CH_3)_2$), 1.78–1.87 (m, 2H, $OCH_2CH_2CH_2Ar$), 2.58 (dd, *J* = 7.8, 7.6 Hz, 2H, $OCH_2CH_2CH_2Ar$), 2.74–2.80 (m, 2H, NCH_2CH_2Ph), 3.42 (dd, *J* = 6.6, 6.3 Hz, 2H, $OCH_2CH_2CH_2Ar$), 3.52–3.58 (m, 4H, OCH_2), 3.60–3.68 (m, 7H, $CH(CH_3)_2$, OCH_2), 3.75 (dd, *J* = 5.6, 5.3 Hz, 2H, OCH_2), 4.01–4.10 (m, 2H, NCH_2CH_2Ph), 6.95–7.07 (m, 6H, Ar-H), 7.08–7.27 (m, 12H, Ar-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = −5.28 ($Si(CH_3)_2$), 18.3 ($SiC(CH_3)_3$), 21.8 ($CH(CH_3)_2$), 25.9 ($SiC(CH_3)_3$), 26.3 ($CH(CH_3)_2$), 31.2 ($OCH_2CH_2CH_2Ar$), 31.6 ($OCH_2CH_2CH_2Ar$), 37.9 (NCH_2CH_2Ph), 46.2 (NCH_2CH_2Ph), 62.7 (CH_2OTBS), 70.1 (OCH_2), 70.4 (OCH_2), 70.6 (OCH_2), 70.7 (2 × OCH_2), 72.6 (OCH_2), 115.3 (d, J_{CF} = 21.1 Hz, 2CH, Ar), 115.5 (C, Ar), 119.7 (2CH, Ar), 121.8 (C, Ar), 126.8 (CH, Ar), 128.3 (d, J_{CF} = 3.7 Hz, C, Ar),

128.3 (2CH, Ar), 128.5 (2CH, Ar), 128.6 (2CH, Ar), 128.7 (2CH, Ar), 129.0 (C, Ar), 130.5 (2CH, Ar), 131.5 (CH, Ar), 133.2 (d, J = 8.0 Hz, 2CH, Ar), 134.6 (C, Ar), 136.1 (C, Ar), 137.2 (C, Ar), 137.6 (C, Ar), 141.2 (C, Ar), 162.3 (d, J_{CF} = 248.1 Hz, C, Ar), 164.6 (CONH).

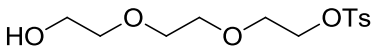
5-(4-Fluorophenyl)-2-isopropyl-1-phenethyl-4-phenyl-*N*-(4-(14,14,15,15-tetramethyl-4,7,10,13-tetraoxahexadecyl)phenyl)-1*H*-pyrrole-3-carboxamide (1-144)



A solution of silyl ether **1-143** (250 mg, 0.31 mmol) in methanol (3 mL) containing a catalytic amount of *p*-TSA•H_2O was stirred at room temperature. After 2 h, the reaction mixture was diluted with ethyl acetate (5 mL), washed with saturated $NaHCO_3$ and saturated NaCl solution. The separated organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated under vacuum. The residue was purified by flash chromatography using pure ethyl acetate to afford **1-144** (170 mg, 79%) as pale yellow colored thick oil. $\mathbf{R_f}$ = 0.24 (only EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.56 (d, J = 7.1 Hz, 6H, $CH(CH_3)_2$), 1.77–1.89 (m, 2H, $OCH_2CH_2CH_2Ar$), 2.31 (br, s, 1H, OH), 2.58 (dd, J = 7.6, 7.6 Hz, 2H, $OCH_2CH_2CH_2Ar$), 2.77 (dd, J = 8.3, 7.6 Hz, 2H, NCH_2CH_2Ph), 3.42 (dd, J = 6.6, 6.3 Hz, 2H, $OCH_2CH_2CH_2Ar$), 3.51–3.75 (m, 12H, OCH_2), 4.05 (dd, J = 8.1, 8.1 Hz, 2H, NCH_2CH_2Ph), 6.81 (br, s, 1H, CONH), 6.84 (d, J = 6.3 Hz, 2H, Ar-H), 6.93–7.06 (m, 6H, Ar-H), 7.08–7.34 (m, 10H, Ar-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 21.8 ($CH(CH_3)_2$), 26.3 ($CH(CH_3)_2$), 31.1 ($OCH_2CH_2CH_2Ar$), 31.6 ($OCH_2CH_2CH_2Ar$), 37.9 (NCH_2CH_2Ph), 46.2 (NCH_2CH_2Ph), 61.7 (CH_2OH), 70.1 (OCH_2), 70.4 (2 × OCH_2), 70.6 (2 × OCH_2), 72.5 (OCH_2), 115.4 (d, J_{CF} = 21.2 Hz, 2CH, Ar), 115.4 (C, Ar), 119.7 (2CH, Ar), 121.8 (C, Ar), 126.6 (CH, Ar), 126.8 (CH, Ar), 128.3 (2CH, Ar), 128.5 (2CH, Ar), 128.6 (2CH, Ar), 128.7 (2CH, Ar), 130.5 (2CH, Ar), 131.48, 133.2 (d, J_{CF} = 8.0 Hz, 2CH, Ar), 134.6 (C, Ar),

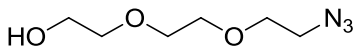
136.1 (C, Ar), 137.2 (C, Ar), 137.6 (C, Ar), 141.2 (C, Ar), 162.3 (d, J_{CF} = 247.4 Hz, C, Ar), 163.5 (CONH); **HRMS** (ESI): $[M+H]^+$ calcd for $C_{43}H_{50}FN_2O_5$ 693.36983, found 693.36979.

2-(2-(2-Hydroxyethoxy)ethoxy)ethyl 4-methylbenzenesulfonate (2-5)[171]



Tosyl chloride (10 g, 52.4 mmol) was added in a mixture of triethylene glycol **2-4** (31.5 g, 210 mmol) and Et_3N (105 mmol) in CH_2Cl_2 (250 mL) at room temperature. The reaction was completed in 1 h (TLC). Then the mixture was washed with 1M $KHSO_4$ solution (150 mL), 5% $NaHCO_3$ solution (150 mL) and saturated NaCl solution (100 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The crude oil was purified by flash chromatography (MeOH/CH_2Cl_2, 1:19) to afford alcohol **2-5** (14.84 g, 93%) as colorless oil. R_f = 0.2 (EtOAc/petroleum ether, 1:4); **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 2.26 (s, 1H, OH), 2.42 (s, 3H, CH_3), 3.55 (dd, *J* = 4.5, 4.5 Hz, 2H, OCH_2), 3.59 (s, 4H, OCH_2), 3.68 (dd, *J* = 9.6, 4.8 Hz, 4H, OCH_2), 4.14 (dd, *J* = 4.8, 4.8 Hz, 2H, OCH_2), 7.32 (d, *J* = 8.1 Hz, 2H, Ar-H), 7.78 (d, *J* = 8.1 Hz, 2H, Ar-H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 21.6 (CH_3), 61.7 (OCH_2), 68.6 (OCH_2), 69.1 (OCH_2), 70.7 (OCH_2), 72.4 (OCH_2), 127.9 (2CH, Ar), 129.8 (2CH, Ar), 132.9 (C, Ar), 144.8 (C, Ar).

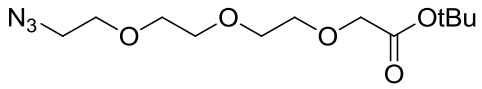
2-(2-(2-Azidoethoxy)ethoxy)ethanol (2-6)[172]



A mixture of tosylate **2-5** (14.84g, 48.7 mmol) and NaN_3 (6.34 g, 97.5 mmol) in DMF (75 mL) was stirred at 50 °C. After 14 h, the reaction mixture was quenched by addition of water (50 mL) and extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with saturated NaCl solution (100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (MeOH/CH_2Cl_2, 1:20) to afford azide **2-6** (7.89 g, 92%) as colorless oil. **R_f** = 0.17 (MeOH/CH_2Cl_2, 1:4); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 2.31 (s, 1H, OH), 3.38 (dd, *J* = 4.9, 4.9 Hz, 2H, OCH_2), 3.58–3.60 (dd, *J* = 4.5, 4.5

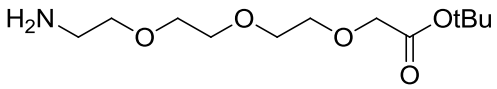
Hz, 2H, OCH_2), 3.65–3.68 (m, 6H, OCH_2), 3.70–3.73 (dd, J = 4.4, 4.4 Hz, 2H, OCH_2); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 50.6 (CH_2N_3), 61.7 (CH_2OH), 70.0 (OCH_2), 70.3 (OCH_2), 70.6 (OCH_2), 72.4 (OCH_2).

tert-Butyl 2-(2-(2-(2-azidoethoxy)ethoxy)ethoxy)acetate (2-7)[172]



NaH (2.67 g, 66.8 mmol, 60 % suspension in oil) was added to a solution of alcohol **2-6** (7.8 g, 44.5 mmol) in DMF (150 mL) at room temperature. The reaction mixture was allowed to stir for 30 min before *tert*-butyl bromoacetate (13.2 mL, 89.0 mmol) was added to the reaction mixture and stirring was continued for 3 h. The reaction mixture was quenched by addition of a small amount of water and then extracted with ethyl acetate (3 × 100 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under vacuum. Purification by flash chromatography of the residual material afforded ester **2-7** (9.78g, 76%) as colorless oil. **R_f** = 0.46 (petroleum ether/EtOAc, 1:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 1.46 (s, 9H, $C(CH_3)_3$), 3.37 (dd, J = 5.1, 5.1 Hz, 2H, CH_2N_2), 3.64–3.73 (m, 10H, OCH_2), 4.01 (s, 2H, OCH_2CO); **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 28.1 ($C(CH_3)_3$), 50.7 (CH_2N_3), 69.0 (OCH_2), 70.0 (OCH_2), 70.6 (OCH_2), 70.7 (3 × OCH_2), 81.5 ($C(CH_3)_3$), 169.6 (CO_2tBu).

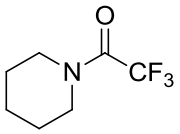
tert-Butyl 2-(2-(2-(2-aminoethoxy)ethoxy)ethoxy)acetate (2-8)[163]



Azide **2-7** (2.31 g, 7.9 mmol) was dissolved in a mixture of THF (23 mL) and H_2O (2.3 mL) and PPh_3 (4.19 g, 16.0 mmol) was added to the mixture which was stirred for 8 h at room temperature. The reaction volume was reduced to ~10 mL on a rotary evaporator, diluted with toluene (10 mL) and concentrated to remove water as azeotropic mixture. This manipulation was repeated once and then the crude residue was purified by flash chromatography

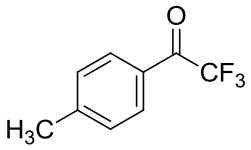
(MeOH/CH_2Cl_2/NH_4OH, 1:9:0.005) which afforded amine **2-8** (1.68 g, 92%) as colorless oil. $\mathbf{R_f}$ = 0.17 (MeOH/CH_2Cl_2/NH_4OH, 1:9:0.005); **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 1.44 (s, 9H, $C(CH_3)_3$), 2.01 (s, 2H, NH_2), 2.86 (dd, *J* = 5.2, 5.2 Hz, 2H, CH_2NH_2), 3.51 (dd, 2H, *J* = 5.2, 5.2 Hz, OCH_2), 3.59–3.71 (m, 8H, OCH_2), 4.00 (s, 2H, OCH_2CO_2tBu); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 28.1 ($C(CH_3)_3$), 41.6 (CH_2NH_2), 69.0 (OCH_2), 70.2 (OCH_2), 70.5 (2 × OCH_2), 70.6 (OCH_2), 73.0 (OCH_2CO), 81.6 ($C(CH_3)_3$), 169.7 (CO_2tBu).

2,2,2-Trifluoro-1-piperidin-1-yl-ethanone (2-10)[98a]



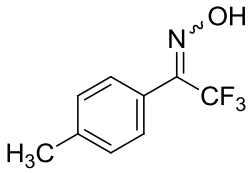
To a solution of piperidine (12.4 mL, 126 mmol) and triethylamine (14.6 mL, 105 mmol) in diethyl ether (6 mL) was added TFAA (14.8 mL, 105 mmol) via dropping funnel at room temperature over 3 h. The reaction mixture was cooled to 0 °C and stirred vigorously for 1 h at room temperature. The mixture was washed with 1N HCl solution (50 mL) and the separated organic layer was dried over Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by high vacuum distillation (40 °C, 0.3 mbar) to furnish **2-10** (17.15 g, 90%) as colorless liquid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.53–1.71 (m, 6H, CH_2), 3.46–3.53 (t, *J* = 5.0 Hz, 2H, NCH_2), 3.54–3.62 (t, *J* = 5.6 Hz, 2H, NCH_2); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 23.9 (CH_2), 25.3 (CH_2), 26.2 (CH_2), 44.7 (NCH_2), 46.9 (q, J_{CF} = 3.7 Hz, NCH_2), 114.7 (q, J_{CF} = 286.2 Hz, CF_3, minor), 116.5 (q, J_{CF} = 287.6 Hz, CF_3, major), 155.5 (q, J_{CF} = 35.7 Hz, C=O, major), 157.9 (q, J_{CF} = 41.0 Hz, C=O, minor).

2,2,2-Trifluoro-1-(4-tolyl)ethanone (2-11)[98a]



A three neck round bottom flask equipped with a reflux condenser, addition funnel and a pressure equalizing bubbler was charged with magnesium turnings (2.47 g, 101.5 mmol) and THF (100 mL) under nitrogen atmosphere. Preparation of Grignard reagent was initiated by addition of a small amount (~1 mL) of 4-bromotoluene **2-9** (12.42 mL, 100.1 mmol) and thereafter the rest of **2-9** in THF (30 mL) was added dropwise using a dropping funnel maintaining gentle refluxing. The mixture was heated to reflux for 1 h and then added to a flask containing a precooled (−78 °C) solution of amide **2-10** in THF (120 mL). The reaction mixture was allowed to stir at room temperature (14 h) overnight, and then quenched by addition of saturated NH_4Cl solution (50 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed successively with 1N HCl (2 × 60 mL), water (2 × 100 mL) and saturated NaCl solution (100 mL). The separated organic layer was dried over $MgSO_4$, filtered and concentrated to afford sufficiently pure ketone **2-11** (18.23 g, 96%) as yellow colored oil. $\mathbf{R_f}$ = 0.58 (diethyl ether/petroleum ether, 2:3); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 2.45 (s, 3H, CH_3), 7.33 (d, J = 8.1 Hz, 2H, Ar-H), 7.06 (d, J = 7.8 Hz, 2H, Ar-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 21.9 (CH_3), 116.7 (d, J_{CF} = 291.3 Hz, CF_3), 127.4 (C, Ar), 129.8 (2CH, Ar), 130.2 (2CH, Ar), 147.0 (C, Ar), 180.1 (d, J_{CF} = 34.4 Hz, C, Ar).

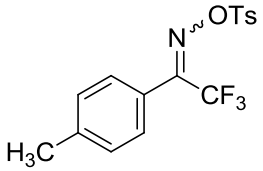
2,2,2-Trifluoro-1-(4-methylphenyl)-1-ethanone oxime (2-12)[98c]



Ketone **2-11**[98a] (18.9 g, 100 mmol) was dissolved in a mixture of pyridine (200 mL) and ethanol (100 mL) wherein hydroxylamine hydrochloride (9.07 g, 130 mmol) was added. The reaction mixture was heated to reflux for 18 h then cooled to the room temperature and ethanol was removed under vacuum. The residual mixture was partitioned between diethyl ether (200 mL) and water (200 mL). The organic layer was separated, washed with 1N HCl (3 × 50 mL) and water (100 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated to afford oxime **2-12** (18.52 g, 91%) as colorless semisolid, pure enough for the next step. $\mathbf{R_f}$ = 0.57

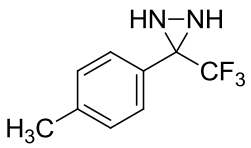
(diethyl ether/petroleum ether, 1:4); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 2.41 (s, 3H, CH_3), 7.29 (d, *J* = 7.8 Hz, 2H, Ar-H), 7.46 (d, *J* = 8.1 Hz, 2H, Ar-H), 9.62 (s, 1H, OH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 21.4 (CH_3), 120.7 (q, J_{CF} = 275.2 Hz, CF_3), 123.1 (C, Ar), 128.6 (2CH, Ar), 129.2 (2CH, Ar), 147.3 (q, J_{CF} = 32.2 Hz, C=N−OH).

2,2,2-Trifluoro-1-(p-tolyl)ethanone *O*-tosyl oxime (2-13)[98a]



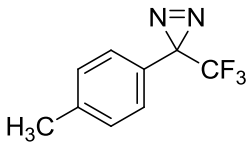
To a solution of oxime **2-12**[98a] (18.52 g, 91.2 mmol) in pyridine (250 mL), tosyl chloride (26.1 g, 136.7 mmol) was added in one portion and the mixture was refluxed for 3 h. The reaction mixture was cooled to the room temperature and the solvent was evaporated under vacuum. The residue was dissolved in diethyl ether (200 mL) and washed successively with 1N HCl (3 × 50 mL) and water (3 × 100 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated in vacuo. The crude material was recrystallized from diethyl ether/hexane to provide tosylate **2-13** (30.14 g, 92%) as white crystalline solid. $\mathbf{R_f}$ = 0.26 (toluene); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 2.39 (s, 3H, CH_3, tosyl), 2.46 (s, 3H, CH_3, toluyl), 7.24–7.34 (m, 4H, Ar-H), 7.37 and 7.88 (4H, AA' and BB' system, tosyl, Ar-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 21.5 (CH_3), 21.7 (CH_3), 119.7 (q, J_{CF} = 277.4 Hz, CF_3), 121.6 (C, Ar), 127.0, 128.4 (2CH, Ar), 129.2 (2CH, Ar), 129.4 (2CH, Ar), 129.8 (2CH, Ar), 130.2, 131.2 (C, Ar), 142.3 (C, Ar), 146.0 (C, Ar), 154.0 (q, J_{CF} = 33.7 Hz, *C*=N).

3-(*p*-Tolyl)-3-(trifluoromethyl)diaziridine (2-14)[98a]



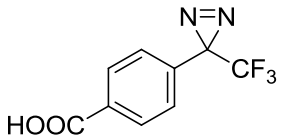
In screw cap bottle (Duran Glass) containing diethyl ether (100 mL) under N_2 atmosphere, ammonia (50 mL) was condensed at −78 °C to which a solution of tosylate **2-13**[98a] (13.1 g, 64.6 mmol) in diethyl ether (100 mL) was added and the bottle was closed with a screw cap under N_2 flow and the mixture stirred at room temperature. After 20 h, the reaction mixture was cooled (−30 °C) and excess of ammonia was evaporated slowly by opening the bottle carefully. The residual solution was washed with water (100 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. The crude product was purified by flash chromatography (diethyl ether/petroleum ether, 1:4) to yield diaziridine **2-14** (12.10 g, 93%) as colorless solid. $\mathbf{R_f}$ = 0.32 (diethyl ether/petroleum ether, 1:4); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 2.18 (d, *J* = 8.3 Hz, 1H, NH-NH), 2.37 (s, 3H, CH_3), 2.75 (d, *J* = 8.1 Hz, 1H, NH-NH), 7.22 (d, *J* = 7.8 Hz, 2H, AA' and BB' system, Ar-H), 7.49 (d, *J* = 8.1 Hz, 2H, AA'BB' system, Ar-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 21.3 (CH_3), 57.9 (q, J_{CF} = 35.9 Hz, Ar*C*(NH-NH)CF_3), 123.6 (q, J_{CF} = 278.1 Hz, CF_3), 128.0 (2CH, Ar), 128.7 (C, Ar), 129.4 (2CH, Ar), 140.2 (C, Ar).

3-(*p*-Tolyl)-3-(trifluoromethyl)-3*H*-diazirine (2-15)[98c]



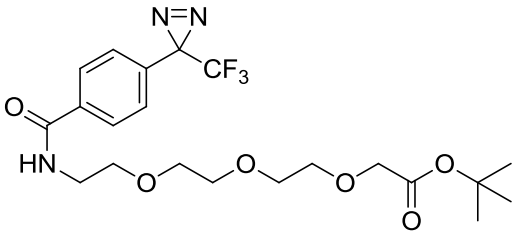
A mixture of diaziridine **2-14**[98a] (5.01 g, 24.7 mmol) and freshly prepared Ag_2O[98c] (22.92 g, 98.9 mmol) in diethyl ether (150 mL) was stirred at room temperature for 3 h. The mixture was filtered through a pad of celite and the filtrate was concentrated under vacuum to afford pure diazirine **2-15** (4.74 g, 95%) as colorless oil which upon storage under −20 °C crystallized as colorless solid. $\mathbf{R_f}$ = 0.7 (diethyl ether/petroleum ether, 1:4); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 2.36 (s, 3H, CH_3), 7.09 and 7.20 (d, *J* = 8.2 Hz, 4H, AA' and BB' system, Ar-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 21.1 (CH_3), 28.4 (q, J_{CF} = 28.4 Hz, Ar*C*(N=N)CF_3), 122.2 (q, J_{CF} = 275.2 Hz, CF_3), 126.1 (C, Ar), 126.4 (2CH, Ar), 129.5 (2CH, Ar), 139.8 (C, Ar).

4-(3-(Trifluoromethyl)-3*H*-diazirin-3-yl)benzoic acid (2-16)[98a]



Toluene derivative **2-15**[98a] (4.18 g, 20.9 mmol) was dissolved in pyridine (80 mL) and water (80 mL) to which $KMnO_4$ (13.19 g, 83.5 mmol) in one portion was added and the mixture was heated at 60 °C for 20 h before it was diluted with water (500 mL). Afterwards, the mixture was acidified to pH ~ 3 using 1N H_2SO_4 resulting in a suspension of MnO_2. Then 20% aq $NaHSO_3$ solution was added to dissolve the precipitated MnO_2. The colorless aqueous solution was extracted with diethyl ether (3 × 100 mL). The combined organic layers were washed with water followed by 0.1N KOH solution (2 × 50 mL). The combined KOH solution was acidified back to pH ~ 3, and extracted with diethyl ether (3 × 70 mL). The combined organic layers were washed with saturated NaCl solution, dried over $MgSO_4$, filtered and concentrated to furnish crude acid which was recrystallized from methanol/water to yield acid **2-16** (2.71 g, 56%) as white solid. $\mathbf{R_f}$ = 0.36 (EtOAc/petroleum ether/AcOH, 1:4:0.001); **^{1}H NMR** (400 MHz, CD_3OD): δ = 7.33 and 8.08 (d, *J* = 8.3 and 8.1 Hz, 4H, AA' and BB' system, Ar-H); **^{13}C NMR** (100 MHz, CD_3OD): δ = 29.5 (q, J_{CF} = 41.0 Hz, *C*(N=N)CF_3), 123.4 (q, J_{CF} = 274.4 Hz, CF_3), 127.5 (2CH, Ar), 131.3 (2CH, Ar), 133.5 (C, Ar), 134.4 (C, Ar), 168.5 (COOH).

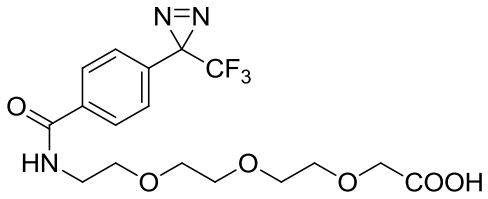
***tert*-Butyl 1-oxo-1-(4-(3-(trifluoromethyl)-3*H*-diazirin-3-yl)phenyl)-5,8,11-trioxa-2-azatridecan-13-oate (2-17)**



To a cooled solution (0 °C) of acid **2-16** (500 mg, 2.2 mmol) and amine **2-8** (572 mg, 2.2 mmol) in CH_2Cl_2 (20 mL) was added DIPEA (757 mL, 4.3 mmol) followed by addition of PyBrOP (1.21 g, 2.6 mmol). The mixture was stirred overnight at room temperature then diluted with

CH_2Cl_2, washed with 1N HCl (20 mL), saturated $NaHCO_3$ (20 mL) and saturated NaCl solution. The separated organic layer was dried over Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by flash chromatography (methanol/CH_2Cl_2, 1:25) to furnish amide **2-17** (760 mg, 73%) as colorless oil. $\mathbf{R_f}$ = 0.37 (methanol/CH_2Cl_2, 1:25); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.45 (s, 9H, $C(CH_3)_3$), 3.61–3.69 (m, 12H, OCH_2), 3.96 (s, 2H, OCH_2CO), 7.03 (1H NH), 7.21 and 7.85 (d, *J* = 8.6 and 8.1 Hz, 2H, AA' and BB' system, Ar-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 28.0 ($C(CH_3)_3$), 28.3 (q, J_{CF} = 40.2 Hz, C(N=N)CF_3), 39.9 (CH_2NHCO), 68.8 (OCH_2), 69.8 (OCH_2), 70.1 (OCH_2), 70.4 (OCH_2), 70.5 (2C, OCH_2), 81.8 ($C(CH_3)_3$), 121.9 (q, J_{CF} = 274.4 Hz, CF_3), 126.4 (2CH, Ar), 127.7 (2CH, Ar), 131.9 (C, Ar), 135.7 (C, Ar), 166.3 (CONH), 169.6 (COO*t*Bu); **HRMS** (ESI): $[M+Na]^+$ calcd for $C_{21}H_{28}N_3F_3O_6Na$ 498.18224, found 498.182063.

1-Oxo-1-(4-(3-(trifluoromethyl)-3*H*-diazirin-3-yl)phenyl)-5,8,11-trioxa-2-azatridecan-13-oic acid (2-18)



A solution of *t*-butyl ester **2-17** (100 mg, 2.1 mmol) in a mixture of TFA (0.5 mL) and CH_2Cl_2 (1.5 mL) was stirred at room temperature for 14 h. The reaction mixture was concentrated under vacuum to remove volatiles, then the residue was purified by flash chromatography (methanol/CH_2Cl_2/AcOH, 1:9:0.01) to yield acid **2-18** (73 mg, 83%) as colorless oil. $\mathbf{R_f}$ = 0.56 (methanol/CH_2Cl_2/AcOH, 1:9:0.01); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 3.55–3.75 (m, 12H, OCH_2), 4.09 (s, 2H, OCH_2CO), 7.19 (s, 1H, NH), 7.20 and 7.87 (d, *J* = 8.6 and 8.1 Hz, 4H, AA' and BB' system, Ar-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 28.3 (q, J_{CF} = 40.3 Hz, C(N=N)CF_3), 39.9 (CH_2NHCO), 68.7 (OCH_2), 69.8 (2 OCH_2), 70.0 (OCH_2), 70.4 (OCH_2), 71.2 (OCH_2), 121.7 (q, J_{CF} = 274.4 Hz, CF_3), 126.4 (2CH, Ar), 127.7 (2CH, Ar), 132.1 (C, Ar), 135.3 (C, Ar), 166.6 (*C*ONH), 172.2 (COOH); **HRMS** (ESI): $[M+Na]^+$ calcd for $C_{17}H_{20}N_3F_3O_6Na$ 442.11964, found 442.120007.

Immobilization of the diazirine containing linker 2-18 on Toyopearl AF amino 650 beads

Toyopearl AF 650 amino beads (1.45 mL, 0.145 mmol, 20% aq ethanol suspensions) were filtered under vacuum on a sintered glass funnel (G-4 type). The beads were washed three times using DMF (3 mL each) and transferred into a Falcon tube to which DMF (3 mL), DIC (337 μL) and linker **2-18** (200 mg, 0.48 mmol) were added. The tube was covered with aluminium foil to protect them from light and shaken at room temperature. After 72 h, the bead suspension was transferred into a sintered glass funnel, filtered and washed with DMF (3 × 5 mL), followed by 50% aq dioxane (3 × 5 mL) and transferred into a new Falcon tube. 50% aq dioxane (5 mL), 10% aq AcOH (135 μL) and DIC (337 μL) were added and the mixture was shaken for 4 h at room temperature in absence of light. The resulting suspension was washed with 50% aq dioxane (3 × 5 mL), which was followed by alternative washing with acetate buffer of pH ~4 (3 × 5 mL) and Tris buffer of pH ~8 (3 × 5 mL). Finally the beads were washed with dd H_2O (3 × 5 mL) and 20% aq ethanol (3 × 5 mL) successively. The obtained dry beads **2-19** were stored in 20% aq ethanol (0.725 mL) as bead suspension (total volume 1.3 mL).

General procedure for the preparation of small molecule immobilized affinity beads.

Affinity linker immobilized beads **2-19** (250 μL, 27.5 μmol) were washed with dd H_2O (3 × 400 μL) followed by 2-propanol (3 × 400 μL) to remove water from the swollen beads and then the beads were transferred into a glass sample vial. A solution of small molecule (1 equiv, 27.5 μmol, according to concentration of beads **2-19** in 20% aq ethanol) in ethanol (250 μL) was added to the dry beads. The solvent was removed by putting the bead suspension under vacuum. The resulting homogenous mixture was exposed to UV light (365 nm, 4 Jcm^{-2}) for 2 h while taking care for irradiation of complete sample. Then the vial was turned occasionally to expose all the beads to the UV light. The resulting beads were washed with 50% aq ethanol, ethanol, DMSO and ethanol (each 3 × 500 μL). These dried beads were then transferred into an Eppendorf tube and stored as suspensions in 20% aq ethanol (200 μL) before they were used for fishing experiment. At this point we assumed that roughly 10 mol% of the small molecule was successfully immobilized on the beads.

SILAC protocol for cells carried by colleague (In German)

1. **Reagenzien und Materialien:**

- DMEM Silac High Glucose (4,5 mg/ml) ohne Arginin, ohne Lysin, ohne L-Glutamin
- Dialysiertes FBS
- L-Glutamin 100x bzw. 200mM
- Aminosäuren Arginin (light, medium, heavy), Lysin (light, medium, heavy)
- Zur Herstellung einer Stock-Lösung werden die lyophilisierten AS in 1 ml PBS aufgenommen.

Stock-Lösung: c(Lys) = 146 mg/ml c(Arg)= 84 mg/ml

Lysin	light (L): Lys 0	Arginin	light: Arg 0
	medium (M): Lys 4		medium: Arg 6
	heavy (H): Lys 8		heavy: Arg 10

- Penicillin/ Streptomycin mit c(Pen)=10000 U/ml, c(Strep)=10000 µg/ml
- EDTA stock 0,5M pH=8, (verdünnt für Zellen: 170 µl EDTA-Stock auf 50 ml PBS) PBS
- Corning Filter systems (Polyethersulfon PES, 0,22µm)
- Mikroskop
- Zellschalen mit Durchmesser 6 cm
- Brutschrank: Bedingungen 37°C, 5% CO2, wasserdampfgesättigt.

2. **Herstellen des Silac Zell-Mediums für Einsatz Zellkultur:**

(Angabe allgemein, und in Klammer unsere eingesetzten Volumina, 190 mL pro Silac Medium L, M, H) Unter der Sterilbank arbeiten! Das DMEM Silac vorlegen (500ml). Dann gibt man L-Glutamin 100x (5 ml) hinzu, damit die Endkonzentration 1% ist. Dann gibt man

Penicillin/Streptomycin 100x (5ml) hinzu, damit die Endkonzentration 1% ist. (insgesamt nun 510 ml Gesamtvolumen). Diese Mischung wird zu 3 gleichen Teilen (jeweils 170 ml) in neue sterile Gefäße überführt. Nun gibt man jeweils die Aminosäure-Stocks hinzu (Light, medium, heavy), so daß die Aminosäuren Arginin und Lysin im Medium nun 1:2000 vorliegen. (95 µl AS-stock auf insgesamt 190 ml Medium). Die Medien werden nun mittels Corning Sterilfiltern (Unterdruck) sterilfiltriert. Nun gibt man jeweils dialysiertes FBS dazu (20 ml), damit die Endkonzentration 10% ist und mischt das Medium gut durch. Das Silac Medium kann bei 4°C gelagert werden.

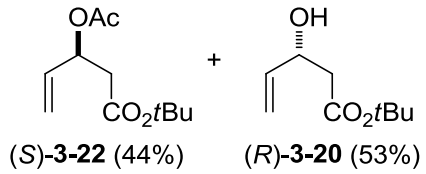
3. **SILAC Zellkultur führen:**

Die Silac-Kultur kann in Kulturschalen (Durchmesser 6 cm) mit 4 ml Kulturmedium geführt werden. Für die Durchführung von Versuchen kann die Zellkultur auf 10 cm Schalen expandiert werden mit 10 mL Kulturmedium. Bei einer Zellyse einer konfluenten 10 cm Schale ist die Proteinausbeute ca. 1,5 mg.

4. **Zellen splitten (6 cm Schale):**

Beispielsweise 3x die Woche 1:4, oder 2x die Woche 1:6. Dies ist abhängig Von der Zellart und der Wachstumsgeschwindigkeit. Das verbrauchte Kulturmedium wird abgezogen. Es wird 2x mit je 2 ml PBS gewaschen. (schwenken und vollständig abziehen d. Flüssigkeit). Nun wird 0,5 ml verdünntes EDTA dazugegeben, auf der Schale verteilt und ca. 10 min bei 37°C inkubiert. Danach wird mittels Mikroskop geprüft, ob sich die Zellen abgelöst haben, ggf. die Schale schwenken und abklopfen. Nun werden jeweils 1,5 ml neues Zellmedium (L,M,H) auf die Schalen gegeben und geschwenkt. (also insgesamt jetzt 2ml). Nun werden die Zellen in der Zellsuspension durch mehrmaliges auf- und abpipettieren vereinzelt. Bei einem Split von 1:4 werden nun 0,5 ml davon in eine neue Kulturschale gegeben, in welcher zuvor schon 3,5 ml des entsprechenden Silac-Mediums vorgelegt wurden. Auch diese Schale wird kurz geschwenkt, damit sich die Zellen gleichmäßig verteilen. Die Zellen werden im Brutschrank bei 37°C inkubiert.

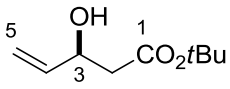
tert-Butyl (3*S*)-3-(acetyloxy)pent-4-enoate (*S*)-3-22[173,174]



(*S*)-**3-22** (44%) (*R*)-**3-20** (53%)

To a suspension of hydroxy ester *rac*-**3-20**[173] (10.0 g, 58.1 mmol), molecular sieves (9.85 g) and amano PS lipase (5.83 g) in pentane (300 mL) was added vinyl acetate (5.36 mL, 58.1 mmol) and the reaction mixture was stirred at 30 °C for 16 h. The reaction mixture was filtered through a pad of celite. The filtrate was concentrated, and the residue purified by flash chromatography (Et_2O/petroleum ether, 1:4) to give (*S*)-acetate **3-22** (5.53 g, 44%) and unreacted alcohol (*R*)-**3-20** (5.35 g, 53%). $\mathbf{R_f}$ = 0.24 (alcohol **3-20)** and 0.56 (acetate **3-22)** (Et_2O/petroleum ether, 1:4); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.42 (s, 9H, $C(CH_3)_3$), 2.03 (s, 3H, $OCOCH_3$), 2.50 (dd, *J* = 15.2, 5.8 Hz, 1H, 2-H), 2.58 (dd, *J* = 15.4, 8.1 Hz, 1H, 2-H), 5.18 (ddd, *J* = 10.4, 1.0, 1.0 Hz, 1H, 5-H), 5.28 **(**ddd, *J* = 17.2, 1.3, 1.0 Hz, 1H, 5-H), 5.54–5.62 (m, 1H, 3-H), 5.80 (ddd, *J* = 16.9, 10.3, 6.1 Hz, 1H, 4-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 21.0 ($OCOCH_3$), 28.0 ($C(CH_3)_3$), 40.6 (C-2), 71.0 (C-3), 81.0 ($C(CH_3)_3$), 117.3 (C-5), 135.1 (C-4); 168.9 (CO_2tBu), 169.8 ($OCOCH_3$).

tert-Butyl (3*S*)-3-hydroxypent-4-enoate (*S*)-3-20

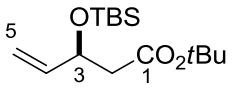


K_2CO_3 (4.01 g, 18.7 mmol) was added to a cooled solution of acetate (*S*)-**3-22** (2.71 g, 19.6 mmol) in methanol (40 mL) at −15 °C. The mixture was stirred for 45 min, before it was filtered through a pad of celite and the filtrate carefully concentrated to a volume of ~10 mL. This solution was diluted with Et_2O (20 mL), washed with water, and saturated NaCl solution. The organic layer was dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude hydroxyester was purified by flash chromatography (diethyl ether/petroleum ether, 3:7) to furnish (*S*)-alcohol (*S*)-**3-20** (2.64 g, 82%) as colorless oil. $\mathbf{R_f}$ = 0.24 (diethyl ether/petroleum ether,1:4); $\mathbf{[\alpha]_D^{20}}$ = −6.6 (*c* 1.0, $CHCl_3$); {ref[173] *ent*-**3-20** $[\alpha]_D^{25}$ = + 7.7 (*c* 3.58, $CHCl_3$)}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.44 (s, 9H, $C(CH_3)_3$), 2.41 (dd, *J* = 16.2, 8.3, Hz, 1H, 2-H), 2,49

(dd, *J* = 4.0, 16.2 Hz, 1H, 2-H), 3.13 (d, *J* = 4.5 Hz, 1H, OH), 4.44−4.50 (m, 1H, 3-H), 5.13 (ddd, *J* = 10.4, 1.5, 1.3 Hz, 1H, 5-H), 5.28 (ddd, *J* = 17.2, 1.5, 1.5, Hz, 1H, 5-H), 5.85 (ddd, *J* = 17.2, 10.6, 5.6 Hz, 1H, 4-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 27.8 ($C(CH_3)_3$), 41.7 (C-2), 68.7 (C-3), 81.1 ($C(CH_3)_3$), 114.8 (C-5), 138.5 (C-4), 171.4 (C-1).

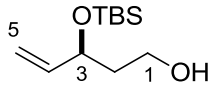
The *ee* of (*S*)-**3-20** after resolution was determined to be 98.5% by chiral GC.

(*S*)-*tert*-Butyl-3-((*tert*-butyldimethylsilyl)oxy)pent-4-enoate (3-23)



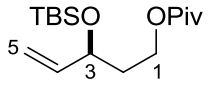
A mixture of alcohol (*S*)-**3-20** (2.95 g, 17.1 mmol), imidazole (1.75 g, 25.7 mmol), and *tert*-butyldimethylsilyl chloride (2.83 g, 18.8 mmol) in DMF (60 mL) was stirred at 50 °C for 3 h. The reaction was quenched by adding water (10 mL), and the mixture extracted with EtOAc (3 × 25 mL). The combined organic layers were washed with saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated in vaccuo. Flash chromatography (Et_2O/petroleum ether, 1:50) provided silyl ether **3-23** (4.59 g, 93%) as a colorless oil. $\mathbf{R}_f$ = 0.17 (Et_2O/petroleum ether, 1:50); $\mathbf{[\alpha]_D^{21}}$ = −3.56 (*c* 1.0, $CHCl_3$) {ref[173] *ent*-**3-23** $[\alpha]_D^{25}$ +3.5 (*c* 1.94, $CHCl_3$)}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 0.03 (s, 3H, $Si(CH_3)_2$), 0.05 (s, 3H, $Si(CH_3)_2$), 0.87 (s, 9H, $SiC(CH_3)_3$), 1.43 (s, 9H, CO_2tBu), 2.33 (dd, *J* = 14.6, 5.8 Hz, 1H, 2-H), 2.33 (dd, *J* = 14.6, 7.3 Hz, 1H, 2-H), 4.49−4.56 (m, 1H, 3-H), 5.04 (ddd, *J* = 10.4, 1.5, 1.3 Hz, 1H, 5-H), 5.19 (ddd, *J* = 17.2, 1.5, 1.3 Hz, 1H, 5-H), 5.82 (ddd, *J* = 16.9, 10.4, 6.3 Hz, 1H, 4-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = −5.0 ($Si(CH_3)_2$), −4.4 ($Si(CH_3)_2$), 18.1 ($SiC(CH_3)_3$), 25.8 ($SiC(CH_3)_3$), 28.1 ($OC(CH_3)_3$), 44.8 (C-2), 70.9 (C-3), 80.4 ($OC(CH_3)_3$), 114.4 (C-5), 140.5 (C-4), 170.3 (C-1); **HRMS** (ESI): $[M+Na]^+$calcd for $C_{15}H_{30}O_3Na$ 309.18564, found 309.185479.

(*S*)-3-((*tert*-Butyldimethylsilyl)oxy)pent-4-en-1-ol (3-24)



To a cooled (−78 °C) solution of ester **3-23** in CH_2Cl_2 (100 mL) was added dropwise a solution of DIBAL-H (61.1 mL, 61.1 mmol, 1M in hexane) using a syringe pump within 40 min. After complete addition, the mixture was allowed to warm to 0 °C over 2 h and then stirred for additional 2 h. The reaction was quenched by slow addition of methanol (3 mL) and saturated NH_4Cl solution (15 mL). After 3 h of vigorous stirring at room temperature, the organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with saturated NaCl solution (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude oil was purified by flash chromatography (ethyl acetate/petroleum ether, 1:9) to afford alcohol **3-24** (2.21 g, 84%) as colorless oil. $\mathbf{R_f}$ = 0.25 (EtOAc/petroleum ether, 1:9); $\mathbf{[\alpha]_D^{21}}$ = −4.99 (*c* 1.0, $CHCl_3$) {ref[175] **3-24** $[\alpha]_D^{29}$ −5.65 (*c* 0.5, MeOH), ref[176] *ent*-**3-24** $[\alpha]_D^{25}$ + 1.9 (*c* 1.2, $CHCl_3$), ref[177] *ent*-**3-24** $[\alpha]_D^{20}$ + 3.3 (*c* 0.94, $CHCl_3$), ref[178] *ent*-**3-24** $[\alpha]_D^{20}$ +7.5 (*c* 0.75, $CHCl_3$)}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 0.05 (s, 3H, $Si(CH_3)_2$), 0.08 (s, 3H, $Si(CH_3)_2$), 0.89 (s, 9H, $C(CH_3)_3$), 1.70 (dddd, *J* = 14.1, 10.1, 6.3, 6.1 Hz, 1H, 2-H), 1.84 (dddd, *J* = 14.1, 8.1, 4.3, 4.5 Hz, 1H, 2-H), 2.28 (s, 1H, OH), 3.70 (ddd, *J* = 10.6, 6.1, 4.3 Hz, 1H, 1-H), 3.80 (ddd, *J* = 11.8, 8.1, 4.0 Hz 1H, 1-H), 4.36–4.44 (m, 1H, 3-H), 5.09 (ddd, *J* = 10.6, 1.5, 1.3 Hz, 1H, 5-H), 5.20 (ddd, *J* = 17.2, 1.5, 1.3 Hz, 1H, 5-H), 5.84 (ddd, *J* = 5.8, 10.6, 17.2 Hz, 1H, 5-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = −5.1 ($Si(CH_3)_2$), −4.4 ($Si(CH_3)_2$), 18.1 (Si*C*$(CH_3)_3$), 25.8 (SiC(*C*$H_3)_3$), 39.1 (C-2), 60.1 (C-1), 73.2 (C-3), 114.4 (C-5), 140.6 (C-4); **HRMS** (ESI): $[M+Na]^+$ calcd for $C_{11}H_{24}O_2SiNa$ 239.14378, found 239.143772.

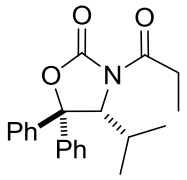
(*S*)-3-((*tert*-butyldimethylsilyl)oxy)pent-4-en-1-yl pivalate (3-25)



Et_3N (1.67 mL, 12.0 mmol), pivaloyl chloride (1.08 mL, 9.0 mmol), and DMAP (73 mg, 0.6 mmol) were added successively to a cooled (ice/water bath) solution of alcohol **3-24** (1.21 g, 6.0 mmol) in CH_2Cl_2 (22 mL) and the reaction mixture was allowed to stir at room temperature for 1 h (TLC control). The mixture was washed with saturated $NaHCO_3$ solution (5 mL), water (5 mL) and saturated NaCl solution. The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated on a rotary evaporator. Purification of the residue by flash chromatography

(Et_2O/petroleum ether, 1:50) yielded pivaloyl ester **3-25** (1.85 g, 97%) as colorless liquid. $\mathbf{R_f}$ = 0.23 (Et_2O/petroleum ether, 1:50); $\mathbf{[\alpha]_D^{20}}$ = −5.35 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 0.02 (s, 3H, $Si(CH_3)_2$), 0.04 (s, 3H, $Si(CH_3)_2$), 0.88 (s, 9H, $SiC(CH_3)_3$), 1.19 (s, 9H, $C(CH_3)_3$, pivaloyl), 1.73–1.84 (m, 2H, 3-H), 4.08 (dddd, *J* = 17.4, 10.7, 6.6, 5.8 Hz, 2H, 1-H), 4.13 (dddd, *J* = 16.9, 10.9, 5.8, 5.8 Hz, 1-H) 4.19–4.27 (m, 1H, 3-H), 5.04 (ddd, *J* = 10.4, 1.0, 1.0 Hz, 1H, 5-H), 5.15 (ddd, *J* = 17.2, 1.5, 1.3 Hz, 1H, 5-H), 5.79 (ddd, *J* = 17.2, 10.4, 6.3 Hz, 1H, 4-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = −5.0 ($Si(CH_3)_2$), −4.4 ($Si(CH_3)_2$), 18.2, ($SiC(CH_3)_3$), 25.8 ($SiC(CH_3)_3$), 27.2 ($C(CH_3)_3$, pivaloyl), 37.0 (C-2), 38.7 ($C(CH_3)_3$, pivaloyl), 61.0 (C-1), 70.7 (C-3), 114.2 (C-5), 141.1 (C-4), 17.4 (C=O); **HRMS** (ESI): $[M+Na]^+$ calcd for $C_{16}H_{32}O_3SiNa$ 323.20129, found 323.201168.

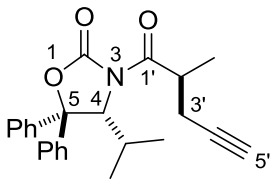
(*R*)-4-Isopropyl-5,5-diphenyl-3-propionyloxazolidin-2-one (3-27)[179]



(4*R*)-4-Isopropyl-5,5-diphenyl-1,3-oxazolidin-2-one **3-26**[143b] (26.01 g, 92.5 mmol) was dissolved in THF (330 mL) and cooled to 0 °C in an ice bath. *n*-BuLi (42.51 mL, 106.3 mmol, 2.5M in hexane) was added dropwise over 30 min and the mixture was stirred for 20 min. Propionyl chloride (10.48 mL, 92.5 mmol) was added within 15 min and the reaction mixture was allowed to stir at room temperature for 1 h. The mixture was diluted with ether (100 mL), excess of propionyl chloride was quenched with saturated NH_4OH solution. The organic layer was separated and the aqueous layer was extracted with diethyl ether (3 × 30 mL). The combined organic layers were washed with aqueous 1M NaOH solution (50 mL), saturated NaCl solution (50 mL), dried over $MgSO_4$, filtered and concentrated under vacuum. The crude solid was purified by flash chromatography (EtOAc/petroleum ether, 1:9) to yield **3-27** (30.1 g, 96%) as a white solid. $\mathbf{R_f}$ = 0.3 (EtOAc/petroleum ether, 1:4); $\mathbf{[\alpha]_D^{24}}$ = +223.15 (*c* 1, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 0.75 (d, *J* = 6.8 Hz, 3H, $CHCH(CH_3)_2$), 0.87 (d, *J* = 7.1 Hz, 3H, $CHCH(CH_3)_2$), 1.08 (t, *J* = 7.6 Hz, 3H, CH_2CH_3), 1.58 (s, H_2O), 1.90–2.02 (m, 1H,

CHC*H*$(CH_3)_2$), 2.72 (ddd, *J* = 17.4, 14.6, 7.3 Hz, 1H, C*H*$_2$CH$_3$), 2.92 (ddd, *J* = 17.2, 14.6, 7.3 Hz, 1H, C*H*$_2$CH$_3$), 5.36 (d, *J* = 3.5 Hz, 1H, C*H*CH$(CH_3)_2$), 7.23–7.41 (m, 8H, Ar-H), 7.44–7.49 (m, 2H, Ar-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 8.6 (CH_2*C*H$_3$), 16.3 (CHCH(*C*H$_3$)$_2$), 21.8 (CHCH(*C*H$_3$)$_2$), 28.9 (*C*H$_2$CH$_3$), 29.9 (CH*C*H$(CH_3)_2$), 64.4 (*C*HCH$(CH_3)_2$), 89.3 (*C*(Ph)$_2$OCO), 125.6 (2CH, Ar), 125.9 (2CH, Ar), 127.9 (CH, Ar), 128.3 (2CH, Ar), 128.5 (CH, Ar), 128.9 (2CH, Ar).

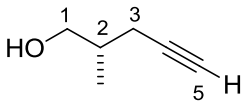
(*R*)-4-Isopropyl-3-((*S*)-2-methylpent-4-ynoyl)-5,5-diphenyloxazolidin-2-one (3-28)



NaHMDS (45 mL, 2M in THF, 90.0 mmol) was added to a solution of propionyl derivative **3-27** (20.01 g, 59.3 mmol) in THF (60 mL) at −78 °C. The mixture was stirred for 2 h at this temperature followed by addition of propargyl bromide (15.1 mL, 178 mmol, 80% w/w in toluene). After complete addition, the mixture was allowed to warm to −15 °C and stirred at this temperature for 20 h. The reaction mixture was diluted with Et_2O (50 mL) and treated with a saturated solution of NH_4Cl (50 mL). The resulting white salt precipitated was dissolved by addition of a small amount of water. The organic layer was separated and the aqueous layer was extracted with Et_2O (3 × 50 mL). The combined organic layers were washed with saturated NaCl solution (50 mL), dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. The crude solid obtained was purified by flash chromatography (Et_2O/petroleum ether, 1:4) to afford alkylated product **3-28** (21.15 g, 95%) as white solid, **m.p.** 166–169 °C; $\mathbf{R_f}$ = 0.36 (ethyl acetate/petroleum ether, 1:20); $\mathbf{[\alpha]_D^{22}}$ = +209.9 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 0.73 (d, *J* = 6.8 Hz, 3H, 4-CH(C*H*$_3$)$_2$), 0.85 (d, *J* = 7.1 Hz, 3H, 4-CH(C*H*$_3$)$_2$), 0.86 (d, *J* = 7.1 Hz, 3H, 2'-CH_3), 1.85–1.98 (m, 1H, 4-C*H*$(CH_3)_2$), 1.92 (dd, *J* = 2.8, 2.5 Hz, 1H, 5'-H), 2.37 (ddd, *J* = 16.7, 6.6, 2.8 Hz, 1H, 3'-H), 2.53 (ddd, *J* = 16.9, 7.1, 2.8 Hz, 1H, 3'-H), 3.82 (m, 1H, 2'-H), 5.33 (d, *J* = 3.3 Hz, 1H, 4-H), 7.18–7.43 (m, 10H, Ar-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 16.2 (2'-CH_3), 4-CH(*C*H$_3$)$_2$), 21.7 (4-CH(*C*H$_3$)$_2$), 22.6 (C-3'), 29.7 (4-*C*H$(CH_3)_2$), 37.1 (C-2'), 64.6

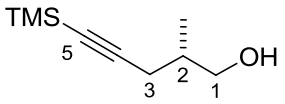
(C-4), 70.0 (C-5'), 81.5 (C-5), 89.4 (C-4'), 125.5 (2CH, Ar), 125.8 (2CH, Ar), 127.9 (CH, Ar), 128.4 (2CH, Ar), 128.5 (CH, Ar), 128.8 (2CH, Ar), 138.0 (C, Ar), 142.2 (C, Ar), 152.7 (C-2), 174.5 (C-1'); **HRMS** (ESI): $[M+Na]^+$ calcd for $C_{24}H_{25}NO_3Na$ 398.17266, found 398.172724.

(2*S*)-2-Methyl-5-(trimethylsilyl)pent-4-ynol (3-29)



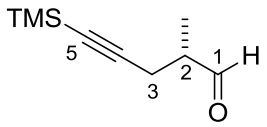
To a cooled solution (salt/ice bath) of oxazolidinone **3-28** (14.83 g, 39.5 mmol) in THF (1100 mL) was added a solution of $NaBH_4$ (7.47 g, 197.5 mmol) in H_2O (280 mL) dropwise at 0 °C within 30 min. The reaction mixture was allowed to warm to room temperature overnight (~12 h), and then quenched by adding saturated NH_4Cl solution. The white salt precipitated was dissolved by adding a small amount of water. Most of the THF was removed carefully under vacuum, and the residual mixture was filtered to recover the precipitated auxiliary. The filtrate was extracted using Et_2O (3 × 150 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuum (carefully). The residue was purified by flash chromatography (Et_2O/petroleum ether, 3:7) to furnish alcohol **3-29** (3.56 g, 92%) as slightly yellow oil. $\mathbf{R_f}$ = 0.31 (Et_2O/petroleum ether, 2:3); $\mathbf{[\alpha]_D^{22}}$ = −14.8 (*c* 1.0, $CHCl_3$) {ref[180] *ent*-**3-29** $[\alpha]_D^{20}$ +11.4 (*c* 1.1, $CHCl_3$)}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.0 (d, *J* = 6.8 Hz, 3H, 2-CH_3), 1.57 (s, br, 1H, OH), 1.82–1.94 (m, 1H, 2-H), 1.97 (dd, *J* = 2.8, 2.5 Hz, 1H, 5-H), 2.20 (ddd, *J* = 16.7, 6.3, 2.5 Hz, 2H, 3-H), 2.27 (ddd, *J* = 16.9, 6.3, 2.8 Hz, 2H, 3-H), 3.56 (d, *J* = 6.3 Hz, 2H, 1-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 16.1 (2-CH_3), 22.2 (C-3), 34.9 (C-2), 66.9 (C-5), 69.6 (C-1), 82.6 (C-4).

(2*S*)-2-Methyl-5-trimethylsilyl-pent-4-yn-1-ol (3-30)



n-BuLi (32.6 mL, 2.5M in hexane, 81.6 mmol) was added dropwise to a solution of alkynol **3-29** (3.64 g, 37.1 mmol) in THF (90 mL) at −78 °C followed by stirring of the mixture for 1 h at the same temperature. Then, trimethylsilyl chloride (9.88 mL, 77.9 mmol) was added slowly and the mixture was allowed to warm to the room temperature within 2 h. The reaction was quenched by addition of 1N HCl (30 mL) and the mixture stirred for additional 2 h to cleave the silyl ether. The mixture was extracted with Et_2O (3 × 60 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Purification of the residue by flash chromatography (Et_2O/petroleum ether, 3:7) afforded alcohol **3-30** (4.99 g, 79 %) as pale yellow oil. $\mathbf{R_f}$ = 0.44 (Et_2O/petroleum ether, 2:3); $\mathbf{[\alpha]_D^{23}}$ = −6.01 (*c* 1, $CHCl_3$) {ref[181] *ent*-**3-30** $[\alpha]_D^{23}$ +6.6 (*c* 1.12, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 0.13 (s, 9H, $Si(CH_3)_3$), 0.98 (d, *J* = 6.8 Hz, 3H, 2-CH_3), 1.64 (s, 1H, OH), 1.81–1.94 (m, 1H, 2-H), 2.22 (dd, *J* = 16.9, 6.3, Hz, 1H, 3-H), 2.28 (dd, *J* = 17.2, 6.6, Hz, 1H, 3-H), 3.55 (d, *J* = 6.6 Hz, 2H, 1-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = −0.07 ($Si(CH_3)_3$), 16.2 (2-CH_3), 23.8 (C-3), 35.01 (C-2), 67.2 (C-1), 86.1 (C-5), 105.4 (C-4).

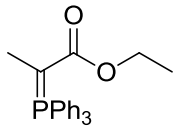
(2*S*)-2-Methyl-5-(trimethylsilyl)pent-4-ynal (3-31)



To a cooled solution (−78 °C) of oxalyl chloride (1.53 mL, 17.8 mmol) in CH_2Cl_2 (75 mL) was slowly added in a dropwise fashion DMSO (2.53 mL, 35.6 mmol) while maintaining the temperature below −75 °C. After being stirred for 15 min at this temperature, a solution of alcohol **3-30** (1.53 g, 14.8 mmol) in CH_2Cl_2 (10 mL) was added over a period of 15 min, before Et_3N (10.3 mL, 74.2 mmol) was added dropwise to the reaction mixture. The mixture was stirred at the same temperature for 1 h and then warmed to room temperature. It was washed with 1N HCl (50 mL), water (50 mL) and saturated NaCl solution (50 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by flash chromatography (Et_2O/petroleum ether, 1:9) to afford aldehyde **3-31** (2.40 g, 96%) as yellow oil. $\mathbf{R_f}$ = 0.25 (Et_2O/petroleum ether, 1:20); $\mathbf{[\alpha]_D^{21}}$ = −8.12 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz,

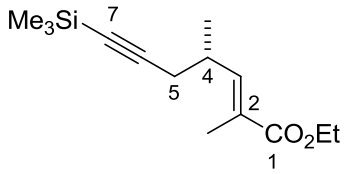
$CDCl_3$): δ = 0.12 (s, 9H, $Si(CH_3)_3$), 1.20 (d, *J* = 7.1 Hz, 3H, 2-CH_3), 2.38 (dd, *J* = 18.4, 8.8, 1H, 3-H), 2.54 (dd, *J* = 18.4, 5.8, 1H, 3-H), 2.48–2.54 (m, 1H, 2-H,), 9.69 (s, 1H, 1-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = −0.0 ($Si(CH_3)_3$), 13.0 (2-CH_3), 21.2 (C-3), 45.1 (C-2), 87.0 (C-5), 103.3 (C-4), 203.2 (C-1).

