SEQUENCE ENGINEERING: FINE TUNING POLYMER PROPERTIES AT THE MICROSTRUCTURAL LEVEL

by

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Sequence, which Nature uses to spectacular advantage, has not been fully exploited in synthetic copolymers. To investigate the effect of sequence and stereosequence on the physical properties of copolymers a family of complex isotactic, syndiotactic and atactic repeating sequence poly(lactic-*co*-glycolic acid) copolymers (RSC PLGAs) were prepared and their NMR and thermal behavior was studied. The unique suitability of polymers prepared from the bioassimilable lactic and glycolic acid monomers for biomedical applications makes them ideal candidates for this type of sequence engineering. Polymers with repeating units of LG, GLG, LLG, LLLG and GLLG (L = lactic, G = glycolic) with controlled and varied tacticities were synthesized by assembly of the corresponding sequence specific, stereopure dimeric, trimeric, tetrameric and hexameric segmer units. Specifically labeled deuterated lactic and glycolic acid segmers were likewise prepared and polymerized. Although the effects of sequence-influenced solution conformation were visible in all resonances of the ^{1}H and ^{13}C NMR spectra, the diastereotopic methylene resonances in the ^{1}H NMR ($CDCl_3$) for the glycolic units of the copolymers proved most sensitive. An octad level of resolution, which corresponds to an astounding 31-atom distance between the most separated stereocenters, was observed in some mixed sequence polymers. Importantly, the level of sensitivity of a particular NMR resonance to small differences in sequence was found to depend on the sequence itself. Thermal properties were also correlated with sequence.

Functionalized RSC PLGAs were also prepared by the introduction of a benzyl-ether substituted monomer, (S)-3-benzyloxy-2-hydroxypropionic acid, derived from serine. A series of dimeric and trimeric based copolymers were assembled with controlled and varied tacticities as well as a sequenced heptamer and decamer copolymer. Deprotection of the hydroxyl groups was accomplished by catalytic hydrogenolysis to yield highly functionalized, hydrophobic polyesters. The NMR spectra for all of the copolymers were consistent with sequence and stereosequence retention. Progress towards the development and incorporation of another functional monomer derived from malic acid was also investigated.

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SYMBOLS AND ABBREVIATIONS

Å	angstrom
AcOH	acetic acid
Adj	adjacent
ADMET	acylic-diene metathesis
ATRP	atom transfer radical polymerization
Bn	benzyl group
BnOH	benzyl alcohol
Br	bromine
brine	saturated aqueous sodium chloride
nBuLi	*n*-butyl lithium
tBuLi	*tert*-butyl lithium
CH_2Cl_2	dichloromethane
$CHCl_3/CDCl_3$	chloroform (d-deuterated)
CH_3CN	acetonitrile
COSY	correlation spectroscopy
CRP	controlled/living radical polymerization
CSA	camphorsulfonic acid
C=O	carbonyl

°C	degrees Celsius
DBU	1,8-diazobicyclo[5.4.0]undec-7-ene
DCC	dicyclohexylcarbodiimide
DIC	diisopropylcarbodiimide
Dist	distant
dioxo	dioxolanone
DMAP	dimethylaminopyridine
DMF	dimethylformamide
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid
DP	degree of polymerization
DPTS	4-(dimethylamino)pyridinium *p*-toluenesulfonate
DSC	differential scanning calorimetry
DVB	divinyl benzene
d	doublet (NMR signal)
dd	doublet of doublets (NMR signal)
dq	doublet of quartets (NMR signal)
D_2O	deuterium oxide
δ	chemical shift
Δ	difference
EDCI	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
EI	electron impact ionization
ES	electrospray ionization

equiv	equivalents
EtOAc	ethyl acetate
Et_3N	triethylamine
Et_2O	diethyl ether
G	glycolic acid unit
G_{d2}	deuterated glycolic acid unit
G^C	glycolic unit of C-side of lactic unit
G^O	glycolic unit of O-side of lactic unit
g	gram
GC	gas chromatography
h	hour
H	proton
H_2	hydrogen gas
H_2O	water
HCl	hydrogen chloride
HETCOR	heteronuclear correlation spectroscopy
HMBC	heteronuclear multiband correlation spectroscopy
HRMS	high resolution mass spectroscopy
Hz	hertz
i	isotactic dyad
J	coupling constant (NMR signal)
kDa	kilodaltons
L	lactic acid unit

L_R	(*R*)-lactic acid unit
L_{rac}	racemic lactic acid unit
$L_{d,rac}$	deuterated racemic lactic acid unit
L^C	lactic unit on C-side of glycolic unit
L^O	lactic unit on O-side of glycolic unit
LDA	lithium diisopropylamide
LiHMDS	lithium hexamethyldisalazide
m	multiplet (NMR signal)
M	molarity
M(x)	malic acid unit
MALDI	matrix assisted laser desorption ionization
MALLS	multiple angle laser light scattering
MeOH	methanol
$MgSO_4$	magnesium sulfate
MHz	megahertz
min	minute
ml/mL	milliliter
mm	millimeter
mm Hg	millimeter mercury
mmol	millimoles
M_n	number average molecular weight
M_w	weight average molecular weight
MS	mass spectroscopy

M+	mass ion
M+Na	mass ion plus sodium
m/z	mass per charge
μm	micrometer
N_2	nitrogen gas
NaCl	sodium chloride
Na_2CO_3	sodium carbonate
$NaHCO_3$	sodium bicarbonate
NH_4Cl	ammonia chloride
NH_4OH	ammonia hydroxide
NMP	nitroxide mediated polymerization
NMR	nuclear magnetic resonance
o	ortho
p	para
[Pd]	palladium catalyst
Pd/C	palladium on activated charcoal
PDI	poly dispersity index
PHB	poly(hydroxybutyrate)
PG	protecting group
PLA	poly(lactic acid)
PLGA	poly (lactic-*co*-glycolic acid)
ppt	precipitate
PPTS	pyridinium *p*-toluene sulfonate

PS	polystyrene
q	quartet (NMR signal)
RAFT	reversible addition-fragmentation polymerization
R_g	radius of gyration
RGD	arginine-glycine-aspartic acid peptide
ROP	ring-opening polymerization
RSC	repeating sequence copolymer
RT	room temperature
s	singlet (NMR signal)
s	syndiotactic
S*(x)	*S*-2,3-dihydroxypropionic acid unit
SAP	segmer assembly polymerization
SEC	size exclusion chromatography
SiR_3	silyl-protecting group
t	triplet (NMR signal)
TBAF	tetrabutylammonium fluoride
TBDPSCl	*t*butyldiphenylsilylchloride
T_{cystal}	crystallization transition temperature
T_g	glass transition temperature
THF	tetrahydrofuran
THP	tetrahydropyran
T_m	melting transition temperature
TOF	time of flight

PREFACE

Rarely does a plan survive inception to fruition and my graduate school experience has been no exception. I arrived with only one intention and that was to claim a piece of science and research as mine. After many years and many struggles I feel that I have accomplished my goal but I have also matured enough to realize this initial intention was narrow-minded and selfish. I have been fortunate enough to be surrounded by great mentors and colleagues with whom I owe a debt of gratitude for my own personal growth and that knowledge is not to be claimed but shared.

I would like to thank my advisor Tara Meyer, who taught me that you cannot always synthesize an answer, sometimes you have to think about it. I have two instances that I will always remember: First, after joining her group she handed me a proposal draft and said "I know you want to do other research but do you think you could get this started for me?" This propelled me into polymer science and altered my future for the better. The second instance was when I presented some complex microstructural interpretations and after surviving many disagreements she smiled and extended her hand in congratulations. For future group members reading this if you every have to give bad news to Tara, show her a pretty NMR spectrum first!

A strong foundation was laid by my mentors from Kent State University, Dr. Mary E. Neubert and Julie Kim. They shaped my technical training, extreme attention to detail and lab

hygiene that have enabled my success at higher levels. Dr. Edwin Gould, who expected nothing less than the best from me and for me.

My colleagues in the Meyer Group deserve a round of thanks. Dan Knapton, Jim Copenhafer and Ken Cutler brought me into the group and helped me get started while trying to impart information that I was years away from understanding. Ben Norris was a great idea man and mental springboard. Rob Walters, who is still helping me today, was a wealth of industrial knowledge even though he had no idea how to take his own NMR spectrum. Jian Li has been a great support on this project and Ryan Weiss, who I know will carry this on into the future. I have also had the privilege of mentoring a great group of undergraduate researchers: Jennifer Burke, Carrie DuMars, David Schafer and Evan Jones.

I would like to thank Dr. George Bandik, Dr. Damaodaran Krishnan, Dr. Joel Gillespie and Fran Nagy from the Chemistry Department for helping as well. Dr. Bandik has inspired most of my teaching and is not-so-silently waiting my return to it. Dr. Krishnan assisted with any NMR problems and loaded pulse sequences that no one else would possibly need. Dr. Gillespie pieced together and maintained many instruments that were crucial for my research. And Fran‘s hard work that keeps the department running smoothly.

My committee members, Drs. Chapman, Horne and Little for not only sitting on my dissertation committee but aiding in my endeavors from learning polymer chemistry, peptide conformation dynamics and future material applications.

Last, but not least, my wife Emily who has supported me throughout graduate school while enduring my ever changing moods and crazy work schedules. Thank you and I cannot wait to move on to a new phase in our lives.

1.0 INTRODUCTION

1.1 SEQUENCE ENGINEERING

Sequence engineering or sequencing are terms readily applied to the preparation of natural materials with exact, well-defined microstructures, i.e. peptides and poly(nucleic acid)s, not synthetic copolymers. Nature exploits sequence to the fullest extent utilizing less than thirty monomers to assemble hundreds of thousands of precise, monodisperse polymers each with a dedicated and specialized function encoded in the sequence/primary structure.[2] This level of exactness, a one-to-one structure-property relationship is rarely found and unfortunately, in many cases, deemed unnecessary in synthetic polymer chemistry.[3] Yet, in order to address the need for more sophisticated materials, sequence engineering is emerging as a new frontier in polymer chemistry.[3,4]

1.1.1 Sequence and Current Polymerization Methodologies

The lack of sequence specific synthetic materials is due, in large part, to the scarcity of polymerization techniques that are amenable to complete microstructural control. While the assemblage of sequenced peptides, polypeptides, and more generalized polyamides is well documented,[5-11] microstrucutral adaptations to the current state of the art synthetic polymerization techniques, i.e. controlled/living radical polymerization (CRP) and ring-opening polymerization (ROP), are far fewer. Microstructural design, therefore, remains largely one dimensional addressing either homopolymer stereosequence motifs or copolymer architectural motifs (Figure 1). However, advances in catalyst design and directing group utilization have enabled the preparation of more two dimensional microstructures.

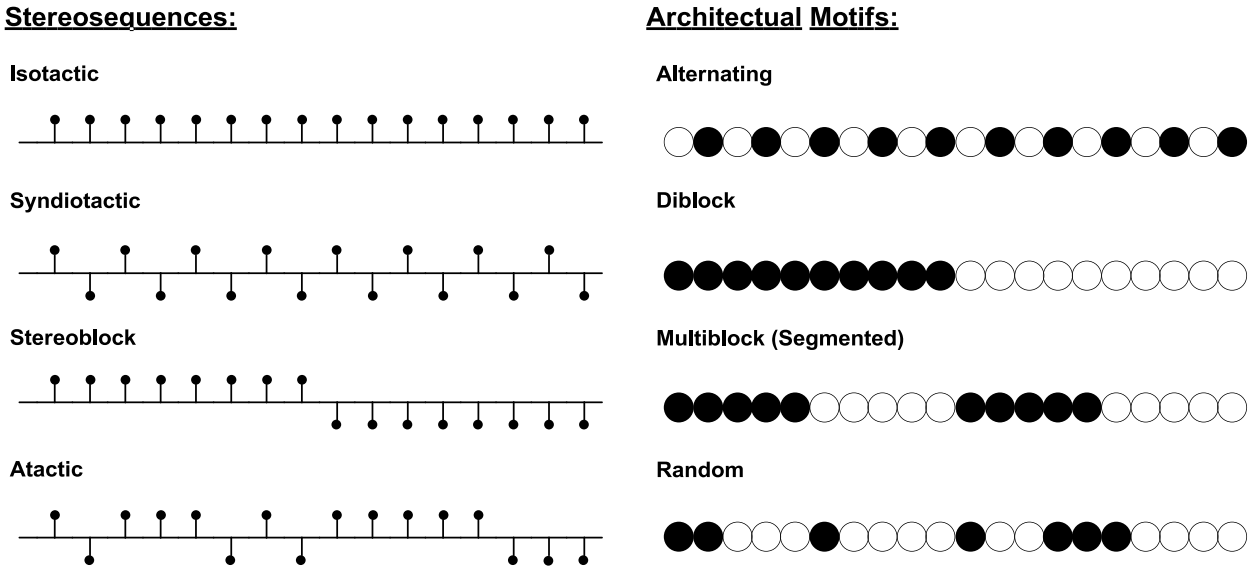


Figure 1. Examples of stereosequences and architectural motifs - filled and open circles represent different monomers.

Polymerization catalysts and catalyst design have advanced significantly since the introduction of Ziegler-Natta catalysts.[12] Utilization of the ruthenium based Grubbs catalysts have led to the development one of the most sequence specific polymerization techniques,

acyclic-diene metathesis (ADMET). Wagener and coworkers have exploited this methodology to prepare precisely functionalized aliphatic polymers from specific α,ω-diolefins.[13-16] Grubbs and coworkers furthered this methodology to generate alternating A-B copolymers by incorporating a diacrylate moiety that slowly and irreversibly inserts into the olefinic polymer backbone.[17] Slugovc and coworkers imparted chain directionality with the preparation of a mixed monomer with a terminal olefin and a terminal acrylate.[18]

Another polymerization technique that has advanced due to catalyst design is ROP. Recent developments in site specific coordination catalysts have enabled progress in stereosequence control, regioselectivity and some two-dimensional microstructure complexity. A large portion of this work involves the preparations of stereosequenced homopolymers poly(lactic acid) (PLA) and poly(3-hydroxybutryrate) (PHB) from cyclic monomeric and dimeric units.[19-22] Simple isotactic,[23,24] syndiotactic,[25] heterotactic[26] and stereoblocked[27] PLA polymers have been prepared in the Coates and Hillmeyer labs while isotactic and syndiotactic PHB has been prepared by Carpentier and coworkers.[28,29] Recently, Coates and coworkers prepared the most complex microstructure, an alternating syndiotactic PHB.[30] While the microstructural control in ROP of cyclic co-monomers remains difficult,[20,31,32] alternating copolymers have been prepared by regiospecific ROP of epoxides in the presence of carbon monoxide or carbon dioxide to generate polyesters[33] or polycarbonates[34,35].

The impact of catalysts on microstructural control diminishes greatly in radical polymerizations. Initially, radical polymerizations were believed to be too fast to control except under specific conditions where the monomer to co-monomer reaction is preferred (reativity ratios), i.e. copolymerization of styrene with diphenylethylene[36] or maleic anhydride[37]. Recent development of CRP techniques such as atom transfer radial polymerization (ATRP), reversible

addition-fragmentation transfer polymerization (RAFT) and nitroxide-mediated polymerization (NMP) have slowed the polymerizations dramatically by shifting the equilibrium towards excess dormant but living chains.[38] These longer reaction times enable microstructural manipulation by complexation of directing groups.

Lewis acid additives, in conjunction with polar-carbonyl containing monomers, have been shown to aid both stereo- and architectural sequence controls in CRPs. Matyaszewski and coworkers utilized yttrium and ytterbium based Lewis acids with dimethylacrylamide to increase isotactic stereosequences upwards of 85% in both RAFT and ATRP.[39] Sawamoto and coworkers were able to achieve 87% isotactic stereosequences of poly(*N*-isopropylacrylamide) using a similar method.[40] Alternating architectural motifs of similarly reactive co-monomers styrene and methylmethacrylate, were possible with the addition of diethylaluminium chloride.[41] Coordination of a bulky fluoroalcohol solvent, Isobe and coworkers were able to prepare predominately syndiotactic poly(acrylates) under both free radical and ATRP conditions.[42,43] Satoh and coworkers utilized bulky side groups generated by hydrogen bonded moieties to synthesize predominately syndiotactic polymers.[44]

Template-assisted polymerization techniques have been developed in an effort to assert complete microstructural control.[45,46] Sawamoto and coworkers have recently created a series of macroinitiator templates for chain-growth polymerizations.[46-48] These macroinitiators possess two polymerization sites: one for cationic polymerization and the second for radical polymerization. The 'template' copolymer is created by cationic polymerization followed by free radical polymerization of the sequenced copolymer. The obvious flaw in this method is that the 'template' copolymer has to be as complex as the desired sequenced copolymer. Avoiding the

synthesis of a complex template, Datta and coworkers have modified DNA for the formation of sequenced polyaniline nanowires.[49,50]

1.1.2 Microstructural Consequences of the Microstructure

The major advantage of newer synthetic polymerization techniques such as CRP is the preparation of well-defined di- and multiblock copolymers and organized macrostructures. The living nature of the polymer chains in CRP enable nearly complete compositional separation of the monomer blocks. Altering the block compositions by covalently linking different block types that would normally disassociate when blended, i.e. hydrophilic with hydrophobic and hard with soft, can generate organized macrostructures such as spherical, rod and lamellar (Figure 2).[51,52] RAFT and ATRP especially, are tolerant to many monomer types and functional groups facilitating chemically active surfaces and stimuli responsive copolymer systems.[51,52] ADMET polymerization as well, has been utilized to determine the effect of sequence length and substitution pattern on lamellar packing and crystal thickness in polyethylene and polypropylene.[13,53]

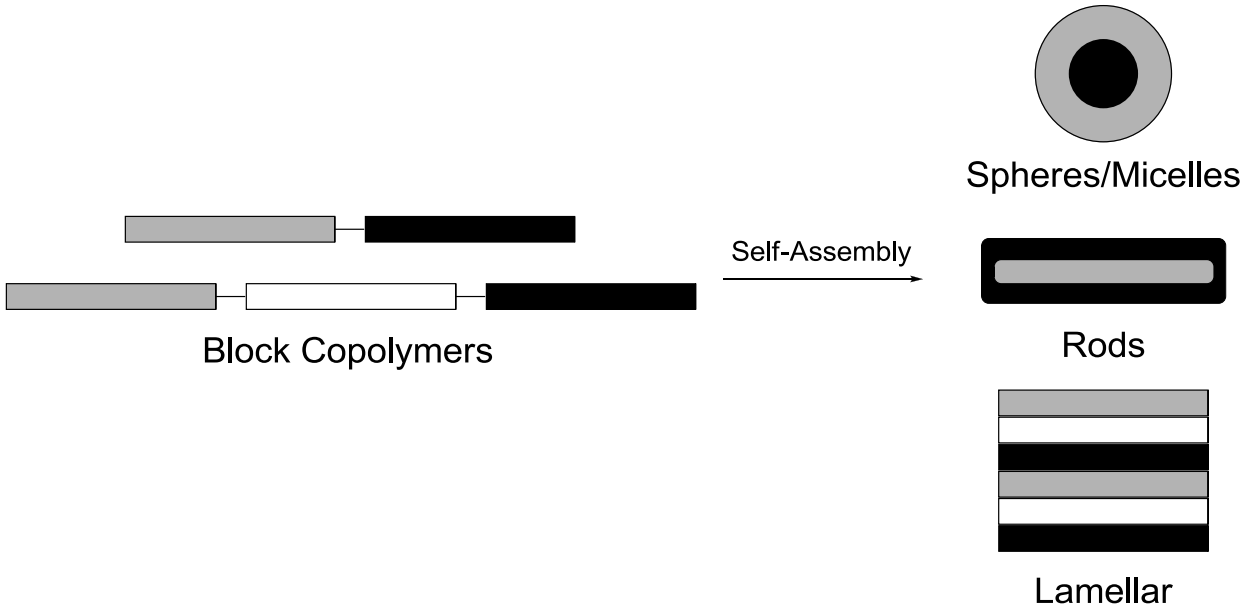


Figure 2. Common macrostructural assembly motifs for block copolymers.

In order for synthetic polymers to access more complex macrostructures and functions, similar to those found in Nature, new adaptations and methodologies are need to address control at the microstructural level. The combination of stereo- and sequence-complexity found in simple natural materials like Gramicidin and spider silk far exceed most of the current "state of the art" synthetics. Gramicidin, a natural antibacterial, has an alternating syndiotactic microstructure which was only recently accessed in the ROP of certain butyrlactones.[28,30] Spider silk, a segmented natural material with hard β-sheet and soft α-helix segments, is tougher than many man-made materials including steel.[54] The evidence is clear for a paradigm shift in polymer chemistry.

1.1.3 Repeating Sequence Copolymers

Research in the Meyer Group focuses on the effect of microstructurally controlled sequences on the physical properties of the corresponding repeating sequence copolymers (RSCs). Families of

RSCs are prepared utilizing segmer assembly polymerization (SAP) in which the segmers, precisely sequenced oligomers that are amenable to further polymerization, are systematically varied (Figure 3). Ward and Meyer reported the synthesis of *o*,*p*-polyaniline, copolymerizing an *ortho*-substituted macromonomer with a trimeric aniline segment, generating regularly spaced *o*-phenylene units.[55] Copenhafer, Walters and Meyer prepared a series of poly(fluorene-*co*-methylene) RSCs by ADMET to examine the effect of fluorene sequence length on optical properties and thermal degradation mechanisms.[56] Norris, Pan and Meyer have applied sequence specificity to oligo(phenylene-vinylene)s as an approach to determine the effect of sequence on conjugated materials.[57] Sequence is rarely applied to conjugated materials and may be a promising approach to advanced organic electronics.

