



INTERNATIONAL DOCTORAL
SCHOOL OF THE USC

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PhD Thesis

Helix Induction Mechanisms in Poly(phenylacetylene)s bearing Oligopeptides as Pendants

Santiago de Compostela, 2022



HELIX INDUCTION MECHANISMS IN POLY(PHENYLACETYLENE)S BEARING OLIGOPEPTIDES AS PENDANTS

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ESCOLA DE DOUTORAMNETO INTERNACIONAL DA UNIVERSIDADE DE
SANTIAGO DE COMPOSTELA
PROGRAMA DE DOUTORAMENTO EN CIENCIA E TECNOLOXÍA QUÍMICA

SANTIAGO DE COMPOSTELA

2022



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**Helix Induction Mechanisms in Poly(phenylacetylene)s bearing Oligopeptides as
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Abbreviations and Acronyms

% v/v	Volume percentage
°C	Celsius degree
1,2-DCE	1,2-Dichloroethane
[α]	Standardized optical rotation
α	Optical rotation
α_{obs}	Angstrom
$\bar{\alpha}$	Optical rotation observed
AFM	Atomic force microscopy
Aib	α -aminoisobutiric acid
AIBN	Azobisisobutironitril
Ala	Alanine
anh.	Anhydride
<i>ap</i>	<i>antiperiplanar</i>
$\Delta^2\text{Phe}$	Z- α - β -Dehydrophenylalanine
BDY	Boradiazaindacene
BiPy	Bipyridine
c	Concentration
<i>c-c</i>	<i>cis-cisoid</i>
<i>c-t</i>	<i>cis-transoid</i>
ca.	Latin expression " <i>circa</i> "; around
CD	Circular dichroism
CHCl ₃	Chloroform
CMPH	See HPMC
CNT	Carbon nanotube
cod	<i>Cis,cis</i> -1,5-cyclo-octadiene
CSP	Chiral stationary phase
CyD	Cyclodextrin
CyHex	Cyclohexanone
δ	Chemical shift
Δ	Heat
d	Doublet

Abbreviations and Acronyms

dd	Double doublet
DCM	Dichloromethane
DIPEA	<i>N,N</i> -Diisopropylethylamine
DLS	Dynamic light scattering
DMF	<i>N,N</i> -Dimethylformamide
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
DSC	Differential scanning calorimetry
E	Energy
ϵ	Dielectric constant
<i>ee</i>	Enantiomeric excess
ECD	Electric circular dichroism
EDC	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
EDX	Energy dispersive X-ray analysis
<i>e.g.</i>	Latin expression “ <i>exempli gratia</i> ”; for example
EIHH	Emulsification-induced-homo-helicity
EPR	Electron paramagnetic resonance
ESI	Electrospray ionization
<i>et al.</i>	Latin expression “ <i>et Alii</i> ”; and others
equiv	Equivalents
Et ₃ N	Triethylamine
ϕ	Phi dihedral angle: torsion angle N-C α
FT-IR	Fourier transform infrared spectroscopy
g	Grams
GPC	Gel performance chromatography
h	Hours
HATU	Azabenzotriazol-1-yl-1,1,3,3-tetramethyluronium hexafluorophosphate
Hept	Heptet
HOBT	1-Hydroxybenzotriazole
HOPG	High oriented pyrolytic graphite
HPLC	High-performance liquid chromatography
HPMC	Helical polymer-metal complex
H ν	Light
HRMS	High resolution mass spectrometry

Hz	Hertz
i.e.	Latin expression " <i>id est</i> "; it is
ICD	Induced circular dichroism
IR	Infrared spectroscopy
<i>it</i> -PMMA	Isotactic poly(methylmethacrylate)
λ	Wavelength
l	Pathlength
LB	Langmuir-Blodget
LC	Liquid crystal
LOD	Limit of detection
LS	Langmuir-Schaefer
M	Molar
<i>M</i> helix	Minus; Counterclockwise helix
M ⁺	Monovalent metal ion
M ²⁺	Divalent metal ion
m	Multiplet
mg	Miligrams
MD	Molecular dynamic
MHz	Megahertz
MIBK	Methyl isobuthyl buthyl ketone
min.	Minutes
mL	Millilitres
MM	Molecular mechanic
mM	Millimolar
μ M	Micromolar
mmol	Milimol
M _n	Number average molecular weight
MO	Molecular orbital
MPA	α -Methoxyphenylacetic acid
m.r.u	Monomeric repeating unit
MTBE	Methyl tert-butyl ether
MTPA	α -Methoxy- α -trifluoromethylphenylacetic acid
M _w	Molecular weight
Na ₂ SO ₃	Sodium sulfite

Abbreviations and Acronyms

NaHCO ₃	Sodium bicarbonate
ν	Wavenumber
nbd	2,5-norboradiene
NMR	Nuclear magnetic resonance
NMP	<i>N</i> -methyl-2-pyrrolidone
NP	Nanoparticle
OEG	Oligo(ethylene glycol)
P	Pressure
PA	Phenylacetylene
PBA	Poly(biarylylacetylene)
PBPA	Poly(biphenylacetylene)
PC	Photoconductivity
PCP	Polymer chiral particle
PDI	Polydispersity
PEA	Phenylethyl alcohol
PEG	Polyethylene glycol
Phe	Phenylalanine
<i>P</i> Helix	Plus; Clockwise helix
PLA	Polylactic
POM	Polarized optic microscopy
PPA	Poly(phenylacetylene)
ppm	Parts per million
PTrMA	Poly(triphenylmethylmethacrylate)
PQX	Poly(quinoxaline-2,3-diyl)s
Pyr	Pyren-1-yl
q	quartet
quint	quintet
QD	Quantum Dots
ROA	Raman optical activity
s	Singlet
SAXS	Small angle X-ray scattering
SC	Stereocomplex
SCF	Self-consistent field method
SDS	Sodium dodecyl sulfate

SEM	Scattering electric microscopy
<i>sp</i>	<i>synperiplanar</i>
st	Elongation
<i>st</i> -PMMA	Syndiotactic poly(methylmethacrylate)
STS	Scanning tunneling spectroscopy
t	Triplet
<i>t-c</i>	<i>trans-cisoid</i>
<i>t-t</i>	<i>trans-transoid</i>
TEM	Transmission electronic microscopy
TBAF	Tetrabutylammonium fluoride
TD-DFT	Time-Dependent Density Functional Theory
TFA	Trifluoroacetic acid
TGA	Thermal gravimetric analysis
THF	Tetrahydrofuran
TMS	Tetramethylsilil
TrMA	Triphenylmethyl methacrylate
u.r.m	See m.r.u
UV-Vis	Ultraviolet-visible
VT-CD	Variable temperature circular dichroism
Val	Valine
VCD	Vibrational circular dichroism
WAXS	Wide angle X-ray scattering
ω	Dihedral angle
XPS	X-ray photoelectron spectroscopy
XRD	X-ray diffraction
ψ	Psi dihedral angle: torsion angle C α -C
ZINDO/S	ZenerQs Intermediate Neglect of Differential Overlap

List of publications

During the development of this Thesis, the following article has been published in scientific journal. Furthermore, the results of this article have been included within this manuscript.

- 1) Rafael Rodríguez, Elena Rivadulla-Cendal, Manuel Fernández-Míguez, Berta Fernández, Emilio Quiñoá, Katsuhiko Maeda and Félix Freire.

Angew. Chem. Int. Ed. **2022**, *61*, e202209953.

Impact factor: 16.823.

Category: Chemistry, multidisciplinary (Q1)

E. R. C. has contributed to the experimental part (synthesis and characterization), discussion of results and the manuscript preparation.

The authorization of the journal can be found in the following link:

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INTRODUCTION

Introduction

The helix is one of the most important structures and it is inherently chiral, left and right-handed scaffolds cannot be superimposed. Thus, it can be found in nature at both microscopic and macroscopic level such as oligomers, peptides, polymers, etc and their assemblies can be optically active due to their helicity. In the 50's, took place the two most important discoveries of molecular biology: the first one was the discovery of the structure of the right-handed α -helix for proteins proposed by Pauling and Corey (1951),¹ and the second one was the double helical structure of DNA proposed by Watson and Crick (1953).² This helical structure is responsible for functions that these macromolecules adopt in living systems like catalysis, genetic information storage, ion transport, recognition, replication, etc.³

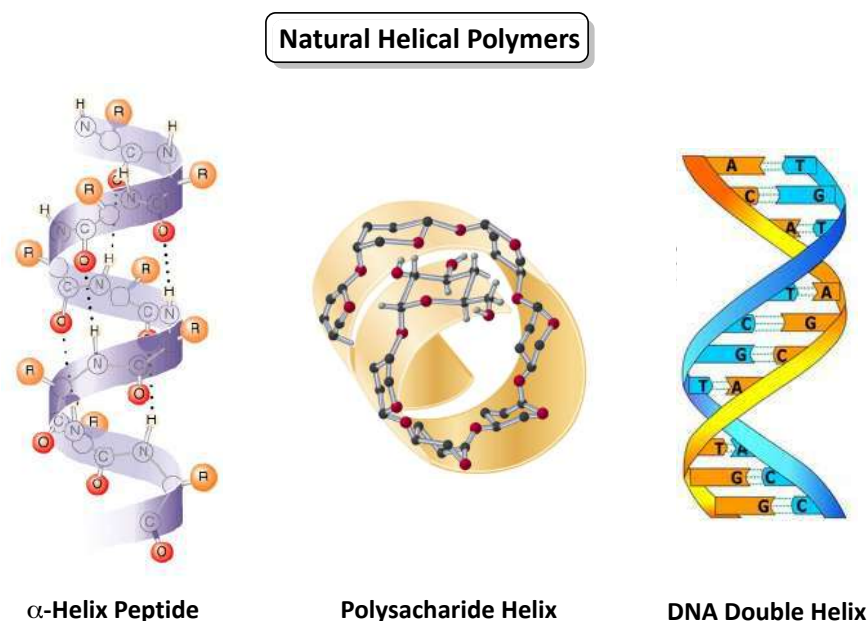


Figure 1. Naturally occurring helical polymers.

Taking these findings into account, the scientific community is making a great effort to emulate these structures; trying to develop new structures with new functionalities.⁴

¹ Pauling, L.; Corey, R. B.; Branson, H. R. *Proc. Natl. Acad. Sci. U. S. A.* **1951**, 37, 205-211.

² Watson, J. D.; Crick, F. H. C. *Nature* **1953**, 171, 737-738.

³ a) Alberts, B.; Johnson, A.; Lewis, J.; Morgan, D.; Raff, M.; Roberts, K.; Walter, P. *Mol. Biol. Cell*, 6th ed.; *Garland Science*: New York, **2014**; b) Saenger, W. *Principles of Nucleic Acid Structure*, 1 ed., Springer-Verlag New York, **1984**, p 556; c) Schulz, G. E.; Schirmer, R. H. *Principles of Protein Structure*, 1 ed., Springer-Verlag New York, **1979**.

⁴ a) Schwartz, E.; Koepf, M.; Kitto, H. J.; Nolte, R. J. M.; Rowan, E. *Polym. Chem.* **2011**, 2, 33-47; b) Yashima, E.; Maeda, K.; Iida, H.; Furusho, Y.; Nagai, K. *Chem. Rev.* **2009**, 109, 6102-6211; c) Liu, J.; Lam, J. W. Y.; Tang, B. Z. *Chem. Rev.* **2009**, 109, 5799-5867; d) Rosen, B. M.; Wilson, C. J.; Wilson, D. A.; Peterca, M.; Imam, M. R.; Percec, V. *Chem. Rev.*

The presence of a helical structure in a non-natural polymer was first described by Natta in 1955: an isotactic poly(propylene) (poly-1).⁵ This polymer presents a mixture of right- and left-handed helices in the solid state, losing the helical structure once the polymer is dissolved. Thereby, poly-1 was the first example of a synthetic helical polymer reported in literature (Figure 2).

In the 60's, the research community achieved to generate polymers that can adopt a helical structure even in solution. In this way, Pino and co-workers carried out the synthesis of a new series of poly-(vinyl) polymers (poly-2) by polymerization of optically active monomers, where the pendant group induces a predominant helical sense, that was determined using optical rotation.⁶ It was not until 70's that the most important advances were made in the helical polymers field. In particular, the groups of Okamoto, Nolte, and Green among others, made some of the most extraordinary progresses.

Nolte and co-workers determined the structure of poly(*tert*-butyl isocyanide) (poly-3) into left- and right-handed helices by chiral HPLC in 1974.⁷ Later, Okamoto's group synthesized the first helical vinyl polymer (poly-4) using an achiral monomeric unit, triphenylmethyl methacrylate (TrMA), and a chiral catalyst —lithium (*R*)-*N*-(1-phenylethyl)anilide and (-)-sparteine-*n*-BuLi complex— able to form a helix with a preferred helical sense in solution induced by the chirality of the catalyst. These results were applied in fields such as HPLC, using the helical polymeric materials as stationary phase (CSP).⁸

In the late 80's, Green and co-workers reported an important discovery in the helical polymer field. They managed to synthesize a new family of helical polymers, the poly(isocyanate)s (poly-5), which helical structure is a mixture of both helical senses (right- and left-handed), in the same helical structure by applying different external stimuli. Furthermore, they reported that this helical interconversion takes place through

⁵ Natta, G.; Pino, P.; Corradini, P.; Danusso, F.; Mantica, E.; Mazzanti, G.; Moraglio, G. *J. Am. Chem. Soc.* **1955**, *77*, 1708-1710.

⁶ Pino, P.; Lorenzi, G. *P. J. Am. Chem. Soc.* **1960**, *82*, 4745-4747.

⁷ Nolte, R. J. M.; Van Beijnen, A. J. M.; Drenth, W. *J. Am. Chem. Soc.* **1974**, *96*, 5932-5933.

⁸ Okamoto, Y.; Suzuki, K.; Ohta, K.; Hatada, K.; Yuki, H. *J. Am. Chem. Soc.* **1979**, *101*, 4763.

the presence of helical reversals.⁹ Thus, poly(isocyanate)s were the first example of dynamic helical polymer, a new family of polymers that includes different kinds of polymers such as poly(acetylene)s^{4c, 10} or poly(silanes).¹¹

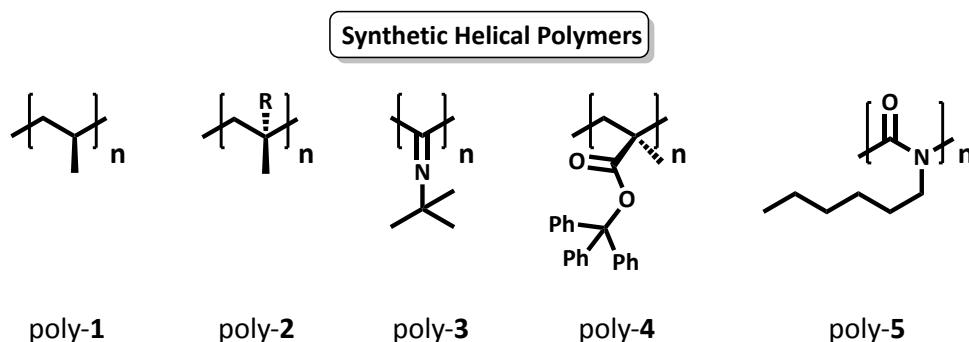


Figure 2. Schematic representation of synthetic helical polymers.

1. Helical Polymers Classification

Synthetic helical polymers can be classified in two main groups according to their dynamic behaviour and their helical properties. These dynamic properties are directly related with the interconversion energy barrier between the *M* and *P* helical states. Thus, when the helix inversion barrier of the polymer is high the *M* and *P* helical states cannot be switched one into the other. These kinds of polymers are known as static helical polymers (Figure 3) and are found in polymers that bear bulky substituents. Otherwise, if a polymer presents a low interconversion barrier, the helical structure can be switched from *M* to *P* helices. This family of polymers is designated as dynamic helical polymers (Figure 4).

1.1. Static Helical Polymers

Static helical polymers are defined as those polymers that keep a rigid structure with a defined helical sense during their synthesis. Thus, these materials present a high interconversion energy barrier between the two orientations of the helix (*M* and *P*) and cannot be modulated using external stimuli once they have been synthesized. These polymers are obtained by a process called “helix-sense-selective polymerization”⁴ⁱ that consists in the polymerization of optically active monomers or achiral monomers using

⁹ Green, M. M.; Andreola, C.; Munoz, B.; Reidy, M. P.; Zero, K. *J. Am. Chem. Soc.* **1988**, *110*, 4063.

¹⁰ Liu, J.; Tang, B. Z. *Acc. Chem. Res.* **2005**, *38*, 745-754.

¹¹ Fujiki, M. *Macromol. Rapid Commun.* **2001**, *22*, 539.

chiral catalysts. Some of the most representative examples of static helical polymers are poly(guanidine)s (poly-6), poly(isiocianurate)s (poly-7), poly(methacrylamide)s (poly-8), poly(methacrylate)s (poly-9) or poly(quinoxaline-2,3-dyl)s (poly-10).^{4b,j}

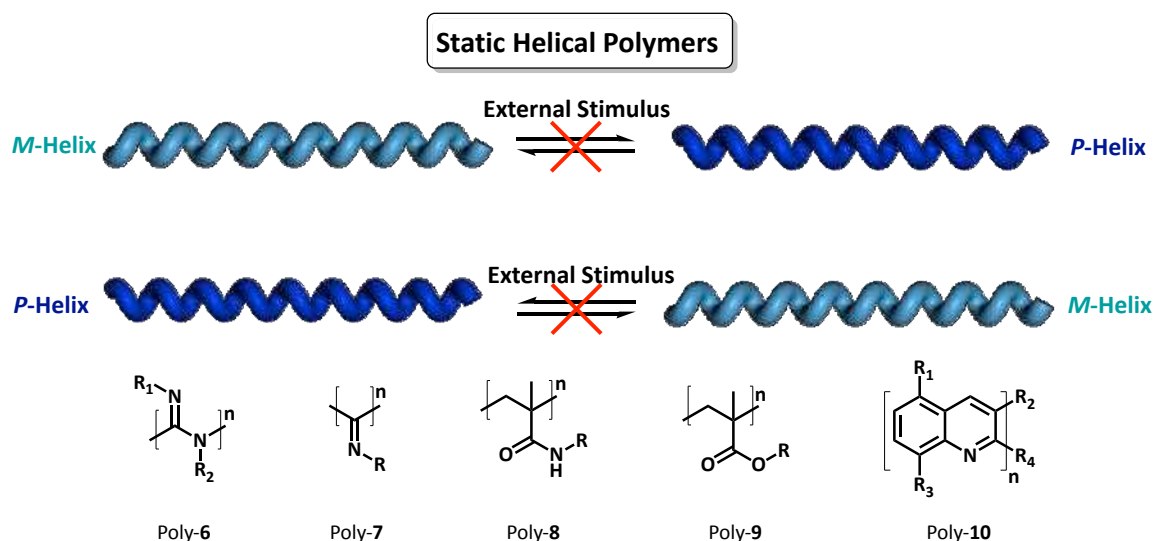


Figure 3. Conceptual representation and some representative scaffolds of the static helical polymers.

1.2. Dynamic Helical Polymers

Dynamic helical polymers are a group of polymers that can adopt both (*P* and *M*) helical structures due to their low interconversion energy barrier. Thereupon, these polymers can be easily switch from left to right-handed helices and *vice versa* by applying different external stimuli such as chiral molecules, metal ions, pH, polarity of the solvent, temperature, etc.^{4e,f,h, 12} Moreover, the two helical senses can coexist within the same polymer chain in similar or different proportion, separated by helical reversal (Figure 4).

There are two different ways to carry out their synthesis:

- *Polymerization of optically active monomers* that acquire preferably one of the two helices (*P* or *M*).¹³
- *Polymerization of optically inactive monomers* where the interaction with a chiral solvent or molecule on a solution provide a specific helical sense due to the establishing of the chiral inducer-polymer complex.¹⁴

¹² Yashima, E.; Maeda, K.; Kishimura, T. *Chem. Eur. J.* **2004**, *10*, 42-51.

¹³ Louzao, I.; Seco, J. M.; Quiñoá, E.; Riguera, R. *Angew. Chem. Int. Ed.* **2010**, *49*, 1430-1433.

¹⁴ Freire, F.; Seco, J. M.; Quiñoá, E.; Riguera, R. *Angew. Chem. Int. Ed.* **2011**, *50*, 11692-11696.

Poly(acetylene)s^{4c, 10} (poly-11), poly(isocyanate)s^{4a} (poly-12) and poly(silane)s¹¹ (poly-13) are usually classified as dynamic ones.

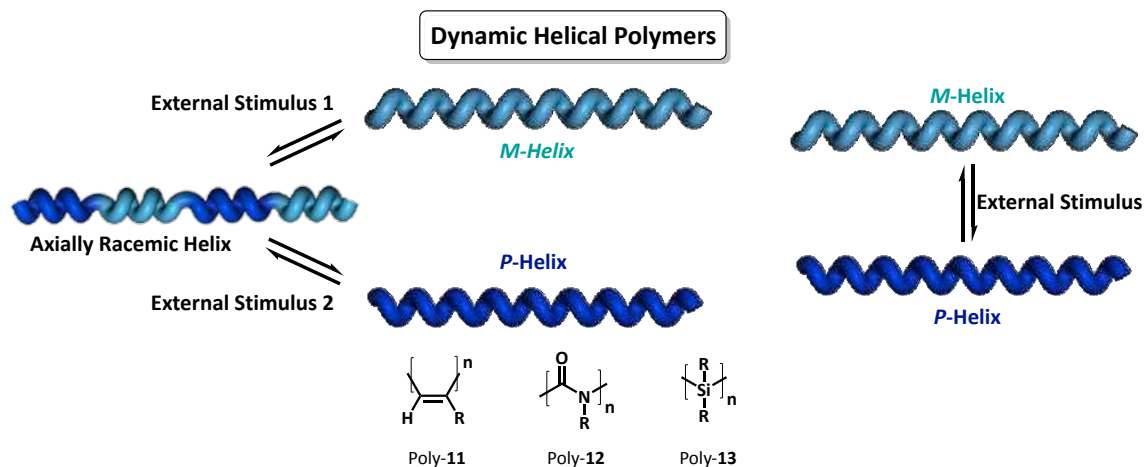


Figure 4. Schematic representation of synthetic helical polymers.

1.3. Foldamers

Foldamers were described by Prof. Samuel Gellman as “polymers with a strong tendency to adopt a specific compact conformation”. Thereby, these macromolecules can be regarded as dynamic helical polymers, which can show a predominant helical sense in solution stabilized by non-covalent interactions between non-adjacent monomeric units (Figure 5). Different examples of foldamers are *meta*-phenylene ethynylenes (poly-14) or quinolinecarboxamides (poly-15) among others.¹⁵

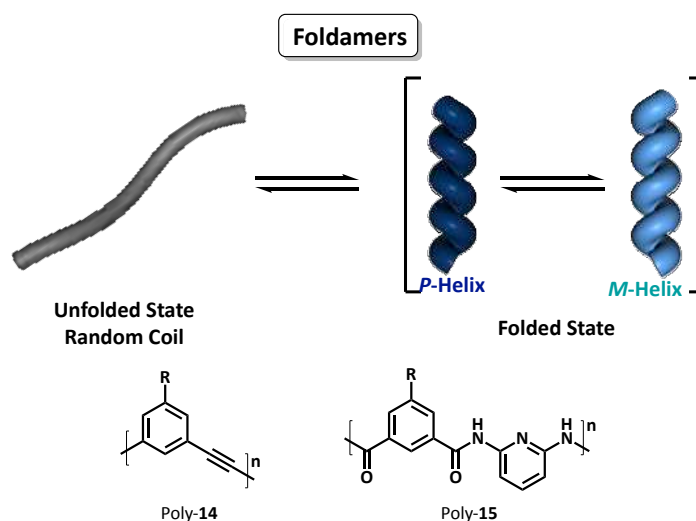


Figure 5. Some examples of foldamers.

¹⁵ (a) Hill, D. J.; Mio, M. J.; Prince, R. B.; Hughes, T. S.; Moore, J. S. *Chem. Rev.* **2001**, *101*, 3893-4012. (b) Appella, D. H.; Christianson, L. A.; Karle, I. L.; Powell, D. R.; Gellman, S. H. *J. Am. Chem. Soc.* **1996**, *118*, 13071-13072.

2. Poly(Acetylene)s

Poly(acetylene)s (PA)s are a family of dynamic helical polymers that exhibit a polyene backbone constituted by π -conjugated double bonds. These polymers can be easily synthesized by polymerization of the corresponding acetylenic monomers (alkyne as polymerizable group). There are several examples of monomers such as aliphatic acetylenes^{4b,c, 10} (m-1), phenylacetylenes (m-2), propargylamides (m-3), propargyl esters (m-4) or propionic esters (m-5) with an alkyne moiety that can provide (PA)s derivatives (Figure 6).

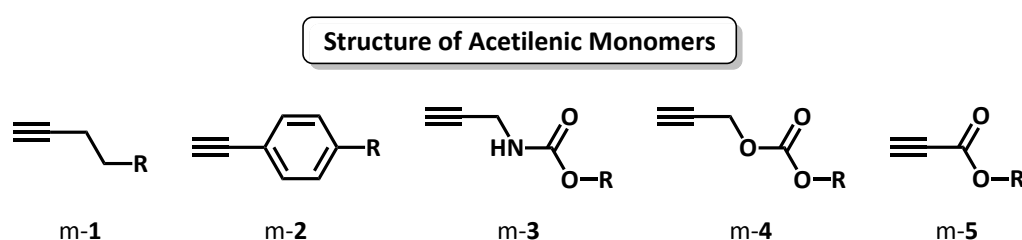


Figure 6. Representative structures of PA family.

Poly(phenylacetylene)s (PPA)s are the most studied (PA)s due to their processability, their solubility in common organic solvents, their stability in air and their easy synthesis among others. Taking all this information into account, these kinds of polymers constitute a potential candidates for several applications such as CSP for HPLC, as chiral sensors, asymmetric electrodes, optical polarizing films, and so on.^{4c, 10}

A remarkable structural characteristic of (PA)s is that they present four possible configurations of the conjugated double bonds of the polyenic main chain —*trans-cisoid* (*t-c*), *trans-transoid* (*t-t*), *cis-cisoid* (*c-c*) and *cis-transoid* (*c-t*) — being only the *c-c* and *c-t* configurations the ones that promote the formation of a helical structure (Figure 7).

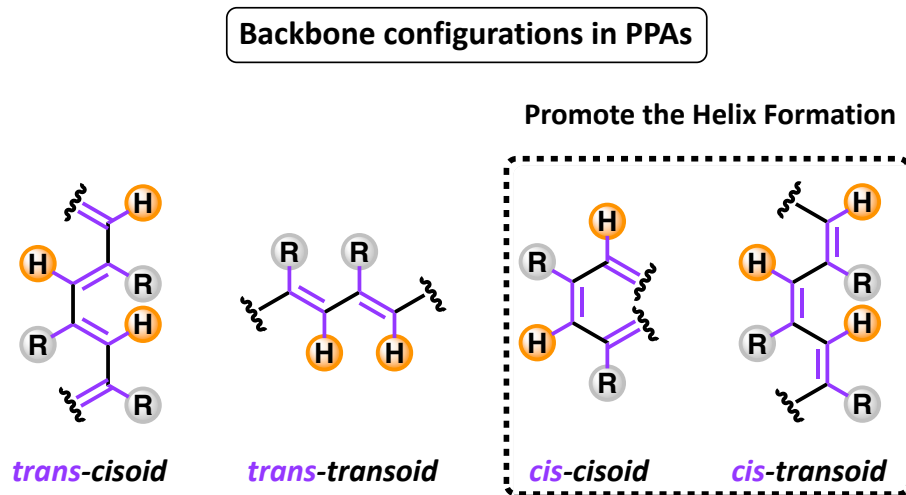


Figure 7. Possible configuration that the polyene backbone of the (PPA)s can adopt.

The most popular catalyst to carry out their polymerization was developed by Noyori and co-workers and consists on a family of Rh (I) catalysts, which produce (PA)s with a high *cis*- content of double bonds. Also, high molecular polymers, in high yield and with low polydispersity are generated by a stereospecific living polymerization reaction.¹⁶

There are different examples of catalyst commercially available that work in organic solvents ($[\text{Rh}(\text{nbd})\text{Cl}]_2$, $[\text{Rh}(\text{cod})\text{Cl}]_2$) or even in water ($[\text{Rh}(\text{cod})(\text{BF}_4)]$).

The polymerization mechanism of (PPA)s using Rh (I) catalysts consists in a 2,1-alkyne insertion (Figure 8). There is steric repulsion between pendant units that lead to a high stereoregular polymer chain and is the responsible of this mechanism.¹⁷

¹⁶ (a) Hirao, K.; Ishii, Y.; Terao, T.; Kishimoto, Y.; Miyatake, T.; Ikariya, T.; Noyori, R. *Macromolecules* **1998**, *31*, 3405. (b) Kishimoto, Y.; Eckerle, P.; Miyatake, T.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1994**, *116*, 12131.

¹⁷ Ke, Z.; Abe, S.; Ueno, T.; Morokuma, K. *J. Am. Chem. Soc.* **2011**, *133*, 7926.

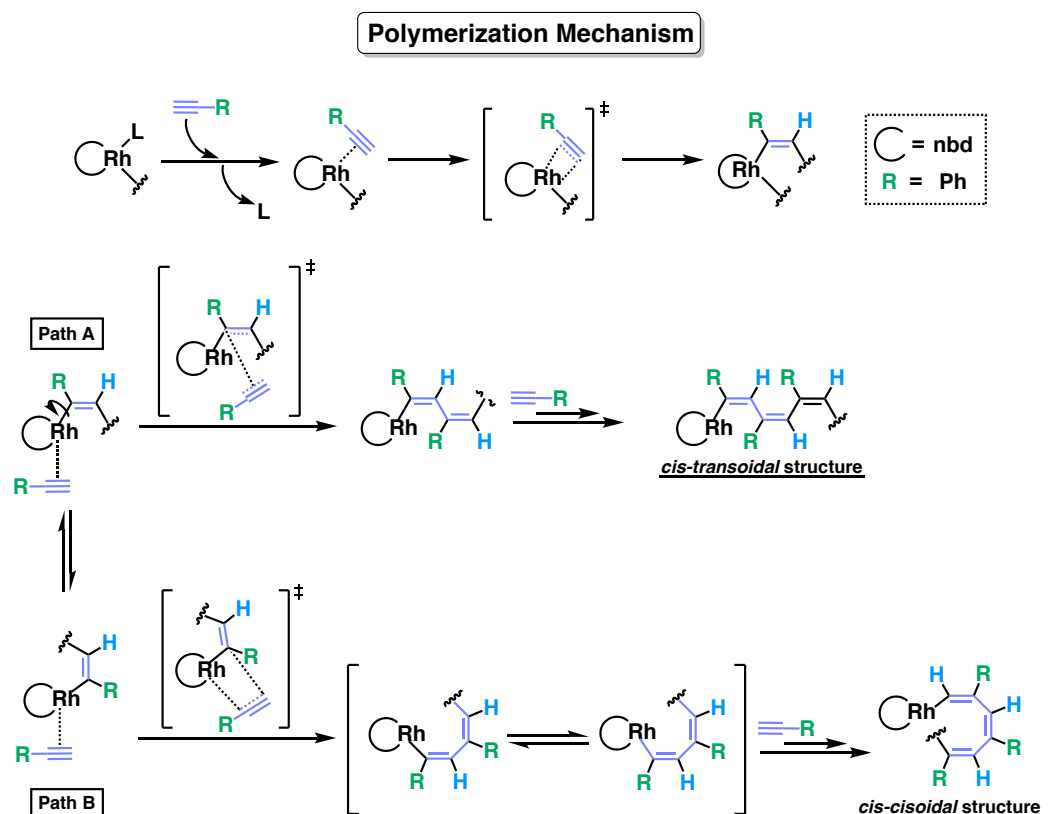


Figure 8. Polymerization mechanism of PA by Rh (I) catalysts.

3. Stability of Poly(PhenylAcetylene)s

Since the discovery of poly(phenylacetylene)s with *cis-cisoidal* or *cis-transoidal* polyene backbone were extensively studied. One of the most important features of these particular helical polymers is their stability and degradation, which is close related to their structure.¹⁸

Percec and co-workers developed different structural studies of a *cis-transoidal* PPA showing a decrease in the *cis*- content of double bonds and in their molecular weight (M_w) once that they are in chloroform solution.^{18f} This degradation process goes through an intramolecular electrocyclization followed by a polymer chain break that produces a 1,3,5-triphenylbenzene.^{18d,f} Moreover, this decomposition occurs indistinctly in solution

¹⁸ (a) Liu, I.; Namikoshi, T.; Zang, Y.; Aoki, T.; Hadano, S.; Abe, Y.; Wasuzu, I.; Tsutsuba, T.; Teraguchi, M.; Kaneko, T. *J. Am. Chem. Soc.* **2013**, *135*, 602. (b) Huang, K.; Mawatari, Y.; Miyasaka, A.; Sadahiro, Y.; Tabata, M.; Kashiwaya, Y. *Polymer* **2007**, *48*, 6366. (c) Miyasaka, A.; Mawatari, Y.; Sone, T.; Tabata, M. *Polym. Degrad. Stab.* **2007**, *92*, 253. (d) Percec, V.; Rudick, J. G. *Macromolecules* **2005**, *38*, 7241. (e) Deng, J.; Tabei, J.; Shiotsuki, M.; Sandra, F.; Masuda, T. *Polymer* **2004**, *45*, 7395. (f) Percec, V.; Rudick, J.; Nomer, P.; Buchowicz, W. *J. Polym. Sci., Part A: Polym. Chem.* **2002**, *40*, 3212. (g) Abdul Kaim, S. M.; Nomura, R.; Masuda, T. *J. Polym. Sci., Part A Polym. Chem.* **2001**, *39*, 3130. (h) Tabata, M.; Tanaka, Y.; Sadahiro, Y.; Sone, T.; Yokota, K.; Miura, I. *Macromolecules* **1997**, *30*, 5200. (i) Matsunami, S.; Watanabe, T.; Kamimura, H.; Kakuchi, T.; Ishii, F.; Tsuda, K. *Polymer* **1996**, *37*, 4853. (j) Simonescu, C. I.; Percec, V.; *Polym. Sci., Part A: Polym. Chem.* **1980**, *18*, 147.

and in solid state and can be affected by the presence of air and/or by heating at 100°C detecting by ^1H NMR experiments.^{18d,f} On the opposite side, this degradation is slowed down in vacuum or under inert atmosphere.¹⁹ Thus, (PPA)s can be considered thermosensitive, and this should be considering during their manipulation.

In addition, Tabata and co-workers reported different examples of *cis-trans* isomerization processes in (PPA)s that can be promoted by external stimuli such as electric field, heating, light and pressurization. There are unpaired electrotrons (radicals), involved in the mechanism of the isomerization, that are stabilized as electrons solitons.^{18b,c,h}

Most recently, a helical-sense selective photodegradation by selective photocyclic aromatization (SCAT) was reported by Liu *et al.* In particular, this reaction depends on the macromolecular structure of the PPA and takes places in the solid state and only with *cis-cisoidal* structures, yielding exclusively a 1,3,5-trisubstituted benzene derivative.^{18a, 20}

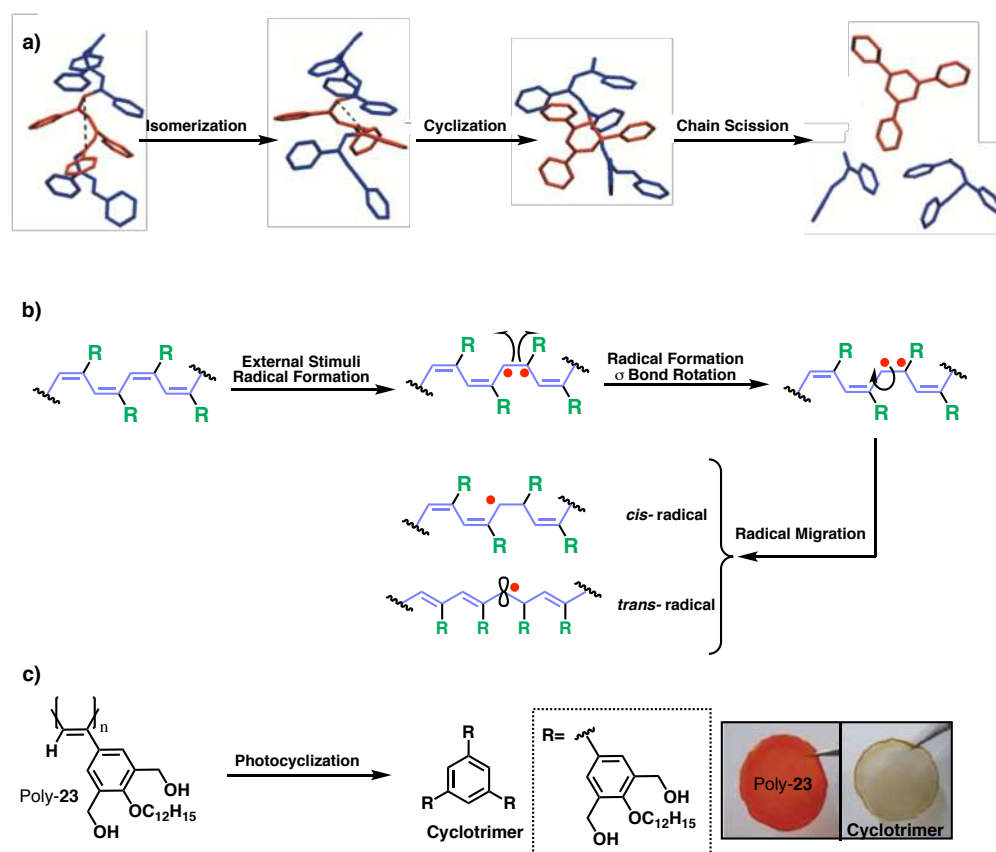


Figure 9. (a) Schematic illustration of the degradation mechanism by means of intramolecular electrocyclization reported by Percec and co-workers. (b) Schematic representation of *cis*- to

¹⁹ Vohlidal, J.; Redrova, D.; Pacovska, M.; Sedlacek, J. *Collect Czech Chem. Commun.* **1993**, 58, 2651-2662.

²⁰ Miyata, M.; Masahiro, T.; Hirimochi, E.; Takashi, K.; Toshiki, A. *Chem. Lett.* **2014**, 43, 1476-1477.

trans- isomerization processes induced by an external stimuli reported by Tabata and co-workers. (c) Schematic illustration of the photocyclic aromatization reaction of *c-c* (PPA)s in the solid state reported by Liu *et al.*

4. Properties of Dynamic Helical Polymers

Dynamic helical polymers have great potential for the development of materials such as chiral sensors, conductive materials, memory storage, optical devices, etc. Their functions are determined by two structural parameters: the helical sense adopted by the PPA (*P* or *M*) and the stretching degree of the polyene chain. Hence, both parameters can be switch by the addition of external stimuli (chiral molecules, metal ions, pH, polarity of the solvent, temperature among others). In the following section the main properties of helical polymers will be discussed in detail.

4.1. Helical Induction

As stated before, a dynamic helical polymer can be synthesized starting from an achiral monomeric unit. These polymers are racemic from the microscopic point of view displaying left- and right-handed helices in the same population. However, the induction of a specific helicity can be promoted by the addition of chiral molecules to the starting axially material, through non-covalent bonding interactions.^{4b,f}

The first example of macromolecular helical induction in (PPA)s was reported by Yashima *et al.*²¹ To develop this work, they used a racemic poly-(4-carboxy)phenylacetylene (poly-**16**) —null CD signal— that can be turned into pure right- or left-handed helices through the formation of a complex with chiral amines. These acid-base interactions are the responsible to induce a specific handedness —CD active determined by the absolute configuration of the chiral amine employed—. ^{21, 22} Based on these findings, this induction phenomenon was applied to carry out other potential materials for chiroptical sensing. Furthermore, this helix induction was also demonstrated to work not only in solution, but also in the gel state, in liquid crystalline phases and even in the solid state.²³

²¹ Yashima, E.; Matsushima, T.; Okamoto, Y. *J. Am. Chem. Soc.* **1995**, *117*, 11596-11597.

²² (a) Hase, Y.; Nagai, K.; Iida, H.; Maeda, K.; Ochi, N.; Sawabe, K.; Sakajiri, K.; Okoshi, K.; Yashima, E. *J. Am. Chem. Soc.* **2009**, *131*, 10719. (b) Yashima, E.; Matsushima, T.; Okamoto, Y. *J. Am. Chem. Soc.* **1995**, *117*, 11596.

²³ Goto, H.; Zhang, H. Q.; Yashima, E. *J. Am. Chem. Soc.* **2003**, *125*, 2516.

4.2. Memory Effect

The chiral induction phenomenon is a dynamic process, this means that when the inductors are removed a disappearance of the induced helical sense is produced. Taking this topic into account, Yashima *et al.* have demonstrated how the poly-(4-carboxy)phenylacetylene (poly-**16**) could keep the induced helical sense after the chiral amine was completely replaced by an achiral one. This process is known as “Memory Effect” and the mechanism can be explained by the stabilization of the helical configuration due to the presence of electrostatic repulsions between the pendant groups.²⁴

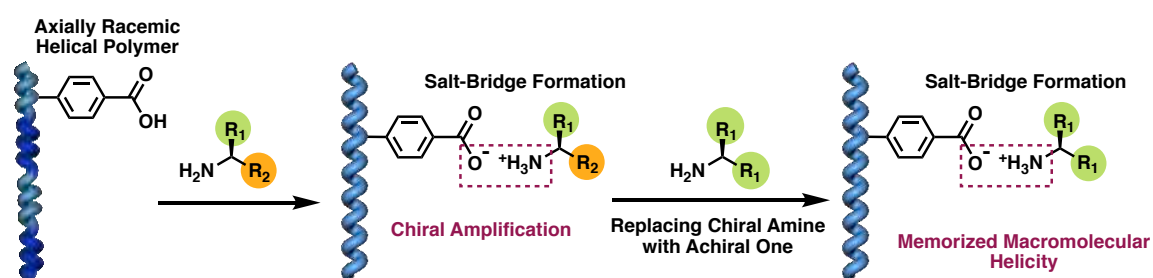


Figure 10. Schematic illustration of the helix induction and memory of macromolecular helicity.

4.3. Chiral Amplification

Chiral amplification is one of the most amazing process in dynamic helical polymers. Basically, this phenomenon consists of a significant increase in the final chiral content when a small amount of an external stimuli (chiral or achiral) is added to the starting axially system. Also, this enhancement is favored by covalent or non-covalent interactions.^{12, 25}

In this case, the addition of a chiral molecule to a polymer that exhibit left- and right-handed helices in the same proportion, will generate a supramolecular complex which is the responsible to induce a specific screw sense (*M* or *P*) to the starting racemic system. Likewise, this helicity is determined by the absolute configuration of the chiral substrate.

Nevertheless, there are other ways to lead a preferred helical sense: for example, a system that, despite of being chiral, presents a conformational equilibrium between two

²⁴ Yashima, E.; Maeda, K.; Okamoto, Y. *Nature* **1999**, 399,449.

²⁵ (a) Palmans, A. R. A.; Meijer, E. W. *Angew. Chem. Int. Ed.* **2007**, 46, 8948-8968. (b) Feringa, B. L.; Van Delden, R. A. *Angew. Chem. Int. Ed.* **1999**, 38, 3418.

or more structures, displaying a new chiral axially racemic scenario. A selective fixation of one of the structures is produced providing a specific handedness.

Another process, known as “Chiral Enhancement”, was demonstrated by our research group through the synthesis of a poly(phenylacetylene) (poly-**17**) bearing α -methoxy- α -phenylacetic acid (MPA) as chiral pendant groups where an achiral external stimulus is able to promote a preferred helical sense.¹⁴ Deep into details, this PPA is highly dynamic, this means it is axially racemic from the macroscopic point of view presenting 50% of left-handed helices and 50% of right-handed helices —null CD signal— due to the presence of two main conformers in equilibrium in equal population in the pendant group: *sp* conformer, where the carbonyl and methoxy groups are *synperiplanar* oriented [dihedral angle for (C=O-C-OMe) ca. 0°] and *ap* conformer, where the the carbonyl and methoxy groups are *antiperiplanar* oriented [dihedral angle for (C=O-C-OMe) ca. 180°]. Aforementioned, the addition of metal ions has an important role in this conformational equilibrium due to their different coordination mode with the pendant group. In particular, the presence of monovalent metal ions (i.e., Li⁺, Na⁺ and Ag⁺) determine the *ap* conformation (*M* helix) owing to the coordination between the metal ion and the pendant group through the carbonyl group and an extra cation- π interaction with the aryl ring of the MPA moiety. On the other hand, the *sp* conformation (*P* helix) is fixed by the addition of divalent metal ions (i.e., M⁺²) that prefer to coordinate both carbonyl and methoxy group.

Interestingly, Aries *et al.* reported a total control on the helical sense of poly-**17** by activation/deactivation of the cation- π interactions.²⁶ They demonstrated how the *ap* conformation can be converted to *sp* by employing an suitable cosolvent that disrupts these cation- π interactions (that stabilizes the *ap* conformation). Hence, if we switch the coordination mode between the pendant group and the metal ion together with the addition of a monovalent metal ion, we will be able to lead the *P* helix or *M* helix in poly-**17**.

²⁶ Arias, S.; Freire, F.; Quiñóá, E.; Riguera, R. *Polym. Chem.* **2015**, *6*, 4725-4733.

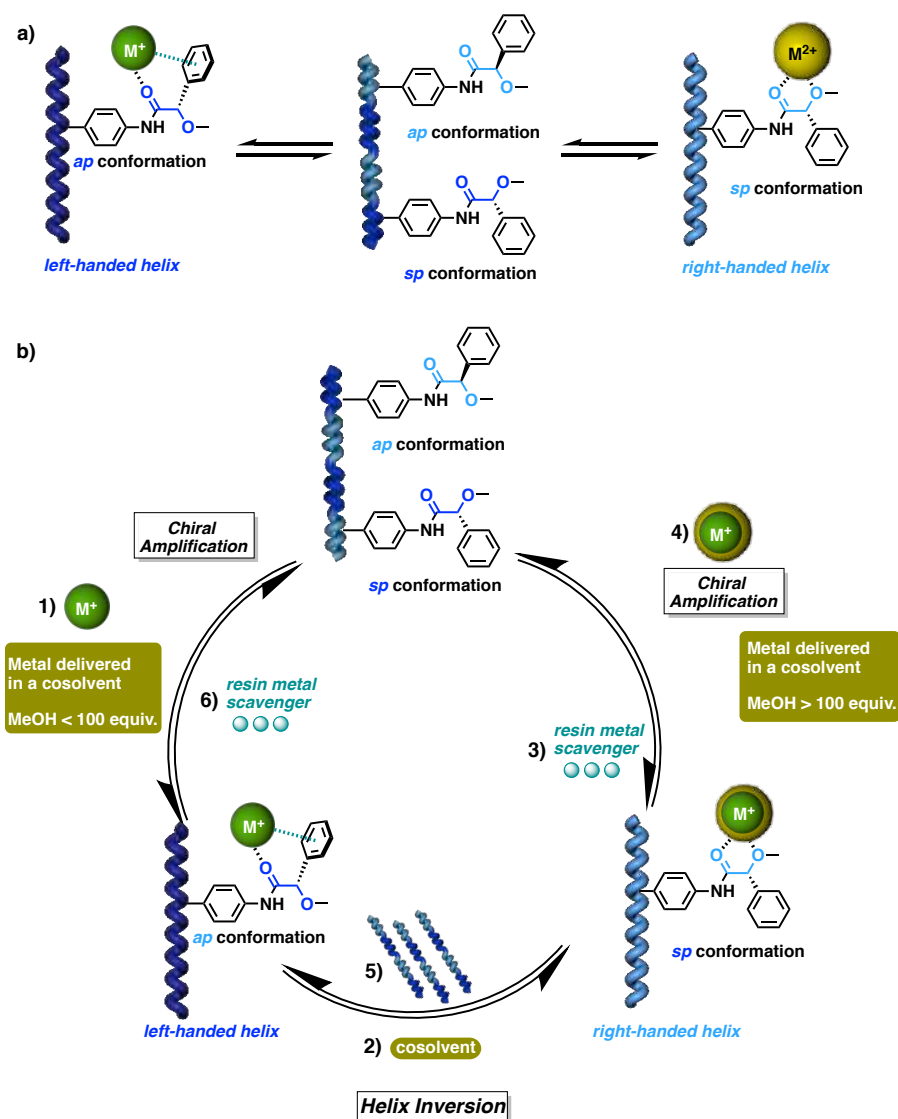


Figure 11. (a) Metal coordination driven chiral amplification process for poly-17. (b) Cation- π driven selection of the left- or right-handed helical sense of poly-17 by activation/deactivation of cation- π interactions.

Chiral amplification studies have been for the first time investigated by Green *et al.* using helical poly(isocyanite)s. These helical systems display left- and right-handed helices in equal proportion, being connected through helical reversals. They discovered three chiral amplification phenomena employing covalent and non-covalent polymeric systems: Sergeants and Soldiers Effect, Majority Rules and Chiral Conflict. These three examples of chiral amplification phenomena will be explained in detail next.

4.4. Sergeants and Soldiers Effect

As mentioned before, the Sergeants and Soldiers Effect is a chiral amplification phenomenon reported by Green *et al.* in 1988. They presented a copolymer composed by achiral isocyanate units (Soldier) and a small percentage of chiral isocyanate (Sergeant) (99%/1% chiral/achiral ratio). This system allowed controlling the helical sense of the polyenic chain by/through a cooperative mechanism. This means that this copolymer showed that Sergeant is able to command the Soldier, where the achiral units adopt the specific helicity of the chiral one.²⁷

From this first study, other Sergeants and Soldiers Effects have been developed in covalent and supramolecular polymers. In 1997, Meijer and co-workers reported this effect in dynamic helical assemblies using 3,3'-diamino-2,2'-bipyridine (poly-**18**) (BiPy) moieties with chiral aliphatic chains (Sergeant) with achiral (Soldiers).²⁸ The chiral units form a helical structure provided by columnar stacks in apolar solvents, which displays a CD response due to π - π^* transition of the bipyridine moiety, while the achiral ones formed racemic helical columnar stacks showing a null CD signal. Nevertheless, the addition of only 2.5% of Sergeant moiety to a hexane solution of the achiral ones (Soldiers) resulted in a significant CD signal, which is comparable with CD response of the pure chiral units in *n*-hexane. This study was the first example of chiral amplification where the Sergeants and Soldiers Effect is operative in dynamic structures of molecular aggregates.

A remarkable aspect of the Sergeants and Soldiers Effect is that although a small percentage of Sergeant is enough to command the helicity of the amplified system, this at the same time is a great drawback since although the system finally presents this chiral amplification effect, it will not be possible to modify the screw sense of the final supramolecular structure.

However, our research group achieved to overcome this handicap applying the Sergeants and Soldiers Effect to the selective chiral amplification reported for poly-**17**.²⁹ For that, poly(phenylacetylene)s copolymer integrated by the combination of achiral

²⁷ (a) Green, M. M.; Park, J.-W.; Sato, T.; Teramoto, A.; Lifson, S.; Selinger, R. L. B.; Selinger, J. V. *Angew. Chem. Int. Ed.* **1999**, *38*, 3138. (b) Green, M. M.; Peterson, N. C.; Sato, T.; Teramoto, A.; Cook, R.; Lifson, S. *Science* **1995**, *268*, 1860. (c) Green, M. M.; Reidy, M. P.; Johnson, R.D.; Darling, G.; O'Leary, D. J.; Willson, G. J. *Am Chem. Soc.* **1989**, *111*, 6452.

²⁸ Palmans, A. R. A.; Meijer, E. W. *Angew. Chem. Int. Ed.* **2007**, *46*, 8948.

²⁹ Bergueiro, J.; Freire, F.; Wendler, E. P.; Seco, J. M.; Quiñoá, E.; Riguera, R. *Chem. Sci.* **2014**, *5*, 2170-2176.

monomer (phenylacetylene derivative) and chiral one (MPA monomer) was designed. Contrary to Green's system, our chiral MPA moiety presents an axially racemic behaviour—two conformers in equal population—, which means that it is not able to organize the helical structure. Thus, the chiral moiety only could be the Sergeant by the addition of a small amount of an achiral agent (i.e., monovalent or divalent metal ions). This external stimulus coordinates to one of the two MPA conformers inducing a specific helical sense not only to the other MPA conformer, but also to the achiral unit. As a result, we have a fully folded state where the handedness is determined by the valance of the metal ion added to the MPA moiety.

Moreover, the reversibility of this phenomenon was also studied. In this way, we are able to recover the initial racemic state if the metal cation is removed from the helical polymer metal complex. Thus, our research group reported for the first time a Sergeants and Soldiers Effect that can be selectively activated/deactivated by the addition or removal of external stimuli.

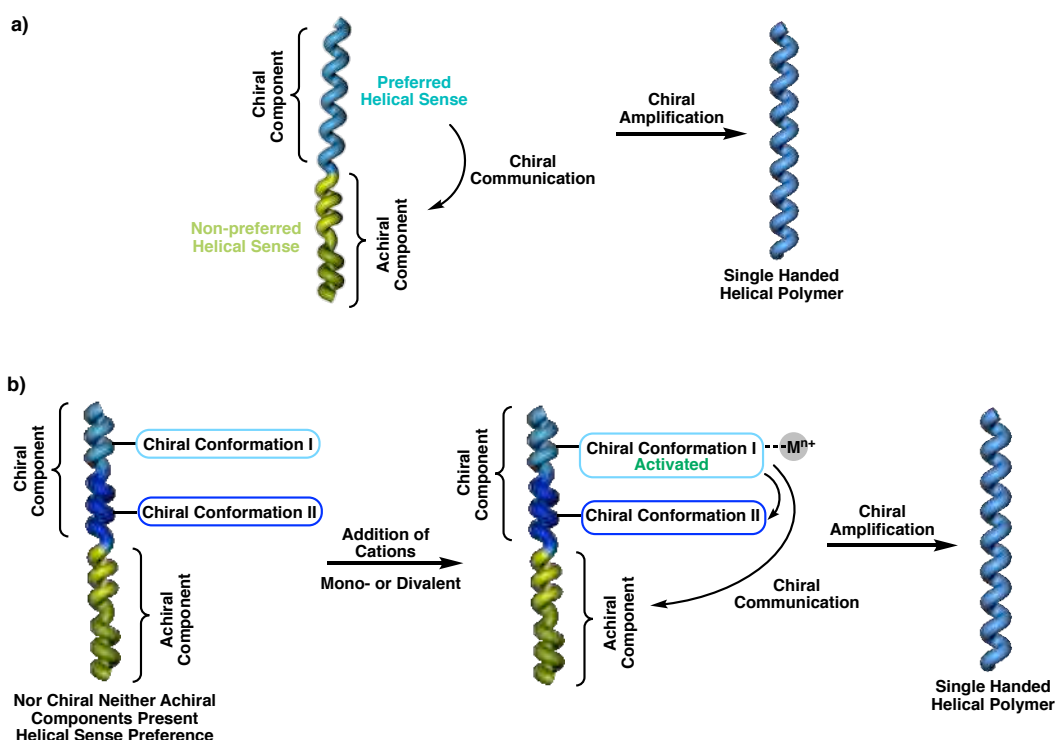


Figure 12. Schematic illustration of the chiral amplification phenomena through the Sergeant and Soldiers effect (a) Classical approach and (b) Metal-driven coordination approach.

Finally, it is important to say that the helicity induced in poly-17 by the addition of monovalent metal ions is produced by the presence of cation- π interactions, which can be disrupted by the addition of a cosolvent. In particular, our group used a single

monovalent cation (i.e., Na^+),³⁰ that in the presence of low amounts of cosolvent, coordinates to the pendant group in the *ap* mode —cation- π interaction on—. Nevertheless, a higher amount of cosolvent disrupt the chelation in *ap* mode and the coordination mode shifts towards the *sp* conformation.

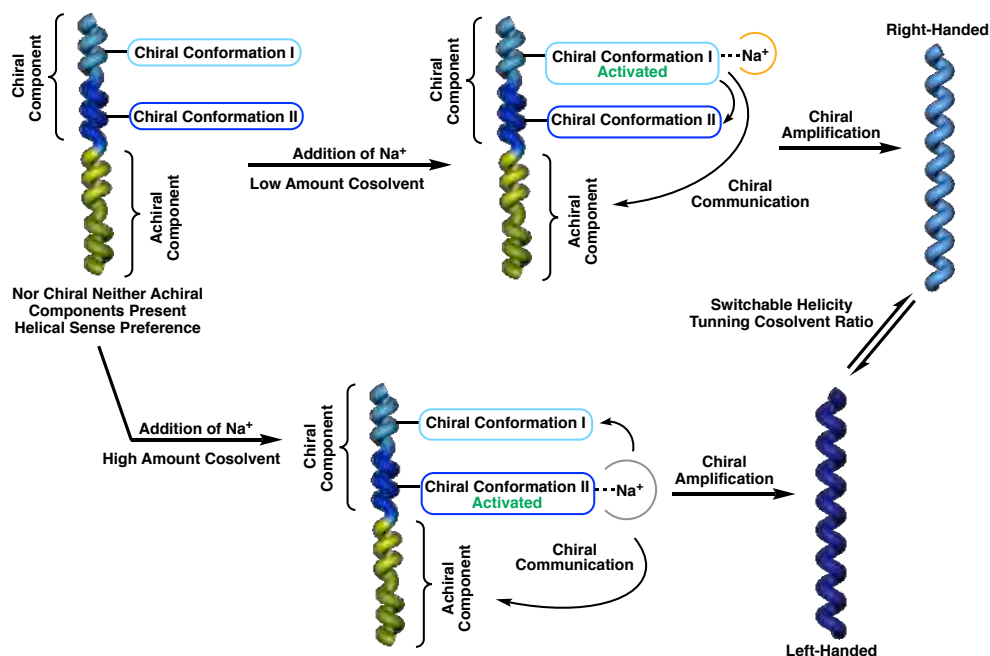


Figure 13. Total control on the helical sense of a PPA through the Sergeant and Soldiers effect by selective tuning of the cation- π interactions.

4.5. Majority Rules

Green *et. al.* discovered another chiral amplification phenomenon through the synthesis of poly(isocyanate)s copolymers consisting in a mixture of (*R*)- and (*S*)-enantiomers that present a small enantiomeric excess (*ee*). They found that this small *ee* is able to generate a predominantly one-handed helical conformation —only a 12% of *ee* is enough to promote a single-handed helical polymer—. ³¹ This means that the minor component adopts the helical sense of the major component in order to avoid the presence of helical reversals. This phenomenon is known as “Majority Rules” and has also been observed for dynamic helical poly(acetylene)s through non-covalent chiral interactions.¹⁴ This study was reported by Yashima and co-workers who synthesized a new racemic PPA (poly-**19**) bearing an aza-18-crown-6-ether —a very common and

³⁰ Arias, S.; Bergueiro, J.; Freire, F.; Quiñoá, E.; Riguera, R. *Small* **2016**, *12*, 238.

³¹ Green, M. M.; Garetz, B. A.; Munoz, B.; Chang, H. P.; Hoke, S.; Cooks, R. G. *J. Am. Chem. Soc.* **1995**, *117*, 4181.

useful functional group involved in host-guest chemistry— as pendant group.³² This polymer generates a one-handed helix once interacts with *L*-Alanine and another natural or non-natural amino, where the final helicity is determined by the absolute configuration of the amino acid. The complex shows an induced circular dichroism (ICD), responsible of a cooperative complexation. Additionally, mixtures of *L*- and *D*-Ala in different ratios were evaluated, where a very small *ee* of chiral guest (less than 0.005%) was able to promote a specific screw sense. For this reason, poly-**19** is considered one of the most sensitive receptors for detecting the amino acids chirality.¹²

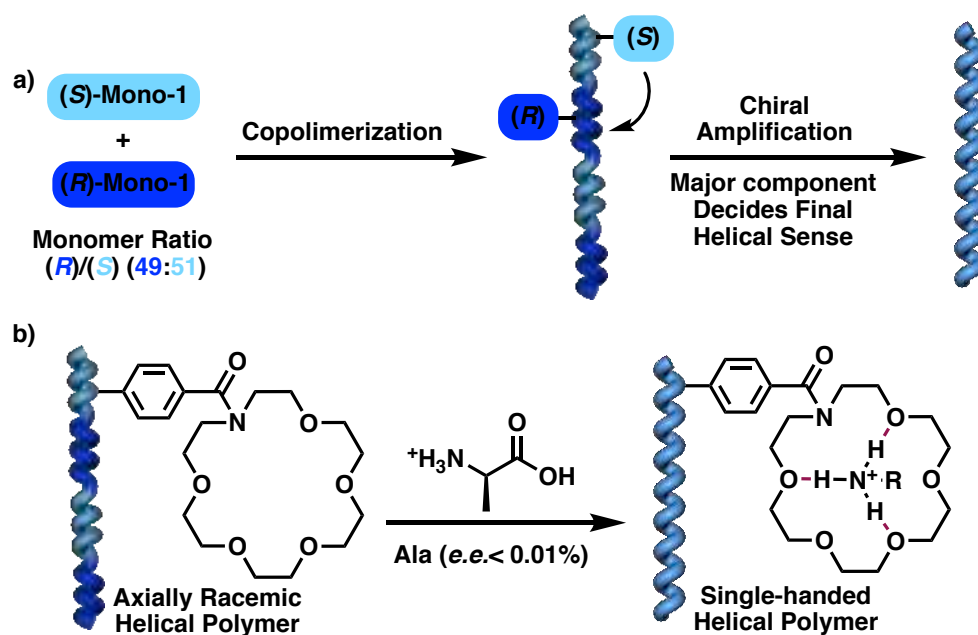


Figure 14. Schematic illustration of the Majority Rules effect in (a) covalent systems and (b) in a supramolecular system.

4.6. Chiral Conflict

Another phenomenon described by Green and co-workers was the “Chiral Conflict” where they studied poly(isocyanate)s systems composed by chiral monomers with a preferential and opposite helical sense at a certain ratio. Due to their different structure these monomers can induce a new chiral communication along the polyenic chain.³³ Thus, depending on the ratio between each chiral unit and playing with temperature they can shift from *P* helix (low temperature) to *M* helix (high temperature) or *vice versa*

³² Nonokawa, R.; Yashima, E. *J. Am. Chem. Soc.* **2003**, *125*, 1278.

³³ Tang, K.; Green, M. M.; Cheon, K. S.; Selinger, J. V.; Garetz, B. A. *J. Am. Chem. Soc.* **2003**, *125*, 7313.

going through a medium stated where the polymer presents an axially racemic behaviour. Moreover, it is possible to modify the starting helicity and the temperature of helical inversion changing the ratio between the comonomers.

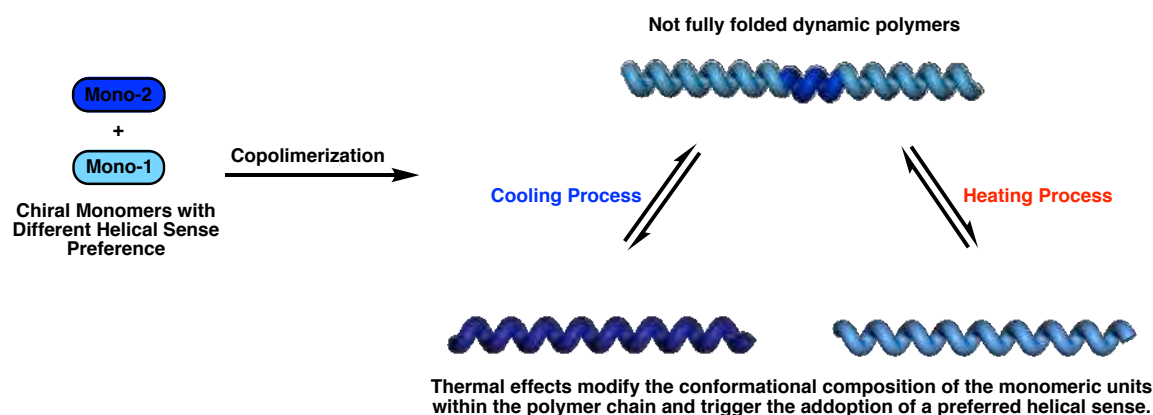


Figure 15. Schematic illustration of the Chiral Conflict and its modulation by thermal effects.

4.7. Domino Effect

Domino Effect is a chiral amplification phenomenon that takes place in covalent³⁴ and supramolecular³⁵ systems such as dynamic helical polymers³⁶ and peptides³⁷. In the particular case of peptides, Inai and co-workers reported the synthesis of several achiral ones, which adopt a mixture of helical senses. However, a preferred handedness can be adopted by the addition of chiral molecules to an unprotected *N*- or *C*-terminal peptides. Specially, this group generated achiral peptides composed by fragments of α -aminoisobutyric acid (Aib) and *Z*- α - β -deshydrophenylalanine (AzPhe) (poly-**20** and poly-**21**). This peptide bears an unprotected amino group, which is able to interact with carboxylic acids through non-covalent acid-base interactions. The absolute configuration of the chiral carboxylic acid leads a specific helicity in the entire peptide.³⁸

³⁴ (a) Obata, K.; Kira, M. *Macromolecules* **1998**, *31*, 4666. (b) Maeda, K.; Matsuda, M.; Nakano, T.; Okamoto, Y. *Polym. J.* **1995**, *27*, 141. (c) Obata, K.; Kabuto, C.; Kira, M. *J. Am. Chem. Soc.* **1997**, *119*, 11345.

³⁵ (a) Inai, Y.; Ousaka, N.; Okabe, T. *J. Am. Chem. Soc.* **2003**, *125*, 8151. (b) Sanji, T.; Takase, K.; Sukaria, H. *J. Am. Chem. Soc.* **2001**, *123*, 12690. (c) Inai, Y.; Tagawa, K.; Takasu, A.; Hirabayashi, T.; Oshikawa, T.; Yamashita, M. *J. Am. Chem. Soc.* **2000**, *122*, 11731.

³⁶ Fukuda, M.; Rodríguez, R.; Fernández, Z.; Nishimura, T.; Hirose, D.; Watanabe, G.; Quiñoá, E.; Freire, F.; Maeda, K. *Chem. Commun.* **2019**, *55*, 7906-7909.

³⁷ (a) Solá, J.; Helliwell, M.; Clayden, J. *J. Am. Chem. Soc.* **2010**, *132*, 4548-4549. (b) Costil, R.; Fernández-Nieto, F.; Atkinson, R.C.; Clayden, J. *Org. Biomol. Chem.* **2018**, *16*, 2757-2761.

³⁸ Ousaka, N.; Inai, Y. *J. Org. Chem.* **2009**, *74*, 1429.

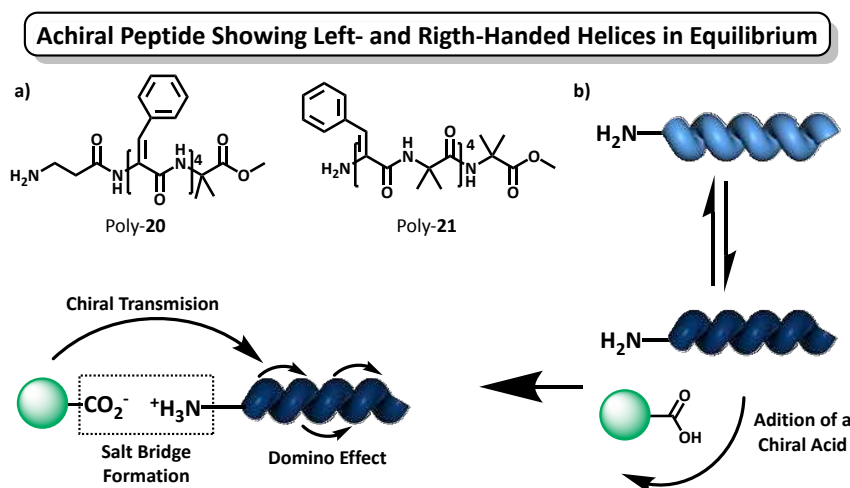


Figure 16. (a) Examples of peptides showing Domino Effect. (b) Schematic illustration of the chiral amplification phenomena through the Domino Effect.

4.8. Chiral Communication through spacers: chiral teleinduction and chiral harvesting

Poly(phenylacetylene)s are dynamic helical polymers with potential applications in different fields such as asymmetric synthesis,³⁹ chiral separations,⁴⁰ sensing,⁴¹ etc., whose helicity and/or length can be by the application of several external stimuli.^{4, 41, 42, 43, 44, 45} In these polymers, the chirality of the pendant groups selectively commands the helical sense of the polyenic skeleton (*P/M* helix)^{4a-e, 42} depending on its *R/S* absolute configuration. Additionally, these changes produced in the helical structure can be also determined by the spatial dispositions adopted by the pendant group. Related to this topic, Yashima⁴⁶ and Nolte^{4j, 47} have reported that the screw sense of polymers bearing more than one chiral center is controlled by the group closer to the backbone. Likewise, Veciana and co-workers⁴⁸ have demonstrated that the effective helical induction

³⁹ (a) Megens, R. P.; Roelfes, G. *Chem. Eur. J.* **2011**, *17*, 8514-8523. (b) Tang, Z.; Iida, H.; Hu, H.-Y.; Yashima, E. *ACS Macro Lett.* **2012**, *1*, 261-265. (c) Iida, H.; Tang, Z.; Yashima, E. *J. Polym. Sci., Part A: Polym. Chem.* **2013**, *51*, 2869-2879.

⁴⁰ Shimomura, K.; Ikai, T.; Kanoh, S.; Yashima, E.; Maeda, K. *Nat. Chem.* **2014**, *6*, 429-434.

⁴¹ (a) Anger, E.; Iida, H.; Yamaguchi, T.; Hayashi, K.; Kumano, D.; Crassous, D.; Vanthuyne, N.; Roussel, C.; Yashima, E. *Polym. Chem.* **2014**, *5*, 4909-4914. (b) Iida, H.; Miki, M.; Iwahana, S.; Yashima, E. *Chem. Eur. J.* **2014**, *20*, 4257-4262.

⁴² Yashima, E.; Ousaka, N.; Taura, D.; Shimomura, K.; Ikai, T.; Maeda, K. *Chem. Rev.* **2016**, *116*, 13752-12990.

⁴³ Sakurai, S.-I.; Okoshi, K.; Kumaki, J.; Yashima, E. *J. Am. Chem. Soc.* **2006**, *128*, 5650-5651.

⁴⁴ Okoshi, K.; Sakurai, S.; Ohsawa, S.; Kumaki, J.; Yashima, E. *Angew. Chem. Int. Ed.* **2006**, *45*, 8173-8176.

⁴⁵ Feringa, B. L. *Acc. Chem. Res.* **2011**, *34*, 504-513.

⁴⁶ Kamikawa, Y.; Kato, T.; Onouchi, H.; Kashiwagi, D.; Maeda, K.; Yashima, E. *J. Polym. Sci. A Polym. Chem.* **2004**, *42*, 4580.

⁴⁷ Cornelissen, J. J. L. M.; Donners, J. J. J. M.; de Gelder, R.; Graswinckel, W. S.; Metselaar, G. A.; Rowan, A. E.; Sommerdijk, N. A. J. M.; Nolte, R. J. M. *Science* **2001**, *293*, 676.

⁴⁸ (a) Ramos, E.; Bosch, J.; Serrano, J. L.; Sierra, T.; Veciana, J. J. *Am. Chem. Soc.* **1996**, *118*, 4703. (b) Amabilino, D. B.; Ramos, E.; Serrano, J. L.; Sierra, T.; Veciana, J. J. *Am. Chem. Soc.* **1998**, *120*, 9126.

decreases when the chiral center is shifted away along the pendant chain. Therefore, it is necessary to place the chiral group close to the backbone in order to achieve an effective helical induction.

Our group have taken one step further in the helicity control of (PPA)s and have reported different remote chiral induction mechanisms. An effective transmission of chiral information from the pendant to the polyenic scaffold was demonstrated by the introduction of both flexible —chiral tele-induction—^{49-, 50, 51, 52, 53, 54, 55} and rigid achiral spacers —chiral harvesting—.^{35a, 36, 38, 56}

In the first mechanism, transmission of the chiral information from a remote position takes place through space, thus overcoming the distance triggered by the spacer. In this way, we have reported an effective chiral induction in two (PPA)s series that bear pendants formed by one or two consecutive glycine residues —acting as an achiral, flexible and well-organized spacers—and (*R*)- or (*S*)- α -methoxy- α -trifluoromethylphenylacetic acid (MTPA) —as the remote chiral inductor— (poly-**22** to poly-**25**, Figure 17a). These glycine residues form a parallel β -sheet structure with the neighboring pendants, stabilizing the helical structure of the polyene by hydrogen bonding and orienting the chiral groups in specific directions. In addition, the helicity of the polyenic chain (*P/M*) can be modulated by the application of different external stimuli (i.e., polarity of the media, metal cations) fixing the conformation of the MTPA moiety connected to the achiral β -sheet spacer.⁵⁴

⁴⁹ Amabilino, D. B.; Ramos, E.; Serrano, J. L.; Sierra, T.; Veciana, J. *Polymer* **2005**, *46*, 1507-1521.

⁵⁰ Gomar-Nadal, E.; Veciana, J.; Rovira, C.; Amabilino, D. B. *Adv. Mater.* **2005**, *17*, 2095-2098.

⁵¹ Percec, V.; Aqad, E.; Petarca, M.; Rudick, J. G.; Lemon, L.; Ronda, J.C.; De, B. B.; Heiney, P. A.; Meijer, E. W. *J. Am. Chem. Soc.* **2006**, *128*, 16365-16372.

⁵² Percec, V.; Petarca, M.; Rudick, J. G.; Aqad, E.; Imam, M. R.; Heiney, P. A. *Chem. Eur. J.* **2007**, *13*, 9572-9581

⁵³ Abe, Y.; Aoki, T.; Jia, H.; Hadano, S.; Namikoshi, T.; Kakihana, Y.; Liu, L.; Zang, Y.; Teraguchi, M.; Kaneko, T. *Chem. Lett.* **2012**, *41*, 244-246.

⁵⁴ Rodríguez, R.; Quiñoá, E.; Riguera, R.; Freire, F. *Chem. Mater.* **2018**, *30*, 2493-2497.

⁵⁵ Rodríguez, R.; Quiñoá, E.; Riguera, R.; Freire, F. *Small* **2019**, *15*, 1805413.

⁵⁶ Fernández, Z.; Fernández, B.; Quiñoá, E.; Riguera, R.; Freire, F. *Chem. Sci.* **2020**, *11*, 7182-7187.

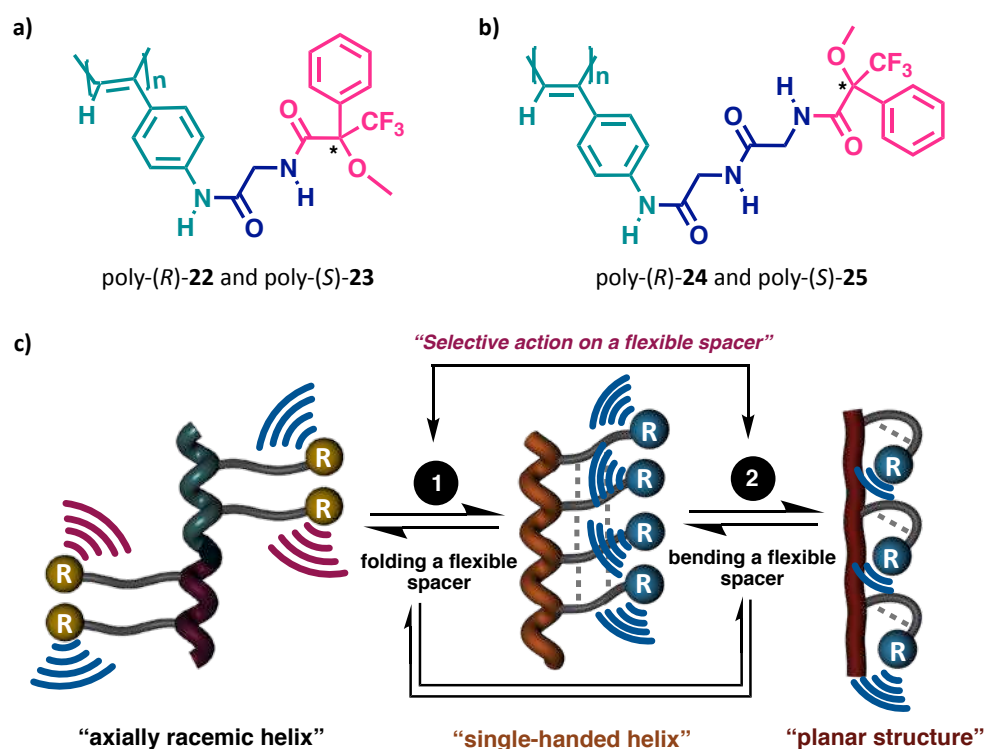


Figure 17. Structure of the polymers with (a) one and (b) two flexible spacers. (c) Conceptual representation of the chiral teleinduction produced in a helical polymer when an achiral flexible linker is fixed by internal supramolecular interactions.

As above mentioned (see section 4.7), these achiral residues can be used as building blocks generating achiral peptides composed by fragments such as α -aminoisobutyric acid (Aib) among others.³⁴⁻³⁷ Clayden and co-workers have reported an interesting work employing this kind of oligopeptides. This research was focused on the membrane phase which requires probes sensitive to conformational change in membrane-active dynamic foldamers. Thus, enantiomers of chiral peptide foldamers bearing bis(pyrene) fluorescent probes were synthesized, analyzed and designed to distinguish between right- and left-handed screw sense conformers of 3_{10} -helical α -aminoisobutyric acid (Aib), both in solution and bilayer membranes. Conformational interchange between *P* and *M* helical sense in Aib foldamers could be monitored in real time by these optimized probes both in organic solvents and bilayers. The mentioned probes were attached to the C-terminus of Aib tetramers presenting different chiral residues at the N-terminus where the two pyrene units located closer allowed to obtain a higher excimer fluorescence than pyrene units spaced further away. In bilayers, fluorescent probes made it possible to

demonstrated for the first time that the chirality of natural phospholipids has a significant influence on the conformation of oligomers in the membrane.⁵⁷

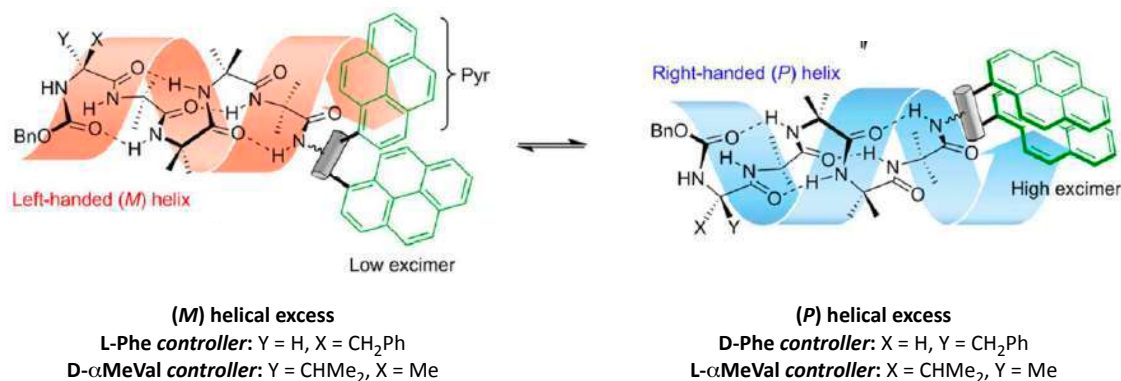


Figure 18. Schematic bis(pyren-1-yl) probe attached to *M* and *P* screw-sense conformers of a controlled Aib₄ helix.

Additionally, our group have described a chiral induction mechanism in poly(phenylacetylene)s whose pendants groups are made by these short oligopeptides [(Aib)_n, (n = 1, 2, 3)] —the achiral units— that place the chiral moiety [(*R*)-MTPA] far away from the helical structure. The chiral information of the MTPA is transmitted along the achiral Aib to the helical scaffold through chiral tele-induction and/or chiral harvesting mechanism depending on the length of the achiral spacer. In addition, these length modifications as well as the application of external stimuli allow us to modify the helical sense of the generated macromolecular gears (Figure 19).⁵⁸

⁵⁷ Lister, F. G. A.; Eccles, N.; Pike, S. J.; Brown, R. A.; Whitehead, G. F. S.; Raftery, J.; Webb, S. J.; Clayden, J. *Angew. Chem. Sci.* **2018**, 9, 6860-6870.

⁵⁸ Suárez-Picado, E.; Rodríguez, R.; Quiñoá, E.; Riguera, R.; Freire, F. *Angew. Chem. Int. Ed.* **2020**, 59, 8616-8622.

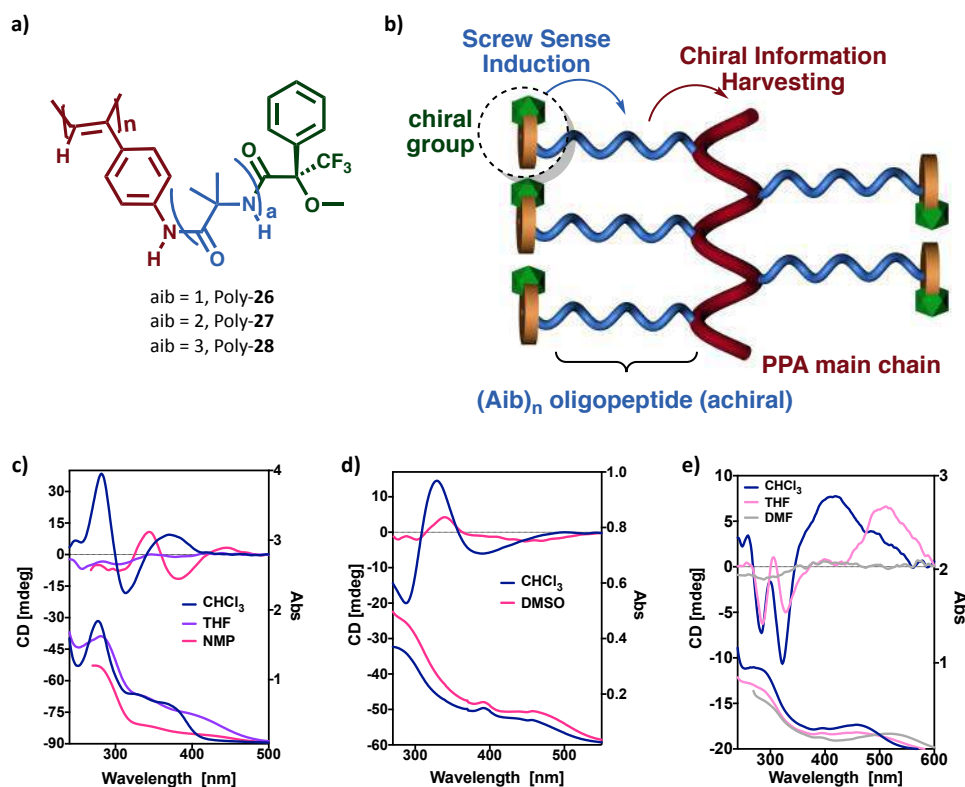


Figure 19. (a) Structures of polymers. (b) Conceptual illustration of the chiral information transmission mechanism. CD/UV-Vis spectra showing (c) the helix inversion and stretching process of poly-26, (d) the stretching process of poly-27 and (e) the three different helical state with different elongation degree of poly-28.

The second mechanism —chiral harvesting— describes how the helix induction is harvested by the polymer main chain when chiral information is transmitted through achiral spacers itself. It is possible to generate a preferred helical structure into the achiral spacer by modifying the chiral center conformation or even just changing its absolute configuration, which in turn will be harvested by polyenic backbone.

Another chiral harvesting process was reported by our group where the arrangement of the achiral spacer within the helical structure is determined by the chiral center which does not generate a conformational change at the achiral spacer. To achieve this goal polymers bearing oligo(*p*-phenyleneethynylene)s ($m = 1, 2, 3$) (OPEs) as rigid spacers —placing the chiral pendant group away from the polyene backbone— were developed. The stacking of the OPE units within the helical scaffold is affected by the arrangement of the chiral moiety, which is further harvested by the polyene backbone giving rise to a preferred *P* or *M* internal helix.^{56, 59}

⁵⁹Fernández, Z.; Fernández, B.; Quiñoá, E.; Freire, F. *J. Am. Chem. Soc.* **2021**, *143*, 20963-20969.

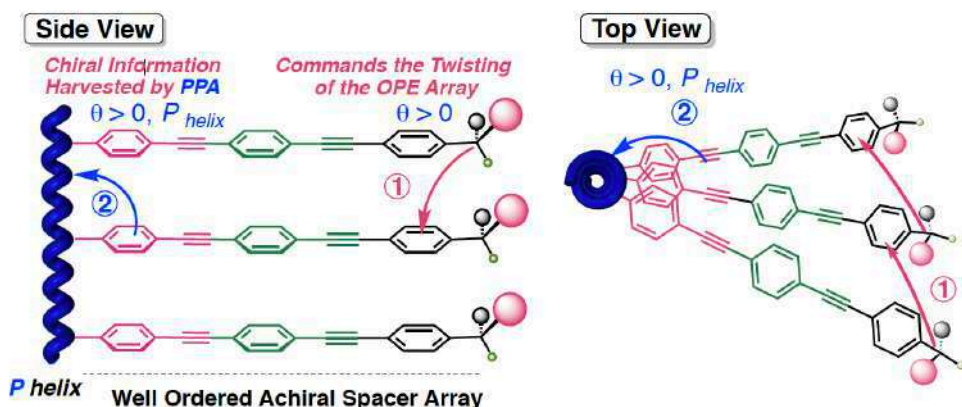


Figure 20. Conceptual side view and top view of the chiral information transmission from stereocenters at the far end of OPE spacers to the polyene backbone via chiral harvesting.

4.9. Helix Inversion

One of the most interesting features of dynamic helical polymers is the helix inversion, a macromolecular process where the control of the helicity between left- and right-handed helical conformations is done by the presence of several external stimuli like changes in solvent polarity⁶⁰ or temperature,⁶¹ addition of anionic species⁶² or metal ions,^{26, 27} pH⁶³ or even light.^{4b, 64}

With this information in mind, our research group developed a polymer formed from the amine of 4-ethynylbenzoic acid with the amino acid (*S*)-phenylglycine methyl ester (PGME) (poly-**29**). This PPA presents two main conformers in equilibrium in equal population in the pendant group: the *syn* conformer, where the two carbonyls are in *synperiplanar* orientation and the *ap* conformer, in which the two carbonyls are *antiperiplanar* oriented. This conformational equilibrium can be modulated by organic solvents with different polarity. In polar solvents (e.g. DMF), the pendant moiety of PGME adopts the *syn* conformation, while in low-polar solvents (e.g. CHCl₃ or THF) the *anti* conformer of the pendant group commands the helical sense displaying a negative CD signal. Also, the addition of metal cation (e.g., Ba²⁺) is able to shift the *ap* conformer

⁶⁰ Maeda, K.; Kamiya, N.; Yashima, E. *Chem. Eur. J.* **2004**, *10*, 4000-4010.

⁶¹ Zhou, Y.; Zhang, C.; Qiu, Y.; Liu, L.; Yang, T.; Dong, H.; Satoh, T.; Okamoto, Y. *Molecules* **2016**, *21*, 11.

⁶² (a) Kakuchi, R.; Shimada, R.; Tago, Y.; Sakai, R.; Satoh, T.; Kakuchi, T. *J. Polym. Sci., Part A: Polym. Chem.* **2010**, *48*, 1683-1689. (b) Kakuchi, R.; Tago, Y.; Sakai, R.; Satoh, T.; Kakuchi, T. *Macromolecules* **2009**, *42*, 4430-4435. (c) Otsuka, I.; Sakai, R.; Satoh, T.; Kakuchi, R.; Kaga, H.; Kakuchi, T. *J. Polym. Sci., Part A: Polym. Chem.* **2005**, *43*, 5855-5863.

⁶³ Janssen, P. G. A.; Ruiz-Carretero, A.; González-Rodríguez, D.; Meijer, E. W. *Angew. Chem. Int. Ed.* **2009**, *48*, 8103-8106.

⁶⁴ Wang, L.; Dong, H.; Li, Y.; Liu, R.; Wnag, Y.-F.; Bisoyi, H. K.; Sun, L.-D.; Yan, C.-H.; Li, Q. *Adv. Mater.* **2005**, *27*, 2065-2069.

of the PGME moiety to the *syn* conformer due to the chelation between the metal cation with the two carbonyl groups. This variation produces a new spatial arrangement of functional bulkier phenyl ring group of the pendant being located on opposite sides for each conformation, which inverts the helicity of the polyenic main chain (Figure 21).⁶⁵

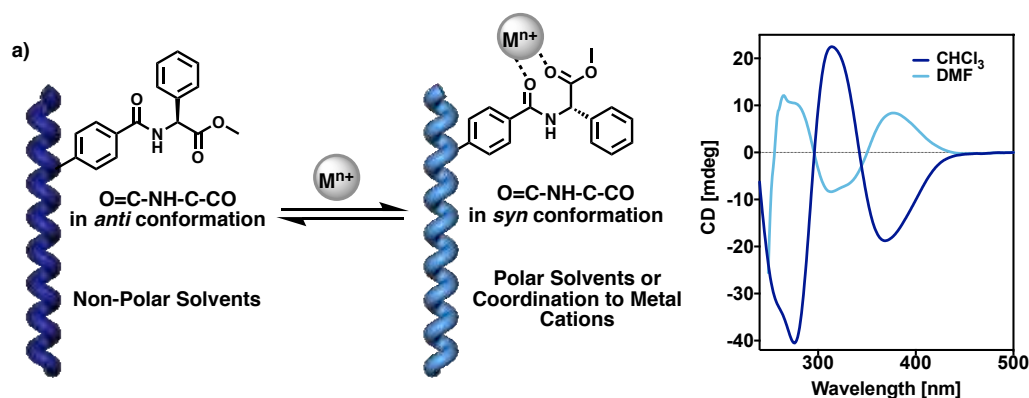


Figure 21. Schematic illustration of the helix inversion process mediated by (a) metal cations or (b) by light in a supramolecular approach.

4.10. Length Control in Poly(PhenylAcetylene)s

The total control of the helical sense is close related to their design, properties and applications. (PPA)s display a dynamic helical structure that can be determined by two properties: the helicity (*P/M*) and the elongation of the polyene backbone (compressed/stretched).^{40, 42a-b, 66, 67, 68} The first one can be monitored by CD spectroscopy that define the presence of a single-handed helix in the polymer and also to evaluate the stimuli-responsive properties of the material. On the other hand, the elongation changes can be monitored by UV-Vis spectroscopy where stretched structures absorb at longer wavelengths due to a higher conjugation of the polyenic chain; also, the bathochromic effect can even be detected by naked eye, making (PPA)s promising materials as colorimetric sensors.

⁶⁵ (a) Louzao, I.; Seco, J. M.; Quiñoá, E.; Riguera, R. *Angew. Chem. Int. Ed.* **2010**, *49*, 1430. (b) Alzubi, M.; Arias, S.; Louzao, I.; Quiñoá, E.; Riguera, R.; Freire, F. *Chem. Commun.* **2017**, *53*, 8573.

⁶⁶ (a) Percec, V.; Peterca, M.; Rudick, J. G.; Aqad, E.; Imam, M. R.; Heiney, P. A. *Chem. Eur. J.* **2007**, *13*, 9572-9581. (b) Percec, V.; Rudick, J. G.; Peterca, M.; Aqad, E.; Imam, M. R.; Heiney, P. A. *J. Polym. Sci., Part A: Polym. Chem.* **2007**, *45*, 4974-4987. (c) Percec, V.; Aqad, E.; Peterca, M.; Rudick, J. G.; Lemon, L.; Ronda, J. C.; De, B. B.; Heiney, P. A.; Meijer, E. W. *J. Am. Chem. Soc.* **2006**, *128*, 16365-16372. (d) V. Percec, J. G. Rudick, M. Peterca, M. Wagner, M. Obata, C. M. Mitchell, W. D. Cho, V. S. K. Balagurusamy and P. A. Heiney, *J. Am. Chem. Soc.* **2005**, *127*, 15257-15264.

⁶⁷ (a) Maeda, K.; Mochizuki, H.; Watanabe, M.; Yashima, E. *J. Am. Chem. Soc.* **2006**, *128*, 7639-765. (b) Yashima, E.; Maeda, K.; Sato, O. *J. Am. Chem. Soc.* **2001**, *123*, 8159-8160.

⁶⁸ Sanda, F.; Terada, K.; Masuda, T. *Macromolecules*, **2005**, *38*, 8149-8154.

Maeda *et al.* reported a series of (PPA)s with tunable degree of elongation and the first colorimetric sensor. In particular, they prepared several (PPA)s (poly-**30**) bearing optically active cyclodextrin (CyD) residues as the pendant groups. Thermal changes and solvent composition (e.g., percentage of water in DMSO) modifies the elongation and helical sense of the polymers. In addition, the polymer shows a colorimetric change from yellow to red in the presence of (*S*)-1-phenylethylamine, while the polymer keeps in yellow in the presence of the enantiomer (Figure 22a).^{47a, 69} The same group developed a poly(phenylacetylene) bearing a peptide pendant (poly-**31**), which is soluble in water and can be modulated by external stimuli like pH, ionic strength and solvent polarity. This promote conformational changes in the peptidic side chain (Figure 22b).⁴⁰

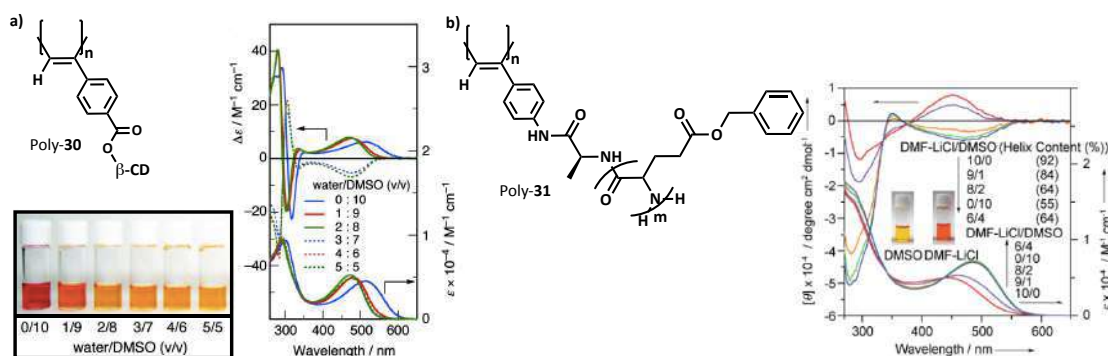


Figure 22. (a) Schematic illustration of the stretching process of poly-**30** by the change in the solvent composition. (b) Schematic illustration of the stretching process of poly-**31** by changes in the polarity of the media and the pH by changing the conformation of the peptidic pendant group.

In relation to this phenomenon, Tabata and co-workers defined a new effect called accordion-like helix oscillation (“HELIOS effect”) in a dynamic poly(acetylene) (poly-**32**) that presents fragments of compressed and stretched helices in the same polyenic chain.⁷⁰ Thus, changing the temperature they can switch the population of the stretched fragments along the main chain axis where higher temperatures increase the stretched fragment.

⁶⁹ Maeda, K.; Mochizuki, H.; Osato, K.; Yashima, E. *Macromolecules* **2011**, *44*, 3217-3226.

⁷⁰ Yoshida, Y.; Mawatari, Y.; Motoshige, A.; Motoshige, R.; Hiraoki, T.; Wagner, M.; Müllen, K.; Tabata, M. *J. Am. Chem. Soc.* **2013**, *135*, 4110.

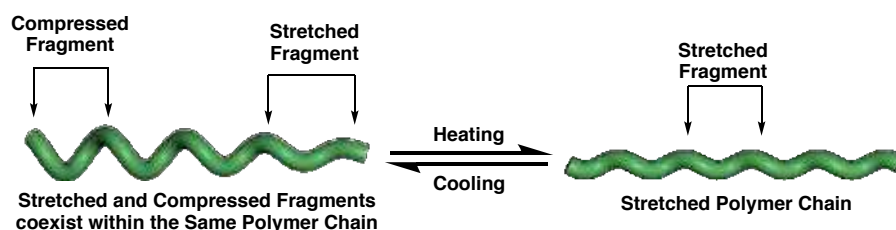


Figure 23. Schematic illustration of the HELIOS effect within a polymer chain.

Leiras *et al.* developed a polymer where the helicity and the backbone elongation can be selectively controlled according to two different stimuli: the polarity and the acceptor/donor character of the organic solvents. This PPA bears the (*R*)- α -methoxy- α -trifluoromethylphenylacetic acid (MTPA) as the pendants (poly-**33**), which presents two different bonds: the first one is the (H-)N-C(=O) amide bond that can be twisted from *cis*- to *trans*- conformation depending on the donor/acceptor properties of the solvent. Hence, when the polymer is dissolved in donor solvents, there is a shift from *trans*-amide to *cis*-amide (stabilized by the presence of the electro withdrawing trifluoromethyl moiety in the pendant group). This means that the amide bond, closed to the polymer, is the responsible to control the elongation of the polymer scaffold, which was easily monitored by UV-Vis spectroscopy. The second bond is the O=C-C-OMe bond that can be switched from *ap* conformation —the carbonyl and methoxy group are *antiperyplanar* oriented—to *sp* one —the carbonyl and methoxy group are *synperyplanar* oriented— depending on the polarity of the solvent. This selective manipulation from *sp* (more polar conformer) to *ap* (less polar solvent) can be easily tuned. Thus, this polymer can adopt four different helical structures through the combination between *cis*-/*trans*- amide and *sp*/*ap* conformers in the second bond.⁷¹

⁷¹ Leiras, S.; Freire, F.; Seco, J. M.; Quiñoá, E.; Riguera, R. *Chem. Sci.* **2013**, 4, 2735-2743.

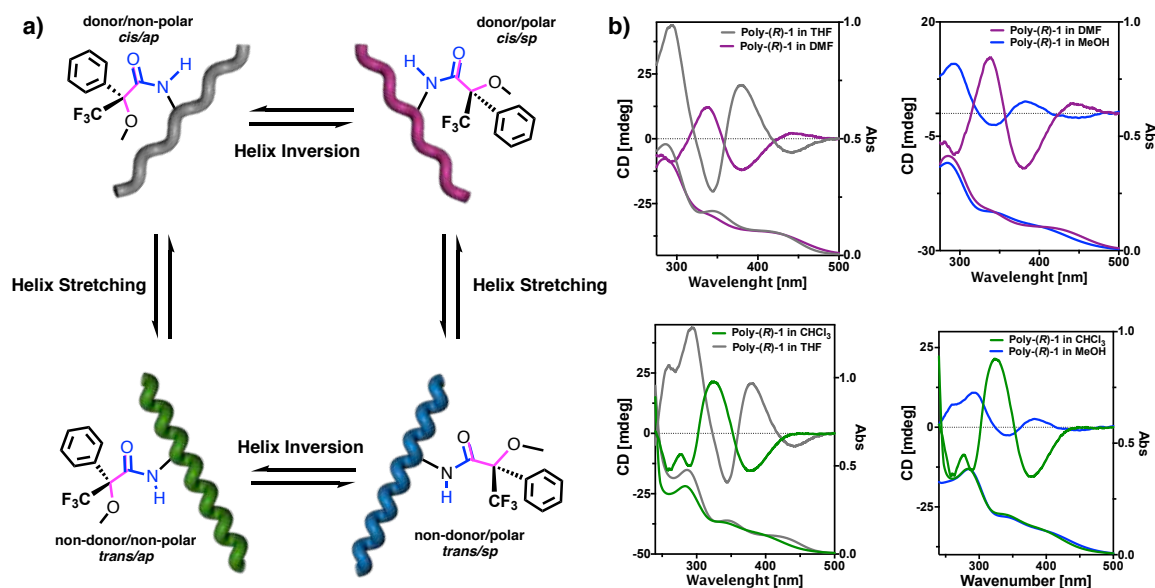


Figure 24. (a) Schematic illustration of the conformational changes in the MTPA moiety of poly-**33** and the effect on the helical scaffold depending on the donor/acceptor and polar character of the solvent. (b) CD and UV-Vis spectra displaying the helical changes of poly-**33** shown in (a).

Most recently, Takata and co-workers reported a new PPA bearing a rotaxane as pendant group (poly-**34**), which can be placed selectively in a remote/close position (compressed/stretched helix) to the polyenic chain. The elongation of this PPA can be also modified by the addition of acidic media or temperature.⁷²

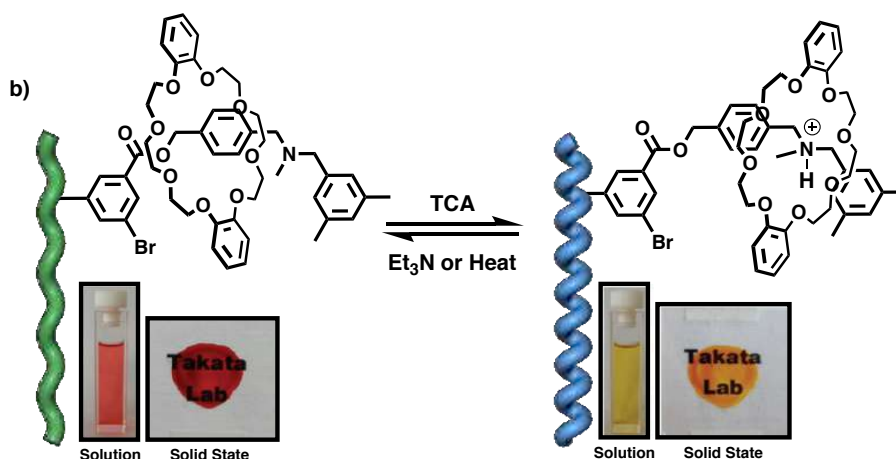


Figure 25. Schematic illustration of the acid-mediated control on the elongation control of poly-**34** bearing a rotaxane as pendant group.

Finally, Rodríguez *et al.* reported the effects of the aromatic substitution pattern (*ortho*-, *meta*- and *para*-) of the pendant (*R*)-MPA residues of (PPA)s not only on the dynamic

⁷² (a) Ishiwari, F.; Nakazono, K.; Koyama, Y.; Takata, T. *Angew. Chem. Int. Ed.* **2017**, *56*, 14858. (b) Zhu, N.; Nakazono, K.; Takata, T. *Chem. Commun.* **2016**, *52*, 3647. (c) Ishiwari, F.; Nakazono, K.; Koyama, Y.; Takata, T. *Chem. Commun.* **2011**, *47*, 11739.

behaviour of polymers but also on their helical pitch (compressed or stretched). Thereby, although *para*- and *meta*-substituted polymers [(poly-35) and (poly-36)] responds to the presence of external stimuli like metal cations, the *meta*-substituted one presents a less dynamic behaviour, displaying a lower response than in the case of poly-35. Also, poly-36 has an equilibrium mixture of two different helical structures: one with a similar helical pitch to the *para*-substituted PPA (poly-28) (*cis-cisoidal* structure), and other more stretched one (*cis-transoidal*). On the opposite side, the *ortho*-substituted system (poly-37) does not respond to the addition of external stimuli due to his quiasi static behaviour, showing a highly stretched structure with an almost planar conformation, which is able to form fibrillar aggregates. These structural changes (dynamic behaviour/elongation) have been shown to be related with the aromatic substitution pattern where the *ortho*- and *meta*-substituted (PPA)s place the pendant moiety outside and close to the backbone.⁷³

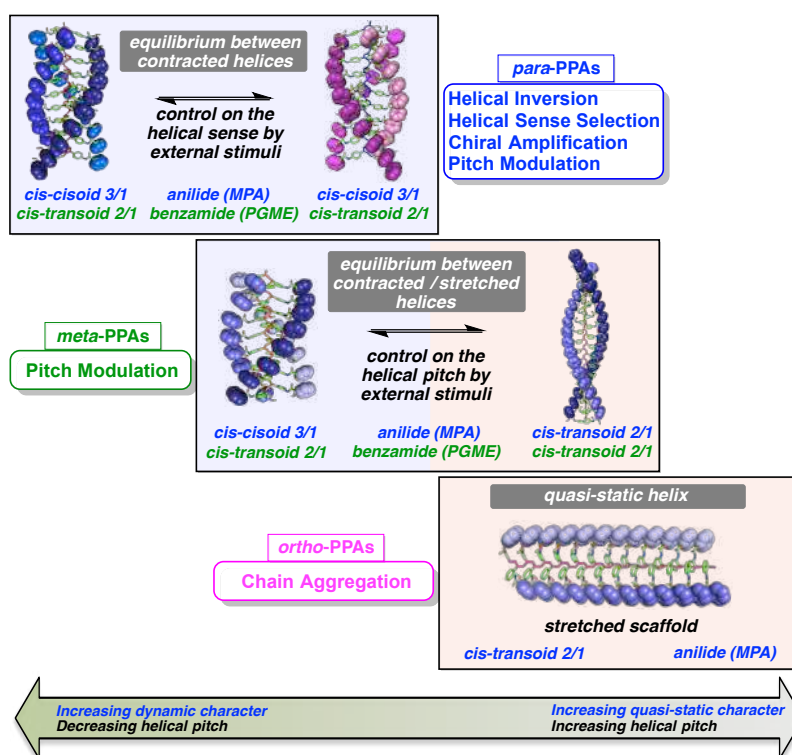


Figure 26. Schematic representation of the effect on aromatic substitution pattern in (PPA)s.

⁷³ Rodríguez, R.; Quiñoá, E.; Riguera, R.; Freire, F. J. *Am. Chem. Soc.* **2016**, *138*, 9620-9628.

5. Structure of (PPA)s

The properties and functions of (PPA)s are closely related to their secondary structure. Therefore, a correct designs and structural knowledge of helical structures is very important to develop polymers with specific functions. The structural elucidation of artificial helical polymers is necessary for understanding the mechanism of helix formation and the helical structure/function relationship. Thus, the secondary structure of a helical polymer can be obtained by the combination of several techniques that are summarized next:

- *Computational calculations*: molecular dynamics (MD), molecular mechanics (MM) and molecular orbital (MO).
- *Diffraction methods*: X-ray diffraction, small angle X-ray scattering (SAXS) and wide angle X-ray scattering (WAXS).
- *Microscopy*: atomic force microscopy (AFM), scanning electron microscopy (SEM), transmission electron microscopy (TEM) and scanning tunnelling microscopy (STM).
- *Spectroscopic techniques*: electronic circular dichroism (ECD), nuclear magnetic resonance (NMR), ultraviolet-visible (UV-Vis), vibrational circular dichroism (VCD), optical activity —optical rotation (OR) and specific rotation (SR)—, Raman and infrared spectroscopies (FT-IR).

5.1. Determination of the *cis* Content in Poly(PhenylAcetylene)s

Polymerization of monosubstituted acetylenes generates conjugated double bonds in the polymer backbone with *cis*- or *trans*-configuration depending on the catalyst employed in the polymerization. In particular, polymers with *trans*-configuration of the double bonds display a planar structure;⁷⁴ while the PPA consisting of *cis*- double bonds shows a less congested helical structure where the dihedral angle (ω_1) of the sigma bond C (sp²) – C (sp²) can acquire values from 0° to 180° determining the helicity [$\omega_1 < 0^\circ$ *M* helix, $\omega_1 > 0^\circ$ *P* helix] and the helical pitch [$\omega_1 < 90^\circ$ *cis-cisoidal*, $\omega_1 > 90^\circ$ *cis-transoidal*] — Rh(I) catalyst provides (PPA)s in high yield and *cis*-content of double bonds—. ⁷⁵

⁷⁴ Natta, G.; Mazzanti, G.; Corradini, P. *Rend. Accad. Nazl. Lincei Rend. Classe Sci. Fis. Mat. Nat.* **1958**, 25, 3.

⁷⁵ (a) Kishimoto, Y.; Eckerle, P.; Miyatake, T.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1994**, 116, 12131. (b) Tabata, M.; Yang, W.; Yokota, K. *Polym. J.* **1990**, 22, 1105. (c) Furlani, A.; Napoletano, C.; Russo, M. V.; Feast, W. J. *Polym. Bull.* 1986, 16, 311. (d) Simionescu, C.I.; Percec, V. *Prog. Polym. Sci.* 1982, 8, 133. (e) Simionescu, C.I.; Percec, V. *J. Polym.*

Related to this information, Percec and co-workers reported how the four different configurations of the conjugated double bonds—*trans-cisoidal* (t-c), *trans-transoidal* (t-t), *cis-cisoidal* (c-c) and *cis-transoidal* (c-t) — can be differentiated by ^1H NMR spectra combining theoretical and experimental results.^{55f,g,h} In polymers with *trans*-configuration of the double bonds, the vinylic proton resonates around 6.20-7.20 ppm. Moreover, the aromatic protons present different pattern in a *trans-cisoidal* or *trans-transoidal* structure: in the first case all the aromatic protons resonate in the same region while in a *trans-transoidal* configuration only two aromatic protons appear upfield shifted with respect to the other aromatic protons.⁷² Otherwise, the vinylic proton of a polymer with *cis*- structure appears around 5.60-5.80 ppm and the aromatic protons also present different splitting pattern. Polyenic chain with *cis-transoidal* configuration display two aromatic protons upfield shifted, while in a PPA with *cis-cisoidal* polyene backbone, only one aromatic proton should be upfield shifted in comparison with the other aromatic protons. ^1H NMR spectra of a PPA with *cis-cisoidal* structure have the vinyl proton at 5.80 ppm; ^1H *ortho*- at 6.70 ppm, ^1H *para*- and *meta*- at 6.85 ppm. In addition, they also propose an equation to determine the *cis*-content of PPA based on this data.

$$\% \text{ cis} = [A_{\text{cis}} / (A_{\text{total}} \times H_{\text{total}})] \times 100$$

Equation 1. Equation used for calculating the % cis of a PPA.

Where A_{cis} is the peak area of the vinyl proton obtained from ^1H NMR (5.6-5.8 ppm), A_{total} is the total area of the observed ^1H -NMR spectrum, and H_{total} is the number of the pendant protons.

Another useful technique to obtain information about the polyenic chain configuration is Raman spectroscopy that shows the resonance bands characteristics of the polyene skeleton in a PPA. A polymer with a *trans-transoidal* structure presents the following bands: *trans*-C=C (1475 cm^{-1}) and *trans*-C-C (1200 cm^{-1}),^{18b,c, 76} while a PPA with a *cis-cisoidal* or *cis-transoidal* configuration displays *cis*-C=C (1530 cm^{-1}), *cis*-C-C (1335 cm^{-1})

Sci.: *Polymer Symposia* **1980**, 67, 43. (f) Simionescu, C. I.; Percec, V. *J. Polym. Sci., Polym. Chem. Ed.* **1980**, 18, 147. (g) Simionescu, C. I.; Percec, V. *J. Polym. Sci., Polym. Lett. Ed.* **1979**, 17, 421. (h) Simionescu, C. I.; Percec, V.; Dumitrescu, S. *J. Polym. Sci., Polym. Chem. Ed.* **1977**, 15, 2497.

⁷⁶ Misayaka, A.; Sone, T.; Mawatari, Y.; Setauesh, S.; Müllen, K.; Tabata, M. *Macromol. Chem. Phys.* **2006**, 207, 1938.

and *cis*-C-H (965 cm^{-1}) bands. Additionally, deformation bands, *trans*-C-H (1015 cm^{-1}) and *cis*-C-H (740 cm^{-1}) can be detected by FT-IR spectroscopy.⁷⁷

With all this previous information in hand, obtained from the combination of NMR, Raman spectroscopy and FT-IR techniques, we are able to distinguish a *cis*- or *trans*-configuration of the double bonds, but is impossible to differentiate *c-c* from *c-t* and *t-t* from *t-c*. Thereby, additional technique is required to define the secondary structure of (PPA)s: Differential Scanning Calorimetry (DSC) whose thermograms are different for polymers with *c-c* and *c-t* structure. The thermogram of a *c-c* (PPA)s shows only an exothermic transition peak around $200\text{--}240^\circ\text{C}$ due to the isomerization process from *c-c* to *t-t*, while (PPA)s with *c-t* configuration present two exothermic bands around 140°C and 240°C , corresponding with the *c-t* to *c-c* and *c-c* to *t-t* isomerization processes respectively. This quality makes DSC an useful technique to diferenciate between the *c-c* and *c-t* scenario.^{78, 79}

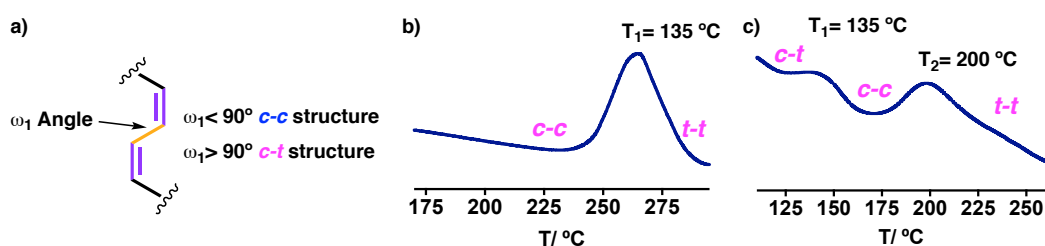


Figure 27. (a) Schematic illustration of the ω_1 angle and the effect over the type of helical scaffold. Representative DSC thermograms of (b) *c-c* structures and (c) *c-t* structures.

Other technique that can provide information about the secondary structure of (PPA)s is UV-Vis spectroscopy that allows us to control the compression or stretching degree of the polymer backbone by comparison with other reported (PPA)s helical structures. Deep into details, a more compressed helix will display a hypsochromic shift in the vinylic region due to a less conjugated helical scaffold. However, a bathochromic effect is observed

⁷⁷ (a) Ito, T.; Shirakawa, H.; Ikeda, S. *J. Polym. Sci., Part A: Polym. Chem.* **1974**, *12*, 11-20. (b) Shirakawa, H.; Ikeda, S. *Polym. J.* **1971**, *2*, 231.

⁷⁸ (a) Motoshige, A.; Mawatari, Y.; Yoshida, Y.; Motoshige, R.; Tabata, M. *Polym. Chem.* **2014**, *5*, 971. (b) Yoshida, Y.; Mawatari, Y.; Motoshige, A.; Motoshige, R.; Hiraoki, T.; Wagner, M.; Müllen, K.; Tabata, M. *J. Am. Chem. Soc.* **2013**, *135*, 4110. (c) Motoshige, A.; Mawatari, Y.; Motoshige, R.; Yoshida, Y.; Tabata, M. *J. Polym. Sci., Part A: Polym. Chem.* **2013**, *51*, 5177.

⁷⁹ Motoshige, R.; Mawatari, Y.; Motoshige, A.; Yoshida, Y.; Sasaki, T.; Yoshimizu, H.; Suzuki, T.; Tsujita, Y.; Tabata, M. *J. Polym. Sci., Part A: Polym. Chem.* **2014**, *52*, 752.

when conjugation of the double bonds increase, which corresponds to a more stretched structure than the previous one.^{80, 81}

5.2. Determination of the Screw Sense of (PPA)s

The helical pitch and the helical handedness excess in the macromolecule structure can be determined by different techniques. The two most common techniques are circular dichroism (CD) and optical rotation that are based on the interaction of the corresponding macromolecules with light.

5.2.1 Circular Dichroism

Circular dichroism (CD) is a very useful technique in the helical polymers field where CD studies allow us to detect the presence of a preferred helical sense in the polymer, namely, it is able to distinguish between the absorption of right-handed circularly polarised light (*R*-CPL) and left-handed circularly polarised light (*S*-CPL) of molecules that bear one or more chiral chromophores (light-absorbing groups). In addition, this technique can be applied to determine the chirality of small molecules or the chiral content and folding of big macromolecules. The CD spectrum not only gives us information about the secondary structure of peptides (being folded in α -helix, β -sheet or random coil) but also about the conformational changes of molecules with different sizes once external stimuli is added. Thereby, kinetic, structural and thermodynamic parameters can be easily obtained from this technique.^{82, 83, 84}

⁸⁰ (a) Percec, V.; Peterca, M.; Rudick, J. G.; Aqad, E.; Imam, M. R.; Heiney, P. A. *Chem. Eur. J.* **2007**, *13*, 9572. (b) Percec, V.; Rudick, J. G.; Peterca, M.; Aqad, E.; Imam, M. R.; Heiney, P. A. *J. Polym. Sci., Part A: Polym. Chem.* **2007**, *45*, 4974. (c) Percec, V.; Aqad, E.; Peterca, M.; Rudick, J. G.; Lemon, L.; Ronda, J. C.; De, B. B.; Heiney, P. A.; Meijer, E. W. *J. Am. Chem. Soc.* **2006**, *128*, 16365. (d) Percec, V.; Rudick, J. G.; Peterca, M.; Wagner, M.; Obata, M.; Mitchell, C. M.; Cho, W. D.; Balagurusamy, V. S. K.; Heiney, P. A. *J. Am. Chem. Soc.* **2005**, *127*, 15257.

⁸¹ Motoshige, A.; Mawatari, Y.; Yoshida, Y.; Matsuyama, C. S.; Tabata, M. *J. Polym. Sci., Part A: Polym. Chem.* **2012**, *50*, 3008.

⁸² (a) Hammes, G. G.; *Circular Dichroism, Optical Rotatory Dispersion, and Fluorescence Polarization, In Spectroscopy for the Biological Sciences*, John Wiley & Sons, Inc. **2005**, p 63. (b) Bereova, N.; Nakanishi, K.; Woody, R. W., *Circular Dichroism: Principles and Applications*, 2nd ed., Wiley-VCH: New York, **2000** p 912.

⁸³ (a) K. Nakanishi, N. Berona, *Circular Dichroism: Principles and Applications*; ed por N. Berova, K. Nakanishi, W. R. Woody, **2000**, Wiley-VCH, 2nd ed, Cap 13, p 361. (b) Harada, N.; Nakanishi, K. *Circular Dichroic Spectroscopy-Exciton Coupling in Organic Stereochemistry*; 2nd ed., University Science Books: Mill Valley, CA, **1983**.

⁸⁴ (a) Suzuki, Y.; Tabei, J.; Shiotsuki, M.; Inai, Y.; Sanda, F.; Masuda, T. *Macromolecules* **2008**, *41*, 1086. (b) Buffeteau, T.; Ducasse, L.; Poniman, L.; Delsuc, N.; Huc, I. *Chem. Commun.* **2006**, 2714-2716. (c) Tang, H.-Z.; Novak, B. M.; He, J.; Polavarapu, P. L. *Angew. Chem. Int. Ed.* **2005**, *44*, 7298. (d) Tanatani, A.; Yokoyama, A.; Azumaya, I.; Takakura, Y.; Mitsui, C.; Shiro, M.; Uchiyama, M.; Muranaka, A.; Kobayashi, N.; Yokozawa, T. *J. Am. Chem. Soc.* **2005**, *127*, 8553. (e) Tabei, J.; Shiotsuki, M.; Sanda, F.; Masuda, T. *Macromolecules* **2005**, *38*, 9448. (f) Kaneko, T.; Umeda, Y.; Yamamoto, T.; Tereguchi, M.; Aoki, T. *Macromolecules* **2005**, *38*, 9420. (g) Takei, F.; Hayashi, H.; Onitsuka, K.; Kobayashi, N.; Takahashi, S. *Angew. Chem. Int. Ed.* **2001**, *40*, 4092.

Thus, the CD spectroscopy gives us information about the response to external stimulus and the folding of helical polymers where the amount of polymer needed is very small (less than 0.1 mg) and the environment conditions to carry out these studies can be easily modified (temperature, solvents...). In helical polymers, the presence of an excess of helical sense and helical changes can be detected by the CD signal of the polymeric main chain.^{4b}

5.2.2 Theoretical Calculations of Circular Dichroism

During the last years, theoretical calculations have attracted the attention of the scientific community for its usefulness in elucidating helical structures. Deep into details, the secondary structure of some helical polymers can be determined by exploring ECD simulation together with MMFF94 energy minimization, where the time-dependent self-consistent field (SCF) ZernerQs Intermediate Neglect of Differential Overlap (ZINDO/S) method is employed. For instance, the formation of two different helical scaffolds (different dihedral angle at the single bond along the main chain) was demonstrated by Masuda and co-workers when working with a series of polymers derived from propargylamides.^{82a}

In the case of (PPA)s, an example has been report focusing on the CD bands corresponding to the pendant and not on those related to the polyenic chain.^{82f} Recently, DFT theoretical studies on oligomers obtained from experimental techniques were used to correlate the CD signal in the vinylic region with the helicity adopted by the poly(phenylacetylene). This occurs when a good match is observed/obtained between the experimental ECD spectra for some (PPA)s – that present a known helical scaffold– and the calculated ECD spectra for small oligomers. To calculate the ECD spectra, the Time-Dependent Density Function Theory (TD-DFT) was employed and the 3-21G basis set with the CAM-B3LYP functional were selected as base. This work was reported by our research group providing that if the first Cotton effect has a negative sing [CD (-)], the polyenic skeleton adopts a *M* internal helix. On the contrary, a *P* internal helix is obtained when the first Cotton effect is positive [CD (+)].⁸⁵

⁸⁵ (a) Fernández, B.; Rodríguez, R.; Rizzo, A.; Quiñoá, E.; Riguera, R.; Freire, F. *Angew. Chem. Int. Ed.* **2018**, *57*, 3666-3670. (b) Fernández, B.; Rodríguez, R.; Quiñoá, E.; Riguera, R.; Freire, F. *ACS Omega* **2019**, *4*, 5233-5240.

From these results, theoretical calculations could have been applied in different works such as predicting the structural and dynamic behaviour by rational design of polymers;⁸⁶ in more complex helices presenting rigid spacers between pendants and the backbone^{56, 57} and even in the formation of supramolecular helical scaffolds.^{87, 88}

5.2.3 Vibrational Circular Dichroism and Raman Optical Activity

Another interesting technique to determine the screw sense in (PPA)s are Vibrational Circular Dichroism (VCD) and Raman Optical Activity, the chiral version of traditional IR and Raman techniques.

On the one hand, VCD is a spectroscopic method to measure the difference in absorbance intensity between left- and right-hand circularly polarized light in the infrared and near infrared regions. This is distinguished from electronic circular dichroism (ECD or CD), which focuses on the ultraviolet region. VCD allows not only direct observation and control of supramolecular chirality, but also to differentiate between different conformations of pendant groups in (polyphenylacetylene)s. Likewise, this technique shows how an achiral solvent can be organized in a helical form by interacting with the helical polymer and displays an interesting sensitivity in the formation of protein fibril structures in solution.^{89, 90, 91}

On the other hand, ROA is more localized, and more reflective of configuration, than VCD. Also, there is a non-equivalence between the scattered and incident circular polarization light beam.⁹² Recently, it has been used not only to define the screw sense of the helix but also to elucidate the helical structure of (PPA)s despite being a weak effect and requiring large amounts of sample.^{93, 94}

⁸⁶ Cobos, K.; Rodríguez, R.; Domarco, O.; Fernández, B.; Quiñoá, E.; Riguera, R.; Freire, F. *Macromolecules* **2020**, *53*, 3182.

⁸⁷ Fernández, B.; Fernández, Z.; Quiñoá, E.; Freire, F. *Molecules* **2021**, *26*, 3530.

⁸⁸ Fernández, Z.; Fernández, B.; Quiñoá, E.; Freire, F. *Angew. Chem. Int. Ed.* **2021**, *60*, 9919.

⁸⁹ Ma, S.; Cao, X.; Mak, M.; Sadik, A.; Walkner, C.; Freedman, T. B.; Lednev, I. K.; Dukor, R. K.; Nafie, L. A. *J. Am. Chem. Soc.* **2007**, *129*, 12364.

⁹⁰ Kurouski, D.; Lombardi, R. A.; Dukor, R. K.; Lednev, I. K.; Nafie, L. A. *Chem. Commun.* **2010**, *46*, 7154.

⁹¹ Nieto-Ortega, B.; Rodríguez, R.; Medina, S.; Quiñoá, E.; Riguera, R.; Casado, J.; Freire, F.; Ramírez, F. J. *J. Phys. Chem. Lett.* **2018**, *9*, 2266.

⁹² Nafie, L. A. *Theor. Chem. Acc.* **2008**, *119*, 39.

⁹³ Li, G.; Kessler, J.; Cheramy, J.; Wu, T.; Poopari, M. R.; Bour, P.; Xu, Y. *Angew. Chem. Int. Ed.* **2019**, *58*, 16495; *Angew. Chem.* **2019**, *131*, 16647.

⁹⁴ Palomo, L.; Rodríguez, R.; Medina, S.; Quiñoá, E.; Casado, J.; Freire, F.; Ramírez, F. J. *Angew. Chem. Int. Ed.* **2020**, *132*, 9165.

5.2.4 Optical rotation

The optical rotation provides the degree of deviation of the polarized light produced when interacts with optically active molecules in solution. This data depends on the concentration, solvent and temperature of the sample and also depends on the length of the cuvette employed to perform the measurement. However, this technique is low sensitivity and a large amount of sample required. In helical polymers, the $[\alpha]$ value is at least one order of magnitude higher than the corresponding monomeric unit. The $[\alpha]$ value is calculated from equation. 2, where α_{obs} is the observed optical rotation (degrees), c is the concentration (g/mL) and l is the path length (length of the cell in dm).

$$[\alpha] = \frac{\alpha_{obs}}{c \cdot l}$$

Equation 2. Equation used for the calculation of the optical rotation.

Nevertheless, the combination of these structural techniques (CD, DSC, IR, NMR and Raman) cannot provide the 3D structure of the polymers so their helical pitch as well as their ω_1 value are unknown. In order to resolve these limitations and achieve the secondary structure of a helical PPA other techniques such as XDR (X-ray diffraction) and AFM (Atomic Force Microscopy) must be applied.^{4b}

5.3. X-ray Diffraction

It is possible to obtain information about the secondary structure of a PPA by X-ray diffraction, where the most important drawback is the preparation of the sample: a uniaxially oriented film of the polymer with a regular helical structure over a long distance. The presence of rigid rods in the polymer promotes the formation of these kind of oriented films with tendency to form lyotropic or thermotropic liquid crystals (LC). Also, they can be fabricated by physical shearing or under electric or magnetic fields.⁹⁵ From these measurements, several data related to the main chain helical structure can be obtained (helix width, helix length, interpendant distances and helical pitch). Nevertheless, not always all these different parameters can be assignable, and even in this best case it is impossible to obtain the helicity of the polymer.

⁹⁵ Yashima, E. *Polym. J.* **2010**, 42, 3-16.

5.4. Atomic Force Microscopy Analysis

Atomic Force Microscopy (AFM) represents the most powerful structural technique to define the helical structure of helical polymer, providing the main structural information like helical sense described by the pendants, helical pitch and packing angle. Nevertheless, the preparation of a high-resolution AFM image is the main disadvantage of this technique being necessary to obtain a 2D-crystal or well-ordered monolayers of the polymer. The different protocols to prepare AFM samples are described next.

5.4.1. Drop-casting and spin coating

The first approach to solve the helical structure by AFM was reported by Yashima and co-workers. They deposited the following three polymers by drop casting on an AFM substrate, in this case, mica: low- and high-molecular-weight poly(4-carboxyphenylacetylene)s (poly-**16**), their salts with (*R*)-(+)-1-(1-naphthyl)ethylamine [(*R*)-**38**] and their corresponding carboxyamides (poly-**39**). Then, an AFM analysis was performed where the helical structure of isolated chains was obtained.⁹⁶ However, the quality of the images was not good enough to obtain reliable values for the helical pitch and packing angle (Figure 28a-b).⁹⁷ That's the reason why they decided to carry out a second approach, introducing a long alkyl chains in the pendant moiety of the PPA, which should promote its self-assembly by interdigitation of the long chain.^{43, 98} Next, the spin coating of a dilute solution of the polymer onto a solid AFM substrate —mica or highly oriented pyrolytic graphite (HOPG)— was made. The substrate was also kept under solvent atmosphere overnight to promote the self-assembly of the polymer chains. From this new methodology, Yashima and co-workers acquired the helical structure of poly-*D*-**40** and poly-*L*-**40**, bearing *D*- and *L*-alanine decyl esters.^{69c} Additionally, AFM analysis showed well-ordered 2D-crystals due to the strong and epitaxial adsorption of the alkyl chains of the pendant on the graphite lattice (Figure 28d). The AFM images of poly-*L*-**40** displayed a helical structure with a helical pitch of 2.34 nm and a packing angle of 40°, where the pendant groups define an external *M* helical structure 11/5, with two residues

⁹⁶ Sakurai, S.-I.; Kuroyanagi, K.; Morino, K.; Kunitake, M.; Yashima, E. *Macromolecules* **2003**, *36*, 9670-9674.

⁹⁷ (a) Sakurai, S.-I.; Ohira, A.; Suzuki, Y.; Fujito, R.; Nishimura, T.; Kunitake, M.; Yashima, E. *J. Polym. Sci. Part A Polym. Chem.* **2004**, *42*, 4621. (b) Nishimura, T.; Maeda, K.; Ohsawa, S.; Yashima, E. *Chem. - A Eur. J.* **2005**, *11*, 1181.

⁹⁸ (a) Nishimura, T.; Takatani, K.; Sakurai, S.; Maeda, K.; Yashima, E. *Angew. Chem. Int. Ed.* **2002**, *41*, 3602-3604. (b) Okoshi, K.; Sakurai, S.; Ohsawa, J. K.; Yashima, E. *Angew. Chem. Int. Ed.* **2006**, *45*, 1245-1248 (c) Ohsawa, S.; Sakurai, S.-I.; Nagai, K.; Banno, M.; Maeda, K.; Kumaki, J.; Yashima, E. *J. Am. Chem. Soc.* **2011**, *133*, 108-114.

per turn (Figure 28d). The internal polyenic backbone shows a *c-t* configuration and describes a right-handed (*P*) helical sense with a pitch of 2.3 nm. From these results, a right-handed helical structure is determined by the polyene backbone, while a left-handed helical array is described by the pendant groups (AFM, Figure 28d).