Ethyl 2-(triphenylphosphoranylidene)propanoate (3-32)[146b]



A mixture of PPh_3 (7.24 g, 27.6 mmol) and ethyl-2-bromopropionate (3.57 mL, 27.6 mmol) was heated at 50 °C in a thick glass screw cap bottle for 10 h. Hexane (20 mL) was added and the hard white solid cake was broken into small pieces, washed in a filtration funnel with hexane (3 × 100 mL) and the dried white solid was dissolved in CH_2Cl_2 (100 mL). This solution was added to a precooled solution of NaOH (1.10 g, 27.6 mmol) in water (100 mL) and the mixture was stirred for 30 min at room temperature. This biphasic mixture was separated and the aqueous layer washed with CH_2Cl_2 (2 × 50 mL). The combined organic layers were washed several times with water until pH of the water phase became neutral. The organic layer was dried over Na_2SO_4, filtered concentrated, and the residue dried under high vacuum to afford stabilized Wittig ylide **3-32** (26.51 g, 96%) as yellow fine powder. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 0.43 (t, *J* = 7.1 Hz, 3H$_{major}$, OCH_2CH_3), 1.22 (t, *J* = 6.82 Hz, 3H$_{minor}$, OCH_2CH_3), 1.58 (d, J_{PH} = 14.4 Hz, 3H$_{minor}$, 3-H), 1.60 (d, J_{PH} = 13.9 Hz, 3H$_{major}$, 3-H), 3.69 (q, *J* = 7.1 Hz, 3H$_{major}$, OCH_2CH_3), 4.03 (q, *J* = 7.1 Hz, 3H$_{minor}$, OCH_2CH_3), 7.41–7.67 (m, 15 H, Ar-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 12.1 (C-3$_{minor}$, *J* = 11.7 Hz), 12.8 (C-3$_{major}$, *J* = 13.8 Hz,), 14.0 (OCH_2CH_3, major), 15.3 (OCH_2CH_3, minor), 31.6 (C-2$_{major}$, J_{CP} = 120.7 Hz), 32.7 (C-2$_{major}$, J_{CP} = 126.6 Hz), 57.2 (OCH_2CH_3, major), 57.9 (OCH_2CH_3, minor), 127.8 (C$_{minor}$, J_{CP} = 90.6 Hz, Ar), 128.3 (C$_{major}$, J_{CP} = 90.8, Hz, Ar), 128.3 (CH$_{major}$, J_{CP} = 12.4 Hz, Ar), 128.4 (CH$_{minor}$, J_{CP} = 12.4 Hz, Ar), 131.4 (CH$_{minor}$, J_{CP} = 2.9 Hz, Ar), 131.4 (CH$_{major}$, J_{CP} = 2.9 Hz, Ar), 133.5 (CH$_{major}$, J_{CP} = 9.5 Hz, Ar), 133.5 (CH$_{minor}$, J_{CP} = 9.5 Hz, Ar).

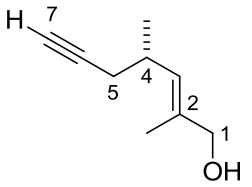
Ethyl (2*E*,4*S*)-2,4-dimethyl-7-(trimethylsilyl)hept-2-en-6-ynoate (3-33)



A mixture of aldehyde **3-31** (2.25 g, 13.4 mmol) and stabilized Wittig reagent **3-32** (7.28 g, 20.1 mmol) in toluene (30 mL) was heated to 80 °C for 12 h. The reaction mixture was cooled to room temperature and filtered through a pad of celite to remove Ph_3PO. The filtrate was concentrated in vacuo, and the residue purified by flash chromatography (diethyl ether/petroleum ether, 1:50) to yield unsaturated ester **3-33** (2.89 g, 86%) as yellow colored oil, *E/Z* ratio 15:1. $\mathbf{R_f}$ = 0.44 (diethyl ether/petroleum ether, 1:25); $\mathbf{[\alpha]_D^{20}}$ = +9.6 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 0.12 (s, 9H, $Si(CH_3)_3$), 1.09 (d, *J* = 6.8 Hz, 3H, 4-CH_3), 1.26 (t, *J* = 7.3 Hz, 3H, OCH_2CH_3), 1.85 (d, *J* = 1.5 Hz, 3H, 2-CH_3), 2.23 (d, *J* = 6.6 Hz, 2H, 5-H), 2.67–2.79 (m, 1H, 4-H), 4.17 (q, *J* = 7.3 Hz, 2H, OCH_2CH_3), 5.56 (ddd, *J* = 10.1, 1.5, 1.3 Hz, 1H, 3-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 0.0 ($Si(CH_3)_3$), 12.6 (2-CH_3), 14.2 (OCH_2CH_3), 19.2 (4-CH_3), 26.7 (C-4), 32.7 (C-5), 60.5 (OCH_2CH_3), 86.4 (C-7), 104.9 (C-6), 127.4 (C-2), 145.2 (C-3), 168.2 (C-1); **HRMS** (ESI): $[M+Na]^+$ calcd for $C_{14}H_{24}O_2SiNa$ 275.14378, found 275.143577.

The *ee* of **3-33** after the Wittig reaction was determined to be 89.8% by chiral GC.

(2*E*,4*S*)-2,4-Dimethylhept-2-en-6-yn-1-ol (3-36)

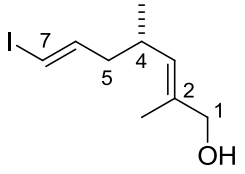


a) *DIBAL-H reduction*: To a cooled (−40 °C) solution of ester **3-33** (1.76 g, 7.4 mmol) in CH_2Cl_2 (40 mL) was added DIBAL-H (18.5 mL, 18.5 mmol, 1M in hexane) over 30 min followed by stirring the mixture for 2 h at the same temperature. Excess of DIBAL-H was quenched by addition of methanol (2 mL) and saturated solution of NH_4Cl (10 mL). The mixture was allowed

to stir vigorously at room temperature for 1 h and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 15 mL) and the combined organic layers were washed with saturated NaCl solution, dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by flash chromatography (EtOAc/petroleum ether, 1:4) to afford the corresponding alcohol (1.35 g, 87%) as colorless oil. $\mathbf{R_f}$ = 0.22 (EtOAc/petroleum ether, 1:4); $\mathbf{[\alpha]_D^{20}}$ = −13.4 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 0.13 (s, 9H, $C(CH_3)_3$), 1.03 (d, *J* = 6.8 Hz, 3H, 4-CH_3), 1.40 (s, 1H, OH), 1.68 (d, *J* = 1.3 Hz, 3H, 2-CH_3), 2.15 (dd, *J* = 19.4, 7.1 Hz, 1H, 5-H), 2.19 (dd, *J* = 18.9, 6.3 Hz, 1H, 5-H), 2.58–2.70 (m, 1H, 4-H), 3.98 (s, 2H, 1-H), 5.24 (ddd, *J* = 9.3, 1.3, 1.3 Hz, 1H, 3-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 0.1 ($Si(CH_3)_3$), 13.9 (2-CH_3), 20.0 (4-CH_3), 27.5 (C-5), 31.7 (C-4), 68.7 (C-1), 85.4 (C-7), 105.9 (C-6), 130.4 (C-3), 134.5 (C-2); **HRMS** (ESI): $[M+Na]^+$ calcd for $C_{12}H_{22}OSiNa$ 233.13321, found 233.133104.

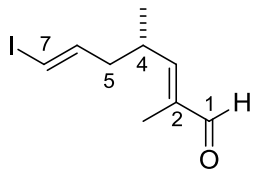
b) *TMS removal*: K_2CO_3 (1.66 g, 12.0 mmol) was added to a solution of the foregoing TMS acetylene (1.01 g, 4.8 mmol) in methanol (15 mL) and the mixture was allowed to stir at room temperature for 3 h. The reaction mixture was filtered through a pad of celite. The filtrate was concentrated and the residual oil purified by flash chromatography (diethyl ether/petroleum ether, 1:4) to furnish alkynol **3-36** (0.628 g, 95%) as colorless oil. $\mathbf{R_f}$ = 0.3 (Et_2O/petroleum ether, 1:4); $\mathbf{[\alpha]_D^{22}}$ = −13.6 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.05 (d, *J* = 6.6 Hz, 3H, 4-CH_3), 1.51 (s, 1H, OH), 1.67 (d, *J* = 1.5 Hz, 3H, 2-CH_3), 1.94 (dd, *J* = 2.8, 2.5 Hz, 1H, 7-H), 2.12 (ddd, *J* = 16.7, 7.1, 2.8 Hz, 1H, 5-H), 2.17 (ddd, *J* = 16.7, 6.3, 2.8 Hz, 1H, 5-H), 2.58–2.70 (m, 1H, 4-H), 3.98 (s, 2H, 1-H), 5.27 (ddd, *J* = 9.3, 1.3, 1.3 Hz, 1H, 3-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 13.8 (2-CH_3), 20.0 (4-CH_3), 26.1 (C-5), 31.3 (C-4), 68.6 (C-1), 69.1 (C-7), 82.9 (C-6), 130.1 (C-3), 134.7 (C-2); **HRMS** (ESI): $[M+Na]^+$ calcd for $C_9H_{14}ONa$ 161.09369, found 161.093613.

(2*E*,4*S*,6*E*)-7-Iodo-2,4-dimethylhepta-2,6-dien-1-ol (3-37)[182]



To a cooled (0 °C) solution of alkynol **3-36** (0.560 g, 4.0 mmol) in THF (5 mL), DIBAL-H (4.05 mL, 1M in hexane, 4.0 mmol) was added and the mixture was stirred for 1 h at room temperature. In another flask, containing Cp_2ZrCl_2 (1.16 g, 4.5 mmol) in THF (10 mL) at 0 °C was added DIBAL-H (4.5 mL, 1M in hexane, 4.5 mmol) and the resulting white suspension of the zirconocene hydrochloride was stirred for 30 min at the same temperature. To this second reaction mixture, the solution from the first reaction flask, containing the di-isobutyl alkoxide of **3-36**, was added dropwise at 0 °C. The reaction mixture was warmed to the room temperature until it became clear (~ 45 min). This mixture of the vinyl alane was cooled to −78 °C before a solution of iodine (2.0 g, 8.0 mmol) in THF (5 mL) was slowly added dropwise. The mixture was allowed to warm to room temperature within 1 h. The reaction was quenched with saturated NH_4Cl solution (5 mL) and extracted with EtOAc (3 ×15 mL). The combined organic layers were washed with 1M $Na_2S_2O_3$ solution, saturated NaCl solution, dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. Purification of the residue by flash chromatography (EtOAc/petroleum ether, 1:4) provided vinyl iodide **3-37** (0.850 g, 79%) as colorless oil. $\mathbf{R_f}$ = 0.33 (EtOAc/petroleum ether, 1:4); $\mathbf{[\alpha]_D^{22}}$ = −0.43 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 0.94 (d, *J* = 6.6 Hz, 3H, 4-CH_3), 1.45 (s, 1H, OH), 1.64 (d, *J* = 1.3 Hz, 3H, 2-CH_3), 1.93–2.08 (m, 2H, 5-H), 2.41–2.54 (m, 1H, 4-H), 3.98 (s, 2H, 1-H), 5.16 (ddd, *J* = 9.3, 1.3, 1.3 Hz, 1H, 3-H), 5.96 (ddd, *J* = 14.4, 1.3, 1.3 Hz, 1H, 7-H), 6.43 (ddd, *J* = 14.4, 7.6, 7.3 Hz, 1H, 6-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 13.9 (2-CH_3), 20.4 (4-CH_3), 31.6 (C-4), 43.5 (C-5), 68.6 (C-1), 75.4 (C-7), 130.5 (C-3), 134.3 (C-2), 144.8 (C-6); **HRMS** (ESI): $[M+Na]^+$ calcd for $C_9H_{15}IONa$ 289.0598, found 289.05864.

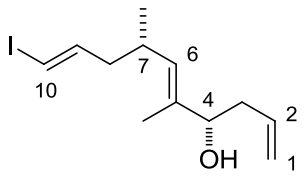
(2*E*,4*S*,6*E*)-7-Iodo-2,4-dimethylhepta-2,6-dienal (3-38)



To a cooled (0 °C) solution of alcohol **3-37** (0.83 g, 3.1 mmol) in CH_2Cl_2 (25 mL) was added Dess-Martin periodinane (1.59 g, 3.8 mmol) and the resulting mixture was allowed to stir at room temperature for 30 min. The reaction mixture was filtered through a pad of celite and the

filtrate washed with a mixture of saturated $NaHCO_3$ solution (5 mL) and 1M $Na_2S_2O_3$ solution (5 mL) followed by washing with saturated NaCl solution. The organic layer was dried over anhydrous Na_2SO_4, filtered, concentrated and the residue purified by flash chromatography (diethyl ether/petroleum ether, 1:20) to furnish aldehyde **3-38** (0.81g, 83%) as purple colored oil. $\mathbf{R_f}$ = 0.30 (diethyl ether/petroleum ether, 1:9); $\mathbf{[\alpha]_D^{20}}$ = 3.38 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.08 (d, *J* = 6.8 Hz, 3H, 4-CH_3), 1.74 (d, *J* = 1.3 Hz, 3H, 2-CH_3), 2.07–2.22 (m, 2H, H-5), 2.72–2.85 (m, 1H, 4-H), 6.06 (ddd, *J* = 14.4, 1.3, 1.01 Hz, 1H, 7-H), 6.21 (ddd, *J* = 9.8, 1.3, 1.3 Hz, 3-H), 6.42 (ddd, *J* = 14.4, 7.6, 7.3 Hz, 1H, 6-H), 9.38 (s, 1H, 1-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 9.4 (2-CH_3), 19.3 (4-CH_3), 32.9 (C-4), 42.5 (C-5), 76.8 (C-7), 138.6 (C-2), 143.2 (C-6), 157.7 (C-3), 195.2 (C-1); **HRMS** (ESI): $[M+Na]^+$ calcd for $C_9H_{13}IONa$ 286.99033, found 286.990534.

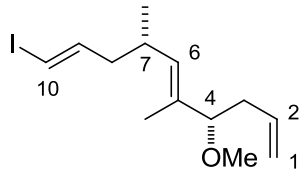
(4*S*,5*E*,7*S*,9*E*)-10-Iodo-5,7-dimethyldeca-1,5,9-trien-4-ol (3-39)



To a cooled (−78 °C) solution of (−)-Ipc_2BOMe (0.860 g, 2.7 mmol) in Et_2O (10 mL) was slowly added a solution of allyl magnesium bromide (2.61 mL, 1M in Et_2O, 2.6 mmol) under nitrogen atmosphere and the mixture allowed to stir at room temperature for 1 h. The resulting mixture was cooled to −90 °C using a toluene/N_2 bath before a solution of aldehyde **3-38** (599 mg, 2.3 mmol) in Et_2O (5 mL) was added dropwise followed by stirring of the mixture for 5 h at the same temperature. The reaction was quenched by adding 10% NaOH solution (5 mL), 40% H_2O_2 solution (5 mL) and the mixture was then stirred overnight at room temperature. The organic layer was separated and the aqueous layer was washed with diethyl ether (3 ×10 mL). The combined organic layers were dried over $MgSO_4$, filtered, concentrated, and the residue was purified by flash chromatography (Et_2O/petroleum ether, 1:4) to afford allylated product **3-39** (461 mg, 66%) as colorless oil. $\mathbf{R_f}$ = 0.20 (diethyl ether/petroleum ether, 1:4); $\mathbf{[\alpha]_D^{21}}$ = 7.56 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 0.95 (d, *J* = 6.8 Hz, 3H, 7-CH_3), 1.61 (s, 1H,

OH), 1.61 (d, *J* = 1.3 Hz, 3H, 5-CH_3), 1.94 (dddd, *J* = 13.9, 8.6, 7.8, 1.3 Hz, 1H, 8-H), 2.04 (dddd, *J* = 13.9, 7.3, 5.8, 1.0 Hz, 1H, 8-H), 2.29 (ddd, *J* = 6.8, 1.3, 1.3 Hz, 1H, 3-H), 2.31 (ddd, *J* = 6.8, 1.3, 1.3 Hz, 1H, 3-H), 2.42–2.53 (m, 1H, 7-H), 4.02 (t, *J* = 6.8 Hz, 4-H), 5.08–5.17 (m, 3H, 1-H, 6-H), 5.73 (dddd, *J* = 16.7, 10.6, 7.3, 7.1 Hz, 1H, 2-H), 5.94 (ddd, *J* = 14.1, 1.3, 1.3 Hz, 1H, 10-H), 6.42 (ddd, *J* = 14.4, 7.6, 7.3 Hz, 1H, 9-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 11.6 (7-CH_3), 20.5 (5-CH_3), 31.7 (C-7), 39.9 (C-3), 43.5 (C-8), 75.4 (C-10), 76.6 (C-4), 117.7 (C-1), 131.5 (C-6), 134.6 (C-2), 144.9 (C-9); **HRMS** (ESI): $[M+Na]^+$ calcd for $C_{12}H_{19}IONa$ 329.03728, found 329.037211.

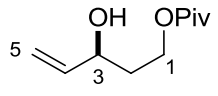
(1*E*,4*S*,5*E*,7*S*)-1-Iodo-7-methoxy-4,6-dimethyldeca-1,5,9-triene (3-16)



Proton sponge (662 mg, 1.1 mmol) and Me_3OBF_4 (228 mg, 1.5 mmol) were added to a solution of alcohol **3-39** (315 mg, 1.0 mmol) in CH_2Cl_2 (10 mL). The reaction mixture was stirred in the dark at room temperature for 3 h, diluted with CH_2Cl_2 (10 mL) and washed subsequently with 1M HCl (5 mL), saturated $NaHCO_3$ (5 mL) and saturated NaCl (5 mL) solution. The organic layer was dried over anhydrous Na_2SO_4, filtered, concentrated in vacuo and the residue purified by flash chromatography (Et_2O/petroleum ether, 1:50) to furnish methyl ether **3-16** (301 mg, 91%) as colorless oil. $\mathbf{R}_f$ = 0.25 (Et_2O/petroleum ether, 1:50); $\mathbf{[\alpha]_D^{21}}$ = −4.23 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 0.97 (d, *J* = 6.8 Hz, 3H, 4-CH_3), 1.52 (d, *J* = 1.3 Hz, 3H, 6-CH_3), 1.94 (dddd, *J* = 14.1, 8.6, 7.3, 1.5 Hz, 1H, 3-H), 2.05 (dddd, *J* = 13.6, 7.3, 5.8, 1.3 Hz, 1H, 3-H), 2.21 (dddd, *J* =14.4, 8.6, 7.3, 1.3 Hz, 1H, 8-H), 2.36 (dddd, *J* = 13.9, 8.1, 6.8, 1.3 Hz, 1H, 8-H), 2.45–2.58 (m, 1H, 5-H), 3.16 (s, 3H, OCH_3), 3.45 (dd, *J* = 7.1, 7.1 Hz, 1H, 7-H), 5.01–5.12 (m, 3H, 5-H, 10-H), 5.69 (dddd, *J* = 17.2, 10.1, 7.1, 6.8 Hz, 1H, 9-H), 5.95 (ddd, *J* = 14.1, 1.5, 1.3 Hz, 1H, 1-H), 6.42 (ddd, *J* = 14.1, 7.6, 7.3 Hz, 1H, 2-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 10.7 (6-CH_3), 20.8 (4-CH_3), 31.8 (C-4), 38.2 (C-8), 43.5 (C-3), 55.6 (OCH_3), 75.4 (C-1), 86.9 (C-7),

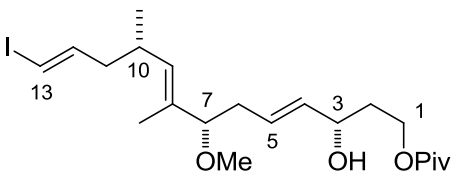
116.5 (C-10), 133.2 (C-6), 134.0 (C-5), 135.0 (C-9), 145.0 (C-2); **HRMS** (ESI): $[M+Na]^+$ calcd for $C_{13}H_{21}IONa$ 343.05293, found 343.052985.

(3*S*)-3-Hydroxypent-4-enyl pivalate (3-46)



A solution of silyl ether **3-25** (0.94 g, 3.1 mmol) and *p*-TSA•H_2O (60 mg, 0.31 mmol) in methanol (10 mL) was stirred at room temperature for 1 h. After TLC showed essentially complete conversion, the mixture was treated with water (5 mL) and extracted with Et_2O (3 × 5 mL). The combined organic layers were washed with saturated NaCl solution (10 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (small filtration column, Et_2O/petroleum ether, 3:7), to give allyl alcohol **3-46** (545 mg, 94%) as colorless oil. $\mathbf{R_f}$ = 0.27 (Et_2O/petroleum ether, 3:7); $\mathbf{[\alpha]_D^{21}}$ = 4.1 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.19 (s, 9H, $C(CH_3)_3$), 1.79 (ddd, *J* = 14.4, 7.6, 5.8 Hz, 1H, 3-H), 1.86 (ddd, *J* = 14.9, 6.3, 6.1 Hz, 1H, 3-H), 2.11 (bs, 1H, OH), 4.11 (ddd, *J* = 11.1, 6.1, 5.5 Hz, 1H, 1-H), 4.15–4.21 (m, 1H, 3-H), 4.26 (ddd, *J* = 11.1, 7.6, 5.6 Hz, 1H, 1-H), 5.11 (ddd, *J* = 10.6, 1.5, 1.3 Hz, 1H, 5-H), 5.23 (ddd, *J* = 17.2, 1.5, 1.3 Hz, 1H, 5-H), 5.86 (ddd, *J* = 17.2, 10.6, 6.1 Hz, 5-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 27.1 ($C(CH_3)_3$), 36.0 (C-2), 38.7 ($C(CH_3)_3$), 61.2 (C-3), 69.9 (C-1), 115.0 (C-5), 140.2 (C-4), 178.8 (C=O); **HRMS** (ESI): $[M+Na]^+$ calcd for $C_{10}H_{18}O_3Na$ 209.11482, found 209.11472.

(3*S*,4*E*,7*S*,8*E*,10*S*,12*E*)-3-Hydroxy-13-iodo-7-methoxy-8,10-dimethyltrideca-4,8,12-trienyl pivalate (3-47)



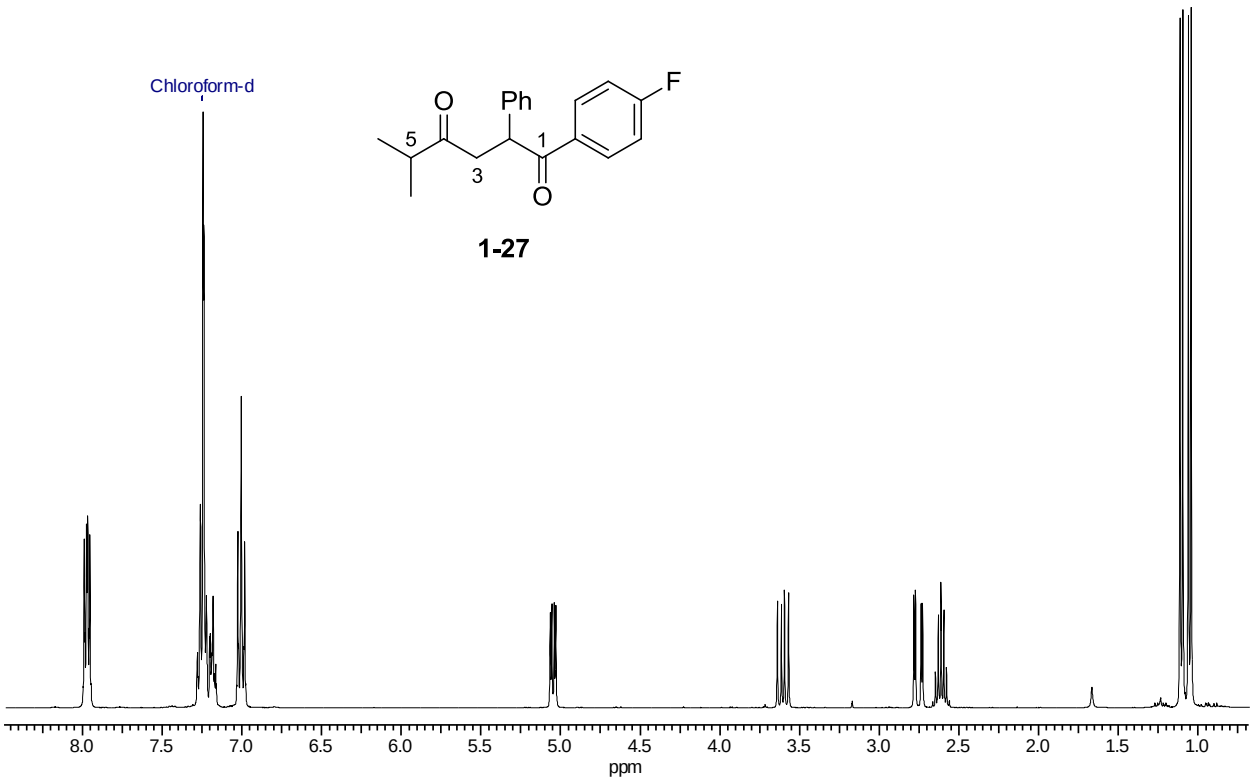
To a solution of triene **3-16** (50 mg, 0.16 mmol) and allyl alcohol **3-46** (58 mg, 0.31 mmol) in dry degassed toluene (2.5 mL) was added Grubb's 2nd catalyst (13 mg, 10 mol%) in toluene (0.5

mL) dropwise at 80 °C. The reaction mixture was stirred at the same temperature for 24 h while the progress of the reaction was checked by TLC. After cooling, the mixture was concentrated in vacuo and the residue purified by flash chromatography (EtOAc/petroleum ether, 1:4) to provide the metathesis product **3-47** (33 mg, 44%) as colorless oil. $\mathbf{R_f}$ = 0.25 (ethyl acetate/petroleum ether, 1:4); $\mathbf{[\alpha]_D^{22}}$ = 11.72 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 0.96 (d, *J* = 6.8 Hz, 3H, 10-CH_3), 1.18 (s, 9H, $C(CH_3)_3$), 1.51 (d, *J* = 1.3 Hz, 3H, 8-CH_3), 1.78–1.85 (m, 2H, 2-H), 1.94 (dddd, *J* = 14.1, 8.8, 8.1, 1.5 Hz, 1H, 11-H), 2.03 (dddd, *J* = 13.9, 7.6, 6.1, 1.3 Hz, 1H, 11-H), 2.17 (ddd, *J* = 13.9, 6.8, 6.6 Hz, 1H, 6-H), 2.32 (ddd, 14.7, 13.9, 7.3 Hz, 1H, 6-H), 2.44–2.56 (m, 1H, 10-H), 3.14 (s, 3H, OCH_3), 3.42 (t, *J* = 6.82 Hz, 1H, 7-H), 4.09 (ddd, *J* = 11.1, 6.1, 6.1 Hz, 1H, 1-H), 4.19 (ddd, *J* = 13.4, 6.3, 6.3 Hz, 1H, 3-H), 4.23 (ddd, *J* = 11.1, 6.6, 6.6 Hz, 1H, 1-H), 5.10 (d, *J* = 9.6 Hz, 1H, 9-H), 5.48–5.64 (m, 2H, 4-H, 5-H), 5.95 (ddd, *J* = 14.4, 1.3, 1.0 Hz, 1H, 13-H), 6.41 (ddd, *J* = 14.4, 7.6, 7.1 Hz, 1H, 12-H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 10.9 (8-CH_3), 20.7 (10-CH_3), 27.2 ($C(CH_3)_3$), 31.8 (C-10), 36.2 (C-2), 36.8 (C-6), 38.7 ($C(CH_3)_3$), 43.4 (C-11), 55.7 (OCH_3), 61.3 (C-1), 69.7 (C-3), 75.5 (C-13), 86.8 (C-7), 128.3 (C-5), 133.3 (C-8), 133.9 (C-9), 134.0 (C-4), 144.9 (C-12), 178.7 (C=O); **HRMS** (ESI): $[M+Na]^+$ calcd for $C_{21}H_{35}IO_4Na$ 501.14722, found 501.147474.

15 Appendix

15.1 NMR-Spectra for important compounds

Additional spectra are included in the supporting information of the published papers from this work and are available free of charge via Internet at DOI: 10.1055/s-0031-1289898 (Synlett) and http://dx.doi.org/10.1016/j.tet.2010.10.028 (Tetrahedron).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O
Ph
F
5
1
3
O
8.0
7.5
7.0
6.5
6.0
5.5
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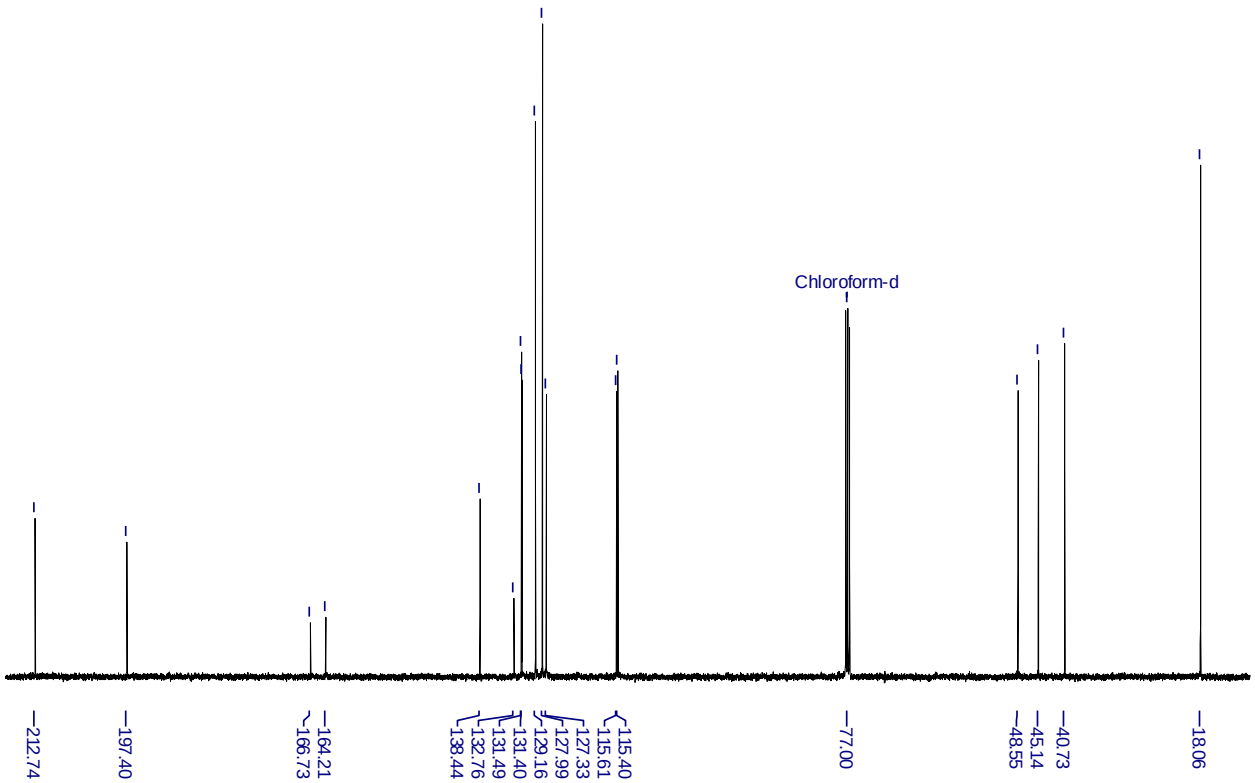
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

1-27


Chloroform-d
212.74
197.40
166.73
164.21
138.44
132.76
131.49
131.40
129.16
127.99
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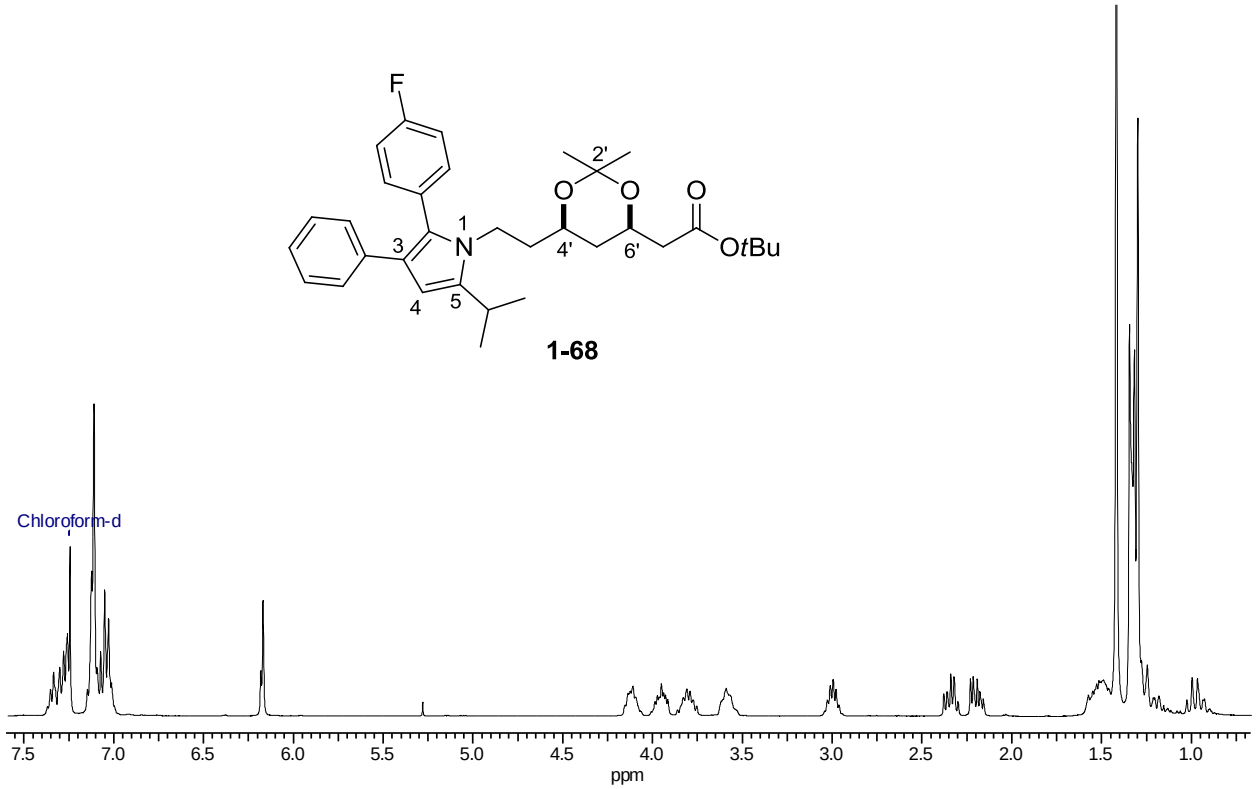
115.40
77.00
48.55
45.14
40.73
18.06


F
2'
O
O
O
1
N
3
4'
6'
OtBu
4
5
Chloroform-d
7.5
7.0
6.5
6.0
5.5
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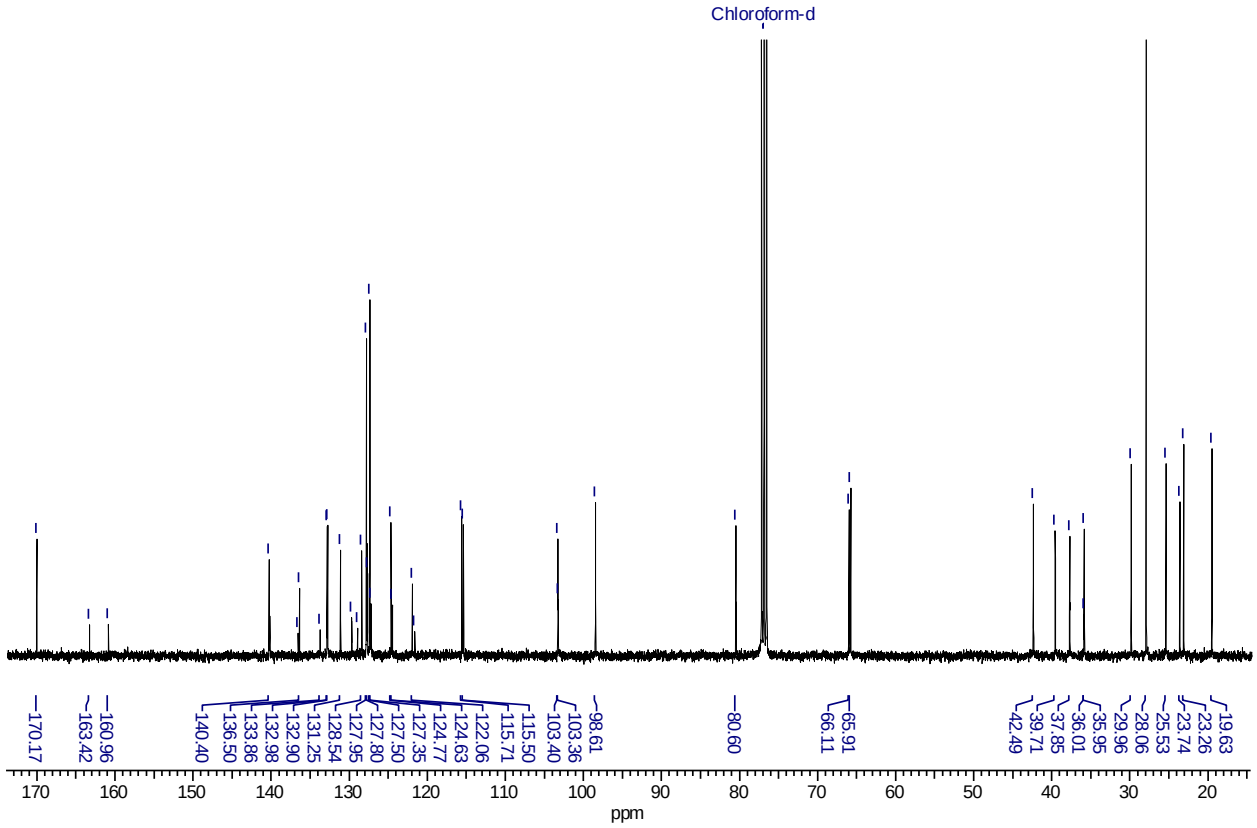
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

1-68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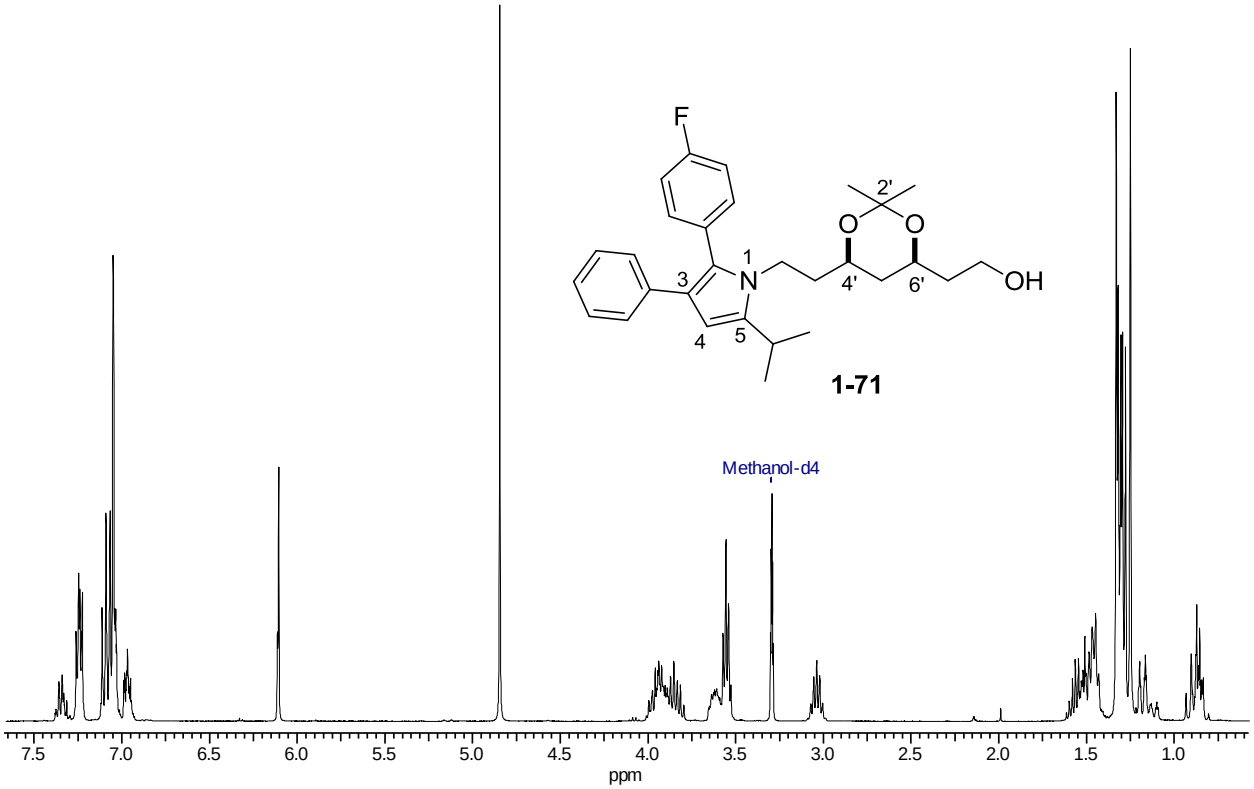
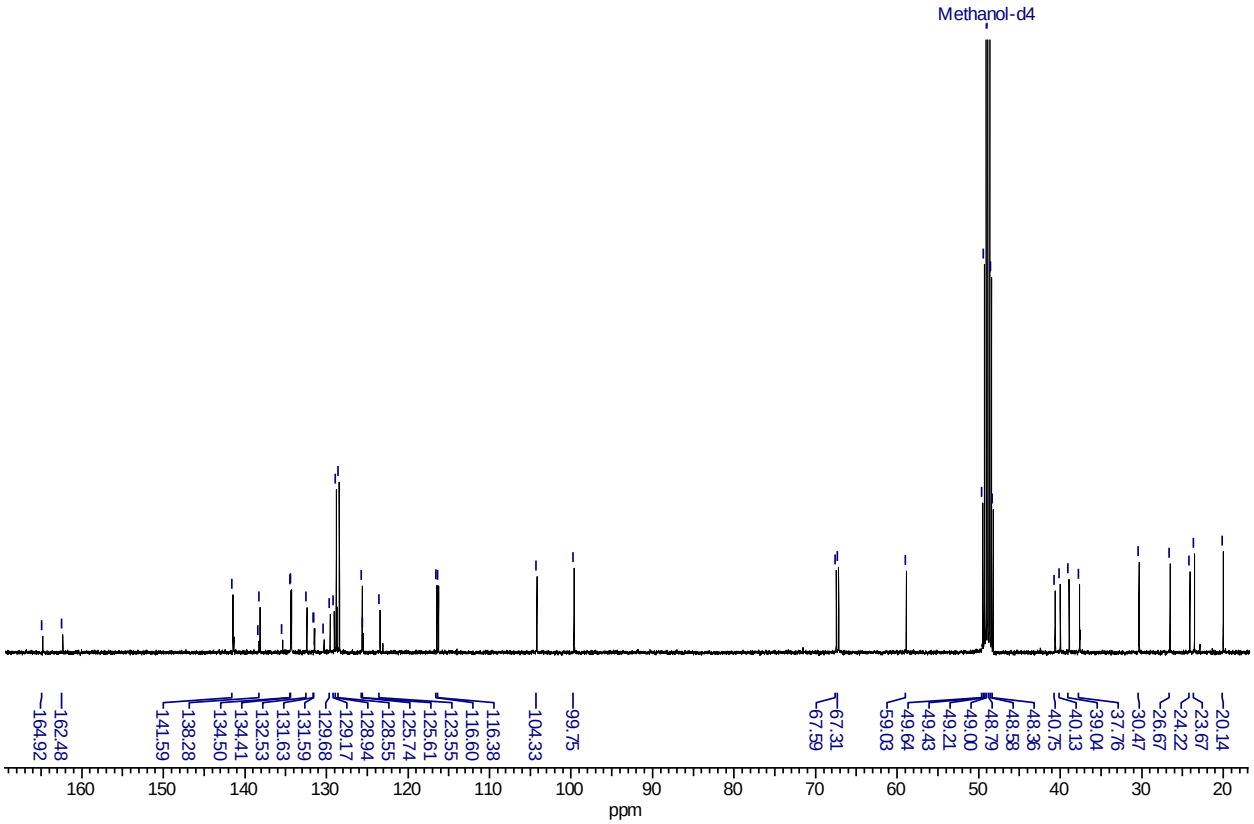
163.42
160.96
140.40
136.50
133.86
132.98
132.90
131.25
128.54
127.95
127.80
127.50
127.35
124.77
124.63
122.06
115.71
115.50
103.40
103.36
98.61
80.60
66.11
65.91
42.49
39.71
37.85
36.01
35.95
29.96
28.06
25.53
23.74
23.26
19.63
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm


F
2'
O
O
1
N
3
4'
6'
OH
4
5
1-71
Methanol-d4
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm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141.59
138.28
134.50
134.41
132.53
131.63
131.59
129.68
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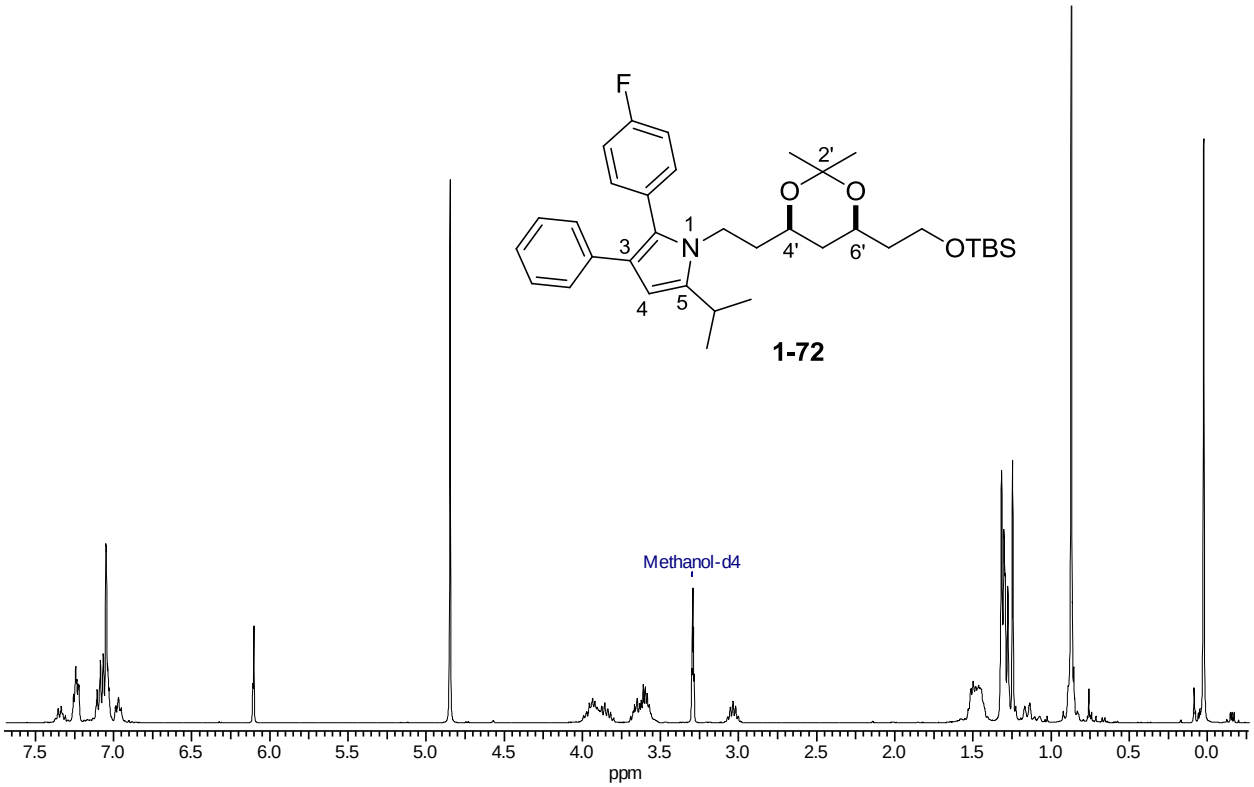
128.55
125.74
125.61
123.55
116.60
116.38
104.33
99.75
67.59
67.31
59.03
49.64
49.43
49.21
49.00
48.79
48.58
48.36
40.75
40.13
39.04
37.76
30.47
26.67
24.22
23.67
20.14
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm


F
2'
O
O
1
N
3
4'
6'
OTBS
4
5
1-72
Methanol-d4
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6.5
6.0
5.5
5.0
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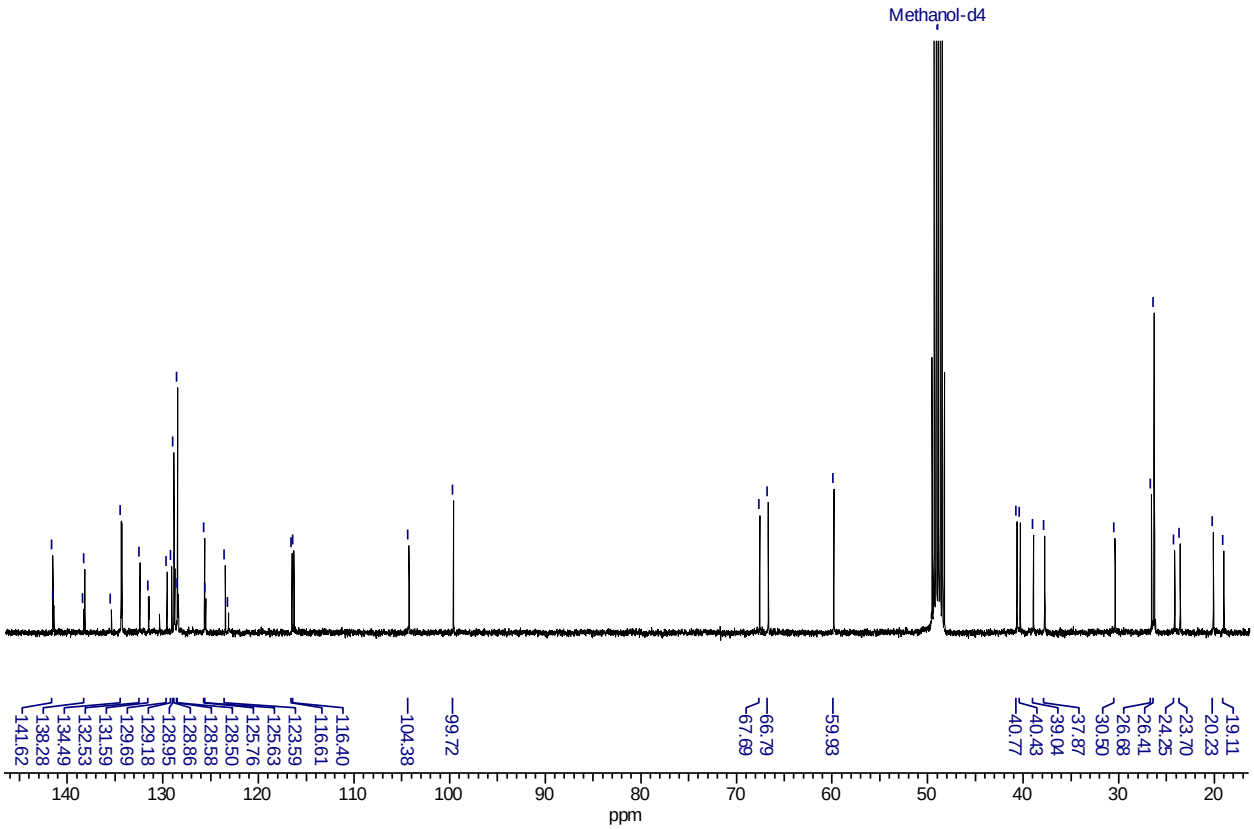
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm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129.69
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128.86
128.58
128.50
125.76
125.63
123.59
116.61
116.40
104.38
99.72
67.69
66.79
59.93
40.77
40.43
39.04
37.87
30.50
26.68
26.41
24.25
23.70
20.23
19.11
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130
120
110
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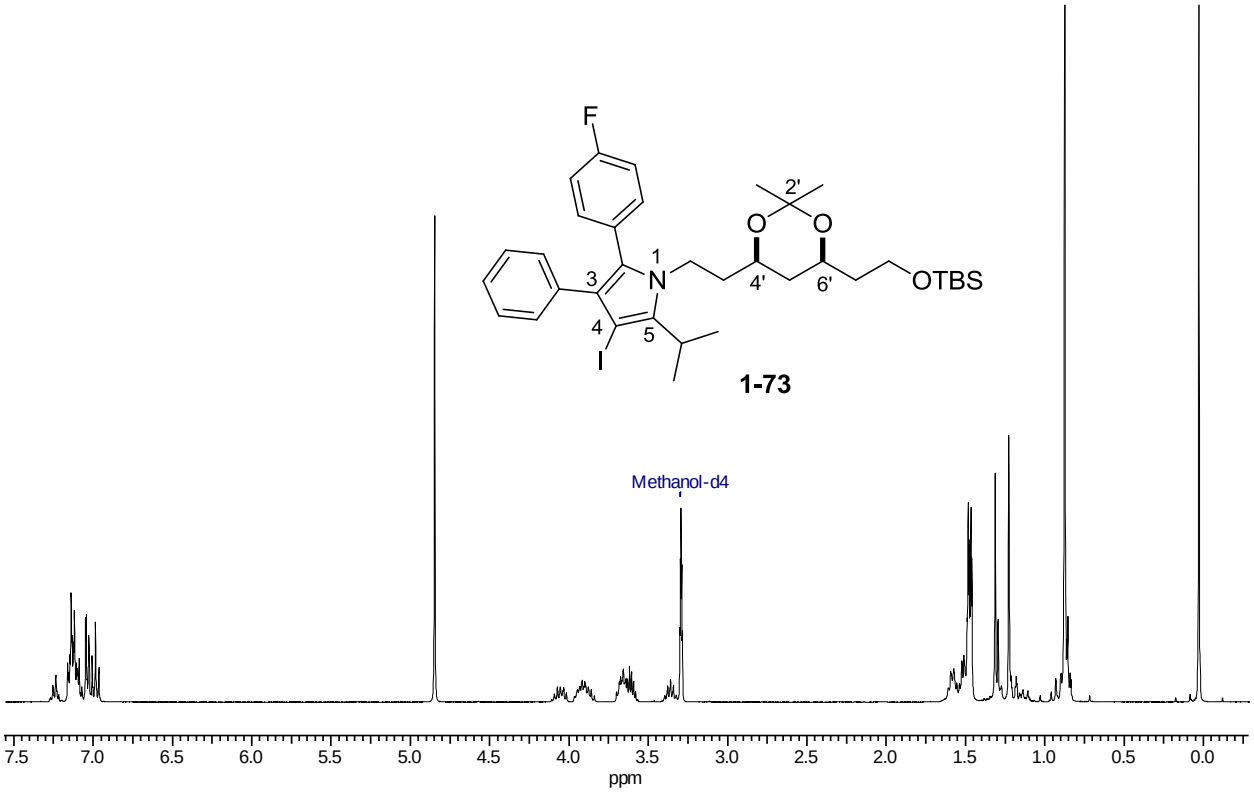
80
70
60
50
40
30
20
ppm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O
O
1
N
3
4'
6'
OTBS
4
5
I
1-73
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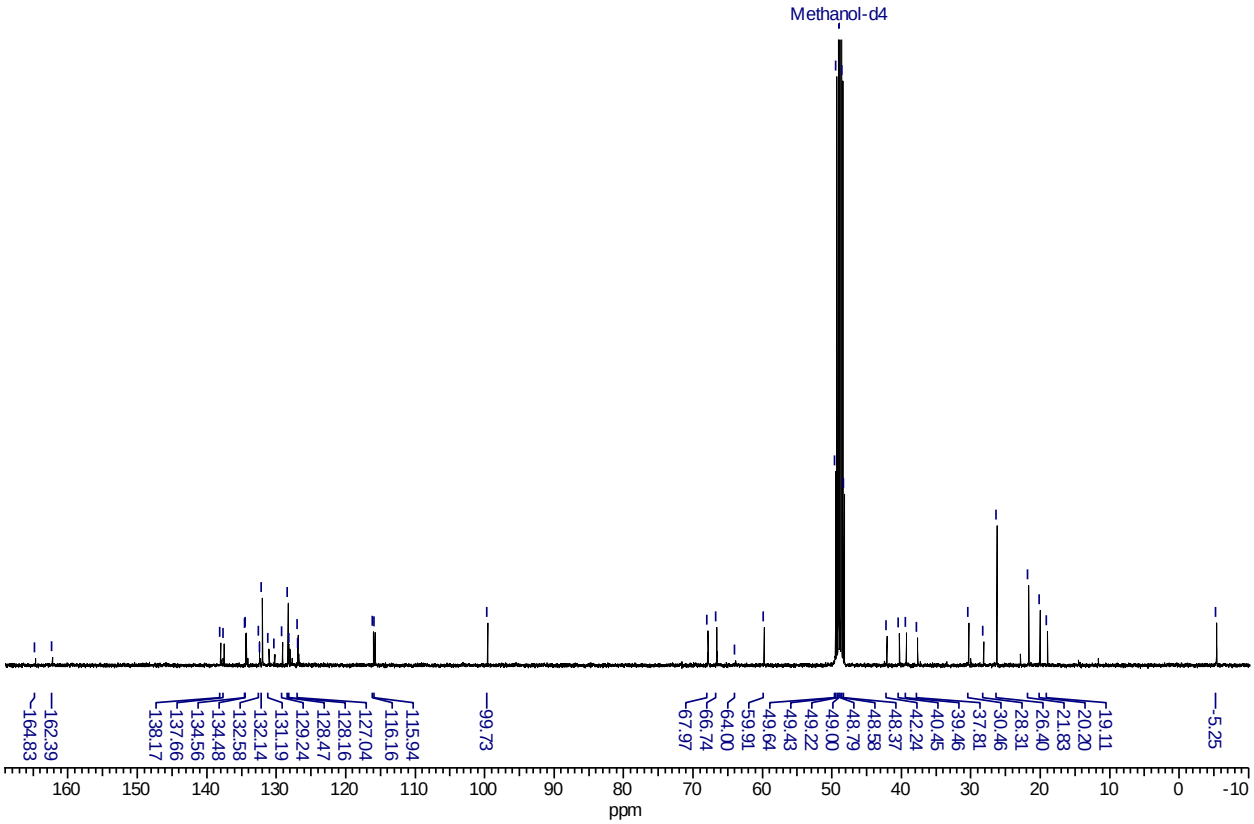
ppm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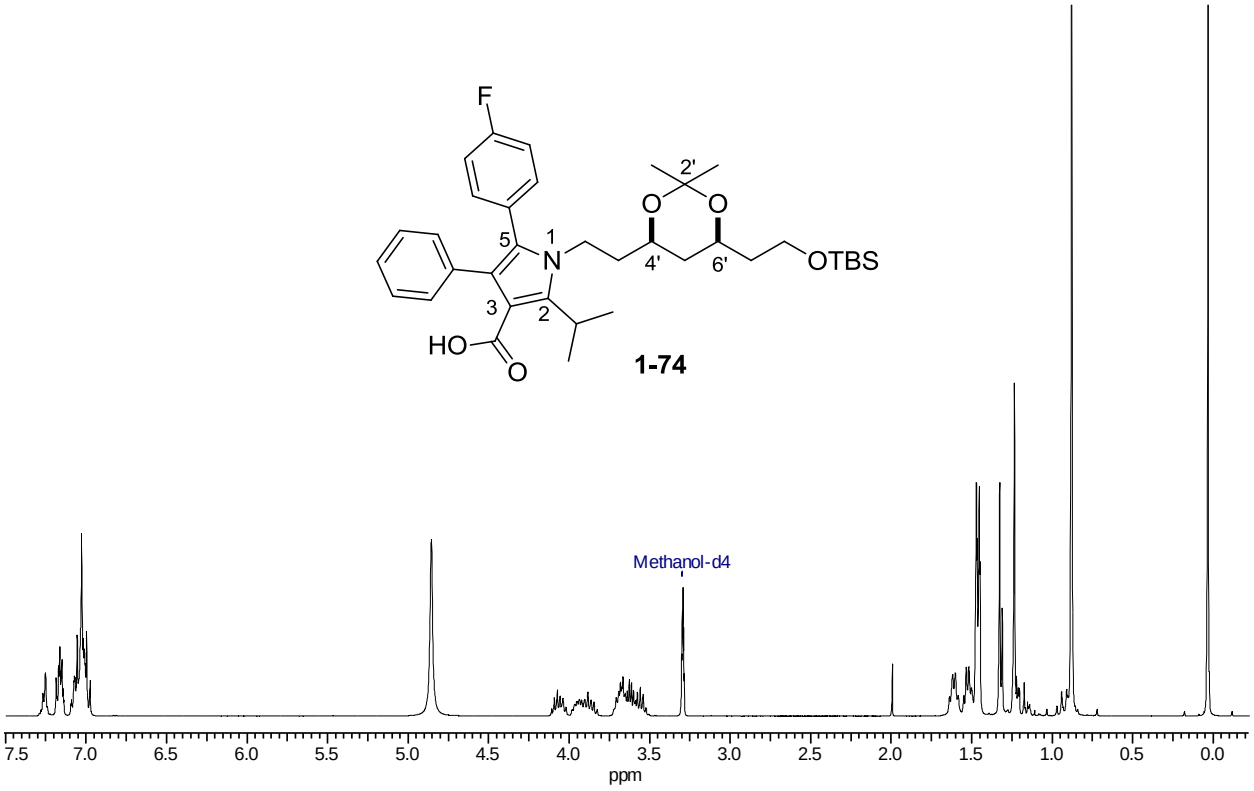
138.17
137.66
134.56
134.48
132.58
132.14
131.19
129.24
128.47
128.16
127.04
116.16
115.94
99.73
67.97
66.74
64.00
59.91
49.64
49.43
49.22
49.00
48.79
48.58
48.37
42.24
40.45
39.46
37.81
30.46
28.31
26.40
21.83
20.20
19.11
5.25
160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
ppm