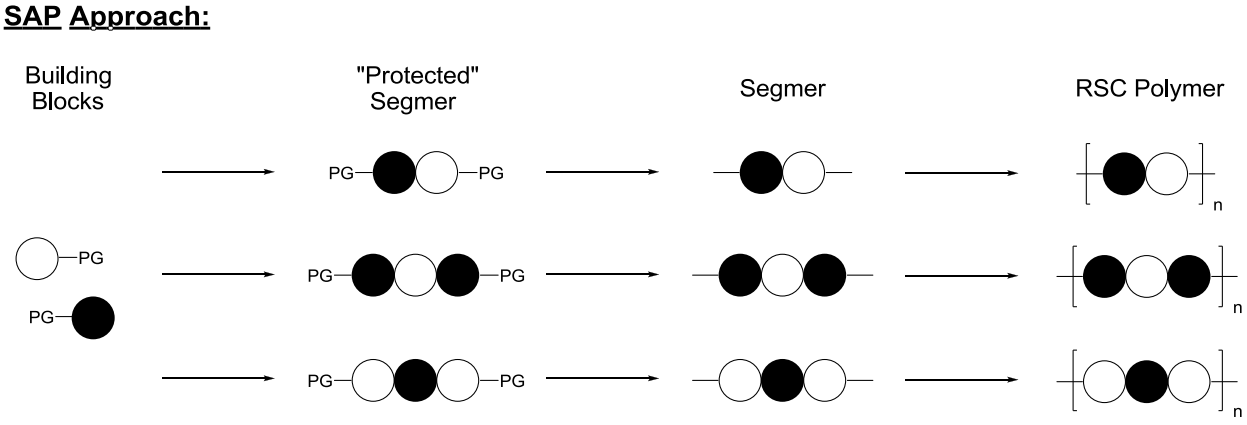
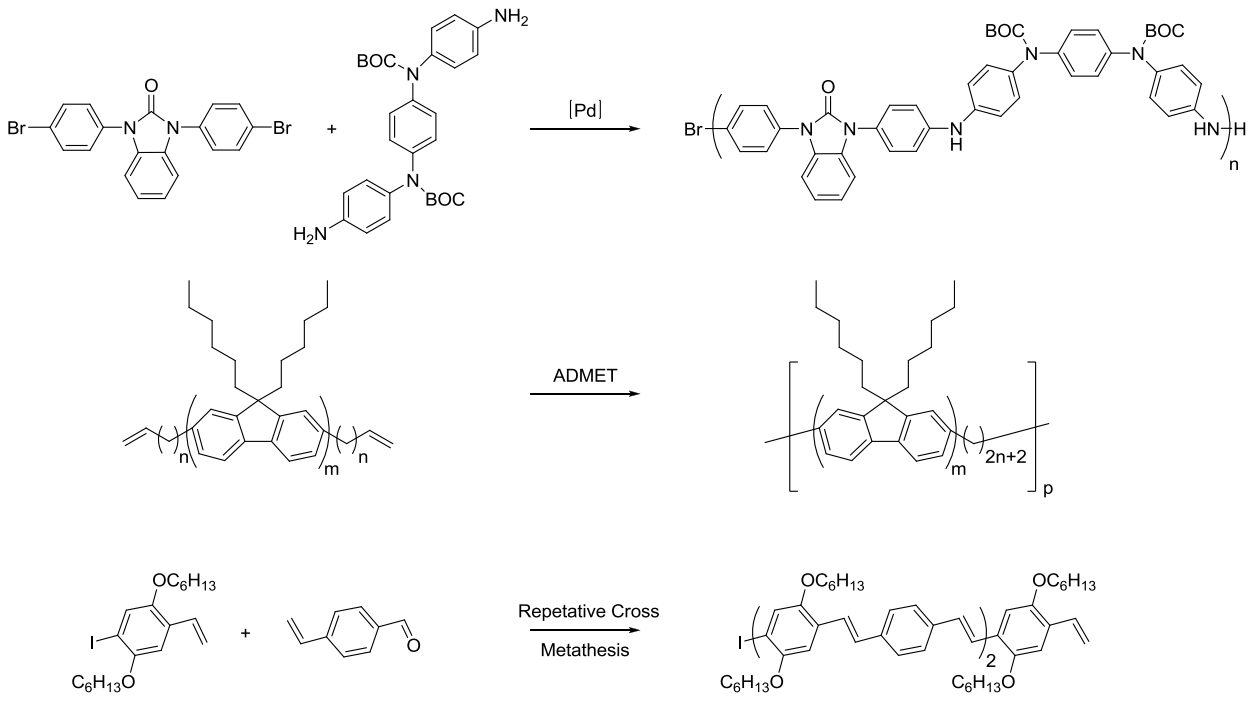


Figure 3. Segmer Assembly Polymerization method.



Scheme 1. Examples of segmers and RSCs prepared by SAP.

1.2 SEQUENCED POLY(LACTIC-CO-GLYCOLIC ACID)S

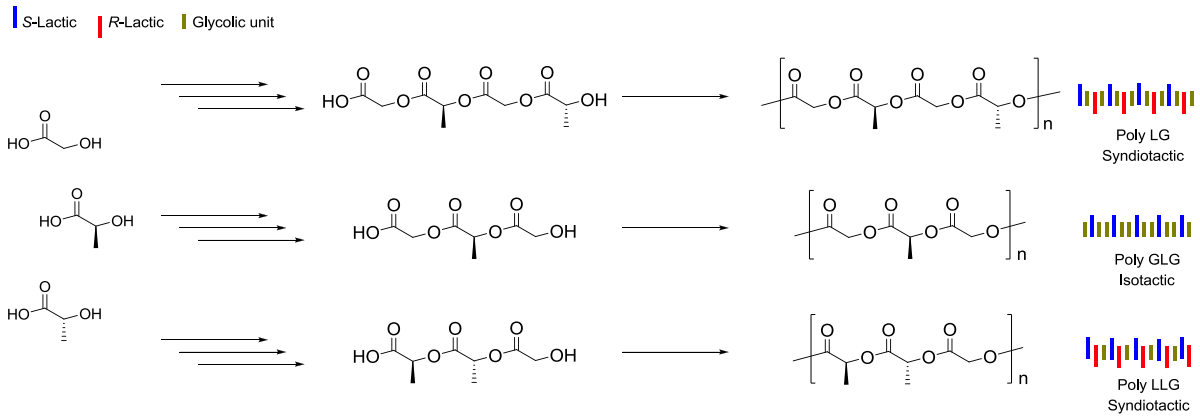
The extensive investigation of poly(lactic-*co*-glycolic acid)s (PLGAs) for *in vivo* applications requiring controlled polymer degradation renders them ideal candidates for the investigation of the role of sequence in polymer properties. The popularity of these polymers for applications such as stem cell scaffolding and drug delivery vehicles stems from the fact that bulk structures made from PLGAs hydrolyze at a moderate rate in the body and the products, lactic and glycolic acid, are bioassimilable.[58-66] Although other polymers are employed for these applications, studies on PLGAs and PLAs represent a significant proportion of all work in the area. The ubiquity of the materials and the special suitability of the monomers to bioengineering applications make the idea of creating repeating sequence copolymers (RSCs) from these

monomers particularly attractive. Finally, there are clear advantages to be realized from the rearrangement of "old" monomers to create new polymers: *economic*, in that the infrastructure that already exists for the large scale synthesis of these old monomers translates into low cost and high availability and *pragmatic*, in that the knowledge base that already exists regarding the suitability of these monomers for particular applications translates into an efficient path to application.

Our approach to the investigation of the role of sequence on the properties of PLGAs is to create and then analyze a family of RSCs. Our methodology, which involves the condensation of preformed segmers, allows for the synthesis of polymers with structural- and stereo-sequences more complex than those previously prepared. Selected examples are presented in Figure 4. Previous efforts to prepare sequenced PLAs and PLGAs have relied on the ring-opening polymerization (ROP) of the cyclic lactide, glycolide, and methyl glycolide dimers.[20-23,25,27,67-75] Despite the laudable success achieved though the sophisticated design of selective catalysts and the exploitation of chain-end control the number and types of sequences that can be prepared is limited by the dimeric form of the ROP monomer and by challenges inherent in programming catalysts to deliver a pattern more complex than alternation. While the strategy we employ in this paper of pre-assembling a sequenced segmer by a condensation mechanism is arguably less efficient than ROP, it is convergent and molecular weights > 20 kDa are routinely achievable. Most importantly this approach is general—*any RSC PLGA envisioned can be prepared.*

The first benefit realized from our creation of a family of PLGA RSCs is the creation of a partial "Rosetta Stone" for the interpretation of NMR data of polymers with complex stereochemical patterns in general and for PLGAs in particular. The most relevant precedents for this work are the extensive investigations of the NMR for PLA of varying

tacticities.[23,25,27,68,76-88] It is worth noting that in the PLA system the ^{13}C NMR spectroscopic shifts have been found to be most sensitive to the relationships between distant stereocenters; differences in relative stereochemistries up to 5-6 units away from the nucleus under observation can be detected.[76,78,79,82,84,86,89] Although the NMR data for PLGAs has likewise been studied, the added complexity introduced by having two variables, sequence and stereochemistry, as well as the fairly modest control of these variables achievable using the common ROP synthetic approach, has inhibited progress. These studies have primarily been limited to the partial assignment of local sequence within otherwise random copolymers.[69,71,74,75,80,90-93] Our approach to preparing PLGAs, which allows for nearly perfect sequence and stereocontrol, greatly expands the database and offers, thereby, a significant advance in the understanding of PLGA NMR data as well as some interesting new conclusions of a more general nature pertaining to sequenced copolymers.



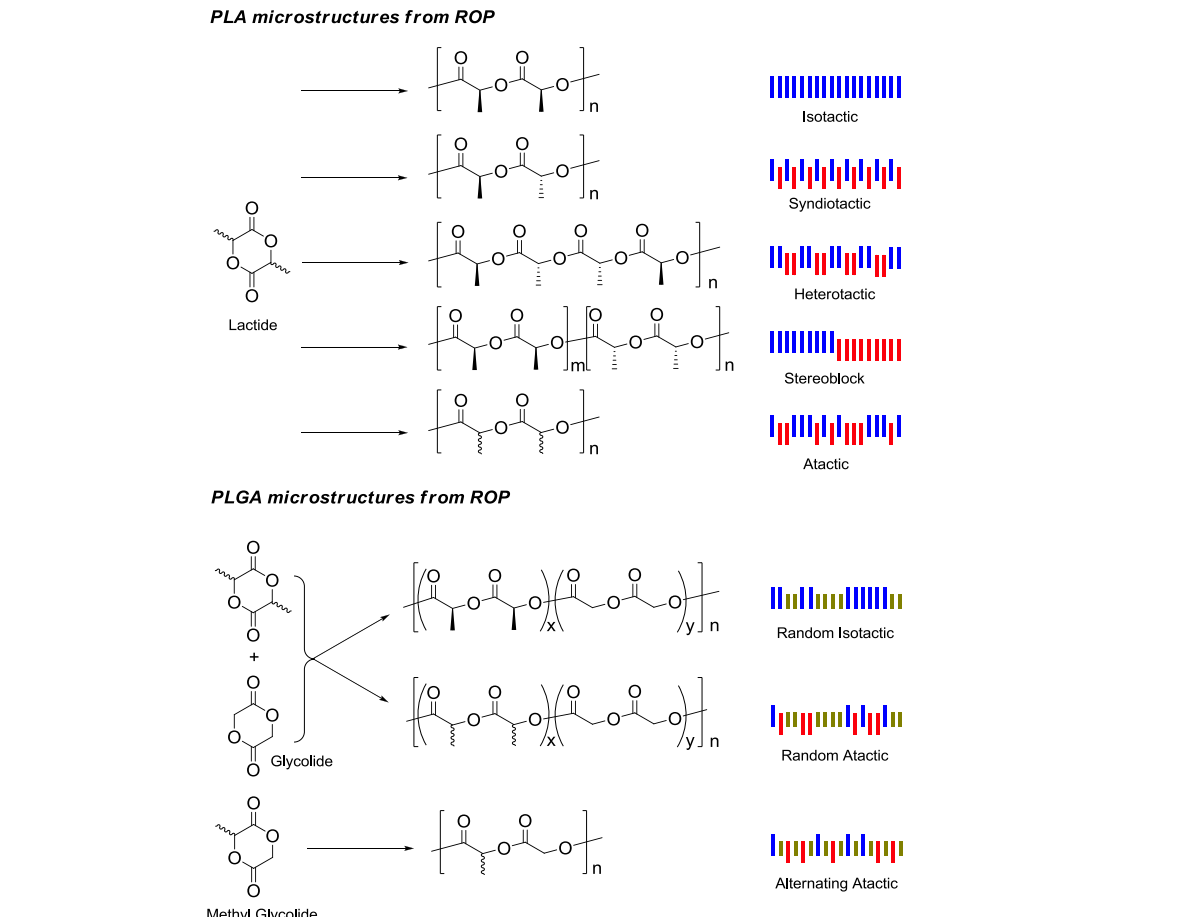
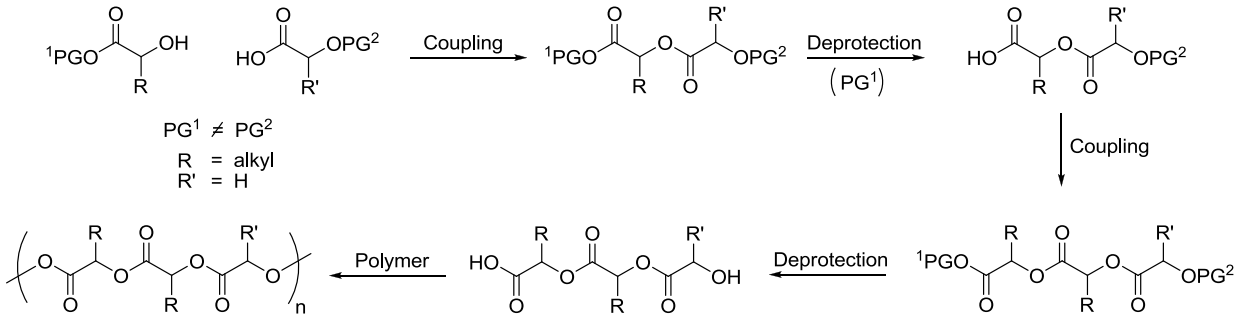


Figure 4. Comparison of complex sequences prepared by segmer assembly with simpler PLA and PLGA microstructures prepared by ring-opening polymerization.[20-23,25,27,75]

2.0 SYNTHESIS OF PLGA RSC – CORRELATION OF SEQUENCED MICROSTRUCTURES WITH NMR SPECTRA AND THERMAL PROPERTIES

2.1 OVERVIEW

A series of RSC PLGAs based on dimeric, trimeric, tetrameric and hexameric repeating units have been prepared by condensation of the pre-formed segmers. Segmers were assembled in a convergent fashion by reacting partly protected subunits to form completely protected products which, after subsequent deprotection of both termini, yielded the desired segmers as α-hydroxy carboxylic acids. This segmer/oligomer assembly methodology, modeled from peptide syntheses, has been well established for lactic and glycolic acids[94,95] as well as hydroxy-alkanoates (Scheme 3).[96,97]



Scheme 2. General scheme for segmer assembly and polymerization.

The key reaction in our RSC assembly is the polymerization. Transesterification, chain transfer and epimerization of the lactic stereocenter are inherent side reactions in ring-opening and traditional condensation polymerizations due to the extremely reactive catalysts or high temperature and high vacuum necessary to drive the equilibrium to polymer formation. Adapting a mild condensation method from Akutsu and Moore,[98,99] we are able to polymerize specific segmers with minimal (< 5%) loss of sequence or stereosequence.

2.2 NAMING CONVENTIONS

Segmers are named by listing the monomers in sequence order from the C-side to the O-side using the abbreviations in Table 1. **Bn-LL$_{rac}$G** is, therefore, a trimer of stereopure L-lactic acid, *rac*-lactic acid and glycolic acid that bears a benzyl protecting group on the carboxylic acid (C-side) terminus. Additionally, the deuterium labeled lactic and glycolic acids are labeled **L$_{d,rac}$** and **G$_{d2}$**, respectively. Polymers are named from the exact segmer used. Thus, the polymer prepared from **LLG** is named **poly LLG** rather than **poly GLL** despite the homology of the two sequences after polymerization i.e. …LLGLLGLLGLLGLLGLLG…

Table 1. Naming conventions for segmers and polymers

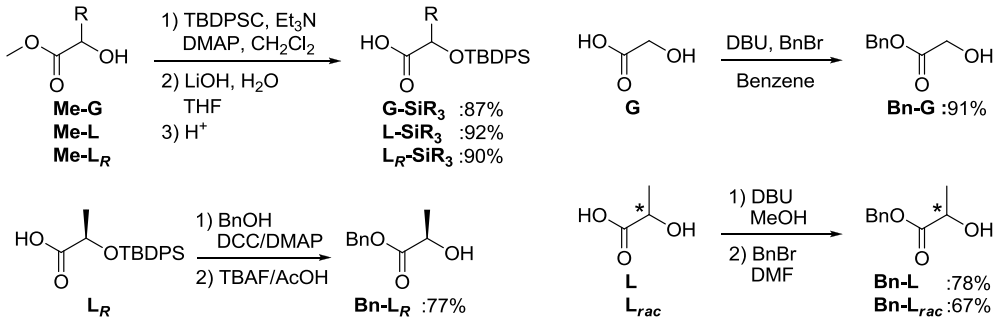
Symbol	Definition
L	L-Lactic unit (*S* configuration)
$\mathbf{L}_{R}$	D-Lactic unit (*R* configuration)
$\mathbf{L}_{rac}$	*rac*-Lactic unit
$\mathbf{L}_{\mathbf{d},rac}$	α-d-*rac*-Lactic unit
G	Glycolic unit
$\mathbf{G}_{\mathbf{d2}}$	α-d,d-Glycolic unit
Bn	Benzyl protecting group
$\mathbf{SiR}_{\mathbf{3}}$	Silyl protecting group (*t*Butyldiphenylsilyl)

2.3 RESULTS

2.3.1 Building Block Syntheses

Orthogonally protected building blocks were prepared in 1 or 2 steps from commercially available materials. Methyl glycolate, methyl (*S*)-lactate and methyl (*R*)-lactate were treated with triethylamine, dimethylaminopyridine (DMAP) and *tert*-butyldiphenylchlorosilane (TBDPSCl) to yield the silyl-protected esters which, after saponification with lithium hydroxide, gave the corresponding silyl-protected acids **G-SiR$_3$**, **L-SiR$_3$** and **L$_R$-SiR$_3$** in 77-92% yields (Scheme 3).[100,101] Benzyl glycolate (**Bn-G**) was prepared by the deprotonation of glycolic acid using 1,8-diazobicyclo[5.4.0]undec-7-ene (DBU) in dry benzene followed by the addition of benzyl bromide. After refluxing for 10 h the product was isolated and purified by vacuum distillation in 91% yield (200 g reaction). Benzyl lactates **Bn-L** and **Bn-L$_{rac}$** were prepared in a similar manner, although the lactic acid starting material which is purchased as a 90% solution in water

must first be dried by addition of DBU and vacuum distillation. Benzyl protection was achieved by treatment with benzyl bromide in dry dimethylformamide (DMF). Products were isolated after vacuum distillation in 70-80% yields (500 g reaction).[102] Due to limited availability of (*R*)-lactic acid, **Bn-L$_R$** was prepared by dicyclohexylcarbodiimide (DCC)/DMAP ester coupling of benzyl alcohol with **L$_R$-SiR$_3$** followed by removal of the silyl protecting group using tetrabutylammonium fluoride (TBAF) buffered with acetic acid to give a 77% yield over 2 steps.



Scheme 3. Preparation of silyl and benzyl protected building blocks.

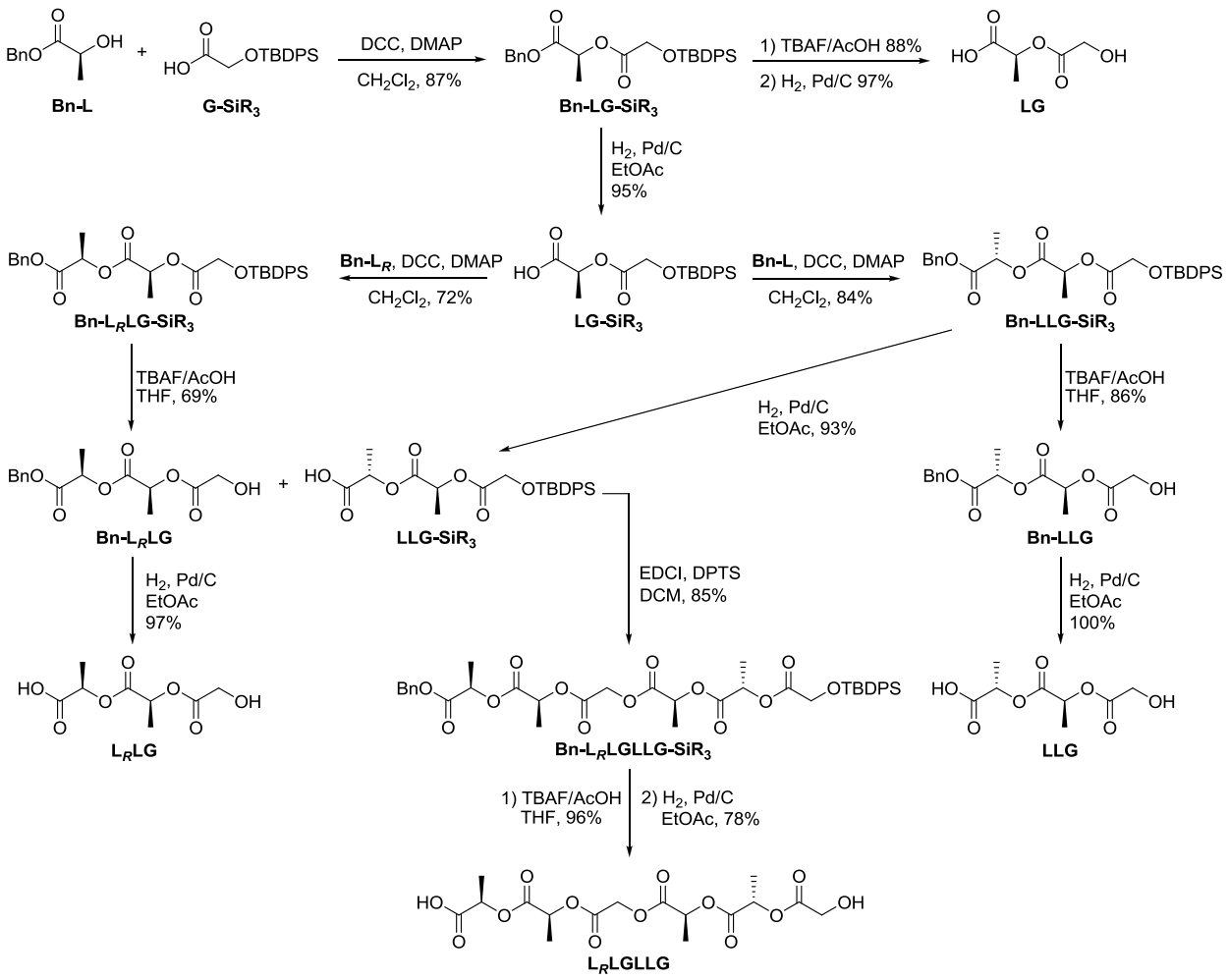
2.3.2 Segmer Assembly

Utilizing the mono-protected building blocks, segmers of any designed sequence and/or stereosequence could be assembled. Scheme 4 is an illustrative example of the level of sequence complexity that can be obtained from 3 simple building blocks. Dimer **Bn-LG-SiR$_3$** was prepared from the coupling of **Bn-L** and **G-SiR$_3$** in an 87% yield.[103] Deprotection of both protecting groups gave segmer **LG** in an 85% yield over 2 steps. To access higher segmers, selective removal of the benzyl-protecting group of **Bn-LG-SiR$_3$** by catalytic hydrogenolysis was used to generate the partially deprotected **LG-SiR$_3$** unit in a 95% yield. **Bn-L** and **Bn-L$_R$** were coupled to **LG-SiR$_3$** to generate di-protected trimers **Bn-LLG-SiR$_3$** and **Bn-L$_R$LG-SiR$_3$** in 84 and 72% yields, respectively. Removal of both protecting groups gave segmers **LLG** and **L$_R$LG**

in 83% and 67% yields. Hexamer **L$_R$LGLLG** was synthesized by coupling partially deprotected trimeric segmers **Bn-L$_R$LG** and **LLG-SiR$_3$** followed by subsequent deprotections in a 75% yield overall. Table 2 lists the corresponding building blocks used to prepare segmers of trimeric length or greater.