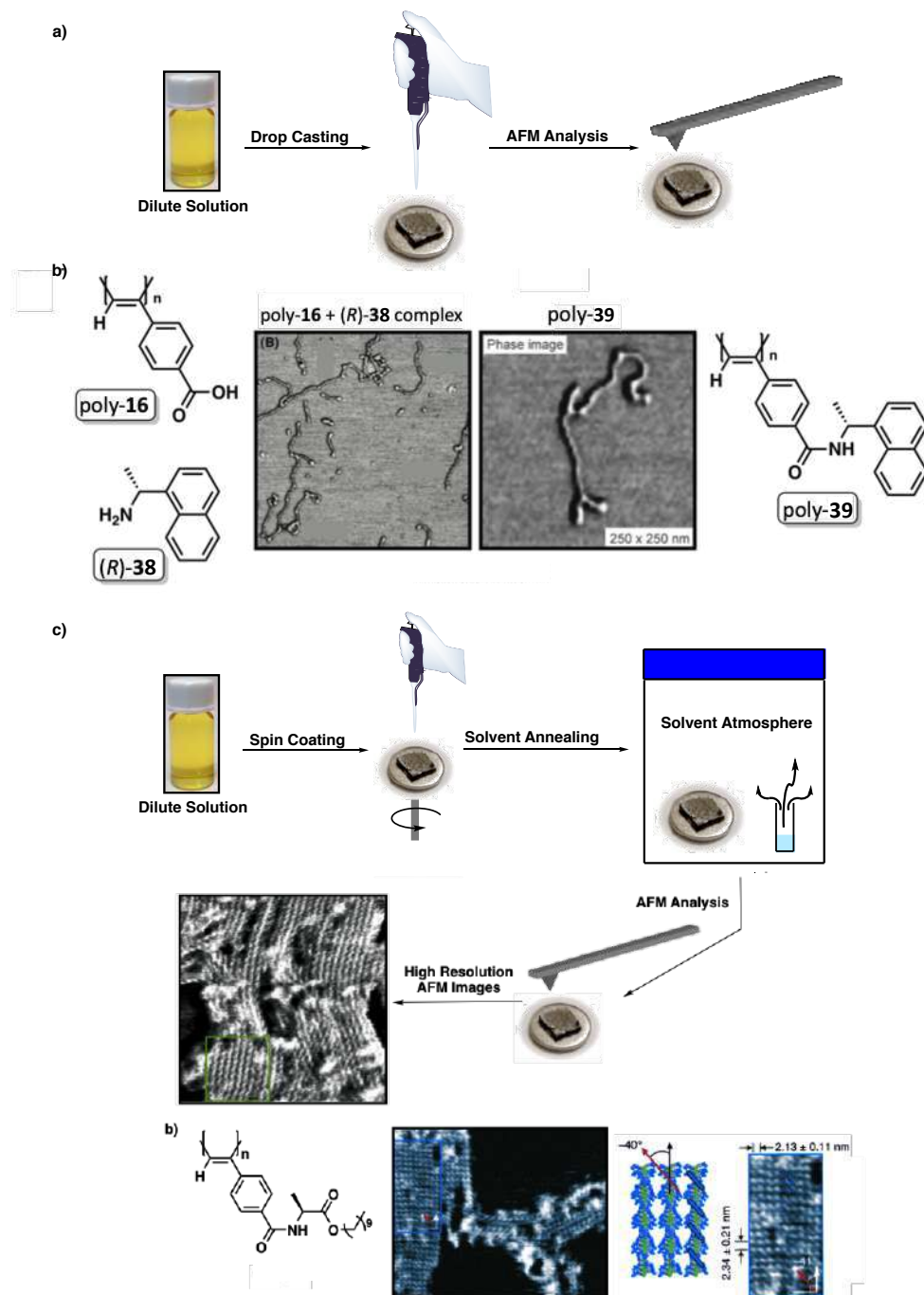


Figure 28. (a) Schematic illustration of the drop casting technique. (b) Structure and AFM image of Poly-16/(*R*)-38)-naphtylethylamine complex and poly-39. (c) Schematic illustration of the spin-coating and solvent exposure process. (d) Structure and AFM images of poly-40.

In parallel to Yashima's work, Percec and co-workers described a similar protocol to produce 2D crystals by spin coating approach, where a dilute solution of the polymer is deposited over the corresponding substrate —either mica or HOPG—. The process is followed by thermal annealing instead of solvent exposure and was applied to a library of dendronized (PPA)s (poly-**41** and poly-**42**) with long alkyl tails, essentials to promote the PPA self-assembly (Figures 29a and 29c).⁹⁹ Despite of the successful creation of 2D-crystals, no high-resolution AFM images could be obtained and therefore, parameters like helical sense, helical pitch and packing angle continue to be unknown (Figure 29).

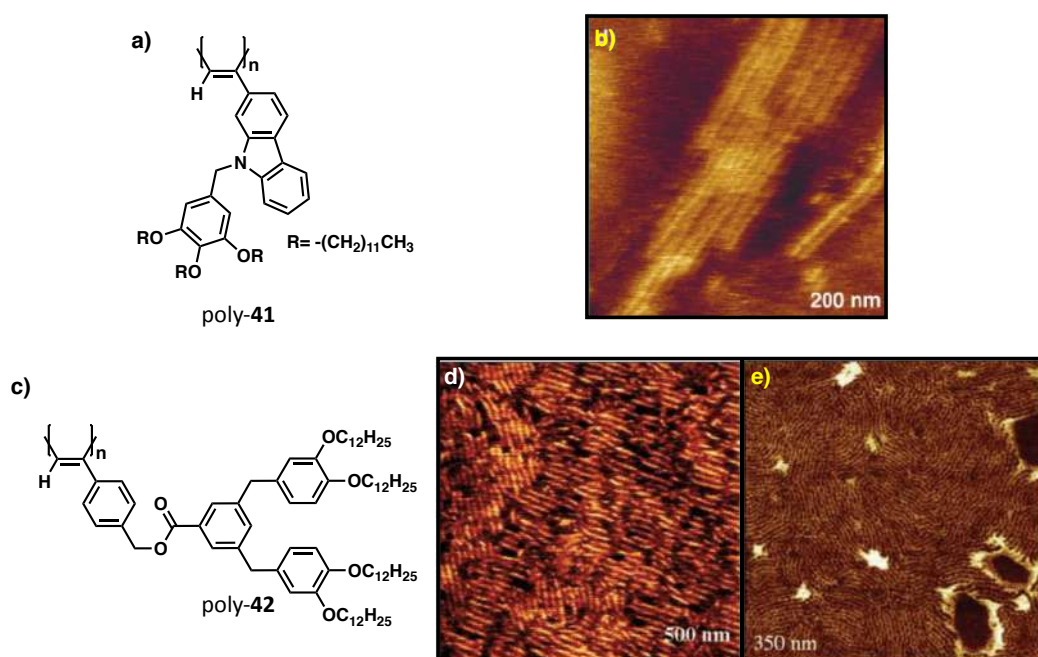


Figure 29. (a) Structure of poly-**41**. (b) AFM of poly-**41** on HOPG after thermal annealing. (c) Structure of poly-**42**. (d) and (e) AFM images of poly-**42** in mica and HOPG respectively after thermal annealing.

5.4.2. Langmuir-Blodgett Monolayers

As previous mentioned, the preparation of PPA monolayers by drop casting and spin coating consists in the evaporation of a solution of the polymer on a solid support where an air/solid interface is formed. In those conditions, the solvent evaporation and the polymer substrate affinity are critical factors.

⁹⁹ (a) Percec, V.; Obata, M.; Rudick, J. G.; De, B. B.; Glodde, M.; Bera, T. K.; Magonov, S. N.; Balagurusamy, V. S. K.; Heiney, P. A. *J. Polym. Sci., Part A: Polym. Chem.* **2002**, *40*, 3509. (b) Percec, V.; Rudick, J. G.; Peterca, M.; Staley, S. R.; Wagner, M.; Obata, M.; Mitchell, C. M.; Cho, W.-D.; Balagurusamy, V. S. K.; Lowe, J. N.; Glodde, M.; Weichold, O.; Chung, K. J.; Ghionni, N.; Magonov, S. N.; Heiney, P. A. *Chem. Eur. J.* **2006**, *12*, 5731. (c) Percec, V.; Rudick, J. G.; Wagner, M.; Obata, M.; Mitchell, C. M.; Cho, W.-D.; Magonov, S. N. *Macromolecules* **2006**, *39*, 7342.

Affortunately it is possible to resort to another procedure, the Langmuir-Blodgett (LB) method, that prepares monolayers in an air/water interface. The formation of Langmuir monolayers starts with dropwise deposition of the target molecule in an organic solvent on a water surface. Next, two processes happen at the same time: the water surface is gradually compressed by the barriers of the LB system and the pressure of the polymer increases until a compact monolayer of molecules is formed. Then, the monolayers are transferred from the air/water interface to the AFM substrate, which was immersed on water (Figure 30a).¹⁰⁰ Although HOPG is adequate for the polymer, its hydrophobic properties are incompatible with its use in LB because the substrate has to be extracted from the water layer. Moreover, it's known that the best AFM images acquired for this family of polymers are obtained when HOPG is used as solid substrate.

Tang and co-workers applied the LB method to different polymers bearing (*L*)-Aline (poly-**43**) and (*L*)-Valine (poly-**44**) methyl ester residues as pendant groups. They achieved the formation of the monolayers, but their qualities were poor and they could not solve the helical structure of the polymer (Figure 30b-c).¹⁰¹

¹⁰⁰ (a) Kawauchi, T.; Kumaki, J.; Kitaura, A.; Okoshi, K.; Kusanagi, H.; Kobayashi, K.; Sugai, T.; Shinohara, H.; Yashima, E. *Angew. Chem. Int. Ed.* **2008**, *47*, 515-519. (b) Roberts, G. G. *Langmuir-Blodgett Films*; Plenum: New York, **1990**.

¹⁰¹ (a) Li, B. S.; Kang, S. Z.; Cheuk, K. K. L.; Wan, L.; Ling, L.; Bai, C.; Tang, B. Z. *Langmuir* **2004**, *20*, 7598. (b) Li, B. S.; Lam, J. W. Y.; Yu Z.-Q.; Tang, B. Z. *Langmuir* **2012**, *28*, 5770.

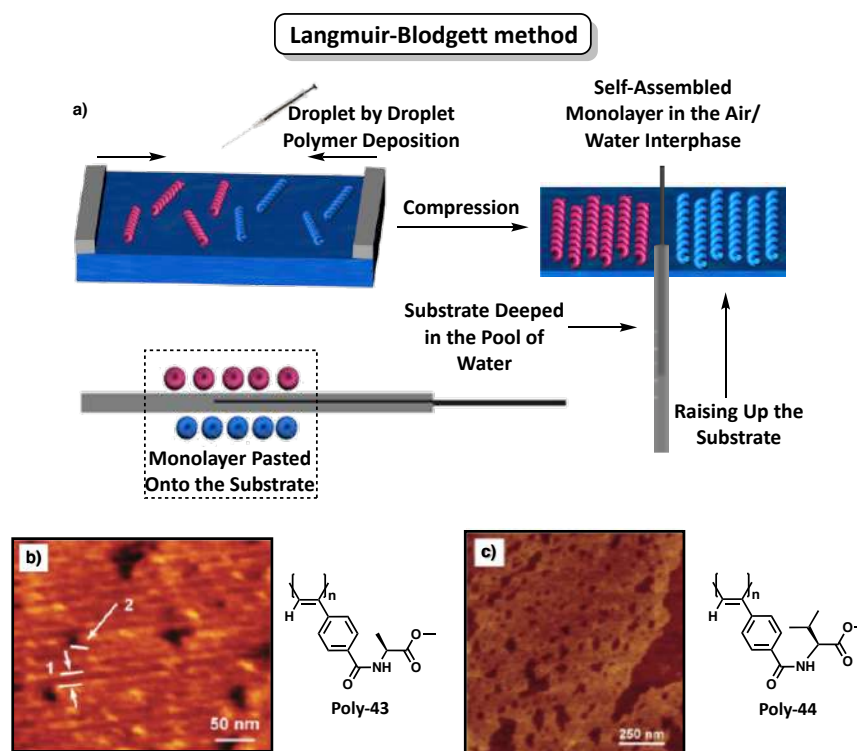


Figure 30. (a) Schematic illustration of the LB technique. Structure and AFM image of (b) poly-43 and (c) poly-44 obtained by LB protocol.

5.4.3. Langmuir–Schaefer

Using Yashima's protocol,^{69c} our research group succeeded applied the spin coating/solvent exposure method to the helically racemic poly-17¹⁴ bearing short pendants, showing that the presence of long alkyl chains is not always necessary for the self-assembly of (PPA)s.

To develop this work, poly-17 was deposited on HOPG, but we did not observe the presence of 2D-crystals, probably due to the highly dynamic behaviour of poly-17. Thus, an alternative methodology, a modification of the LB method, was employed to prepare a well-ordered monolayer of poly-17 and consequently elucidate the secondary structure of this poly(phenylacetylene): the Langmuir-Schaefer (LS) protocol¹⁰² where the monolayer is directly exfoliated from the air/water interphase by the AFM substrate instead of immersing the substrate on water to get the transference of the monolayer (Figure 31a). In addition, HOPG can be used as AFM substrate, which is more convenient for preparing a self-assembled monolayer of a PPA.

¹⁰² Ulman, A. An Introduction to ultrathin, Organic Films-From Langmuir-Blodgett to Self-Assembly, *Academic Press*, New York, **1991**.

The application of LS method to poly-**17** allowed us to acquire well-ordered monolayers for this polymer making possible to measure different helical parameters and getting its helical structure where it was found that poly-**17** is folded in enantiomeric 2D crystals, which are made of helices with same scaffold but different helical sense (Figure 31b).¹⁰³

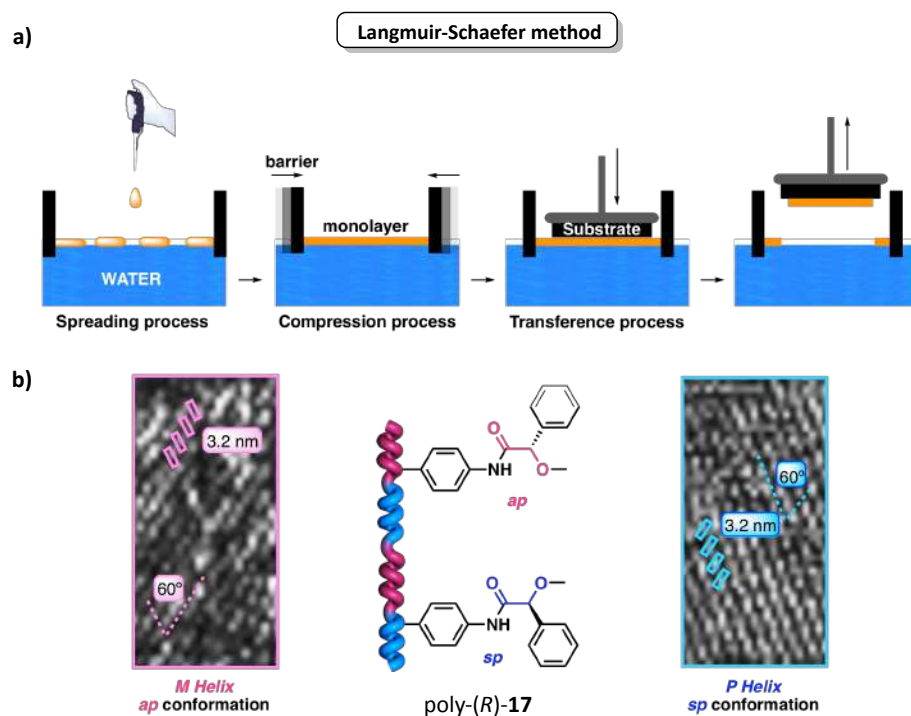


Figure 31. (a) Langmuir-Schaefer procedure. (b) Helical structure and AFM images of poly-**17** in *ap* and *sp* conformation monolayers obtained by Langmuir-Schaefer.

5.5. Architecture of (PPA)s

In polymers field, there is an important structural feature related to the architecture of poly(phenylacetylene)s that is intrinsically to all (PPA)s and is not always taking into account. Every helical scaffold is always constituted by two “coaxial helices”: an internal helix described by the polyene backbone and an external one defined by the orientation of the pendant groups around the axis of the backbone, and due to its peripheral position. In particular, the first one depends on the ω_1 dihedral angle that determines not only the presence of a *c-c* or *c-t* structure but also the helical sense — $\omega_1 < 0$ generates *M* helices and $\omega_1 > 0$ generates *P* helices—. This internal helix can be easily studied by CD and UV-Vis spectroscopy. Otherwise, the second coaxial helix can be

¹⁰³ Rodríguez, R.; Ignés-Mullol, J.; Sagués, F.; Quiñoá, E.; Riguera, R.; Freire, F. *Nanoscale* **2016**, *8*, 3362.

obtained by AFM analysis once the polymer is deposited onto the corresponding substrate (Figure 32).

Interestingly, the helical sense of these two coaxial helices can be coincident or not, depending on the configuration of the conjugated double bonds of the PPA. As mentioned above in this section, the secondary structure of a PPA can not be elucidate just by CD spectroscopy, this means that it must be combined with other techniques like AFM, where the helicity observed corresponds to the external helix, the one described by the pendant groups. It's known that a polymer with *c-c* structure ($\omega_1 < 90^\circ$) displays a compressed helix with a three residues per turn (3/1 helix) where the internal helix and the external helix are coincident (e.g., negative CD signal for the *M* internal helix and *M* external helix in AFM). However, (PPA)s with *c-t* scaffolds ($\omega_1 > 90^\circ$) describe a stretched helix with two residues per turn (2/1 helix) where the internal helix and the external one rotates in opposite ways (e.g., negative CD signal for the *M* helix and *P* external helix in AFM). In case of having information from a single technique [CD (internal helix), AFM (external helix)], DSC is an useful technique to correlate the thermogram with the configuration of the polyene main chain (*c-c* or *c-t*).

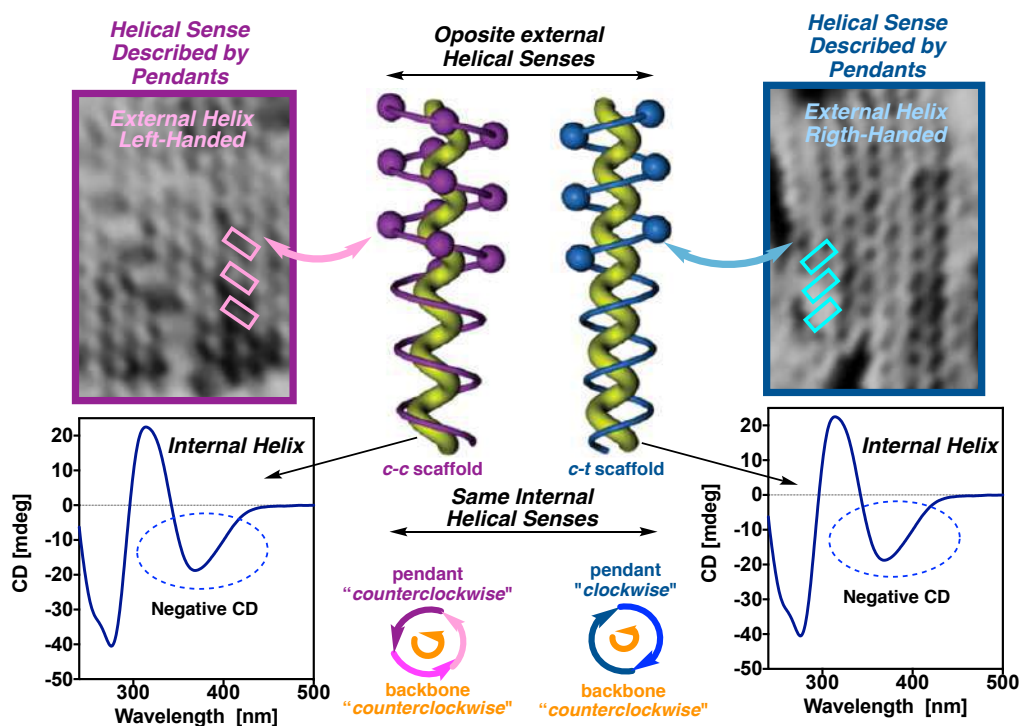


Figure 32. Schematic illustration of the different architectures in *c-c* and *c-t* scaffold. Effect on the coaxial helices, CD spectra and AFM analysis.

The structural elucidation of a PPA, combining information from several structural techniques, was reported by our group for the polymer poly-(*R*)-**17**/ M^{n+} complex.¹⁴ AFM studies indicated the presence of well-ordered 2D-crystals after a dilute solution of the helical polymer-metal complex (HPMC) was spin coated onto HOPG and kept under a THF atmosphere overnight, providing good quality monolayers.

This procedure allowed us to obtain several helical parameters such as the helical pitch (around 3.2 nm), the packing angle (close to 60°), and the screw sense (right-handed helix in case of poly-**17**/ M^{+2} complex and left-handed helix in the case of poly-**17**/ M^+ complex) (Figure 33). In addition, we have demonstrated that the helix inversion was triggered by precise tuning of the cation- π with polar solvents in poly-**17**/ Na^+ complexes could be maintained in the 2D-crystals.¹⁴

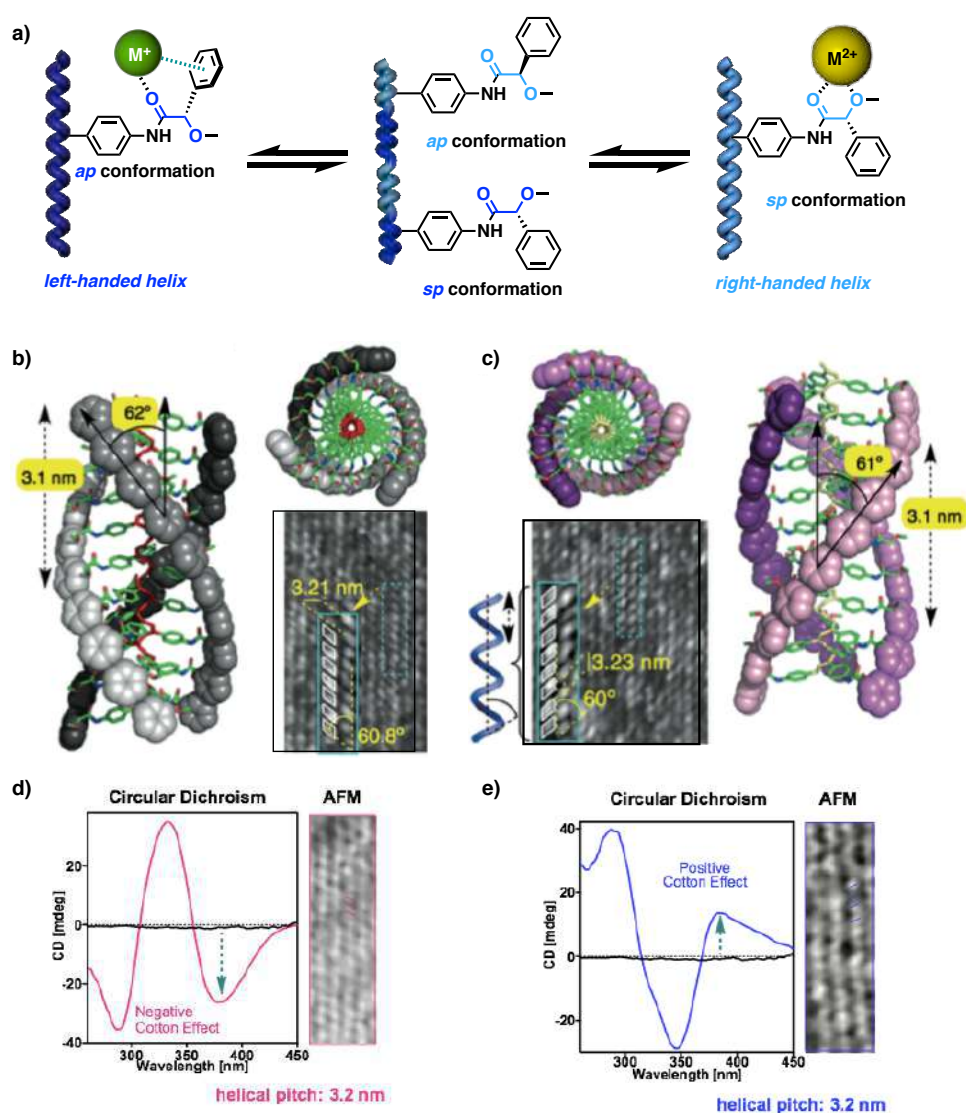


Figure 33. (a) Conceptual representation of the conformational equilibrium of poly-**17** and the selective chiral amplification mediated by metal ions. (b) 2D-crystals and 3D model poly-**17**/ M^+

complex. (c) 2D-crystals and 3D model poly-**17**/ M^{2+} complex. (d) AFM and CD spectra of poly-**17**/ Na^+ cation- π interaction activated. (e) AFM and CD spectra of poly-**17**/ Na^+ cation- π deactivated.

6. Supramolecular Assemblies of Helical Polymers

During the last 60 years a few new concepts of supramolecular chemistry were introduced: one is macromolecules,^{104, 105} whose importance was recognized in the 1953 Nobel Prize to Staudinger, and the other two are molecular recognition and supramolecular assembly, which gave the 1987 Nobel Prize to Cram, Lehn, and Pedersen.¹⁰⁶

Different architectures (films, layers, membranes, spheres, etc.) can be adopted by supramolecular assemblies depending on the physical interactions (supramolecular) or chemical (covalent bonds) that keep the different molecular components together. Moreover, the introduction of optically active components can transfer chiral information to the assembly.^{107, 108}

In the next section the most common supramolecular assemblies —fibers, gels and particles— will be discussed in detail.

6.1. Fibbers, superhelices and double helices

Poly(phenylacetylene)s can self-assemble into fibber-like structures by supramolecular interactions between the pendants of different chains. For polymeric aggregation, appropriate functional groups on the pendant group and adequate complementary

¹⁰⁴ (a) Percec, V. Hierarchical Macromolecular Structures: 60 Years after the Staudinger Nobel Prize I. *Advances in Polymer Science*, 261, Springer, New York, **2013**. (b) Percec, V. Hierarchical Macromolecular Structures: 60 Years after the Staudinger Nobel Prize II. *Advances in Polymer Science*, 262, Springer, New York, **2013**.

¹⁰⁵ (a) Lenh, J. M. Supramolecular Chemistry. Concepts and Perspectives. Wiley-VCH, Weinheim, Germany, **1995**. (b) Steed, J. W.; Atwood, J. L. Supramolecular Chemistry. John Wiley & Sons Ltd: West Sussex, United Kingdom, **2009**. (c) Cragg, P. J. A Practical Guide to Supramolecular Chemistry. John Wiley & Sons Ltd: West Sussex, United Kingdom, **2005**.

¹⁰⁶ (a) Li, A. D. Q. *Molecular Self-Assembly: Advances and Applications*. Taylor & Francis Group, LLC, Boca Ratón, Florida, **2013**. (b) Loh, X. J.; Scherman, O. A. *Polymeric and Self Assembled Hydrogels*. The Royal Society of Chemistry, Cambridge, **2013**. (c) Harada, A. *Supramolecular Polymer Chemistry*. Wiley-VCH, Weinheim, Germany, **2012**. (d) Hadjichristidis, N.; Hirao, A.; Tezuka, Y.; Prez, F. D. *Complex Macromolecular Architectures*. John Wiley & Sons (Asia) Pte Ltd. **2011**. (e) Hao, J. *Self-Assembled Structures Properties and Applications in Solution and on Surfaces*. Taylor & Francis Group, LLC, Boca Ratón, Florida, **2010**. (f) Geckeler, K. E.; Nishide, H. *Advanced Nanomaterials*. (Volumes I and II). Wiley-VCH, Weinheim, Germany, **2010**. (g) Ozin, G. A.; Arsenault, A. C.; Cadernatiri, L. *Nanochemistry: A Chemical Approach to Nanomaterials*. The Royal Society of Chemistry, Cambridge, **2010**. (h) Lee, Y. S. *Self-Assembly and Nanotechnology. A Force Balance Approach*. John Wiley & Sons, Inc. Hoboken, New Jersey, **2008**. (i) Rotello, V. M., Thayumanavan, S. *Molecular Recognition and Polymers*. Hoboken, New Jersey, **2008**. (j) Kickelbick G. *Hybrid Materials. Synthesis, Characterization, and Applications*. Wiley-VCH, Weinheim, Germany, **2007**.

¹⁰⁷ Freire, F.; Quiñóá, E.; Riguera, R. *Chem. Rev.* **2016**, *116*, 1242-1271.

¹⁰⁸ Yashima, E.; Ousaka, N.; Taura, D.; Shimomura, K.; Ikai, T.; Maeda, K. *Chem. Rev.* **2016**, *116*, 1375-13990.

between the interacting chains are required.^{4d, 107, 79} A good example of the abovementioned requirements is represented by the formation of stereocomplexes (SCs) which are supramolecular aggregates formed by the interaction between complementary and stereoregular helical polymers with different physical properties — i.e. better mechanical and thermal resistance as well as a slower degradation process— to the starting polymers. Moreover, Van der Waals forces (weak) and electrostatic interactions (strong) are the main interactions in the formation of SCs.¹⁰⁹

The first example of a SC formation was reported in the late 50's and it consisted in a SC formed by poly(methylmethacrylate)s¹¹⁰ —interaction of a syndiotactic poly(methylmethacrylate) (*st*-PMMA) with an isotactic PMMA (*it*-PMMA)—. Over the years and to this day more several examples of SCs have been reported, being the case of SCs formed by polylactic (PLA)¹¹¹ and some polypeptides.¹¹²

Working on this topic, our group reported the first example of a SC formed by (PPA)s. The starting polymers are two helical poly(phenylacetylene)s, poly-(*R*)-**33** and poly-(*S*)-**33**, derived from (*R*) and (*S*)- α -methoxy- α -trifluoromethylphenylacetic acid (MTPA) respectively. In these polymers the modulation of the *cis*-/ *trans*- conformation in the amide of the pendant group plays an important role. When these polymers are dissolved in a donor solvent⁷¹ (e.g., THF), the amides groups, which are located on the crest of the helix, adopt a *cis*- conformation inducing a stretching in the polymer backbone. Due to their spatial localitation, these amide groups form supramolecular interaction with the complementary helical polymer. Thus, the combination of the enantiomeric polymer chains results in a supramolecular fiber-like aggregate that, at higher concentrations, generate gels (Figure 34). This stereocomplex formation process can be manipulated in a reversible way through modifications in the properties of the organic solvent or in the temperature.¹¹³

¹⁰⁹ (a) Bertin, A. *Macromol. Chem. Phys.* **2012**, 213, 2329. (b) Slager, J.; Domb, A. J. *Adv. Drug Delivery Rev.* **2003**, 55, 549-583.

¹¹⁰ (a) Fox, T. G.; Garrett, B. S.; Goode, W. E.; Gratch, S.; Kincaid, J. F.; Spell, A.; Stroupe, J. D. *J. Am. Chem. Soc.* **1958**, 80, 1768-1769. (b) Hatada, K.; Kitayama, T. *Polym. Int.* **2000**, 49, 11-47. (c) Brinkhuis, R. H. G.; Schouten, A. J. *Macromolecules* **1992**, 25, 6173-6178. (d) Špeváček, J.; Scheinder, B. *Adv. Colloid Interface Sci.* **1987**, 27, 81-150.

¹¹¹ (a) Akagi, T.; Fujiwara, T.; Akashi, M. *Angew. Chem. Int. Ed.* **2012**, 51, 5493. (b) Furuhashi, Y.; Kimura, Y.; Yoshie, N. *Polym. J.* **2006**, 38, 1061. (c) Tsuji, H. *Macrom. Biosci.* **2005**, 5, 569.

¹¹² (a) Nakayama, H. Manaka, T.; Iwamoto, M.; Kimura, S. *Soft. Matter.* **2012**, 8, 3387. (b) Pauling, L.; Corey, R. B. *Proc. Natl. Acad. Sci. U.S.A.* **1953**, 39, 253.

¹¹³ Leiras, S.; Freire, F.; Quiñoá, E.; Riguera, R. *Chem. Sci.* **2015**, 6, 246.

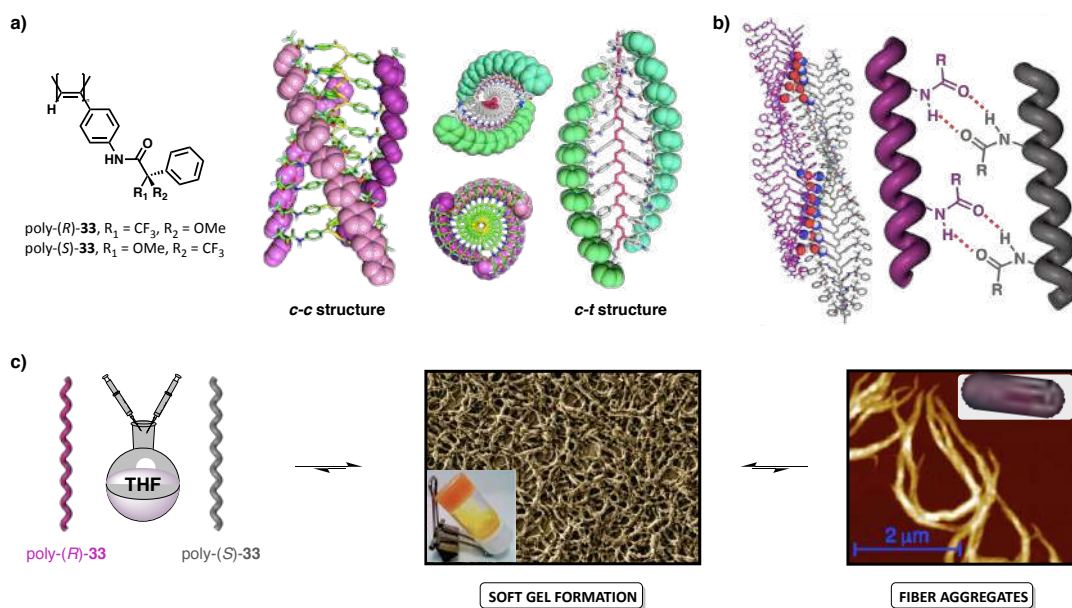


Figure 34. (a) Structure and schematic illustration of the *c-c* and *c-t* structures adopted by poly-33. (b) Structural model of the polymeric self-assembly. (c) Stereocomplex formation and SEM images of the soft gel and fiber aggregates.

Recently, new SCs based on polycarbonates were reported by Auriemma *et al.* and Liu *et al.*, consisting in a mixture of enantiometric pure polymers where crystals of the SC were also obtained.¹¹⁴

Other examples of fiber-like aggregates based on (PPA)s different from SCs can be found in literature. In this way, a polymer bearing menthoxycarbonylamino groups (poly-45) were reported by Shinohara, Shigekawa and co-workers.¹¹⁵ They used Scanning Tunnelling Microscopy (STM) to display the formation of double helical structures when a solution of poly-45 was drop-cast onto HOPG substrate. Therefore, they found that the interaction between the double helical structure and the scanning probe gave mobility to these macromolecules. As a result of these modifications during the STM measurement, the double helical structure was loosened. (Figure 35).

¹¹⁴ (a) Auriemma, F.; De Rosa, C.; Di Caprio, M. R.; Di Girolamo, R.; Coates, G. W. *Macromolecules* **2015**, *48*, 2534-2550. (b) Auriemma, F.; De Rosa, C.; Di Caprio, M. R.; Di Girolamo, R.; Ellis, W. C.; Coates, G. W. *Angew. Chem. Int. Ed.* **2015**, *54*, 1215-1218. (c) Liu, Y.; Ren, W.-M.; Wang, M.; Liu, C.; Lu, X.-B. *Angew. Chem. Int. Ed.* **2015**, *54*, 2241-2244.

¹¹⁵ Shinohara, K.; Yasuda, S.; Kato, G.; Fujita, M.; Shigekawa, H. *J. Am. Chem. Soc.* **2001**, *123*, 3619-3620.

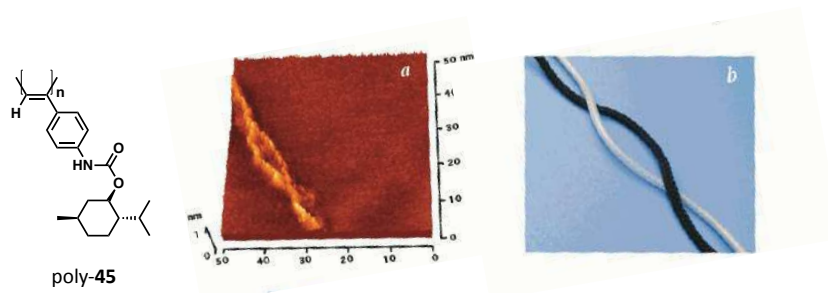


Figure 35. Structure of poly-45. (a) STM image of the supramolecular helical assembly and (b) conceptual representation of the assembly generated.

Related to these findings, the effect in the supramolecular aggregation of (PPA)s bearing different methyl ester aminoacids as pendant group [e.g. valine (poly-46)] was reported by Tang and co-workers (Figure 36).^{72, 47, 116} The researchers found that changing the conditions of deposition the polymers could adopt intramolecular/intermolecular hydrogen bonds leading to different types of supramolecular structures.

On one side, the formation of intermolecular hydrogen bonds interactions is favored by the pendant groups when a high concentration of poly-46 is dissolved in low polar solvents (Figure 36a). Likewise, when solutions of those (PPA)s are drop-casted and slowly evaporated on mica, high order aggregates, such as fibbers with different length and diameters, could be observed by AFM (Figure 36d and 36e).⁷²

Otherwise, when poly-46 is dissolved in polar solvents different supramolecular aggregates are generated due to their amphipathic character (non-polar backbone and polar pendants). This produces the formation of micelle-like structures, with the apolar polyenic backbone in the core and polar amino acid pendants pointing out to the shell (Figure 32b). The pendants outside of these micelles interact through hydrogen bonds, holding them together and triggering larger micelles that collapse to produce fibber-like structures (Figure 36c).⁷²

¹¹⁶ (a) Cheuk, K. K. L.; Li, B. S.; Lam, J. W. Y.; Xie, Y.; Tang, B. Z. *Macromolecules* **2008**, *41*, 5997-6005. (b) Li, B.S.; Cheuk, K. K. L.; Ling, L.; Chen, J. Xiao, X.; Bai, C.; Tang, B. Z. *Macromolecules* **2003**, *36*, 77-85. (c) Li, B. S.; Chreuk, K. K. L.; Yang, D.; Lam, J. W. Y.; Wan, L. J.; Bai, C.; Tang, B. Z. *Macromolecules* **2003**, *36*, 5447-5450. (d) Li, B. S.; Cheuk, K. K. L.; Salhi, F.; Lam, J. W. Y.; Cha, J. A. K.; Xiao, X.; Bai, C, Tang, B. Z. *Nano Lett.* **2001**, *1*, 323-328.

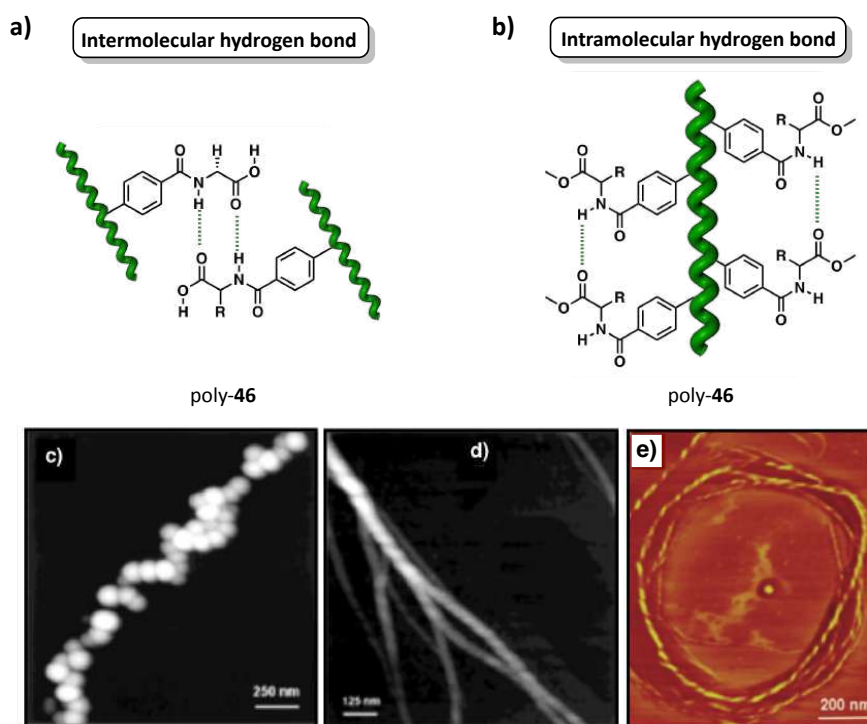


Figure 36. Schematic representation of (a) intermolecular hydrogen bonds between the pendant groups of different helices responsible for the formation of high-order aggregate, (b) intramolecular hydrogen bonds between the pendant groups stabilizing the helical structure of the PPA. AFM images of (c) pearl-like and (d-e) fiber-like structures.

It's possible to find a third example of supramolecular aggregates based on (PPA)s that can form fiber-like helical aggregates or superhelices but, in this case, their aggregation process takes place in a semiplanar structure instead of a helical one. Working on this idea, Yashima and co-workers reported a representative example of planar-mediated aggregation induced by the size of the pendants. They studied (PPA)s bearing bulky groups like cyclodextrins (CyD) as pendant moieties that aggregate into long and well-defined fiber-like structures.^{4d, 69b, 107} Sakurai *et al.* reported another example where poly-19/Alanine complexes generate superhelical structures once deposited onto mica.¹¹⁷

In 1998, Nolte *et al.* described the first example of helical superstructures formed by synthetic helical polymers.¹¹⁸ One feature of these superhelices is that the helical sense can be totally controlled once they are formed in aqueous media. An amphiphilic block copolymer (poly-47)—composed of a hydrophobic tail of flexible polystyrene, and a hydrophilic rigid-rod helical poly(isocyanopeptide) bearing a negative charged group on

¹¹⁷ Sakurai, S. I.; Kuroyanagi, K.; Nonokawa, R.; Yashima, E. *J. Polym. Sci. Part A Polym. Chem.* **2004**, 42, 5838.

¹¹⁸ Cornelissen, J. J. L. M.; Fischer, M.; Sommerdijk, N. A. J. M.; Nolte, R. J. M. *Science* **1998**, 280, 1427-1430.

the side chain— is used to get their self-assembly. Amazingly, the right-handed helical structure of the amphiphilic copolymer results in the formation of helical superstructures that present an opposite helical sense (left-handed superhelix) (Figure 37).

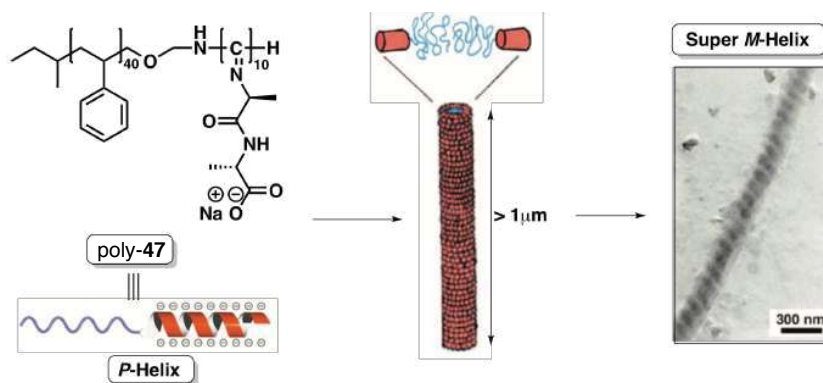


Figure 37. Schematic illustration of the formation of superhelix by self-assembly of an amphiphilic polymer.

Another interesting example of supramolecular helical assemblies was reported by Cheng and co-workers.¹¹⁹ They crystallized chiral but non-helical main chain LC polyesters (poly-48), obtaining flat-elongated and left-handed helical lamellar single crystals (Figure 38).

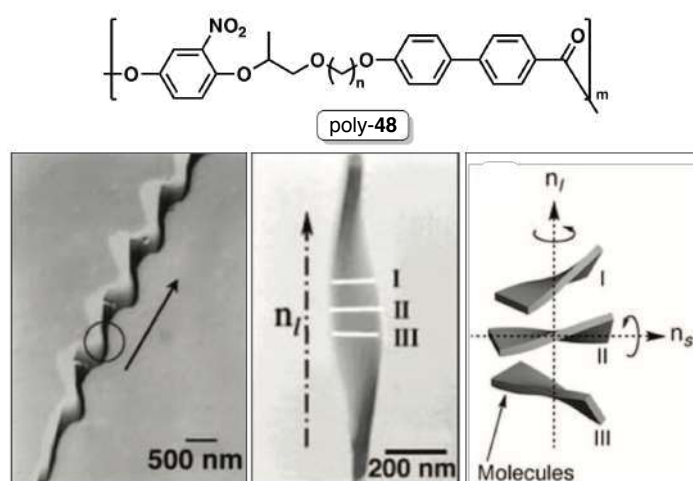


Figure 38. TEM images and schematic drawings of a twist model of a double-twisted helical lamellar crystal.

¹¹⁹ (a) Lotz, B.; Cheng, S. Z. D. *Polymer* **2005**, 46, 577-610. (b) Li, C. Y.; Cheng, S. Z. D.; Ge, J. J.; Bai, F.; Zhang, J. Z.; Mann, I. K.; Chien, L. C.; Harris, F. W.; Lotz, B. *J. Am. Chem. Soc.* **2000**, 122, 72-79. (c) Li, C. Y.; Yan, D.; Cheng, S. Z. D.; Bai, F.; He, T.; Chien, L. C.; Harris, F. W.; Lotz, B. *Macromolecules* **1999**, 32, 524-527.

Finally, Akagi and co-workers described supramolecular assemblies based on (PPA)s polymerized in liquid crystal phases with chiral dopant agents (axially chiral binaphthyl derivatives).¹²⁰ These structures grow from single polymers chains to produce polymer bundles that in a final step self-assemble to form spiral structures (Figure 39).

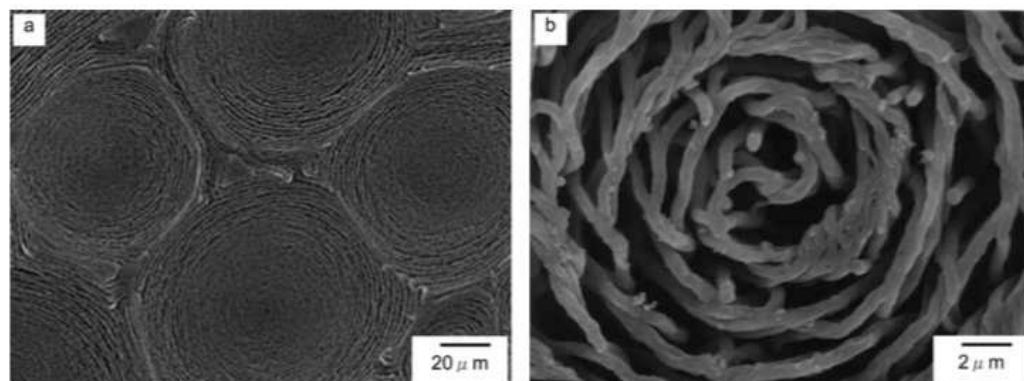


Figure 39. (a-b) SEM images of superhelical structures obtained by synthesis of polyacetylene in liquid crystals.

6.2. Nanostructures based on (PPA)s

Micro- and nanostructured materials present different and several features compared with bulk materials. Polymer nanoparticles are included in this kind of nanoarchitectures and can be defined as nanospheres or nanocapsules made by a polymeric cover with a specific size range (10–1000 nm). Nanospheres are spherical and solid, and they are commonly used to adsorb molecules on their surface or encapsulate them inside. However, nanocapsules are colloidal particles consisting in a hollow core surrounded by the polymeric membrane. These vesicular systems are usually employed to encapsulate substances into their cavity.¹²¹

During the last years, these materials have been studied and prepared in multiples sizes (bulk, micro, nano) and morphologies developing important properties and functions for being applied in fields such as controlled release, drug delivery, liquid chromatography, self-assembly materials, and so on.¹²² In the same way, chirality can be incorporated into

¹²⁰ Akagi, K. *Chem. Rev.* **2009**, *109*, 5354.

¹²¹ Reese, C. E.; Asher, S. A. *J. Colloid Interface Sci.* **2002**, *248*, 41.

¹²² (a) Li, W.; Huang, H.; Li, Y.; Deng J. P. *Polym. Chem.* **2014**, *5*, 1107-1118. (b) Song, C.; Liu, X.; Liu, D.; Ren, C.; Yang, W.; Deng, J. P. *Macromol. Rapid Commun.* **2013**, *34*, 1426-1445.

these nanostructures (nanofibers, nanospheres, nanotubes, etc) providing applications in catalysis, chiral sensing, enantiomeric separation, etc.

Polymer particles can be prepared through two main protocols: emulsification method and emulsion polymerization.

6.2.1. Emulsification method

This methodology consists in the emulsification of a performed polymer chains into micelles. Following this technique, polymer chiral particles (PCPs) were prepared by Zhang *et al.* Firstly, they synthesized the polymer using a Rh(I) catalyst in an organic solvent (poly-**49**) (Figure 40). Then, a concentrated polymer solution in THF was added droplet-by-droplet onto an aqueous solution of the surfactant, sodium dodecyl sulphate (SDS), getting nanoparticles which size depends on the emulsifier concentration: lower polymer particle size with an increasing concentration of surfactant due to the higher number of micelles in the medium.¹²³

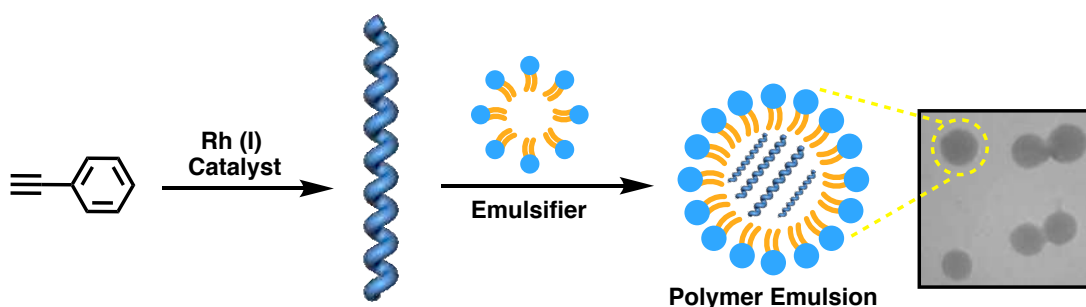


Figure 40. Schematic illustration of the emulsification driven polymer particle formation.

A few years ago, Deng and co-workers applied emulsification-induced homo-helicity effect to prepare PCPs using an axially racemic helical polymer (mixture of right- and left-handed helical sense) (poly-**50**).¹²⁴ Thus, in the presence of chiral additive the polymer is emulsified in micelles and will experiment a single-handed helical sense induction upon the emulsification process, achieving optically active polymer nanoparticles (Figure 41).

¹²³ Zhang, Y.; Luo, X.; Deng, J.; Yang, W. *Macromol. Chem. Phys.* **2011**, 212, 353-360.

¹²⁴ Zhao, B.; Deng, J.; Deng, J. P. *Macromol. Rapid Commun.* **2016**, 37, 568-574.

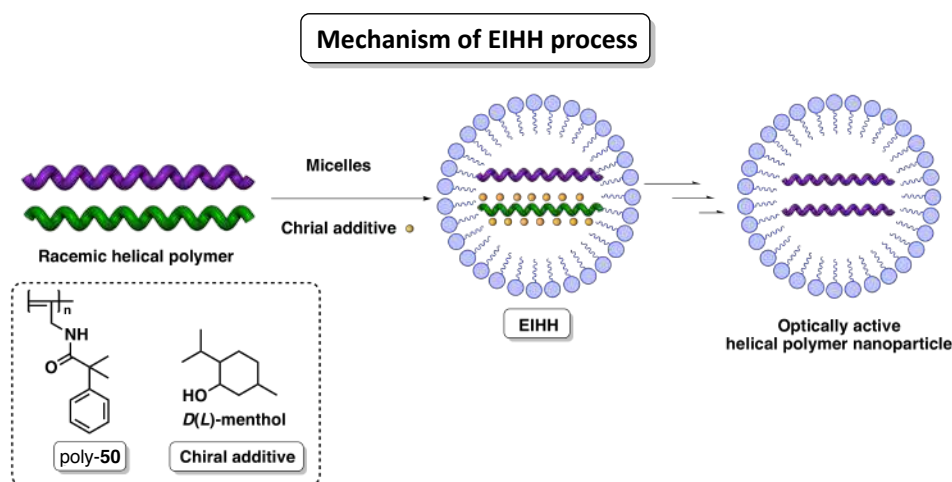


Figure 41. Schematic illustration displaying proposed mechanism of the EIHH process (ref. 93 and 94).

6.2.2. Emulsion polymerization

This methodology consists in a polymerization process carried out in a heterogeneous media, frequently an aqueous and a non-aqueous phases.¹²⁵ This protocol requires a monomeric unit with low solubility in water, a water-soluble initiator and emulsifier.

Deng and co-workers investigated this method to form optically active polymer nanoparticles derived from substituted acetylenic monomers using either chiral monomers or chiral emulsifiers.¹²⁶ In most cases, the generated (P)As show a preferred helical sense, resulting in chiral nanoparticles.^{97b} Thereby, while the monomer insoluble in water stays trapped inside the micelle, the hydrophobic Rh (I) catalyst is dispersed into the micelles, which contains the monomer. In consequence, the polymerization occurs inside the micelle getting the polymer particles with small diameter.^{97c}

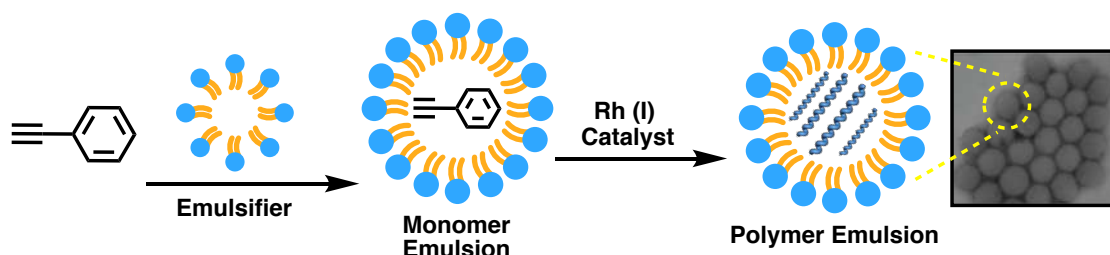


Figure 42. Schematic illustration of the emulsion polymerization process.

¹²⁵ Chern, C. S. *Prog. Polym. Sci.* **2006**, *31*, 443-486.

¹²⁶ (a) Deng, J.; Chen, B.; Luo, X.; Yang, W. *Macromolecules* **2009**, *42*, 933-938. (b) Chen, B.; Deng, J.; Tong, L.; Yang, W. *Macromolecules* **2010**, *43*, 9613-9619. (c) Chen, B.; Liu, X.; Xu, C.; Song, C.; Luo, X.; Yang, W.; Deng, J. *Macromol. Chem. Phys.* **2012**, *213*, 603-609.

6.3. Nanostructuration based on helical polymers by cross-linked agents

The first example of chiral polymer nanoparticles generated by using metal cations as supramolecular cross-linking agents was developed by our group. The chiral amplification phenomenon of poly-**17** (see the section 4.3) is promoted by the addition of metal ions that act not only as helical inducer¹⁴ but also as a cross-linking agent.¹²⁷ The interaction between the polymer and the metal ion —as a cross-linking agent— forms nanospheres whose size and chiral content can be controlled by the nature of the metal ion, the polymer/metal ratio and the solvent properties (Figure 43a).

These nanospheres presented the ability to encapsulate iron oxide magnetic nanoparticles, organic molecules (e.g., fluorescent dyes) or quantum dots (Figure 43d). Moreover, it was possible to obtain other types of nanostructures like nanotubes or toroidal nanostructures by variation of the solvent (Figure 43d-e).¹²⁸ Finally, the chirality of the nanoparticles in both monovalent¹²⁹ and divalent¹³⁰ HMPCs can be switched in a reversible way modifying in the coordination mode between the metal and the pendant moiety.

¹²⁷ Freire, F.; Seco, J. M.; Quiñoá, E.; Riguera, R. *J. Am. Chem. Soc.* **2012**, *134*, 19374-19383.

¹²⁸ Arias, S.; Freire, F.; Quiñoá, E.; Riguera, R. *Angew. Chem. Int. Ed.* **2014**, *53*, 13720.

¹²⁹ (a) Arias, S.; Bergueiro, J.; Freire, F.; Quiñoá, E.; Riguera, R. *Small* **2016**, *12*, 238. (b) Arias, S.; Núñez-Martínez, M.; Quiñoá, E.; Riguera, R.; Freire, F. *Small* **2017**, *13*, 1602398.

¹³⁰ Arias, S.; Núñez-Martínez, M.; Quiñoá, E.; Riguera, R.; Freire, F. *Polym. Chem.* **2017**, *8*, 3740.

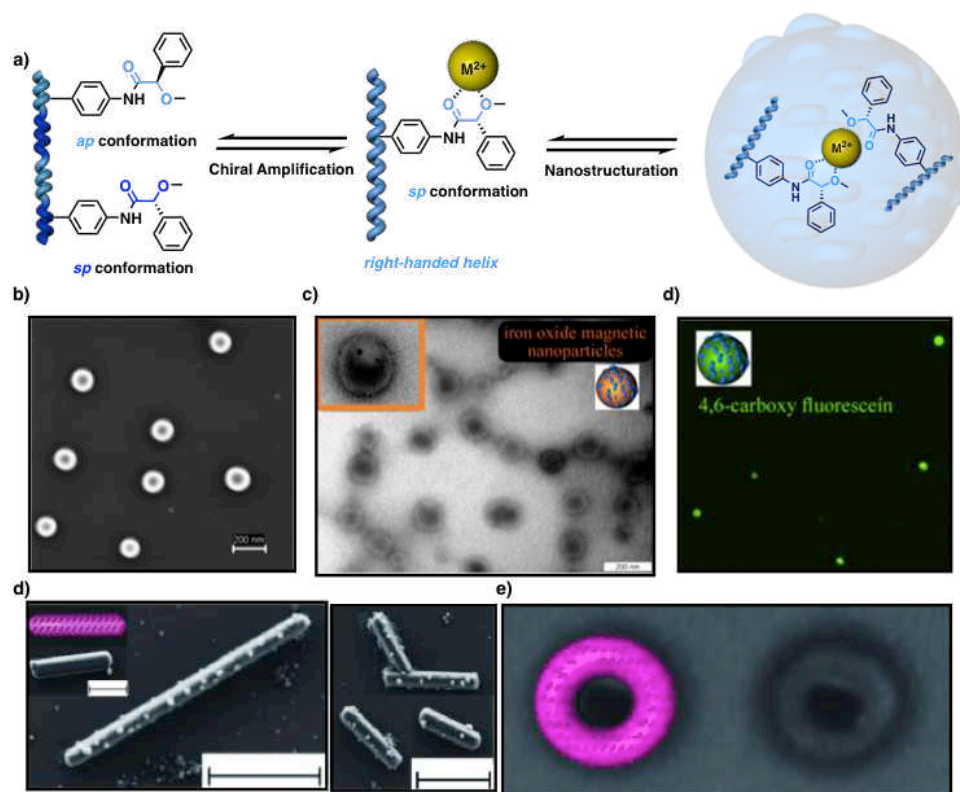


Figure 43. (a) Schematic illustration of the metal coordination driven formation of nanospheres based on HPMCs. (b) SEM images of nanospheres based on HPMCs. (c) TEM image showing FeNPs encapsulated within a HPMC nanosphere. (d) Confocal image of HPMCs nanospheres showing fluorescence due to the encapsulation of fluorescein and SEM images of nanotubes based on HPMCs. (e) SEM images of nanotorus based on HPMCs.

7. Applications of (PPA)s

Helical polymers based on (PPA)s are interesting and promising materials due to their chiral nature and the possibility to manipulate their helical parameters. For instance, the potential functions of optically active helical polymers —asymmetric catalysis, chiral recognition and chiral sensing among others— will be discussed next.

7.1. Sensors

A remarkable feature of (PPA)s is the opportunity to modify the helical sense or the helical scaffold of the polymer by the interaction with external stimulus, being also possible to detect these small variations by CD and UV-Vis techniques. For this reason, during the last decade dynamic helical polymers have been employed as optical and

chiroptical sensors to detect species like anions,¹³¹ metal ions,^{14, 29, 44a} solvent properties⁵⁰ or even act as thermal sensors.⁴⁰

As it was mentioned previously, our research group reported a PPA, poly-**17**, that displays large chiral amplification phenomena when interacts with monovalent and divalent metal ions, acquiring *M* or *P* helix respectively and making poly-**17** a suitable sensor for the valence of metal ions.¹⁴ In addition, we have developed several polymers (poly-**29** and poly-**33**) as solvent sensors: poly-**29** is able to identify the polarity of the solvent (polar/non-polar)^{65a} producing different CD spectra while poly-**33** can classify solvents according to the polar/non-polar donor/non-donor properties showing four different helical structures.⁷¹

Otherwise, optical sensors are related to the presence of the conjugated double bonds of the polyenic chain where a colorimetric change from yellow to red is observed when a compressed helical structure moves to a stretched one. As aforementioned, Yashima and co-workers reported this colorimetric change on solution of a PPA (poly-**30**) bearing a bulky group (β -cyclodextrins) at the pendant moiety. Thus, when the polymer interacts with some alcohols the colour for the polymer's solution goes from yellow to red and can also be observed by changes in the solvent composition or by thermal modifications of the media where it is dissolved.^{47a, 69}

Working on colorimetric detection systems, different polymers can be used as colorimetric sensors for anions —not only in organic solvents but also in aqueous media— were carried out by Kakuchi and co-workers. They prepared poly-**51** bearing an urea group adequate to interact with anions. These interactions are responsible of colorimetric changes due to an elongation in the polyene backbone minimizing the generated repulsions (Figure 44).¹³¹

¹³¹ (a) Sakai, R.; Barasa, E. B.; Sakai, N.; Sato, S.-I.; Satoh, T.; Kakuchi, T. *Macromolecules* **2012**, *45*, 8221-8227. (b) Sakai, R.; Sakai, N.; Satoh, T.; Li, W.; Zhang, A.; Kakuchi, T. *Macromolecules* **2011**, *44*, 4249-4257. (c) Sakai, R.; Okade, S.; Barasa, E. B.; Kakuchi, R.; Ziabka, M.; Umeda, S.; Tsuda, K.; Satoh, T.; Kakuchi, T. *Macromolecules* **2010**, *43*, 7406-7411. (d) Qu, Y.; Hua, J.; Jiang, Y.; Tian, H. *J. Polym. Sci., Part A: Polym. Chem.* **2009**, *47*, 1544-1552. (e) Kakuchi, R.; Nagata, S.; Tago, Y.; Sakai, R.; Otsuka, I.; Satoh, T.; Kakuchi, T. *Macromolecules* **2009**, *42*, 1476-1481. (f) Kakuchi, R.; Kodama, T.; Shimada, R.; Tago, Y.; Sakai, R.; Satoh, T.; Kakuchi, T. *Macromolecules* **2009**, *42*, 3892. (g) Kakuchi, R.; Nagata, S.; Saki, R.; Otsuka, I.; Nakada, H.; Satoh, T.; Kakuchi, T. *Chem. Eur. J.* **2008**, *14*, 10259-10266.

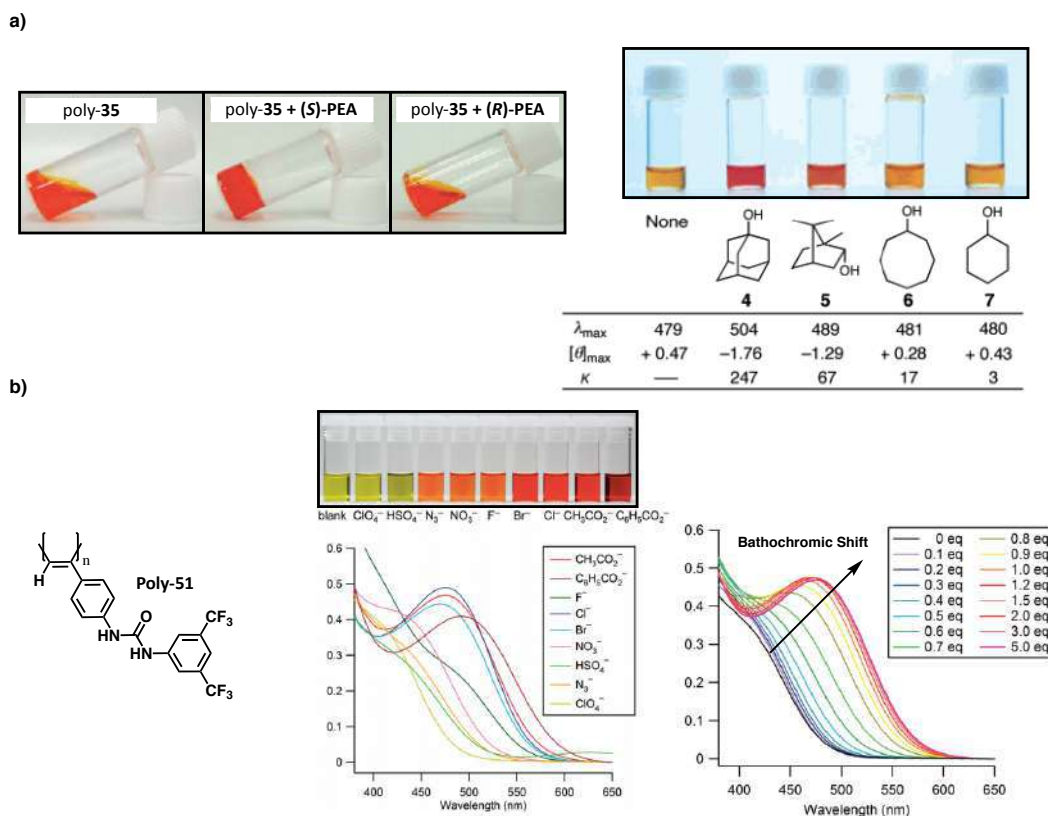


Figure 44. (a) Enantioselective gelation and colorimetric detection of different alcohols with similar structures by poly-30. (b) Structure and schematic illustration of poly-51 detecting different anions and titration with acetate anion showing bathochromic shift in the polyenic region with increasing amounts of anion.

7.2. Chiral Recognition

The separation of enantiomers and the determination of their enantiomeric excess (*ee*) by high-performance liquid chromatography (HPLC) using a chiral stationary phase (CSP) is a powerful technique in analytical and industrial scales.^{132, 133} A remarkable aspect is that it is necessary to have a CSP with excellent chiral recognition ability towards a variety of racemates in order to obtain an appropriate separation of enantiomers by HPLC.

At the present time, there are several chiral CSPs commercially available and based on small molecules and in polymers (artificial helical polymers, polysaccharides and proteins).¹³⁴ Okamoto and co-workers reported the first example of enantioseparation based on helical polymers where a chiral poly(metacrylate) (poly-52) bearing (*R*)-

¹³² Andersson, S.; Allenmark, S. G. *Journal of Biochemical and Biophysical Methods* **2002**, 54, 11-23.

¹³³ Liu, Y.; Lantz, A. W.; Armstrong, D. W. *J. Liq. Chromatogr. Relat. Technol.* **2004**, 27, 1121-1178.

¹³⁴ (a) Yamamoto, C.; Okamoto, Y. *Bull. Chem. Soc. Jpn.* **2004**, 77, 227-257. (b) Blaschke, G. *Angew. Chem. Int. Ed.* **1980**, 19, 13-24. (c) Nakano, T. *J. Chromatogr. A.* **2001**, 906, 205-225.

phenylacetylcarbamoyl pendant groups was employed as CSP for HPLC resolving mixtures of different racemates, including molecule **53** (Figure 45a).¹³⁵

More recently, Maeda and co-workers reported an axially racemic helical polymer that bears a bisphenol derivative as pendant group (poly-**54**), whose helical sense can be switched from *P* to *M* helix or *vice versa* when interacts with (*R*)- or (*S*)-phenylethanol (**55**) respectively. The fact that poly-**54** keeps its helicity, once the chiral alcohol has been removed, constitute the first example of an induced helical polymer where the memorized handedness is able to separate racemates (e.g., *trans*-stilbene **56**). Moreover, they found that the screw sense of the system is the responsible to define the elution order of the *trans*-stilbene enantiomers (Figure 45b).⁴⁰

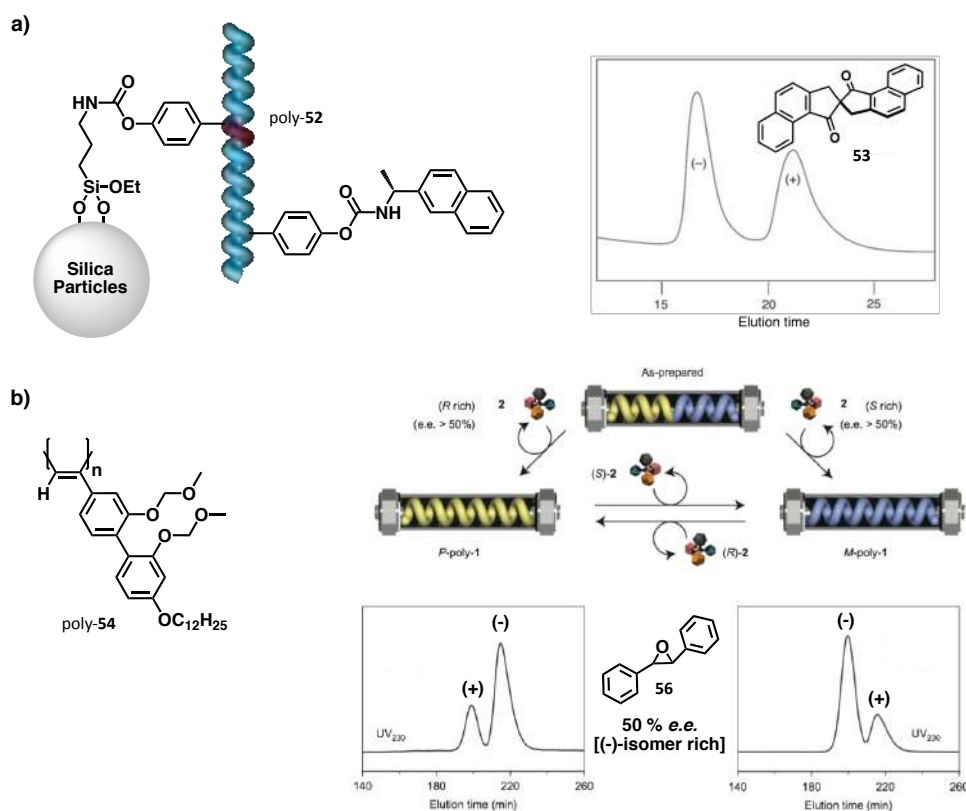


Figure 45. (a) Structure of poly-**52** and chromatogram showing the separation of the enantiomers of **53**. (b) Structure of poly-**54** and conceptual representation of the chiral amplification and memory of macromolecular helicity process and their implication in the separation of **56**.

With this aforementioned information in hand, a new CSP system based on a PPA derivative, poly-**17**, was performed by Freire and Maeda. The addition of achiral metal ions to poly-**17** in solution allows us to control its helicity (*P* or *M* helix),¹⁴ making this PPA

¹³⁵ Yashima, E.; Huang, S.; Okamoto, Y. *J. Chem. Soc., Chem. Commun.* **1994**, 1811-1812.

suitable for using as CSP for HPLC. In addition, this system can be also studied in the enantiodiscrimination process when it presents an axially racemic state due to the absence of the metal ion.¹³⁶ They also demonstrated that if the macromolecular helicity of this polymer is switched, the elution order of enantiomers of a racemate could be inverted. This study represents the first example of a CSP for HPLC able to switch in a reversible way its chiral recognition ability by controlling the helical sense of the PPA. Finally, they showed how the retention time of the two enantiomers of an optically active molecule could be inverted or affected depending on the helical scaffold adopted by the system (Figure 46).

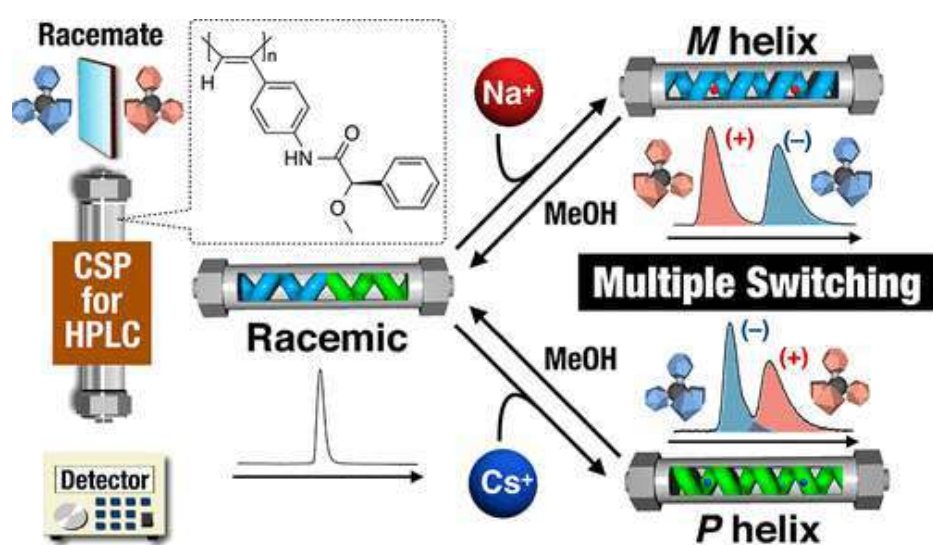


Figure 46. Schematic illustration of the three-state switchable CSP based on poly-17 (ref. 107).

Recently, Wan and co-workers have reported six proline-derived acetylene polymers bearing either two stereocenters where its chiral discriminating property was evaluated by using several aromatic racemates as CSPs for HPLC. They proved that both the helical sense of the main chain and the elution order of analytes were determined by the configuration of the stereocenter adjacent to polymer mainchain, while that of the remote one affected the arrangement of pendants and the scope of analytes that could be discriminated.¹³⁷

Yashima and co-workers have showed the chiral abilities when used as CSPs for HPLC of a series of *cis*-poly(biphenylacetylene) (PBPA) derivatives bearing chiral and achiral

¹³⁶ Hirose, D.; Isobe, A.; Quiñoá, E.; Freire, F.; Maeda, K. *J. Am. Chem. Soc.* **2019**, *141*, 8592-8598.

¹³⁷ G. Shi, Y. Li, X. Dai, J. Shen, X. Wan. *Chirality* **2022**, *34*, 574-586.

pendant groups at the 4'-position of the biphenyl units through an amide or carbamate linkage. These (PBPA)s exhibited an excess one-handed helice —via covalent and non-covalent chiral interactions with chiral alcohols [(*R*)- and (*S*)-PEA]— when homochiral *L*-amino acid residues were introduced into the pendants groups (Figure 47b). Likewise, two-state helical conformational changes were observed, being regulated by on/off switching of the intramolecular H-bonding formations (Figure 47c). These helical conformations depended on the solvent medium —less polar and polar solvents for the extended and contracted helices, respectively—but not on the pendant *L*-amino acid residues. Finally, the chiral recognition abilities of the (PBPA)s were significantly influenced by the kinds of *L*-amino acid residues.¹³⁸

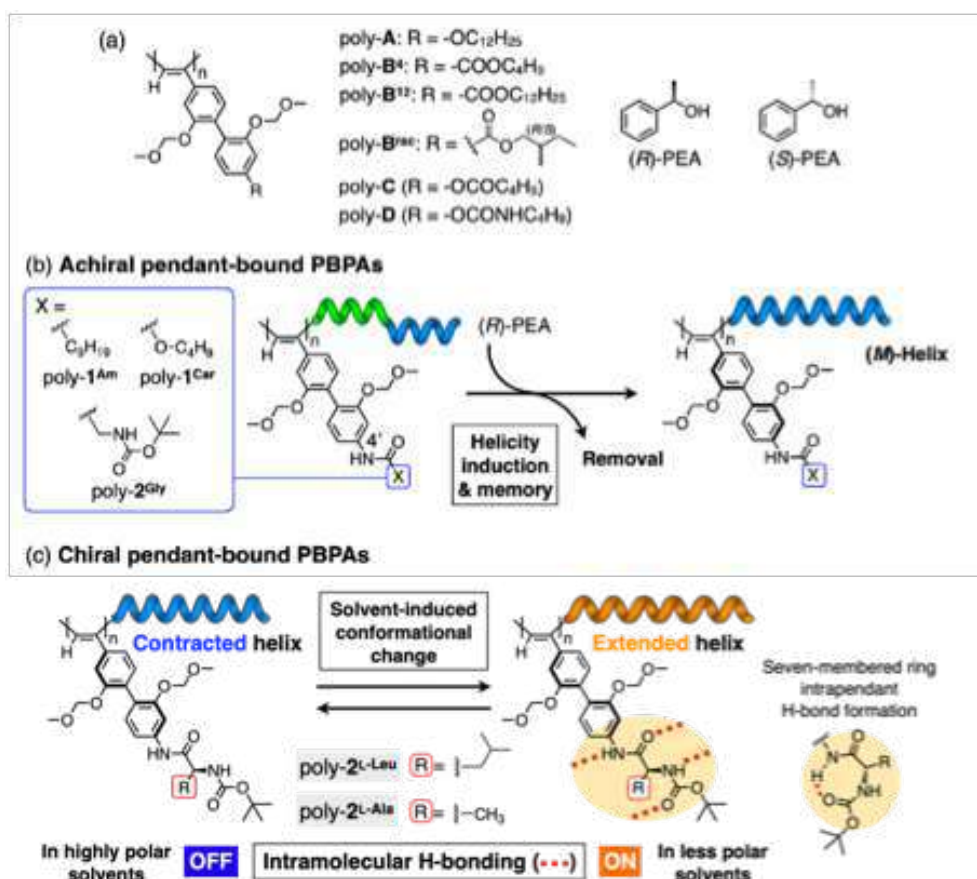


Figure 47. (a) Structures of PBPA (poly-A — poly-D) and optically active [(*R*)- and (*S*)-PEA]. (b) Schematic illustration of macromolecular helicity induction and subsequent helicity memory in achiral pendant-bound (PBPA)s. (c) Schematic illustration of the solvent-induced conformational changes in chiral pendant-bound PBPA between contracted and extended helices.

¹³⁸ Ikai, T.; Okuda, S.; Aizawa, M.; Yashima, E. *Macromolecules* **2022**, *55*, 7023-7031.

7.3. Asymmetric Catalysis

During the last decades, asymmetric catalysis has attracted the attention of the scientific community, more precisely, asymmetric reactions where helical polymers can be used to obtain enantiopure compounds.^{39a, 139} The chirality of the catalyst and the monomer design play an important role to develop these asymmetric reactions successfully. Related to this topic, Pu and co-workers demonstrated how highly enantioselective reactions (i.e. organozinc additions to carbonyl compounds,¹⁴⁰ epoxidations, hetero-Diels-Alder reactions,¹⁴¹ Michael additions, reductions, etc) can be performed by polymers and chiral binaphthyl molecules.

The first approach of an asymmetric reaction forming C-C bonds was reported by Reggeline *et al.* who synthesized a new helical poly(methacrylate)s (poly-**57**) bearing one or two pyridyl groups acting as a chiral polymeric ligand in the asymmetric allylic alkylation reaction. Moreover, poly-**57** was prepared by the helix-sense-selective polymerization or copolymerization with TrMA.¹⁴²

Since this pioneering discovery different systems like poly(quinoxaline)s,¹⁴³ poly(isocyanide)s,^{4a} peptides¹⁴⁴ or poly(phenylacetylene)s have been applied in this field.^{4d, 79}

The first asymmetric reaction performed by a PPA was reported by Yashima and co-workers. They prepared poly-**58** that bears an aminoalcohol as pendant group and was used as asymmetric inductor in the addition reaction of diethylzinc to benzaldehyde, generating non-racemic 1-phenylethanol up to 49% *ee*.¹⁴⁵ In this way, the same group applied (PPA)s bearing cinchona alkoid pendants as a chiral inductor and connected via amide linkage to the phenyl rings (poly-**59**). These systems were applied in different

¹³⁹ (a) Miller, S. J. *Nat. Chem.* **2012**, *4*, 344. (b) Ito, H. *Nat. Chem.* **2012**, *4*, 438.

¹⁴⁰ Yu, H.-B.; Hu, Q.-S.; Pu, L. *Tetrahedron Lett.* **2000**, *41*, 1681-1685.

¹⁴¹ Z. Gong, Pu, L. *Tetrahedron Lett.* **2000**, *41*, 2327-2331.

¹⁴² (a) Megens, R. P.; Roelfes, G. *Chem. Eur. J.* **2011**, *17* (31), 8514. (b) Reggeline, M.; Schultz, M.; Holbach, M. *Angew. Chemie Int. Ed.* **2002**, *41*, 1614-1617. (c) Reggeline, M.; Doerr, S.; Klusmann, M.; Schultz, M.; Holbach, M. *Proc. Natl. Acad. Sci.* **2004**, *101*, 5461-5466.

¹⁴³ (a) Yamamoto, T.; Sugimoto, M. *Angew. Chem. Int. Ed.* **2009**, *48*, 539-542. (b) Yamamoto, T.; Murakami, R.; Sugimoto, M. *J. Am. Chem. Soc.* **2017**, *139*, 2557-2560.

¹⁴⁴ Maeda, K.; Tanaka, K.; Morino, K.; Yashima, E. *Macromolecules* **2007**, *40*, 6783.

¹⁴⁵ Yashima, E.; Maeda, Y.; Okamoto, Y. *Polymer Journal* **1999**, *31*, 1033-1036.

reactions obtaining the best result (77% yield and up to 94% *ee*) for the Henry reaction between 4-nitrobenzaldehyde and nitromethane.¹⁴⁶

Zhang *et al.* prepared chiral polymer particles formed by substituted poly(acetylene) that bears *L*-proline as pendant group. These particles were used as a chiral heterogeneous organocatalyst to catalyse an asymmetric aldol reaction, getting a significant catalytic efficiency (76% yield and 80% *ee*). Thus, the methodology of this study provided new opportunities for designing and preparation new polymer-based organocatalysts.¹⁴⁷

Moreover, Takata *et al.* prepared a copolymer series (poly-**60**) bearing two comonomers with similar structure where the chiral monomers act as helical sense preference inductor and the achiral monomers bears the catalytic unit. Thus, the enantioselectivity of the reaction is provided by the macromolecular helicity of the system.^{146a}

¹⁴⁶ (a) Takata, L. M. S.; Iida, H.; Shimomura, K.; Hayashi, K.; Dos Santos, A. A.; Yashima, E. *Macromol. Rapid Commun.* **2015**, *36*, 2047. (b) Tang, Z.; Iida, H.; Hu, H. Y.; Yashima, E. *ACS Macro Lett.* **2012**, *1*, 261. (c) Miyake, G. M.; Iida, H.; Hu, H. Y.; Tang, Z.; Chen, E. Y. X.; Yashima, E. *J. Polym. Sci. Part A Polym. Chem.* **2011**, *49*, 5192. (d) Miyake, G. M.; Iida, H.; Hu, H. Y.; Tang, Z.; Chen, E. Y. X.; Yashima, E. *J. Polym. Sci. Part A Polym. Chem.* **2011**, *49*, 5192.

¹⁴⁷ Zhang, D. Y.; Zhang, H. Y.; Song, C.; Yang, W. T.; Deng, J. P. *Synthetic. Met.* **2012**, *162*, 1858-1863.

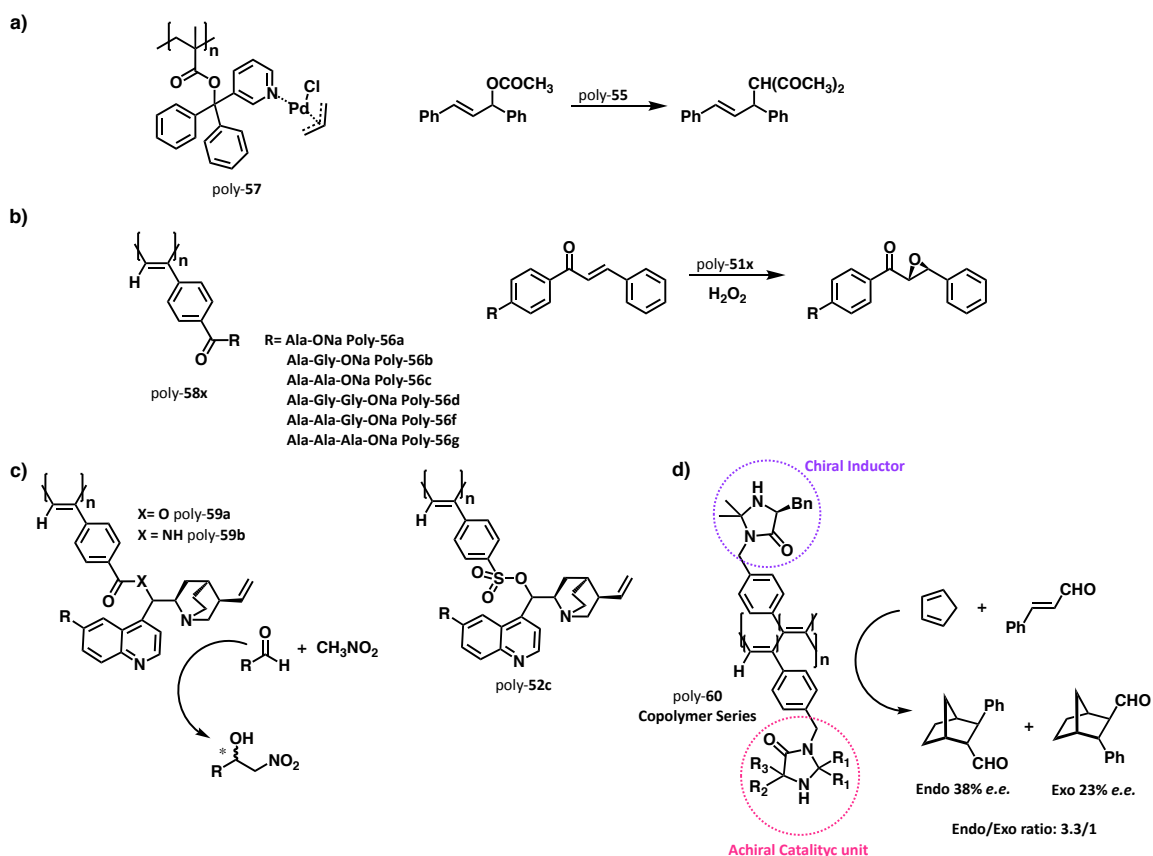


Figure 48. Schematic illustration showing the structure of and the catalysed reaction for (a) poly-57. (b) poly-58. (c) poly-59 and poly-60 copolymer series.

Suginome and co-workers have reported a new way of single-handed screw-sense induction in poly(quinoxaline-2,3-diyl)s (PQX) bearing only achiral substituents. This was favored due to chiral non-bonding interaction with *N*-protected amino acid methyl esters used as chiral additives in achiral solvents. In addition, the effects of achiral solvents have been shown to be significant owing to the better screw-sense induction obtained with ether solvents (MTBE) than with halogenated solvents (CHCl_3). Furthermore, phosphine ligands were employed to generate PQXphos —acting as a helically dynamic ligand—, together with a chiral additive (*L*- or *D*-Ac-Pro-OMe) led to a highly enantioselective Suzuki–Miyaura coupling reaction with up to 95% enantiomeric excess.¹⁴⁸

¹⁴⁸ Ikeda, S.; Takeda, R.; Fujie, T.; Ariki, N.; Nagata, Y.; Suginome, M. *Chem. Sci.*, **2021**, *12*, 8811.

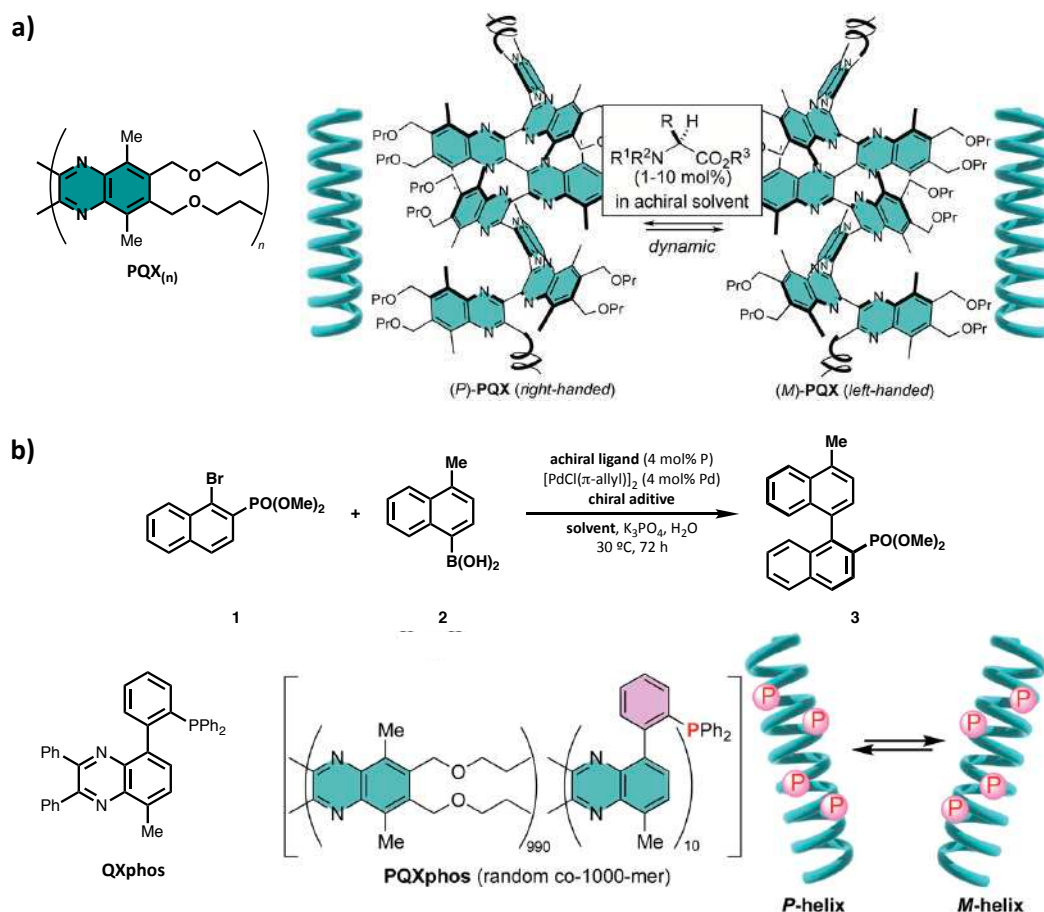


Figure 49. (a) Two enantiomeric (*P*- and *M*-) conformations of achiral PQQ, of which equilibrium is shifted by *N*-protected amino acid esters used as additives in an achiral solvent. (b) Asymmetric Suzuki–Miyaura coupling in the presence of achiral phosphine ligands including PQXphos with chiral additives.

Until recently, optically active monomers were indispensable for the production of helical polymers since racemic monomers are optically inactive and hence show no chiral functions. However, Yashima and co-workers have just published an unprecedented enantioselectivity of a PPA triggered by the polymerization of a dynamically racemic monomer units (Figure 50a). These dynamically racemic helical polymers could be transformed into both right- and left-handed helical polymers by non-covalent interaction with a chiral alcohol. These helical polymers showed the ability to memorize its macromolecular helicity and the axial chirality induced in the pendants after complete removal of the chiral alcohol. Finally, catalytic asymmetric reaction was carried out with high enantioselectivity (up to 86% *e.e.*).¹⁴⁹

¹⁴⁹ Ikai, T.; Ando, M.; Ito, M.; Ishidate, R.; Suzuki, N.; Maeda, K.; Yashima, E. *J. Am. Chem. Soc.* **2021**, *143*, 12725-12735.

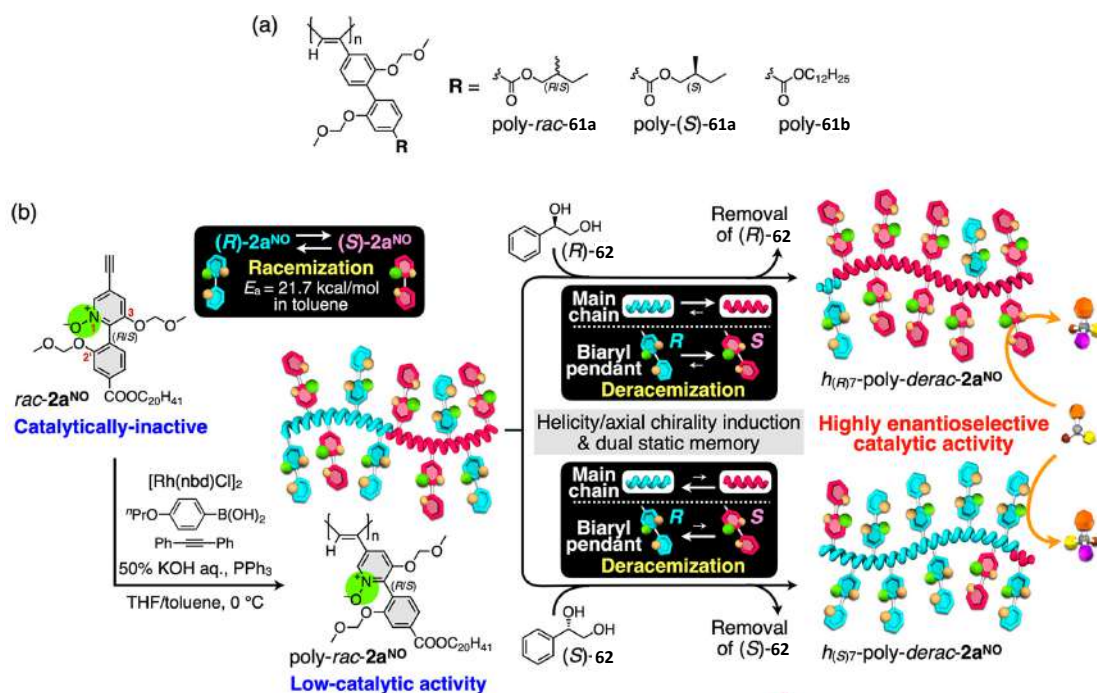


Figure 50. (a) Structures of poly(biphenylacetylene) (PBPA) derivatives. (b) Schematic illustration of emergence of a highly enantioselective catalytic activity in a racemic helical polymer composed of dynamically racemic 2-arylpyridyl-*N*-oxide monomer units.

More specifically, these helical poly-(biarylacetylene) (PBA) are composed of axially chiral, but fully racemic 2-arylpyridyl-*N*-oxide monomer units with *N*-oxide moieties located in the vicinity of the helical polymer structure (Figure 50a).

OBJECTIVES

Objectives

The helix is one of the topological structures and it is inherently chiral; therefore, biological molecules, supramolecules, oligomers, polymers, and their assemblies can be optically active —despite lacking stereogenic centers in their components— when they adopt a preferred-handed helical conformation. A large number of artificial helical polymers and oligomers with controlled helicity have been synthesized, not only to mimic biological helices, but also to develop chiral materials with functionally. More specifically, poly(phenylacetylene)s (PPA)s are a family of dynamic helical polymers where the screw sense, elongation of the polyenic main chain or even both, can be modified by the action of different external stimuli such as pH, polarity of the solvent, temperature, chiral additives or metal, among others. This property makes these materials very helpful in different fields such as sensing, asymmetric catalysis or chiral templates.

These interesting properties make (PPA)s excellent candidates for mimicking biomolecules and their interactions. However, dynamic helical polymers bearing multi-chiral pendants in which the power of the chiral center located at a remote position remains unexplored. In this context, this Doctoral Thesis is focused in developing new methodologies and systems to solve this handicap and evaluate the stimuli-responsive abilities of these materials.

The objectives can be classified in four main topics:

CHAPTER I: Full Control of the “Chiral-Overpass” Effect in Helical Polymers: *P/M* Screw Sense Induction by Remote Chiral Centers After Bypassing the First Chiral Residue

In literature, it is described that the handedness of helical polymers is governed by the helicity of the pendants. In particular, those structures constituted by pendants with more than one chiral residue present preferentially one helical sense determined by the first chiral moiety, which is attached to the polyenic skeleton.

However, the screw sense of poly(phenylacetylene)s with pendants composed by two chiral centers can be tamed by the “chiral-overpass” inductive mechanism where the application of different external stimuli (e.g. metal cations) is necessary to fix a bent

conformation in the pendant group, placing the second chiral center in a closer position to the polyene framework, now being responsible for the helicity adopted by the polymer.

The objective of this chapter is to take a step forward in the control of the “chiral-overpass” effect. A new system based on (PPA)s with two different chiral centers is described: the first chiral moiety is an alanine group, known to be part of polyalanines that are involved in turns (e.g. in α helices); and the second one is the α -methoxy- α -methylacetic acid (MPA) group which display switchable conformation from *synperiplanar* to *antiperiplanar*. The combination of elements provided us a multi-switchable “chiral-overpass” induction system. With this idea in mind, we want to corroborate if it is possible to achieve not only a selective activation/deactivation of the “chiral-overpass” effect but also to know if we are able to acquire a full control over the handedness of the polymers.

Publication associated with this objective: Rodríguez, R.; Rivadulla-Cendal, E.; Fernández-Míguez, M.; Fernández, B.; Quiñoá, E.; Maeda, K.; Freire, F. *Angew. Chem. Int. Ed.* **2022**, *61*, e202209953.

CHAPTER II: Diastereomeric Multi-Chiral Pendant Groups: Their Key Role in Stimuli-Responsive Polymeric Properties

A variety biological processes are dependent on the dynamism of helical structures. This is one of the reasons why new artificial helical systems, such as dynamic helical polymers, have been developed to mimic interesting biological properties. Because of the difference in stability between the two possible enantiomeric or diastereomeric helices, helical systems bearing more than one chiral unit (i.e., multi-chiral pendant groups) are scarcely studied. As previously stated, the absolute configuration of the chiral residue closest to the polymeric main chain determines the screw sense of most helical polymers. This fact leaves the second one with low-to-null impact on the handedness of the macromolecule.

The aim of this new project is to explore the limits of the impact of diastereomeric multi-chiral pendants in the screw sense induction and stimuli-responsive nature of the (PPA)s. Therefore, we have synthesized a new family of diastereomeric (PPA)s bearing a pendant group composed by two chiral groups: the first residue is *L*-valine group —that it is known

to promote β -sheet conformations— while the second chiral group is a bulky (*R* or *S*)- α -methoxy- α -phenylacetic acid. We have studied their dynamic behavior where variations in their stimuli-responsive properties will be found due to their diastereomeric relationship. Eventually, the conformational change at the glycine residue dictated the arrangement of the pendant group, which will adopt two possible conformations depending on the orientation of the amide groups: *synperiplanar* and *antiperiplanar* conformations when carbonyl groups are oriented in the same and opposite directions, respectively. This selective disposition of the pendant group will be modulated by changes in the polarity of the solvent.

Publication associated with this objective: Rodríguez, R.; Rivadulla-Cendal, E.; Quiñoá, E.; Freire, F. *Chirality* **2022**, *Submitted*.

CHAPTER III: Greasing Macromolecular Gears: Inclusion of Flexible Spacers

In nature, helical structures are commonly adopted by biomacromolecules and their functions are directly related to them. The fact that some significant biological processes are known to depend on the dynamism of these helical motifs has motivated the development of novel materials —such as foldamers or helical polymers— that adopt helical structures capable of emulating biological properties.

The screw sense of helical systems built from chiral monomers cannot be switched due to the different stability of the two possible diastereomeric helices (left- and right-handed). Nevertheless, polymers or foldamers based on non-chiral units can overcome this issue —by applying external stimuli— as a result of their low energy barrier interconversion between the *P* and *M* helices.

In literature, there are several examples of oligomers formed by achiral residues —used as building blocks— whose helicity can be selectively controlled when a chiral amino acid is supramolecularly interacting or covalently linked at one of the two edges of the sequence (*N*- or *C*-terminus). As previous mentioned in the introduction, a series of (PPA)s showed the ability to control the helicity/elongation degree in some of them via chiral harvesting mechanism. The pendants were based on a chiral moiety (MTPA) at the *N*-terminus of an achiral Aib oligopeptide chain and a 4-ethynylalaniline group at the *C*-

terminus of these peptides. Unfortunately, the handedness of the bulkier peptides could not be selectively modulated due to their low flexibility. For this reason, the main objective of this chapter is to try to release the steric stress generated in these previous systems by introducing a flexible linker between the backbone and the Aib foldamer. Accordingly, the chiral information from a remote position will be transferred to the helical scaffold through chiral harvesting mechanism. Then, the stimuli-responsive nature of the synthesized (PPA)s, their structure and how the conformational changes on the MTPA moiety can affect to their helical behavior will be studied.

CHAPTER IV: Multi-helical Scaffolds (up to Five Helices) from Chiral (PPA)s bearing a Gly-AA as Pendant

In recent years, our group has successfully demonstrated the chiral teleinduction mechanism from a remote chiral center to the inner helix. Basically, these helical motifs were formed by achiral peptidic linkers (i.e., glycine residues), *N*-attached to the distant chiral moiety (e.g. MPA, MTPA) and *C*-linked to the polyene main chain through a peptide bond. These systems adopt a rigid and well-organized β -sheet structure due to the arrangement of the flexible glycine spacers along the pendants. Their helical scaffold can be selectively folded into right- or left-handed helices due to changes in solvent polarity. This property is also accompanied, in some cases, by changes in the elongation of the backbone.

Taking these findings into account, the goal is to prepare new helical polymers capable of forming a well-organized β -sheet like orientation in order to obtain an efficient transmission of chiral information through teleinduction mechanism. For this purpose, these (PPA)s will bear an achiral linker (glycine unit) capped at the end of the edge by different chiral centers (*L*-valine and *L*-phenylalanine amino acids). We will see that the effect of these remote chiral groups on the final folding of the polymers results in the generation of up to five different helical structures due to the formation of a multi-conformational pendant group (*anti-anti* conformation corresponding to a highly compressed helix, *syn-syn* and *syn-anti* conformations related to a more stretched scaffold, and γ -turn-*syn*/ γ -turn-*anti* conformations associated with a stretched helix).

Lastly, these new helical structures will also exhibit different mode of connection to the polyene main chain (i.e., anilide and benzamide) that will play a crucial role in their stimulus-response properties.

CHAPTER I

*Full Control of the Chiral Overpass Effect in Helical Polymers: P/M Screw Sense
Induction by Remote Chiral Centers After Bypassing the First Chiral Residue*

Chapter I. Full Control of the Chiral Overpass Induction Effect in Helical Polymers: *P/M* Screw Sense Induction by Remote Chiral Centers After Bypassing the First Chiral Residue.

Adapted from:

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Angew. Chem. Int. Ed., **2022**, *61*, e202209953.

Abstract

In helical polymers, helical sense induction is usually commanded by teleinduction mechanism, where the largest substituent of the chiral residue directly attached to the main chain is the one that commands the helical sense. In this work, different helical structures with different helical senses are induced in a helical polymer [poly(phenylacetylene)] when the conformational composition of two different dihedral angles of a pendant group with more than two chiral residues is tamed. Thus, while the dihedral angle at chiral residue **1** [(*S*)- or (*R*)-alanine], attached to the backbone, produces an extended or bent conformation in the pendant resulting in two scaffolds with different stretching degree, the second dihedral angle at chiral residue **2** [(*R*)- or (*S*)-methoxyphenylacetamide] places the substituents of this chiral center in a different spatial orientation, originating opposite helical senses at the polymer that are induced through a total control of the “chiral overpass effect”.

Introduction

During the last decade, the field of helical polymers has flourished in the preparation of new architectures with defined macromolecular structure (i.e., handedness and elongation degree) that mimic the natural ones —peptides, saccharides or nucleic acids amongst others—, drawing the attention of the scientific community for their potential applications as chiral materials.¹ It should be noted that these systems have been successfully applied in different fields such as asymmetric synthesis,² sensing,³ chiroptical switches,⁴ switchable chiral stationary phases for HPLC,⁵ chiral templates,⁶ spin filters,⁷ CPL sources⁸ and biological applications⁹ among others.

Since the applications mentioned above directly rely on the secondary structure exhibited by these macromolecules, the preparation of defined compressed/stretched

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scaffolds with preferred *P/M* handedness is a matter of great interest to obtain chiral materials with enhanced properties.

Among helical polymers, poly(phenylacetylene)s (PPA)s¹⁰ represent an appealing family of compounds where both structural features, elongation and handedness, can be modulated either separately or together by the application of proper external stimuli.¹¹ The adoption of a screw sense excess in a PPA can be achieved following different strategies such as supramolecular interactions with either chiral or achiral moieties, as well as by the inclusion of a single chiral center with a preferred conformation at the pendant group of the polymer.¹² Remarkably, further modifications on the conformational composition of the pendant group can lead to helix induction,¹³ helix inversion¹⁴ or even to modifications on the stretching degree of the polymer backbone.^{3a, 15}

Unfortunately, when the pendant is composed by two or more chiral centers, the one closest to the polymer backbone is most likely to control the handedness of the polymer, while the other center has low-to-null impact on the structural features of the helical structure.¹⁶ Interestingly, our group has recently reported the “chiral overpass” inductive mechanism. To activate such an effect, a bent conformation must be fixed at the pendant group through an external stimulus (i.e., metal cations). This geometry locates the second chiral moiety closer to the polyene backbone, now being responsible for the helical sense adopted by the polymer.¹⁷ In this system, by changing the absolute configuration of the second chiral residue, it is possible to invert the helical sense of the PPA.

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¹¹ a) S. Leiras, E. Suárez-Picado, E. Quiñoá, R. Riguera, F. Freire. *Giant*, **2021**, *7*, 100068; b) Y. Song, S. Kang, S. Kang, Y. Lee. *Angew. Chem. Int. Ed.*, **2020**, *59* (51), 22968-22972; c) V. Percec, J. G. Ruick, M. Peterca, P. A. Heiney. *J. Am. Chem. Soc.*, **2008**, *130*, 7503-7508; d) S. Leiras, F. Freire, J. M. Seco, E. Quiñoá, R. Riguera. *Chem. Sci.*, **2013**, *4*, 2735-2743; e) K. Maeda, H. Mochizuki, M. Watanabe, E. Yashima. *J. Am. Chem. Soc.*, **2006**, *128*, 7639-7650; f) K. Maeda, N. Kamiya, E. Yashima. *Chem. Eur. J.*, **2004**, *10*, 4000-4010.

¹² a) K. Cobos, R. Rodríguez, O. Domarco, B. Fernández, E. Quiñoá, R. Riguera, F. Freire. *Macromolecules*, **2020**, *53*, 3182-3193; b) R. Rodríguez, E. Quiñoá, R. Riguera, F. Freire. *J. Am. Chem. Soc.*, **2016**, *138*, 9620.

¹³ a) F. Freire, J. M. Seco, E. Quiñoá, R. Riguera. *Angew. Chem. Int. Ed.*, **2011**, *50*, 11692-11696; b) V. Percec, E. Aqad, M. Peterca, J. G. Rudick, L. Lemon, J. C. Ronda, B. B. De, P. A. Heiney and E. W. Meijer. *J. Am. Chem. Soc.*, **2006**, *128*, 16365-16732.

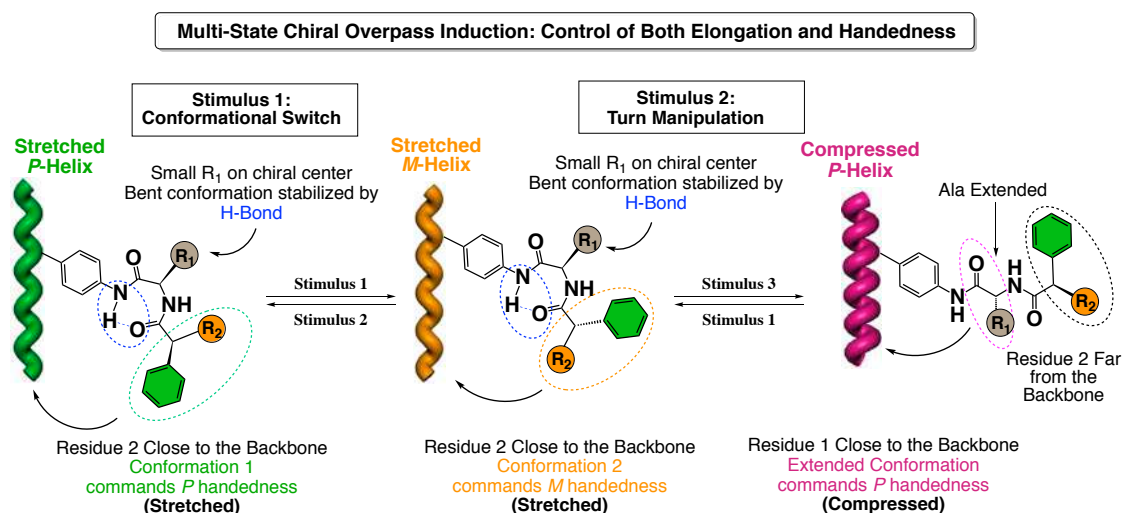
¹⁴ a) X. Guan, S. Wang, G. Shi, J. Zhang, X. Wan. *Macromolecules*, **2021**, *54*, 4592-4600; b) T. Van Leeuwen, G. H. Heideman, D. Zhao, S. J. Wezenberg, B. L. Feringa. *Chem. Commun.*, **2017**, *53*, 6393-6396; c) M. Alzubi, S. Arias, I. Louzao, E. Quiñoá, R. Riguera, F. Freire. *Chem. Commun.*, **2017**, *53*, 8573-8576; d) I. Louzao, J. M. Seco, E. Quiñoá, R. Riguera. *Angew. Chem. Int. Ed.*, **2010**, *49*, 1430-1433.

¹⁵ a) Z. Fernández, B. Fernández, E. Quiñoá, F. Freire. *J. Am. Chem. Soc.*, **2021**, *143*, 20962-20969; b) R. Rodríguez, E. Suárez-Picado, E. Quiñoá, R. Riguera, F. Freire. *Angew. Chem. Int. Ed.*, **2020**, *59*, 8616-8622; c) N. Zhu, K. Nakazono, T. Takata. *Chem. Commun.*, **2016**, *52*, 3647-3649; d) V. Percec, J. G. Rudick, M. Petarca, M. Wagner, M. Obata, C. M. Mitchell, W-D. Cho, V. S. K. Balagurusamy, P. A. Heiney. *J. Am. Chem. Soc.*, **2005**, *127*, 15257-15264.

¹⁶ J. W. Y. Lam, B. Z. Tang. *Acc. Chem. Res.*, **2005**, *38*, 745-754.

¹⁷ E. Suárez-Picado, E. Quiñoá, R. Riguera, F. Freire. *Angew. Chem. Int. Ed.*, **2020**, *59*, 4537-4543.

Herein we want to take a step forward by doing a selective conformational control of two different dihedral angles. Thus, while the first dihedral angle will be responsible for the activation/deactivation of the chiral overpass induction, the second dihedral angle, located on chiral residue two, will be the cause of the *P/M* helical sense induced in the PPA when the chiral overpass effect is activated. To do that, we envisaged a monomer unit that combines an amino acid involved in structural motifs such as turns^{4a, 18} and β -sheets^{4b, 18} together with a conformationally switchable arylacetic acid.^{11, 12a, 14c, 19} Therefore, while playing with the conformation of the amino acid it is possible to activate (γ -turn)/deactivate (extended) the chiral overpass effect, conformational changes at the arylacetic group will position the aryl ring in opposite directions and thus inducing a *P* or an *M* helical sense at the PPA without changing the absolute configuration of the second residue (Scheme 1).



Scheme 1. Conceptual representation of multi-state chiral overpass-induction controlling both stretching and handedness.

¹⁸ a) T. Ikai, S. Okuda, M. Aizawa, E. Yashima. *ChemRxiv*. 10.26434/chemrxiv-2022-kzrz; b) H. Choi, S. Ogi, N. Ando, S. Yamaguchi. *J. Am. Chem. Soc.*, **2021**, *143*, 2953-2961; c) R. Rodríguez, E. Quiñoá, R. Riguera, F. Freire. *Small*, **2019**, *15*, 1805413.

¹⁹ a) Z. Fernández, B. Fernández, E. Quiñoá, R. Riguera, F. Freire. *Chem. Sci.*, **2020**, *11*, 7182-7187; b) M. Fukuda, R. Rodríguez, Z. Fernández, T. Nishimura, D. Hirose, G. Watanabe, E. Quiñoá, F. Freire, K. Maeda. *Chem. Commun.*, **2019**, *55*, 7906-7909.

Results and discussion

A set of monomers made up of all possible diastereoisomers of the 4-ethynylanilides of (*S*)- or (*R*)-Alanine (Ala) derivatized at the *N*-terminus with the two enantiomeric forms (*R*)- or (*S*)- α -methoxy- α -phenylacetic acid (MPA) —m-(*S*)-Ala-(*R*)-MPA; m-(*S*)-Ala-(*S*)-MPA; m-(*R*)-Ala-(*R*)-MPA; m-(*R*)-Ala-(*S*)-MPA—(Figure 1) were prepared following a multistep synthetic protocol (see SI).

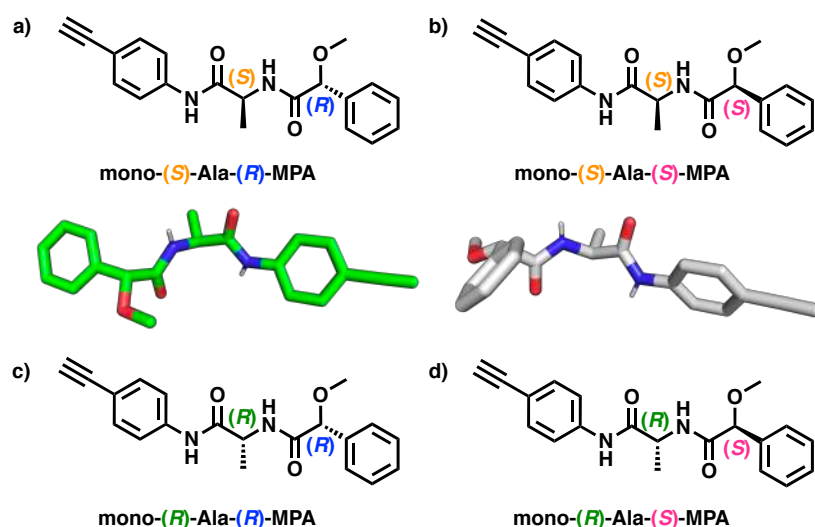


Figure 1. Structures of monomers employed in this work. (a) mono-(*S*)-Ala-(*R*)-MPA and its X-ray structure. (b) mono-(*S*)-Ala-(*S*)-MPA and its X-ray structure. (c) mono-(*R*)-Ala-(*R*)-MPA and (d) mono-(*R*)-Ala-(*S*)-MPA.

Crystal structures of m-(*S*)-Ala-(*R*)-MPA and m-(*S*)-Ala-(*S*)-MPA were obtained, and their X-Ray studies showed extended structures of the two chiral residues (see Figures S13 and S14).²⁰ These monomers were polymerized using $[\text{Rh}(\text{nbd})\text{Cl}]_2$ as catalyst,²¹ which produced the corresponding polymers (Figure 2) in high yield, low polydispersity (see Table S2) and *cis*-stereoregularity of double bonds as inferred by ^1H -NMR^{22, 23} (see Figure S15 and S16) and Raman (see Figure S17).²³ Differential Scanning Calorimetry (DSC) experiments

²⁰ Deposition numbers 2180644 and 2180647 contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.

²¹ a) N. S. L. Tan, A. B. Lowe. *Angew. Chem. Int. Ed.*, **2020**, 59, 5008-5021; b) Z. Ke, S. Abe, T. Ueno, K. Morokuma. *J. Am. Chem. Soc.*, **2011**, 133, 7926.

²² a) C. I. Simionescu, V. Percec, S. Dumitrescu. *J. Polym. Sci. Polym. Chem. Ed.*, **1977**, 15, 2497-2509.

²³ a) C. I. Simionescu, V. Percec. *Progress in polyacetylene chemistry. Progress in Polymer Science*, **1892**, 8, 133-214; b) H. Shirakawa, T. Ito, S. Ikeda. *Polym. J.*, **1973**, 4, 460-462.

showed the presence of two consecutive exothermic peaks for both polymers suggesting the adoption of *cis-transoidal* (*c-t*) stretched structures ($\omega_1 > 90^\circ$, see Fig. S18).²⁴

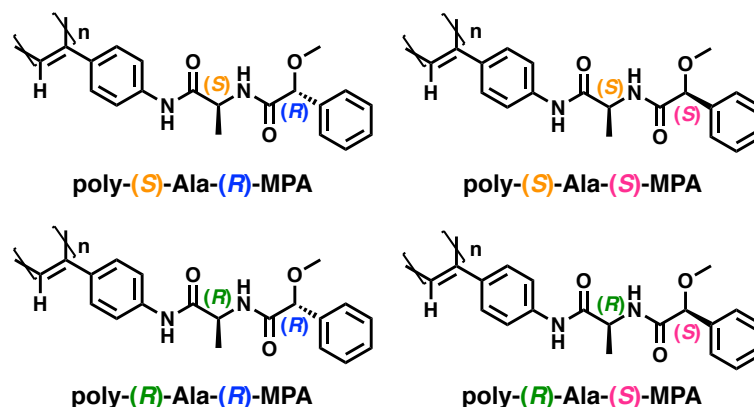


Figure 2. Structures of the polymers employed in this work.

Chiral overpass studies were then performed by ECD, UV-Vis and VCD. To carry them out, polymers poly-(S)-Ala-(R)-MPA and poly-(S)-Ala-(S)-MPA were dissolved in CHCl_3 and DMSO. These solvents were chosen to promote the formation and disruption of a bent structure at the pendant. Thus, while CHCl_3 favors a bent structure, most probably stabilized by intra-pendant hydrogen bonds to form a γ -turn mimetic motif at the pendant, DMSO disrupts these supramolecular bonds due to its interaction with the anilide groups. As a result, a β -sheet mimetic motif is generated at the pendant (extended structure).¹⁸ ECD/UV-Vis spectra of poly-(S)-Ala-(S)-MPA in CHCl_3 and DMSO depict a variation in the stretching degree in total agreement with the presence of a bent and extended structure at the pendant group, respectively (Figure 3b). To corroborate the presence of this equilibrium between bent and extended structures promoted by the activation/deactivation of an intramolecular hydrogen bond, external stimuli such as F^- (added as TBAF salt) or TFA, which act as hydrogen bond disruptors,^{4b, 11a} were added to the CHCl_3 solution of poly-(S)-Ala-(S)-MPA giving rise to an ECD/UV-Vis pattern resembling that obtained in DMSO (Figure 3c). Moreover, addition of metal cations (i.e., Li^+ and Ba^{2+} perchlorate salts, 10 mg/mL MeOH solutions) to a solution of poly-(S)-Ala-(S)-MPA in CHCl_3 also promoted the adoption of compressed helices analogous to the previous ones. The reason lies in the coordination of the metal ions with the $\text{C}=\text{O}$ groups that promote the

²⁴ L. Liu, T. Namikoshi, Y. Zang, T. Aoki, S. Hadano, Y. Abe, I. Wasuzu, T. Tsutsuba, M. Teraguchi, T. Kaneko. *J. Am. Chem. Soc.*, **2013**, 135, 602-605.

formation of an extended structure in the pendant (Figure 3d).^{13a, 14b, 14c} Analogous studies were carried out for the other polymer counterparts displayed in Figure 2, which show the same stretching effects and opposite helical sense of the (PPA)s due to enantio/diastereomeric relationships (See Figures S22 and S23).

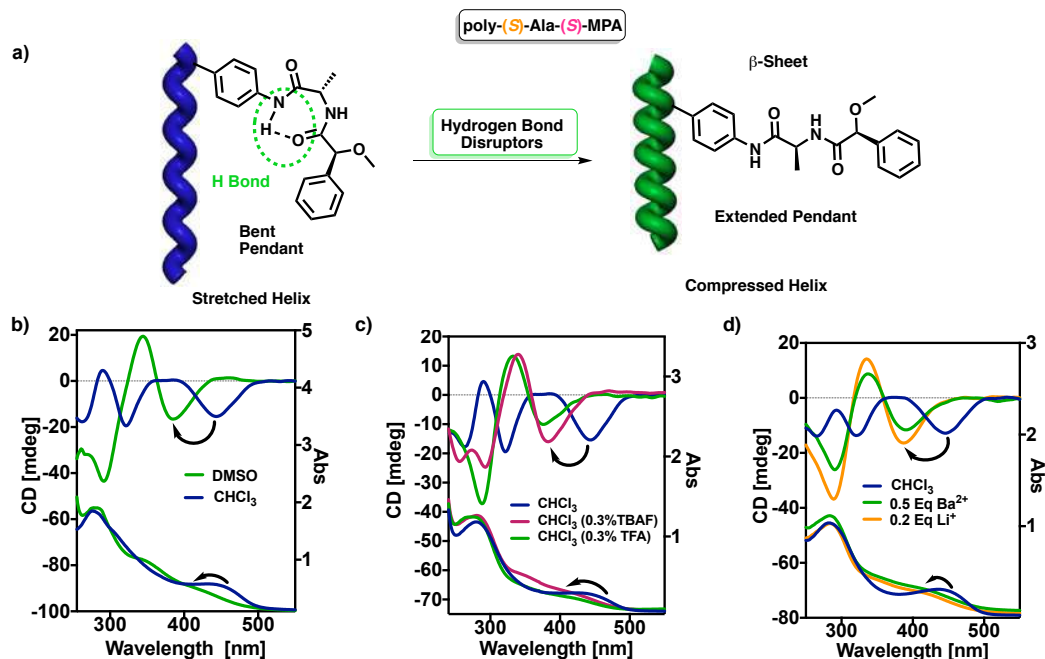


Figure 3. (a) Conceptual representation of the conformational manipulation from bent to stretched pendant group of poly-(S)-Ala-(S)-MPA. ECD/UV-Vis and spectroscopy monitoring of the above process triggered by (b) polar effects, (c) hydrogen bond disruptors (TFA/TBAF) and (d) metal coordination.

To further corroborate that PPA compression/stretching is due to selective manipulation between a bent and an extended structure in the pendant (Figure 4a), VCD spectroscopy studies were carried out. This technique is a powerful tool in the structural elucidation of supramolecular and covalent helical polymers.^{19b, 25} Comparison of the VCD patterns of poly-(S)-Ala-(R)-MPA and poly-(S)-Ala-(S)-MPA in CDCl₃ and DMSO-d₆ reveals a totally different dichroic spectra when shifting from a bent (CHCl₃) to an extended conformation at the pendant (DMSO) in both cases (Figures 4b-c) Therefore, VCD is a useful technique to elucidate structural variations at the pendant group.²⁶

²⁵ M. A. Martínez, A. Doncel-Giménez, J. Cerdá, J. Calbo, R. Rodríguez, J. Aragón, J. Crassous, E. Ortí, L. Sánchez. *J. Am. Chem. Soc.*, **2021**, *143*, 13281-13291; b) E. E. Greciano, R. Rodríguez, K. Maeda, L. Sánchez. *Chem. Commun.*, **2020**, *56*, 2244-2247; c) K. Maeda, T. Miyagawa, A. Furuko, H. Onouchi, E. Yashima. *Macromolecules*, **2015**, *48*, 4281-4293; d) Y. Hase, K. Nagai, K. Maeda, N. Ochi, K. Sawaba, K. Sakajiri, K. Okoshi, E. Yashima. *J. Am. Chem. Soc.*, **2009**, *131*, 10719-10732.

²⁶ a) B. Fernández, R. Rodríguez, E. Quiñoá, R. Riguera, F. Freire. *ACS Omega*, **2019**, *4*, 5233-5240; b) B. Fernández, R. Rodríguez, A. Rizzo, E. Quiñoá, R. Riguera, F. Freire. *Angew. Chem. Int. Ed.*, **2018**, *57*, 3666-3670.

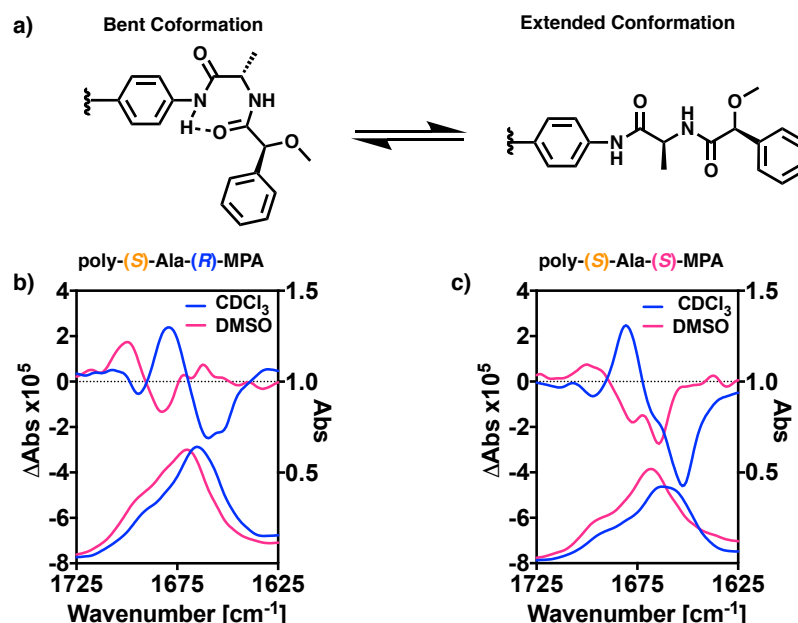


Figure 4. (a) Conceptual representation of bent and extended conformations in the pendant groups. VCD/IR spectroscopy monitoring the dichroic inversion related to the conformational switch triggered by polar effects of (b) poly-(S)-Ala-(R)-MPA and (c) of poly-(S)-Ala-(S)-MPA.

Computational DFT studies were carried out on monomers *m*-(S)-Ala-(R)-MPA and *m*-(S)-Ala-(S)-MPA using the wB97XD functional together with the 6-31G(d,p) basis set. As input, the structures of the monomers were introduced with a γ -turn conformation at the alanine residue. The obtained optimized geometries indicated that the chirality of the Ala promotes in the γ -turn a specific angle of -65° , independent of the absolute configuration of the second chiral center (i.e., the MPA moiety), maintaining in both cases an *ap* conformation in the MPA moiety (see Figures 5c-d and Figure S24).

Comparison of the calculated γ -turn VCD pattern with the experimental ones obtained for poly-(S)-Ala-(R)-MPA and poly-(S)-Ala-(S)-MPA in CHCl₃ shows a good match between theoretical and experimental data, and almost identical for both polymers. This fact indicates that the VCD pattern (bisignate) observed for either poly-(S)-Ala-(R)-MPA and poly-(S)-Ala-(S)-MPA in CHCl₃ is governed by the presence of a bent structure at the pendant in this solvent (γ -turn a specific angle of -65°), whose $-/+$ sign is unaffected by the absolute configuration of the MPA moiety (Figures 5a-b).

Next, to further confirm that bent and extended conformations at the pendants have different VCD patterns, theoretical studies were carried out on mimetics of multiparallel β -sheet motifs of monomers *m*-(S)-Ala-(R)-MPA and *m*-(S)-Ala-(S)-MPA (see Figure S24).

These studies show a good match between theoretical —using B3LYP functional with the 6-31G(d,p) basis set— and experimental studies performed in DMSO, which confirms this extended structure at the pendant (Figures 5b-c). Interestingly, in the VCD pattern of an extended structure for poly-(*S*)-Ala-(*R*)-MPA and poly-(*S*)-Ala-(*S*)-MPA is possible to observe the opposite orientation of the carbonyl band of the MPA (ca. 1670 cm⁻¹) due to their enantiomeric relationship [Figures 4b-c (DMSO) and Figure 5].

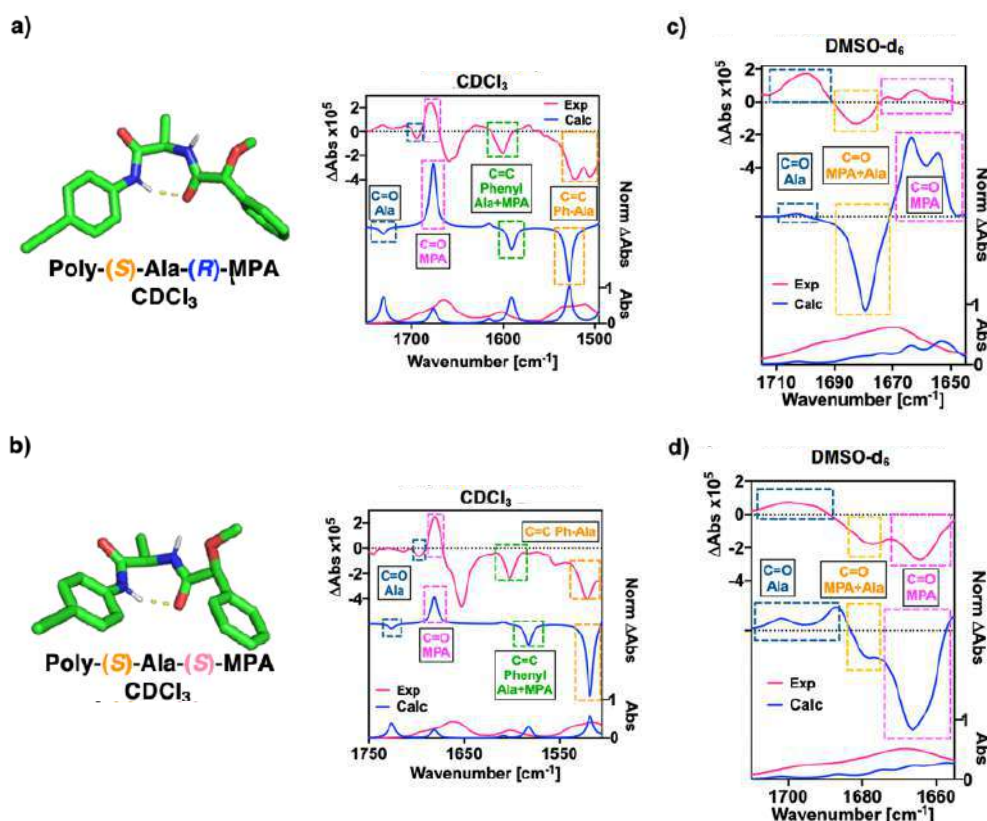


Figure 5. (a) and (b) Computed structures for bent conformations (γ-turn) of m-(*S*)-Ala-(*R*)-MPA and m-(*S*)-Ala-(*S*)-MPA and comparison of experimental vs calculated VCD/IR spectra with the corresponding polymers poly-(*S*)-Ala-(*R*)-MPA and poly-(*S*)-Ala-(*S*)-MPA in CDCl₃. (c) and (d) Computed vs experimental VCD/IR spectra of the extended conformation of poly-(*S*)-Ala-(*R*)-MPA and poly-(*S*)-Ala-(*S*)-MPA in DMSO-d₆.

ECD studies were performed for these polymers in CHCl₃ and DMSO to determine how the conformational changes at the pendant affect to the helical sense excess of the polyene main chain. As expected, when the pendant group adopts an extended structure —poly-(*S*)-Ala-(*R*)-MPA and poly-(*S*)-Ala-(*S*)-MPA dissolved in DMSO—, the helical sense is induced by the chiral residue closest in sequence to the polyene backbone, in this case the alanine group (Figure 6a). As a result, a *M* helical sense is induced in poly-(*S*)-Ala-(*R*)-MPA

and poly-(*S*)-Ala-(*S*)-MPA even though the absolute configuration of the second chiral residue, i.e. MPA, is different in both. On the contrary, when these studies are carried out in CHCl_3 , a helical sense inversion happens when the absolute configuration of MPA changes (Figure 6d). This outcome confirms the activation of the chiral overpass effect in CHCl_3 due to the presence of a bent structure in the pendant. Similar effects were obtained for the enantiomeric series poly-(*R*)-Ala-(*R*)-MPA and poly-(*R*)-Ala-(*S*)-MPA, with opposite helicities induced in the (PPA)s due to the enantiomeric relationships (see Figures S22 and S23).