F
2'
O
O
5
1
N
4'
6'
OTBS
3
2
HO
O
1-74
Methanol-d4
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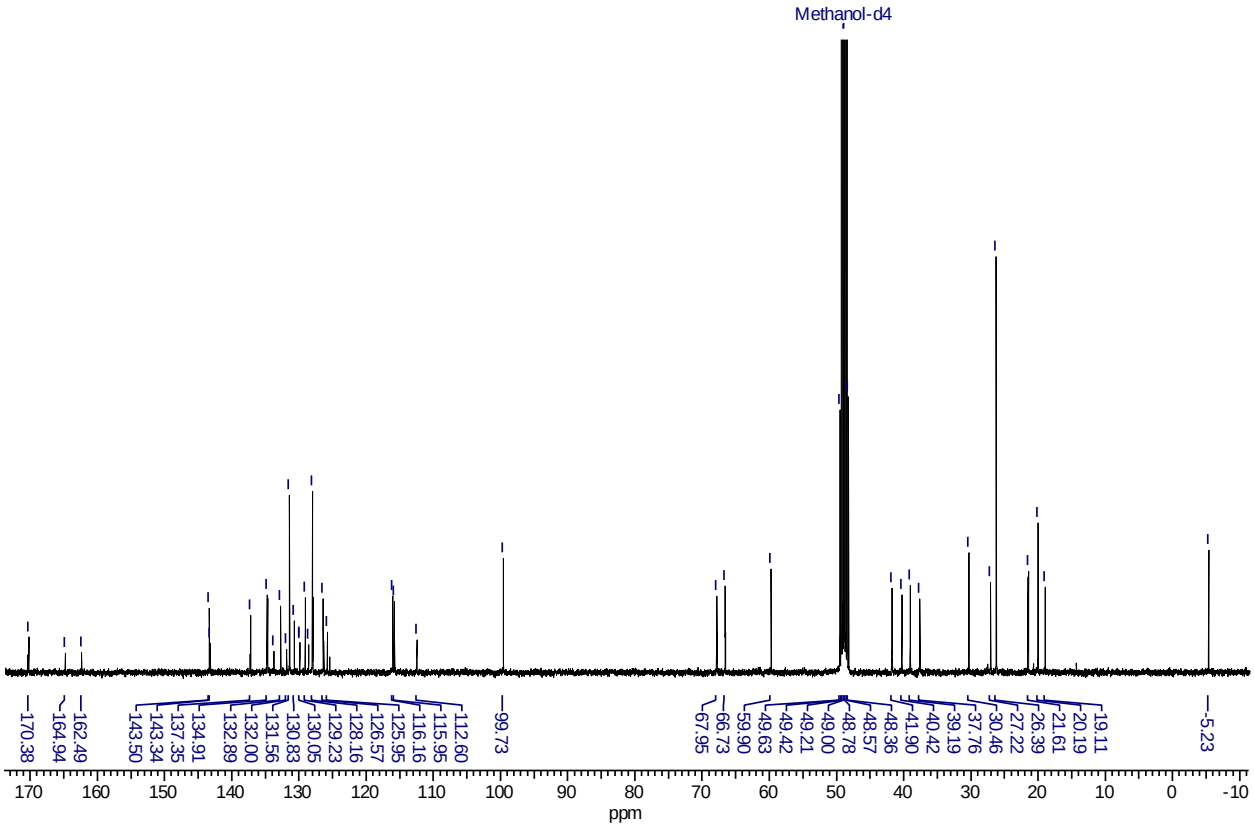
ppm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162.49
143.50
143.34
137.35
134.91
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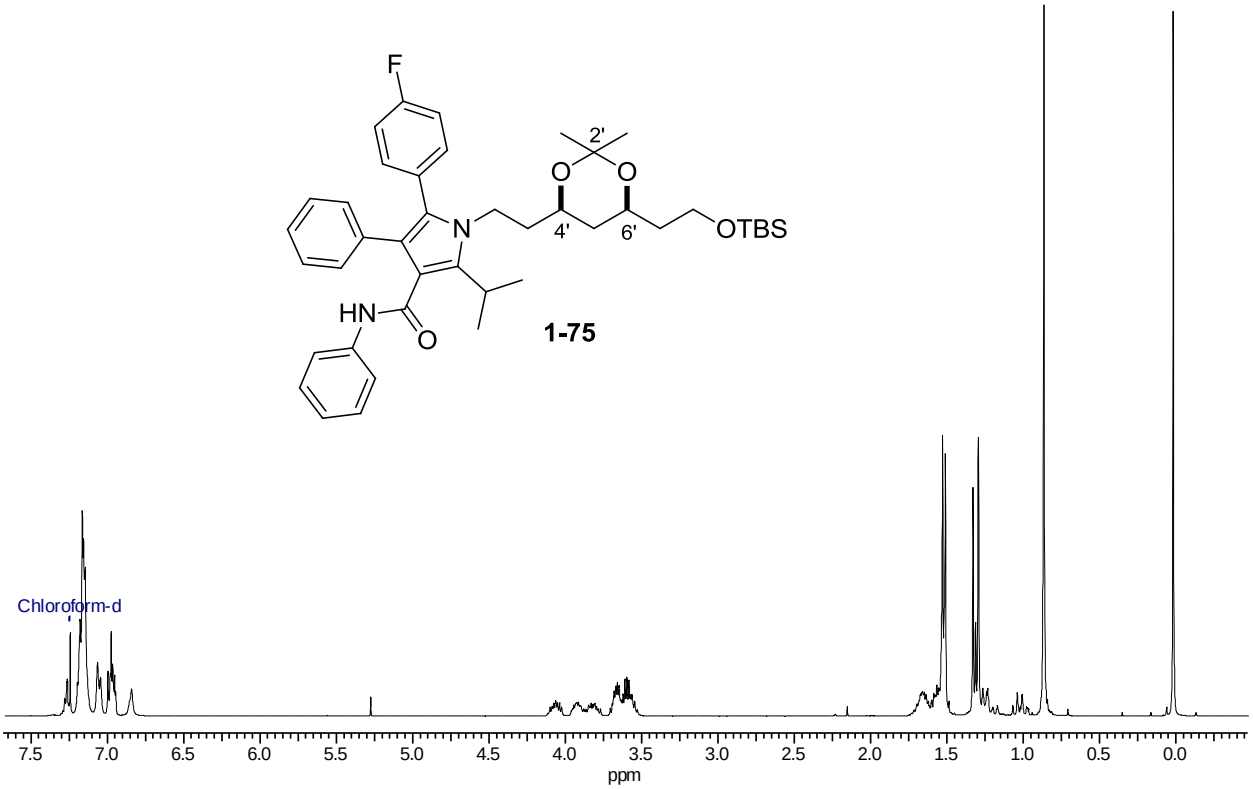
132.00
131.56
130.83
130.05
129.23
128.16
126.57
125.95
116.16
115.95
112.60
99.73
67.95
66.73
59.90
49.63
49.42
49.21
49.00
48.78
48.57
48.36
41.90
40.42
39.19
37.76
30.46
27.22
26.39
21.61
20.19
19.11
-5.23
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
ppm


F
2'
O
O
N
4'
6'
OTBS
HN
O
1-75
Chloroform-d
7.5
7.0
6.5
6.0
5.5
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4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
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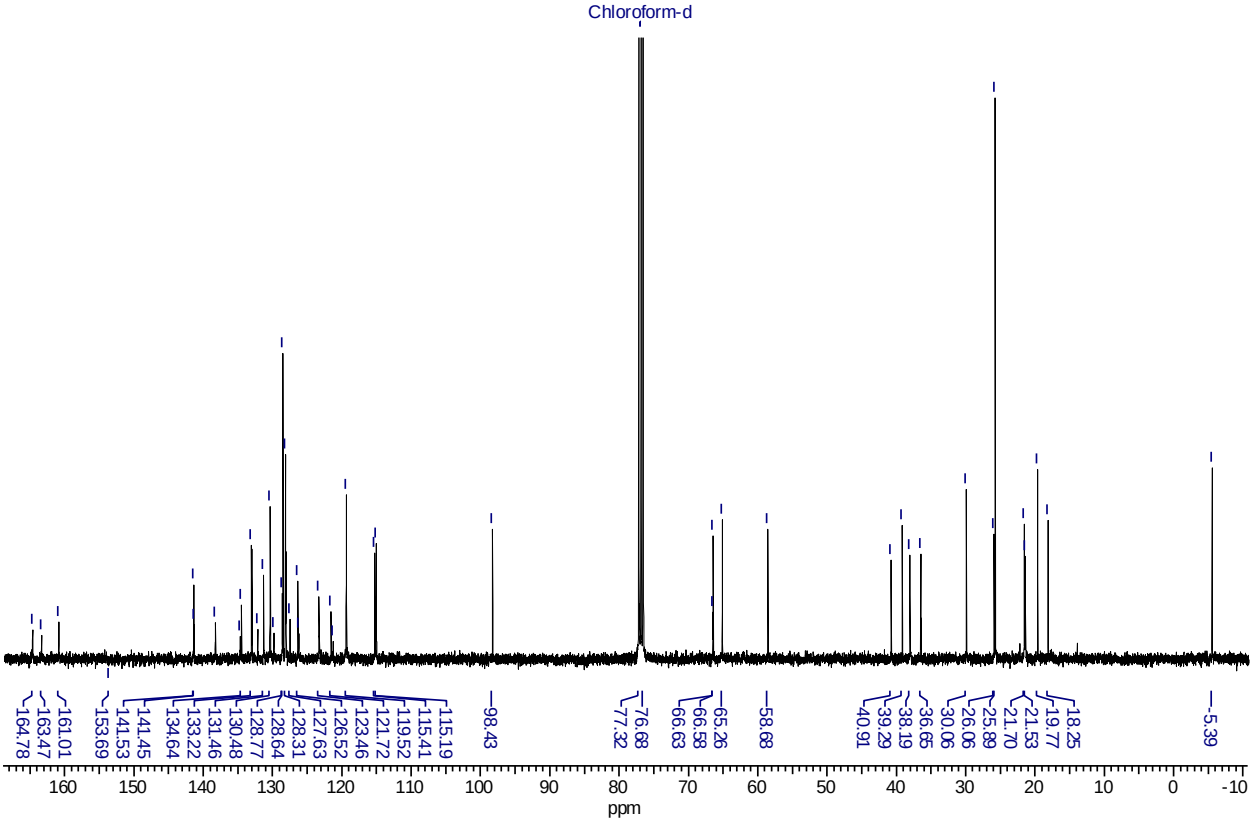
0.0
ppm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131.46
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128.64
128.31
127.63
126.52
123.46
121.72
119.52
115.41
115.19
98.43
77.32
76.68
66.63
66.58
65.26
58.88
40.91
39.29
38.19
36.65
30.06
26.06
25.89
21.70
21.53
19.77
18.25
-5.39
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130
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90
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20
10
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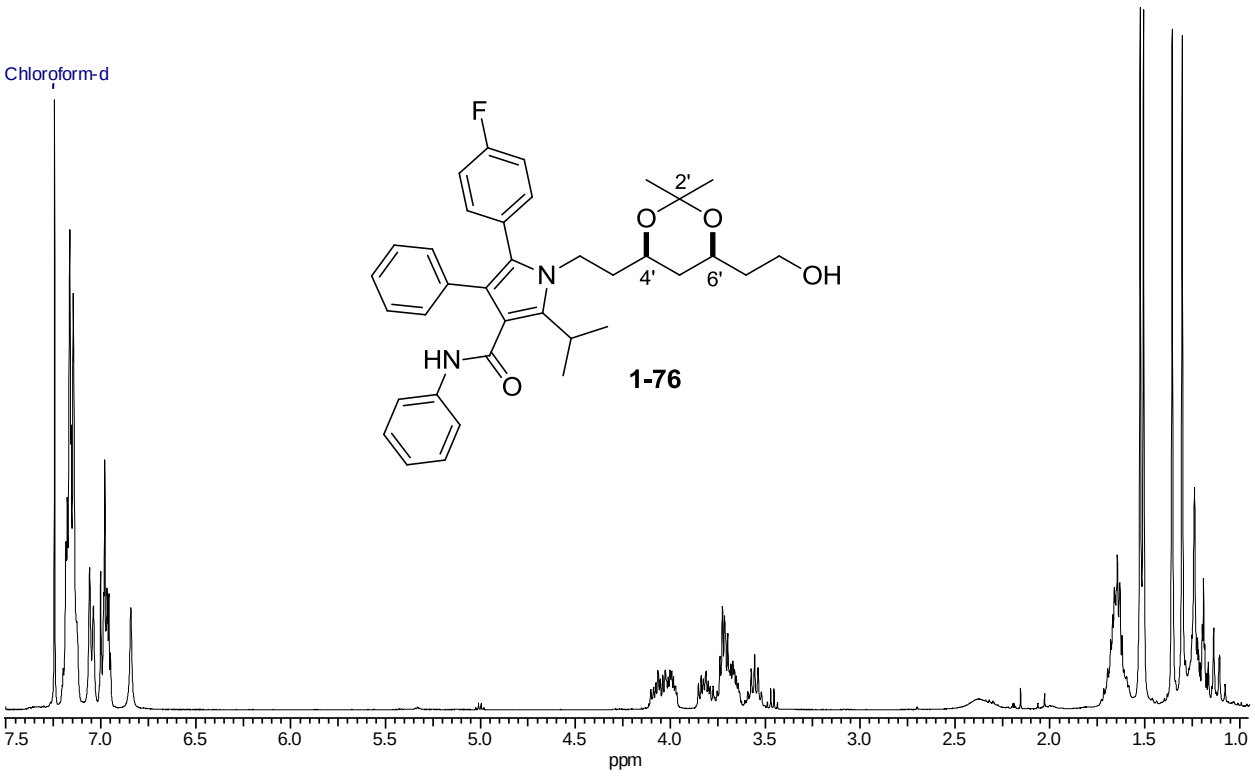
-10
ppm


Chloroform-d
F
2'
O
O
N
4'
6'
OH
HN
O
1-76
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
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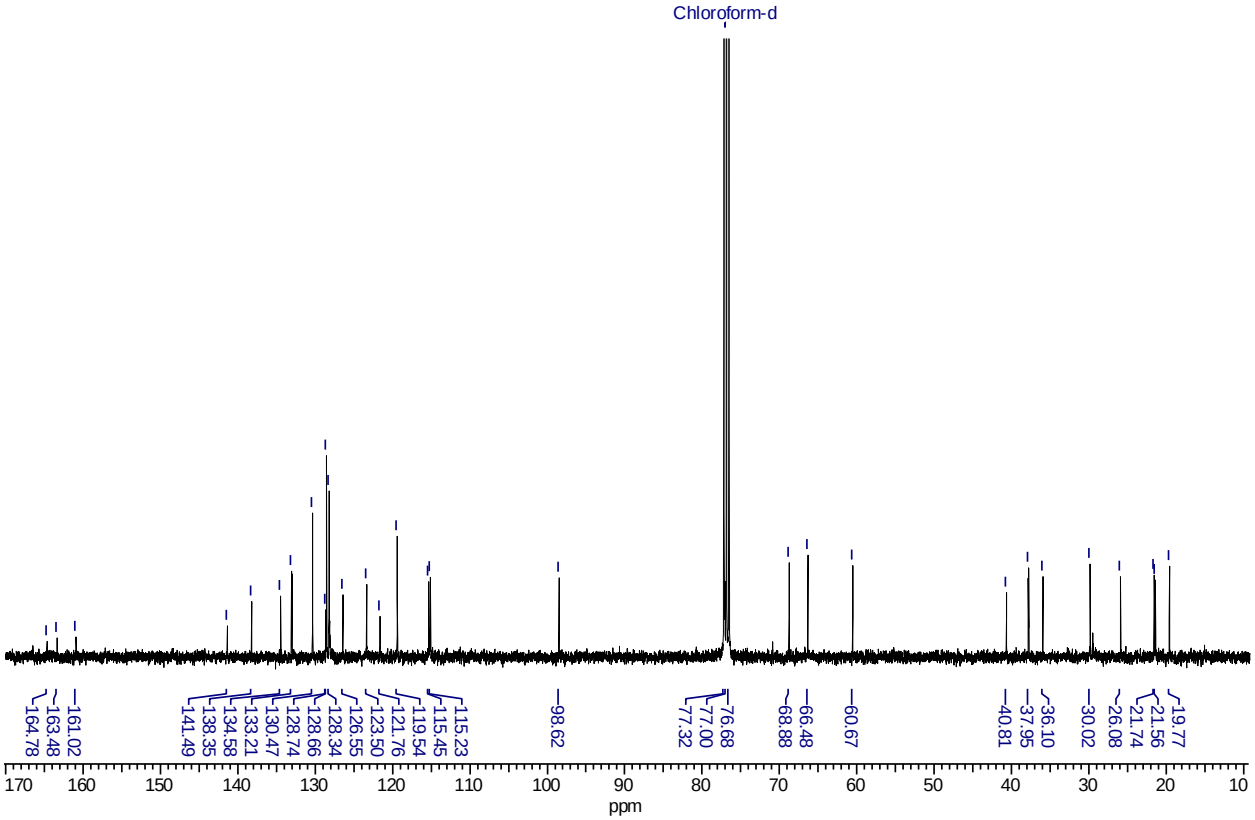
1.5
1.0
ppm


Chloroform-d
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138.35
134.58
133.21
130.47
128.74
128.66
128.34
126.55
123.50
121.76
119.54
115.45
115.23
98.62
77.32
77.00
76.68
68.88
66.48
60.67
40.81
37.95
36.10
30.02
26.08
21.74
21.56
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150
140
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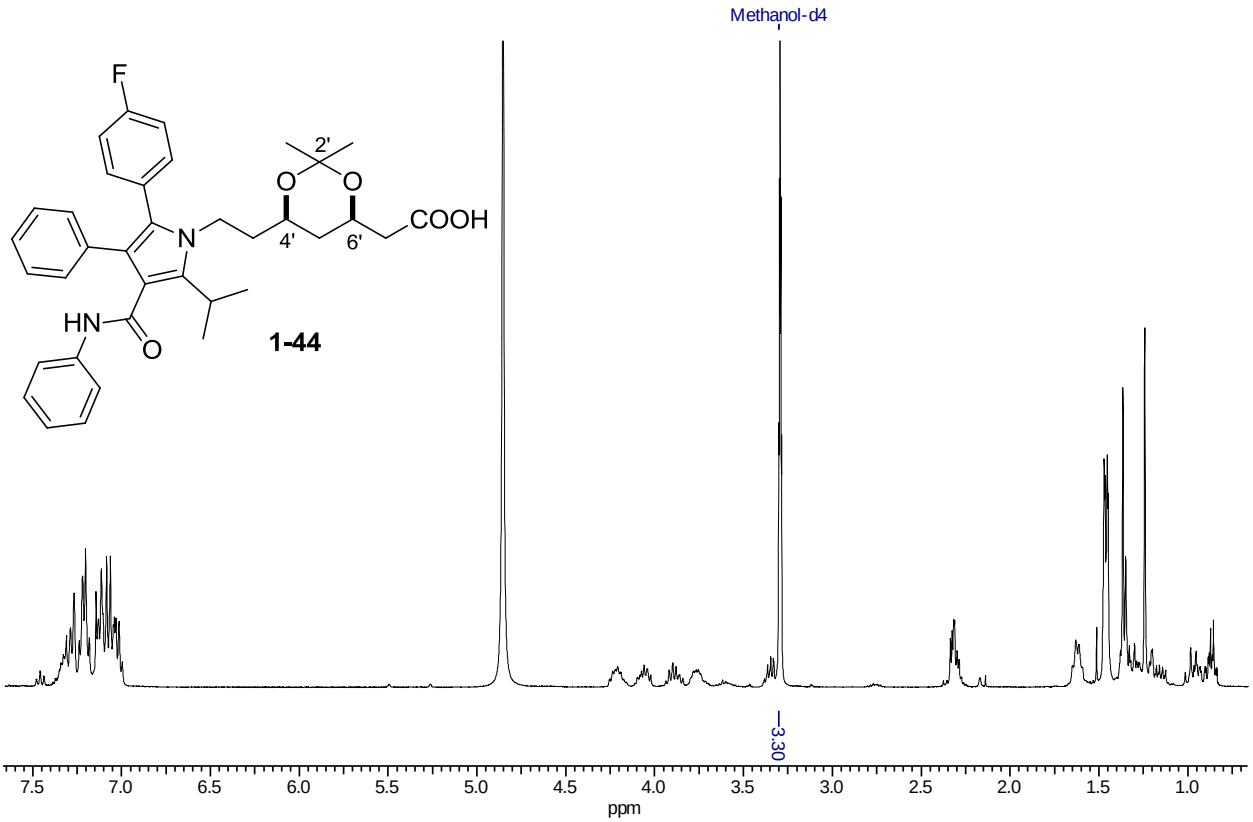
70
60
50
40
30
20
10
ppm


Methanol-d4
F
2'
O
O
COOH
N
4'
6'
HN
O
1-44
3.30
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
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3.0
2.5
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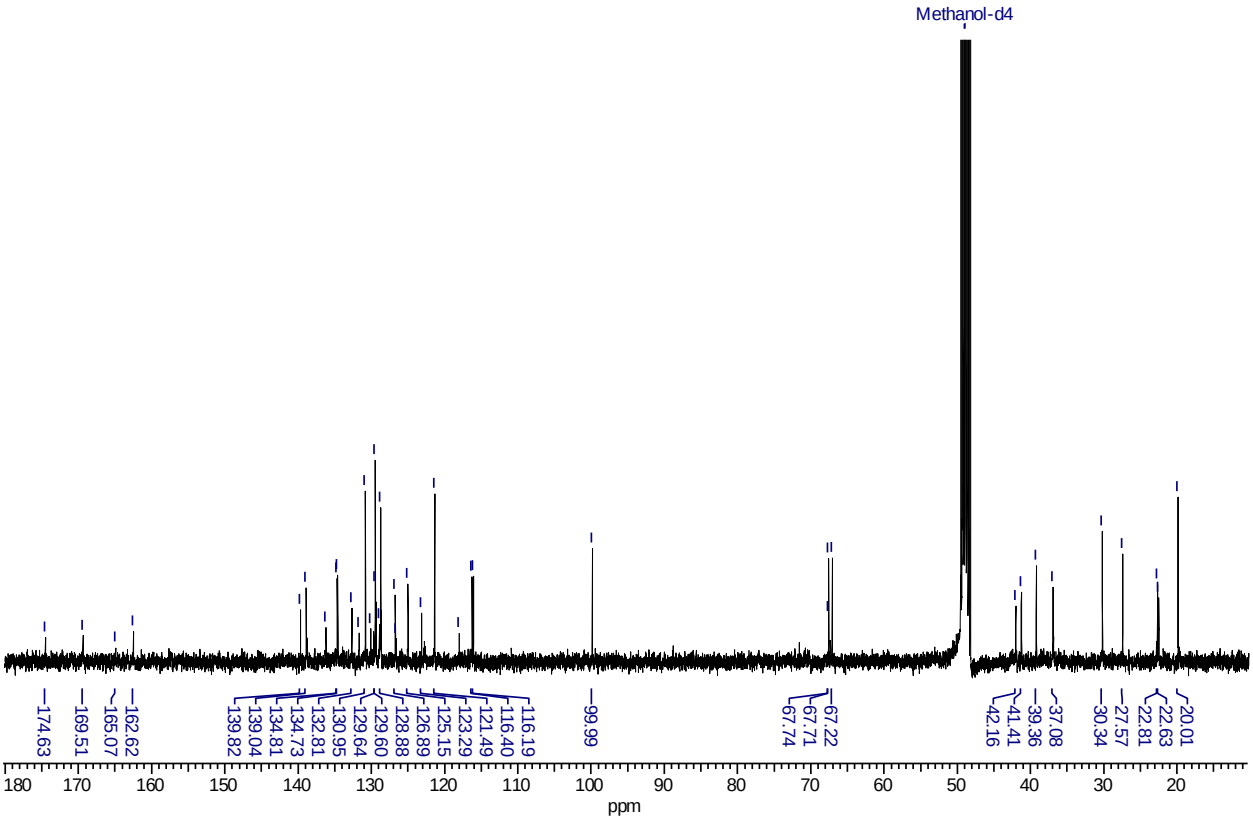
1.5
1.0
ppm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132.81
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129.64
129.60
128.88
126.89
125.15
123.29
121.49
116.40
116.19
99.99
67.74
67.71
67.22
42.16
41.41
39.36
37.08
30.34
27.57
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22.63
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160
150
140
130
120
110
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90
80
70
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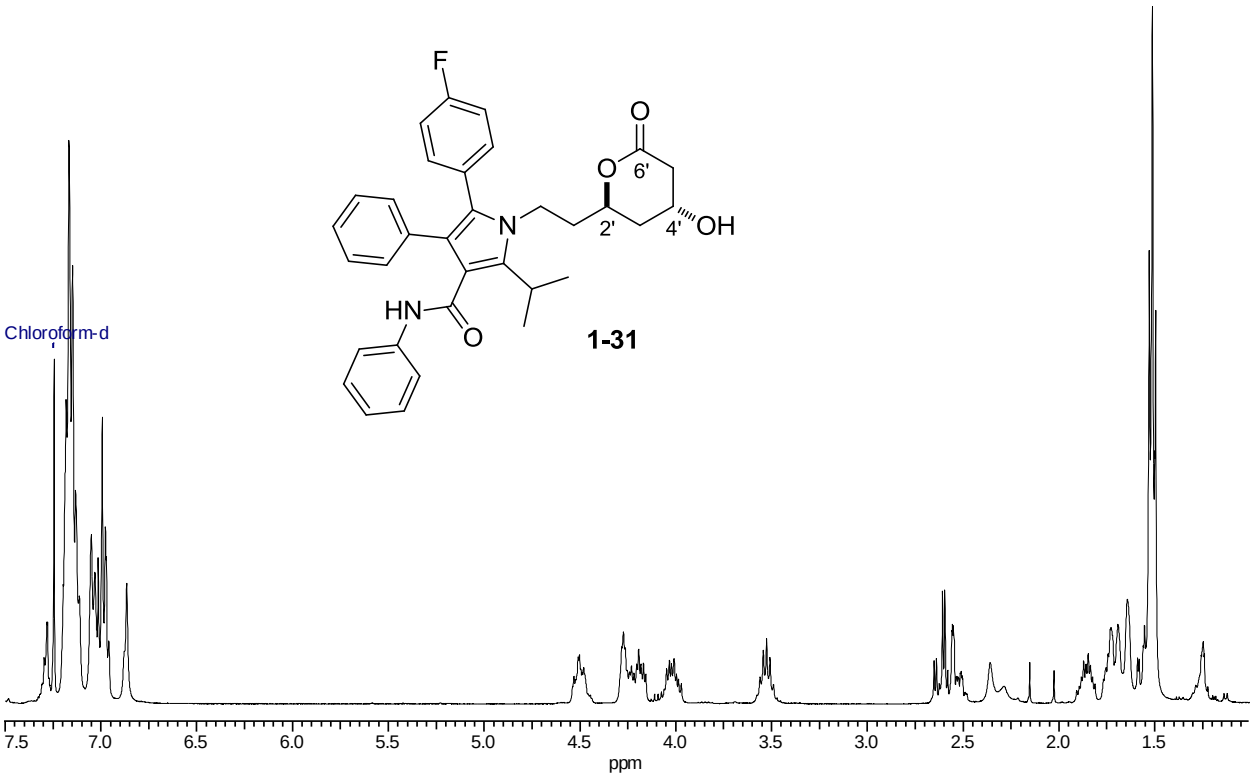
50
40
30
20
ppm


F
O
O
6'
N
2'
4'
OH
HN
O
1-31
Chloroform-d
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5.5
5.0
4.5
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3.5
3.0
2.5
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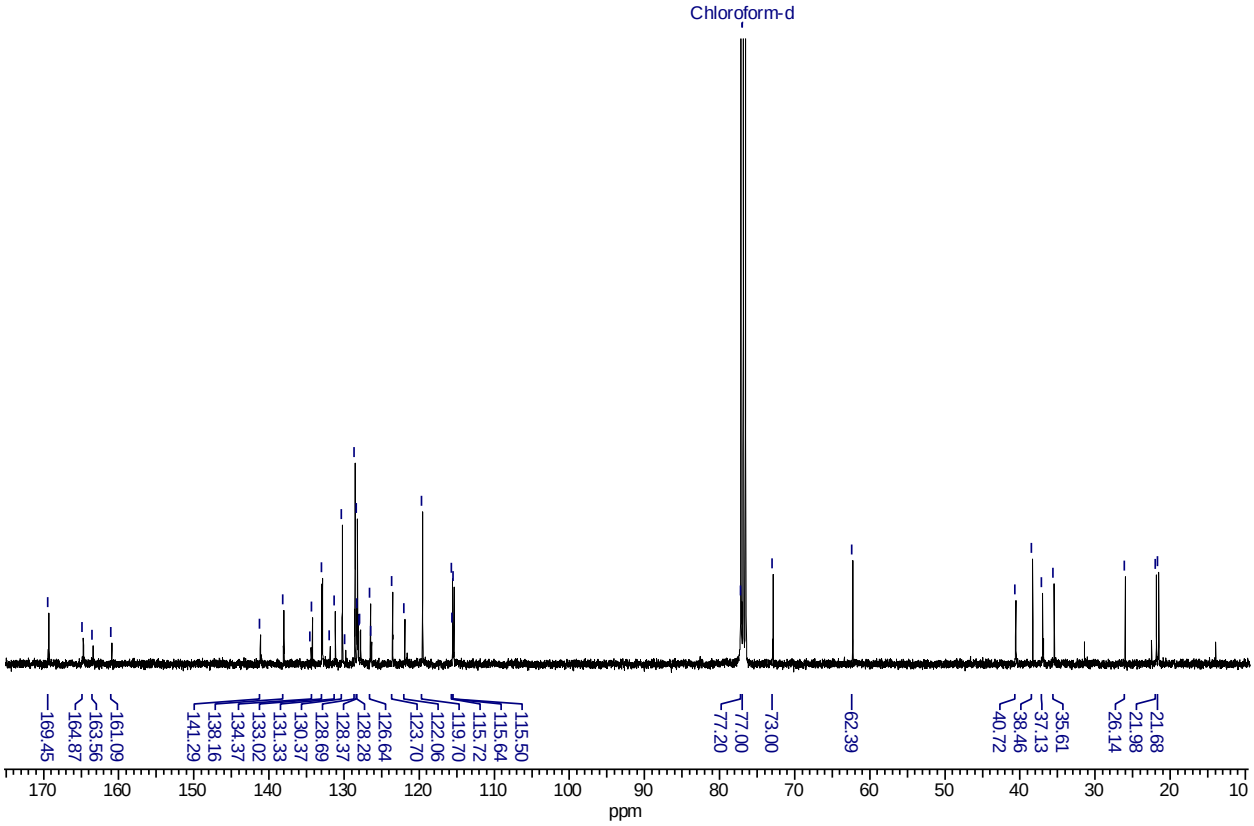
ppm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128.37
128.28
126.64
123.70
122.06
119.70
115.72
115.64
115.50
77.20
77.00
73.00
62.39
40.72
38.46
37.13
35.61
26.14
21.98
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150
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70
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30
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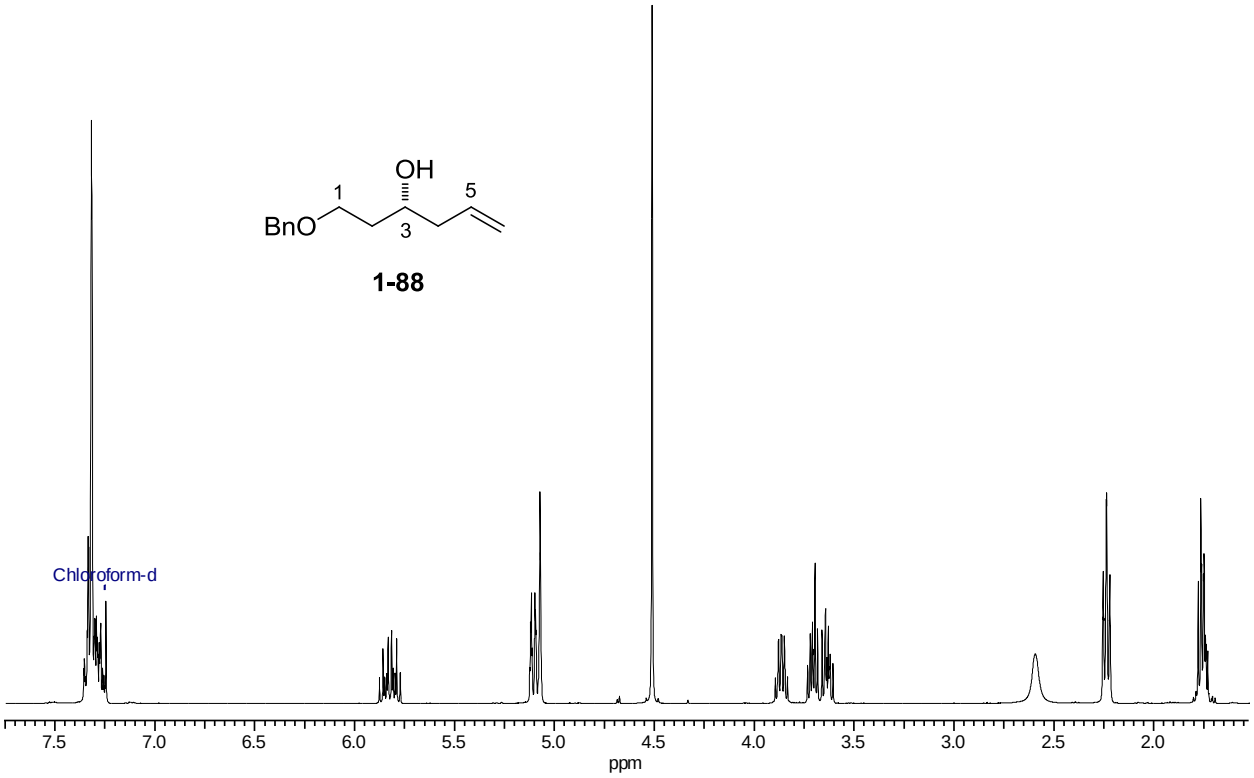
10
ppm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1
5
BnO
3
1-88
Chloroform-d
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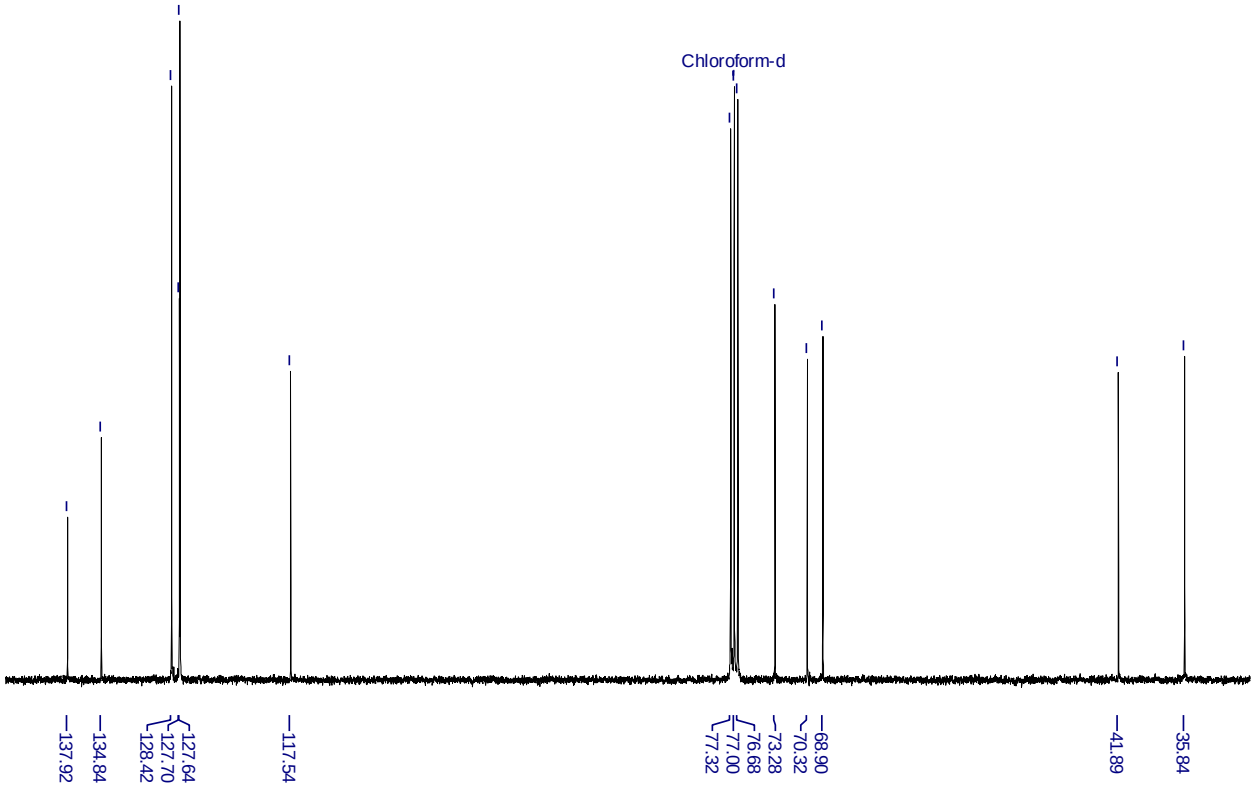
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
ppm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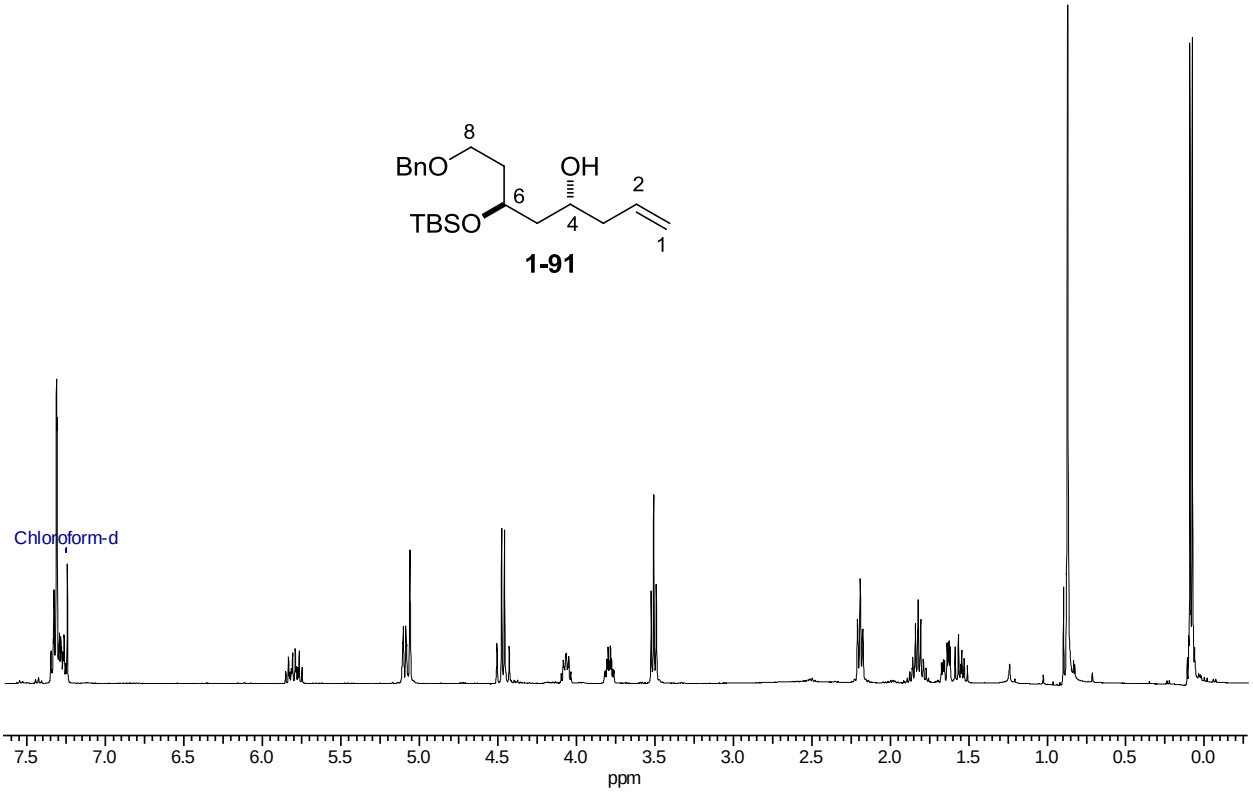
127.64
117.54
77.32
77.00
76.68
73.28
70.32
68.90
41.89
35.84


8
BnO
OH
2
6
TBSO
4
1
1-91
Chloroform-d
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
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2.5
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1.5
1.0
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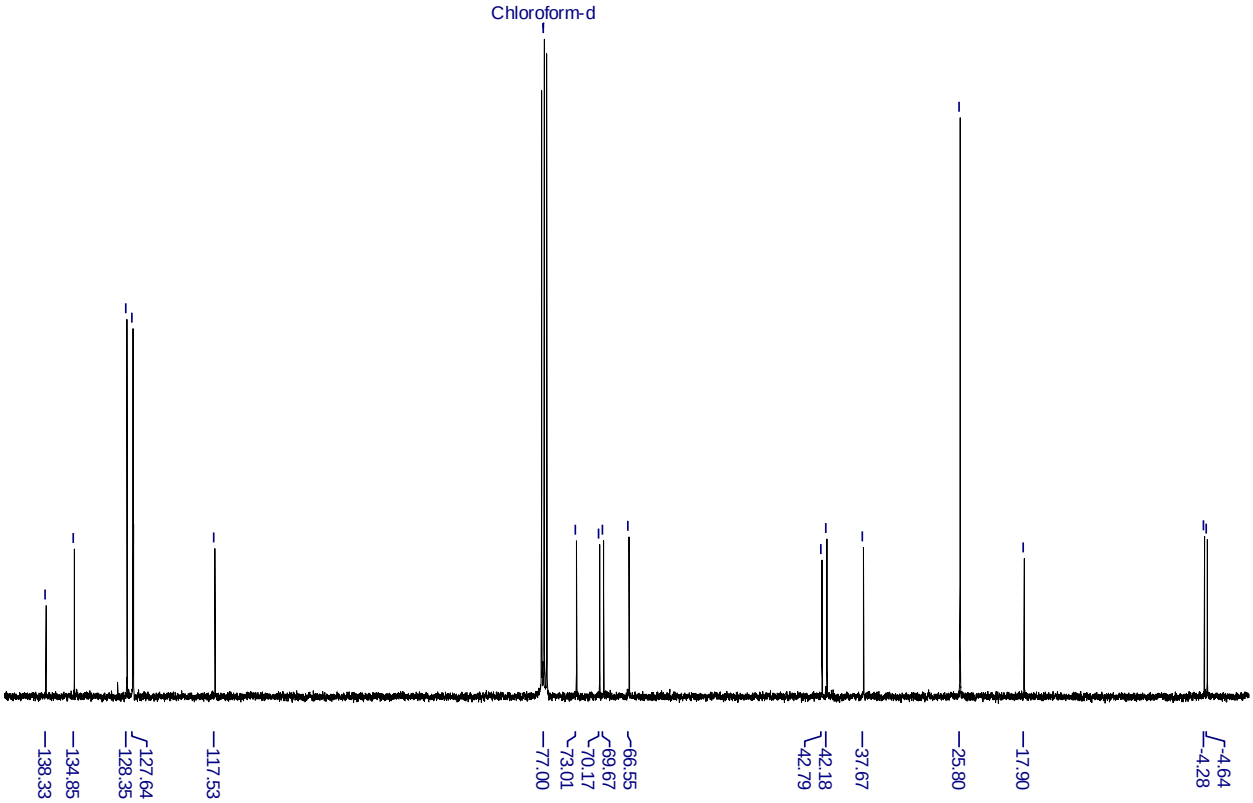
0.0
ppm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117.53
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73.01
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69.67
66.55
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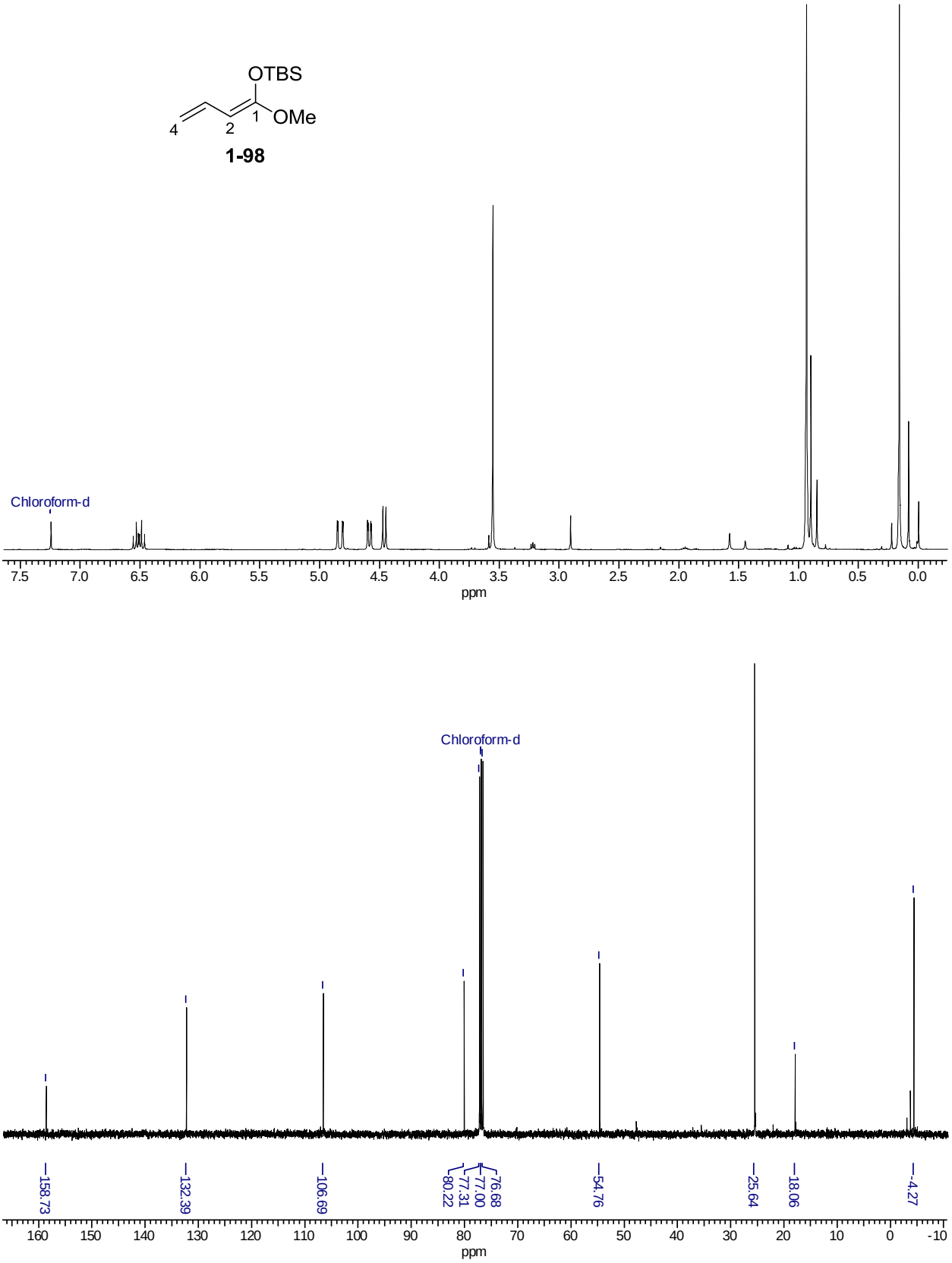
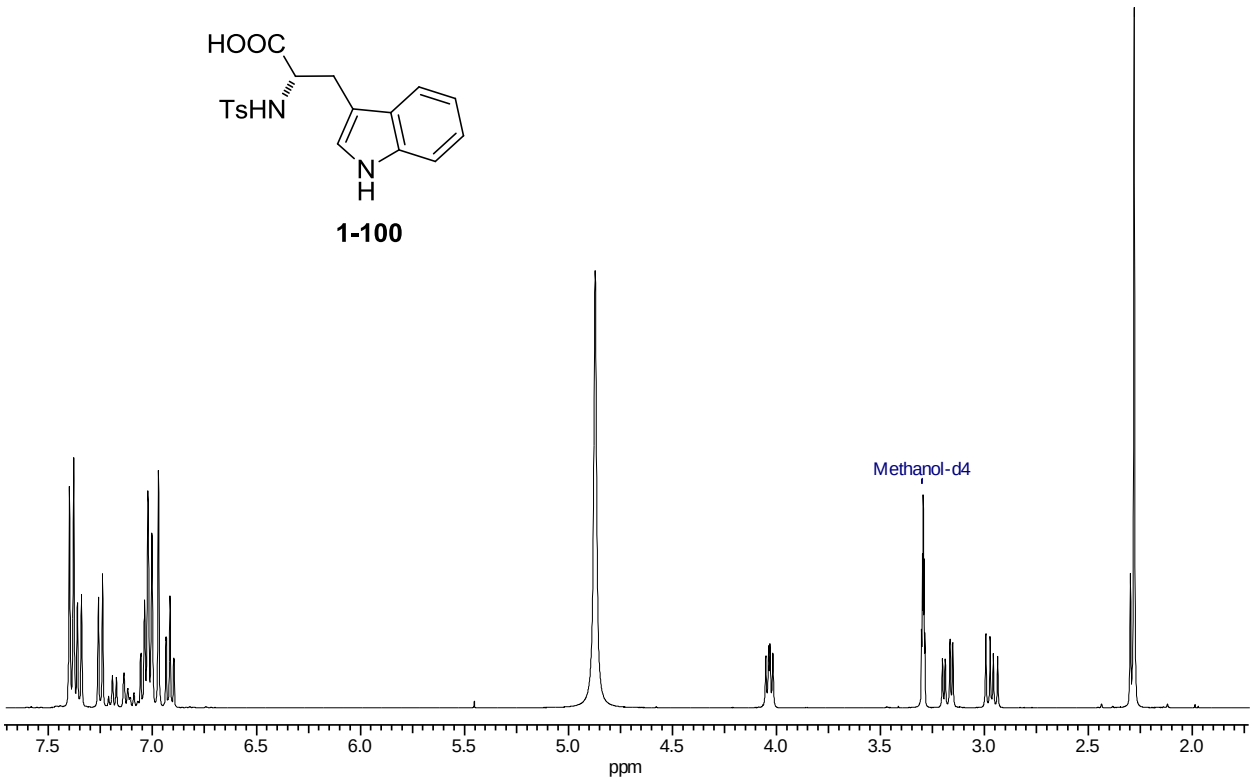
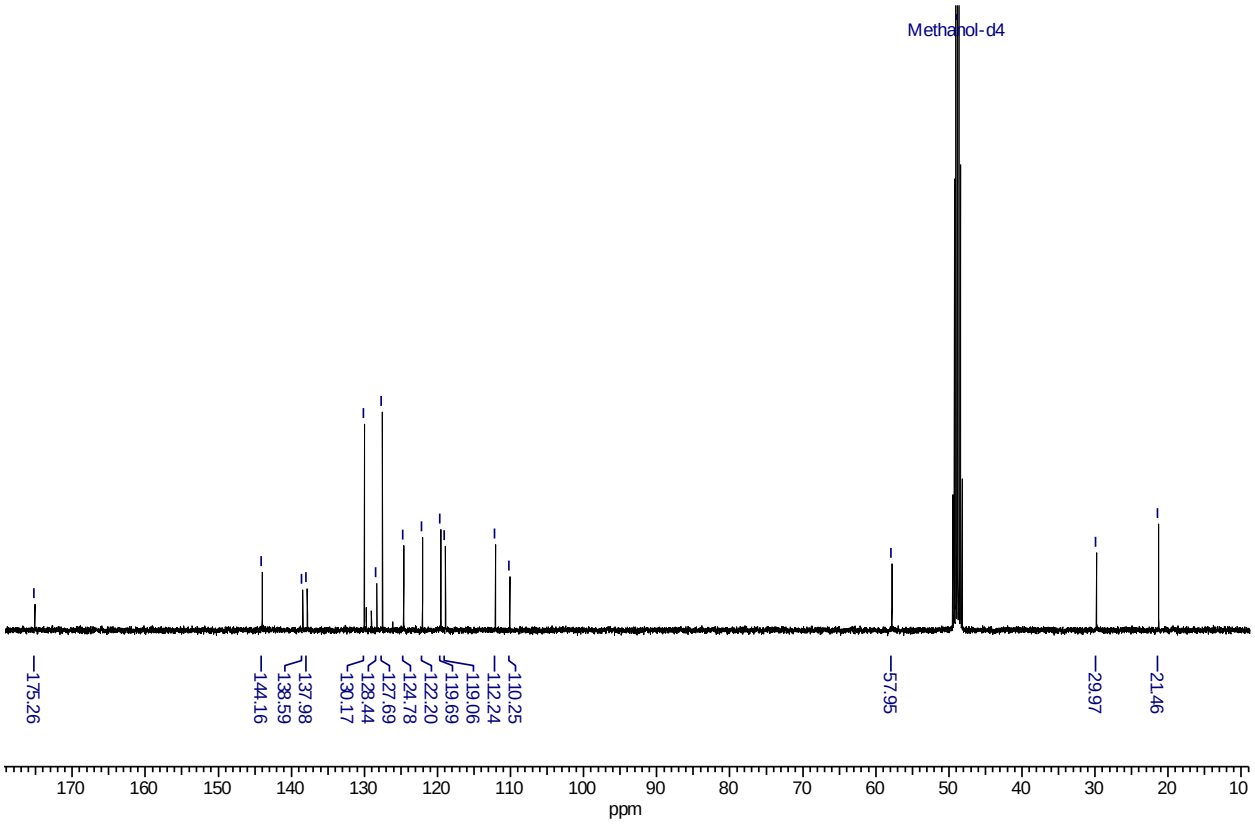
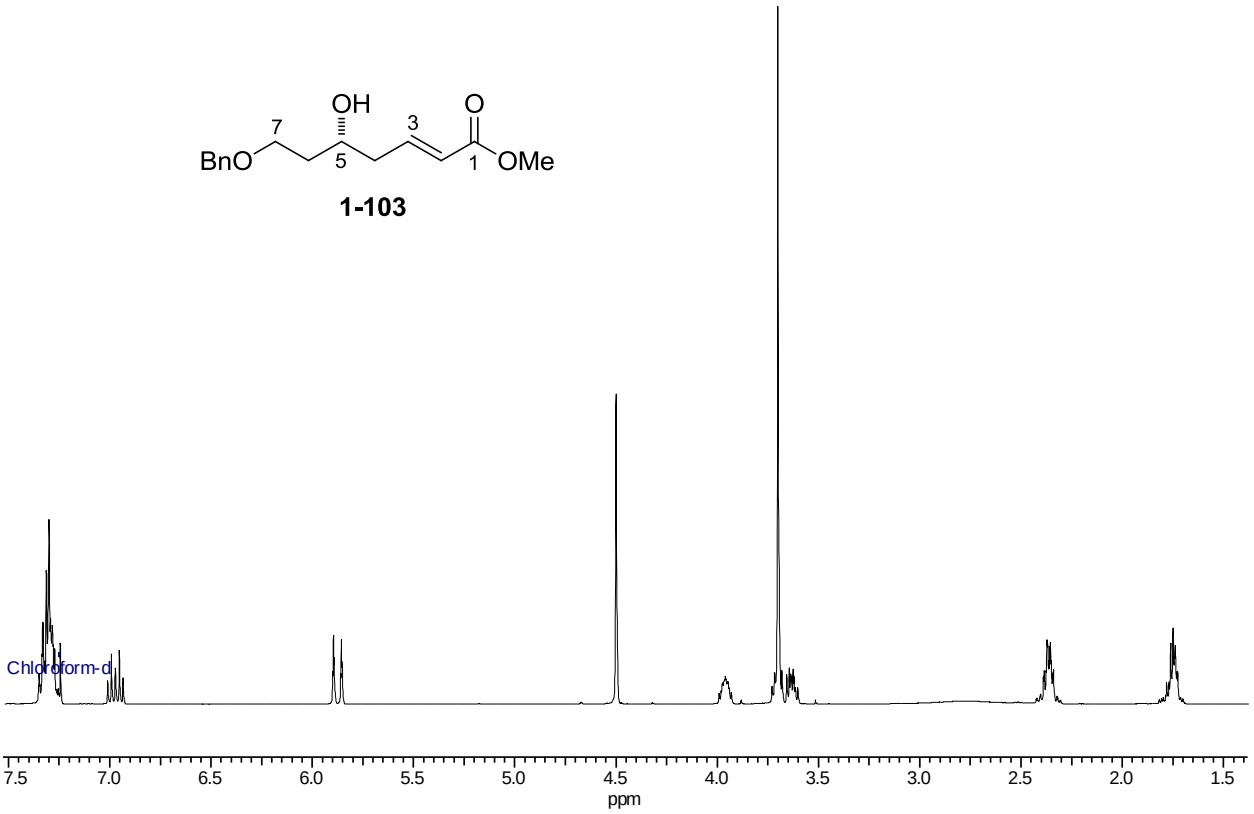
42.18
37.67
25.80
17.90
-4.28
-4.64