Table 2. Segmers and corresponding building blocks

Segmer	Building Blocks	Segmer	Building Blocks
GLG	G + LG	**GLGL$_R$**	GL + GL$_R$
GL$_{rac}$G	G + L$_{rac}$G	**LLLG**	LLL + G
LLG	L + LG	**LLL$_{rac}$G**	LL + L$_{rac}$G
LL$_R$G	LL$_R$ + G	**LL$_{rac}$LG**	LL$_{rac}$L + G
LL$_{rac}$G	L + L$_{rac}$G	**L$_{rac}$LLG**	L$_{rac}$L + LG
L$_{rac}$LG	L$_{rac}$ + LG	**L$_{rac}$L$_{rac}$LG**	L$_{rac}$L$_{rac}$L + G
L$_{rac}$L$_{rac}$G	L$_{rac}$ + L$_{rac}$G	**GLLG**	G + LLG
LLL	L + LL	**GL$_R$LG**	GL$_R$ + LG
LL$_{rac}$L	L + L$_{rac}$L	**GLL$_{rac}$G**	G + LL$_{rac}$G
L$_{rac}$L$_{rac}$L	L$_{rac}$ + L$_{rac}$L	**LLGLL$_R$G**	LLG + LL$_R$G



Scheme 4. Synthesis of dimeric, trimeric and hexameric segmers.

2.3.3 Stereochemical preferences

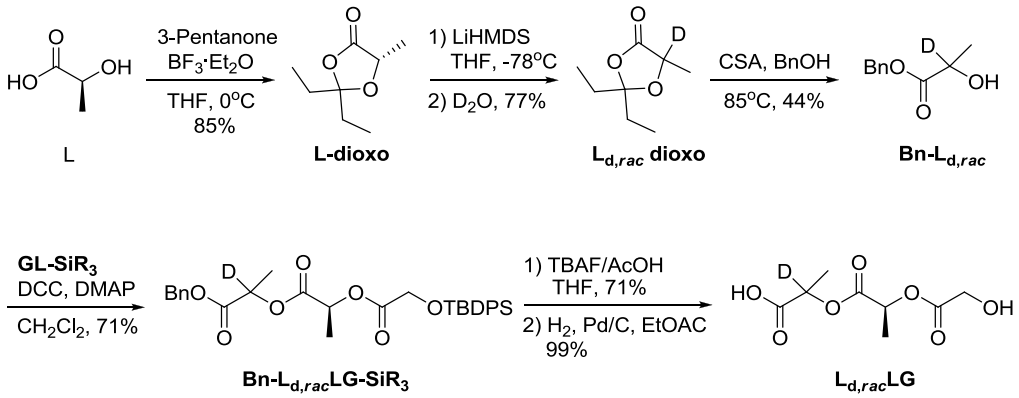
It should be noted that in the preparation of segmers from the racemic precursors, there is a slight preference, 60:40, for the formation of units with different stereocenters i.e. **LL$_R$G** and **L$_R$LG** are favored over **LLG** and **L$_R$L$_R$G** in **L$_{rac}$L$_{rac}$G**. This preference can be clearly seen in the copolymer spectrum as well as in the spectra for **poly L$_{rac}$LLG** and **LL$_{rac}$LG**. The synthesis of the oligomer **L$_{rac}$LG** and **LLL$_{rac}$G** also results in a slight bias towards **L$_R$LG** over **LLG** and **LLL$_R$G** over **LLLG** but it is difficult to detect by NMR once polymerized.

2.3.4 Deuterium Labeled Segmer Synthesis

A complementary subset of deuterium labeled segmers was prepared by incorporation of deuterium labeled monomers. Vert and coworkers have previously attempted deuterium exchange with both lactide[104] and glycolide[105] utilizing a High-temperature Solid-state Catalytic Isotope Exchange (HSCIE) methodology. This approach, however, yielded little exchange and a mixture of deuterated products. Realizing the difficulty of such an endeavor, our approach focused on deuterium exchange utilizing established enolate chemistry.[106,107]

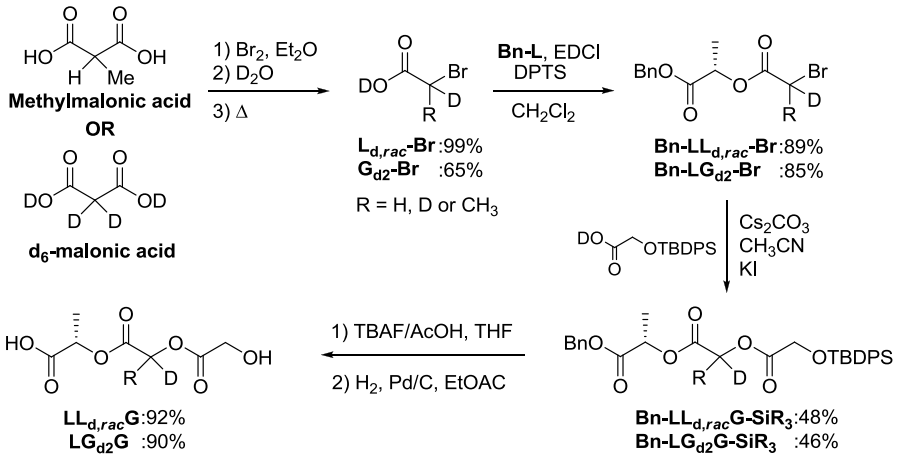
Utilizing Seebach's dioxolanone methodolgy,[106,107] racemic α-deuterated benzyl lactate (**Bn-L$_{d,rac}$**) was prepared in three steps from lactic acid (Scheme 5). Condensation of the dehydrated lactic acid with 3-pentanone using boron triflouride generated **L-dioxo** in an 85% yield.[108] **L-dioxo** was treated with lithium hexamethyldisalazide (LiHMDS) to generate a lactic enolate that when quenched with deuterium oxide afforded **L$_{d,rac}$-dioxo** in a 77% yield with >85% deuterium incorporation.[109,110] Camphorsulfonic acid mediated transesterification with benzyl alcohol gave **Bn-L$_{d,rac}$** in 44% yield and segmer **L$_{d,rac}$LG** was prepared similarly to **LLG**

in a 50% yield. Similar attempts with **G-dioxo** and **L-chlorophenyldioxo** (Figure 5), synthesized for stereospecific deuterium incorporation, resulted in the deprotection of the acids without deuterium exchange.



Scheme 5. Synthesis of segmer $L_{d,rac}$LG from lactic acid utilizing dioxolanone protecting group.

Highly enolizable malonic acids provided a more generalized approach to prepare deuterated monomers of both L and G with nearly complete deuterium exchange and good yields. Deuterium labeled 2-bromopropionic acid and bromoacetic acid (**$L_{d,rac}$-Br** and **G_{d2}-Br**) were prepared in three steps according to the procedure of Hoberman (Scheme 6).[111,112] Commercially available methylmalonic acid and *per*-deuterated malonic acid were treated with bromine in dry ether to generate the bromomalonic acids in quantitative yields. Treatment with deuterium oxide facilitated deuterium exchange. Decarboxylation followed by distillation under reduced pressure gave **$L_{d,rac}$-Br** and **G_{d2}-Br** in 99 and 65% yields, respectively, with > 99% deuterium incorporation. **$L_{d,rac}$-Br** and **G_{d2}-Br** were coupled with **L-Bn** under mild esterification conditions to give bromo-dimers **Bn-L$L_{d,rac}$-Br** and **Bn-LG_{d2}-Br** in 89 and 85% yields, respectively. The bromo-dimers were treated with cesium carbonate, potassium iodide and deuterated **G-SiR_3** in dry acetonitrile to give **Bn-L$L_{d,rac}$G-SiR_3** and **Bn-LG_{d2}G-SiR_3** in 48 and 46% yields, respectively. After subsequent deprotections, segmers **L$L_{d,rac}$G** and **LG_{d2}G** were isolated in 92 and 90% yields, respectively.



Scheme 6. Synthesis of segmers $\mathbf{LL_{d,rac}G}$ and $\mathbf{LG_{d2}G}$ utilizing malonic acids.

Other di-protected monomers were prepared and screened under deuterium exchange enolate conditions, lithium diisopropylamide (LDA) or LiHMDS and quenched with D_2O or *d*-acetic acid, to much less effect (Figure 5). Dispiroketals, **BisTHP-L** and **BisTHP-G** were synthesized according to procedures by Ley and coworkers, involving acid catalyzed condensation of lactic and glycolic acid with a di-THP protecting group **BisTHP**.[113,114] Deuterium exchange (>80%) proceeded with **BisTHP-L** and **BisTHP-G** using LDA and D_2O in good yield (70%). However the synthesis and purification of **BisTHP** was not amenable to the multigram scale up necessary. Di-protected benzyl monomers, $\mathbf{Bn\text{-}L\text{-}SiR_3}$ and $\mathbf{Bn\text{-}G\text{-}SiR_3}$ were synthesized in good yield using previously discussed silyl-protecting reaction and THP protected **Bn-L-THP** was prepared in quantitative yield according to procedures by Yoshikoshi, et. al.[115] All of the benzyl monomers deprotected without exchange when treated with LDA and D_2O. Switching to LiHMDS prevented the undesired silyl deprotection of $\mathbf{Bn\text{-}L\text{-}SiR_3}$ and $\mathbf{Bn\text{-}G\text{-}SiR_3}$ however, deuterium exchange was not observed.

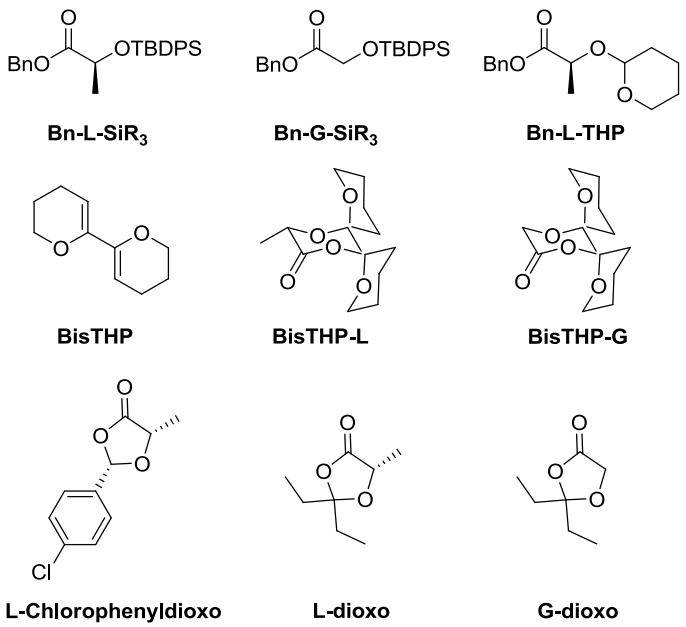
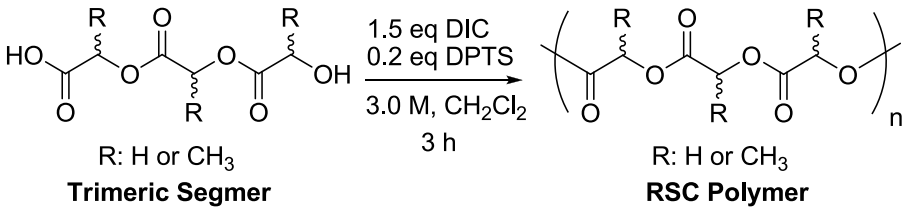


Figure 5. Di-protected monomers prepared for deuterium exchange.

2.3.5 Polymerization conditions and molecular weight determinations

Polymerization conditions, utilizing mild esterification reagents 1,3 diispropylcarbodiimide (DIC) and 4-(dimethylamino)pyridinium *p*-toluenesulfonate (DPTS), were adapted from Moore and Akutsu (Scheme 7).[98,99] In this way, for example, **poly LLG** was prepared by the DIC/DPTS-mediated condensation of the fully deprotected **LLG** segmer. Initially DCC and DMAP were screened as plausible polymerization catalysts but the polymer yields and molecular weights were found unreliable (Table 3).[103] All polymers were isolated as colorless solids by precipitation into methanol and purified by re-precipitation from methylene chloride into methanol to give yields ranging from 50 to 99% (Table 4 and Table 5). It should be noted that we did not observe significant sequence preferences when assembling segmers with racemic units into polymers. We have found that the inherent but slight preferences for alternation of stereochemical centers that were observed in selected segmer preparations can be minimized in

the polymer preparation by coupling segmers bearing L groups on one terminus and G's on the other.



Scheme 7. PLGA RSC polymerization conditions.

Molecular weights for the polymers were determined by both size exclusion chromatography (SEC) and multi-angle laser light scattering (MALLS). Relative molecular weights were obtained by SEC in both THF and $CHCl_3$ vs. polystyrene standards with the number average molecular weights (M_n) ranging from 8.0 – 55.0 kDa in THF and 19.3 – 42.3 kDa in $CHCl_3$. Absolute M_ns were determined for **poly LG**, **GLG**, **LLG** and **L*rac*LG,** using SEC-MALLS. The dramatic lack of correlation between the SEC molecular weights in the two solvents and the differences between these molecular weights and the absolute M_ns determined by MALLS, makes it clear that the R_g of the polymers is extremely sequence and solvent dependent. The SEC molecular weights must, therefore, be regarded with special care. By interpolation of the SEC and SEC-MALLS data obtained, however, we can say with a high degree of confidence that the majority of the polymers prepared have an absolute molecular weight > 15 kDa which corresponds to a DP > 200 (based on the count of glycolic and lactic units). This conclusion is further substantiated by the lack of endgroups observed in the NMRs of these polymers. Previous studies by others on related polymers have shown microstructure dependent SEC behavior.[116,117]

The molecular weights of the RSCs, while lower than those routinely achieved by ring-opening of lactides and glycolides, are respectable for a condensation polymerization on the 1-2

g scale that we are currently employing. Moreover, it worth noting again that *polymers with the sequence complexity of those reported herein cannot be produced by any known ROP catalytic system.*

Table 3. PLGA RSC characterization data for DCC/DMAP polymerizations.

		THF		
Polymer	Yield (%)[a]	M_n (kDa)[b]	PDI[b]	DP[c]
LG	42	15.6	1.7	240
L*rac*G	28	9.25	1.4	71
LLG	41	12.9	1.6	191
GLG	80	12.4	1.6	198

[a]Isolated after 2x precipitation in MeOH; [b]Determined by SEC relative to PS standards; [c]DP from SEC data based on the number of lactic and glycolic monomers.

Table 4. PLGA RSC characterization data from ref 93.

Polymer	Yield (%)[a]	THF M_n (kDa)[b]	THF PDI[b]	$CHCl_3$ M_n (kDa)[b]	$CHCl_3$ PDI[b]	$CHCl_3$ Absolute M_n[c]	$CHCl_3$ DP[d,e]
LG	63	27.4	1.3	33.3	1.3	13.4	512 (206)
L*rac*G	52	28.8	1.3	34.3	1.4	---	527
GLG	78	26.2	1.2	36.2	1.4	19.4	577 (309)
GL*rac*G	60	21.4	1.3	27.5	1.4	---	439
LLG	70	41.2	1.2	41.8	1.3	23.1	620 (343)
LL*R*G	71	29.0	1.4	42.3	1.3	---	628
L*R*LG	59	30.6	1.4	39.8	1.4	---	591
L*rac*L*rac*G	65	30.5	1.4	35.2	1.3	---	522
LL*rac*G	50	17.8	1.4	19.3	1.6	---	286
L*rac*LG	83	27.4	1.4	40.5	1.4	25.9	601 (384)
L$_{d,rac}$LG	99	32.8	1.3	31.7	1.5	---	468
LL$_{d,rac}$G	62	29.6	1.4	33.7	1.4	---	498
GLG$_{d2}$	52	15.2	1.4	25.3	1.5	---	400
GLGL*R*	65	12.3	1.5	21.1	1.4	---	324
LLGLL*R*G	70	30.0	1.4	32.0	1.5	---	475
L*R*LGLLG	63	30.1	1.4	39.8	1.3	---	591

[a]Isolated after 2x precipitation in MeOH; [b]Determined by SEC relative to PS standards; [c]Determined by SEC-MALLS; [d]DP from SEC data based on number of lactic and glycolic monomers; [e](DP) from SEC-MALLS data based on number of lactic and glycolic monomers.

Table 5. Miscellaneous RSC characterization data.

Polymer	Yield (%)[a]	THF Mn (kDa)[b]	PDI[b]	DP[c]
LLLG	85	55.0	1.5	802
LLL$_{rac}$G	58	8.5	1.4	124
LL$_{rac}$LG	71	32.9	1.6	480
L$_{rac}$LLG	61	11.7	1.4	171
L$_{rac}$L$_{rac}$LG	68	32.3	1.8	471
GLLG	88	13.0	1.6	200
GL$_R$LG	87	13.3	1.7	204
GLL$_{rac}$G	68	7.9	1.7	121
LL	28	22.2	1.4	308
L$_R$L	43	7.9	1.5	110
LL$_R$	36	14.8	1.3	205
LLL	42	24.0	1.3	333
LL$_{rac}$L	49	15.3	1.3	212
L$_{rac}$L$_{rac}$L	63	27.9	1.3	387

[a]Isolated after 2x precipitation in MeOH; [b]Determined by SEC relative to PS standards;
[c]DP from SEC data based on the number of lactic and glycolic monomers.

2.3.6 MALDI-TOF Mass Spectroscopy.

MALDI TOF analysis confirms the sequence fidelity of the PLGA RSCs. Using conditions optimized for PLGAs,[118,119] the analysis of selected copolymers was carried out. The masses of the chains present in **poly LG**, for example, differ in molecular weight by increments of exactly 58 amu, corresponding with the glycolic unit, and 72 amu, corresponding to the lactic unit (Figure 6). Moreover, chains differing by exactly one segmer weight (L + G = 130 amu) dominate, which is consistent with synthesis by assembly of segmers. Analogously, the envelope of masses present in the spectrum of **poly GLG** differ in molecular weight by a pattern of G, L and G molecular weights with a predomination of chains differing by exactly a segmer weight. Unfortunately, an analysis of the absolute molecular weights did not correspond to chemically reasonable endgroups. It seems likely that there is some degradation of the samples in the experiment. Full MALDI spectra are available in the appendix.

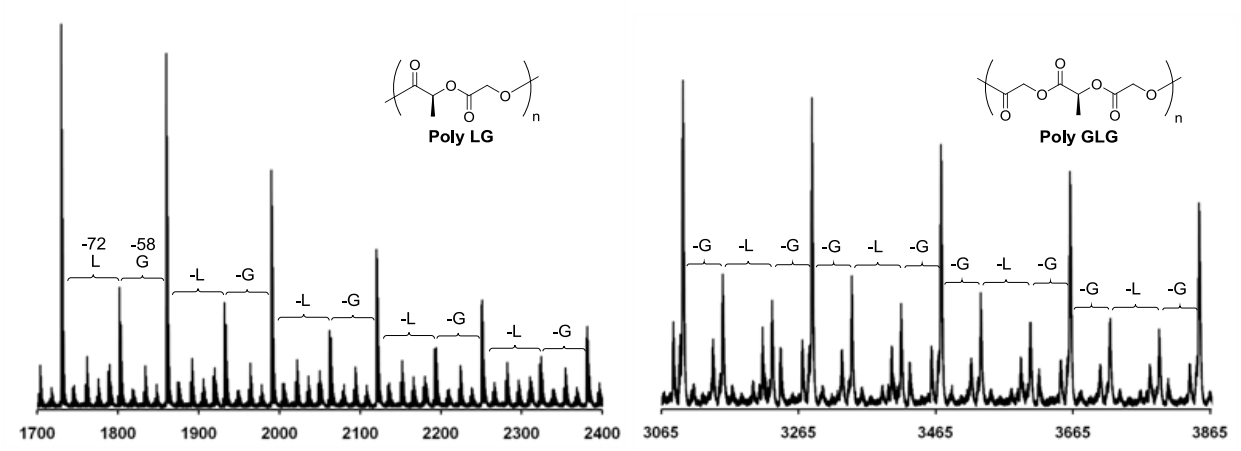


Figure 6. MALDI TOF patterns for **poly LG** (top) and **poly GLG** (bottom).