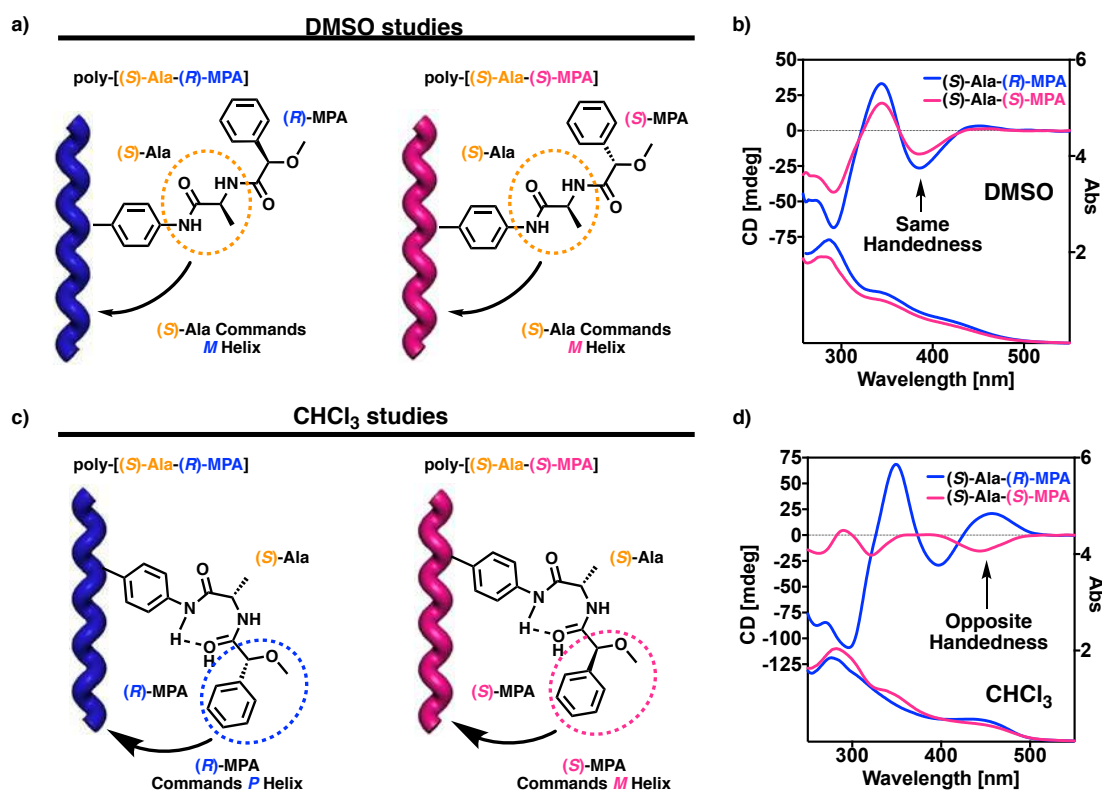


Figure 6. Conceptual representation and ECD of the activation and deactivation of the chiral overpass by controlling the presence of (a-b) an extended (DMSO) conformation or (c-d) a bent conformation (γ -turn, CHCl_3) in the pendants of poly-(*S*)-Ala-(*R*)-MPA and poly-(*S*)-Ala-(*S*)-MPA.

Next, the total control of the chiral overpass effect was explored by playing with the conformational composition of the MPA moiety while the alanine fragment remains in a bent structure. To do that it is necessary to have two solvents that do not disrupt the intrapendant hydrogen bond of alanine, but at the same time possess different polarities to play with the *antiperiplanar*/*synperiplanar* conformational equilibrium of the MPA moiety. Thus, while an *antiperiplanar* conformation is favored in low-polar solvents, an increase in the solvent polarity favors the adoption of a *synperiplanar* conformation in this fragment.

To achieve this goal, CHCl_3 was chosen as low-polar solvent while cyclohexanone and acetone were selected as polar solvents. ECD and UV-Vis studies of poly-(*S*)-Ala-(*R*)-MPA and poly-(*S*)-Ala-(*S*)-MPA in these solvents indicate the presence of a scaffold with similar elongation but opposite helical sense (Figure 7). Thus, a positive ECD band centered at 448 nm was obtained for poly-(*S*)-Ala-(*R*)-MPA in CHCl_3 indicating the adoption of a *P* helix by the polyene backbone, while a negative band is obtained for poly-(*S*)-Ala-(*R*)-MPA in acetone or cyclohexanone, indicative of a *M* helicity (Figure 7a).²⁶

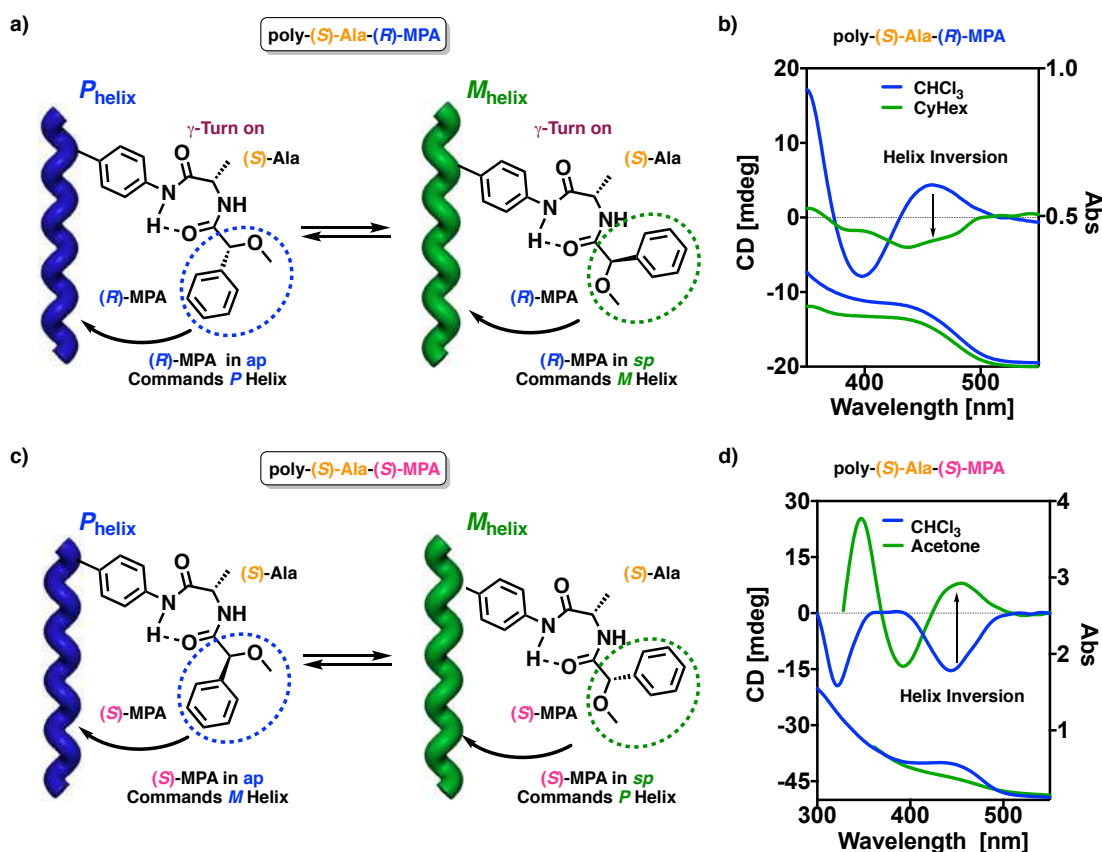


Figure 7. Conceptual representation of the chiral overpass induction by conformational modulation of the second chiral center monitored by ECD/UV-Vis spectra of (a-b) poly-(*S*)-Ala-(*R*)-MPA and (c-d) poly-(*S*)-Ala-(*S*)-MPA (CyHex and acetone, respectively).

This helical inversion is a consequence of a conformational change in the MPA fragment, from *antiperiplanar* (CHCl_3) to *synperiplanar* (acetone or cyclohexanone), which places its aromatic ring in different orientations, producing the inversion. In the case of poly-(*S*)-Ala-(*S*)-MPA, the results were the opposite, showing a negative ECD band centered at 448 nm when dissolved in CHCl_3 (*M* helix), while a positive band (*P* helix) is obtained when dissolved in acetone or cyclohexanone (Figure 7d). These studies were also carried out for

the enantiomeric series —poly-(*R*)-Ala-(*R*)-MPA and poly-(*R*)-Ala-(*S*)-MPA (Figures S22 and S23)— obtaining, as expected, a total control of the helix, inducing *P* and *M* helices in the PPA by a total control of the chiral overpass effect. Moreover, it should be noted that poly-(*S*)-Ala-(*R*)-MPA and poly-(*R*)-Ala-(*R*)-MPA have identical behavior, inducing a *P* helix in CHCl₃ and a *M* helix in acetone. In turn, polymers poly-(*S*)-Ala-(*S*)-MPA and poly-(*R*)-Ala-(*S*)-MPA showed opposite helical sense inductions, *M* helix in CHCl₃ and *P* helix in acetone, due to the opposite configuration of the second chiral residue (MPA) (Figure 7).

Finally, we proceeded to do the structural elucidation of the polymers using atomic force microscopy (AFM) and the information previously obtained from Raman, DSC, IR, ECD and VCD studies. AFM allowed us to directly visualize the macromolecular helical structures adopted by the polymers²⁷ following the protocol developed by the groups of Yashima²⁸ and Percec.²⁹ High-resolution AFM images were obtained from dilute solutions of poly-(*S*)-Ala-(*S*)-MPA (0.05 mg/mL, CHCl₃) and poly-(*S*)-Ala-(*S*)-MPA/Li⁺ complex in 1/1 (mol/mol) ratio that were spin coated onto freshly cleaved highly oriented pyrolytic graphite (HOPG). These images showed, as expected, the presence of a compressed poly-(*S*)-Ala-(*S*)-MPA/Li⁺ complex and a stretched helical scaffold for poly-(*S*)-Ala-(*S*)-MPA (Figures 8, S25 and S26). In both cases, *cis-transoidal* scaffolds were obtained with *P* orientation of the external helix and *M* orientation of the internal one. These helices showed different helical pitches and packing angles. Thus, values of 4.8 nm and 50° were obtained for poly-(*S*)-Ala-(*S*)-MPA/Li⁺ complex (compressed helix), while 5.8 nm and 40° were obtained for poly-(*S*)-Ala-(*S*)-MPA (stretched helix).

Combining all the structural data allowed us to construct *cis-transoidal* helical structures with dihedral angles between conjugated double bonds of $\omega_1 = -160^\circ$ and $\omega_2 = -170^\circ$ for the compressed and stretched helices, and where the internal and external helices rotate in opposite directions (P_{ext}/M_{int}).^{27b}

²⁷ a) A. Yurtsever, S. Das, T. Nishimura, R. Rodríguez, D. Hirose, K. Miyata, A. Sumino, T. Fukuma, K. Maeda. *Chem. Commun.*, **2021**, 57, 122266-122269; b) F. Freire, E. Quiñoá, R. Riguera. *Chem. Commun.*, **2017**, 53, 481-492; c) R. Rodríguez, J. Ignés-Mullol, F. Sagués, E. Quiñoá, R. Riguera, F. Freire. *Nanoscale*, **2016**, 8, 3362-3367.

²⁸ a) J. Kumaki. *Polym. J.*, **2016**, 48, 3-14; b) E. Yashima. *Polymer Journal*, **2010**, 42, 3-16; c) J. Kumaki, S.-I. Sakurai, E. Yashima. *Chem. Soc. Rev.*, **2009**, 38, 737-746; d) S. Sakurai, K. Okoshi, J. Kumaki, E. Yashima. *J. Am. Chem. Soc.*, **2006**, 128, 5650-5651; e) S.-I. Sakurai, K. Okoshi, J. Kumaki, E. Yashima. *Angew. Chem. Int. Ed.*, **2006**, 45, 1245-1248.

²⁹ a) V. Percec, J. G. Rudick, M. Peterca, S. R. Staley, M. Wagner, M. Obata, C. M. Mitchell, W.-D. Cho, V. S. K. Balagurusamy, J. N. Lowe, M. Glodde, O. Weichold, K. J. Chung, N. Ghionni, S. N. Magonov, P. A. Heiney. *Chem. - Eur. J.*, **2006**, 12, 5731-5746; b) V. Percec, J. G. Rudick, M. Wagner, M. Obata, C. M. Mitchell, W.-D. Cho, S. N. Magonov. *Macromolecules*, **2006**, 39, 7342.

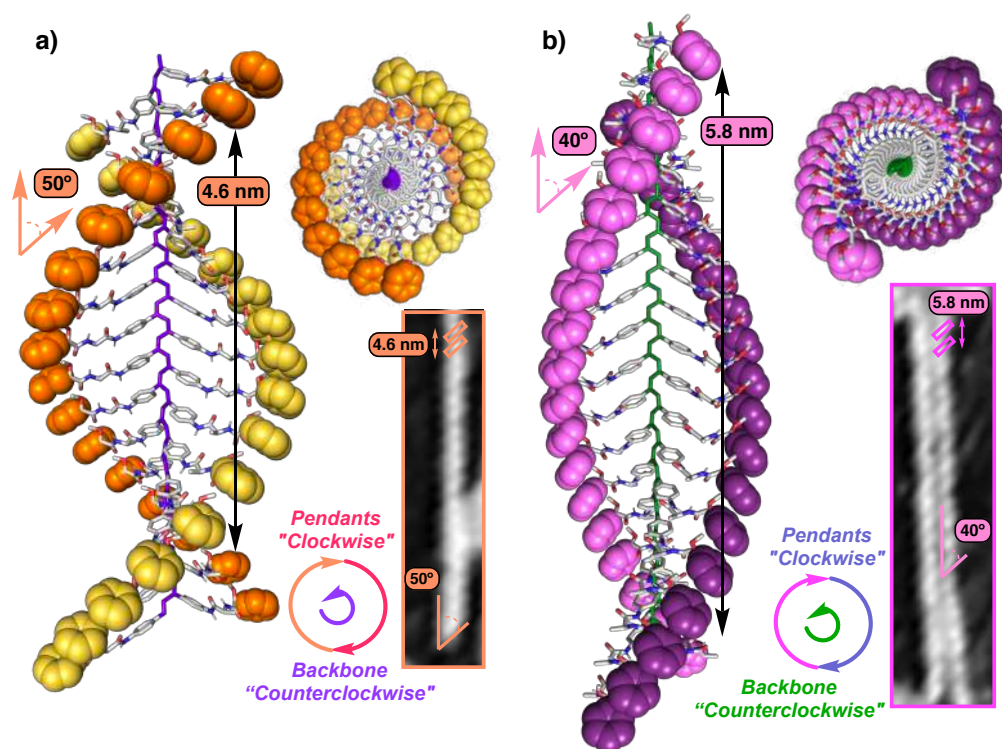


Figure 8. AFM Images and 3D-models of (a) compressed and (b) stretched *M* helices of poly-(*S*)-Ala-(*S*)-MPA obtained from CHCl_3 and $\text{CHCl}_3/\text{Li}^+$ solutions (HPOG as substrate).

Conclusions

In conclusion, this work demonstrates how the chiral overpass induction effect can be totally tamed, by introducing in the pendant groups of (PPA)s two chiral residues, which show independent and selective conformational control. As a result, it is possible to selectively induce an excess of *P* or *M* helical sense in the PPA main chain by varying the conformational composition at the second chiral residue through a chiral overpass effect. This polymer switch is achieved by a thorough design of the monomeric repeating unit. In our case, an alanine residue in either (*S*) or (*R*) configuration was introduced to link the pendant group to the PPA backbone through an anilide linkage and to play between an extended and a bent structure due to a conformational control in this group. Moreover, a second chiral residue consisting of (*R*)- or (*S*)- α -methoxyphenyl acetic acid was added to the pendant through the *N*-terminus of the aniline. This second chiral residue shows a conformational composition between two major conformers that places the bulkiest substituent, phenyl, in opposite directions and will allow the helical sense of the PPA to be controlled by means of a chiral overpass effect that occurs when alanine adopts a bent structure. As a result, when alanine adopts an extended structure, the second chiral

residue is placed far from the polyene backbone. Thus, the helical sense adopted by the PPA is commanded by the chirality of the alanine, while changes in the absolute configuration of the second chiral center or conformational changes at this residue does not affect the helical sense of the PPA. In contrast, when alanine adopts a bent structure, both conformational changes and changes in the absolute configuration of the MPA moiety result in a helix inversion in the PPA. This fact indicates that a total control of chiral overpass effect is achieved.

To our knowledge, this is the first time that a chiral overpass effect has been tamed, making it possible to induce both helical senses in the PPA by changes in the conformational composition of the second chiral residue (MPA). As a remarkable result, three different helices are produced in the PPA by varying the conformational composition in the monomer repeating unit. This unique and novel helical sense control portrayed here opens promising prospects in advanced helical sense control of (PPA)s and can be applied to develop new multi-stimuli responsive chiral polymeric materials with enhanced applications as sensors, as chiroptical switches or in chiral recognition, among many others. Efforts in those directions are currently underway in our laboratory.

CHAPTER II

*Diastereomeric Multi-Chiral Pendant Groups: Their Key Role in Stimuli-Responsive
Polymeric Responses*

Chapter II. Diastereomeric Multi-Chiral Pendant Groups: Their Key Role in Stimuli-Responsive Polymeric Responses.

Adapted from:

Rafael Rodríguez, Elena Rivadulla-Cendal, Emilio Quiñoá and Félix Freire.

Chirality, 2022, Submitted.

Abstract

Chiral information transmission in helical polymers bearing multi-chiral pendant groups is usually determined by the absolute configuration of the first chiral center. The second chiral residue usually has low-to-null influence in the macromolecular handedness of the polymer, due to its remote position respect to the polyene main chain. Here we demonstrate how the stimuli-responsive properties of diastereomeric polymers, obtained by changing the absolute configuration of the second chiral center, are different due to the unlike properties of diastereoisomers.

Introduction

Helical macromolecules have attracted the attention of the scientific community due to the properties and functionalities associated with this structural motif.^{1, 2} In consequence, a large variety of non-natural foldamers and helical polymers have been studied during the last decades. In the special case of helical polymers, families such as poly(isocyanide)s,³ poly(isocyanate)s,⁴ poly(diphenylacetylene)s,^{5, 6} or poly(acetylene)s,^{7, 8} among others, provide a large variety of helical scaffolds with different static/dynamic which properties find applications in different fields such as asymmetric catalysis,^{9, 10, 11, 12, 13} chiral recognition,^{14, 15} CPL sources,^{5, 6, 15, 16} chiroptical switches^{17, 18} or chiral stationary phases for HPLC among others.^{19, 20, 21} To be functional, these helical polymers must adopt macromolecular helical structures with screw sense excess. This can be achieved using supramolecular interactions with different external stimuli,^{22, 23} by controlling the conformational composition of the pendant groups^{24, 25, 26, 27} or by means of different chiral

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communication mechanism like Sergeants and Soldiers Effect,^{28, 29, 30, 31} Majority Rules,^{32, 33} Chiral Coalition,³⁴ Chiral Harvesting^{35, 36, 37} or Chiral Teleinduction³⁸ among others.

Most of the screw sense control studies in helical polymers have been done with pendant groups possessing a single chiral center, without paying attention to multi-chiral pendant groups. This fact is due to the control exercised by the first chiral center attached to the polymerizable functional group in the monomer, which is usually located close to the helix backbone on the macromolecular scaffold. This fact makes the other chiral centers present in the pendant group have a low-to-null impact on the net helicity of the system due to their remote location with respect to the polymer main chain.^{39, 40, 41, 42, 43} Our group has recently developed different protocols to modulate this effect and surpass the command of the first chiral center through a conformational control of the linkage between the different chiral residues. Allowing, in certain conformations, to place the second chiral center close to the polyene backbone resulting in the so-called chiral overpass effect.^{44, 45} In particular, we used as pendants dipeptide sequences or peptidomimetics that are involved in structural motifs such as turns, different from the classical β -sheet orientation found in these polymers. As a result, when the pendant adopts a bent conformation, the second chiral center occupies a position closer to the polymer main chain allowing it to dominate the handedness of the helix.

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Herein, we want to explore how the point chirality of the second residue affects the stimuli-responsive properties of a poly(phenylacetylene) (PPA) where the first chiral residue commands the helix through the adoption of a β -sheet conformation in the pendant group.^{38, 40, 41, 43} It is well known that physical and chemical properties of diastereomers are different, and therefore, the stimuli-responsive properties of diastereomeric (PPA)s towards solvent polarity can also be different. To study that, we designed a phenylacetylene monomer that bears the anilide of (*S*)-valine connected to the (*R*) or (*S*)- α -methoxy- α -phenylacetic acid (MPA) —m-(*S,R*)-**1**, m-(*S,S*)-**2**— (Figure 1a). In the corresponding polymers —poly-(*S,R*)-**1**, poly-(*S,S*)-**2**—, valine must govern the helix resorting to its two major conformations —*syn* and *anti*—, controlled by solvent polarity. The role of the second chiral center is just to alter the polarity of the polymers due to their diastereomeric relationship. As a result, the *syn/anti* conformational control of the valine residue in the two diastereomeric polymers can be produced at different solvent polarities, allowing us to detect a certain solvent.

Results and discussion

To test our hypothesis monomers, m-(*S,R*)-**1**, m-(*S,S*)-**2**, were prepared according to the protocol shown in the Supporting Information (SI). Next, the corresponding polymers, poly-(*S,R*)-**1**, poly-(*S,S*)-**2**, were prepared by using a Rh(I) catalyst —(i.e., [Rh(nbd)Cl]₂)— which produces the desired (PPA)s with a high *cis*- content of the conjugated double bonds as inferred by ¹H NMR and Raman (see Figures S7-S9).^{46, 47}

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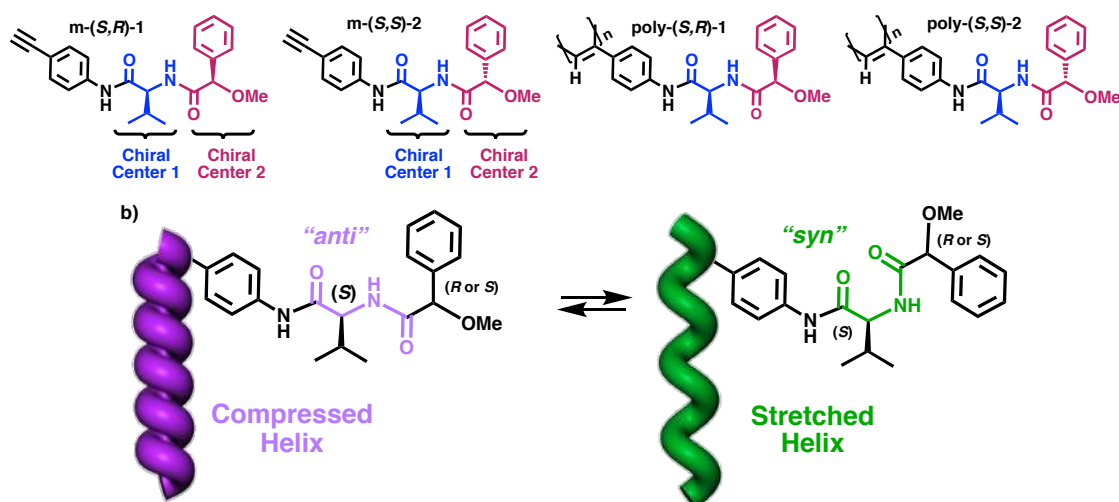


Figure 1. (a) Chemical structures of m-(S,R)-1, m-(S,S)-2, poly-(S,R)-1, poly-(S,S)-2. (b) *syn/anti* conformation of the valine residue in poly-(S,R)-1, poly-(S,S)-2.

ECD studies of poly-(S,R)-1, poly-(S,S)-2 were carried out in solvents with different polarity such as DCM, CHCl₃, THF, DMF and DMSO (Figure 2). In low polar solvents, e.g., DCM and CHCl₃, both polymers show ECD traces composed by two strong negative Cotton effects with maxima at 228 and 288 nm that corresponds to a compressed *M* helix.^{48, 49} This structure is adopted when the two amides of the valine residue are *anti* oriented, conformation that is favored for (PPA)s derivatized with amino acids in low-polar solvents (Figure 2a).^{50, 51, 52, 53} To corroborate the presence of a helical structure, optical rotation (OR) measurements were done for poly-(S,R)-1, poly-(S,S)-2 in DCM and the corresponding monomers. The values obtained for the polymers are much higher than those obtained for the monomers, indicating the presence of a helix (see Table S3).

Interestingly, the ECD traces obtained for poly-(S,R)-1, poly-(S,S)-2 in a medium polar solvent like THF are completely different. Thus, while poly-(S,R)-1 shows a spectrum similar to that obtained in low-polar solvents (see above), poly-(S,S)-2 shows a more stretched helix with three consecutive and alternating -/+/- Cotton effects with maxima at 280, 345 and 290 nm (Figure 2c), indicating the adoption of a preferred stretched *M*-helix.^{48, 49} This

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helical stretching is associated to an *anti* to *syn* conformational change at the valine residue, conformation favored in (PPA)s derivatized with amino acids in polar solvents. Therefore, both polymers show different stimuli-responsive properties towards THF due to their diastereomeric relationship.

When analogous ECD studies are carried out in more polar solvents such as DMSO or DMF, both polymers show similar ECD traces with three consecutive and alternating -/+/- Cotton effects with maxima at 280, 345, and 390 nm, virtually identical to that observed for poly-(*S,S*)-2 in THF. As a result, poly-(*S,R*)-1 and poly-(*S,S*)-2 adopt stretched *M*-helical scaffold in polar solvents due to the *syn* conformation of the valine residue.

Comparison of the UV-Vis spectra for poly-(*S,R*)-1 and poly-(*S,S*)-2 in DCM and DMSO shows a large bathochromic shift of the polyene band from 310 nm in DCM to 425 nm in DMSO in agreement with the ECD observations (Figure 2d and Figure S12).

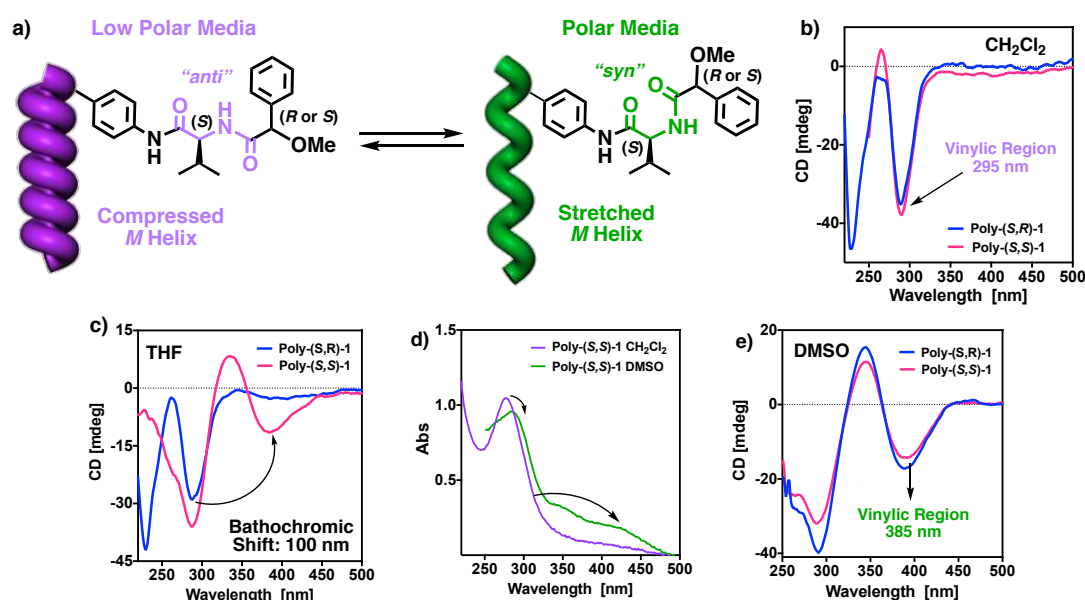


Figure 2. (a) Schematic illustration of the helical transformation of poly-(*S,R*)-1 and poly-(*S,S*)-2 triggered by polarity effects. ECD spectra in (b) DCM, (c) THF and (d) DMSO ($c = 0.3$ mg/mL).

Next, we decided to demonstrate the presence of the *anti* to *syn* conformational change by adding different stimuli such as TBAF, TFA or Ba(ClO₄)₂ to a DCM solution of poly-(*S,R*)-1 and poly-(*S,S*)-2. From previous studies it is known that these stimuli produce conformational changes at the pendant, *anti* to *syn*, by interacting with the amide groups.^{44, 50-53} Here, we show that the compressed *M*-helix is transformed into the

stretched one when these stimuli are present, corroborating the *anti* to *syn* conformational change at the pendant (Figures 3a-c).

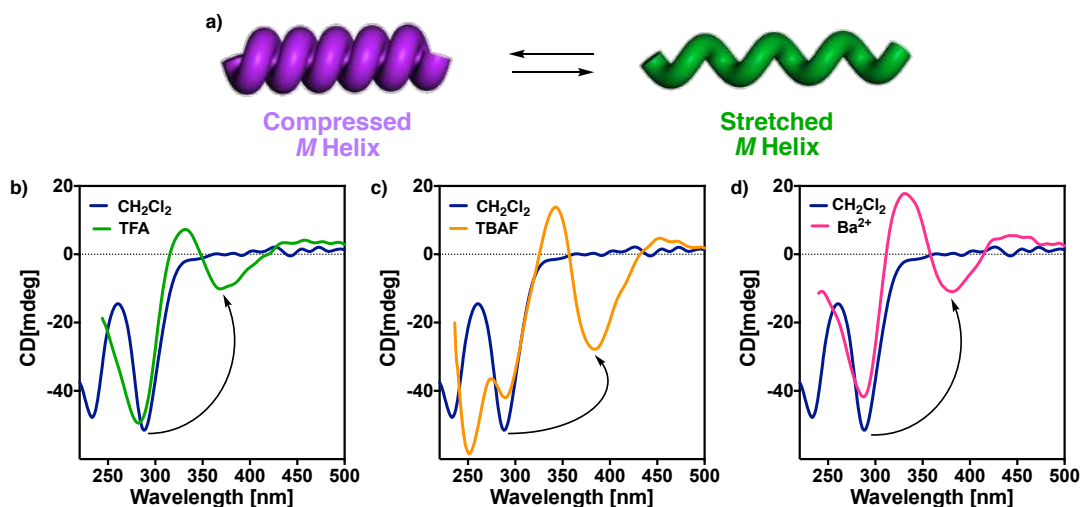


Figure 3. (a) Schematic illustration of the elongation of poly-(*S,S*)-**2** monitored by ECD after interacting with (b) TFA, (c) TBAF and (d) metal coordination (i.e., Ba^{2+}) (0.3 mg/mL, DCM).

Conclusions

In conclusion, we have demonstrated that although the helical senses induced in helical polymers possessing multi-chiral pendants groups is governed by the chiral center places closer to the backbone, the chiral centers placed in remote positions can have important consequences in the stimuli-responsive properties although their influence in the helical sense induction is limited. In this work, two different (PPA)s bearing as pendant (*S*)-Valine-(*R*)-MPA and (*S*)-Valine-(*S*)-MPA were prepared. The helical sense in all the solvents tested is commanded by the (*S*)-valine obtaining a *M* helix in all cases. However, this helix is compressed in low-polar solvents and stretched in polar solvents, difference attributed to an *anti* to *syn* conformational change produced at the pendant group. This *anti* to *syn* conformational change is activated by the solvent polarity, and because the two diastereomeric polymers, poly-(*S,R*)-**1** and poly-(*S,S*)-**2** have different physical properties, the value of the dielectric constant of the solvent needed to produce this conformational change is different for both polymers. As a result, these two polymers show different stimuli-responsive properties in THF. While poly-(*S,R*)-**1** adopts a compressed helix due to an *anti*-conformation at the pendant, in poly-(*S,S*)-**2** an *anti* to *syn* conformational change is triggered producing a stretched helix. Consequently, these two polymers allow to sense THF due to the different helical scaffolds induced by a different conformational

composition at the pendants. We believe these findings will encourage the scientific community to study more complex multi-chiral pendant groups and their potential impact in the folding/stimuli-responsive nature of the polymers. Efforts in that direction are currently ongoing in our laboratory.

CHAPTER III

Greasing Macromolecular Gears: Inclusion of Flexible Spacers

Chapter III. Greasing Macromolecular Gears: Inclusion of Flexible Spacers.

Abstract

A macromolecular gear formed by a helical poly(phenylacetylene) (PPA) backbone with short oligopeptide helices as phenyl rings substituents is described. The acetylene group introduced at the C- terminus of a short oligopeptide composed by achiral gly-Aib_n units ($n = 1-4$) derivatized at the N- terminus by a single enantiomer (*S*)- α -methoxy- α -trifluoromethylphenylacetic acid (MTPA) is polymerized to form this macromolecular gear. The introduction of the flexible glycine linker into the classical 3₁₀-helix foldamer adopted by the aminoisobutyric (Aib) sequence, results into an improved helix induction from the end capping MTPA moiety towards the poly(phenylacetylene) (PPA) framework. Additionally, the systems exhibit helix inversion or modifications of the stretching degree of the PPA skeleton triggered by either thermal or polar effects.

Introduction

Nature has thrived on the development of intricate macromolecular structures that are able to translate information through complex conformational changes. G-protein coupled receptors and transmembrane receptors represent archetypal examples of this type of naturally occurring systems.^{1, 2} Peptides, DNA or saccharides are further examples of biomacromolecules adopting helical structures —whose function is directly related to their helical structure—. Unfortunately, due to the homochirality of nature, only one set of enantiomers is used in each case, and therefore the above-mentioned biomolecules are exclusively composed by (*L*)-aminoacids or (*D*)-Sugars. As a result, the biopolymers obtained present only one single-handed helicity —triggered by the chirality of the constituent building blocks— limiting their applications as chiral materials.

Consequently, artificial helical systems able to translate chiral responses have attracted the attention of the scientific community not only to mimic natural systems,³ but also to exploit them as chiral materials suitable for sophisticated tasks such as catalyzed

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asymmetric reactions,⁴ chiral recognition⁵ or generation of chiroptical switches among many others.⁶

Such artificial helical polymers represent unique platforms to study asymmetry amplification through different mechanisms.³ If the polymer is composed by non-chiral building blocks, the interconversion energy barrier between *P/M* is low and the interaction with chiral additives is enough to promote the adoption of a preferred handedness.³ Working on this topic, Green and co-workers developed several pioneering approaches based on copolymerization strategies, being Sergeant and Soldiers⁷ and Majority Rules⁸ the most commonly applied. The former is based on the copolymerization of achiral building blocks with a small amount of a chiral congener, while the latter relies on the copolymerization of an enantioenriched mixture of a monomer. Both strategies resulted successful in the adoption of single-handed helices, thus inspiring their application in supramolecular polymers and complex coordination compounds.

Remarkably, if the helical structure is composed by chiral monomers, the polymer adopts a preferred handedness that can be enhanced⁹ or inverted¹⁰ by applying proper internal or external stimuli.

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Another unique example of asymmetry induction —reported by Inai and coworkers in folded synthetic oligomers (Foldamers)—¹¹ is the “Domino effect”.¹² These foldamers are based on non-natural amino acids or combinations of natural and non-natural amino acids that fold into helical structures mimicking natural peptides (e.g., α -aminoisobutyric acid (Aib) and α,β -didehydrophenylalanine). This effect is based on the adoption of a preferred-handed helix in foldamers composed by achiral building blocks via supramolecular interactions of chiral compounds at either the *N*- or *C*- terminus.¹⁴

This pioneering discovery promoted the application of these systems as efficient chiral communicators. Toniolo,¹³ Yashima¹⁴ and Clayden¹⁵ reported several models of chiral information transmission through these moieties by including chiral centers within the foldamer sequence.

Interestingly, further manipulation of foldamer handedness can also be obtained by controlling the hydrogen bonding network of the helical scaffold by pH modifications or photochemical triggers. Unfortunately, often as a result, changes in the helical sense of the oligopeptide require changes in the absolute configuration of the peptide or in the net number of atoms in the foldamer.^{6b}

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Recently, we have shown that the introduction of a single enantiomer of α -methoxy- α -trifluoromethylphenylacetic acid (MTPA)¹⁶ at the *N*-terminus of an achiral Aib oligopeptide, allowed the selective preparation of the *P/M* helical senses of the oligopeptide by tuning the conformational composition of the terminal MTPA. Upon polymerization of the monomers through the alkyne site at the *N*-terminus, efficient asymmetry induction was observed in the resulting poly(phenylacetylene) (PPA) backbone.¹⁷

Additional modifications of the conformational composition of the MPTA moiety were effectively transmitted to the PPA skeleton, only resulting in helix inversion in the case of the shorter linker bearing a single Aib unit. The longer counterparts —carrying two or three Aib units— result in stretching of the polyene backbone rather than inversion of the helix. Despite the effective transmission of chiral information, lack of flexibility results in stretching of the polymer backbone and inefficient chiral stimuli-response readout. The main reason behind this phenomenon is the lack of flexibility in the connection between the bulky peptide and the PPA skeleton, which is not able to accommodate new conformations of the peptide chain.¹⁷

We envision here that the introduction of a flexible linker between the PPA backbone and the Aib foldamer should release steric stress, therefore resulting in (PPA)s with higher dynamism, enhanced chiral content and, accordingly, improved stimuli-responsive nature. As a flexible linker, we selected a simple glycine (gly) unit, as it has been used previously as effective linker in (PPA)s^{6b, 18} and also fits well with the 3_{10} helical structure adopted by Aib foldamers. In fact, it acts as a chiral communication conductor, as demonstrated by Clayden and coworkers.¹⁹

In addition, introduction of a 4-ethynylaniline group at the *C*-terminus of these peptides and subsequent rhodium-catalyzed polymerization produces the corresponding poly(phenylacetylene) (PPA).²⁰

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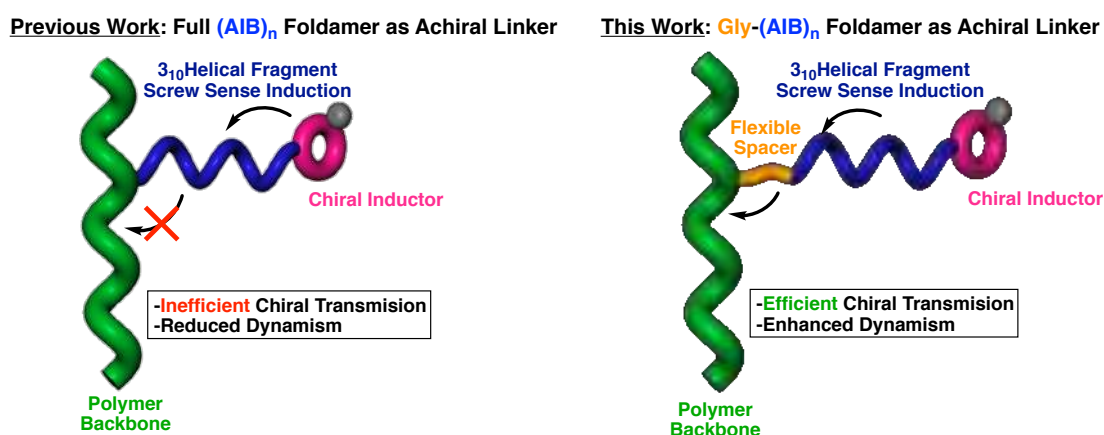
¹⁷ Rodríguez, R.; Suárez-Picado, E.; Quiñoá, E.; Riguera, R.; Freire, F. *Angew. Chem. Int. Ed.* **2020**, *59*, 8616-8622.

¹⁸ Rodríguez, R.; Quiñoá, E.; Riguera, R.; Freire, F. *Small* **2019**, *15*, 1805413.

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In this way, polarity-induced conformational changes in the MTPA unit produce screw sense changes in the oligopeptide that are transmitted to the poly(phenylacetylene) backbone as changes on the elongation and/or sense of the helix.



Scheme 1. Schematic illustration of the impact of the flexible linker in the transmission of chiral information through the Aib foldamer towards the PPA backbone in a polymeric macromolecular gear.

Results and discussion

The designed monomers (Figure 1a) were prepared via a multistep synthetic route depicted in the SI, and were fully characterized through a battery of NMR, HRMS and X-ray diffraction experiments.

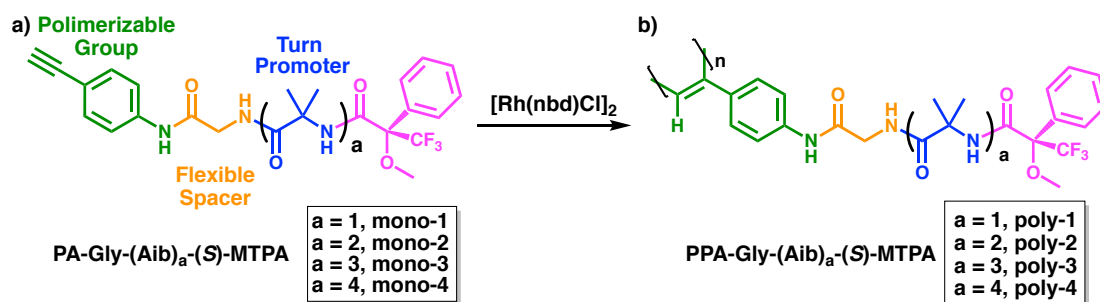


Figure 1. (a) Foldamers PA-(Aib)_n-(S)-MTPA (a = 1, 2, 3, 4). (b) Poly(phenylacetylene)s (S)-MTPA-(Aib)_n-PPA (a = 1, 2, 3, 4).

The adoption of helical structures by different monomers in the solid state was determined by X-ray diffraction of single crystals of the monomers, grown by slow evaporation of DCM/hexane solutions. The 3_{10} -helical structures were stabilized by the presence of consecutive *i*, *i*+3 hydrogen bonds. Interestingly, *P* and *M* helical structures were present in all the crystals, the screw sense being dependent on the conformation of the chiral MTPA moiety.

X-ray diffraction of mono-**1** showed the coexistence of *P* and *M* helices in solid state. These structures were stabilized by O=C-C-OMe dihedral angles of -173° and $+152^\circ$ for *P* and *M* helices, respectively (Figure 2a and Table S1). In the case of mono-**2**, X-ray diffraction showed a *P*- 3_{10} helix stabilized by a single intramolecular hydrogen bond between *i* and *i*+3 residues. The right-handed orientation of the 3_{10} helix was promoted by an *antiperiplanar* orientation between the carbonyl and methoxy groups of the (*S*)-MTPA residue (O=C-C-OMe dihedral angle: -172°). Similar to mono-**1**, a second structure —*M*- 3_{10} helix— was found in solid state, stabilized by an *ap*_{OMe} conformation whose O=C-C-OMe angle was $+162^\circ$ (Figure 2b and Table S2).

Remarkably, X-ray experiments showed, for mono-**3**, the coexistence in the same crystal unit of four independent molecules, related two by two by hydrogen bonds. Each pair displayed the two helical senses —*P* and *M*— of the 3_{10} helix, stabilized by two consecutive *i*, *i*+3 hydrogen bonds. The chiral (*S*)-MTPA residue in the *P* and *M* helices showed O=C-C-OMe dihedral angles of -174° and $+161^\circ$, respectively (Figure 2c and Table S3). Finally, X-ray diffraction of mono-**4** also showed the *P*- and *M*- 3_{10} helices. Both structures were stabilized by an *ap*_{OMe} conformation of the (*S*)-MTPA residue. As in the previous cases, opposite O=C-C-OMe angles were found: -176° for *P*- 3_{10} helix and $+151^\circ$ for *M*- 3_{10} helix (Figure 2d and Table S4).

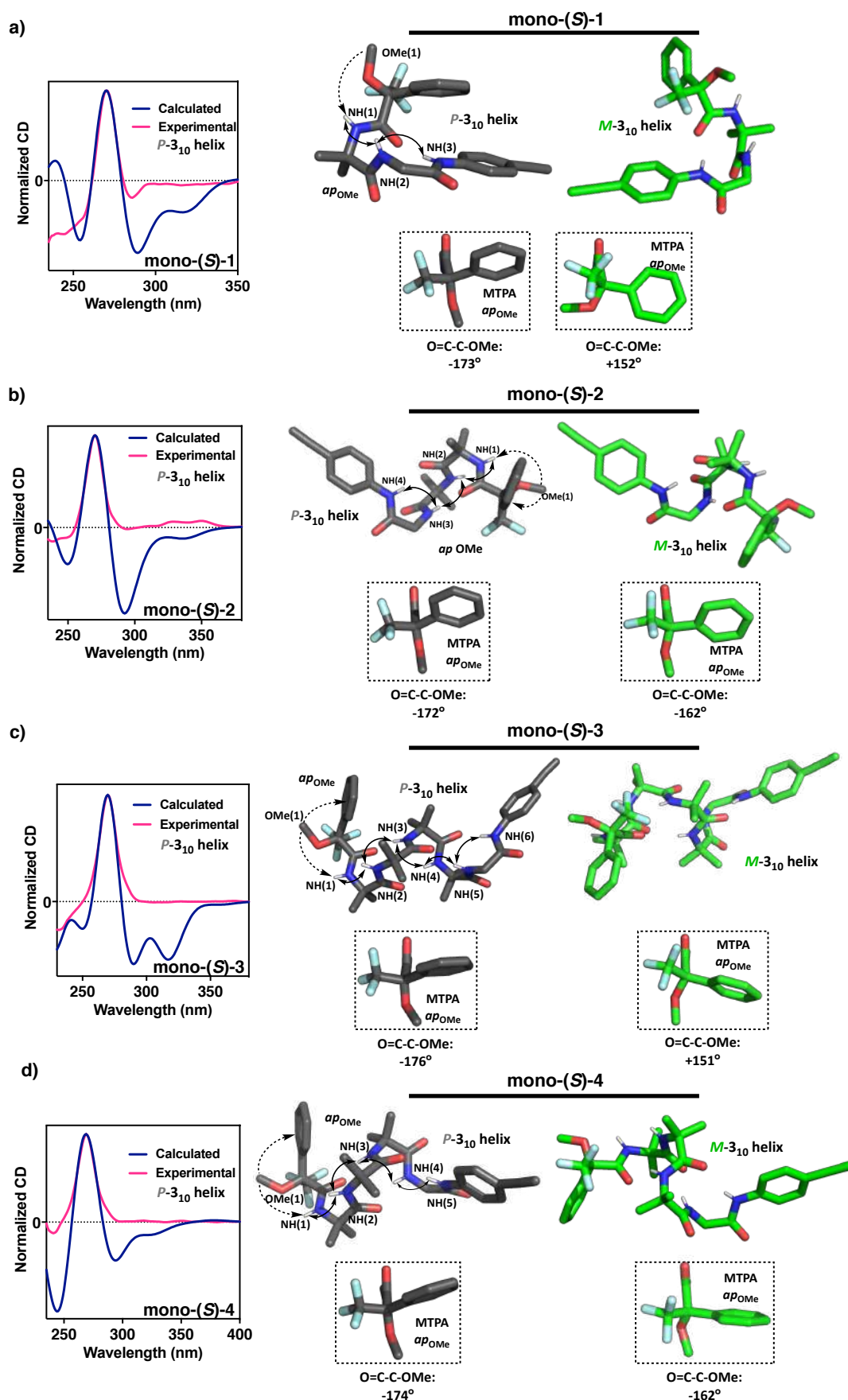


Figure 2. X-ray structures showing the representative NOEs found in solution and experimental vs computed CD spectra of (a) mono-1, (b) mono-2, (c) mono-3 and (d) mono-4.

To determine the folding and dynamic behavior in solution, NMR, ECD and Raman experiments in different solvents were carried out for the corresponding monomers. Remarkably, NMR experiments, together with theoretical calculations, revealed that the structures found in solution were virtually identical to those present in the solid state (See Figures 2a-d and SI). A detailed description of key NMR signals confirming the abovementioned structures is shown next.

2D-NMR (NOESY) in THF- d_8 of mono-**1** displayed strong sequential NH-NH cross peaks indicating the presence of a very stable β -turn structure. (Figure S37a, S38a-b). In addition, amide NH(1)/OMe(1) cross peak demonstrated a preferred *ap*_{OMe} conformation at the chiral (*S*)-MTPA residue (Figure S37c, S38c). Moreover, ECD experiments in the same solvent showed a positive Cotton effect at 270 nm, confirming the *ap*_{OMe} conformation (Figure 2a). Additionally, strong cross peaks between the flexible glycine unit with its neighboring amides —CH₂-NH(3) and CH₂-NH(2)— were observed (Figure S37b). All these data verified that oligomer mono-**1** presents, in polar solvents, a *P* β -turn twisted structure, in agreement with that obtained from the X-ray studies (Figure 2a).

ECD studies of mono-**1** in other solvents (e.g., CDCl₃) revealed its static behavior (positive CD spectrum) due to the absence of a conformational switch at the chiral (*S*)-MTPA moiety. 1D and 2D-NOESY NMR experiments were carried out to further confirm the *ap*_{OMe} conformation adopted by mono-**1** in CDCl₃. As in the case of polar solvents, strong sequential NH-NH and amide NH(1)/OMe(1) cross peaks were observed (see SI Figures S41a-b, S42). Analogous set of NMR, CD and computational studies were carried out for the corresponding counterparts (mono-**2** to mono-**4**) to determine the folding of these structures in solution. Remarkably, these monomers showed similar behavior in solution, folding into a preferred *P*-handed 3_{10} -helix independently of the solvent used.

1D and 2D-NOESY NMR experiments of mono-**2**, mono-**3** and mono-**4** in THF- d_8 showed strong sequential NH-NH cross peaks that together with other NOEs corroborated the presence of a *P*- 3_{10} helix in solution (Figures S45a and S46a-d, Figures S53a and S54a-c, Figures S61a and S62, respectively). The absence of long distance NOEs for OMe(1) together with NOEs between OMe(1) with amide NH(1) indicated a major *antiperiplanar* orientation between methoxy and carbonyl groups in the MTPA moiety that commands a *P*- 3_{10} helix in these three oligomers (Figure 2b-d, and Figures S45b and S46e, Figures S53b and S54d, Figures S61b and S62e, respectively). In all cases, strong cross peaks were again

observed between the flexible glycine unit with its neighboring amides —CH₂-NH(4) and CH₂-NH(3) for mono-**2** (Figures S45c and S46f); CH₂-NH(5) and CH₂-NH(4) for mono-**3** (Figures S53d and S54e) and CH₂-NH(6) and CH₂-NH(5) for mono-**4** (Figure S61d)—.

TD-DFT studies using CAM-B3LYP method, together with the 6-31+G** basis, were performed for the different monomers (mono-**1** to mono-**4**). The optimized structures were in good agreement with those found in the solid state, also in perfect agreement with the cross peaks found through the NMR studies. The computed vs experimental ECD spectra of the monomers are shown in Figure 2, and they exhibit a good match between both spectra and thus confirm the existence of such structures both solution and in the solid state (see Figures 2a-d).

Raman spectroscopy has recently been applied as an effective tool to study the folding of Aib oligomers into 3₁₀-helices. These studies were performed in our monomer set (mono-**1** to mono-**4**) showing in all cases amide I bands at 1670 cm⁻¹, value considered as 3₁₀ helix marker (see Figure S23a).²¹

The corresponding polymers (poly-**1** to poly-**4**, Figure 1b) were prepared by Rh(I) catalyzed polymerization of the terminal alkyne contained in the C-terminus of the foldamers.²⁰ The polymers were obtained in high yield, with high content of *cis* double bonds as inferred by ¹H NMR spectra (see Figures S19-22) and Raman (see Figures S23b-e) experiments. For all the polymers, an efficient chiral transmission from the MTPA moiety towards the PPA backbone was found. This fact indicated the presence of a well-folded structures of the pendant groups in solution. Additionally, subtle changes in the polarity of the media produced conformational changes in the MTPA moiety, resulting in helical inversion and/or variations of the elongation of the PPA skeleton. A detailed explanation of the features of each polymer can be found next.

As depicted in Figure 3, poly-**1** showed an effective asymmetry induction from the MTPA moiety, through the achiral gly-Aib fragment, towards the polyene backbone as inferred by the presence of an active ECD trace with predominant macromolecular screw sense. As an example, the presence of a positive Cotton effect centered at 375 nm in MeOH— ascribed to the polymer main chain— indicated the presence of a *P* helix. Interestingly, the polymer presented dynamic behavior as demonstrated by ECD studies in different

²¹ Lizio, M. G.; Andrushchenko, V.; Pike, S. J.; Peters, A. D.; Whitehead, G. F. S.; Vitorica-Yrezabal, I. J.; Mutter, S. T.; Clayden, J.; Bour, P.; Blanch, E. W.; Webb, S. J. *Chem. Eur. J.* **2018**, *24*, 9399-9408.

solvents. Thus, solvents with low polarity (e.g., CHCl_3 or DCM) induced a *M* helix, while more polar ones (e.g., DMF, DMSO, NMP) promoted a *P* helix thus affording inversed CD spectra as shown in Figure 3b. VT-CD experiments carried out in low polar solvents (e.g., CHCl_3 and DCM) showed a concomitant helical inversion (see Figures 26a and S26b) of the PPA framework as the temperature increased. Additionally, the UV-Vis studies showed a bathochromic shift in the chromophoric main chain region (from $\lambda = 395$ to 455 nm) as the polarity of the corresponding solvent increased (see Figure S25b), indicative of an elongation of the polyene backbone.

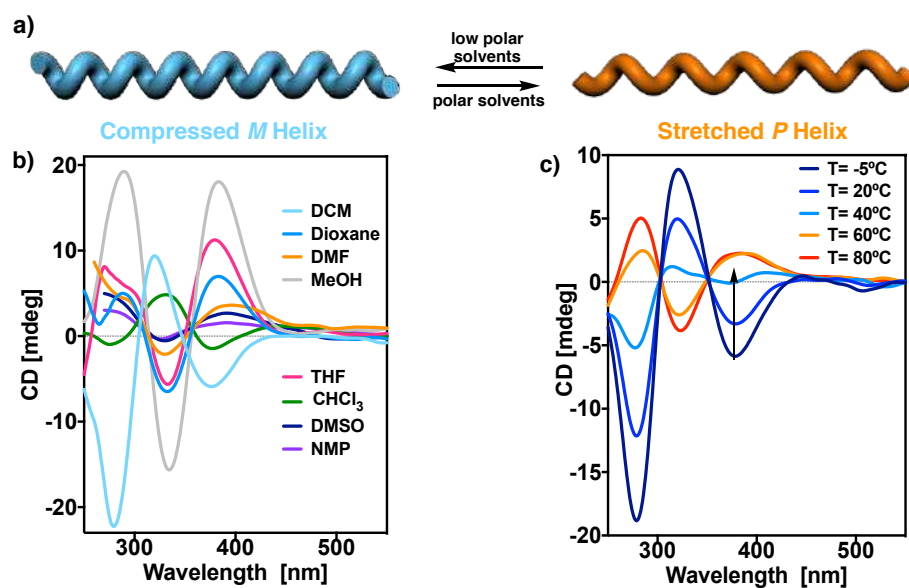


Figure 3. (a) Conceptual illustration of the stretching process of (S)-MTPA-Aib-gly-PPA. (b) CD and (c) VTCD spectra of poly-1 showing the helix inversion process.

CD studies of poly-2 in different solvents showed the existence of a preferred-handed macromolecular helical structure, whose elongation and handedness were affected by the nature of the solvent. Consequently, for the majority of solvent tested, CD experiments showed a positive Cotton effect with maxima at $\lambda = 470$ nm — *P* helix, CD(+), that is shifted 95 nm compared with the abovementioned counterpart poly-1— indicative of stretched *P* skeleton (Figure 4b). Importantly, CHCl_3 and DCM were able to trigger a helix inversion process as demonstrated by ECD experiments — *M* helix, CD(—) — (Figure 4). Strikingly, VT-CD experiments showed two different scenarios depending on the solvent used. A temperature-dependent helix inversion was observed in CHCl_3 : at 60°C the Cotton effect ascribed to the polymer main chain was positive, while at low temperature (i.e., $T = -5^\circ\text{C}$)

was negative, therefore indicating an inversion from *P* to *M* helix (Figure S28a). Interestingly, a stretching of the PPA skeleton was triggered in DCM as revealed by the large bathochromic shift in the vinylic region (from $\lambda = 445$ to $\lambda = 430$ nm) of the CD spectra (Figure S28b).

Although the (*S*)-MTPA chiral unit is separated from the backbone by one glycine and two achiral Aib residues, it is still able to induce a preferred helical sense in the polyene chain. Other modifications in the conformational composition of the MTPA moiety result in helix inversion, an effect not obtained for the previously reported counterpart.¹⁷

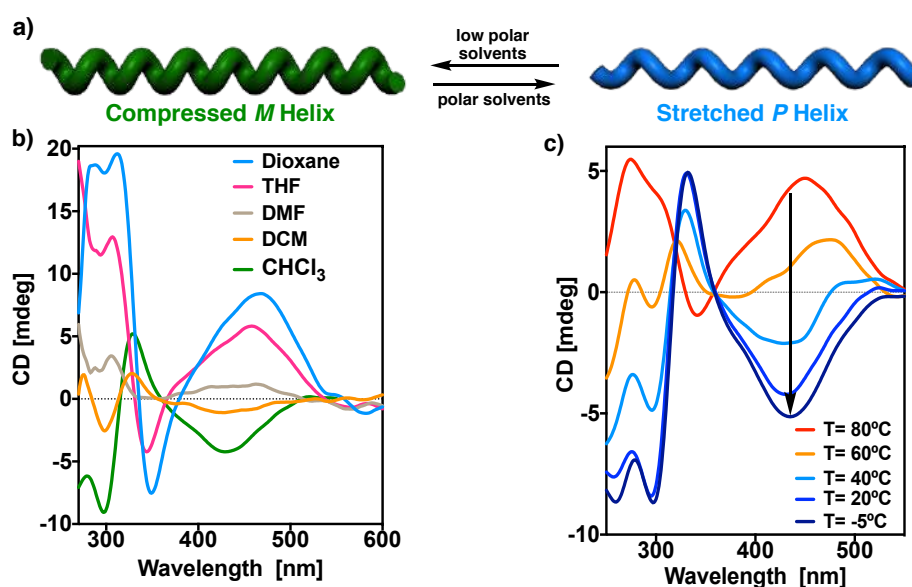


Figure 4. (a) Conceptual illustration of the stretching process of (*S*)-MTPA-(Aib)₂-gly-PPA. (b) CD and (c) VTCD spectra of poly-2 showing the helix inversion process.

CD studies of poly-3 in different solvents showed the presence of a preferred helical structure that generated, in all cases, a strong negative Cotton effect in the vinylic region —*M* helix, CD(–)— (Figure 5b). While the polymer displayed in all cases a *M* helical structure, variations in the polarity of the media modified the elongation degree of the polymer as concluded by both ECD and UV-Vis experiments (Figure 5b-c). Thus, in low-polar solvents (i.e., CHCl₃), the conjugated PPA backbone had a maximum in absorption at $\lambda = 455$ nm, while in more polar solvents such as NMP, it underwent a bathochromic shift of 30 nm ($\lambda = 485$ nm), indicative of the presence of a more stretched helix (Figure 5c). Interestingly, the introduction of glycine as flexible spacer allowed efficient transmission of chiral information and increased tolerance to solvents, as described below. Our previous

system bearing a pure Aib foldamer linker, with virtually the same length, was not able to transmit chiral information in polar solvents (e.g., DMF and NMP) due to the lack of flexibility of the more rigid fragment, therefore emphasizing the effectiveness of the introduction of glycine in our foldamer design.¹⁷

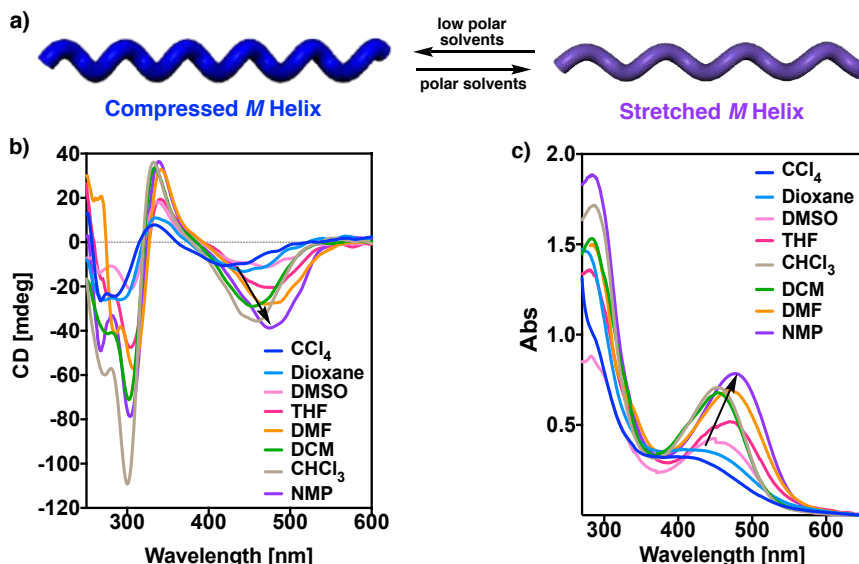


Figure 5. (a) Conceptual illustration of the stretching process of (*S*)-MTPA-(Aib)₃-gly-PPA. (b) CD and (c) UV-Vis spectra of poly-**3** displaying the stretching process.

Finally, CD studies of poly-**4** showed a CD response in all the solvents tested, indicating an effective transmission of chiral information through the non-chiral foldamer sequence, implying the presence of a well-ordered 3_{10} -helix structure in the pendant groups. However, subtle differences were found in the spectral pattern depending on the solvent used, indicating that the system was more dynamic than expected. The subtle but important differences in the ECD/UV-Vis spectral patterns for the solvents tested are displayed in Figure 6b-c. In DCM and acetone, poly-**4** showed a first small Cotton effect centered at $\lambda = 570$ nm and 565 nm followed by consecutive strong positive and negative bands at $\lambda = 515$ and 345, and 480 and 345 nm, respectively. This spectral pattern was modified in more polar solvents (i.e., DMF), where the first Cotton effect at higher wavelengths disappeared and only a broad positive Cotton effect with two maxima appeared ($\lambda = 435$ and 525 nm, Figure 6b and S30). The presence of two maxima in the region ascribed to the polymer main chain indicated the presence of an equilibrium between two helical scaffolds with same handedness but different stretching degree. This

effect has been previously reported for other (PPA)s bearing meta-substitution patterns.²² Finally, in CHCl_3 , only a broad positive Cotton effect was detected in the main chain region with absorption until 600 nm, indicative of a more elongated helical structure. Parallel UV-Vis studies displayed in Figure 6c showed the differences in absorption maxima for the above-mentioned solvents. This variation in absorption had a strong macroscopic outcome, shifting the color of the solutions from yellow to orange to deep red what makes this system a nice example of dynamic multistate chiroptical switch.

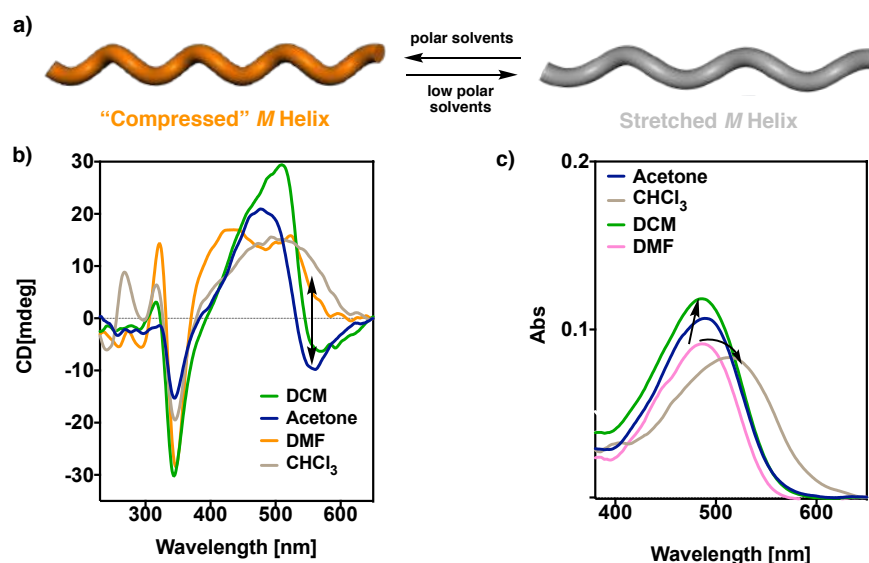


Figure 6. (a) Conceptual illustration of the stretching process of poly-4. (b) CD and (c) UV-Vis spectra of poly-4.

Conclusions

We have demonstrated that the introduction of glycine as a flexible spacer at the *N*-terminus of short non-chiral Aib oligomers ($n = 1, 2, 3, 4$) end capped with a single enantiomer of MTPA allows the selective folding of the chain into *P* or *M* helical senses, by simply playing with the polarity of the solvent. This action is due to the conformational change produced in the chiral MTPA unit of mono-**1-4** series that is transmitted to the oligopeptide chain via screw sense induction.

Introduction of a 4-ethynylaniline group at the *C*-terminus of those oligopeptides followed by rhodium-catalyzed polymerization of the alkyne produced the corresponding poly(phenylacetylene)s (PPA)s —poly-**1** to poly-**4**— that were shown to act as a

²² Rodríguez, R.; Quiñoá, E.; Riguera, R.; Freire, F. J. *Am. Chem. Soc.* **2016**, *138*, 9620-9628.

macromolecular gear, where the helical sense/elongation of the polyenic skeleton is controlled by the helical sense of the oligopeptide chain that in turn, obeys the conformational composition of the terminal (*S*)-MTPA unit, shifted by the polarity of the media. In this way, solvent polarity changes make the oligopeptide substituents of the PPA —(*S*)-MTPA-(Aib)_{*n*}-PPA (*n* = 1, 2)— to vary their *P/M* screw sense preference, triggering a structural change on the polyenic skeleton —helical sense and/or elongation—.

Interestingly, the two first counterparts of the series (poly-**1** and poly-**2**) display effective chiral communication between the MTPA moiety towards the polymer skeleton. Strikingly, the presence of the flexible glycine allows the system to display dynamic behavior promoting helix inversion under proper circumstances (i.e., DCM as solvent and thermal treatment). The last two components of the series (poly-**3** and poly-**4**) exhibit also strong chiral information harvesting through the well-folded non-chiral fragment. The presence of larger pendants reduces the dynamicity of the corresponding (PPA)s, which do not display clear helix inversions, but do show interesting variations in the degree of elongation. The chiral communication process reported here contributes to the development on new stimuli-responsive materials with potential application as sensors, chiral stationary phases for HPLC, and logic devices among others.

CHAPTER IV

*Multi-Helical Scaffolds (up to Five Helices) from Chiral (PPA)s bearing a Gly-AA as
Pendant.*

Chapter IV. Multi-Helical Scaffolds (up to Five Helices) from Chiral (PPA)s bearing a Gly-AA as Pendant.

Abstract

Helical sense of chiral poly(phenylacetylene)s is usually controlled by taming the conformational composition at the chiral pendant group. Sometimes, the *P/M* helical sense control can be accompanied by variation on the elongation of the polymer, although is not possible to control both parameters (elongation and helical sense) independently. Herein, we will show how up to five different helical structures can be obtained from a PPA that bears the anilide of the Gly-AA-Boc (AA = Phe, Val) as pendant. In this polymer it is possible to control the conformational composition of the two amino acid residues independently, which results in a full control of the polymer elongation (gly, achiral residue) —three scaffolds: helix **1-3**—and the helical sense (AA, chiral amino acid) —*P/M* screw sense excess—.

Introduction

Biological macromolecules, such as DNA, peptides, polysaccharides and proteins, adopt one-handed helical structures predetermined by the chirality of their constituent units. In addition, part of these biomacromolecules such as proteins combine different structural motifs (i.e., helices, loops, turns, β -sheets) to be folded into high-order macromolecular structures (tertiary and quaternary structures) which are responsible of the protein function.¹⁻⁴

Due to this fact, the scientific community has developed a large number of artificial helical structures (i.e. helical polymers or oligomers) with a preferred helicity to study the application/function of these new scaffolds. Among them, dynamic helical polymers, like poly(phenylacetylene)s [(PPA)s], represent an attractive research topic due to their stimuli-responsive properties and their different applications such as sensors,⁵ chiroptical switches,⁶⁻⁸ chiral stationary phases⁹ or chiral catalyst,¹⁰⁻¹⁵ among others.

In most of these polymers, the handedness of the helical polymers is induced by the chiral pendant group directly attached to the poly(phenylacetylene) backbone. Further changes in the conformational composition of the pendant group by the application of external stimuli could result in changes in the helical parameters of the PPA —elongation and/or sense—, as a result, these polymers can act as stimuli-responsive materials.

During the last decades, some research groups have been working in the introduction of achiral flexible spacers between the chiral center and the pendant group, obtaining that as the chiral center is being placed further from the polyene backbone, the helix induction

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is vanished, resulting in a racemic helical conformation.^{16, 17, 18, 19, 20, 21} Therefore, these studies suggest that the best folding for a PPA is obtained when the distance between the backbone and the chiral motif is as small as possible. For this reason, the closer is the pendant to the polyene framework, the better is the helical control.^{22, 23} Nonetheless, during these studies it was also found that a full helical sense control can be achieved in (PPA)s that bears an achiral spacer between the chiral center and the polyene backbone if this achiral spacer adopts a well-ordered structural motif —helix, β -sheet, turn, tilting degree—. ^{20, 21, 24-29, 30-32} Moreover, these materials can work as stimuli responsive materials if the addition of external stimuli can alter the secondary structure adopted by the achiral spacer either by acting directly on this motif, or by modifying the conformational composition at the chiral fragment which is further effectively transmitted to the achiral spacer.³⁰

From these materials, we wanted to highlight a previously reported anilide-PPA, which contains an achiral glycine connected to the polyene backbone through the *N*-terminus, and derivatized with a chiral (*R* or *S*)- α -methoxyphenyl acetic acid (MPA) or a chiral (*R* or *S*)- α -methoxy- α -trifluoromethylphenyl acetic acid (MTPA) derivative at the *C*-terminus. In these (PPA)s, a screw sense excess is obtained due to the presence of a well folded extended structure at the pendant (β -sheet mimetic), which is stabilized by hydrogen bond (H-bonds) interactions between neighboring pendants — n^{th} and $(n+2)^{\text{th}}$ or n^{th} and $(n+3)^{\text{th}}$,

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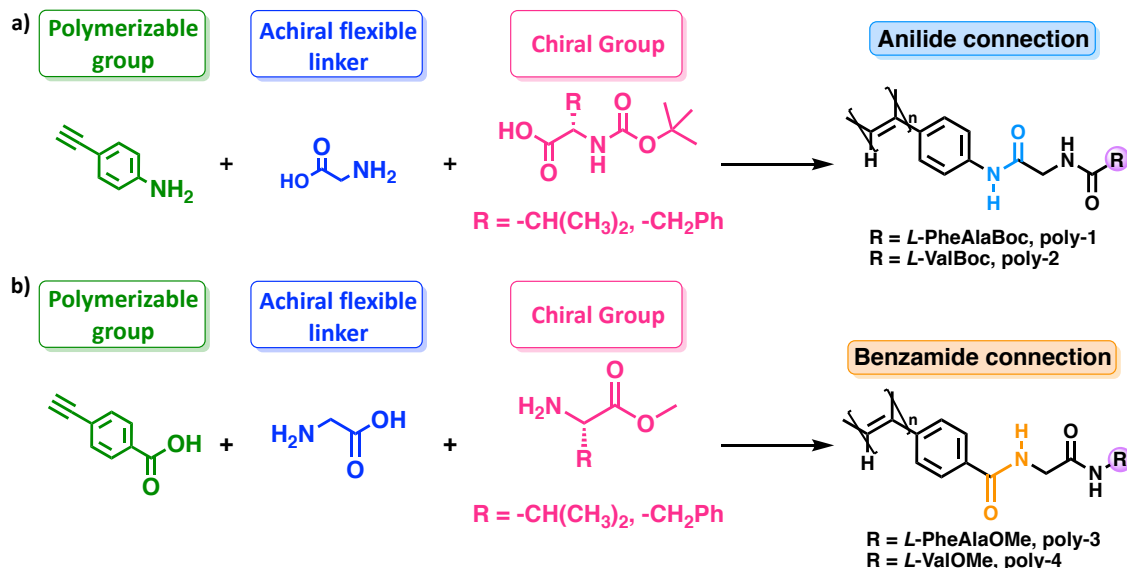
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transforming the flexible spacer into a rigid one.^{20, 23} Remarkably, in such systems, the helix induction is produced through a tele-induction mechanism, being the screw sense preference lost when two glycine residues are introduced in the achiral spacer.

In this work, we wanted to do a step forward in the preparation of stimuli-responsive materials using remote helical sense control of (PPA)s. Thus, we aim to prepare a pendant group consisting of an achiral spacer and a chiral residue, which can adopt different structural motifs under different external stimuli. Considering our expertise in (PPA)s derivatized with amino acids, and the information obtained from literature, we envisioned an PPA bearing either a Gly-Phe or a Gly-Val as pendant groups, connected to the polyene backbone through the *N*- (anilide-PPA) or *C*-terminus (benzamide) (Scheme 1). Thus, if we can control the conformational composition at the pendant group, we will be able to generate different extended and bent structures at the pendant group that result in the adoption of different helical scaffolds. In our design, the glycine residue has been chosen as flexible and achiral spacer, which can be involved either into extended or bent structures, while the phenylalanine and the valine has been selected due to the presence their bulky side chain, needed to have a good tele-induction.



Scheme 1. Schematic illustration of the components that form the pendant groups of the polymers bearing glycine spacers: (a) anilide-(PPA)s and (b) benzamide-(PPA)s.

Results and discussion

Thus, monomers mono-*L*-1 and mono-*L*-2, containing the anilide of a Gly-Phe-Boc and a Gly-Val-Boc dipeptide respectively (Figure 1a), and monomers mono-*L*-3 and mono-*L*-4

containing the benzamide of a Gly-Phe-OMe and a Gly-Val-OMe dipeptide, containing a benzamide connection (Figure 1b) were prepared by using solution peptide chemistry (see SI for details). In these monomers, the chiral residue —*L*-pheanylalanine or *L*-valine amino acids— used as chiral inductor is located at the opposite end of the polymerizable group in the dipeptide, the 4-ethynylanilide for *N*-connection and 4-ethynylbenzamide for the *C*-connection (Figure 1).

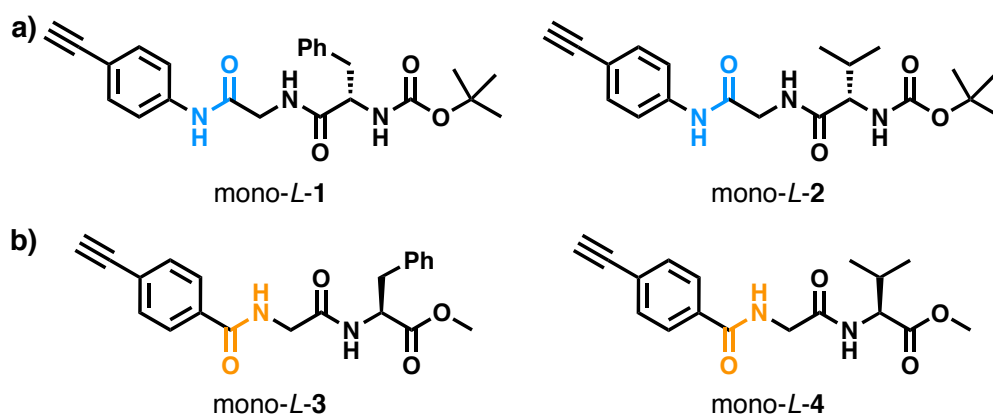


Figure 1. Structures of monomers bearing pendant groups with a spacer formed by one glycine unit (a) *N*- and (b) *C*-attached to the backbone.

Next, monomers (**1-4**) were submitted to polymerization by using $[\text{Rh}(\text{nbd})\text{Cl}]_2$ as catalyst in THF (see SI for details). The corresponding polymers, [poly-*L*-(**1-4**)] were obtained in high yield and high *cis* content of double bonds (see SI for details) (Figure 2).

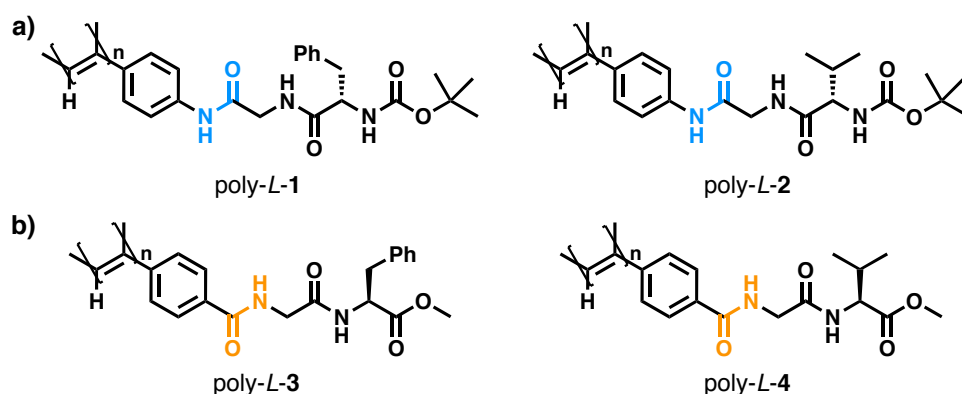


Figure 2. Chemical structure of polymers, poly-*L*-(**1-4**).

Next, ECD studies in different solvents were carried out for poly-*L*-(**1-4**) to determine the dynamic behavior of these polymers.

Anilide PPAs: In the case of anilide-(PPA)s, such as poly-*L*-**1** and poly-*L*-**2**, three helical scaffolds, with different elongation degrees were obtained, fact that indicates as expected the presence of different structural motifs at the pendant groups.

Thus, a highly compressed helix was adopted by poly-*L*-**1** and poly-*L*-**2** in low-polar and non-donor solvents such as chloroform (CHCl₃) or dichloromethane (CH₂Cl₂) (Figure 3). The presence of a helical structure was corroborated by optical rotation measurements, where the values obtained for poly-*L*-**1** and poly-*L*-**2** are one order of magnitude higher than those obtained for the corresponding monomers, mono-*L*-**1** and mono-*L*-**2** (see SI Table S3). These compressed helices were obtained due to the presence of an extended conformation at the pendant group, where the two amino acid residues adopted an *anti*-conformation between amide groups. This *anti*_{gly}-*anti*_{phe/val} conformation at the pendant group is the less congested one, placing the chiral group and the larger substituents in the most remote possible position (Figure 3). As a result, a highly compressed helix was formed (helix **1**), where polyene bands located at 288 nm reveals a poor conjugation between double bonds, result of the compressed helix, and where the negative sign of the ECD spectra indicated a *M* orientation of the polyene backbone (Figure 3). Very similar results were obtained for poly-*L*-**1** and poly-*L*-**2** indicating a structural behavior that can be extrapolated to other anilide-gly-aa dipeptides.

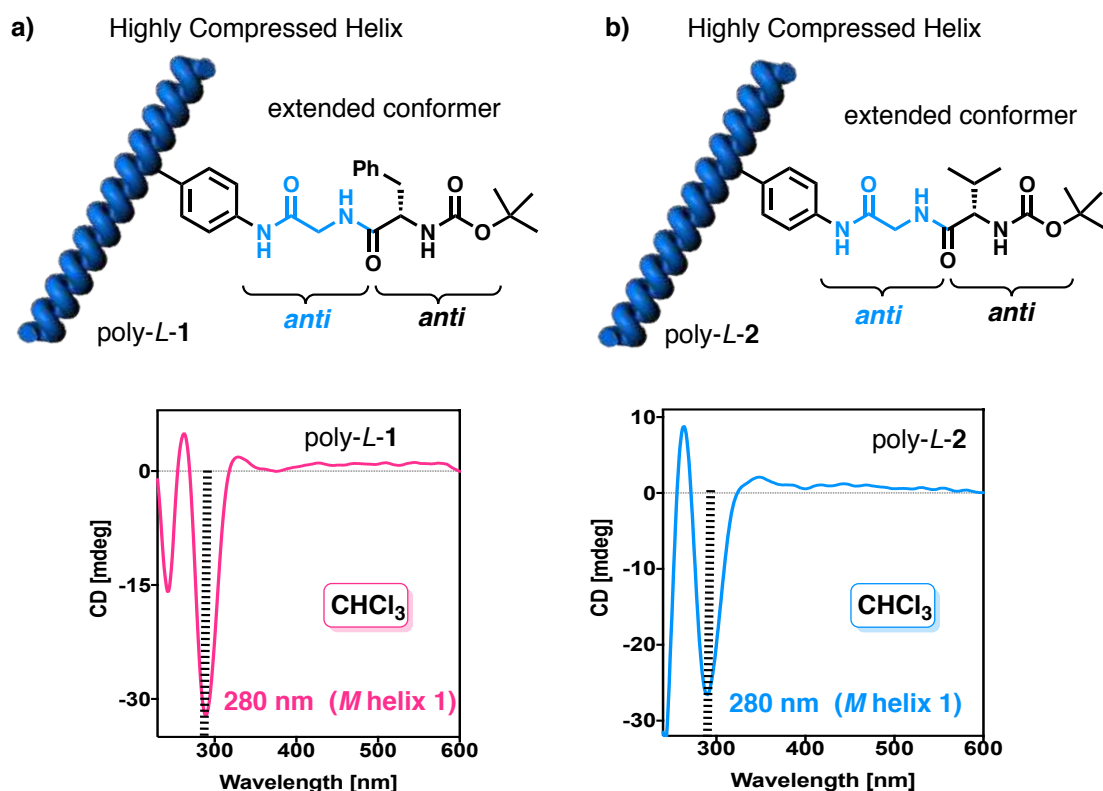


Figure 3. ECD spectra of (a) poly-L-1 and (b) poly-L-2 in CHCl_3 indicating the presence of a highly compressed helix (helix 1).

However, when polymers poly-L-1 and poly-L-2 were dissolved in more polar solvents such as THF, a bathochromic shift of the polyene band from 280 nm to 380 nm was observed, revealing the presence of a more elongated helix (helix 2) (Figure 4). In this case, the helical sense induced in the polyene band of the PPA was kept into a counterclockwise orientation (*M* helix 2), as inferred from the negative sign of the Cotton band at 380 nm (Figure 4). This helical sense can be explained by a *anti* to *syn* conformational change at the glycine residue, remaining the chiral residue, Phe or Val, in an *anti*-conformation. Analogous results were obtained for poly-L-1 and poly-L-2 indicating a structural behavior that can be extrapolated to other anilide-gly-aa dipeptides.

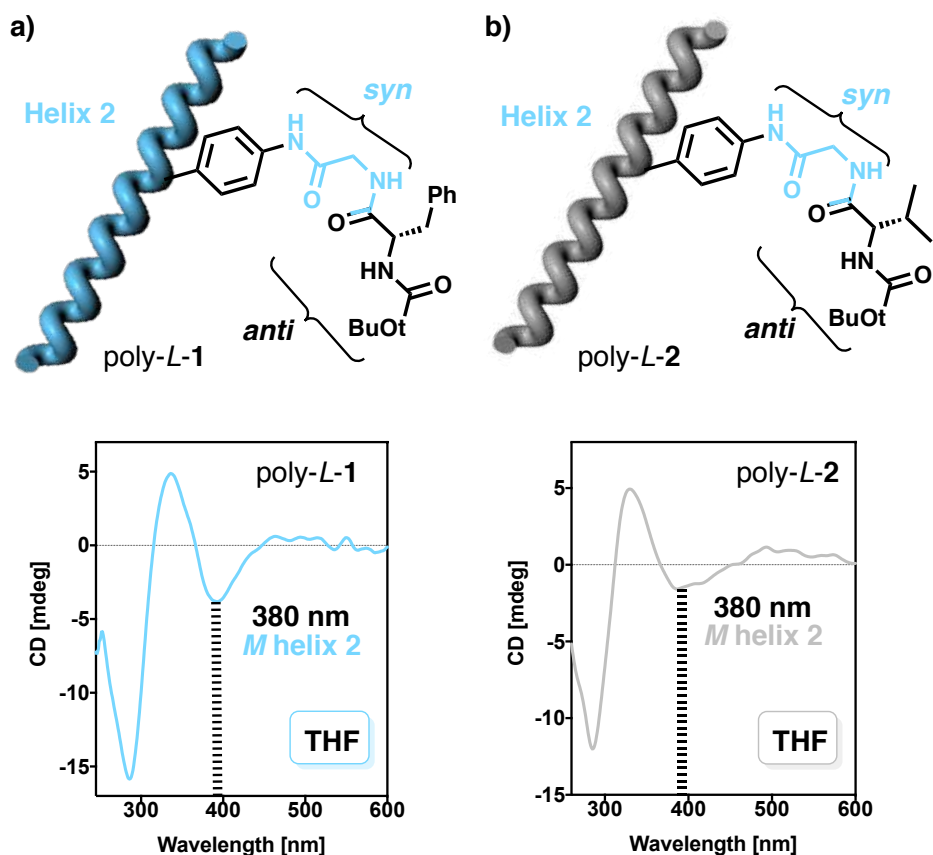


Figure 4. ECD spectra of (a) poly-L-1 and (b) poly-L-2 in THF showing the presence of a more stretched helix (helix 2).

Interestingly, the *M* helical sense adopted by poly-L-1 and poly-L-2 can be inverted by using MeOH as solvent to dissolve the polymers. In this case, a positive Cotton band was obtained for the polyene band at 380 nm, indicative of the presence of a *P* helix 2 (Figure 5). This change in the screw sense of poly-L-1 and poly-L-2, without modifying the polymer scaffold was due to an *anti* to *syn* conformational change at the chiral residue, preserving the *syn* conformation of the glycine residue. Thus, while in THF the pendant group of poly-L-1 and poly-L-2 adopted a preferred *syn*_{gly}-*anti*_{phe/val} conformation, in MeOH, the pendant adopted a preferred *syn*_{gly}-*syn*_{phe/val} conformation.

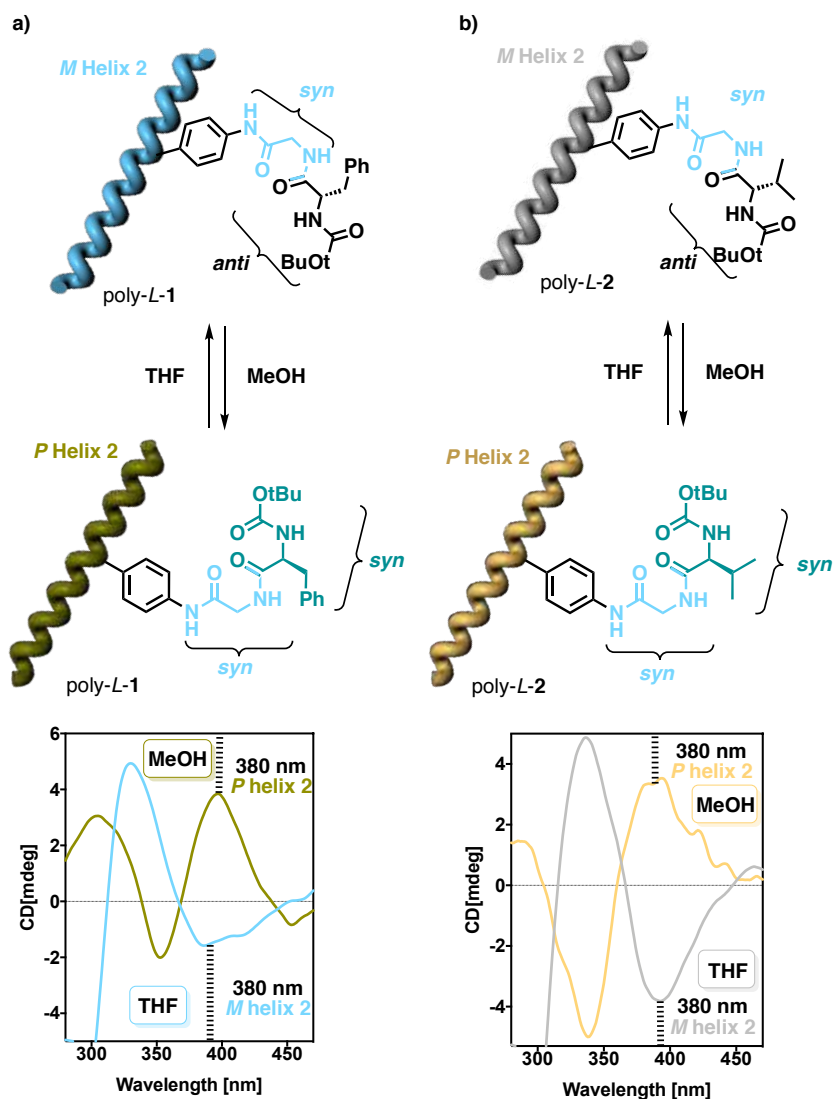


Figure 5. ECD spectra of (a) poly-L-1 and (b) poly-L-2 in THF and MeOH which reflected a conformational change at the chiral residue in the pendant (helix 2).

To corroborate the presence of a *syn*_{gly}-*anti*_{phe/val} and a *syn*_{gly}-*syn*_{phe/val} conformation at the pendant group, Ba(ClO₄)₂ was added as external stimulus to a chloroform solution of poly-L-1 and poly-L-2, where the pendant adopted a preferred *anti*_{gly}-*anti*_{phe/val} conformation. From previous studies, it is known that this metal produced a tripodal chelate with (PPA)s bearing dipeptides at the pendant.²⁷ It was found that a low equivalents of Ba(ClO₄)₂ —poly-L-(1-2)/Ba²⁺ 1/0.75 mol/mol ratio— a tripodal chelate was formed between the dipeptide pendant group and the metal ion. As consequence, an *anti* to *syn* conformational change is produced at the two amino acids, which results in an elongation of the polymer scaffold from helix 1 (280 nm) to helix 2 (380nm), accompanied with a helix inversion, from *M* to *P* (Figure 6).

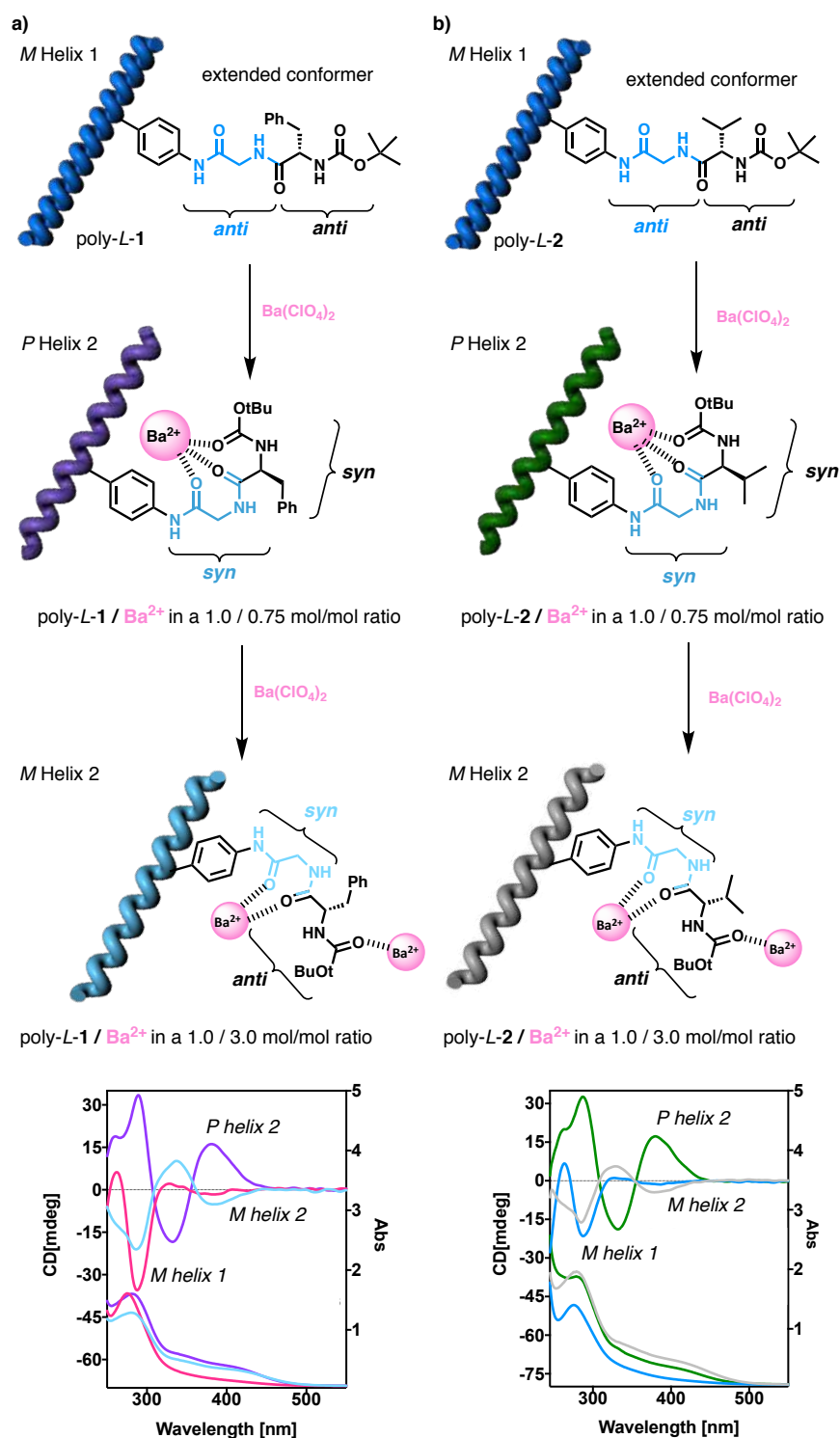


Figure 6. ECD spectra of (a) poly-L-1 and (b) poly-L-2 in chloroform before and after addition of different equivalents of $\text{Ba}(\text{ClO}_4)_2$.

From literature, it is known that the tripodal chelate between a dipeptide pendant a the Ba^{2+} ion can be disrupted by addition of an extra amount of $\text{Ba}(\text{ClO}_4)_2$. In that case, one Ba^{2+} ion should coordinate the glycine residue maintaining a *syn* conformation (helix 2),

while another metal ion will coordinate the Boc group producing a conformational shift from *syn* (*M*) to *anti* (*P*) into the chiral amino acid. As expected, when the amount of $\text{Ba}(\text{ClO}_4)_2$ increased until reach a poly-*L*-(**1-2**)/ Ba^{2+} 1/3 mol/mol ratio, a helix inversion was produced, from *P* to *M*, while no changes in the polymer elongation were produced.

As expected therefore, by playing with the proportion poly-*L*-(**1-2**)/ Ba^{2+} mol/mol ratio in chloroform, was possible to obtain either the *P* (1/0.75 mol/mol ratio) or *M* (1/3 mol/mol ratio) helical sense of an elongated helix (helix **2**) in a similar manner than when the polymers were dissolved in THF (*M* helix **2**) or MeOH (*P* helix **2**) (Figure 6). Intriguingly, poly-*L*-**1** and poly-*L*-**2** showed a similar behavior and stimuli responsive properties towards solvents and Ba^{2+} ions, which indicated that this structural behavior that can be extrapolated to other (PPA)s bearing anilide-gly-aa dipeptides as pendants.

Finally, a third helical scaffold was obtained when poly-*L*-**1** and poly-*L*-**2** were dissolved in ketone solvents (acetone, benzylacetone, butanone...). In these solvents, poly-*L*-**1** and poly-*L*-**2** adopted the most stretched scaffold as inferred from the bathochromic shift of the polyene band in the ECD spectra ($\lambda = 450 \text{ nm}$), which suggested a more conjugation of the polyene backbone (Figure 7). This stretching of the helical scaffold can be only explained by the adoption of a bent structure at the dipeptide pendant group, which located the pendant group close to the backbone inducing a polymer elongation to release the steric hindrance generated. Considering either the twisted conformation adopted by the pendant in THF (*syn*_{gly}-*anti*_{phe/val}) or MeOH (*syn*_{gly}-*syn*_{phe/val}) and the acidity of the anilide group, which can interact easily with anions and even be deprotonated by mild bases, a bent structure had to be adopted by the dipeptide in acetone stabilized probably by a hydrogen bond between the NH of the anilide and the carbonyl group of the chiral amino acid. This bent structure at the pendant affected only to the elongation of the PPA, and not to the *P/M* helical sense, because the glycine residue involved in this structural motif had no helix induction power.

By looking at the ECD spectra of poly-*L*-**1** and poly-*L*-**2** in acetone was possible to observe that both polymers adopted a similar scaffold (elongation) but with opposite helical sense (Figure 7). This fact was due to a different conformation at the chiral moiety, being *anti* for the Phe residue of poly-*L*-**1** and *syn* for the Val residue of poly-*L*-**2**.

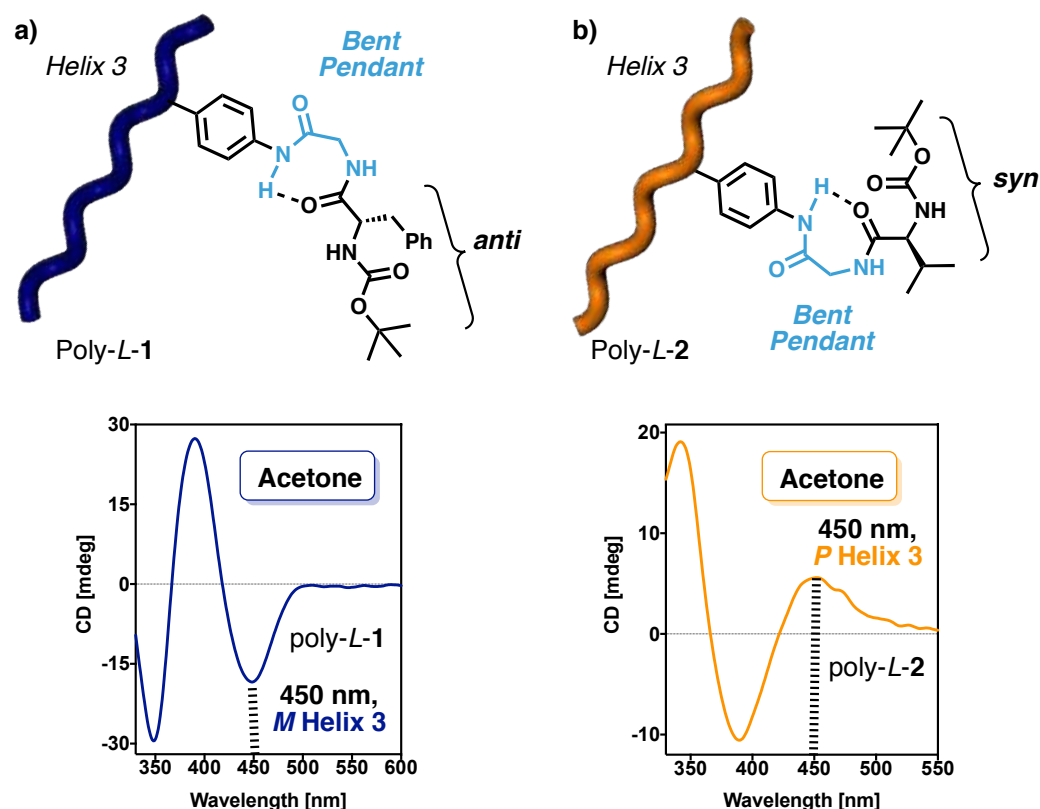


Figure 7. ECD spectra of (a) poly-L-1 and (b) poly-L-2 in Acetone displaying the presence of the most stretched helix (helix 3).

To demonstrate that this stretched helix 3 was formed due to an intra-pendant hydrogen bond interaction that forced a bent structure, a H-bond disruptor such as TBAF was added to a solution of poly-L-1 and poly-L-2 in acetone. TBAF is a source of fluoride anions, which interact strongly with amide groups and are frequently used to disrupt H-bond interactions between amide groups. ECD studies before and after addition of TBAF showed a structural change in poly-L-1 and poly-L-2 once the fluoride anions were present in solution (Figure 8). In this case, a compression of the helical scaffold from helix 3 to helix 2 was obtained, indicative of a *syn* conformation at the glycine residue. In both polymers, a *P* helix 2 was obtained which reveals a *syn*_{gly}-*syn*_{phe/val} conformation at the pendant group for both polymers.

Moreover, ECD studies of poly-L-1 and poly-L-2 in acetone disclosed that while the same bent conformation was stabilized in the achiral glycine residue for both polymers, a different *syn* or *anti* conformation was stabilized at the chiral amino acid. Therefore,

considering this fact and the similar stimuli responsive properties shown by poly-L-1 and poly-L-2, it is expected to induce either a *P* or *M* helical sense in the helical scaffold helix.

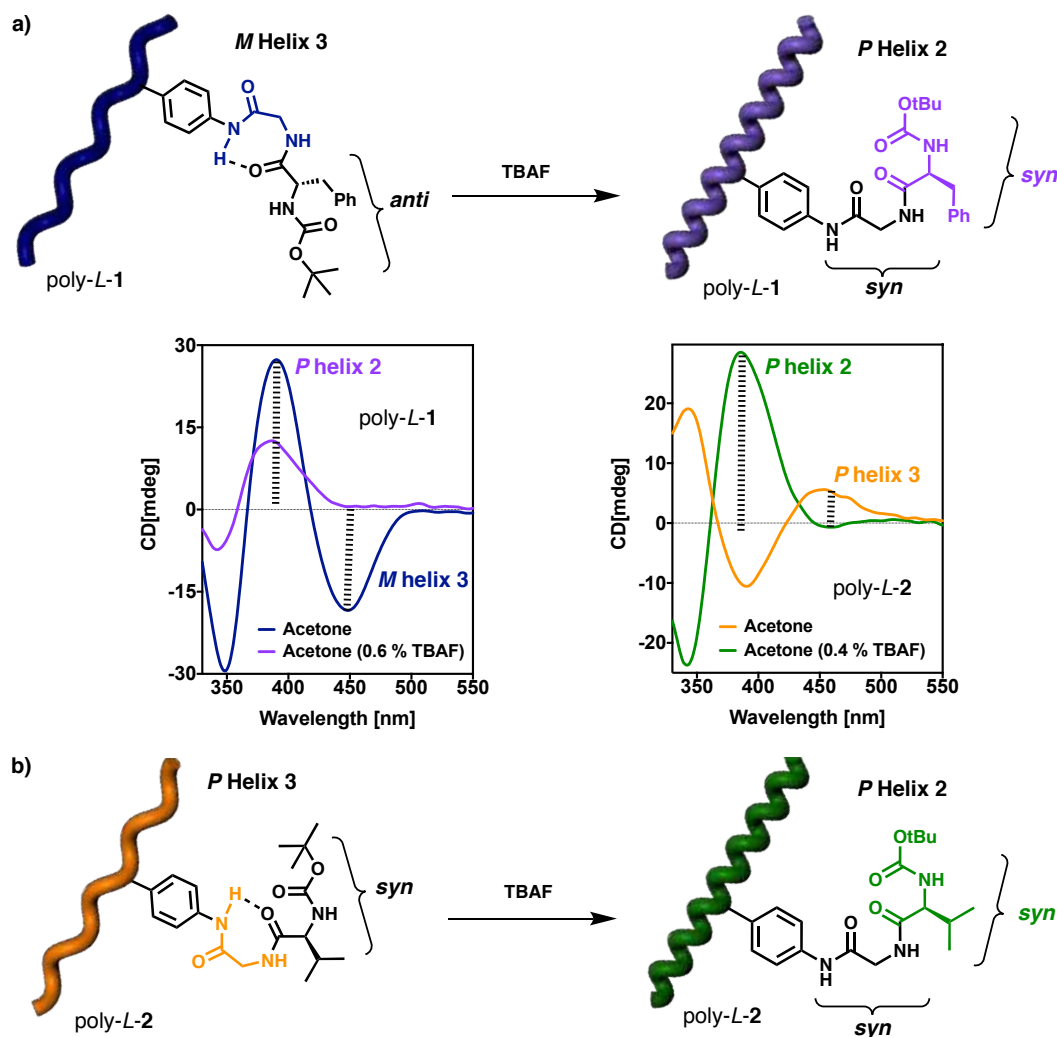


Figure 8. ECD spectra of (a) poly-L-1 and (b) poly-L-2 in Acetone before and after the addition of TBAF.

Thus, poly-L-1 and poly-L-2 were dissolved in different solvents and different additives were added to achieve this goal, a *P* helix 3 for poly-L-1 and a *M* helix 3 for poly-L-2. Therefore, a *P* helix 3 was induced in poly-L-1 in THF after addition of TBAF (Figure 9), demonstrating the dynamic behavior of this helical scaffold (helix 3) where the two *P* and *M* helical senses can be selectively induced for poly-L-1. Regretfully, *M* helix 3 for poly-L-2 could not be obtained.

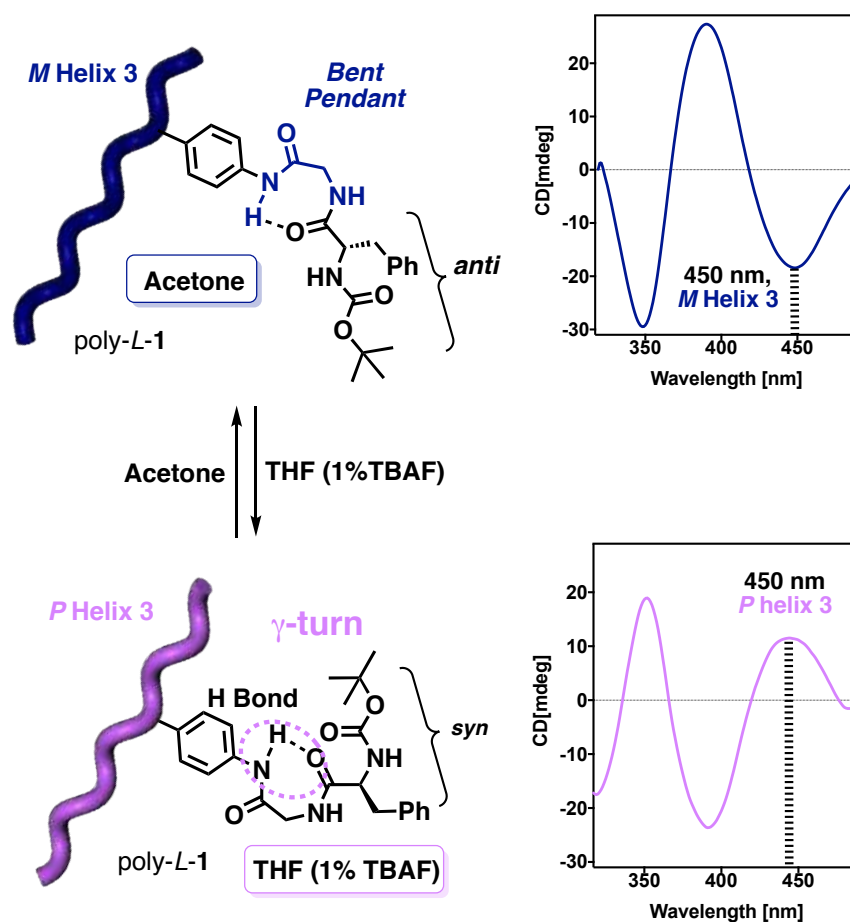


Figure 9. Conceptual illustration of the structure and ECD spectra of poly-L-1 after the addition of TBAF in THF which reflected a conformational change at the chiral residue in the pendant.

Benzamide PPAs: In the case of benzamide-(PPA)s, such as poly-L-3, the scaffold variability was drastically reduced. ECD studies showed that PPA in all solvents tested the same *M* helical sense ($ECD_{380} < 0$) was induced in the PPA (Figure 10). This fact indicated that in Gly-AA dipeptides connected through the *N*-terminus to a poly(phenylacetylene) backbone (benzamide linkage) the conformational variability at the pendant group is reduced to the classical extended β -sheet orientation. DSC studies suggested the presence of a *cis-transoidal* polyene backbone. Moreover, UV-Vis and ECD studies show small bathochromic effect when poly-L-3 was dissolved in polar solvents, this fact was due to a slight stretching of the polyene scaffold. *Cis-transoidal* structures are in general stretched helices where small variations in the dihedral angle between conjugated double bonds results in large variations in the UV-Vis band of the polyene backbone.

Thus, in this polymer variations in solvent polarity or donor character did not affect to the conformational composition of the gly-Phe dipeptide. This fact was probably due to

the less acidic character of the benzamide connection in comparison to the anilide one, and therefore intra-pendant hydrogen bonds were less favored.

No ECD studies could be performed for poly-*L*-4 due to solubility problems.

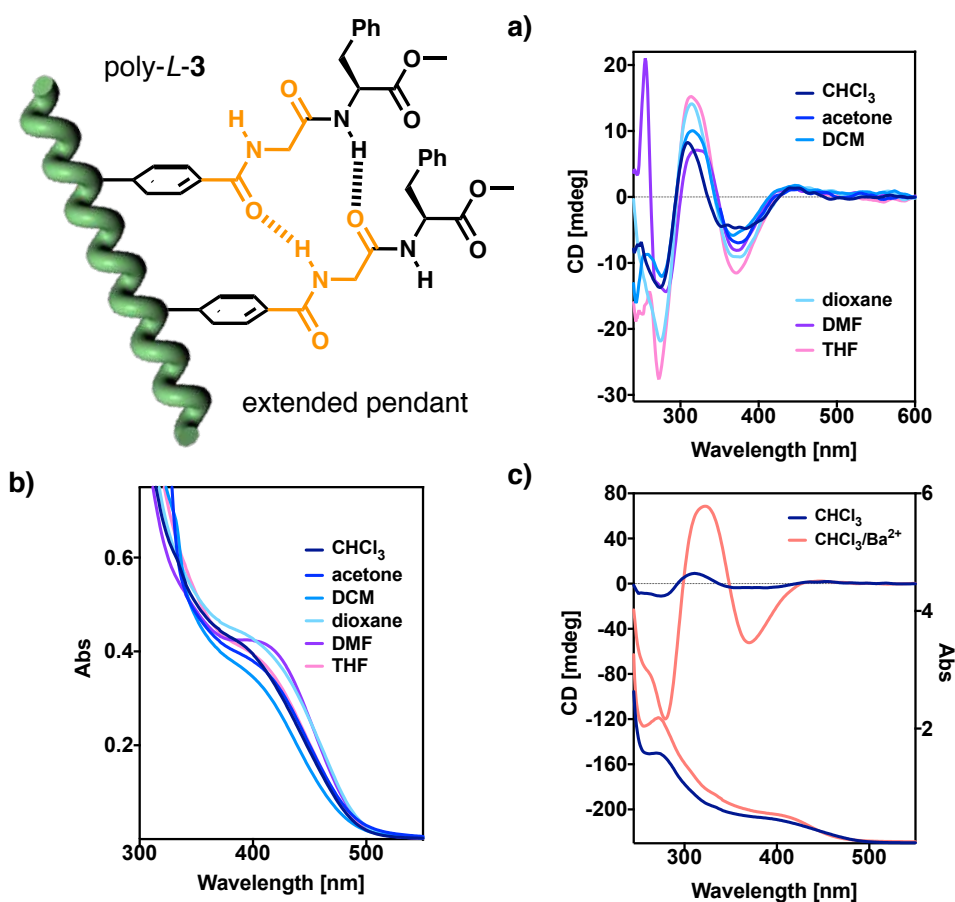


Figure 10. (a) ECD and (b) UV-Vis spectra of poly-*L*-3 in different solvents. (c) ECD spectra of poly-*L*-3 in CHCl₃ before and after the addition of TBAF.

Conclusions

In conclusion, in this work we have demonstrated that the introduction of a flexible and an achiral spacer between the chiral center and the polyene backbone can result not only in an effective helix induction due to a correct transmission of the chiral information from the chiral pendant to the polyene backbone, but also in the possibility of creating different helical scaffolds with different elongations as consequence of different structural arrangements —extended, bent structures— at the achiral spacer. More precisely, we have been able to create five different helical structures for a PPA that bears the anilide of a gly-AA-Boc dipeptide (AA = Phe, Val) — *M* helix 1, *P* helix 2, *M* helix 2, *P* helix 3, *M* helix

3—, by playing with the conformational composition at the glycine residue which allowed us to create three different scaffolds (from compressed to stretched: helix **1**, helix **2**, helix **3**), and the conformational composition at the chiral amino acid which allowed us to play with the *P/M* helical orientation of the different scaffolds.

RESUMO

Resumo

Esta tese doutoral titulada: “Mecanismos de indución helicoidal en poli(fenilacetileno)s portando oligopéptidos como cadeas laterais”, inclúe catro proxectos de investigación nos que se abordarán tanto o estudo das estruturas, o comportamento dos polímeros helicoidais covalentes como os mecanismos de transferencia da información quiral nos mesmos. Finalmente, a información recadada nestas pescudas será combinada, xerando así un novo material no que estes motivos están presentes. A continuación expoñeranse os resultados máis relevantes de cada capítulo.

Capítulo I. Control Total do Efecto *Sorpasso* Quiral en Polímeros Helicoidais: Indución do Sentido Helicoidal *P/M* por Centros Quirais Remotos Despois de Pasar por Alto o Primeiro Residuo Quiral.

Neste traballo estudáronse as propiedades e o comportamento dinámico dunha serie de polímeros helicoidais que conteñen cadeas laterais con dous centros quirais. O obxectivo é observar cambios estruturais sobre a hélice comparando os novos resultados cos polímeros que conteñen cadeas laterais máis sinxelas (formadas por un único centro quiral). En bibliografía existen varios exemplos de poli(fenilacetileno)s que conteñen máis dun centro quiral nas súas cadeas laterais pero a súa helicidade esta gobernada polo centro quiral máis próximo ó esqueleto helicoidal, sendo o responsable de que o polímero presente un sentido de xiro helicoidal preferente (*P* ou *M* dependendo da configuración absoluta de dito centro quiral). Para sintetizar estas macromoléculas, realizouse previamente un deseño e síntese dos correspondentes monómeros. Estas unidades están formadas por un aminoácido como primeiro residuo quiral (*S*- e/ou *R*-alanina) e polo ácido (*R* ou *S*)- α -metoxi- α -fenilacético (MPA) como segunda unidade quiral, conformando así a cadea lateral dun total de catro monómeros [(*S*)-ala-(*S*)-MPA, (*S*)-ala-(*R*)-MPA, (*R*)-ala-(*S*)-MPA e (*R*)-ala-(*R*)-MPA]. A continuación, levouse a cabo a polimerización destes catro monómeros empregando un catalizador de rodio (I) que proporciona polímeros helicoidais en bo rendemento, baixa polidispersidade e alto contido *cis*- dos dobres enlaces conxugados, responsables de adoptar unha estrutura helicoidal. Unha vez sintetizados, caracterizáronse medinte diferentes técnicas tales como RMN, IR, GPC, TGA, DCS, Raios-X, VCD, Raman, UV-Vis, e ECD, entre outras.

Os estudos de Raios-X da parella de enantiómeros (*S*)-ala-(*S*)-MPA e (*S*)-ala-(*R*)-MPA amosaron unha estrutura estendida en forma de lámina β dos dous residuos (a alanina e o ácido MPA). Sen embargo, entre todas as técnicas nomeadas, foi o Dicroísmo Circular o que nos permitiu realizar un estudo conformacional e analizar o carácter helicoidal dos polímeros en disolución para coñecer de primeira man se estas macromoléculas presentan un sentido de xiro helicoidal maioritario e, ó mesmo tempo, identificar qué residuo quiral goberna a helicidade destes polímeros helicoidais.

No referente ó estudo conformacional, estes experimentos mostraron diferenzas substanciais no pregamento final dos polímeros. No sistema homoquiral (*S*)-ala-(*S*)-MPA disolventes pouco polares (cloroformo) promoveron a formación dunha estrutura xirada na cadea lateral debido á formación de enlaces de hidróxeno intramoleculares, mentres que disolventes máis polares (DMSO) interactúan cos grupos anilida e por conseguinte rompen ditos enlaces supramoleculares, ocasionando a adopción dunha estrutura estendida en forma de lámina β . Este cambio de estrutura na cadea lateral foi facilmente rexistrado mediante estudos de ECD/UV-Vis en ambos disolventes que amosaron unha variación no grado de elongación dos polímeros en total acordo coa presenza das estruturas estendida e xirada: hélices máis estiradas en estruturas xiradas (cloroformo) e hélices máis comprimidas en estruturas estendidas (DMSO).

Para corroborar a presenza deste equilibrio entre as estruturas xirada e estendida promovido pola activación/desactivación do enlace de hidróxeno intramolecular, engadíronse estímulos externos como o ácido trifluoroacético (TFA) ou catións metálicos $[(\text{BaClO}_4)_2]$ a unha disolución do polímero (*S*)-ala-(*S*)-MPA en cloroformo. O resultado foi un espectro de ECD/UV-Vis parecido ó obtido en DMSO, é dicir, observouse o cambio dunha hélice estirada cunha conformación xirada da cadea lateral a unha hélice comprimida cunha conformación estendida. Os mesmos estudos leváronse a cabo para o outro sistema homoquiral [(*R*)-ala-(*R*)-MPA] onde se observaron os mesmos efectos de estiramento e sentidos helicoidais opostos debido a súa relación enantio/diastereomérica.

No referente ó carácter helicoidal dos polímeros realizáronse estudos de ECD en cloroformo e DMSO co fin de determinar cómo os cambios conformacionais na cada lateral poden afectar ó exceso do sentido helicoidal do esqueleto poliénico. Estes estudos permitíronnos tamén identificar se este exceso é debido a influencia do primeiro residuo quiral ou se, pola contra, ten lugar o chamado efecto *sorpasso* quiral sendo o segundo

residuo o que comandaría o sentido de xiro. Tal e como se agardaba, cando a cadea lateral adopta un estrutura estendida (DMSO) o sentido helicoidal está determinado polo residuo quiral máis achegado ó esqueleto poliénico (a alanina). Como consecuencia, ambos polímeros amosaron un efecto Cotton negativo (hélice *M*) a pesar de que a configuración absoluta do segundo grupo quiral (MPA) é diferente. Pola contra, en cloroformo produciuse una inversión do sentido helicoidal ó cambiar a configuración absoluta do MPA, pasando dunha hélice *M* a unha hélice *P*. Este feito demostra a activación do efecto *sorpasso* quiral en cloroformo debido á formación da estrutura xirada na cadea lateral, colocando o segundo residuo máis próximo a cadea polimérica e sendo responsable da helicidade destes polímeros.

Non só se demostrou que o efecto *sorpasso* quiral ten lugar senón que se logrou un control total sobre o mesmo mentres o fragmento de alanina permanece nunha estrutura xirada. Isto foi posible xogando coa composición conformacional do MPA mediante cambios na polaridade do disolvente que non provocasen a rotura do enlace intramolecular que mantén o xiro no fragmento da alanina. Desde xeito, mentres disolventes pouco polares como cloroformo favorecen unha conformación *antiperiplanar* no MPA, un incremento na polaridade do disolvente (ciclohexanona e acetona) favorece a adopción dunha conformación *sinperiplanar* no MPA. Os espectros de ECD para os polímeros en cloroformo, acetona e ciclohexanona amosaron (PPA)s con grados de elongación similares pero con sentidos helicoidais opostos: os sistemas heteroquirais adoptaron unha hélice *P* en cloroformo e unha hélice *M* en acetona o ciclohexanona. Esta inversión de helicidade é ocasionada polo cambio conformacional no segundo residuo quiral (MPA) cando pasa dunha conformación *antiperiplanar* (cloroformo) a unha *sinperiplanar* (acetona o ciclohexanona) colocando o anel aromático en diferentes orientacións, producindo así a inversión. No caso dos polímeros homoquirais os resultados foron opostos xa que muda a configuración absoluta do segundo grupo quiral que é o que goberna a helicidade: adopta unha hélice *M* en cloroformo e unha hélice *P* en acetona o ciclohexanona.

Polo tanto, neste traballo demostramos cómo cambios conformacionais en cadeas laterais que presentan dous centros quirais inflúen no sentido de xiro de xeito diferente a cando só existe un único centro quiral, conseguindo incluso que a unidade quiral máis alonxada do esqueleto poliénico sexa capaz de adoptar una estrutura específica e inducir

unha helicidade predominante no polímero, superando de maneira efectiva á orde que o primeiro grupo quiral puidera inducir sobre o mesmo.

Capítulo II. Cadeas Laterais Multi-quirais Diastereoméricas: O seu Papel Clave nas Respostas Poliméricas Sensibles a Estímulos

Como se mencionou con anterioridade, a helicidade da meirande parte dos poli(fenilacetileno)s que conteñen máis dun centro quiral está determinada pola configuración absoluta do residuo quiral máis próximo á cadea polimérica. Sen embargo, no primeiro capítulo desta tese de doutoramento demostrouse non só que o segundo residuo é capaz de comandar o sentido de xiro senón que tamén somos capaz de obter un control total sobre o chamado efecto indutivo *sorpasso* quiral.

Neste novo traballo estudáronse as propiedades de resposta a estímulos en polímeros diastereoméricos, novamente con dous grupos quirais formando a súa cadea lateral, obtidos ó cambiar a configuración absoluta do segundo residuo quiral. Sábese que as propiedades químicas e físicas dos compostos diastereoméricos son diferentes, e polo tanto, espérase que as súas propiedades de resposta a estímulos, como a polaridade dos disolventes, sexan diferentes. Para levar a cabo este propósito, deseñamos un monómero de fenilacetileno que contén un aminoácido como primeiro residuo quiral (*L*-valina) conectado ó ácido (*R*)/(*S*)- α -metoxi- α -fenilacético (MPA) como segunda unidade quiral, conformando así a cadea lateral dun total de dous monómeros con relación diastereomérica [(*S*)-val-(*S*)-MPA, (*S*)-val-(*R*)-MPA]. A continuación, levouse a cabo a súa polimerización [obtendo deste xeito poli-(*S*)-val-(*S*)-MPA e poli-(*S*)-val-(*R*)-MPA] empregando o catalizador de rodio (I) anteriormente descrito. Este polímeros amosaron a presenza de dous conformacións —*sin* e *anti*— nas súas cadeas laterais controladas pola polaridade do disolvente sendo a valina (o primeiro residuo quiral) quen debe gobernar á helicidade. Pola contra, o papel do segundo residuo quiral é simplemente alterar a polaridade dos polímeros debido a súa relación diastereomérica.

Os estudos de ECD de ambos polímeros permitiron revelar diferenzas significativas do seu pregamento final segundo ó medio de disolución. Atopáronse dous efectos Cotton negativos fortes para ambos polímeros en disolventes pouco polares (DCM/cloroformo),

correspondentes a unha hélice *M* comprimida. Esta estrutura prodúcese cando as dúas amidas do grupo valina están orientadas en posición *anti*.

Pola contra, cando se realizaron os estudos de ECD para poli-(*S*)-val-(*S*)-MPA e poli-(*S*)-val-(*R*)-MPA en disolventes de polaridade media (THF) obtivéronse espectros completamente diferentes: mentres o polímero (*S*)-val-(*R*)-MPA mostrou un comportamento similar ó obtido en DCM/cloroformo, o polímero (*S*)-val-(*S*)-MPA presentou unha hélice máis estirada indicando a formación dunha hélice preferentemente *M* cun máximo a 390 nm. Este estiramento helicoidal é debido ó cambio conformacional de *anti* a *sin* no residuo de valina. De xeito análogo obtivéronse trazas de ECD similares para ambos polímeros en disolventes máis polares como DMF ou DMSO: unha estrutura helicoidal estirada *M* cun máximo a 390 nm correspondente as dúas amidas orientadas en conformación *sin*. No referente ó grado de elongación dos dous polímeros os espectros de UV-Vis amosaron un efecto batocrómico dende os 310 nm (DCM) ós 425 nm (DMSO) en total concordancia cos resultados obtidos mediante ECD. Finalmente, estes cambios conformacionais —de *anti* a *sin*— na cadea lateral puideron corroborarse cando se engadiron diferentes estímulos externos (TBAF, TFA ou perclorato de bario) a sendas disolucións de polímero en DCM. Estes estímulos externos interactúan cos grupos amida producindo un desprazamento no espectro de ECD dende unha hélice *M* comprimida a unha hélice estirada e de igual sentido de xiro.

Polo tanto, neste traballo demostramos as diferentes propiedades de resposta dos dous polímeros á estímulos, como a polaridade do disolvente, debido á súa relación diastereomérica. Así mesmo, corroborouse que estes cambios na polaridade do disolvente permiten controlar o cambio conformacional *anti/sin* no residuo de valina en ambos polímeros sendo capaz de detectar así un disolvente determinado.

Capítulo III. Engraxando Engrenaxes Macromoleculares: Inclusión de Espazadores Flexibles

En bibliografía existen varios exemplos de oligopéptidos (por exemplo, foldámeros) capaces de adquirir unha estrutura helicoidal en disolución estabilizada por enlaces de hidróxeno. Deste xeito, foldámeros formados por residuos aquirais de glicina presentan enerxías de interconversión de hélices *M* ou *P* moi baixas, o que facilita a súa aplicación

como sensores en presenza de diferentes estímulos externos. Existen varios exemplos de péptidos helicoidais onde a helicidade está determinada polo centro quiral conectado a un dos dous posibles extremos da cadea (C- ou N-terminal). Esta funcionalización permite que a estrutura helicoidal adopte unha helicidade preferente dacordo coa configuración absoluta e a conformación que adquira a unidade ópticamente activa. Este ordeamento estrutural sobre as unidades aquirais que forman o resto do esqueleto denomínase “Efecto Dominó” e foi amplamente estudado en foldámeros formados por grupos aquirais derivados do ácido α -aminoisobutírico (Aib), onde de maneira similar, a helicidade é definida polo centro quiral localizado nun dos seus extremos.

Tendo en conta esta información, neste capítulo da Tese explícase o deseño, síntese e estudo estrutural de catro oligopéptidos cunha hélice manipulable mediante estímulos externos. A cadea lateral destes foldámeros está formada por un espazador aquiral de glicina, que aportará flexibilidade, e diferente número de residuos aquirais ($n = 1, 2, 3, 4$) do ácido α -aminoisobutírico funcionalizado no seu extremo N-terminal por unha unidade quiral [o ácido α -metoxi- α -trifluoroacético (MTPA)] que promoveran a formación dunha hélice 3_{10} .

Os catro monómeros derivados de fenilacetileno caracterizáronse mediante diversas técnicas (IR, Raios-X, RMN...). Deste xeito, cristais dos monómeros obtidos por evaporación nunha mestura de diclorometano/hexano foron difractados observando a presenza de varias estrutura macromoleculares con sentidos de xiro opostos. Por unha parte os monómeros formados por unha, dúas e catro unidades quirais de Aib amosaron a coexistencia de dúas estruturas en estado sólido con helicidade opostas (P e M). En ditas estruturas a unidade quiral (MTPA) adquire unha conformación *antiperiplanar* entre os grupos metoxi e trifluoro responsable de que estes tres oligopéptidos adopten en disolución unha estrutura P - 3_{10} . A diferenza entre ambas estruturas, e polo tanto a que ocasiona os dous sentidos de xiro mencionados, é o ángulo dihedral $O=C-C-OMe$, practicamente oposto para cada estrutura. Finalmente a caracterización por Raios-X do monómero composto por tres residuos de Aib revelou a coexistencia no mesmo cristal de catro estruturas independentes relacionadas dúas a dúas por enlaces de hidróxeno. Cada parella amosou os dous sentidos helicoidais dunha hélice 3_{10} estabilizada por os enlaces de hidróxeno entre os residuos i e $i+3$. Novamente observouse unha conformación *antiperiplanar* nas dúas estruturas. Así mesmo, empregáronse outras técnicas como RMN,

ECD e Raman para estudar o comportamento dinámico e o pregamento destes oligómeros en disolución. Os estudos de RMN de NOE en diferentes disolventes amosaron os correspondentes picos de cruce entre os protóns que se sitúan preto no espazo, permitindo corroborar a adopción da conformación *antiperiplanar* descrita anteriormente. A adopción dunha hélice 3_{10} foi confirmada mediante a técnica de infravermello Raman, observando a banda responsable deste tipo de estruturas aproximadamente a 1670 cm^{-1} .

Por último realizáronse estudos de ECD para avaliar o comportamento helicoidal dos poli(fenilacetileno)s obtidos tras a polimerización dos correspondentes monómeros. Os polímeros formados por unha glicina e unha e dúas unidades aquirais de Aib (poli-**1** e poli-**2**) amosaron comportamentos análogos segundo o disolvente empregado: en disolventes de baixa polaridade (DCM/ CHCl_3) ambos polímeros amosaron a formación dunha hélice *M* na rexión vinílica ($\lambda = 380\text{ nm}$), mentres que en medios máis polares (DMF/THF) observouse unha inversión da helicidade (hélice *P*). Pola contra, os polímeros constituídos por un maior número de residuos (poli-**3** e poli-**4**) demostraron ser tamén uns sistemas eficientes para a transmisión da información quiral a pesar da posición aloxada do centro quiral ó esqueleto polimérico. Poli-**3** mostrou un carácter estático (hélice *M*) independentemente da polaridade do medio e unha variación da elongación mentres que poli-**4** amosou un carácter dinámico coa presenza dun equilibrio entre dúas estruturas helicoidais ca mesma helicidade pero diferente grao de elongación en disolventes máis polares.

Polo tanto, neste traballo demostramos que a introdución dunha glicina como espazador flexible no extremo *N*- dun oligómero formado por residuos de Aib non quirais entre a unidade polimerizable e o indutor quiral permiten o pregamento selectivo nun sentido de xiro *P* ou *M* simplemente modificando a polaridade do disolvente. Estes sistemas actúan como engraxes macromoleculares onde a helicidade e/ou elongación do esqueleto poliénico é controlado pola composición conformacional da unidade de MTPA.

Capítulo IV. Estruturas Multi-Helicoidais (ata Cinco Hélices) a partir de (PPA)s quirais cun Gly-AA como cadea lateral.

O noso grupo de investigación demostrou nos últimos anos a indución efectiva da helicidade —mediante o mecanismo da teleindución— en (PPA)s con cadeas laterais formadas por espaciadores flexibles aquirais conectados á cadea lateral mediante conexión *N*-terminal e funcionalizados no extremo *C*-terminal por un grupo quiral (por exemplo, MPA ou MTPA). Nestes polímeros obtense un exceso da helicidade debido a formación dunha estrutura estendida ben pregada e estabilizada por enlaces de hidróxeno na cadea lateral. Sen embargo, cando se introduciu unha segunda unidade aquiral de glicina na cadea lateral a transmisión da información quiral a través do espazo diminuíu de maneira drástica.

Neste traballo demos un paso máis na preparación de materiais sensibles a estímulos empregando o control remoto da helicidade dos (PPA)s. Sinterizáronse poli(fenilacetileno)s portando cadeas laterais cun espazador aquiral de glicina e un residuo quiral (aminoácidos de *L*-valina e *L*-fenilalanina) conectados á cadea poliénica mediante conexión *N*-terminal (anilida) o *C*-terminal (benzamida) que adoptaran diferentes motivos estruturais baixo diferentes estímulos externos.

En primeiro lugar realizáronse estudos de ECD para avaliar o comportamento helicoidal dos polímeros que presentan conexión anilida (poli-1 e poli-2). Para estes polímeros observouse a formación de tres andamios helicoidais con diferentes grados de elongación dependendo da polaridade do medio: unha hélice altamente comprimida (hélice **1**, $\lambda = 280$ nm) en disolventes pouco polares (cloroformo ou diclorometano); unha estrutura menos comprimida (hélice **2**, $\lambda = 380$ nm) en disolventes polares (THF ou metanol) e unha terceira hélice estirada (hélice **3**, $\lambda = 450$ nm) en disolventes máis polares (acetona). A adopción destas tres estruturas helicoidais é consecuencia dos cambios producidos na composición conformacional da cadea lateral que dependen da disposición adoptada polos grupos carbonilos: teremos unha conformación *anti*_{gly}-*anti*_{phe/val} a $\lambda = 280$ nm (hélice **1**), unha conformación *sin*_{gly}-*sin*_{phe/val}/*sin*_{gly}-*anti*_{phe/val} a $\lambda = 380$ nm (hélice **2**) e una disposición xiro γ _{gly}-*sin*_{phe/val}/xiro γ _{gly}-*anti*_{phe/val} a $\lambda = 450$ nm (hélice **3**). No referente ó sentido helicoidal adquirido por estas estruturas obtivéronse hélices con xiro á esquerda (hélice *M*) cando poli-1 e poli-2 foron disoltos en CHCl₃/DCM (*anti-anti*) e THF (*sin-anti*).

Sen embargo, produciuse unha inversión da helicidade, de *M* a *P*, cando poli-**1** e poli-**2** foron disoltos en metanol debido ó cambio conformacional, de *sin-anti* (*M*) a *sin-sin* (*P*) dos grupos carbonilo, producido na cadea lateral. A formación das distintas composicións conformacionais corroborouse medinte a aplicación de estímulos externos tales como a adición de ións metálicos (sales de litio ou bario).