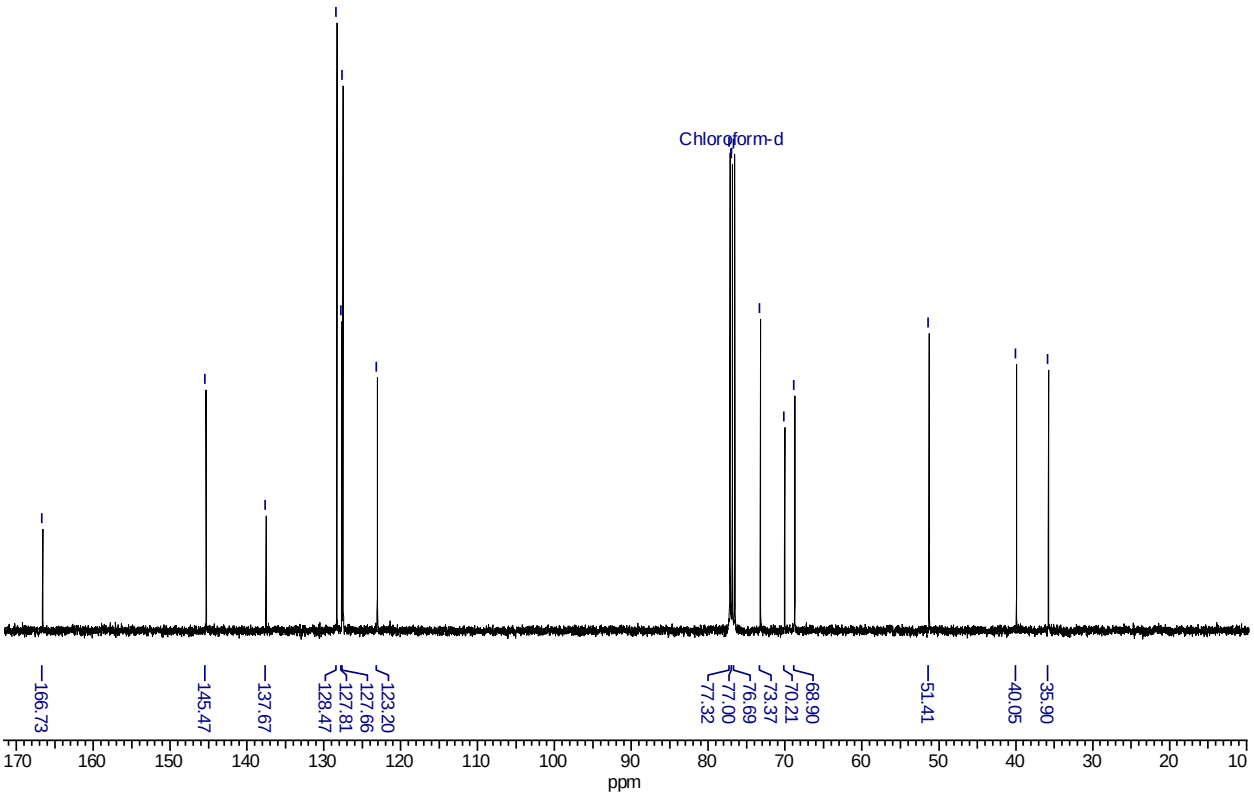

OTBS
OMe
1
2
4
1-98
Chloroform-d
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm
Chloroform-d
158.73
132.39
106.69
80.22
77.31
77.00
76.68
54.76
25.64
18.06
-4.27
160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
ppm

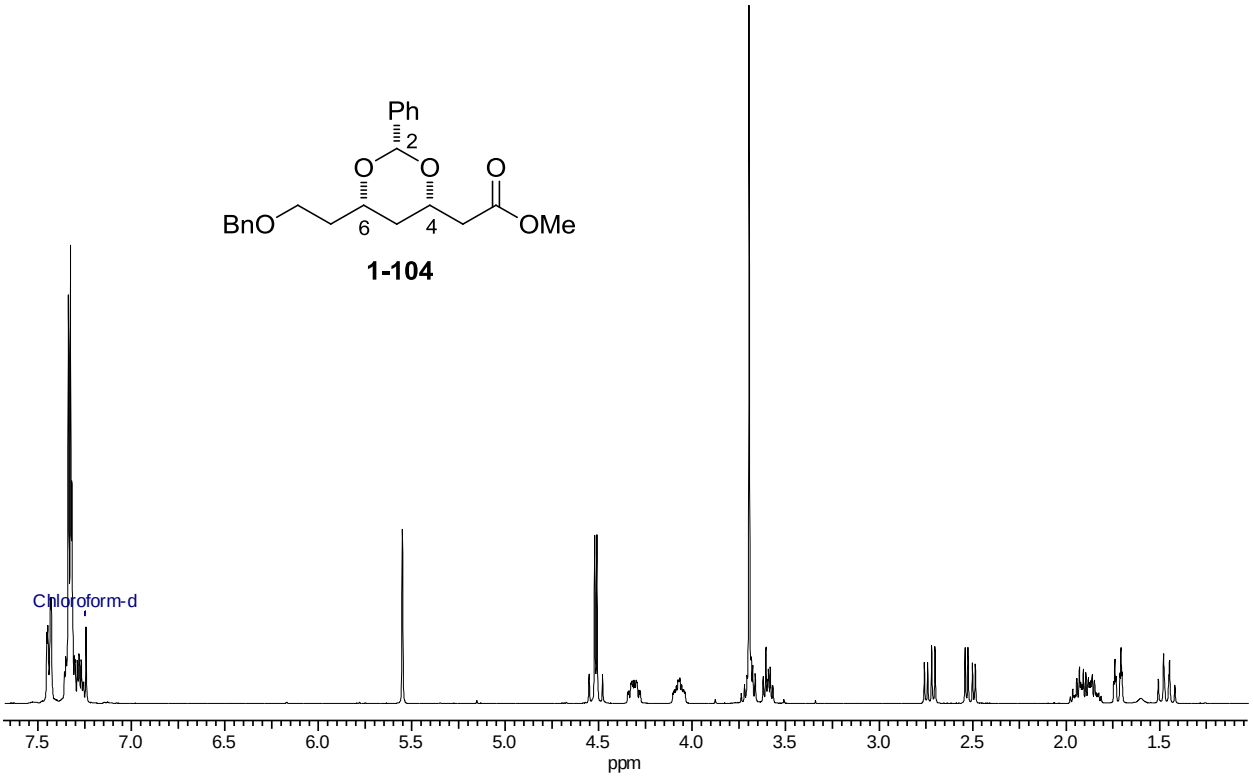

HOOC
TsHN
N
H
Methanol-d4
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
ppm

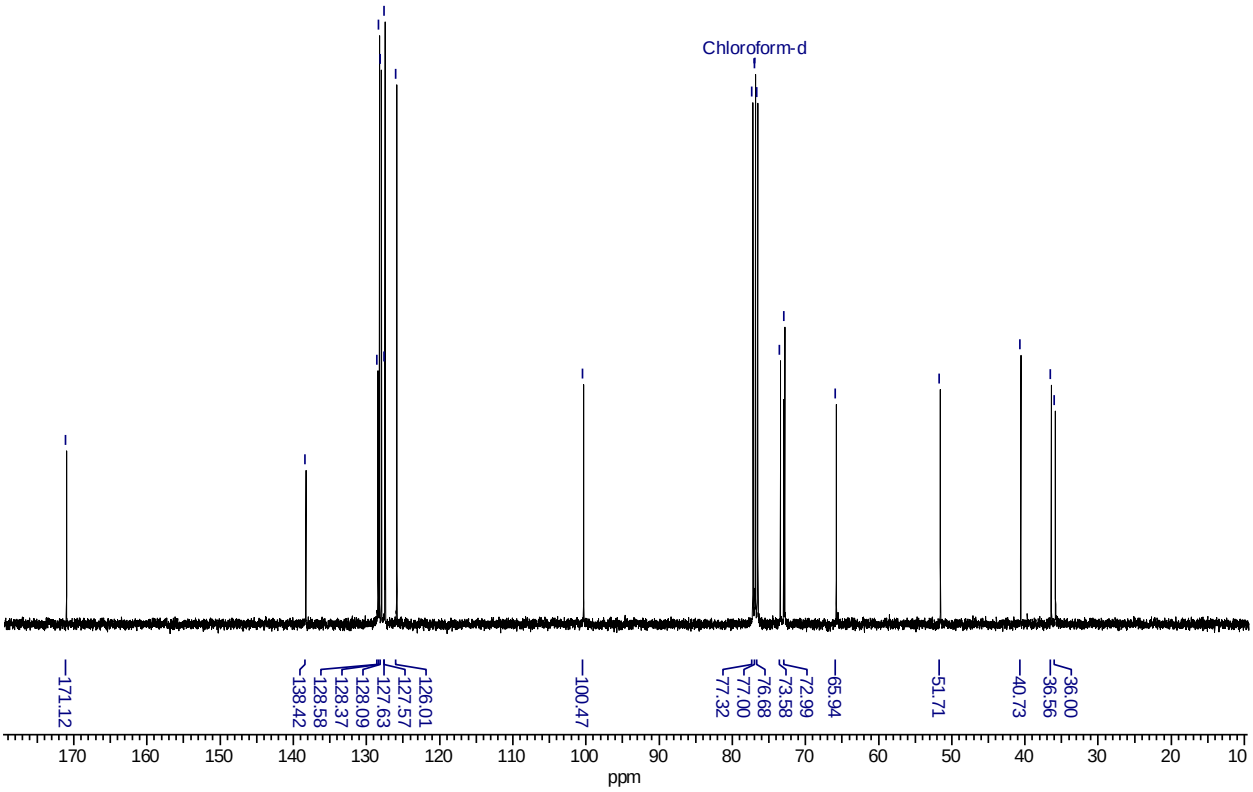
1-100

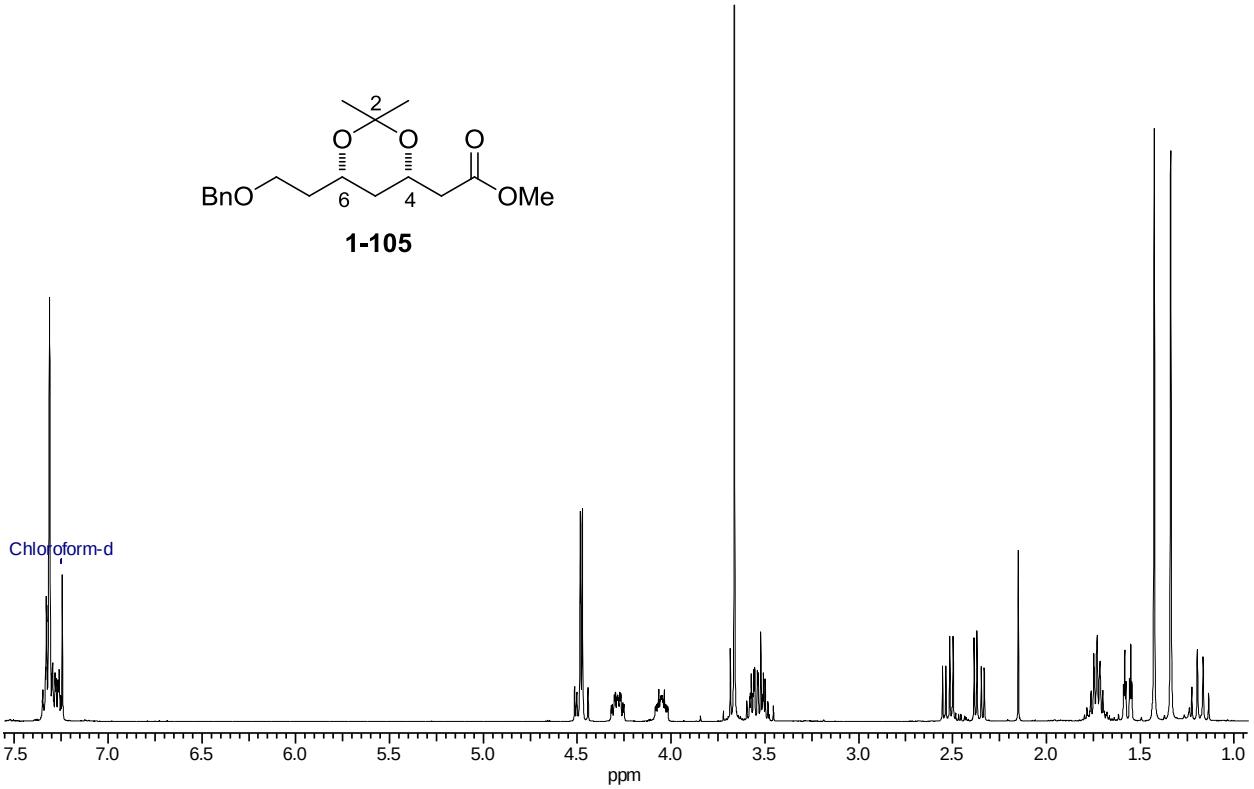

Methanol-d4
175.26
144.16
138.59
137.98
130.17
128.44
127.69
124.78
122.20
119.69
119.06
112.24
110.25
57.95
29.97
21.46
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


OH
O
7
3
BnO
5
1
OMe
1-103
Chloroform-d
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm

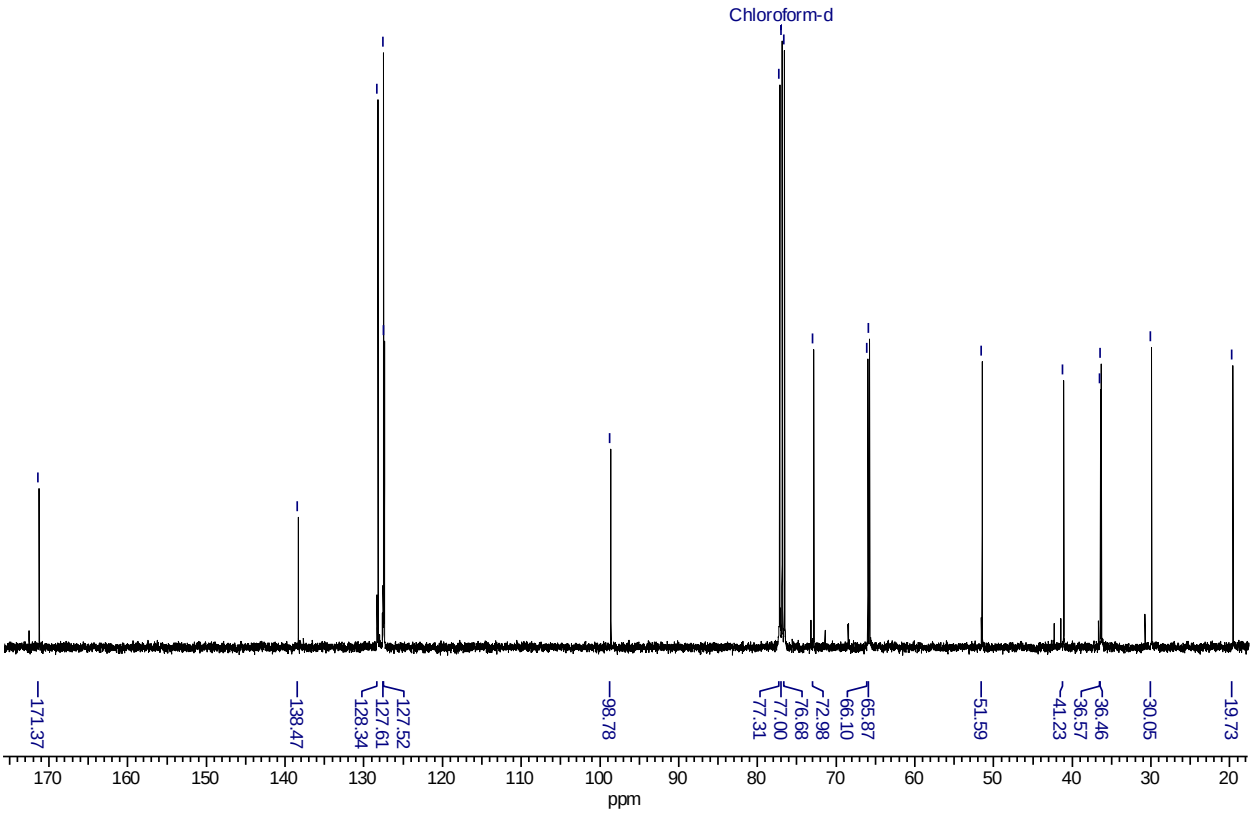

Chloroform-d
166.73
145.47
137.67
128.47
127.81
127.66
123.20
77.32
77.00
76.69
73.37
70.21
68.90
51.41
40.05
35.90
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

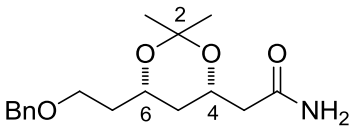

Ph
2
O
O
O
BnO
6
4
OMe
1-104
Chloroform-d
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm


Chloroform-d
171.12
138.42
128.58
128.37
128.09
127.63
127.57
126.01
100.47
77.32
77.00
76.68
73.58
72.99
65.94
51.71
40.73
36.56
36.00
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


2
O
O
O
BnO
6
4
OMe
Chloroform-d
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

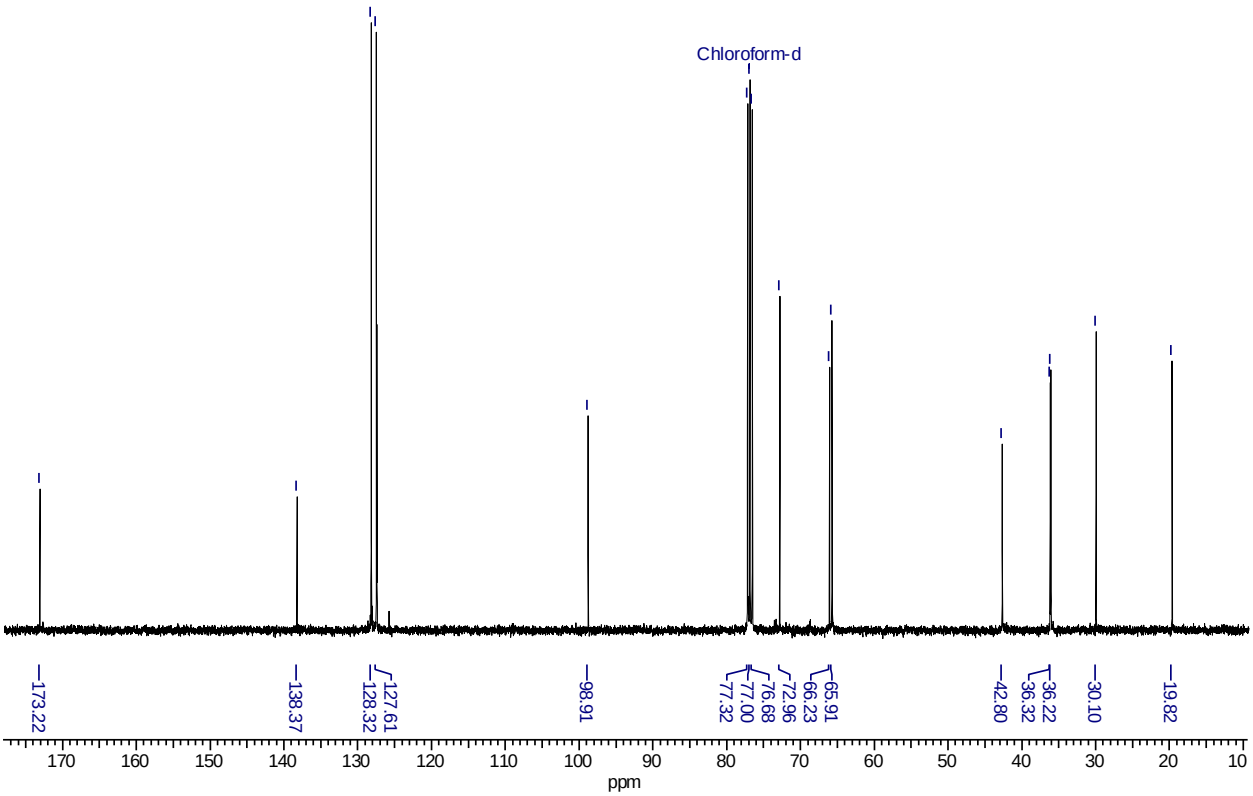
1-105

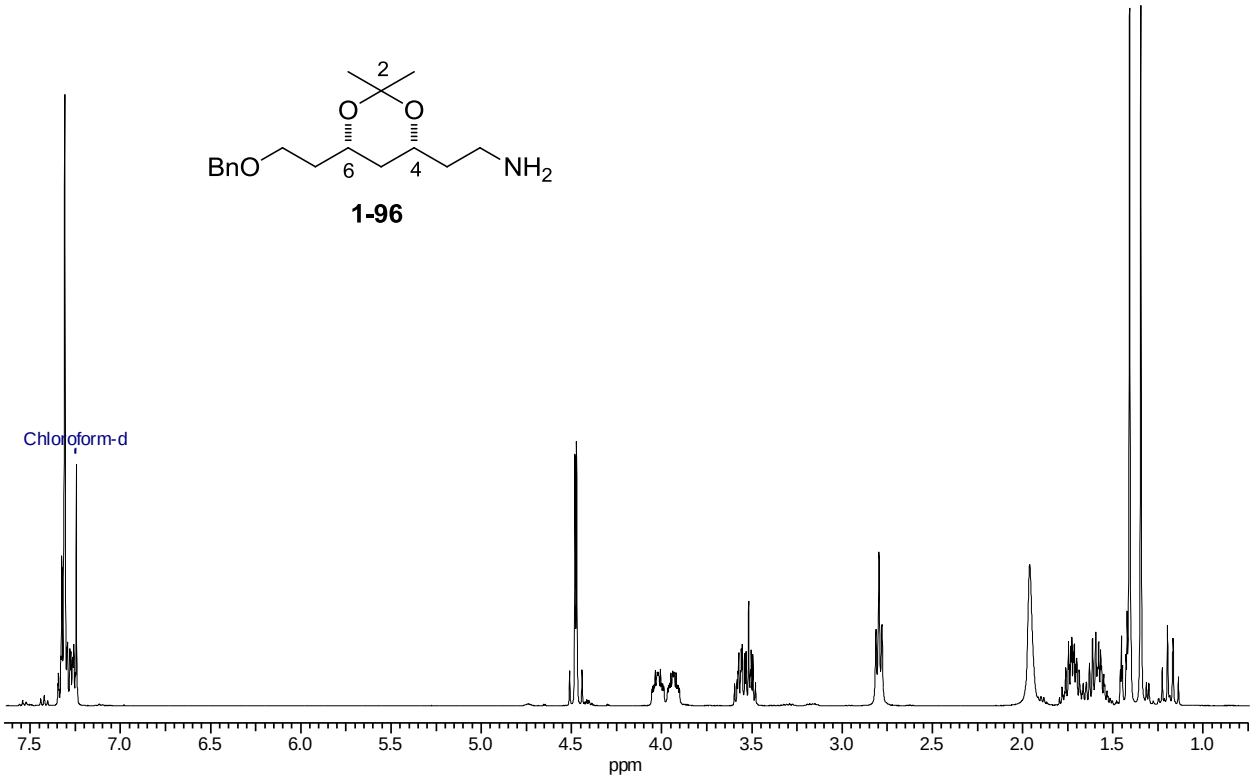

Chloroform-d
171.37
138.47
128.34
127.61
127.52
98.78
77.31
77.00
76.68
72.98
66.10
65.87
51.59
41.23
36.57
36.46
30.05
19.73
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

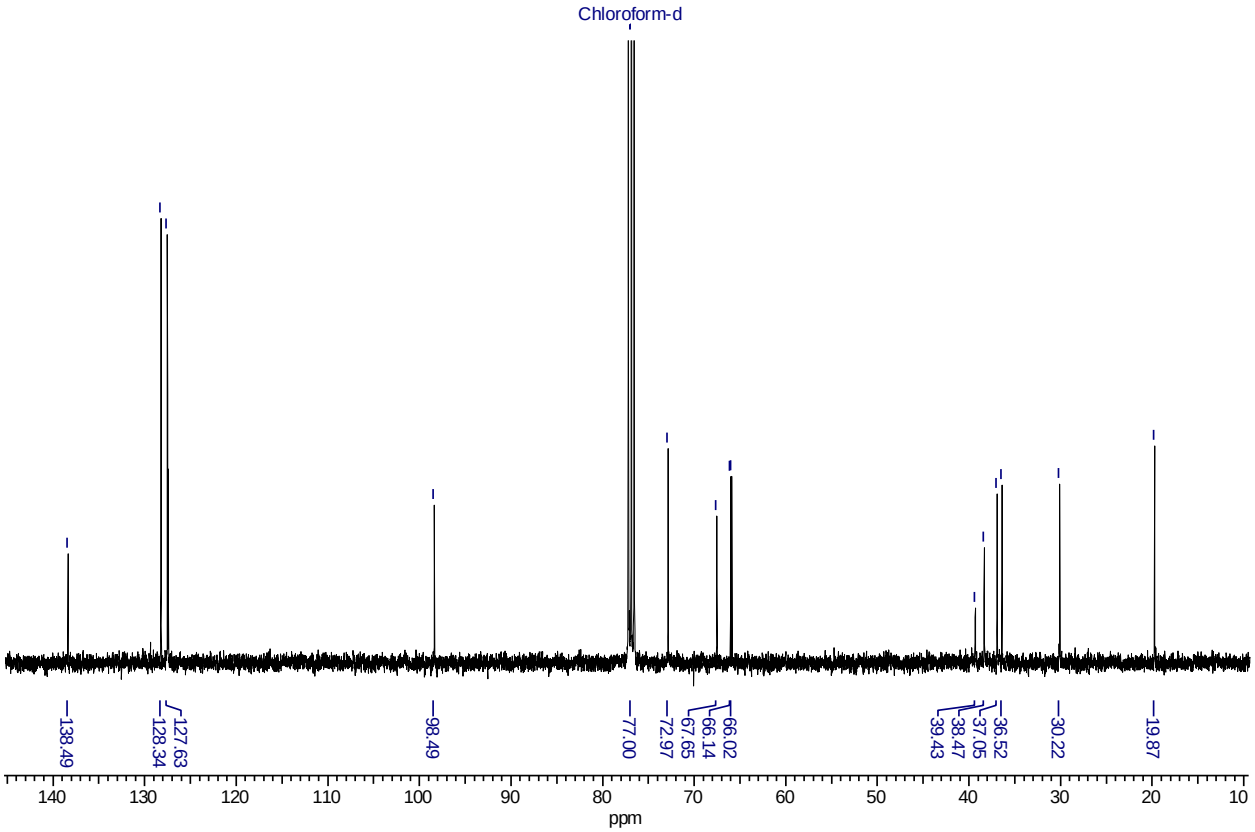

2
O
O
O
BnO
6
4
NH2

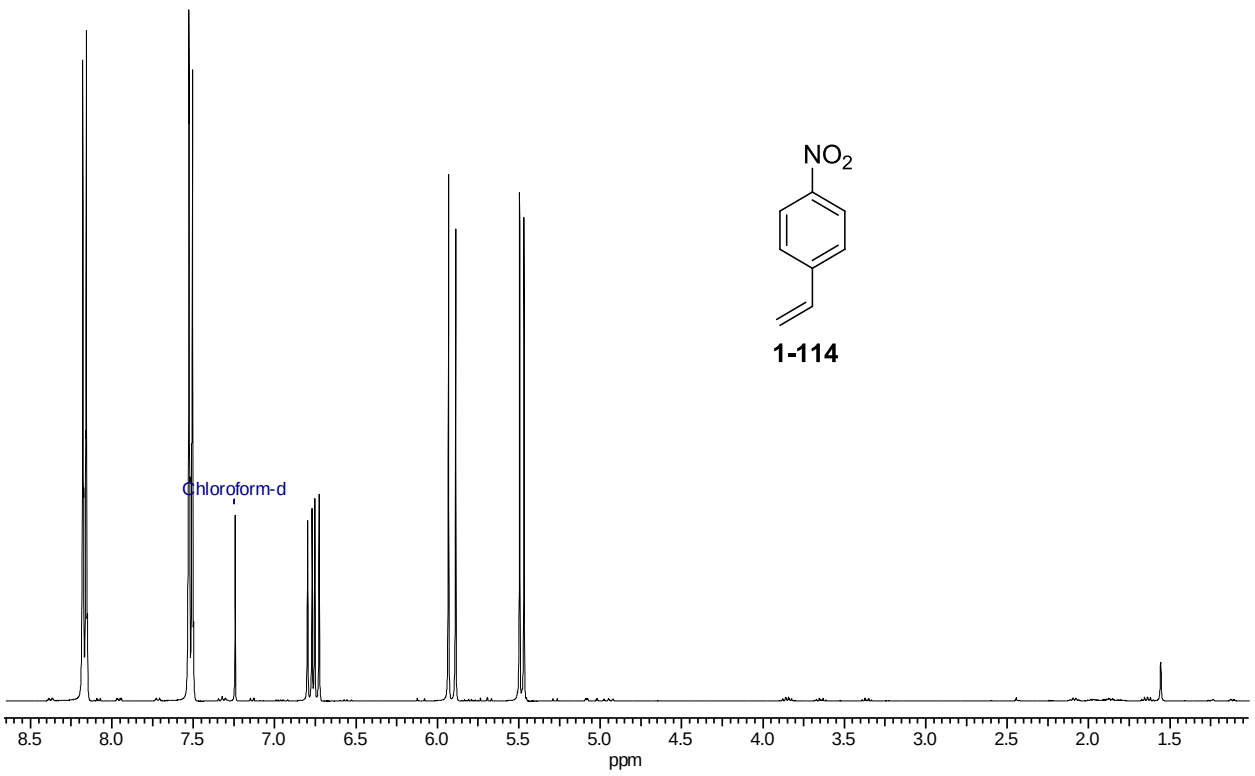
1-106

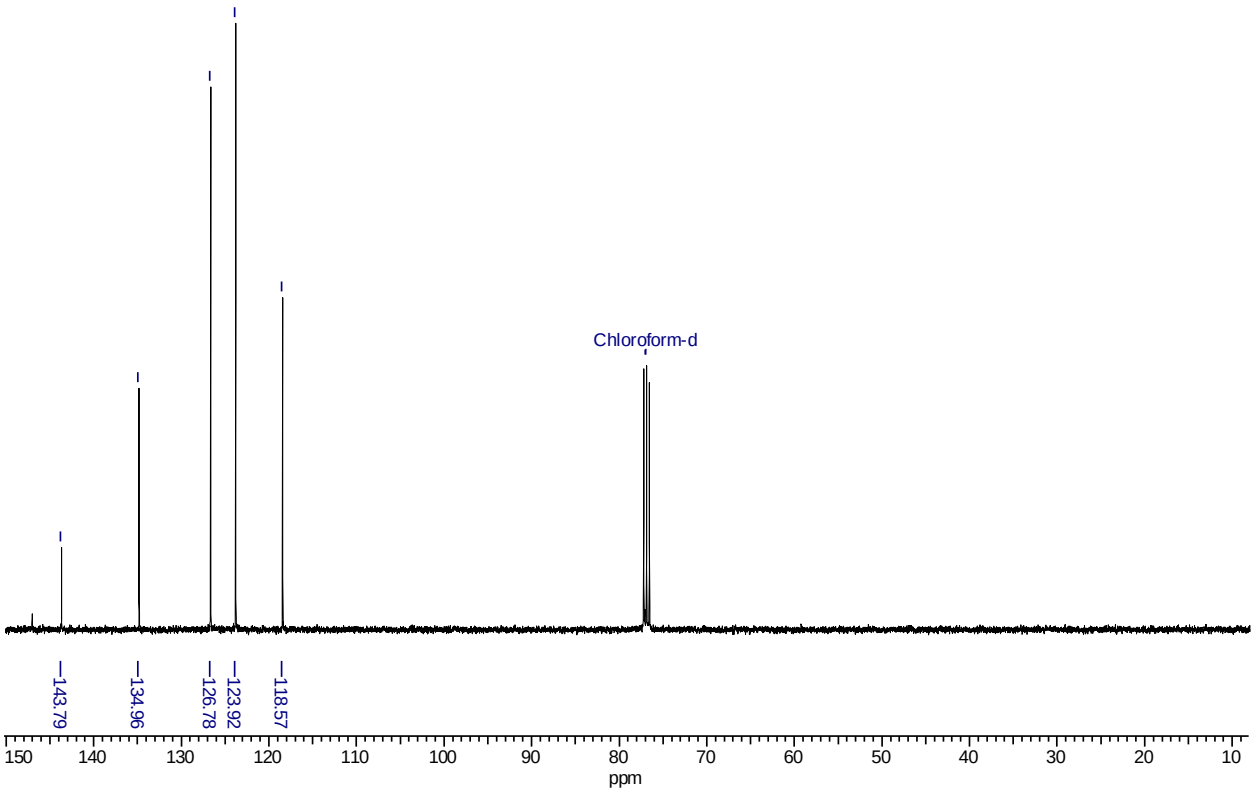
Chloroform-d
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

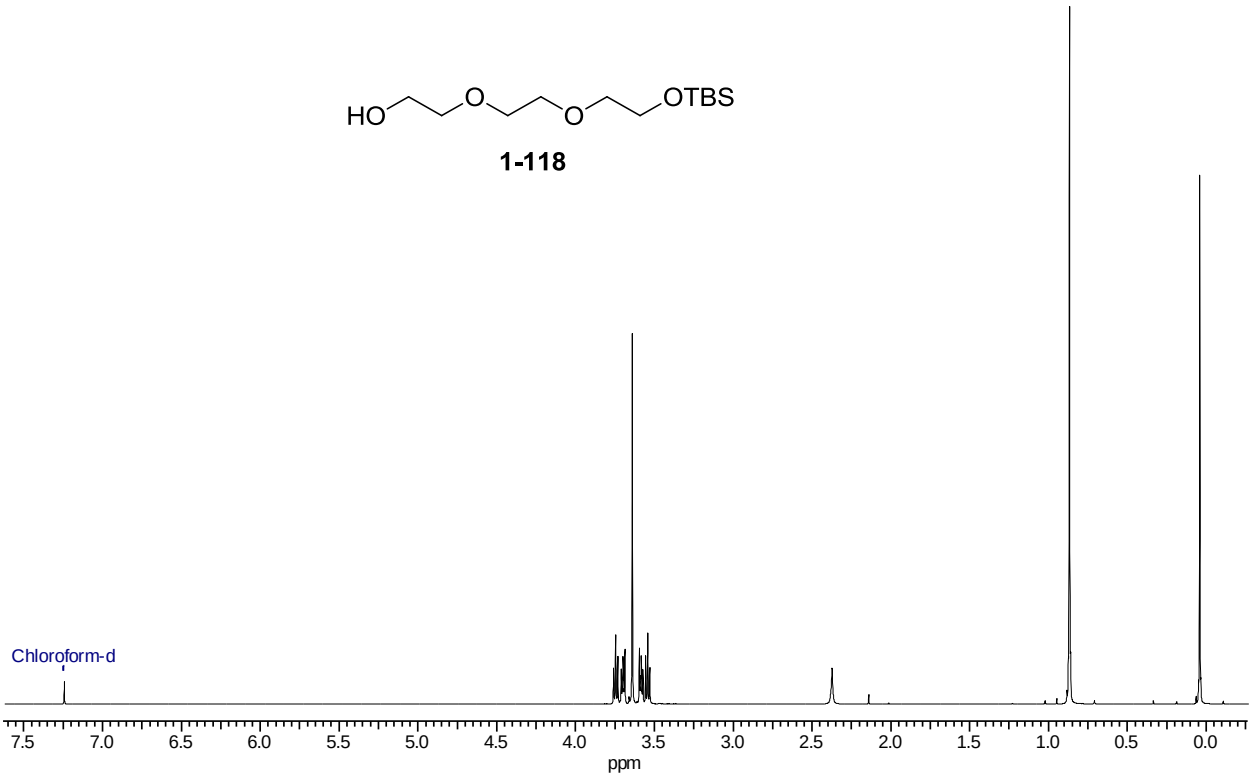

Chloroform-d
173.22
138.37
128.32
127.61
98.91
77.32
77.00
76.68
72.96
66.23
65.91
42.80
36.32
36.22
30.10
19.82
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

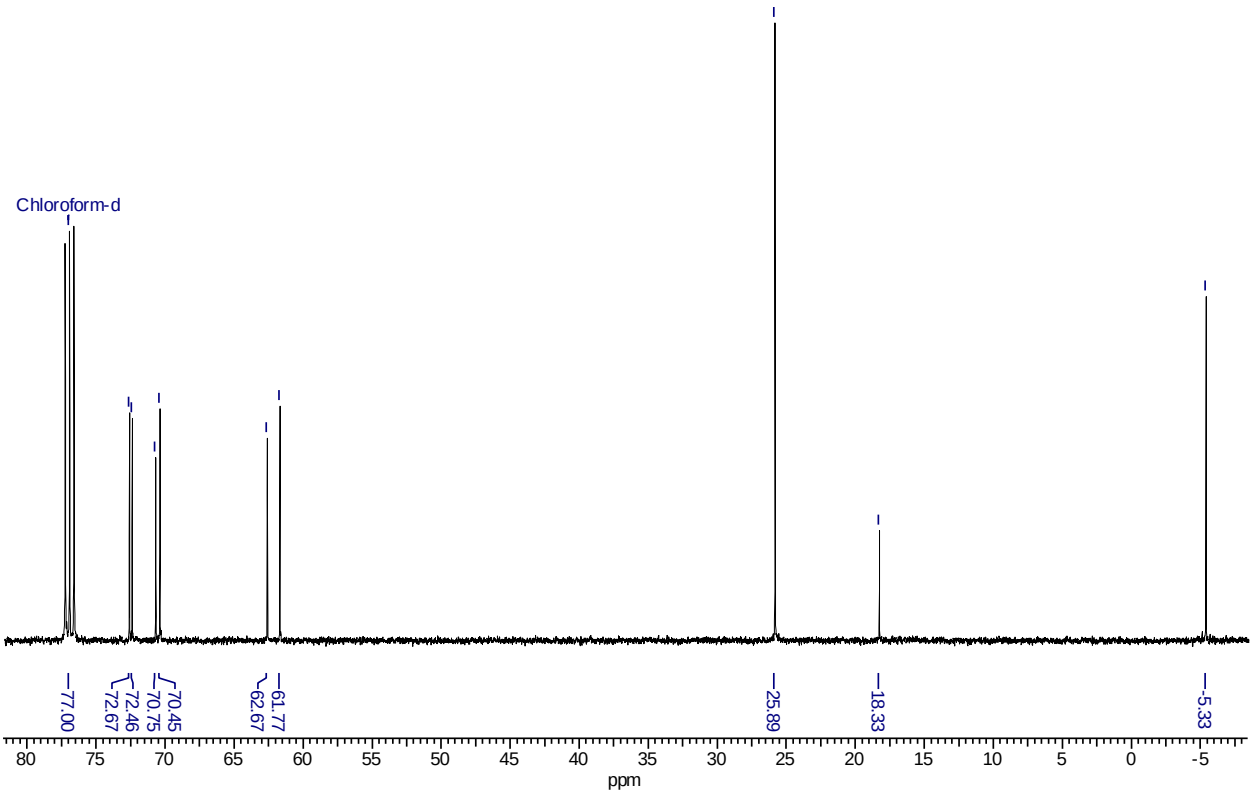

2
O
O
BnO
6
4
NH2
1-96
Chloroform-d
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

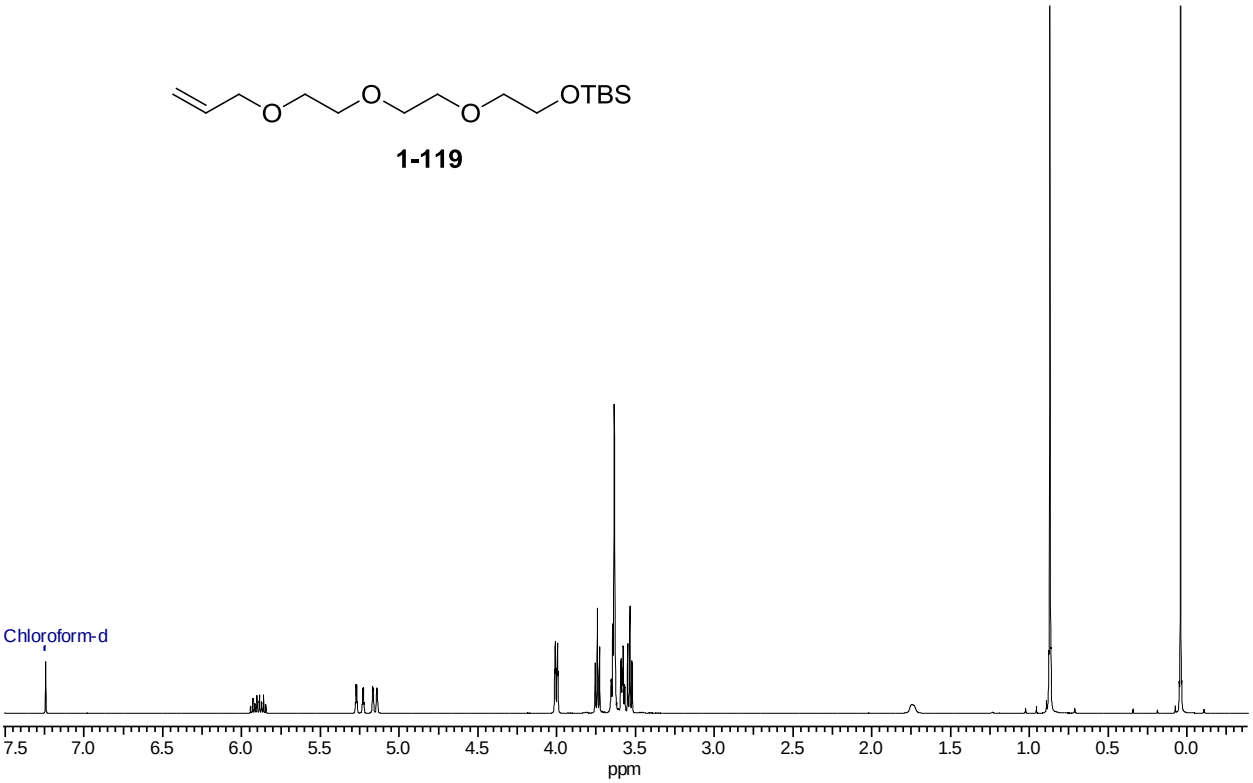

Chloroform-d
138.49
128.34
127.63
98.49
77.00
72.97
67.65
66.14
66.02
39.43
38.47
37.05
36.52
30.22
19.87
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

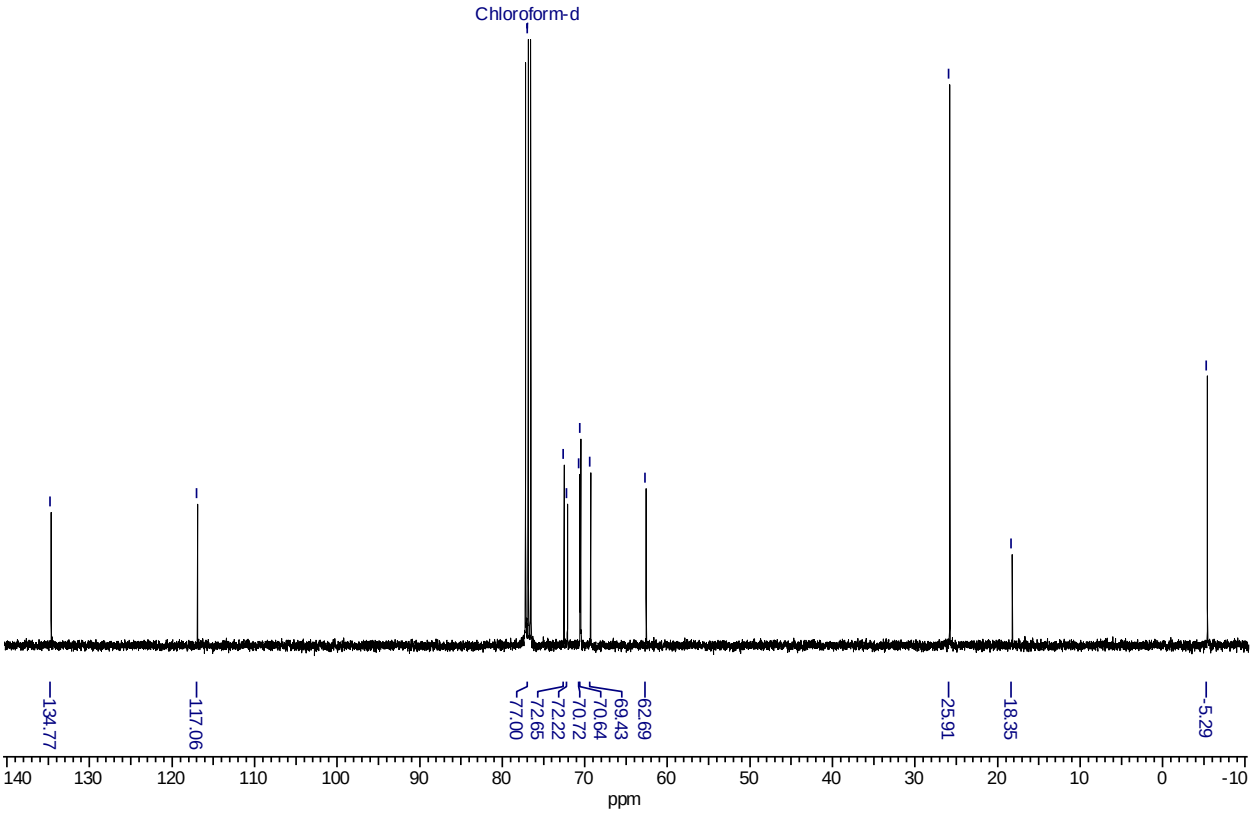

NO2
1-114
Chloroform-d
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm

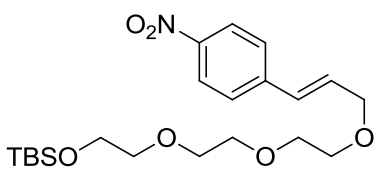

Chloroform-d
143.79
134.96
126.78
123.92
118.57
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


HO
O
O
OTBS
1-118
Chloroform-d
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm


Chloroform-d
77.00
72.67
72.46
70.75
70.45
62.67
61.77
25.89
18.33
-5.33
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
-5
ppm

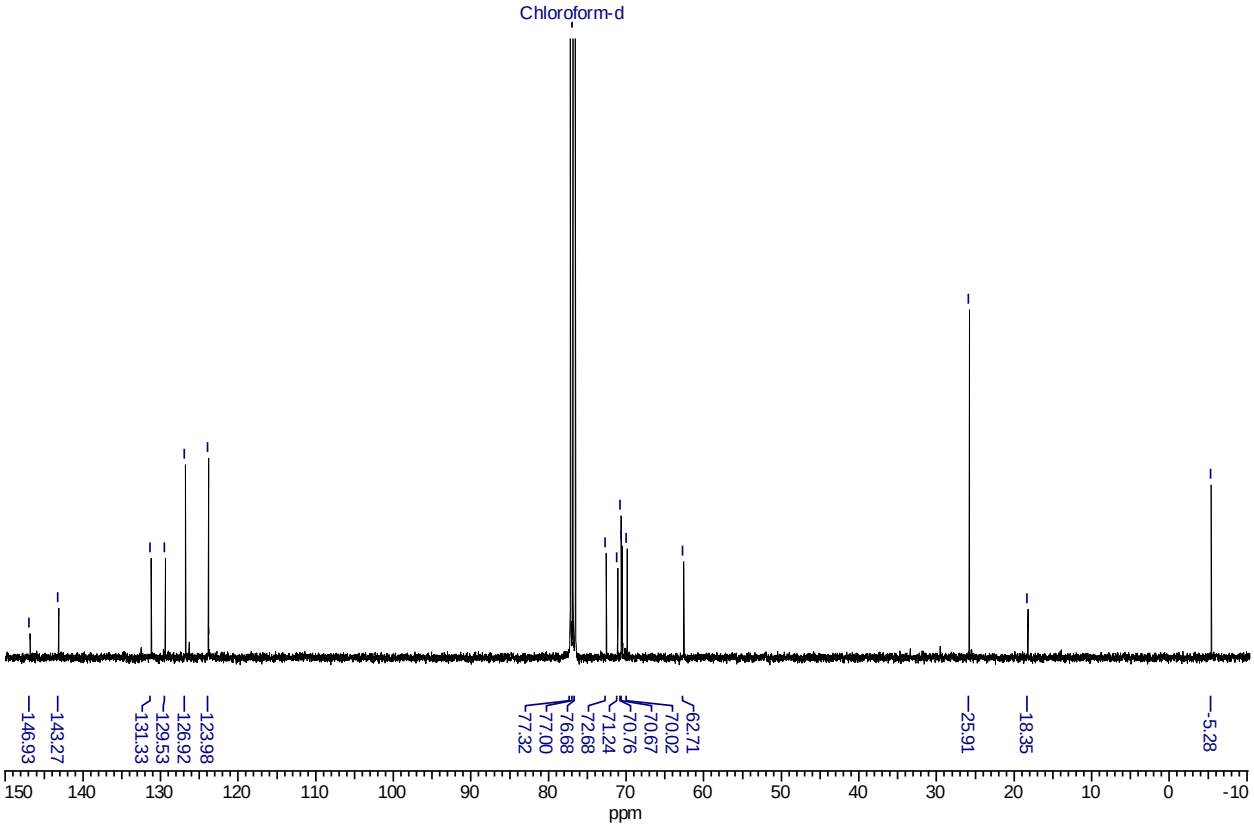

OTBS
O
O
O
1-119
Chloroform-d
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm

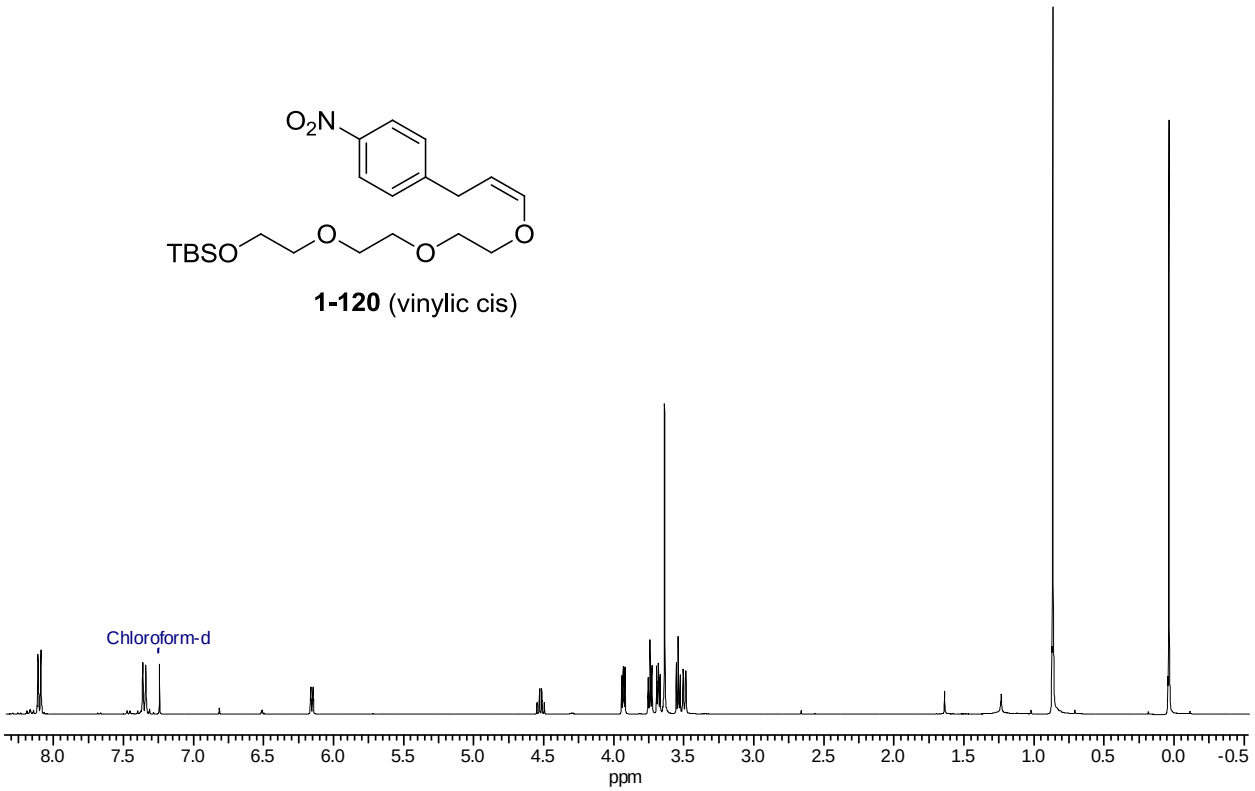

Chloroform-d
134.77
117.06
77.00
72.65
72.22
70.72
70.64
69.43
62.69
25.91
18.35
-5.29
140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
ppm