2.3.7 Thermal Properties.

Differential scanning calorimetry (DSC) was performed on polymer samples and annealed films. The glass transition temperature (T_g) varied slightly due to changes in the sequence composition and stereosequence (Tables 6 and 7). The T_gs for high L content isotactic PLGA RSCs, **poly LG**, **LLG** and **LLLG** were around 57 °C approaching the T_gs for isotactic PLA RSCs **poly LL** and **LLL** around 60 °C. While remaining isotactic, increasing the G content, **poly GLG**, or the number of G-G linkages, **poly GLLG**, the T_g decreased to 50 °C and 46 °C, respectively. Within each series, except GLG and GLLG, the T_g was dependent on stereosequence. Isotactic polymers possessed the highest T_g (57-58 °C for PLGA RSCs and 59-61 °C for PLA RSCs), the atactic polymers possessed intermediate T_gs (51-55 °C) and the syndiotactic polymers possessed the lowest T_gs (46-50 °C). For the GLG and GLLG series, changes in stereochemistry did not significantly change T_gs; **poly GLG** and **GL*rac*G** both exhibit a T_g of 50 °C while **poly GLLG**, **GL*R*LG** and **GLL*rac*G** exhibit T_gs of 46 °C, 44 °C and 45 °C respectively. A possible contributing factor to the lower T_gs of the GLLG series is their molecular weight (~ 10 kDa) while the remaining series are much higher (~ 30 kDa).

The PLA RSCs exhibit a T_m as well as a crystallization transition ($T_{crystal}$) similar to reported PLA transitions (Table 7).[23,25] The T_ms for **poly LL** and **LLL**, 164 °C and 163 °C respectively, were only slightly lower than the T_m for high molecular weight PLA prepared by ROP, 175 °C.[9] Randomization of the stereosequence in **poly L*rac*L*rac*L** lowered the T_m to 124 °C and no melting transition was found for **poly LL*rac*L**. Syndiotactic PLA RSCs **poly L*R*L** and **LL*R*** exhibit T_ms at 138 °C and 148 °C while the T_m for predominately syndiotactic ROP PLA is 153 °C.[11] The 10 °C difference between **poly L$_R$L** and **LL*R*** can be attributed to their lower molecular weights, 7.9 kDa and 14.8 kDa respectively. Interestingly, of the PLGA RSCs, T_ms

were only found for the syndiotactic LLG polymers, **poly L$_R$LG** and **LL$_R$G**, at 154 °C and 158 °C, respectively. The crystallization temperatures were constant around 110 °C for **poly LL**, **LLL** and **LL$_R$** while lower for **poly L$_{rac}$L$_{rac}$L** at 77 °C.

Polymer films were prepared by drop-casting from methylene chloride into DSC pans, drying under vacuum and annealing at 85 °C for 3 h. Annealing had little effect on the transitions for **poly LL$_R$G** and **L$_R$LG** but the T_gs for all of the remaining annealed samples dropped and became less sequence sensitive. A new melting transition appeared for **poly LLG** at 114 °C, which is much lower than that observed for **poly LL$_R$G** and **L$_R$LG**.

Given the regularity of the stereopure PLGA RSCs, the lack of crystallization is somewhat surprising. Although annealing did promote crystallization in the case of **poly LLG**, other sequences did not exhibit melting points despite repeated efforts. We do not rule out the potential for crystallinity, however, as we suspect that we may not have discovered the proper thermal conditions to promote the longer range organization of the chains. Notably, Coates and coworkers did not observe crystal formation for the predominantly heterotactic sequenced PLA.[23]

Table 6. Thermal properties for PLGA RSCs

	M_n[a]	Precipitate		Annealed[b]	
Polymer	(kDa)	T_g (°C)	T_m (°C)	T_g (°C)	T_m (°C)
LG	27.4	57[c]	ND	49[d]	ND
L*rac*G	28.8	55[c]	ND	48[d]	ND
GLGL*R*	12.3	50[c]	ND	---	---
GLG	26.2	50[c]	ND	43[d]	ND
GL*rac*G	21.4	50[c]	ND	---	---
LLG	41.2	57[c]	ND	50[d]	114[c]
L*R*LG	30.6	50[c]	154[d]	---	---
LL*R*G	29.0	48[c]	158[d]	48[d]	155[d]
LLGLL*R*G	30.0	52[c]	ND	48[d]	ND
L*R*LGLLG	30.1	52[c]	ND	48[c]	ND
L*rac*L*rac*G	30.5	51[c]	ND	47[d]	ND
L*rac*LG	27.4	51[c]	ND	48[d]	ND
LL*rac*G	17.8	53[c]	ND	48[d]	ND
LLLG	55.0	58[c]	ND	56[d]	ND
LLL*rac*G	8.5	51[c]	ND	50[d]	ND
LL*rac*LG	32.9	54[c]	ND	50[d]	ND
L*rac*LLG	11.7	51[c]	ND	50[d]	ND
L*rac*L*rac*LG	32.3	53[c]	ND	49[d]	ND
GLLG	13.0	46[c]	ND	---	---
GL*R*LG	13.3	44[c]	ND	---	---
GLL*rac*G	7.9	45[c]	ND	---	---

[a]Number average molecular weights determined by SEC in THF vs PS standards. [b]Polymer films were drop-cast into DSC pans, dried under vacuum and annealed at 85°C for 3 h; [c]Transitions were measured in second heating cycle; [d]Transitions were measured in the first cycle.

Table 7. Thermal properties of PLA RSCs

		Precipitate			Annealed[b]		
Polymer	Mn[a] (kDa)	T_g (°C)[c]	$T_{crystal}$ (°C)[c]	T_m (°C)[c]	T_g (°C)[d]	$T_{crystal}$ (°C)[d]	T_m (°C)[d]
LL	22.2	61	110	164	---	---	---
L*R*L	7.9	46	ND	138	---	---	---
LL*R*	14.8	46	110	148	---	---	---
LLL	24.0	59	109	163	55	ND	164
LL*rac*L	15.3	52	ND	ND	52	ND	ND
L*rac*L*rac*L	27.9	50	77	124	52	ND	ND

[a]Number average molecular weights determined by SEC in THF vs PS standards. [b]Polymer films were drop-cast into DSC pans, dried under vacuum and annealed at 85°C for 3 h; [c]Transitions were measured in second heating cycle; [d]Transitions were measured in the first cycle.

2.4 MICROSTRUCTURAL ANALYSIS

2.4.1 Dimeric L_xG RSCs.

Our major discovery in the study of the alternating **poly L_xG** series polymers for **poly LG**, **L*rac*G** and **GLGL*R*** was the surprisingly high sensitivity of the glycolic methylene protons for the relative stereochemistry of the neighboring lactic units (Figure 7).[103] The difference in the methylene signals of isotactic **poly LG** (δ 4.86 and 4.63, Δ = 0.23 ppm) and syndiotactic **poly GLGL*R*** (δ 4.81 and 4.69, Δ = 0.12 ppm) are particularly illustrative. While each spectrum contains a pair of doublets, as would be predicted for the clearly diastereotopic methylene protons, the chemical shifts are dramatically different.

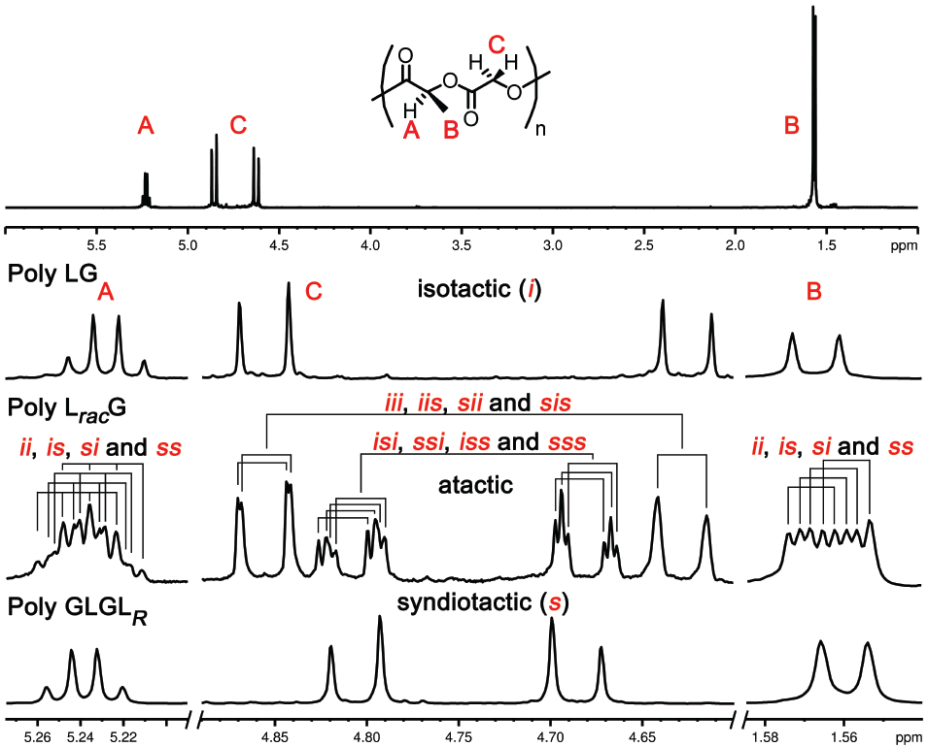


Figure 7. (Top) Full spectrum of **poly LG**; (Bottom) expansions of selected regions for **poly LG, L$_{rac}$G** and **GLGL$_R$.** ^{1}H NMR spectra at 600 MHz in $CDCl_3$**.**

Each of these alternating copolymers possesses a unique stereosequence that can be encoded using the widely accepted convention of assigning relative stereochemistries in polymers as either *i* for neighboring units with the same absolute stereochemistry or *s* for the opposite. Using this coding system, and focusing on a *tetrad* level of resolution, the stereochemistry of **poly LG** can, for example, be expressed as *iii* and **poly GLGL$_R$** as *sss* (Figure 8 and Table 8).

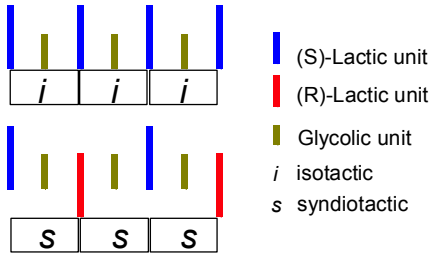


Figure 8. Example of tetrad stereosequence encoding for **poly LG** (all isotactic) and **GLGL$_R$** (all syndiotactic)**.**

Table 8. Tetrad assignments for stereosequences of polymers from the **poly L_xG** series

	LG	**$L_{rac}G$**	**$GLGL_R$**	**60% LG + 40% $L_{rac}G$**	
Tetrads	*i i i*	*i i i*	*s s s*	*i i i*	Major
		i i s		*i i s*	Minor
		s i i		*s i i*	Minor
		s i s		*s s i*	Minor
		i s i		*i s s*	Minor
		s s i			
		i s s			
		s s s			

We focus on the tetrad level because we can clearly see this level of resolution for some sequences present in the more complex spectrum of atactic **poly $L_{rac}G$** (Figure 7)**.** Using the data from the stereopure polymers and from a sequence-weighted copolymer prepared by mixing **LG** and **$L_{rac}G$** in a 60:40 ratio, we were able to make a nearly complete assignment of the signals. We see that the methylene resonances divide into two regions based on the relative stereochemistry of the closest neighboring lactic units: *i*-centered (outer signals) and *s*-centered (inner signals). The resonances for each of the *s*-centered tetrads, *sss*, *ssi*, *iss* and *isi*, can be clearly differentiated while those for the *i*-centered tetrads, *iii*, *iis*, *sii* and *sis*, overlap such that the effective resolution is expressed at a lesser diad or triad level.

The other resonances in the spectra of the dimeric polymers also show stereosequence-dependent chemical shifts, though none exhibit as high a level of sensitivity/interpretability as the methylene protons. A clear chemical shift difference was noted, for example, between the methine and methyl groups from syndiotactic **poly $GLGL_R$** and isotactic **poly LG**. The smaller chemical shift range, however, limits the resolution of the stereosequences present in **poly $L_{rac}G$** to the triad level. In the ^{13}C NMR spectra the L-carbonyl resonances were clearly resolved to the

triad level while the G-carbonyl, L-methyl and L-methine resonances were nearly resolved triads (Figure 9). The *s*-carbonyl resonances for both L and G appeared upfield relative to the *i*-stereoisomer. In contrast, the *s*-methine and *s*-methyl resonances were downfield of the *i*-versions. Interestingly, the methylene resonance, which was so sensitive in the ^{1}H NMR data, was only a broad singlet in the ^{13}C NMR spectrum.

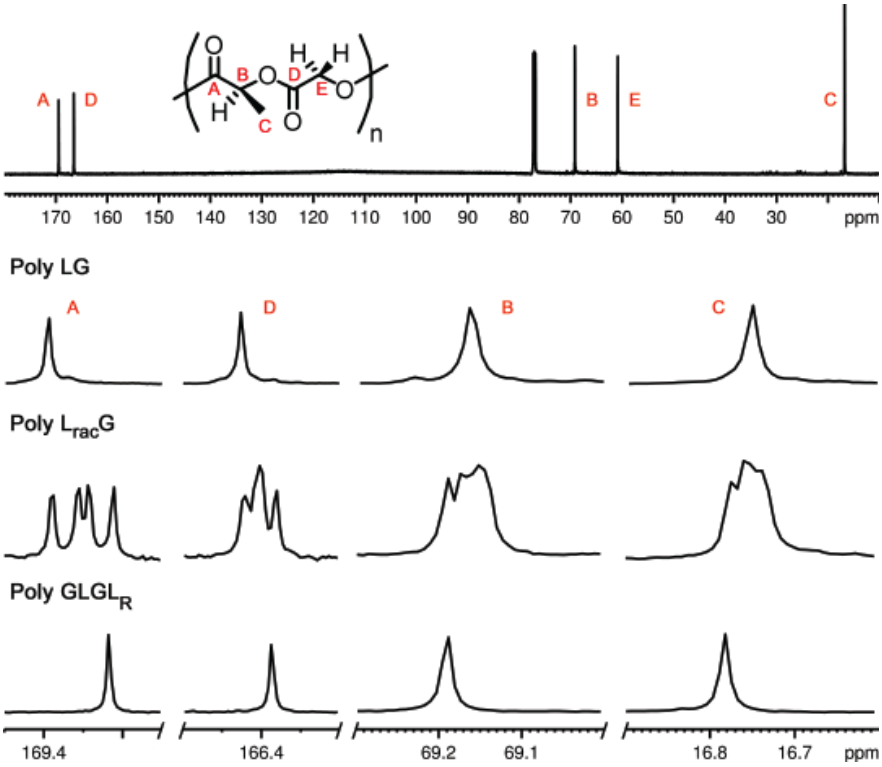


Figure 9. (Top) Full spectrum of **poly LG**; (Bottom) expansions of selected regions for **poly LG**, **L$_{rac}$G** and **GLGL$_R$**. ^{13}C NMR spectra at 150 MHz in $CDCl_3$.

2.4.2 Trimeric GL$_x$G RSCs.

In moving from a dimer-based **LG** copolymer to a trimer-based copolymer, additional complexity was introduced both in the architecture and in the resulting NMR spectra. The third monomer presents the possibility of two different structural sequences, **GLG** or **LLG**, and

multiplies the number of possible stereoisomers. It should be noted again that the choice to refer to a particular sequence as **GLG** rather than **GGL** was based on the unit actually used in the synthesis. Once polymerized, of course, such differences are irrelevant since **poly GLG** would necessarily be the same in all respects as **poly GGL** except in the identity of the endgroups; both would have a repeating sequence of –GGLGGLGGLGGLGGLGGL- in the backbone.

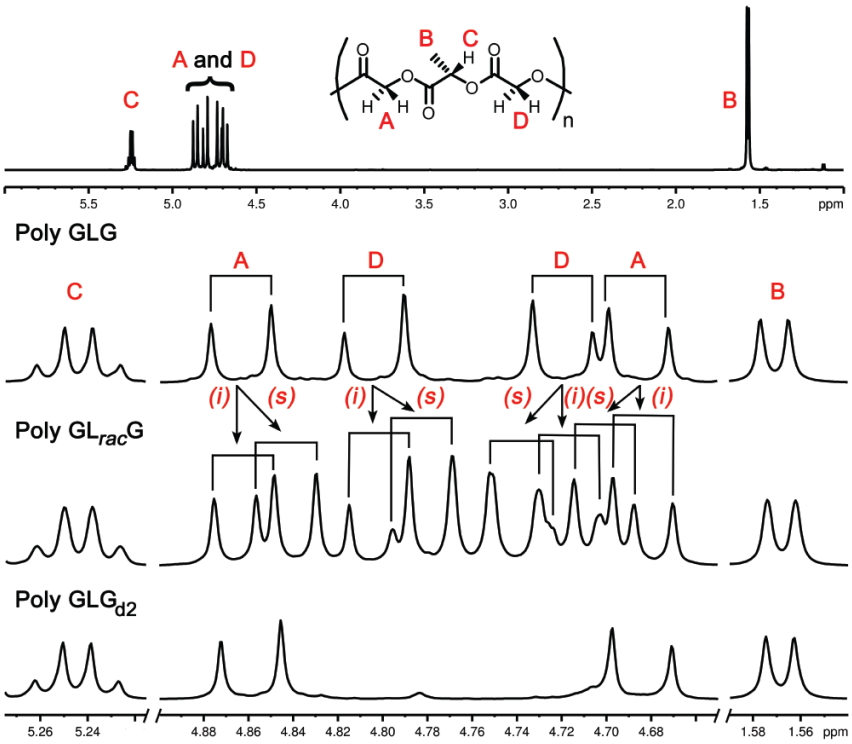


Figure 10. (Top) Full spectrum of **poly GLG**; (Bottom) expansions of selected regions for **poly GLG**, **GL$_{rac}$G** and **GLG$_{d2}$**. ^{1}H NMR spectra at 600 MHz in $CDCl_3$.

Analysis of the NMR spectra of **poly GLG** in both the stereopure and racemic forms required that we first assign the resonances for the two chemically distinct G monomers. The G units are inequivalent due to the intrinsic lack of symmetry of the polyester chain, which has a distinct C- and O-terminus for each polymer and for each sequence within the polymer. We can differentially label the G's then as either being connected to the C-terminus of the lactic residue (G^C) or the O-terminus (G^O). This inequivalence was expressed both in the ^{1}H NMR spectrum

(two pairs of doublets, Figure 10) and in the ^{13}C NMR spectrum (C=O, δ 166.5 and 166.4; δ 60.9 and 60.7, Figure 11). The assignment of the resonances of **poly GLG** was facilitated by comparison with the spectrum of the polymer that was selectively deuterated at G^O, **poly GLG$_{d2}$**. The inner pair of doublets were absent from the ^1H NMR spectrum and the downfield methylene resonance was not present in ^{13}C NMR spectrum. Further confirmation of the assignment came from the 2D Heteronuclear Multiple Bond Coherence (HMBC) NMR spectrum of **poly GLG** in which a 3-bond correlation of the L-carbonyl with the outer pair of doublets from the methylene protons of G^C was observed along with the correlation between the G^O carbonyl and the L-methine (Figure 12).[76,81,120,121]

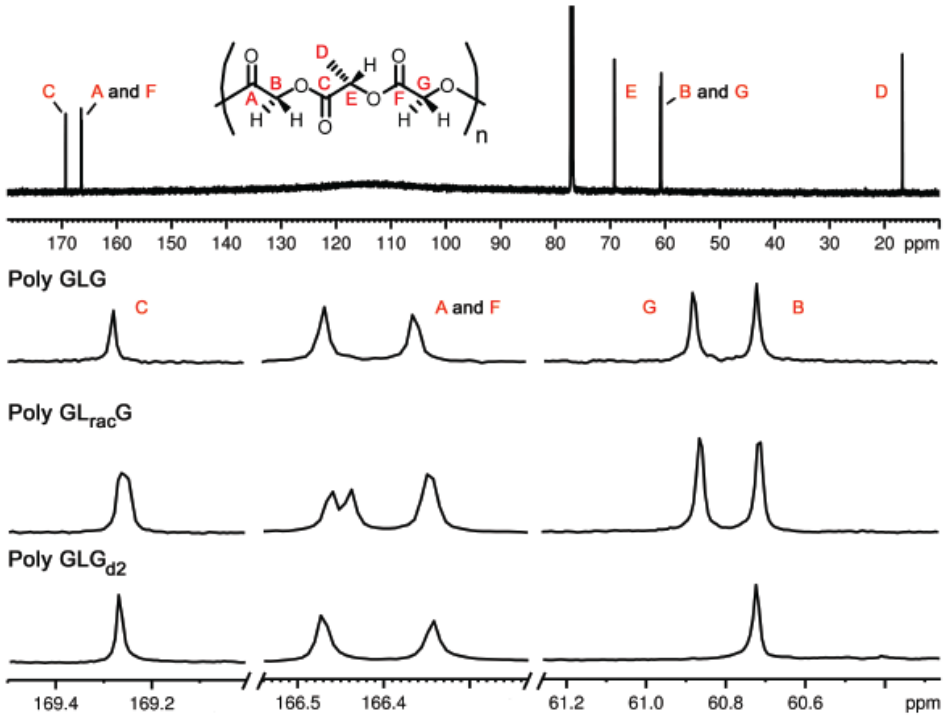


Figure 11. (Top) Full spectrum of poly **GLG**; (Bottom) expansions of selected regions for **poly GLG, GL$_{rac}$G** and **GLG$_{d2}$**. ^{13}C NMR spectra at 150 MHz in $CDCl_3$.

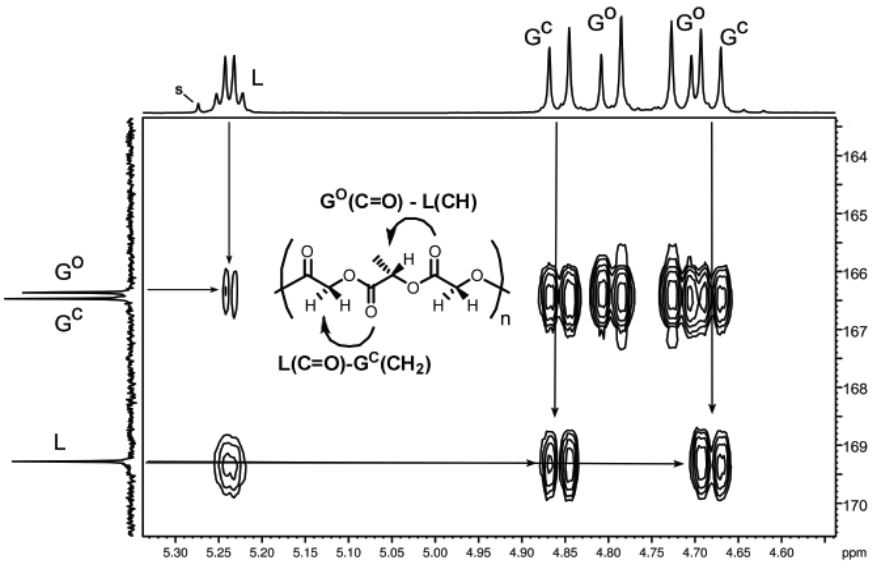


Figure 12. 2D HMBC ^{1}H-^{13}C correlation NMR spectrum for **poly GLG** in $CDCl_3$ (700 MHz, ^{1}H; 175 MHz ^{13}C). The detailed cross peaks correspond to 3-bond correlations between the L-carbonyl with the G^C methylenes and the G^O carbonyl with the L-methine.