Curiosamente poli-**1** e poli-**2** amosaron a formación dunha terceira estrutura helicoidal —estabilizada por enlace de hidróxeno intramolecular— en disolventes máis polares, como a acetone, cunha elongación similar pero con sentidos de xiro opostos debido a diferente conformación da unidade quiral: *anti* na fenilalanina de poli-**1** e *sin* na valina de poli-**2**. A formación desta hélice **3** tamén puido ser corroborada mediante a adición dun disruptor de enlaces de hidróxeno como son as sales de TBAF que ó ser engadido a unha disolución destes polímeros en acetona produciu a rutura de este enlace intramolecular dando lugar á hélice **2**.

Finalmente os estudos de ECD para os polímeros portando os aminoácidos quirais conectados ó esqueleto polimérico mediante conexión benzamida (poli-**3** e poli-**4**) mostraron a formación dun único andamio helicoidal (hélice *M*) para poli-**3** debido a formación dunha estrutura ben pregrada como é a lámina beta. Desafortunadamente, non se puido estudar o carácter helicoidal de poli-**4** debido a súa alta insolubilidade.

Polo tanto, neste traballo demostramos que a introdución dun espazador aquiral e flexible entre o centro quiral e o esqueleto poliínico resulta non só nunha correcta transmisión da información quiral a través do espazo senón tamén na posibilidade de crear diferentes estruturas poliméricas con diferentes elongacións como consecuencia de diferente disposición estrutural, estendida ou xirada, adoptada polo espazador aquiral. Así mesmo, o carácter ácido da amida dos sistemas que presentan conexión anilida demostrou xogar un papel fundamental na adopción das diferentes estruturas helicoidais.

CONCLUSIONS

Conclusions

This thesis is focused on the development of new synthetic chiral materials based on poly(phenylacetylene)s (PPA)s bearing two types of pendant groups: one formed by more than one chiral center and another one constituted by flexible linkers and a chiral motif located in remote position to the polyene main chain. Their chiral information transmission mechanisms, dynamic helical behavior and stimuli-responsive properties were studied, leading to promising new materials for the future rational design of novel smart materials with specific properties.

Through the different chapters, it was described the synthesis and characterization of new dynamic *para*-substituted (PPA)s. This finding open new possibilities of applications for these materials.

Following, the main conclusions for each chapter are summarized below.

Chapter I. Full Control of the Chiral Overpass Effect in Helical Polymers: *P/M* Screw Sense Induction by Remote Chiral Centers After Bypassing the First Chiral Residue.

This work demonstrates how the chiral overpass induction effect can be totally tamed, by introducing in the pendant groups of (PPA)s two chiral residues, which show independent and selective conformational control. As a result, it is possible to selectively induce an excess of *P* or *M* helical sense in the PPA main chain by varying the conformational composition at the second chiral residue through a chiral overpass effect. This polymer switch is achieved by a thorough design of the monomeric repeating unit. In our case, an alanine residue in either (*S*) or (*R*) configuration was introduced to link the pendant group to the PPA backbone through an anilide linkage and to play between an extended and a bent structure due to a conformational control in this group. Moreover, a second chiral residue consisting of (*R*)- or (*S*)- α -methoxyphenyl acetic acid was added to the pendant through the *N*-terminus of the aniline. This second chiral residue shows a conformational composition between two major conformers that places the bulkiest substituent, phenyl, in opposite directions and will allow the helical sense of the PPA to be controlled by means of a chiral overpass effect that occurs when alanine adopts a bent structure. As a result, when alanine adopts an extended structure, the second chiral residue is placed far from the polyene backbone. Thus, the helical sense adopted by the

PPA is commanded by the chirality of the alanine, while changes in the absolute configuration of the second chiral center or conformational changes at this residue does not affect the helical sense of the PPA. In contrast, when alanine adopts a bent structure, both conformational changes and changes in the absolute configuration of the MPA moiety result in a helix inversion in the PPA. This fact indicates that a total control of chiral overpass effect is achieved.

To our knowledge, this is the first time that a chiral overpass effect has been tamed, making it possible to induce both helical senses in the PPA by changes in the conformational composition of the second chiral residue (MPA). As a remarkable result, three different helices are produced in the PPA by varying the conformational composition in the monomer repeating unit. This unique and novel helical sense control portrayed here opens promising prospects in advanced helical sense control of (PPA)s and can be applied to develop new multi-stimuli responsive chiral polymeric materials with enhanced applications as sensors, as chiroptical switches or in chiral recognition, among many others.

Chapter II. Diastereomeric Multi-Chiral Pendant Groups: Their Key Role in Stimuli-Responsive Polymeric Responses.

In this chapter, it has demonstrated that although the helical senses induced in helical polymers possessing multi-chiral pendants groups is governed by the chiral center places closer to the backbone, the chiral centers placed in remote positions can have important consequences in the stimuli-responsive properties although their influence in the helical sense induction is limited. In this work, two different (PPA)s bearing as pendant (*S*)-Valine-(*R*)-MPA and (*S*)-Valine-(*S*)-MPA were prepared. The helical sense in all the solvents tested is commanded by the (*S*)-valine obtaining a *M* helix in all cases. However, this helix is compressed in low-polar solvents and stretched in polar solvents, difference attributed to an *anti* to *syn* conformational change produced at the pendant group. This *anti* to *syn* conformational change is activated by the solvent polarity, and because the two diastereomeric polymers, poly-(*S,R*)-**1** and poly-(*S,S*)-**2** have different physical properties, the value of the dielectric constant of the solvent needed to produce this conformational change is different for both polymers. As a result, these two polymers show different

stimuli-responsive properties in THF. While poly-(*S,R*)-**1** adopts a compressed helix due to an *anti*-conformation at the pendant, in poly-(*S,S*)-**2** an *anti* to *syn* conformational change is triggered producing a stretched helix. Consequently, these two polymers allow to sense THF due to the different helical scaffolds induced by a different conformational composition at the pendants. We believe these findings will encourage the scientific community to study more complex multi-chiral pendant groups and their potential impact in the folding/stimuli-responsive nature of the polymers.

Chapter III. Greasing Macromolecular Gears: Inclusion of Flexible Spacers

We have demonstrated that the introduction of glycine as a flexible spacer at the *N*-terminus of short non-chiral Aib oligomers ($n = 1, 2, 3, 4$) end capped with a single enantiomer of MTPA allows the selective folding of the chain into *P* or *M* helical senses, by simply playing with the polarity of the solvent. This action is due to the conformational change produced in the chiral MTPA unit of mono-**1-4** series that is transmitted to the oligopeptide chain via screw sense induction.

Introduction of a 4-ethynylaniline group at the *C*-terminus of those oligopeptides followed by rhodium-catalyzed polymerization of the alkyne produced the corresponding poly(phenylacetylene)s (PPA)s —poly-**1** to poly-**4**— that were shown to act as a macromolecular gear, where the helical sense/elongation of the polyenic skeleton is controlled by the helical sense of the oligopeptide chain that in turn, obeys the conformational composition of the terminal (*S*)-MTPA unit, shifted by the polarity of the media. In this way, solvent polarity changes make the oligopeptide substituents of the PPA —(*S*)-MTPA-(Aib)_{*n*}-PPA ($n = 1, 2$)— to vary their *P/M* screw sense preference, triggering a structural change on the polyenic skeleton —helical sense and/or elongation—.

Interestingly, the two first counterparts of the series (poly-**1** and poly-**2**) display effective chiral communication between the MTPA moiety towards the polymer skeleton. Strikingly, the presence of the flexible glycine allows the system to display dynamic behavior promoting helix inversion under proper circumstances (i.e., DCM as solvent and thermal treatment). The last two components of the series (poly-**3** and poly-**4**) exhibit also strong chiral information harvesting through the well-folded non-chiral fragment. The presence of larger pendants reduces the dynamicity of the corresponding (PPA)s, which do not

display clear helix inversions, but do show interesting variations in the degree of elongation. The chiral communication process reported here contributes to the development on new stimuli-responsive materials with potential application as sensors, chiral stationary phases for HPLC, and logic devices among others.

Chapter IV. Multi-Helical Scaffolds (up to Five Helices) from Chiral (PPA)s bearing a Gly-AA as Pendant.

In this work we have demonstrated that the introduction of a flexible and an achiral spacer between the chiral center and the polyene backbone can result not only in an effective helix induction due to a correct transmission of the chiral information from the chiral pendant to the polyene backbone, but also in the possibility of creating different helical scaffolds with different elongations as consequence of different structural arrangements —extended, bent structures— at the achiral spacer. More precisely, we have been able to create five different helical structures for a PPA that bears the anilide of a gly-AA-Boc dipeptide (AA = Phe, Val) — *M* helix **1**, *P* helix **2**, *M* helix **2**, *P* helix **3**, *M* helix **3**—, by playing with the conformational composition at the glycine residue which allowed us to create three different scaffolds (from compressed to stretched: helix **1**, helix **2**, helix **3**), and the conformational composition at the chiral amino acid which allowed us to play with the *P/M* helical orientation of the different scaffolds.

EXPERIMENTAL SECTION

CHAPTER I

1. Materials and methods

CD measurements were done in a Jasco-720.

UV spectra were registered in a Jasco-630.

The optical rotation was measured in a Jasco P-2000.

NMR experiments were measured in a Varian 300 operating at 300 MHz for proton NMR and 75 MHz for carbon. CDCl_3 signal ($\delta = 77.2$ ppm) was used as standard for ^{13}C experiments.

Raman spectra were carried out in a Renishaw confocal Raman spectrometer (Invia Reflex model), equipped with two lasers (diode laser 785 nm and Ar laser 514 nm).

DSC traces were obtained in a DSC Q200 Tzero Technology (TA Instruments, New Castle, UK), equipped with a refrigerated cooling system RCS90 (TA Instruments, New Castle, UK), using a Tzero low-mass aluminium pan.

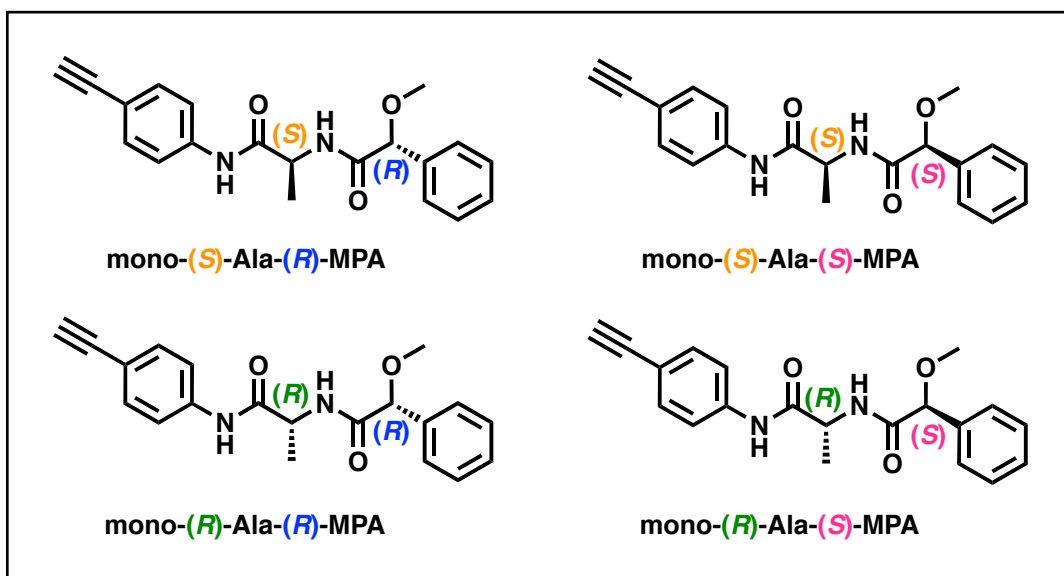
TGA traces were obtained in a TGA Q5000 (TA Instruments, New Castle, UK) using a platinum pan.

GPC studies were carried out in a Waters Alliance equipped with Phenomenex GPC columns.

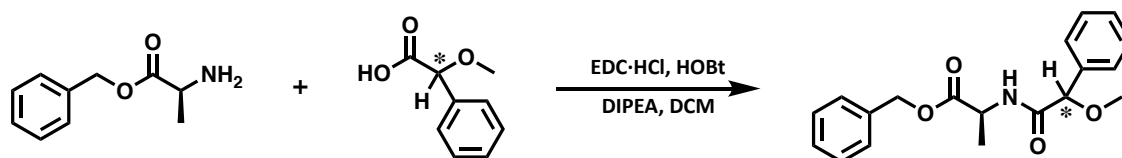
AFM measurements were performed in a MultiMode V Scanning Probe Microscope (Veeco Instruments) in air at rt with standard silicon cantilevers and super-sharp cantilevers in tapping mode using 12 μm scanners. Nanoscope processing software and WSxM 4.0 Beta 1.0 [4] (Nanotec Electronica, S.L.) were used for image analysis.

VCD spectra were recorded in a jasco FVS-6000 over an average of 6000 scans using a cell equipped with BaF_2 lens and a Teflon spacer generating a 150 μm path length.

2. Synthesis of monomers



The monomers employed in this work have been prepared according to the following synthetic scheme.

Benzyl [(*R*)- and (*S*)-2-methoxy-2-phenylacetyl]-(*S*)-alaninate

N-(3-Dimethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride (EDC·HCl, 0.34 g, 1.05 equiv), Hydroxybenzotriazole (HOBt, 0.24 g, 1.05 equiv), (*R*)- or (*S*)-2-methoxy-2-phenylacetic acid (0.31 g, 1.10 equiv) and diisopropyltriethylamine (DIPEA, 0.36 mL, 1.20 equiv) were dissolved in 17 mL of DCM, and the mixture was stirred for 20 min to activate the acid. Then, (*S*)-alanine benzyl ester *p*-toluensulfonate salt (0.60 g, 1.00 equiv) and diisopropyltriethylamine (DIPEA, 0.30 mL, 1.00 equiv) were added and the reaction mixture was stirred 48h. Then the solvent was evaporated at reduced pressure and the crude was diluted in DCM, the organic layer was washed with HCl 1M, saturated solution of NaHCO₃ and brine. The combined organic layers were dried over anhyd. Na₂SO₄, filtered and the solvent was evaporated at reduced pressure. The crude product was chromatographed on silica gel (40-63 mesh) with hexane/ethyl acetate (7/3) as eluent obtaining benzyl [(*R*) or (*S*)-2-methoxy-2-phenylacetyl]-(*S*)-alaninate in 91 and 85 % yield (0.51 g and 0.49 g, respectively).

NMR data of [(*R*)-2-methoxy-2-phenylacetyl]-(*S*)-alaninate

^1H NMR (300 MHz, CDCl_3) δ (ppm): 7.36 (m, 10H), 5.15 (q, 2H), 4.66 (m, 2H), 3.35 (s, 3H), 1.49 (d, $J=7.2$ Hz, 3H).

^{13}C NMR (75 MHz, CDCl_3) δ (ppm): 172.4, 170.1, 136.8, 135.4, 128.6, 128.6, 128.6, 128.4, 128.2, 127.4, 83.7, 67.1, 57.0, 47.7, 18.4.

HRMS (ESI) m/z calc for $\text{C}_{19}\text{H}_{21}\text{NO}_4$ [$\text{M}+\text{H}$]: 328.1471, found: 328.1543.

$\alpha_{\text{D}}^{20} = -92$ ($c = 10$ mg/mL, CHCl_3).

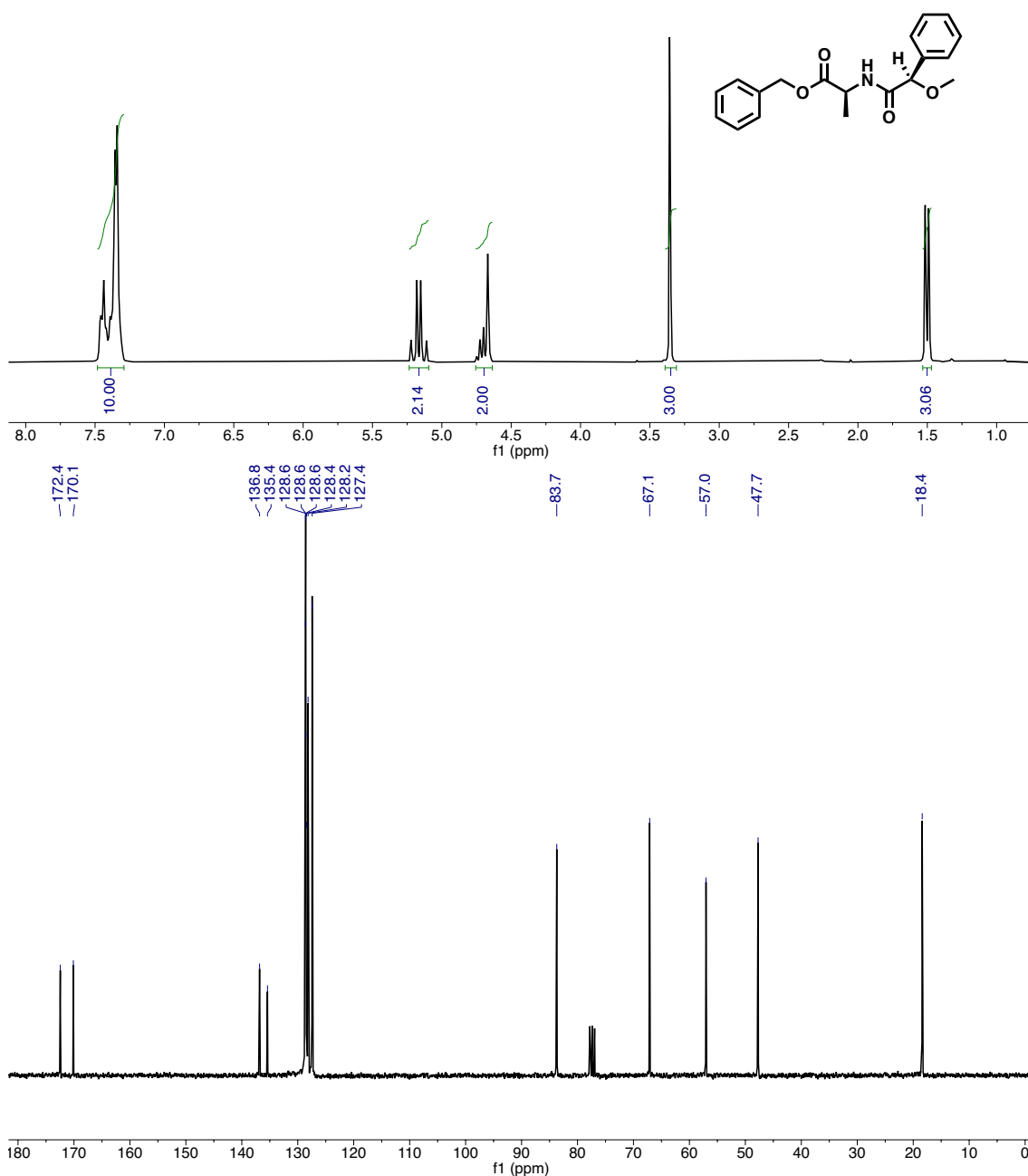


Figure S1. (a) ^1H -NMR and (b) ^{13}C -NMR of [(*R*)-2-methoxy-2-phenylacetyl]-(*S*)-alaninate in CDCl_3 .

NMR data of [(S)-2-methoxy-2-phenylacetyl]-(S)-alaninate

^1H NMR (300 MHz, CDCl_3) δ (ppm): 7.35 (m, 10H), 5.14 (q, 2H), 4.66 (m, 2H), 3.32 (s, 3H), 1.47 (d, $J=7.2$ Hz, 3H).

^{13}C NMR (75 MHz, CDCl_3) δ (ppm): 172.6, 170.3, 137.0, 135.4, 128.6, 128.6, 128.4, 128.1, 127.0, 83.7, 67.1, 57.4, 47.7, 18.2.

HRMS (ESI) m/z calc for $\text{C}_{19}\text{H}_{21}\text{NO}_4$ $[\text{M}+\text{H}]$: 328.1471, found: 328.1543.

$\alpha_D^{20} = +96$ ($c = 10$ mg/mL, CHCl_3).

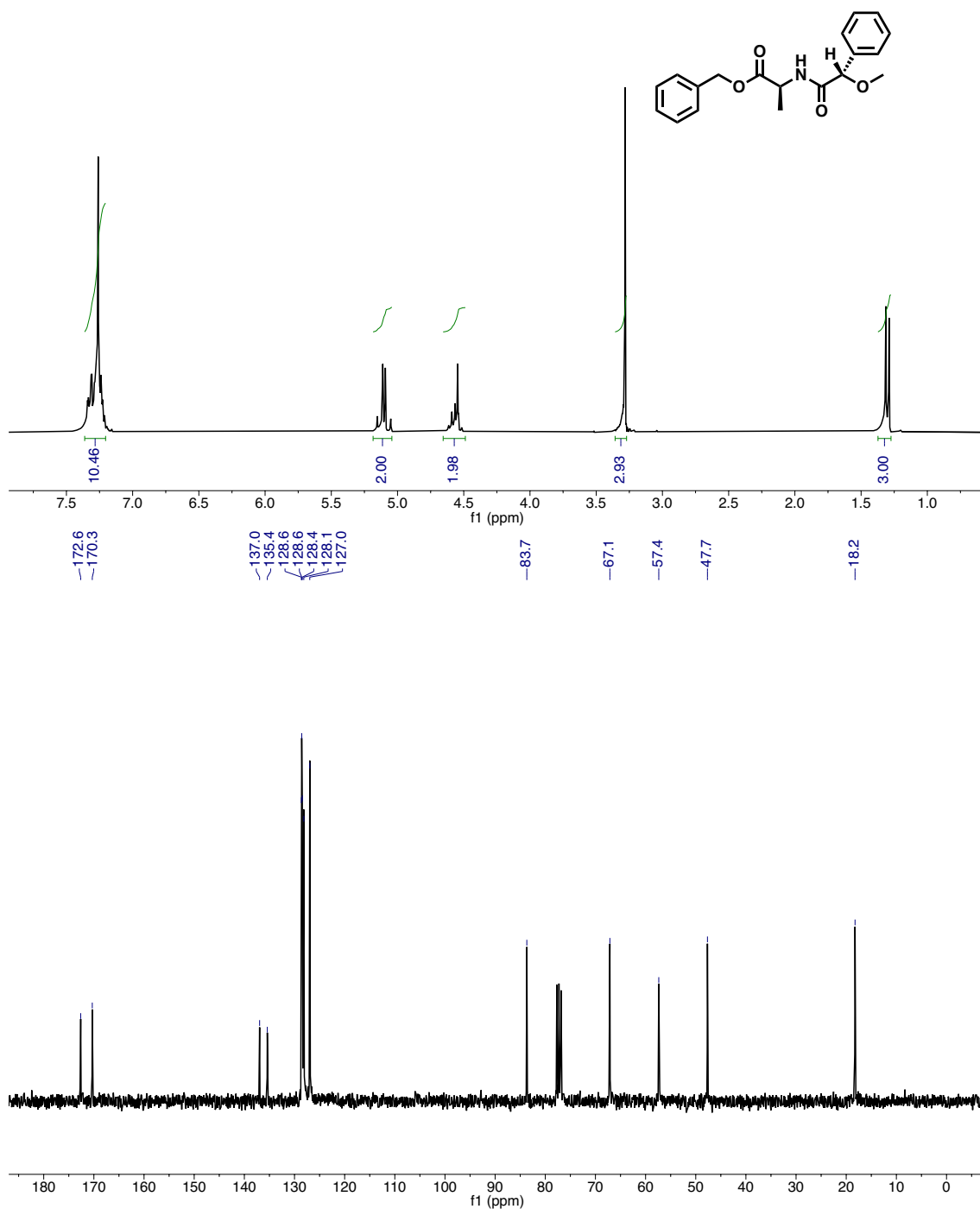
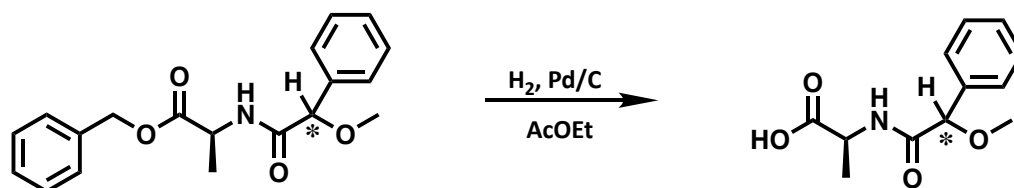


Figure S2. (a) ^1H -NMR and (b) ^{13}C -NMR of [(S)-2-methoxy-2-phenylacetyl]-(S)-alaninate in CDCl_3 .

[(*R*)- and (*S*)-2-methoxy-2-phenylacetyl]-(*S*)-alanine

Pd/C (0.12 g) was suspended in 30 ml of EtOAc and submitted to three cycles of vacuum/purge with hydrogen. Then the Pd/C suspension was stirred under hydrogen atmosphere for 20 min and next a solution of benzyl [(*R*)- or (*S*)-2-methoxy-2-phenylacetyl]-(*S*)-alaninate (0.45 g, 1.37 mmol) in 15 mL of EtOAc was injected to the reaction vessel via syringe. After one hour TLC analysis showed no presence of the starting material and the suspension was filtered through celite and washed thoroughly with EtOAc, obtaining [(*R*)- and (*S*)-2-methoxy-2-phenylacetyl]-(*S*)-alanine in quantitative yield (0.32 g both compounds).

NMR data of [(*R*)-2-methoxy-2-phenylacetyl]-(*S*)-alanine

^1H NMR (300 MHz, CDCl_3) δ (ppm): 8.66 (s, 1H), 7.36 (m, 6H), 4.65 (s, 1H), 4.54 (quint, $J=7.3$ Hz, 1H), 3.34 (s, 3H), 1.50 (d, $J=7.2$ Hz, 3H).

^{13}C NMR (75 MHz, CDCl_3) δ (ppm): 175.7, 171.4, 136.7, 129.0, 128.9, 127.8, 83.8, 57.3, 48.2, 18.4.

HRMS (ESI) m/z calc for $\text{C}_{12}\text{H}_{15}\text{NO}_4$ [$\text{M}+\text{H}$]: 238.1001, found: 238.1074.

$\alpha_D^{20} = -85$ ($c = 10$ mg/mL, MeOH).

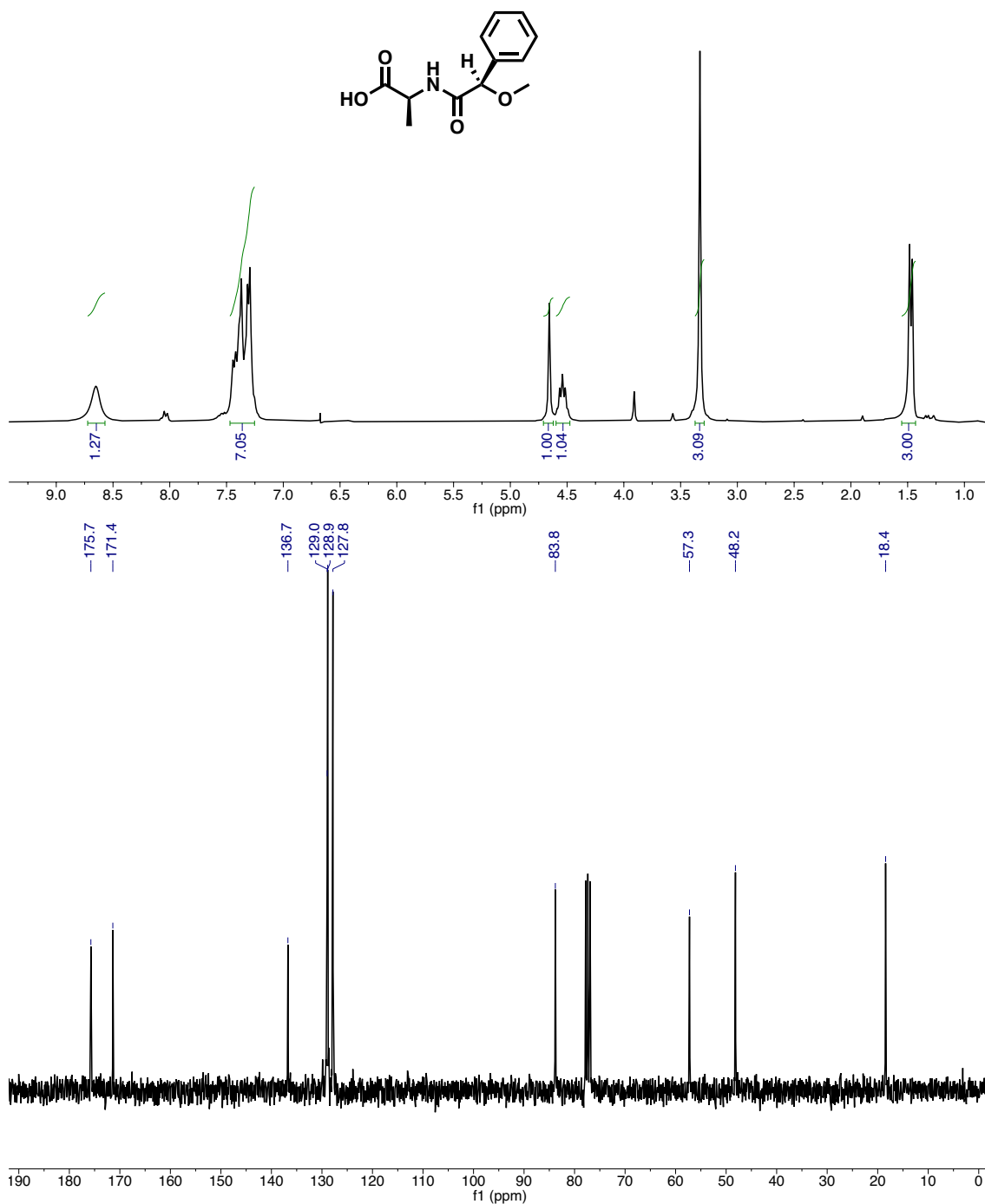


Figure S3. (a) ^1H -NMR and (b) ^{13}C -NMR of [(*R*)-2-methoxy-2-phenylacetyl]-(*S*)-alanine in CDCl_3 .

NMR data of [(S)-2-methoxy-2-phenylacetyl]-(S)-alanine

^1H NMR (300 MHz, CDCl_3) δ (ppm): 9.14 (s, 1H), 7.37 (m, 7H), 4.68 (s, 1H), 4.58 (quint, $J=7.3$ Hz, 1H), 3.40 (s, 3H), 1.45 (d, $J=7.2$ Hz, 3H).

^{13}C NMR (75 MHz, CDCl_3) δ (ppm): 176.1, 171.3, 136.5, 128.7, 127.1, 83.4, 57.3, 47.8, 18.0.

HRMS (ESI) m/z calc for $\text{C}_{12}\text{H}_{15}\text{NO}_4$ $[\text{M}+\text{H}]$: 238.1001, found: 238.1074.

$\alpha_{\text{D}}^{20} = +81$ ($c = 10$ mg/mL, MeOH).

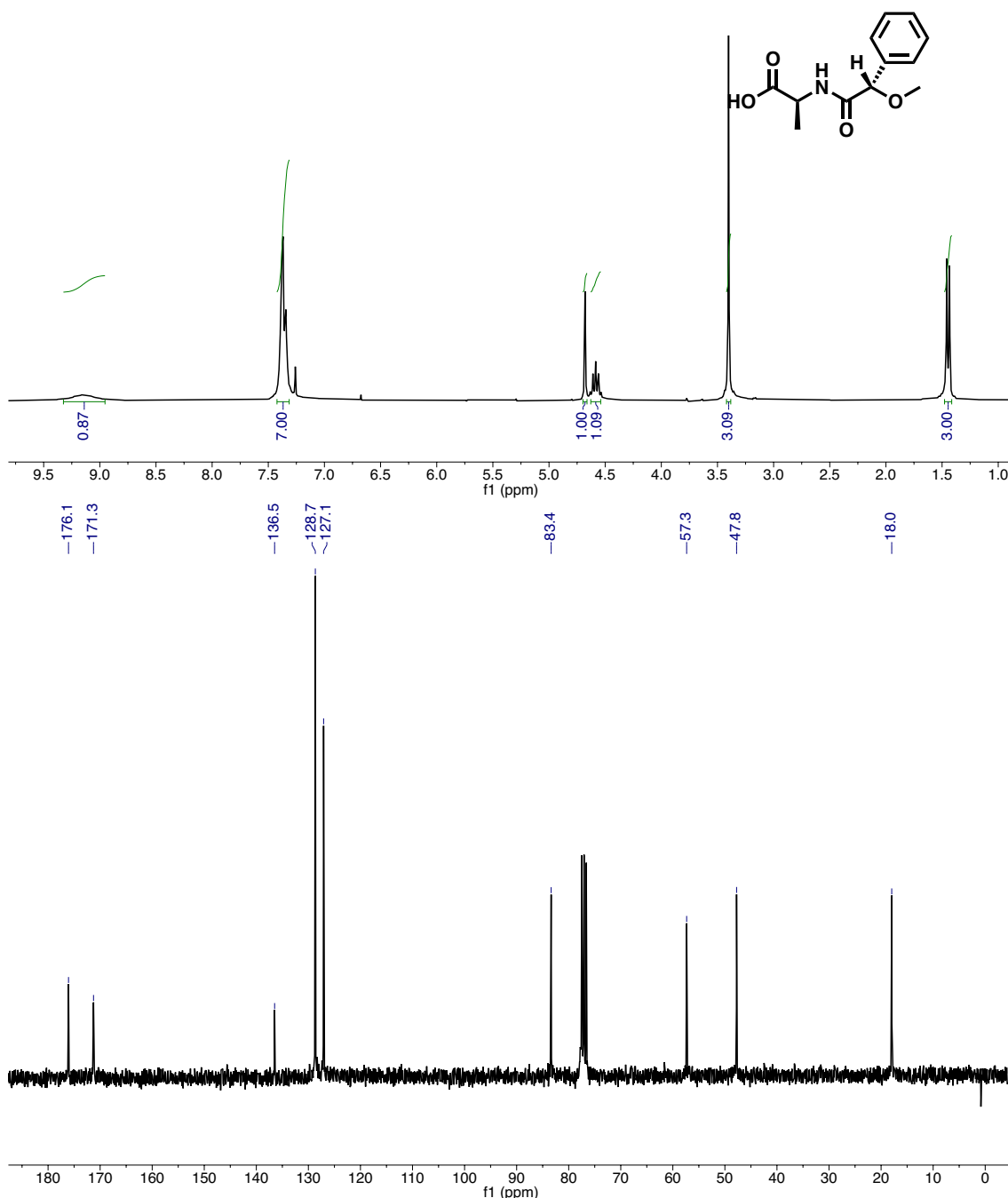
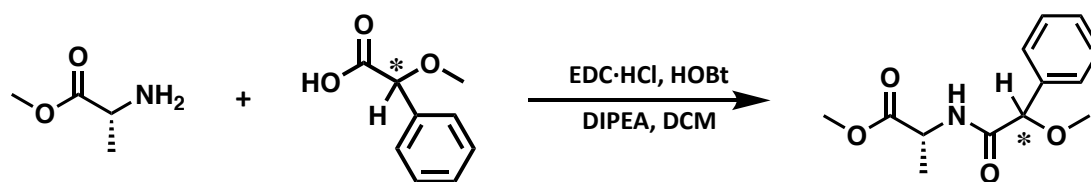


Figure S4. (a) ^1H -NMR and (b) ^{13}C -NMR of [(S)-2-methoxy-2-phenylacetyl]-(S)-alanine in CDCl_3 .

Methyl [(*R*)- and (*S*)-2-methoxy-2-phenylacetyl]-(*R*)-alaninate

N-(3-Dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (EDC·HCl, 0.86 g, 1.05 equiv), Hydroxybenzotriazole (HOBt, 0.61 g, 1.05 equiv), (*R*)- or (*S*)-2-methoxy-2-phenylacetic acid (0.78 g, 1.10 equiv) and diisopropyltriethylamine (DIPEA, 0.90 mL, 1.20 equiv) were dissolved in 45 mL of DCM, and the mixture was stirred for 20 min to activate the acid. Then, methyl (*R*)-alaninate (0.60 g, 1.00 equiv) and diisopropyltriethylamine (DIPEA, 0.75 mL, 1.00 equiv) were added and the reaction mixture was stirred 48h. Then the solvent was evaporated at reduced pressure and the crude was diluted in DCM, the organic layer was washed with HCl 1M, saturated solution of NaHCO₃ and brine. The organic layer was dried over anhyd. Na₂SO₄, filtered and the solvent was evaporated at reduced pressure. The crude product was chromatographed on silica gel (40-63 mesh) with hexane/ethyl acetate (7/3) as eluent obtaining methyl [(*R*)- and (*S*)-2-methoxy-2-phenylacetyl]-(*R*)-alaninate in 84 and 88 % yield (0.91 g and 0.95 g, respectively).

NMR data of [(*R*)-2-methoxy-2-phenylacetyl]-(*R*)-alaninate

^1H NMR (300 MHz, CDCl_3) δ (ppm): 7.31 (m, 6H), 4.59 (s, 1H), 4.52 (quint, $J=7.5$ Hz, 1H), 3.68 (s, 3H), 3.33 (s, 3H), 1.33 (d, $J=7.2$ Hz, 3H).

^{13}C NMR (75 MHz, CDCl_3) δ (ppm): 173.5, 170.7, 137.2, 128.8, 128.7, 127.3, 83.9, 57.6, 52.7, 47.8, 18.4.

HRMS (ESI) m/z calc for $\text{C}_{13}\text{H}_{17}\text{NO}_4$ [$\text{M}+\text{H}$]: 252.1158, found: 252.1230.

$\alpha_{\text{D}}^{20} = -90$ ($c = 10$ mg/mL, CHCl_3).

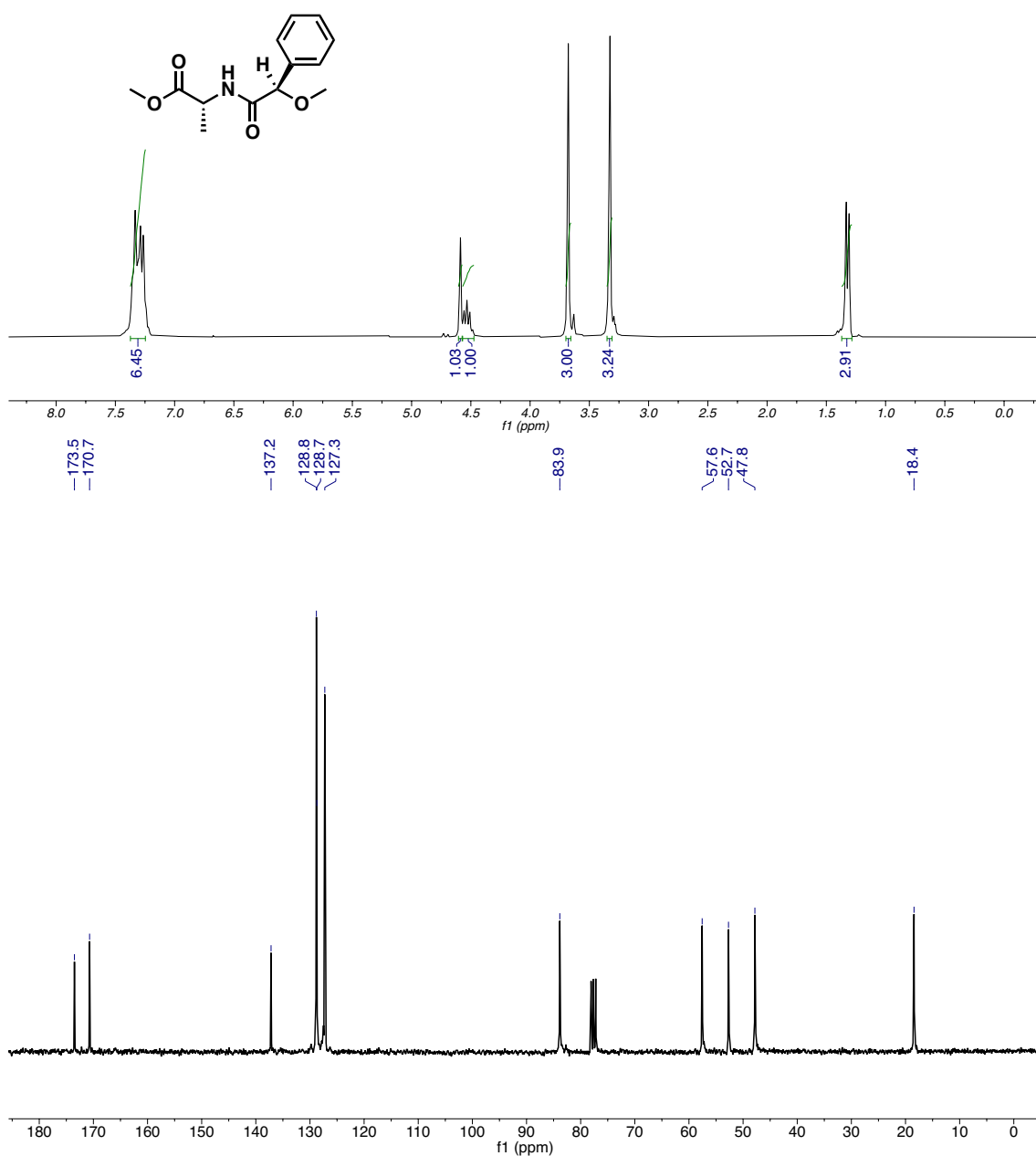


Figure S5. (a) ^1H -NMR and (b) ^{13}C -NMR of [(*R*)-2-methoxy-2-phenylacetyl]-(*R*)-alaninate in CDCl_3 .

NMR data of [(*S*)-2-methoxy-2-phenylacetyl]-(*R*)-alaninate

^1H NMR (300 MHz, CDCl_3) δ (ppm): 7.34 (m, 6H), 4.56 (m, 2H), 3.67 (s, 3H), 3.32 (s, 3H), 1.45 (d, $J=7.1$ Hz, 3H).

^{13}C NMR (75 MHz, CDCl_3) δ (ppm): 173.4, 170.4, 137.1, 128.8, 127.7, 83.9, 57.3, 52.7, 47.9, 18.7.

HRMS (ESI) m/z calc for $\text{C}_{13}\text{H}_{17}\text{NO}_4$ [$\text{M}+\text{H}$]: 252.1158, found: 252.1230.

$\alpha_D^{20} = +117$ ($c = 10$ mg/mL, CHCl_3).

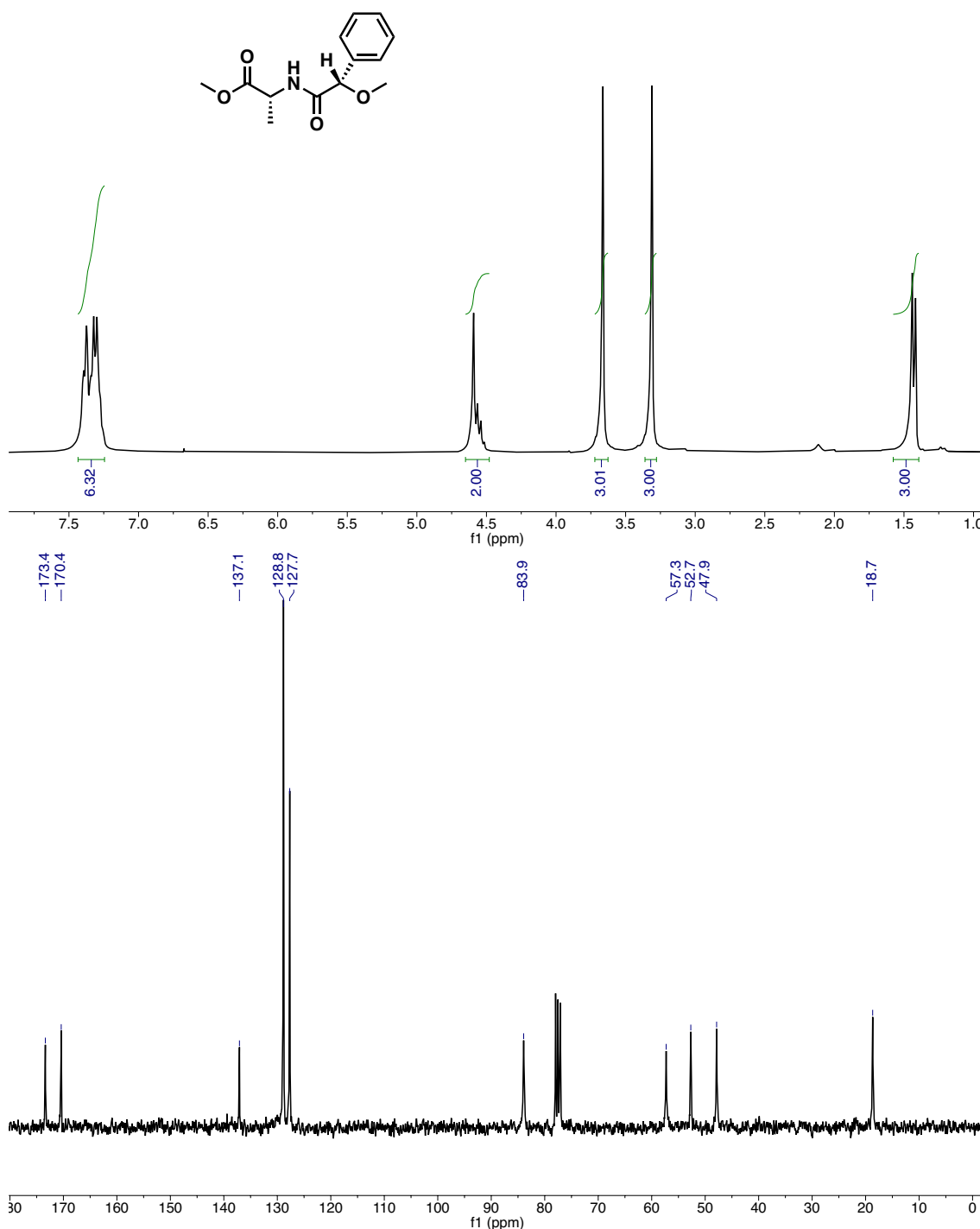
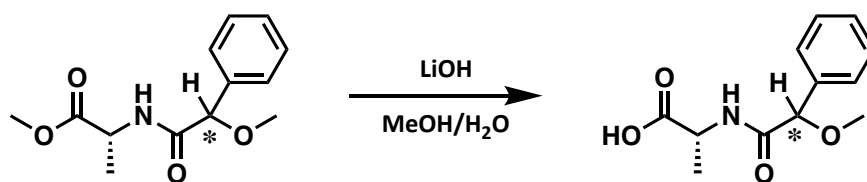


Figure S6. (a) ^1H -NMR and (b) ^{13}C -NMR of [(*S*)-2-methoxy-2-phenylacetyl]-(*R*)-alaninate in CDCl_3 .

[(*S*)- and (*R*)-2-methoxy-2-phenylacetyl]-(*R*)-alaninate

Once obtained the corresponding methyl [(*R*)- and (*S*)-2-methoxy-2-phenylacetyl]-(*R*)-alaninate (0.50 g, 1.00 equiv), it was dissolved in a mixture of MeOH/H₂O (95/5) (40 mL) and lithium hydroxide was added (LiOH, 0.24 g, 5.00 equiv). After 30 minutes the solvent was removed under reduced pressure. The residue was redissolved in a small amount of water and acidified to pH = 1. After extracting with ethyl acetate (4 times), the solution was dried over Na₂SO₄. Next, the organic solvent was removed obtaining the corresponding [(*S*)- and (*R*)-2-methoxy-2-phenylacetyl]-(*R*)-alaninate in 98 and 96 % yield (0.46 g and 0.45 g, respectively).

NMR data of [(*R*)-2-methoxy-2-phenylacetyl]-(*R*)-alaninate

^1H NMR (300 MHz, CDCl_3) δ (ppm): 8.76 (s, 1H), 7.36 (m, 7H), 4.65 (s, 1H), 4.52 (quint, $J=7.2$ Hz, 1H), 3.34 (s, 3H), 1.33 (d, $J=7.2$ Hz, 3H).

^{13}C NMR (75 MHz, CDCl_3) δ (ppm): 175.9, 171.0, 136.4, 128.7, 128.6, 127.5, 83.4, 56.9, 47.8, 18.2.

HRMS (ESI) m/z calc for $\text{C}_{12}\text{H}_{15}\text{NO}_4$ [$\text{M}+\text{H}$]: 238.1001, found: 238.1074.

$\alpha_D^{20} = -61$ ($c = 10$ mg/mL, CHCl_3).

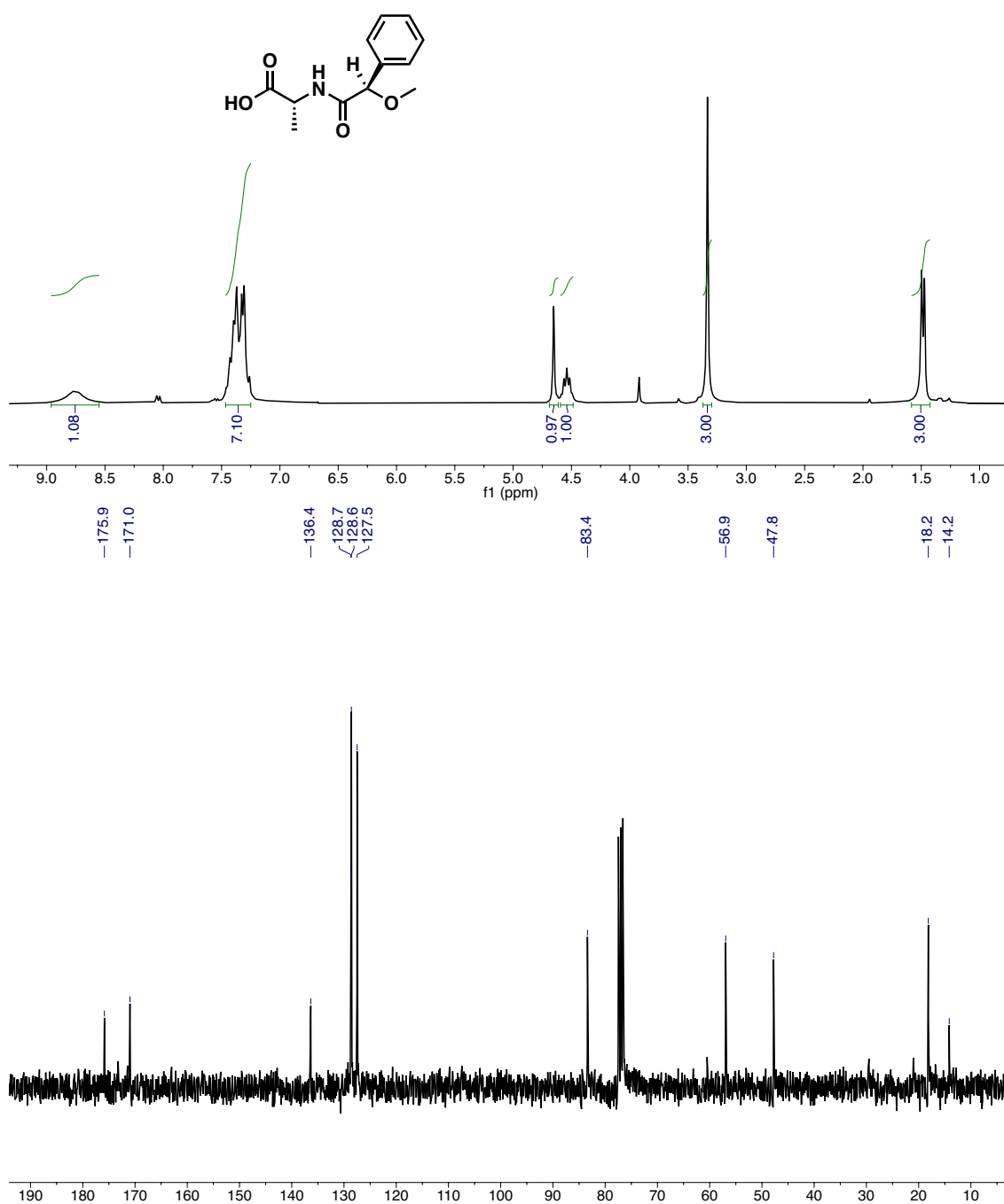


Figure S7. (a) ^1H -NMR and (b) ^{13}C -NMR of [(*R*)-2-methoxy-2-phenylacetyl]-(*R*)-alaninate in CDCl_3 .

NMR data of [(S)-2-methoxy-2-phenylacetyl]-(R)-alaninate

^1H NMR (300 MHz, CDCl_3) δ (ppm): 11.03 (s, 1H), 7.40 (m, 6H), 4.67 (s, 1H), 4.56 (quint, $J=7.3$ Hz, 1H), 3.33 (s, 3H), 1.45 (d, $J=7.1$ Hz, 3H).

^{13}C NMR (75 MHz, CDCl_3) δ (ppm): 176.4, 171.4, 136.6, 129.0, 128.9, 127.9, 83.7, 57.2, 48.1, 18.5.

HRMS (ESI) m/z calc for $\text{C}_{12}\text{H}_{15}\text{NO}_4$ $[\text{M}+\text{H}]$: 238.1001, found: 238.1074.

$\alpha_{\text{D}}^{20} = +121$ ($c = 10$ mg/mL, CHCl_3).

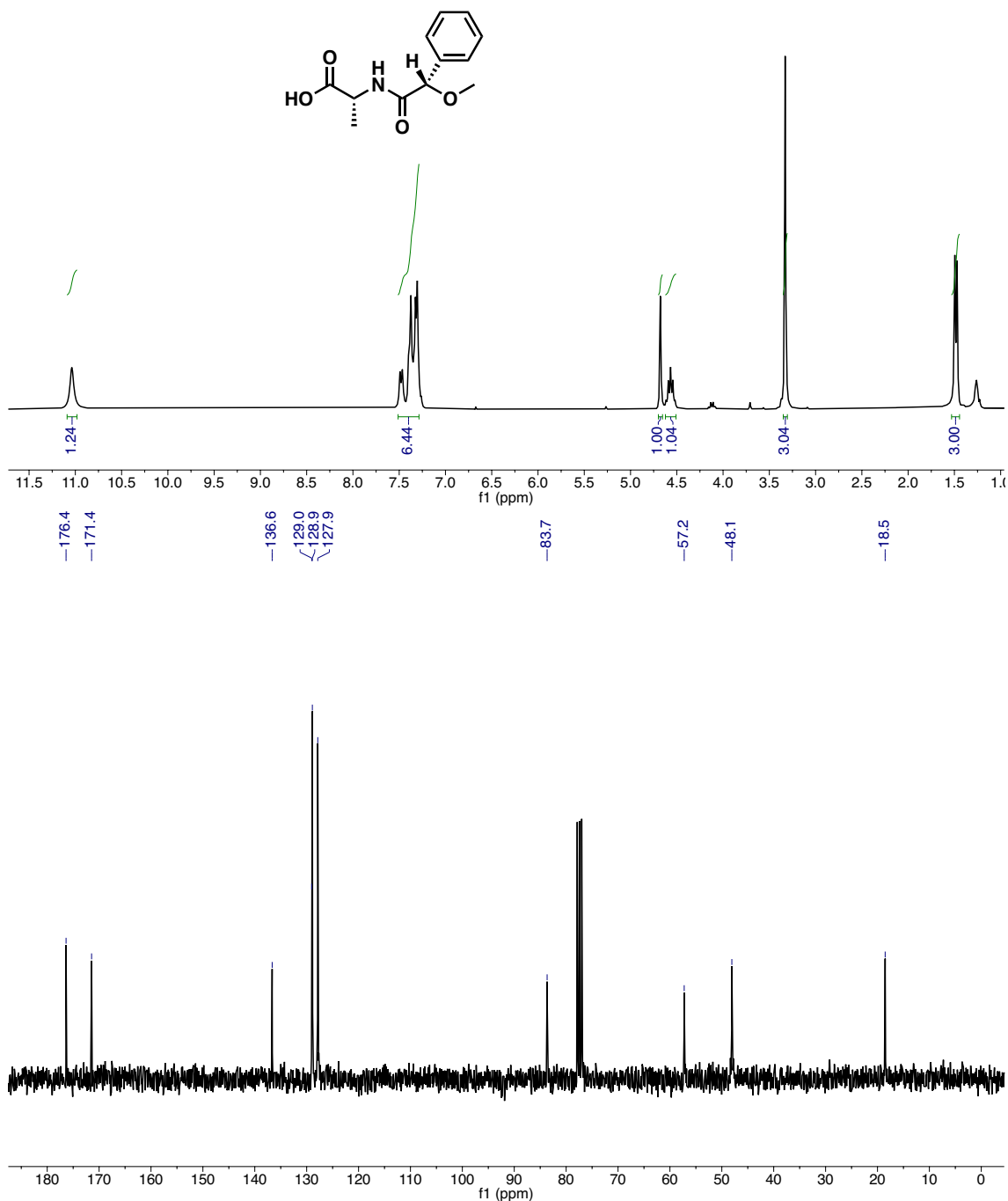
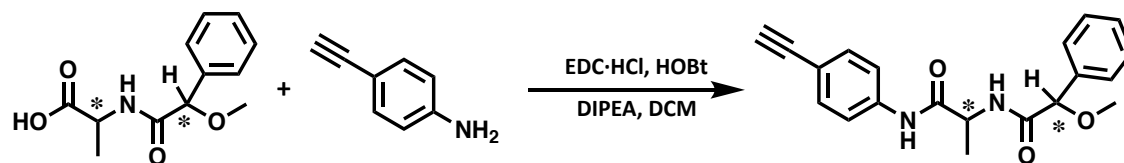


Figure S8. (a) ^1H -NMR and (b) ^{13}C -NMR of [(S)-2-methoxy-2-phenylacetyl]-(R)-alaninate in CDCl_3 .

(*S*) and (*R*)-*N*-(4-ethynylphenyl)-2-[(*S*)-phenylacetamido]propanamide and (*R*)-2-methoxy-2-phenylacetamido]propanamide



N-(3-Dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (EDC·HCl, 0.23 g, 1.05 equiv), Hydroxybenzotriazole (HOBt, 0.16 g, 1.05 equiv), the corresponding [(*R*)- and (*S*)-2-methoxy-2-phenylacetyl]-(*S*)-alanine and [(*R*)- and (*S*)-2-methoxy-2-phenylacetyl]-(*R*)-alanine (0.30 g, 1.10 equiv) and diisopropyltriethylamine (DIPEA, 0.24 mL, 1.20 equiv) were dissolved in 15 mL of DCM, and the mixture was stirred for 20 min to activate the acid. Then, 4-ethynylaniline (0.13 g, 1.00 equiv) was added and the reaction mixture was stirred overnight. Then, the reaction mixture was washed with HCl 1M (x3), saturated solution of NaHCO₃ and brine. The organic layer was dried over anhyd Na₂SO₄, filtered and the solvent was evaporated at reduced pressure. The crude product was chromatographed on silica gel (40-63 mesh) with hexane/ethyl acetate (7/3) as eluent obtaining the corresponding monomers mono-(*S*)-Ala-(*R*)-MPA-**1**, mono-(*S*)-Ala-(*S*)-MPA-**2**, mono-(*R*)-Ala-(*R*)-MPA-**3** and mono-(*R*)-Ala-(*S*)-MPA-**4** in 82, 82, 81 and 77 % yield (0.35 g, 0.35 g, 0.34 g and 0.33 g, respectively).

NMR data of mono-**1** (*S*)-Ala-(*R*)-MPA

^1H NMR (300 MHz, CDCl_3) δ (ppm): 9.27 (s, 1H), 7.62 (d, $J=7.6$ Hz, 1H), 7.42 (m, 9H), 4.72 (quint, $J=7.1$ Hz, 1H), 4.62 (s, 1H), 3.34 (s, 3H), 3.05 (s, 1H), 1.41 (d, $J=6.7$ Hz, 3H).

^{13}C NMR (75 MHz, CDCl_3) δ (ppm): 171.2, 170.3, 138.6, 136.6, 132.8, 128.9, 128.8, 127.5, 119.9, 117.4, 83.6, 83.5, 57.1, 49.5, 18.3.

HRMS (ESI) m/z calc for $\text{C}_{20}\text{H}_{20}\text{N}_2\text{O}_3$ $[\text{M}+\text{H}]$: 337.1474, found: 337.1547.

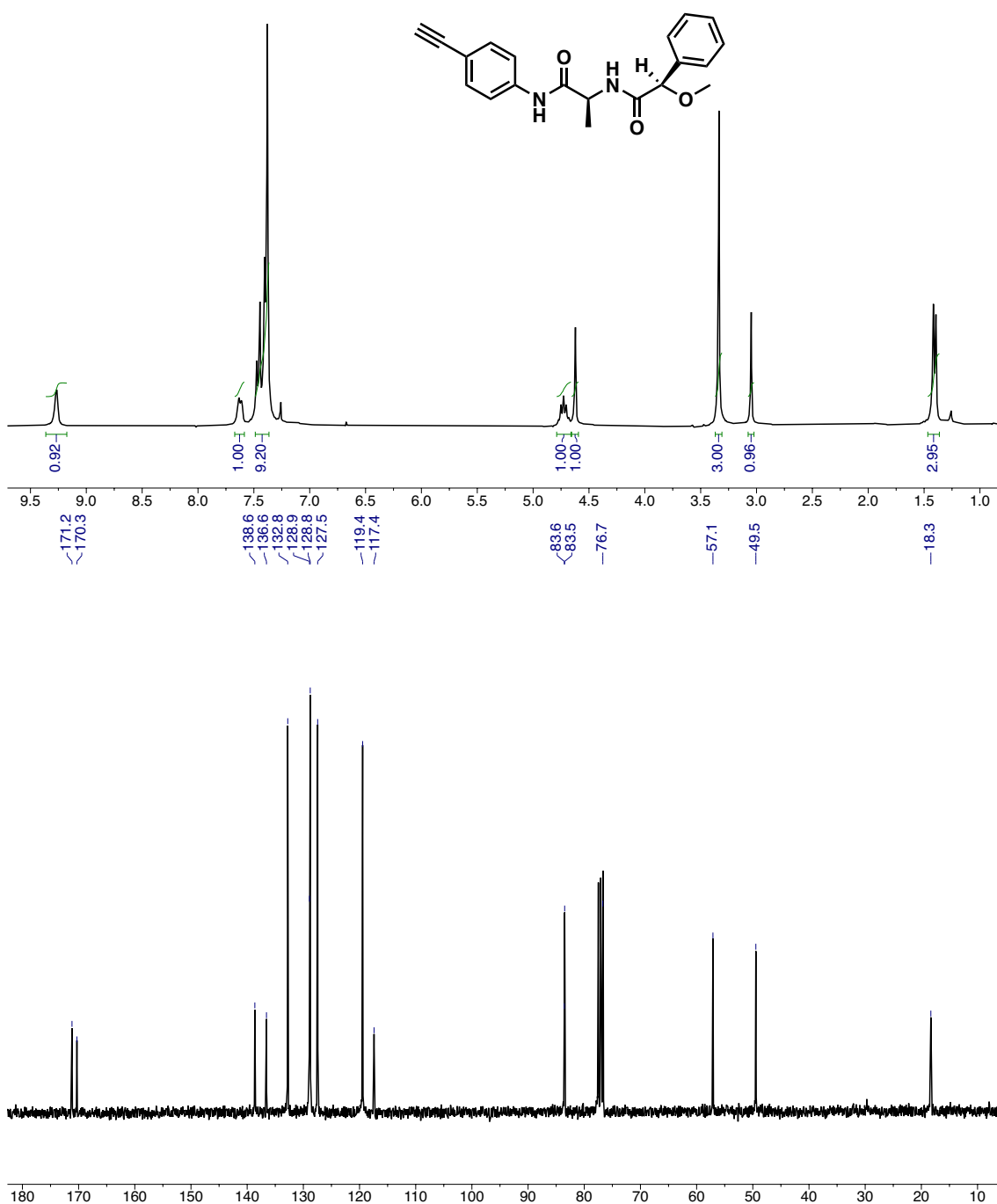


Figure S9. (a) ^1H -NMR and (b) ^{13}C -NMR spectra of mono-**1** (*S*)-Ala-(*R*)-MPA-1 in CDCl_3 .

NMR data of mono-**2** (S)-Ala-(S)-MPA

^1H NMR (300 MHz, CDCl_3) δ (ppm): 9.52 (s, 1H), 7.81 (d, $J=7.7$ Hz, 1H), 7.47 (d, 2H), 7.38 (m, 7H), 4.81 (quint, $J=6.9$ Hz, 1H), 4.61 (s, 1H), 3.32 (s, 3H), 3.07 (s, 1H), 1.38 (d, $J=6.8$ Hz, 3H).

^{13}C NMR (75 MHz, CDCl_3) δ (ppm): 171.3, 171.0, 139.1, 137.0, 133.0, 129.2, 129.1, 127.8, 119.8, 117.7, 83.9, 77.2, 57.4, 49.8, 19.3.

+HRMS (ESI) m/z calc for $\text{C}_{20}\text{H}_{20}\text{N}_2\text{O}_3$ $[\text{M}+\text{H}]$: 337.1474, found: 337.1547.

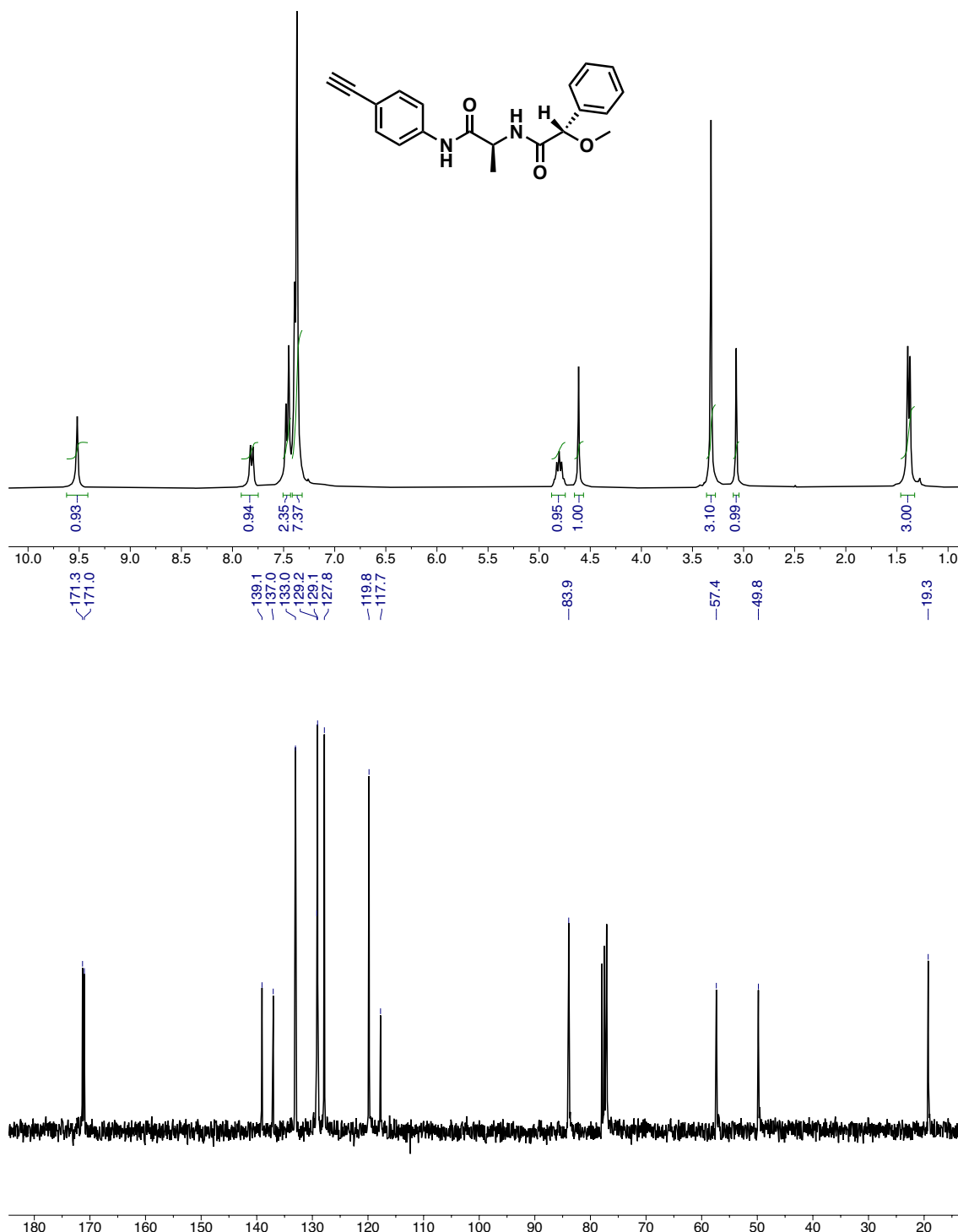


Figure S10. (a) ^1H -NMR (b) ^{13}C -NMR spectra of mono-(S)-Ala-(S)-MPA-**2** in CDCl_3 .

NMR data of mono-**3** (*R*)-Ala-(*R*)-MPA

^1H NMR (300 MHz, CDCl_3) δ (ppm): 9.42 (s, 1H), 7.74 (d, $J=7.8$ Hz, 1H), 7.45 (d, 2H), 7.37 (m, 7H), 4.78 (quint, $J=7.2$ Hz, 1H), 4.61 (s, 1H), 3.32 (s, 3H), 3.06 (s, 1H), 1.39 (d, $J=6.8$ Hz, 3H).

^{13}C NMR (75 MHz, CDCl_3) δ (ppm): 171.4, 170.8, 139.0, 137.0, 133.0, 129.2, 129.1, 127.8, 119.8, 117.7, 83.9, 57.4, 49.8, 19.0.

HRMS (ESI) m/z calc for $\text{C}_{20}\text{H}_{20}\text{N}_2\text{O}_3$ $[\text{M}+\text{H}]$: 337.1474, found: 337.1547.

$\alpha_{\text{D}}^{20} = +99$ ($c = 10$ mg/mL, CHCl_3).

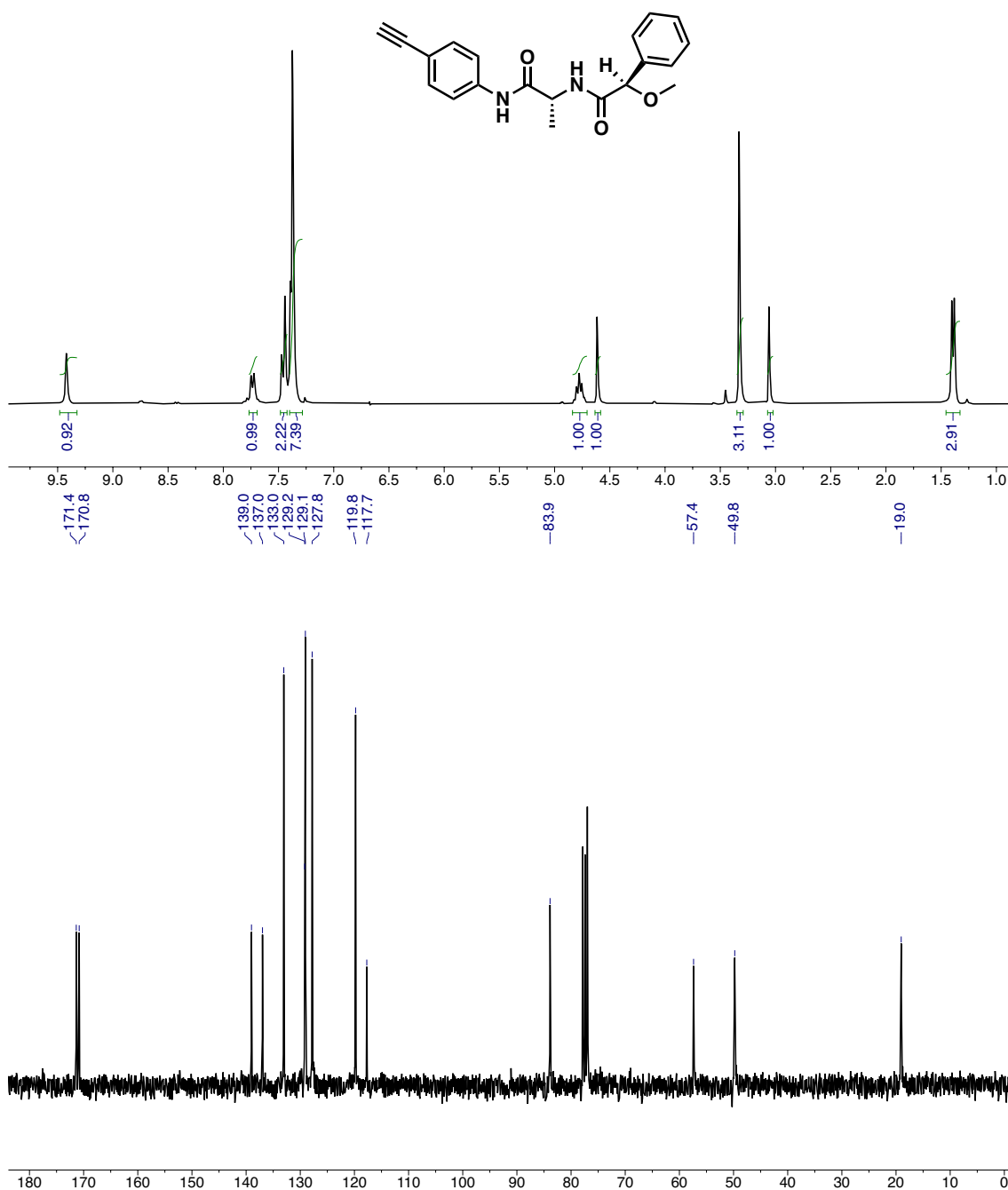


Figure S11. (a) ^1H -NMR and (b) ^{13}C -NMR spectra of mono-(*R*)-Ala-(*R*)-MPA-**3** in CDCl_3 .

NMR data of mono-**4** (*R*)-Ala-(*S*)-MPA

^1H NMR (300 MHz, CDCl_3) δ (ppm): 8.90 (s, 1H), 7.56 (d, $J=8.0$ Hz, 1H), 7.31 (m, 7H), 7.15 (d, 2H), 4.78 (quint, $J=7.2$ Hz, 1H), 4.67 (s, 1H), 3.34 (s, 3H), 3.03 (s, 1H), 1.52 (d, $J=6.7$ Hz, 3H).

^{13}C NMR (75 MHz, CDCl_3) δ (ppm): 171.3, 170.1, 138.4, 136.5, 132.7, 129.0, 128.8, 127.6, 119.4, 117.2, 83.6, 83.5, 76.5, 56.9, 49.2, 18.3.

HRMS (ESI) m/z calc for $\text{C}_{20}\text{H}_{20}\text{N}_2\text{O}_3$ $[\text{M}+\text{H}]^+$: 337.1474, found: 337.1547.

$\alpha_{\text{D}}^{20} = +138$ ($c = 10$ mg/mL, CHCl_3).

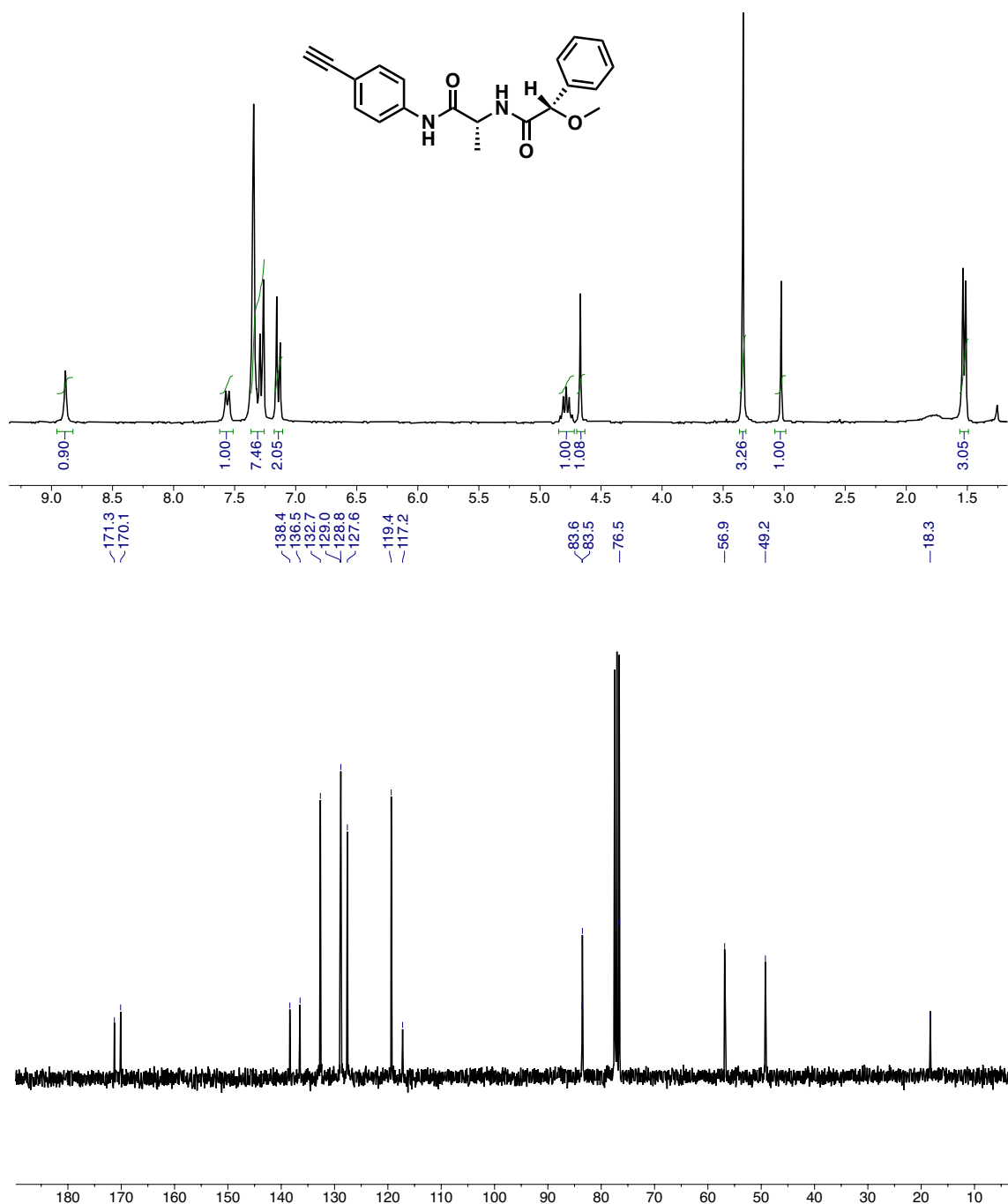


Figure S12. (a) ^1H -NMR and (b) ^{13}C -NMR spectra of mono-(*R*)-Ala-(*S*)-MPA-**4** in CDCl_3 .

3. X-ray structures of the monomers

Single crystals of monomers were grown by slow evaporation of the corresponding monomer solutions in a mixture of DCM/hexanes. The crystallographic data is depicted below in detail.

- Crystal data structure refinement for mono-(*S*)-Ala-(*R*)-MPA-1

Crystal data

$C_{20}H_{20}N_2O_3$
 $M_r = 336.38$
 Monoclinic, $P2_1$
 $a = 13.1471$ (17) Å
 $b = 4.8734$ (5) Å
 $c = 13.4977$ (17) Å
 $\beta = 90.328$ (10)°
 $V = 864.80$ (18) Å³
 $Z = 2$

$F(000) = 356$
 $D_x = 1.292$ Mg m⁻³
 Cu $K\alpha$ radiation, $\lambda = 1.54178$ Å
 Cell parameters from 1672 reflections
 $\theta = 3.3\text{--}65.8^\circ$
 $\mu = 0.71$ mm⁻¹
 $T = 100$ K
 Needle, clear colourless
 $0.18 \times 0.02 \times 0.02$ mm

Data collection

Bruker D8 VENTURE PHOTON-III 14
 diffractometer
 Radiation source: microfocus sealed tube, Incoatec
 $I\mu S$ 3.0
 Multilayer mirror monochromator
 Detector resolution: 7.3910 pixels mm⁻¹
 φ or ω oscillation scans
 Absorption correction: multi-scan
SADABS2016/2 - Bruker AXS area detector scaling
 and absorption correction

$T_{\min} = 0.71$, $T_{\max} = 0.99$
 12358 measured reflections
 3312 independent reflections
 2187 reflections with $I > 2\sigma(I)$
 $R_{\text{int}} = 0.124$
 $\theta_{\max} = 72.1^\circ$, $\theta_{\min} = 3.3^\circ$
 $h = -16 \rightarrow 16$
 $k = -6 \rightarrow 6$
 $l = -16 \rightarrow 13$

Refinement

Refinement on F^2
 Least-squares matrix: full
 $S = 1.00$
 3312 reflections
 234 parameters
 1 restraint
 Primary atom site location: dual
 Secondary atom site location: difference Fourier map
 Hydrogen site location: mixed
 H atoms treated by a mixture of independent and
 constrained refinement

$R[F^2 > 2\sigma(F^2)] = 0.061$
 $wR(F^2) = 0.171$
 $w = 1/[\sigma^2(F_o^2) + (0.079P)^2]$
 where $P = (F_o^2 + 2F_c^2)/3$
 $(\Delta/\sigma)_{\max} < 0.001$
 $\Delta\rho_{\max} = 0.20$ e Å⁻³
 $\Delta\rho_{\min} = -0.24$ e Å⁻³
 Absolute structure: Flack x determined using 695
 quotients $[(I^+)-(I^-)]/[(I^+)+(I^-)]$ (Parsons, Flack and
 Wagner, Acta Cryst. B69 (2013) 249-259).
 Absolute structure parameter: 0.2 (5)

Special details

Geometry. All e.s.d.'s (except the e.s.d. in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell e.s.d.'s are taken into account individually in the estimation of e.s.d.'s in distances, angles and torsion angles; correlations between e.s.d.'s in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell e.s.d.'s is used for estimating e.s.d.'s involving l.s. planes.

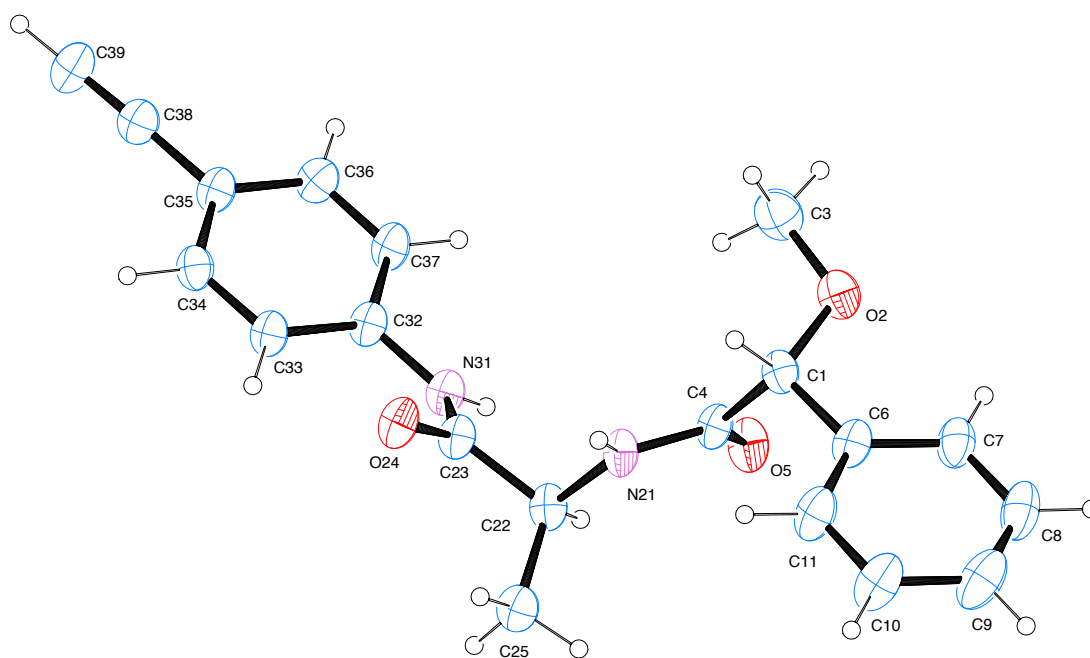


Figure S13. ORTEP representation of mono-(*S*)-Ala-(*R*)-MPA-1 conformation obtained from X-ray studies.

- Crystal data structure refinement for mono-(*S*)-Ala-(*S*)-MPA-2

Crystal data

$C_{20}H_{20}N_2O_3$
 $M_r = 336.38$
 Orthorhombic, $P2_12_12_1$
 $a = 4.9369$ (3) Å
 $b = 12.8572$ (8) Å
 $c = 26.7636$ (15) Å
 $V = 1698.81$ (18) Å³
 $Z = 4$
 $F(000) = 712$

$D_x = 1.315$ Mg m⁻³
 Cu $K\alpha$ radiation, $\lambda = 1.54178$ Å
 Cell parameters from 5261 reflections
 $\theta = 3.3$ – 76.0°
 $\mu = 0.72$ mm⁻¹
 $T = 100$ K
 Needle, clear colourless
 $0.12 \times 0.06 \times 0.02$ mm

Data collection

Bruker D8 VENTURE PHOTON-III 14
 diffractometer
 Radiation source: microfocus sealed tube, Incoatec
 $I\mu S$ 3.0
 Multilayer mirror monochromator
 Detector resolution: 7.3910 pixels mm⁻¹
 φ or ω oscillation scans
 Absorption correction: multi-scan
 SADABS2016/2 - Bruker AXS area detector scaling
 and absorption correction

$T_{min} = 0.87$, $T_{max} = 0.99$
 19261 measured reflections
 3478 independent reflections
 3104 reflections with $I > 2\sigma(I)$
 $R_{int} = 0.071$
 $\theta_{max} = 74.5^\circ$, $\theta_{min} = 3.3^\circ$
 $h = -6 \rightarrow 5$
 $k = -15 \rightarrow 16$
 $l = -33 \rightarrow 33$

Refinement

Refinement on F^2
 Least-squares matrix: full

$R[F^2 > 2\sigma(F^2)] = 0.036$
 $wR(F^2) = 0.094$

$S = 1.03$
 3478 reflections
 234 parameters
 0 restraints
 Primary atom site location: dual
 Secondary atom site location: difference Fourier map
 Hydrogen site location: mixed
 H atoms treated by a mixture of independent and
 constrained refinement

$w = 1/[\sigma^2(F_o^2) + (0.0449P)^2 + 0.2271P]$
 where $P = (F_o^2 + 2F_c^2)/3$
 $(\Delta/\sigma)_{\max} < 0.001$
 $\Delta\rho_{\max} = 0.17 \text{ e } \text{\AA}^{-3}$
 $\Delta\rho_{\min} = -0.18 \text{ e } \text{\AA}^{-3}$
 Absolute structure: Flack x determined using 1198
 quotients $[(I+)-(I-)]/[(I+)+(I-)]$ (Parsons, Flack and
 Wagner, Acta Cryst. B69 (2013) 249-259).
 Absolute structure parameter: 0.21 (18)

Special details

Geometry. All e.s.d.'s (except the e.s.d. in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell e.s.d.'s are taken into account individually in the estimation of e.s.d.'s in distances, angles and torsion angles; correlations between e.s.d.'s in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell e.s.d.'s is used for estimating e.s.d.'s involving l.s. planes.

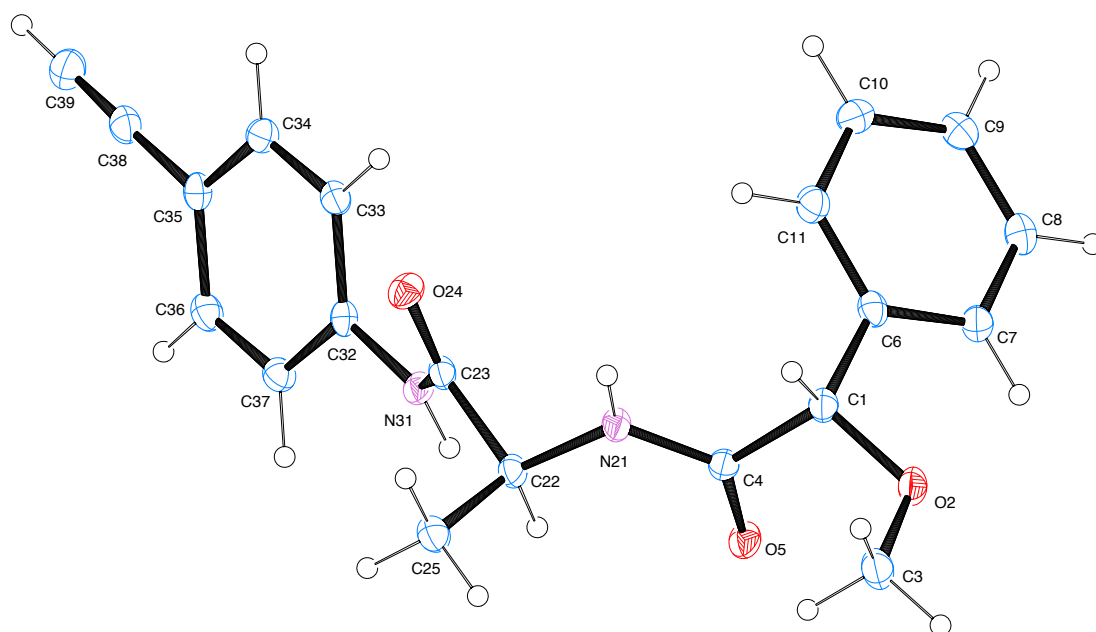
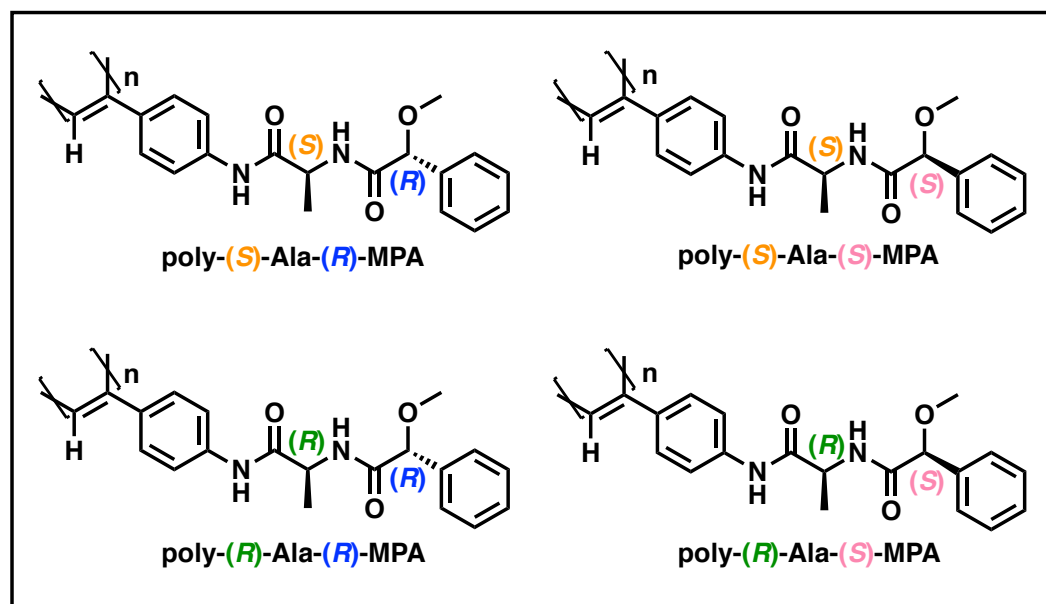


Figure S14. ORTEP representation of mono-(*S*)-Ala-(*S*)-MPA-2 conformation obtained from X-ray studies.

4. Synthesis of polymer derivatives



General procedure for polymerization

The reaction flask (sealed ampoule) was dried under vacuum and argon flushed for three times before monomer was added as a solid. Then, the flask was evacuated on a vacuum line and flushed with dry argon (three times). Dry THF was added with a syringe and then triethylamine was added dropwise via syringe. A solution of rhodium norbornadiene chloride dimer, $[\text{Rh}(\text{nbd})\text{Cl}]_2$, in THF was added at 30°C. The reaction mixture was stirring at 30°C for 6h. Then, the resulting polymer was diluted in DMF and it was precipitated in a large amount of methanol or ether, centrifuged (2 times), reprecipitated in hexane and centrifuged again.

Table S1. Polymerization conditions for poly-(S)-Ala-(R)-MPA-1, poly-(S)-Ala-(S)-MPA-2, poly-(R)-Ala-(R)-MPA-3 and poly-(R)-Ala-(S)-MPA-4.

Polymer	Monomer (mg)	Monomer (mmol)	$[\text{Rh}(\text{nbd})\text{Cl}]_2$ (mg)	THF (ml)	Et_3N (μl)	Yield (%)
poly-(S)-Ala-(R)-MPA-1	70	$2,1 \cdot 10^{-4}$	0.96	0.42	3	82
poly-(S)-Ala-(S)-MPA-2	70	$2,1 \cdot 10^{-4}$	0.96	0.42	3	89
poly-(R)-Ala-(R)-MPA-3	70	$2,1 \cdot 10^{-4}$	0.96	0.42	3	84
poly-(R)-Ala-(S)-MPA-4	70	$2,1 \cdot 10^{-4}$	0.96	0.42	3	72

5. GPC Experiments

The molecular weight (M_n) of all polymers was estimated by GPC with THF as eluent at flow rate 1 ml/min at concentration 0.5 mg/ml using narrow polystyrene standards (PSS) as calibrants.

Table S2. GPC data of poly-(*S*)-Ala-(*R*)-MPA-1, poly-(*S*)-Ala-(*S*)-MPA-2.

Polymer	M_n	M_w	PDI
poly-(<i>S</i>)-Ala-(<i>R</i>)-MPA-1	14220	26619	1.33
poly-(<i>S</i>)-Ala-(<i>S</i>)-MPA-2	14401	35117	2.27

6. NMR Experiments

The polymers display NMR (vinyl protons, δ = 5.7-5.8 ppm) indicative of a *cis*- polyene backbone.

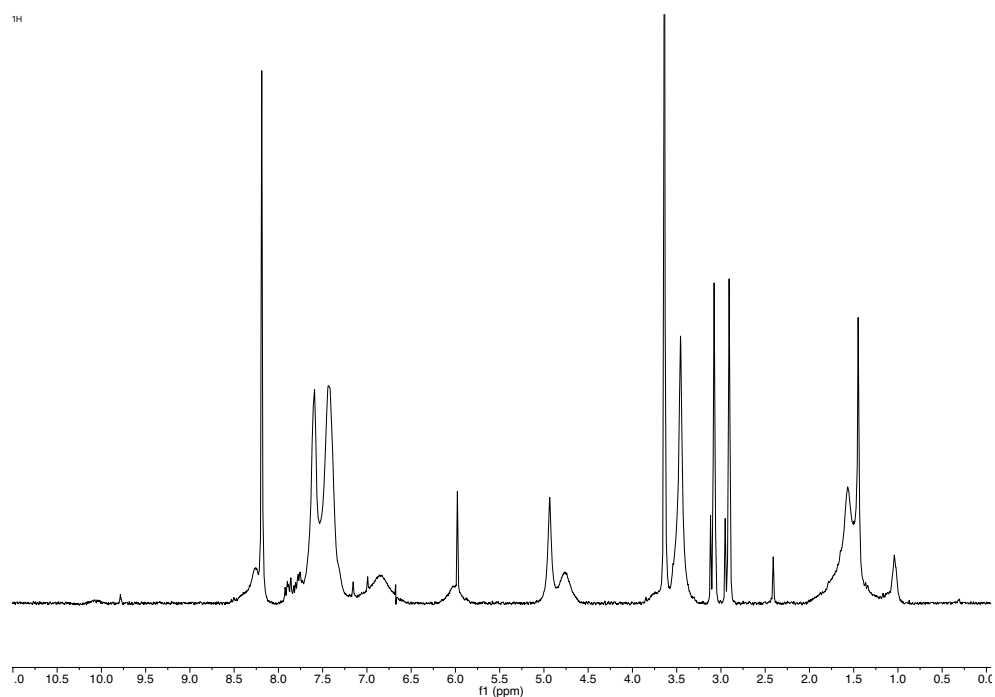


Figure S15. ^1H -NMR spectra of poly-(*S*)-Ala-(*R*)-MPA-1 (DMF- d_7 , 300 MHz).

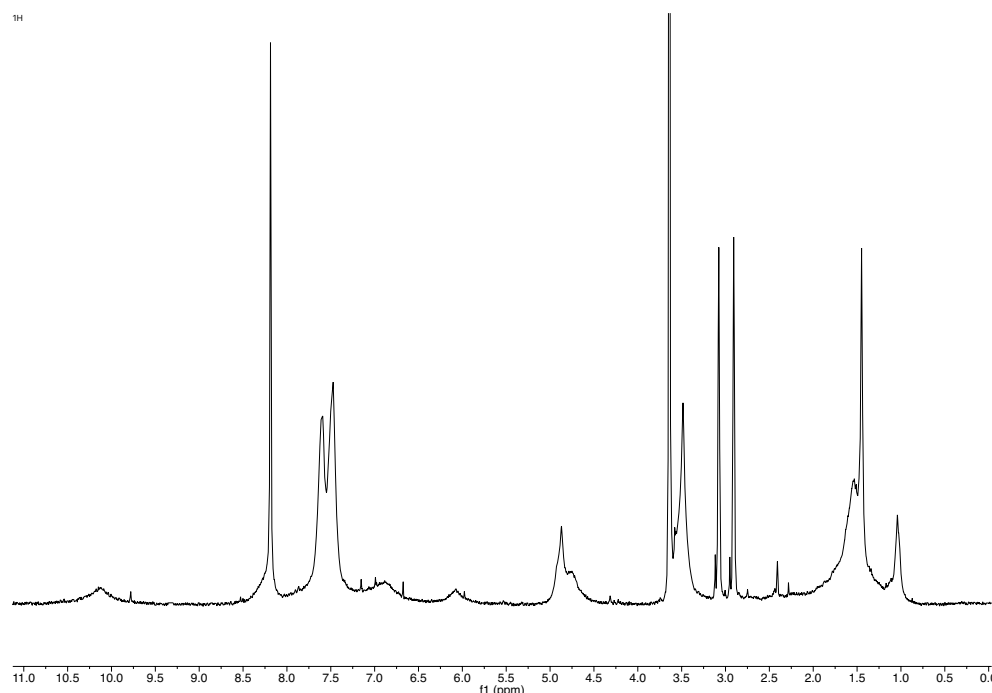


Figure S16. ^1H -NMR spectra of poly-(*S*)-Ala-(*S*)-MPA-2 (DMF- d_7 , 300 MHz).

7. Raman Experiments

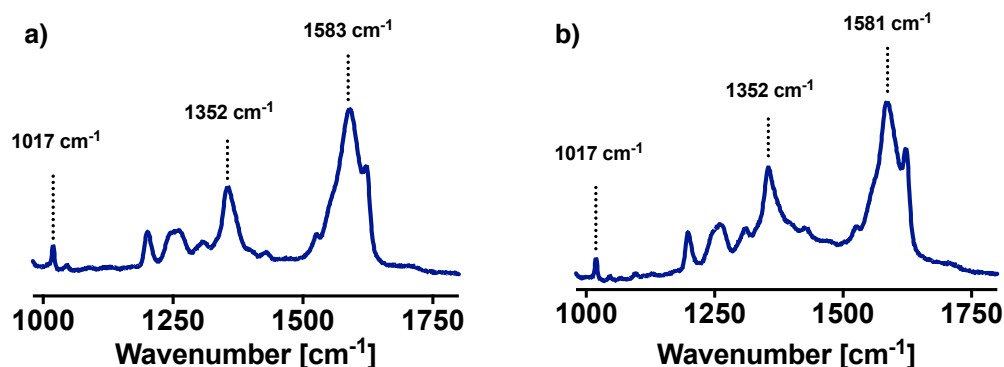


Figure S17. Raman spectra of (a) poly-(*S*)-Ala-(*S*)-MPA-1 and (b) poly-(*S*)-Ala-(*R*)-MPA-2 showing the characteristic bands of a *cis*-polyene backbone.

8. DSC Studies

DSC experiments have been used to determine the configuration of the polymer skeleton in poly(phenylacetylenes) due to the different thermogram pattern for a *cis-cisoidal* or a *cis-transoidal* polyene backbone. For detailed explanation of thermal transitions in PPA's.^[S1] Both DSC traces were recorded using a heating rate of 10°C/min and showed the characteristic thermogram of a *c-t* polymer backbone with the corresponding transitions from *c-t* to *c-c* and a final isomerization from *c-c* to *t-t*.

^{S1} For detailed DSC studies on (PPA)s see: Liu, L.; Namikoshi, T.; Zang, Y.; Aoki, T.; Hadano, S.; Abe, Y.; Wasuzu, I.; Tsutsuba, T.; Teraguchi, M.; Kaneko, T. *J. Am. Chem. Soc.*, **2013**, 135, 602.

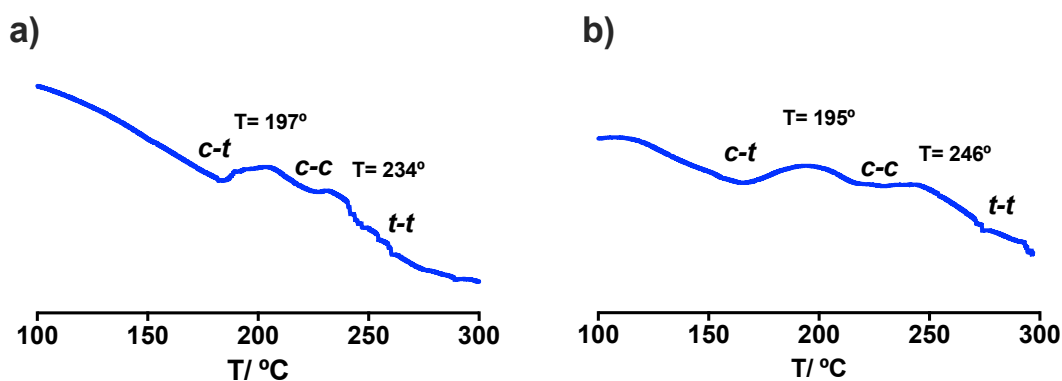


Figure S18. DSC trace of (a) poly-(S)-Ala-(R)-MPA-1 and (b) poly-(S)-Ala-(S)-MPA-2.

9. Thermogravimetric studies

TGA studies were carried out to determine the thermal stability of the polymers. As a general protocol a polymer sample was kept in a platinum pan and heated from 40 $^{\circ}\text{C}$ to 800 $^{\circ}\text{C}$ with a heating rate of 10 $^{\circ}\text{C}/\text{min}$.

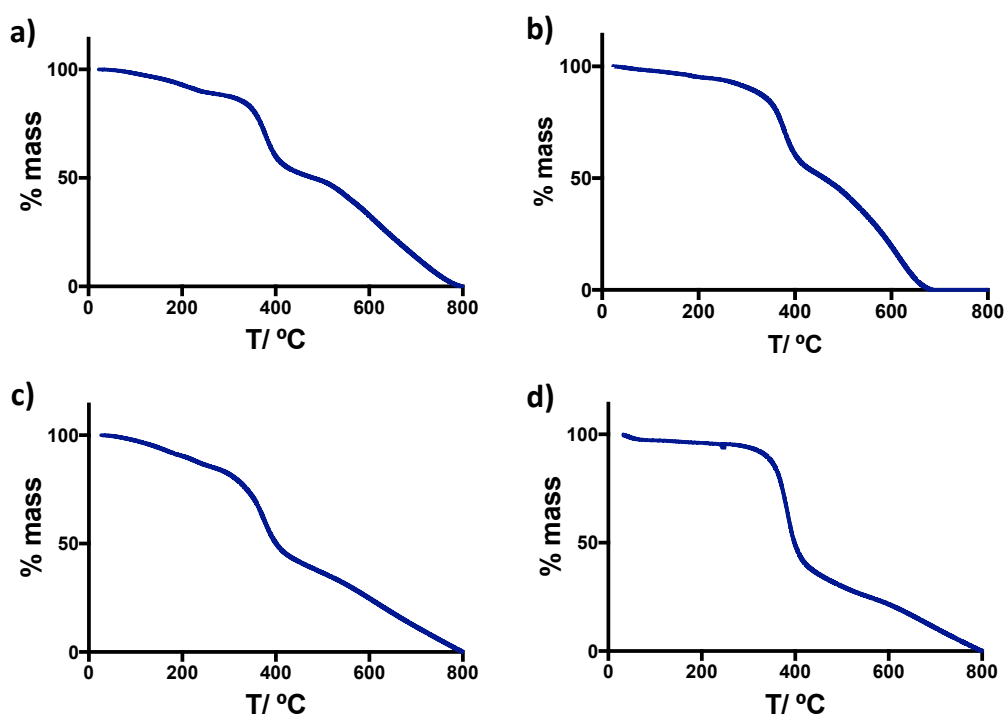


Figure S19. TGA thermograms of (a) poly-(S)-Ala-(R)-MPA-1. (b) poly-(S)-Ala-(S)-MPA-2. (c) poly-(R)-Ala-(R)-MPA-3 and (d) poly-(R)-Ala-(S)-MPA-4.

10. CD/UV-Vis studies in different solvents

Poly-(S)-Ala-(R)-MPA-1, poly-(S)-Ala-(S)-MPA-2, poly-(R)-Ala-(R)-MPA-3 and poly-(R)-Ala-(S)-MPA-4 were measured by CD and UV-Vis in different organic solvents in order to evaluate their helical behavior [PPA] = 0.3 mg/mL, 1 mm cuvette.

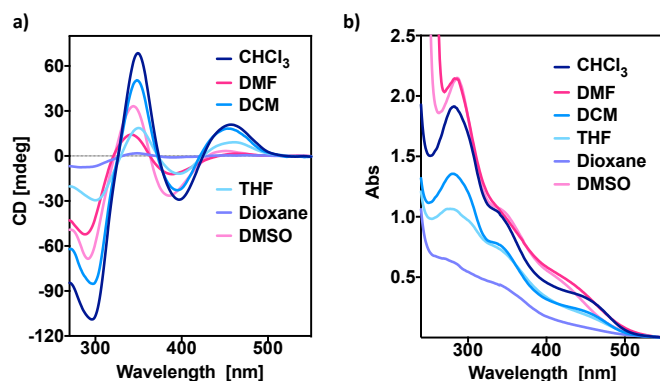


Figure S20. (a) CD and (b) UV-Vis spectra for poly-(S)-Ala-(R)-MPA-1.

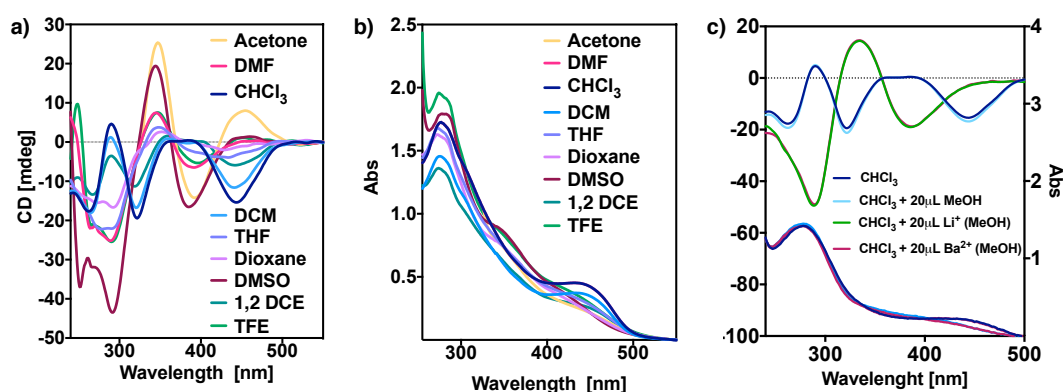


Figure S21. (a) CD and (b) UV-Vis spectra for poly-(S)-Ala-(S)-MPA-2. (c) CD/UV-Vis spectra of poly-(S)-Ala-(S)-MPA-2 in CHCl_3 showing the null impact of MeOH cosolvent in the final structure of poly-(S)-Ala-(S)-MPA-2 after metal coordination (ca. 2 equiv).

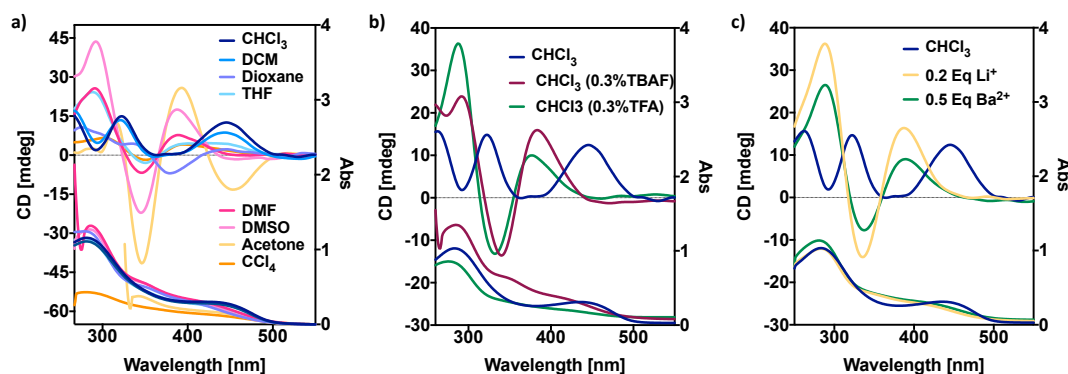


Figure S22. (a) CD and UV-Vis spectra for poly-(R)-Ala-(R)-MPA-3 in different solvents. (b) Hydrogen bond disruptors and (c) Metal coordination.

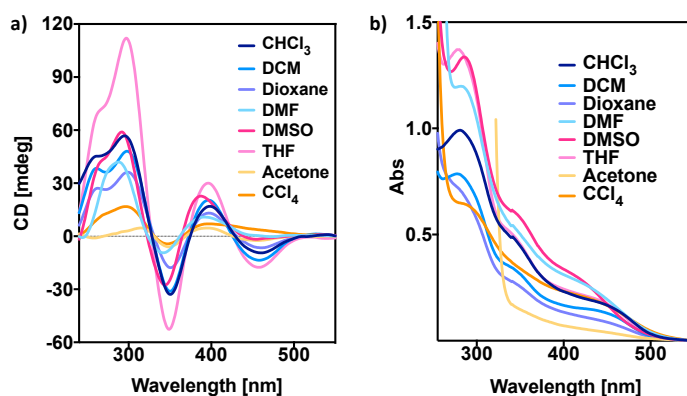


Figure S23. (a) CD and (b) UV-Vis spectra for poly-(*R*)-Ala-(*S*)-MPA-4.

11. Density functional theory-based computations

Gaussian-16 (G16RevC.01) was used to compute the different molecules. The wB97XD functional together with the basis set 6-31G(d,p)^[S2] was used to perform the DFT^[S3] calculations of the γ -turn monomers. To reduce computational costs, the β -sheet aggregates of the extended molecules were calculated with the B3LYP functional and the same 6-31g(d,p) basis set. Geometry optimizations and frequency calculations of the harmonic VCD were performed in all cases without imaginary frequencies. Polarizable Continuum Model (PCM) was employed for the solvent correction.^[S4]

IR and VCD plots are built using a Gaussian band shape of 4 cm⁻¹ full width at half-maximum to reproduce the shape of the experimental spectra.

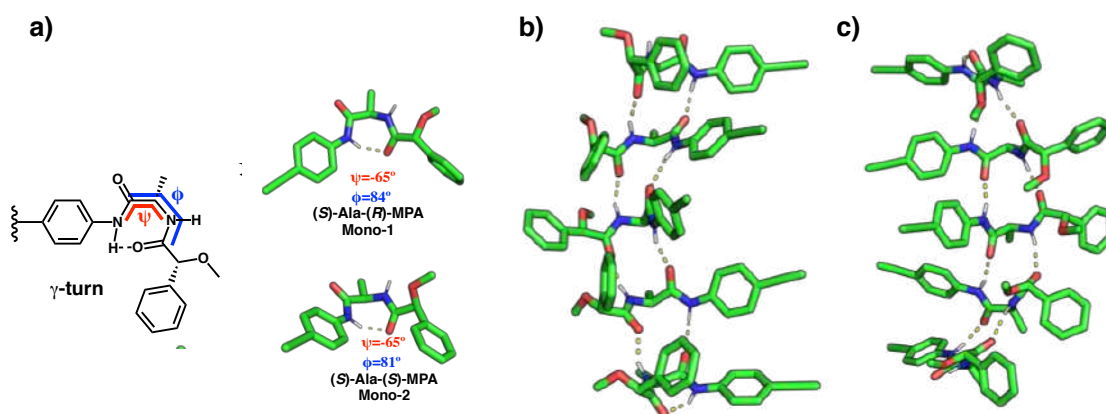


Figure S24. (a) Assignment of dihedral angles and optimized geometries in γ -turn conformations for mono-1 and mono-2. Optimized geometry of β -sheet aggregate of (b) *m*-(*S*)-Ala-(*R*)-MPA-1 and (c) *m*-(*S*)-Ala-(*S*)-MPA-2.

^{S2} Geerlings, P.; De Proft, F.; Langenaeker, W. *Chem. Rev.*, **2003**, 103, 5, 1793-1874.

^{S3} Hohenberg, P.; Kohn, W. *Phys. Rev.*, **1964**, 136, B864-B871.

^{S4} Cossi, M.; Barone, V.; Cammi, R.; Tomasi, J. *Chem. Phys. Lett.*, **1996**, 255, 327-335.

12. Atomic Force Microscopy (AFM) measurements

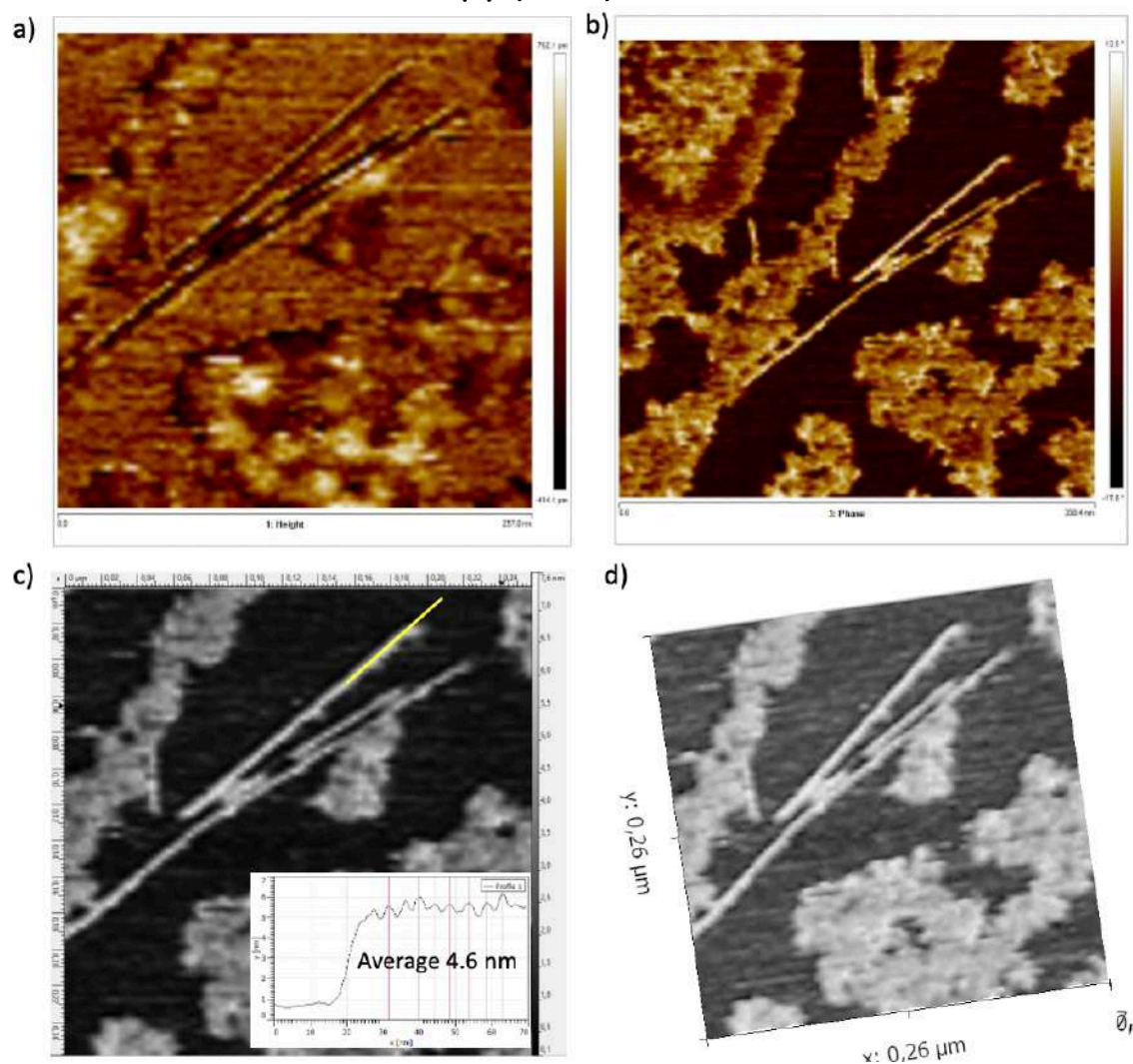


Figure S25. (a) Height and (b) Phase AFM images for the compressed helix of poly-(S)-Ala-(S)-MPA-2. (c) Profile describing the helical pitch of the helix and 3D projection.

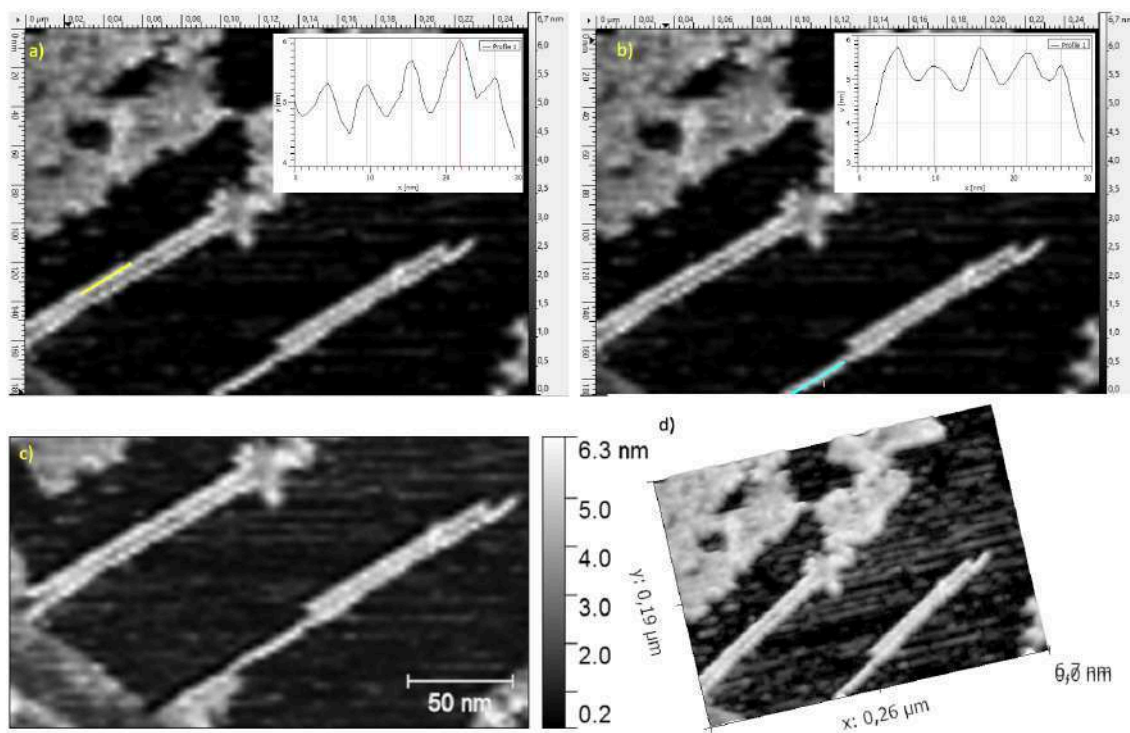


Figure S26. (a-c) height profiles describing the helical pitch of the helix and (d) 3D projection AFM images for the stretched helix of poly-(S)-Ala-(S)-MPA-2.

EXPERIMENTAL SECTION

CHAPTER II

1. Materials and methods

CD measurements were done in a Jasco-720.

UV spectra were registered in a Jasco-630.

The optical rotation was measured in a Jasco P-2000.

NMR experiments were measured in a Varian 300 operating at 300 MHz for proton NMR and 75 MHz for carbon. CDCl_3 signal ($\delta = 77.2$ ppm) was used as standard for ^{13}C experiments.

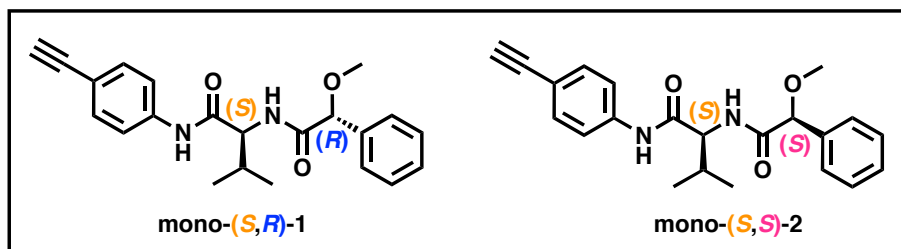
FT-IR measurements were carried out on a Bruker IFS-66v while Raman spectra were carried out in a Renishaw confocal Raman spectrometer (Invia Reflex model), equipped with two lasers (diode laser 785 nm and Ar laser 514 nm).

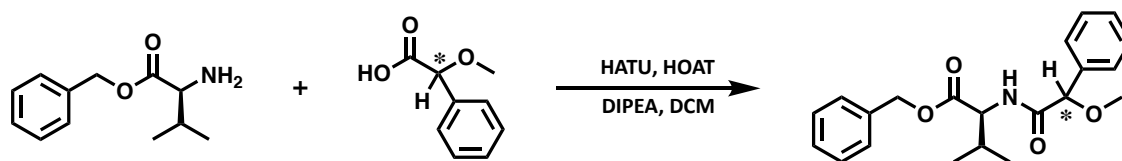
DSC traces were obtained in a DSC Q200 Tzero Technology (TA Instruments, New Castle, UK), equipped with a refrigerated cooling system RCS90 (TA Instruments, New Castle, UK), using a Tzero low-mass aluminium pan.

TGA traces were obtained in a TGA Q5000 (TA Instruments, New Castle, UK) using a platinum pan.

GPC studies were carried out in a Waters Alliance equipped with Phenomenex GPC columns.

2. Synthesis of monomers



Benzyl [(*R*)- and (*S*)-2-methoxy-2-phenylacetyl]-(*S*)-valinate

(2-(7-Aza-1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (HATU, 2.60 g, 1.20 equiv), 1-hydroxy-7-azabenzotriazole (HOAT, 0.90 g, 1.20 equiv), (*R*)- or (*S*)-2-methoxy-2-phenylacetic acid (1.00 g, 1.20 equiv) and diisopropyltriethylamine (DIPEA, 1.25 mL, 1.20 equiv) were dissolved in 30 mL of DCM, and the mixture was stirred for 20 min to activate the acid. Then, (*S*)-valine benzyl ester hydrochloride (1.40 g, 1.00 equiv) was added and the reaction mixture was stirred 48h. Then the solvent was evaporated at reduced pressure and the crude was diluted in DCM, the organic layer was washed with HCl 1M, saturated solution of NaHCO₃ and brine. The combined organic layers were dried over anhyd. Na₂SO₄, filtered and the solvent was evaporated at reduced pressure. The crude product was chromatographed on silica gel (40-63 mesh) with hexane/ethyl acetate (7/3) as eluent obtaining benzyl [(*R*) or (*S*)-2-methoxy-2-phenylacetyl]-(*S*)-valinate in 91 and 85 % yield (1.05 g and 0.98 g, respectively).

NMR data of [(*R*)-2-methoxy-2-phenylacetyl]-(*S*)-valinate

^1H NMR (300 MHz, CDCl_3) δ (ppm): 7.39 – 7.14 (m, 12H), 5.11 (q, $J=12.2$ Hz, 1.5 Hz, 2H), 4.62 – 4.49 (m, 2H), 3.30 (d, $J=1.5$ Hz, 3H), 2.23 – 1.96 (m, 1H), 0.75 (m, 5H).

^{13}C NMR (75 MHz, CDCl_3) δ (ppm): 171.6, 170.6, 137.1, 135.3, 128.5, 128.5, 128.4, 128.4, 128.3, 126.8, 101.0, 83.9, 67.0, 57.3, 56.3, 31.4, 18.9, 17.4.

HRMS (ESI) m/z calc for $\text{C}_{21}\text{H}_{25}\text{NO}_4$ [$\text{M}+\text{H}$]: 328.1471, found: 328.1584.

$\alpha_{\text{D}}^{20} = -87$ ($c = 10$ mg/mL, CHCl_3).

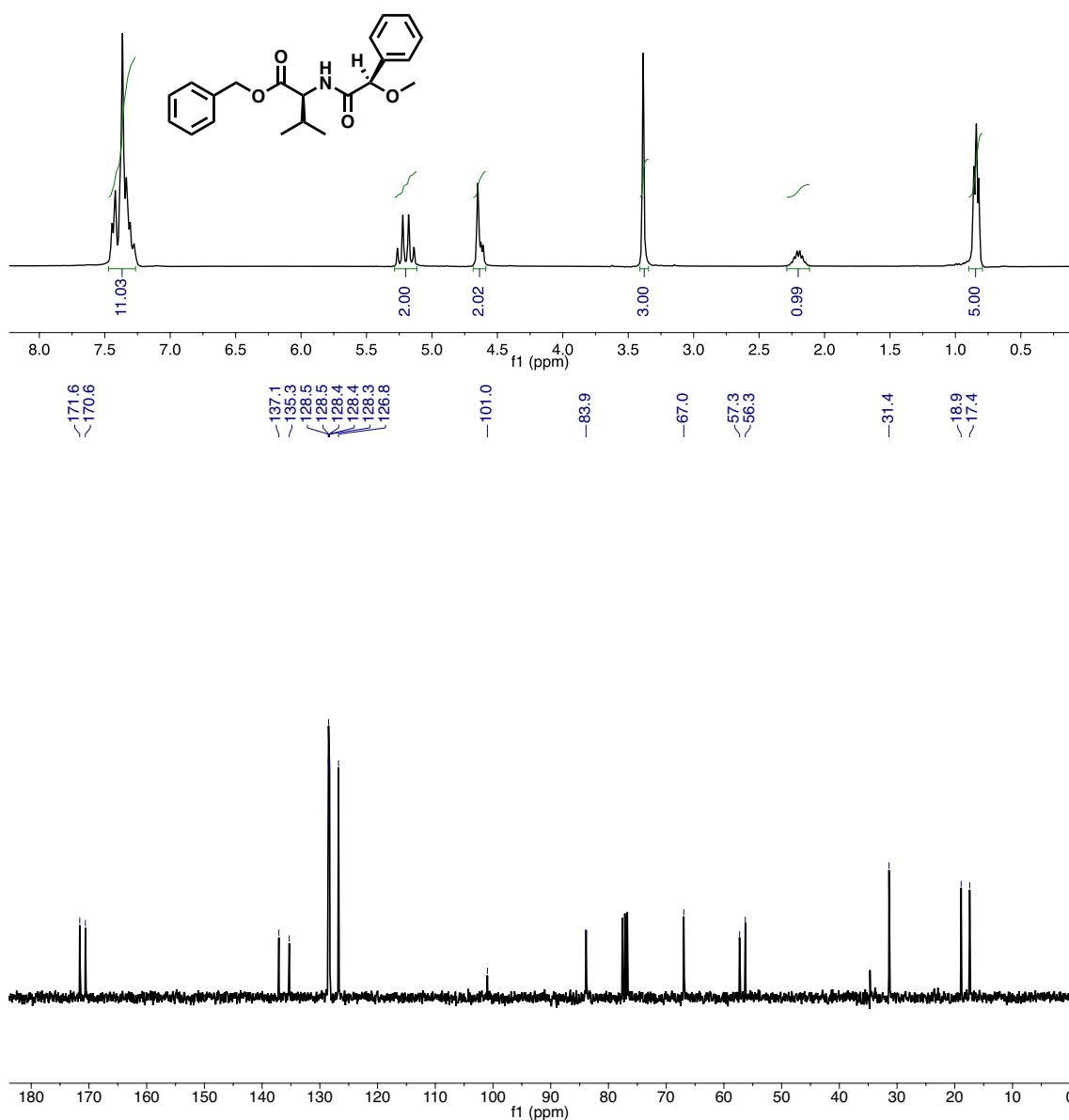


Figure S1. (a) ^1H -NMR and (b) ^{13}C -NMR of [(*R*)-2-methoxy-2-phenylacetyl]-(*S*)-valinate in CDCl_3 .

NMR data of [(S)-2-methoxy-2-phenylacetyl]-(S)-valinate

^1H NMR (300 MHz, CDCl_3) δ (ppm): 7.45 – 7.29 (m, 11H), 7.24 (d, $J=10.0$ Hz, 1H), 5.14 (q, 2H), 4.66 (s, 1H), 4.60 (dd, $J=9.2, 4.7$ Hz, 1H), 3.39 (s, 3H), 2.35 – 2.18 (m, 1H), 0.95 (dd, $J=17.3, 6.9$ Hz, 5H).

^{13}C NMR (75 MHz, CDCl_3) δ (ppm): 171.5, 170.6, 136.9, 135.5, 128.7, 128.6, 128.5, 128.5, 127.4, 83.9, 67.1, 57.3, 56.8, 31.4, 19.2, 17.8.

HRMS (ESI) m/z calc for $\text{C}_{21}\text{H}_{25}\text{NO}_4$ $[\text{M}+\text{H}]$: 328.1471, found: 328.1543.

$\alpha_D^{20} = +36$ (c = 10 mg/mL, CHCl_3).