O2N
TBSO
O
O
O

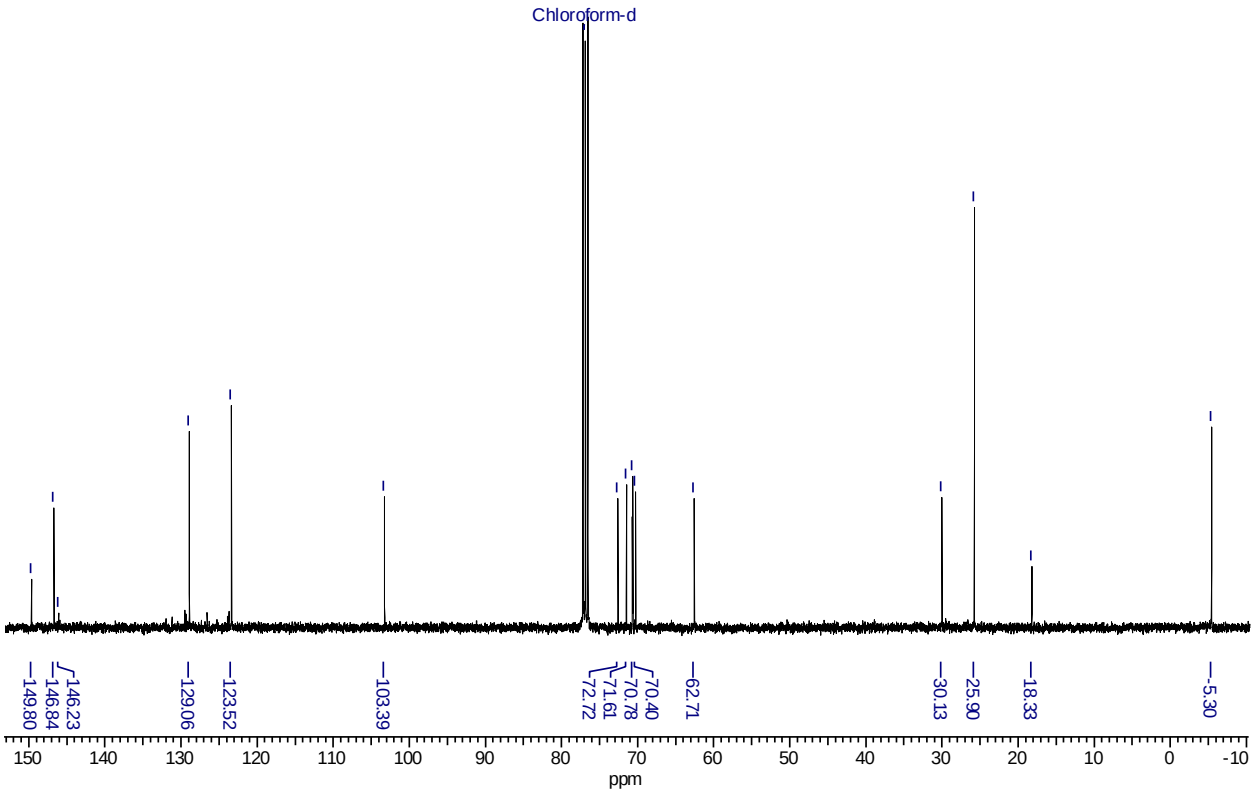
1-120 (trans)

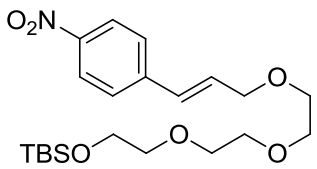
Chloroform-d
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm


Chloroform-d
146.93
143.27
131.33
129.53
126.92
123.98
77.32
77.00
76.68
72.68
71.24
70.76
70.67
70.02
62.71
25.91
18.35
-5.28
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
ppm

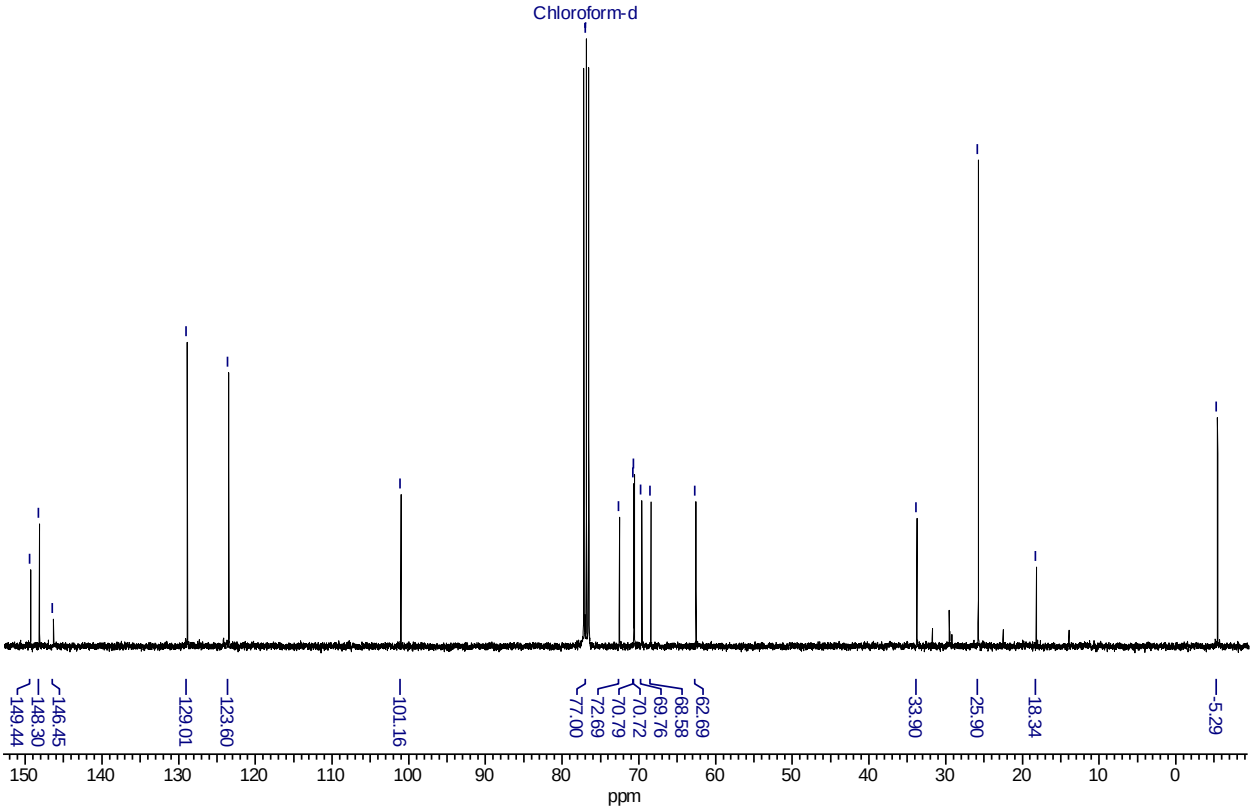


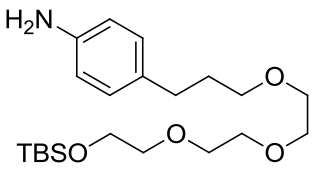
1-120 (vinylic cis)





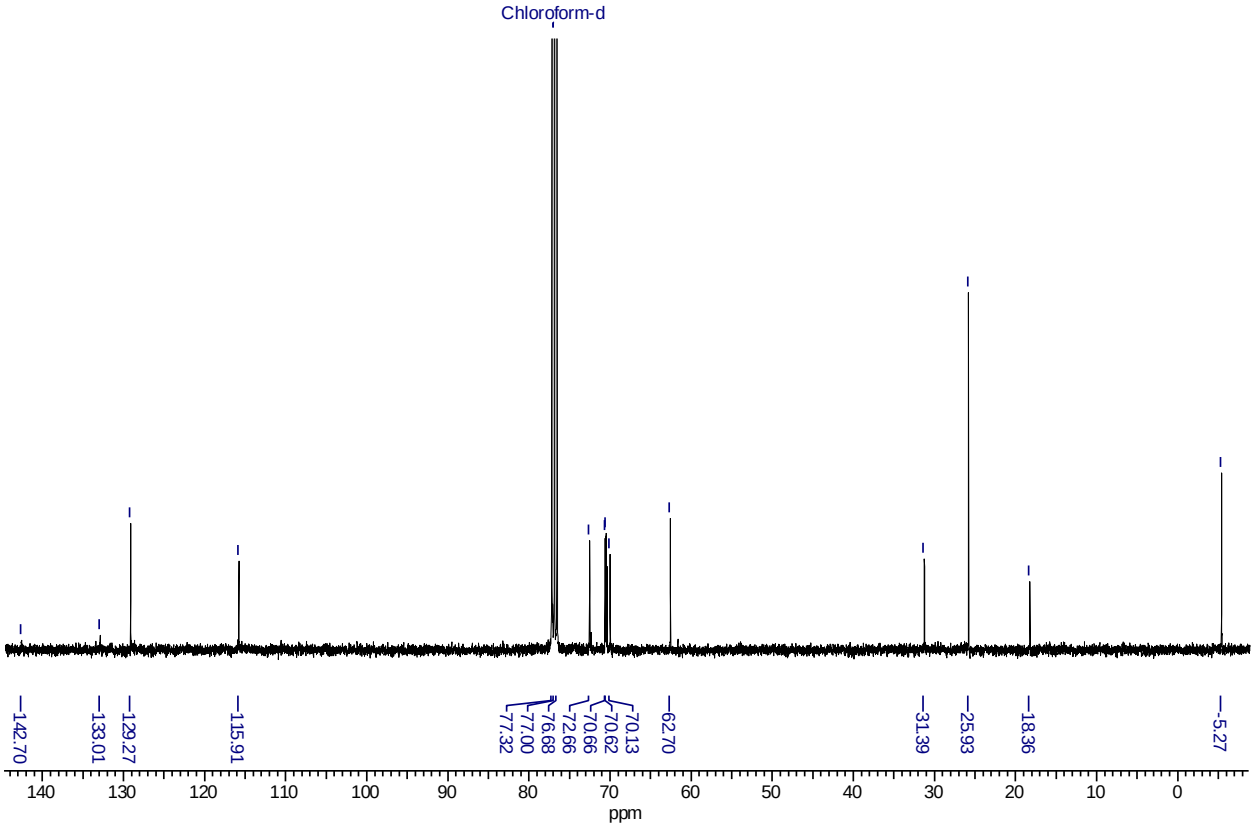
1-120 (vinylic trans)

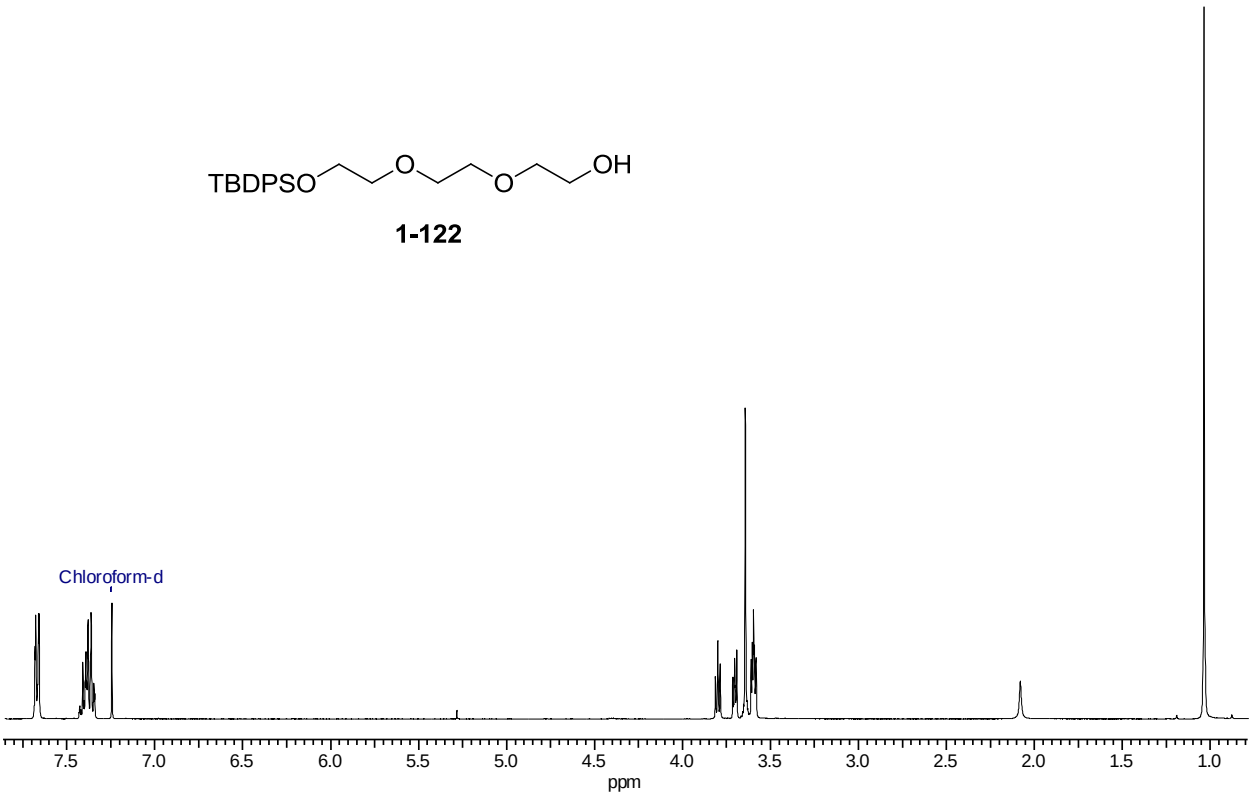


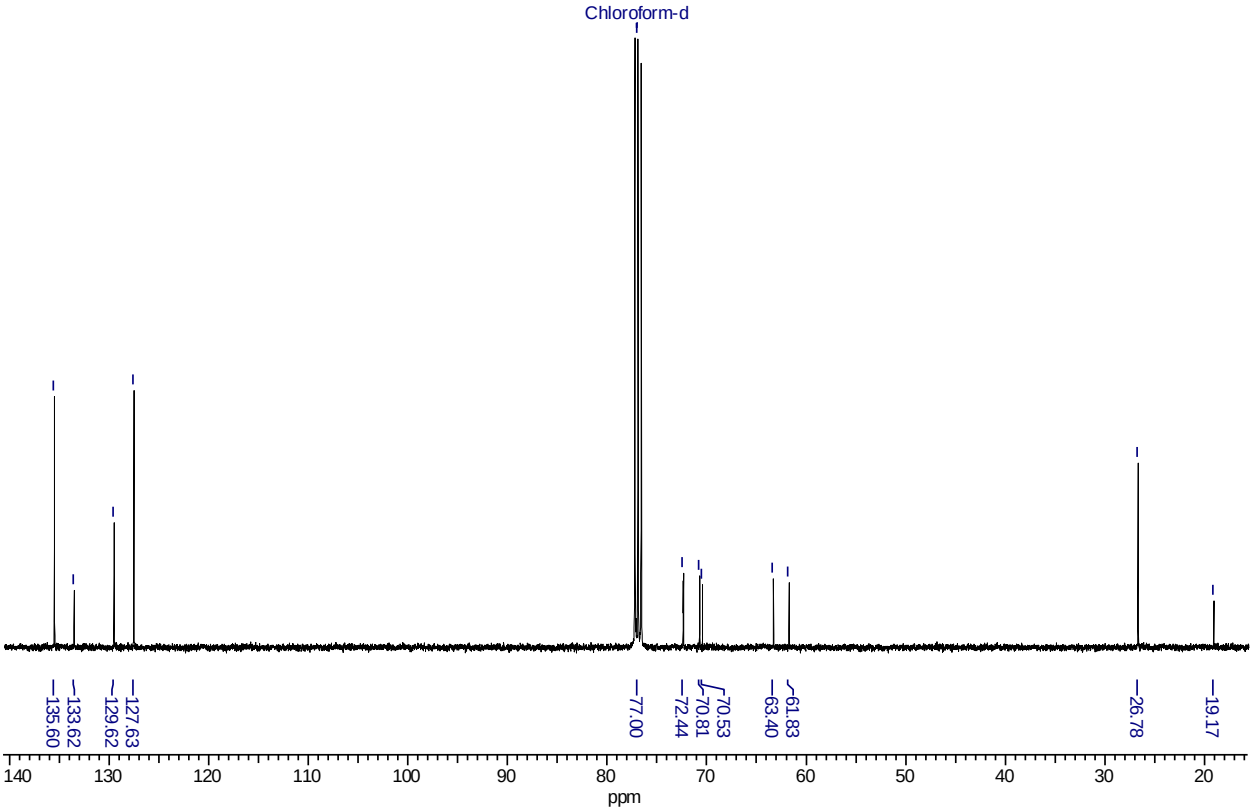

H2N
O
O
O
TBSO

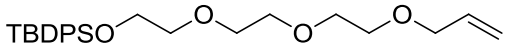
1-121

Chloroform-d
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm


Chloroform-d
142.70
133.01
129.27
115.91
77.32
77.00
76.68
72.66
70.66
70.62
70.13
62.70
31.39
25.93
18.36
-5.27
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

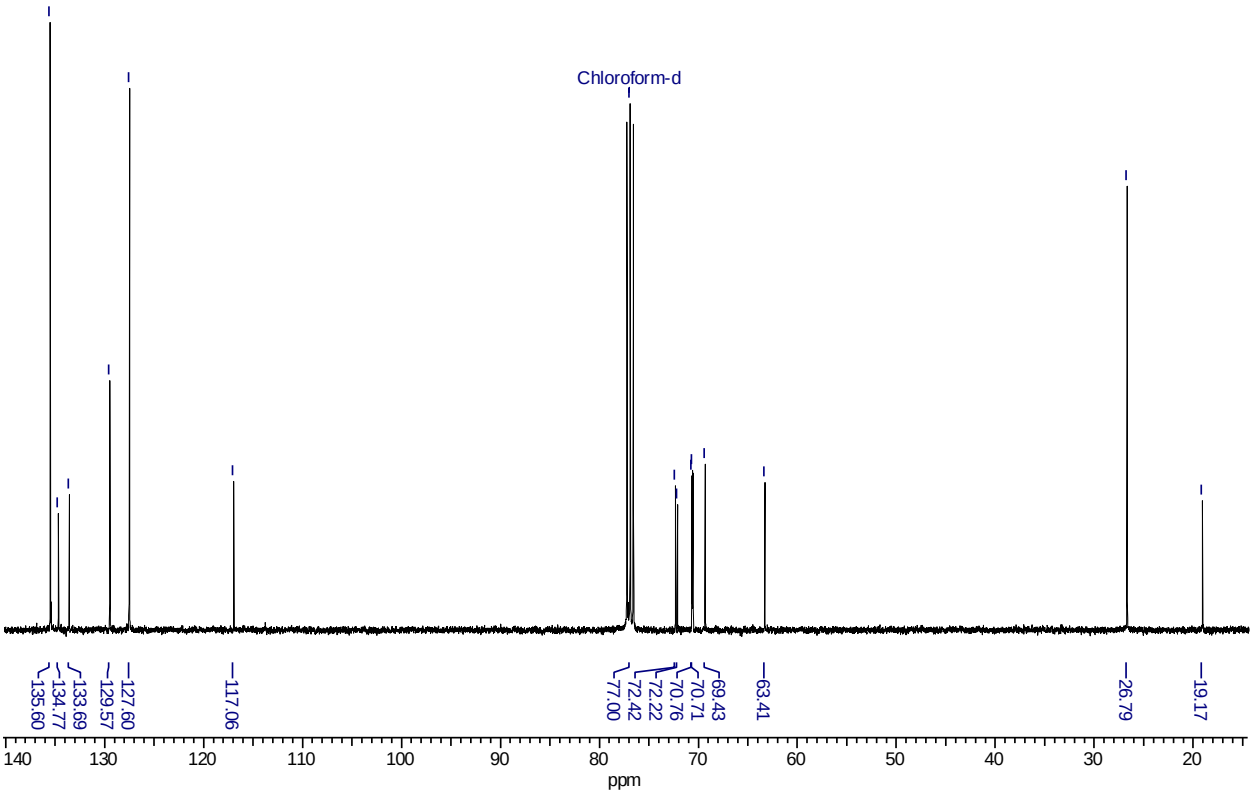

TBDPSO
O
O
OH
1-122
Chloroform-d
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

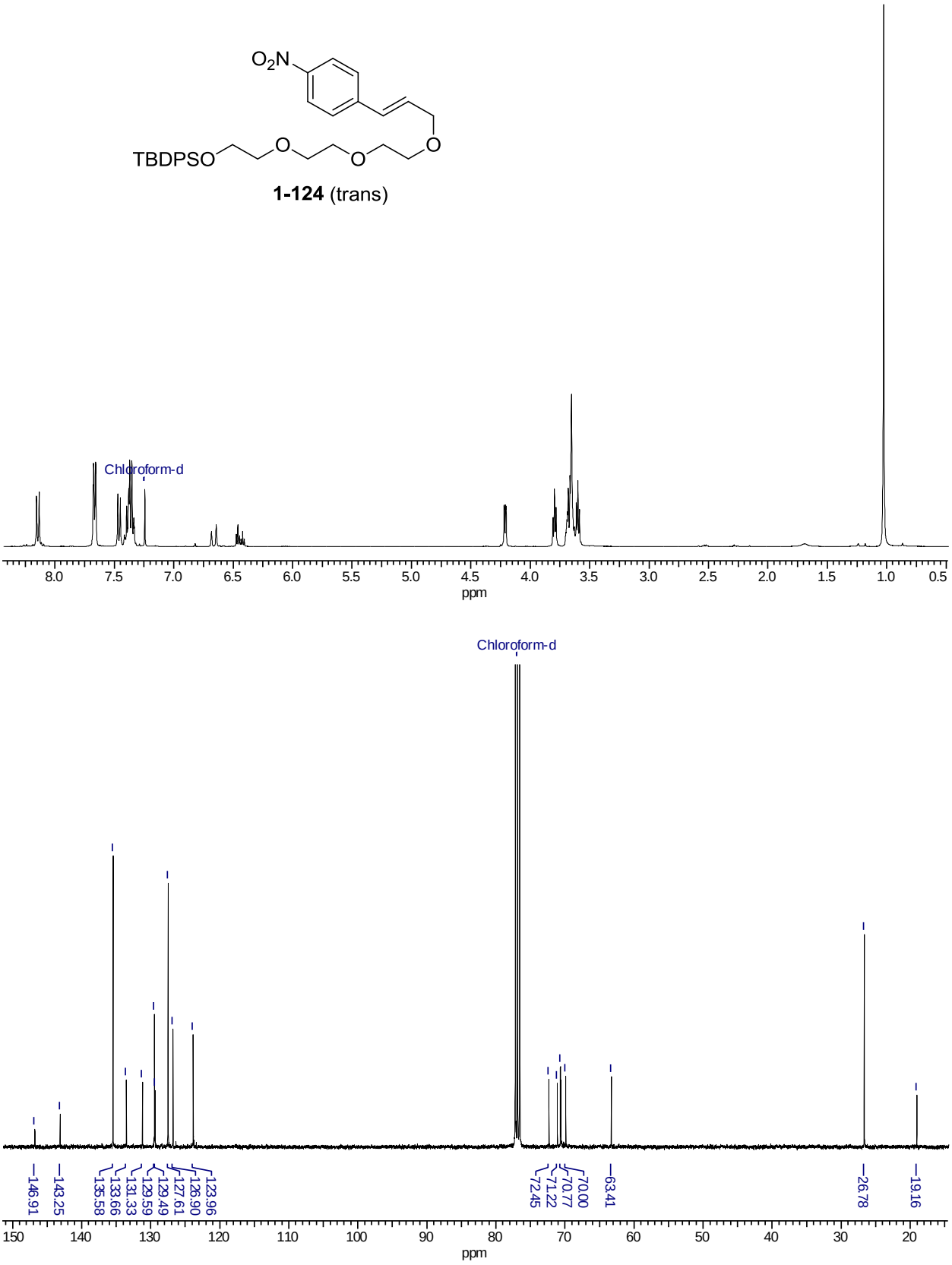

Chloroform-d
135.60
133.62
129.62
127.63
77.00
72.44
70.81
70.53
63.40
61.83
26.78
19.17
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

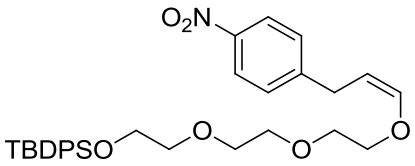

TBDPSO
O
O
O

1-123

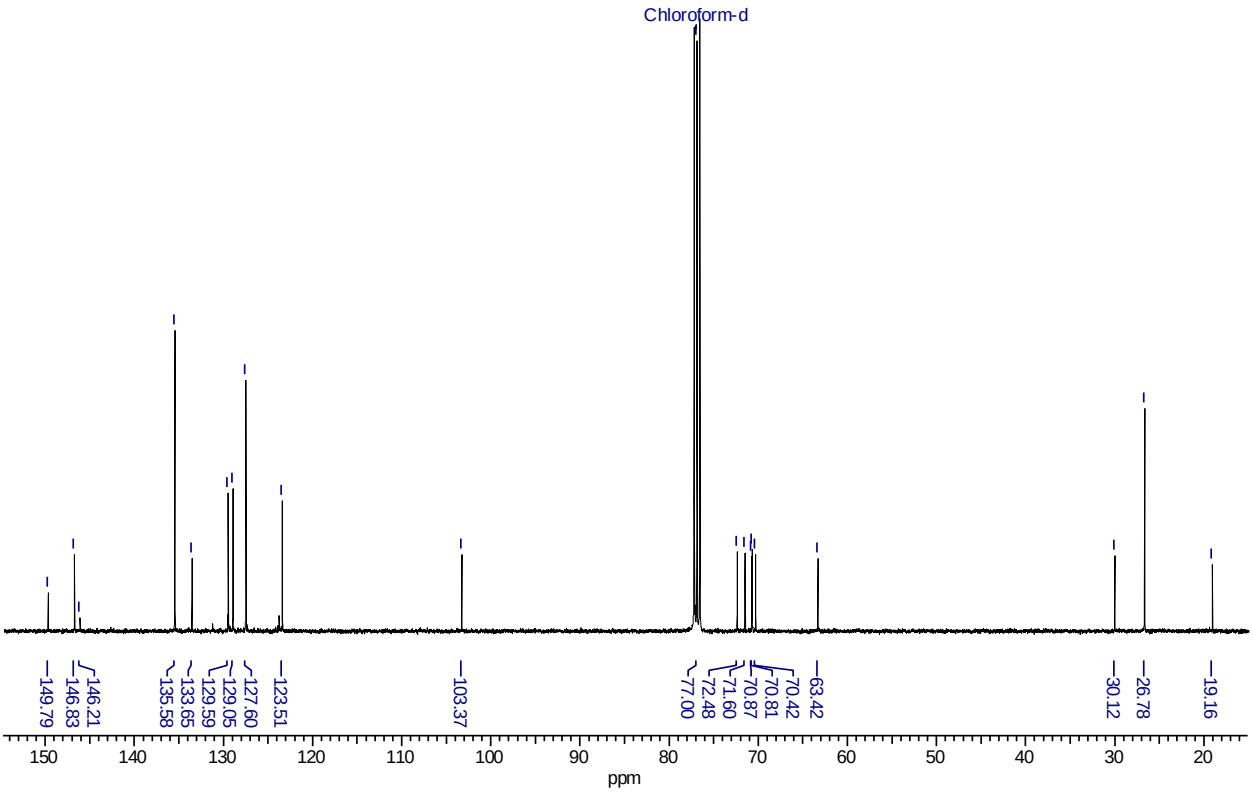
Chloroform-d
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

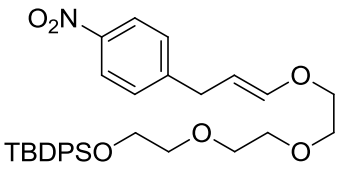

Chloroform-d
135.60
134.77
133.69
129.57
127.60
117.06
77.00
72.42
72.22
70.76
70.71
69.43
63.41
26.79
19.17
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm


O2N
TBDPSO
O
O
O
1-124 (trans)
Chloroform-d
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
Chloroform-d
146.91
143.25
135.58
133.66
131.33
129.59
129.49
127.61
126.90
123.96
72.45
71.22
70.77
70.00
63.41
26.78
19.16
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

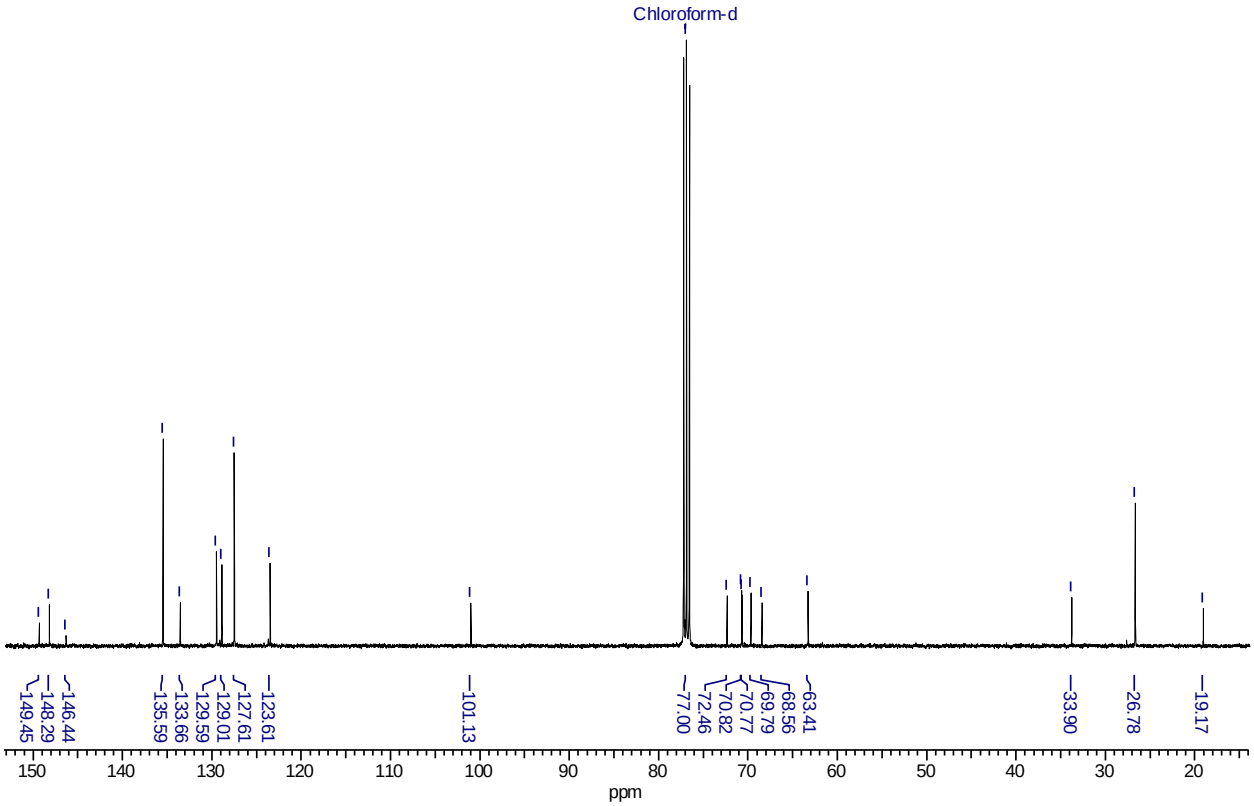


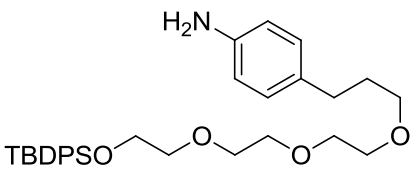
1-124 (vinylic cis)





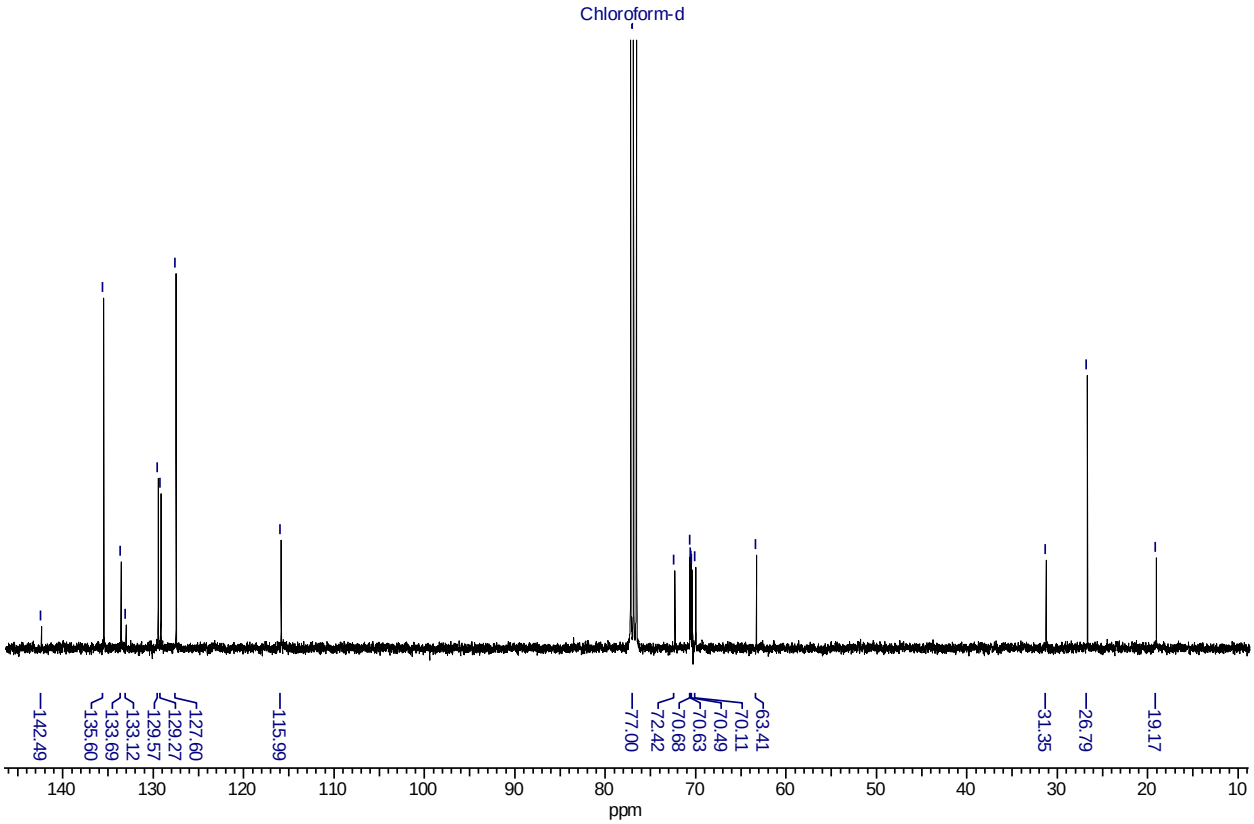
1-124 (vinylic trans)

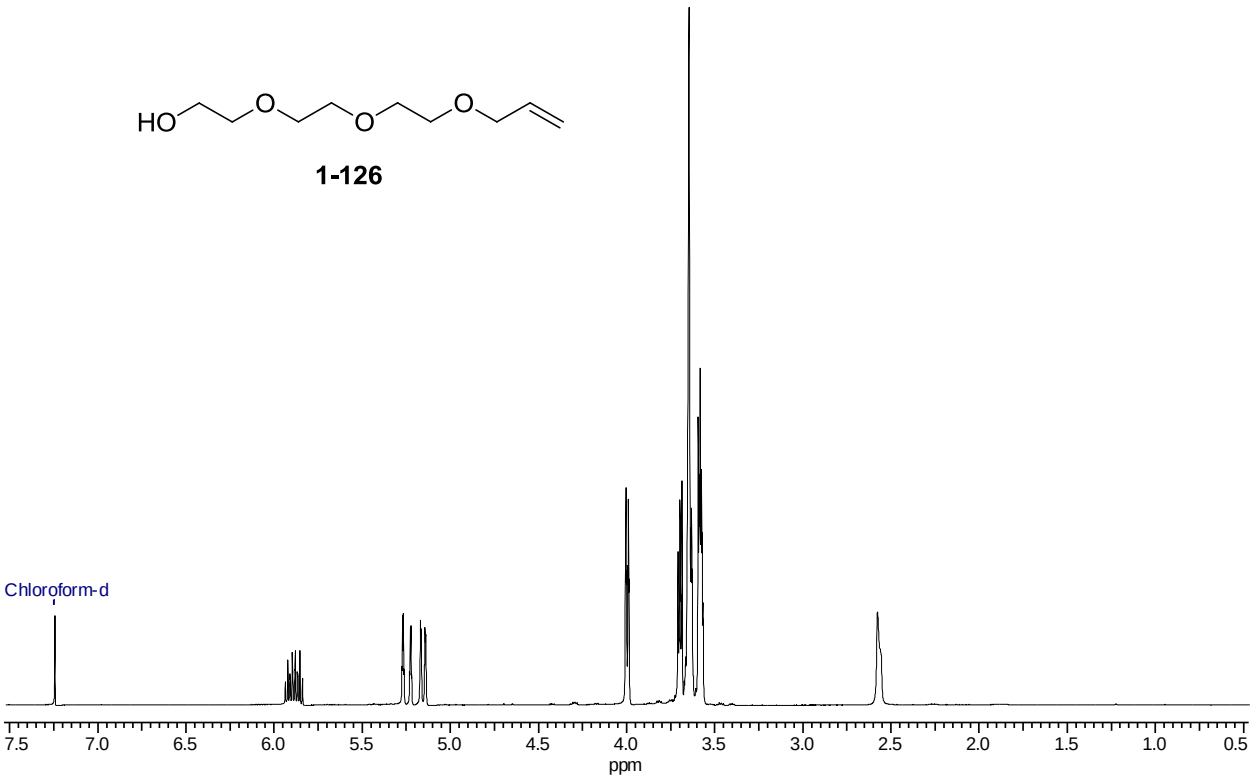


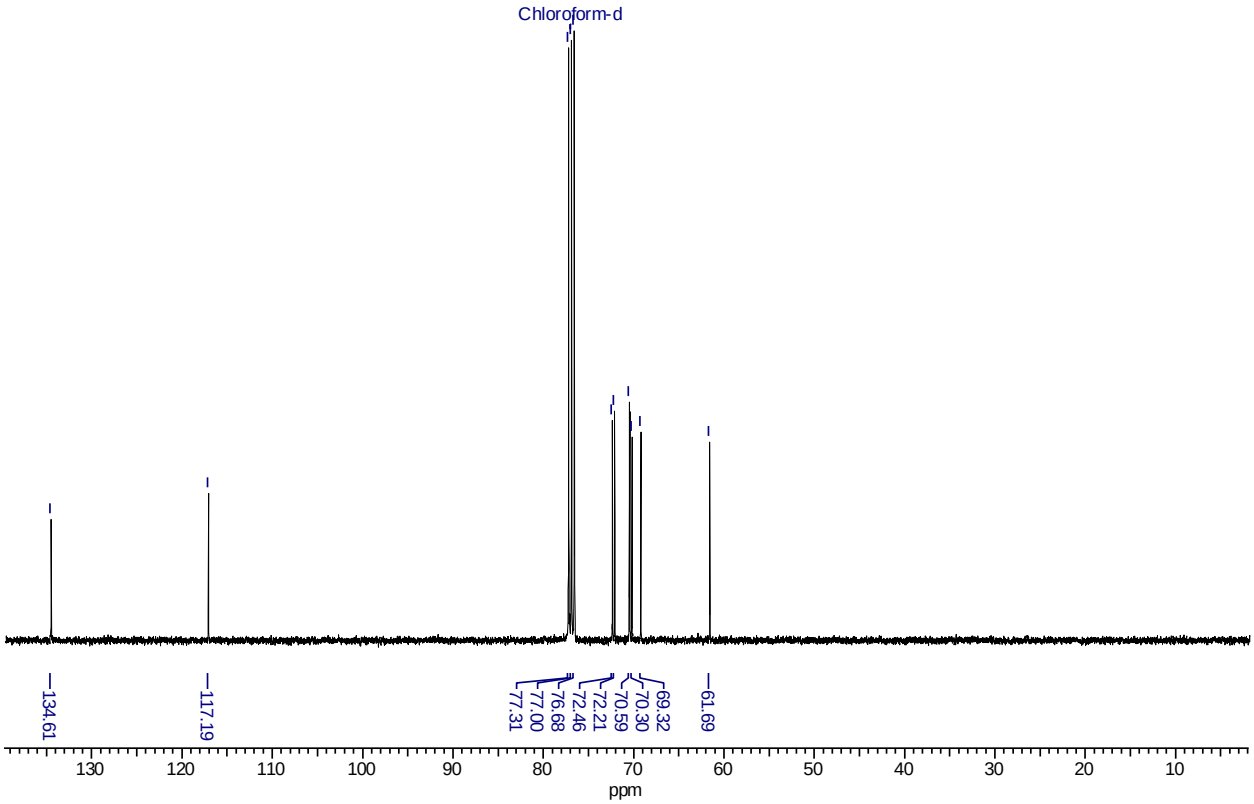

H2N
TBDPSO
O
O
O

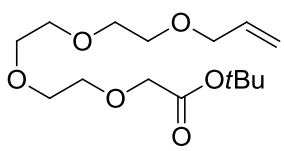
1-125

Chloroform-d
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm


Chloroform-d
142.49
135.60
133.69
133.12
129.57
129.27
127.60
115.99
77.00
72.42
70.68
70.63
70.49
70.11
63.41
31.35
26.79
19.17
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

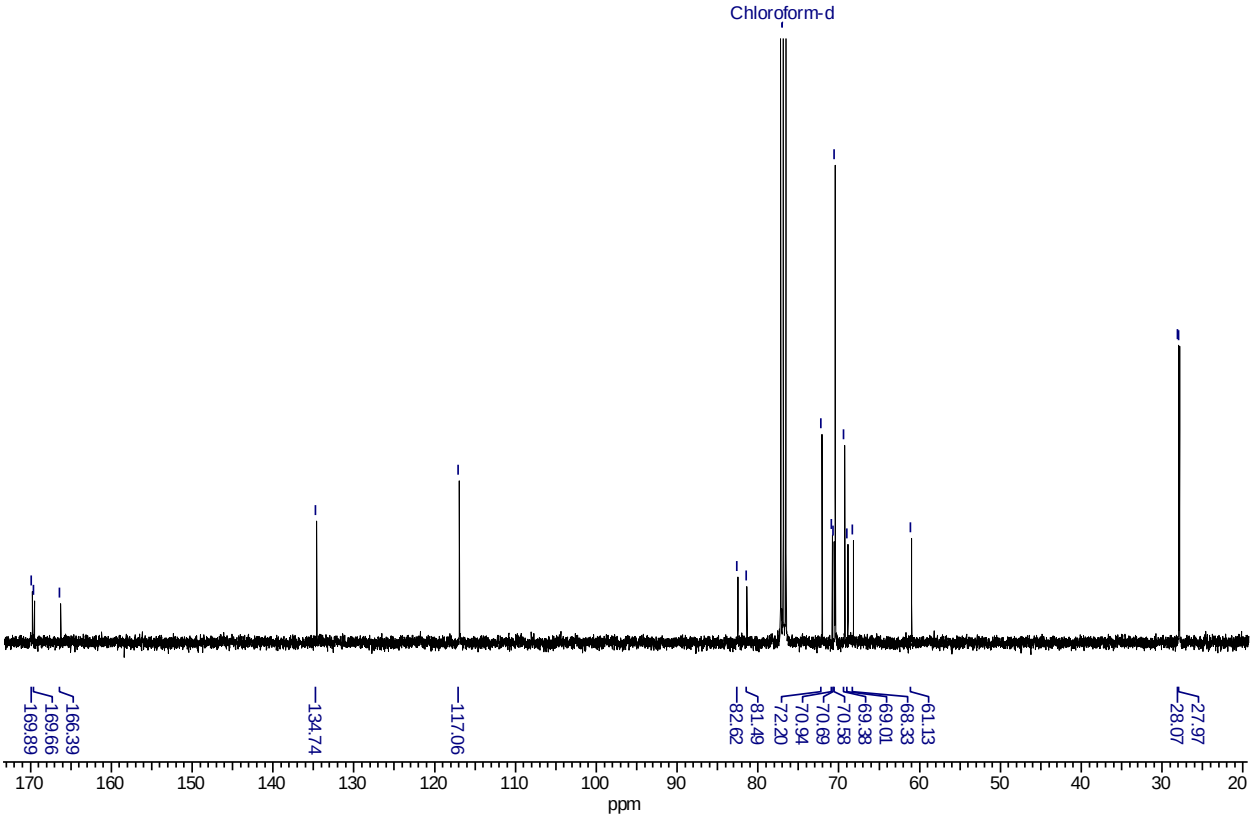

HO
O
O
O
1-126
Chloroform-d
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

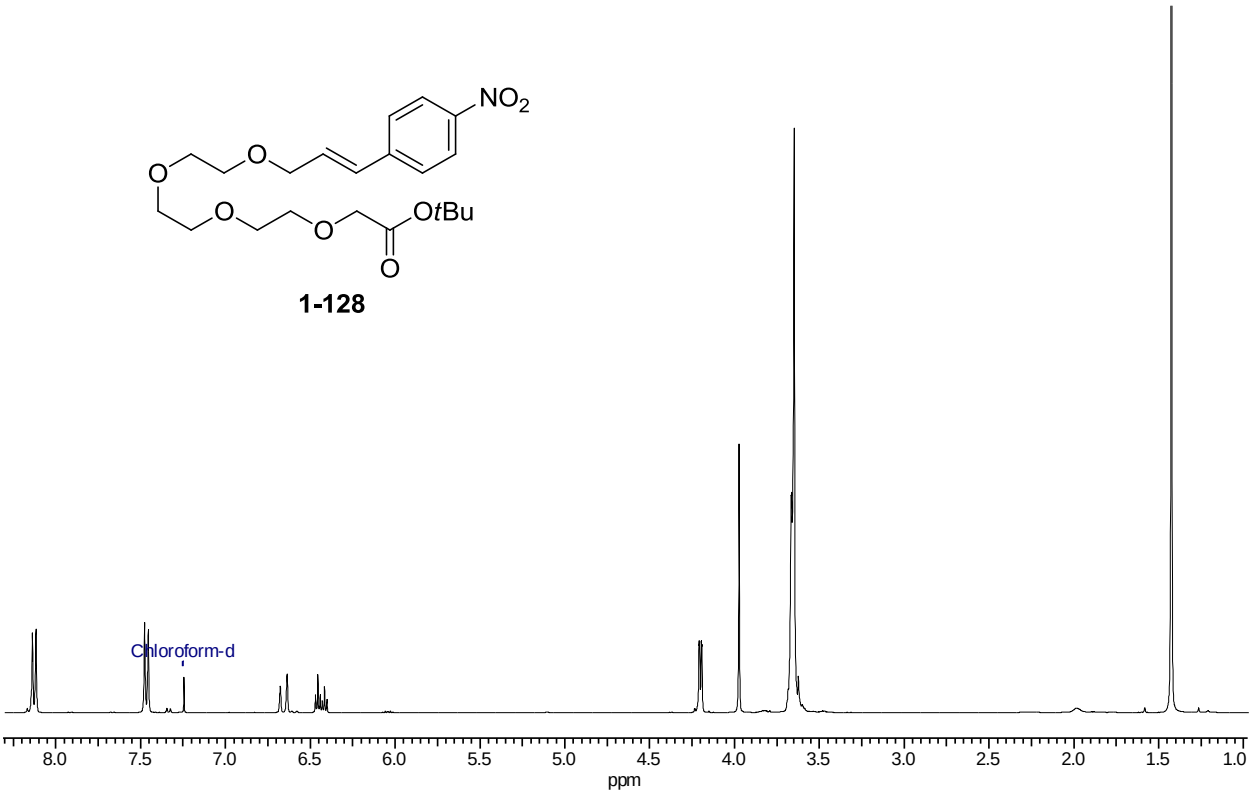

Chloroform-d
134.61
117.19
77.31
77.00
76.68
72.46
72.21
70.59
70.30
69.32
61.69
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

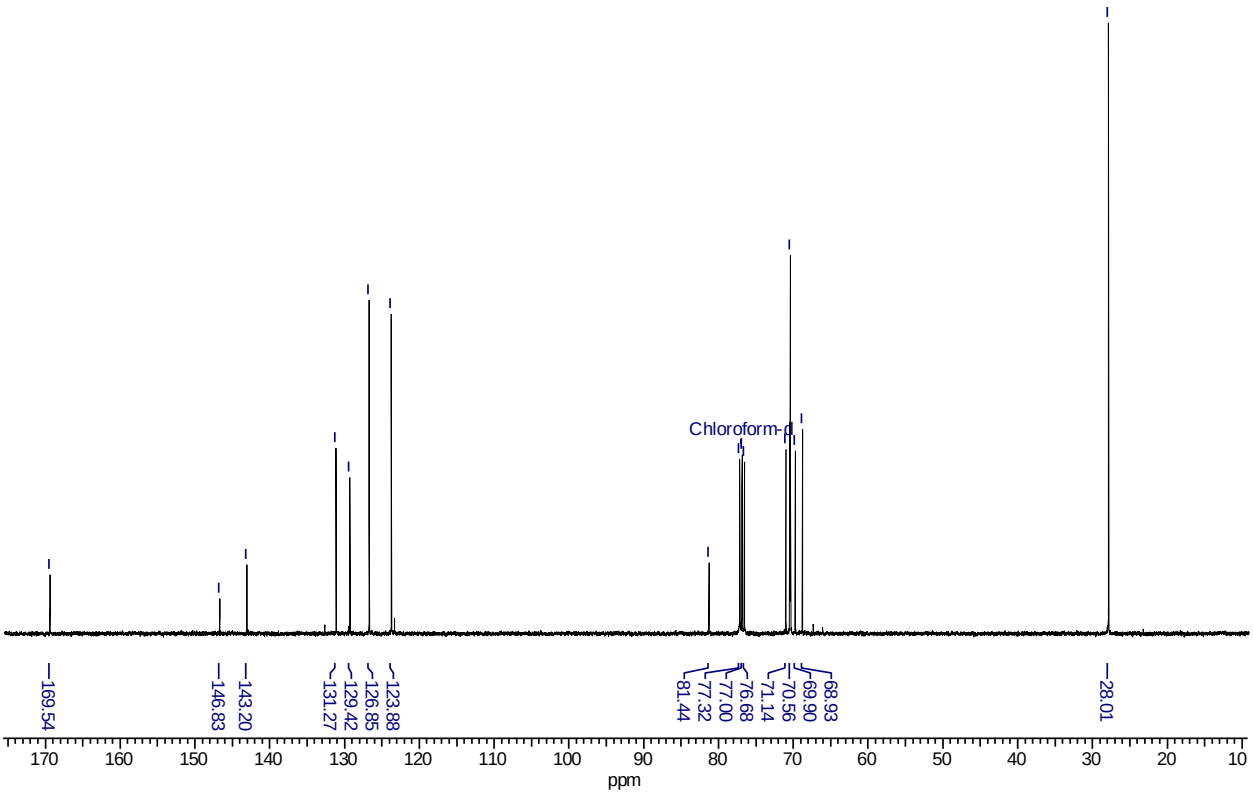

O
O
O
O
O
O
OtBu

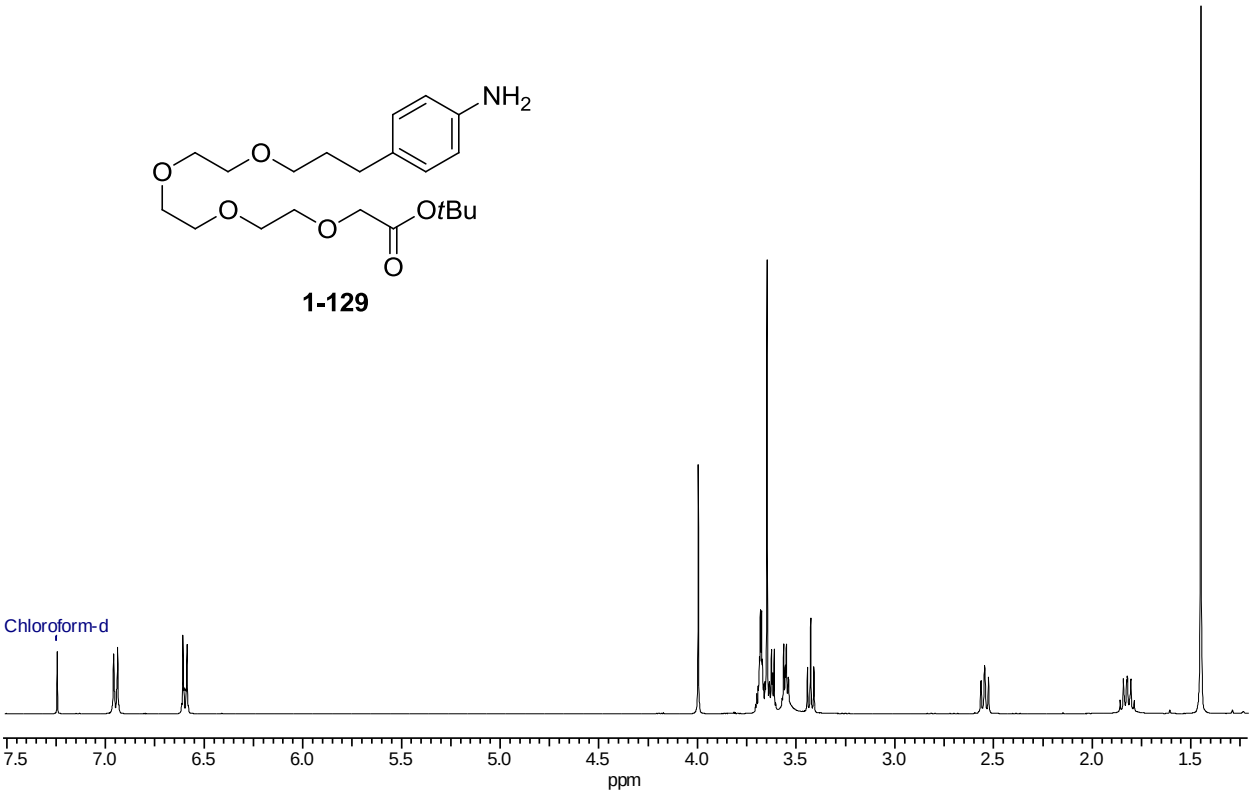
1-127

Chloroform-d
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm

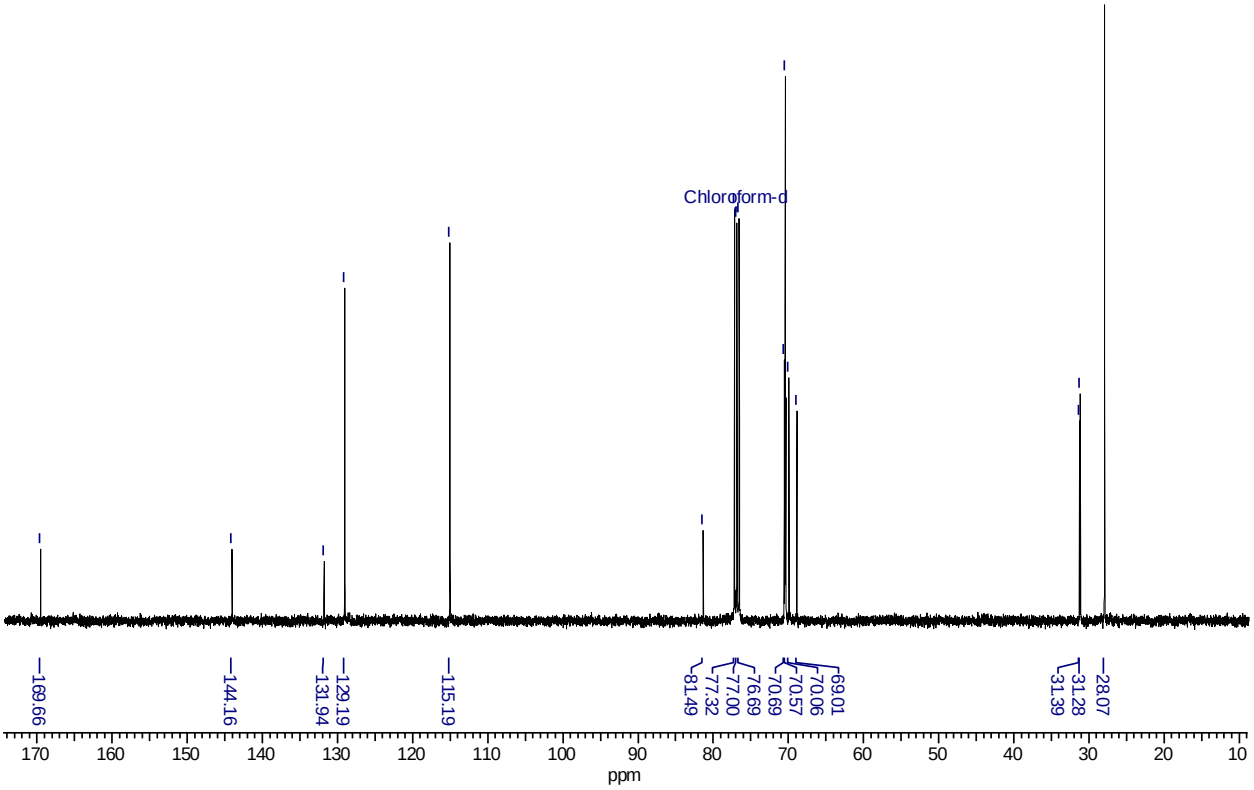

Chloroform-d
169.89
169.66
166.39
134.74
117.06
82.62
81.49
72.20
70.94
70.69
70.58
69.38
69.01
68.33
61.13
28.07
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