Spectra of **poly GL*rac*G** established that the chemical shifts of the G resonances were only modestly sensitive to the tacticity of the polymer. More sensitive than the methyl and methine resonances, which exhibited only a slight broadening, the methylene region exhibited 8 pairs of doublets, which given the inequivalence of the two G units, is consistent with a dyad level of resolution. In other words the chemical shifts of the G resonances depend only upon the relative stereochemistries of the two closest L units. The peaks labeled as *i*-centered resonances corresponded well with the isotactic **poly GLG** standard. The slightly shifted pattern of two pairs of doublets was assigned to the *s* dyad. Partially resolved dyads were likewise visible in the ^{13}C NMR spectrum where the lactic carbonyl appeared to broaden while 3 resonances, two at ca. δ 166.5 and a broadened resonance about δ 166.4 were observed for the glycolic carbonyls.

2.4.3 Trimeric L_xL_xG RSCs.

In moving from the **poly GLG** series to the other trimeric series, **poly LLG**, we must again address the nomenclature and consider the stereochemical implications of the second L unit in the series. The two L units are necessarily inequivalent and are designated as L^O or L^C in relation to the G unit. L^O is connected to the G through the O-terminus and the L^C is connected through the C-terminus. Since the monomer used to prepare these polymers is **LLG** rather than **LGL**, however, the L^O unit will be listed first in the series i.e. L^OL^CG. With these designations in mind, the stereochemical variants of **poly L_xL_xG** can be considered. In Figure 13, our approach to assigning tacticity patterns is illustrated. In the case of **poly L_RLGLLG**, for example, the sequence yields two types of G-centered octads, one of which has an *issiiss* pattern. A subset tetrad pattern of *sii* is recognized from the larger pattern if the relationships from only the nearest four neighbor L's are considered. Interestingly, the same pattern can be reasonably used as a reference for either L^O or L^C despite the shift in the "center" of the sequence. The lack of symmetry in the number of relationships considered relevant on each side of the L center is countered by the fact that the relationships chosen for the polyad maximize the number of adjacent vs. distant interactions, on the assumption (substantiated by the data), that the adjacent relationships will be more influential than the distant ones.

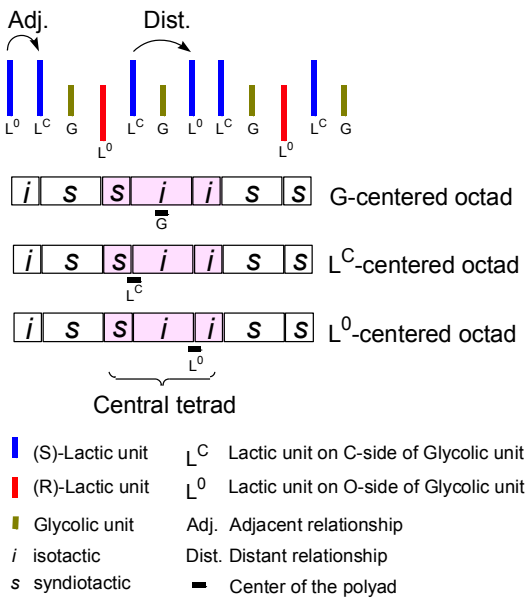


Figure 13. Example of octad-level stereosequence encoding for **poly $L_RL_SGL_SL_SG$**. The central tetrads for each type of unit are defined as including one distant and two adjacent relationships.

In considering the stereochemical possibilities for the **poly L_xL_xG** series we have found it useful to divide the polymers into three families: L^O-variable (**poly L_xLG**); L^C-variable (**poly LL_xG**); and (L^O+L^C)-variable (**poly L_xL_xG**). Table 9 shows the stereochemical possibilities for the first two families at the tetrad, hexad and octad levels. It is important to note that **poly LLG, L_RLG**, and **L_RLGLLG** exhibit all of the stereochemical variations possible in **poly $L_{rac}LG$** at the tetrad level. Likewise **poly LLG**, **LL_RG**, and **$LLGLL_RG$** exhibit the possible tetrad level variations in **poly $LL_{rac}G$.** Stereosequence-specific shading in Table 9 illustrates the hierarchical relationship of the hexads and octads to their parent tetrads.

Table 9. Listing of select polyads for specific **poly L_xL_xG** repeating sequence copolymers[a]

	Poly LLG	Poly L_RLG (LL_RG)	Poly L_RLGLLG	Poly $L_{rac}LG$	Poly $LLGLL_RG$	Poly $LL_{rac}G$
Tetrads	*i i i*	*s s s*	*s i i* *i s s*	*i i i* *s i i* *i s s* *s s s*	*i i s* *s s i*	*i i i* *i i s* *s s i* *s s s*
Hexads	*i i i i i*	*s s s s s*	*i s i i s* *s i s s i*	*i i i i i* *i i i i s* *s s i i i* *s s i i s* *i i s s i* *i i s s s* *s s s s i* *s s s s s*	*s i i s s* *i s s i i*	*i i i i i* *s i i i i* *i i i s s* *s i i s s* *i s s i i* *s s s i i* *i s s s s* *s s s s s*
Octads	*i i i i i i i*	*s s s s s s s*	*i s s i i s s* *s i i s s i i*	*s i i i i i* *s i i i s s* *i i i i s s* *i i i i i i* *s s s i i i* *i s s i i i* *s s s i i s s* *i s s i i s s* *s i i s s i i* *i i i s s i i* *i i i s s s s* *s i i s s s s* *s s s s s s s* *i s s s s s s* *i s s s s i i* *s s s s s i i*	*s s i i s s i* *i i s s i i s*	*i i i i i i i* *s s i i i i i* *s s i i i i s* *i i i i i i s* *i i i i s s i* *s s i i s s i* *s s i i s s s* *i i i i s s s* *i i s s i i i* *s s s s i i i* *i i s s i i s* *s s s s i i s* *i i s s s s s* *s s s s s s i* *s s s s s s s*

[a]Tetrads subsets are identified by color within the hexad and octad tacticity patterns.

The ^{1}H NMR spectra of the glycolic methylene regions of these trimeric series are spectacularly informative—*octad-level resolution of individual stereosequences is observed in some cases*. By comparison with the spectra of **poly LLG, L$_{R}$LG**, and **L$_{R}$LGLLG,** and **L$_{rac}$LG** for the L^{O}-variable family (Figure 14) and **poly LLG**, **LL$_{R}$G**, and **LLGLL$_{R}$G** and **LL$_{rac}$G** for the L^{C}-variable family (Figure 15), it was determined that the chemical shifts of these resonances were inherently hierarchical and facile to interpret.

Beginning by focusing on the L^{O}-variable family (Figure 14), we can assign the resonances from the stereopure standards. The spectrum of the simplest sequence, isotactic **poly LLG,** exhibits a pair of well-separated doublets for the diastereotopic G methylene protons. **Poly L$_{R}$LG**, the fully syndiotactic sequence also exhibits a single pair of doublets while **poly L$_{R}$LGLLG** exhibits two pairs of doublets which is consistent with expectations for this more complex sequence (see Table 9). Although these are stereopure standards with an "infinite" pattern, the resonances are labeled in the figures at the tetrad level for reasons that become clear in the analysis of the racemic variants (*vide infra*).

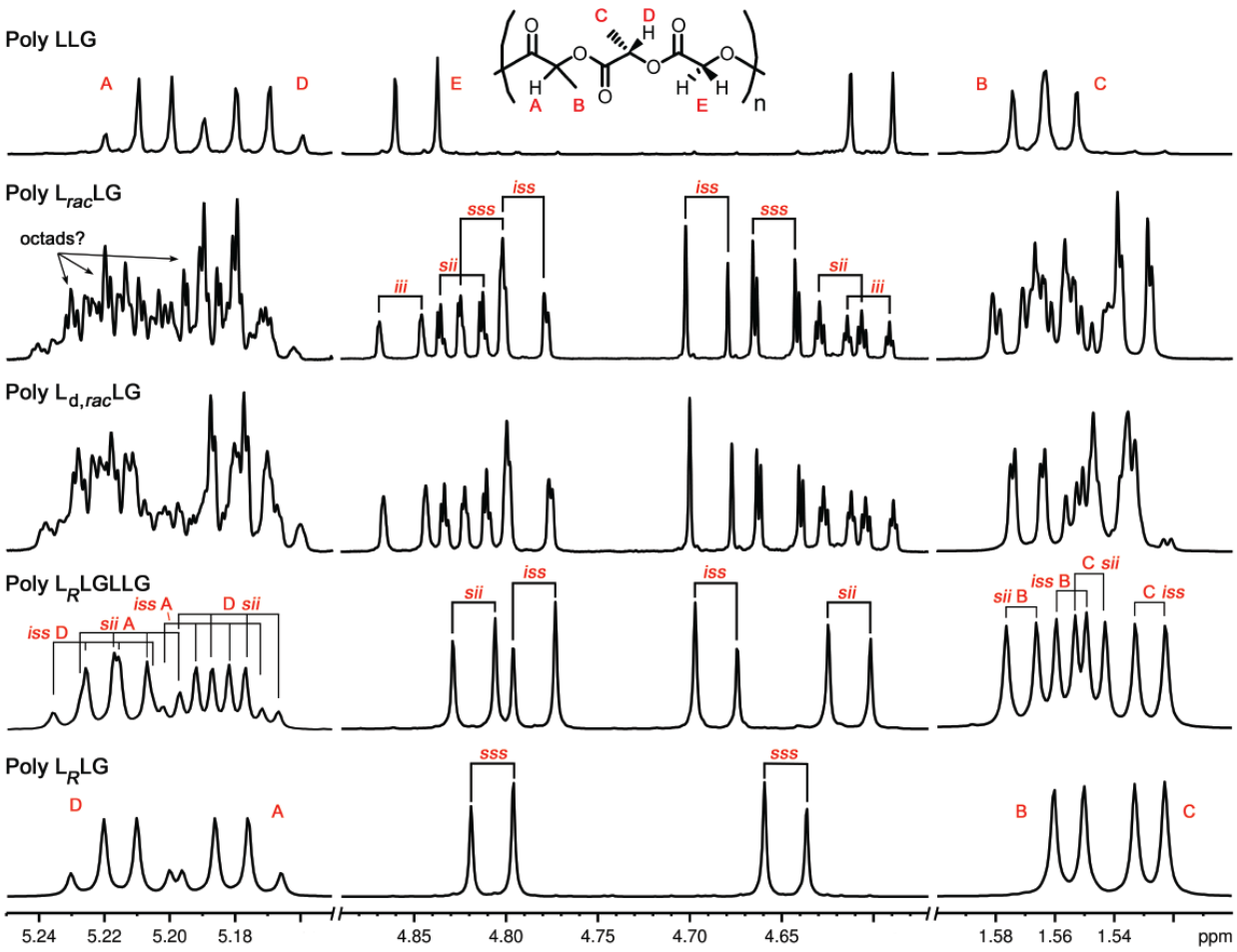


Figure 14. ^{1}H NMR spectra of L^{O}-variable LLG polymers at 700 MHz in $CDCl_3$. Comparisons of the expansions of selected regions for **poly LLG**, **L$_{rac}$LG**, **L$_{d,rac}$LG**, **L$_R$LGLLG**, and **L$_R$LG**.

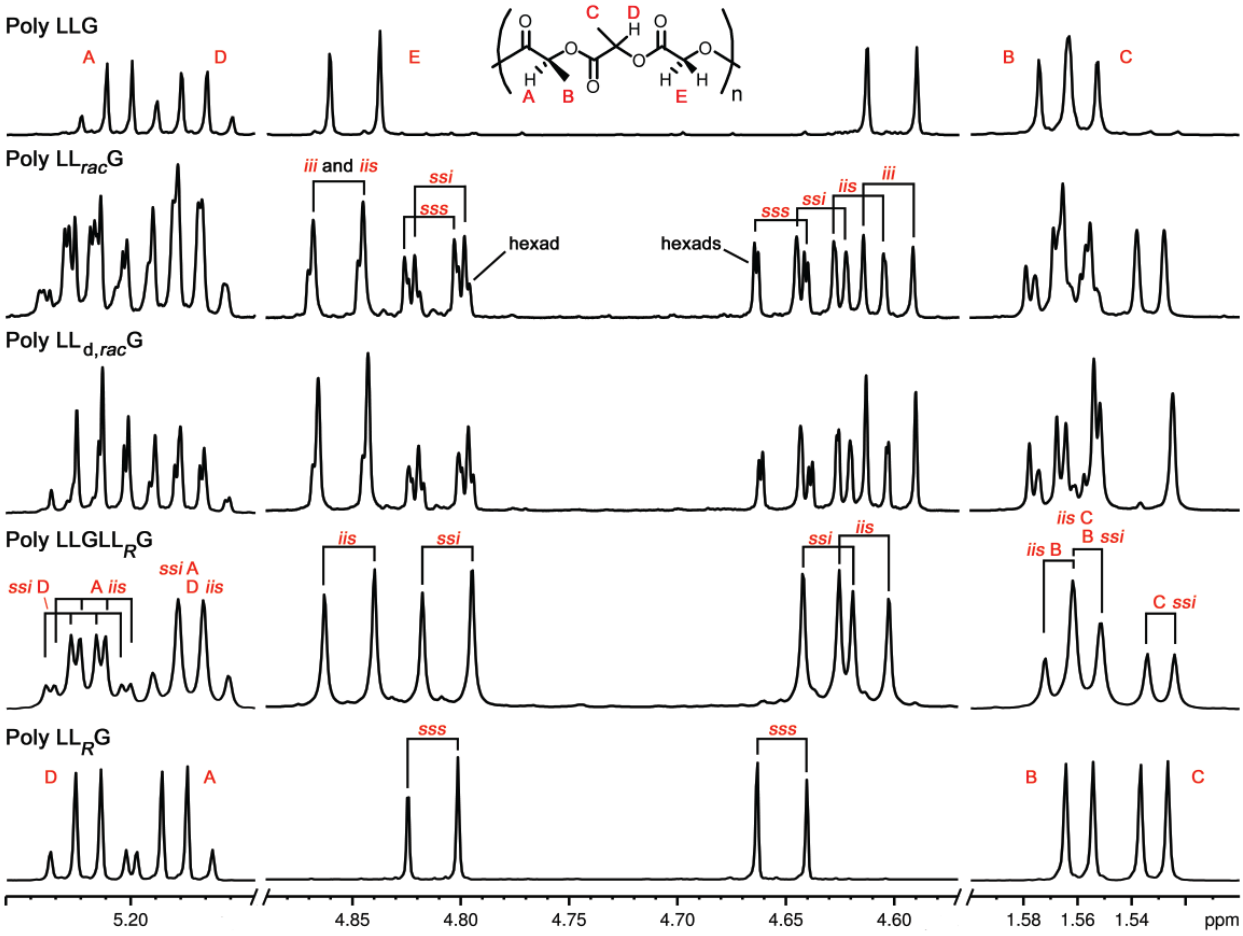


Figure 15. ^{1}H NMR spectra of L^{C}-variable LLG polymers at 700 MHz in $CDCl_3$. Comparisons of the expansions of selected regions for **poly LLG**, **LL$_{rac}$G**, **LL$_{d,rac}$G**, **LLGLL$_R$G**, and **LL$_R$G**.

The analysis of spectrum of **poly L*rac*LG** reveals the useful hierarchical nature of the shift pattern in the methylene region: the gross shifts are determined by the central tetrad relationships while the fine shifts are determined by more distant ones. The methylene region of this polymer manifests as well-separated sets of pairs of doublets, one pair for each of the resolved stereosequences. By comparison of the stereosequence standards and the spectrum of **poly L*rac*LG,** it is clear that the resonances are grouped by the central tetrad relationships, *iii*, *sss*, *iss*, and *sii* into four well-separated regions. Within these tetrad-controlled shift regions, the "fine" chemical shifts are then determined by the relative stereochemistries of L units beyond the central four.

The degree of resolution of longer range relationships in the methylene region is clearly sequence dependent. Focusing on the upfield proton of the G methylene of **poly L*rac*LG** several levels of resolution can be identified (Figure 16). In the case of the *iii* set, for example, there are four nearly resolved doublets, the number that would be expected if there was a doublet present for each of the four possible octad level sequences. Although we do not have standards with sufficient complexity to label the individual sequences, the extremely high level of resolution is striking. The other three sets of doublets in the same region of this spectrum exhibit varying sensitivities ranging from the tetrad to hexad to octad level.

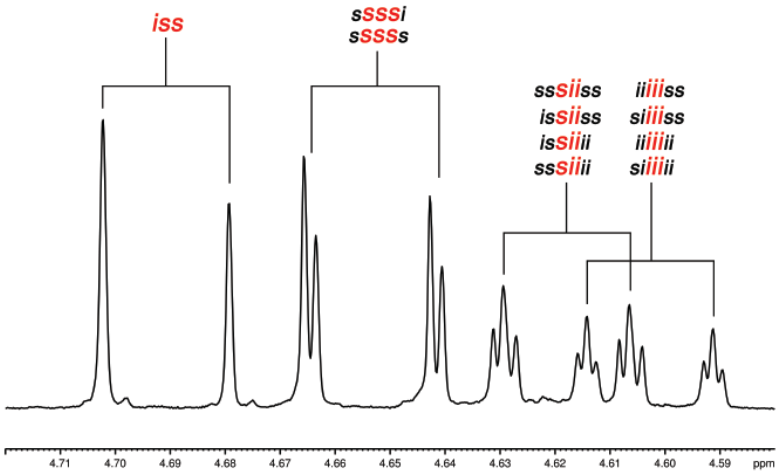


Figure 16. ^{1}H NMR expansion for the upfield diastereotopic proton of the glycolic methylenes of **poly L$_{rac}$LG**. The level of sensitivity for sequence ranges from tetrad (*sii*, *iii*) to hexad (*sss*) to octad (*iss*) depending on the core tetrad sequence.

A similar hierarchical pattern is observed in the methylene region of **poly LL$_{rac}$G** (Figure 15). Sets of pairs of doublets corresponding to the expected tetrads, *iii*, *sss*, *ssi*, and *iis*, can be easily assigned. Within these sets, further resolution of certain sequences is observed. It should be noted that the spectra of **poly L$_R$LG** and **LL$_R$G** (Figures 14 & 15) are identical as would be predicted from their enantiomeric relationship.

Changing the NMR solvent from $CDCl_3$ to d_6-DMSO dramatically decreases the resolution of the spectra (Figure 17). The chemical shift range of the methylene (and other regions) is decreased and sequence resolution is reduced.

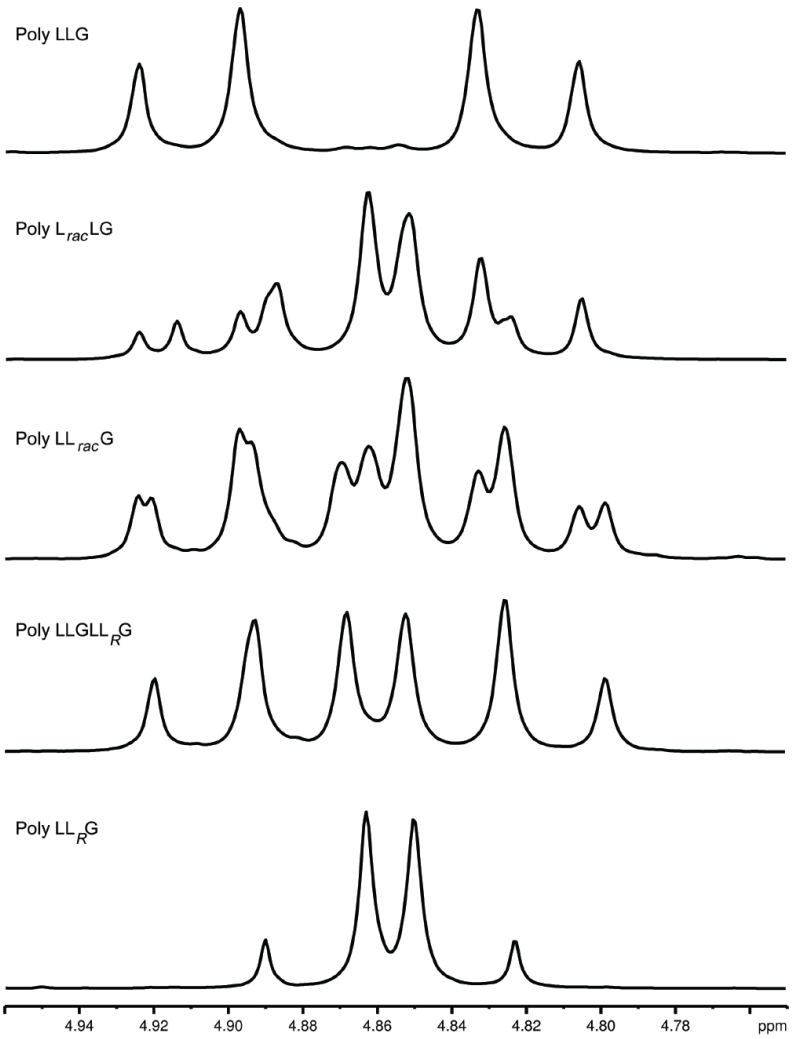


Figure 17. ^{1}H NMR spectra of the methylene region for selected LLG polymers at 600 MHz in d_6-DMSO.

We were also able to make significant progress in assigning the methyl and methine regions of the trimeric series of polymers. These regions are inherently more difficult to interpret because of the presence of the two inequivalent lactic units, the relatively small chemical shift range, and the lack of an hierarchical shift pattern. Primary differentiation of L^O vs. L^C in the fully sequenced polymers **poly LLG**, **L*R*LG** and **L*R*LGLLG** was accomplished using a combination of 2D NMR techniques. Methine resonances were assigned by 2D HMBC NMR spectra where a correlation between the G carbonyl and the L^C methine was observed. Frustrating facile assignment, the relative chemical shifts of the L^O and L^C methines were not consistent throughout the stereochemical series. As Figure 18 illustrates, in isotactic **poly LLG** the L^C resonance is upfield of the L^O resonance but the order is reversed in syndiotactic **poly L*R*LG**. In polymers that contain mixed stereochemical relationships, **poly L*R*LGLLG**, and multiple mixed relationships, **poly L*rac*LG** and **L*rac*L*rac*G**, the 2D correlations showed that the chemical shifts of the L^O and L^C methines were extremely sequence dependent and likely to invert chemical shift order from sequence to sequence. By coupling the assignments of the methine region with 2D COSY NMR spectroscopy, however, the methyl region could be assigned. Unlike the methine resonances, the L^O methyl resonances were always downfield of the corresponding L^C resonances.