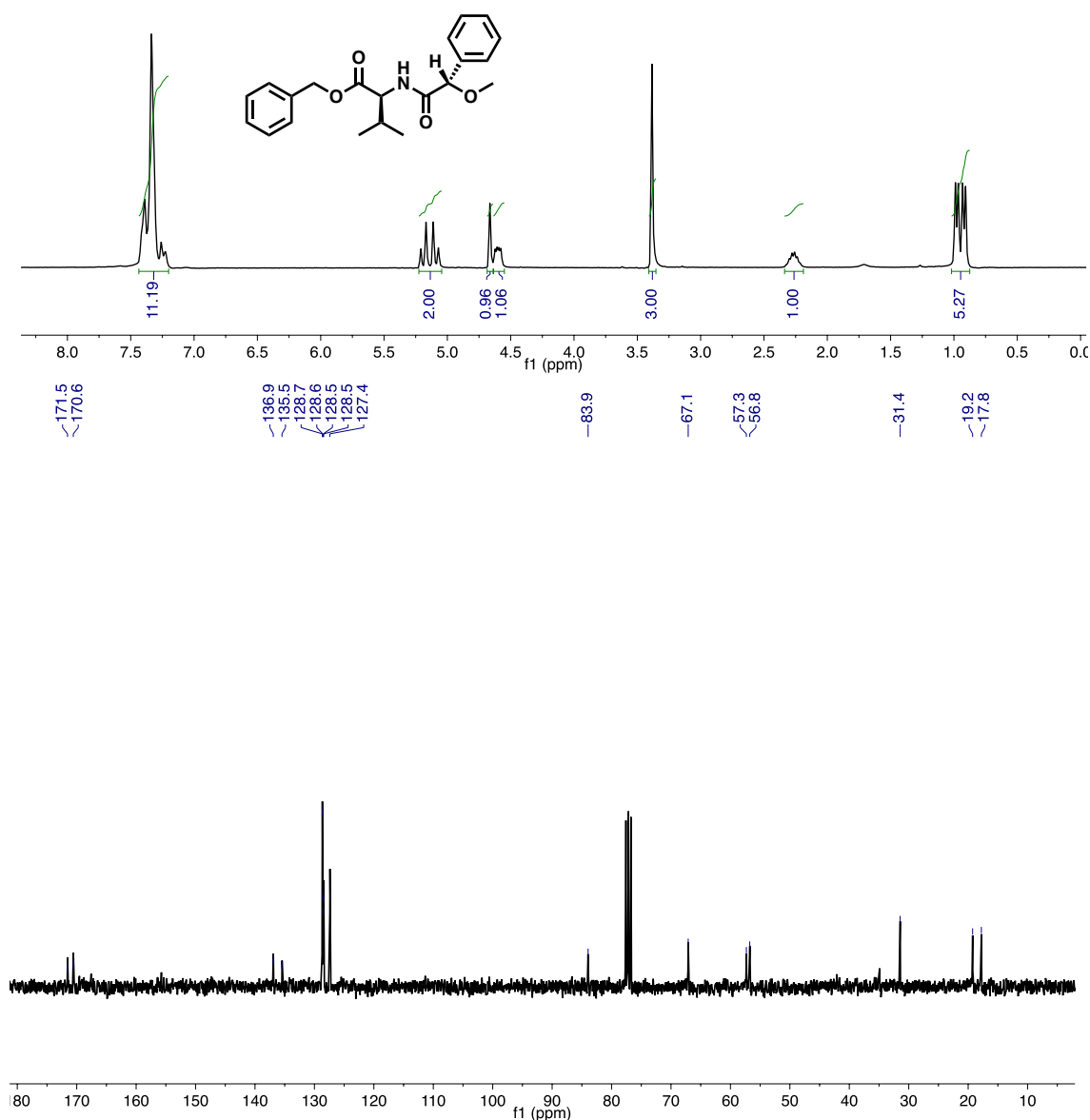
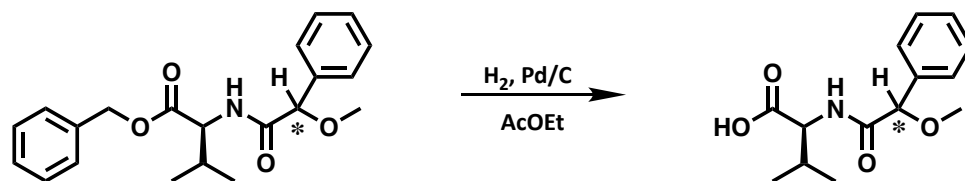


Figure S2. (a) ^1H -NMR and (b) ^{13}C -NMR of [(S)-2-methoxy-2-phenylacetyl]-(S)-valinate in CDCl_3 .

[(*R*)- and (*S*)-2-methoxy-2-phenylacetyl]-(*S*)-valine

Pd/C (0.12 g) was suspended in 30 ml of EtOAc and submitted to three cycles of vacuum/purge with hydrogen. Then the Pd/C suspension was stirred under hydrogen atmosphere for 20 min and next a solution of benzyl [(*R*)- or (*S*)-2-methoxy-2-phenylacetyl]-(*S*)-valinate (0.50 g, 1.41 mmol) in 15 mL of EtOAc was injected to the reaction vessel via syringe. After one hour TLC analysis showed no presence of the starting material and the suspension was filtered through celite and washed thoroughly with EtOAc, obtaining [(*R*)- and (*S*)-2-methoxy-2-phenylacetyl]-(*S*)-valine in quantitative yield (0.37 g both compounds).

NMR data of [(*R*)-2-methoxy-2-phenylacetyl]-(*S*)-valine

^1H NMR (300 MHz, CDCl_3) δ (ppm): 9.56 (s, 1H), 7.44 – 7.26 (m, 6H), 4.71 (s, 1H), 4.55 (dd, $J=9.1$ Hz, 4.6 Hz, 1H), 3.37 (s, 3H), 2.36 – 2.20 (m, 1H), 0.99 (dd, $J=9.6$ Hz, 6.8 Hz, 5H).

^{13}C NMR (75 MHz, CDCl_3) δ (ppm): 175.4, 171.4, 136.6, 128.7, 127.5, 83.7, 57.2, 56.8, 31.2, 19.2, 17.7.

HRMS (ESI) m/z calc for $\text{C}_{14}\text{H}_{19}\text{NO}_4\text{Na}$ [$\text{M}+\text{Na}$]: 288.1207, found: 288.1206.

$\alpha_D^{20} = -88$ ($c = 10$ mg/mL, CHCl_3).

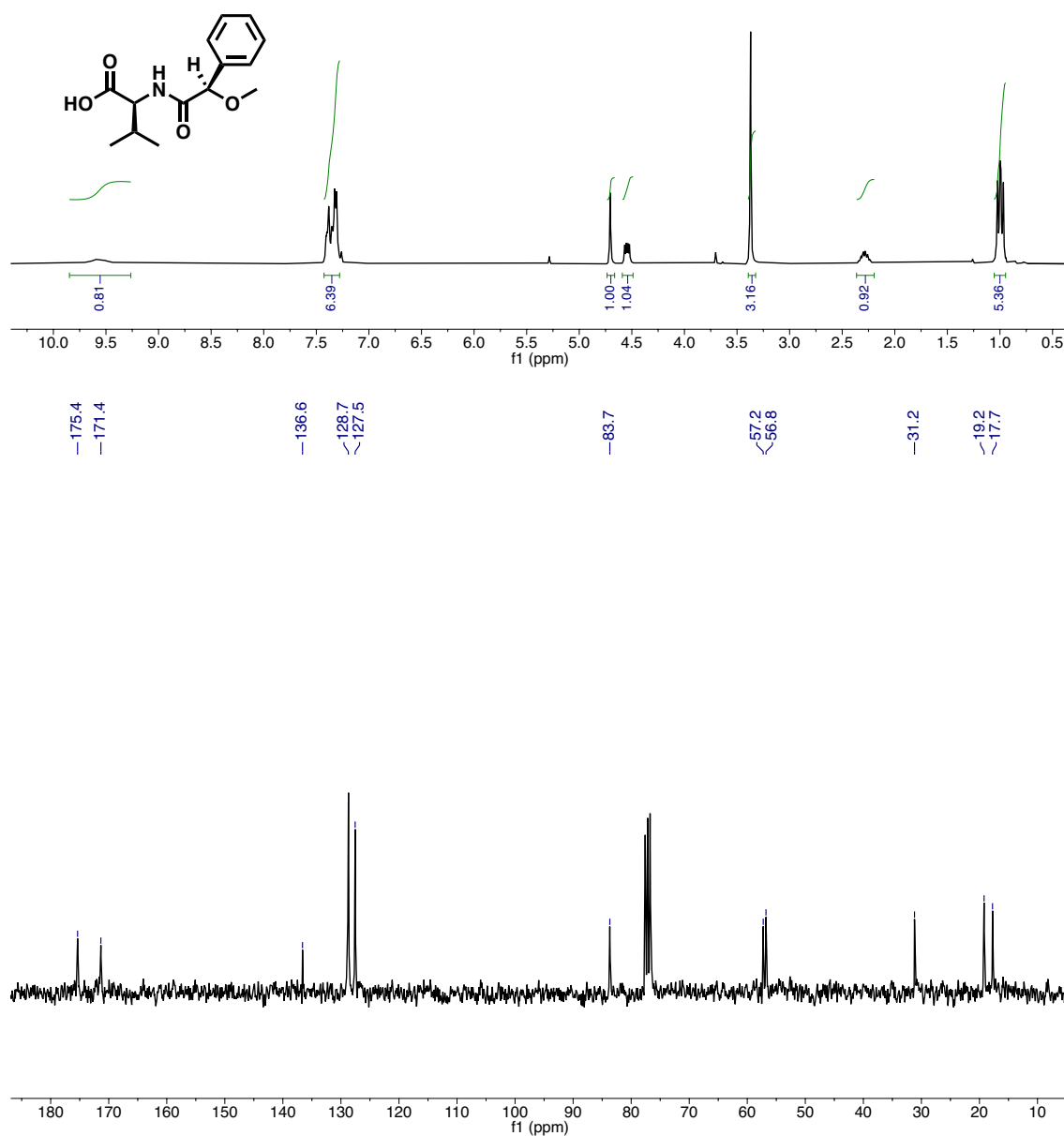


Figure S3. (a) ^1H -NMR and (b) ^{13}C -NMR of [(*R*)-2-methoxy-2-phenylacetyl]-(*S*)-valine in CDCl_3 .

NMR data of [(S)-2-methoxy-2-phenylacetyl]-(S)-valine

^1H NMR (300 MHz, CDCl_3) δ (ppm): 10.42 (s, 1H), 7.38 (dd, $J=18.5$ Hz, 7.5 Hz, 6H), 4.72 (d, $J=1.5$ Hz, 1H), 4.63 – 4.52 (m, 1H), 3.40 (s, 3H), 2.31 – 2.14 (m, 1H), 0.90 (dd, $J=15.2$ Hz, 6.8 Hz, 5H).

^{13}C NMR (75 MHz, CDCl_3) δ (ppm): 175.1, 171.7, 136.9, 128.7, 127.1, 83.7, 57.4, 56.5, 31.3, 19.0, 17.5.

HRMS (ESI) m/z calc for $\text{C}_{14}\text{H}_{19}\text{NO}_4\text{Na}$ [$\text{M}+\text{Na}$]: 288.1207, found: 288.1205.

$\alpha_{\text{D}}^{20} = +62$ ($c = 10$ mg/mL, CHCl_3).

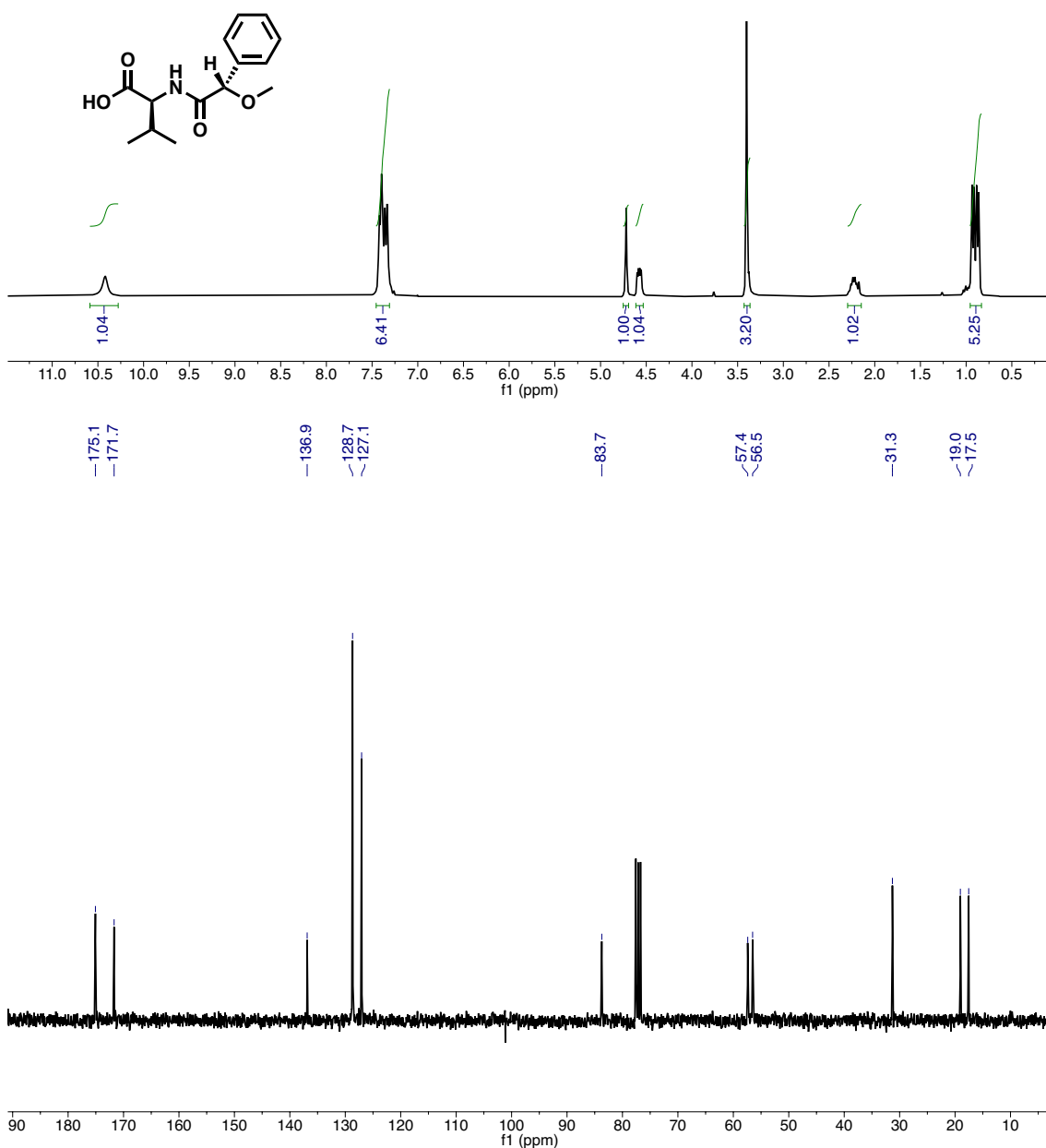
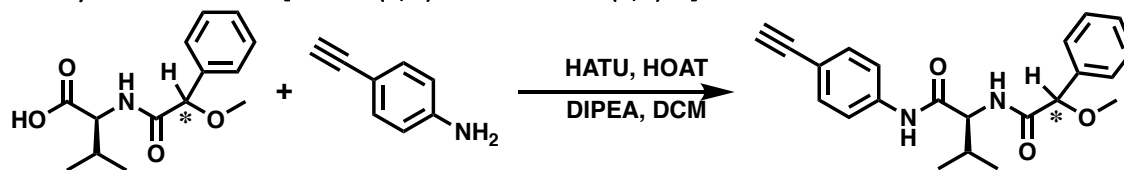


Figure S4. (a) ^1H -NMR and (b) ^{13}C -NMR of [(S)-2-methoxy-2-phenylacetyl]-(S)-valine in CDCl_3 .

(*S*) and (*R*)-*N*-(4-ethynylphenyl)-2-[(*S*)- and (*R*)-2-methoxy-2-phenylacetamido]-3-methylbutanamide—[mono-(*S,R*)-1 and mono-(*S,S*)-2]



(2-(7-Aza-1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (HATU, 0.36 g, 1.20 equiv), 1-hydroxy-7-azabenzotriazole (HOAT, 0.13 g, 1.20 equiv), the corresponding [(*R*)- and (*S*)-2-methoxy-2-phenylacetyl]-(*S*)-valine and [(*R*)- and (*S*)-2-methoxy-2-phenylacetyl]-(*R*)-valine (0.25 g, 1.20 equiv) and diisopropyltriethylamine (DIPEA, 0.16 mL, 1.20 equiv) were dissolved in 20 mL of DCM, and the mixture was stirred for 20 min to activate the acid. Then, 4-ethynylaniline (0.09 g, 1.00 equiv) was added and the reaction mixture was stirred overnight. Then, the reaction mixture was washed with HCl 1M (x3), saturated solution of NaHCO₃ and brine. The organic layer was dried over anhyd Na₂SO₄, filtered and the solvent was evaporated at reduced pressure. The crude product was chromatographed on silica gel (40-63 mesh) with hexane/ethyl acetate (7/3) as eluent obtaining the corresponding monomers mono-(*S,R*)-1 and mono-(*S,S*)-2 in 80 and 82% yield (0.27 g and 0.28 g, respectively).

NMR data of mono-(*S,R*)-**1**

^1H NMR (300 MHz, CDCl_3) δ (ppm): 9.06 (s, 1H), 7.57 (d, $J=9.2$ Hz, 1H), 7.43 – 7.27 (m, 5H), 7.20 (d, $J=8.2$ Hz, 2H), 7.10 (d, $J=8.4$ Hz, 2H), 4.67 (s, 1H), 4.61 (t, $J=8.3$ Hz, 1H), 3.33 (s, 3H), 3.01 (s, 1H), 2.20 (hept, $J=6.8$ Hz, 1H), 1.03 (dd, $J=6.8$ Hz, 2.4 Hz, 5H).

^{13}C NMR (75 MHz, CDCl_3) δ (ppm): 171.2, 169.5, 138.3, 136.5, 132.5, 128.8, 128.7, 127.6, 119.4, 117.1, 83.6, 58.7, 56.9, 31.1, 19.3, 18.4.

HRMS (ESI) m/z calc for $\text{C}_{22}\text{H}_{24}\text{N}_2\text{O}_3$ [$\text{M}+\text{Na}^+$]: 387.1679, found: 387.1683.

$\alpha_{\text{D}}^{20} = -118$ ($c = 10$ mg/mL, CHCl_3).

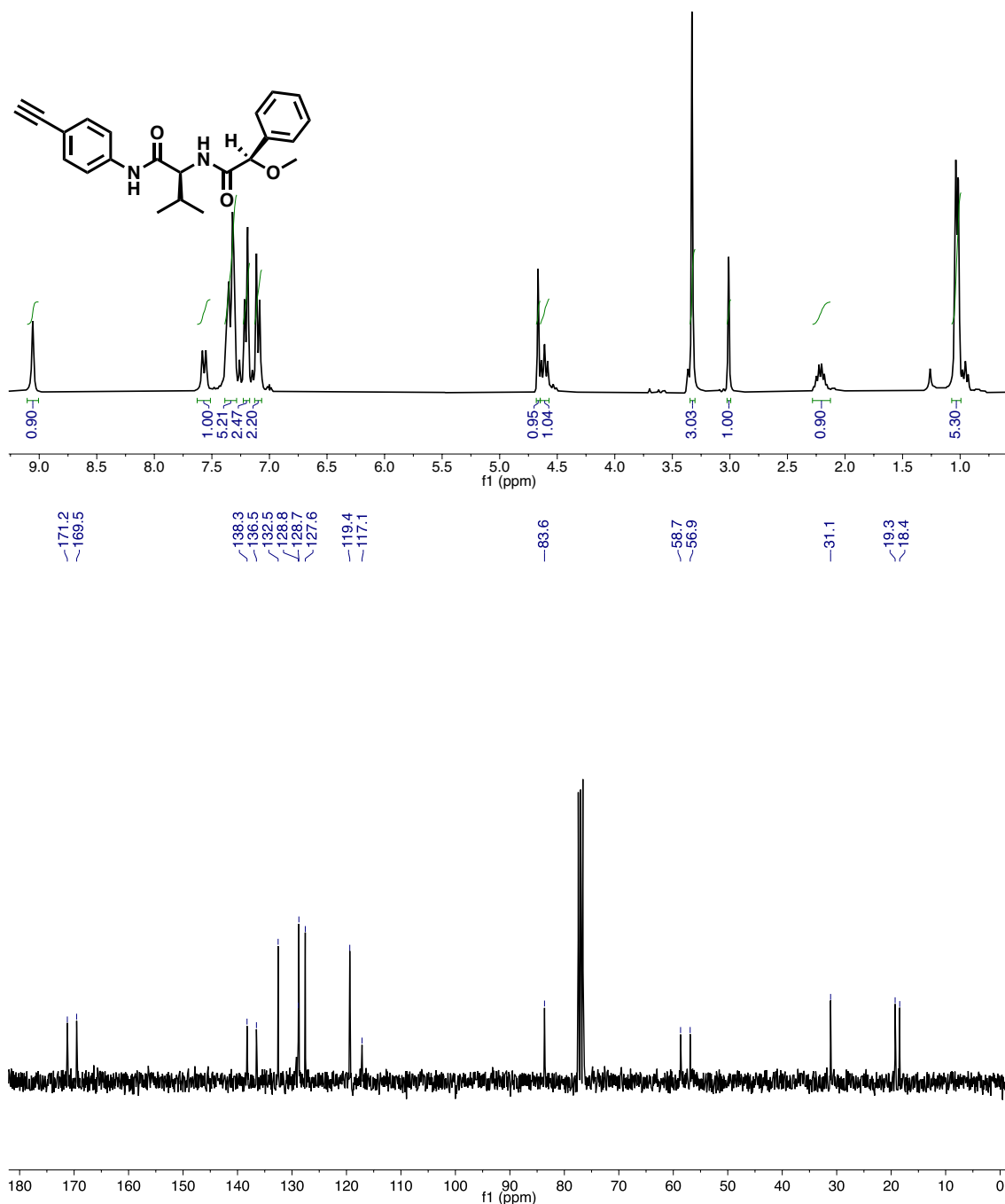


Figure S5. (a) ^1H -NMR and (b) ^{13}C -NMR spectra of *m*-(*S,R*)-**1** in CDCl_3 .

NMR data of mono-(*S,S*)-2

^1H NMR (300 MHz, CDCl_3) δ (ppm): 9.09 (s, 1H), 7.60 – 7.30 (m, 11H), 4.64 (s, 1H), 4.45 (dd, $J=9.0$ Hz, 7.5 Hz, 1H), 3.38 (s, 3H), 3.06 (s, 1H), 2.10 (hept, $J=6.7$ Hz, 1H), 0.88 (dd, $J=14.1$ Hz, 6.7 Hz, 7H).

^{13}C NMR (75 MHz, CDCl_3) δ (ppm): 171.4, 169.8, 138.5, 136.9, 132.9, 128.9, 128.8, 127.4, 119.8, 117.7, 83.9, 83.7, 59.0, 57.3, 31.2, 19.3, 18.5.

HRMS (ESI) m/z calc for $\text{C}_{22}\text{H}_{24}\text{N}_2\text{O}_3$ $[\text{M}+\text{Na}^+]$: 387.1679, found: 387.1684.

$\alpha_D^{20} = -87$ ($c = 10$ mg/mL, CHCl_3).

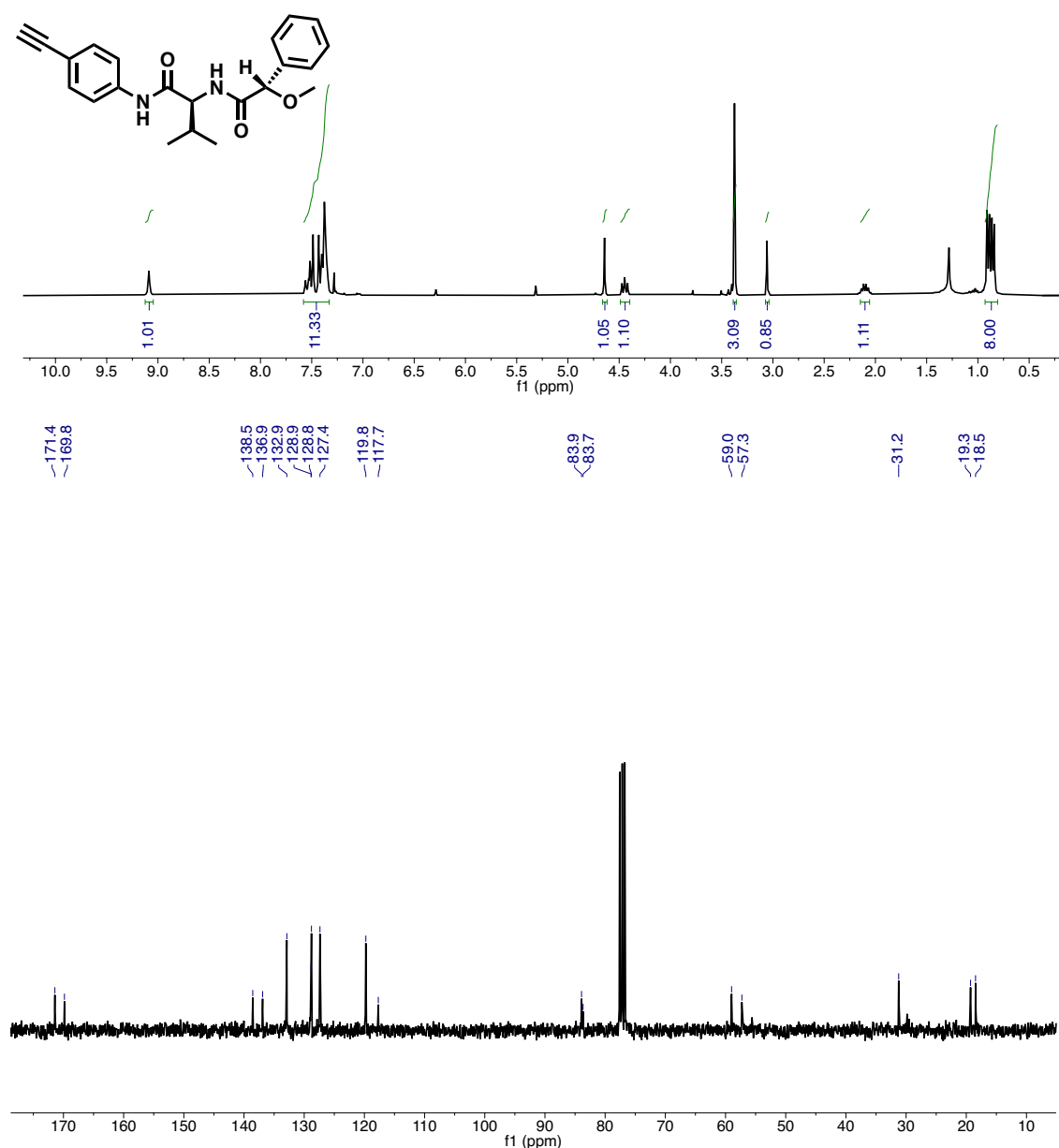
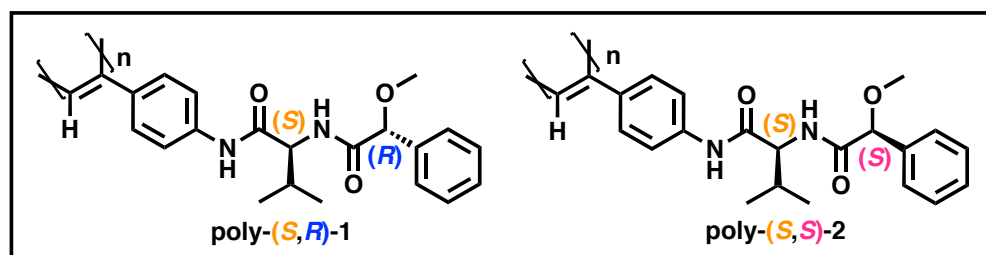


Figure S6. (a) ^1H -NMR and (b) ^{13}C -NMR spectra of m-(*S,S*)-2 in CDCl_3 .

3. Synthesis of polymer derivatives



General procedure for polymerization

The reaction flask (sealed ampoule) was dried under vacuum and argon flushed for three times before monomer was added as a solid. Then, the flask was evacuated on a vacuum line and flushed with dry argon (three times). Dry THF was added with a syringe and then triethylamine was added dropwise via syringe. A solution of rhodium norbornadiene chloride dimer, $[\text{Rh}(\text{nbd})\text{Cl}]_2$, in THF was added at 30°C. The reaction mixture was stirring at 30°C for 6h. Then, the resulting polymer was diluted in THF and it was precipitated in a large amount of methanol, centrifuged (2 times), reprecipitated in hexane and centrifuged again.

Table S1. Polymerization conditions for poly-(*S,R*)-1 and poly-(*S,S*)-2.

Polymer	Monomer (mg)	Monomer (mmol)	$[\text{Rh}(\text{nbd})\text{Cl}]_2$ (mg)	THF (ml)	Et_3N (μl)	Yield (%)
poly-(<i>S,R</i>)-1	70	$1,9 \cdot 10^{-4}$	0.88	0.38	2.70	83
poly-(<i>S,S</i>)-2	70	$1,9 \cdot 10^{-4}$	0.88	0.38	2.70	87

4. GPC Experiments

The molecular weight (M_n) of all polymers was estimated by GPC with THF as eluent at flow rate 1 ml/min at concentration 0.5 mg/ml using narrow polystyrene standards (PSS) as calibrants.

Table S2. GPC data of poly-(*S,R*)-1 and poly-(*S,S*)-2.

Polymer	M_n	M_w	PDI
poly-(<i>S,R</i>)-1	190000	376000	1.98
poly-(<i>S,S</i>)-2	61000	89900	1.47

5. NMR Experiments

The polymers display NMR (vinyl protons, δ = ca. 5.8 ppm) indicative of a *cis*- polyene backbone.

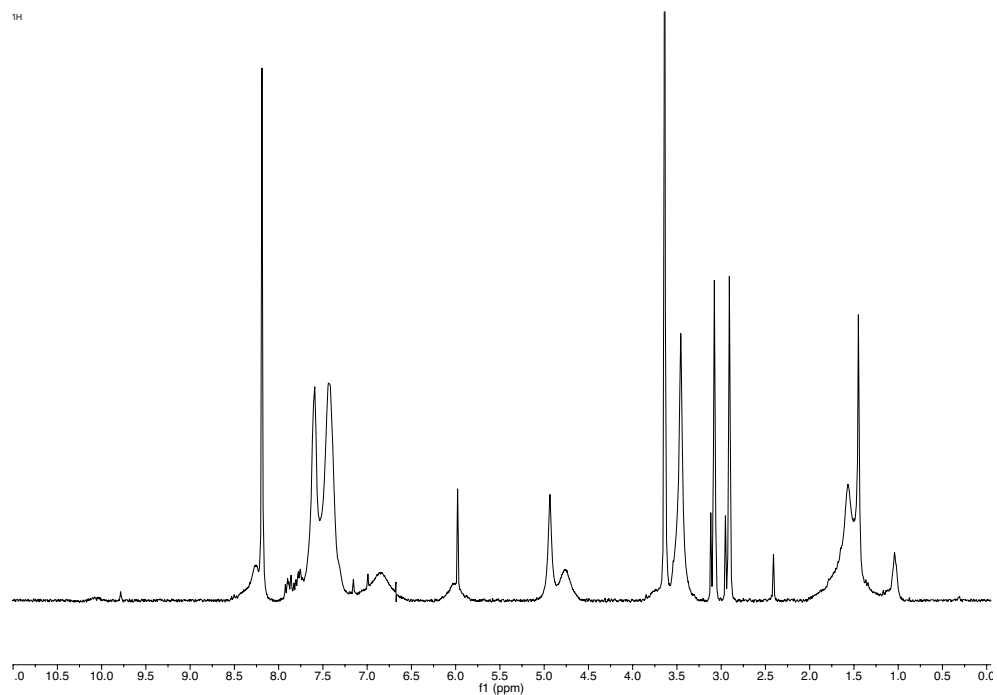


Figure S7. ^1H -NMR spectra of poly-(*S,R*)-**1** (DMF- d_7 , 300 MHz).

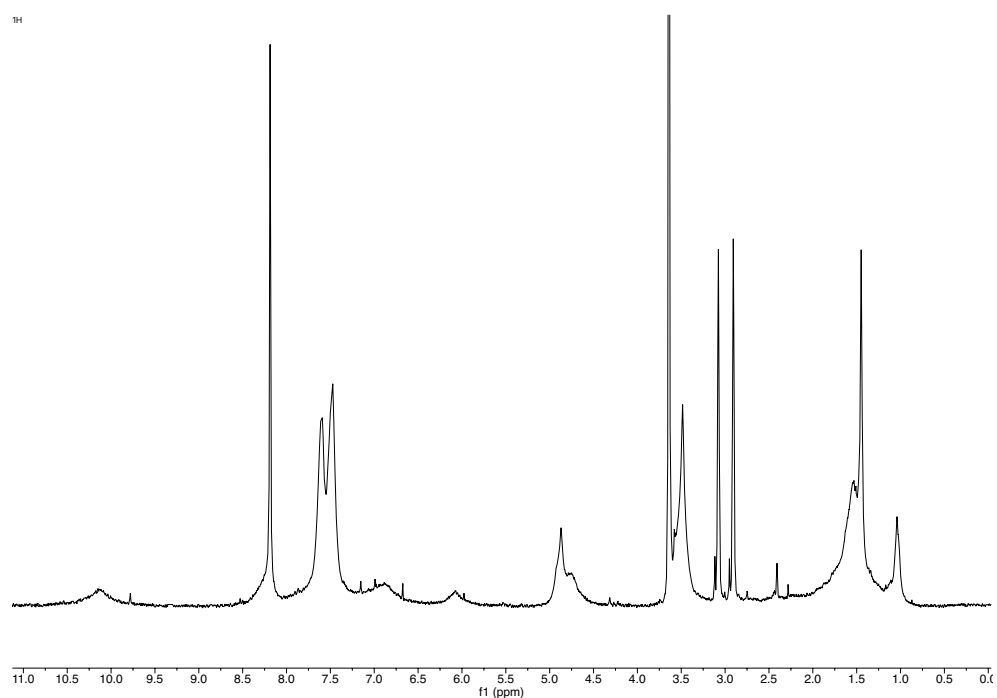


Figure S8. ^1H -NMR spectra of poly-(*S,S*)-**2** (DMF- d_7 , 300 MHz).

6. Raman Experiments

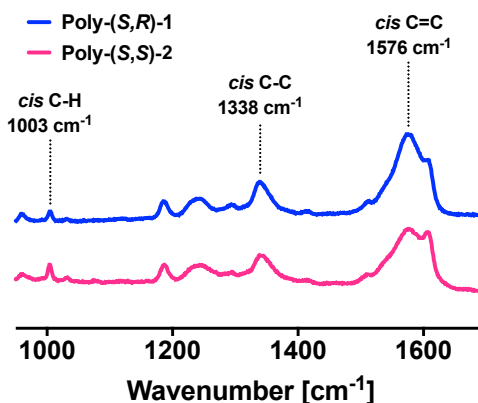


Figure S9. Raman spectra of (a) poly-(*S,R*)-1 and (b) poly-(*S,S*)-2 showing the characteristic bands of a *cis*-polyene backbone (from lower to higher wavenumbers: *cis*-C-H, *cis*-C-C and *cis*-C=C).

7. DSC Studies

DSC experiments have been used to determine the configuration of the polymer skeleton in poly(phenylacetylenes) due to the different thermogram pattern for a *cis-cisoidal* or a *cis-transoidal* polyene backbones. For detailed explanation of thermal transitions in PPA's see ref S1. Both DSC traces were recorded using a heating rate of 10°C/min and showed thermograms referable to *c-c* and *c-t* polymer backbones in DCM and DMF, respectively. The sample prepared annealed in DCM show a single thermal transition centered at 220 compatible with a *cis-cisoidal* scaffold. The sample annealed in DMF display two consecutive thermal transitions centered at 158 and 215°C ascribable to *cis-transoidal* polyene skeleton.^[S1]

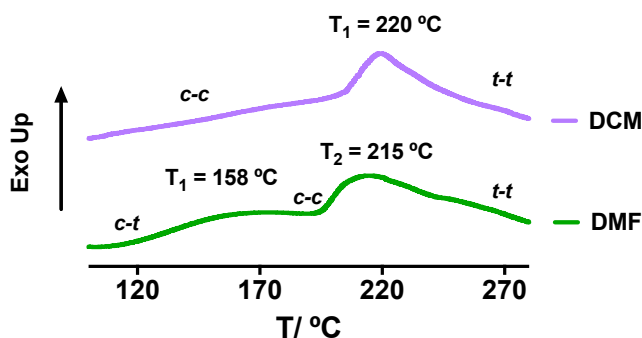


Figure S10. Comparison of the DSC traces of poly-(*S,R*)-1 in compressed and stretched forms.

^{S1} Liu, L.; Namikoshi, T.; Zang, Y.; Aoki, T.; Hadano, S.; Abe, Y.; Wasuzu, I.; Tsutsuba, T.; Teraguchi, M.; Kaneko, T. *J. Am. Chem. Soc.* **2013**, *135*, 602-605.

8. Thermogravimetric studies

TGA studies were carried out to determine the thermal stability of the polymers. As a general protocol a polymer sample was kept in a platinum pan and heated from 40°C to 800°C with a heating rate of 10°C/min.

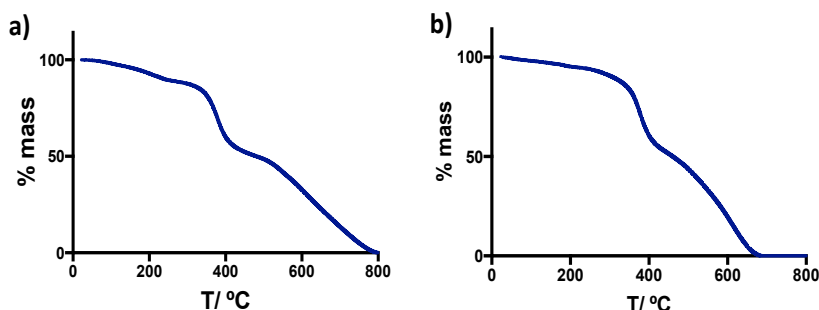


Figure S11. TGA thermograms of (a) poly-(*S,R*)-1 and (b) poly-(*S,S*)-2.

9. CD/UV-Vis studies in different solvents

Poly-(*S,R*)-1 and poly-(*S,S*)-2 were measured by CD and UV-Vis in different organic solvents to evaluate their helical behavior [PPA] = 0.3 mg/mL, 1 mm cuvette.

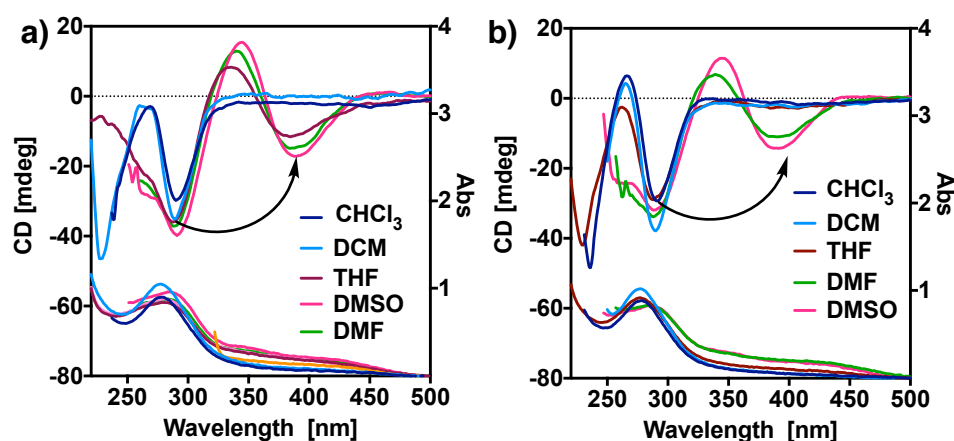


Figure S12. ECD and UV-Vis spectra for (a) poly-(*S,R*)-1 and (b) poly-(*S,S*)-2.

10. Optical rotation studies

Table S3. Comparison of the Optical Rotation data of stretched and compressed helical structures of poly-(*S,R*)-1 and poly-(*S,S*)-2.

mono-(<i>S,R</i>)-1	poly-(<i>S,R</i>)-1	mono-(<i>S,S</i>)-2	poly-(<i>S,S</i>)-2
$\alpha_D^{20} = -118$ (10 mg/mL, CHCl ₃)	Compressed (DCM) $\alpha_D^{20} = -407$ (10 mg/mL)	$\alpha_D^{20} = -87$ (10 mg/mL, CHCl ₃)	Compressed (DCM) $\alpha_D^{20} = -378$ (c= 10 mg/mL)
	Stretched (DMF) $\alpha_D^{20} = -473$ (c= 10 mg/mL)		Stretched (DMF) $\alpha_D^{20} = -369$ (c= 10 mg/mL)

11. IR experiments

IR experiments of poly-(*S,S*)-**2** were measured in CHCl_3 and DMSO as representative examples of low polar and polar solvents that promote *anti* and *syn* conformations in the pendant groups, respectively.

Clear variations in the Amide II stretching band can be observed in the figure depicted below. This variation in wavenumber is associated with a weaker hydrogen bond pattern within pendant groups, which is in keeping the adoption of the *syn* conformation in DMSO.

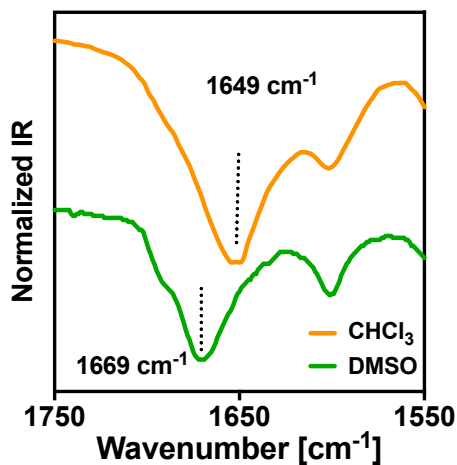


Figure S13. IR spectra of poly-(*S,S*)-**2** ($c = 5 \text{ mg/mL}$, 0.1 mm path length).

EXPERIMENTAL SECTION

CHAPTER III

1. Materials and Methods

CD measurements were done in a Jasco-720.

UV spectra were registered in a Jasco V-630.

The optical rotation was measured in a Jasco P-2000.

NMR experiments were measured in a Varian 300 operating at 300 MHz for proton NMR, 75 MHz for carbon and 282 MHz for fluorine. CDCl₃ signal (δ = 77.2 ppm) was used as standard for ¹³C experiments.

FT-IR measurements were carried out on a Bruker IFS-66v while Raman spectra were carried out in a Renishaw confocal Raman spectrometer (Invia Reflex model), equipped with two lasers (diode laser 785 nm and Ar laser 514 nm).

DSC traces were obtained in a DSC Q200 Tzero Technology (TA Instruments, New Castle, UK), equipped with a refrigerated cooling system RCS90 (TA Instruments, New Castle, UK), using a Tzero low-mass aluminium pan.

TGA traces were obtained in a TGA Q5000 (TA Instruments, New Castle, UK) using a platinum pan.

For molecular modelling we used Spartan 10 (MMFF94). As a molecular visualization system we used PyMOL.

2. Synthesis of monomers

The monomers employed in this work (mono-**1** to mono-**4**) have been prepared according the following synthetic scheme/following three different general methods. For a detailed explanation of each method see below:

- **General Protocol 1: Acylation with Br-Aib-Br or (S)-MTPA-Cl.**

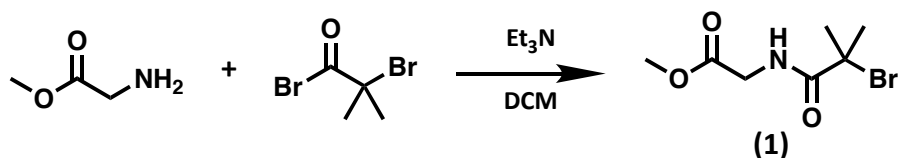
To a solution of the corresponding amine in DCM both Br-Aib-Br/(S)-MTPA-Cl and triethylamine were added. The mixture was stirred for 1 hour. Next, the organic layer was washed with 1M HCl and, if needed, the crude was purified by column chromatography.

- **General Protocol 2: Bromide-azide exchange**

To a solution of the corresponding bromide in DMSO sodium azide was added and the mixture was stirred at 80°C for 2 hours. Next, the organic layer was diluted with ethyl acetate and washed with water at least 5 times. The organic layer was dried with anhydrous Na₂SO₄. Evaporation of the organic layer yielded the corresponding azide.

- **General Protocol 3: Staudinger reduction**

To a solution of the corresponding azide in MeOH/H₂O (95/5 V/V) triphenylphosphine was added and the mixture was refluxed for 2 hours. Next, the organic layer was evaporated at reduced pressure and the crude was diluted with ethyl acetate and extracted with water. The organic layer containing the corresponding amide was used for acylation.

Methyl (2-bromo-2-methylpropanoyl)glycinate (1)

General Protocol 1: glycine methyl ester hydrochloride (2.00 g, 15.90 mmol, 1.00 equiv) in DCM (160 mL) was added to triethylamine (5.55 mL, 39.80 mmol, 2.50 equiv) and α -bromoisobutyryl bromide (1.97 mL, 15.90 mmol, 1.00 equiv), the solution was stirred at rt for 2h. Then, the organic layer was washed with HCl 1M (3 x 50 mL), dried with anhydrous Na₂SO₄ and the organic layer was evaporated to obtain pure methyl (2-bromo-2-methylpropanoyl)glycinate (**1**) in 94 % yield (3.55 g).

Methyl (2-bromo-2-methylpropanoyl)glycinate (**1**)

^1H NMR (300 MHz, CDCl_3) δ (ppm): 7.27 (s, 1H), 3.83 (d, $J=5.4$ Hz, 2H), 3.55 (s, 3H), 1.75 (s, 6H).

^{13}C NMR (75 MHz, CDCl_3) δ (ppm): 172.7, 170.1, 61.1, 52.5, 42.1, 32.3.

HRMS (ESI) m/z calc for $\text{C}_7\text{H}_{12}\text{BrNO}_3$ $[\text{M}+\text{H}]$: 238.0001, found: 238.0073.

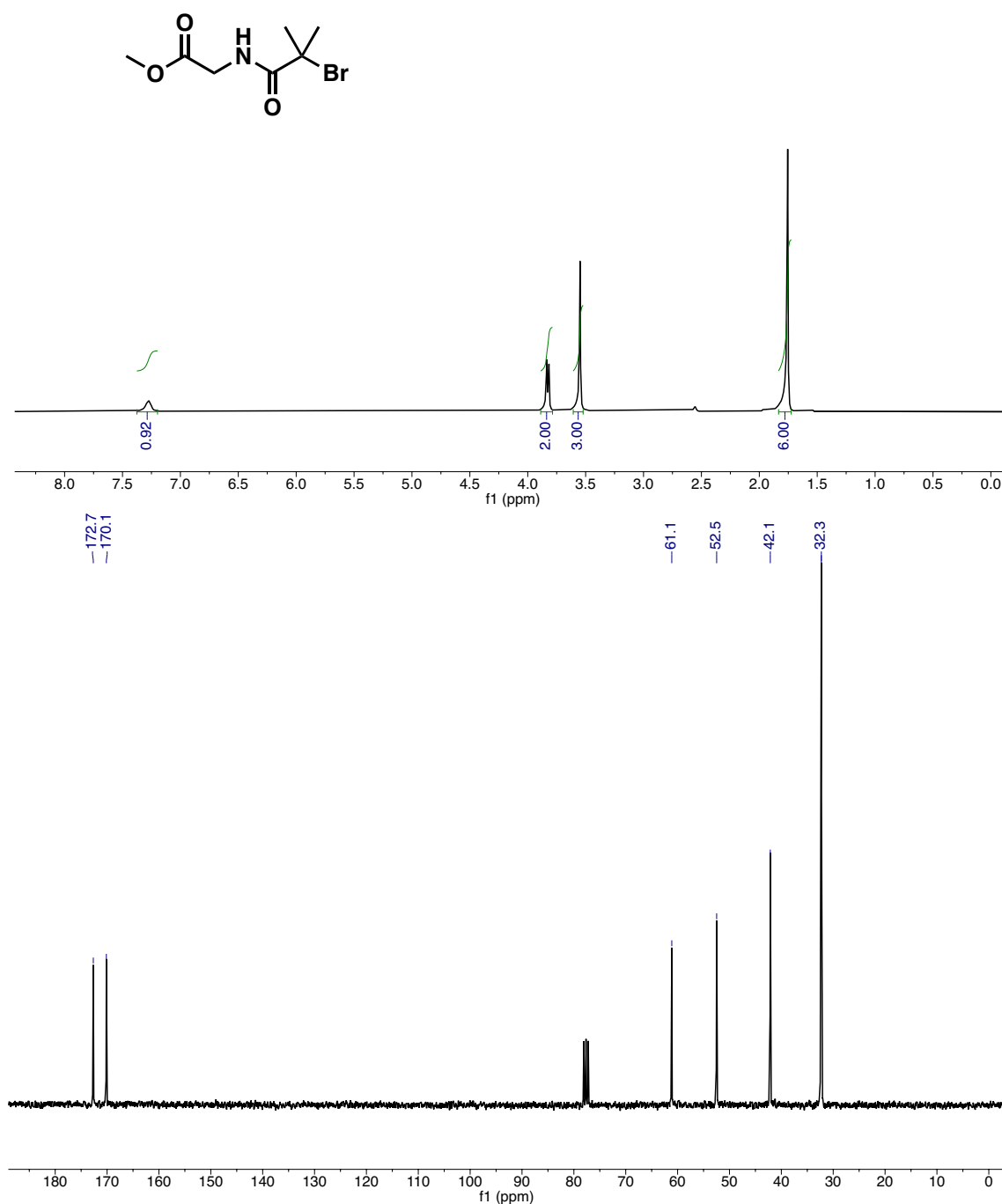
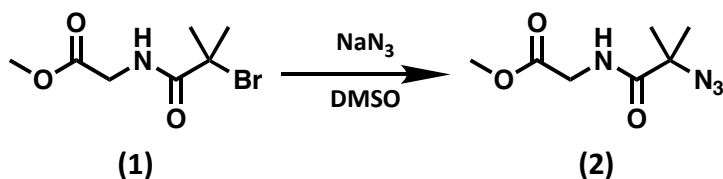


Figure S1. (a) ^1H -NMR and (b) ^{13}C -NMR spectra of **1** in CDCl_3 .

Methyl (2-azido-2-methylpropanoyl)glycinate (2)



General Protocol 2: methyl (2-bromo-2-methylpropanoyl)glycinate (**1**, 0.50 g, 2.10 mmol, 1.00 equiv) was dissolved in 10 mL of DMSO and to this solution sodium azide (0.16 g, 2.50 mmol, 1.20 equiv) was added. The mixture was stirred at 80°C for 2 hours. Then, it was diluted with 50 mL of ethyl acetate, extracted with water (5 x 25 mL) and dried with anhydrous Na₂SO₄. The organic layer was evaporated to obtain methyl (2-azido-2-methylpropanoyl)glycinate (**2**) in 95 % yield (0.40 g).

Methyl (2-azido-2-methylpropanoyl)glycinate (**2**)

^1H NMR (300 MHz, CDCl_3) δ (ppm): 7.31 (t, $J=5.7$ Hz, 1H), 3.71 (d, $J=5.7$ Hz, 2H), 3.43 (s, 3H), 1.65 (s, 6H).

^{13}C NMR (75 MHz, CDCl_3) δ (ppm): 172.2, 169.7, 60.3, 51.9, 41.7, 31.7.

HRMS (ESI) m/z calc for $\text{C}_7\text{H}_{12}\text{N}_4\text{O}_3$ $[\text{M}+\text{Na}]$: 223.0909, found: 223.0802.

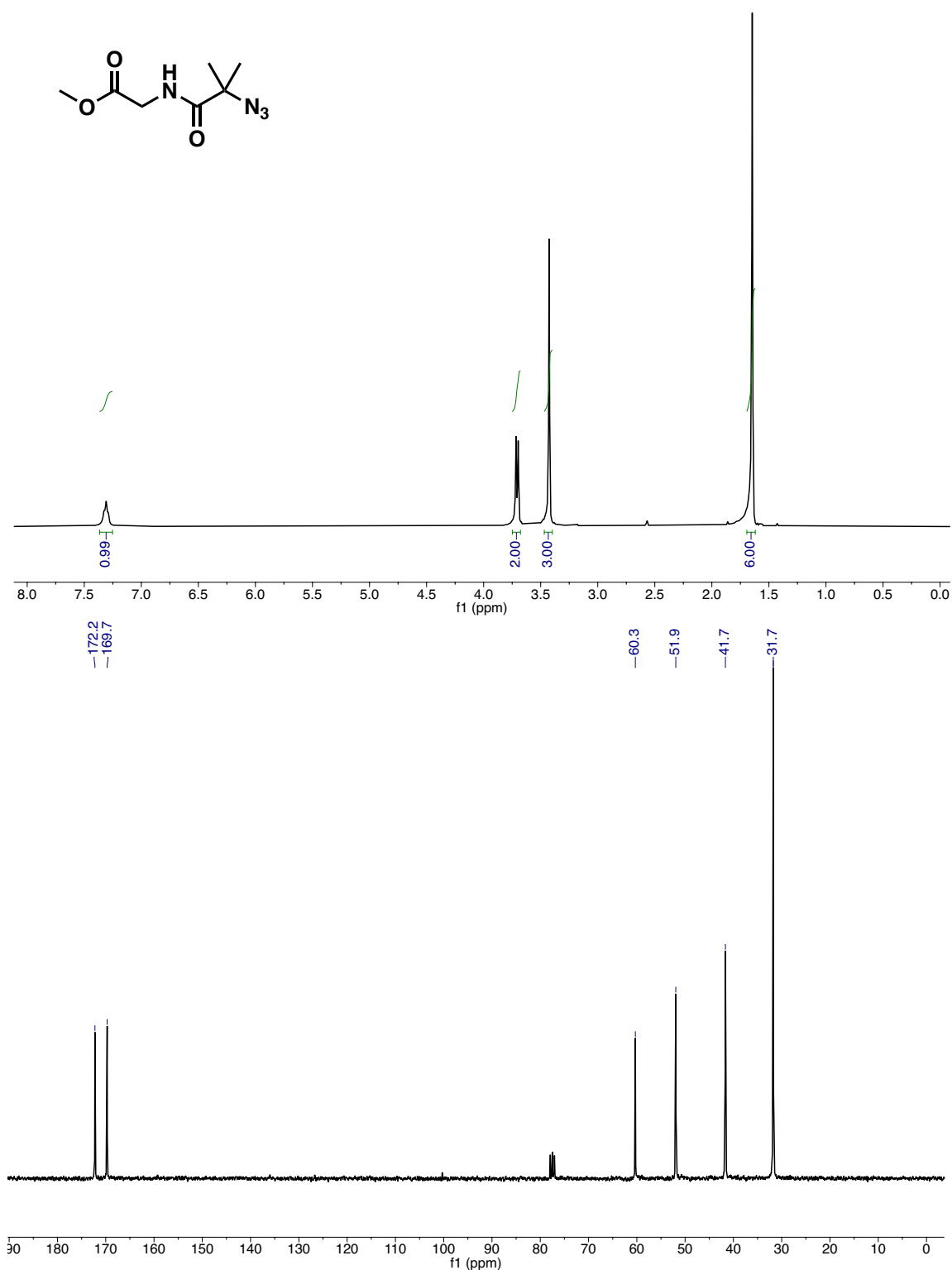
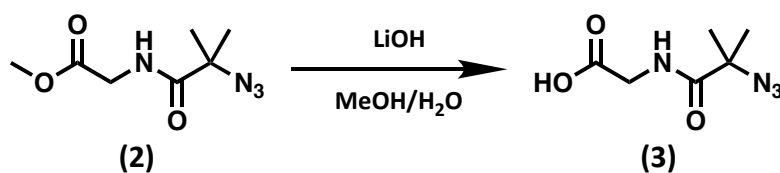


Figure S2. (a) ^1H -NMR and (b) ^{13}C -NMR spectra of **2** in CDCl_3 .

(2-azido-2-methylpropanoyl)glycine (**3**)

Methyl (2-azido-2-methylpropanoyl)glycinate (**2**, 0.40 g, 2.00 mmol, 1.00 equiv) was dissolved in a mixture of MeOH/H₂O (95/5) (50 mL) and lithium hydroxide was added (LiOH, 0.24 g, 10.00 mmol, 5.00 equiv). After 30 minutes the solvent was removed under reduced pressure. The residue was redissolved in a small amount of water and acidified to pH = 1. After extracting with ethyl acetate (4 times), the solution was dried over Na₂SO₄. Next, the organic solvent was removed obtaining **3** in 91 % yield (0.34 g).

(2-azido-2-methylpropanoyl)glycine (**3**)

^1H NMR (300 MHz, CDCl_3) δ (ppm): 9.19 (s, 1H), 7.25 (t, $J=5.3$ Hz, 1H), 3.99 (d, $J=5.5$ Hz, 2H), 1.49 (s, 6H).

^{13}C NMR (75 MHz, CDCl_3) δ (ppm): 173.6, 172.3, 64.1, 41.3, 24.3

HRMS (ESI) m/z calc for $\text{C}_6\text{H}_{10}\text{N}_4\text{O}_3$ $[\text{M}+\text{H}]$: 187.0753, found: 187.0826.

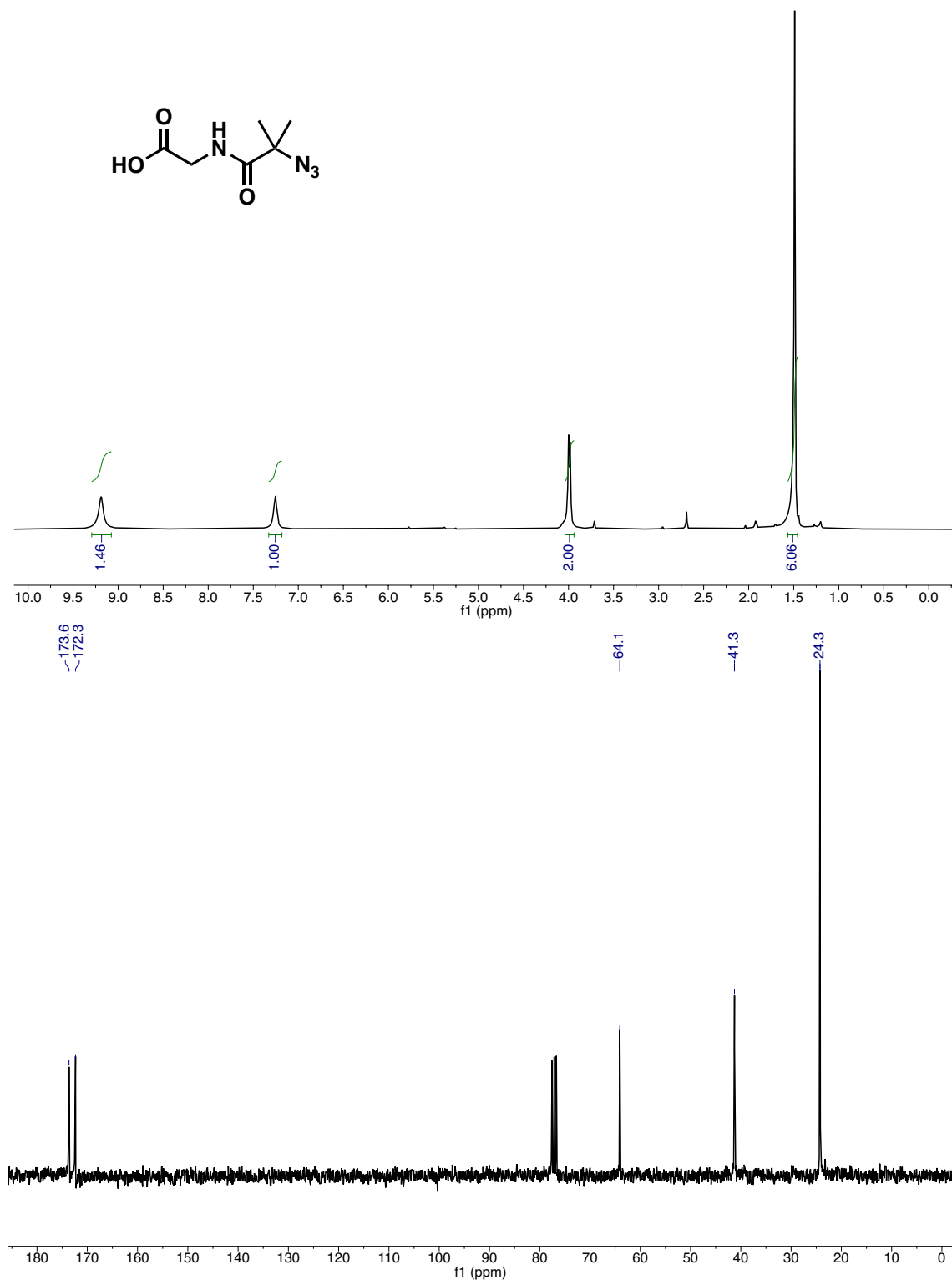
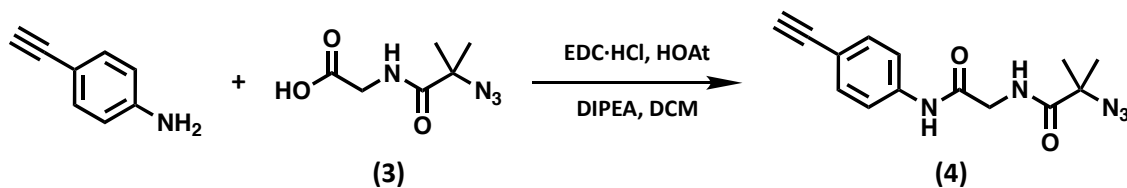


Figure S3. (a) ^1H -NMR and (b) ^{13}C -NMR spectra of **3** in CDCl_3 .

2-azido-*N*-(2-((4-ethynylphenyl)amino)-2-oxoethyl)-2-methylpropanamide (**4**)

N-(3-Dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (EDC·HCl, 0.29 g, 1.05 equiv), 1-Hydroxy-7-azabenzotriazole (HOAt, 0.21 g, 1.05 equiv), (2-azido-2-methylpropanoyl)glycine (**3**, 0.30 g, 1.10 equiv) and diisopropyltriethylamine (DIPEA, 0.31 mL, 1.20 equiv) were dissolved in 15 mL of DCM, and the mixture was stirred for 20 min to activate the acid. Then, 4-ethynylaniline (0.17 g, 1.00 equiv) was added and the reaction mixture was stirred 48h. Then the solvent was evaporated at reduced pressure and the crude was diluted in DCM, the organic layer was washed with HCl 1M, saturated solution of NaHCO₃ and brine. The organic layer was dried over anhyd. Na₂SO₄, filtered and the solvent was evaporated at reduced pressure. The crude product was chromatographed on silica gel (40-63 mesh) with hexane/ethyl acetate (1/1) as eluent obtaining **4** in 59 % yield (0.25 g).

2-azido-*N*-(2-((4-ethynylphenyl)amino)-2-oxoethyl)-2-methylpropanamide (**4**)

^1H NMR (300 MHz, CDCl_3) δ (ppm): 9.07 (s, 1H), 7.59-7.48 (m, 3H), 7.43 (d, $J=8.7$ Hz, 2H), 4.16 (d, $J=5.1$ Hz, 2H), 3.05 (s, 1H), 1.57 (s, 6H).

^{13}C NMR (75 MHz, CDCl_3) δ (ppm): 173.6, 166.5, 138.1, 132.9, 119.4, 117.9, 83.2, 64.0, 44.3, 24.6.

HRMS (ESI) m/z calc for $\text{C}_{14}\text{H}_{15}\text{N}_5\text{O}_2$ $[\text{M}+\text{H}]$: 286.1226, found: 286.1299.

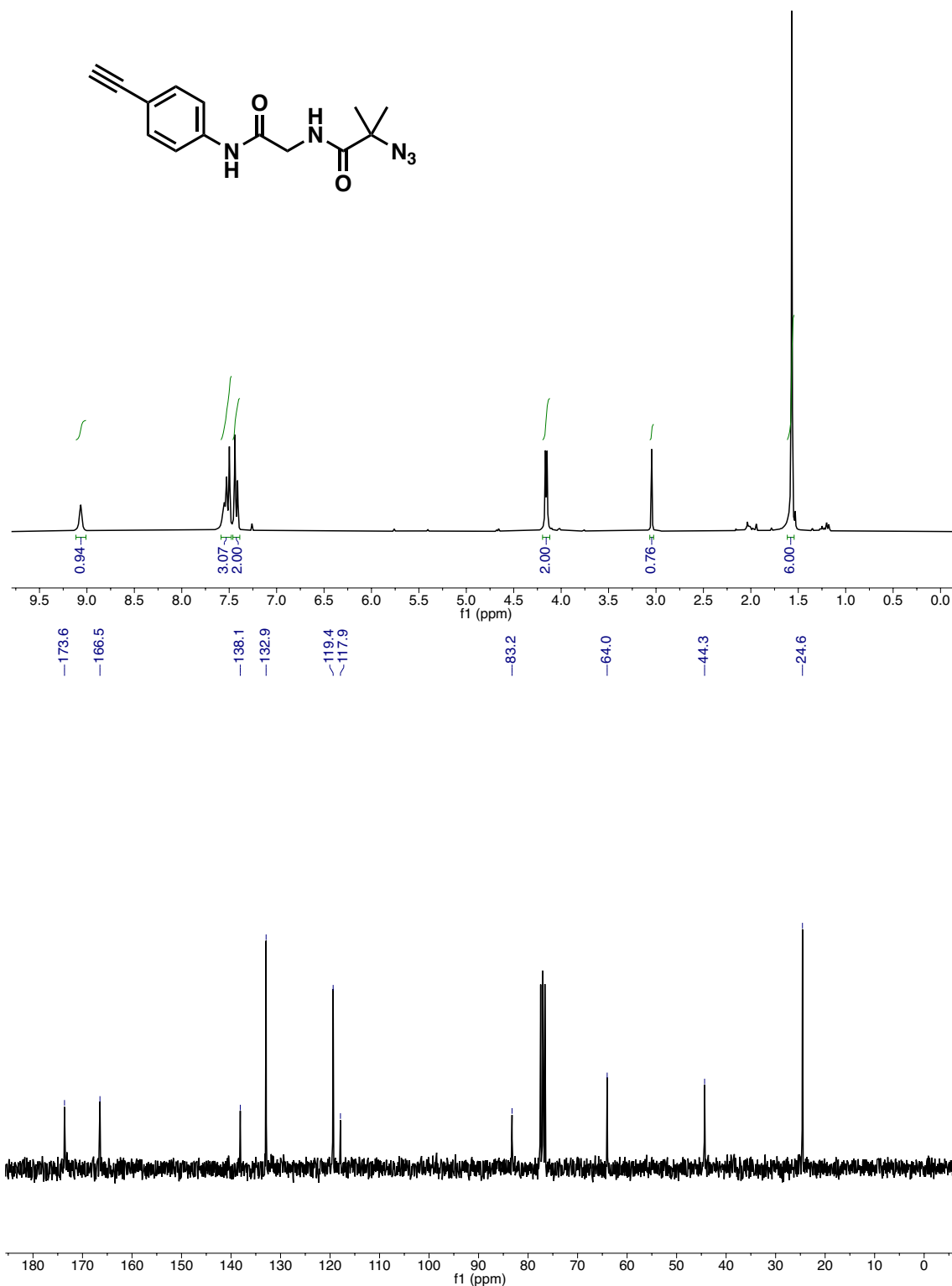
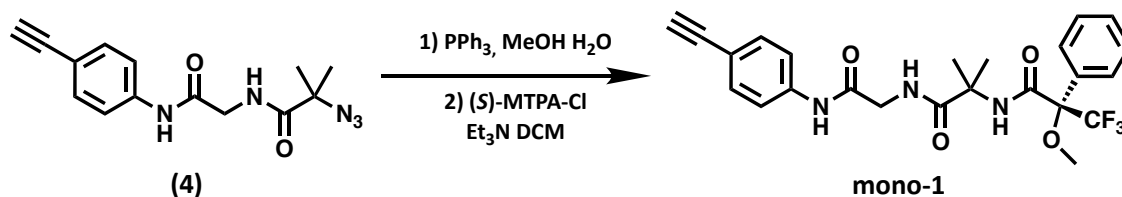


Figure S4. (a) ^1H -NMR and (b) ^{13}C -NMR spectra of **4** in CDCl_3 .

(S)-N-(1-((2-((4-ethynylphenyl)amino)-2-oxoethyl)amino)-2-methyl-1-oxopropan-2-yl)-3,3,3-trifluoro-2-methoxy-2-phenylpropanamide (mono-1)

General Protocol 3: 2-azido-*N*-(2-((4-ethynylphenyl)amino)-2-oxoethyl)-2-methylpropanamide (**4**, 0.25 g, 1.00 equiv) and triphenylphosphine (0.24 g, 1.05 equiv) were dissolved in 30 mL of MeOH/water solution (95/5) and this mixture was refluxed for 2 h. Next, the organic layer was evaporated, diluted with water (20 mL) and extracted with ethyl acetate (5 x 30 mL).

The organic layer was dried with anhydrous Na₂SO₄ and used for acylation with (*S*)-MTPA-Cl without further purification. The ethyl acetate was evaporated to yield 2-amino-*N*-(2-((4-ethynylphenyl)amino)-2-oxoethyl)-2-methylpropanamide in 89 % yield (0.20 g).

(*S*)-MTPA-Cl was prepared according to our previously reported method.^[S1] (*S*)- α -methoxy- α -trifluoromethylphenylacetic acid was dissolved in hexane, then oxalyl chloride and DMF were subsequently added. This mixture was stirred at rt for 30 minutes. Next, the solution was filtrated and the organic layer was evaporated. The crude was diluted in DCM (10 mL) and combined with the solution that contains the amine, and then Et₃N (0.13 mL, 1.20 equiv) was added. The mixture was stirred at rt for 1 h and the organic layer was evaporated and the crude was purified by chromatographic column using silica gel (40-63 mesh) as stationary phase with a mixture of hexane/ethyl acetate (3/7) as eluent, obtaining mono-**1** in 74 % yield (0.31 g).

¹H NMR (750 MHz, CDCl₃) δ (ppm): 8.68 (s, 1H), 7.46 (d, *J*=7.3 Hz, 2H), 7.45 (d, *J*=2.3 Hz, 2H), 7.43 (s, 1H), 7.37–7.31 (m, 3H), 7.24 (d, *J*=8.7 Hz, 2H), 6.59 (t, *J*=6.3 Hz, 1H), 4.17 (dd, *J*=17.3 Hz, 6.7 Hz, 1H), 3.95 (dd, *J*=17.2 Hz, 6.0 Hz, 1H), 3.36 (s, 3H), 3.00 (s, 1H), 1.62 (s, 3H), 1.58 (s, 3H).

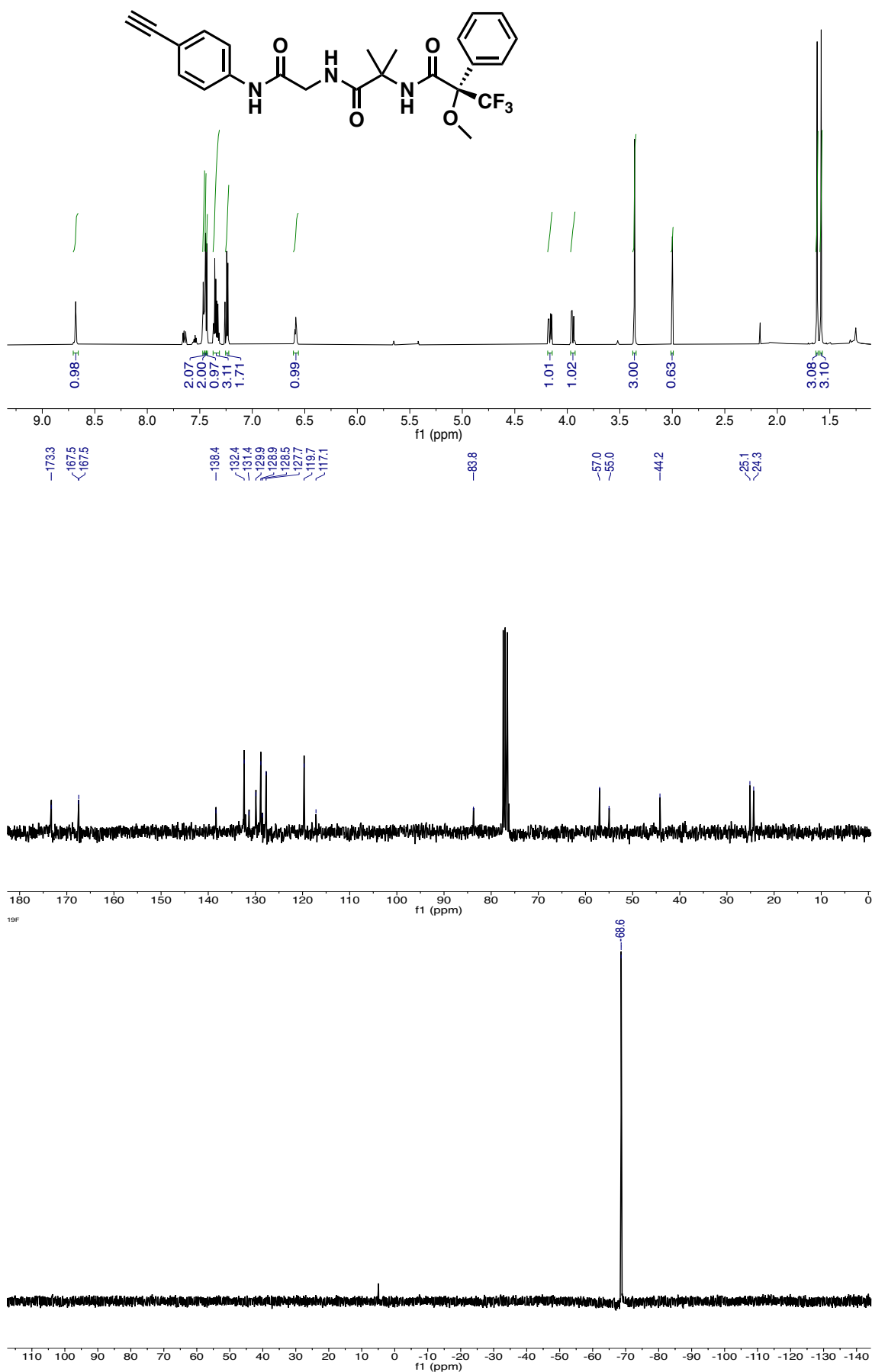
¹³C NMR (75 MHz, CDCl₃) δ (ppm): 173.3, 167.5, 167.5, 138.4, 132.4, 131.4, 129.9, 128.9, 128.5, 127.7, 119.7, 117.1, 83.8, 57.0, 55.0, 44.2, 25.1, 24.3.

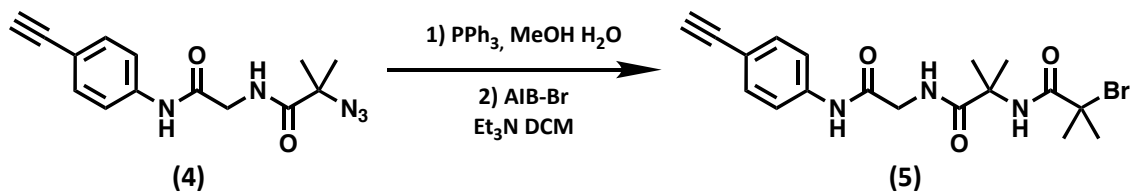
¹⁹F NMR (282 MHz, CDCl₃) δ (ppm): - 68.6.

HRMS (ESI) *m/z* calc for C₂₄H₂₄F₃N₃O₄ [M+H]: 476.1719, found: 476.1792.

α_D^{20} = -96 (*c* = 10 mg/mL, CHCl₃).

^{S1} Leiras, S.; Freire, F.; Seco, J. M.; Quiñoá, E.; Riguera, R. *Chem. Sci.* **2013**, *4*, 2735.

Figure S5. (a) ^1H -NMR, (b) ^{13}C -NMR and (c) ^{19}F -NMR spectra of mono-1 in CDCl_3 .

2-bromo-*N*-(1-((2-((4-ethynylphenyl)amino)-2-oxoethyl)amino)-2-methyl-1-oxopropan-2-yl)-2-methylpropanamide (5)

General protocol 3: 2-azido-*N*-(2-((4-ethynylphenyl)amino)-2-oxoethyl)-2-methylpropanamide (**4**, 0.25 g, 1.00 equiv) and triphenylphosphine (0.24 g, 1.05 equiv) were dissolved in 30 mL of MeOH/water solution (95/5) and this mixture was refluxed for 2 h. Next, the organic layer was evaporated, diluted with water (20 mL) and extracted with ethyl acetate (5 x 30 mL).

The organic layer was dried with anhydrous Na_2SO_4 and used for coupling with α -bromoisobutyryl bromide without further purification. The ethyl acetate was evaporated to yield 2-amino-*N*-(2-((4-ethynylphenyl)amino)-2-oxoethyl)-2-methylpropanamide in 89 % yield (0.20 g).

Following General Protocol 1, 2-amino-*N*-(2-((4-ethynylphenyl)amino)-2-oxoethyl)-2-methylpropanamide (0.20 g, 1.00 equiv) in DCM (10 mL) was added triethylamine (0.27 mL, 2.50 equiv) and α -bromoisobutyryl bromide (0.10 mL, 1.05 equiv). The solution was stirred at rt for 1 h. Then, the organic layer was washed with HCl 1M (3 x 20 mL), dried with anhydrous Na_2SO_4 and was evaporated to obtain **5** in 86 % yield of pure product (0.31 g).

2-bromo-*N*-(1-((2-((4-ethynylphenyl)amino)-2-oxoethyl)amino)-2-methyl-1-oxopropan-2-yl)-2-methylpropanamide (5)

^1H NMR (300 MHz, CDCl_3) δ (ppm): 8.83 (s, 1H), 7.76 (d, $J=8.7$ Hz, 2H), 7.42 (d, $J=8.7$ Hz, 2H), 6.99 (s, 1H), 6.59 (t, $J=5.2$ Hz, 1H), 4.10 (d, $J=6.2$ Hz, 2H), 3.03 (s, 1H), 1.94 (s, 6H), 1.58 (s, 6H).

^{13}C NMR (75 MHz, CDCl_3) δ (ppm): 173.4, 167.3, 138.6, 132.6, 119.7, 112.0, 83.6, 61.1, 57.5, 44.3, 31.9, 24.9.

HRMS (ESI) m/z calc for $\text{C}_{18}\text{H}_{22}\text{BrN}_3\text{O}_3$ $[\text{M}+\text{H}]$: 408.0858, found: 408.0917

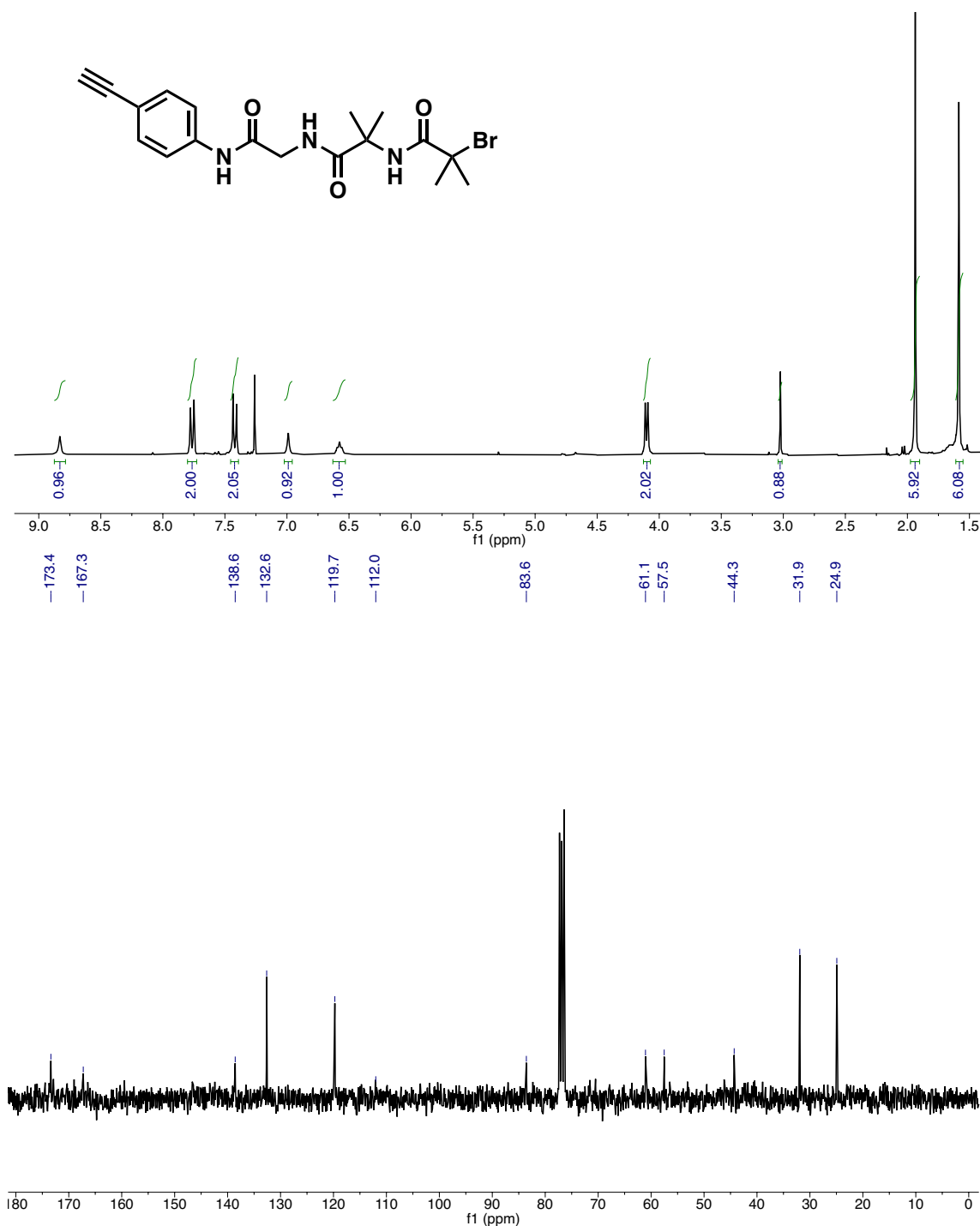
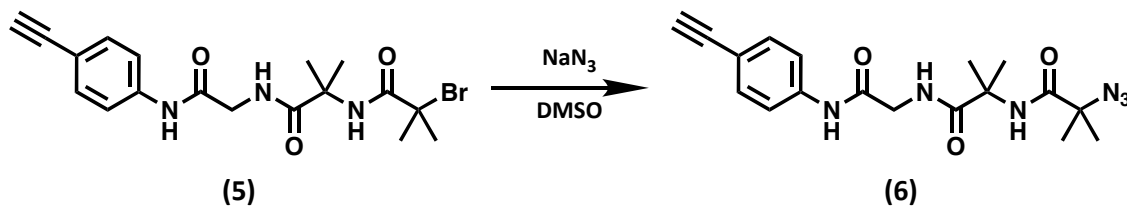


Figure S6. (a) ^1H -NMR and (b) ^{13}C -NMR spectra of 5 in CDCl_3 .

2-azido-*N*-(1-((2-((4-ethynylphenyl)amino)-2-oxoethyl)amino)-2-methyl-1-oxopropan-2-yl)-2-methylpropanamide (6)



General Protocol 2: 2-bromo-*N*-(1-((2-((4-ethynylphenyl)amino)-2-oxoethyl)amino)-2-methyl-1-oxopropan-2-yl)-2-methylpropanamide (**5**, 0.25 g, 0.61 mmol, 1.00 equiv) was dissolved in 5 mL of DMSO and to this solution sodium azide (0.05 g, 0.74 mmol, 1.20 equiv) was added. The mixture was stirred at 80°C for 2 hours. Then, it was diluted with 25 mL of ethyl acetate, extracted with water (5 x 15 mL) and dried with anhydrous Na₂SO₄. The organic layer was evaporated to obtain **6** in 93 % yield (0.21 g).

2-azido-*N*-(1-((2-((4-ethynylphenyl)amino)-2-oxoethyl)amino)-2-methyl-1-oxopropan-2-yl)-2-methylpropanamide (6)

^1H NMR (300 MHz, CD_3OD) δ (ppm): 9.42 (s, 1H), 8.40 (t, $J=5.9$ Hz, 1H), 8.12 (s, 1H), 7.85 (d, $J=8.7$ Hz, 2H), 7.42 (d, $J=8.8$ Hz, 2H), 3.95 (d, $J=5.9$ Hz, 2H), 3.61 (s, 1H), 1.52 (d, $J=2.8$ Hz, 12H).

^{13}C NMR (75 MHz, CD_3OD) δ (ppm): 179.8, 177.8, 172.8, 142.5, 136.0, 123.5, 121.9, 86.8, 80.7, 67.4, 60.6, 47.3, 27.6, 27.1.

HRMS (ESI) m/z calc for $\text{C}_{18}\text{H}_{22}\text{N}_6\text{O}_3$ $[\text{M}+\text{H}]^+$: 371.1753, found: 371.1826.

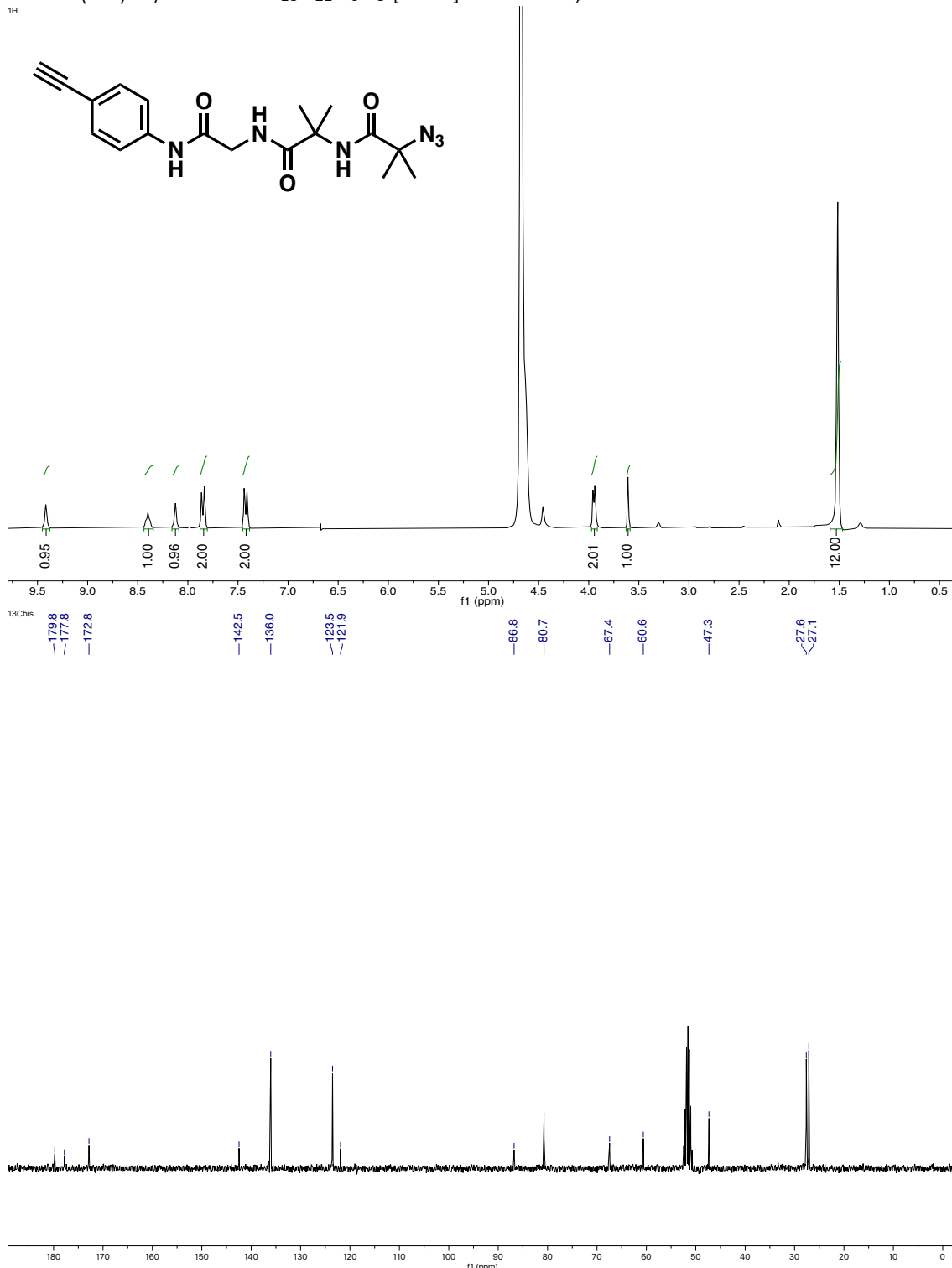
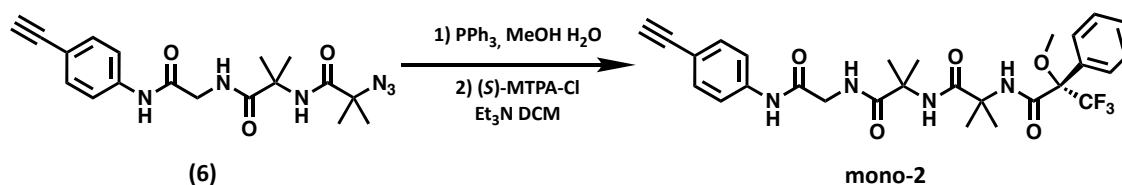


Figure S7. (a) ^1H -NMR and (b) ^{13}C -NMR spectra of **6** in CD_3OD .

(*S*)-*N*-(1-((-1-((2-((4-ethynylphenyl)amino)-2-oxoethyl)amino)-2-methyl-1-oxopropan-2-yl)-amino)-2-methyl-1-oxopropan-2-yl)-3,3,3-trifluoro-2-methoxy-2-phenylpropanamide (mono-2)



General Protocol 3: 2-azido-*N*-(1-((2-((4-ethynylphenyl)amino)-2-oxoethyl)amino)-2-methyl-1-oxopropan-2-yl)-2-methylpropanamide (**6**, 0.21 g, 1.00 equiv) and triphenylphosphine (0.16 g, 1.05 equiv) were dissolved in 30 mL of MeOH/water solution (95/5) and this mixture was refluxed for 2 h. Next, the organic layer was evaporated, diluted with water (20 mL) and extracted with ethyl acetate (5 x 30 mL).

The organic layer was dried with anhydrous Na₂SO₄ and used for acylation with (*S*)-MTPA-Cl without further purification. The ethyl acetate was evaporated to yield 2-amino-*N*-(1-((2-((4-ethynylphenyl)amino)-2-oxoethyl)amino)-2-methyl-1-oxopropan-2-yl)-2-methylpropanamide in 92 % yield (0.18 g).

(*S*)-MTPA-Cl was prepared according to our previously reported method,^[S1] (*S*)-α-methoxy-α-trifluoromethylphenylacetic acid was dissolved in hexane, and oxalyl chloride and DMF were subsequently added. This mixture was stirred at rt for 30 minutes, then the solution was filtrated and the organic layer was evaporated. The crude was diluted in DCM (10 mL) and combined with PA-gly-(Aib)₂-NH₂, and then Et₃N (0.09 mL, 1.20 equiv) was added. The mixture was stirred at rt for 1 h and the organic layer was evaporated and the crude was purified by chromatographic column using silica gel (40-63 mesh) as stationary phase with a mixture of hexane/ethyl acetate (3/7) as eluent, obtaining mono-**2** in 78 % yield (0.23 g).

¹H NMR (750 MHz, CDCl₃) δ (ppm): 8.87 (s, 1H), 7.82 (d, *J*=8.7 Hz, 2H), 7.60 (s, 1H), 7.56 (t, *J*=6.3 Hz, 1H), 7.43–7.35 (m, 7H), 6.29 (s, 1H), 4.05 (dd, *J*=17.2 Hz, 7.0 Hz, 1H), 3.66 (dd, *J*=17.2 Hz, 5.7 Hz, 1H), 3.29 (s, 3H), 3.00 (s, 1H), 1.58 (s, 3H), 1.54 (s, 3H), 1.51 (s, 3H), 1.45 (s, 3H).

¹³C NMR (75 MHz, CDCl₃) δ (ppm): 174.4, 174.2, 168.7, 168.1, 139.5, 132.8, 131.3, 130.4, 129.4, 127.8, 119.9, 117.3, 84.2, 57.6, 57.5, 55.2, 44.4, 26.3, 25.8, 24.9, 24.0.

¹⁹F NMR (282 MHz, CDCl₃) δ (ppm): - 68.1.

HRMS (ESI) *m/z* calc for C₂₈H₃₁F₃N₄O₅ [M+H]: 561.2247, found: 561.2319.

α_D²⁰ = +24 (c = 10 mg/mL, CHCl₃).

^{S1} Leiras, S.; Freire, F.; Seco, J. M.; Quiñoá, E.; Riguera, R. *Chem. Sci.* **2013**, *4*, 2735.

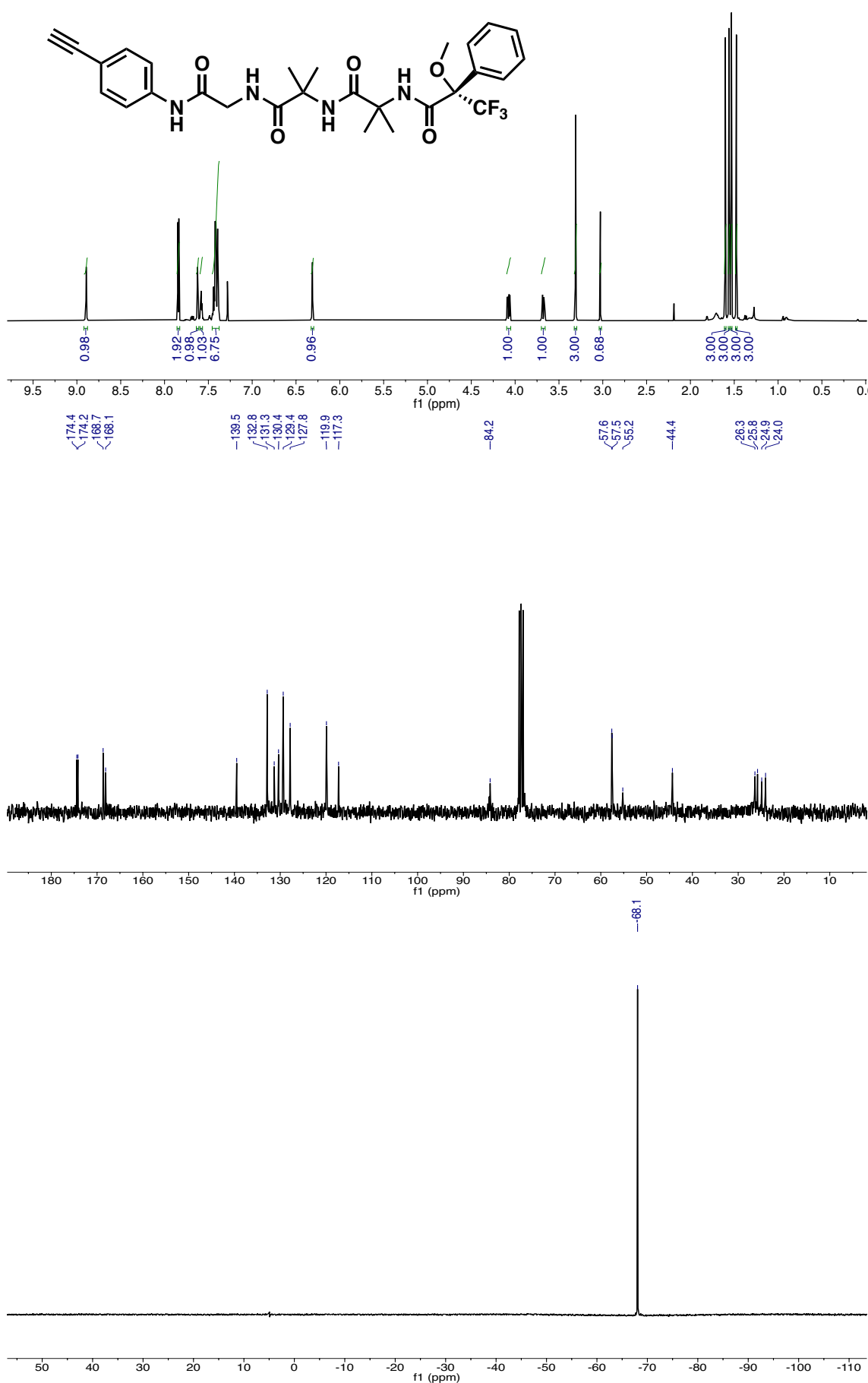
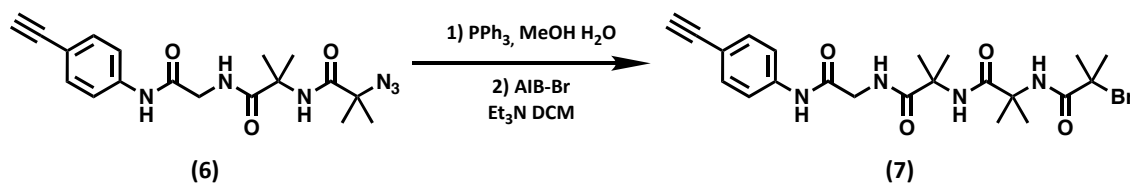


Figure S8. (a) ¹H-NMR, (b) ¹³C-NMR and (c) ¹⁹F-NMR spectra of mono-2 in CDCl₃.

2-bromo-*N*-(1-((1-((2-((4-ethynylphenyl)amino)-2-oxoethyl)amino)-2-methyl-1-oxopropan-2-yl)amino)-2-methyl-1-oxopropan-2-yl)-2-methylpropanamide (7)



General Protocol 3: 2-azido-*N*-(1-((1-((2-((4-ethynylphenyl)amino)-2-oxoethyl)amino)-2-methyl-1-oxopropan-2-yl)amino)-2-methylpropanamide (**6**, 0.21 g, 1.00 equiv) and triphenylphosphine (0.16 g, 1.05 equiv) were dissolved in 30 mL of MeOH/water solution (95/5) and this mixture was refluxed for 2 h. Next, the organic layer was evaporated, diluted with water (20 mL) and extracted with ethyl acetate (5 x 30 mL).

The organic layer was dried with anhydrous Na₂SO₄ and used for acylation with (*S*)-MTPA-Cl without further purification. The ethyl acetate was evaporated to yield 2-amino-*N*-(1-((1-((2-((4-ethynylphenyl)amino)-2-oxoethyl)amino)-2-methyl-1-oxopropan-2-yl)amino)-2-methylpropanamide in 92 % yield (0.18 g).

Following General Protocol 1, 2-amino-*N*-(1-((1-((2-((4-ethynylphenyl)amino)-2-oxoethyl)amino)-2-methyl-1-oxopropan-2-yl)amino)-2-methylpropanamide (0.18 g, 1.00 equiv) in DCM (10 mL) was added triethylamine (0.18 mL, 2.50 equiv) and α-bromoisobutyryl bromide (0.07 mL, 1.05 equiv). The solution was stirred at rt for 1 h. Then, the organic layer was washed with HCl 1M (3 x 20 mL), dried with anhydrous Na₂SO₄ and was evaporated to obtain **7** in 86 % yield of pure product (0.22 g).

2-bromo-*N*-(1-((1-((2-((4-ethynylphenyl)amino)-2-oxoethyl)amino)-2-methyl-1-oxopropan-2-yl)amino)-2-methyl-1-oxopropan-2-yl)-2-methylpropanamide (7)

^1H NMR (300 MHz, DMF-d_7) δ (ppm): 9.45 (s, 1H), 8.40 (s, 1H), 8.26 (s, 1H), 8.02 (m, 3H), 7.47 (d, $J=8.4$ Hz, 2H), 4.01 (s, 1H), 3.93 (d, $J=6.3$ Hz, 2H), 1.93 (s, 6H), 1.54 (s, 6H), 1.46 (s, 6H).

^{13}C NMR (75 MHz, DMF-d_7) δ (ppm): 180.1, 179.2, 176.3, 173.0, 144.2, 136.8, 123.6, 121.3, 88.0, 83.1, 64.7, 61.7, 61.2, 48.2, 34.8, 29.1, 28.2.

HRMS (ESI) m/z calc for $\text{C}_{22}\text{H}_{29}\text{BrN}_4\text{O}_4$ $[\text{M}+\text{H}]$: 493.1372, found: 493.1445.

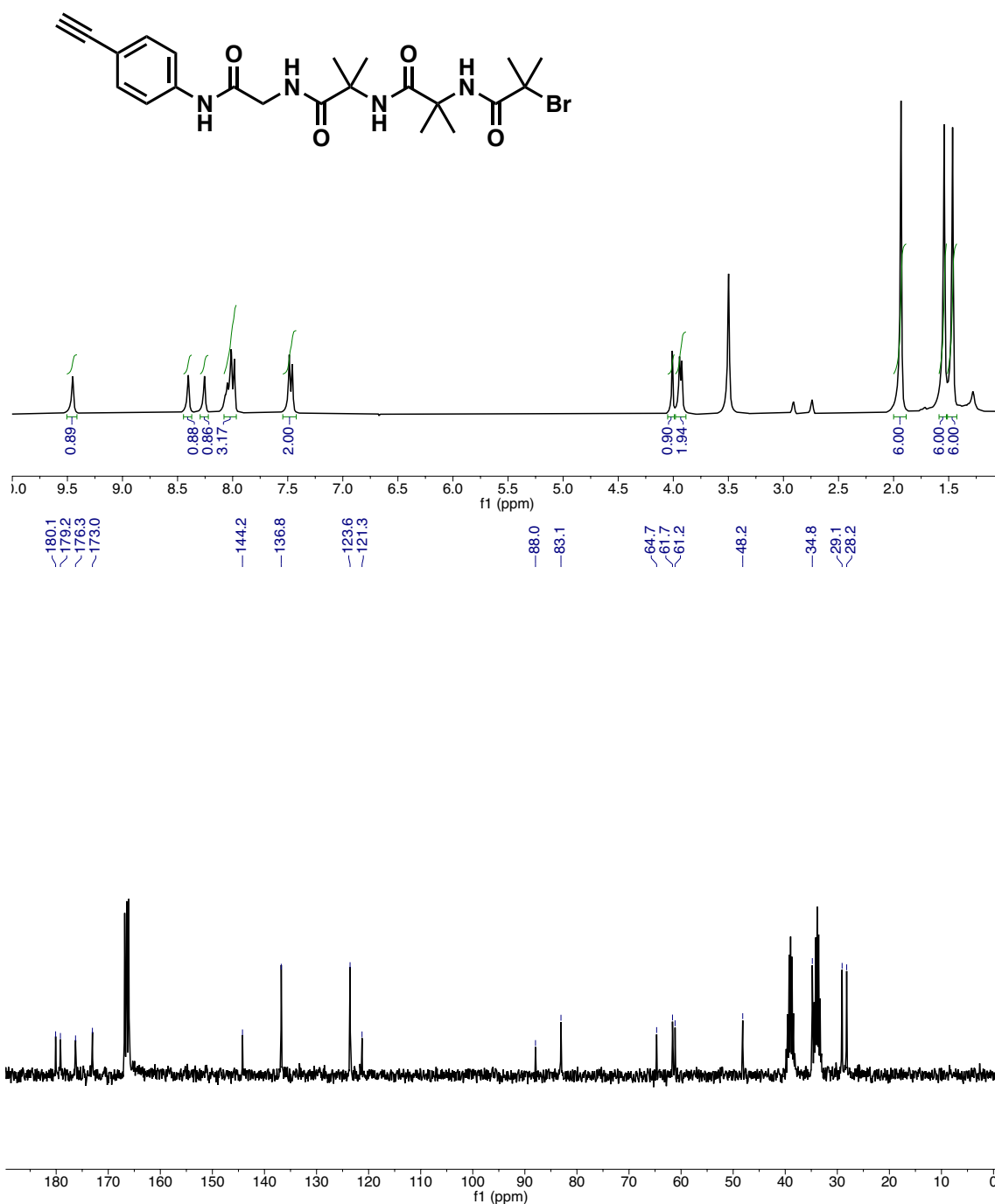
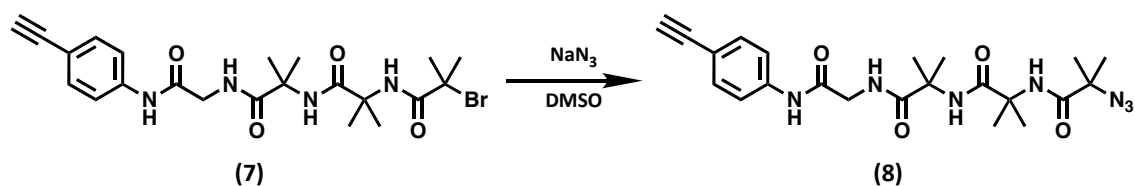


Figure S9. (a) ^1H -NMR and (b) ^{13}C -NMR spectra of 7 in DMF-d_7 .

2-azido-*N*-(1-((1-((2-((4-ethynylphenyl)amino)-2-oxoethyl)amino)-2-methyl-1-oxopropan-2-yl)amino)-2-methyl-1-oxopropan-2-yl)-2-methylpropanamide (**8**)



General Protocol 2: 2-bromo-*N*-(1-((1-((2-((4-ethynylphenyl)amino)-2-oxoethyl)amino)-2-methyl-1-oxopropan-2-yl)amino)-2-methyl-1-oxopropan-2-yl)-2-methylpropanamide (**7**, 0.22 g, 1.00 equiv) was dissolved in 5 mL of DMSO and to this solution sodium azide (0.03 g, 1.20 equiv) was added. The mixture was stirred at 80°C for 2 h. Then, it was diluted with 25 mL of ethyl acetate, extracted with water (5 x 15 mL) and dried with anhydrous Na₂SO₄. The organic layer was evaporated to obtain **8** in 98 % yield (0.20 g) .

2-azido-*N*-(1-((1-((2-((4-ethynylphenyl)amino)-2-oxoethyl)amino)-2-methyl-1-oxopropan-2-yl)amino)-2-methyl-1-oxopropan-2-yl)-2-methylpropanamide (**8**)

^1H NMR (300 MHz, DMF- d_7) δ (ppm): 9.46 (s, 1H), 8.46 (s, 1H), 8.30 (s, 1H), 8.08 (t, $J=6.3$ Hz, 1H), 8.00 (d, $J=8.7$ Hz, 2H), 7.47 (d, $J=8.3$ Hz, 2H), 4.01 (s, 1H), 3.93 (d, $J=6.3$ Hz, 2H), 1.49 (m, 18H).

^{13}C NMR (75 MHz, DMF- d_7) δ (ppm): 180.1, 179.2, 177.8, 173.0, 144.2, 136.8, 123.5, 121.3, 88.0, 83.0, 68.2, 61.4, 61.1, 48.1, 29.1, 28.5, 28.0.

HRMS (ESI) m/z calc for $\text{C}_{22}\text{H}_{29}\text{N}_7\text{O}_4$ $[\text{M}+\text{H}]$: 456.2281, found: 456.2354.

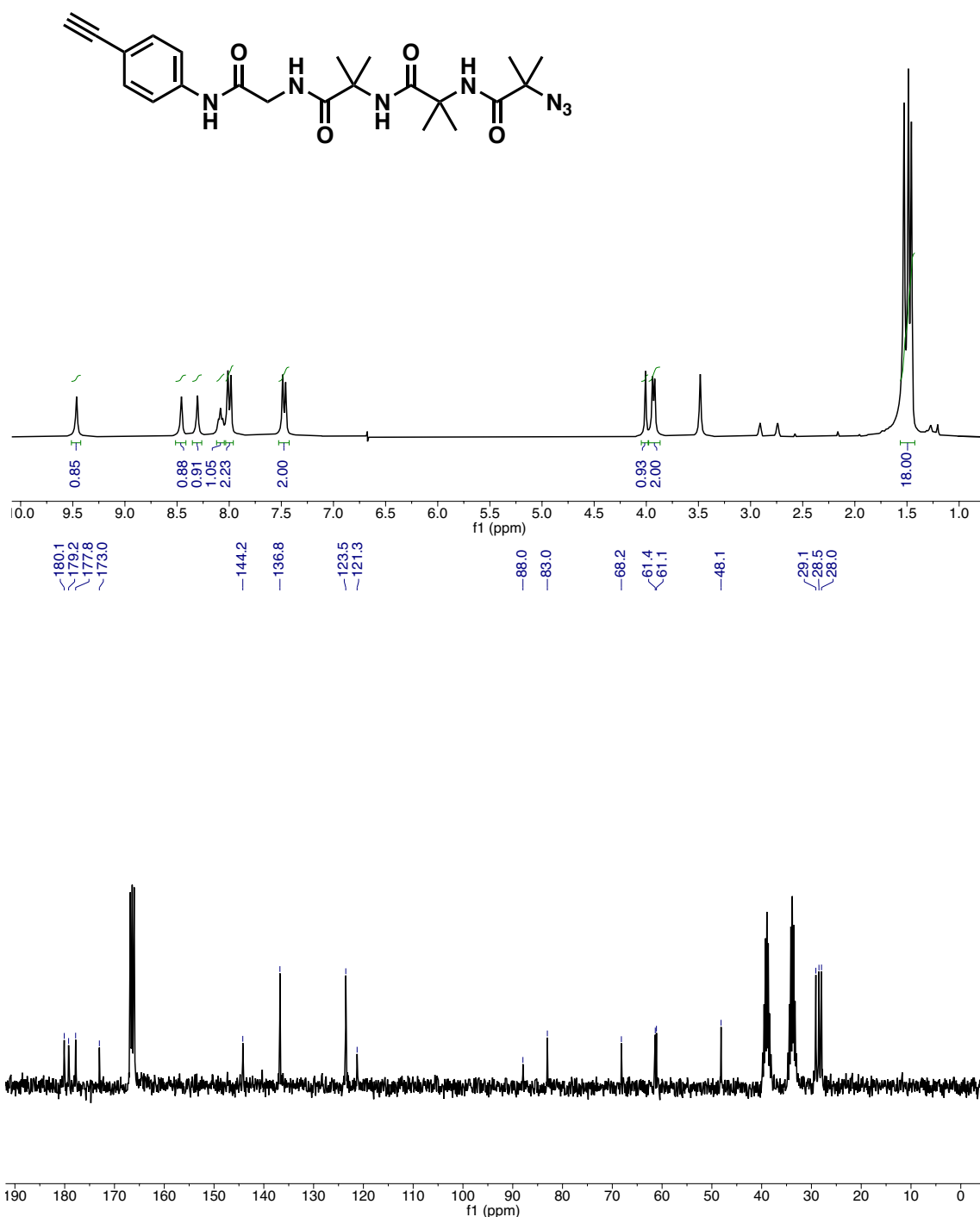
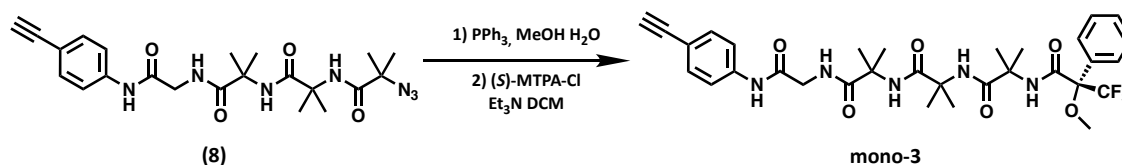


Figure S10. (a) ^1H -NMR and (b) ^{13}C -NMR spectra of **8** in DMF- d_7 .

(*S*)-*N*-(1-((1-((1-((2-((4-ethynylphenyl)amino)-2-oxoethyl)amino)-2-methyl-1-oxopropan-2-yl)amino)-2-methyl-1-oxopropan-2-yl)amino)-2-methyl-1-oxopropan-2-yl)-3,3,3-trifluoro-2-methoxy-2-phenylpropanamide (mono-3)



General Protocol 3: 2-azido-*N*-(1-((1-((2-((4-ethynylphenyl)amino)-2-oxoethyl)amino)-2-methyl-1-oxopropan-2-yl)amino)-2-methyl-1-oxopropan-2-yl)-2-methylpropanamide (**8**, 0.20 g, 1.00 equiv) and triphenylphosphine (0.12 g, 1.05 equiv) were dissolved in 30 mL of MeOH/water solution (95/5) and this mixture was refluxed for 2 h. Next, the organic layer was evaporated, diluted with water (20 mL) and extracted with ethyl acetate (5 x 30 mL). The organic layer was dried with anhydrous Na₂SO₄ and used for acylation with (*S*)-MTPA-Cl without further purification. The ethyl acetate was evaporated to yield 2-amino-*N*-(1-((1-((2-((4-ethynylphenyl)amino)-2-oxoethyl)amino)-2-methyl-1-oxopropan-2-yl)amino)-2-methyl-1-oxopropan-2-yl)-2-methylpropanamide in 94 % yield (0.18 g).

(*S*)-MTPA-Cl was prepared according to our previously reported method,^[S1] (*S*)- α -methoxy- α -trifluoromethylphenylacetic acid was dissolved in hexane, and oxalyl chloride and DMF were subsequently added. This mixture was stirred at rt for 30 minutes, then the solution was filtrated and the organic layer was evaporated. The crude was diluted in DCM (10 mL) and combined with PA-gly-(Aib)₃-NH₂, and then Et₃N (0.07 mL, 1.20 equiv) was added. The mixture was stirred at rt for 1 h and the organic layer was evaporated and the crude was purified by chromatographic column using silica gel (40-63 mesh) as stationary phase with a mixture of hexane/ethyl acetate (1/1) as eluent, obtaining mono-**3** in 88 % yield (0.23 g).

¹H NMR (750 MHz, CDCl₃) δ (ppm): 9.03 (s, 1H), 7.91 (d, *J*=8.7 Hz, 2H), 7.75 (t, *J*=6.4 Hz, 1H), 7.60 (s, 1H), 7.44 (m, 5H), 7.42 (d, *J*=8.6 Hz, 2H), 7.22 (s, 1H), 6.28 (s, 1H), 4.21 (dd, *J*=17.2 Hz, 6.8 Hz, 1H), 3.88 (dd, *J*=17.3 Hz, 5.4 Hz, 1H), 3.38 (s, 3H), 3.03 (s, 1H), 1.54 (s, 3H), 1.52 (s, 3H), 1.49 (s, 3H), 1.42 (s, 3H), 1.38 (s, 3H), 1.30 (s, 3H).

¹³C NMR (75 MHz, CDCl₃) δ (ppm): 175.6, 175.1, 174.1, 169.1, 167.5, 139.6, 132.8, 131.5, 130.3, 129.3, 127.9, 120.0, 117.2, 84.2, 76.5, 57.5, 57.4, 57.2, 55.2, 44.3, 26.0, 25.9, 25.4, 24.7, 24.6, 24.1.

¹⁹F NMR (282 MHz, CDCl₃) δ (ppm): - 67.9.

HRMS (ESI) *m/z* calc for C₃₂H₃₈F₃N₅O₆ [M+H]: 646.2774, found: 646.2847.

α_D^{20} = +28 (c = 10 mg/mL, CHCl₃).

^{S1} Leiras, S.; Freire, F.; Seco, J. M.; Quiñoá, E.; Riguera, R. *Chem. Sci.* **2013**, *4*, 2735.

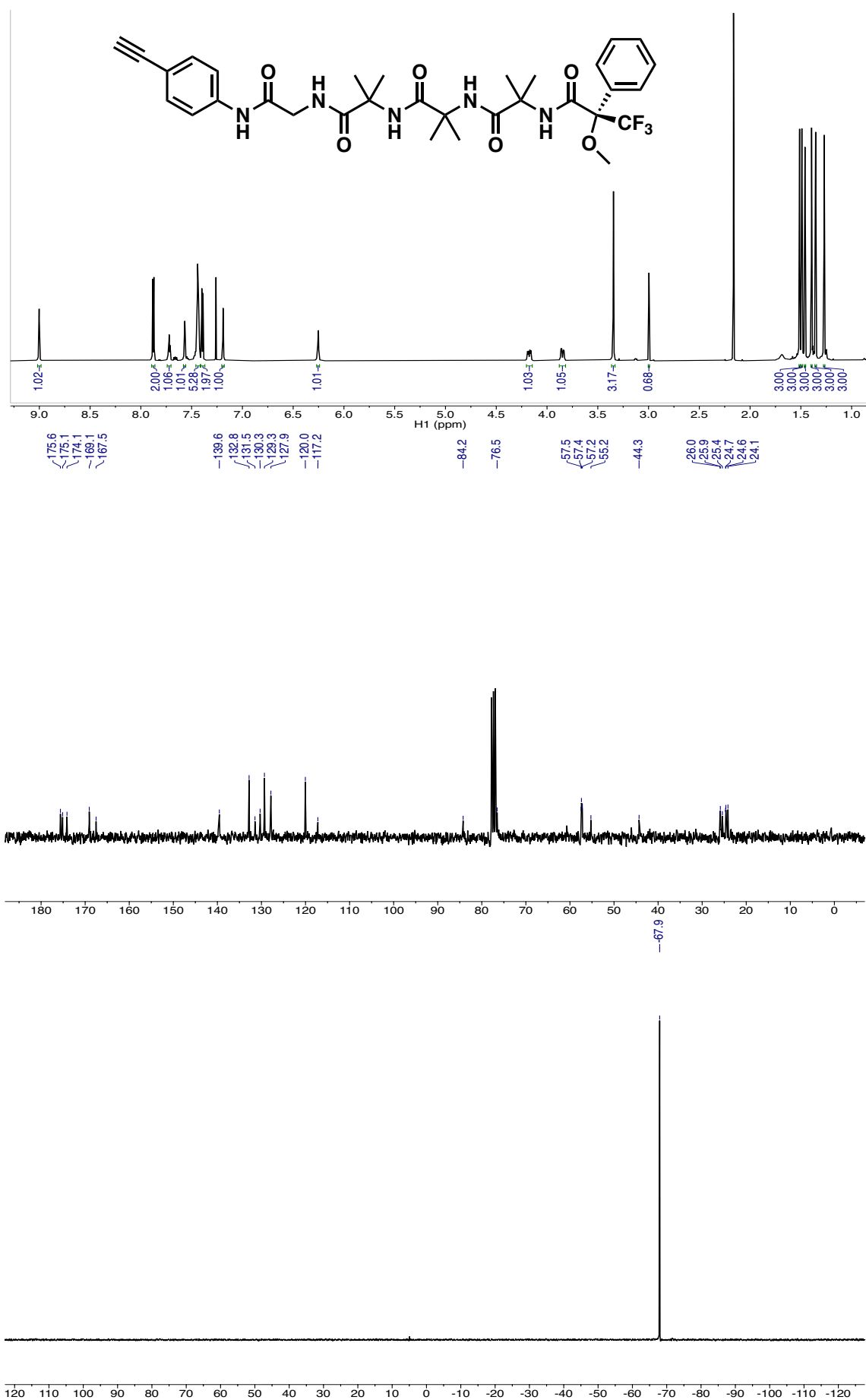
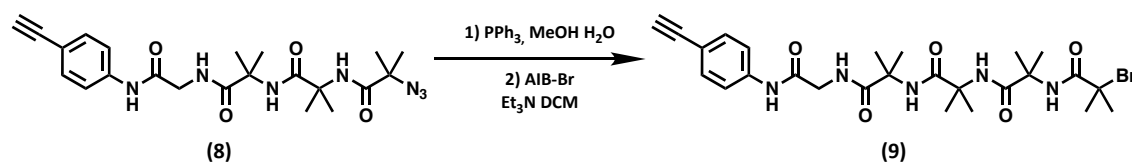


Figure S11. (a) ¹H-NMR, (b) ¹³C-NMR and (c) ¹⁹F-NMR spectra of mono-3 in CDCl₃.

2-bromo-*N*-(1-((1-((1-((2-((4-ethynylphenyl)amino)-2-oxoethyl)amino)-2-methyl-1-oxopropan-2-yl)amino)-2-methyl-1-oxopropan-2-yl)amino)-2-methyl-1-oxopropan-2-yl)-2-methylpropanamide (9)



General Protocol 3: 2-azido-*N*-(1-((1-((1-((2-((4-ethynylphenyl)amino)-2-oxoethyl)amino)-2-methyl-1-oxopropan-2-yl)amino)-2-methyl-1-oxopropan-2-yl)-2-methylpropanamide (8, 0.20 g, 1.00 equiv) and triphenylphosphine (0.12 g, 1.05 equiv) were dissolved in 30 mL of MeOH/water solution (95/5) and this mixture was refluxed for 2 h. Next, the organic layer was evaporated, diluted with water (20 mL) and extracted with ethyl acetate (5 x 30 mL). The organic layer was dried with anhydrous Na₂SO₄ and used for acylation with (*S*)-MTPA-Cl without further purification. The ethyl acetate was evaporated to yield 2-amino-*N*-(1-((1-((1-((2-((4-ethynylphenyl)amino)-2-oxoethyl)amino)-2-methyl-1-oxopropan-2-yl)amino)-2-methyl-1-oxopropan-2-yl)-2-methylpropanamide in 94 % yield (0.18 g).

Following General Protocol 1, 2-amino-*N*-(1-((1-((1-((2-((4-ethynylphenyl)amino)-2-oxoethyl)amino)-2-methyl-1-oxopropan-2-yl)amino)-2-methyl-1-oxopropan-2-yl)-2-methylpropanamide (0.18 g, 1 equiv) in DCM (10 mL) was added triethylamine (0.14 mL, 2.50 equiv) and α-bromoisobutyryl bromide (0.05 mL, 1.05 equiv). The solution was stirred at rt for 1 h. Then, the organic layer was washed with HCl 1M (3 x 20 mL), dried with anhydrous Na₂SO₄ and was evaporated to obtain **9** in 88 % yield of pure product (0.21 g).

2-bromo-*N*-(1-((1-((1-((4-ethynylphenyl)amino)-2-oxoethyl)amino)-2-methyl-1-oxopropan-2-yl)amino)-2-methyl-1-oxopropan-2-yl)amino)-2-methylpropanamide (**9**)

^1H NMR (300 MHz, CDCl_3) δ (ppm): 9.03 (s, 1H), 7.88 (m, 3H), 7.40 (m, 3H), 6.95 (s, 1H), 6.43 (s, 1H), 4.06 (d, $J=6.3$ Hz, 2H), 3.00 (s, 1H), 1.94 (s, 6H), 1.56 (s, 6H), 1.47 (s, 6H), 1.43 (s, 6H).

^{13}C NMR (75 MHz, CDCl_3) δ (ppm): 176.4, 175.8, 175.2, 172.9, 169.6, 139.1, 132.9, 120.4, 117.7, 84.0, 59.9, 57.5, 57.3, 56.4, 44.5, 31.1, 25.5, 25.3, 24.8.

HRMS (ESI) m/z calc for $\text{C}_{26}\text{H}_{36}\text{BrN}_5\text{O}_5$ [$\text{M}+\text{H}$]: 578.1900, found: 578.1973.

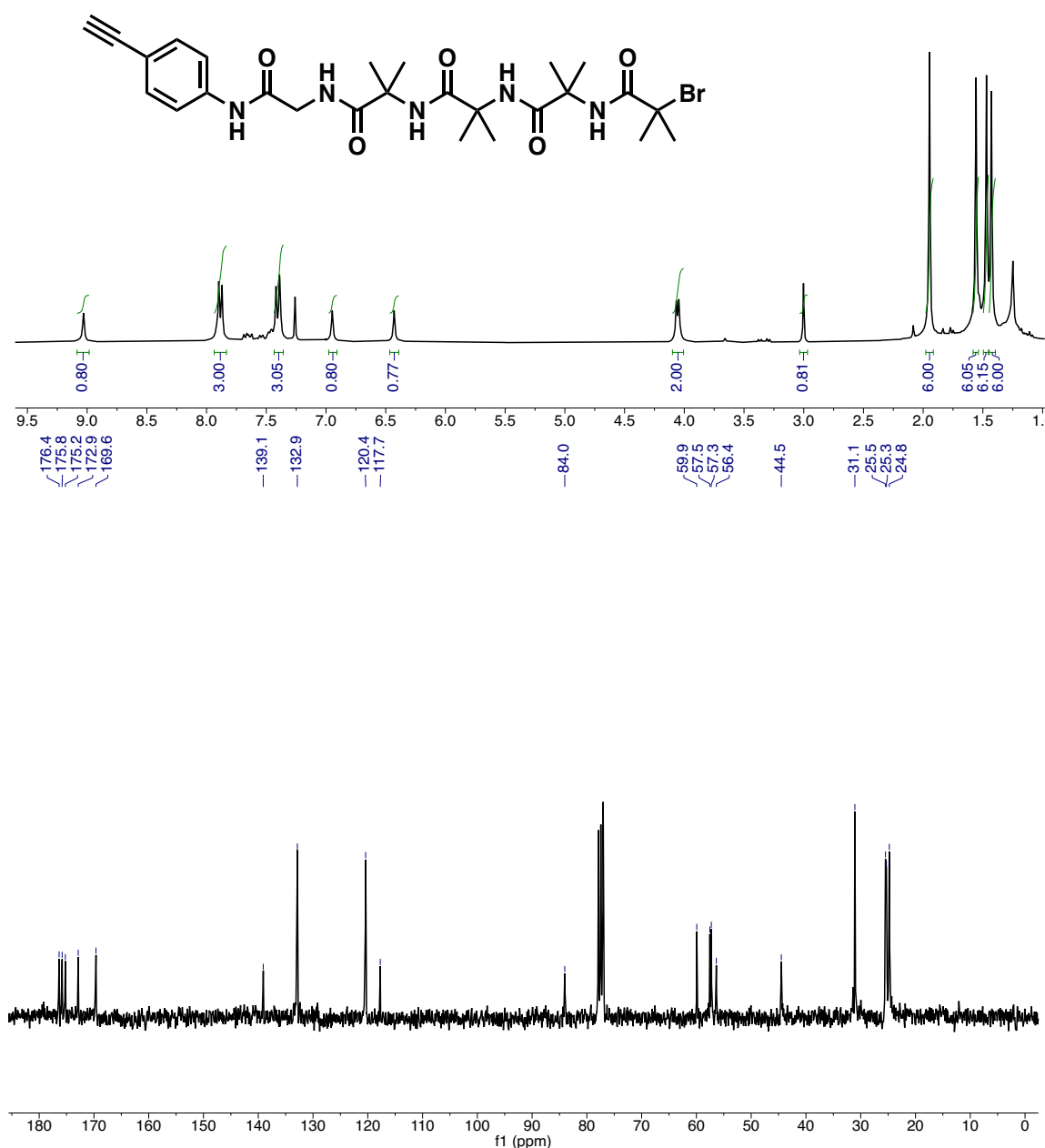
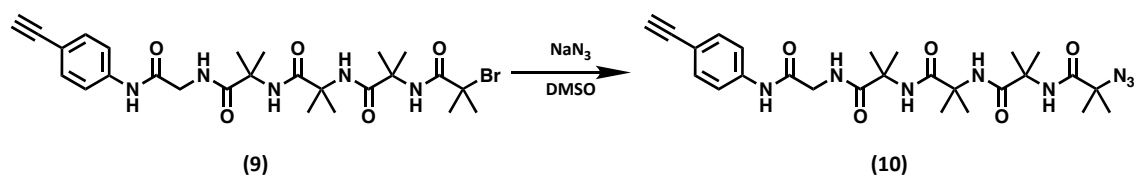


Figure S12. (a) ^1H -NMR and (b) ^{13}C -NMR spectra of **9** in CDCl_3 .

2-azido-*N*-(1-((1-((1-((2-((4-ethynylphenyl)amino)-2-oxoethyl)amino)-2-methyl-1-oxopropan-2-yl)amino)-2-methyl-1-oxopropan-2-yl)amino)-2-methyl-1-oxopropan-2-yl)-2-methylpropanamide (**10**)



General Protocol 2: 2-bromo-*N*-(1-((1-((1-((2-((4-ethynylphenyl)amino)-2-oxoethyl)amino)-2-methyl-1-oxopropan-2-yl)amino)-2-methyl-1-oxopropan-2-yl)amino)-2-methyl-1-oxopropan-2-yl)-2-methylpropanamide (**9**, 0.21 g, 1.00 equiv) was dissolved in 5 mL of DMSO and to this solution sodium azide (0.03 g, 1.20 equiv) was added. The mixture was stirred at 80°C for 2 h. Then, it was diluted with 25 mL of ethyl acetate, extracted with water (5 x 15 mL) and dried with anhydrous Na₂SO₄. The organic layer was evaporated to obtain **10** in 97 % yield (0.19 g).

2-azido-*N*-(1-((1-((1-((2-((4-ethynylphenyl)amino)-2-oxoethyl)amino)-2-methyl-1-oxopropan-2-yl)amino)-2-methyl-1-oxopropan-2-yl)amino)-2-methyl-1-oxopropan-2-yl)-2-methylpropanamide (**10**)

^1H NMR (300 MHz, CD_3OD) δ (ppm): 9.33 (s, 1H), 8.26 (t, $J=6.2$ Hz, 1H), 7.93 (s, 1H), 7.89-7.78 (m, 4H), 7.40 (d, $J=8.7$ Hz, 2H), 3.99 (d, $J=6.2$ Hz, 2H), 3.40 (s, 1H), 1.53 (d, $J=6.9$ Hz, 12H), 1.43 (d, $J=7.7$ Hz, 12H).

^{13}C NMR (75 MHz, CD_3OD) δ (ppm): 176.9, 176.3, 175.7, 173.4, 169.2, 138.7, 132.0, 119.8, 117.9, 82.9, 76.7, 63.4, 56.9, 56.7, 43.5, 24.2, 24.0, 23.4, 23.2.

HRMS (ESI) m/z calc for $\text{C}_{26}\text{H}_{36}\text{N}_8\text{O}_5$ $[\text{M}+\text{H}]^+$: 541.2809, found: 541.2881.

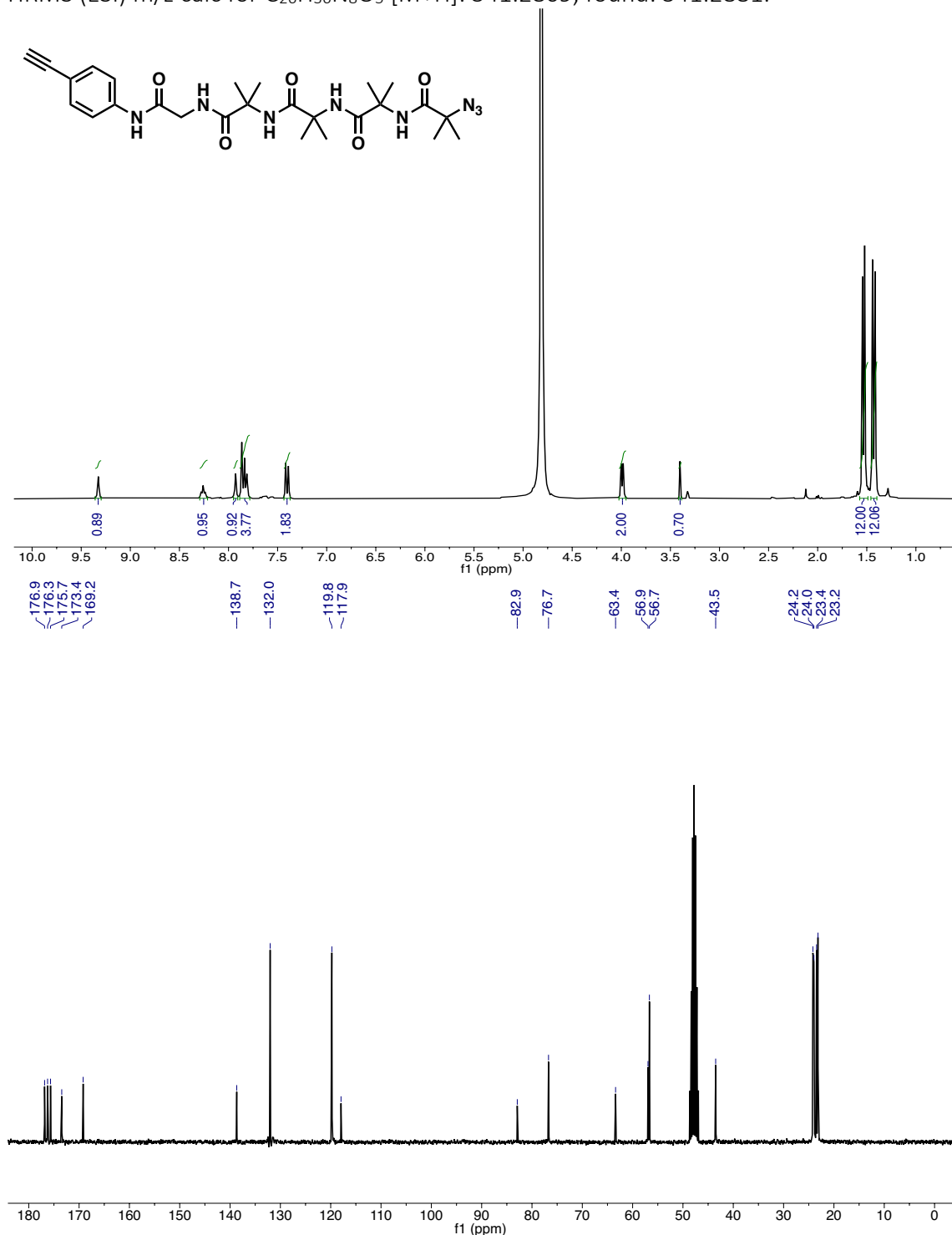
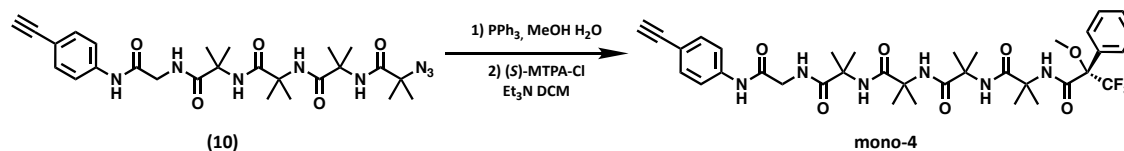


Figure S13. (a) ^1H -NMR and (b) ^{13}C -NMR spectra of **10** in CD_3OD .