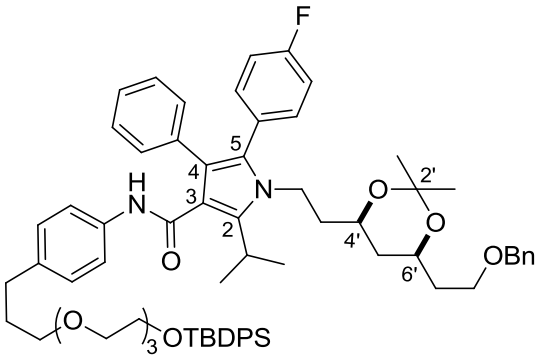

NO2
O
O
O
O
OtBu
O
1-128
Chloroform-d
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm


Chloroform-d
169.54
146.83
143.20
131.27
129.42
126.85
123.88
81.44
77.32
77.00
76.68
71.14
70.56
69.90
68.93
28.01
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


NH2
O
O
O
O
OtBu
O
Chloroform-d
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm

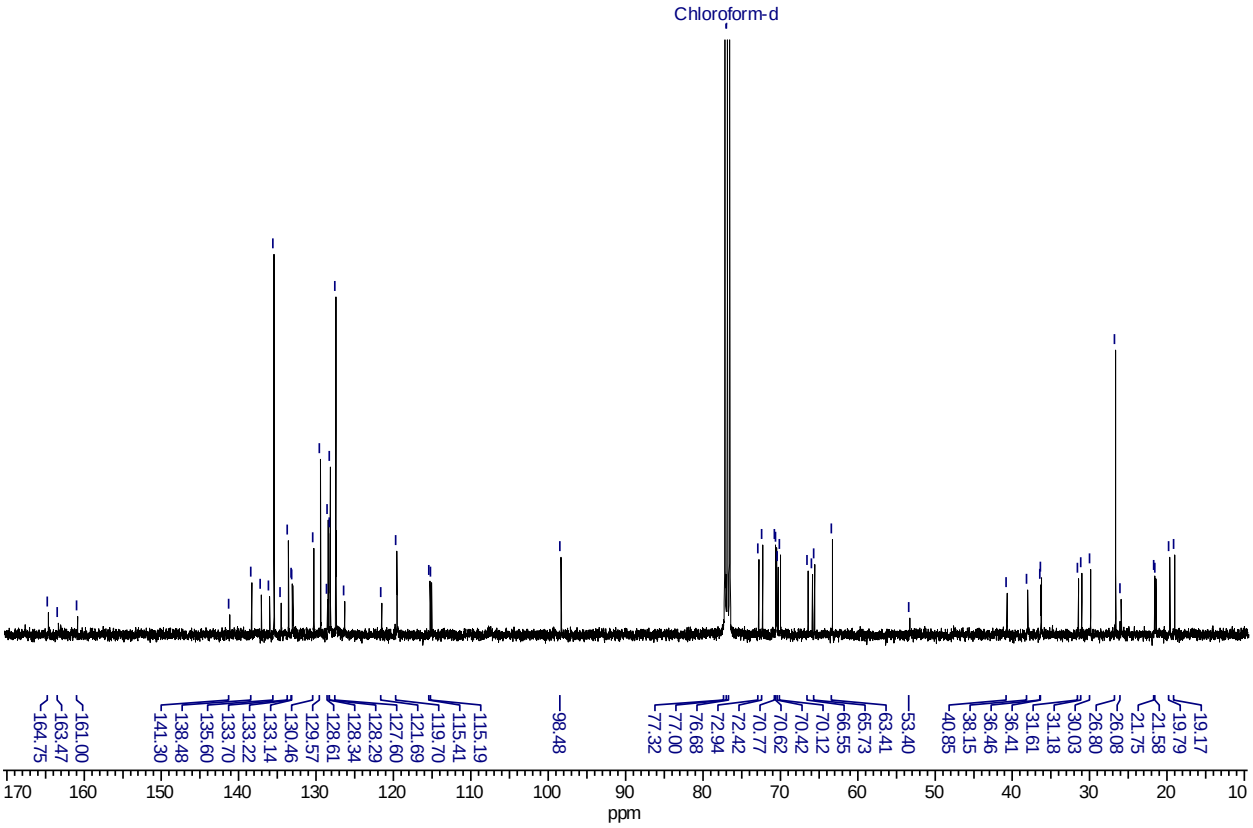
1-129

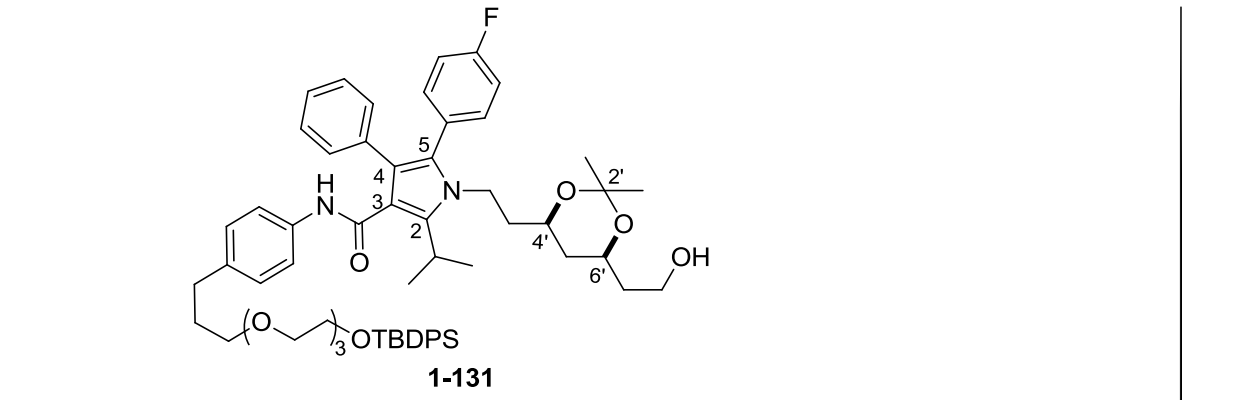

Chloroform-d
169.66
144.16
131.94
129.19
115.19
81.49
77.32
77.00
76.69
70.69
70.57
70.06
69.01
31.39
31.28
28.07
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


F
5
4
3
2
H
N
O
N
2'
O
O
4'
6'
OBn
O
3
OTBDPS

1-130

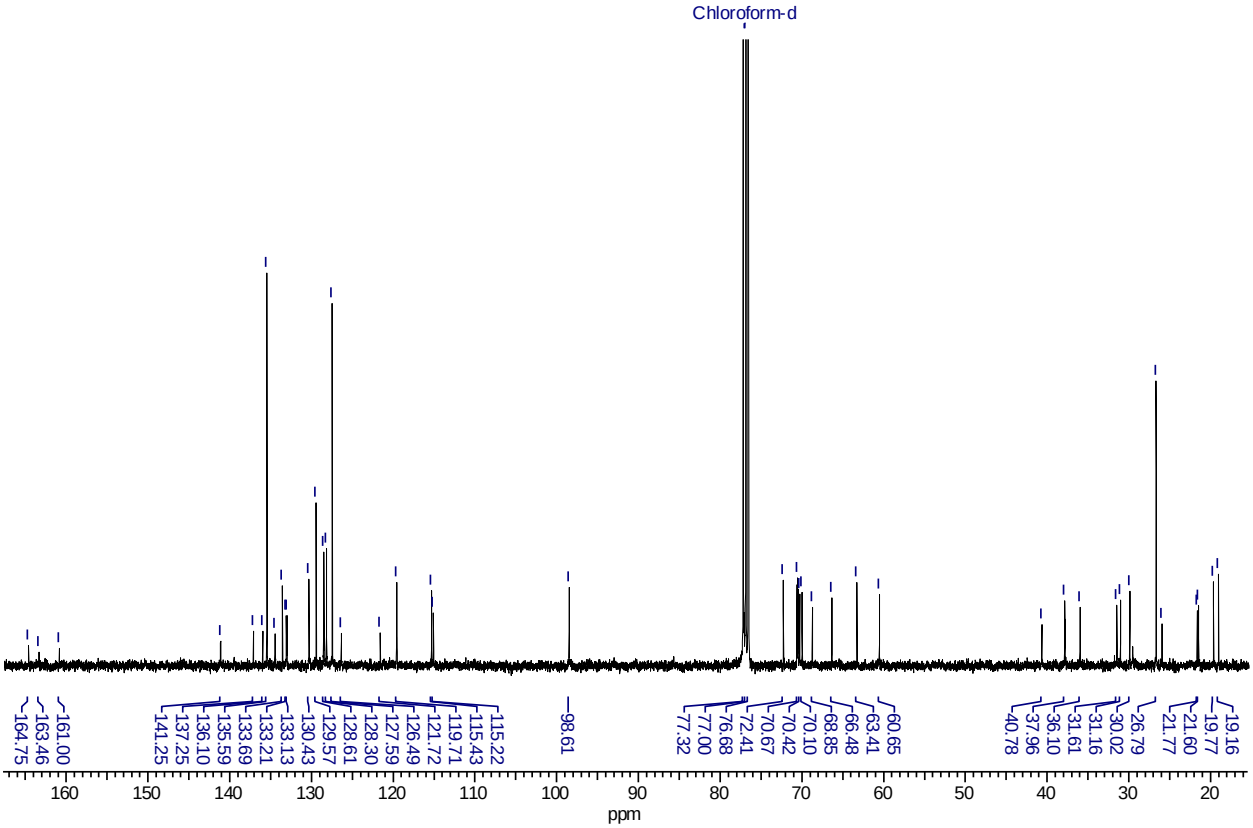
Chloroform-d
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

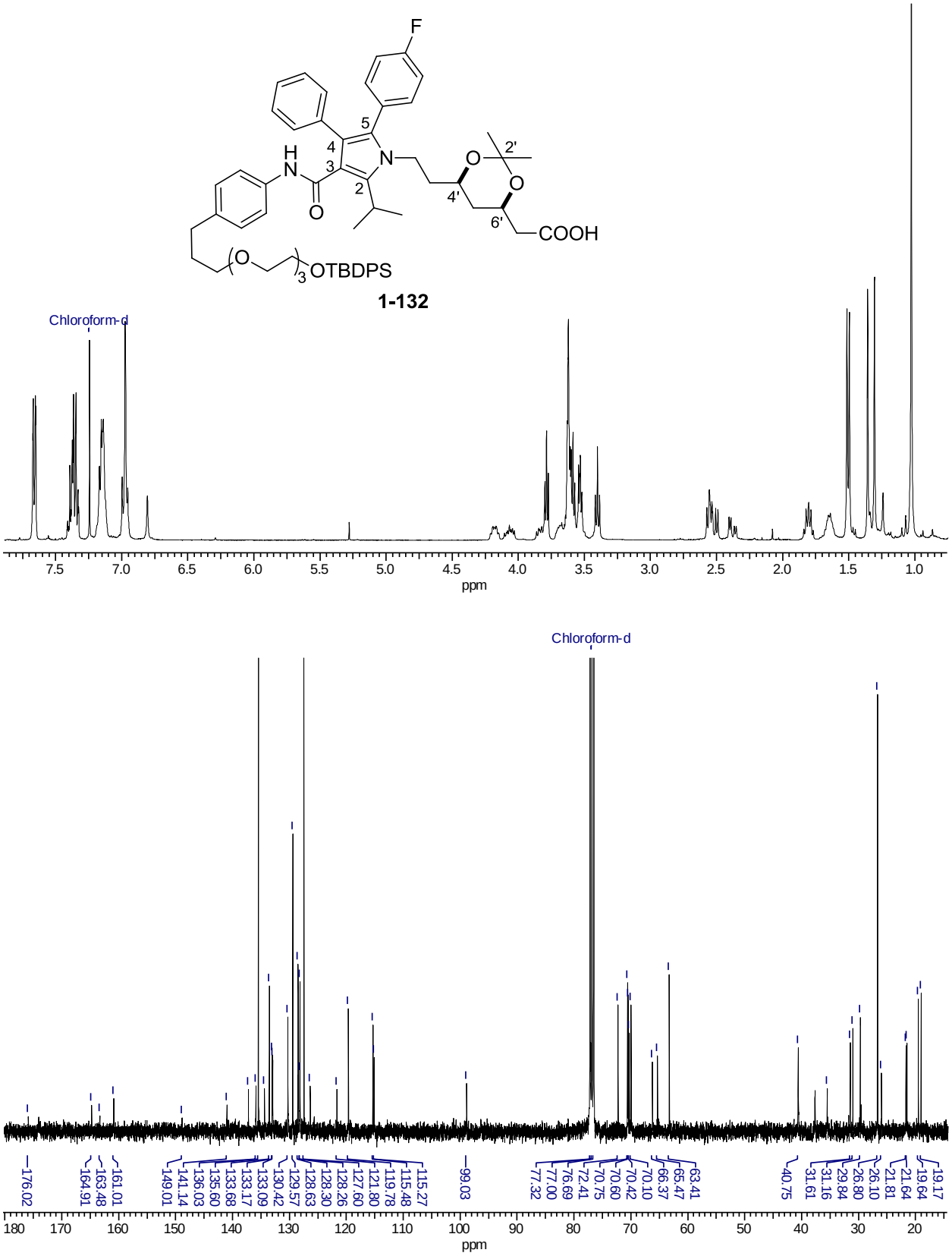

Chloroform-d
164.75
163.47
161.00
141.30
138.48
135.60
133.70
133.22
133.14
130.46
129.57
128.61
128.34
128.29
127.60
121.69
119.70
115.41
115.19
98.48
77.32
77.00
76.68
72.94
72.42
70.77
70.62
70.42
70.12
66.55
65.73
63.41
53.40
40.85
38.15
36.46
36.41
31.61
31.18
30.03
26.80
26.08
21.75
21.58
19.79
19.17
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

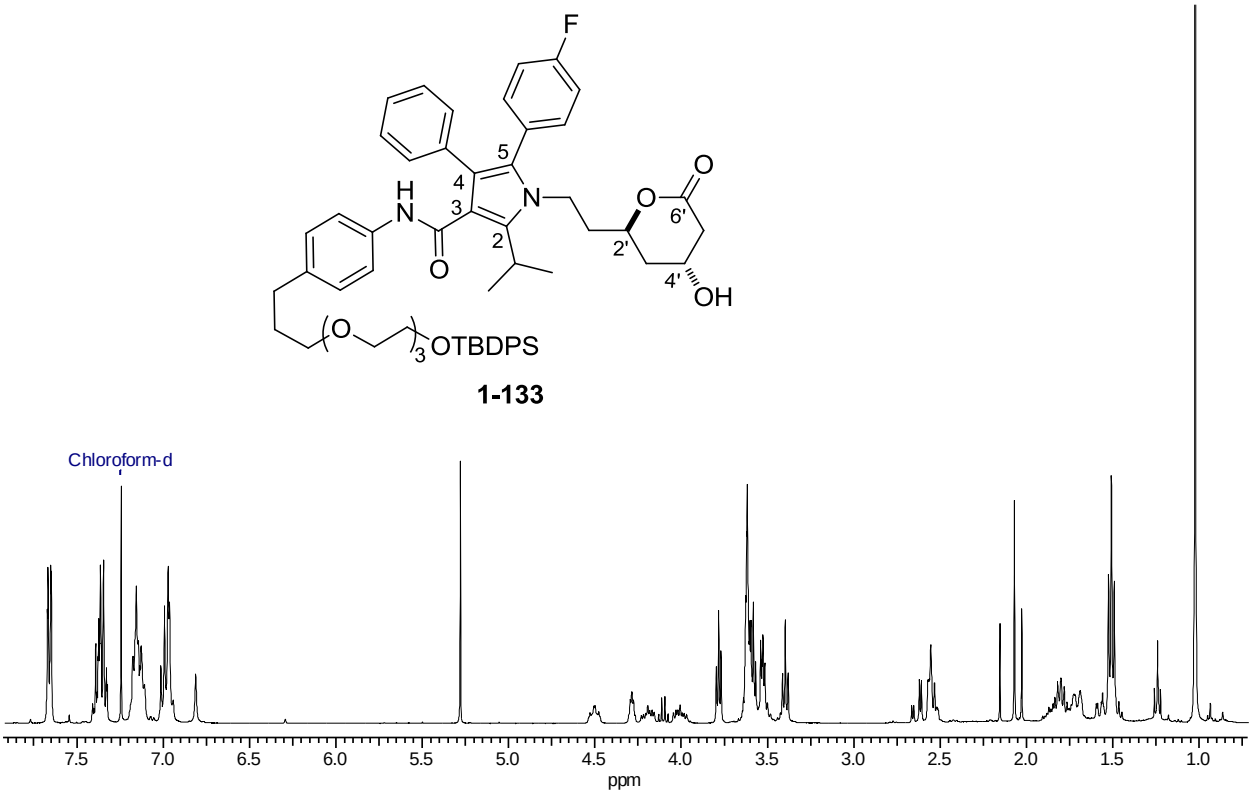

F
5
4
3
2
H
N
N
O
O
2'
O
4'
6'
OH
O
3
OTBDPS

1-131

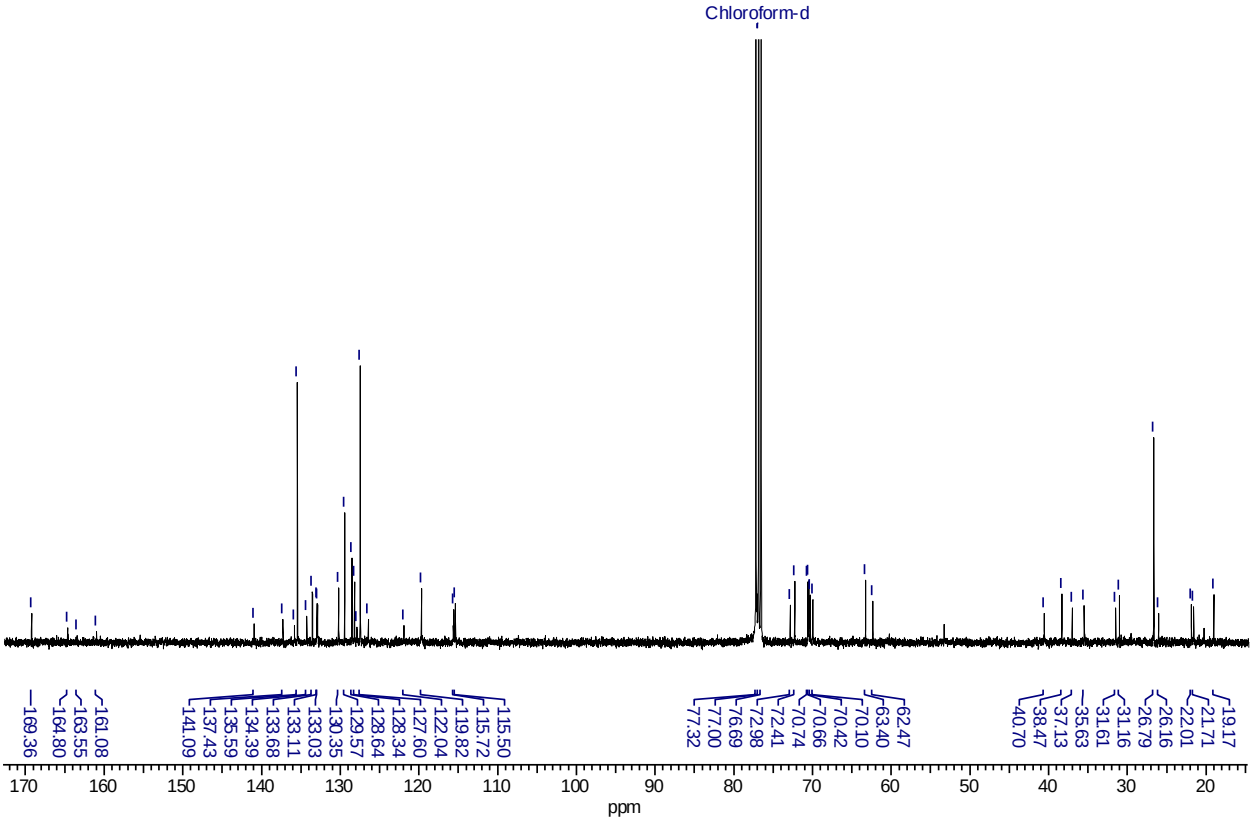
Chloroform-d
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

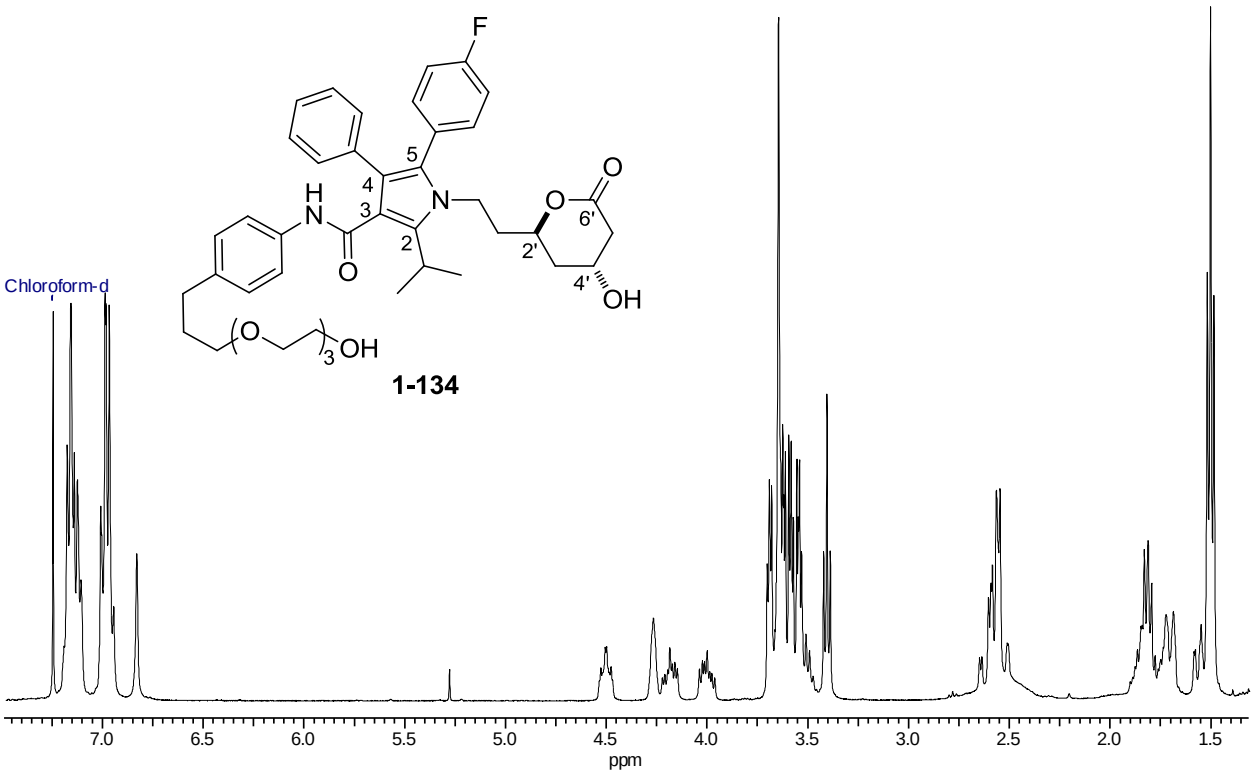

Chloroform-d
164.75
163.46
161.00
141.25
137.25
136.10
135.59
133.69
133.21
133.13
130.43
129.57
128.61
128.30
127.59
126.49
121.72
119.71
115.43
115.22
98.61
77.32
77.00
76.68
72.41
70.67
70.42
70.10
68.85
66.48
63.41
60.65
40.78
37.96
36.10
31.61
31.16
30.02
26.79
21.77
21.60
19.77
19.16
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm


F
5
4
3
2
H
N
N
O
O
2'
O
4'
6'
COOH
O
3
OTBDPS
1-132
Chloroform-d
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
Chloroform-d
176.02
164.91
163.48
161.01
149.01
141.14
136.03
135.60
133.68
133.17
133.09
130.42
129.57
128.63
128.30
128.26
127.60
121.80
119.78
115.48
115.27
99.03
77.32
77.00
76.69
72.41
70.75
70.60
70.42
70.10
66.37
65.47
63.41
40.75
31.61
31.16
29.84
26.80
26.10
21.81
21.64
19.64
19.17
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

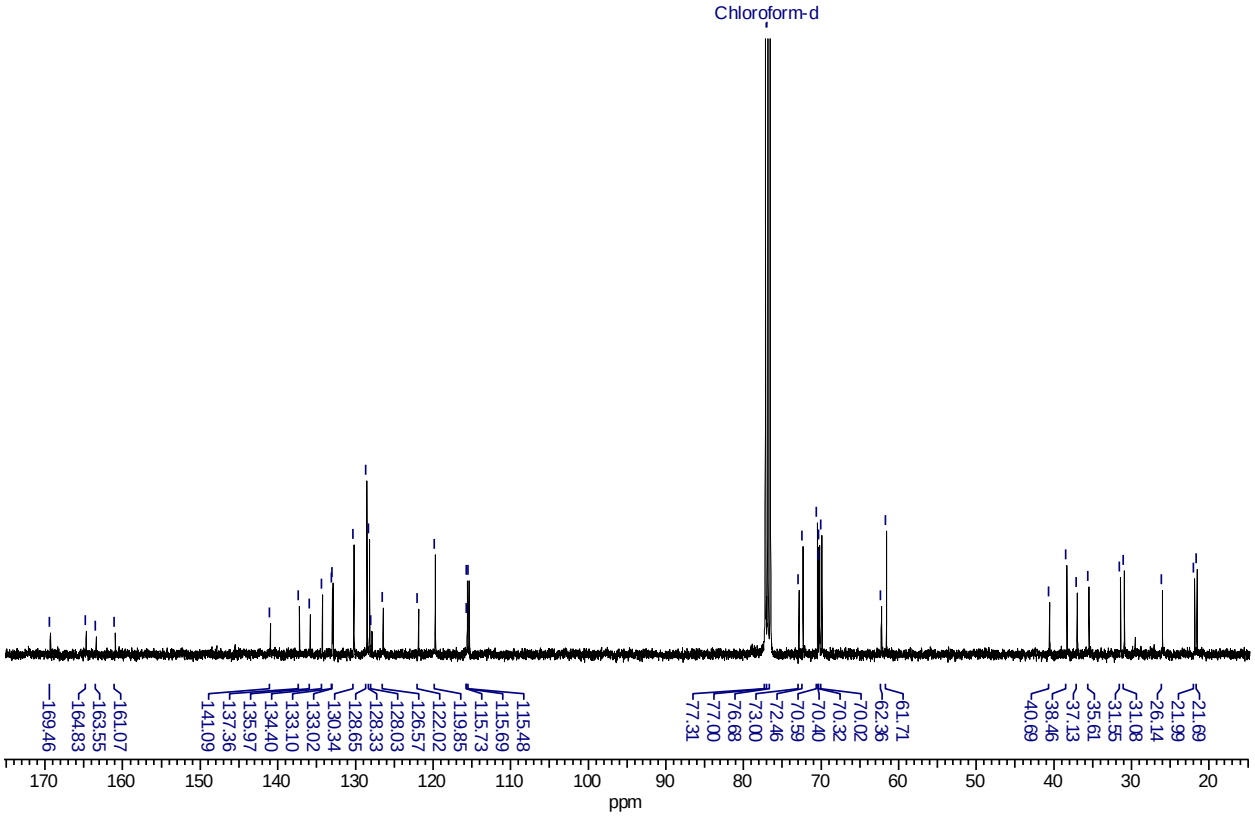

F
5
4
3
H
N
N
2
O
O
O
6'
2'
4'
OH
O
3
OTBDPS
Chloroform-d
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

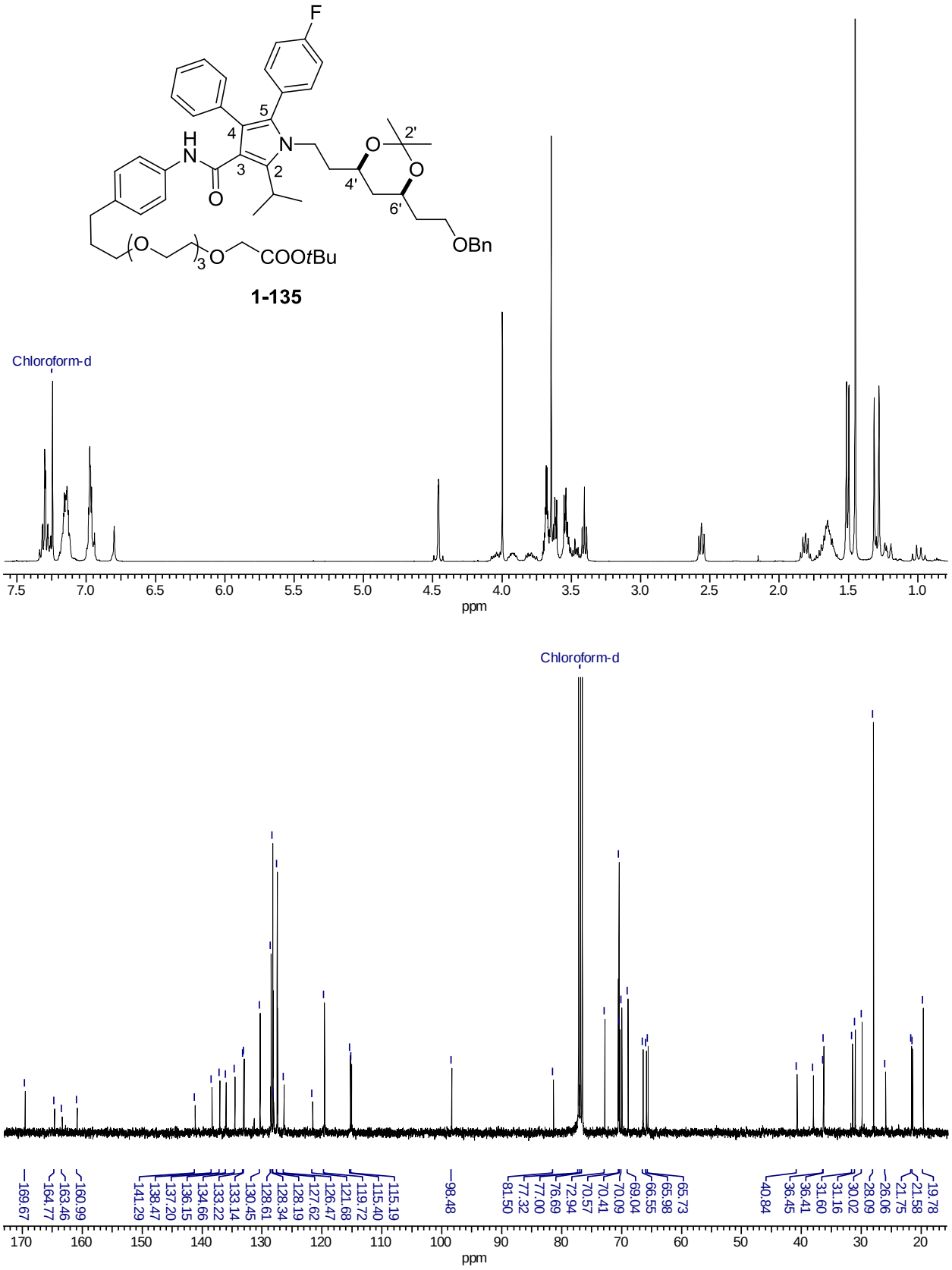
1-133

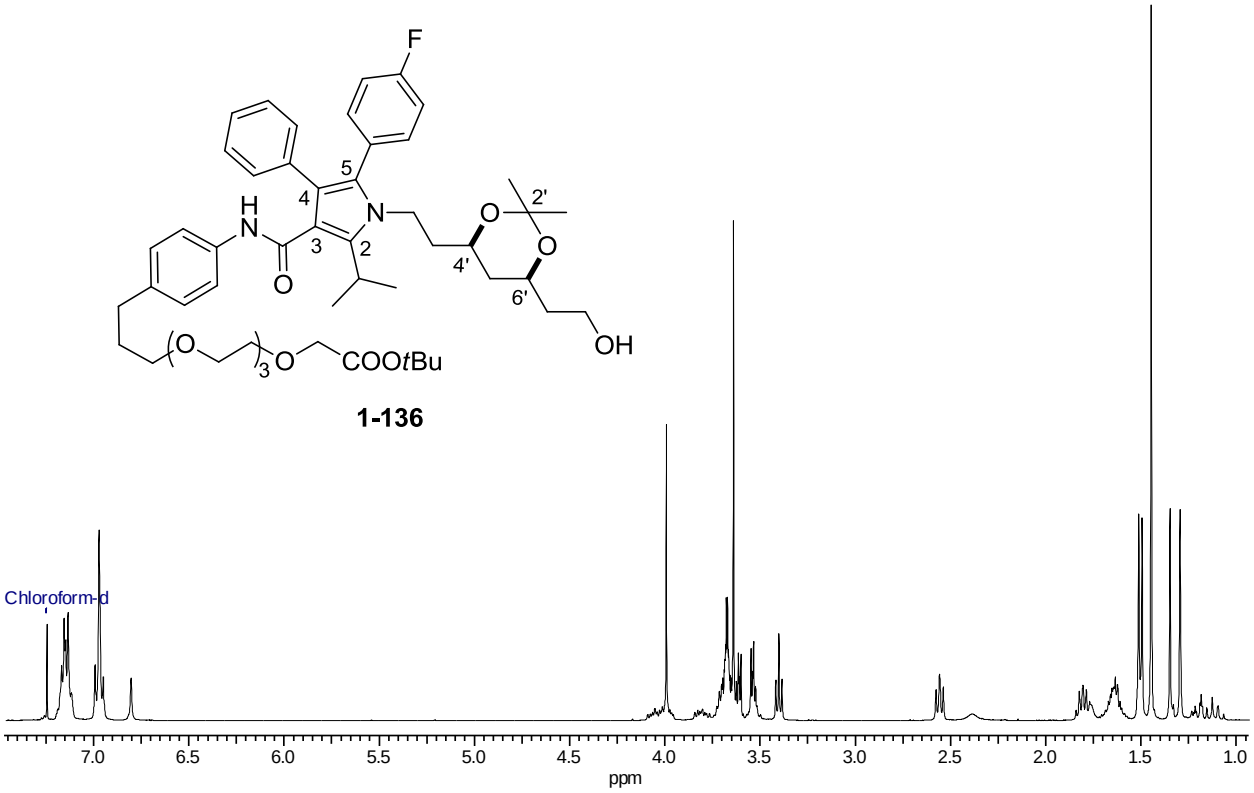

Chloroform-d
169.36
164.80
163.55
161.08
141.09
137.43
135.59
134.39
133.68
133.11
133.03
130.35
129.57
128.64
128.34
127.60
122.04
119.82
115.72
115.50
77.32
77.00
76.69
72.98
72.41
70.74
70.66
70.42
70.10
63.40
62.47
40.70
38.47
37.13
35.63
31.61
31.16
26.79
26.16
22.01
21.71
19.17
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

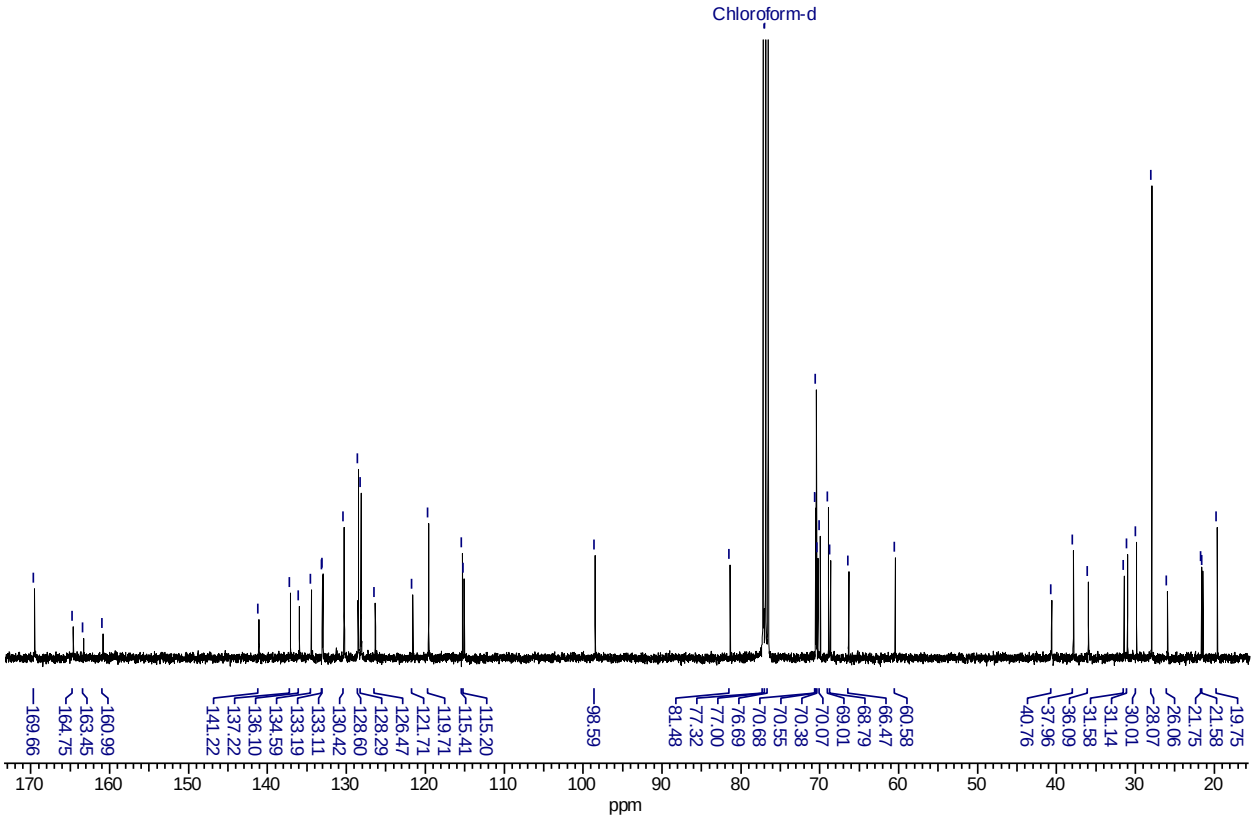

F
5
4
3
2
H
N
N
O
O
O
6'
2'
4'
OH
O
3
OH
Chloroform-d
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm

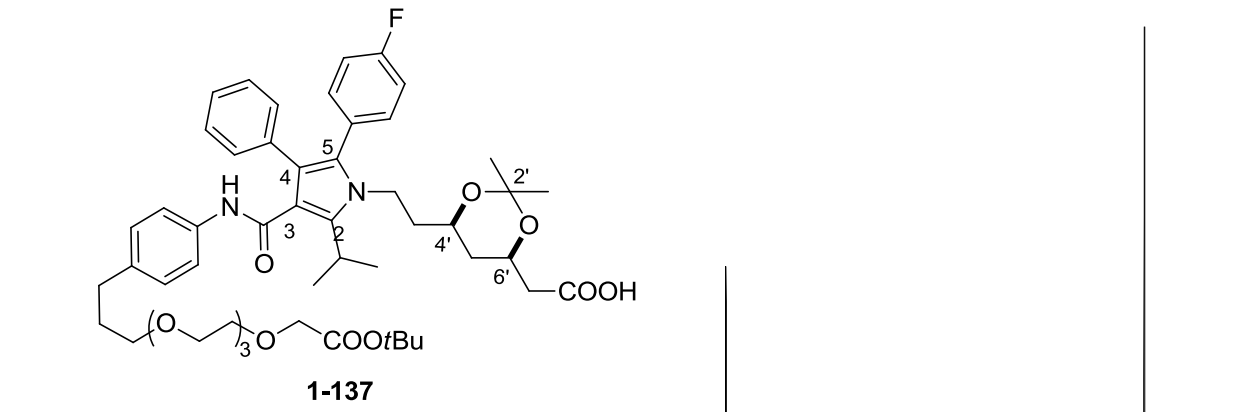
1-134


Chloroform-d
169.46
164.83
163.55
161.07
141.09
137.36
135.97
134.40
133.10
133.02
130.34
128.65
128.33
128.03
126.57
122.02
119.85
115.73
115.69
115.48
77.31
77.00
76.68
73.00
72.46
70.59
70.40
70.32
70.02
62.36
61.71
40.69
38.46
37.13
35.61
31.55
31.08
26.14
21.99
21.69
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm


F
5
4
H
N
3
2
N
O
2'
O
O
4'
6'
OBn
O
3
O
COO*t*Bu
1-135
Chloroform-d
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
ppm
Chloroform-d
169.67 164.77 163.46 160.99 141.29 138.47 137.20 136.15 134.66 133.22 133.14 130.45 128.61 128.34 128.19 127.62 126.47 121.68 119.72 115.40 115.19 98.48 81.50 77.32 77.00 76.69 72.94 70.57 70.41 70.09 69.04 66.55 65.98 65.73 40.84 36.45 36.41 31.60 31.16 30.02 28.09 26.06 21.75 21.58 19.78
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20
ppm

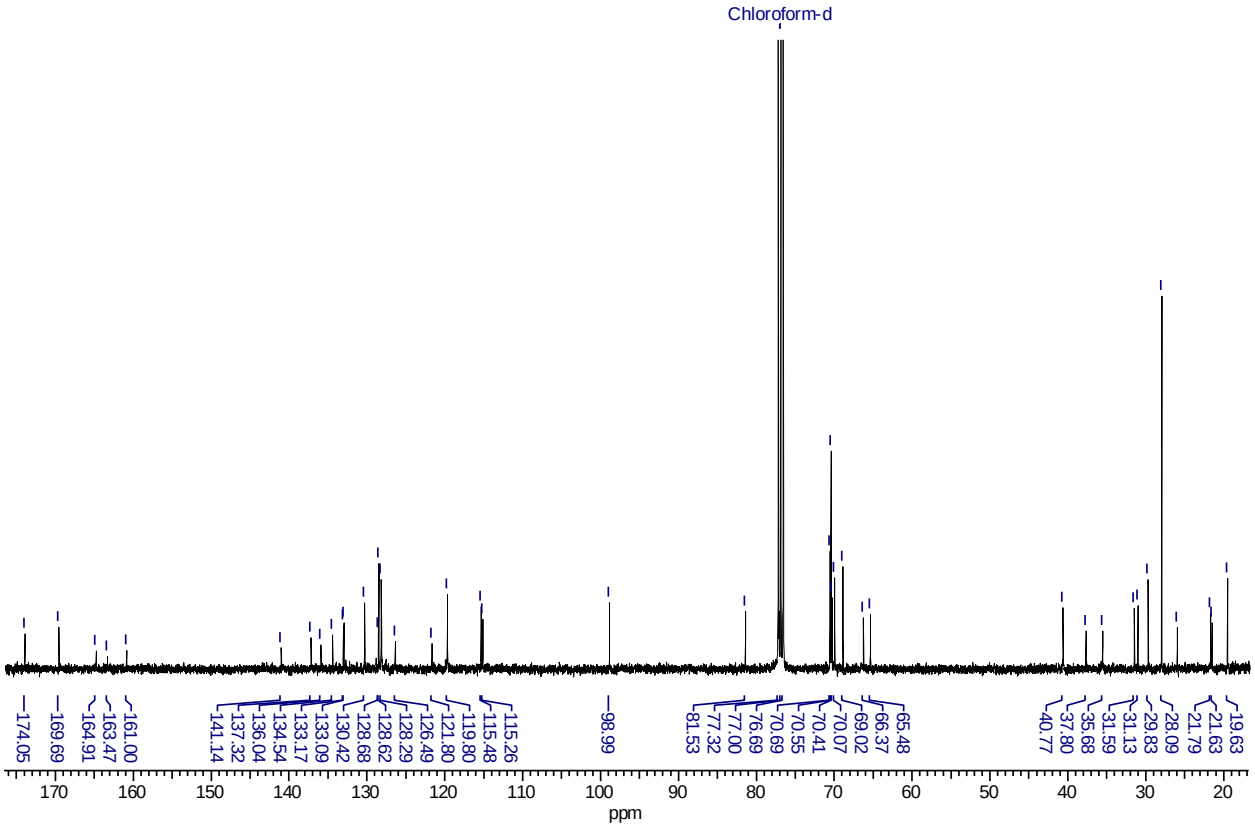

F
5
4
H
N
3
2
N
O
2'
O
4'
O
6'
OH
O
3
O
COO*t*Bu
1-136
Chloroform-d
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

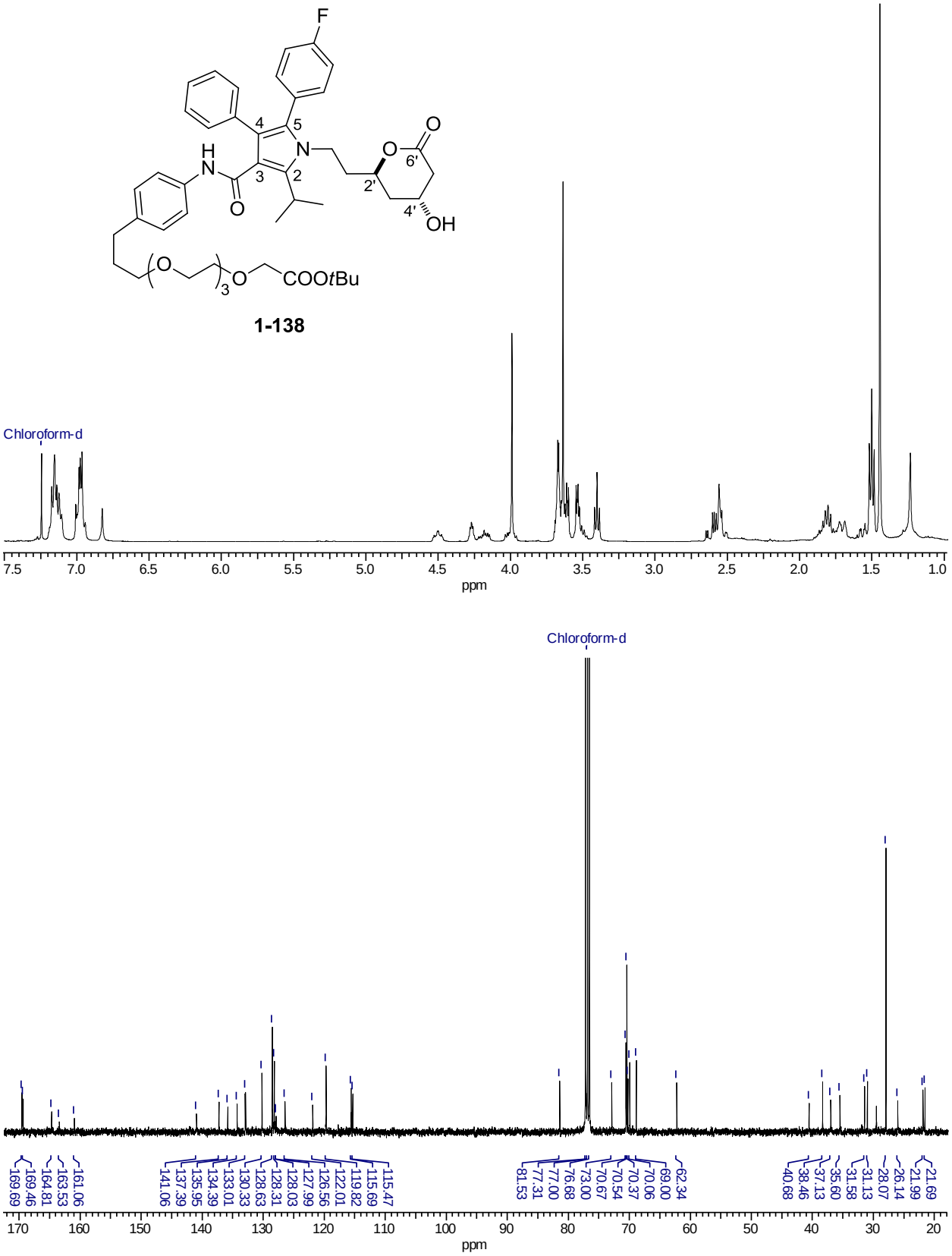

Chloroform-d
169.66
164.75
163.45
160.99
141.22
137.22
136.10
134.59
133.19
133.11
130.42
128.60
128.29
126.47
121.71
119.71
115.41
115.20
98.59
81.48
77.32
77.00
76.69
70.68
70.55
70.38
70.07
69.01
68.79
66.47
60.58
40.76
37.96
36.09
31.58
31.14
30.01
28.07
26.06
21.75
21.58
19.75
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

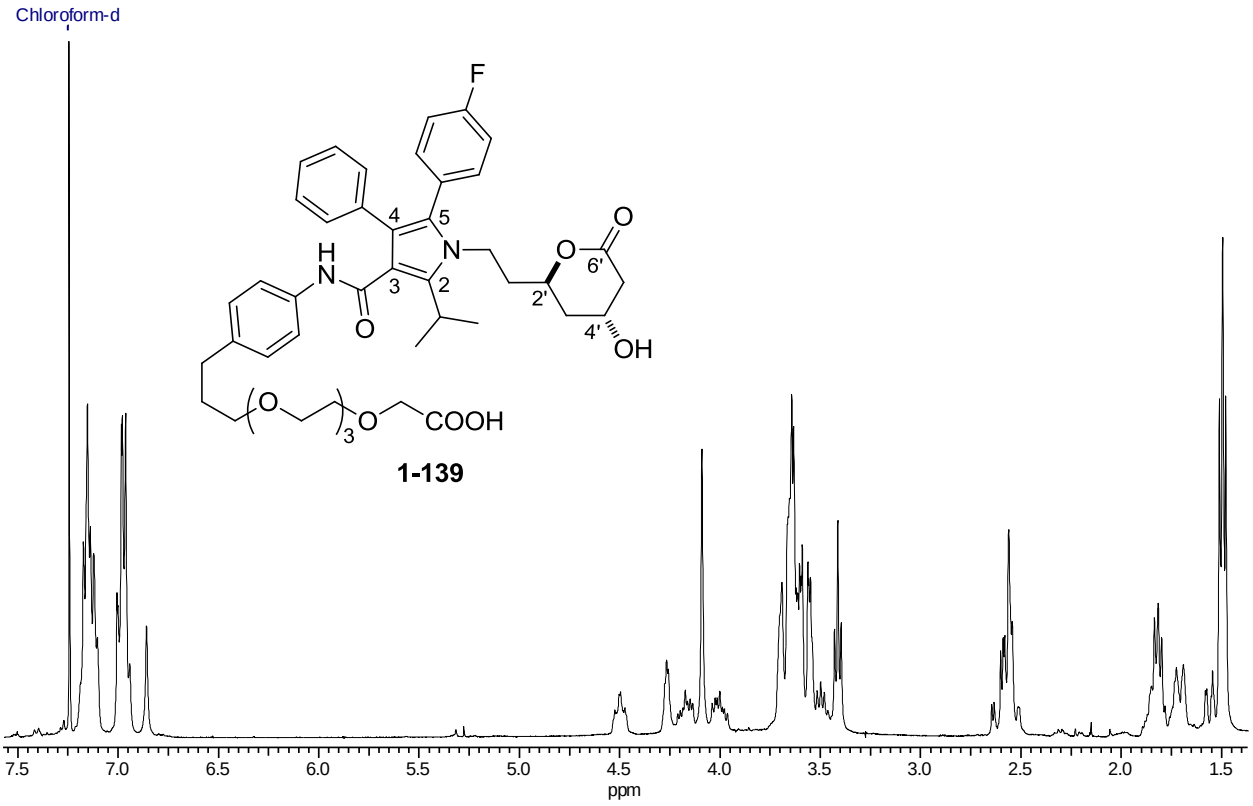

F
5
4
H
N
3
2
N
O
2'
O
O
4'
6'
COOH
O
O
3
O
COOtBu

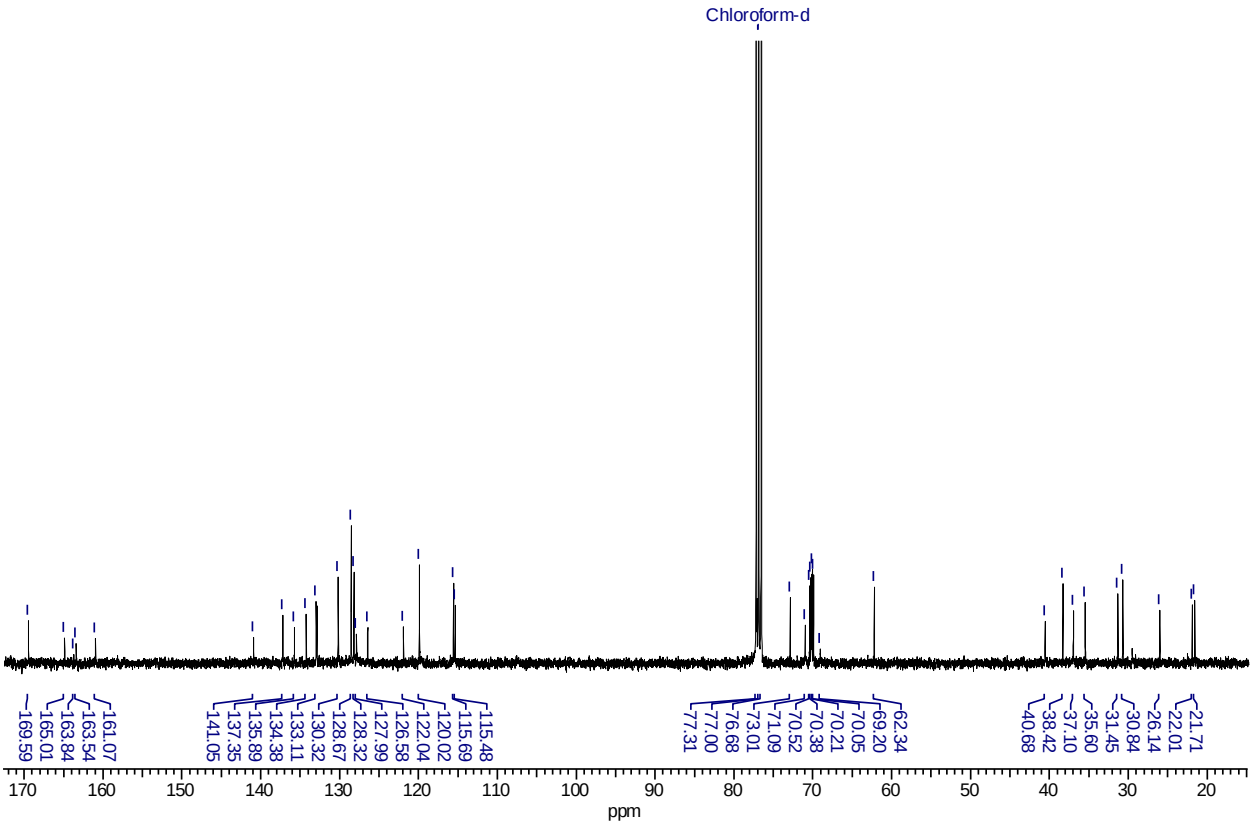
1-137

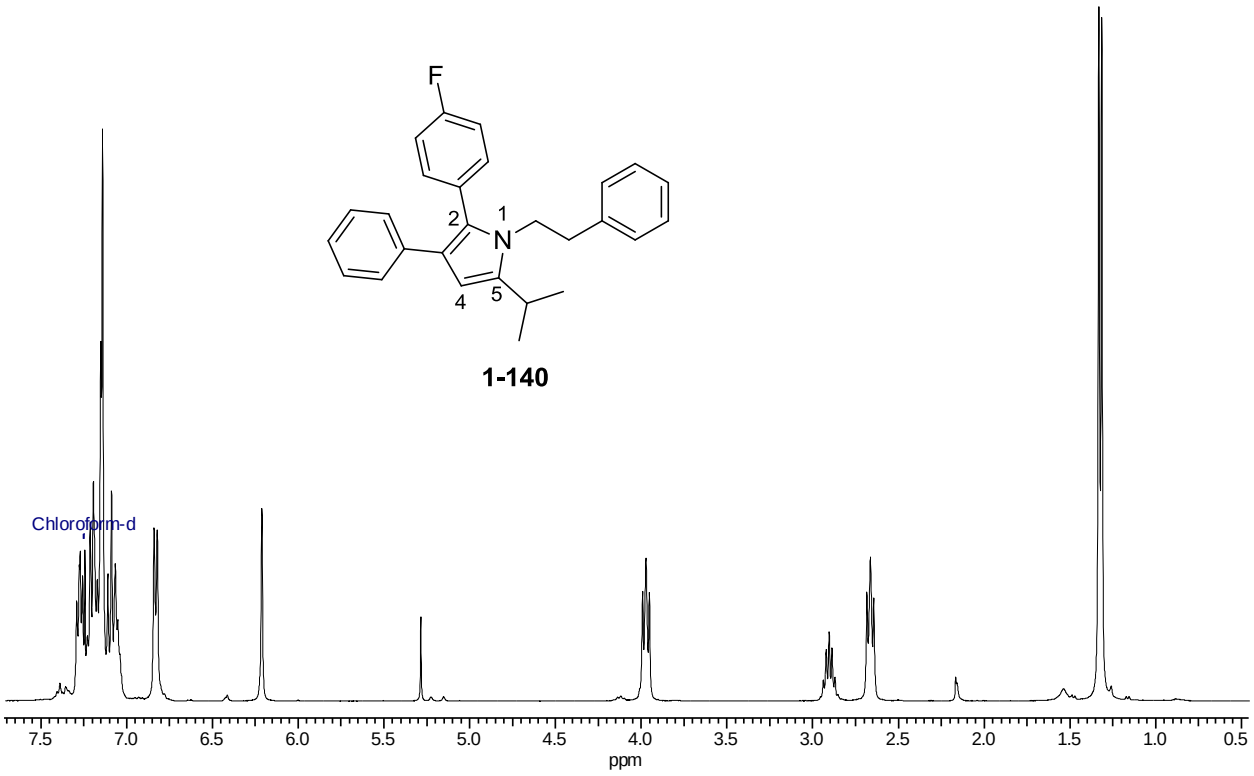
Chloroform-d
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