Although complete interpretation of the methine and methyl regions for **poly L*rac*LG** and **LL*rac*G** could not be accomplished, it was clear that the sequence resolution of both regions was greater than a tetrad level. It should be noted that neither homonuclear decoupling nor 2D NMR was of much use in interpreting these spectra further. The chemical shift envelope for each type of signal was large enough to render the complete homonuclear decoupling of the regions impractical while the small chemical shift range and sequence-dependent shift inversions (*vide*

supra) hindered the interpretation of 2D spectra. The relatively modest simplification of the spectra for the selectively deuterated polymers **poly $L_{d,rac}$LG** and **$LL_{d,rac}$G,** however, establishes the sensitivity of these signals for the stereochemical relationships of lactic units beyond the tetrad level in the chain. Moreover, by simple counting of the resonances and the comparison of the spectra with the stereosequence standards, it is clear that some sequences are actually resolved to a hexad or even octad level.

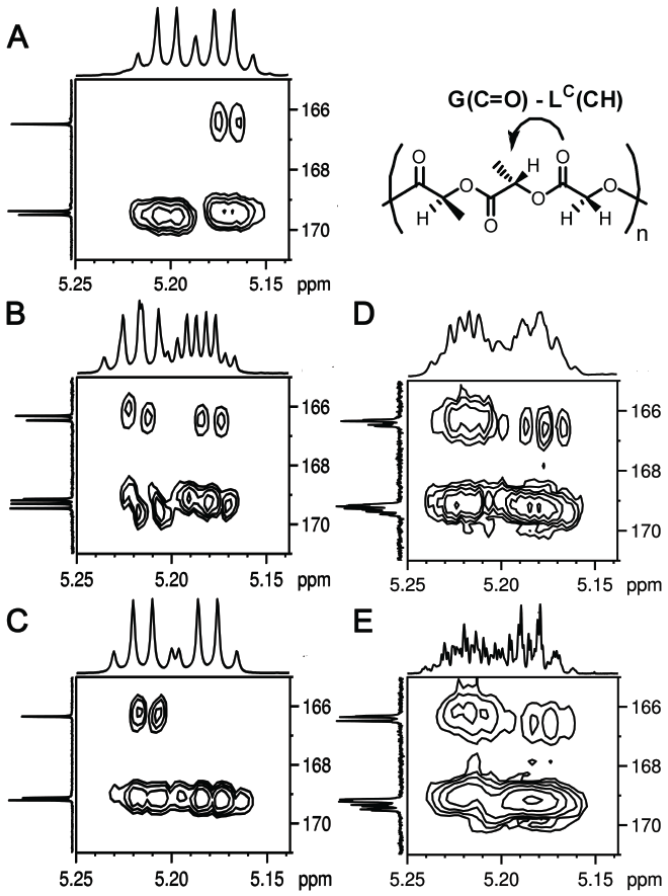


Figure 18. 2D HMBC ^{1}H-^{13}C correlation NMR spectra at 700 MHz in $CDCl_3$ for **poly LLG** (A), **L$_R$LGLLG** (B), **L$_R$LG** (C), **L$_{rac}$L$_{rac}$G** (D) and **L$_{rac}$LG** (E).

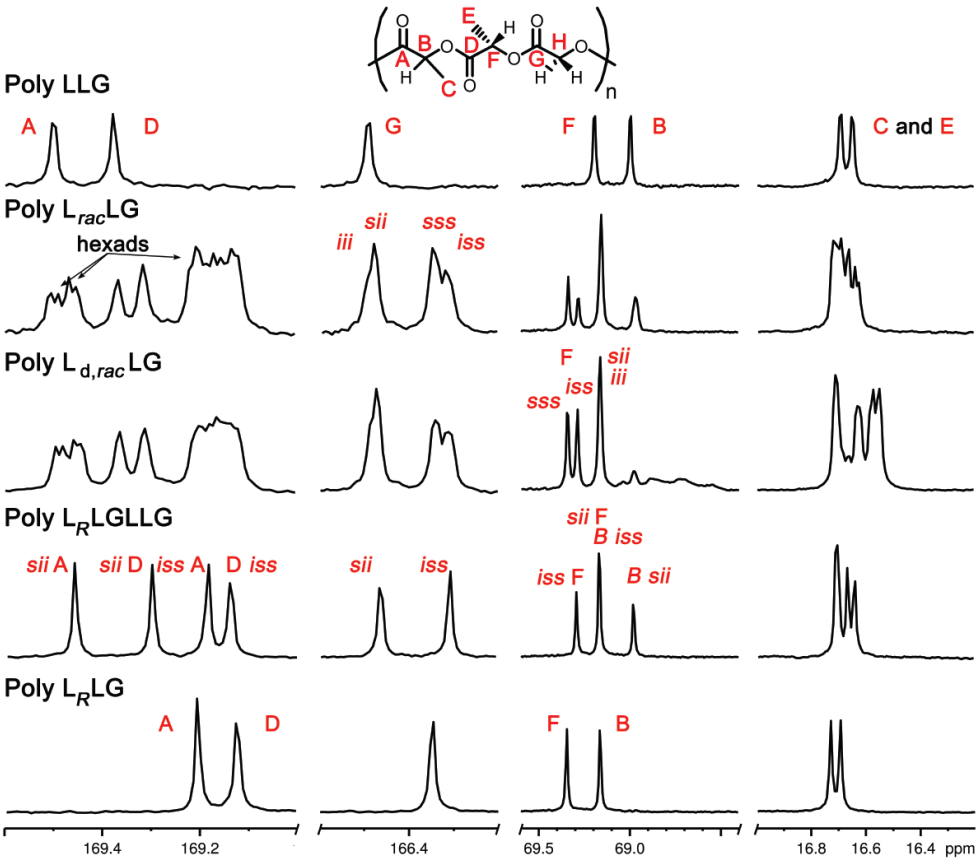


Figure 19. ^{13}C NMR spectra of L^{O}-variable LLG polymers at 175 MHz in $CDCl_3$. Comparisons of the expansions of selected regions for **poly LLG**, **L$_{rac}$LG**, **L$_{d,rac}$LG**, **L$_R$LGLLG**, and **L$_R$LG**.

Chemical shifts in the ^{13}C NMR spectra of **poly L_{rac}LG** and **LL_{rac}G** showed primarily a tetrad level of resolution. Partial assignment was accomplished by comparison with the stereopure and deuterated RSCs (Figure 19 and 20) and by 2D HMBC NMR as described earlier. Analysis of the stereopure RSCs established that the L^O carbonyl resonance was generally downfield of the L^C resonance and the L carbonyl resonances were more sensitive to stereochemistry than the ^{13}C NMR resonances for other groups. The presence of >8 lactic carbonyl signals in the spectra of both **poly L_{rac}LG** and **LL_{rac}G** was consistent with a higher than tetrad (mixed hexad/octad) level of resolution, although it was not possible to make individual assignments due to overlap. It is also of note that, in both the L and G carbonyl regions, the *i*-centered resonances were downfield of the *s*-centered resonances. Methine L^O and L^C resonances were assigned by comparison to the deuterium labeled polymers as the deuterium-substituted carbons exhibited much lower intensities due to slow relaxation. These signals clearly resolved to a slightly more than tetrad level for RSCs incorporating racemic units. The methyl region also showed a greater than tetrad level of resolution but the small chemical shift range made individual assignments in this region impractical.

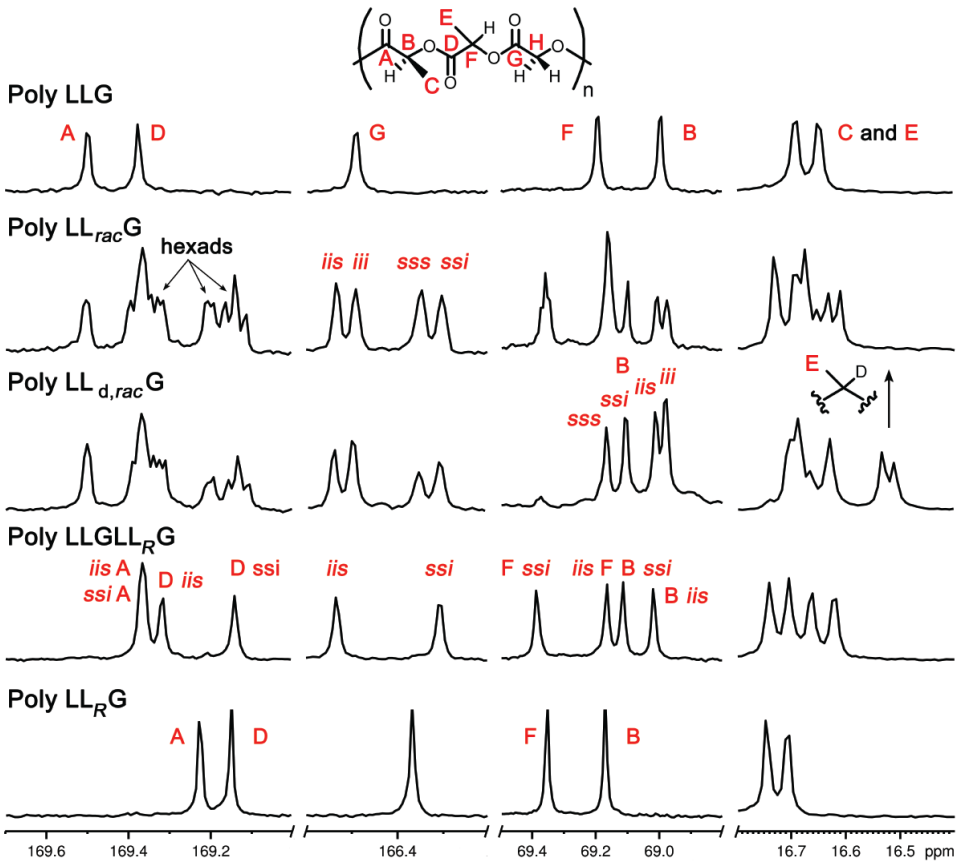


Figure 20. ^{13}C NMR spectra of L^{C}-variable LLG polymers at 175 MHz in $CDCl_3$. Comparisons of the expansions of selected regions for **poly LLG**, **LL$_{rac}$G**, **LL$_{d,rac}$G**, **LLGLL$_R$G**, and **LL$_R$G**.

2.4.4 Tetrameric GL$_x$L$_x$G RSCs

The GL$_x$L$_x$G series, which has an alternating dimeric LLGG motif, combines the nomenclature and stereochemical implications from both L$_x$L$_x$G and GL$_x$G series. The individual L and G units are inequivalent with the L units designated as L^{O} or L^{C} in relation to the GG unit while the G units are designated G^{O} or G^{C} in relation to the LL unit. G^{C} is connected through the C-terminus to L^{O} that is connected to L^{C} and finally G^{O}, which is connected through the O-terminus of L^{C} and the C-terminus to G^{C}. The monomer GLLG is therefore G^{C}L^{O}L^{C}G^{O}. Fortunately, the addition of a second G unit does not overly complicate the core polyad when making tacticity

assignments. Utilizing the same approach as with L_xL_xG, Figure 21 illustrates the central *ssi* tetrad of a *issii* hexad. Again, even though the "center" of the sequence shifts for each unit, the central tetrad remains the same for all of the units when maximizing adjacent versus distant interactions.

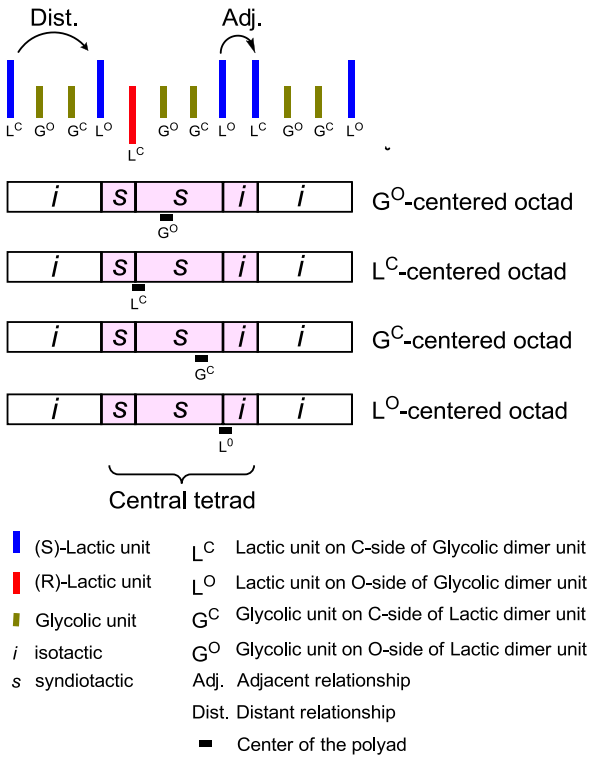


Figure 21. Example of hexad-level stereosequence encoding for **poly GLL$_{rac}$G**. The central tetrads for each unit are defined as including one distant and two adjacent relationships.

The chemical shift trends displayed in the ^{1}H NMR and ^{13}C NMR spectra for **poly GLLG**, **GLL$_{rac}$G** and **GL$_R$LG** are consistent with both the L_xL_xG and GL_xG series (Figure 22 and 23). The spectrum for isotactic **poly GLLG** exhibited two quartets in the lactic methine region, two pairs of well separated doublets from the glycolic methylenes and two doublets from the lactic methyls. 2D HMBC and COSY NMR confirmed that like L_xL_xG, the L^O methine resonance was downfield of the L^C resonance and that when the stereosequence was altered to syndiotactic in **poly GL$_R$LG** the resonances switched order. The L^O methyl resonances remained

downfield of the L^C resonance although the chemical shifts moved upfield for the syndiotactic variant. Just as in the GL_xG series, the outer pair of methylene doublets correspond to G^C and the inner pair correspond to G^O. Predictably, the chemical shift differences for both pairs of doublets decreased in syndiotactic **poly GL$_R$LG**. Utilizing these standards the methylene resonances for atactic **poly GLL$_{rac}$G**, which possess 4 of the 8 possible tetrads for GL_xL_xG: *iii*, *iis*, *ssi* and *sss*, were assigned. The hierarchical order for *i*-centered and *s*-centered polyads was observed. Although the ^{1}H NMR spectrum for **poly GLL$_{rac}$G** was nearly resolved to the tetrad level, the ^{13}C NMR spectrum was only resolved to the dyad level.

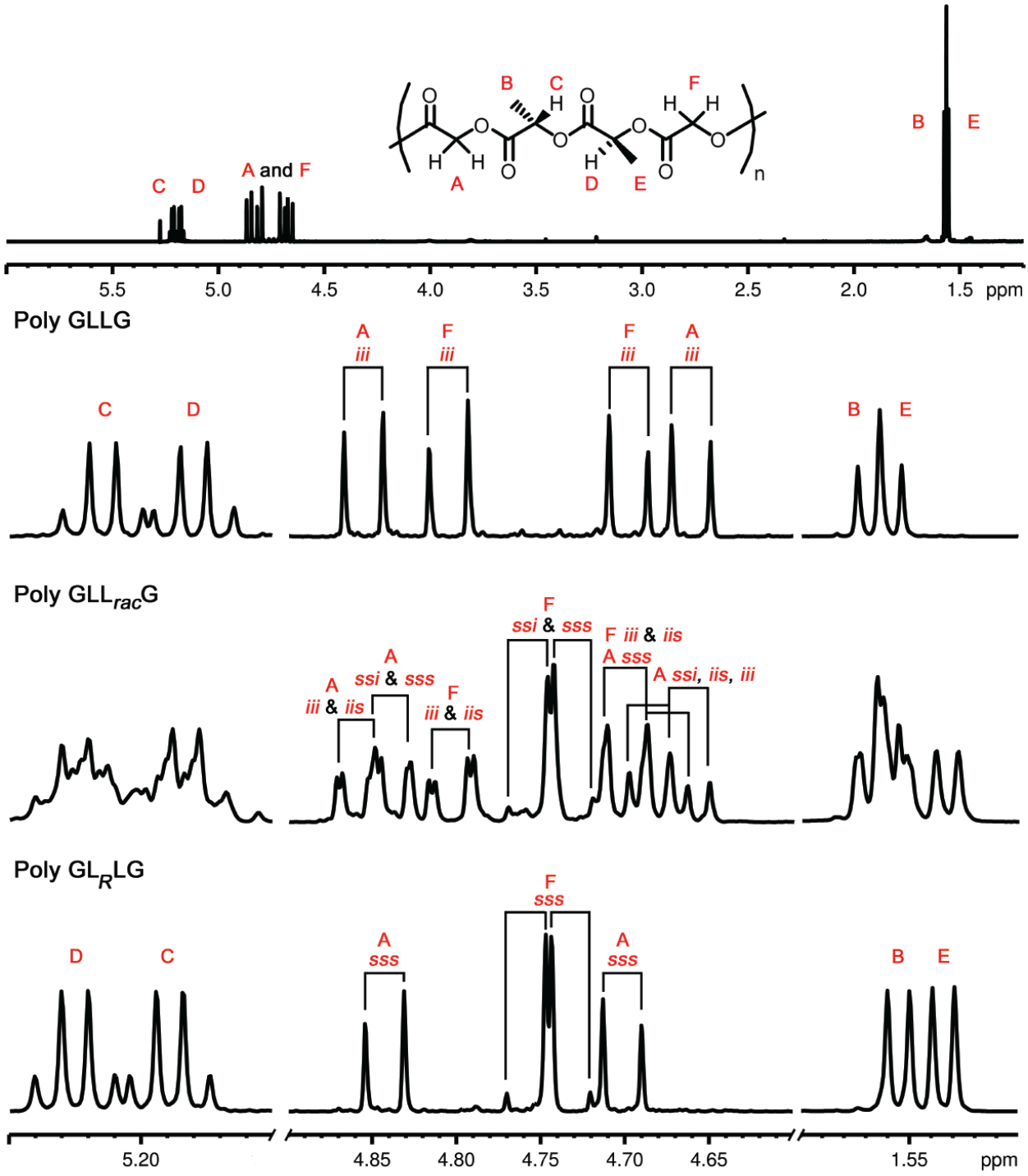


Figure 22. ^{1}H NMR spectra of GL_xL_xG polymers at 700 MHz in $CDCl_3$. Comparisons of the expansions of selected regions for **poly GLLG**, **GLL$_{rac}$G** and **GL$_R$LG**.

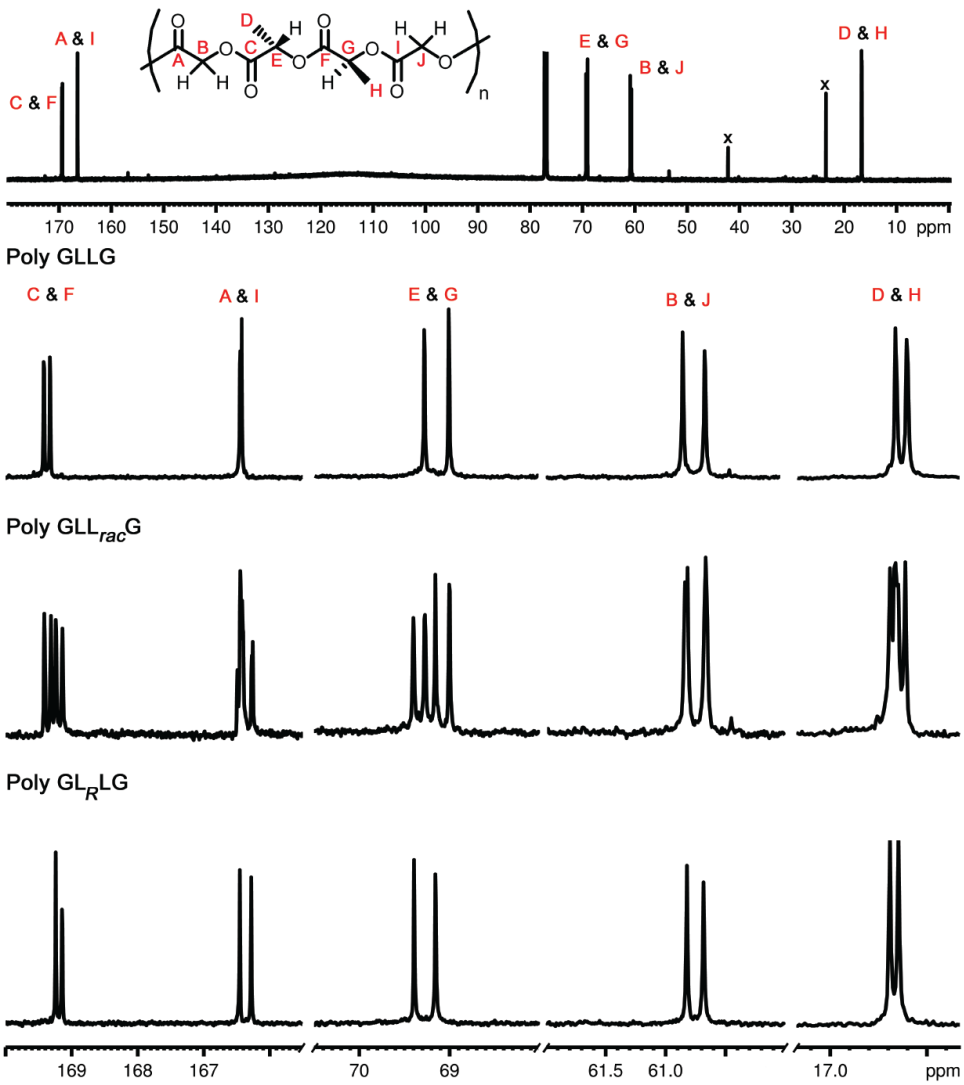


Figure 23. ^{13}C NMR spectra of GL_xL_xG polymers at 175 MHz in $CDCl_3$. Comparisons of the expansions of selected regions for **poly GLLG**, **GLL$_{rac}$G** and **GL$_R$LG**.