(*S*)-*N*-(1-((1-((1-((1-((2-((4-ethynylphenyl)amino)-2-oxoethyl)amino)-2-methyl-1-oxopropan-2-yl)amino)-2-methyl-1-oxopropan-2-yl)amino)-2-methyl-1-oxopropan-2-yl)amino)-2-methyl-1-oxopropan-2-yl)-3,3,3-trifluoro-2-methoxy-2-phenylpropanamide (mono-4)



General Protocol 3: 2-azido-*N*-(1-((1-((1-((2-((4-ethynylphenyl)amino)-2-oxoethyl)amino)-2-methyl-1-oxopropan-2-yl)amino)-2-methyl-1-oxopropan-2-yl)amino)-2-methyl-1-oxopropan-2-yl)-2-methylpropanamide (**10**, 0.15 g, 1.00 equiv) and triphenylphosphine (0.08 g, 1.05 equiv) were dissolved in 30 mL of MeOH/water solution (95/5) and this mixture was refluxed for 2 h. Next, the organic layer was evaporated, diluted with water (20 mL) and extracted with ethyl acetate (5 x 30 mL).

The organic layer was dried with anhydrous Na₂SO₄ and used for acylation with (*S*)-MTPA-Cl without further purification. The ethyl acetate was evaporated to yield 2-amino-*N*-(1-((1-((1-((2-((4-ethynylphenyl)amino)-2-oxoethyl)amino)-2-methyl-1-oxopropan-2-yl)amino)-2-methyl-1-oxopropan-2-yl)amino)-2-methyl-1-oxopropan-2-yl)-2-methylpropanamide in 91 % yield (0.13 g).

(*S*)-MTPA-Cl was prepared according to our previously reported method,^[S1] (*S*)-α-methoxy-α-trifluoromethylphenylacetic acid was dissolved in hexane, and oxalyl chloride and DMF were subsequently added. This mixture was stirred at rt for 30 minutes, then the solution was filtrated and the organic layer was evaporated. The crude was diluted in DCM (10 mL) and combined with PA-gly-(Aib)₄-NH₂, and then Et₃N (0.04 mL, 1.20 equiv) was added. The mixture was stirred at rt for 1 h and the organic layer was evaporated and the crude was purified by chromatographic column using silica gel as stationary phase with a mixture of hexane/ethyl acetate (20/80) as eluent, obtaining mono-4 in 86 % yield (0.16 g).

¹H NMR (500 MHz, DMF-d₇) δ (ppm): 9.19 (s, 1H), 8.77 (s, 1H), 8.19 (s, 1H), 7.99 (t, *J*=6.3 Hz, 1H), 7.87 (d, *J*=8.7 Hz, 2H), 7.73 (s, 1H), 7.52-7.47 (m, 3H), 7.43-7.35 (m, 3H), 7.33 (d, *J*=8.6 Hz, 2H), 3.79 (qd, *J*=17.2 Hz, 6.2 Hz, 2H), 3.35 (s, 1H), 3.32 (s, 3H), 1.42 (s, 6H), 1.38 (d, *J*=4.6 Hz, 6H), 1.28 (d, *J*=4.8 Hz, 6H), 1.23 (s, 3H), 1.19 (s, 3H).

¹³C NMR (500 MHz, DMF-d₇) δ (ppm): 177.1, 176.2, 175.6, 175.4, 169.1, 167.5, 140.3, 133.4, 132.8, 130.1, 129.2, 128.1, 119.7, 117.4, 84.0, 79.1, 57.6, 57.2, 57.0, 57.0, 55.3, 44.2, 25.5, 25.1, 25.0, 24.7, 24.4, 24.0

¹⁹F NMR (750 MHz, DMF-d₇) δ (ppm): -68.8.

HRMS (ESI) *m/z* calc for C₃₆H₄₅F₃N₆O₇ [M+H]: 731.3302, found: 731.3375.

α_D²⁰ = -10 (c = 10 mg/mL, DMF).

^{S1} Leiras, S.; Freire, F.; Seco, J. M.; Quiñoá, E.; Riguera, R. *Chem. Sci.* **2013**, *4*, 2735.

Figure S14. (a) ^1H -NMR, (b) ^{13}C -NMR and (c) ^{19}F -NMR spectra of mono-**4** in DMF- d_7 .

3. X-ray structure of monomers

Single crystals of monomers were grown by slow evaporation of the corresponding monomer solutions in a mixture of DCM/hexanes. The crystallographic data is depicted below in detail.

- Crystal data structure refinement for mono-1

Crystal data

$C_{24}H_{24}F_3N_3O_4$
 $M_r = 475.46$
 Monoclinic, $P2_1$
 Hall symbol: $P\ 2_1yb$
 $a = 8.9570\ (2)\ \text{\AA}$
 $b = 10.3765\ (3)\ \text{\AA}$
 $c = 25.8476\ (7)\ \text{\AA}$
 $\beta = 94.880\ (2)^\circ$
 $V = 2393.63\ (11)\ \text{\AA}^3$
 $Z = 4$

$F(000) = 992$
 $D_x = 1.314\ \text{Mg m}^{-3}$
 Cu $K\alpha$ radiation, $\lambda = 1.54178\ \text{\AA}$
 Cell parameters from 9965 reflections
 $\theta = 3.4\text{--}74.6^\circ$
 $\mu = 0.90\ \text{mm}^{-1}$
 $T = 100\ \text{K}$
 Plate, colourless
 $0.19 \times 0.14 \times 0.02\ \text{mm}$

Data collection

Bruker D8 VENTURE PHOTON III-14
 diffractometer
 Radiation source: INCOATEC microfocus sealed
 tube, Incoatec λ S 3.0
 Incoatec multilayer mirror monochromator
 Detector resolution: $7.3910\ \text{pixels mm}^{-1}$
 ω and ϕ scans
 Absorption correction: multi-scan
 BRUKER SADABS2016/2

$T_{\min} = 0.780$, $T_{\max} = 0.929$
 57121 measured reflections
 9623 independent reflections
 8795 reflections with $I > 2\sigma(I)$
 $R_{\text{int}} = 0.056$
 $\theta_{\max} = 74.5^\circ$, $\theta_{\min} = 1.7^\circ$
 $h = -11 \rightarrow 11$
 $k = -12 \rightarrow 12$
 $l = -31 \rightarrow 32$

Refinement

Refinement on F^2
 Least-squares matrix: full
 $R[F^2 > 2\sigma(F^2)] = 0.041$
 $wR(F^2) = 0.099$
 $S = 1.04$
 9623 reflections
 637 parameters
 1 restraint
 0 constraints
 Primary atom site location: dual
 Secondary atom site location: dual
 Hydrogen site location: mixed

H atoms treated by a mixture of independent and
 constrained refinement
 $w = 1/[\sigma^2(F_o^2) + (0.034P)^2 + 1.7568P]$
 where $P = (F_o^2 + 2F_c^2)/3$
 $(\Delta/\sigma)_{\max} = 0.001$
 $\Delta\rho_{\max} = 0.74\ \text{e \AA}^{-3}$
 $\Delta\rho_{\min} = -0.22\ \text{e \AA}^{-3}$
 Absolute structure: Flack x determined using 3763
 quotients $[(I^+)-(I^-)]/[(I^+)+(I^-)]$ (Parsons, Flack and
 Wagner, Acta Cryst. B69 (2013) 249-259).
 Absolute structure parameter: $-0.12\ (7)$

X-ray structures

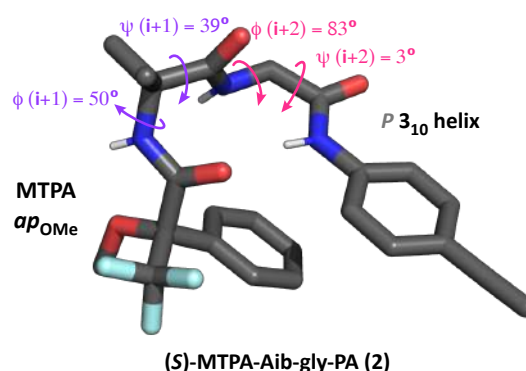
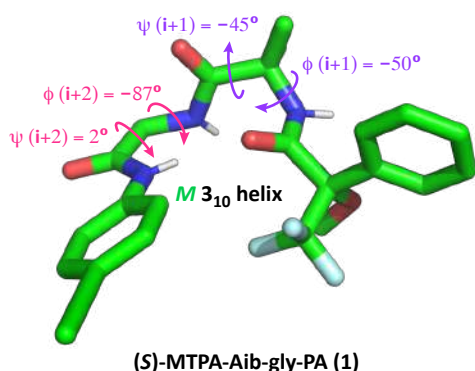


Table S1. Torsion Angle Values (deg) for mono-1 structures.

mono-1	$\psi\ (i+1)$	$\phi\ (i+1)$	$\psi\ (i+2)$	$\phi\ (i+2)$	O=C-C-OMe
ap_{OMe} P- 3_{10} helix	39°	50°	3°	83°	-173°
ap_{OMe} M- 3_{10} helix	-45°	-50°	2°	-87°	$+152^\circ$

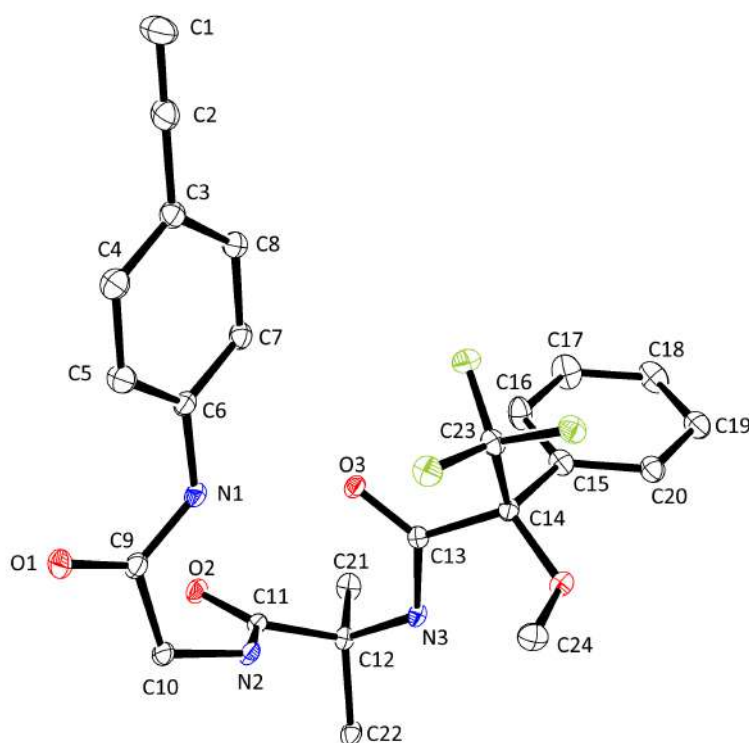


Figure S15. ORTEP representation of the mono-1 conformation obtained from X-ray studies.

• Crystal data structure refinement for mono-2

Crystal data

$C_{28}H_{31}F_3N_4O_5$

$M_r = 560.57$

Monoclinic, $P2_1$

$a = 10.5078$ (3) Å

$b = 16.7772$ (4) Å

$c = 16.2881$ (4) Å

$\beta = 92.6903$ (15)°

$V = 2868.29$ (13) Å³

$Z = 4$

$F(000) = 1176$

$D_x = 1.298$ Mg m⁻³

Cu $K\alpha$ radiation, $\lambda = 1.54178$ Å

Cell parameters from 9847 reflections

$\theta = 4.2\text{--}77.2^\circ$

$\mu = 0.87$ mm⁻¹

$T = 100$ K

Plate, clear colourless

$0.26 \times 0.25 \times 0.02$ mm

Data collection

Bruker D8 VENTURE PHOTON-III C14
diffractometer

Radiation source: microfocus sealed tube, Incoatec

$I\mu S$ 3.0

Multilayer mirror monochromator

Detector resolution: 7.3910 pixels mm⁻¹

φ or ω oscillation scans

Absorption correction: multi-scan

SADABS2016/2 - Bruker AXS area detector scaling
and absorption correction

$T_{\min} = 0.77$, $T_{\max} = 0.99$

87447 measured reflections

12164 independent reflections

9778 reflections with $I > 2\sigma(I)$

$R_{\text{int}} = 0.098$

$\theta_{\max} = 79.9^\circ$, $\theta_{\min} = 2.7^\circ$

$h = -13 \rightarrow 13$

$k = -21 \rightarrow 21$

$l = -19 \rightarrow 20$

Refinement

Refinement on F^2

Least-squares matrix: full

$R[F^2 > 2\sigma(F^2)] = 0.053$

$wR(F^2) = 0.128$

$S = 1.03$

12164 reflections

756 parameters

1 restraint

Primary atom site location: dual

Secondary atom site location: difference Fourier map

Hydrogen site location: mixed

H atoms treated by a mixture of independent and
constrained refinement

$w = 1/[\sigma^2(F_o^2) + (0.0414P)^2 + 1.7094P]$

where $P = (F_o^2 + 2F_c^2)/3$

$(\Delta/\sigma)_{\max} < 0.001$

$\Delta\rho_{\max} = 0.24$ e Å⁻³

$\Delta\rho_{\min} = -0.27$ e Å⁻³

Extinction correction: *SHELXL2018/3* (Sheldrick
2018)

Extinction coefficient: 0.0032 (3)

Absolute structure: Flack x determined using 3805
quotients $[(I^+)-(I^-)]/[(I^+)+(I^-)]$ (Parsons, Flack and
Wagner, Acta Cryst. B69 (2013) 249-259).

Absolute structure parameter: 0.06 (13)

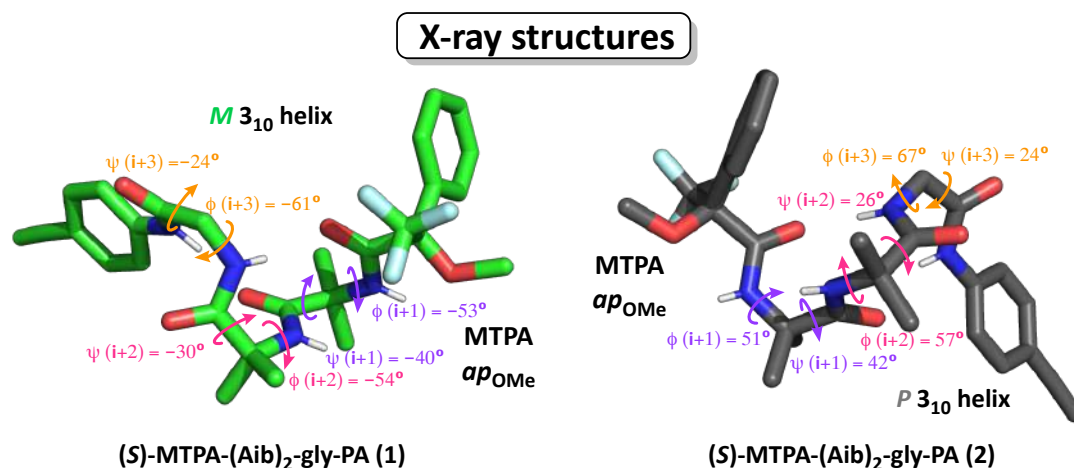


Table S2. Torsion Angle Values (deg) for mono-2 structures.

mono-2	ψ (i+1)	ϕ (i+1)	ψ (i+2)	ϕ (i+2)	ψ (i+3)	ϕ (i+3)	O=C-C-OMe
ap _{OMe} P-3 ₁₀ helix	42°	51°	26°	57°	24°	67°	-172°
ap _{OMe} M-3 ₁₀ helix	-40°	-53°	-30°	-54°	-24°	-61°	+162°

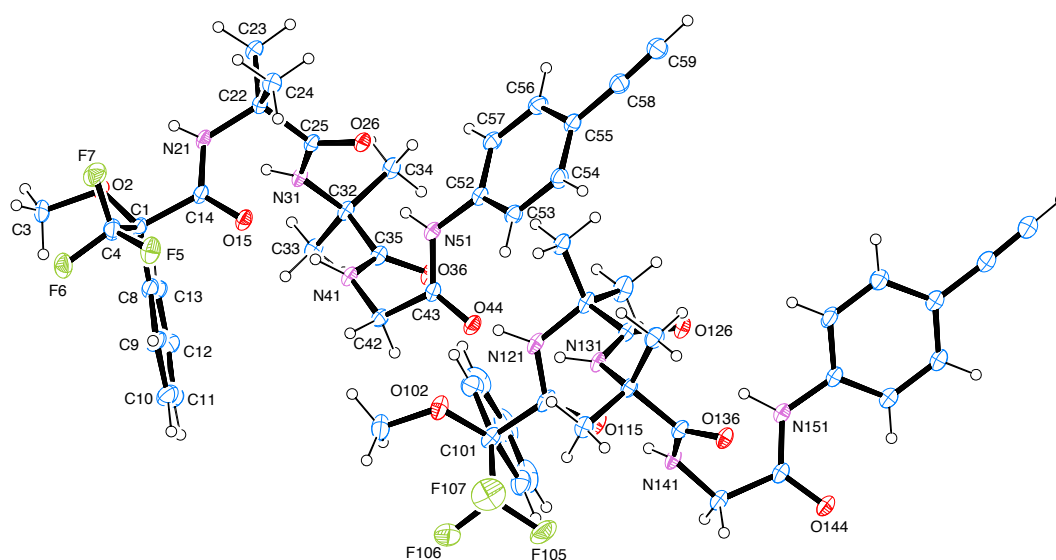


Figure S16. ORTEP representation of the mono-2 (1) and mono-2 (2) conformations obtained from X-ray studies.

- Crystal data structure refinement for mono-3

Crystal data	
Chemical formula	$4(\text{C}_{32}\text{H}_{38}\text{F}_3\text{N}_5\text{O}_6) \cdot \text{C}_6\text{H}_{14}$
M_r	2668.87
Crystal system, space group	Monoclinic, $P2_1$
Temperature (K)	100
a, b, c (Å)	19.5189 (4), 12.6667 (2), 30.3879 (6)
β (°)	96.154 (1)
V (Å ³)	7469.8 (2)
Z	2
Radiation type	Cu $K\alpha$
μ (mm ⁻¹)	0.77
Crystal size (mm)	0.16 × 0.13 × 0.03
Data collection	
Diffractometer	Bruker D8 VENTURE PHOTON III-14
Absorption correction	Multi-scan BRUKER SADABS2016/2
$T_{\min}, T_{\max}$	0.815, 0.929
No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	160851, 29357, 20666
R_{int}	0.120
$(\sin \theta/\lambda)_{\text{max}}$ (Å ⁻¹)	0.617
Refinement	
$R[F^2 > 2\sigma(F^2)], wR(F^2), S$	0.070, 0.205, 1.02
No. of reflections	29357
No. of parameters	1858
No. of restraints	167
H-atom treatment	H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{\text{max}}, \Delta\rho_{\text{min}}$ (e Å ⁻³)	0.60, -0.30
Absolute structure	Flack x determined using 7386 quotients $[(I^+)-(I^-)]/[(I^+)+(I^-)]$ (Parsons, Flack and Wagner, Acta Cryst. B69 (2013) 249-259).
Absolute structure parameter	-0.07 (11)

X-ray structures

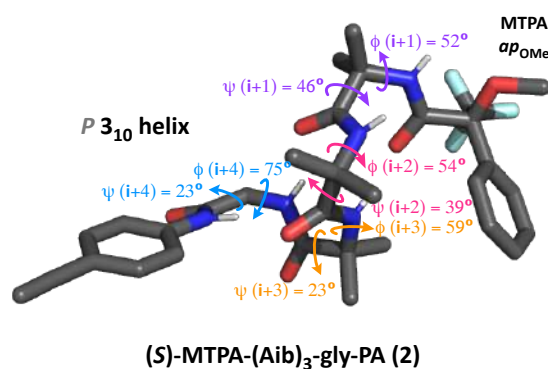
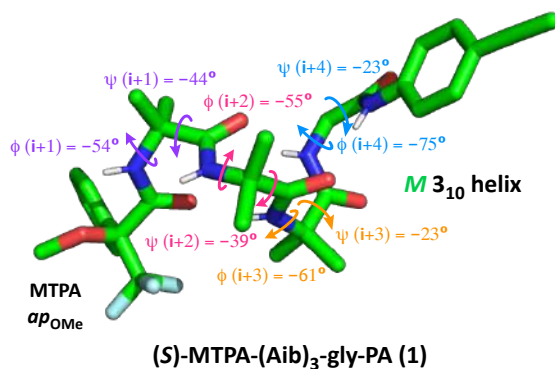
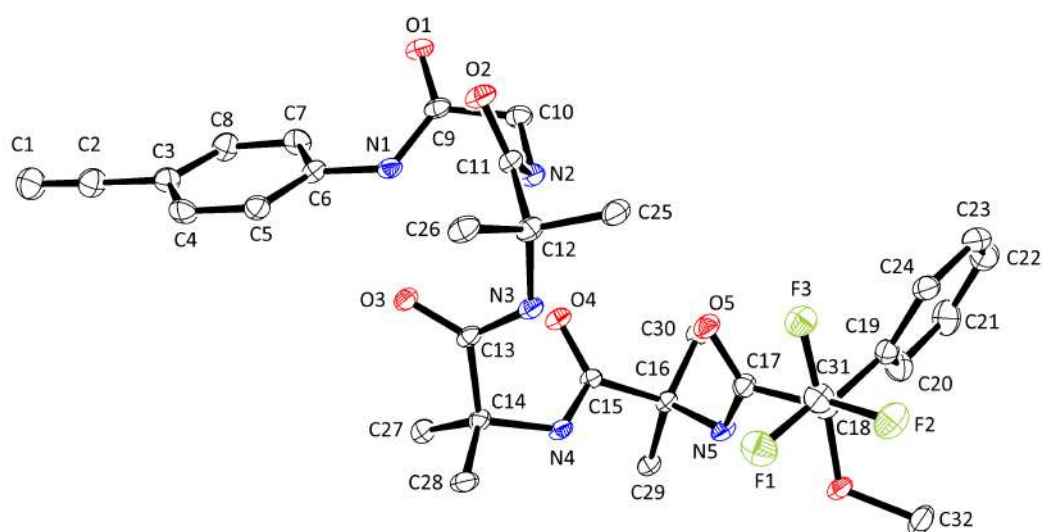


Table S3. Torsion Angle Values (deg) for mono-3 structures.

mono-3	$\psi(i+1)$	$\phi(i+1)$	$\psi(i+2)$	$\phi(i+2)$	$\psi(i+3)$	$\phi(i+3)$	$\psi(i+4)$	$\phi(i+4)$	O=C-C-OMe
ap_{OMe} $P\text{-}3_{10}$ helix	46°	52°	39°	54°	23°	59°	23°	75°	-174°
ap_{OMe} $M\text{-}3_{10}$ helix	-44°	-54°	-39°	-55°	-23°	-61°	-23°	-75°	+161°

a)



b)

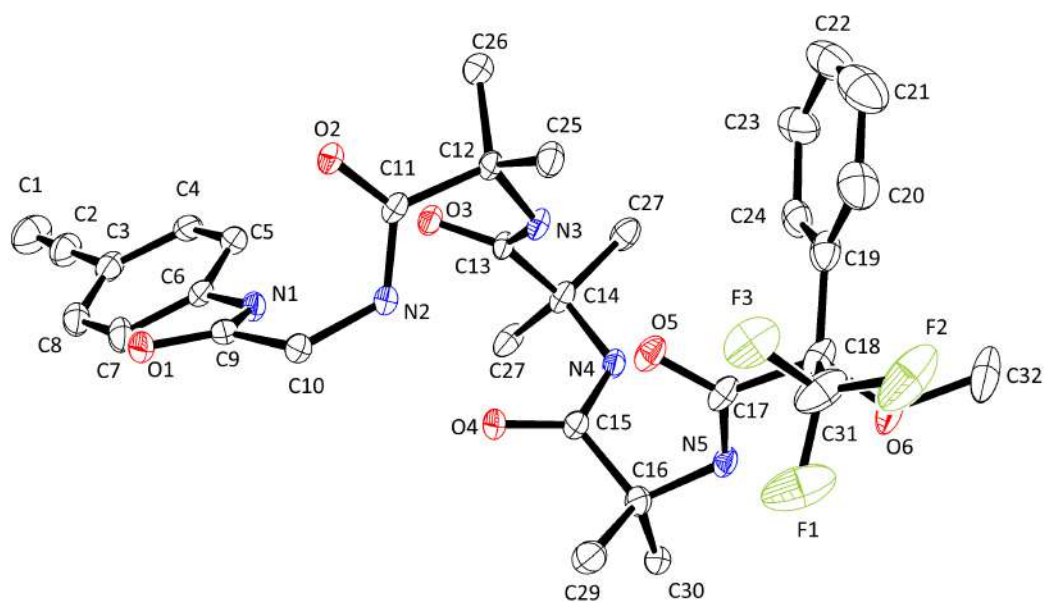


Figure S17. ORTEP representation of the (a) mono-3 (1) and (b) mono-3 (2) conformations obtained from X-ray studies.

- Crystal data structure refinement for mono-4

Crystal data	
Chemical formula	C ₃₆ H ₄₅ F ₃ N ₆ O ₇
<i>M_r</i>	730.78
Crystal system, space group	Monoclinic, <i>C</i> 2
Temperature (K)	100
<i>a</i> , <i>b</i> , <i>c</i> (Å)	24.270 (2), 17.4849 (15), 22.8343 (19)
β (°)	118.769 (3)
<i>V</i> (Å ³)	8493.8 (12)
<i>Z</i>	8
Radiation type	Cu <i>K</i> α
μ (mm ⁻¹)	0.75
Crystal size (mm)	0.24 × 0.02 × 0.02
Data collection	
Diffractometer	?
Absorption correction	—
No. of measured, independent and observed [<i>I</i> > 2 σ (<i>I</i>)] reflections	23164, 5169, 3245
<i>R</i> _{int}	0.107
$\theta_{\max}$ (°)	40.0
(sin θ/λ) _{max} (Å ⁻¹)	0.417
Refinement	
<i>R</i> [<i>F</i> ² > 2 σ (<i>F</i> ²)], <i>wR</i> (<i>F</i> ²), <i>S</i>	0.113, 0.330, 1.21
No. of reflections	5169
No. of parameters	918
No. of restraints	642
H-atom treatment	H-atom parameters constrained
$\Delta\rho_{\max}$, $\Delta\rho_{\min}$ (e Å ⁻³)	0.89, -0.37
Absolute structure	Flack <i>x</i> determined using 1063 quotients [(<i>I</i> +)−(<i>I</i> −)]/[(<i>I</i> +) + (<i>I</i> −)] (Parsons, Flack and Wagner, Acta Cryst. B69 (2013) 249–259).
Absolute structure parameter	−0.1 (2)

X-ray structures

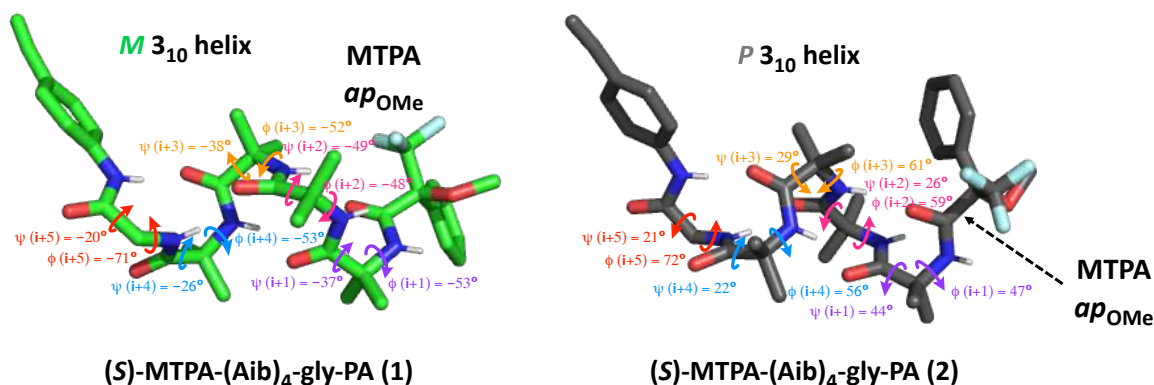


Table S4. Torsion Angle Values (deg) for mono-4 structures.

mono-4	ψ (i+1)	ϕ (i+1)	ψ (i+2)	ϕ (i+2)	ψ (i+3)	ϕ (i+3)	ψ (i+4)	ϕ (i+4)	ψ (i+5)	ϕ (i+5)	O=C-C-OMe
<i>ap</i> _{OMe} <i>P</i> -3 ₁₀ helix	44°	47°	26°	59°	29°	61°	22°	56°	21°	72°	-176°
<i>ap</i> _{OMe} <i>M</i> -3 ₁₀ helix	-37°	-53°	-49°	-48°	-38°	-52°	-26°	-53°	-20°	-71°	+151°

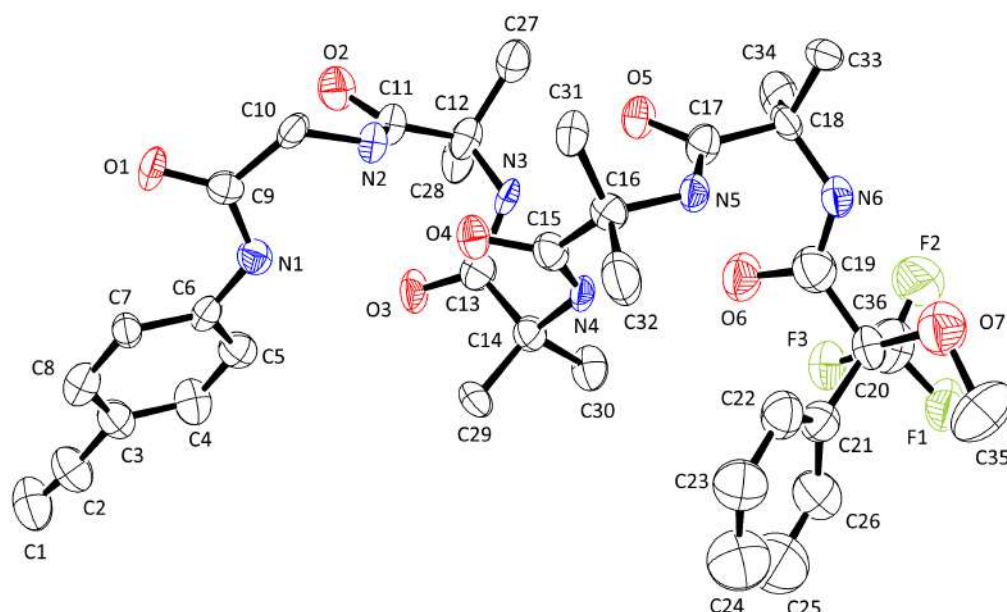


Figure S18. ORTEP representation of the mono-**4** conformation obtained from X-Ray studies.

4. Synthesis of polymers

General procedure for polymerization

The reaction flask (sealed ampoule) was dried under vacuum and argon flushed for three times before monomer was added as a solid. Then, the flask was evacuated on a vacuum line and flushed with dry argon (three times). Dry THF/DMF was added with a syringe and then triethylamine was added dropwise via syringe. A solution of rhodium norbornadiene chloride dimer, $[\text{Rh}(\text{nbd})\text{Cl}]_2$, in THF or DMF was added at 30°C. The reaction mixture was stirring at 30°C for 6h. Then, the resulting polymer was diluted in CH_2Cl_2 and it was precipitated in a large amount of methanol, centrifuged (2 times), reprecipitated in hexane and centrifuged again. The conditions for the polymerization and the respectively yields are described below in Table S5.

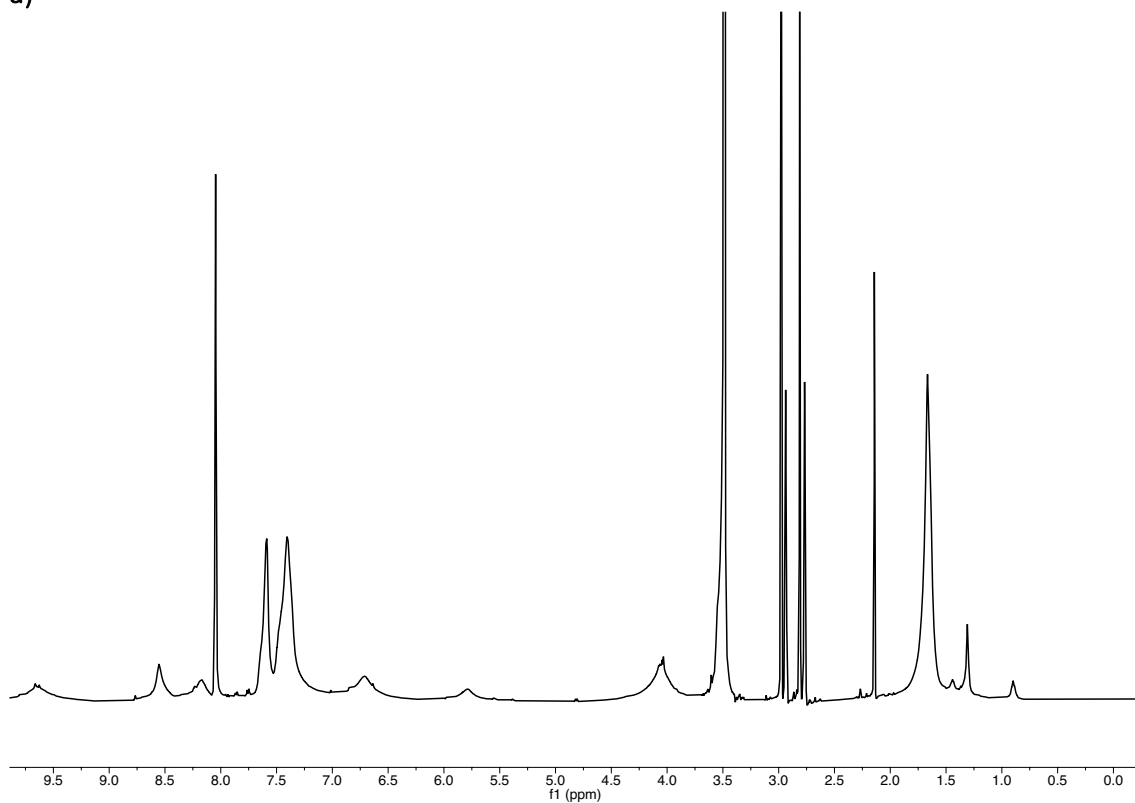
Table S5. Conditions for the polymerization of poly-**1**, poly-**2**, poly-**3** and poly-**4**.

Polymer	Monomer (mg)	Monomer (mmol)	$[\text{Rh}(\text{nbd})\text{Cl}]_2$ (mg)	THF (ml)	DMF (ml)	Et_3N (μl)	Yield (%)
poly- 1	70	0.15	0.70	0.30	-	2.05	83
poly- 2	70	0.12	0.57	0.25	-	1.74	90
poly- 3	70	0.11	0.50	-	0.20	1.51	87
poly- 4	70	0.09	0.44	-	0.20	1.33	74

5. NMR characterization

The polymers display NMR (vinyl protons, $\delta = 5.7$ - 5.8 ppm) indicative of a *cis*- polyene backbone.

a)



b)

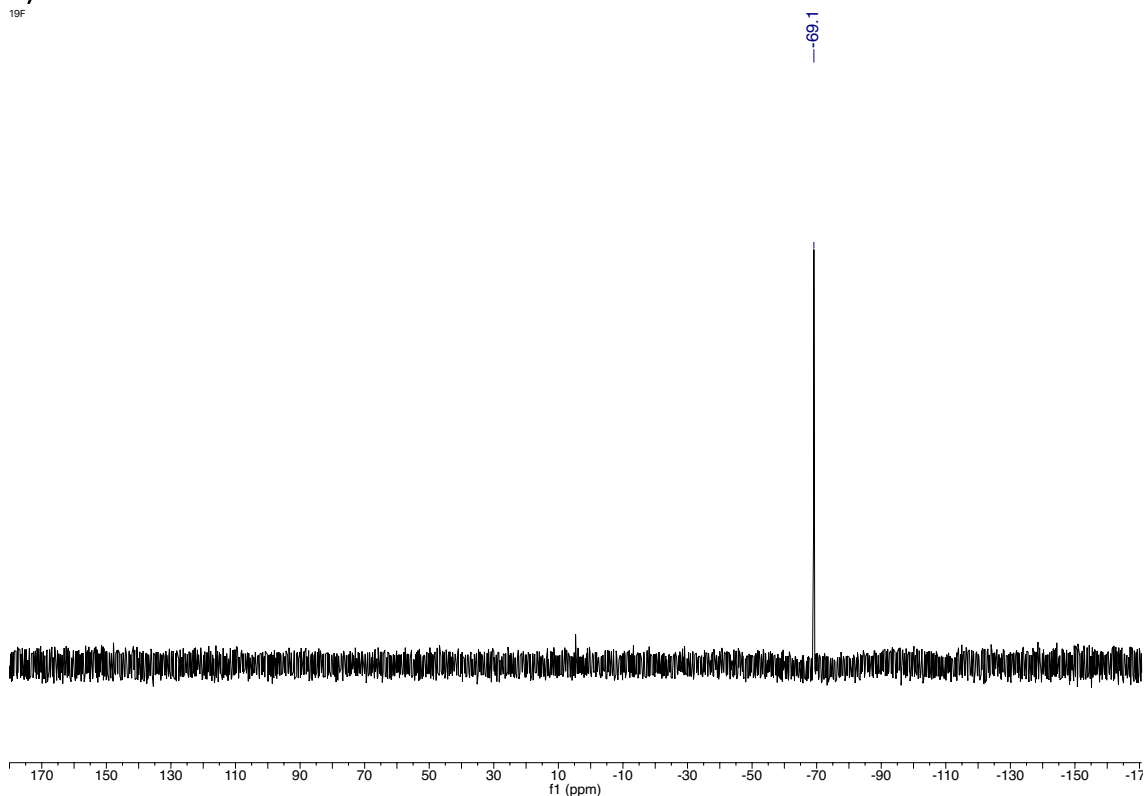
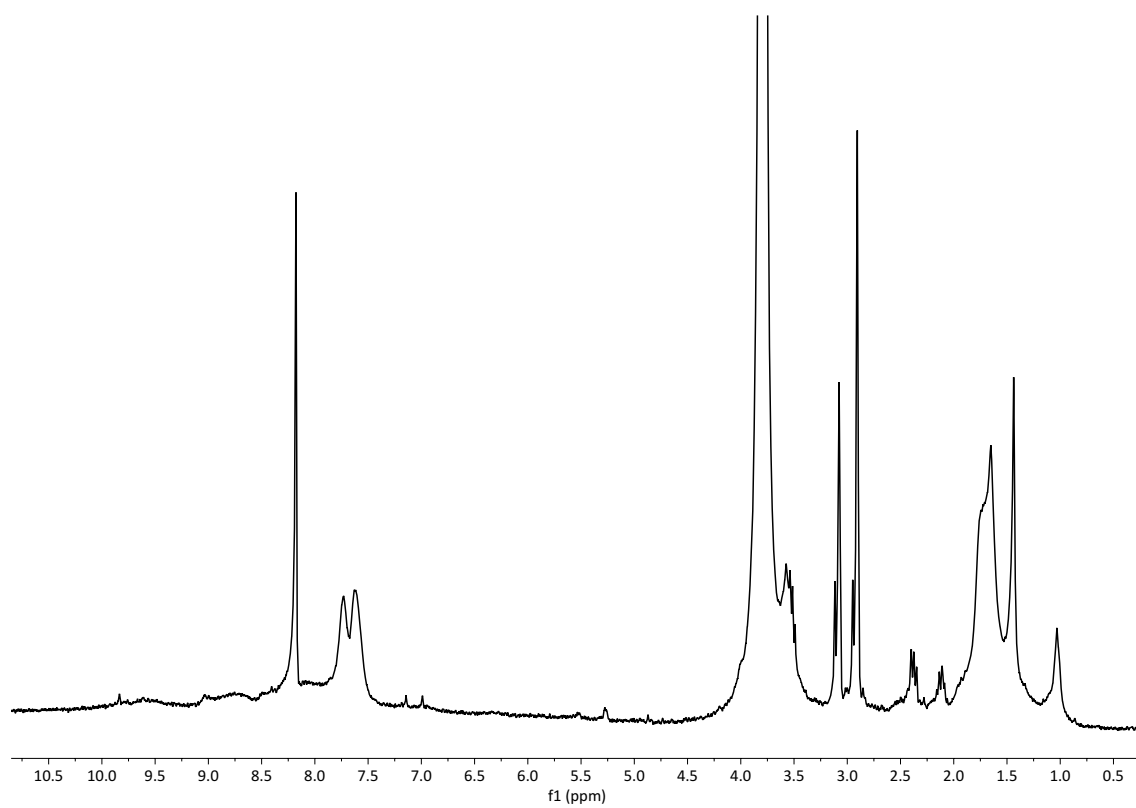


Figure S19. (a) ^1H -NMR (300 Mz, DMF-d_7) and (b) ^{19}F (282 Mz, DMF-d_7) of poly-1.

a)



b)

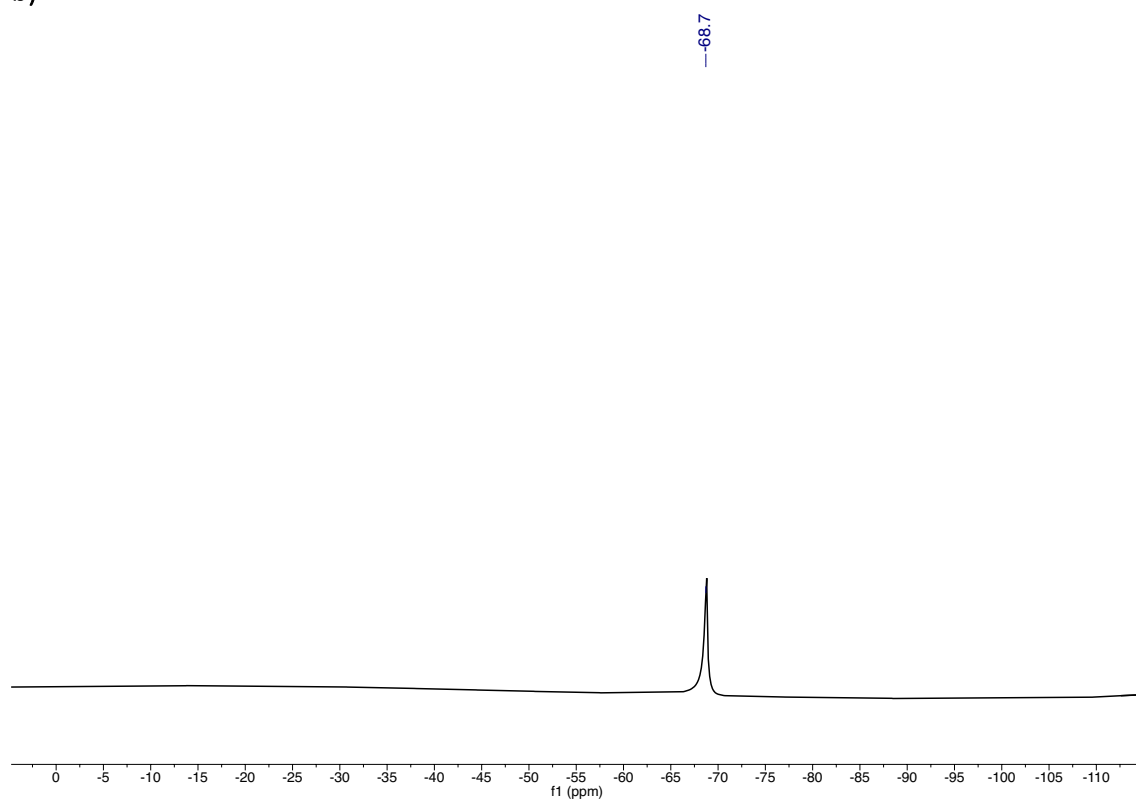


Figure S20. (a) ^1H -NMR (300 Mz, DMF-d_7) and (b) ^{19}F (705 Mz, DMF-d_7) of poly-2.

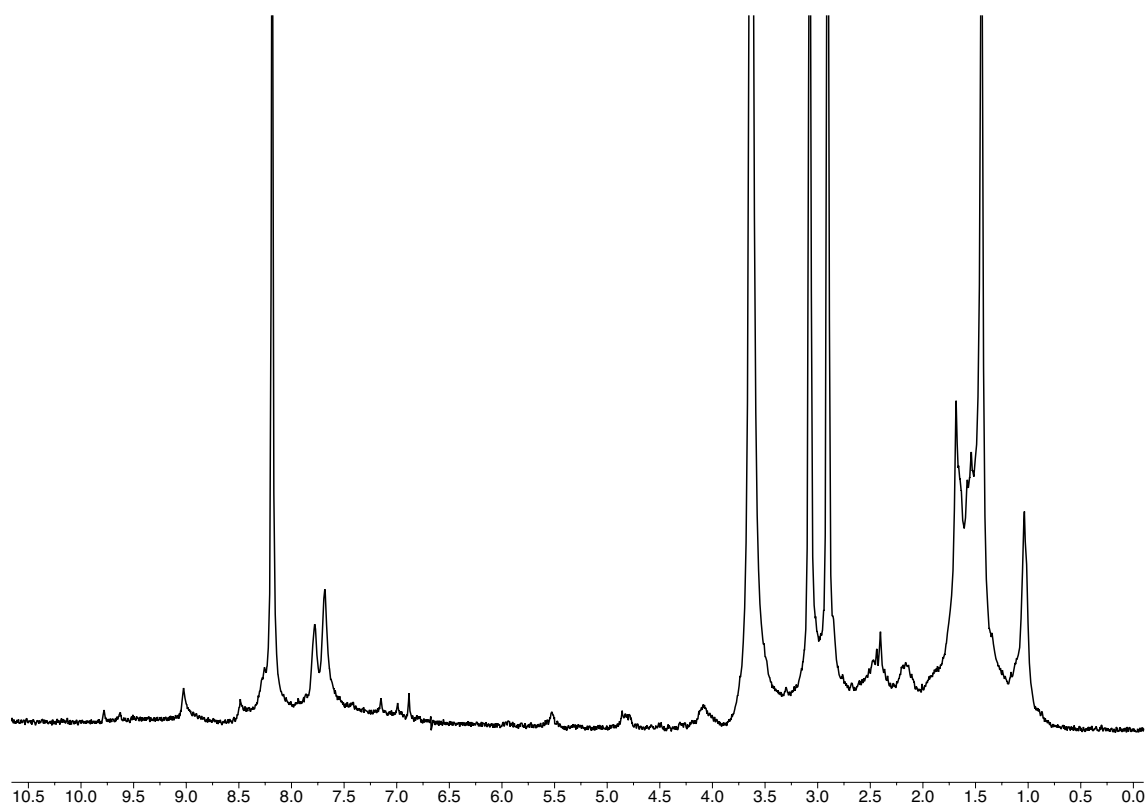


Figure S21. ^1H -NMR of poly-3 (300 Mz, DMF-d_7).

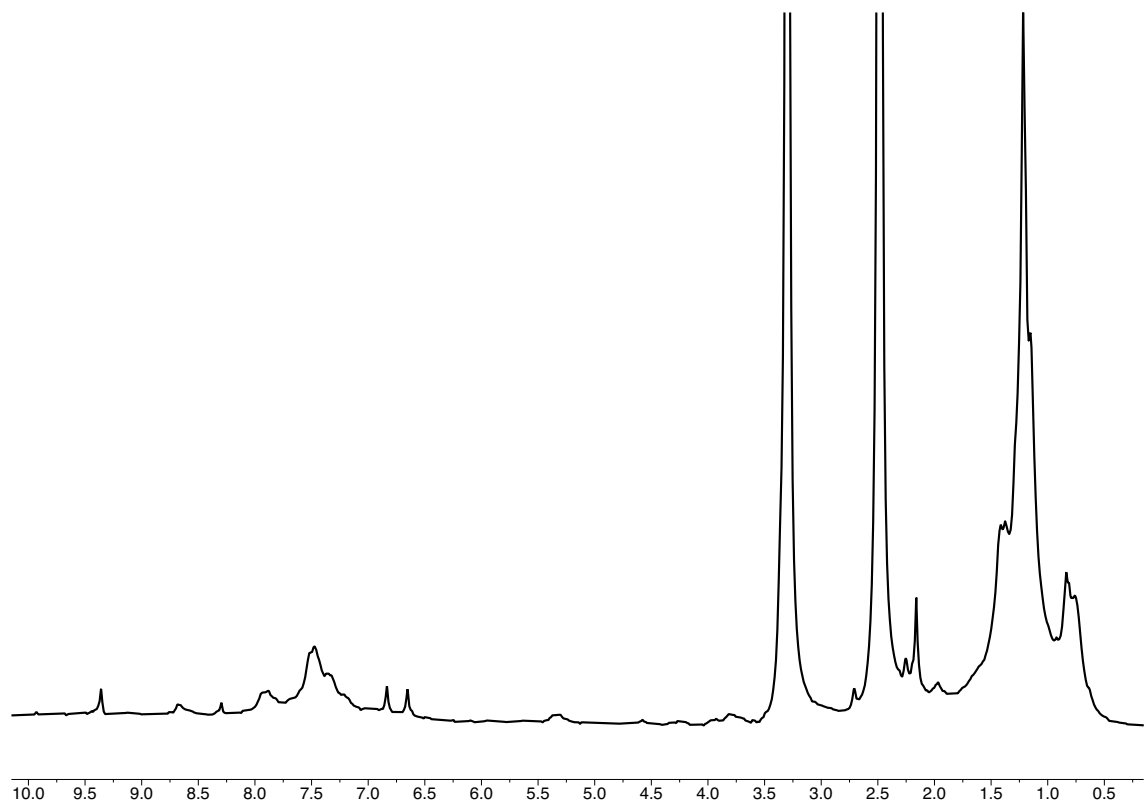


Figure S22. ^1H -NMR of poly-4 (300 Mz, DMSO-d_6).

6. Raman characterization of monomers and polymers

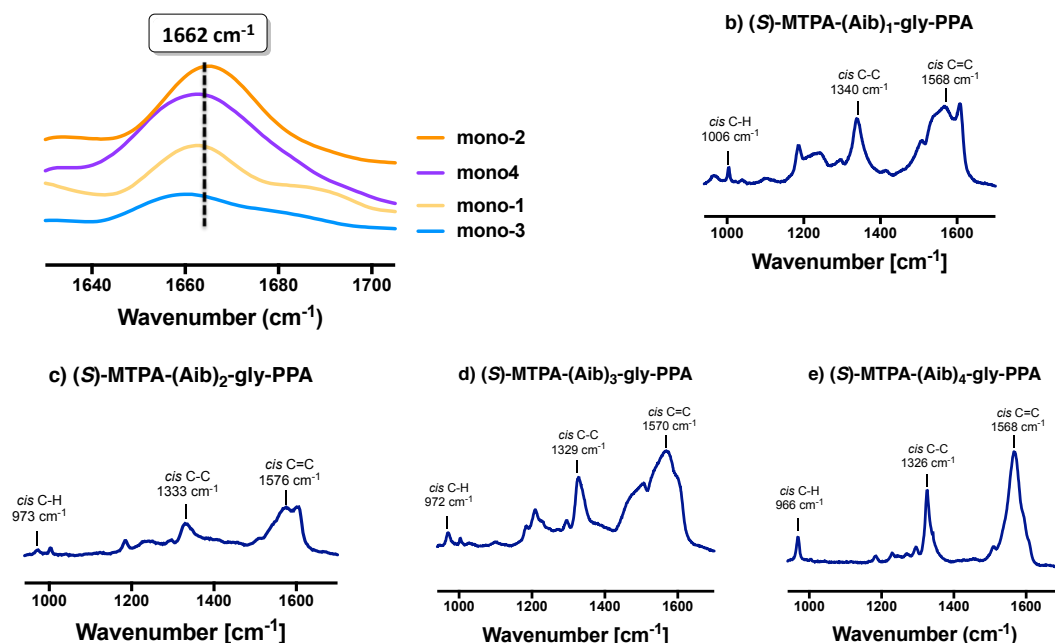


Figure S23. Raman spectra of (a) monomers mono-1 — mono-4, (b) poly-1, (c) poly-2, (d) poly-3 and (e) poly-4 showing the characteristic bands of a *cis*-polyene backbone.

7. ECD Theoretical Calculations

ECD theoretical calculations of the (S)-MTPA-(Aib)_n-gly-PA, (*n* = 1, 2, 3, 4) were performed using as input structural data obtained from X-ray (see Tables S1-S4).

All computations were carried out using Gaussian-16 (G16RevC.01).^[S2] Geometry optimization, as well as ECD theoretical calculations (80 excitation energies), were performed by using the DFT CAM-B3LYP/6-31+G**^[S3-S5] methodology. Frequency calculations on the optimized geometries revealed no imaginary frequencies, indicating that the calculated structures correspond, at least, to local minima on the potential energy surface. The energies shown are the thermally corrected energies at 298K.

^{S2} Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Petersson, G. A.; Nakatsuji, H.; Li, X.; Caricato, M.; Marenich, A. V.; Bloino, J.; Janesko, B. G.; Gomperts, R.; Mennucci, B.; Hratchian, H. P.; Ortiz, J. V.; Izmaylov, A. F.; Sonnenberg, J. L.; Williams-Young, D.; Ding, F.; Lipparini, F.; Egidi, F.; Goings, J.; Peng, B.; Petrone, A.; Henderson, T.; Ranasinghe, D.; Zakrzewski, V. G.; Gao, J.; Rega, N.; Zheng, G.; Liang, W.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Throssell, K.; Montgomery Jr., J. A.; Peralta, J. E.; Ogliaro, F.; Bearpark, M. J.; Heyd, J. J.; Brothers, E. N.; Kudin, K. N.; Staroverov, V. N.; Keith, T. A.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A. P.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Millam, J. M.; Klene, M.; Adamo, C.; Cammi, R.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Farkas, O.; Foresman, J. B.; Fox, D. J. Gaussian 16 Revision C.01. Gaussian Inc: Wallingford CT 2019.

^{S3} Runge, E.; Gross, E. *Phys. Rev. Lett.* **1984**, *52*, 997–1000.

^{S4} Yanai, Y.; Tew, D. P.; Handy, C. C. A. *Chem. Phys. Lett.* **2004**, *393*, 51-57.

^{S5} Peach, M. J. G.; Helgaker, T.; Salek, P.; Keal, T. W.; Lutnaes, O. B.; Tozer, D. J.; Handy, N. C. *Phys. Chem. Chem. Phys.* **2006**, *8*, 558-562.

Table S7. Calculated energy difference for the two *sp/ap* conformers of each *P/M*-turn in terms of the enthalpy (ΔH) and Gibbs free energy (ΔG), where *sp* conformations were considered the zero as *ap* configuration are the most stable in all cases.

monomer	<i>P/M</i> -turn	ΔH (kcal.mol ⁻¹)	ΔG (kcal.mol ⁻¹)
mono-1	<i>P</i> turn	4.4	3.7
	<i>M</i> turn	3.2	3.1
	stretched	4.0	3.8
mono-2	<i>P</i> turn	4.5	4.3
	<i>M</i> turn	4.9	4.3
	stretched	3.6	3.1
mono-3	<i>P</i> turn	4.5	4.8
	<i>M</i> turn	2.9	4.0
	stretched	1.4	0.7
mono-4	<i>P</i> turn	4.6	5.6
	<i>M</i> turn	3.5	3.7
	stretched	2.1	1.6

Considering the shape of the experimental spectra, the theoretical ECDs were built from the calculated rotational strengths assuming a Gaussian band shape with a half width at half height of 0.62 eV. For a more efficient correlation between the theoretical and the experimental results and considering the known differences of DFT in getting accurate ECD spectra, we adjusted each theoretical spectra with correlation factors obtained for comparison (between theory and experiment) of the wavelength and intensity at maximum/minimum corresponding to the first Cotton effect.

In this way, we evaluated a correction factor for lambda as the difference between the theoretical and experimental wavelengths, and we shifted the rest of the theoretical spectrum accordingly. Regarding the intensity, from the above comparison we rescaled the theoretical values to get experimental intensity at the first Cotton effect.

8. CD experiments of monomers

CD studies of the monomers were carried out in different solvents (1 mm cuvette).

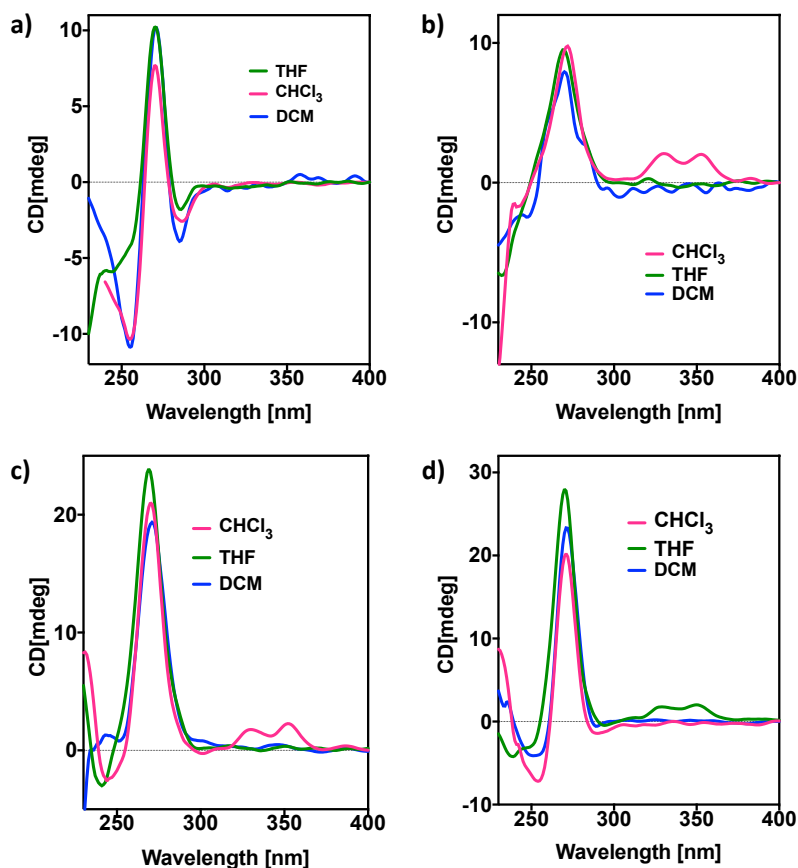


Figure S24. CD spectra in different solvents of (a) mono-1 (0.6 mg/ml), (b) mono-2 (0.6 mg/ml), (c) mono-3 (0.9 mg/ml) and (d) mono-4 (0.9 mg/ml).

Additional CD/UV experiments of poly-1

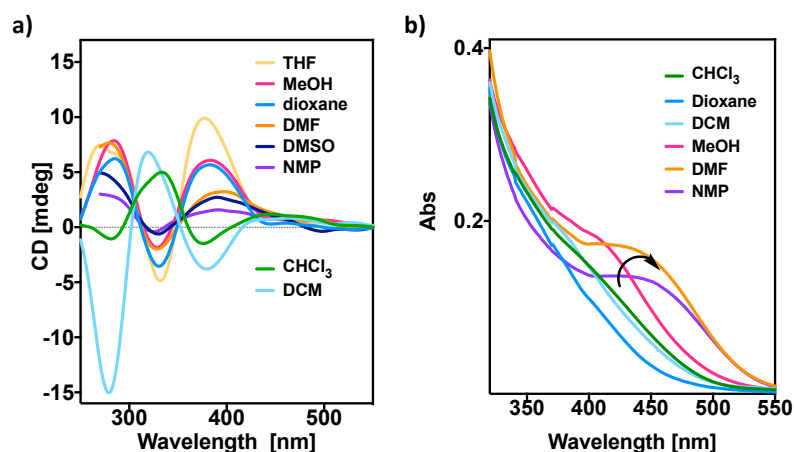


Figure S25. (a) CD spectra of poly-1 in different solvents and (b) UV-Vis spectra showing a bathochromic shift from compressed helix in low polar solvents to stretched helix in polar solvents (0.3 mg/mL, 1 mm cuvette).

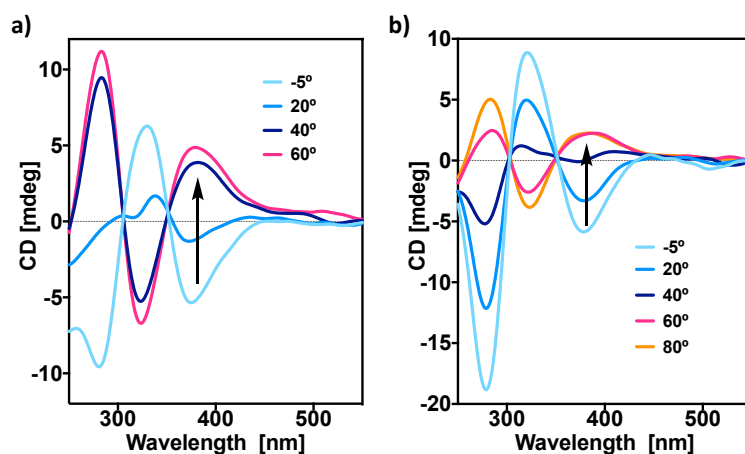


Figure S26. VT-CD of poly-1 in (a) CHCl_3 and (b) DCM (0.3 mg/mL, 1 mm cuvette).

Additional CD/UV experiments of poly-2

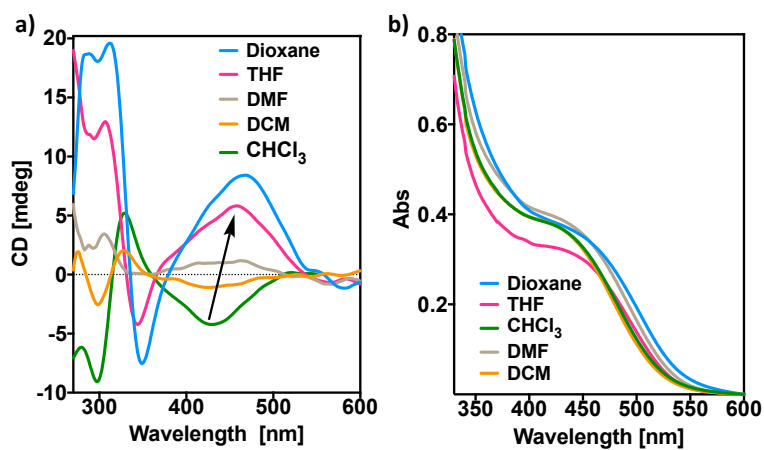


Figure S27. (a) CD and (b) UV-Vis spectra of poly-2 in different solvents (0.15 mg/mL, 1 cm cuvette).

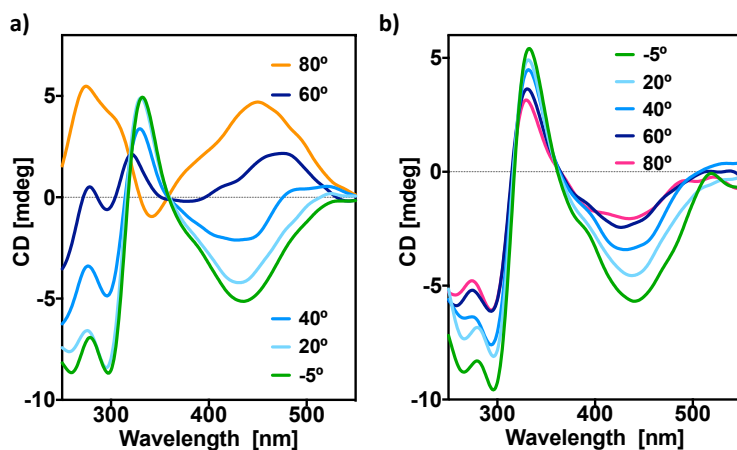


Figure S28. VT-CD of poly-2 in (a) CHCl_3 and (b) DCM (0.3 mg/mL, 1 cm cuvette).

Additional CD/UV experiments of poly-3

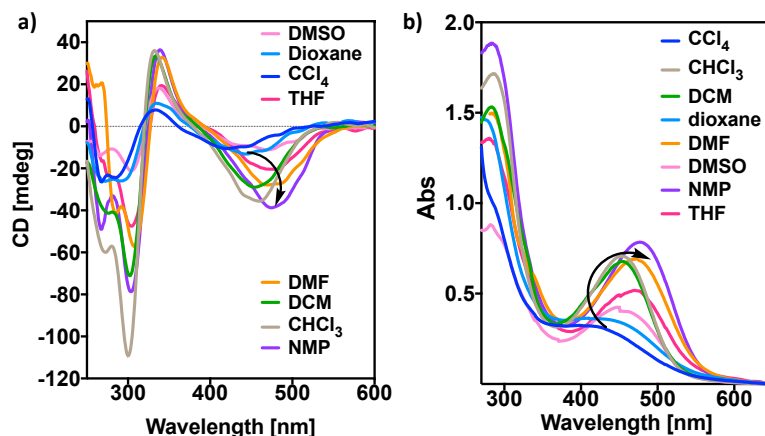


Figure S29. (a) CD spectra of poly-3 in different solvents and (b) UV-Vis spectra showing a bathochromic shift from compressed helix in low polar solvents to stretched helix in polar solvents (0.1 mg/mL, 1 cm cuvette).

Additional CD/UV experiments of poly-4

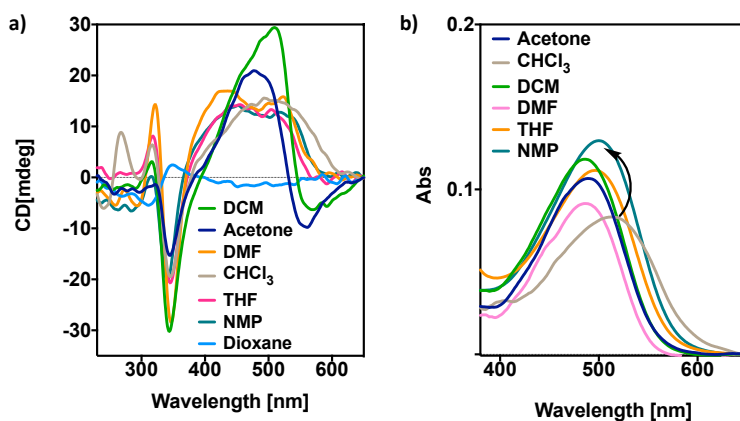


Figure S30. (a) CD spectra of poly-4 in different solvents and (b) UV-Vis spectra showing a stretching process of the PPA skeleton (0.2 mg/mL, 1 mm cuvette).

9. DSC Studies

DSC experiments have been used to determine the configuration of the polymer skeleton in poly(phenylacetylenes) due to the different thermogram pattern for a *cis-cisoidal* or a *cis-transoidal* polyene backbone. For detailed explanation of thermal transitions in PPA's. Both DSC traces were recorded using a heating rate of 10°C/min and showed the characteristic thermogram of a *c-t* polymer backbone with the corresponding transitions from *c-t* to *c-c* and a final isomerization from *c-c* to *t-t*.^[56]

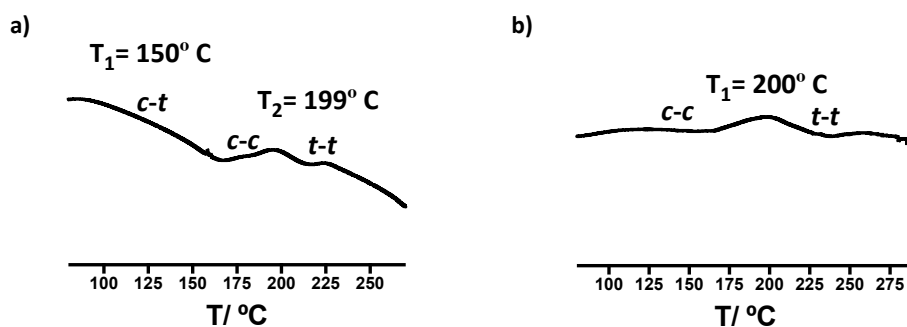


Figure S31. DSC trace of (a) poly-1 and (b) poly-2.

10. Thermal studies

TGA studies were carried out to determine the thermal stability of the polymers. As a general protocol a polymer sample was kept in a platinum pan and heated from 40°C to 800°C with a heating range of 10°C/min.

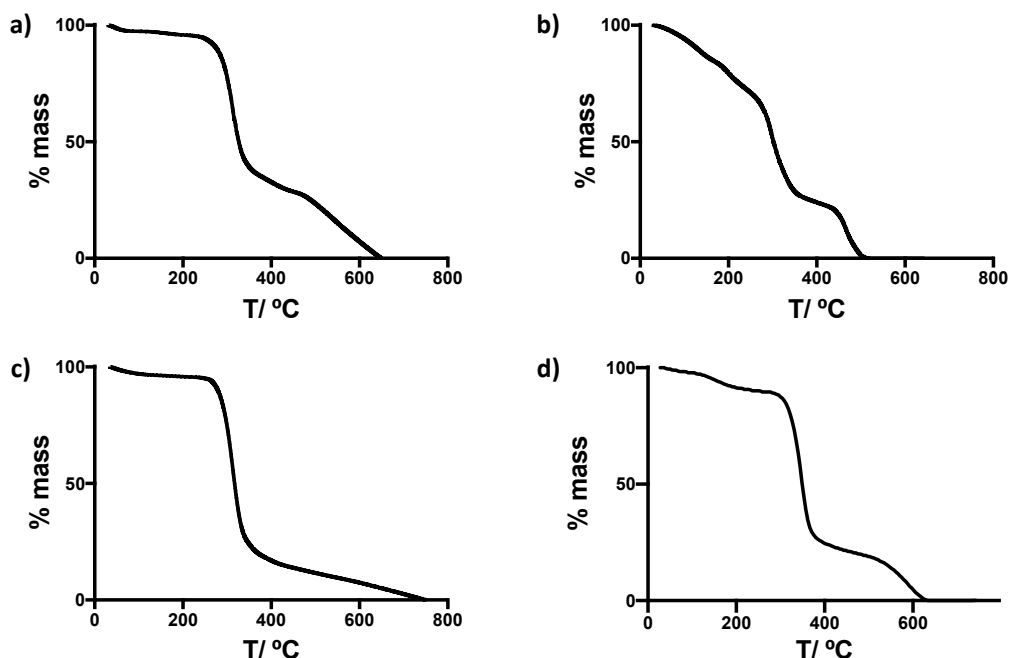


Figure S32. TGA thermograms of (a) poly-1. (b) poly-2. (c) poly-3 and (d) poly-4.

⁵⁶ For detailed DSC studies on (PPA)s see: Liu, L.; Namikoshi, T.; Zang, Y.; Aoki, T.; Hadano, S.; Abe, Y.; Wasuzu, I.; Tsutsuba, T.; Teraguchi, M.; Kaneko, T. *J. Am. Chem. Soc.* **2013**, *135*, 602.

11. IR studies of monomers

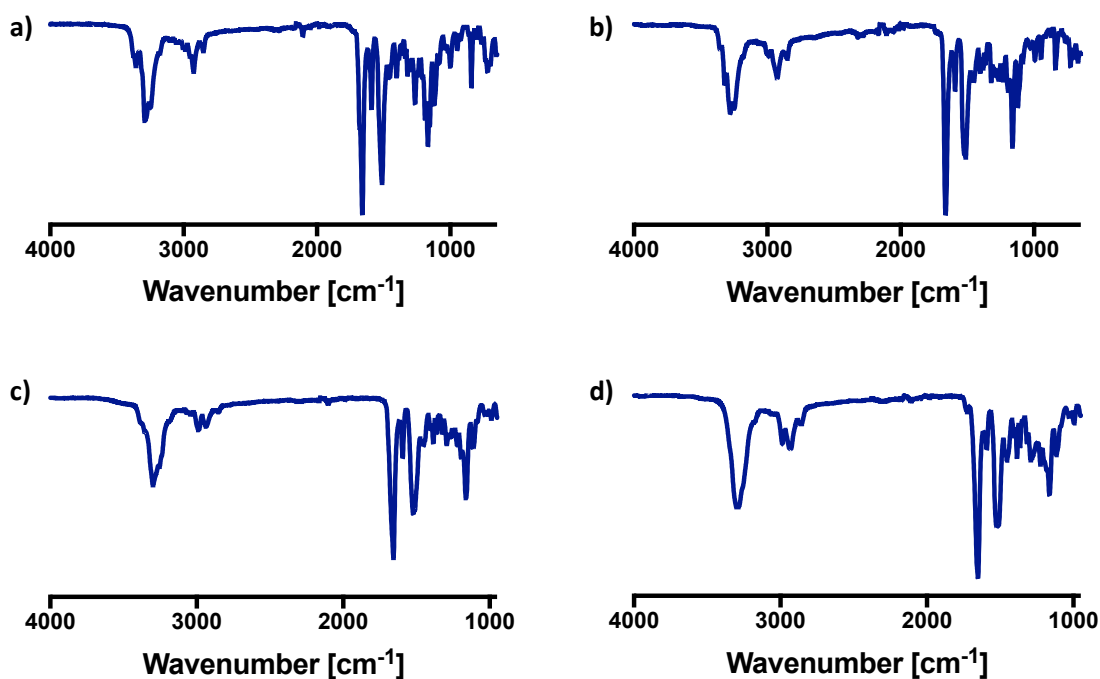


Figure S33. IR spectra of (a) mono-1. (b) mono-2. (c) mono-3 and (d) mono-4.

12. IR studies of polymers

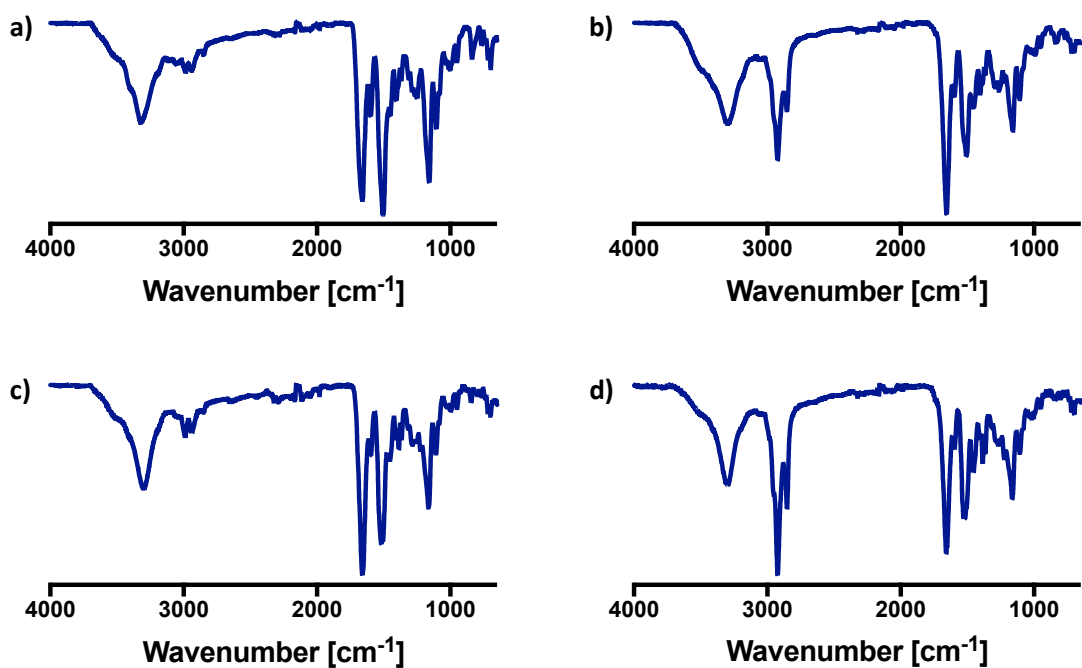


Figure S34. IR spectra of (a) poly-1. (b) poly-2. (c) poly-3 and (d) poly-4.

13. NMR studies of mono-1

Experiments 1D and 2D-NMR in THF- d_8 were carried out to confirm the presence of the *P* torsion of mono-1. Thus, 2D-NOESY spectra were obtained in order to observe the corresponding cross peaks that are indicated below at Figure S35.

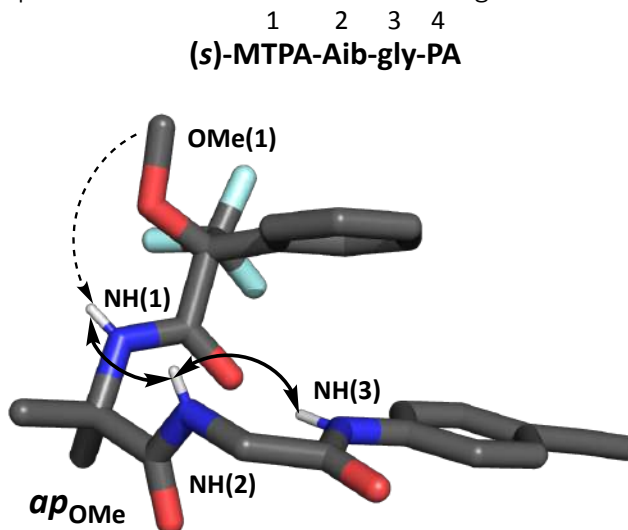


Figure S35. Representative NOEs of mono-1 in THF- d_8 .

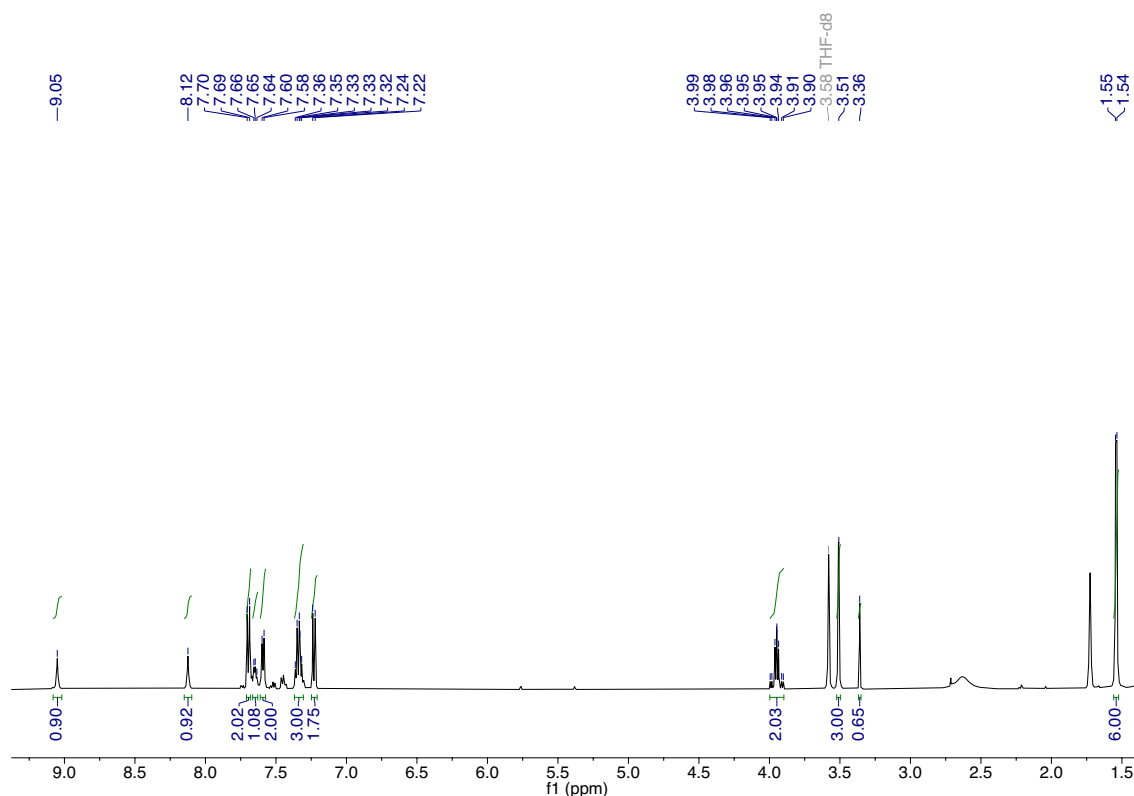
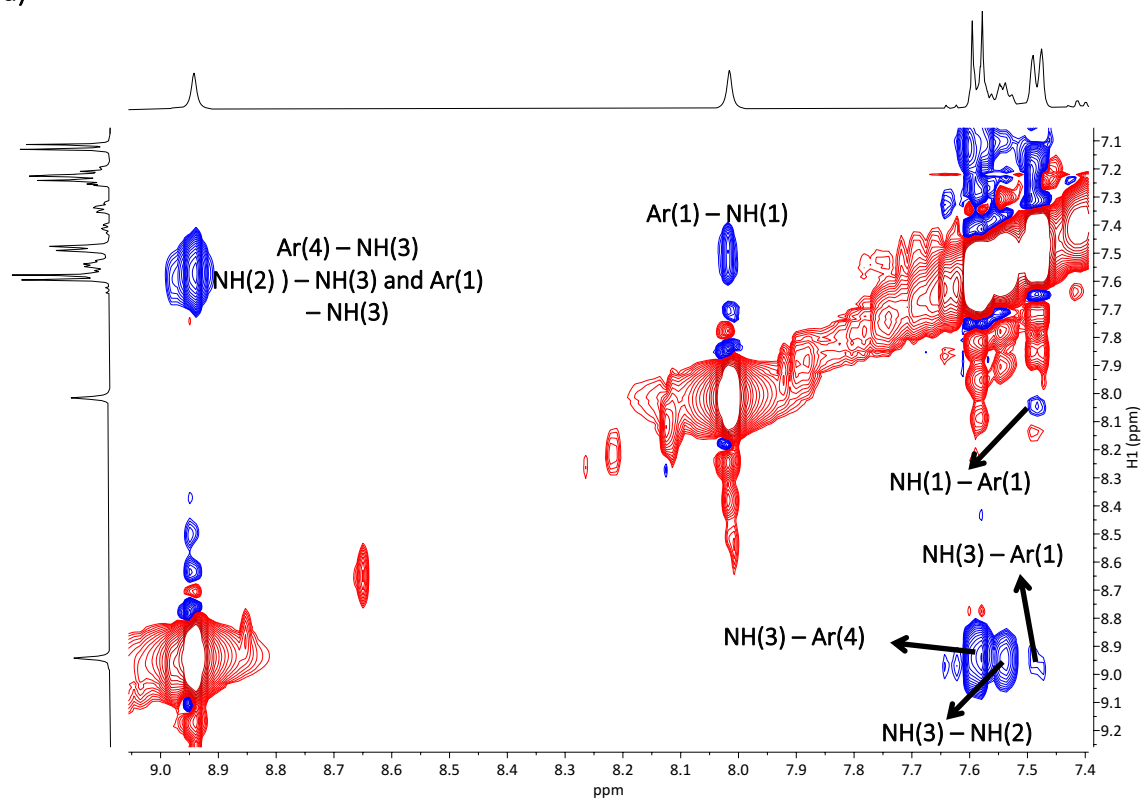


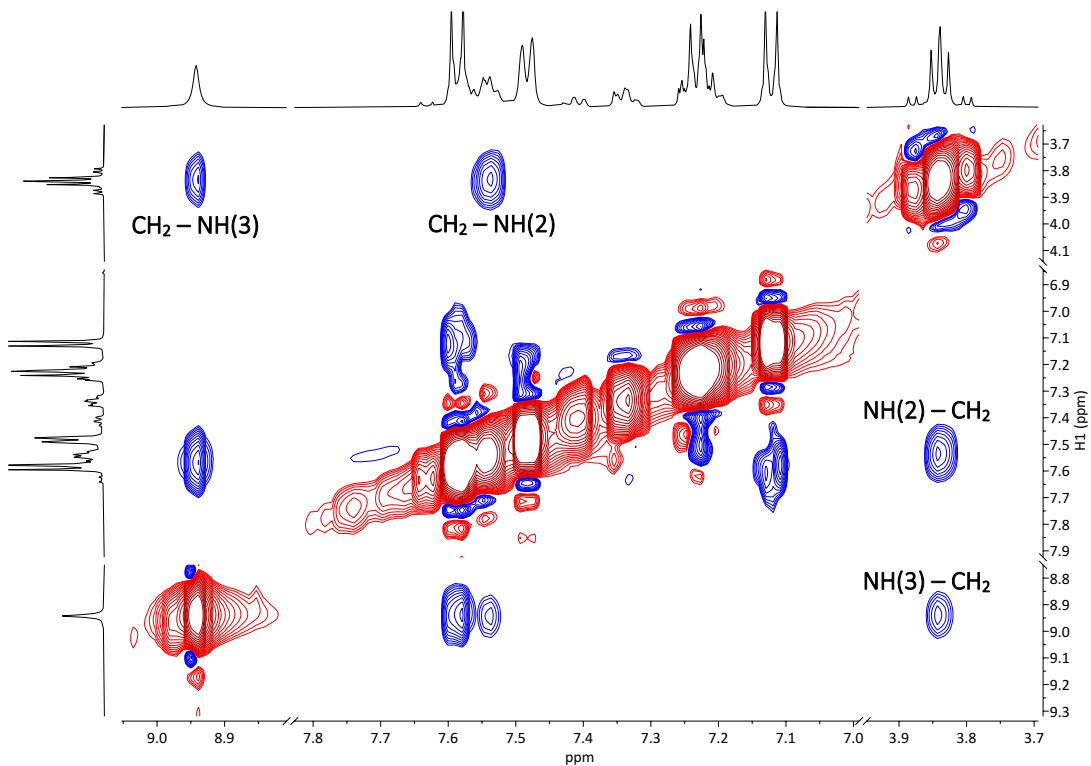
Figure S36. ^1H NMR of mono-1 in THF- d_8 at 268 K.

^1H NMR (500 MHz, THF- d_8) δ (ppm): 9.05 (s, 1H), 8.12 (s, 1H), 7.70 (d, $J=8.7$ Hz, 2H), 7.64 (t, $J=5.9$ Hz, 1H), 7.59 (d, $J=6.9$ Hz, 2H), 7.37 – 7.31 (m, 3H), 7.23 (d, $J=8.7$ Hz, 2H), 4.00 – 3.90 (m, 2H), 3.51 (s, 3H), 3.36 (s, 1H), 1.54 (d, $J=4.8$ Hz, 6H).

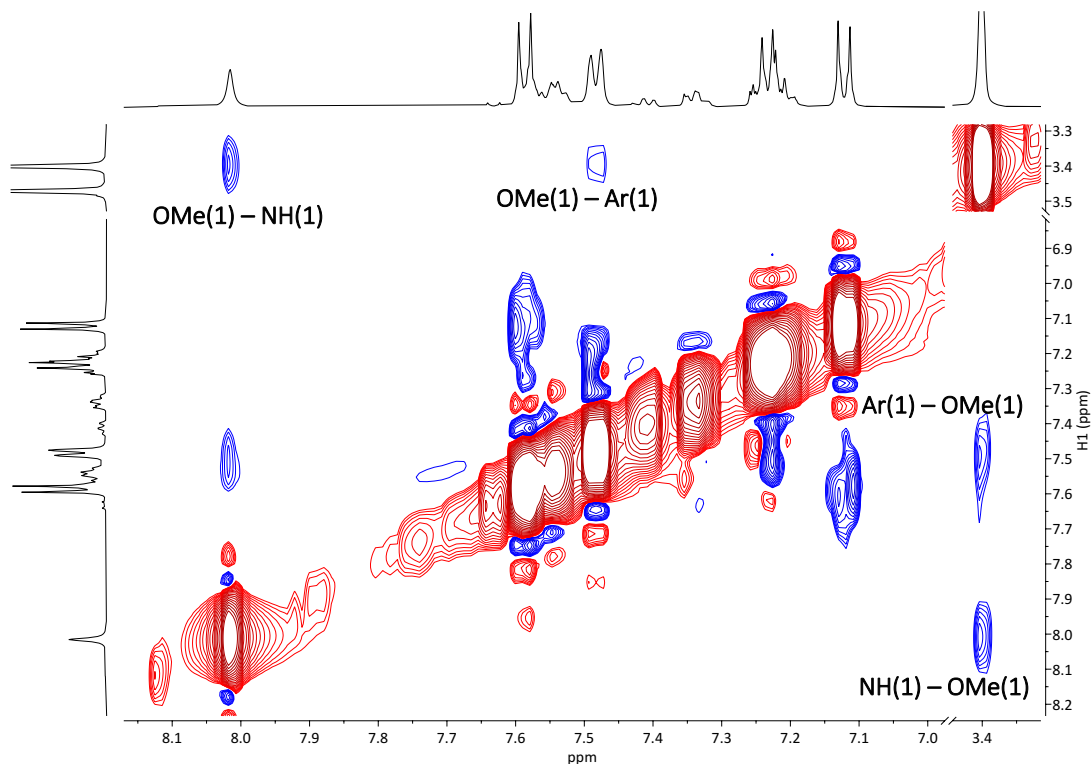
a)



b)



c)



d)

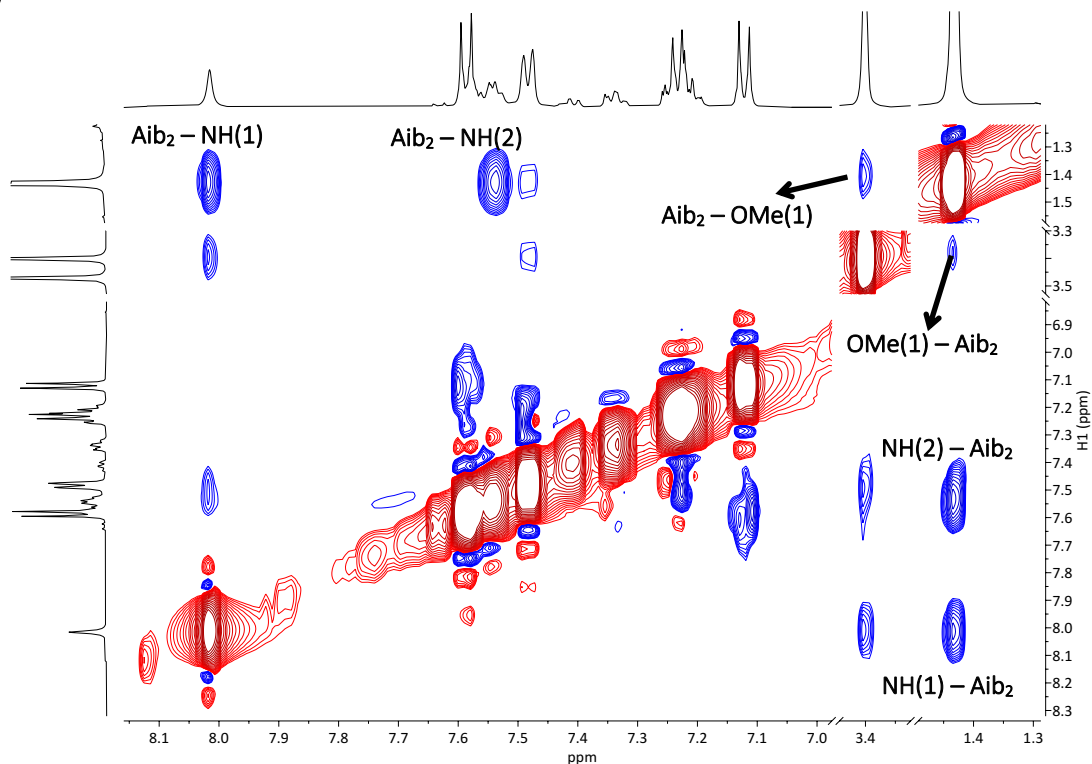
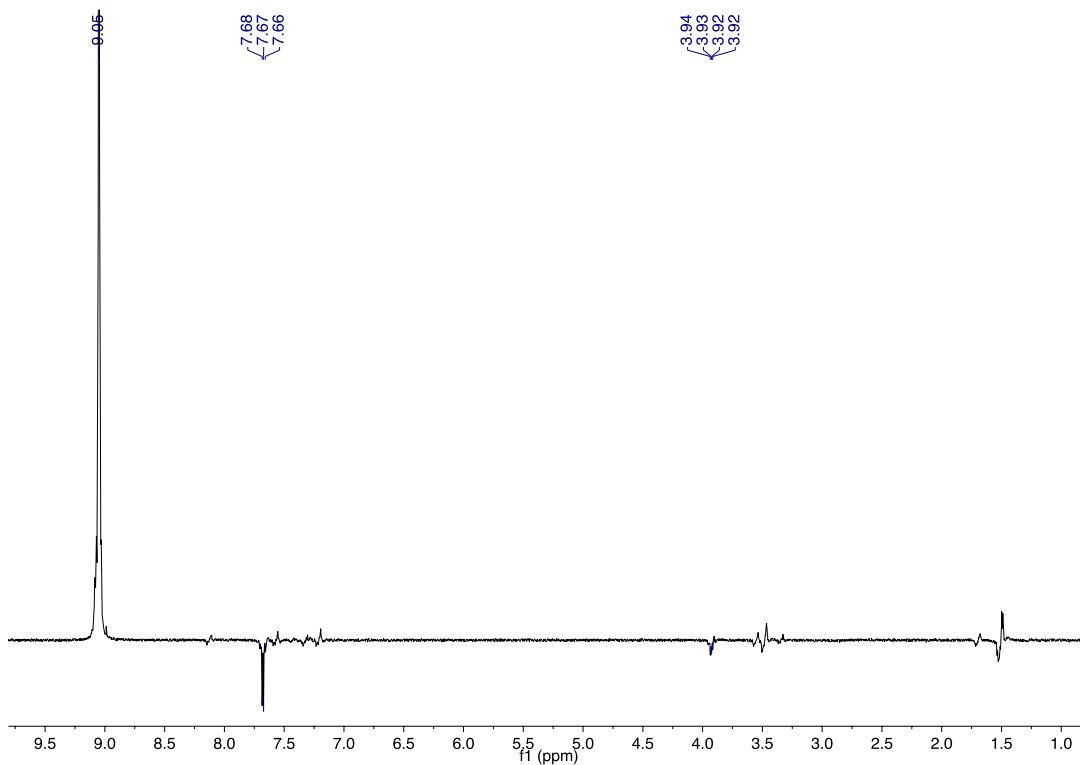


Figure S37. 2D-NOESY of mono-**1** in THF- d_8 at 268 K showing the cross peaks (a) NH(3)-Ar(4), NH(3)-Ar(1), NH(3)-NH(2), NH(1)-Ar(1), (b) CH₂ (gly)-NH(3), CH₂ (gly)-NH(2), (c) OMe(1)-NH(1), OMe(1)-Ar(1), (d) OMe(1)-Aib₂, Aib₂-NH(1), Aib₂-NH(2).

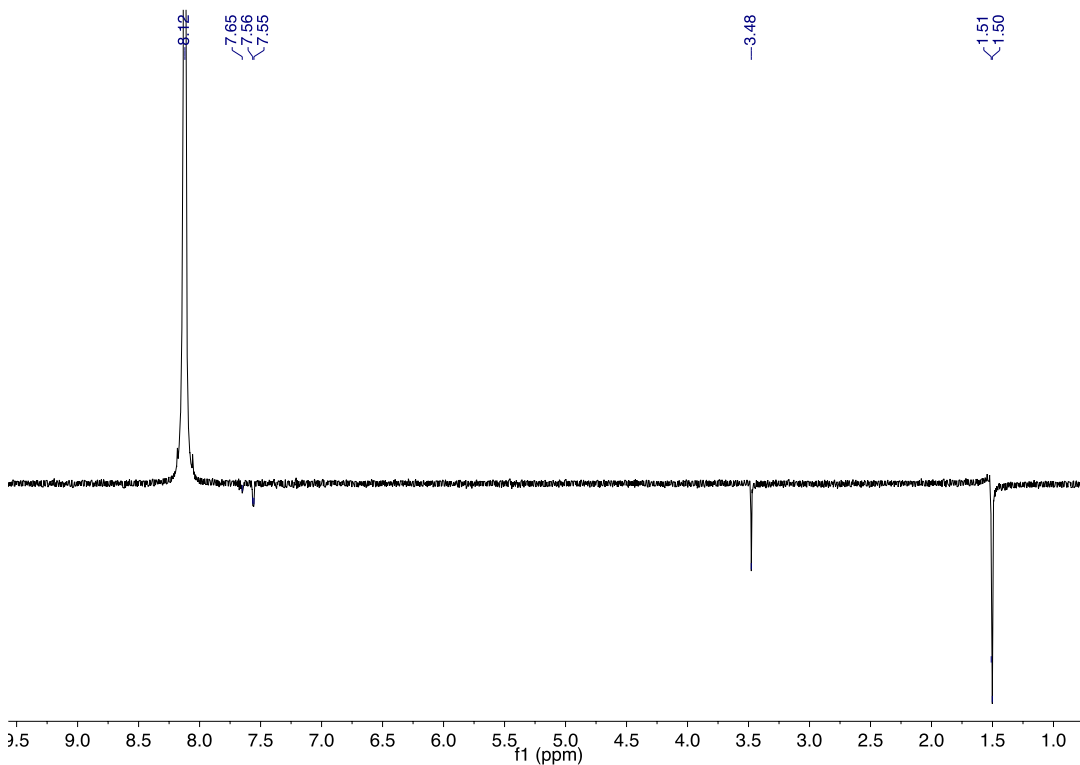
1D-NMR experiments (NOESY) of mono-1 in THF-d₈

1D-NMR experiments (NOESY) of mono-1 in THF-d₈ were carried out where selective signals were irradiated (positive signal) in order to observe the coupled protons of the molecule that are closed in space (negative signal).

a)



b)



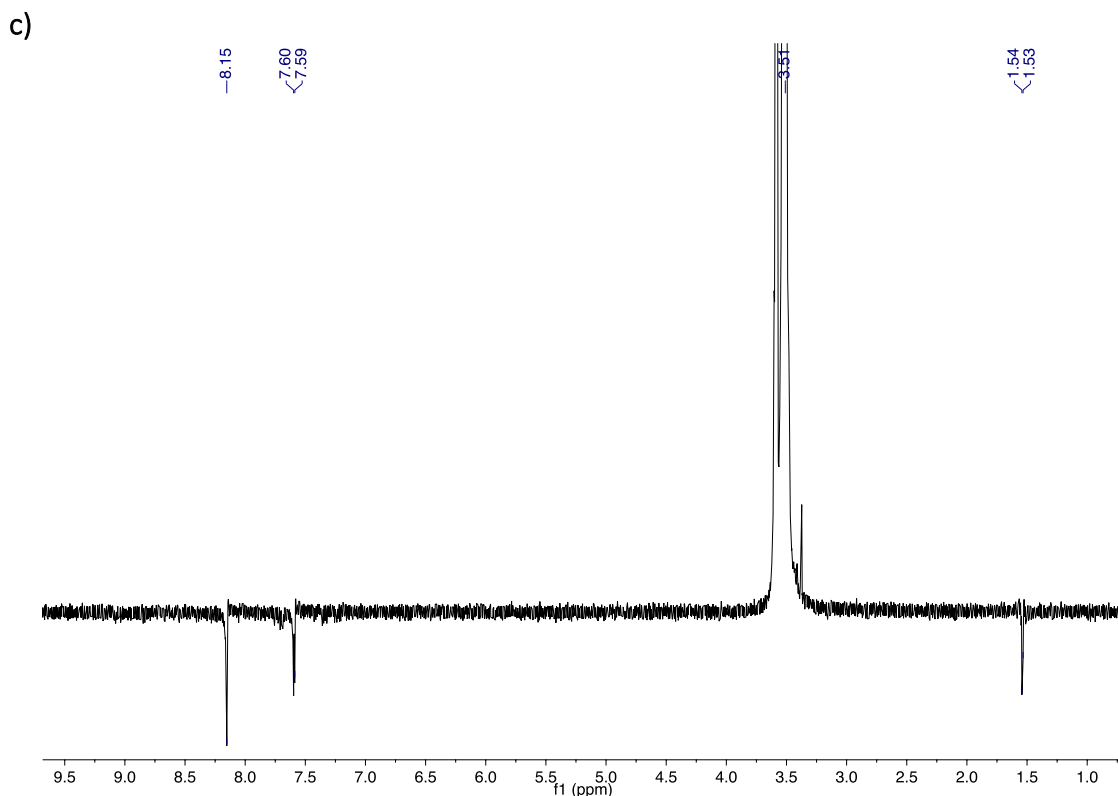


Figure S38. 1D-NMR experiments (NOESY) of mono-**1** in THF- d_8 at 268 K showing the cross peaks that (a) NH(3) is close in space to protons of Ar(4), NH(2) and CH₂ (gly), (b) NH(1) is close in space to protons of Ar(1), NH(2), OMe(1) and Aib₂, (c) OMe(1) is close in space to protons of NH(1), Ar(1) and Aib₂.

1D and 2D-NMR experiments (NOESY) in CDCl₃ showed a strong sequential NH-NH cross peaks, OMe(1)-NH(1) and OMe(1)-NH(2) confirming the presence of the *M* torsion. These NMR experiments confirm the *ap*_{OMe} conformation adopted by mono-**1** in CDCl₃, as well as in THF- d_8 .

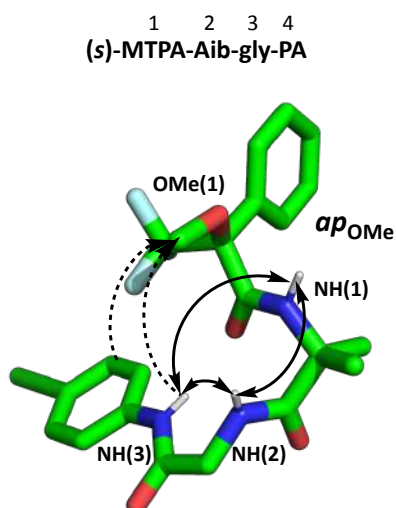


Figure S39. Representative NOEs of mono-**1** in CDCl₃.

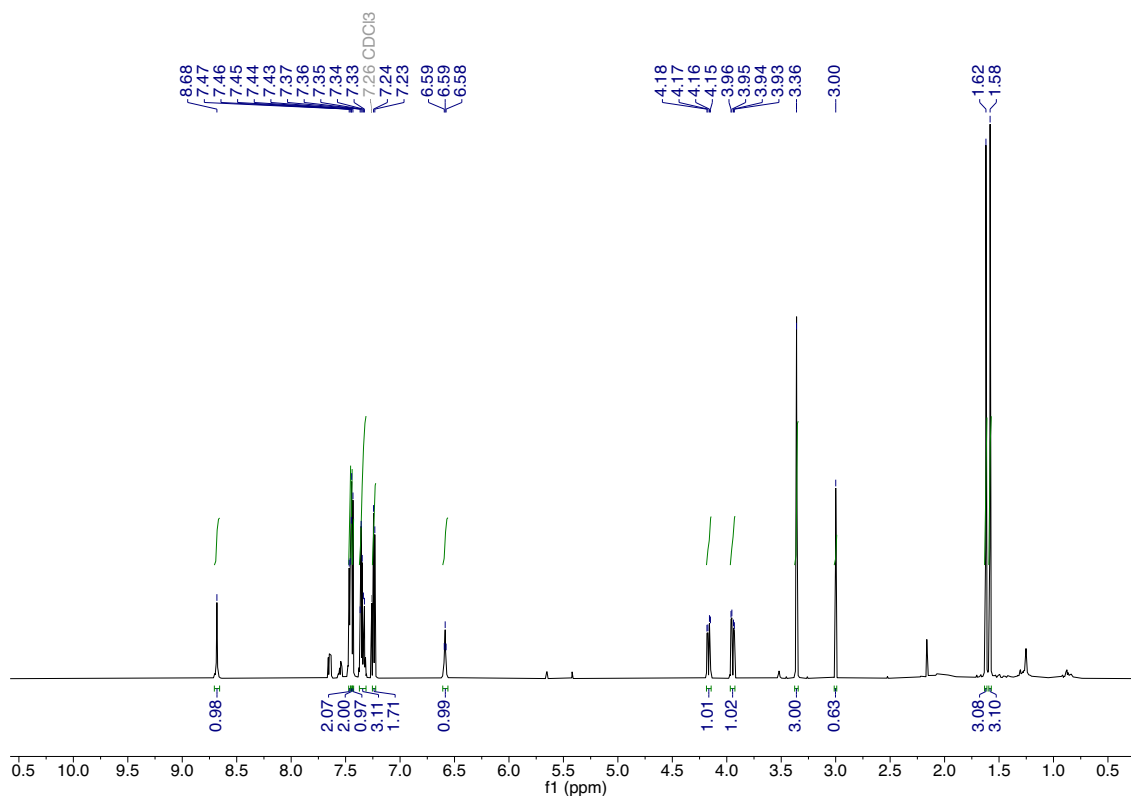
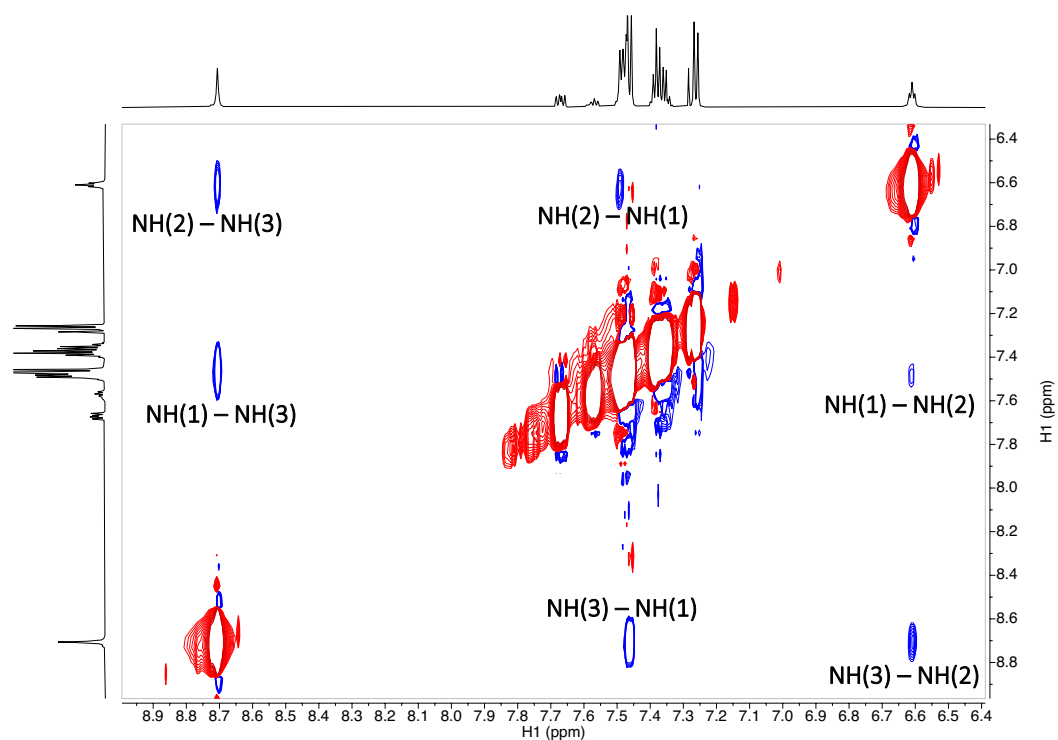


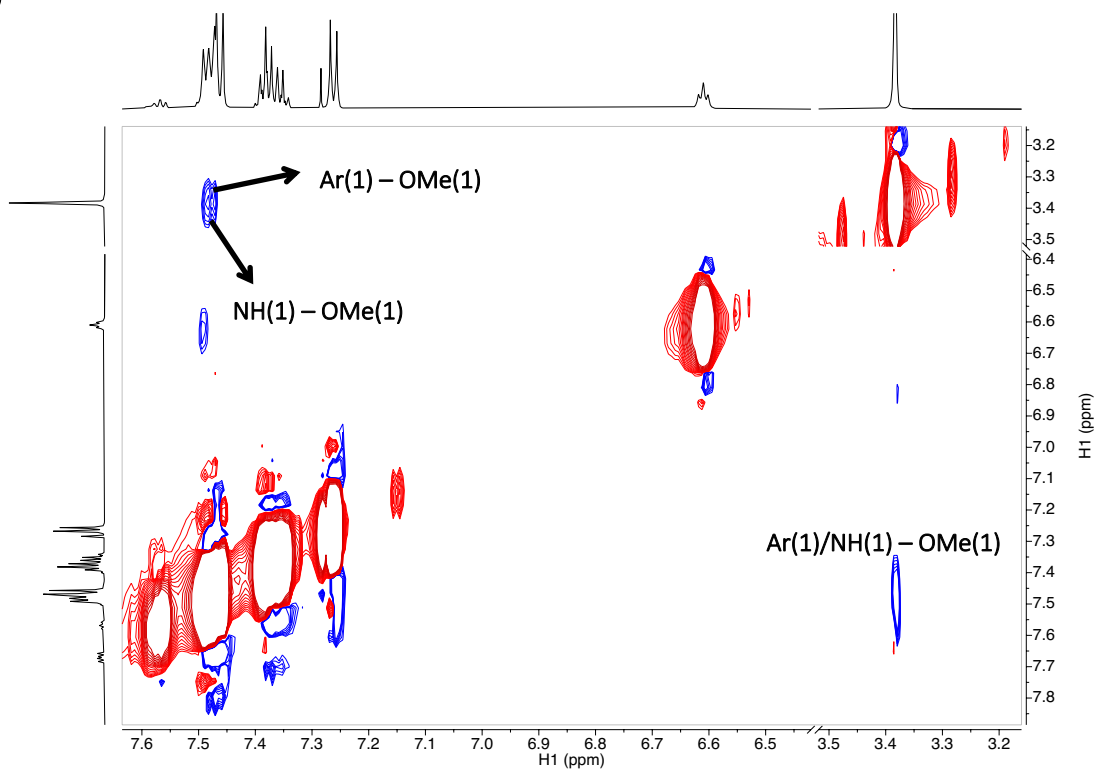
Figure S40. ^1H NMR of mono-**1** in CDCl_3 at 268 K.

^1H NMR (750 MHz, CDCl_3) δ (ppm): 8.68 (s, 1H), 7.46 (d, $J = 7.3$ Hz, 2H), 7.45 (d, $J = 2.3$ Hz, 2H), 7.43 (s, 1H), 7.37–7.31 (m, 3H), 7.24 (d, $J = 8.7$ Hz, 2H), 6.59 (t, $J = 6.3$ Hz, 1H), 4.17 (dd, $J = 17.3$ Hz, 6.7 Hz, 1H), 3.95 (dd, $J = 17.2$ Hz, 6.0 Hz, 1H), 3.36 (s, 3H), 3.00 (s, 1H), 1.62 (s, 3H), 1.58 (s, 3H).

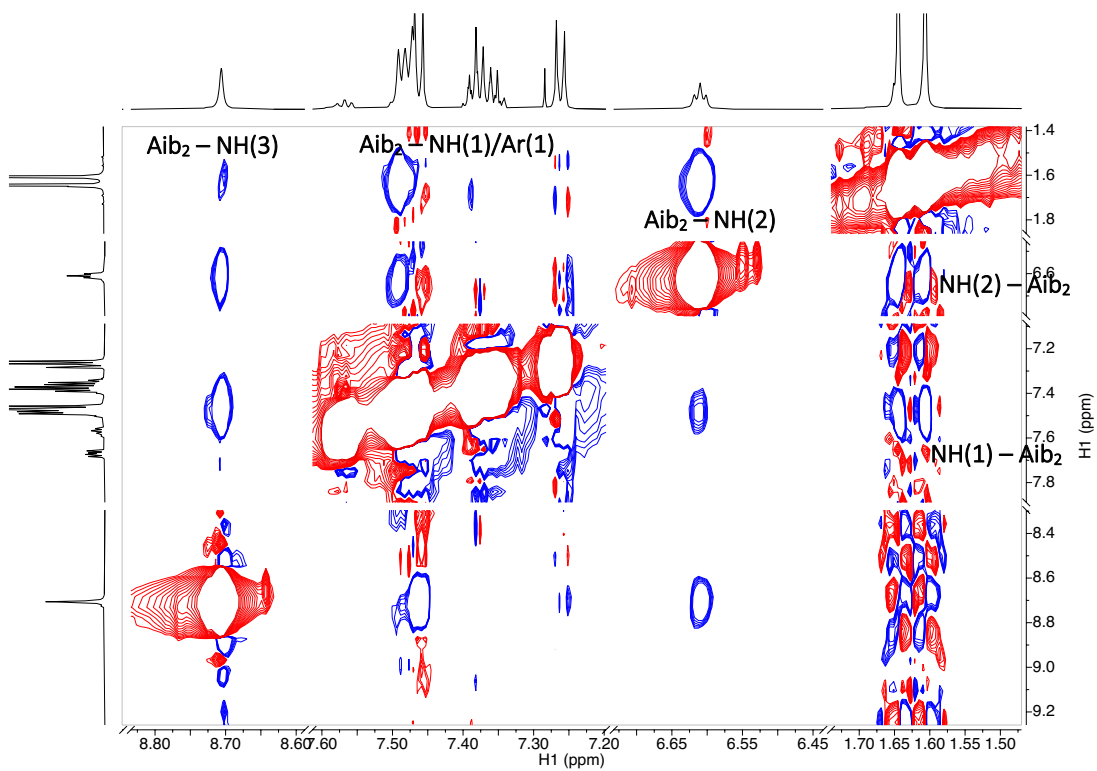
a)



b)



c)



d)

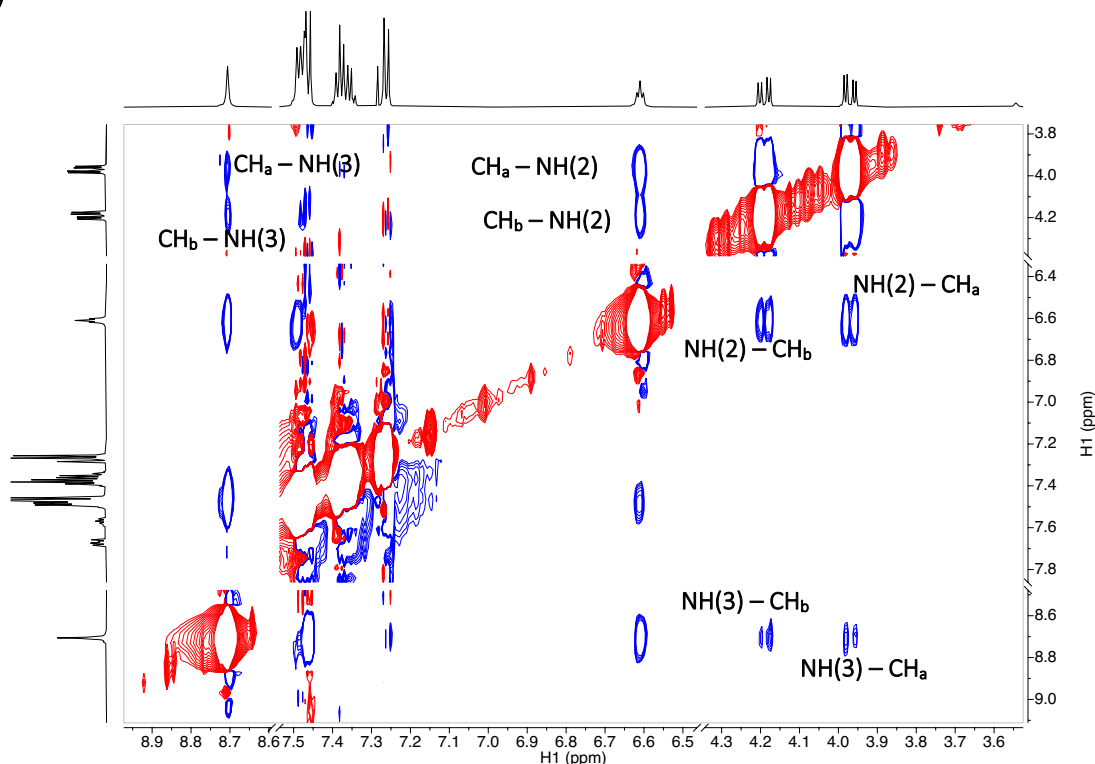
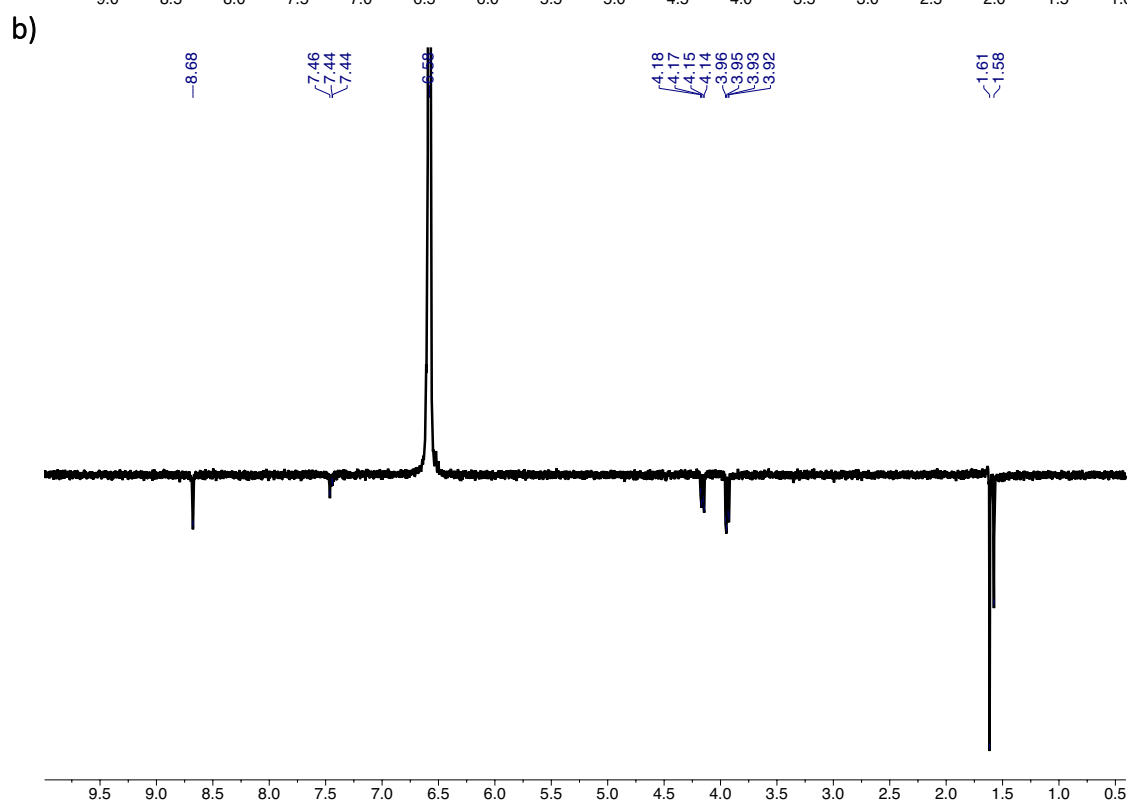
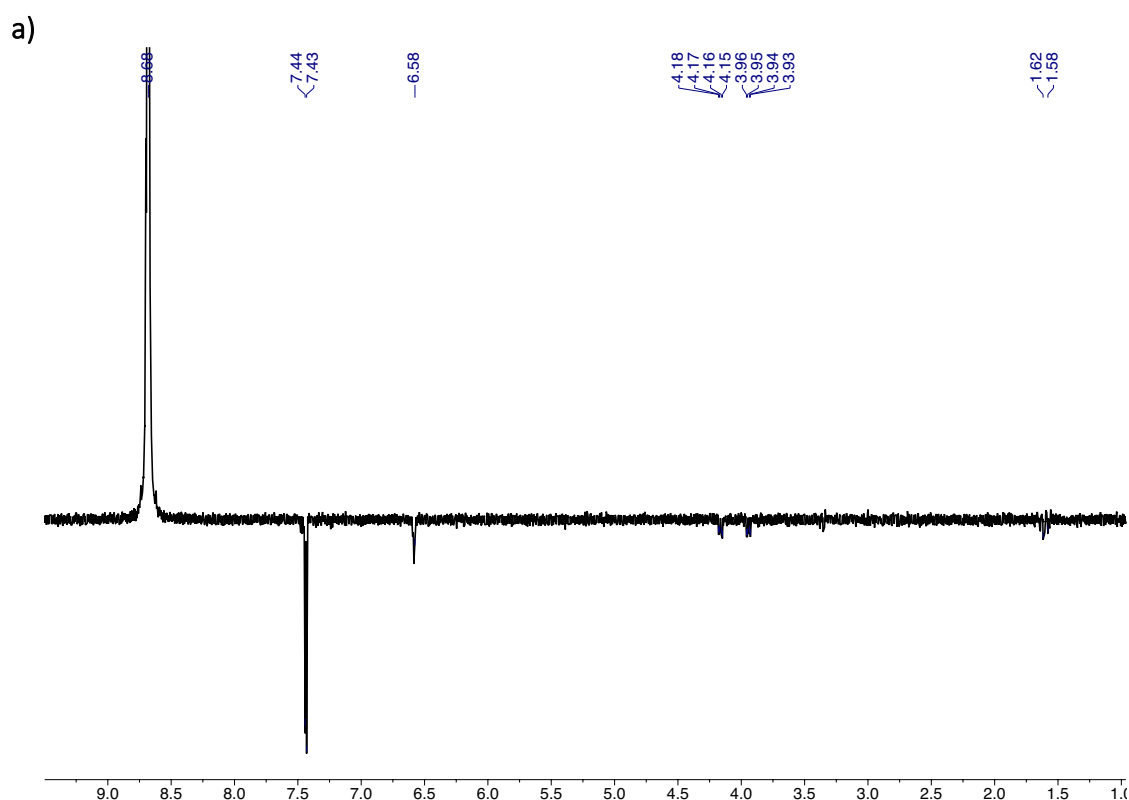


Figure S41. 2D-NOESY of mono-**1** in CDCl_3 at 268 K showing the cross peaks (a) all NH-NH cross peaks: NH(1)-NH(2), NH(1)-NH(3), NH(2)-NH(3), (b) OMe(1)-NH(1), OMe(1)-Ar(1), (c) Aib₂-NH(3), Aib₂-NH(1), Aib₂-Ar(1), Aib₂-NH(2), (d) CH₂ (gly)-NH(3), CH₂ (gly)-NH(2).

1D-NMR experiments (NOESY) of mono-**1** in CDCl_3

1D-NMR experiments (NOESY) of mono-**1** in CDCl_3 were carried out where selective signals were irradiated (positive signal) in order to observe the coupled protons of the molecule that are closed in space (negative signal).



c)

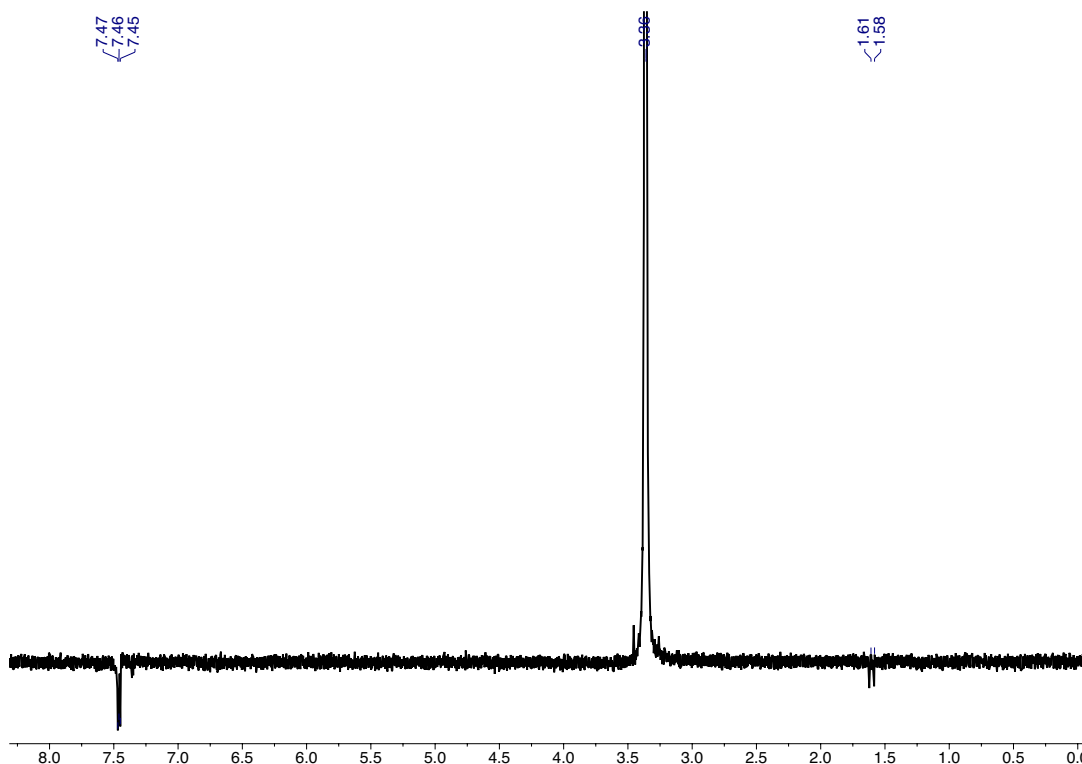


Figure S42. 1D-NMR experiments (NOESY) of mono-1 in CDCl_3 at 268 K showing the cross peaks that (a) NH(3) is close in space to protons of Ar(4), NH(1), NH(2), CH_2 (gly) and Aib₂, (b) NH(2) is close in space to protons of NH(3), NH(1), CH_2 (gly) and Aib₂, (c) OMe(1) is close in space to protons of Ar(1), NH(1) and Aib₂.

14. NMR studies of mono-2

1D and 2D-NOESY NMR experiments of mono-2 in THF-d_8 show strong sequential NH-NH cross peaks which confirms the presence of P -3₁₀ helix of the oligomer in solution. The ap_{OMe} conformation at the pendant group was confirmed by the presence of NOE cross peaks between the anilide (NH1) and the methoxy group.

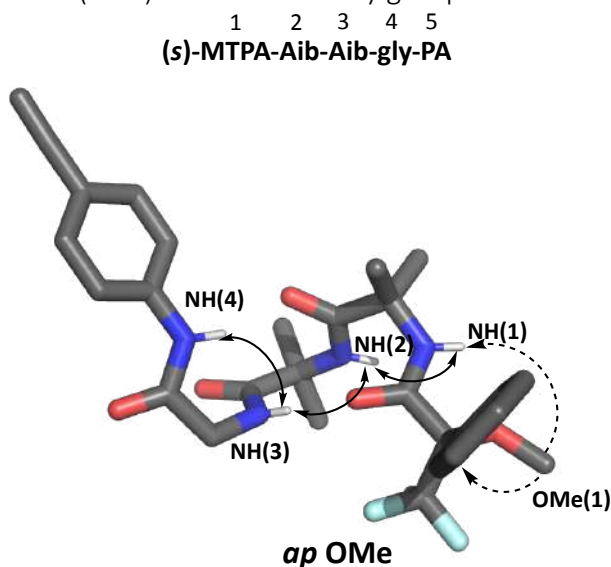


Figure S43. Representative NOEs of mono-2 in THF-d_8 .

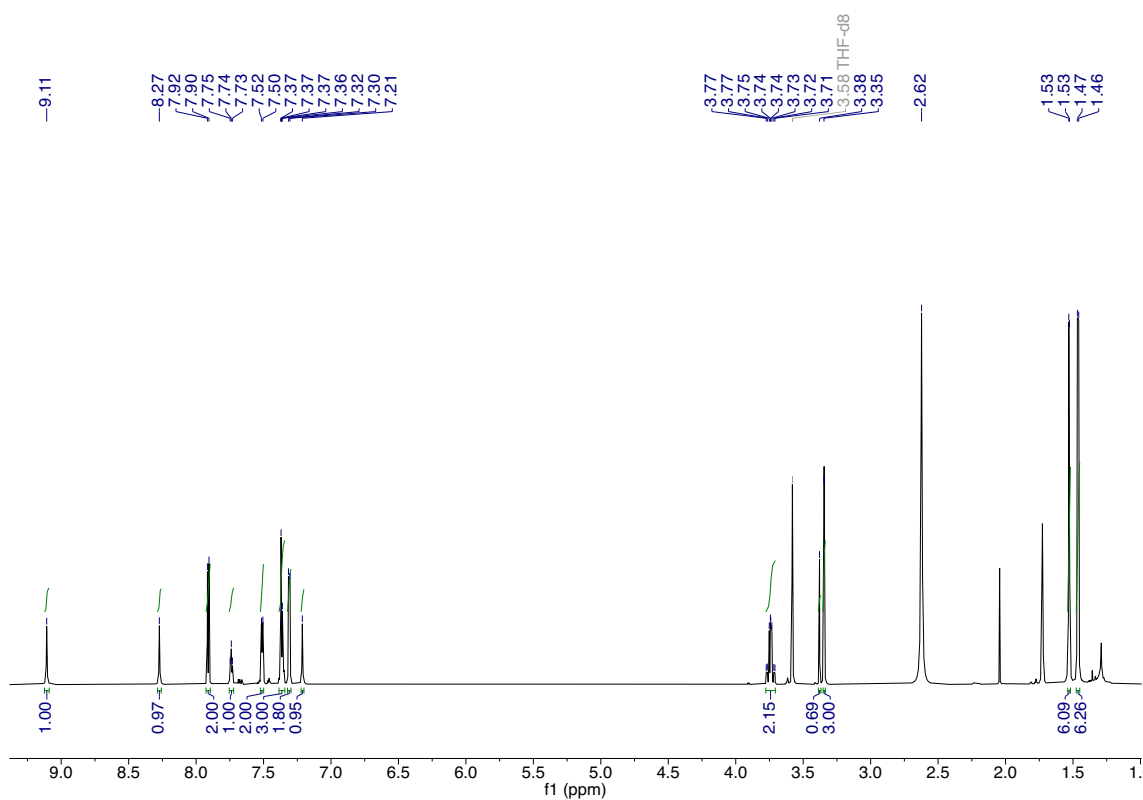
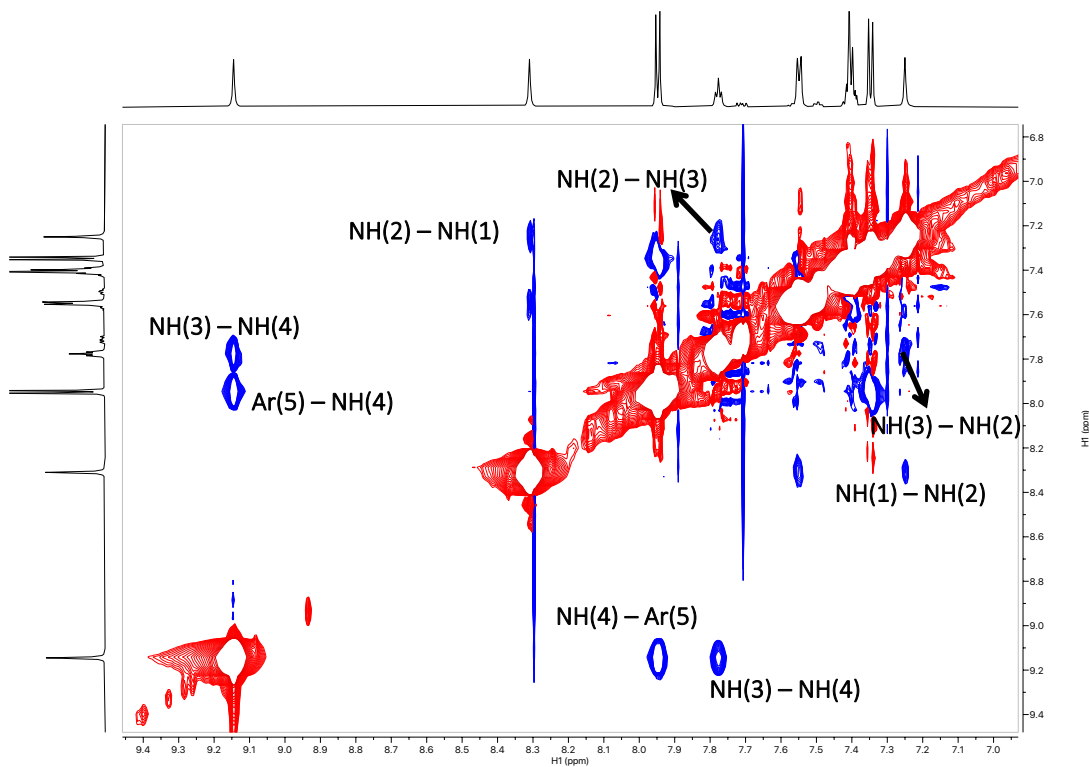


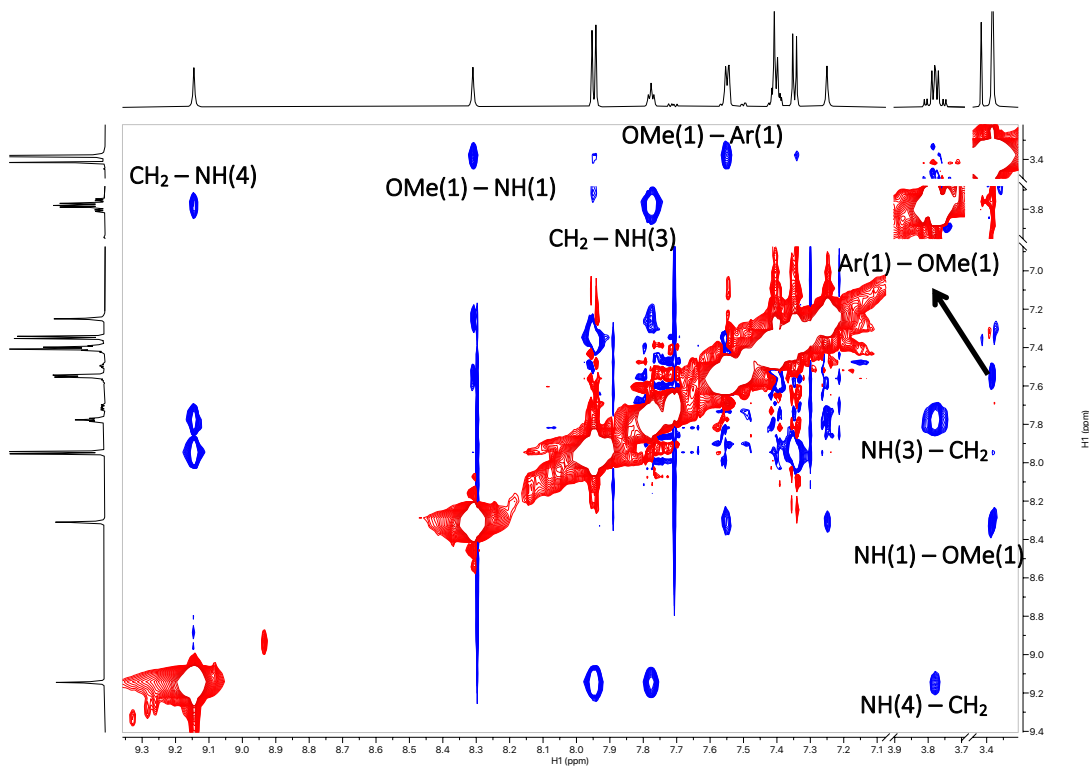
Figure S44. ^1H NMR of mono-2 (THF-d_8 , 268 K).