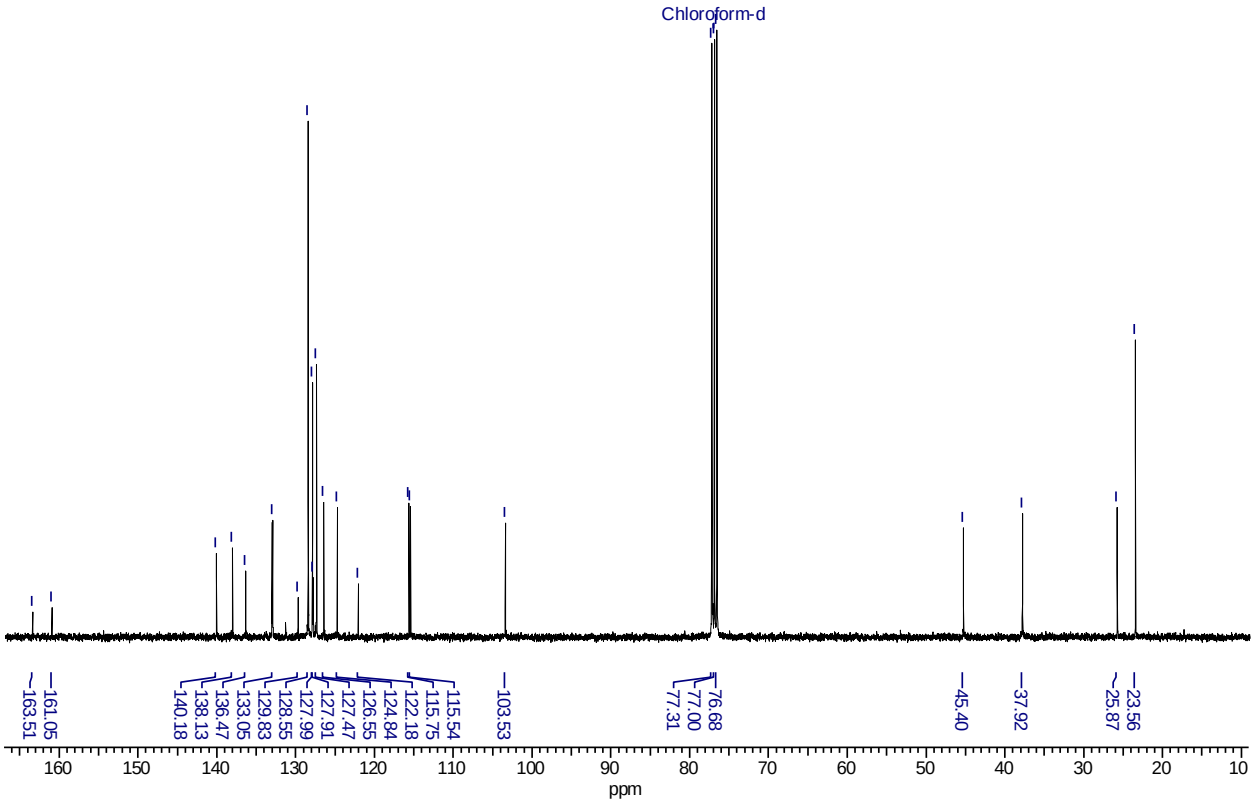

Chloroform-d
174.05
169.69
164.91
163.47
161.00
141.14
137.32
136.04
134.54
133.17
133.09
130.42
128.68
128.62
128.29
126.49
121.80
119.80
115.48
115.26
98.99
81.53
77.32
77.00
76.69
70.69
70.55
70.41
70.07
69.02
66.37
65.48
40.77
37.80
35.68
31.59
31.13
29.83
28.09
21.79
21.63
19.63
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

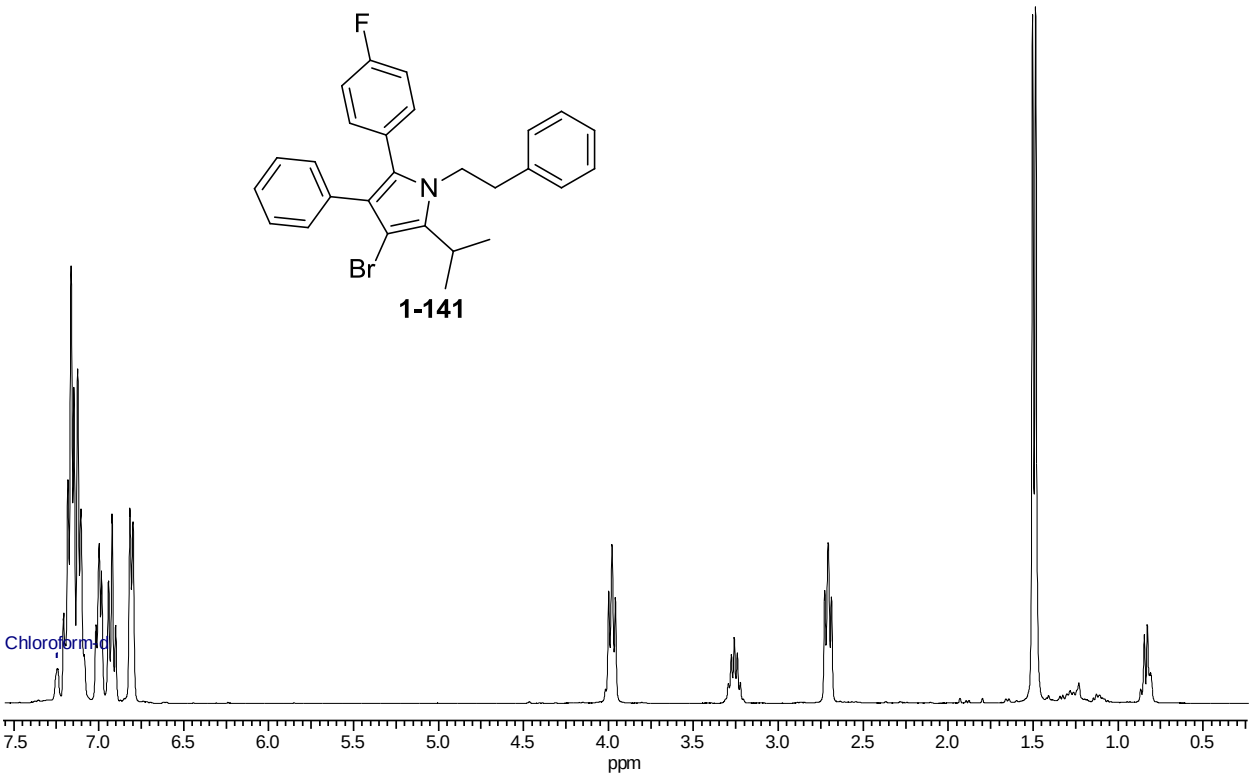

F
4
5
N
O
6'
H
N
3
2
2'
O
4'
OH
O
3
O
COO*t*Bu
1-138
Chloroform-d
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
ppm
Chloroform-d
169.69 169.46 164.81 163.53 161.06 141.06 137.39 135.95 134.39 133.01 130.33 128.63 128.31 128.03 127.99 126.56 122.01 119.82 115.69 115.47 81.53 77.31 77.00 76.68 73.00 70.67 70.54 70.37 70.06 69.00 62.34 40.68 38.46 37.13 35.60 31.58 31.13 28.07 26.14 21.99 21.69
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20
ppm

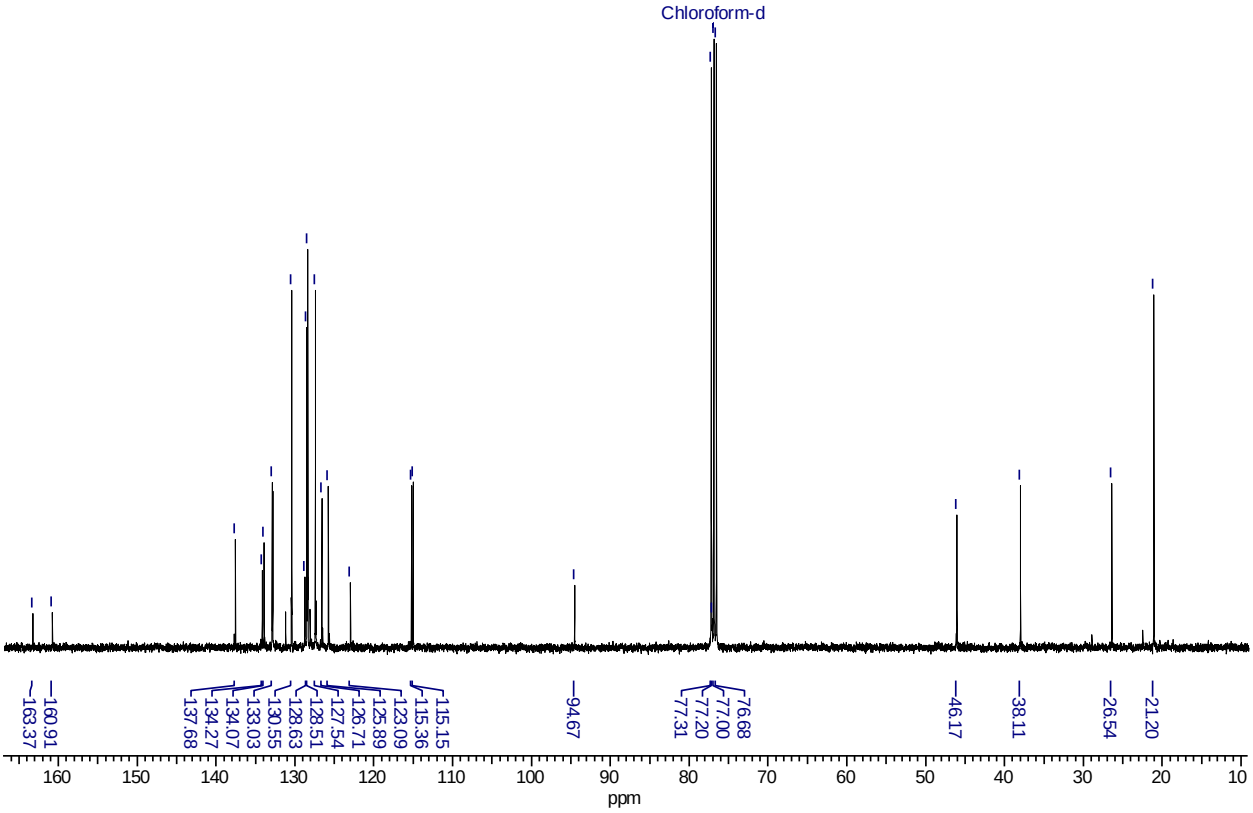

Chloroform-d
F
4
5
N
O
6'
H
N
3
2
2'
4'
OH
O
O
O
3
O
COOH
1-139
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm

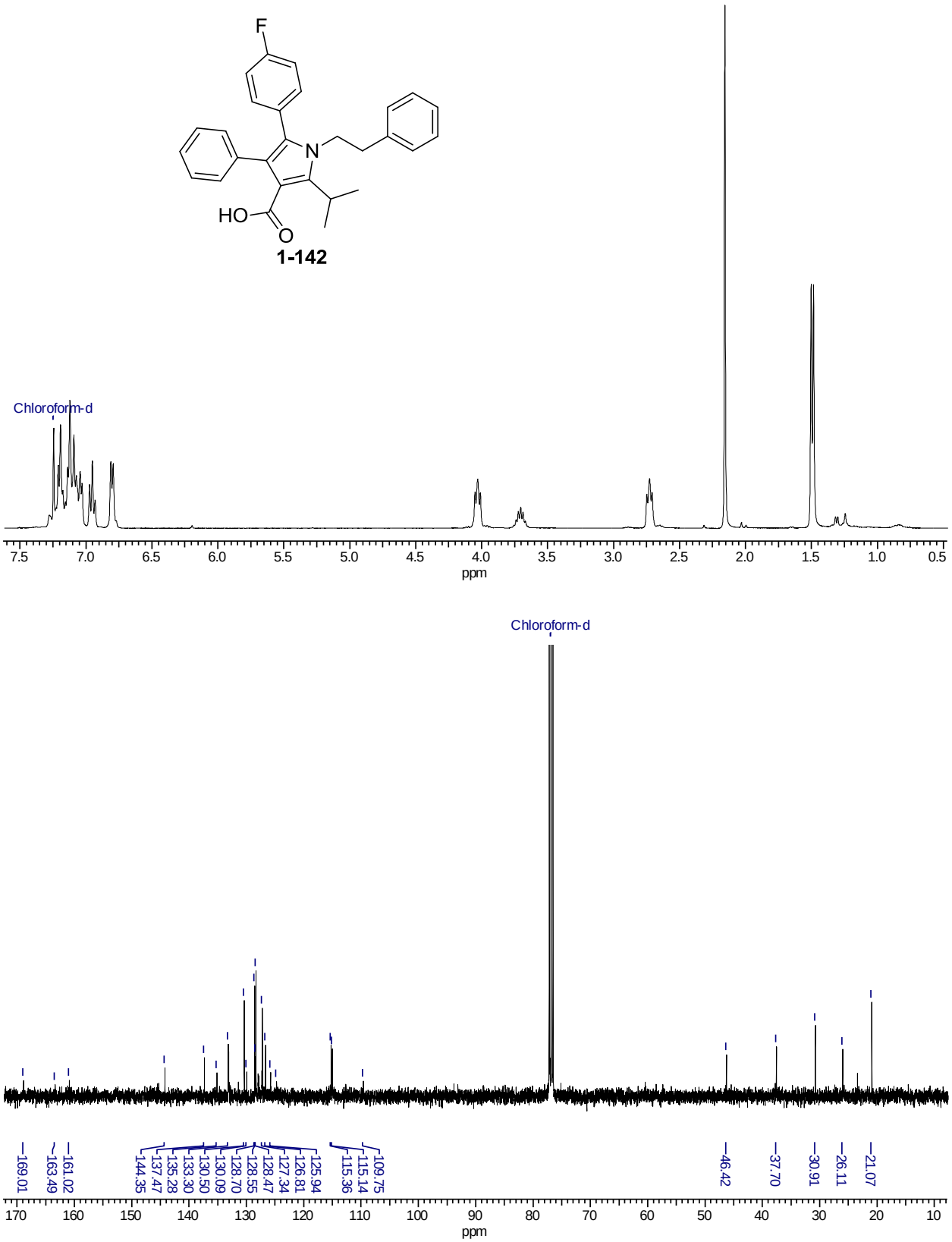

Chloroform-d
169.59
165.01
163.84
163.54
161.07
141.05
137.35
135.89
134.38
133.11
130.32
128.67
128.32
127.99
126.58
122.04
120.02
115.69
115.48
77.31
77.00
76.68
73.01
71.09
70.52
70.38
70.21
70.05
69.20
62.34
40.68
38.42
37.10
35.60
31.45
30.84
26.14
22.01
21.71
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

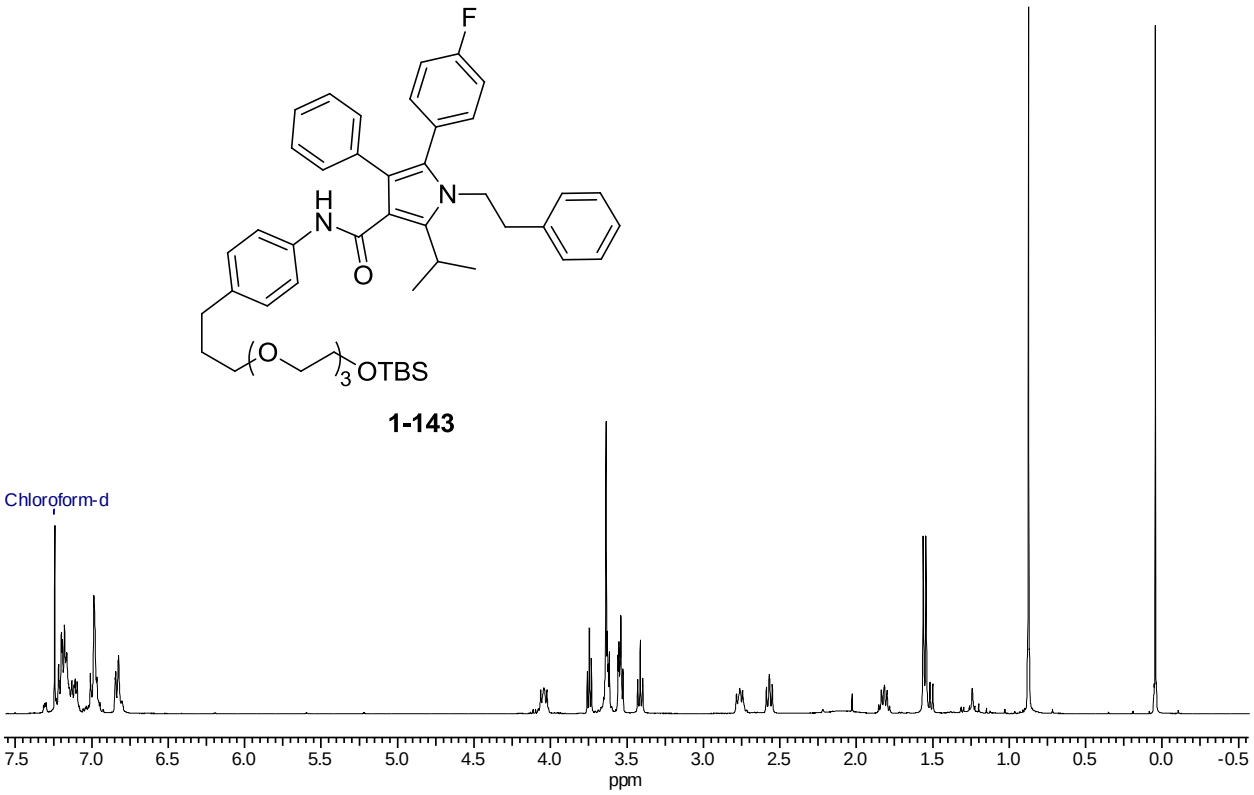

F
2
1
N
4
5
1-140
Chloroform-d
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

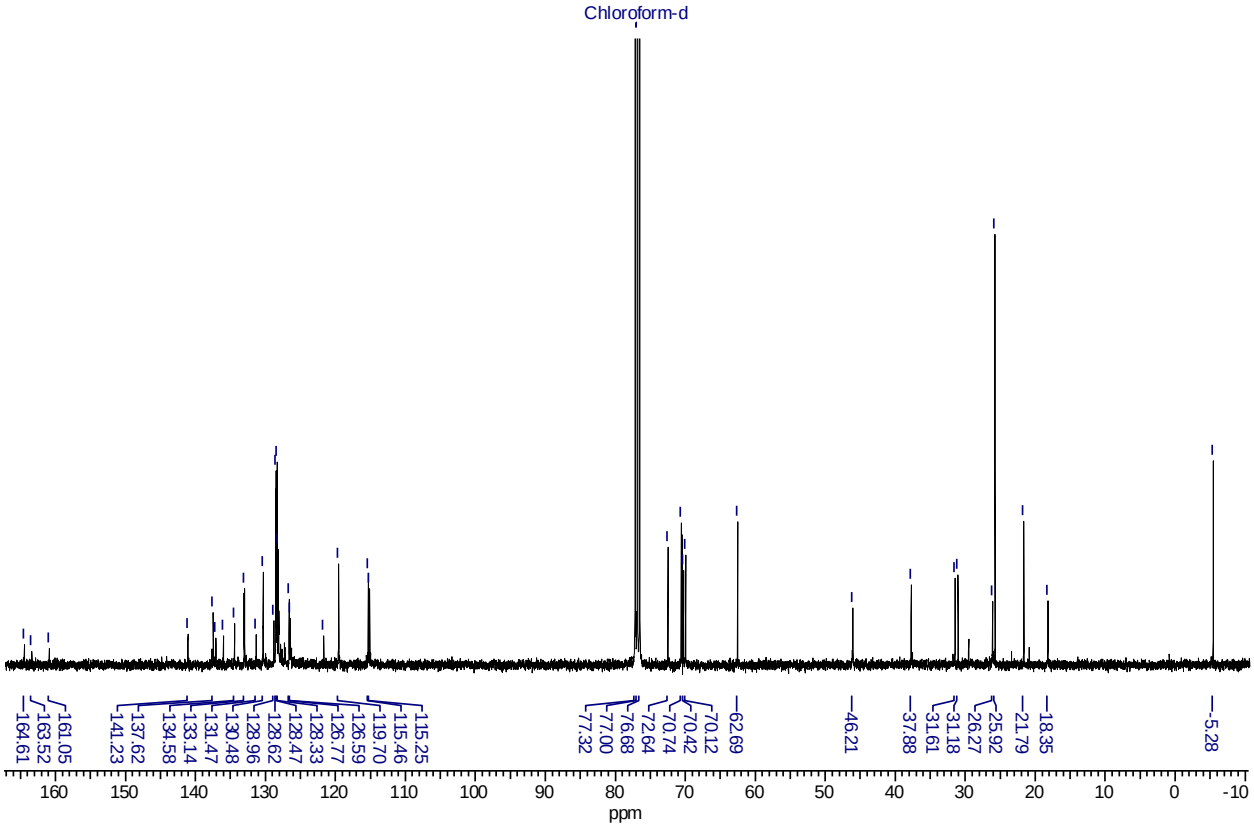

Chloroform-d
163.51
161.05
140.18
138.13
136.47
133.05
129.83
128.55
127.99
127.91
127.47
126.55
124.84
122.18
115.75
115.54
103.53
77.31
77.00
76.68
45.40
37.92
25.87
23.56
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

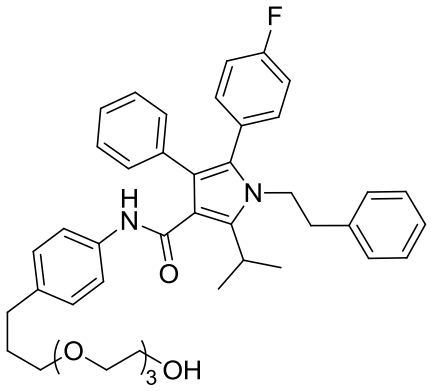

F
N
Br
1-141
Chloroform-d
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm


Chloroform-d
163.37
160.91
137.68
134.27
134.07
133.03
130.55
128.63
128.51
127.54
126.71
125.89
123.09
115.36
115.15
94.67
77.31
77.20
77.00
76.68
46.17
38.11
26.54
21.20
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

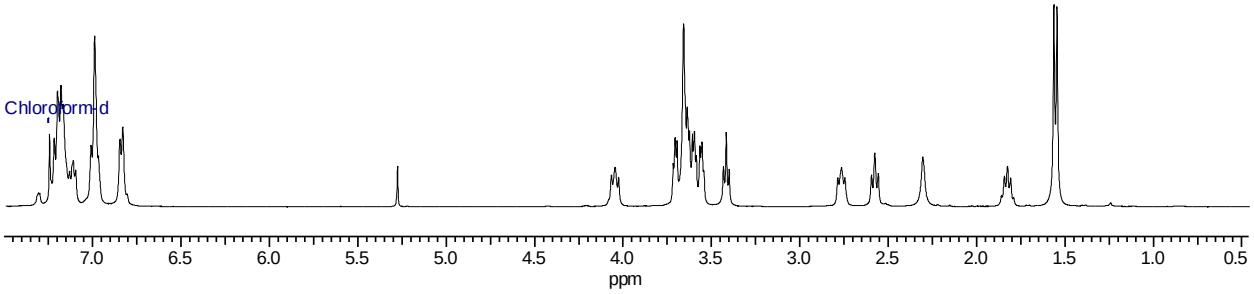

F
N
HO
O
1-142
Chloroform-d
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
ppm
Chloroform-d
169.01
163.49
161.02
144.35
137.47
135.28
133.30
130.50
130.09
128.70
128.55
128.47
127.34
126.81
125.94
115.36
115.14
109.75
46.42
37.70
30.91
26.11
21.07
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
ppm

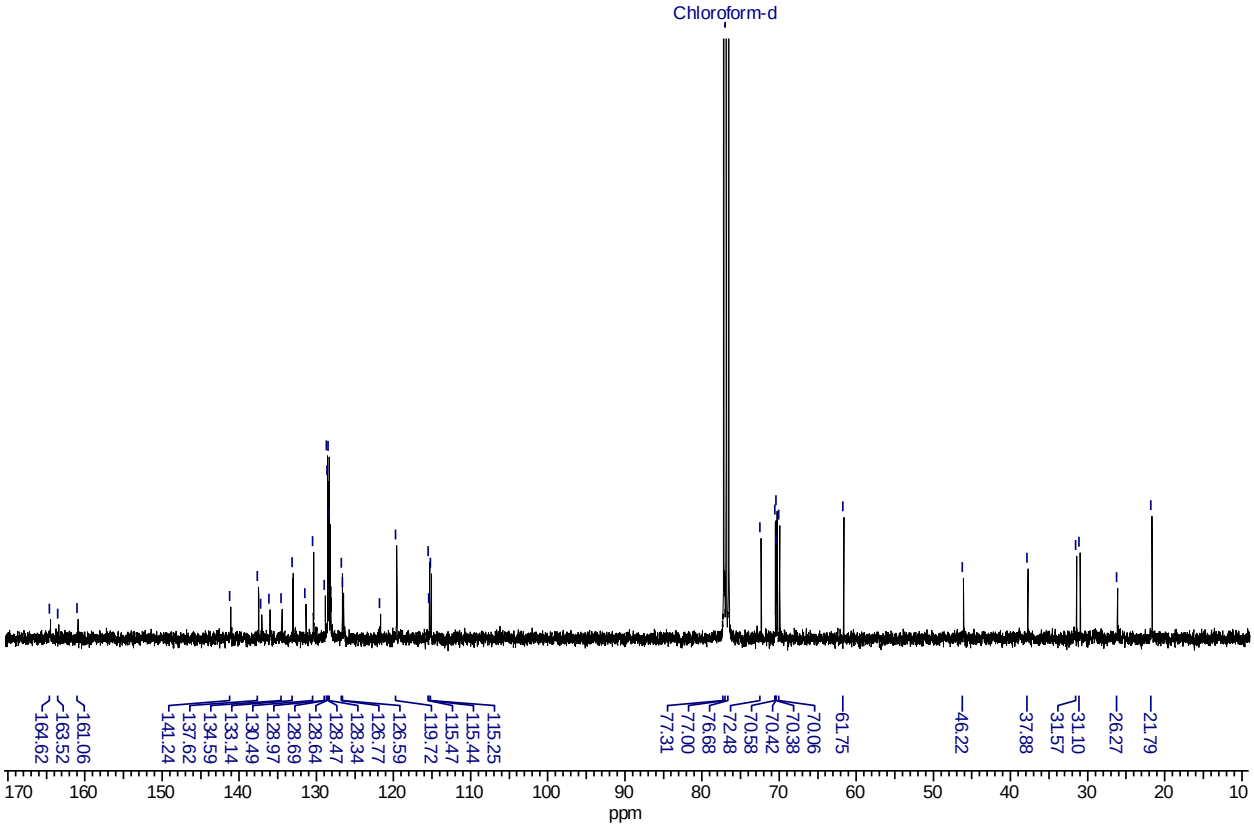

F
H
N
N
O
O
3
OTBS
1-143
Chloroform-d
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
ppm

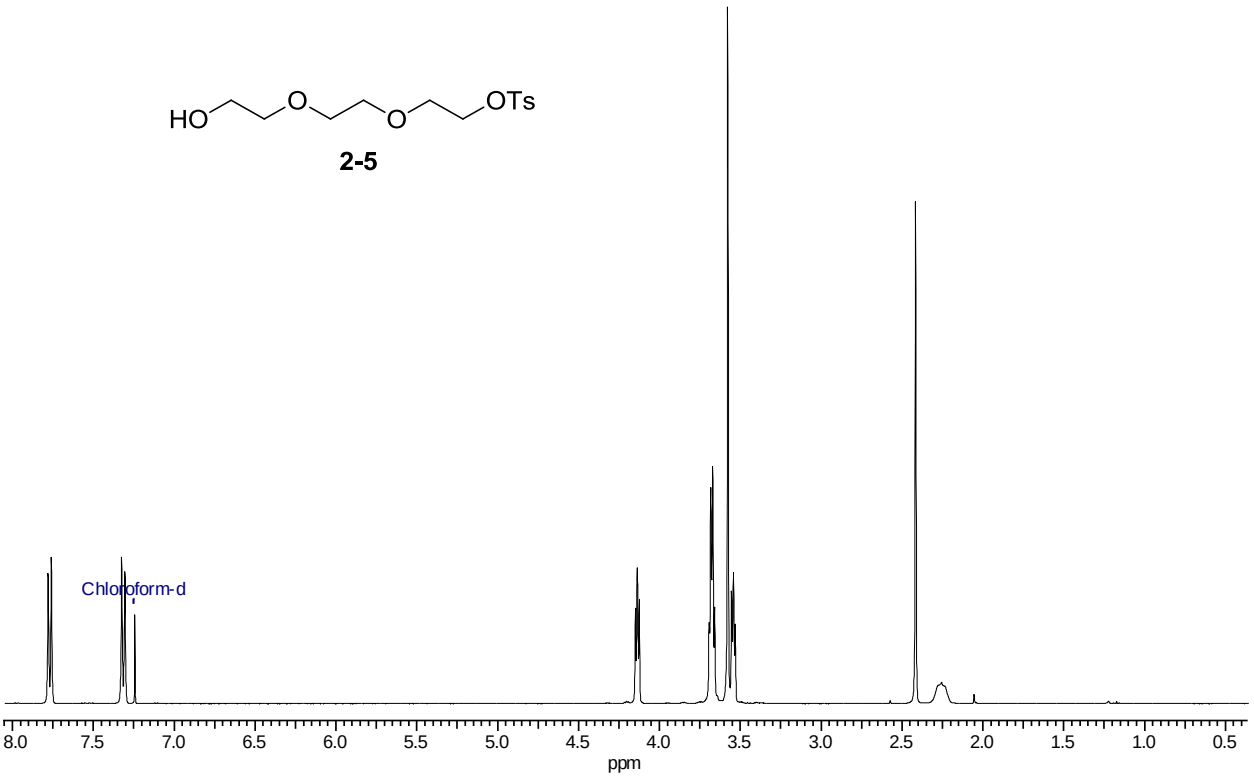

Chloroform-d
164.61
163.52
161.05
141.23
137.62
134.58
133.14
131.47
130.48
128.96
128.62
128.47
128.33
126.77
126.59
119.70
115.46
115.25
77.32
77.00
76.68
72.64
70.74
70.42
70.12
62.69
46.21
37.88
31.61
31.18
26.27
25.92
21.79
18.35
-5.28
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
ppm

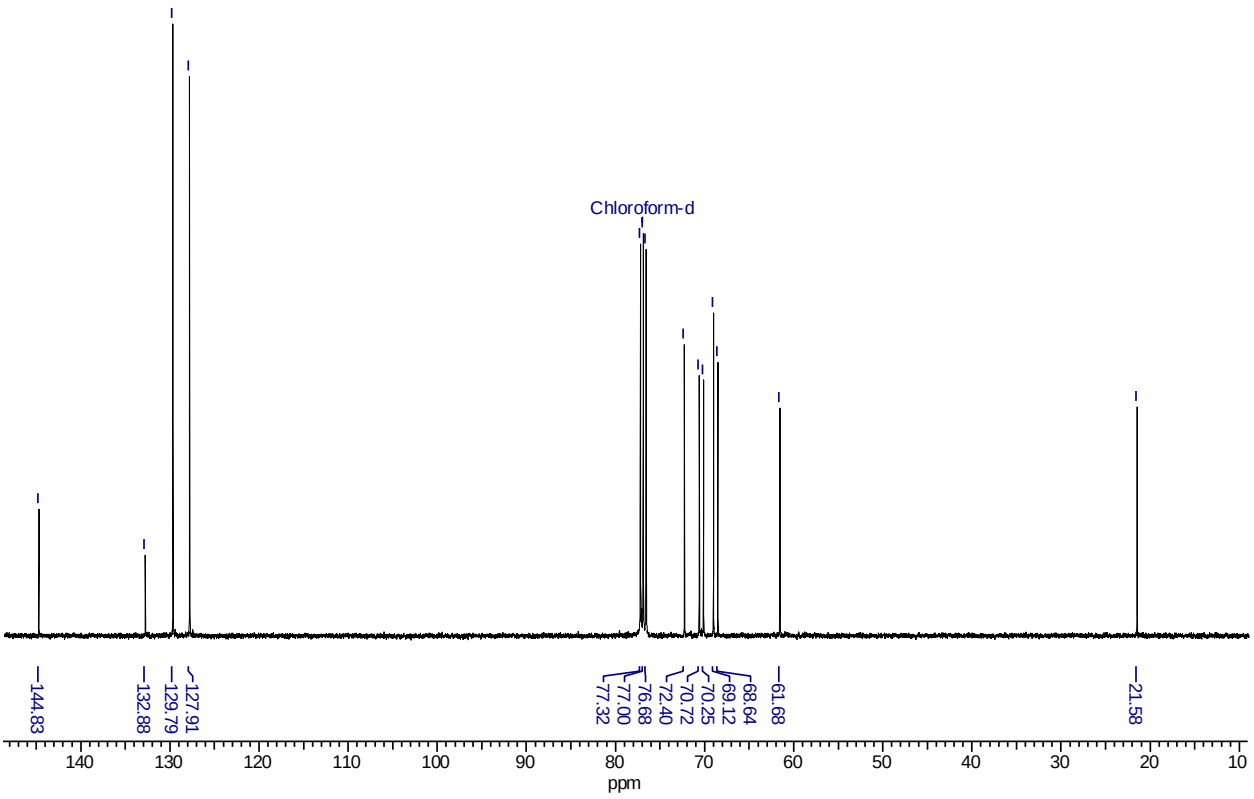

F
H
N
N
O
O
3
OH

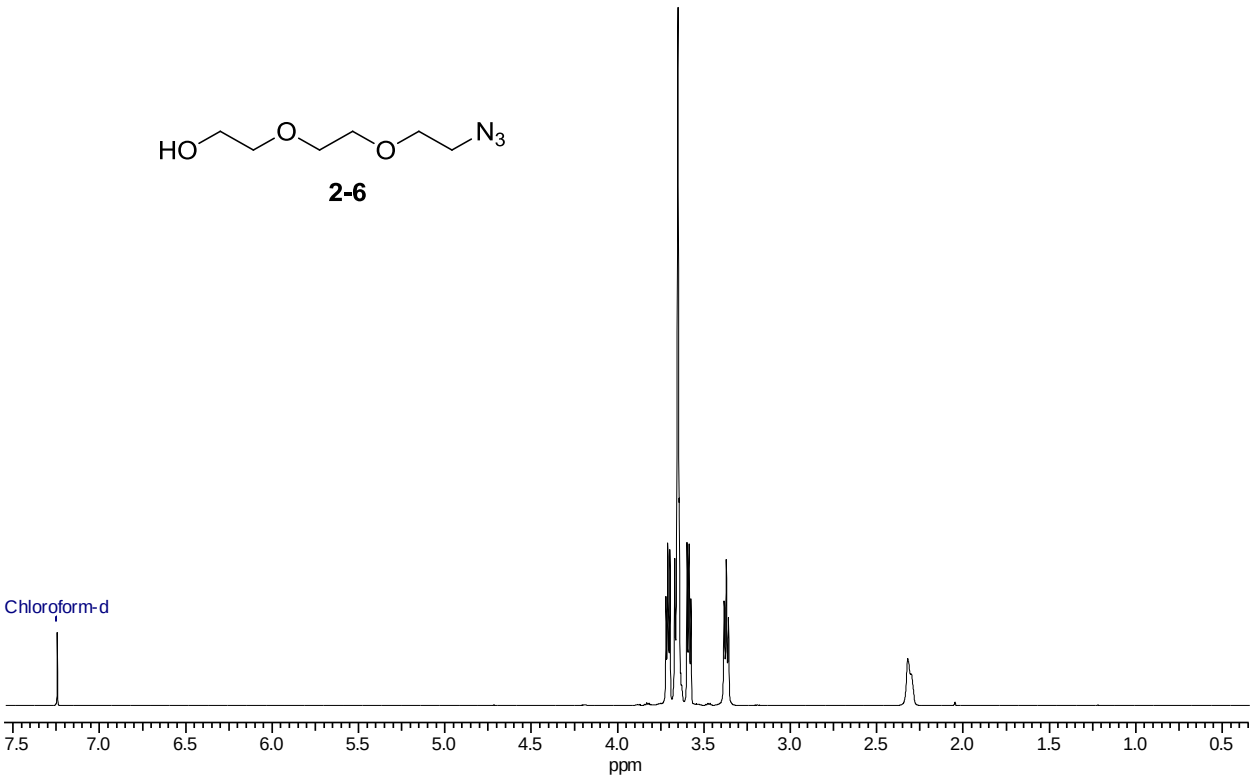
1-144

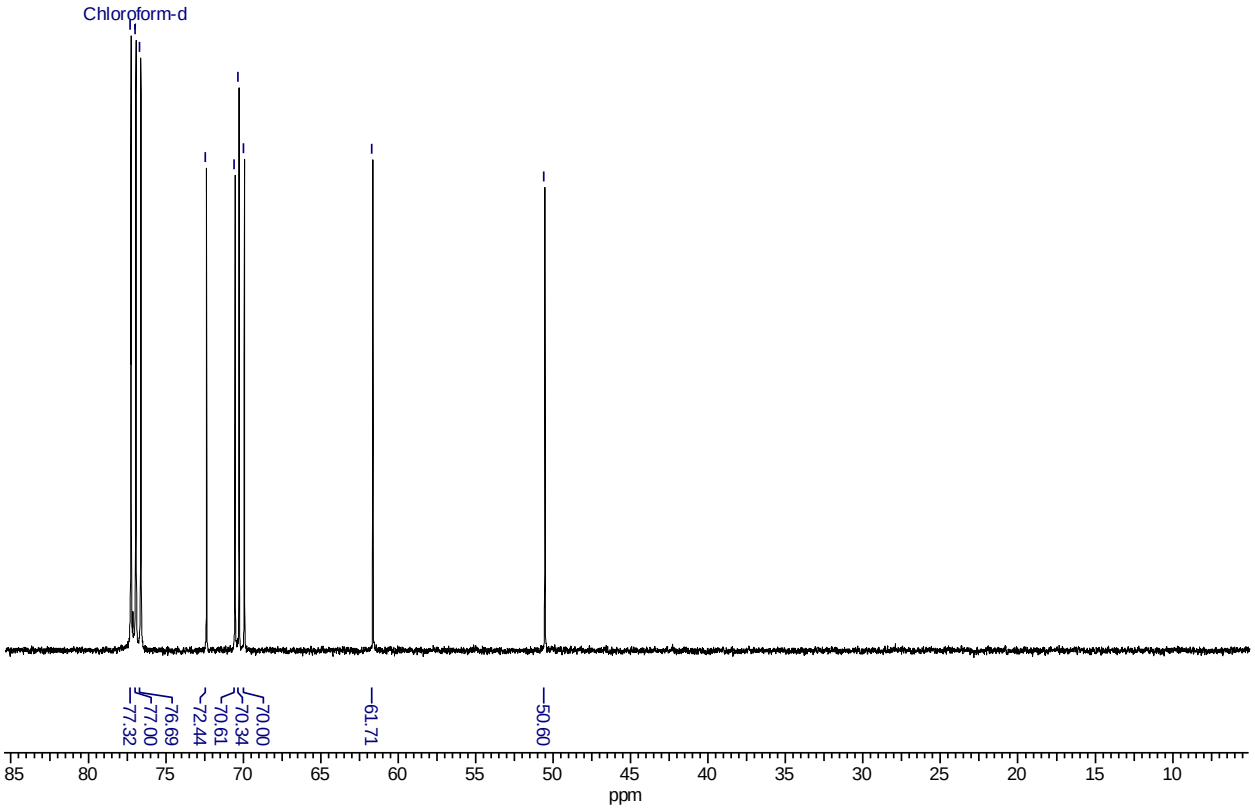

Chloroform-d
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

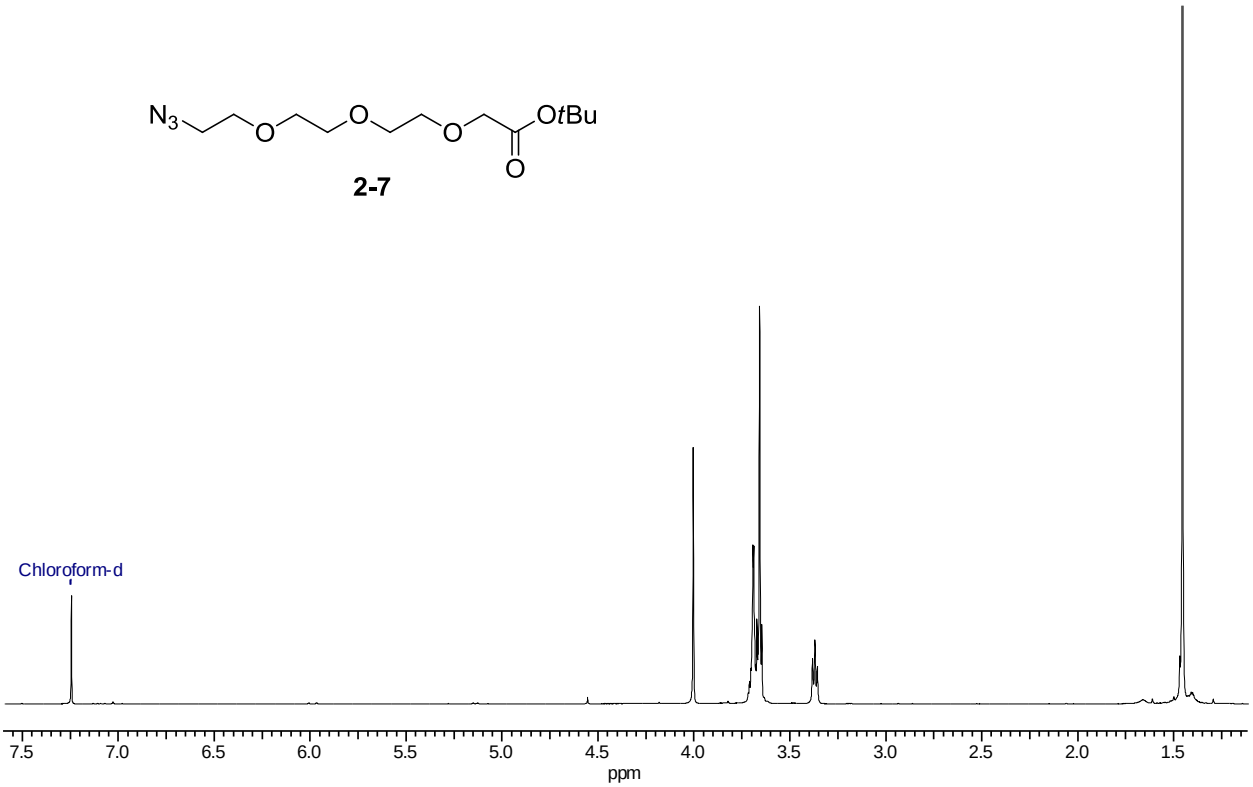

Chloroform-d
164.62
163.52
161.06
141.24
137.62
134.59
133.14
130.49
128.97
128.69
128.64
128.47
128.34
126.77
126.59
119.72
115.47
115.44
115.25
77.31
77.00
76.68
72.48
70.58
70.42
70.38
70.06
61.75
46.22
37.88
31.57
31.10
26.27
21.79
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

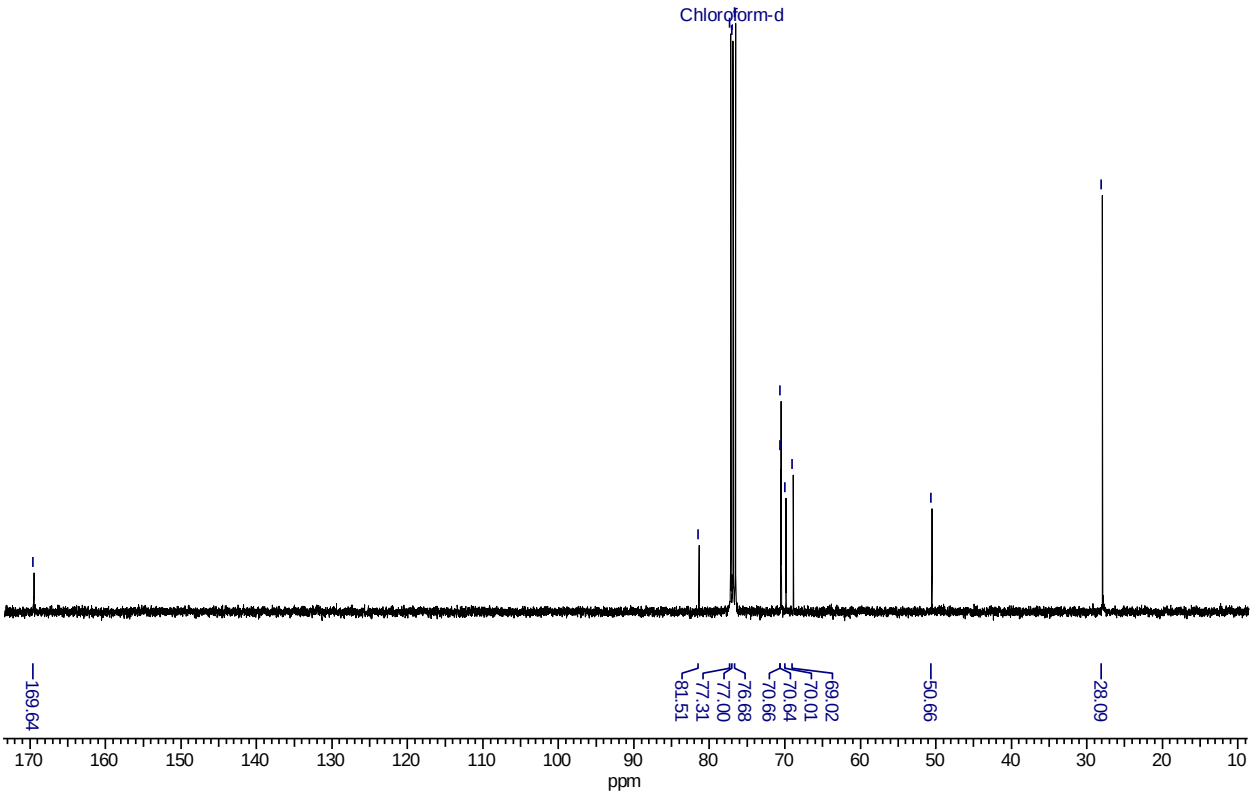

HO
O
O
OTs
2-5
Chloroform-d
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

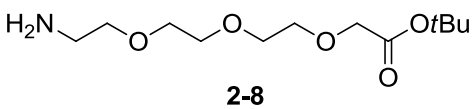

Chloroform-d
144.83
132.88
129.79
127.91
77.32
77.00
76.68
72.40
70.72
70.25
69.12
68.64
61.68
21.58
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


HO
O
O
N3
2-6
Chloroform-d
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm


Chloroform-d
77.32
77.00
76.69
72.44
70.61
70.34
70.00
61.71
50.60
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
ppm

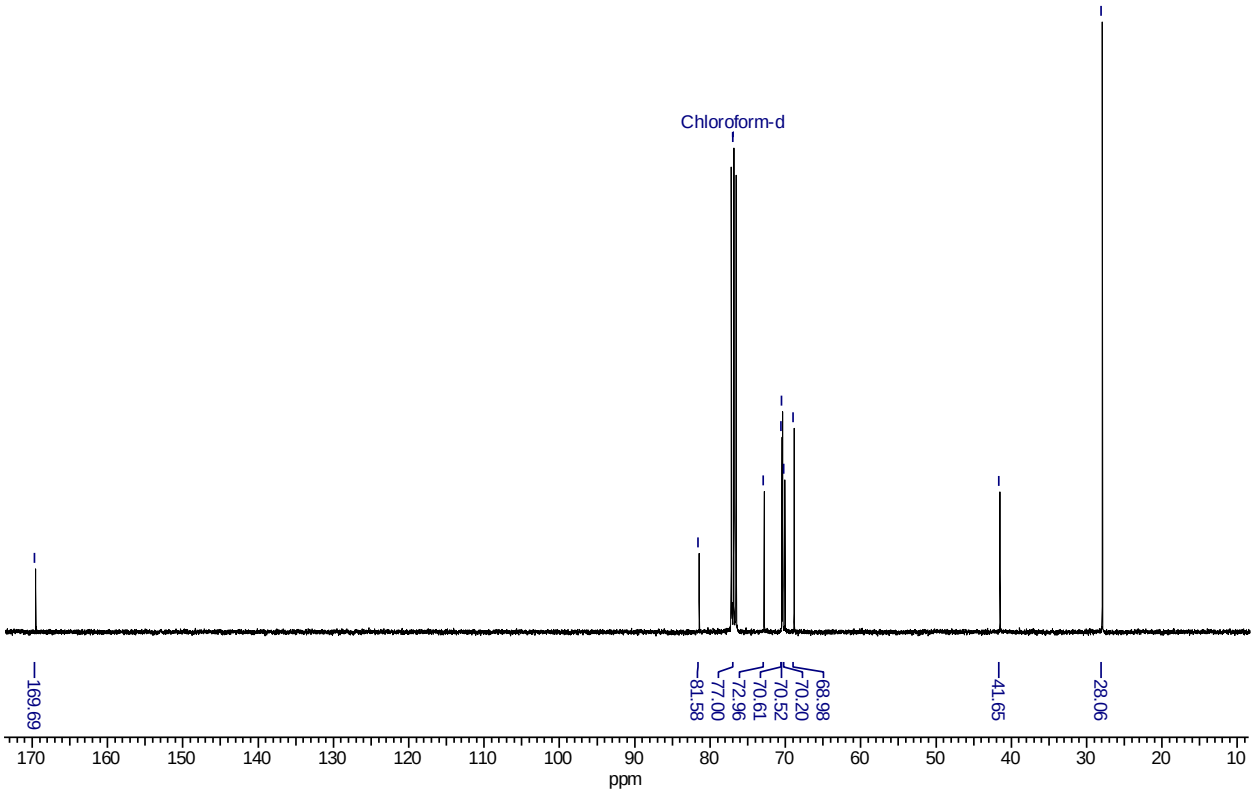

N3
O
O
O
OtBu
O
2-7
Chloroform-d
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm

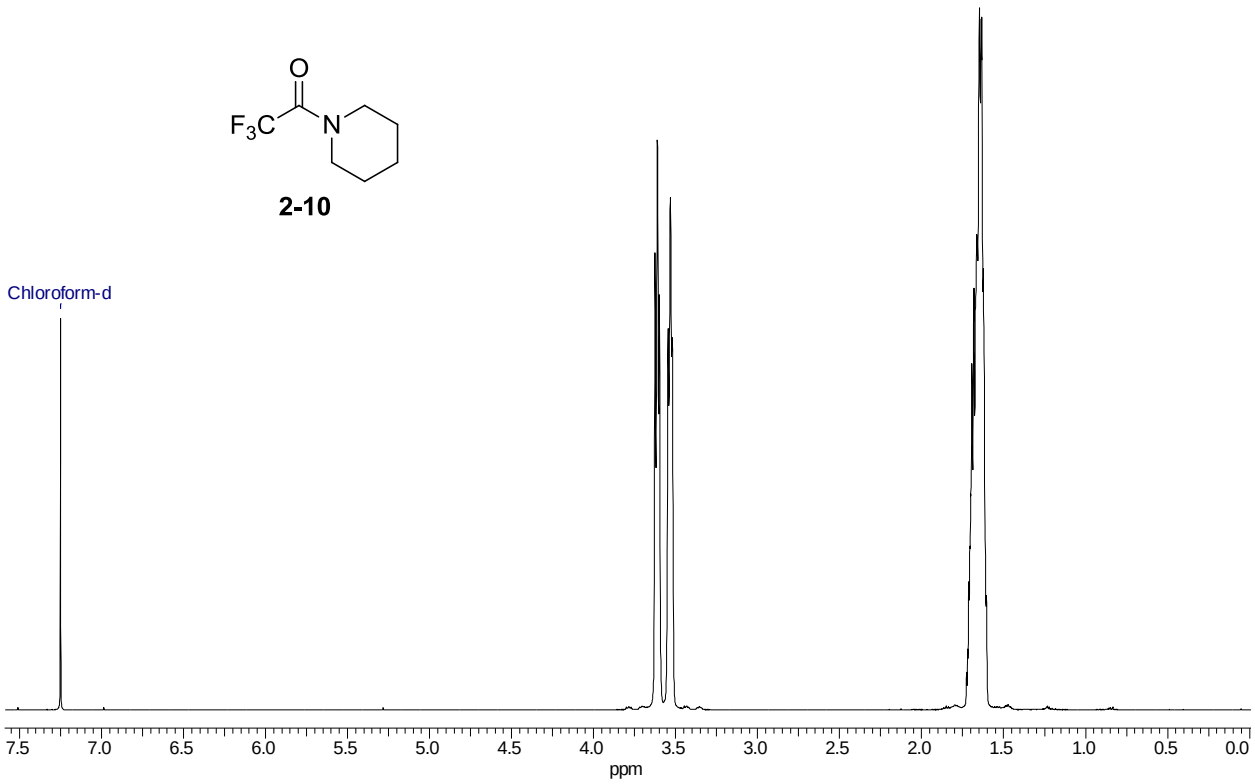

Chloroform-d
169.64
81.51
77.31
77.00
76.68
70.66
70.64
70.01
69.02
50.66
28.09
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

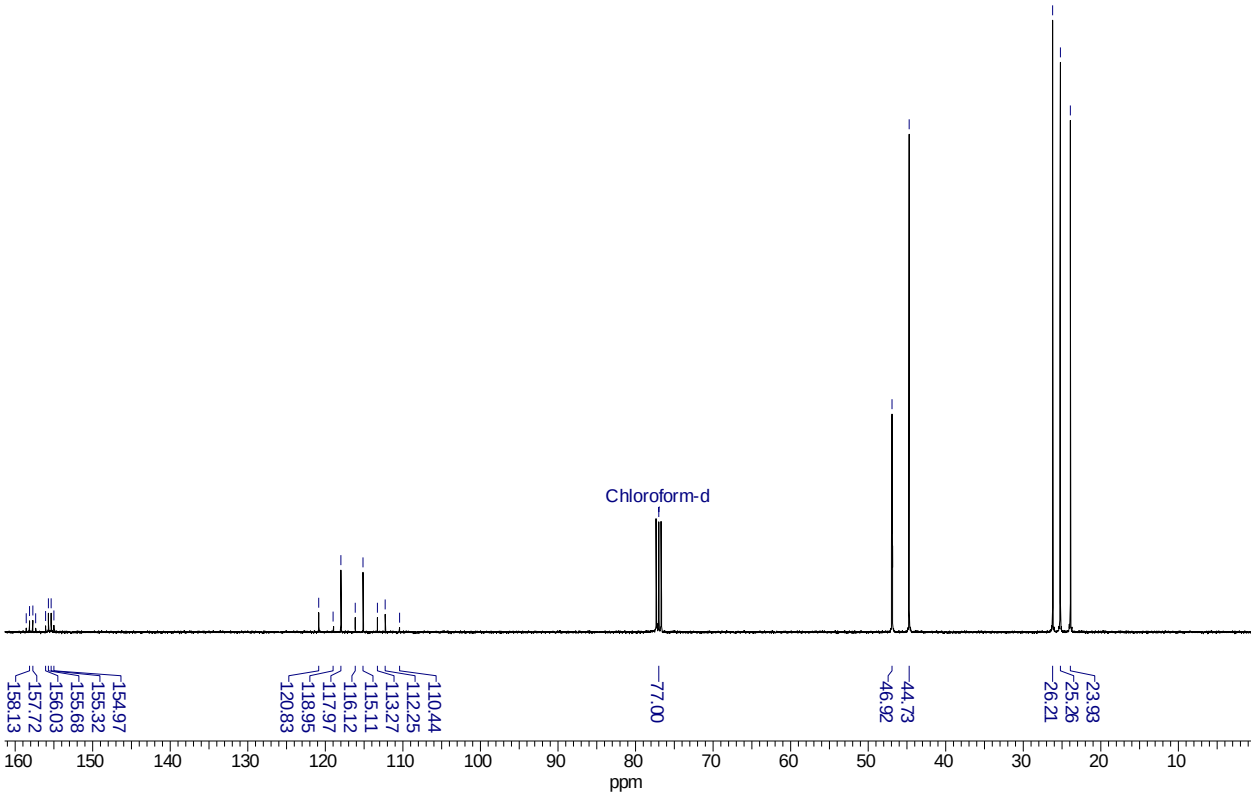

H2N
O
O
O
OtBu
O

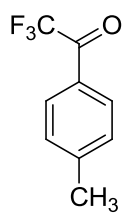
2-8

Chloroform-d
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm


Chloroform-d
169.69
81.58
77.00
72.96
70.61
70.52
70.20
68.98
41.65
28.06
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