2.4.5 Tetrameric $L_xL_xL_xG$ RSCs

The **poly LLLG** series was prepared specifically as an attempt to distinguish microstructural information without the assemblage of multiple stereosequenced standards, 32 possible hexads in this case. The series was compromised of only isotactic **poly LLLG** and atactic **poly L_{rac}LLG**, **LL_{rac}LG**, **LLL_{rac}G** and **$L_{rac}L_{rac}$LG**. The ^{1}H NMR spectrum for **poly LLLG** exhibited a single pair of doublets in the methylene region as expected while the remaining atactic copolymers displayed 4 pairs of doublets indicating a nearly resolved hexad-level of resolution (Figure 24). In the preparation of racemic **LLLG** segmers a stereochemical preference for alternating L stereocenters was evident (Section 2.3.3) and could be utilized to partially assign the methylene region. In **poly L_{rac}LLG** the *iiiii* and *iissi* resonances could be distinguished as smaller than the preferred the *siiii* and *sissi* resonances. The hierarchical order of *i*-centered and *s*-centered polyad resonances also aided assignment. Resonances for **poly LL_{rac}G** displayed preferences but because all of the polyads are *i*-centered perfect assignment was not possibility. Although **poly LLL_{rac}G** should have exhibited preferred stereosequence formation, upon polymerization all resonances were equivalent, however *i*-centered and *s*-centered polyad resonances could be distinguished.

The interpretation and assignment of the L methines and methyls was much more difficult. The primary challenge relative to the more easily interpreted spectra for the L_2 series (**poly L_xL_xG** and **GL_xL_xG**) was loss of strong differentiation between the lactic units. For the L_2 RSCs each L has a different unit both before and after. For the L_3 series (**poly $L_xL_xL_xG$**), two of the three Ls are preceded by an L unit and 2 of the three are followed by an L unit. This lack of differentiation is reflected in the extensive overlap of resonances in the methine and methyl regions in both 1D and 2D NMR spectra.

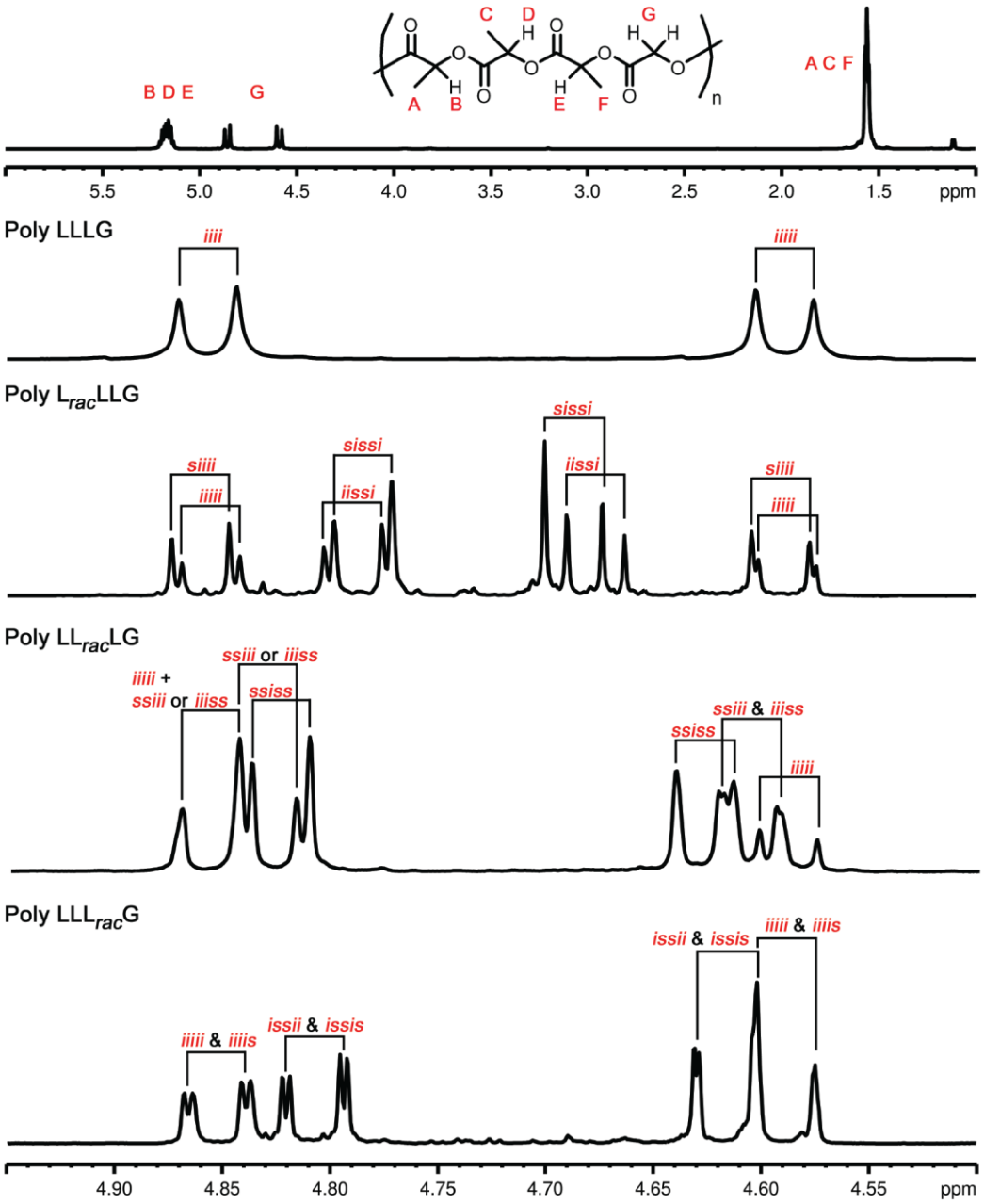


Figure 24. ^{1}H NMR spectra of LLLG polymers at 600 MHz in $CDCl_3$. Comparisons of the expansions of selected regions for **poly LLLG**, **L$_{rac}$LLG, LL$_{rac}$LG** and **LLL$_{rac}$G**.

2.4.6 PLA RSCs – L_xL_x and L_xL_xL

Although not the main focus of our research, several stereosequenced and stereo-randomized PLA RSCs were investigated. Comparison of chemical shifts for the simple stereosequenced isotactic **poly LL** and **LLL** and syndiotactic **poly LL*R*** and **L*R*L** were similar to those reported by Ovitt and Coates.[25] The syndiotactic methine and methyl resonances are slightly upfield of the isotactic PLA resonances in the ^{1}H NMR spectrum, opposite the pattern established in the PLGA RSCs (Figure 25). In the ^{13}C NMR spectrum, the *s*-carbonyl is upfield of the *i*-carbonyl while the *s*-methine is downfield of the *i*-methine and both methyl resonances exhibit a similar chemical shift.

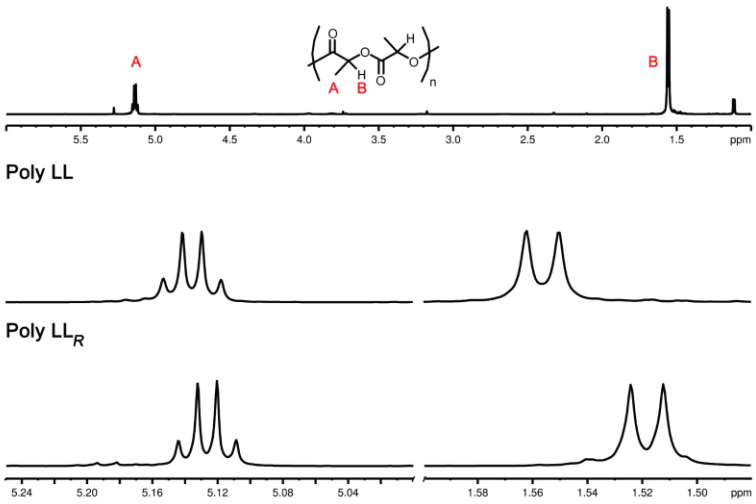


Figure 25. ^{1}H NMR of **poly LL** and **poly LL*R*** at 600 MHz in $CDCl_3$.

Interpretation and partial assignment of the NMR spectra for randomized PLAs, **poly LL*rac*L** and **L*rac*L*rac*L**, was completed according to methods developed by Zell, et al.[76] Although PLA lacks a comonomer frame of reference, which we have utilized to great extent in the microstructural assignment of PLGA RSCs, Zell and coworkers determined that the directionality in the ^{1}H NMR was different than that of the ^{13}C NMR. The ^{1}H NMR proceeds

through the O-terminus while the ^{13}C NMR proceeds through the C-terminus of a central pairwise relationship. Illustrated in Figure 26, the ^{1}H resonance of the central *sis* tetrad of *ssiss* would correlate to the *ssi* resonance in the ^{13}C NMR spectrum. This difference in correlation enables partial assignment of the ^{1}H and ^{13}C methine resonances utilizing HETCOR experiments, 2D heteronuclear correlation NMR, as according to Chisholm[122] and Zell.[76]

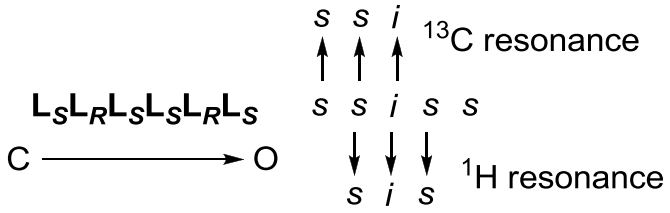


Figure 26. Directionality and correlation of NMR resonances in PLA

Focusing on a tetrad level of resolution, the possible stereochemical relationships for **poly LL$_{rac}$L** were determined by inspection of the 4 possible hexads (*iiiii*, *iiiss*, *ssiii* and *ssiss*) and the 3 component tetrads (a, b and c) of each hexad (Figure 27). The *iiiii* hexad contains 3 *iii* tetrads; *iiiss* contains *iii* (a), *iis* (b) and *iss* (c) tetrads; *ssiii* contains *ssi* (a), *sii* (b) and *iii* (c); and *ssiss* contains *ssi* (a), *sis* (b) and *iss* (c). Due to directionality, ^{1}H NMR resonance of tetrad c will correlate to the ^{13}C resonance of tetrad b and the ^{1}H NMR resonance of tetrad b will correlate to the ^{13}C resonance of tetrad a. Tetrads *sii* and *sis* are of particular interest: 1) the ^{1}H NMR resonances only correlate to the ^{13}C NMR resonance for *ssi* and 2) the ^{1}H NMR chemical shifts of the *sii* and *sis* resonances are the downfield (δ= 5.18) of the remaining resonances (δ= 5.13), determined by stereosequence selectivity of PLA prepared by *rac*- vs. *meso*-lactide. Assignment of the methine region for ^{1}H and ^{13}C NMR spectra of **poly LL$_{rac}$L** were based on these correlations confirming the newer assignments by Zell[76] and the original assignments of Kricheldorf (Figure 28).[83] The ^{1}H and ^{13}C NMR spectra for **poly L$_{rac}$L$_{rac}$L**, which introduces two additional tetrads *sss* and *isi*, were assigned in a similar manner (Figure 29).

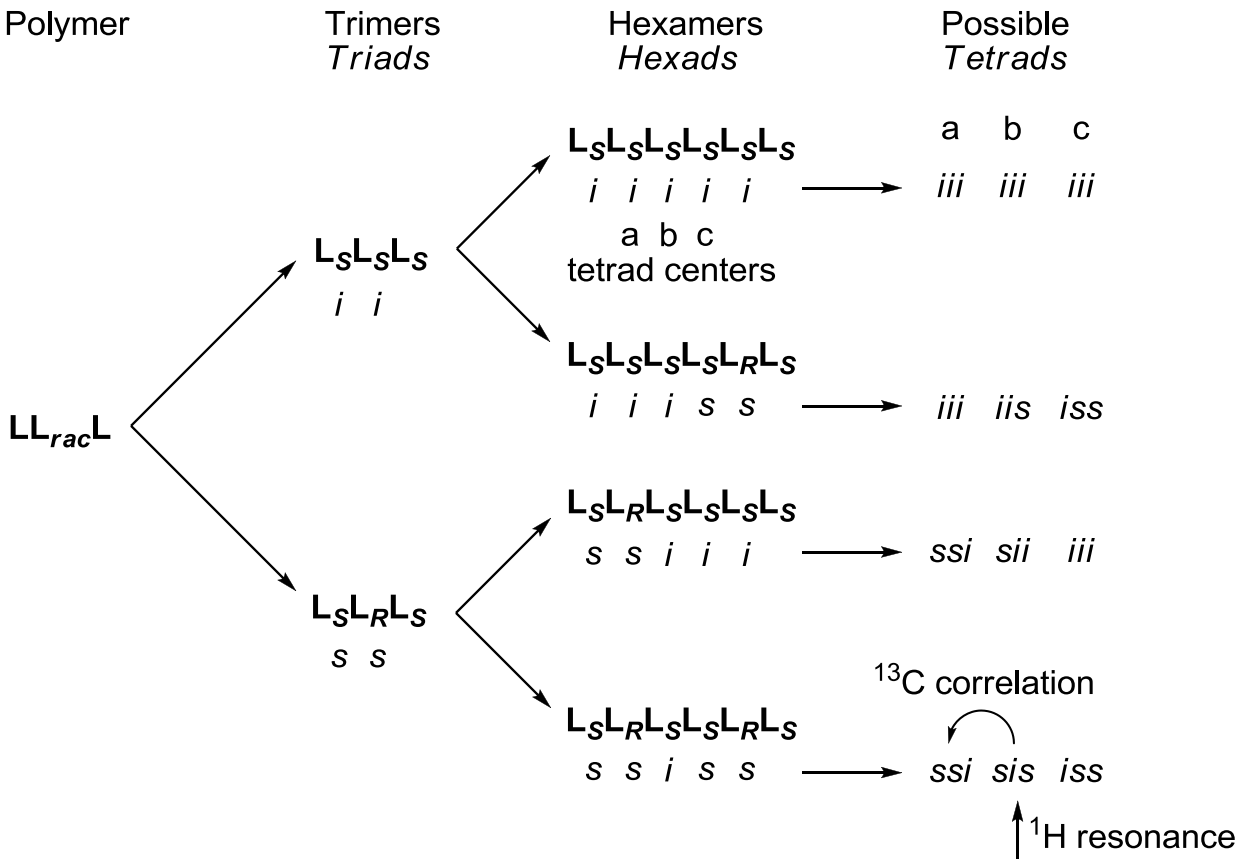


Figure 27. Stereochemical possibilities for **poly LL$_{rac}$L**

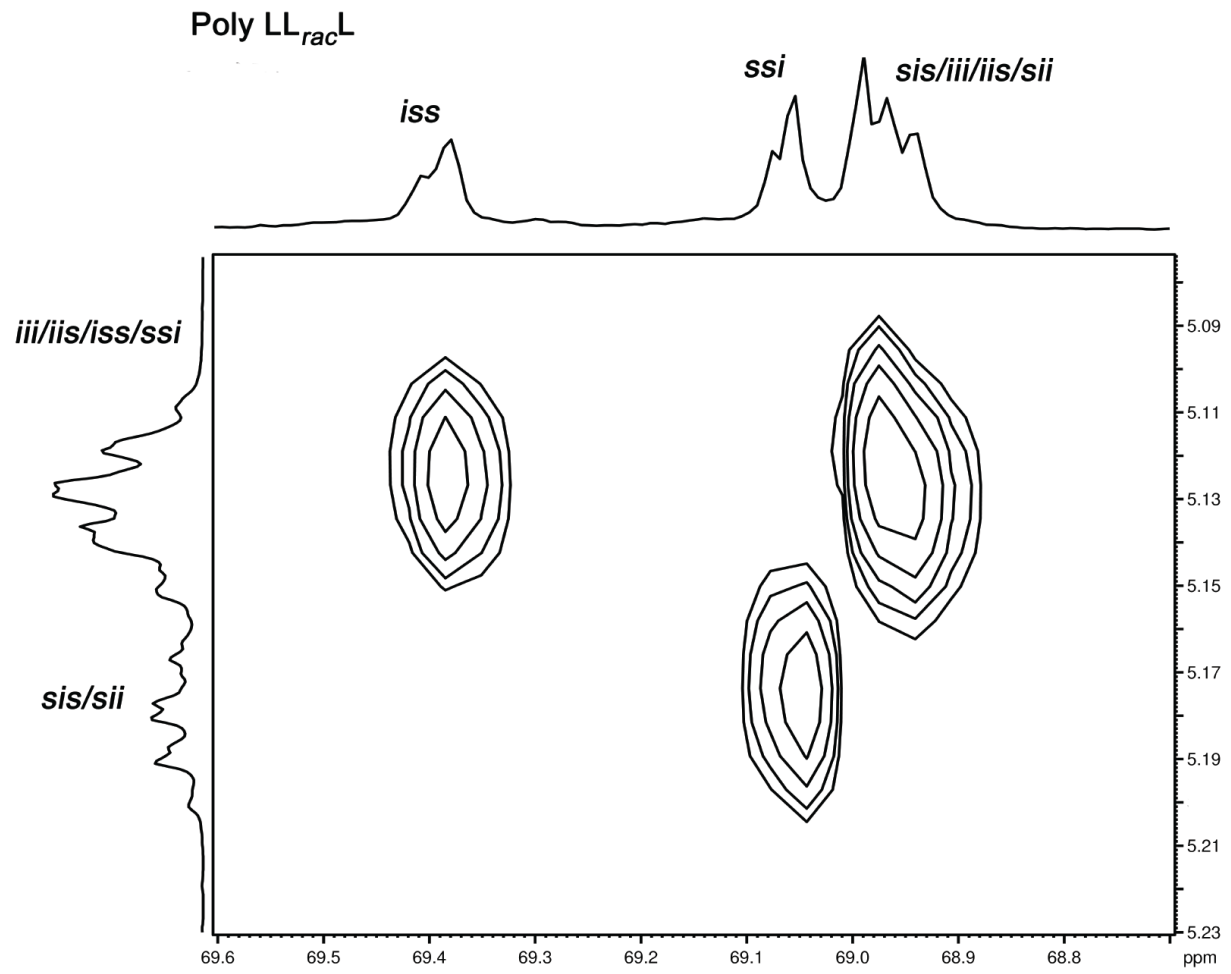


Figure 28. HETCOR NMR spectrum of **poly LL$_{rac}$L** at 700 MHz (^{1}H) and 175 MHz (^{13}C) in $CDCl_3$.

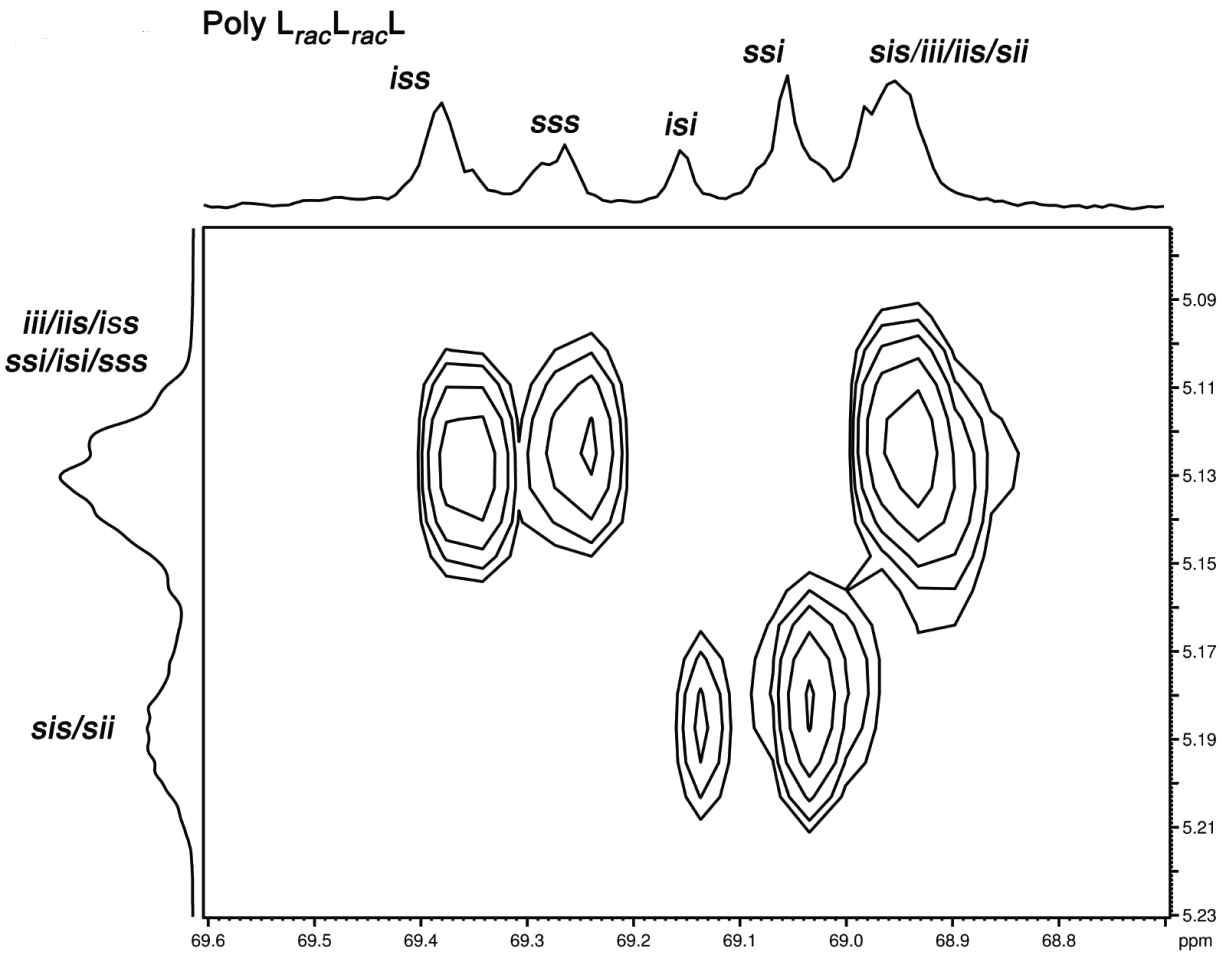


Figure 29. HETCOR NMR spectrum of **poly L$_{rac}$L$_{rac}$L** at 700 MHz (^{1}H) and 175 MHz (^{13}C) in $CDCl_3$.