^1H NMR (750 MHz, THF-d_8) δ (ppm): 9.11 (s, 1H), 8.27 (s, 1H), 7.91 (d, $J=8.6$ Hz, 2H), 7.74 (t, $J=6.3$ Hz, 1H), 7.51 (d, $J=7.9$ Hz, 2H), 7.39 – 7.34 (m, 3H), 7.31 (d, $J=8.6$ Hz, 2H), 7.21 (s, 1H), 3.78 – 3.71 (m, 2H), 3.38 (s, 1H), 3.35 (s, 3H), 1.53 (d, $J=3.7$ Hz, 6H), 1.46 (d, $J=7.5$ Hz, 6H).

a)



b)



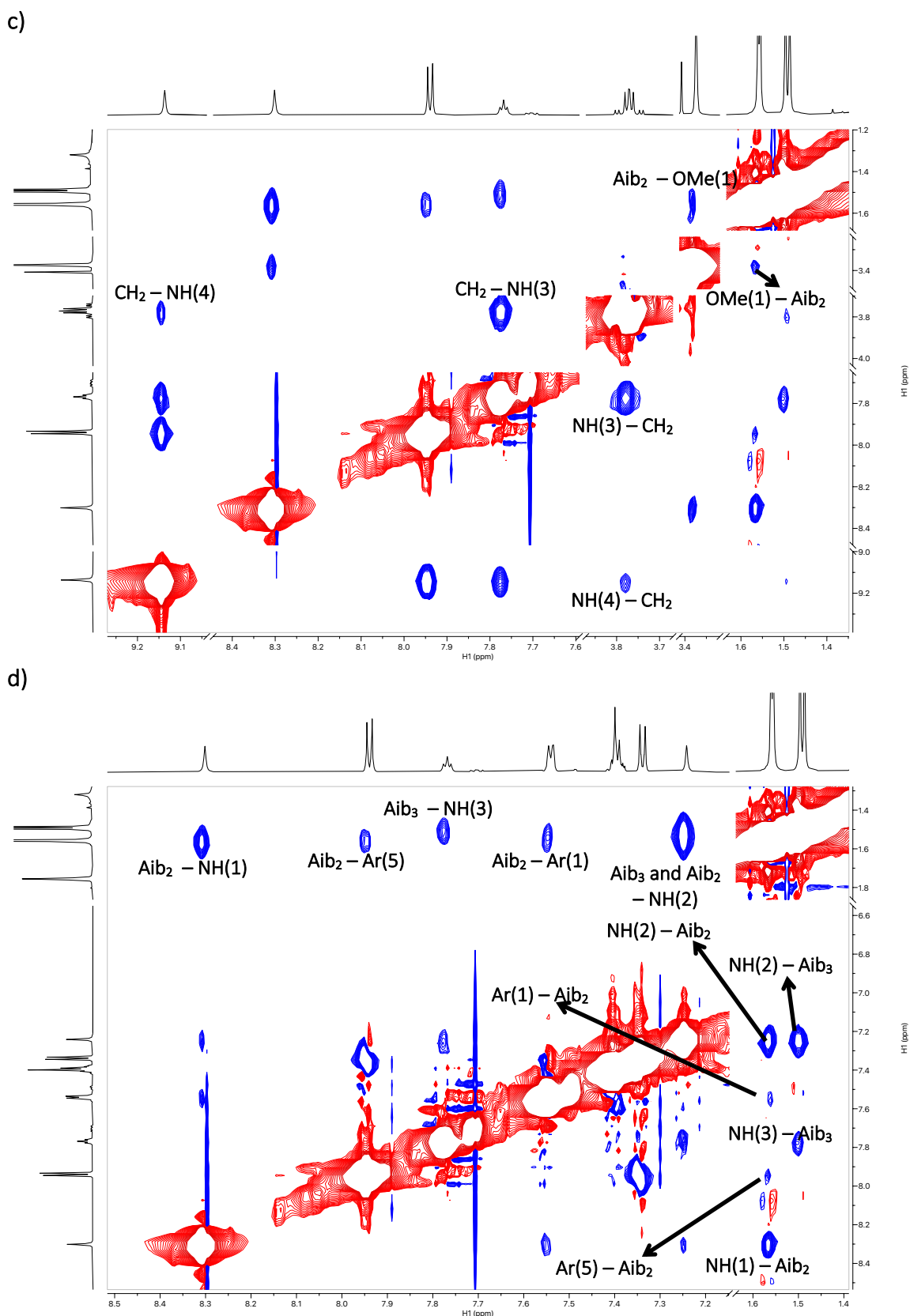
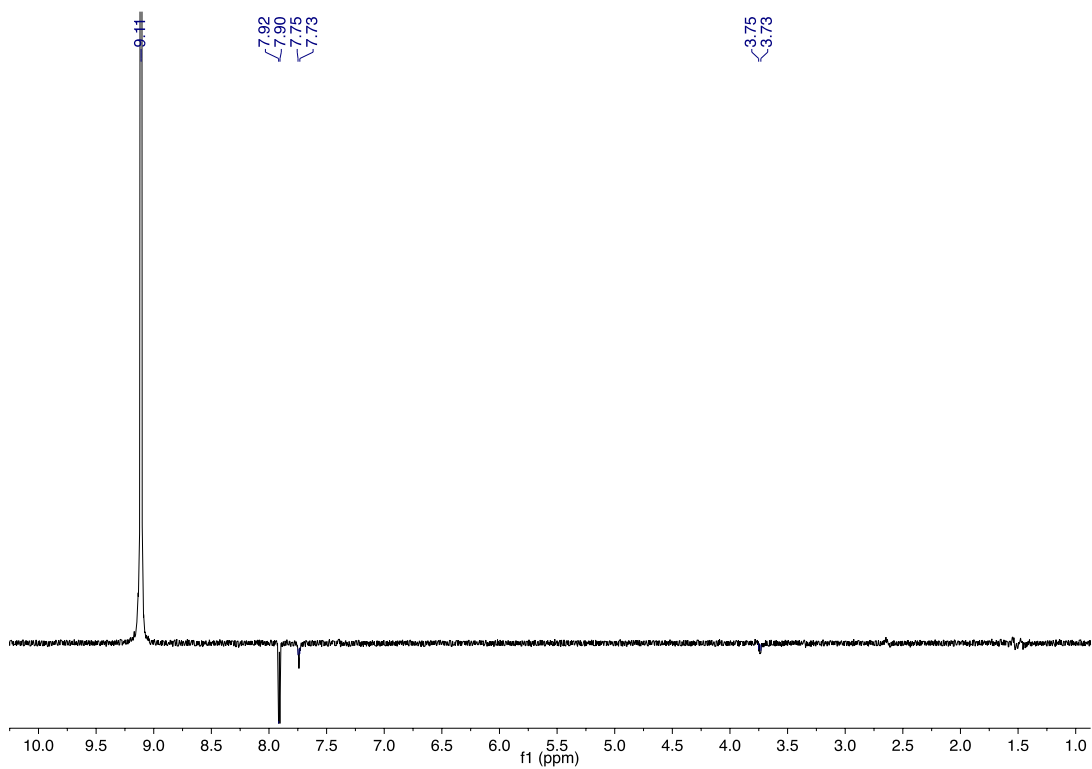


Figure S45. 2D-NOESY of mono-2 in THF- d_8 at 268 K showing (a) all NH-NH cross peaks: NH(4)-NH(3), NH(3)-NH(2) and NH(1)-NH(2), (b) NH(4)-CH₂ (gly), NH(3)-CH₂ (gly), NH(1)-OMe(1) and Ar(1)-OMe(1), (c) NH(4)-CH₂ (gly), NH(3)-CH₂ (gly), Aib₂-OMe(1), (d) Aib₃-NH(3), Aib₃-NH(2), Aib₂-NH(2), Aib₂-NH(1), Ar(1)-Aib₂, Ar(5)-Aib₂.

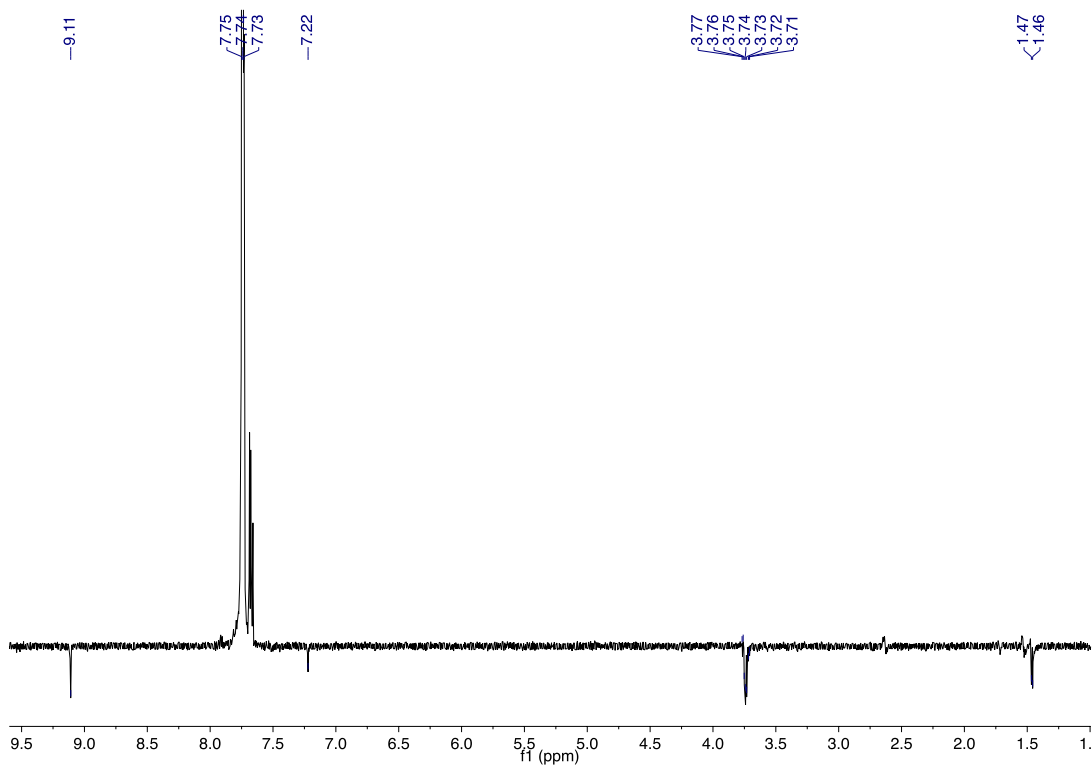
1D-NMR experiments (NOESY) of mono-2 in THF-d₈

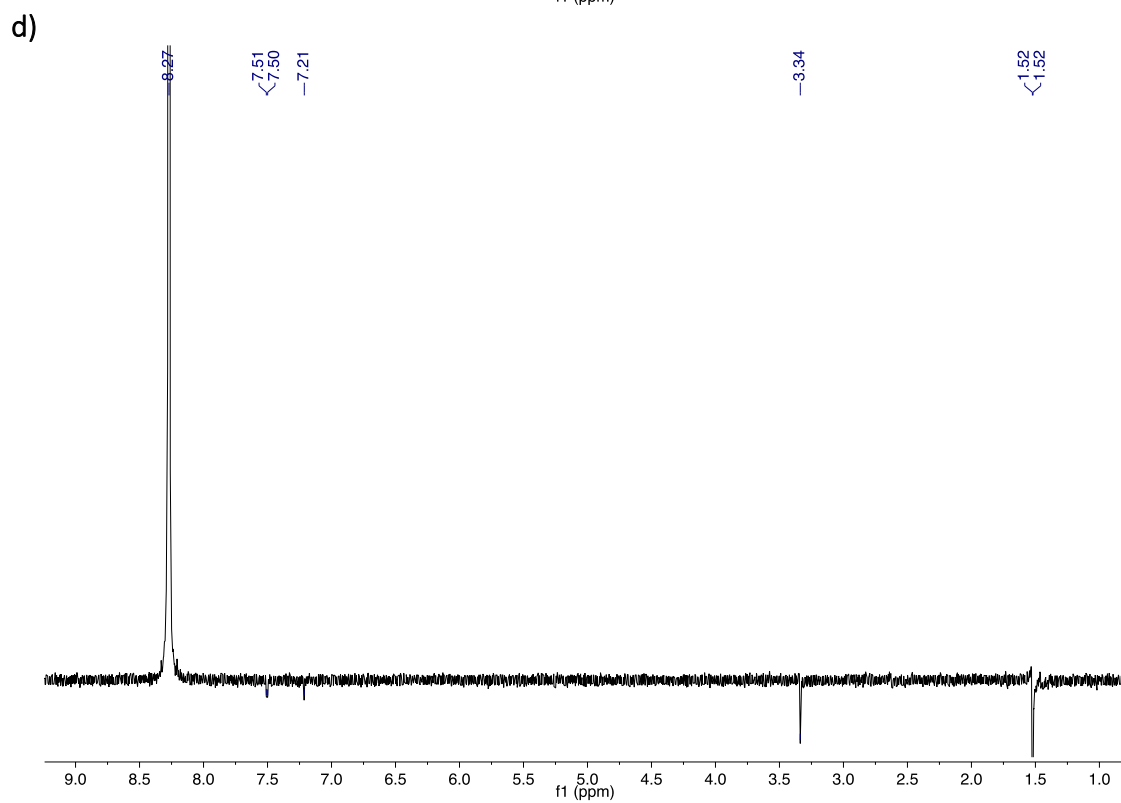
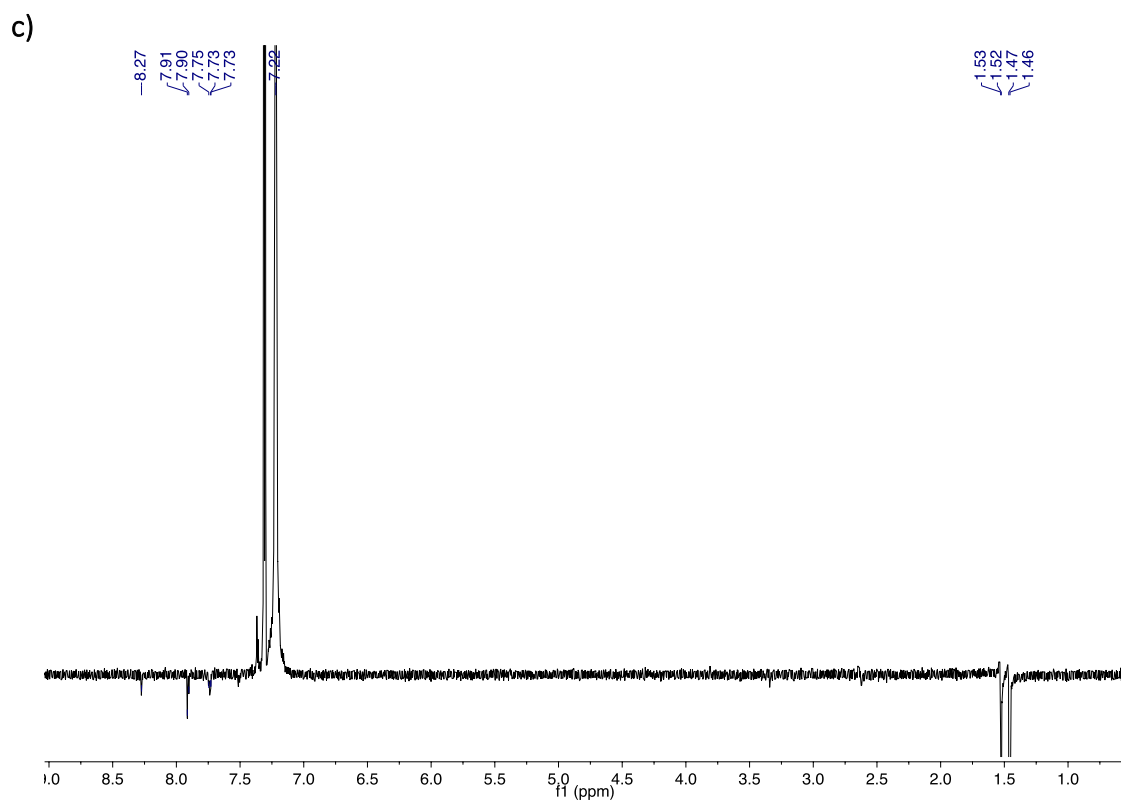
1D-NMR experiments (NOESY) of mono-2 in THF-d₈ were carried out where selective signals were irradiated (positive signal) to observe the coupled protons of the molecule that are closed in space (negative signal).

a)



b)





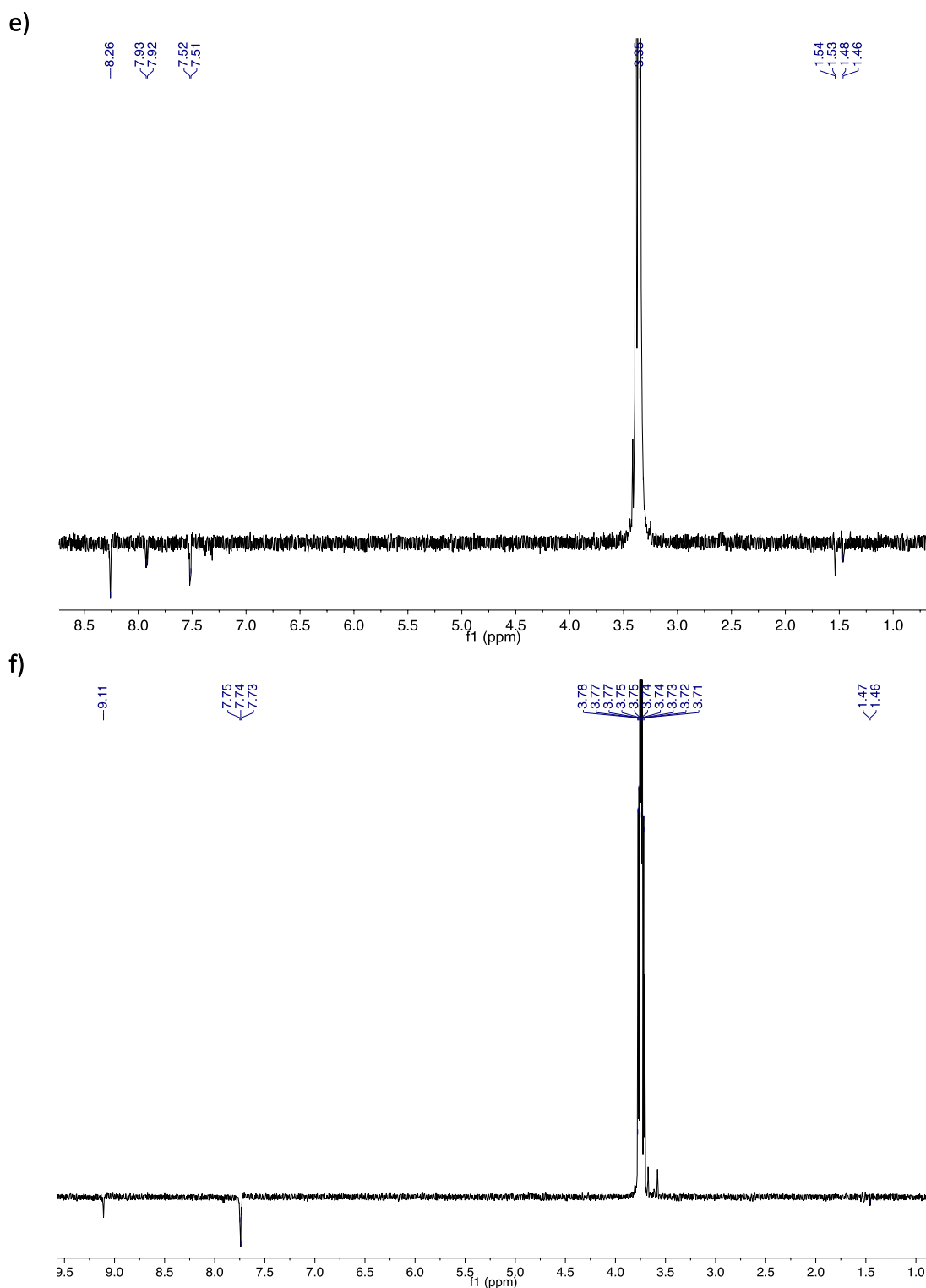


Figure S46. 1D-NMR experiments (NOESY) of mono-**2** in THF- d_8 at 268 K showing the cross peaks that (a) NH(4) is close in space to protons of Ar(5), NH(3) and CH₂ (gly), (b) NH(3) is close in space to protons of NH(4), NH(2), CH₂ (gly) and Aib₃, (c) NH(2) is close in space to protons of NH(3), NH(1), Aib₂ and Aib₃, (d) NH(1) is close in space to protons of NH(2), Ar(1), OMe(1) and Aib₂, (e) OMe is close in space to protons of NH(1), Ar(1), Aib₂ and Aib₃, (f) CH₂ (gly) is close in space to protons of NH(4), NH(3) and Aib₃.

1D and 2D-NOESY NMR experiments of mono-2 in CDCl₃ show the same strong sequential NH-NH and OMe(1)-NH(1) cross peaks than mono-2 in THF-d₈ confirming the *ap*_{OMe} conformation.

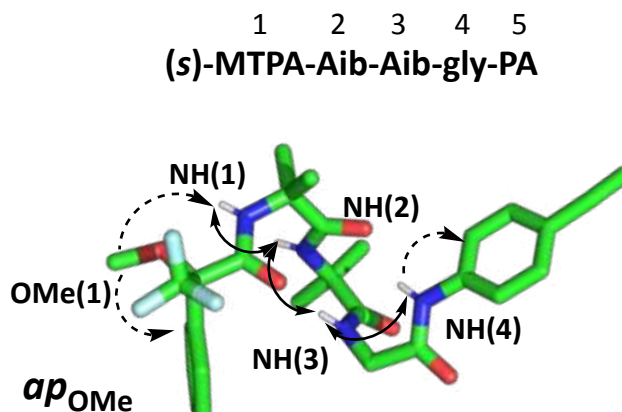


Figure S47. Representative NOEs of mono-2 in CDCl₃.

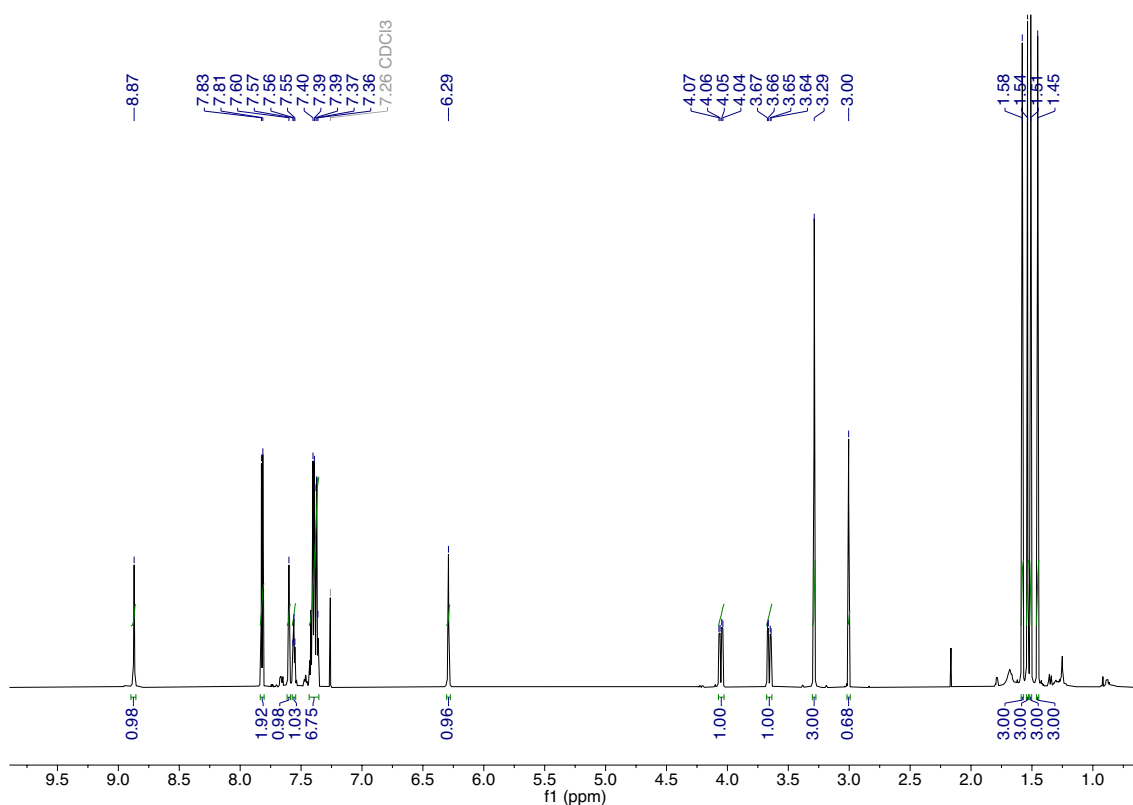
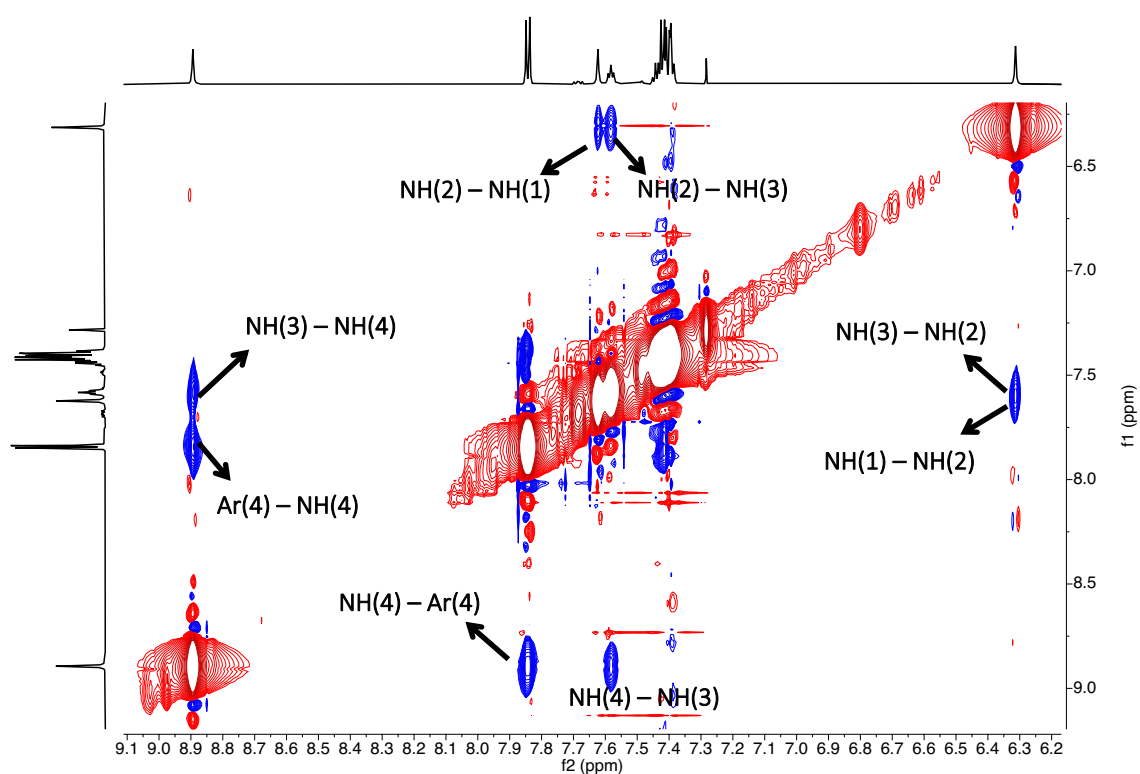


Figure S48. ¹H NMR of mono-2 in CDCl₃ at 268 K.

¹H NMR (750 MHz, CDCl₃) δ (ppm): 8.87 (s, 1H), 7.82 (d, *J*=8.7 Hz, 2H), 7.60 (s, 1H), 7.56 (t, *J*=6.3 Hz, 1H), 7.43 – 7.35 (m, 7H), 6.29 (s, 1H), 4.05 (dd, *J*=17.2 Hz, 7.0 Hz, 1H), 3.66 (dd, *J*=17.2 Hz, 5.7 Hz, 1H), 3.29 (s, 3H), 3.00 (s, 1H), 1.58 (s, 3H), 1.54 (s, 3H), 1.51 (s, 3H), 1.45 (s, 3H).

a)



b)

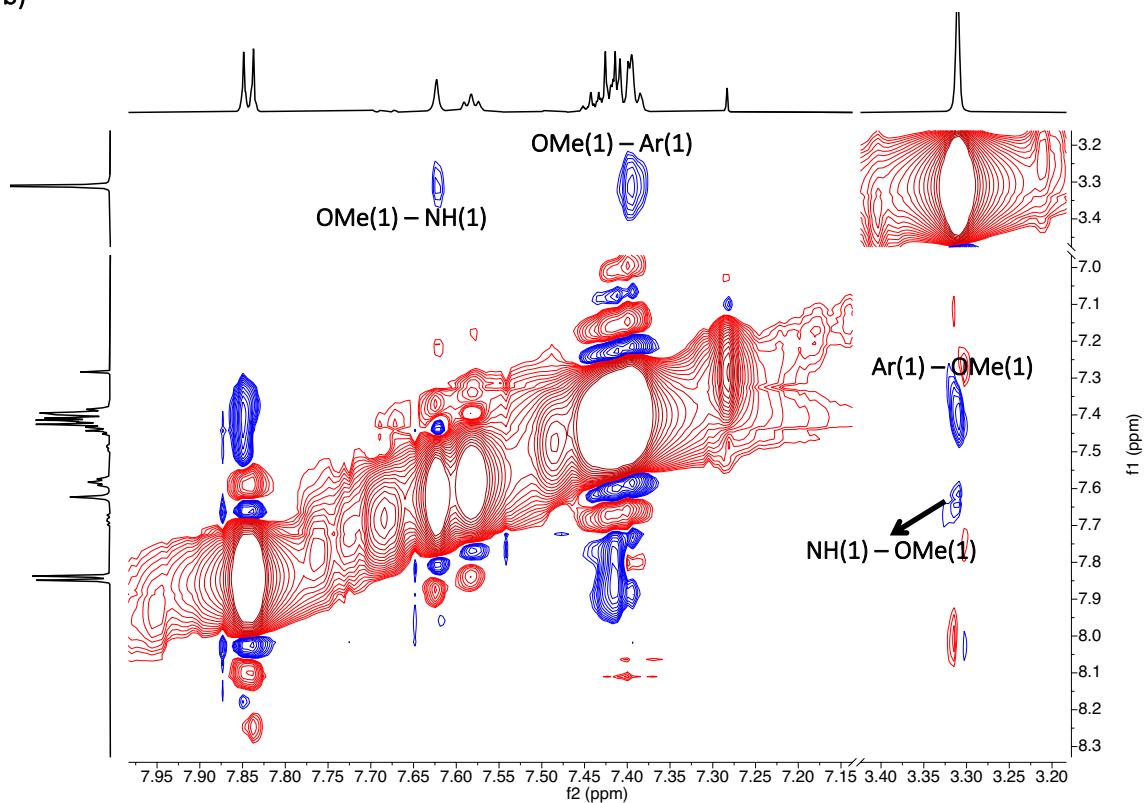
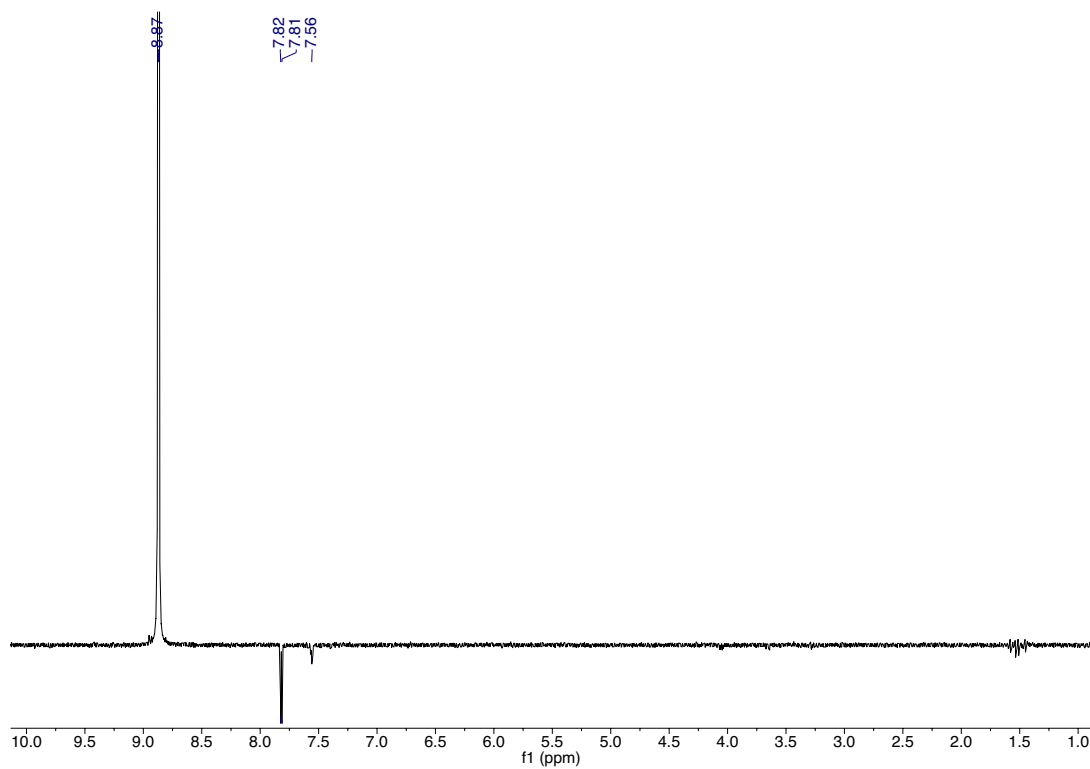
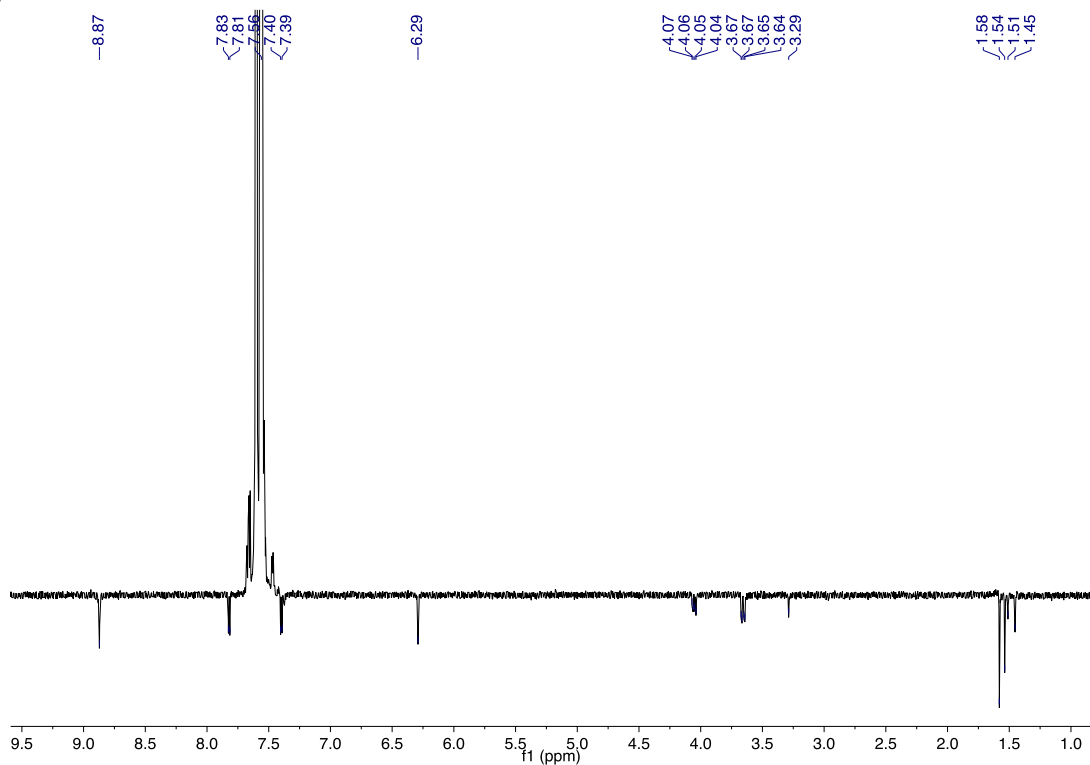


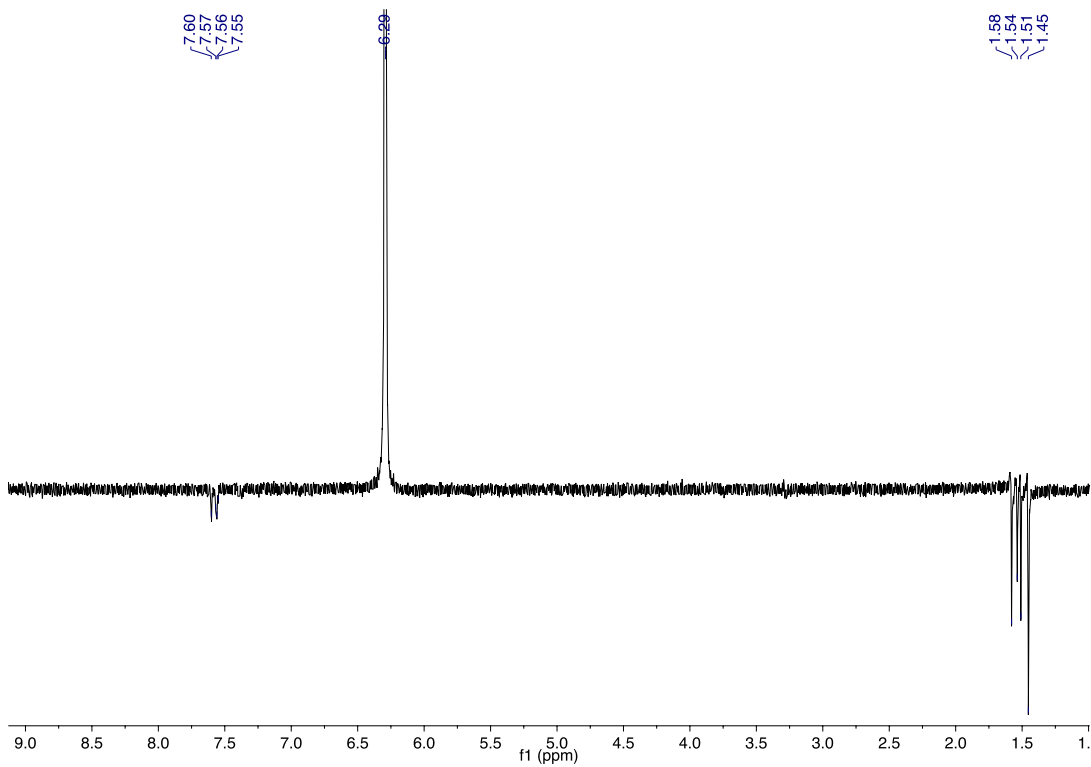
Figure S49. 2D-NOESY of mono-2 in CDCl₃ at 268 K showing (a) all NH-NH cross peaks: NH(4)-NH(3), NH(3)-NH(2), and NH(1)-NH(2), (b) OMe(1)-NH(1), OMe(1)-Ar(1).

1D-NMR experiments (NOESY) of mono-2 in CDCl₃

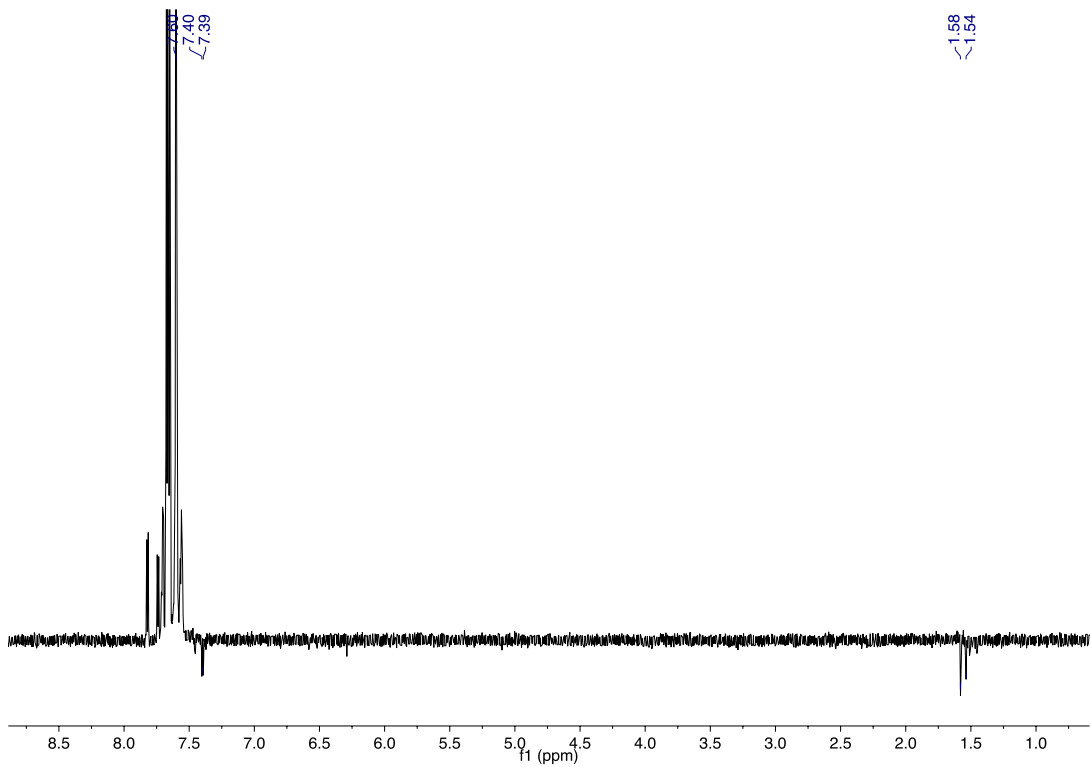
1D-NMR experiments (NOESY) of mono-2 in CDCl₃ were carried out where selective signals were irradiated (positive signal) in order to observe the coupled protons of the molecule that are closed in space (negative signal).

a)**b)**

c)



d)



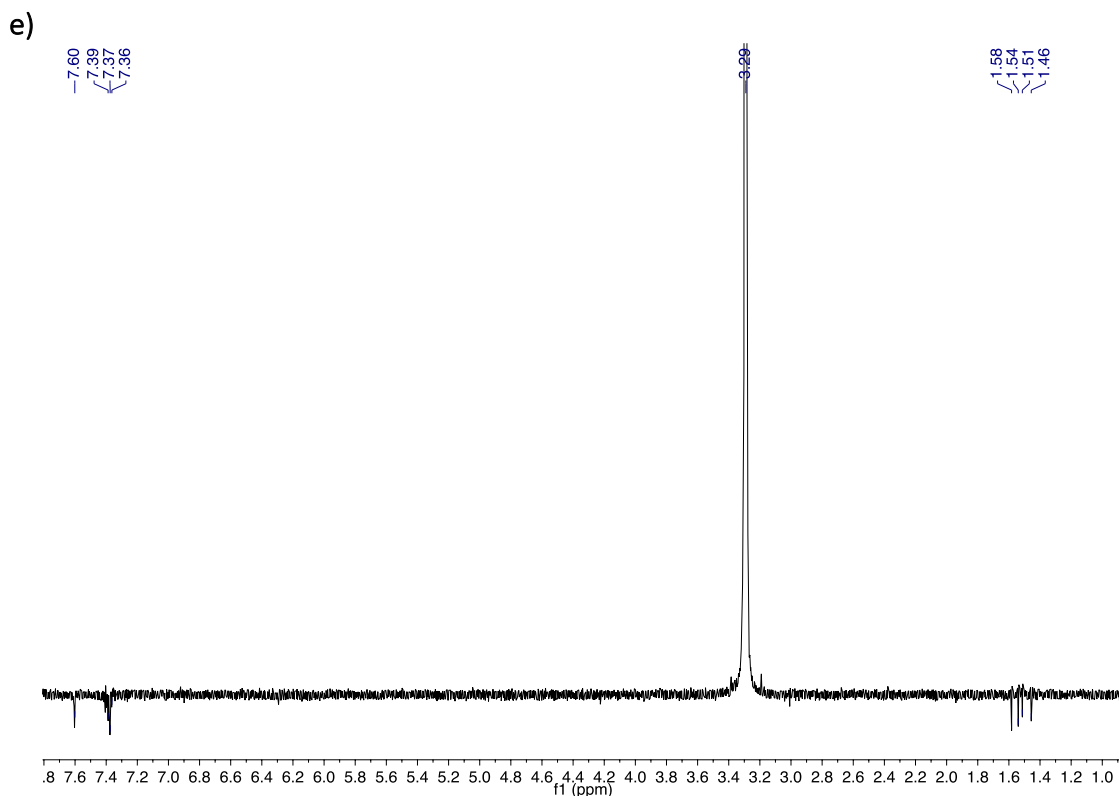


Figure S50. 1D-NMR experiments (NOESY) of mono-2 in CDCl_3 at 268 K showing the cross peaks that (a) NH(4) is close in space to protons of Ar(4) and NH(3), (b) NH(3) is close in space to protons of NH(4), Ar(5), NH(2), CH_2 (gly), Aib₂ and Aib₃, (c) NH(2) is close in space to protons of NH(1), NH(3), Aib₂ and Aib₃, (d) NH(1) is close in space to Ar(1) and Aib₂, (e) OMe is close in space to protons of NH(1), Ar(1), Aib₂ and Aib₃.

15. NMR studies of mono-3

1D and 2D-NOESY NMR experiments of mono-3 in THF-d_8 show strong sequential NH-NH cross peaks which confirms the presence of P -3₁₀ helix of the oligomer in solution. The ap_{OMe} conformation at the pendant group was confirmed by the presence of NOE cross peaks between the anilide (NH1) and the methoxy group.

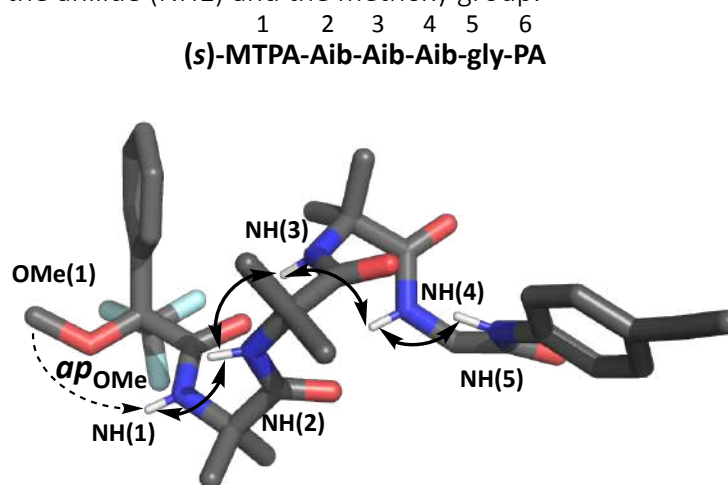


Figure S51. Representative NOEs of mono-3 in THF-d_8 .

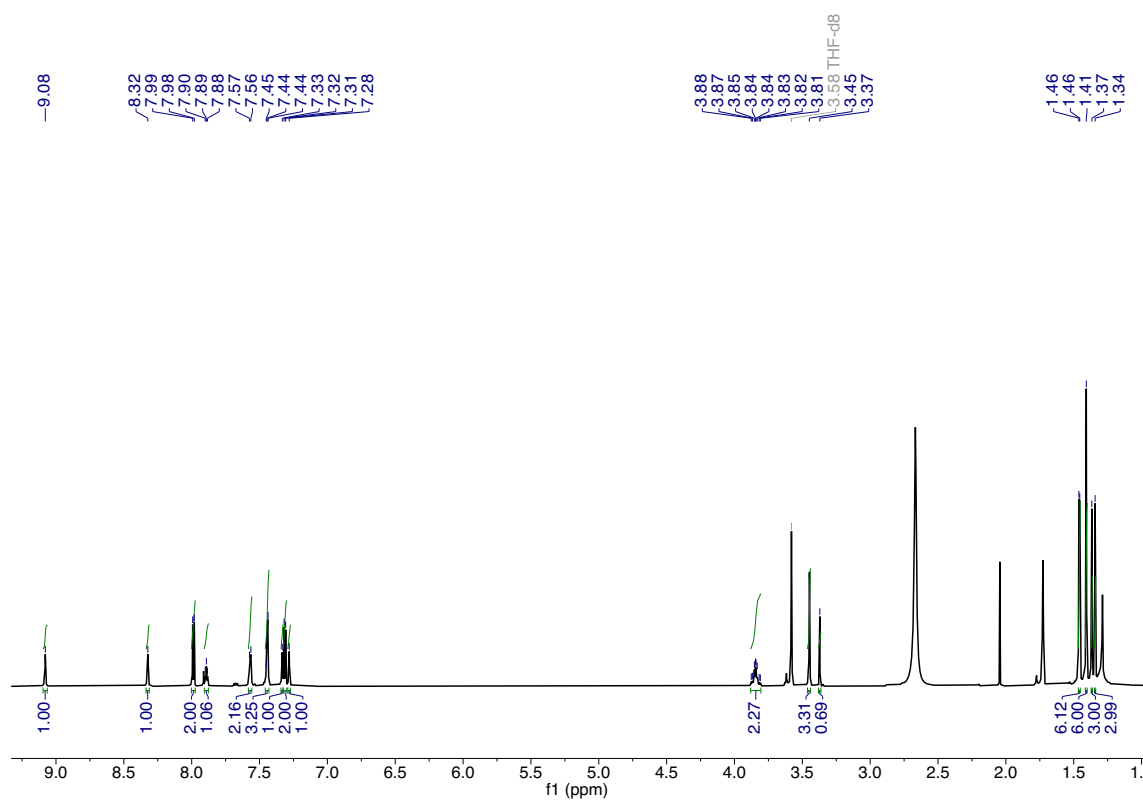
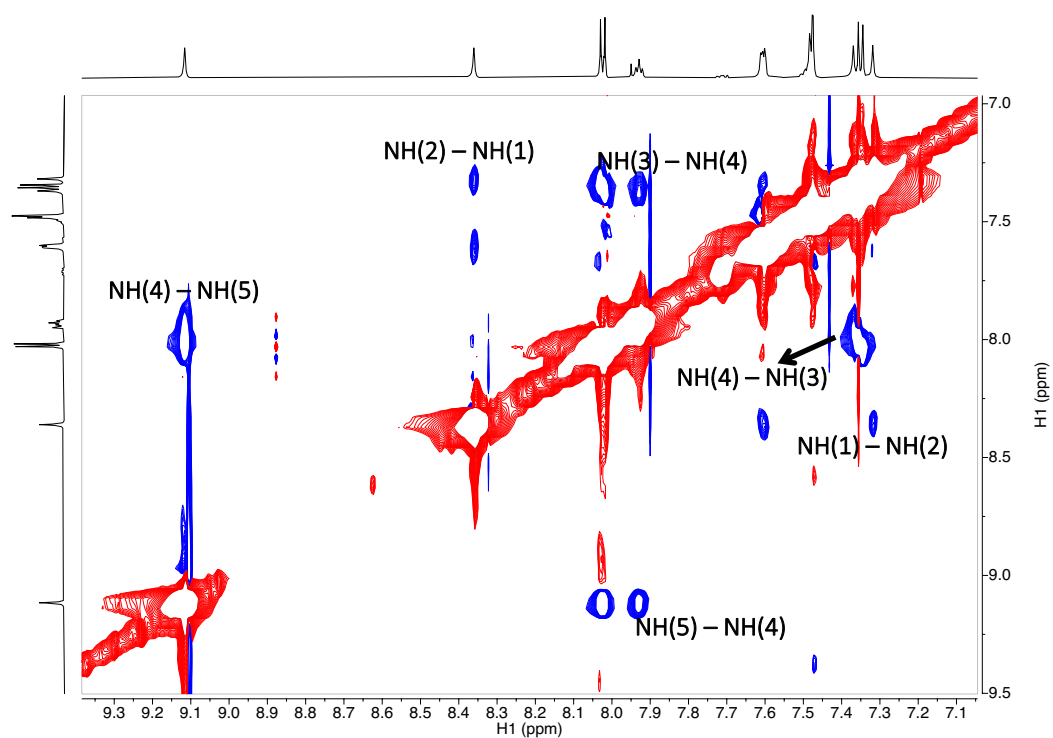


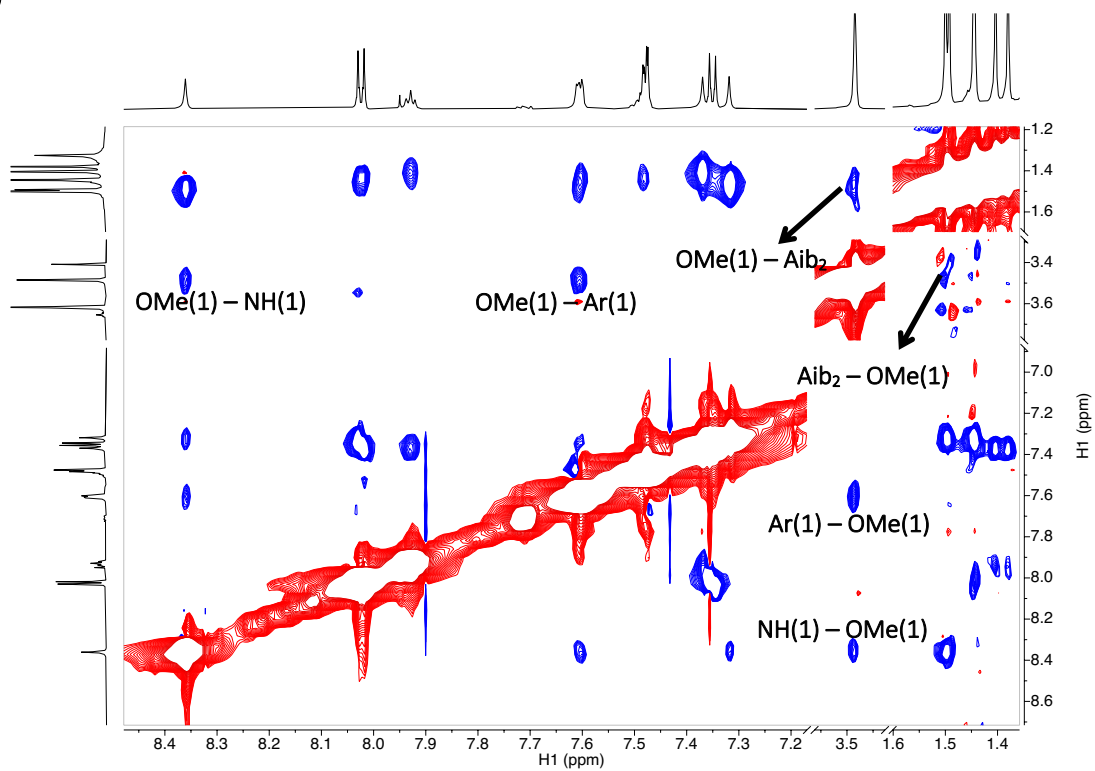
Figure S52. ^1H NMR of mono-**3** (THF- d_8 , 268 K).

^1H NMR (750 MHz, THF- d_8) δ = 9.08 (s, 1H), 8.32 (s, 1H), 7.99 (d, J =8.7 Hz, 2H), 7.89 (t, J =6.4 Hz, 1H), 7.57 (d, J =7.8 Hz, 2H), 7.44 (m, 3H), 7.33 (s, 1H), 7.31 (d, J =8.7 Hz, 2H), 7.28 (s, 1H), 3.88 – 3.81 (m, 2H), 3.45 (s, 3H), 3.37 (s, 1H), 1.46 (d, J =5.1 Hz, 6H), 1.41 (s, 6H), 1.37 (s, 3H), 1.34 (s, 3H).

a)



b)



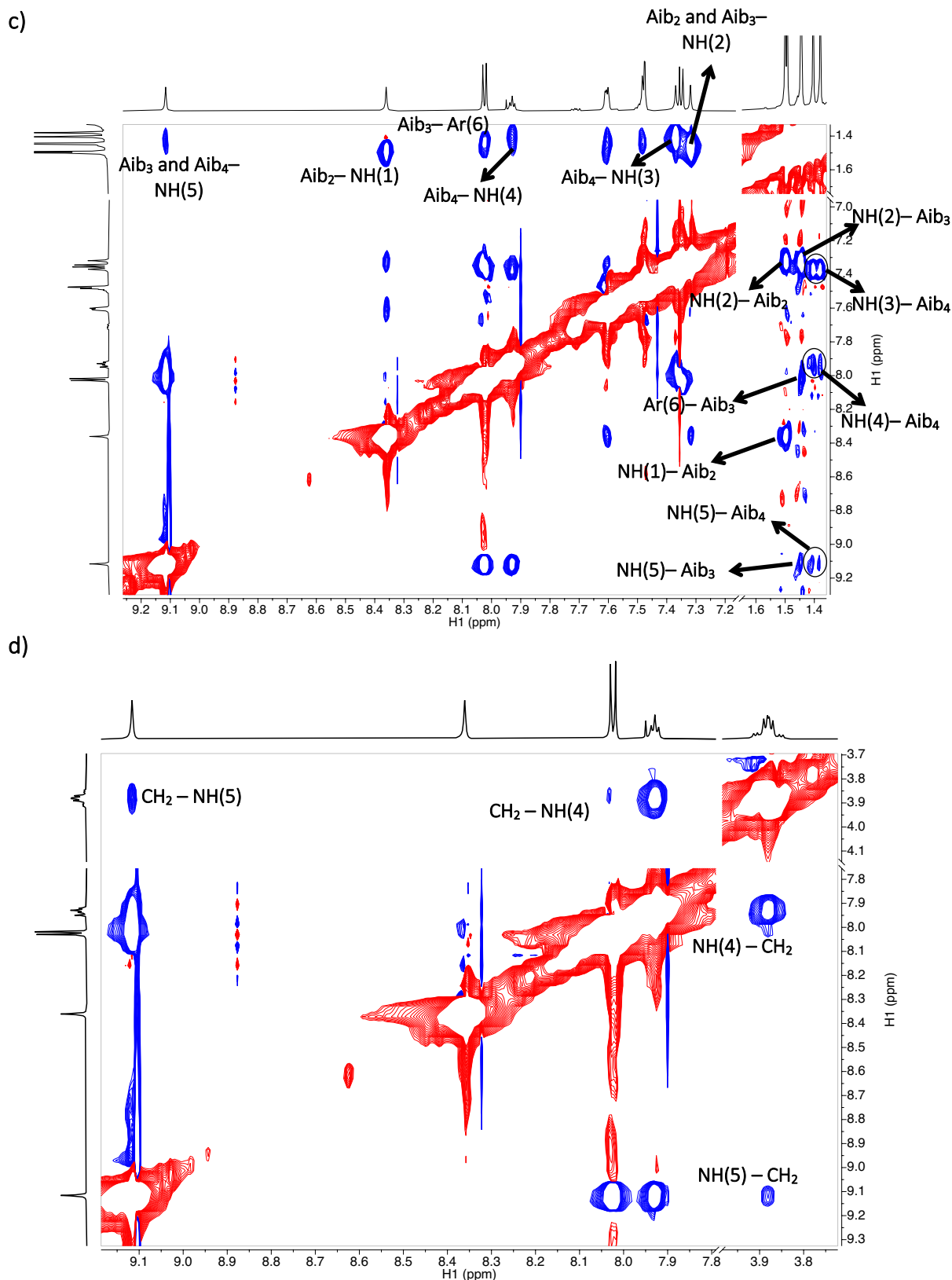
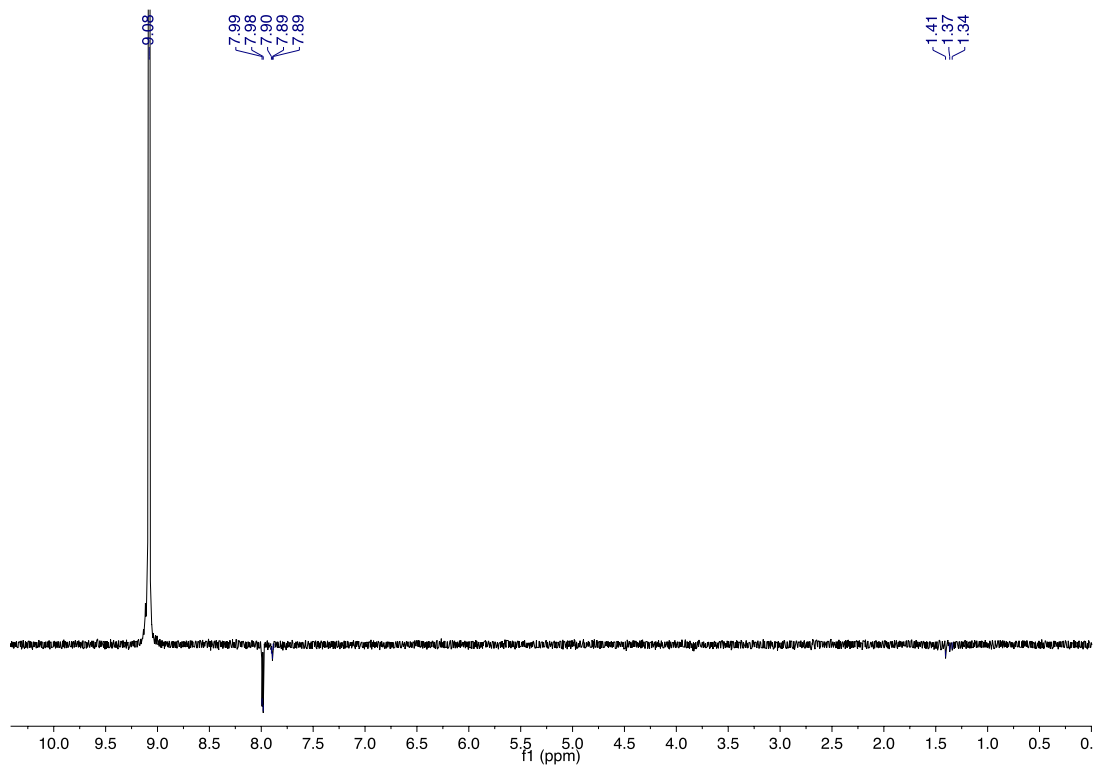
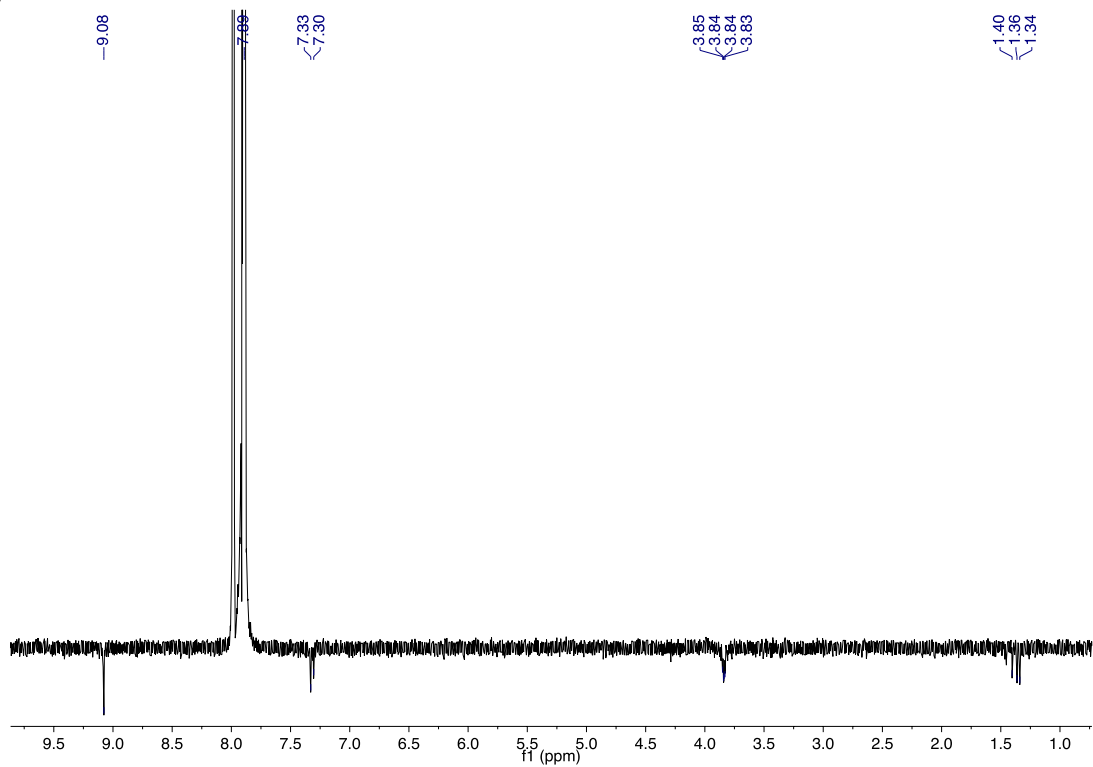
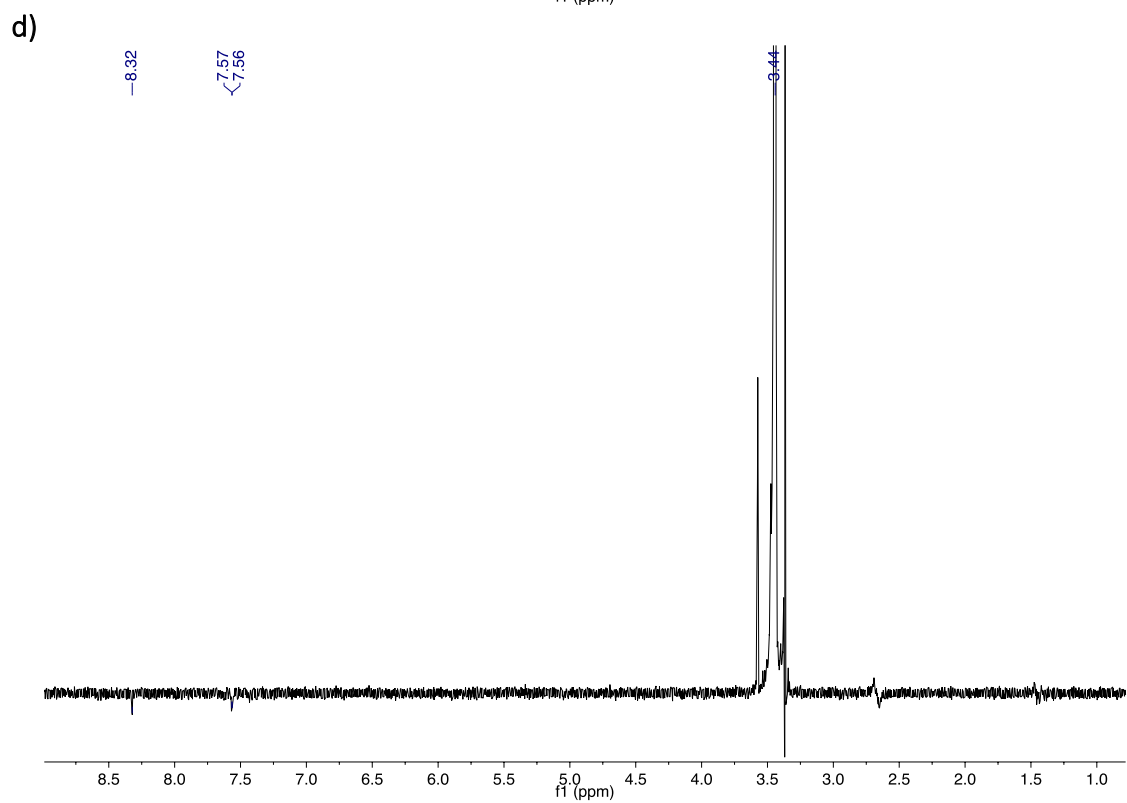
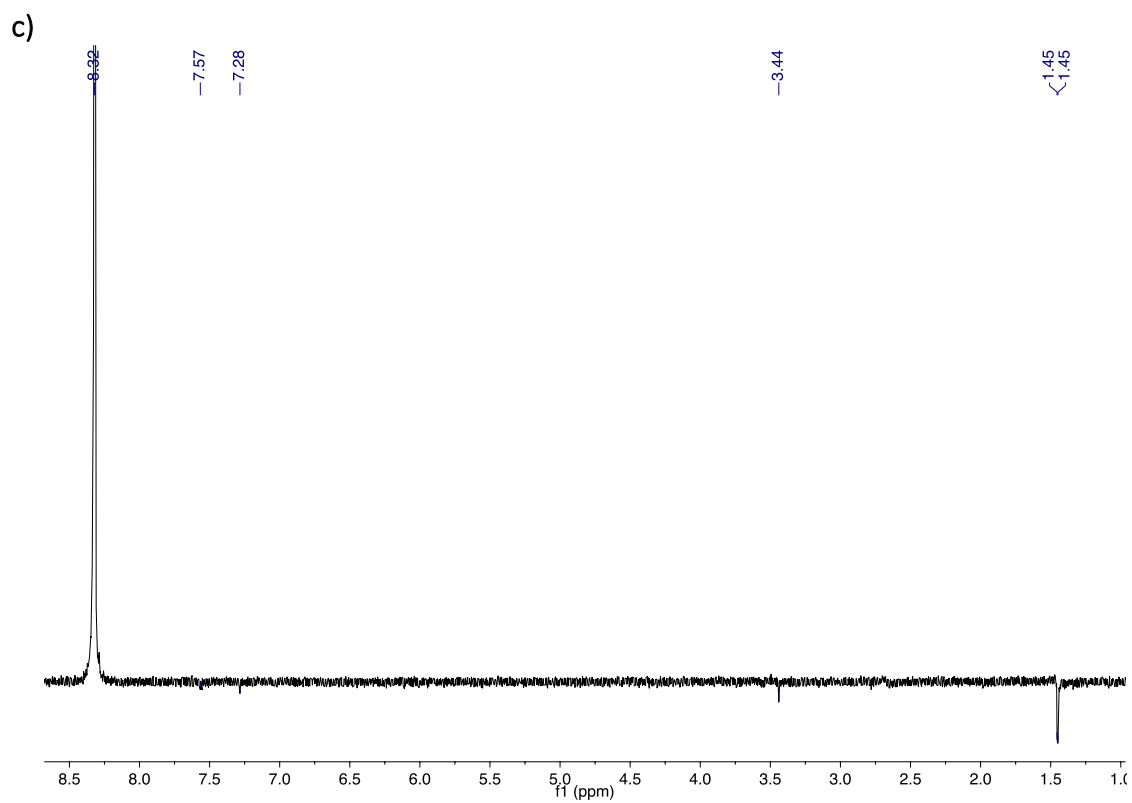


Figure S53. 2D-ROESY of mono-**3** in THF- d_8 at 268 K showing (a) all NH-NH cross peaks: NH(5)-NH(4), NH(4)-NH(3), NH(2)-NH(1), (b) OMe(1)-NH(1), OMe(1)-Ar(1) and OMe(1)-Aib₂, (c) all Aib-NH cross peaks: NH(5)-Aib₄, NH(5)-Aib₃, Ar(6)-Aib₃, NH(4)-Aib₄, NH(3)-Aib₄, NH(2)-Aib₂, NH(2)-Aib₃ and NH(1)-Aib₂, (d) NH(5)-CH₂ (gly), NH(4)-CH₂ (gly).

1D-NMR experiments (NOESY) of mono-3 in THF-d₈

1D-NMR experiments (NOESY) of mono-**3** in THF-d₈ were carried out where selective signals were irradiated (positive signal) in order to observe the coupled protons of the molecule that are closed in space (negative signal).

a)**b)**



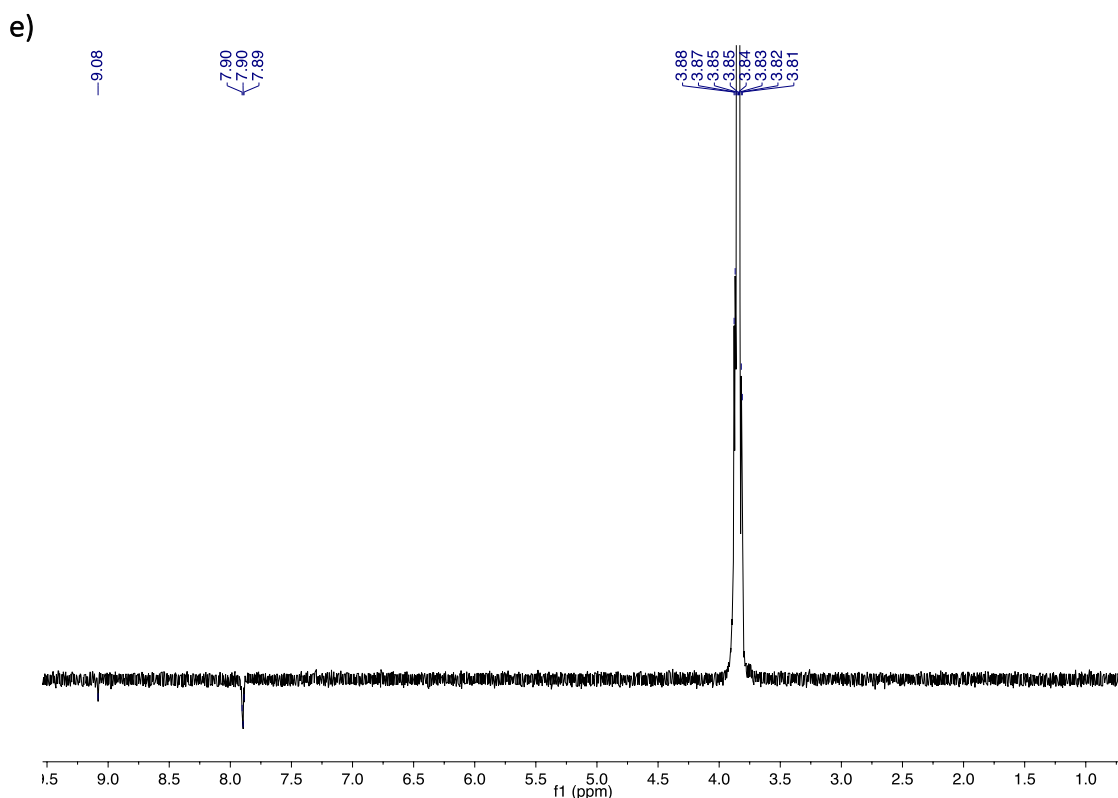


Figure S54. 1D-NMR experiments (NOESY) of mono-3 in THF- d_8 at 268 K showing the cross peaks that (a) NH(5) is close in space to protons of Ar(6), NH(4), Aib₃ and Aib₄, (b) NH(4) is close in space to protons NH(5), Ar(6), NH(3), CH₂ (gly), and Aib₄, (c) NH(1) is close in space to protons NH(2), Ar(1), OMe(1) and Aib₂, (d) OMe is close in space to protons NH(1) and Ar(1), (e) CH₂ (gly) is close in space to protons NH(5) and NH(4).

1D and 2D-NOESY NMR experiments of mono-3 in CDCl₃ show in a similar manner to the other (S)-MTPA-(Aib)_n-gly-PA ($n = 1, 2$) oligomers studied strong sequential NH-NH and OMe(1)-NH(1) cross peaks, confirming the presence of ap_{OMe} and $M-3_{10}$ helical structure of the polymer in solution.

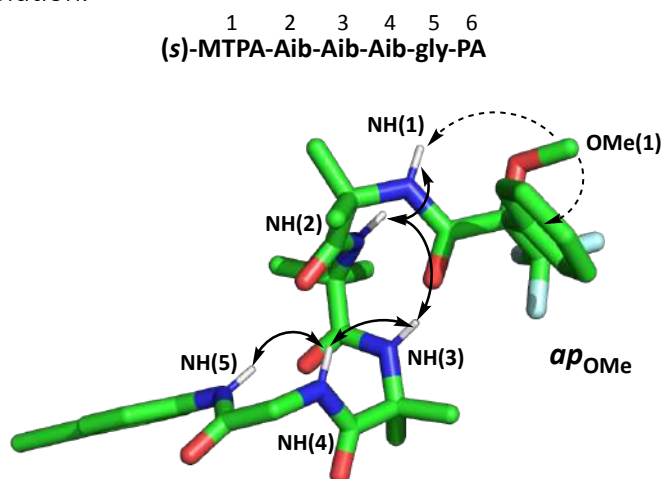


Figure S55. Representative NOEs of mono-3 in CDCl₃.

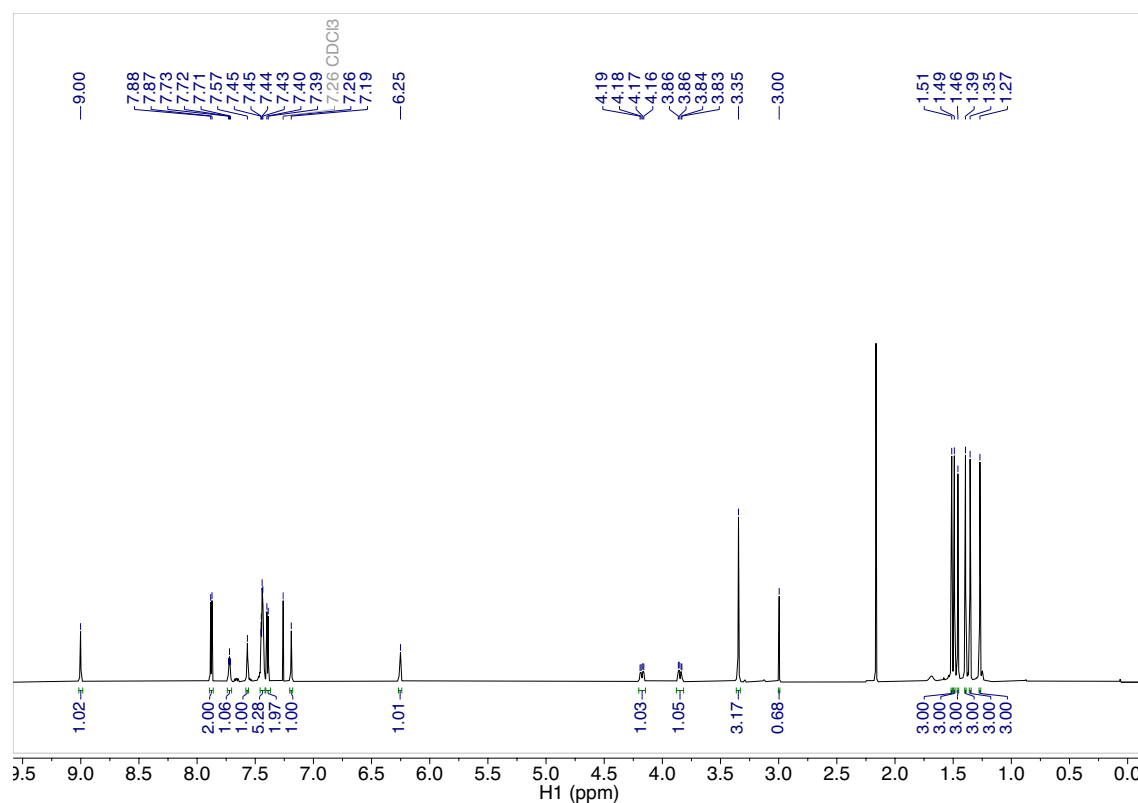
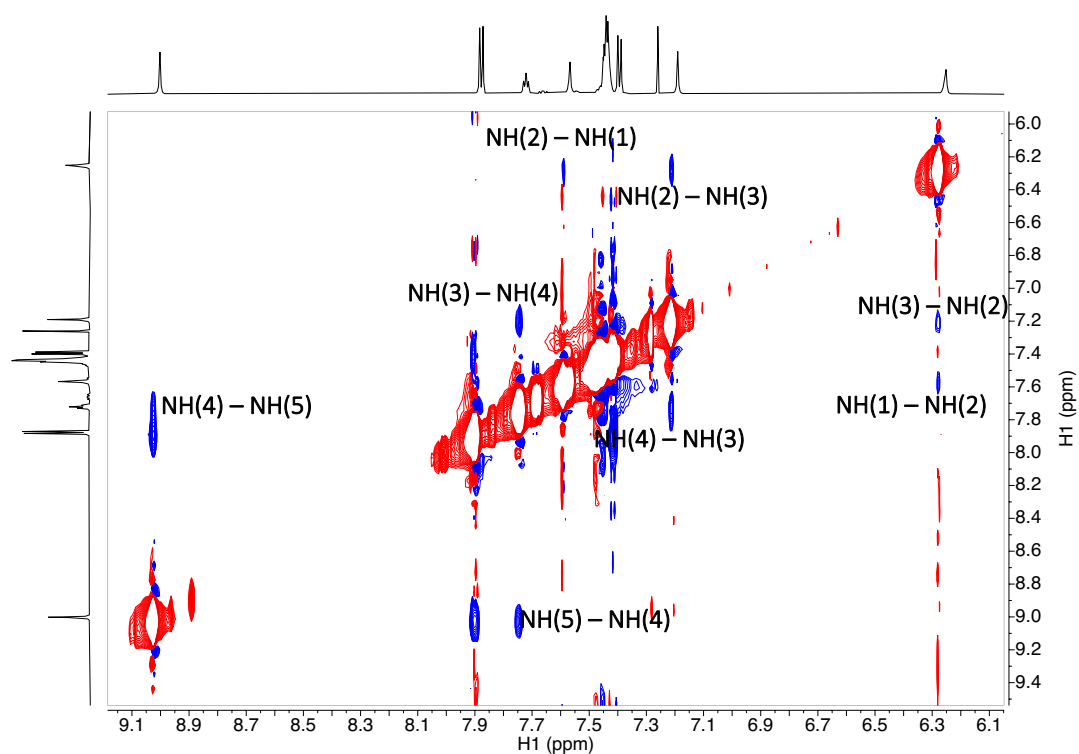


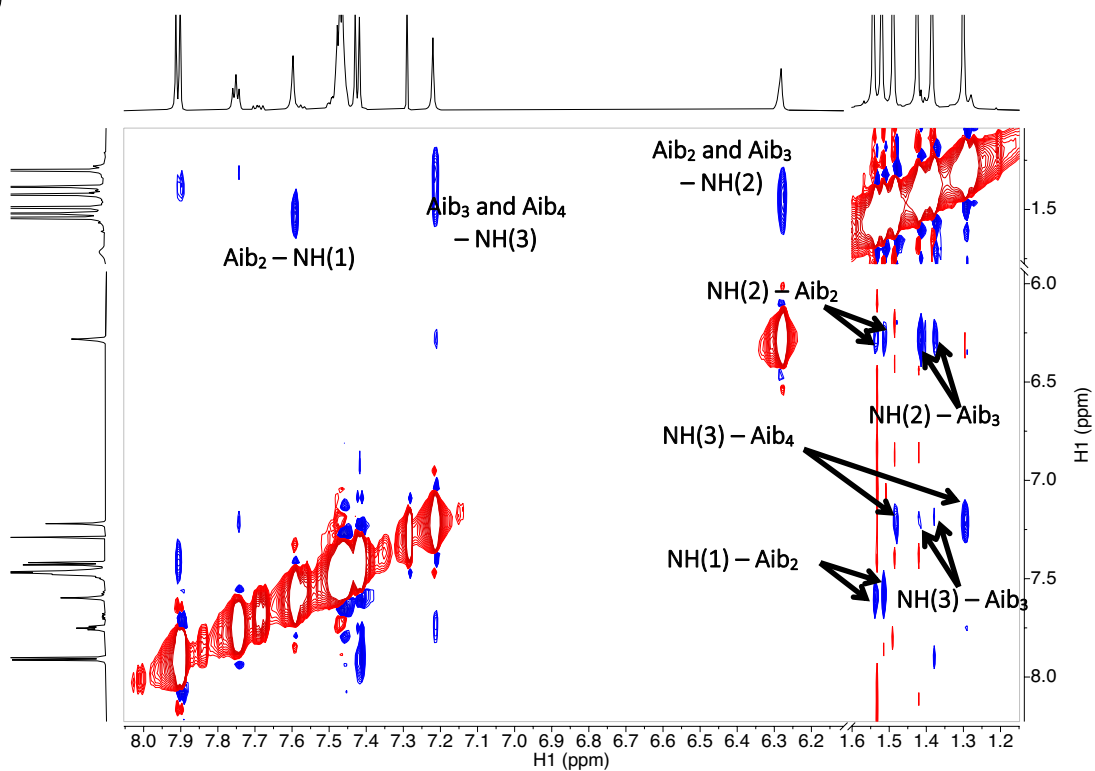
Figure S56. ^1H NMR of mono-3 in CDCl_3 at 268 K.

^1H NMR (750 MHz, CDCl_3) δ (ppm): 9.00 (s, 1H), 7.88 (d, $J=8.7$ Hz, 2H), 7.72 (t, $J=6.4$ Hz, 1H), 7.57 (s, 1H), 7.44 (m, 5H), 7.39 (d, $J=8.6$ Hz, 2H), 7.19 (s, 1H), 6.25 (s, 1H), 4.18 (dd, $J=17.2$ Hz, 6.8 Hz, 1H), 3.85 (dd, $J=17.3$ Hz, 5.4 Hz, 1H), 3.35 (s, 3H), 3.00 (s, 1H), 1.51 (s, 3H), 1.49 (s, 3H), 1.46 (s, 3H), 1.39 (s, 3H), 1.35 (s, 3H), 1.27 (s, 3H).

a)



b)



c)

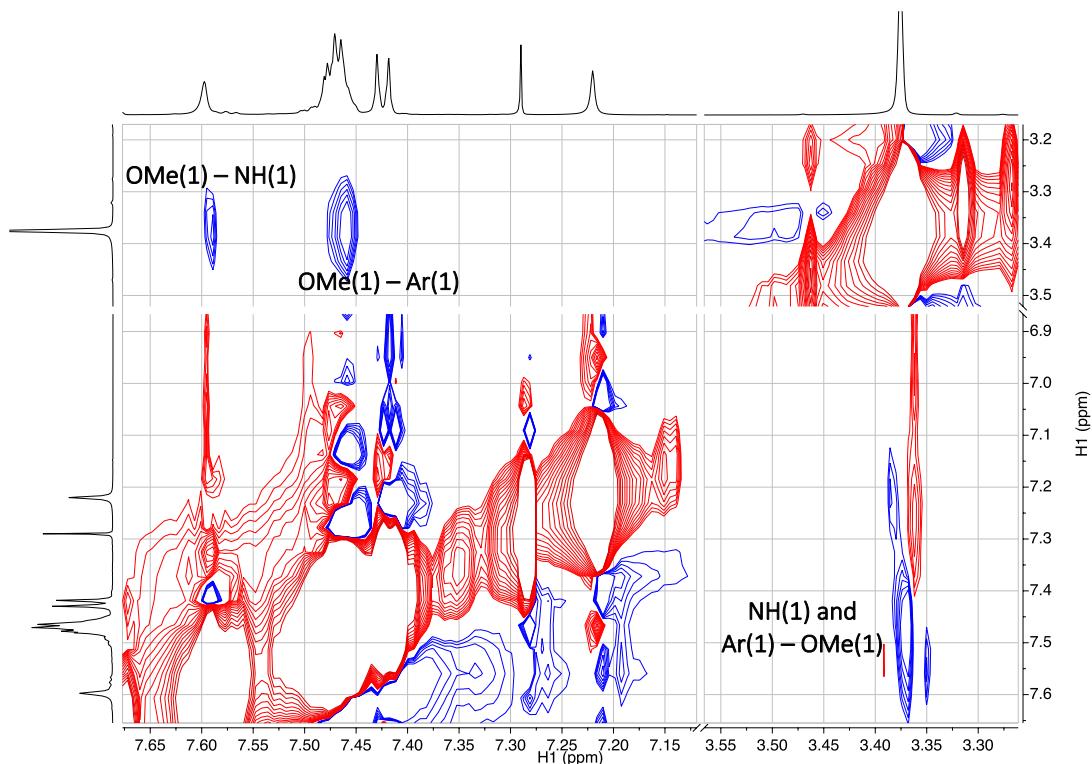
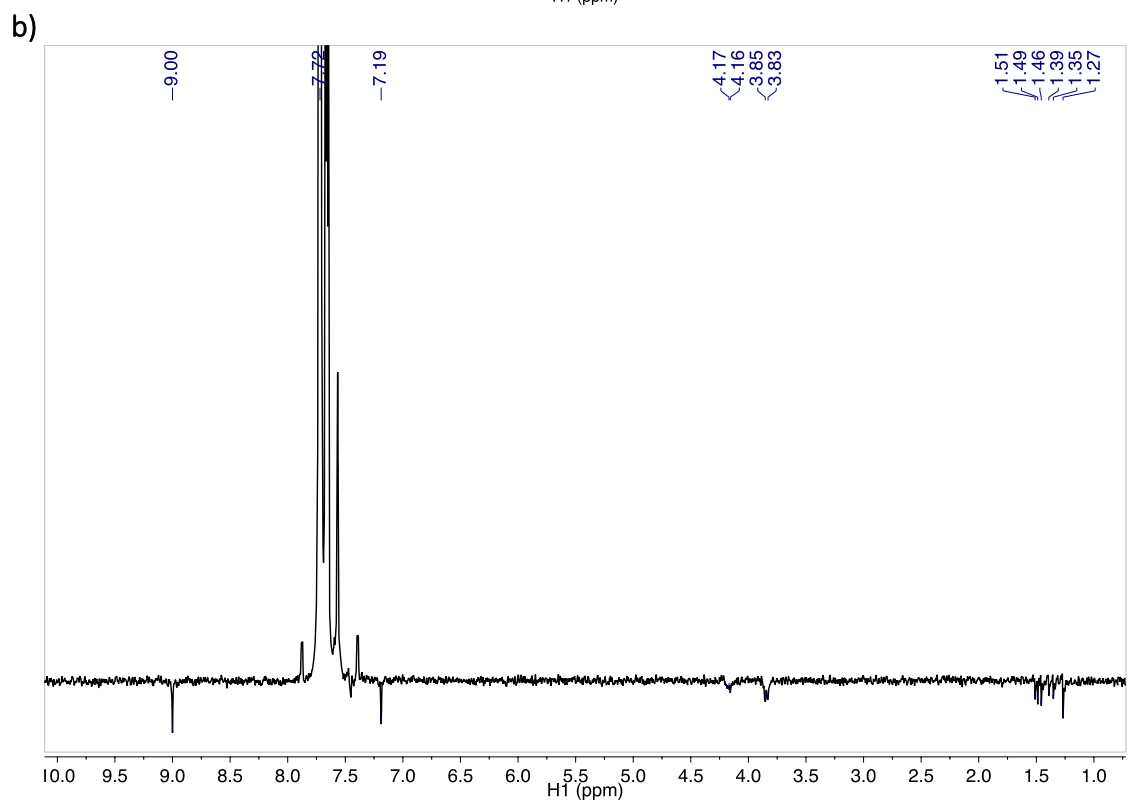
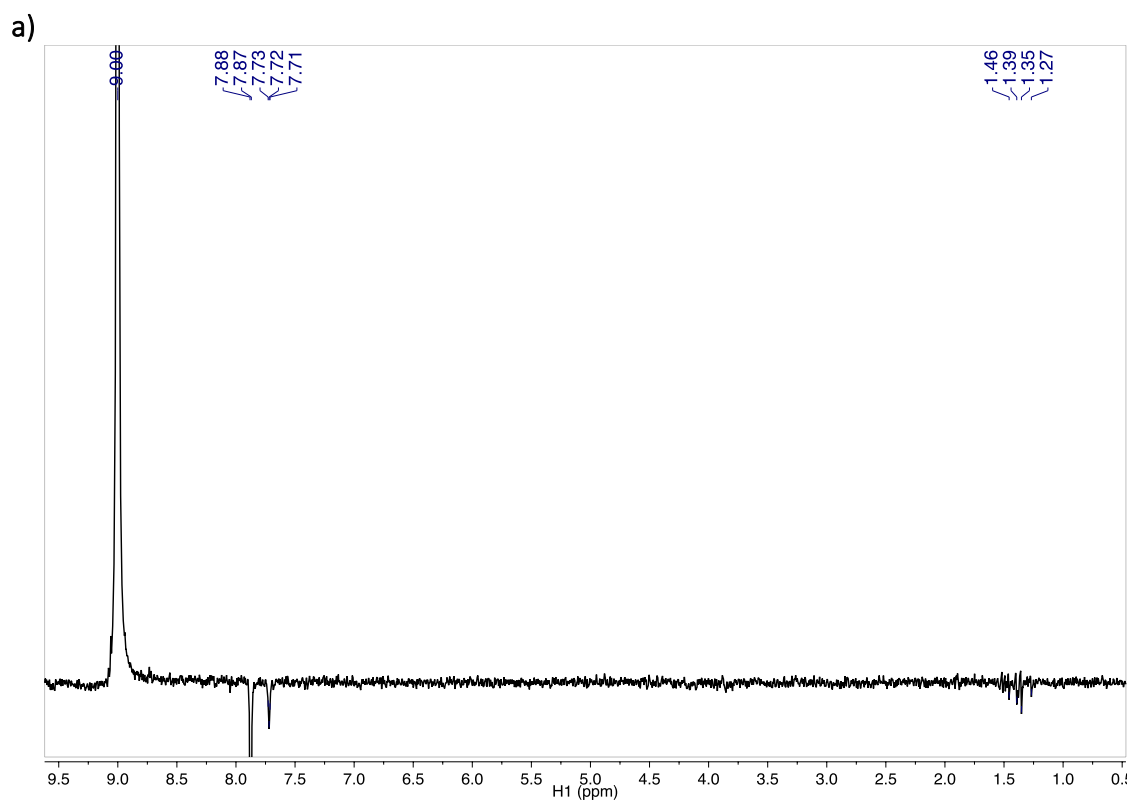


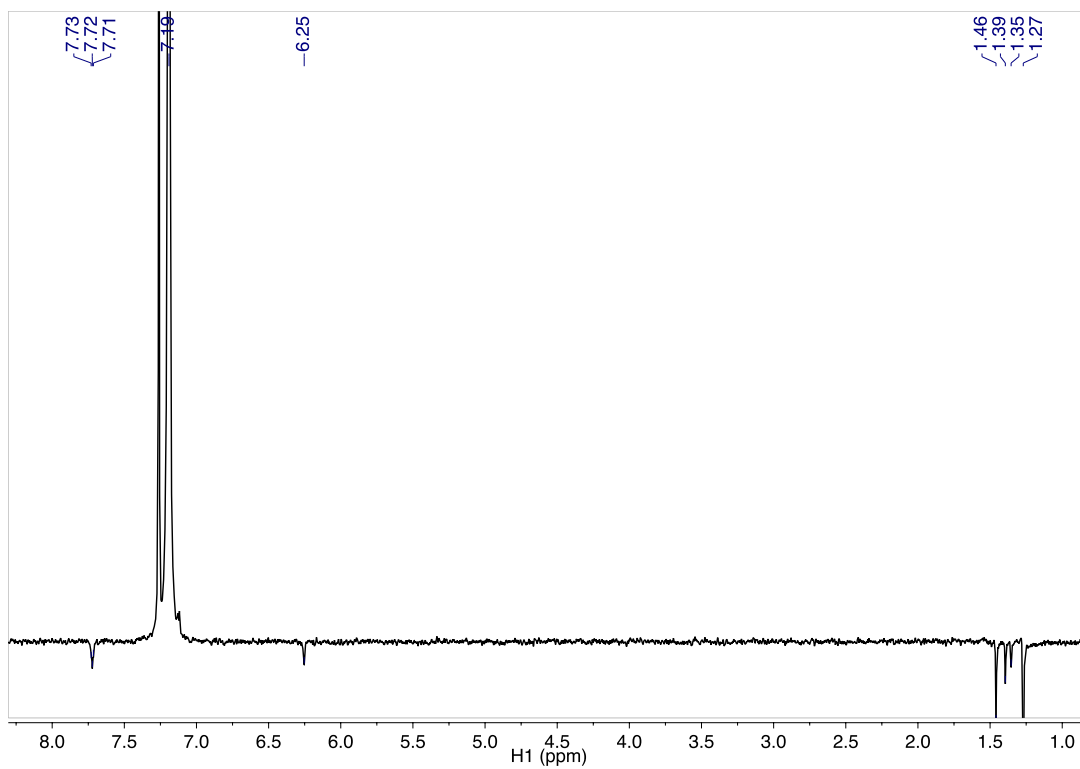
Figure S57. 2D-NOESY of mono-**3** in CDCl_3 at 268 K showing (a) all NH-NH cross peaks: NH(5)-NH(4), NH(4)-NH(3), NH(3)-NH(2), NH(2)-NH(1), (b) NH(1)-Aib₂, NH(2)-Aib₂, NH(2)-Aib₃, NH(3)-Aib₃ and NH(3)-Aib₄, (c) OMe(1)-NH(1) and OMe(1)-Ar(1).

1D-NMR experiments (NOESY) of mono-**3** in CDCl_3

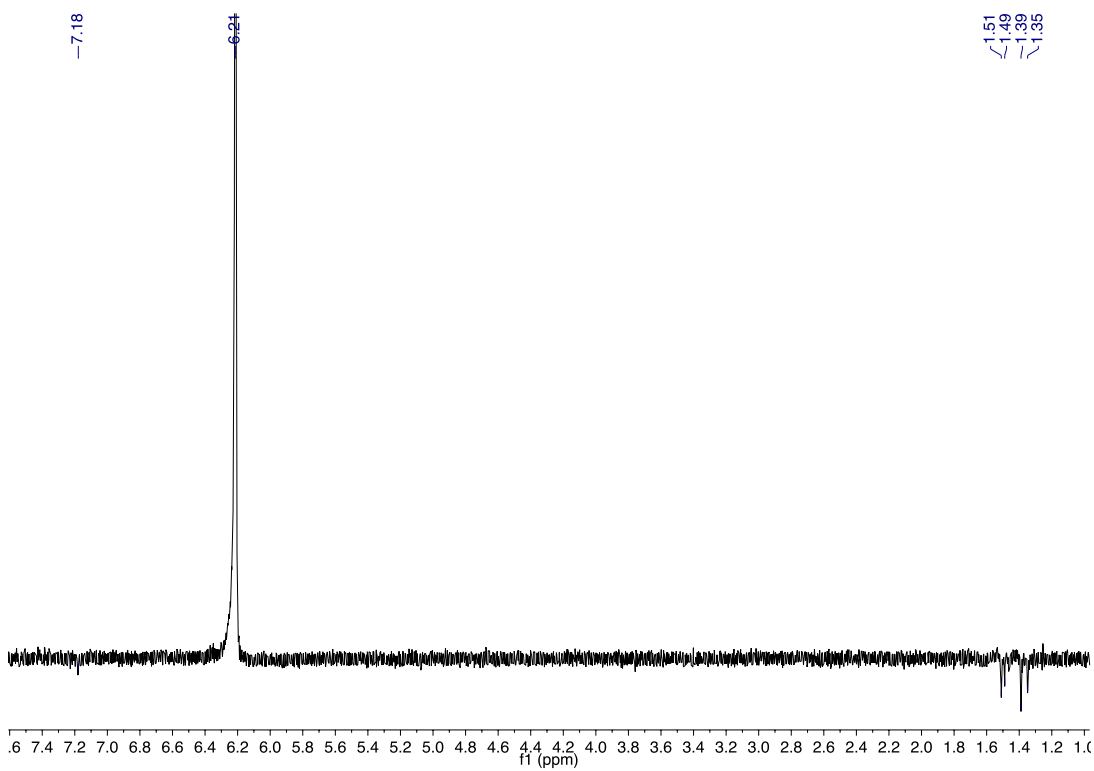
1D-NMR experiments (NOESY) of mono-**3** in CDCl_3 were carried out where selective signals were irradiated (positive signal) in order to observe the coupled protons of the molecule that are closed in space (negative signal).



c)



d)



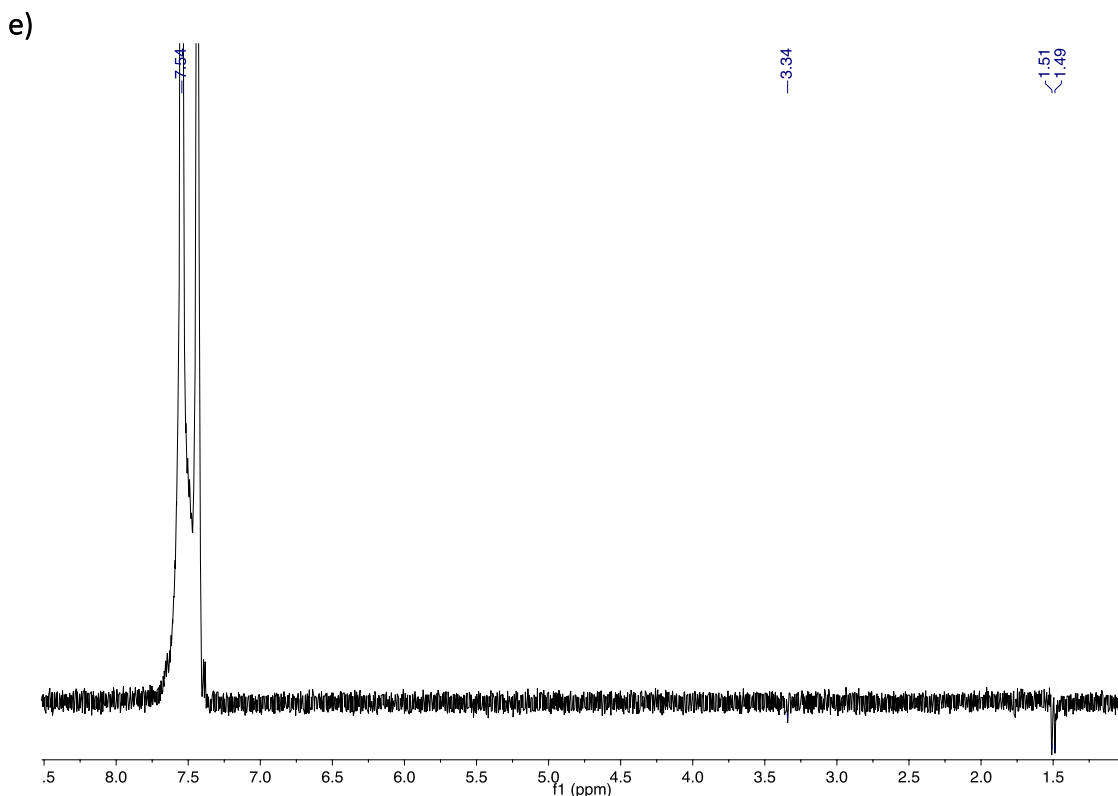


Figure S58. 1D-NMR experiments (NOESY) of mono-**3** in CDCl_3 at 268 K showing the cross peaks that (a) NH(5) is close in space to protons of Ar(6), NH(4), Aib₂ and Aib₄, (b) NH(4) is close in space to protons NH(5), NH(3), CH₂ (gly), Aib₂, Aib₃ and Aib₄, (c) NH(3) is close in space to protons NH(4), NH(2), Aib₃ and Aib₄, (d) NH(2) is close in space to protons NH(3), Aib₂ and Aib₃, (e) NH(1) is close in space to protons of OMe(1) and Aib₂.

16. NMR studies of mono-4

1D and 2D-NOESY NMR experiments of mono-**4** in THF-d_8 show strong sequential NH-NH cross peaks which confirms the presence of P -3₁₀ helix of the oligomer in solution. The ap_{OMe} conformation at the pendant group was confirmed by the presence of NOE cross peaks between the anilide (NH1) and the methoxy group.

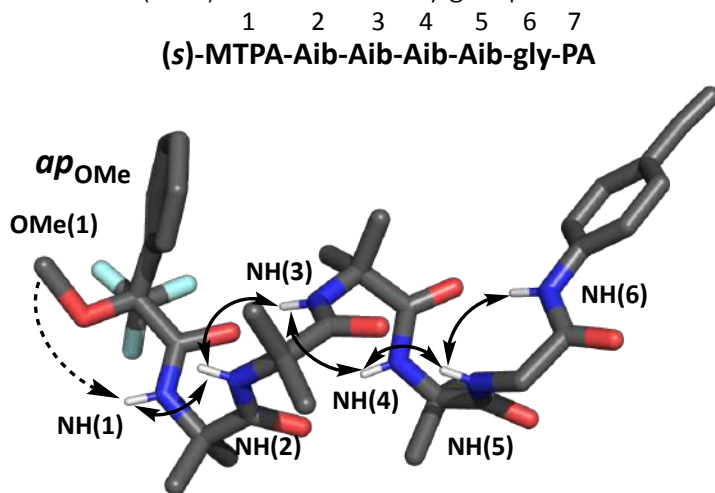


Figure S59. Representative NOEs of mono-**4** in THF-d_8 .

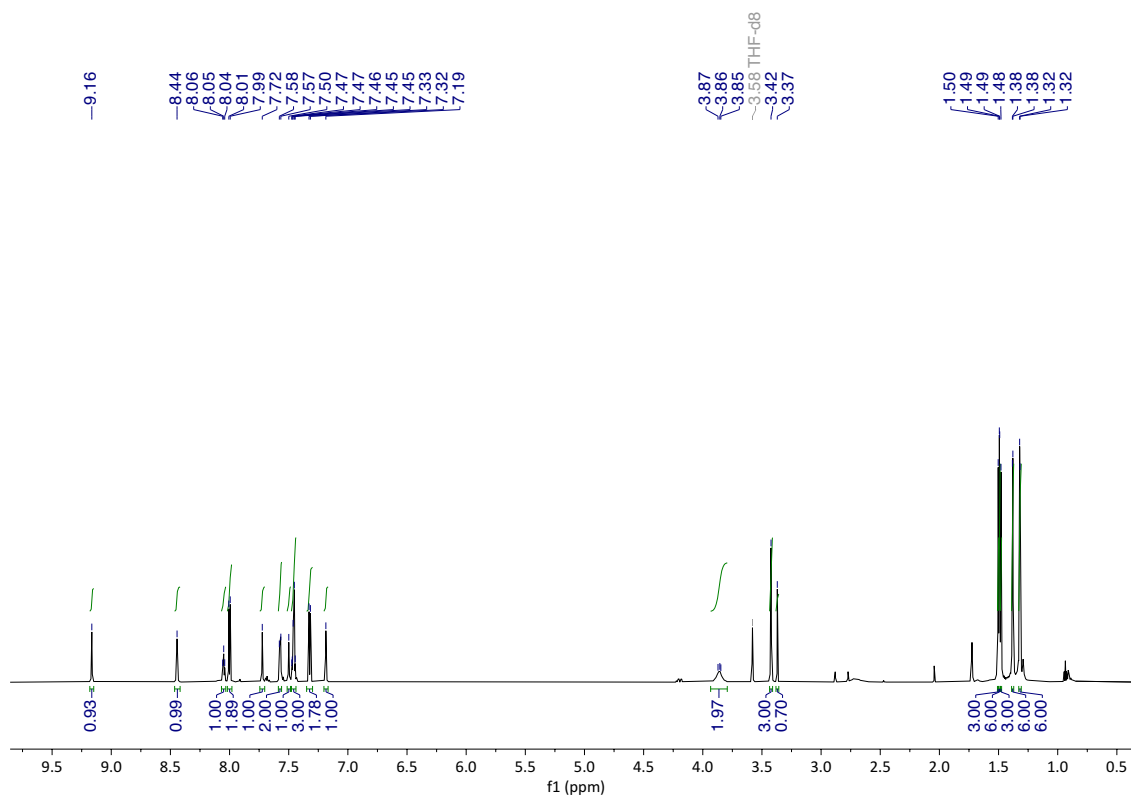
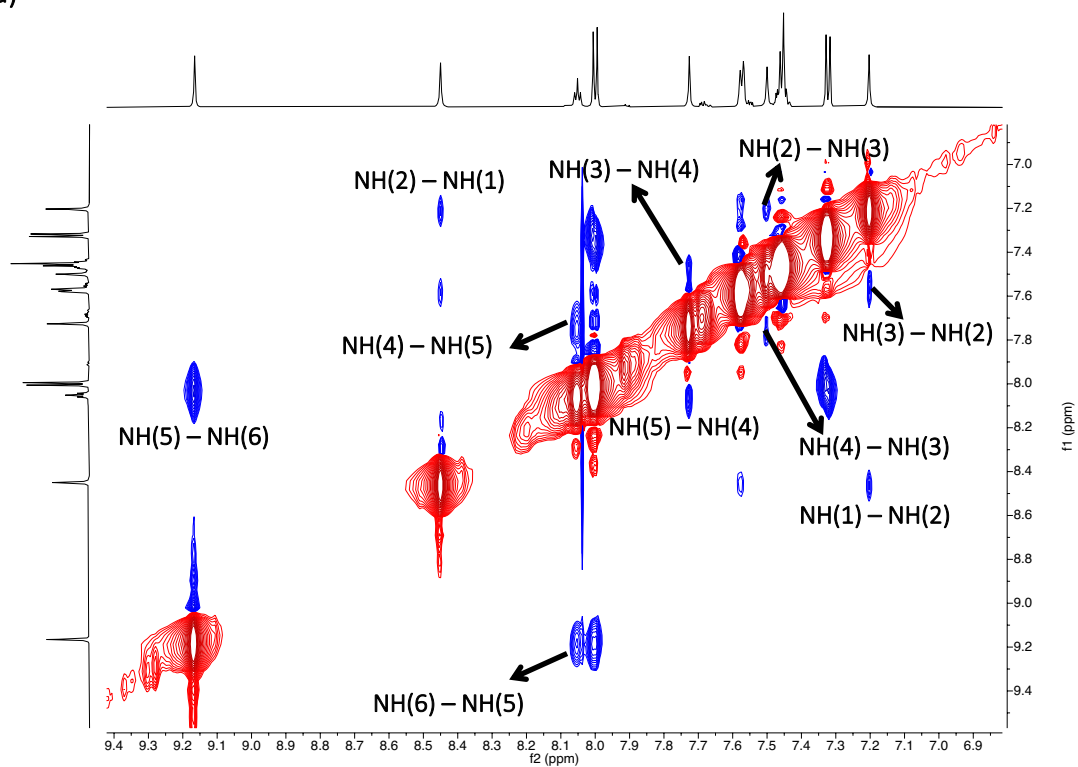


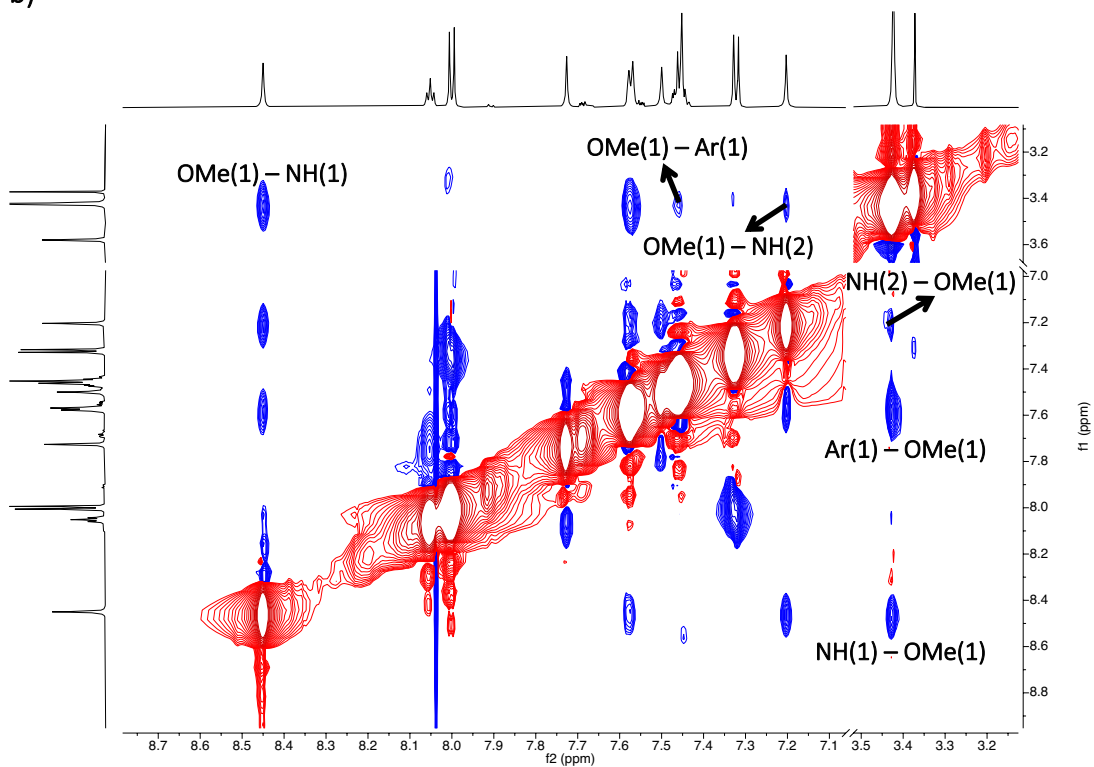
Figure S60. ^1H NMR of mono-**4** (THF- d_8 , 268 K).

^1H NMR (750 MHz, THF- d_8) δ = 9.16 (s, 1H), 8.44 (s, 1H), 8.05 (t, J =6.4 Hz, 1H), 8.00 (d, J =8.7 Hz, 2H), 7.72 (s, 1H), 7.57 (d, J =9.5 Hz, 2H), 7.50 (s, 1H), 7.48 – 7.44 (m, 3H), 7.32 (d, J =8.7 Hz, 2H), 7.19 (s, 1H), 3.93 – 3.79 (m, 2H), 3.42 (s, 3H), 3.37 (s, 1H), 1.50 (s, 3H), 1.49 (d, J =2.4 Hz, 6H), 1.48 (s, 3H), 1.38 (d, J =3.0 Hz, 6H), 1.32 (d, J =2.6 Hz, 6H).

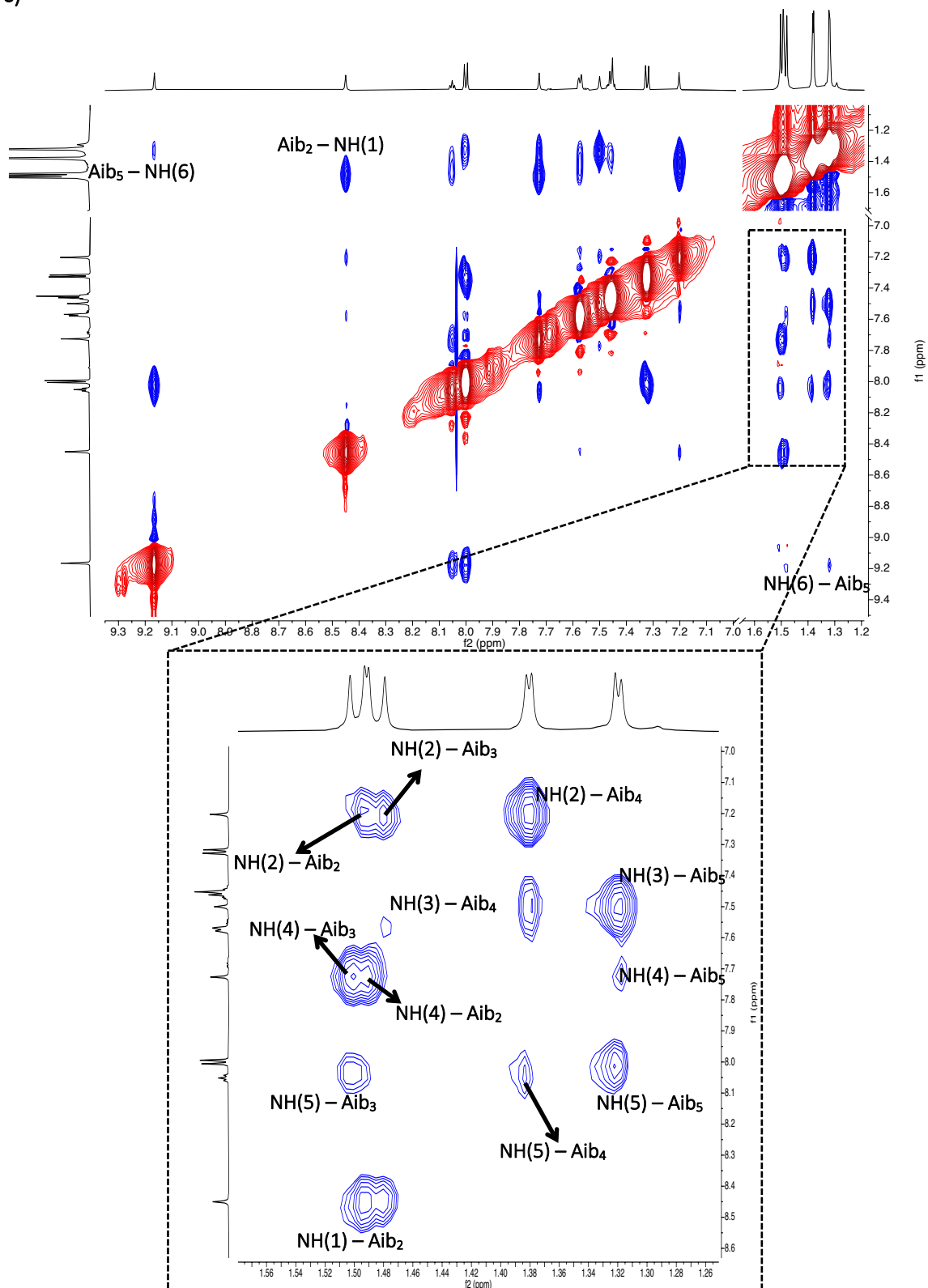
a)



b)



c)



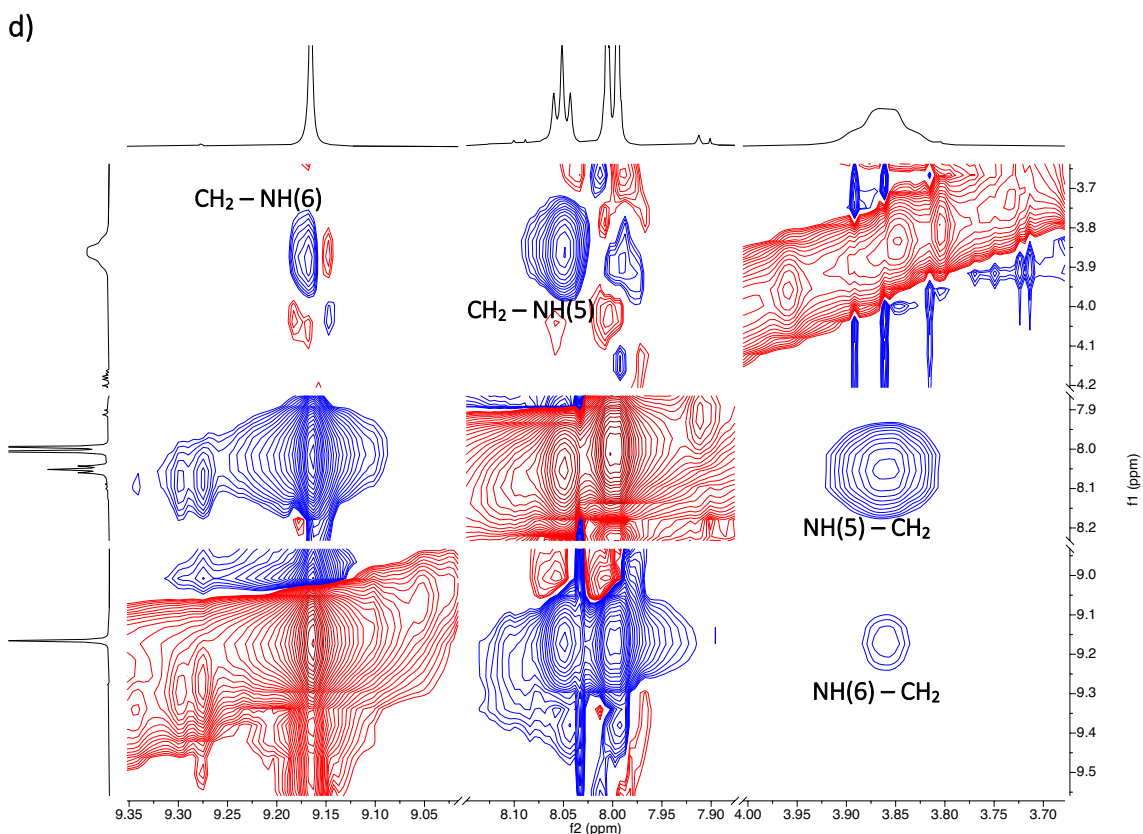
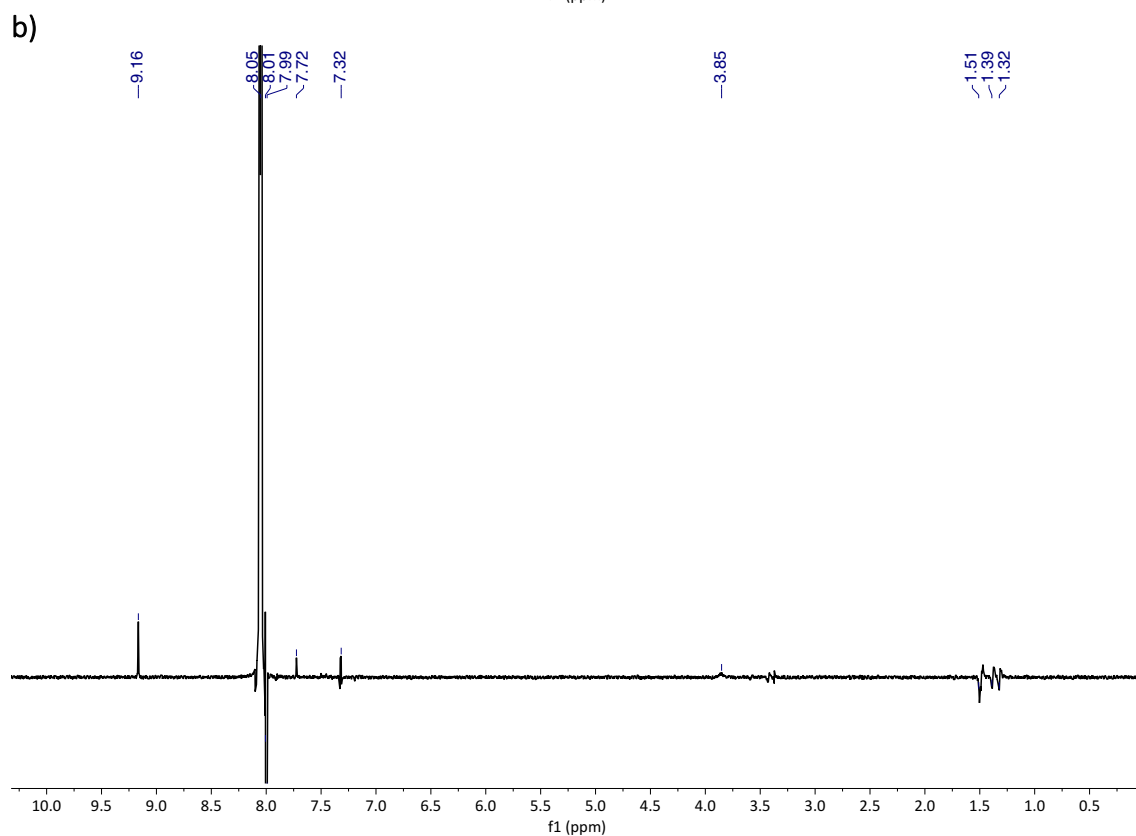
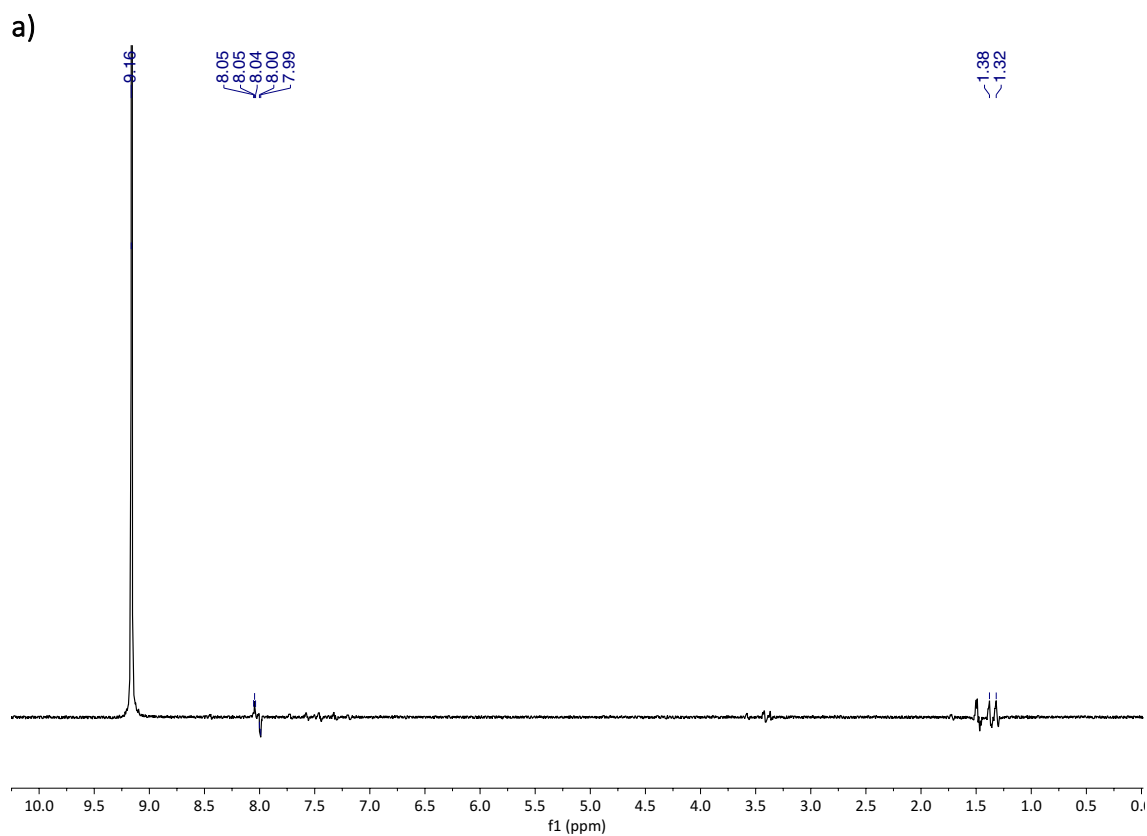
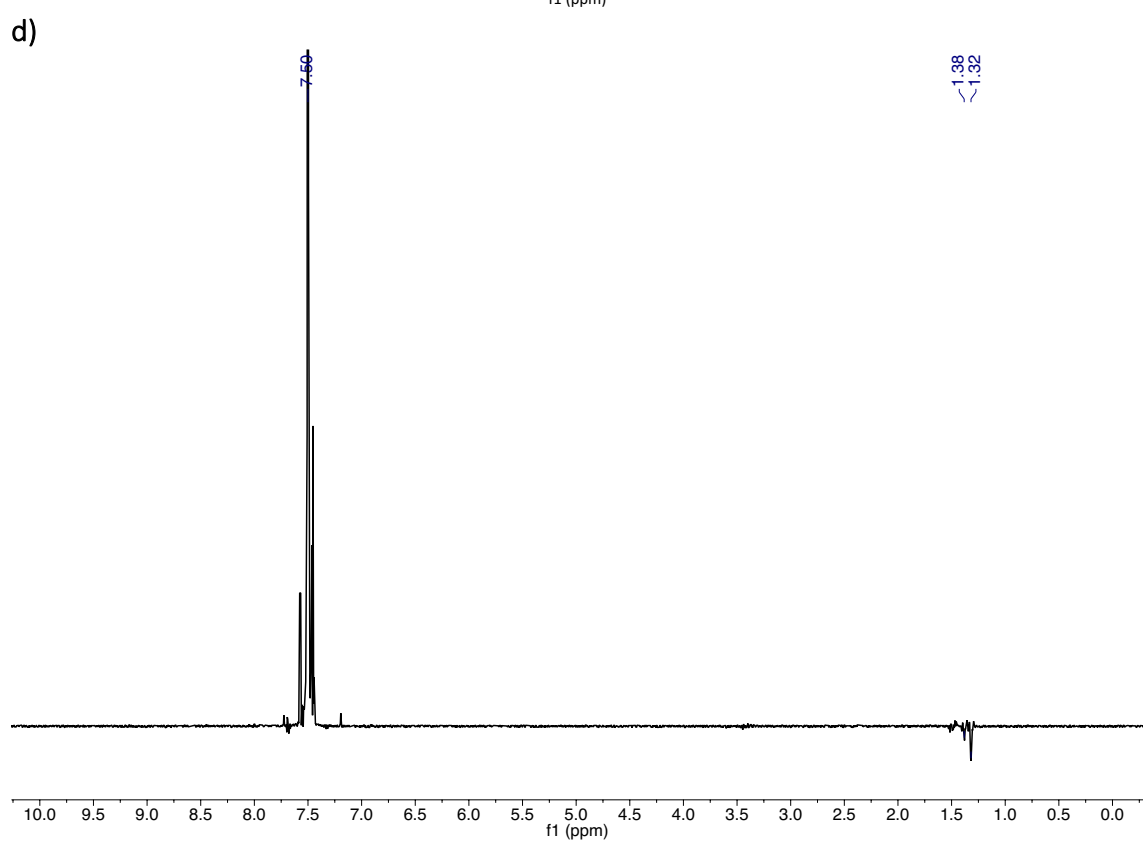
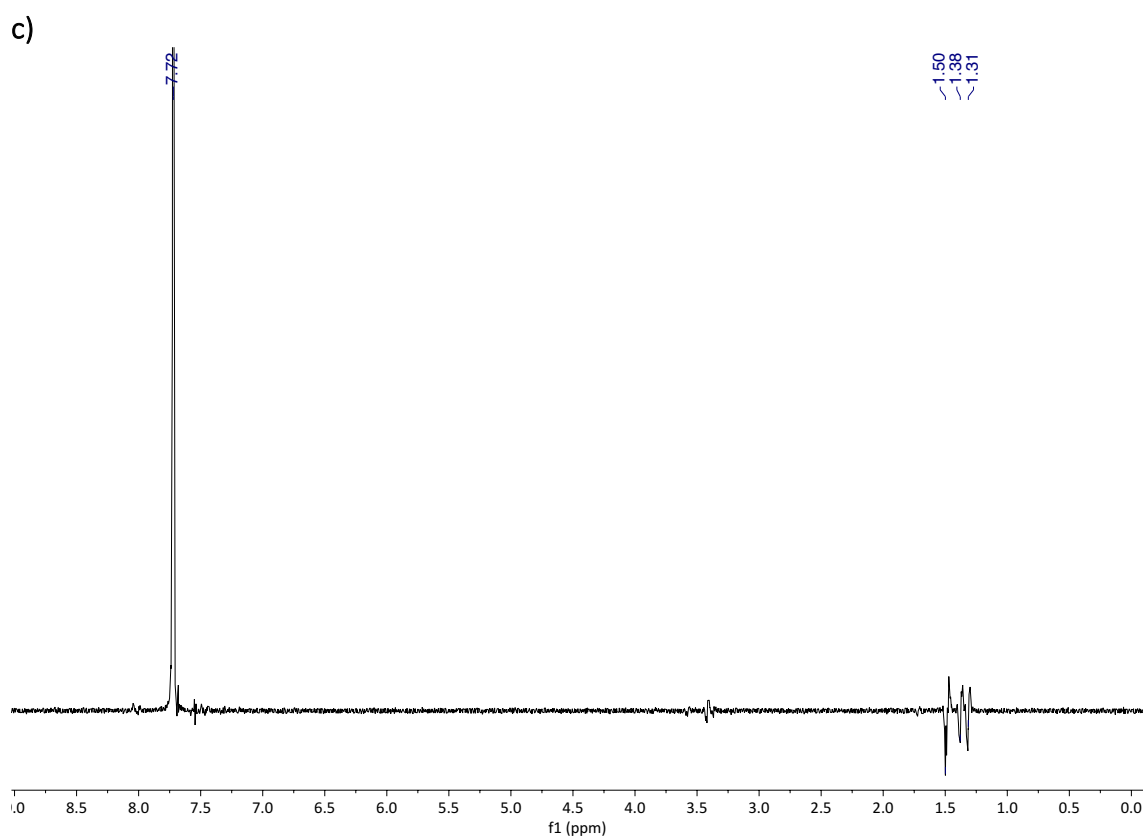


Figure S61. 2D-ROESY of mono-**4** in THF- d_8 at 268 K showing (a) all NH-NH cross peaks: NH(6)-NH(5), NH(5)-NH(4), NH(4)-NH(3), NH(3)-NH(2), NH(2)-NH(1), (b) OMe(1)-NH(1), OMe(1)-Ar(1) and OMe(1)-NH(2), (c) all Aib-NH cross peaks: NH(6)-Aib₅, NH(5)-Aib₃, NH(5)-Aib₄, NH(5)-Aib₅, NH(4)-Aib₂, NH(4)-Aib₃, NH(4)-Aib₅, NH(3)-Aib₄, NH(3)-Aib₅, NH(2)-Aib₂, NH(2)-Aib₃, NH(2)-Aib₄ and NH(1)-Aib₂, (d) NH(6)-CH₂ (gly), NH(5)-CH₂ (gly).