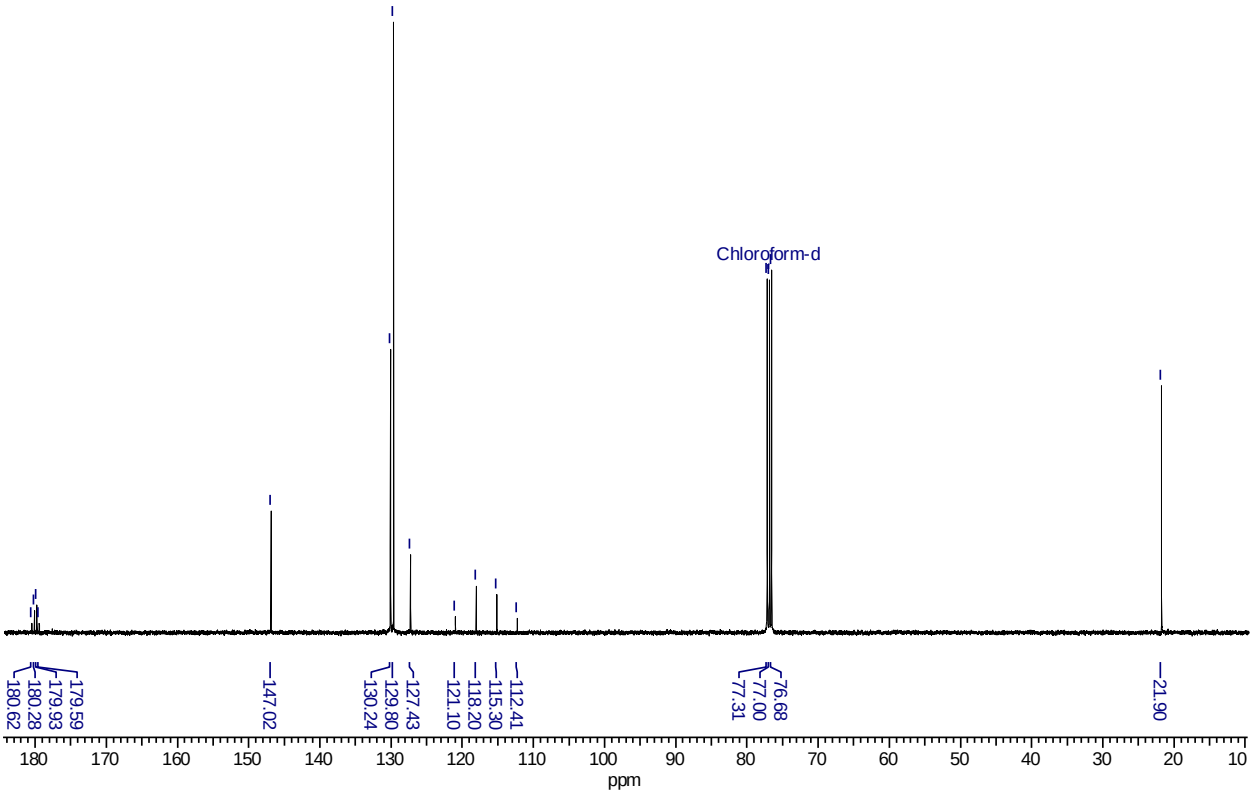

O
F3C
N
2-10
Chloroform-d
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm

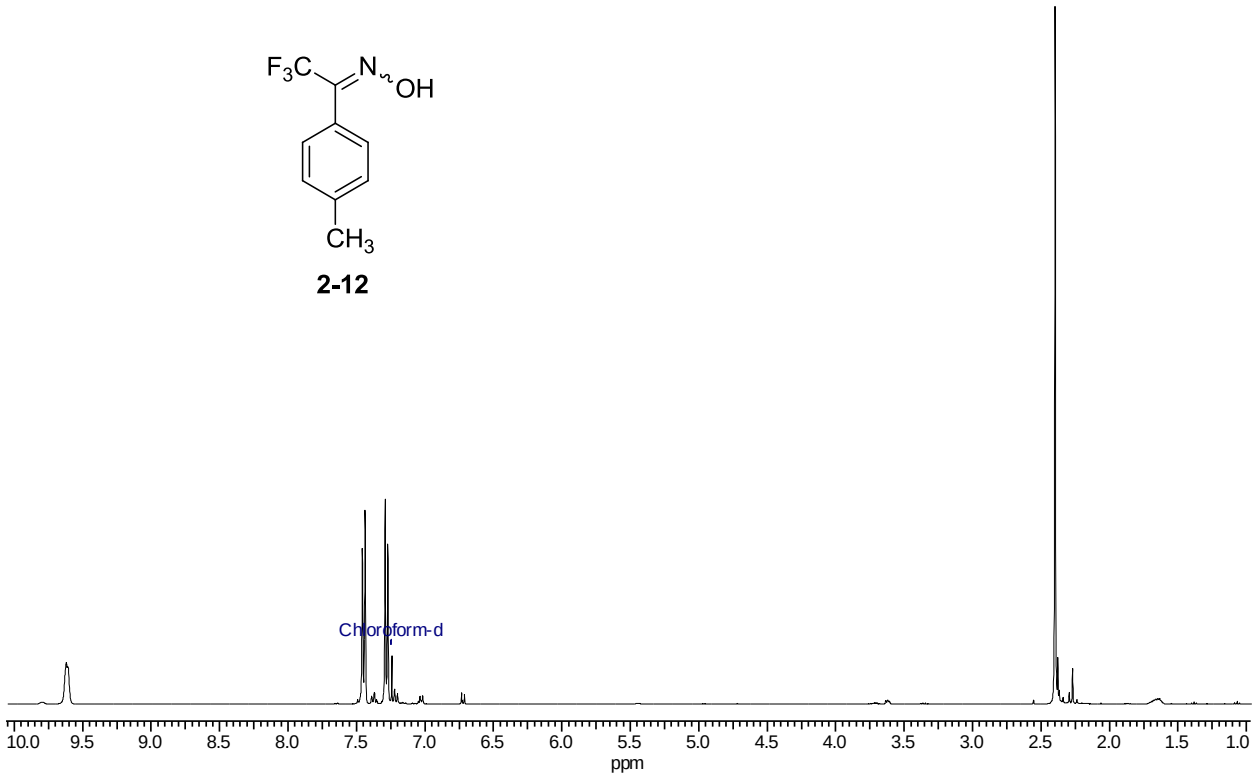

Chloroform-d
158.13
157.72
156.03
155.68
155.32
154.97
120.83
118.95
117.97
116.12
115.11
113.27
112.25
110.44
77.00
46.92
44.73
26.21
25.26
23.93
160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
ppm


F3C
O
CH3

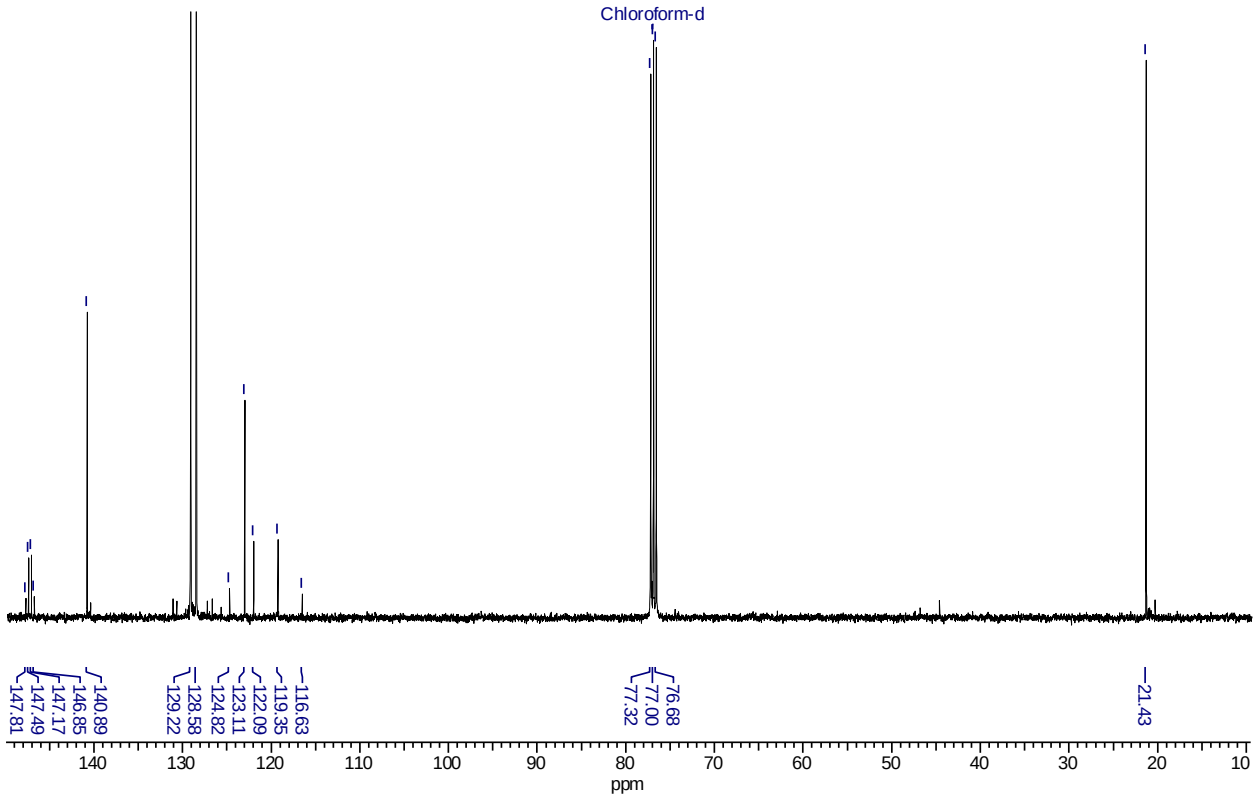
2-11

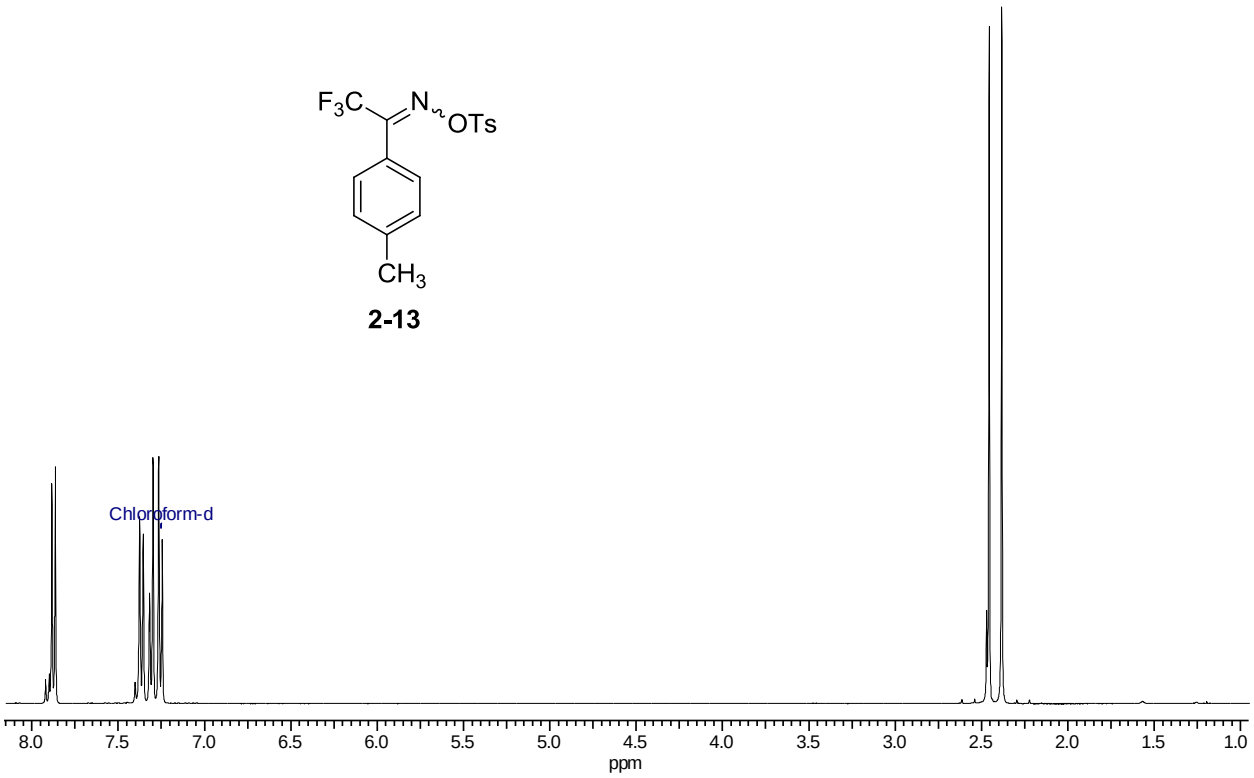
Chloroform-d
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

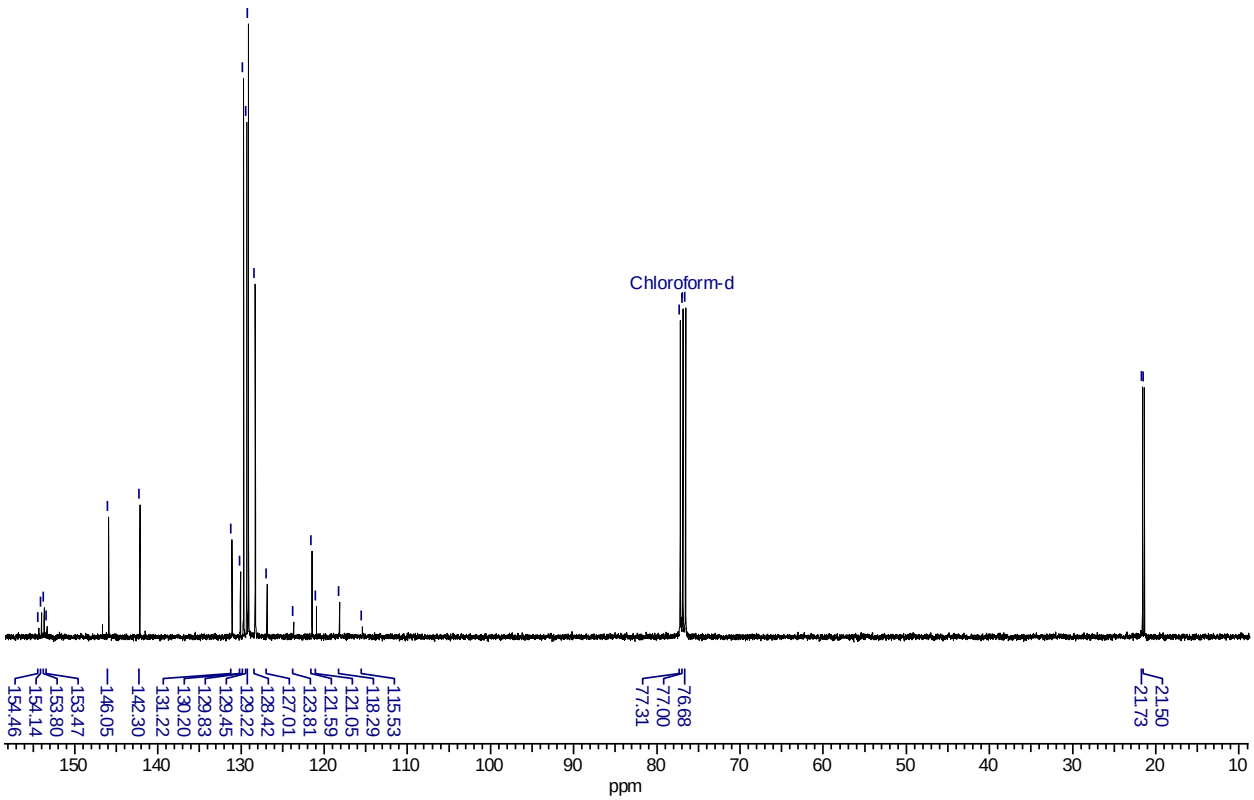

Chloroform-d
180.62
180.28
179.93
179.59
147.02
130.24
129.80
127.43
121.10
118.20
115.30
112.41
77.31
77.00
76.68
21.90
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

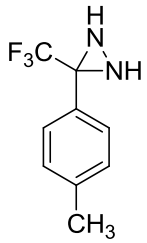

F3C
N
OH
CH3
Chloroform-d
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
ppm

2-12


Chloroform-d
147.81
147.49
147.17
146.85
140.89
129.22
128.58
124.82
123.11
122.09
119.35
116.63
77.32
77.00
76.68
21.43
140 130 120 110 100 90 80 70 60 50 40 30 20 10
ppm

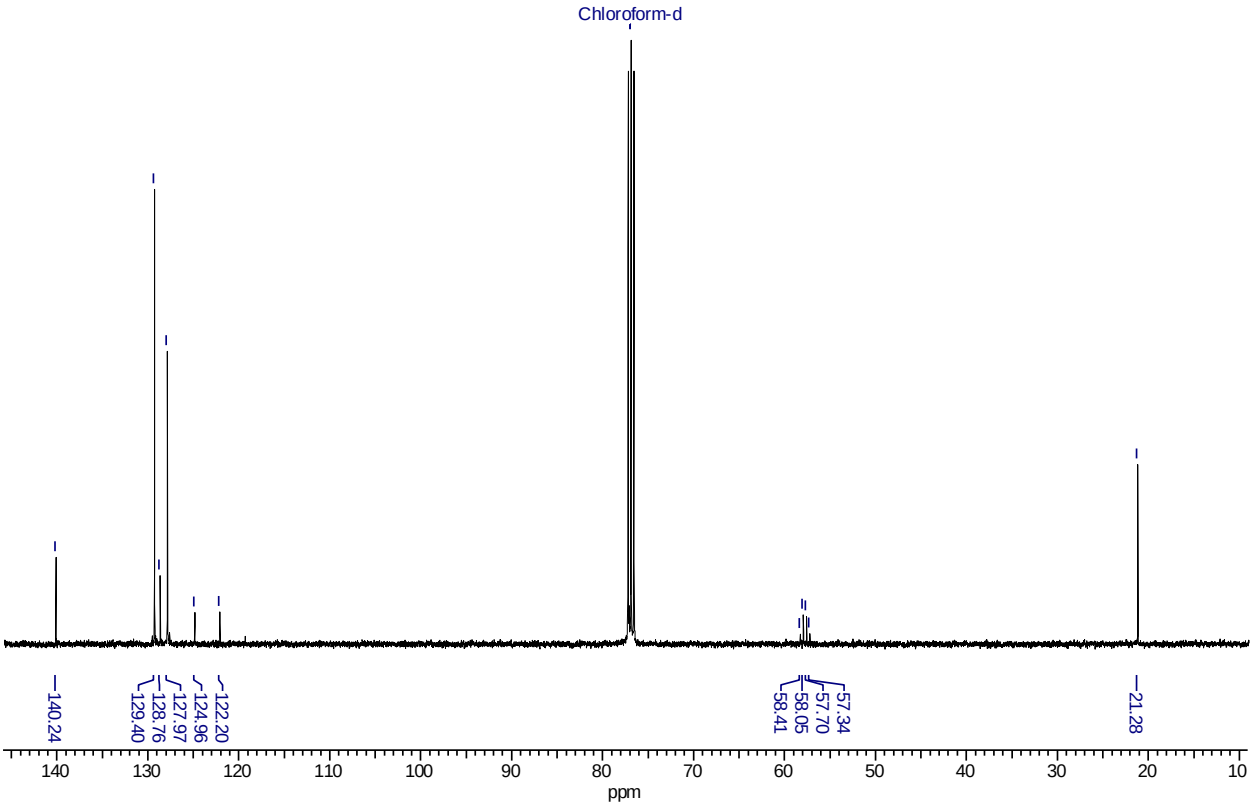

F3C
N
OTs
CH3
2-13
Chloroform-d
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

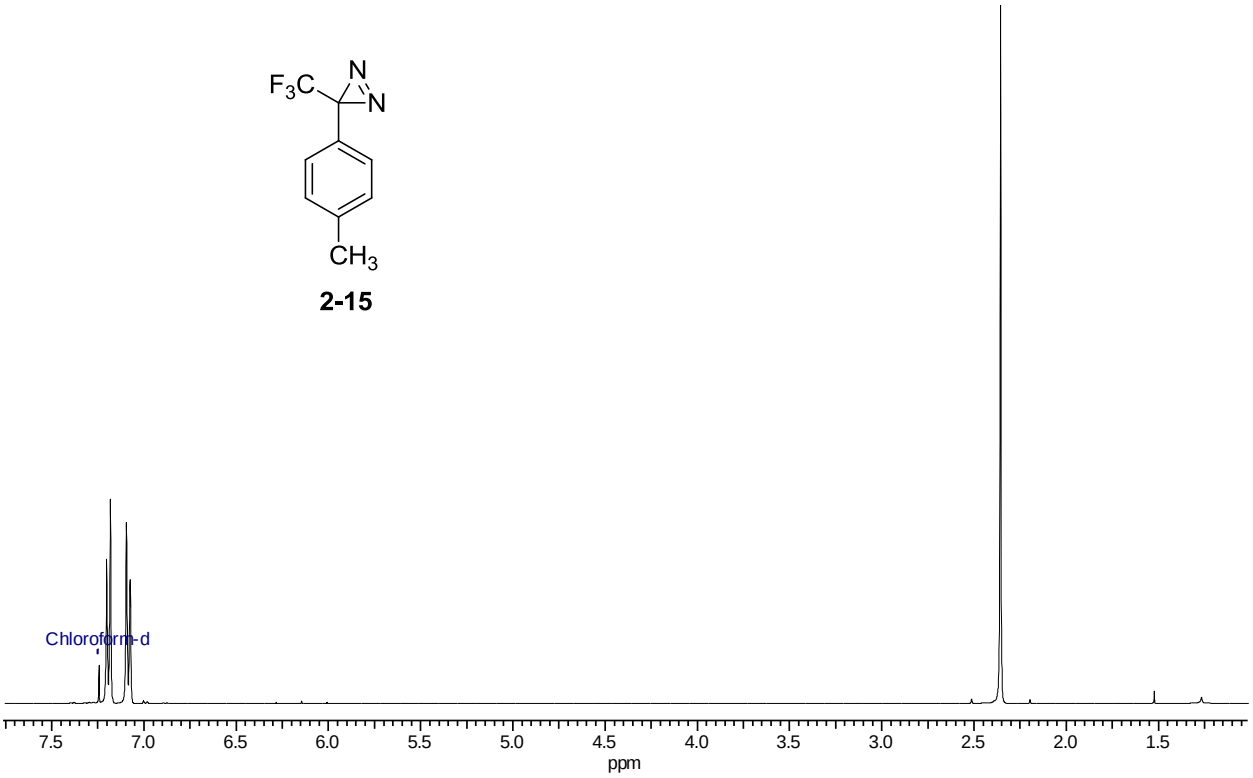

Chloroform-d
154.46
154.14
153.80
153.47
146.05
142.30
131.22
130.20
129.83
129.45
129.22
128.42
127.01
123.81
121.59
121.05
118.29
115.53
77.31
77.00
76.68
21.73
21.50
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


H
N
F3C
NH
CH3

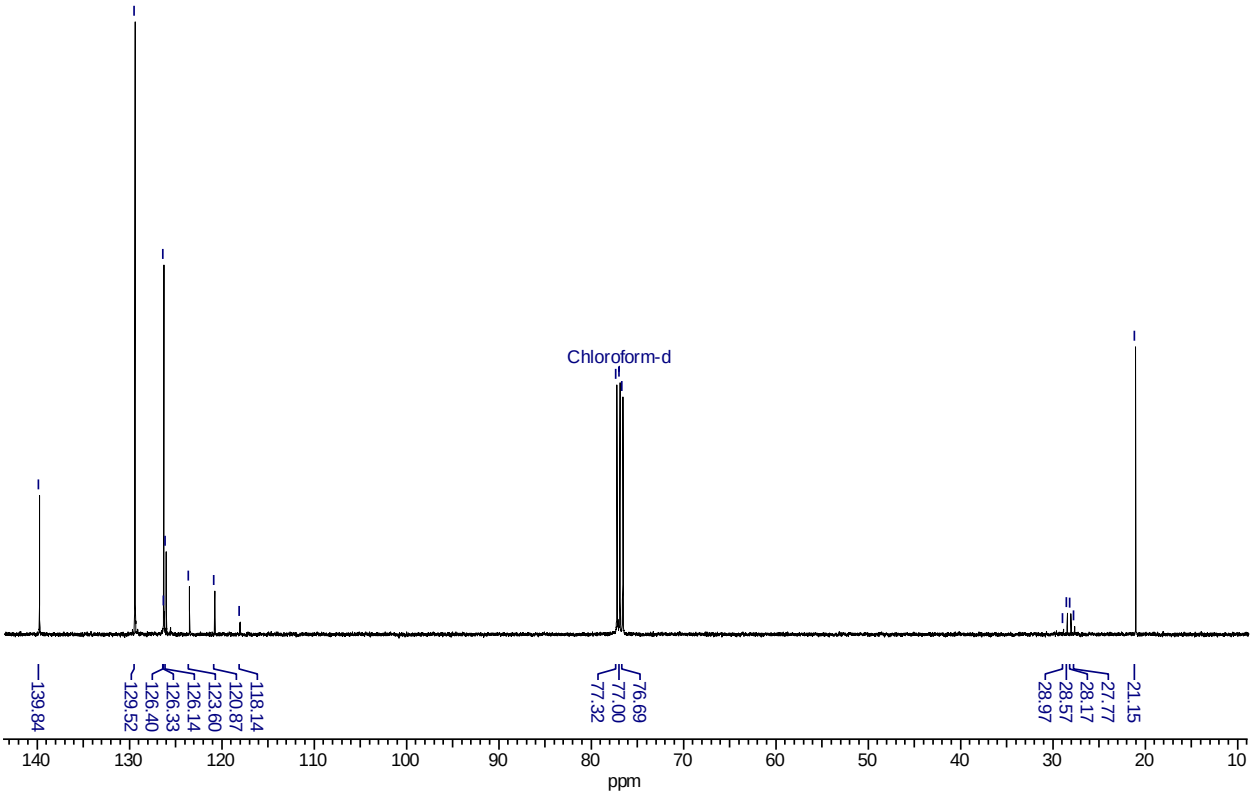
2-14

Chloroform-d
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm


Chloroform-d
140.24
129.40
128.76
127.97
124.96
122.20
58.41
58.05
57.70
57.34
21.28
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


F3C
N
N
CH3
Chloroform-d
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm

2-15


Chloroform-d
139.84
129.52
126.40
126.33
126.14
123.60
120.87
118.14
77.32
77.00
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28.97
28.57
28.17
27.77
21.15
140
130
120
110
100
90
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70
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30
20
10
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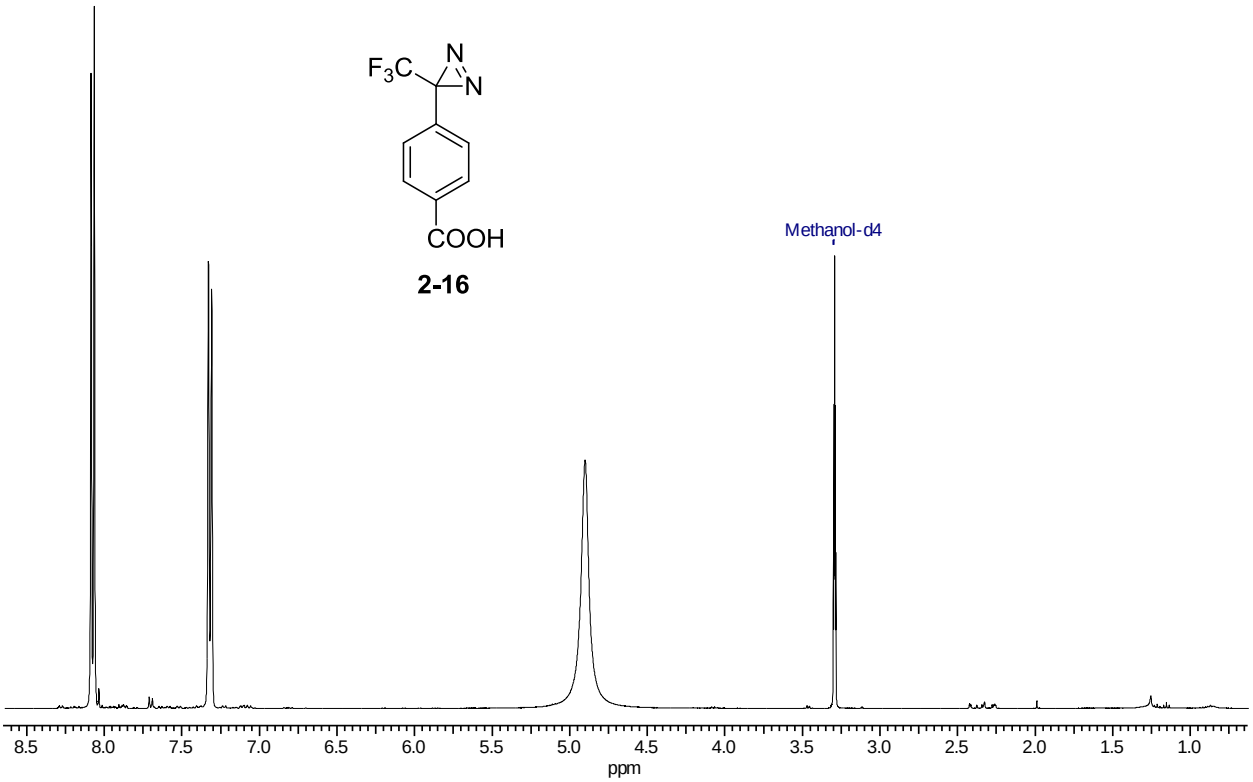
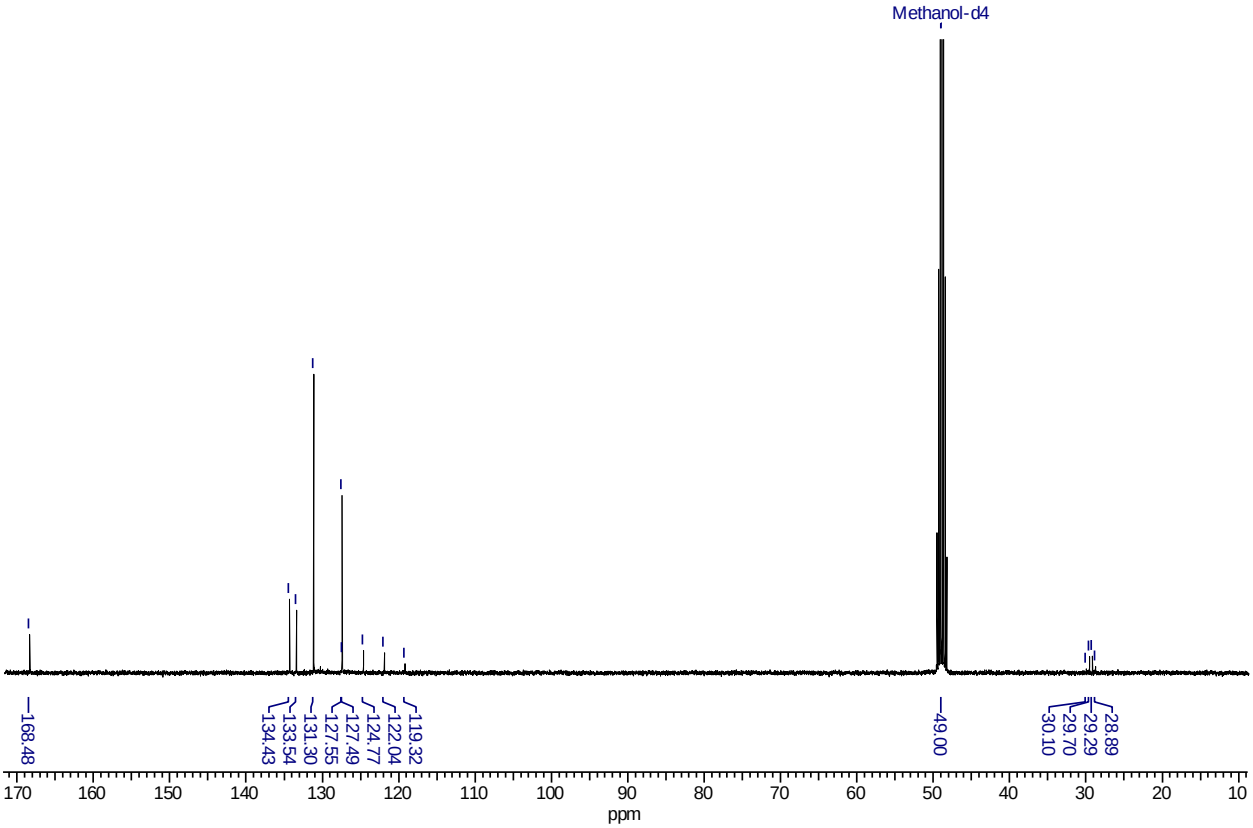

F3C
N
N
COOH
2-16
Methanol-d4
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm


Methanol-d4
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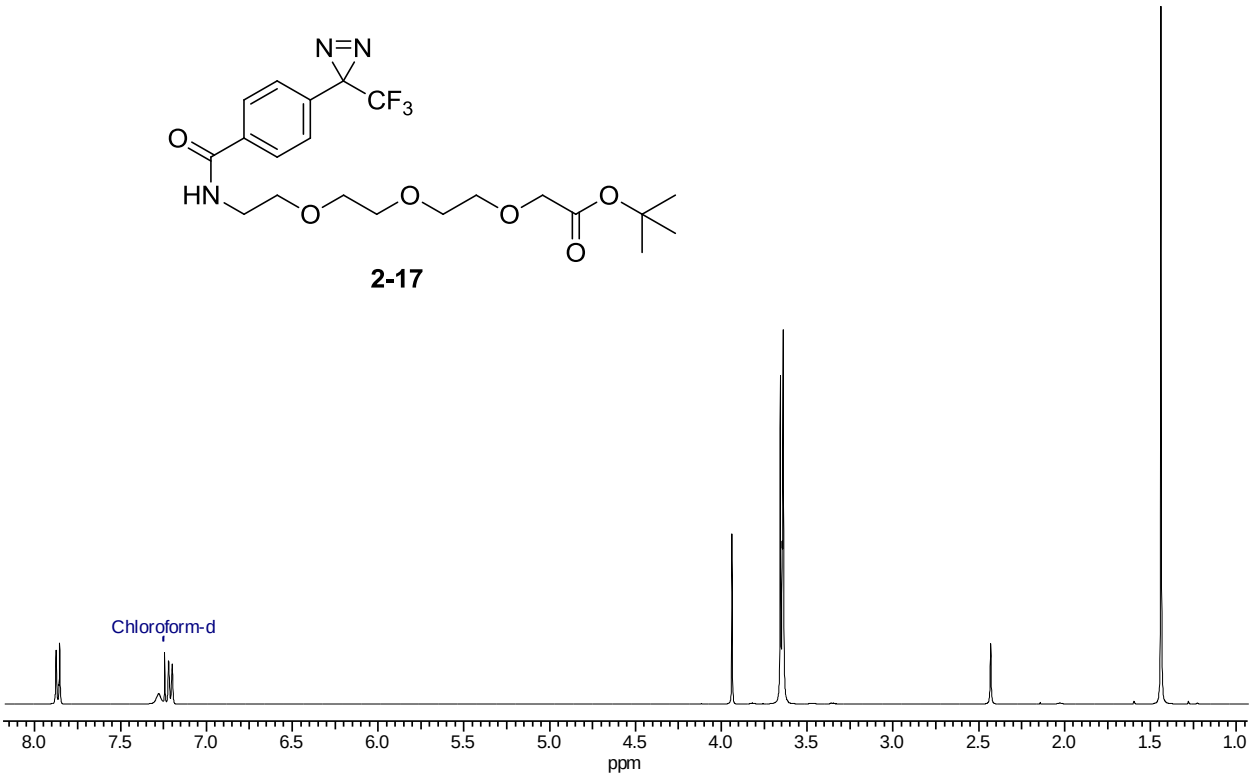
134.43
133.54
131.30
127.55
127.49
124.77
122.04
119.32
49.00
30.10
29.70
29.29
28.89
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm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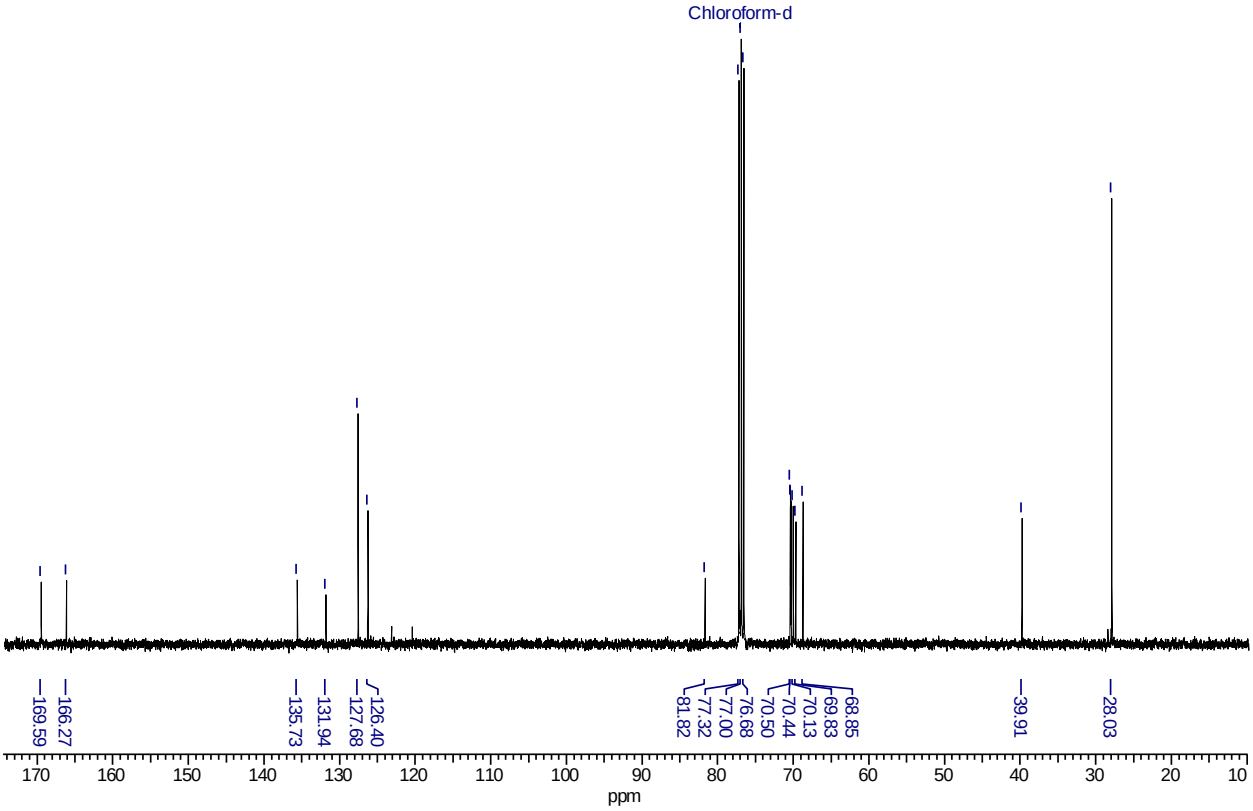
CF3
O
HN
O
O
O
O
O
Chloroform-d
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

2-17


Chloroform-d
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166.27
135.73
131.94
127.68
126.40
81.82
77.32
77.00
76.68
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70.44
70.13
69.83
68.85
39.91
28.03
170
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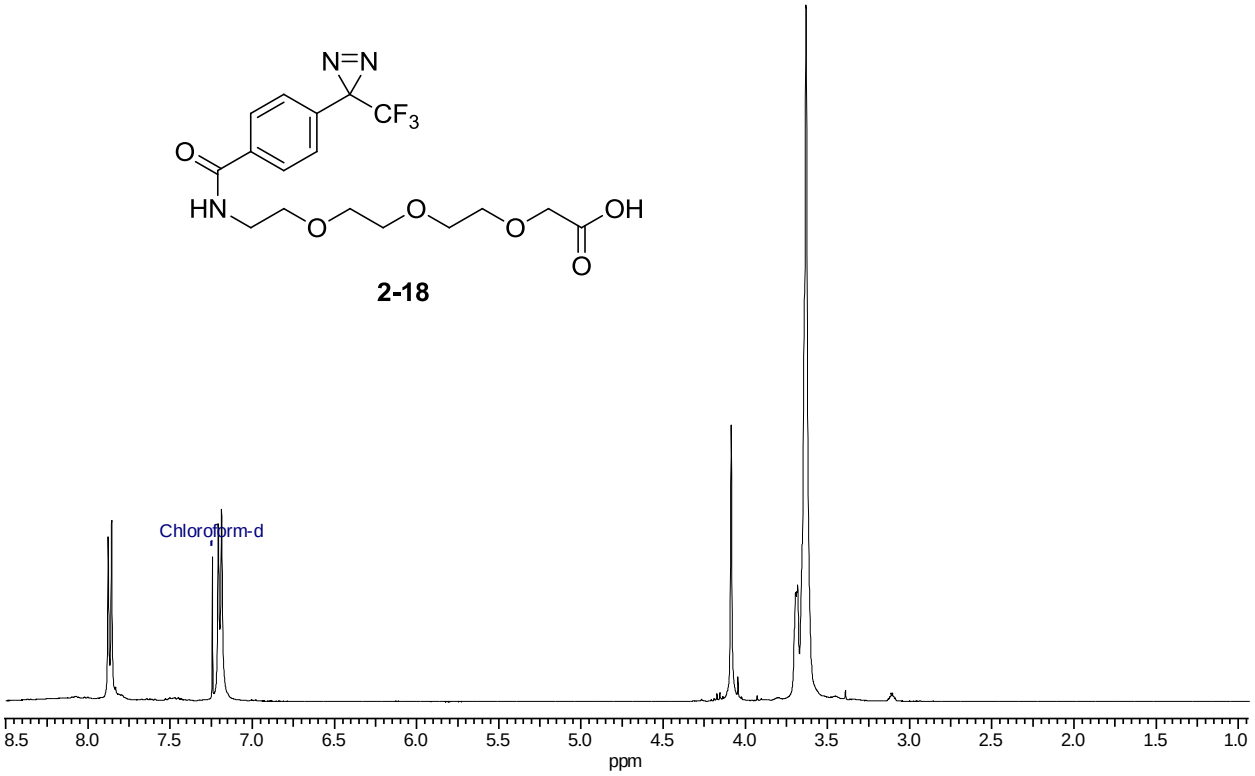
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm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CF3
O
HN
O
O
O
OH
O
Chloroform-d
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8.0
7.5
7.0
6.5
6.0
5.5
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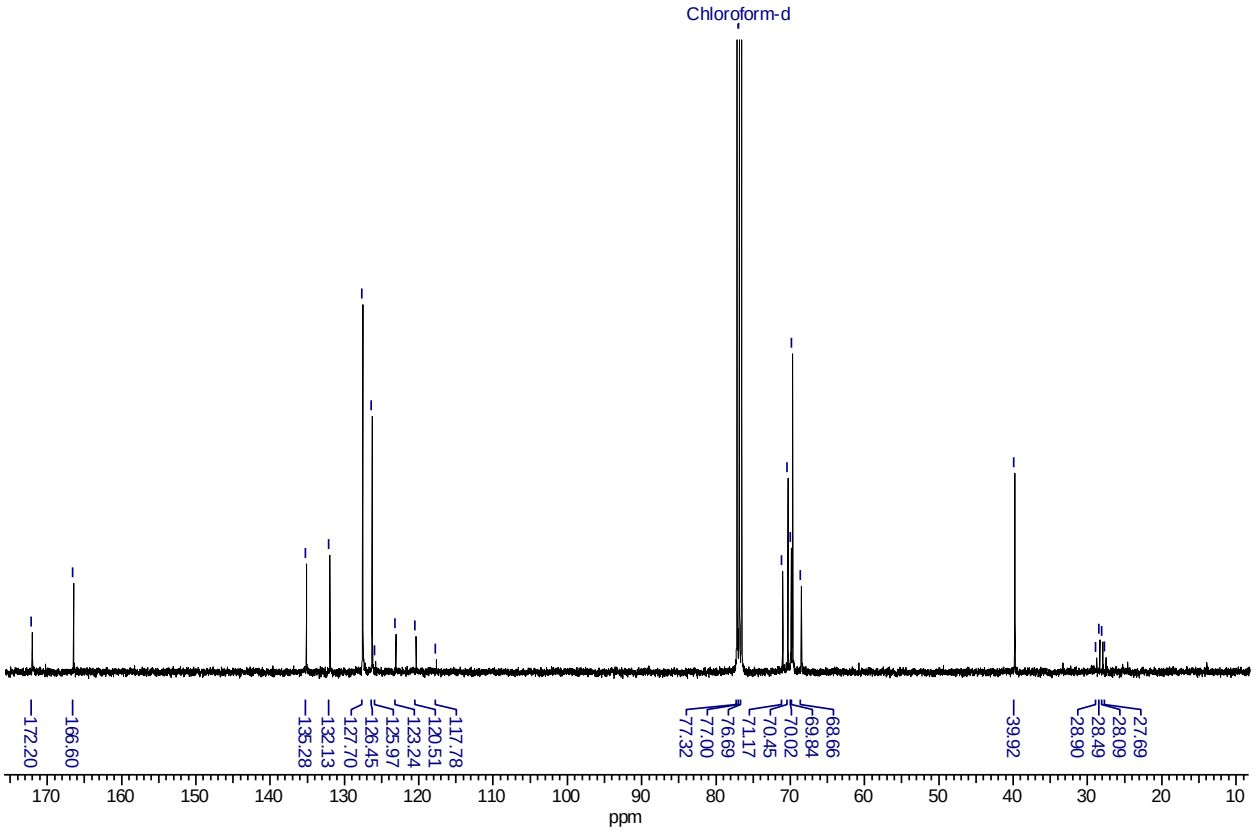
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

2-18


Chloroform-d
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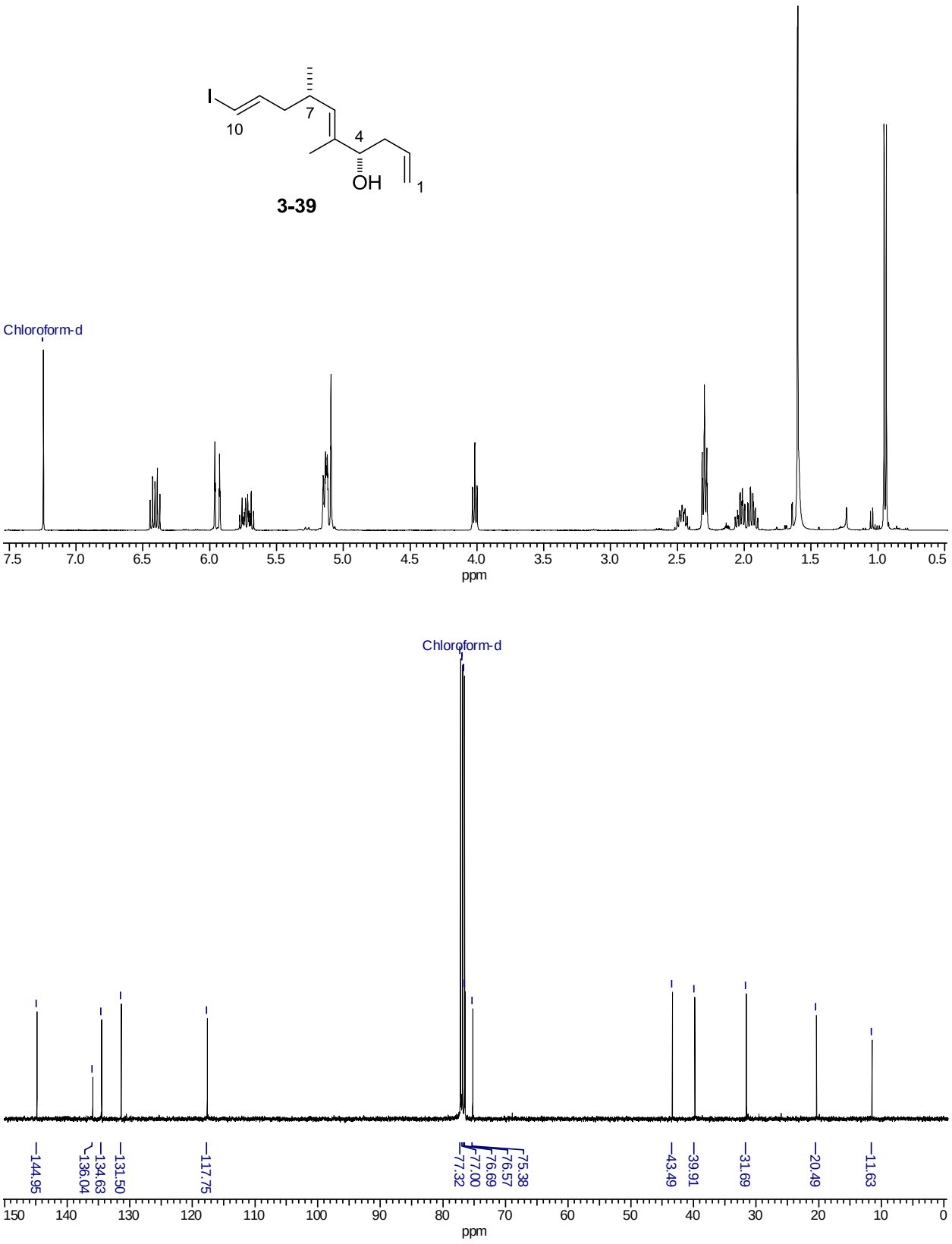
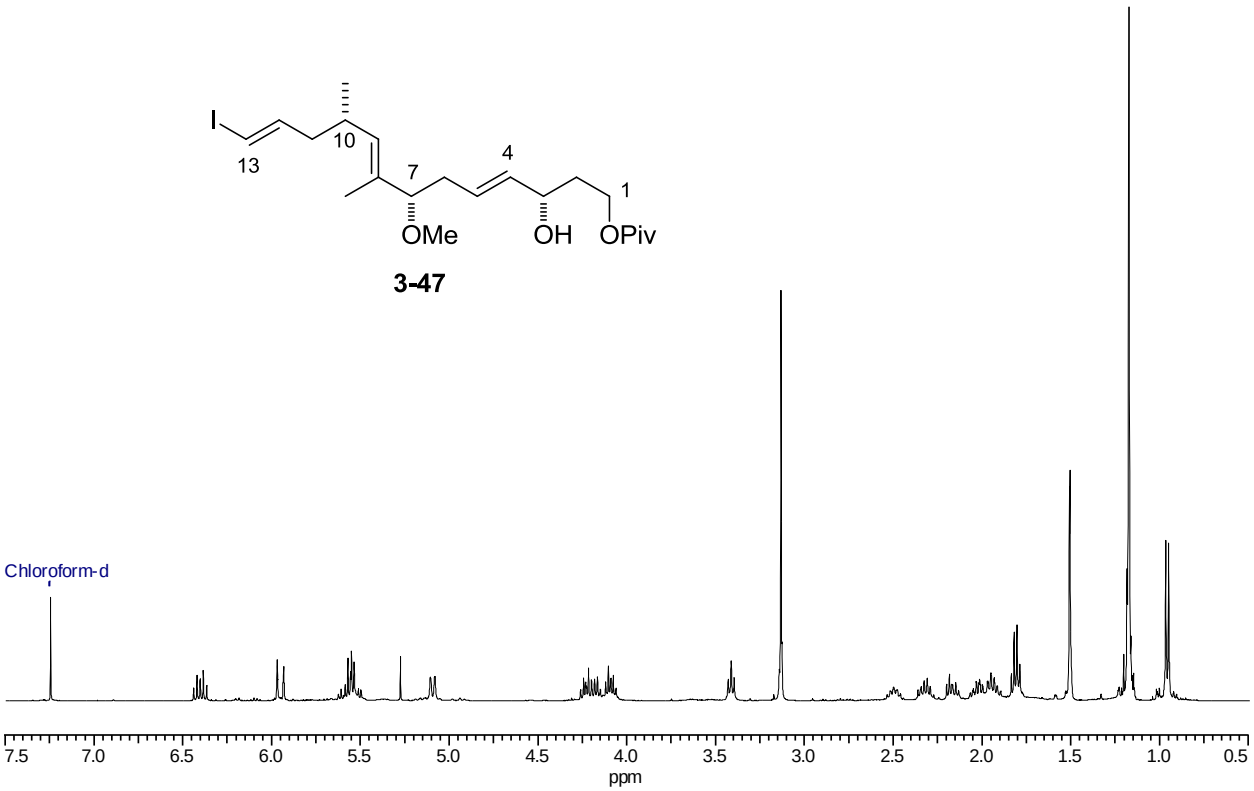
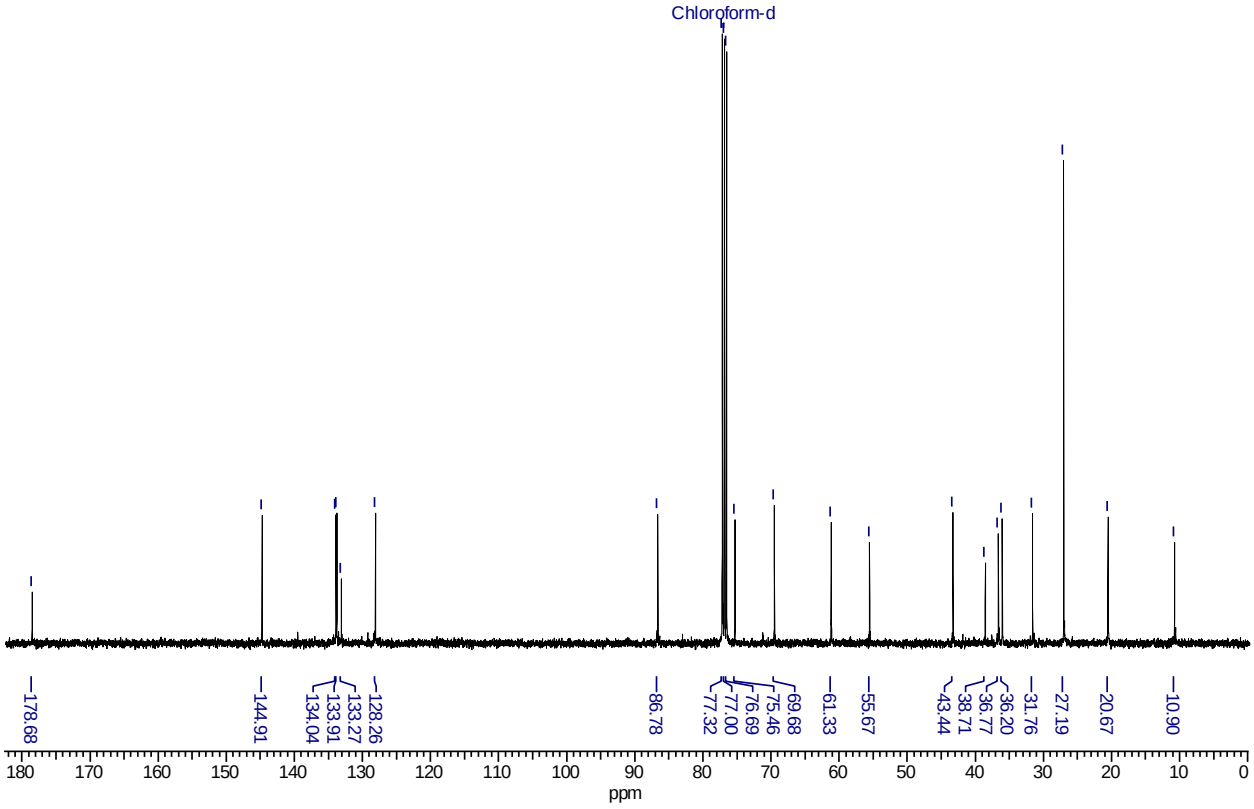
166.60
135.28
132.13
127.70
126.45
125.97
123.24
120.51
117.78
77.32
77.00
76.69
71.17
70.45
70.02
69.84
68.66
39.92
28.90
28.49
28.09
27.69
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


I
10
7
4
OH
1
3-39
Chloroform-d
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
ppm
Chloroform-d
144.95
136.04
134.63
131.50
117.75
77.32
77.00
76.69
76.57
75.38
43.49
39.91
31.69
20.49
11.63
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm


I
13
10
7
4
1
OMe
OH
OPiv
3-47
Chloroform-d
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
ppm


Chloroform-d
178.68
144.91
134.04
133.91
133.27
128.26
86.78
77.32
77.00
76.69
75.46
69.68
61.33
55.67
43.44
38.71
36.77
36.20
31.76
27.19
20.67
10.90
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm

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