1D-NMR experiments (ROESY) of mono-**4** in THF- d_8

1D-NMR experiments (ROESY) of mono-**4** in THF- d_8 were carried out where selective signals were irradiated (positive signal) in order to observe the coupled protons of the molecule that are closed in space (negative signal).





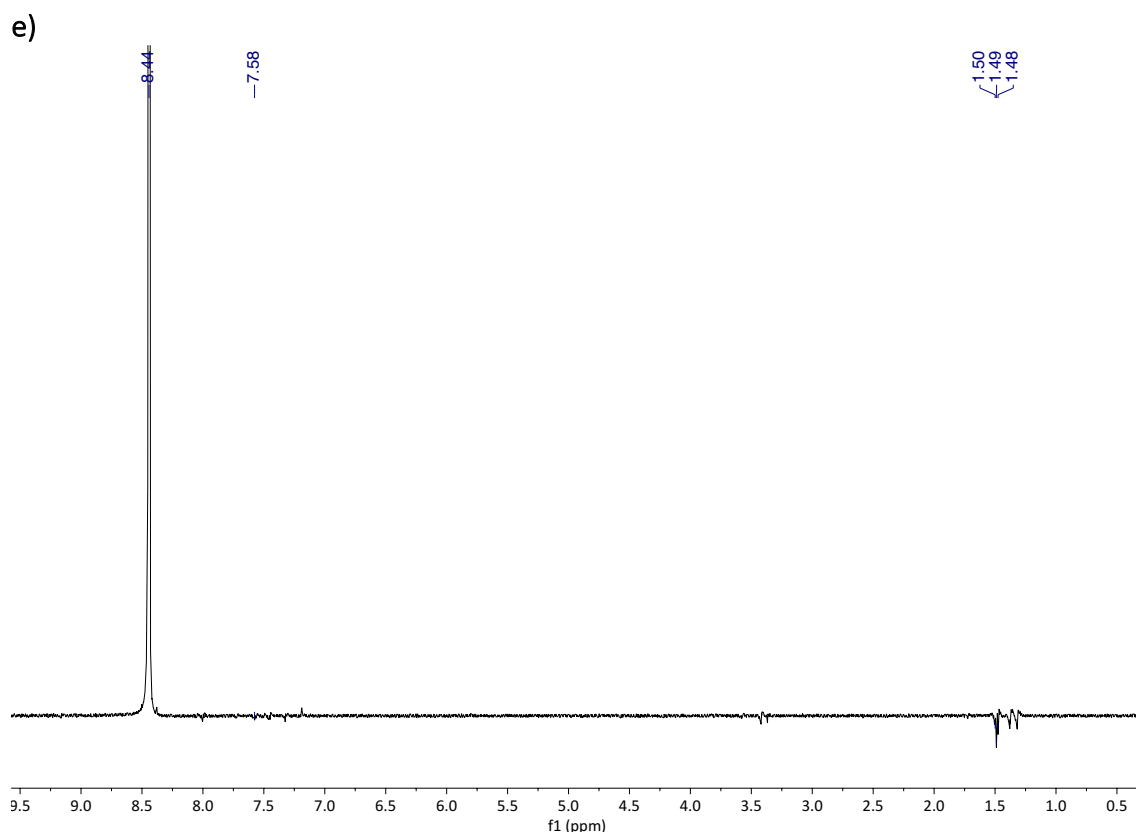


Figure S62. 1D-NMR experiments (ROESY) of mono-**4** in THF- d_8 at 268 K showing the cross peaks that (a) NH(6) is close in space to protons of Ar(6), NH(5), Aib₄ and Aib₅, (b) NH(5) is close in space to protons NH(6), Ar(6), NH(4), CH₂ (gly), Aib₃, Aib₄ and Aib₅, (c) NH(4) is close in space to protons Aib₃, Aib₄ and Aib₅, (d) NH(3) is close in space to protons Aib₃ and Aib₄, (e) NH(1) is close in space to protons Ar(1), OMe(1), Aib₂ and Aib₃.

1D and 2D-NOESY NMR experiments of mono-**4** in CDCl₃ show in a similar manner to the other (*S*)-MTPA-(Aib)_{*n*}-gly-PA (*n* = 1, 2, 3) oligomers studied strong sequential NH-NH and OMe(1)-NH(1) cross peaks, confirming the presence of *ap*_{OMe} and *M*-3₁₀ helical structure of the polymer in solution.

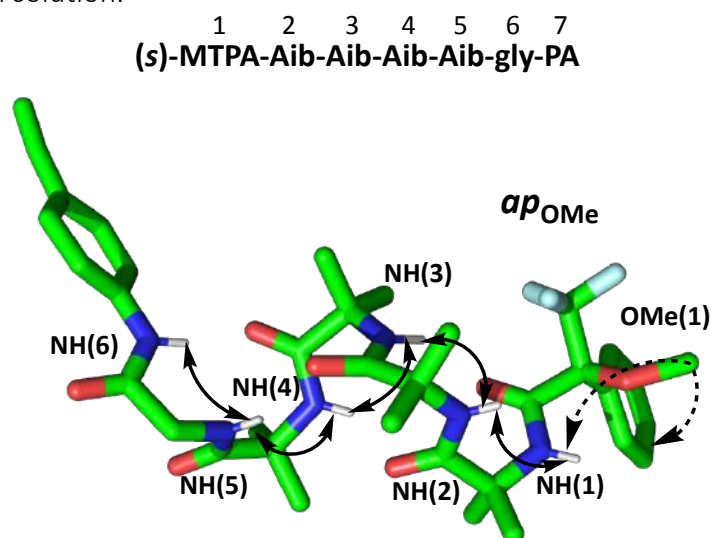


Figure S63. Representative NOEs of mono-**4** in CDCl₃.

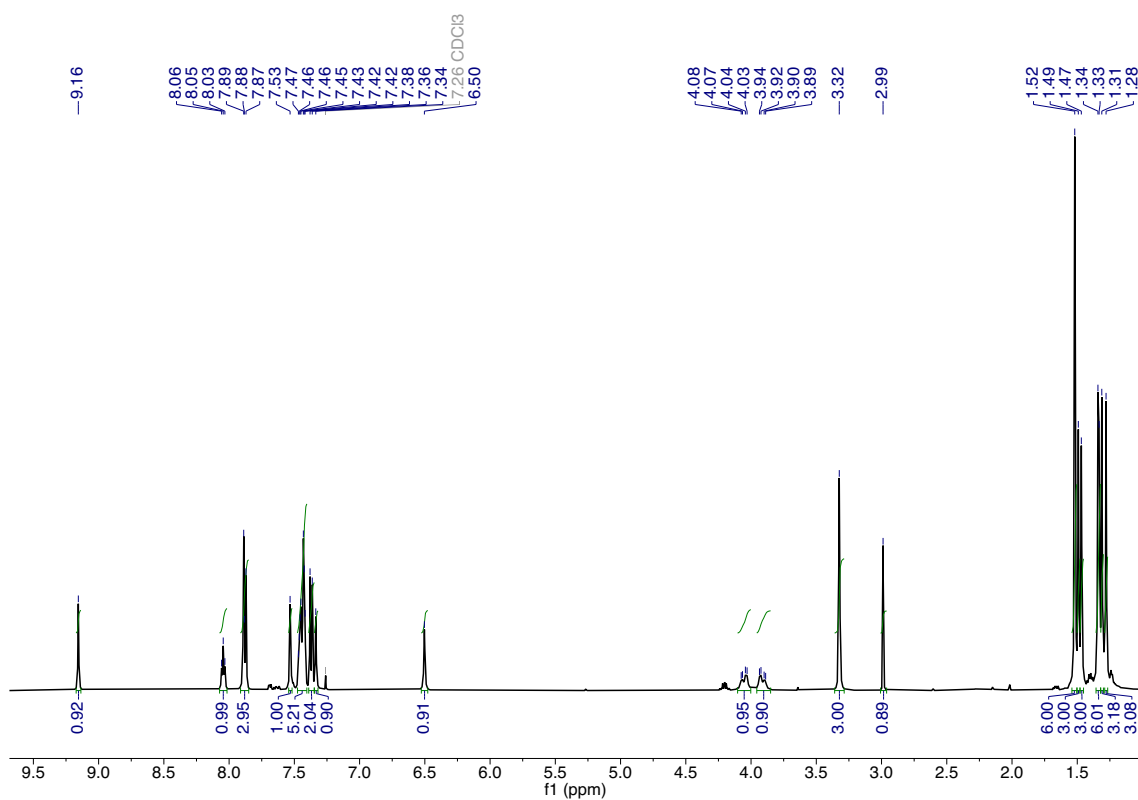
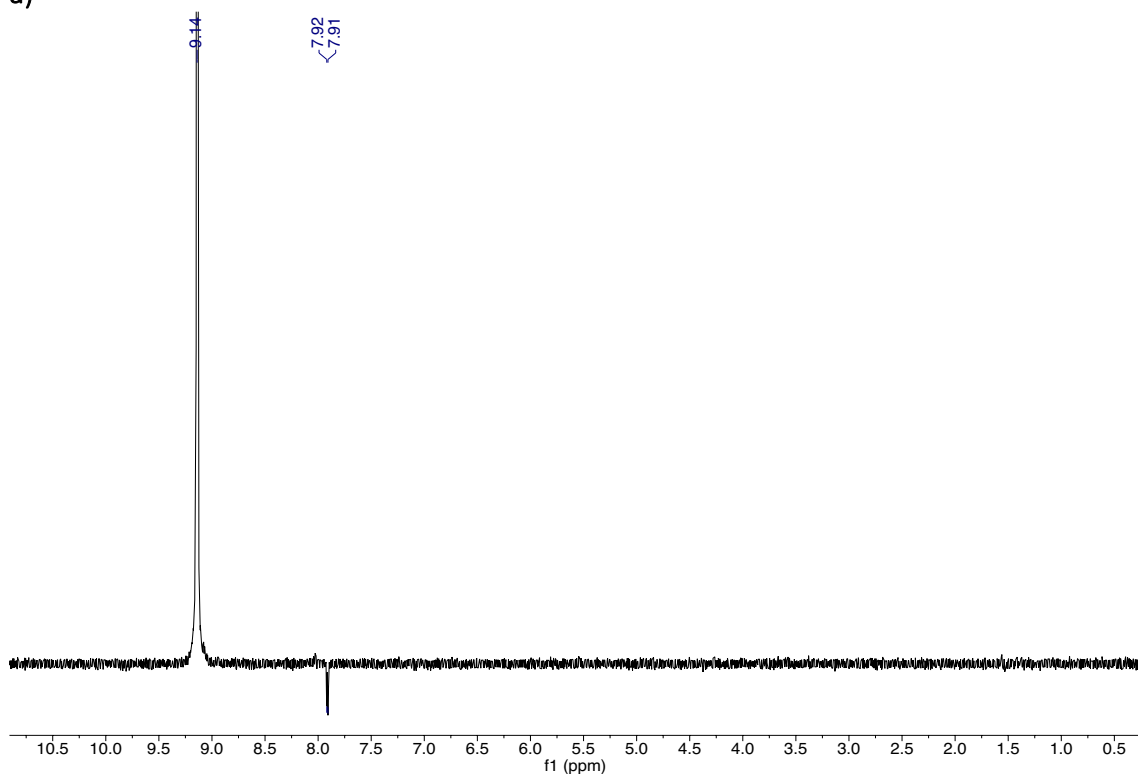


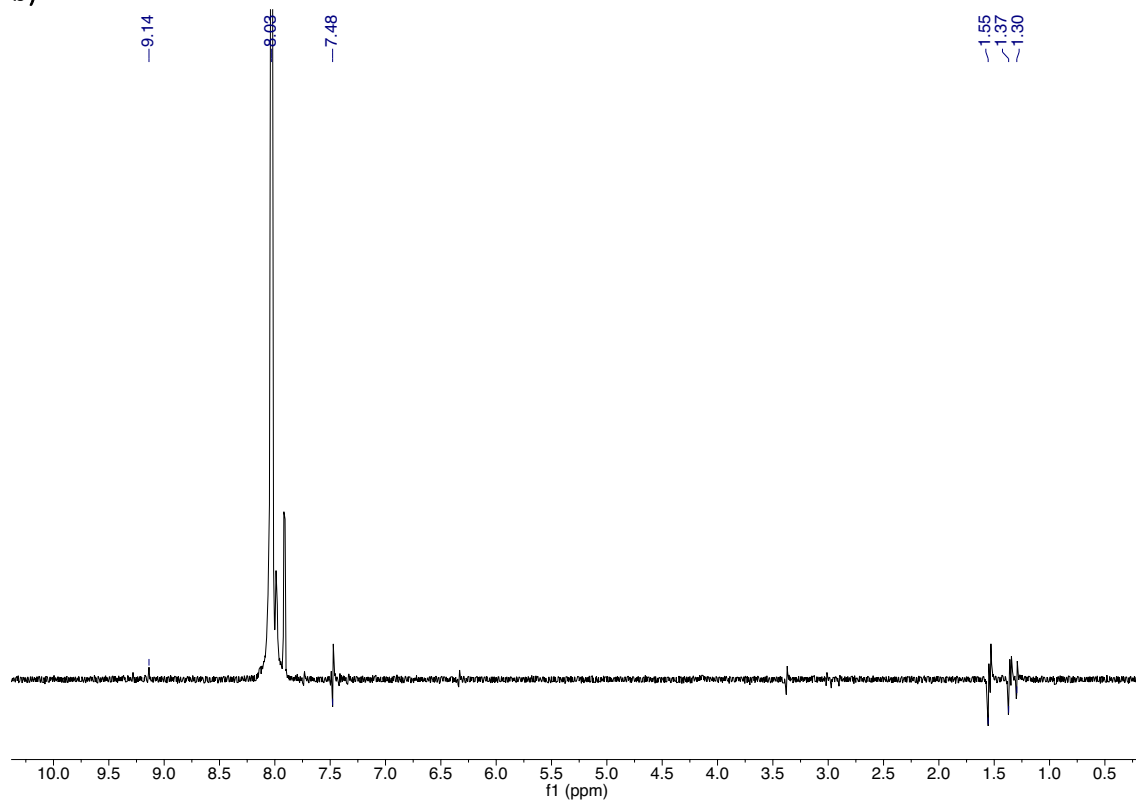
Figure S64. ¹H NMR of mono-4 in CDCl₃ at 268 K.

¹H NMR (500 MHz, CDCl₃) δ = 9.16 (s, 1H), 8.05 (t, J =6.3 Hz, 1H), 7.88 (d, J =8.8 Hz, 3H), 7.53 (s, 1H), 7.49 – 7.40 (m, 5H), 7.37 (d, J =8.4 Hz, 2H), 7.34 (s, 1H), 6.50 (s, 1H), 4.05 (dd, J =17.0 Hz, 6.2 Hz, 1H), 3.91 (dd, J =17.7 Hz, 5.8 Hz, 1H), 3.32 (s, 1H), 2.99 (s, 1H), 1.52 (s, 6H), 1.49 (s, 3H), 1.47 (s, 3H), 1.34 (d, J =4.5 Hz, 6H), 1.31 (s, 3H), 1.28 (s, 3H).

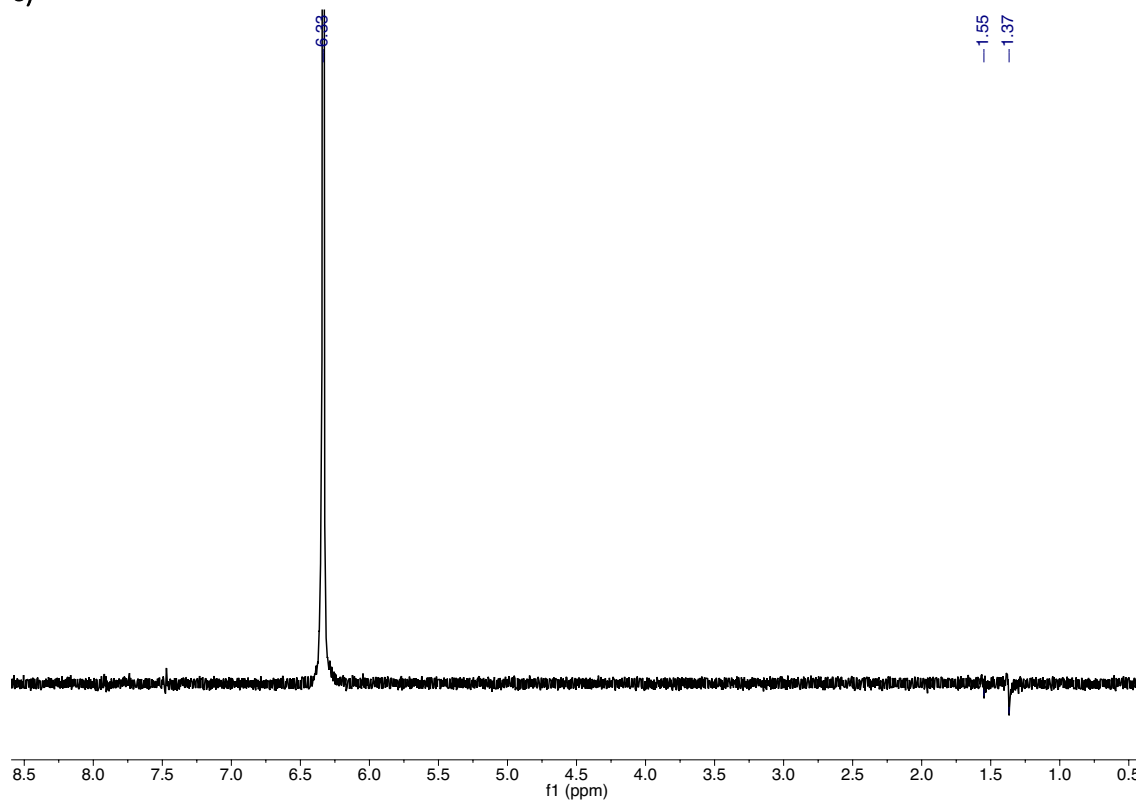
a)



b)



c)



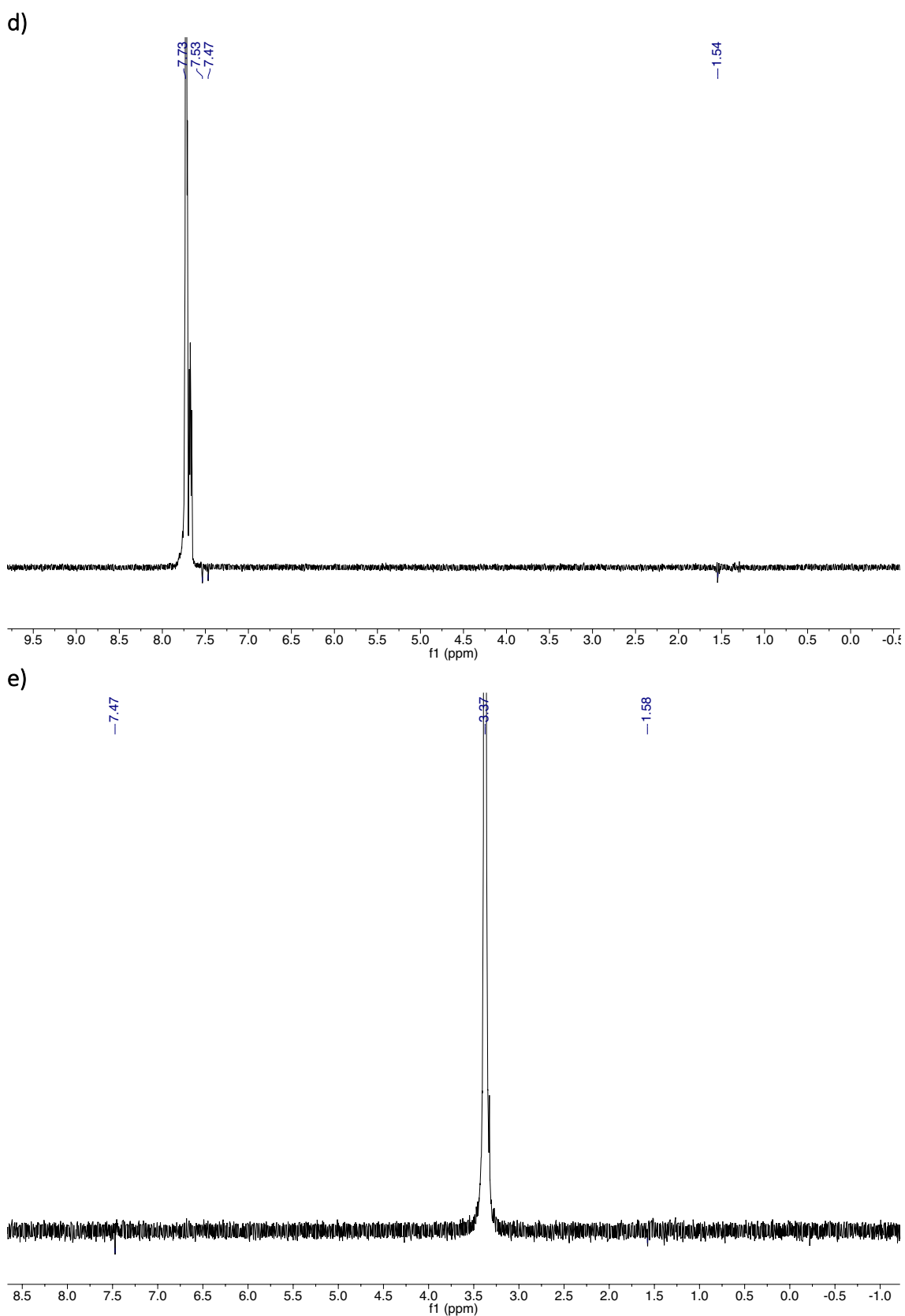


Figure S65. 1D-NMR experiments (ROESY) of mono-**4** in CDCl_3 at 268 K showing the cross peaks that (a) NH(6) is close in space to protons of Ar(6), (b) NH(5) is close in space to protons NH(6), NH(4), Aib₅, Aib₄ and Aib₃, (c) NH(2) is close in space to protons Aib₃ and Aib₂, (d) NH(1) is close in space to protons Ar(1) and Aib₂, (e) OMe(1) is close in space to protons Ar(1) and Aib₂.

EXPERIMENTAL SECTION

CHAPTER IV

1. Materials and methods

CD measurements were done in a Jasco-720.

UV spectra were registered in a Jasco-630.

The optical rotation was measured in a Jasco P-2000.

NMR experiments were measured in a Varian 300 operating at 300 MHz for proton NMR and 75 MHz for carbon. CDCl_3 signal ($\delta = 77.2$ ppm) was used as standard for ^{13}C experiments.

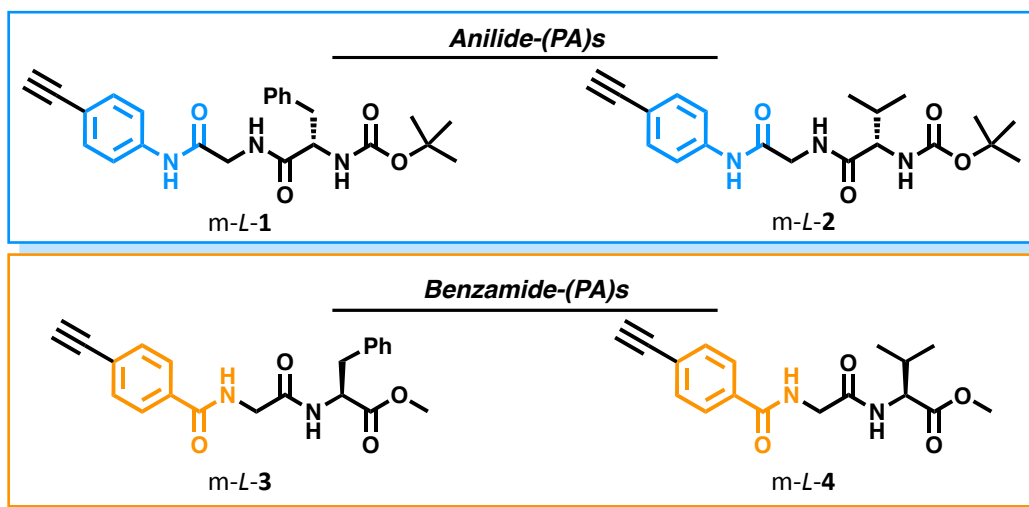
FT-IR measurements were carried out on a Bruker IFS-66v while Raman spectra were carried out in a Renishaw confocal Raman spectrometer (Invia Reflex model), equipped with two lasers (diode laser 785 nm and Ar laser 514 nm).

DSC traces were obtained in a DSC Q200 Tzero Technology (TA Instruments, New Castle, UK), equipped with a refrigerated cooling system RCS90 (TA Instruments, New Castle, UK), using a Tzero low-mass aluminium pan.

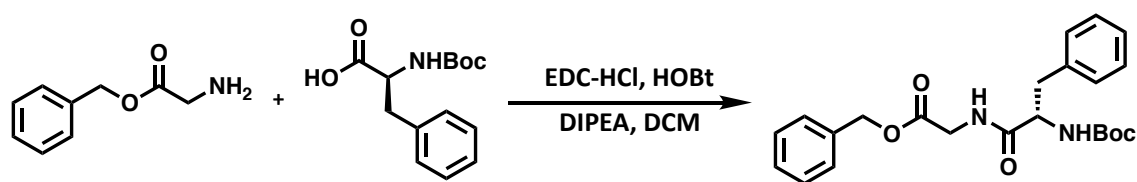
TGA traces were obtained in a TGA Q5000 (TA Instruments, New Castle, UK) using a platinum pan.

GPC studies were carried out in a Waters Alliance equipped with Phenomenex GPC columns.

2. Synthesis of monomers



The monomers employed in this work have been prepared according the following synthetic scheme.

Benzyl (tert-butoxycarbonyl)-L-phenylalanylglycinate (**1**)

N-(3-Dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (EDC·HCl, 0.69 g, 1.05 equiv), Hydroxybenzotriazole (HOBT, 0.49 g, 1.05 equiv), (tert-butoxycarbonyl)-*L*-phenylalanine (1.00 g, 1.10 equiv) and diisopropyltriethylamine (DIPEA, 0.72 mL, 1.20 equiv) were dissolved in 40 mL of DCM, and the mixture was stirred for 20 min to activate the acid. Then, benzyl glycinate (1.16 g, 1.00 equiv) and diisopropyltriethylamine (DIPEA, 0.60 mL, 1.00 equiv) were added and the reaction mixture was stirred overnight. Then the solvent was evaporated at reduced pressure and the crude was diluted in DCM, the organic layer was washed with HCl 1M, saturated solution of NaHCO₃ and brine. The combined organic layers were dried over anhyd Na₂SO₄, filtered and the solvent was evaporated at reduced pressure. The crude product was chromatographed on silica gel (40-63 mesh) with hexane/ethyl acetate (4/6) as eluent obtaining **1** in 53 % yield respectively of pure product (0.75 g).

Benzyl (tert-butoxycarbonyl)-L-phenylalanylglycinate (**1**)

^1H NMR (300 MHz, CDCl_3) δ (ppm): 7.40 – 7.16 (m, 10H), 6.91 (t, $J=5.4$ Hz, 1H), 5.33 (s, 1H), 5.14 (s, 2H), 4.49 (s, 1H), 4.01 (t, $J=5.2$ Hz, 2H), 3.14 (m, 1H), 2.98 (m, 1H), 1.37 (s, 9H).

^{13}C NMR (75 MHz, CDCl_3) δ (ppm): 172.0, 169.5, 155.6, 136.8, 135.2, 129.3, 128.6, 128.5, 128.3, 126.8, 80.1, 67.1, 55.5, 41.3, 38.5, 28.2.

HRMS (ESI) m/z calc for $\text{C}_{23}\text{H}_{28}\text{N}_2\text{O}_5$ $[\text{M}+\text{H}]$: 413.2013, found: 413.2071.

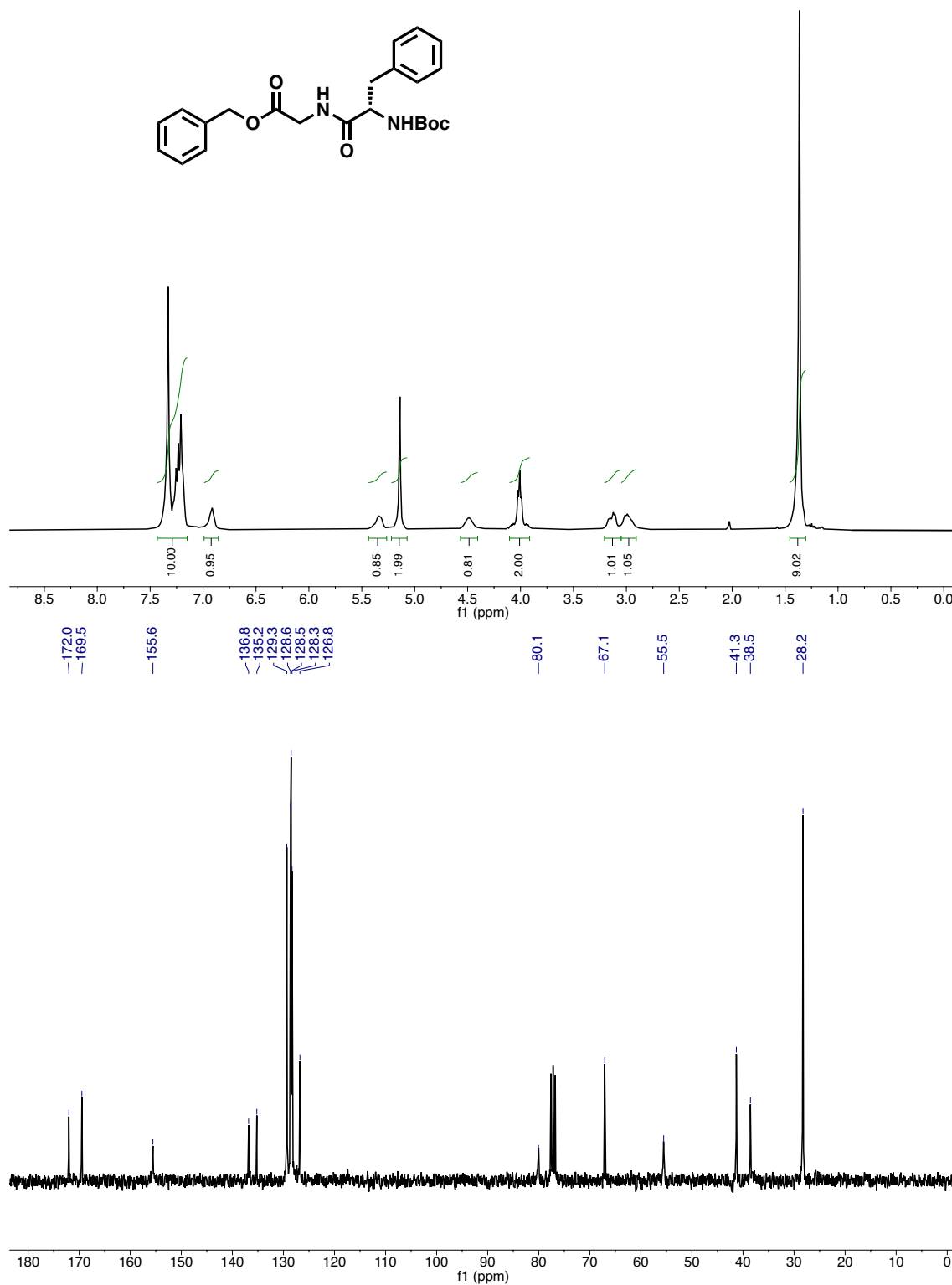
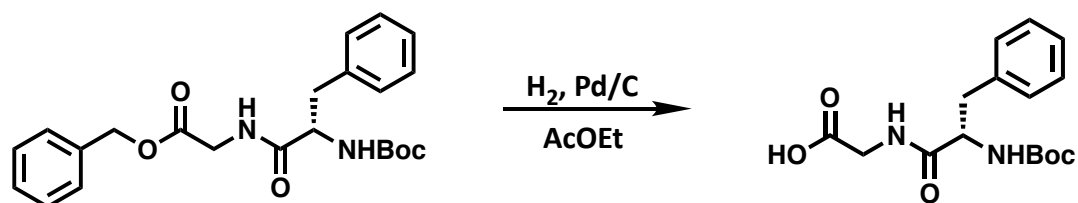


Figure S1. a) ^1H -NMR and b) ^{13}C -NMR spectra of **1** in CDCl_3 .

(tert-butoxycarbonyl)-L-phenylalanylglycine (**2**)

Pd/C (0.16 g) was suspended in 40 mL of EtOAc and submitted to three cycles of vacuum/purge with hydrogen. Then the Pd/C suspension was stirred under hydrogen atmosphere for 20 min and next a solution of benzyl (tert-butoxycarbonyl)-L-phenylalanylglycinate (**1**, 0.75 g, 1.82 mmol) in 15 mL of EtOAc was injected to the reaction vessel via syringe. After one hour TLC analysis showed no presence of the starting material and the suspension was filtered through celite and washed thoroughly with EtOAc, obtaining **2** in quantitative yield.

(tert-butoxycarbonyl)-L-phenylalanylglycine (**2**)

^1H NMR (300 MHz, CDCl_3) δ (ppm): 9.36 (s, 1H), 7.43 – 7.04 (m, 6H), 5.72 (s, 1H), 4.58 (s, 1H), 4.14 – 3.83 (m, 2H), 3.10 (d, $J=13.8$ Hz, 1H), 2.91 (d, 1H), 1.33 (s, 9H).

^{13}C NMR (75 MHz, CDCl_3) δ (ppm): 172.6, 172.2, 156.0, 136.6, 129.3, 128.5, 126.8, 80.4, 55.4, 41.4, 38.7, 28.2.

HRMS (ESI) m/z calc for $\text{C}_{16}\text{H}_{22}\text{N}_2\text{O}_5$ $[\text{M}+\text{H}]$: 323.1543, found: 323.1601.

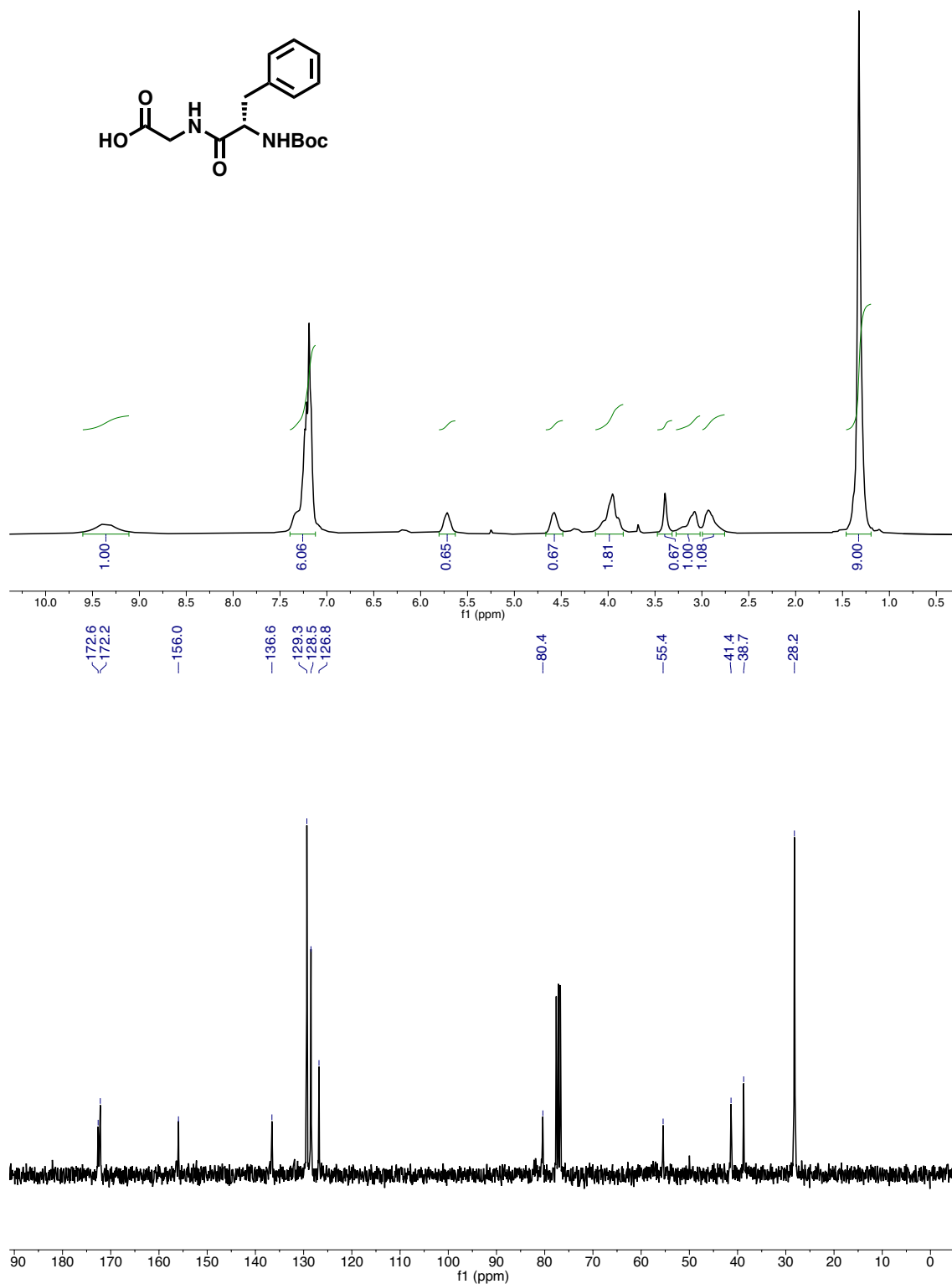
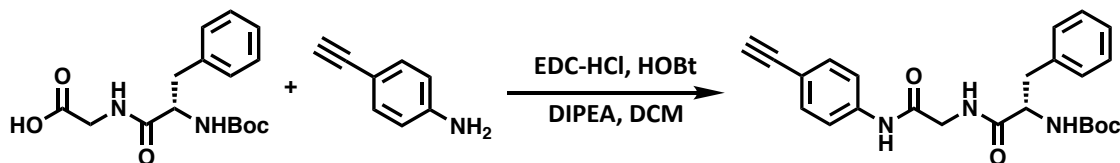


Figure S2. a) ^1H -NMR and b) ^{13}C -NMR spectra of **2** in CDCl_3 .

tert-butyl (S)-1-((2-((4-ethynylphenyl)amino)-2-oxoethyl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate [m-(L)-1]



N-(3-Dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (EDC·HCl, 0.25 g, 1.05 equiv), Hydroxybenzotriazole (HOBT, 0.18 g, 1.05 equiv), (tert-butoxycarbonyl)-*L*-phenylalanylglycine (**2**, 0.45 g, 1.10 equiv) and diisopropyltriethylamine (DIPEA, 0.27 mL, 1.20 equiv) were dissolved in 15 mL of DCM, and the mixture was stirred for 20 min to activate the acid. Then, 4-ethynylaniline (0.15 g, 1.00 equiv) was added and the reaction mixture was stirred overnight. Then, the reaction mixture was washed with HCl 1M (x3), saturated solution of NaHCO₃ and brine. The combined organic layers were dried over anhyd Na₂SO₄, filtered and the solvent was evaporated at reduced pressure. The crude product was chromatographed on silica gel (40-63 mesh) with hexane/ethyl acetate (6/4) as eluent obtaining m-(L)-1 in 53 % yield respectively of pure product (0.28 g).

tert-butyl (S)-1-((2-((4-ethynylphenyl)amino)-2-oxoethyl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate [m-(L)-**1**]

^1H NMR (300 MHz, CDCl_3) δ (ppm): 8.94 (s, 1H), 7.57 (d, $J=8.3$ Hz, 2H), 7.40 (d, $J=8.4$ Hz, 2H), 7.31 – 7.11 (m, 5H), 5.23 (s, 1H), 4.35 (q, $J=6.7$ Hz, 1H), 4.09 (dd, $J=16.6, 5.8$ Hz, 2H), 3.95 (dd, $J=16.7, 5.5$ Hz, 1H), 3.14 (dd, $J=13.8, 6.1$ Hz, 1H), 3.03 – 2.92 (m, 1H), 2.98 (s, 1H), 1.36 (s, 9H).

^{13}C NMR (75 MHz, CDCl_3) δ (ppm): 172.8, 167.6, 156.2, 138.5, 136.4, 133.1, 129.4, 129.1, 127.5, 120.0, 118.1, 83.7, 81.2, 77.1, 56.9, 44.4, 38.2, 28.5.

HRMS (ESI) m/z calc for $\text{C}_{24}\text{H}_{27}\text{N}_3\text{O}_4$ [$\text{M}+\text{Na}$]: 444.2016, found: 444.1894.

$\alpha_{\text{D}}^{20} = +25$ ($c = 10$ mg/mL, CHCl_3).

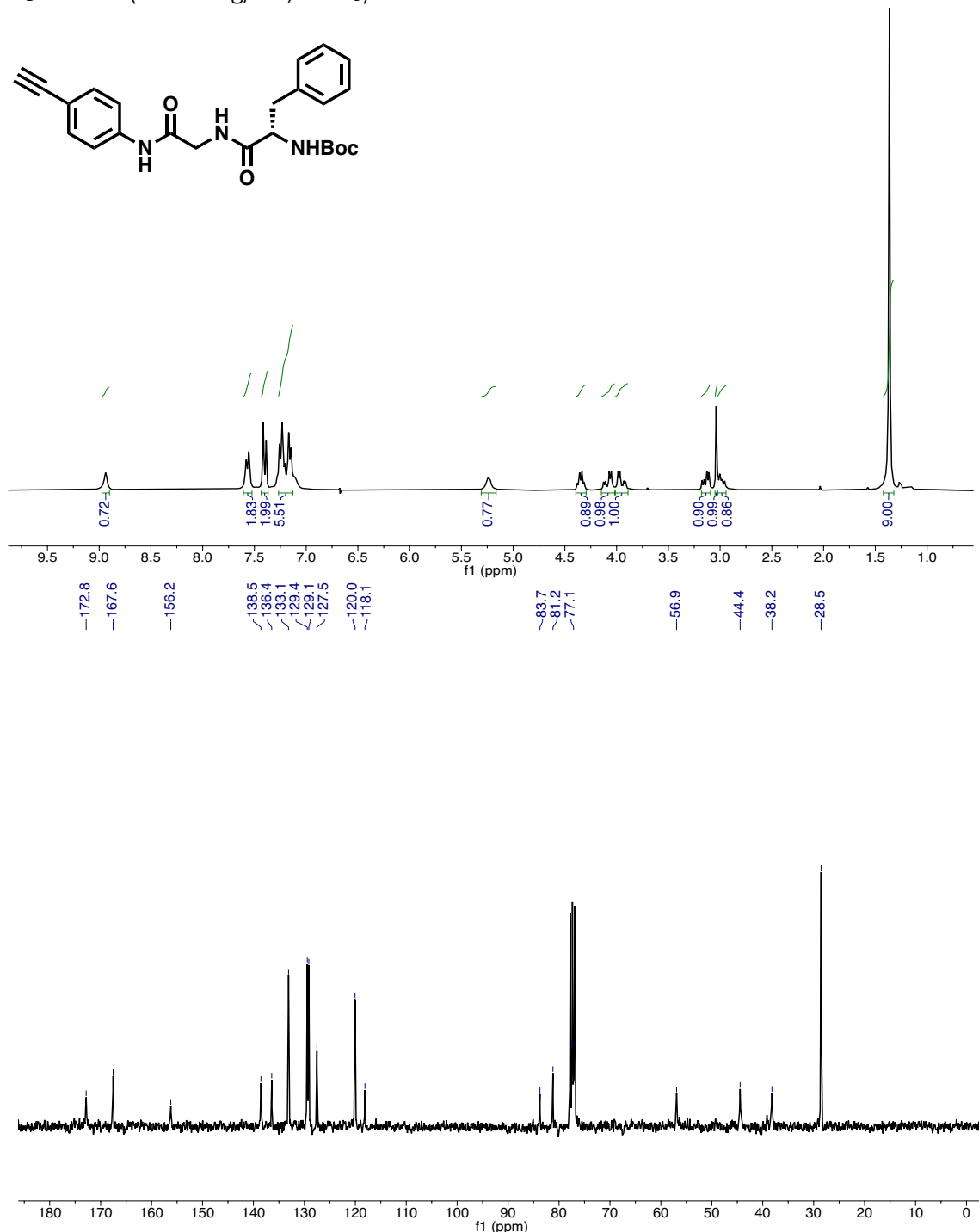
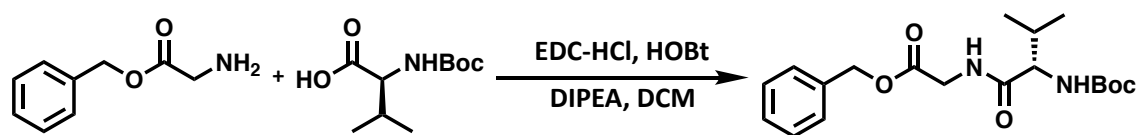


Figure S3. a) ^1H -NMR and b) ^{13}C -NMR spectra of m-(L)-**1** in CDCl_3 .

Benzyl (tert-butoxycarbonyl)-L-valylglycinate (**3**)

N-(3-Dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (EDC-HCl, 1.19 g, 1.05 equiv), Hydroxybenzotriazole (HOBT, 0.84 g, 1.05 equiv), (tert-butoxycarbonyl)-*L*-valine (1.42 g, 1.10 equiv) and diisopropyltriethylamine (DIPEA, 1.24 mL, 1.20 equiv) were dissolved in 60 mL of DCM, and the mixture was stirred for 20 min to activate the acid. Then, benzyl glycylglycinate (2.00 g, 1.00 equiv) and diisopropyltriethylamine (DIPEA, 1.00 mL, 1.00 equiv) were added and the reaction mixture was stirred overnight. Then the solvent was evaporated at reduced pressure and the crude was diluted in DCM, the organic layer was washed with HCl 1M, saturated solution of NaHCO₃ and brine. The combined organic layers were dried over anhyd Na₂SO₄, filtered and the solvent was evaporated at reduced pressure. The crude product was chromatographed on silica gel (40-63 mesh) with hexane/ethyl acetate (4/6) as eluent obtaining **3** in 63 % yield respectively of pure product (1.36 g).

Benzyl (tert-butoxycarbonyl)-L-valylglycinate (**3**)

^1H NMR (300 MHz, CDCl_3) δ (ppm): 7.36 – 7.29 (m, 5H), 6.93 (s, 1H), 5.24 (d, $J=9.0$ Hz, 1H), 5.14 (s, 2H), 4.19 – 3.91 (m, 3H), 2.12 (hept, $J=6.8$ Hz, 1H), 1.41 (s, 9H), 0.93 (dd, $J=14.9, 6.7$ Hz, 6H).

^{13}C NMR (75 MHz, CDCl_3) δ (ppm): 172.1, 169.5, 155.9, 135.1, 128.6, 128.5, 128.3, 79.8, 67.1, 59.7, 41.2, 31.0, 28.3, 19.2, 17.7.

HRMS (ESI) m/z calc for $\text{C}_{19}\text{H}_{28}\text{N}_2\text{O}_5$ $[\text{M}+\text{H}]$: 365,1998, found: 365,2071.

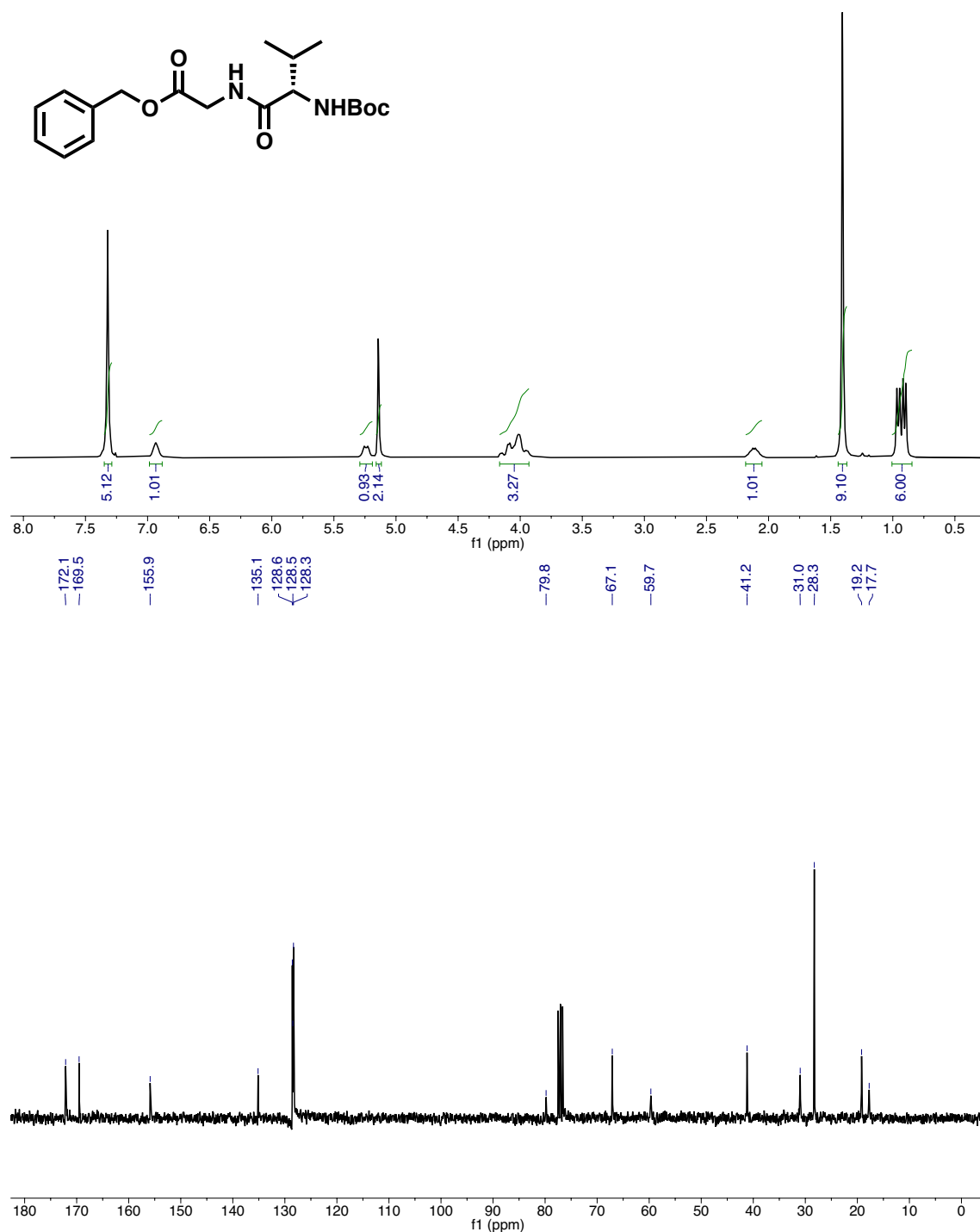
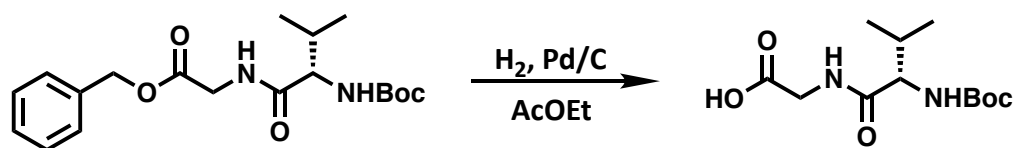


Figure S4. a) ^1H -NMR and b) ^{13}C -NMR spectra of **3** in CDCl_3 .

(tert-butoxycarbonyl)-L-valylglycine (**4**)

Pd/C (0.33 g) was suspended in 80 mL of EtOAc and submitted to three cycles of vacuum/purge with hydrogen. Then the Pd/C suspension was stirred under hydrogen atmosphere for 20 min and next a solution of benzyl (tert-butoxycarbonyl)-L-valylglycinate (**3**, 1.36 g, 3.75 mmol) in 30 mL of EtOAc was injected to the reaction vessel via syringe. After one hour TLC analysis showed no presence of the starting material and the suspension was filtered through celite and washed thoroughly with EtOAc, obtaining **4** in quantitative yield.

(tert-butoxycarbonyl)-*L*-valylglycine (**4**)

^1H NMR (300 MHz, CDCl_3) δ (ppm): 10.40 (s, 1H), 7.46 (s, 1H), 5.71 (d, $J=9.1$ Hz, 1H), 4.09 – 3.78 (m, 2H), 3.34 (s, 1H), 2.16 – 1.85 (s, 1H), 1.33 (s, 9H), 0.86 (t, $J=8.2$ Hz, 6H).

^{13}C NMR (75 MHz, CDCl_3) δ (ppm): 173.0, 172.1, 156.3, 80.0, 59.7, 41.1, 31.1, 28.2, 19.0, 18.0.

HRMS (ESI) m/z calc for $\text{C}_{12}\text{H}_{22}\text{N}_2\text{O}_5$ $[\text{M}+\text{H}]$: 275.1529, found: 275.1601.

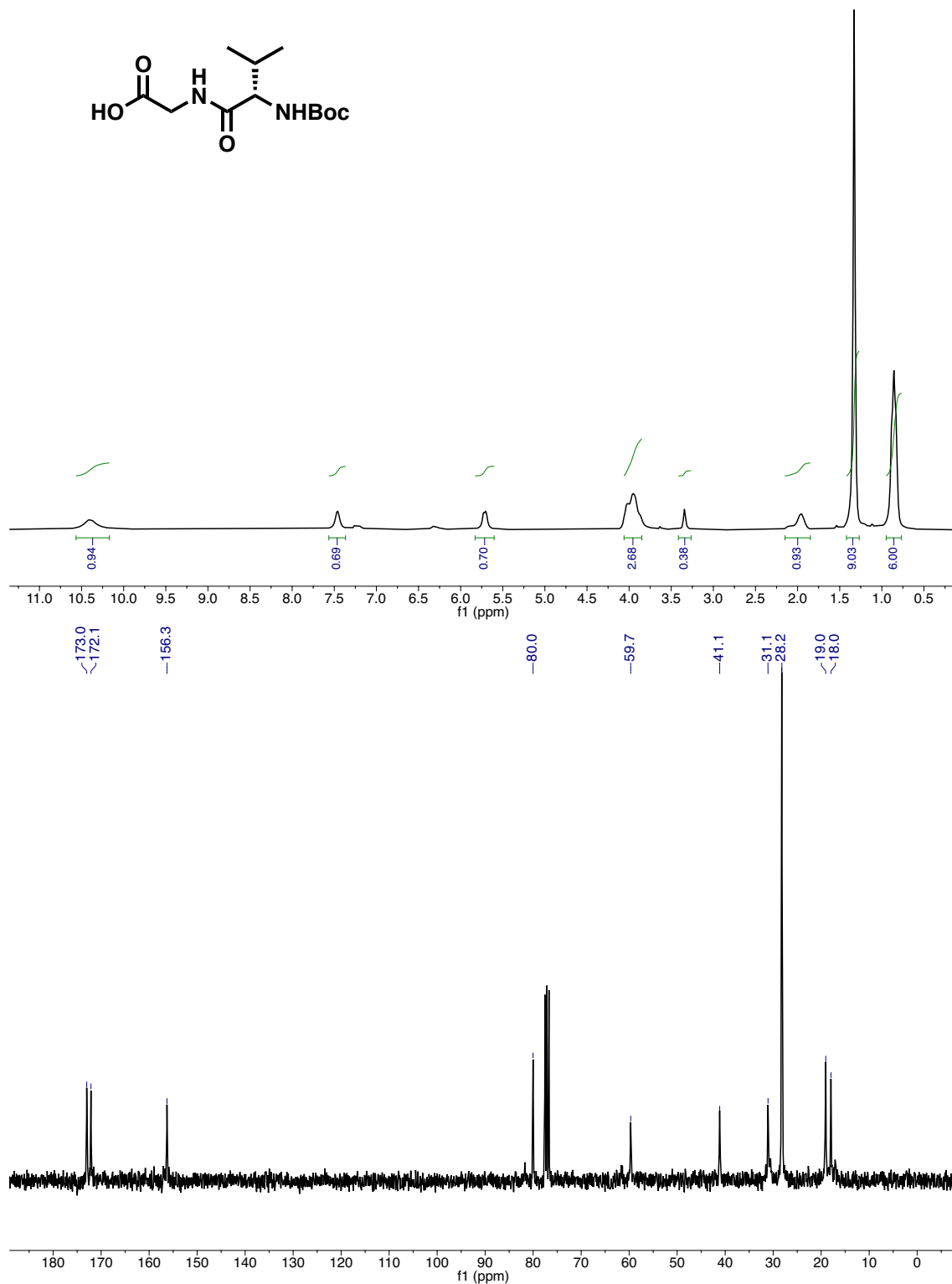
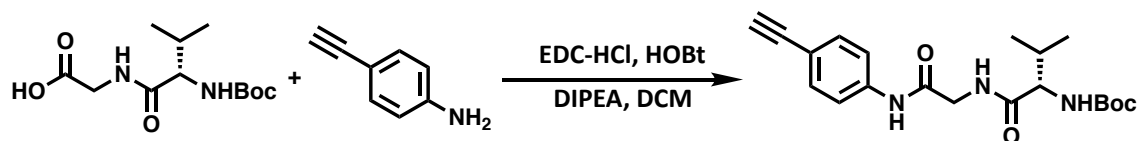


Figure S5. a) ^1H -NMR and b) ^{13}C -NMR spectra of **4** in CDCl_3 .

tert-butyl (S)-1-((2-((4-ethynylphenyl)amino)-2-oxoethyl)amino)-3-methyl-1-oxobutan-2-yl)carbamate [m-(L)-2]



N-(3-Dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (EDC·HCl, 0.33 g, 1.05 equiv), Hydroxybenzotriazole (HOBT, 0.23 g, 1.05 equiv), (tert-butoxycarbonyl)-*L*-valylglycine (**4**, 0.50 g, 1.10 equiv) and diisopropyltriethylamine (DIPEA, 0.34 mL, 1.20 equiv) were dissolved in 20 mL of DCM, and the mixture was stirred for 20 min to activate the acid. Then, 4-ethynylaniline (0.19 g, 1.00 equiv) was added and the reaction mixture was stirred overnight. Then, the reaction mixture was washed with HCl 1M (x3), saturated solution of NaHCO₃ and brine. The combined organic layers were dried over anhyd Na₂SO₄, filtered and the solvent was evaporated at reduced pressure. The crude product was chromatographed on silica gel (40-63 mesh) with hexane/ethyl acetate (1/1) as eluent obtaining m-(L)-2 in 59 % yield respectively of pure product (0.36 g).

tert-butyl (S)-1-((2-((4-ethynylphenyl)amino)-2-oxoethyl)amino)-3-methyl-1-oxobutan-2-yl)carbamate [m-(L)-2]

^1H NMR (300 MHz, CDCl_3) δ (ppm): 9.15 (s, 1H), 7.53 (m, 3H), 7.36 (d, $J=8.2$ Hz, 2H), 5.42 (d, $J=7.3$ Hz, 1H), 4.22 – 3.89 (m, 3H), 3.02 (s, 1H), 2.15 – 2.02 (hept, 1H), 1.38 (s, 9H), 0.92 (t, $J=7.5$ Hz, 6H).

^{13}C NMR (75 MHz, CDCl_3) δ (ppm): 173.4, 167.9, 156.6, 138.5, 133.1, 120.1, 118.1, 83.7, 80.7, 77.1, 61.1, 44.3, 30.9, 28.6, 19.6, 18.4.

HRMS (ESI) m/z calc for $\text{C}_{20}\text{H}_{27}\text{N}_3\text{O}_4$ [$\text{M}+\text{Na}$]: 396.2043, found: 396.1894.

$\alpha_{\text{D}}^{20} = +43$ ($c = 10$ mg/mL, CHCl_3).

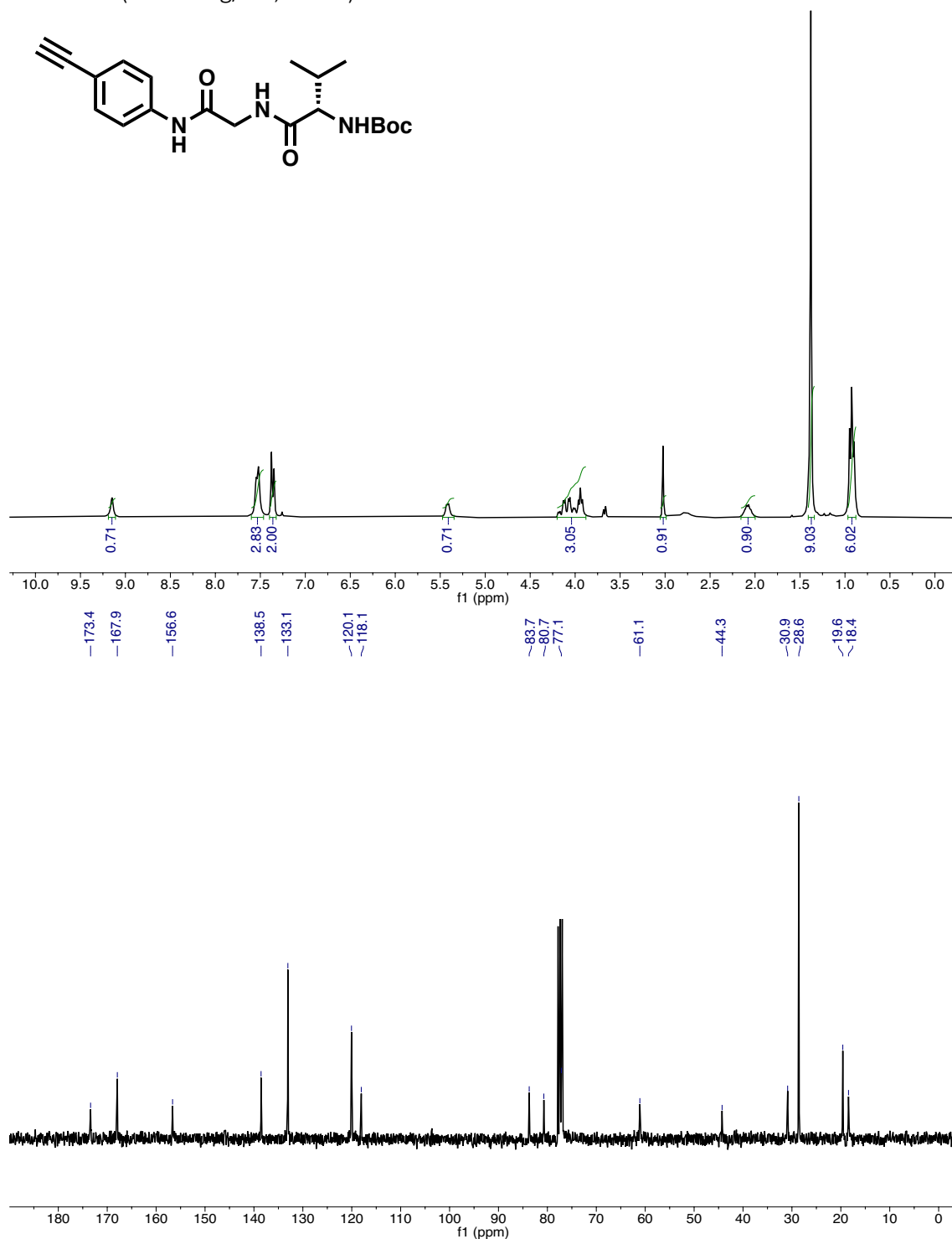
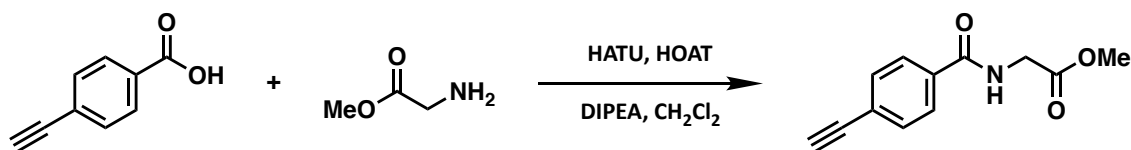


Figure S6. a) ^1H -NMR and b) ^{13}C -NMR spectra of m-(L)-2 in CDCl_3 .

Methyl (4-ethynylbenzoyl)glycinate (**5**)

2-(7-Aza-1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium (HATU, 2.49 g, 1.05 equiv), 1-Hydroxy-7-azabenzotriazole (HOAT, 0.89 g, 1.05 equiv), 4-ethynylbenzoic acid (2.00 g, 1.10 equiv) and diisopropyltriethylamine (DIPEA, 1.30 mL, 1.20 equiv) were dissolved in 60 mL of DCM, and the mixture was stirred for 20 min to activate the acid. Then, methyl glycinate (0.78 g, 1.00 equiv) was added and the reaction mixture was stirred overnight. Then the solvent was evaporated at reduced pressure and the crude was diluted in DCM, the organic layer was washed with HCl 1M, saturated solution of NaHCO₃ and brine. The organic layer was dried over anhyd. Na₂SO₄, filtered and the solvent was evaporated at reduced pressure. The crude product was chromatographed on silica gel (40-63 mesh) with hexane/ethyl acetate (7/3) as eluent obtaining **5** in 42 % yield (1.23 g).

Methyl (4-ethynylbenzoyl)glycinate (**5**)

^1H NMR (300 MHz, CDCl_3) δ (ppm): 7.72 (d, $J=8.6$ Hz, 2H), 7.46 (d, $J=8.7$ Hz, 2H), 7.16 (s, 1H), 4.15 (d, $J=5.3$ Hz, 2H), 3.72 (s, 3H), 3.20 (s, 1H).

^{13}C NMR (75 MHz, CDCl_3) δ (ppm): 170.5, 166.9, 133.5, 132.2, 127.1, 125.6, 82.7, 79.9, 52.4, 41.7.

HRMS (ESI) m/z calc for $\text{C}_{12}\text{H}_{11}\text{NO}_3$ [$\text{M}+\text{H}$]: 218.0817, found: 218.0812.

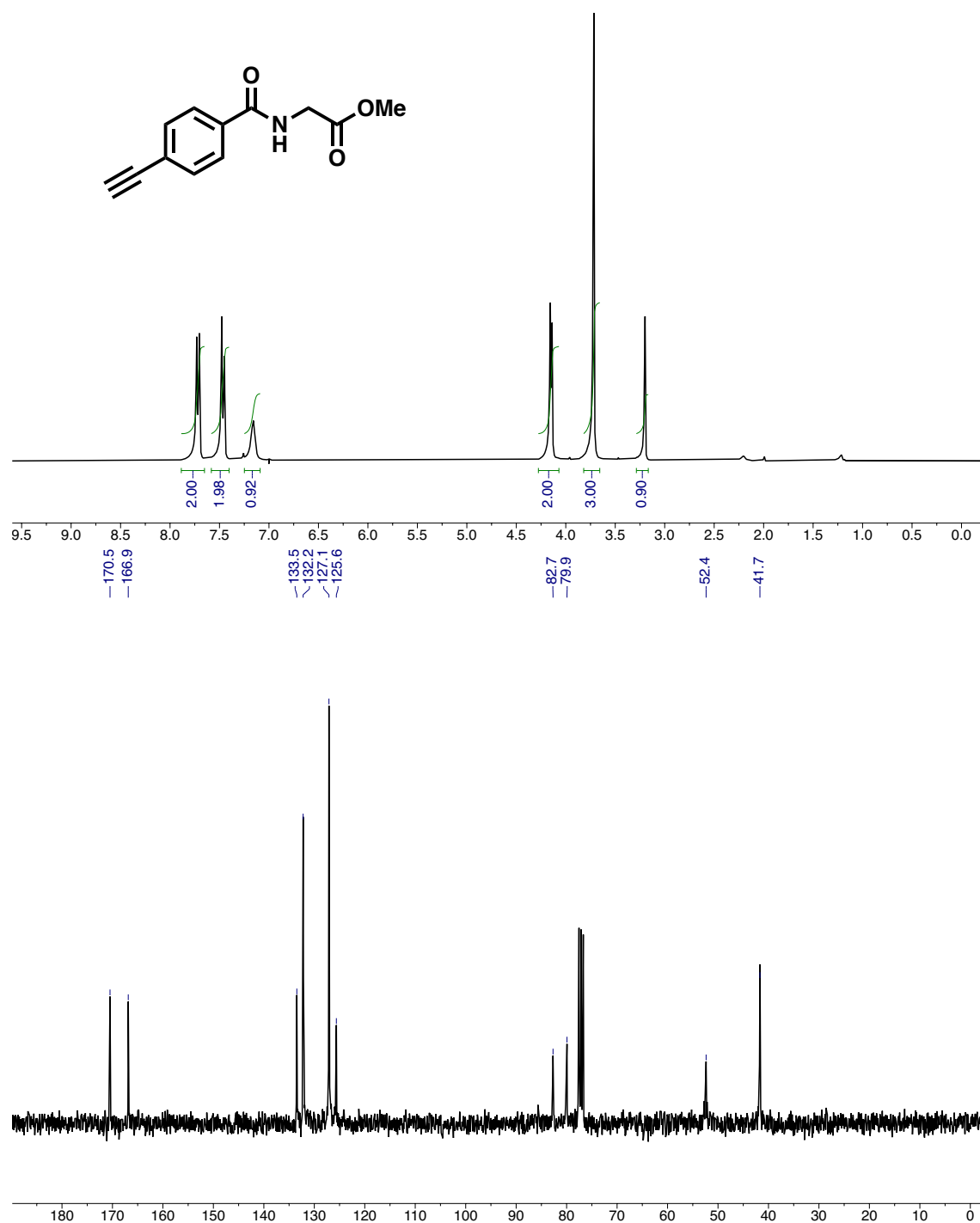
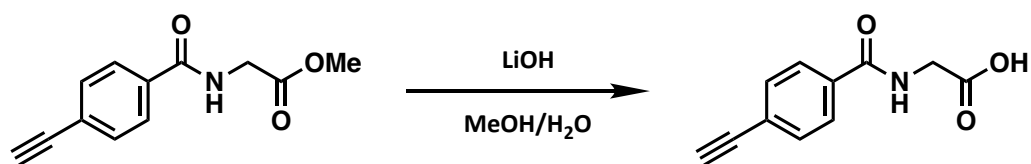


Figure S7. a) ^1H -NMR and b) ^{13}C -NMR spectra of **5** in CDCl_3 .

(4-ethynylbenzoyl)glycine (6)

Methyl (4-ethynylbenzoyl)glycinate (**5**, 0.56 g, 1.00 equiv) was dissolved in a mixture of MeOH/H₂O (95/5) (40 mL) and lithium hydroxide was added (LiOH, 0.31 g, 5.00 equiv). After 30 minutes the solvent was removed under reduced pressure. The residue was redissolved in a small amount of water and acidified to pH = 1. After extracting with ethyl acetate (4 times), the solution was dried over Na₂SO₄. Next, the organic solvent was removed obtaining the corresponding product in 98 % yield (**6**, 0.52 g).

(4-ethynylbenzoyl)glycine (**6**)

^1H NMR (300 MHz, CD_3OD) δ (ppm): 7.82 (d, $J=8.6$ Hz, 2H), 7.53 (d, $J=8.6$ Hz, 2H), 4.10 (s, 2H), 3.67 (s, 1H).

^{13}C NMR (75 MHz, CD_3OD) δ (ppm): 171.7, 168.2, 133.6, 131.7, 127.1, 125.8, 82.1, 79.8, 40.9.

HRMS (ESI) m/z calc for $\text{C}_{11}\text{H}_9\text{NO}_3$ [$\text{M}+\text{H}$]: 204.0661, found: 204.0656.

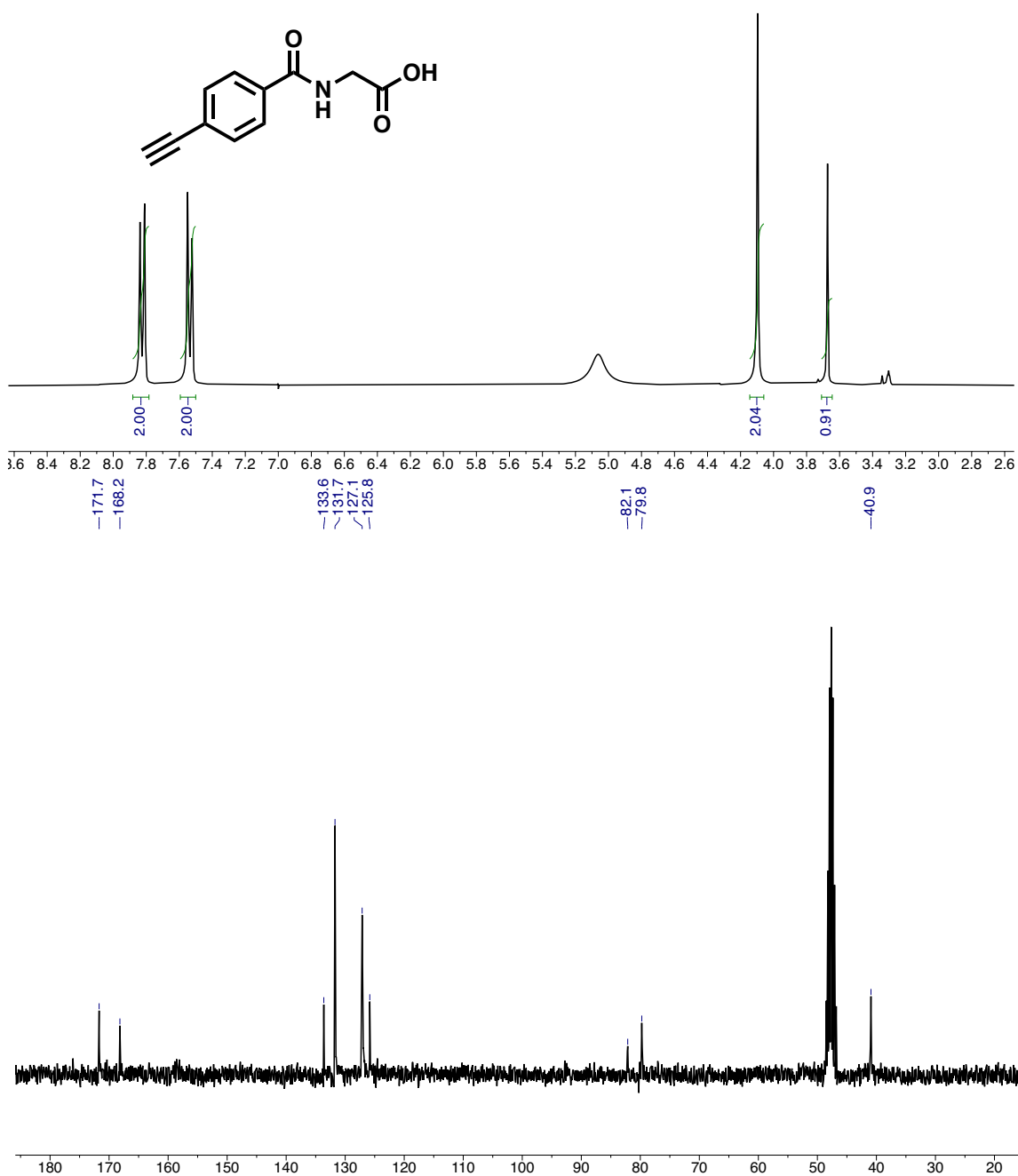
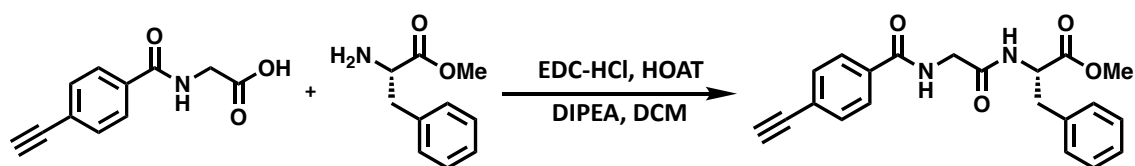


Figure S8. a) ^1H -NMR and b) ^{13}C -NMR spectra of **6** in CD_3OD .

Methyl (4-ethynylbenzoyl)glycyl-*L*-phenylalaninate [m-(*L*)-3]

N-(3-Dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (EDC·HCl, 0.08 g, 1.05 equiv), 1-Hydroxy-7-azabenzotriazole (HOAT, 0.06 g, 1.05 equiv), (4-ethynylbenzoyl)glycine (**6**, 0.09 g, 1.10 equiv) and diisopropyltriethylamine (DIPEA, 0.08 mL, 1.30 equiv) were dissolved in 10 mL of DCM, and the mixture was stirred for 20 min to activate the acid. Then, methyl *L*-phenylalaninate (0.09 g, 1.00 equiv) was added and the reaction mixture was stirred overnight. Then, the reaction mixture was washed with HCl 1M (x3), saturated solution of NaHCO₃ and brine. The organic layer was dried over anhyd Na₂SO₄, filtered and the solvent was evaporated at reduced pressure. The crude product was chromatographed on silica gel (40-63 mesh) with hexane/ethyl acetate (1/1) as eluent obtaining the corresponding product in 89 % yield [m-(*L*)-**3**, 0.11 g].

Methyl (4-ethynylbenzoyl)glycyl-L-phenylalaninate [m-(L)-3]

^1H NMR (300 MHz, CDCl_3) δ (ppm): 7.74 (d, 2H), 7.52 (m, 3H), 7.15 (m, 6H), 4.84 (q, 1H), 4.04 (t, 2H), 3.66 (s, 3H), 3.20 (s, 1H), 3.07 (qd, 2H).

^{13}C NMR (75 MHz, CDCl_3) δ (ppm): 171.9, 169.4, 167.0, 135.9, 133.3, 132.2, 129.2, 128.6, 127.3, 127.1, 125.6, 82.8, 79.9, 53.6, 52.4, 43.6, 37.8.

HRMS (ESI) m/z calc for $\text{C}_{21}\text{H}_{20}\text{N}_2\text{O}_4$ $[\text{M}+\text{H}]$: 365.1501, found: 365.1495.

$\alpha_{\text{D}}^{20} = +50$ ($c = 10$ mg/mL, CHCl_3).

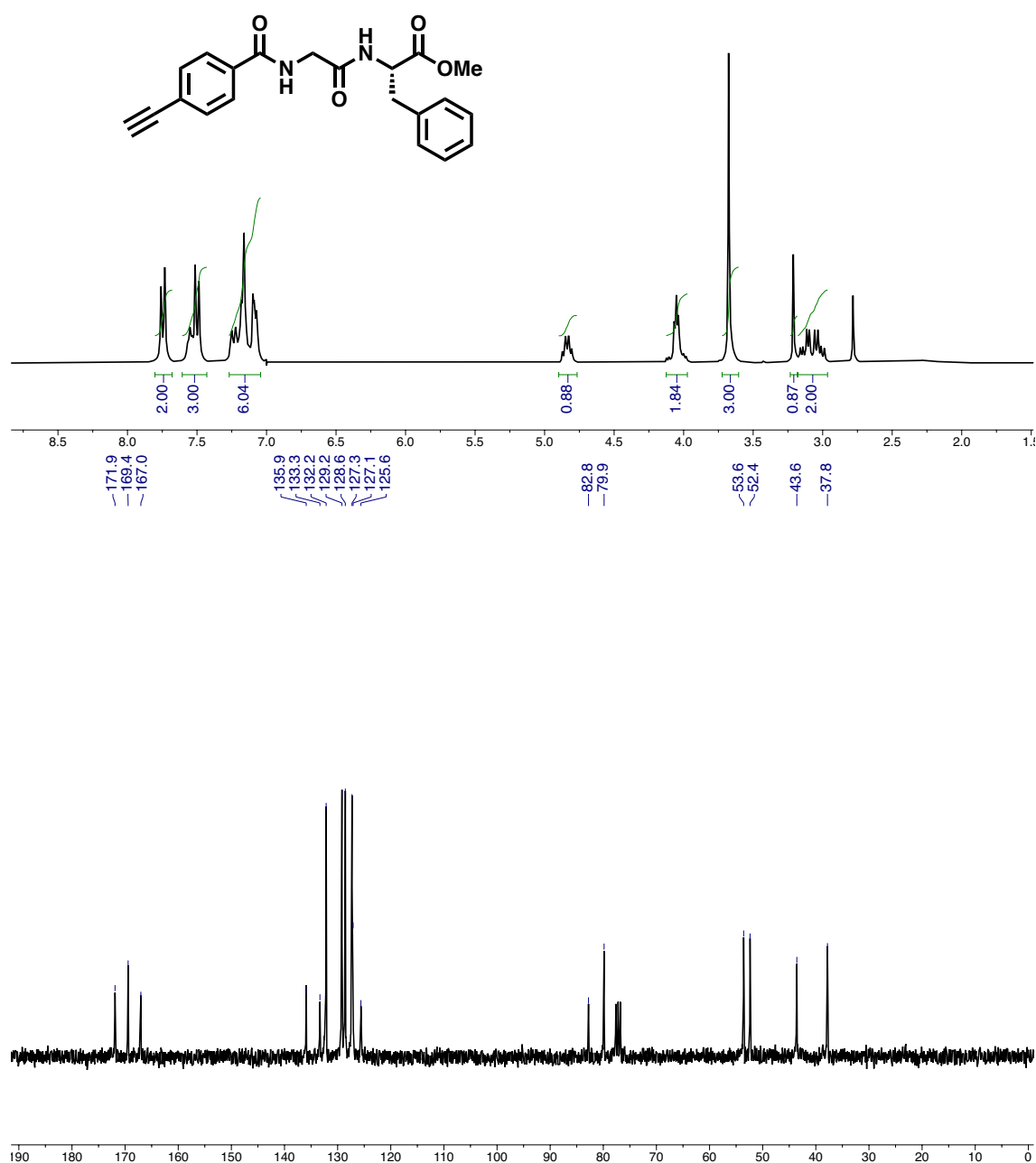
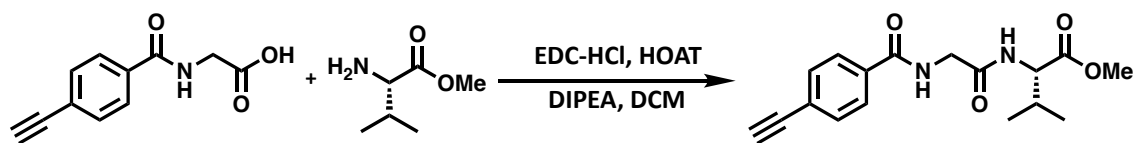


Figure S9. a) ^1H -NMR, and b) ^{13}C -NMR spectra of m-(L)-3 in CDCl_3 .

Methyl (4-ethynylbenzoyl)glycyl-*L*-valinate [m-(*L*)-4]

N-(3-Dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (EDC·HCl, 0.12 g, 1.05 equiv), 1-Hydroxy-7-azabenzotriazole (HOAT, 0.08 g, 1.05 equiv), (4-ethynylbenzoyl)glycine (**6**, 0.13 g, 1.10 equiv) and diisopropyltriethylamine (DIPEA, 0.12 mL, 1.30 equiv) were dissolved in 10 mL of DCM, and the mixture was stirred for 20 min to activate the acid. Then, methyl *L*-valinate (0.10 g, 1.00 equiv) was added and the reaction mixture was stirred overnight. Then, the reaction mixture was washed with HCl 1M (x3), saturated solution of NaHCO₃ and brine. The organic layer was dried over anhyd Na₂SO₄, filtered and the solvent was evaporated at reduced pressure. The crude product was chromatographed on silica gel (40-63 mesh) with hexane/ethyl acetate (1/1) as eluent obtaining the corresponding product in 82 % yield [m-(*L*)-**4**, 0.15 g].

Methyl (4-ethynylbenzoyl)glycyl-L-valinate [m-(L)-**4**]

^1H NMR (300 MHz, CDCl_3) δ (ppm): 7.77 (d, $J=8.4$ Hz, 2H), 7.68 (s, 1H), 7.49 (d, $J=8.4$ Hz, 2H), 7.36 (d, $J=8.6$ Hz, 1H), 4.51 (dd, $J=8.6, 5.1$ Hz, 1H), 4.22 (d, $J=5.0$ Hz, 2H), 3.70 (s, 3H), 3.19 (s, 1H), 2.16 (hept, $J=5.2$, 1H), 0.91 (dd, $J=9.9, 6.8$ Hz, 6H).

^{13}C NMR (75 MHz, CDCl_3) δ (ppm): 172.1, 169.4, 167.1, 133.4, 132.2, 127.2, 125.6, 82.7, 79.6, 57.6, 52.2, 43.7, 31.0, 19.0, 17.8.

HRMS (ESI) m/z calc for $\text{C}_{17}\text{H}_{20}\text{N}_2\text{O}_4$ [M+H]: 317.1501, found: 317.1493.

$\alpha_D^{20} = +5$ ($c = 5$ mg/mL, CHCl_3).

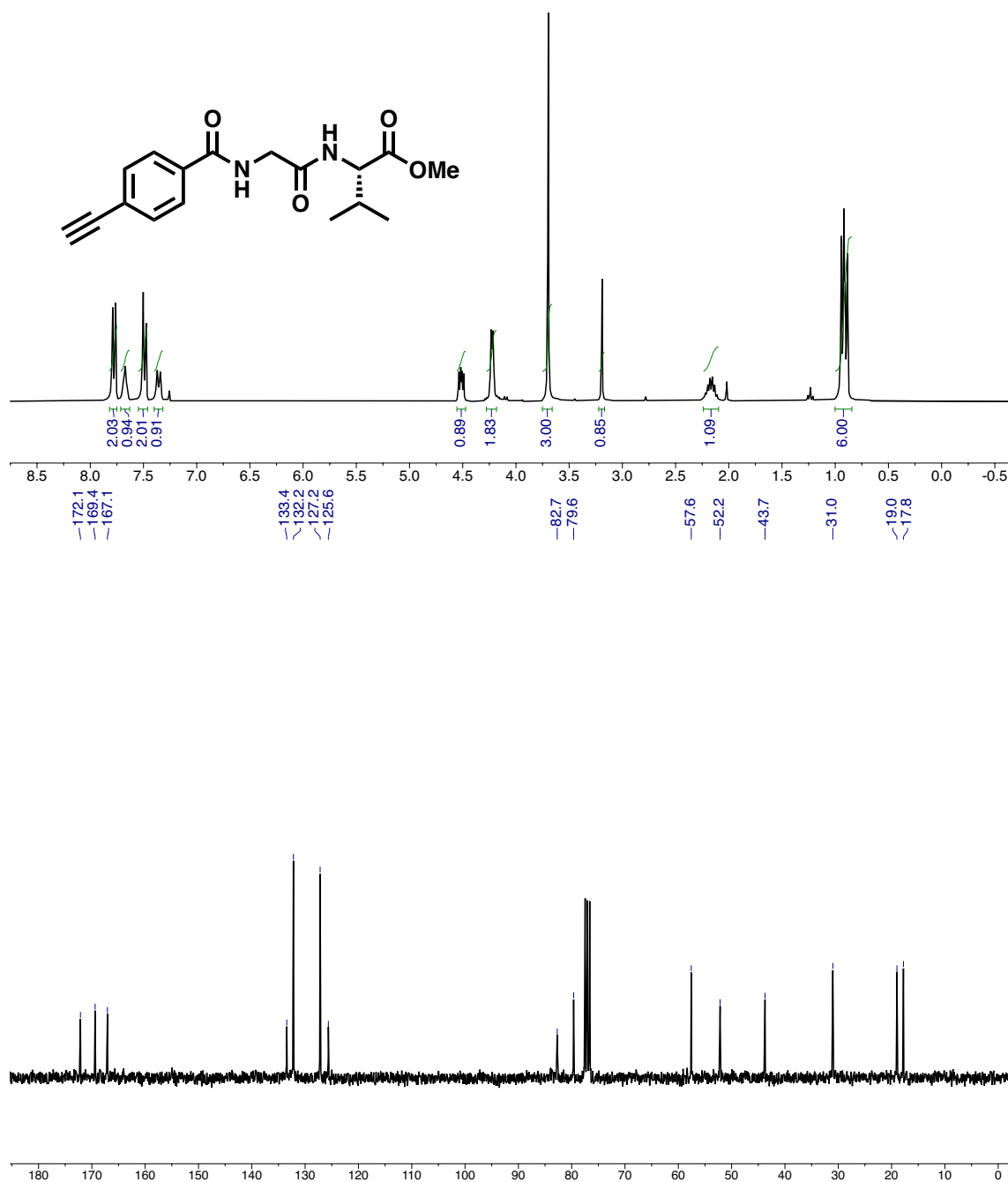
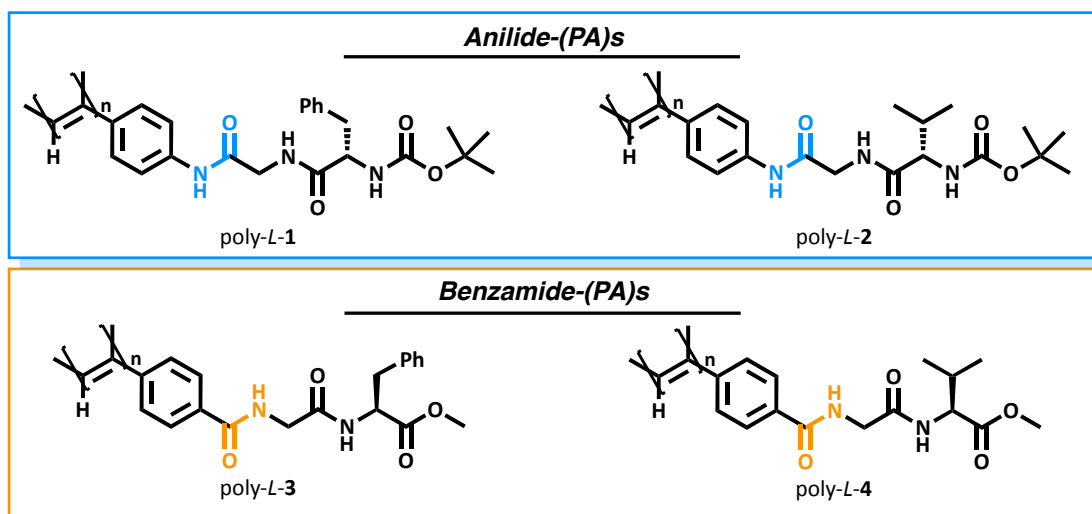


Figure S10. a) ^1H -NMR and b) ^{13}C -NMR spectra of m-(L)-**4** in CDCl_3 .

3. Synthesis of polymers



General procedure for polymerization

The reaction flask (sealed ampoule) was dried under vacuum and argon flushed for three times before monomer was added as a solid. Then, the flask was evacuated on a vacuum line and flushed with dry argon (3 times). Dry THF was added with a syringe and then triethylamine was added dropwise via syringe. A solution of rhodium norbornadiene chloride dimer, $[\text{Rh}(\text{nbd})\text{Cl}]_2$, in THF was added at 30°C. The reaction mixture was stirring at 30°C for 6h. Then, the resulting polymers were diluted in DCM and it was precipitated in a large amount of methanol, centrifuged (2 times), reprecipitated in hexane and centrifuged again.

Table S1. Polymerization conditions for poly-L-1—poly-L-4.

Polymer	Monomer (mg)	Monomer (mmol)	$[\text{Rh}(\text{nbd})\text{Cl}]_2$ (mg)	THF (ml)	Et_3N (μl)	Yield (%)
Poly-L-1	80	0.19	0.87	0.38	2.65	89
Poly-L-2	70	0.19	0.86	0.37	2.61	79
Poly-L-3	68	0.19	0.85	0.40	2.60	87
Poly-L-4	70	0.22	1.02	0.44	3.08	93

4. NMR Experiments

The polymers display NMR (vinyl protons, $\delta = 5.7\text{--}5.8$ ppm) indicative of a *cis*- polyene backbone.

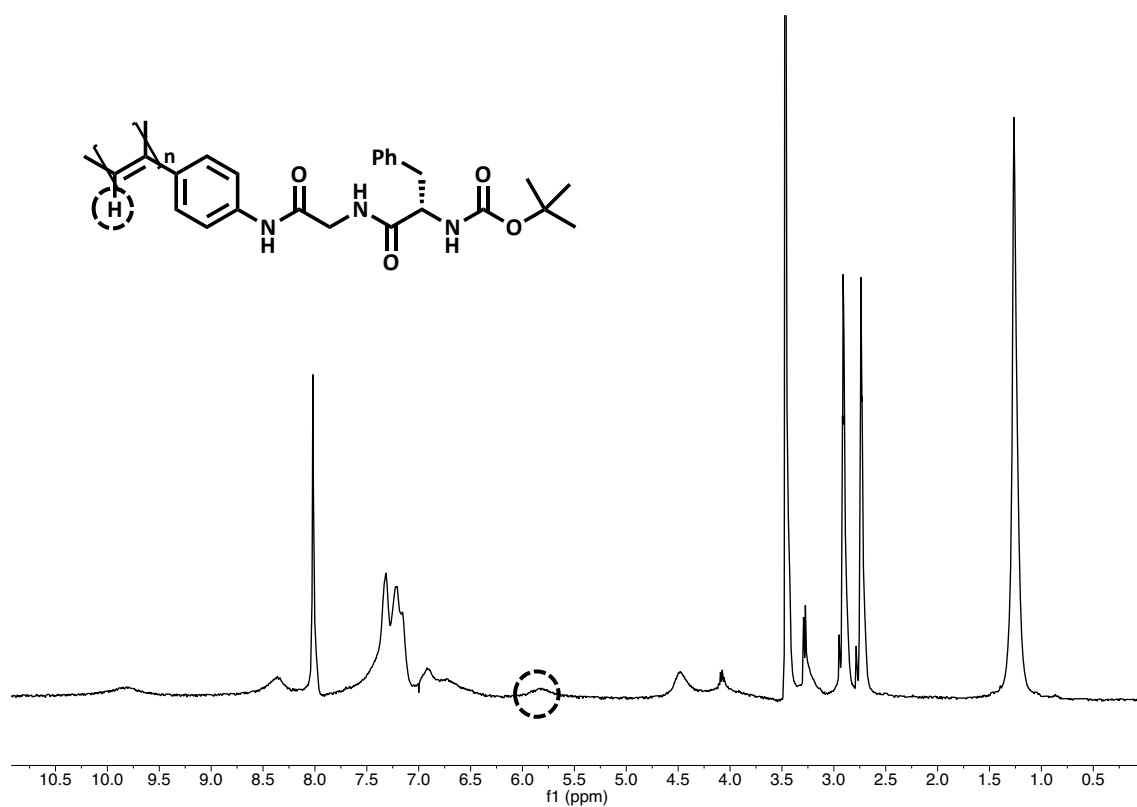


Figure S11. ¹H-NMR spectra of poly-L-1 in CDCl₃.

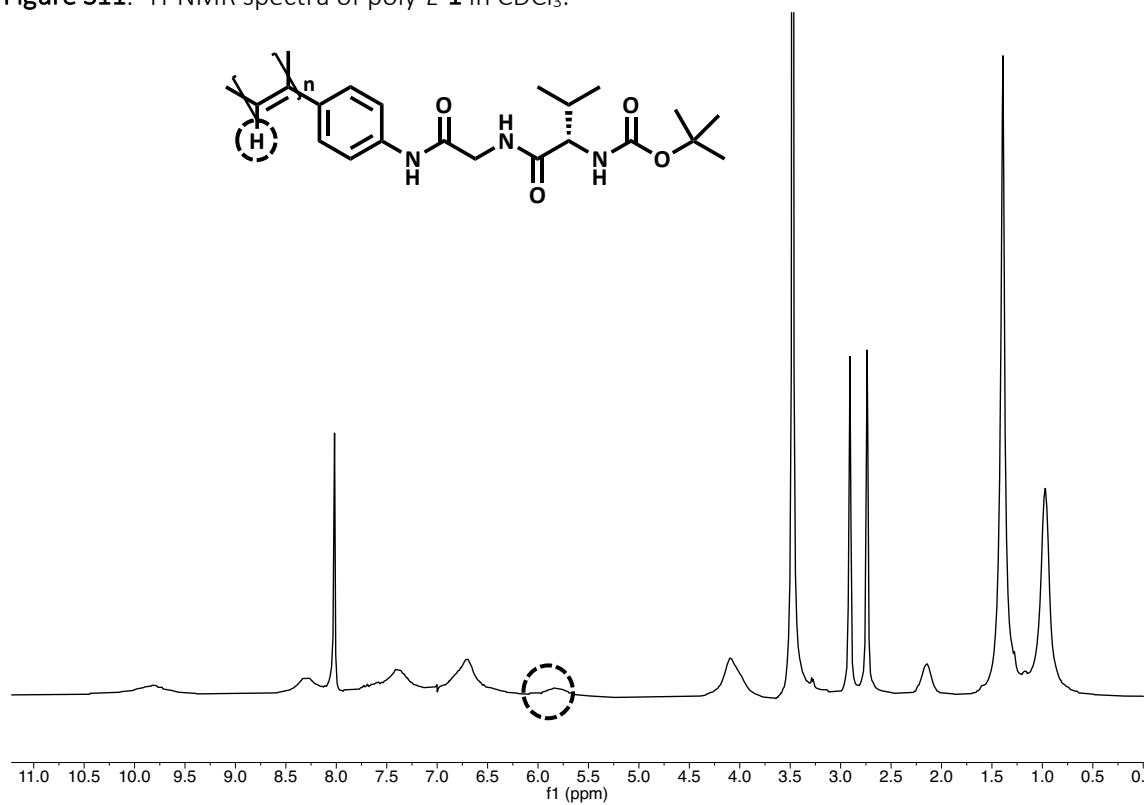


Figure S12. ¹H-NMR spectra of poly-L-2 in DMF-d₇.

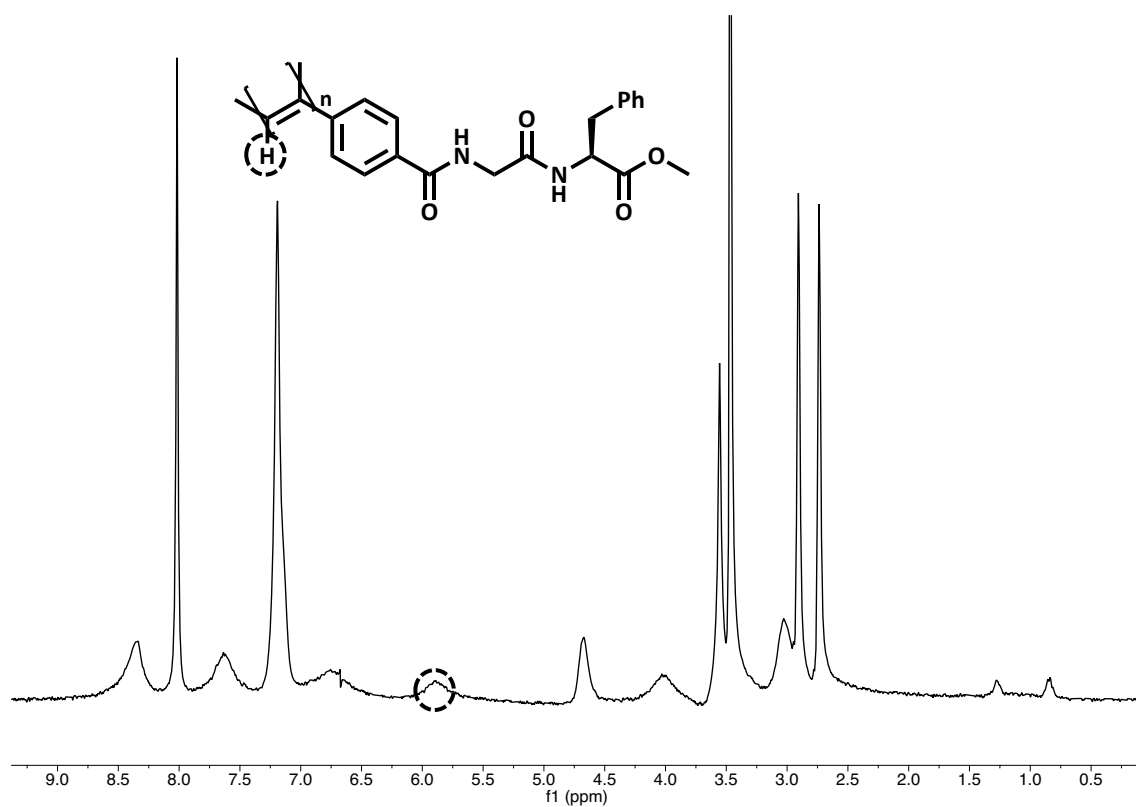


Figure S13. ^1H -NMR spectra of poly-L-3 in CDCl_3 .

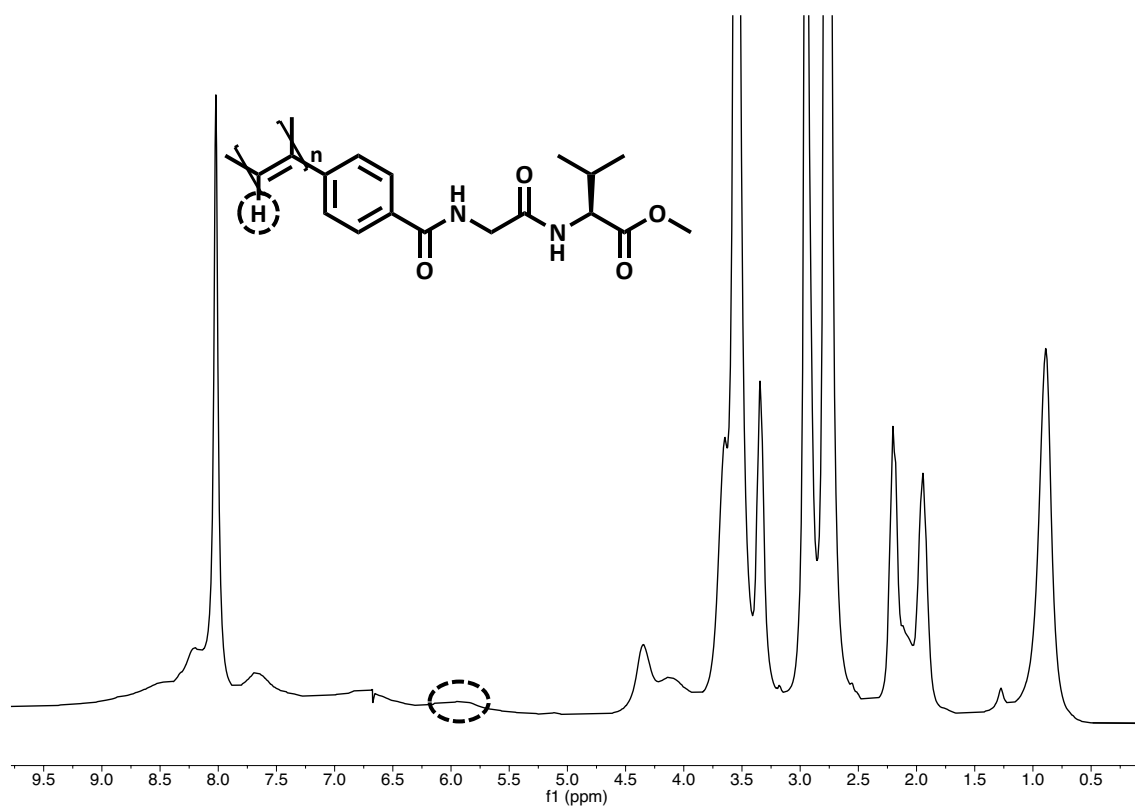


Figure S14. ^1H -NMR spectra of poly-L-4 in DMF-d_7 .

5. Determination of the molecular weight of the polymers. GPC Experiments

The molecular weight (M_n) of all polymers was estimated by GPC with THF as eluent at flow rate 1 ml/min at concentration 0.5 mg/ml using narrow polystyrene standards (PSS) as calibrants.

Table S2. GPC data of poly-L-1 to poly-L-4.

Polymer	M_n	M_w	PDI
Poly-L-1	27182	39832	1.46
Poly-L-2	12142	20848	1.24
Poly-L-3	31333	90041	2.87
Poly-L-4	—	—	—

6. Raman experiments

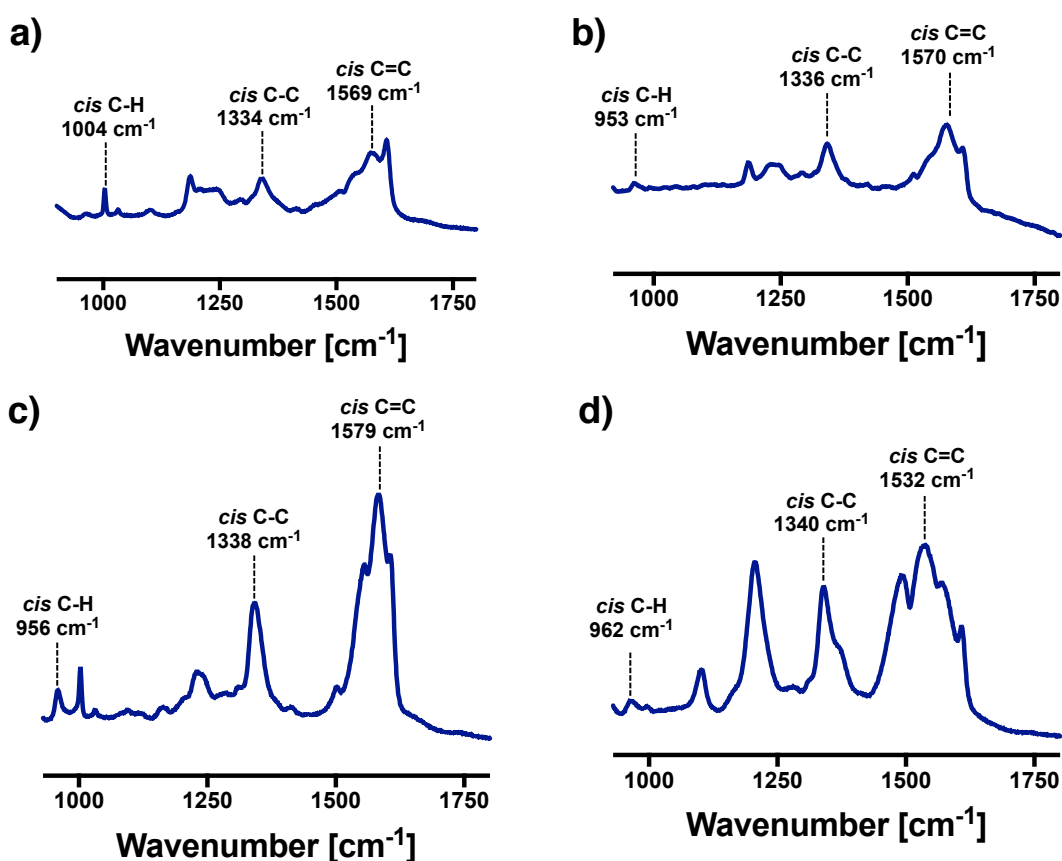


Figure S15. Raman spectra of (a) poly-L-1. (b) poly-L-2. (c) poly-L-3 and (d) poly-L-4 showing the characteristic bands of a *cis*-polyene backbone.

7. Thermal studies

DSC studies were carried out to determine the configuration of the polymer skeleton in (PPA)s due to the different thermogram pattern for *cis-cisoidal* (c-c) or a *cis-transoidal* (c-t) polyene backbone. For detailed explanation of thermal transitions in poly(phenylacetylene)s see ref. S1. As a general protocol a polymer sample was kept in an aluminum pan and heated from 40°C to 350°C with a heating rate of 10°C/min (Figure S16).^[S1]

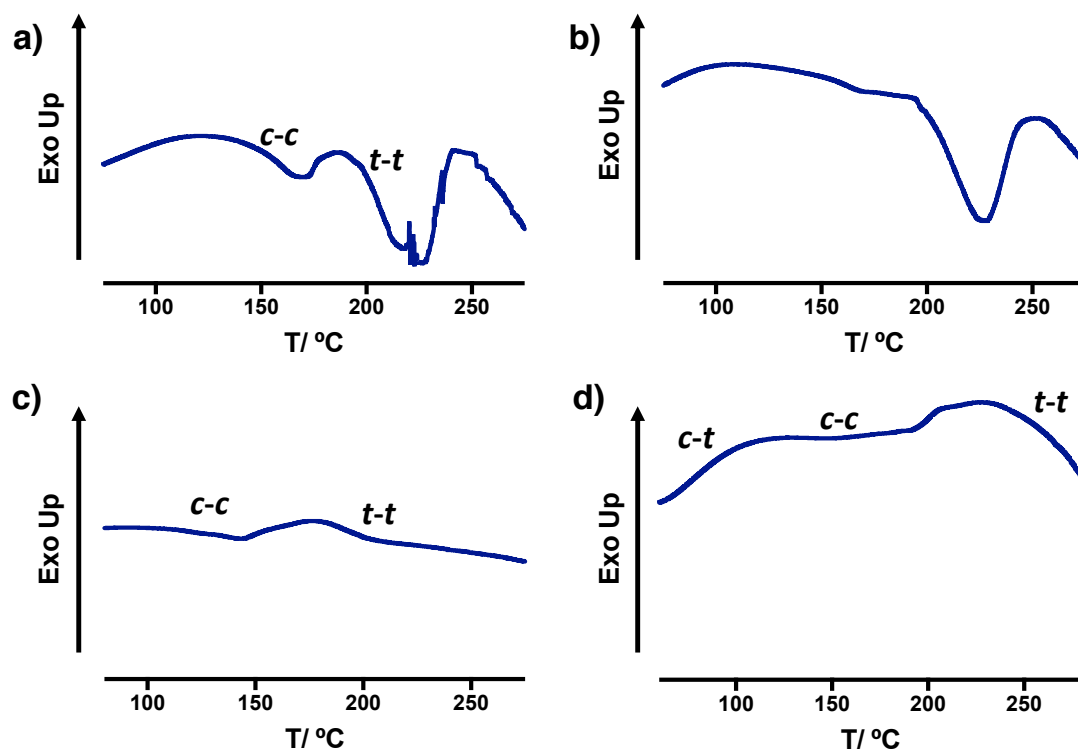


Figure S16. DSC thermograms of (a) poly-L-1. (b) poly-L-2. (c) poly-L-3 and (d) poly-L-4.

^{S1} Liu, L.; Namikoshi, T.; Zang, Y.; Aoki, T.; Hadano, S.; Abe, Y.; Wasuzu, I.; Tsutsuba, T.; Teraguchi, M.; Kaneko, T. *J. Am. Chem. Soc.* **2013**, *135*, 602-605.

TGA studies were carried out in order to determine the thermal stability of the polymers. As a general protocol a polymer sample was kept in a platinum pan and heated from 40°C to 800°C with a heating rate of 10°C/min.

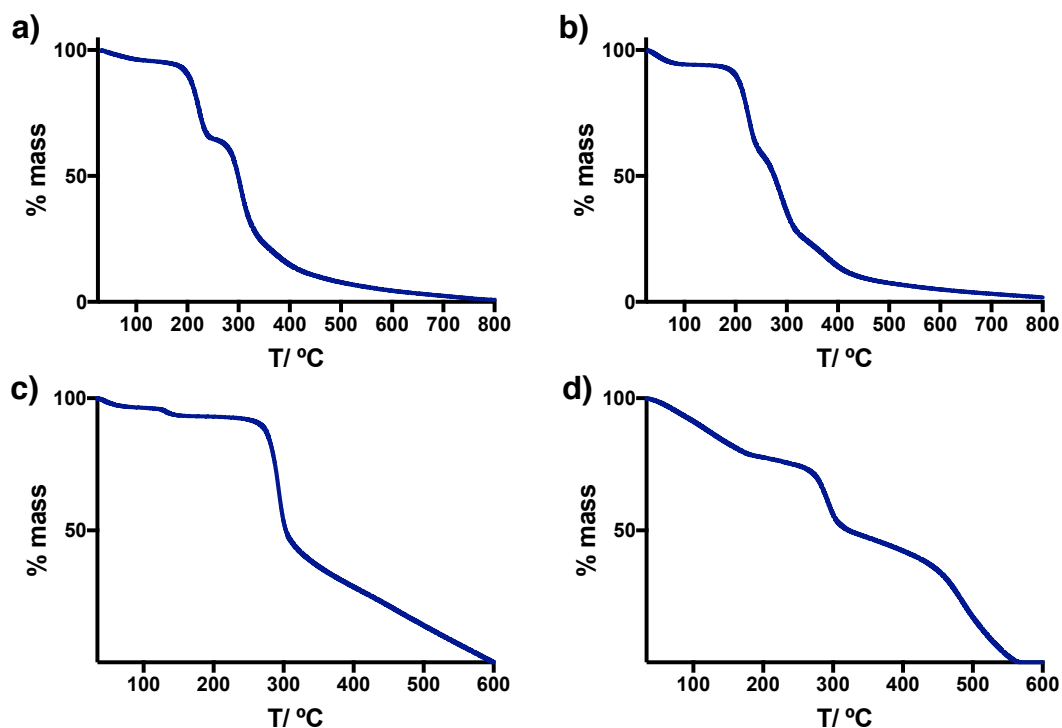


Figure S17. DSC thermograms of (a) poly-L-1. (b) poly-L-2. (c) poly-L-3 and (d) poly-L-4.

8. IR studies of monomers

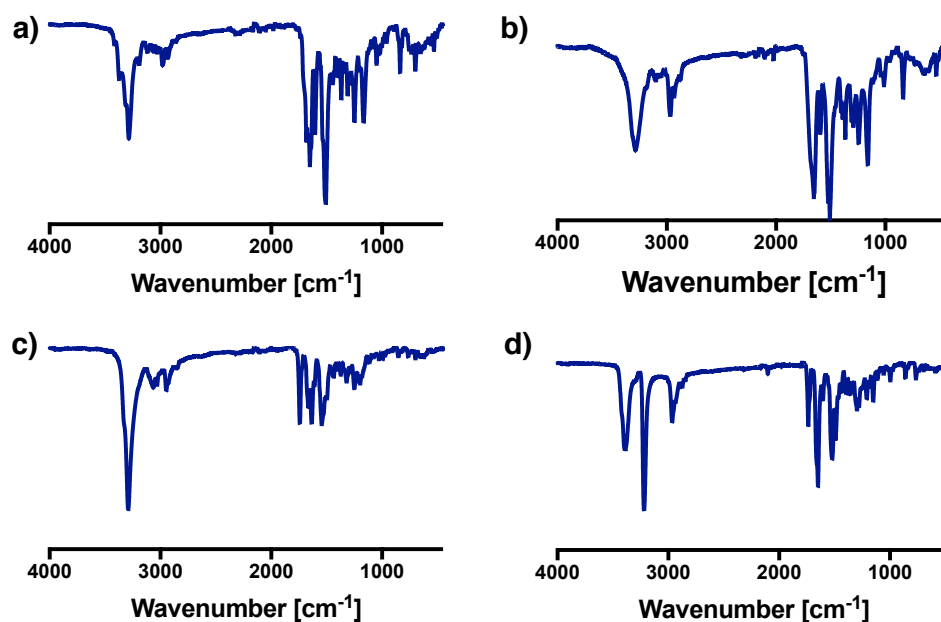


Figure S18. IR spectra of (a) m-L-1. (b) m-L-2. (c) m-L-3 and (d) m-L-4.

9. IR studies of polymers

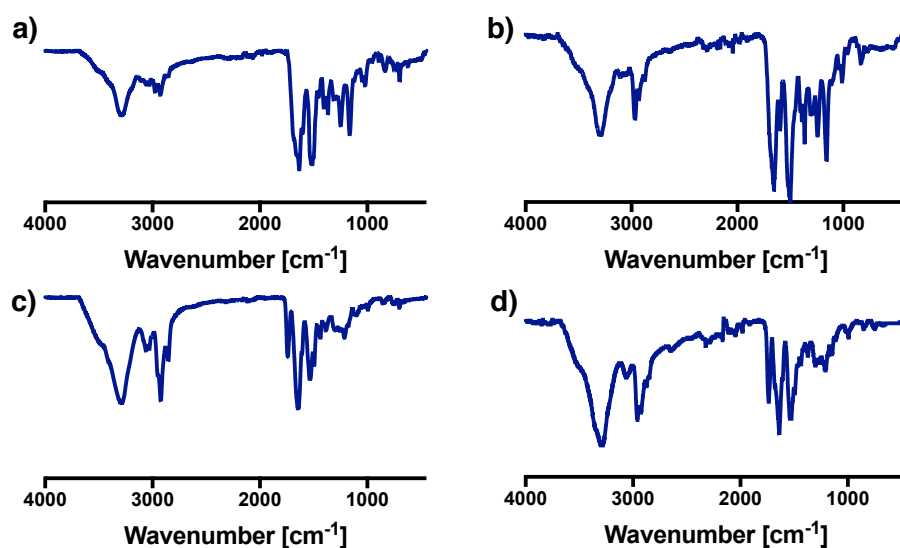


Figure S19. IR spectra of a) poly-L-1, b) poly-L-2, c) poly-L-3 and d) poly-L-4.

10. CD/UV-Vis experiments in different solvents

Poly-L-1—poly-L-4 were measured by CD and UV-Vis in different organic solvents in order to evaluate their helical behavior (CD/UV-Vis studies of poly-L-4 could not be measured due to the high insolubility presented by this polymer).

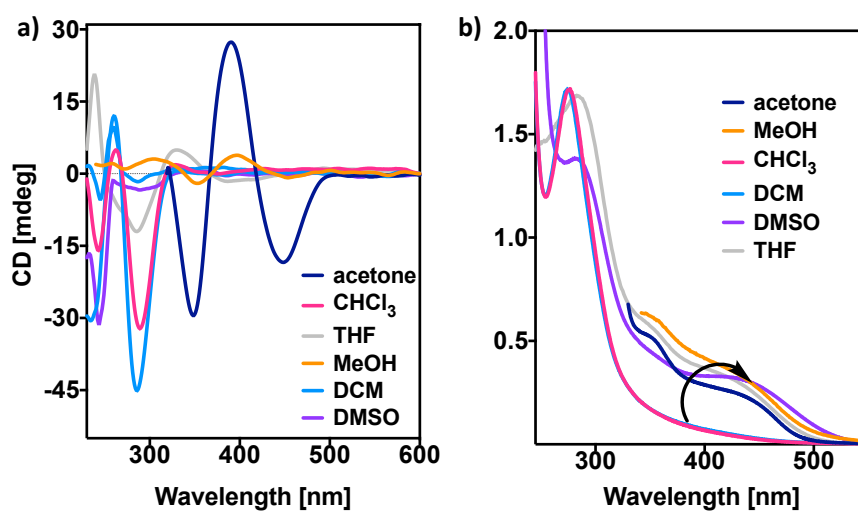


Figure S20. (a) CD and (b) UV-Vis spectra for poly-L-1 [PPA] = 0.5 mg/ml.

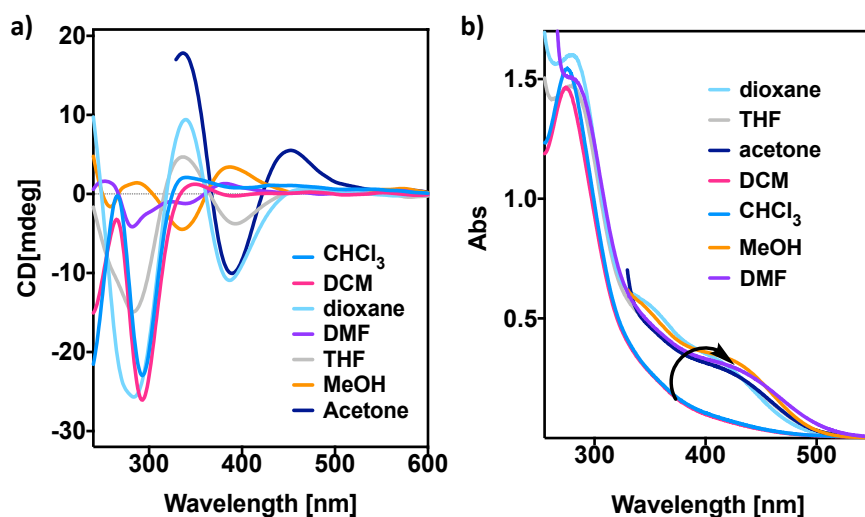


Figure S21. (a) CD and (b) UV-Vis spectra for poly-L-2 [PPA] = 0.5 mg/ml.

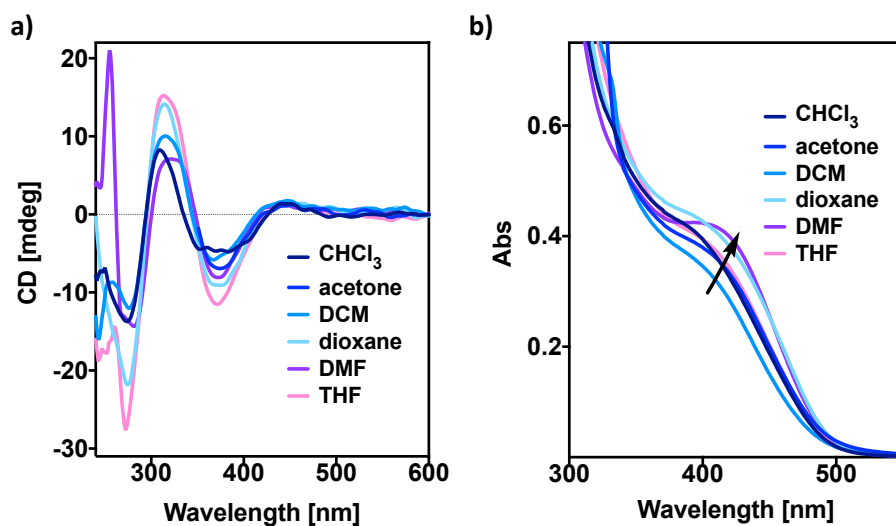


Figure S22. (a) CD and (b) UV-Vis spectra for poly-L-3 [PPA] = 0.5 mg/ml.

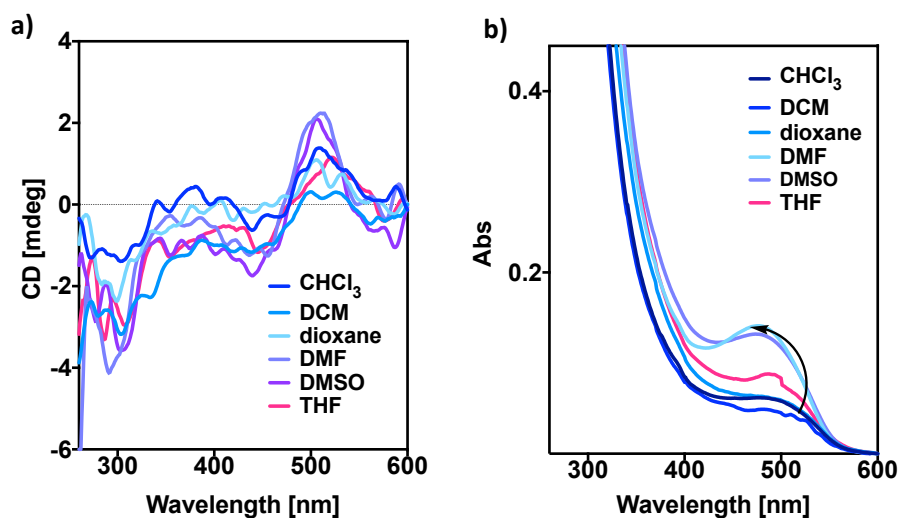


Figure S23. (a) CD and (b) UV-Vis spectra for poly-L-4 [PPA] = 0.5 mg/ml.

Additional CD studies in different cetones for poly-L-1 and poly-L-2

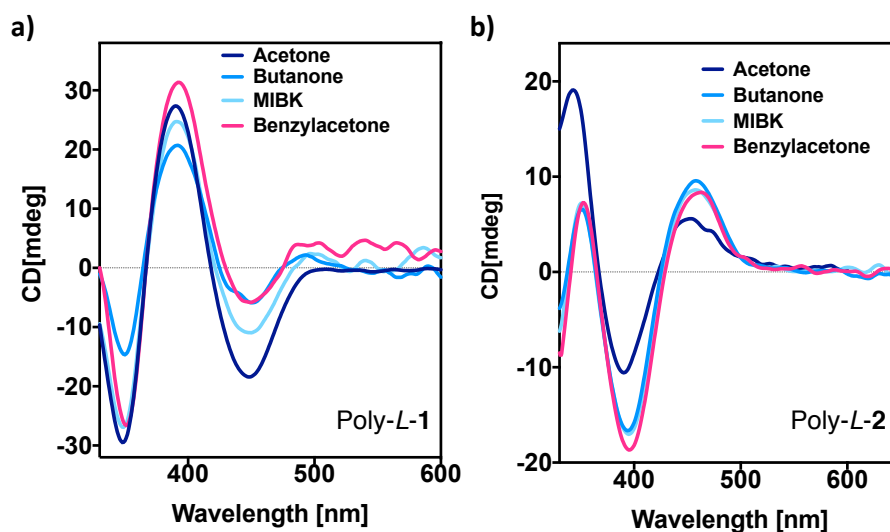


Figure S24. CD spectra of (a) poly-L-1 and (b) poly-L-2 [PPA] = 0.5 mg/ml.

11. Optical Rotation measurements

Table S3. Comparison of the Optical Rotation data of stretched and compressed helical structures of poly-L-1 and poly-L-2.

poly-L-1	poly-L-2
Highly Compressed (DCM) $\alpha_D^{20} = -106$ (10 mg/mL)	Highly Compressed (DCM) $\alpha_D^{20} = -39$ (10 mg/mL)
Compressed (THF) $\alpha_D^{20} = -32$ (10 mg/mL)	Compressed (THF) $\alpha_D^{20} = -98$ (10 mg/mL)
Stretched (Acetone) $\alpha_D^{20} = -16$ (c= 10 mg/mL)	Stretched (Acetone) $\alpha_D^{20} = +53$ (c= 10 mg/mL)
mono-L-1	mono-L-2
Highly Compressed (DCM) $\alpha_D^{20} = +15$ (10 mg/mL)	Highly Compressed (DCM) $\alpha_D^{20} = +39$ (10 mg/mL)
Compressed (THF) $\alpha_D^{20} = +11$ (10 mg/mL)	Compressed (THF) $\alpha_D^{20} = +22$ (10 mg/mL)
Stretched (Acetone) $\alpha_D^{20} = +16$ (c= 10 mg/mL)	Stretched (Acetone) $\alpha_D^{20} = +42$ (c= 10 mg/mL)



Helical polymers, covalent and supramolecular, have attracted the scientific community's attention due to the structure/function relationship found in helical biomacromolecules such as DNA, peptides or proteins, among others. Inspired by these works, this Doctoral Thesis is focused on the development of new synthetic chiral materials based on poly(phenylacetylene)s (PPA)s bearing two types of pendant groups: one formed by multi-chiral pendants and the other consisting of a single chiral motif separated from the polyene main chain by flexible linkers. Their chiral information transmission mechanisms, dynamic helical behavior and stimuli-responsive properties were studied, leading to promising new materials for the future rational design of novel smart materials with specific properties.