2.4.7 Mixed sequences and stereosequences

The chemical shifts for stereopure dimeric and trimeric copolymers are compiled in Tables 10 and 11. It should be emphasized that these are stereopure samples and exact matches to unknowns will not be expected unless the sequences of the spectra compared are homologous at or beyond the level of resolution observed. For convenience, however, the polyads with more complex sequences have been labeled at the tetrad level.

Table 10. ^{1}H NMR chemical shifts of specific sequences from RSCs standards

		Methine[a]				Methylene[b]		Methyl[c]		
Sequence	Polyad	L^O	L	L^C	G	$H^{downfield}$	$H^{upfield}$	L^O	L	L^C
LG	all *i*		5.225			4.860	4.626		1.568	
	all *s*		5.239			4.807	4.686		1.560	
GLG	all *i*		5.244		G^C	4.864	4.686		1.57	
					G^O	4.804	4.720			
LLG	all *i*[d]	5.205		5.175		4.853	4.602	1.572		1.561
	iis[e]	5.215		5.176		4.852	4.611	1.567		1.557
	sii[f]	5.212		5.182		4.818	4.613	1.571		1.548
	ssi[e]	5.176		5.219		4.806	4.634	1.557		1.529
	iss[f]	5.187		5.221		4.785	4.686	1.554		1.528
	all *s*[g]	5.182		5.216		4.813	4.652	1.559		1.532
GLLG	all *i*[h]	5.21		5.18	G^C	4.855	4.661	1.569		1.559
					G^O	4.806	4.669			
	all *s*[i]	5.20		5.23	G^C	4.843	4.702	1.555		1.534
					G^O	4.759	4.732			

[a] quartet ^{3}J = 7.0- 7.2 Hz; [b] pair of doublets, ^{3}J = 15.6 – 16.2 Hz; [c] doublet ^{3}J = 7 – 7.2 Hz; [d]from **poly LLG**; [e]central tetrads from **poly LLGLL$_R$G** sequences *ss*<u>*ii*</u>*ssi* and *ii*<u>*ss*</u>*iis*; [f]central tetrads from **poly L$_R$LGLLG** sequences *iss*<u>*ii*</u>*ss* and *sii*<u>*ss*</u>*ii*; [g]from **poly L$_R$LG** and **LL$_R$G**; [h]from **poly GLLG**; [i]from **poly GL$_R$LG**

Table 11. ^{13}C NMR chemical shifts of specific sequences from RSCs standards

		L Carbonyl			G Carbonyl			Methine		
Sequence	Polyad	L^O	L	L^C	G^O	G	G^C	L^O	L	L^C
LG	all *i*		169.38			166.43			69.15	
	all *s*		169.24			166.38			69.19	
GLG	all *i*		169.28		166.37		166.47		69.24	
LLG	all *i*[a]	169.50		169.37		166.49		68.98		69.18
	iis[b]	169.36		169.32		166.53		69.02		69.16
	sii[c]	169.46		169.30		166.47		68.98		69.17
	ssi[b]	169.36		169.14		166.31		69.11		69.39
	iss[c]	169.18		169.14		166.31		69.17		69.29
	all *s*[d]	169.22		169.14		166.36		69.17		69.35
GLLG	all *i*[e]	169.42		169.33	166.42		166.45	69.0		69.27
	all *s*[f]	169.24		169.14	166.28		166.45	69.15		69.39

[a] from **poly LLG**; [b]central tetrads from **poly LLGLL$_R$G** sequences *ss*<u>*ii*</u>*ssi* and *ii*<u>*ss*</u>*iis* ; [c]central tetrads from **poly L$_R$LGLLG** sequences *iss*<u>*ii*</u>*iss* and *sii*<u>*ss*</u>*ii*; [d]from **poly L$_R$LG** and **LL$_R$G**; [e]from **poly GLLG**; [f]from **poly GL$_R$LG**

Using these spectral tables as a guide and focusing on the methylene region, it is possible to interpret the spectra of samples that contain more than one structural sequence and of samples that contain multiple stereosequences. In a sample comprising a mixture of different structural sequences, in this case a mixture of **poly LG**, **GLG** and **LLG**, resonances for each sequence can easily be distinguished (Figure 30).

A more stringent test is the assignment of the methylene region of **poly L$_{rac}$L$_{rac}$G.** This spectrum is complicated due to the number of possible polyads (8 at the tetrad level) and the presence of multiple levels of resolution for each polyad. Nevertheless, it is possible to make a fairly complete assignment of the sequences present at the tetrad level (Figure 31).

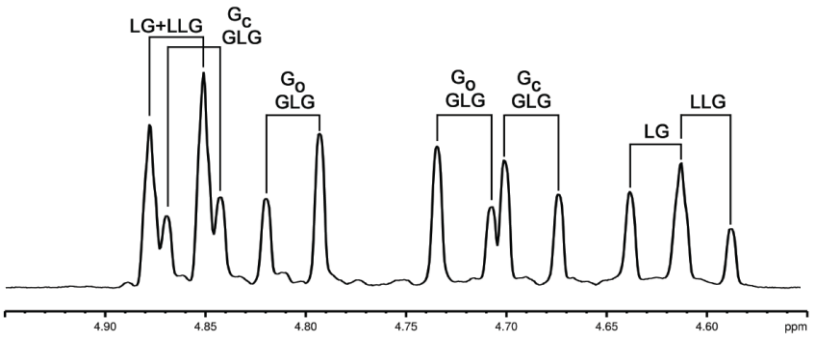


Figure 30. Glycolic methylene region of a mixed ^{1}H NMR spectrum for mixed sample (1:1:1) of **poly LG**, **GLG** and **LLG** at 600 MHz in $CDCl_3$.

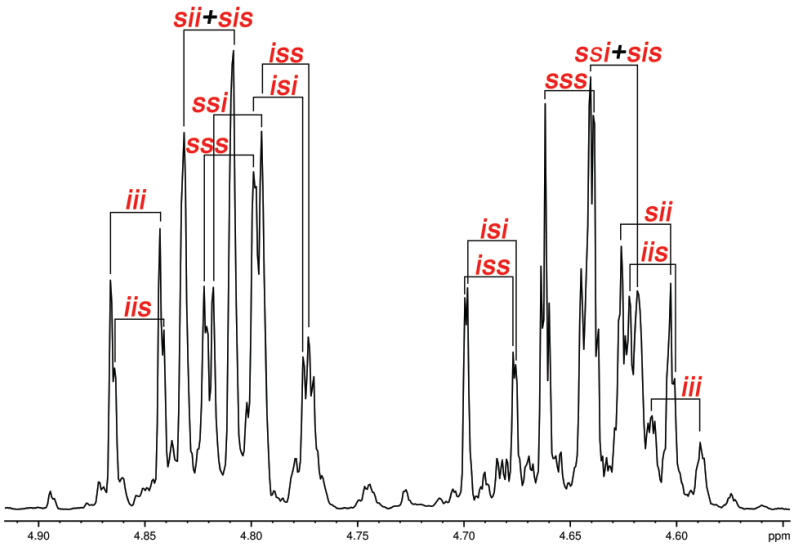


Figure 31. Glycolic methylene region of **poly $L_{rac}L_{rac}G$** at 700 MHz in $CDCl_3$.

2.5 DISCUSSION

2.5.1 Polymerization methods

We are able routinely to prepare RSC PLGAs with DPs > 200 on a per monomer basis with a > 95% sequence fidelity. Previously, we were successful in preparing RSC PLGAs using DCC/DMAP but the DPs were significantly lower.[103] The newly adopted DIC/DPTS method, first developed by Stupp and Moore, utilizes DPTS instead of DMAP in order to suppress chain terminating *N*-acylurea byproducts, neutralize the reaction pH and minimize depolymerization.[99,123] Similar methods were used by Hawker and coworkers in the preparation of well-defined oligomers of lactic acid and caprolactone.[95,97] Examination of the NMR spectra establishes that under the specified reaction conditions, neither sequence scrambling nor epimerization are significant problems although in select samples mistakes (< 5%) can be observed. The spectrum of **poly LG** (Figure 7, methylene region), for example, shows contamination by syndiotactic sequences.

2.5.2 Sequence and Thermal Properties

Sequence was found to have a dramatic effect on the thermal properties of PLGA. In random PLGAs the material properties are primarily dependent on the length of the lactic blocks which generate preferential packing domains.[74] Others have reported that as glycolic content increases the T_g drops to as low as 36 °C at a 50% glycolic unit incorporation.[74,91,124] RSC PLGAs, on the other hand, maintained T_gs at or above 50 °C even when the glycolic unit content exceeded 60%. As long as the uniformity of the structural sequence remained, altering the stereosequence only

slightly lowered the T_g. Most of the polymers remained amorphous even after annealing. **Poly LLG**, **L_RLG** and **LL_RG** were the only polymers that displayed a melting transition and **poly LLG** only crystallized after annealing. Although sequence- and stereoregularity should promote crystallinity, it is clear that it is challenging for these polymers to exhibit long range order based on these relatively short sequences.

2.5.3 Sequence and NMR

Our synthetic approach, which allowed for the creation of an unprecedented array of polymer microstructures, facilitates the understanding of the NMR assignments for specific PLGA sequences. The polymers prepared serve as a partial Rosetta Stone for the assignment of PLGA NMR data. Prior assignments of the NMR resonances for PLGA have been based on random copolymers (and a very small set of easily prepared well-defined homo- and copolymers). While this approach has led to significant understanding for a variety of polymers, it is worth noting that controversies over assignments of stereochemistry in the closely related but obviously simpler PLA system have taken years and the input of several groups to resolve.[76,78,81,125] The fact that PLGA has the potential for both structural and stereosequence variability complicates the issue significantly. However, we have been able, using our family of RSCs, not only to make assignments but also to develop a deeper understanding of the issues involved in the interpretation of NMRs of RSCs.

While the complexity of PLGAs make the assignment of NMR resonances more challenging than in PLAs, our studies have also shown that the copolymer structure offers compensatory advantages that facilitate interpretation. The most important advantage offered by the copolymer is the exquisite sensitivity of the methylenic protons of the glycolic units to

sequence and stereochemistry. The chemical shift range is relatively large and the shifts appear to depend on stereosequence in a hierarchical fashion: the gross chemical shift is determined by the central polyad while the fine chemical shift depends on longer range relationships. The sensitivity of this signal to stereosequence is much greater than any other ^{1}H NMR resonance or the classically more informative ^{13}C NMR resonances. The second compensatory advantage of PLGAs over PLAs (and other well-studied vinyl polymers) is a function of the fact that the resonances for the two monomers are necessarily distributed over a larger chemical shift range than the resonances for any single monomer and the fact that the polymers are unsymmetric—each monomer and each polymer has distinct C and O termini. Using 2D NMR, these differences were exploited to allow for the definitive assignment of resonances.

The most intriguing single result of the NMR studies of these RSC PLGAs, and one that is applicable beyond the narrow scope of these polymers, is the unambiguous demonstration that chemical shift resolution in a polymer bearing multiple sequences *depends on the exact sequence*. Although investigators who have previously analyzed polymers with complex stereosequences have proposed shift assignments based on different levels of resolution in some cases,[77,82] the range of sequence specific polymers available in our system gives a particularly dramatic validation of the hypothesis. The clearest illustration in our system was found in the methylene region of **poly L*rac*LG**. Examining the upfield proton, four groups of doublets are visible (Figure 16). The leftmost group that corresponds to the *iss* tetrad is a simple doublet with no fine structure; this signal is resolved only to the tetrad level. The next group is a barely resolved pair of doublets that corresponds to the gross shift of the *sss* tetrad but which is resolved to a hexad level. The final groups, which exhibit gross chemical shifts consistent with *iii* and *sii* tetrads, exhibit four nearly resolved pairs of doublets which correspond to the much higher octad

level of resolution. An octad level of resolution maps to an impressive distance along the backbone of *31 atoms* between the most separated stereocenters. Such sequence-dependent resolution occurs throughout these spectra although individual signals exhibit varying levels of sensitivity.

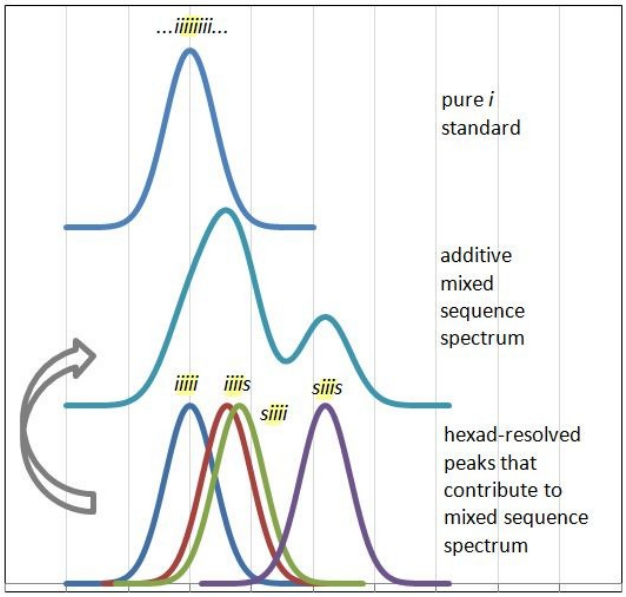


Figure 32. Simulated NMR spectra highlighting the challenges inherent in comparing a standard with perfect stereosequence control to a sample with multiple resolved sequences. Although all sequences share the same "*iii*" central tetrad and exhibit similar chemical shifts, the shifts of the nearly hexad-resolved sequences create a pattern that does not show an easily interpretable correspondence with the standard.

Another important lesson learned from the study of RSC PLGAs is that there are some inherent limitations in our ability to make accurate assignments--limitations that are general to the use of exact sequence RSCs as a key to the interpretation of the NMR spectra of samples with mixed sequence chains, no matter what polymer is involved. The first order approach to assigning spectra, and one that works in some cases, is to assign the resonances for specific sequences by comparison of the chemical shifts with those of a stereopure standard. Our analysis of the extensive database of shifts for the polymers described herein, however, highlights the potential for misinterpretation in systems where the sensitivity of a resonance to stereochemistry

is high and not yet understood. The difficulties are illustrated in the simulated spectrum depicted in Figure 32. If a stereosequence with only "*i*" relationships, for example, is compared to a sample that contains several stereosequences, no peak with a 1:1 shift correspondence to the standard will be found despite the fact that the sample contains a significant (25% in this case) proportion of the "*i*" sequence in the form of "*iiiii*" at a hexad level of resolution. A similar problem would occur if the mixed sample contained only *iiiis* and *siiis* sequences. Despite the fact that both share the same *iii* central tetrad, the shift of neither peak would correspond with that of the "all *i*" standard.

The lack of correlation between stereopure standards and the resonances for individual sequences can thus be attributed to a combination of two phenomena: 1) a full set of standards is not available i.e. sequences longer than those prepared as standards can be distinguished in mixtures and 2) the ultimate sensitivity of the chemical shift for a particular sequence in a mixture e.g. tetrad, hexad, etc. is determined by the inherent resolution of the NMR spectrum. We see the effects of both of these phenomena in our spectra in that the shifts of our standards do not exactly match those observed in our mixed sequence polymers. To achieve a 100% correlation it would have been necessary in the case of **poly $\mathbf{L}_{rac}\mathbf{L}_{rac}\mathbf{G}$,** for example, to prepare all 32 possible octad sequences. As the synthesis of all of these sequenced polymers is impractical, it was necessary to extrapolate from the observed trends from the available standards in assigning certain sequences. The second phenomenon that results in chemical shift miscorrelation, the fact that the certain chemical shift differences are on the same order of magnitude as the peak widths, is a universally recognized spectroscopic challenge and could be overcome by a combination of expanding the database of sequences and "fitting" the mixed

spectra. Although the lack of long-sequence standards prevented an analysis of this depth, these phenomena were taken into account when assignments were made.

The broad manifestation of these chemical shift correlation phenomena in our data can readily be observed in the stacked plots of ^{1}H NMR spectra for the PLGA RSCs (Figures 14 & 15). The fact that peaks labeled as arising from the same tetrad do not always "line up" is due to the peak matching problems just described, not to poor chemical shift calibration. It should be noted that these issues disproportionally complicate the interpretation of the methine and methyl regions because those regions span a smaller chemical shift range and are not as hierarchical as the methylene region.

The analysis of the NMR data for these polymers has also given us some insight into the specific interpretation of the spectra of PLGAs. In particular, we note that the shift range observed for differing stereosequences within the same structural sequence overlaps exactly with the chemical shift range observed for differing structural sequences. Given the similarity of the monomers involved it is, perhaps, not surprising that structural sequence does not introduce a larger perturbation. The bottom line is that, for PLGAs, stereosequence is extremely important in determining the NMR spectral pattern.

2.5.4 Sequence and Conformation

One inescapable conclusion to be drawn from the solution phase behavior of these PLGA RSCs, both NMR and SEC, is that the conformations of these polyesters are sequence dependent. Conformational differences must, for example, be responsible for the differences in chemical environment exhibited by the diastereotopic methylene protons imbedded in different

stereosequences. Conformation is also likely to be responsible for the sequence dependence of the SEC—the R_g is determined by the shape assumed by the polymer in solution.

Although the homology of the monomers in these polymers with those in amino acids, specifically alanine and glycine, renders the sequence-dependence of the conformations unsurprising, the fact that the effect is so strong, given the lack of amide-mediated hydrogen bonding, is perhaps less expected. Indeed, it is common practice to substitute the ester analog of an amino acid into a peptide to determine the importance of a particular amino acid to the tertiary structure of a protein.[126,127]

Although we cannot yet correlate our NMR spectra with specific conformational preferences the data suggests that there is much to be learned. The fact that we observe a sequence-specific sensitivity to stereochemistry is, for example, intriguing. Such behavior could arise either because specific sequences create conformations that place the diastereotopic methylene protons in better positions to "observe" distant stereochemical relationships or it could arise because certain sequences simply have stronger conformational preferences (or both). Also relevant to the understanding of the rules governing the preferred conformations in this system is the observation that the chemical shift difference between the two methylenic protons on a particular carbon was consistently smaller for *s*-centered polyads than *i*-centered polyads. An analogous trend has been well-documented in vinyl polymers such as polypropylene.[128,129]

2.6 CONCLUSIONS

The solution phase conformations for RSC PLGAs were found to be extremely sequence and stereosequence dependent, analogous to peptides. To access these RSC PLGAs, we have

developed a methodology that allows the preparation of complex sequenced copolymers of lactic and glycolic acids from simple mono-protected building blocks. The method is general, convergent, and allows for the synthesis of sequences unavailable by other methods such as ROP. Although RSC synthesis can be used to make stereopure NMR standards, the inherent resolution of specific sequences must be taken into account as the level of resolution for a particular nucleus may be sequence dependent. Improved thermal properties were also a direct result of the uniformity of polymer sequence.

2.7 EXPERIMENTAL SECTION

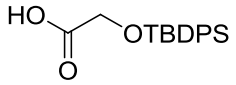
Materials. 4-(Dimethylamino)pyridinium *p*-toluenesulfonate (DPTS) was synthesized according to reported literature procedure.[99] Ethyl acetate, methylene chloride, acetonitrile and triethylamine were distilled under nitrogen from calcium hydride. THF was passed through activated alumina using a SPS 400 (Innovative Technology). Lactic acid was purified for dioxolanone synthesis by vacuum distillation of a commercially available 90% solution (Acros) followed by recrystallization in benzene with ether and hexanes. All other reagents were purchased and used without further purification. Column chromatography was performed using EMD 60 Å, 40-63 μm standard grade silica.

NMR Spectroscopy. ^{1}H (300, 400, 600 and 700 MHz) and ^{13}C (75, 100, 150 and 175 MHz) NMR spectra were recorded with Bruker spectrometers in $CDCl_3$ or DMSO and calibrated to the residual solvent peaks. 2D NMR experiments were recorded with Bruker 600 and 700 MHz NMR spectrometers equipped with a 5 mm gradient probe using HMBC, HMQC and ^{1}H decoupled HETCOR gradient pulse sequences.

Molecular weight analysis. Molecular weights and polydispersities were acquired on a Waters GPC (THF and $CHCl_3$) with Jordi 500 Å, 1000 Å and 10000 Å divinylbenzene (DVB) columns and refractive index detector (Waters) was calibrated to polystyrene standards. Absolute molecular weights were performed by Impact Analytical, Inc using Waters Alliance Separations Module 2695, PLGel 5 μm Mixed-C column, Waters 2414 DRI and Wyatt Dawn EOS (690 nm) detectors. MALDI-TOF MS analysis was performed with a Voyager DE-STR instrument (Applied Biosystems) equipped with a 337-nm nitrogen laser. An accelerating voltage of 25 kV was applied. Mass spectra were recorded in the reflection mode (1000 shots). The polymer samples were dissolved in THF at a concentration of 1 mg/ml. The cationization agents used were potassium trifluoroacetate or sodium trifluoroacetate dissolved in THF at a concentration of 1 mg/ml. The matrix trans-2-(3-(4-tert-butylphenyl)-2-methyl-2-propenylidene)malononitrile (DCTB) was dissolved in THF at a concentration of 40 mg/ml. Solutions of matrix (10 mL), salt (1 mL), and polymer (5 mL) were mixed, and the mixture was spotted by hand onto a stainless-steel MALDI target and left to dry. Baseline corrections and data analysis were performed by using Data Explorer version 4.0 from Applied Biosystems.[118]

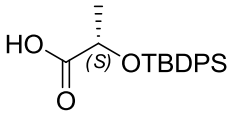
Thermal Analysis. Differential scanning calorimetry (DSC) measurements were performed with a Perkin Elmer Pyris 6 DSC. Standard data were collected with a heating and cooling rate of 10°C/min and data was collected from the second cycle. Annealed samples were prepared by drop- casting (CH_2Cl_2) into DSC pans, drying under vacuum for 24 h, and annealing at 85 °C for 3 h. The data for annealed samples was collected on the first run.

2.7.1 General procedures for the preparation of TBDPS-protected acids

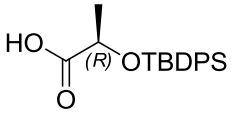


G-SiR$_3$. Methyl glycolate (4.63 g, 51.4 mmol), Et_3N (15.7 ml, 113 mmol) and 4-(dimethylamino)pyridine (DMAP) (3.05 g, 25 mmol) were combined in 200 ml of dry CH_2Cl_2 under N_2. After cooling the reaction mixture to 0°C, *t*-butyldiphenylchlorosilane (TBDPSCl) (15.5 g, 56.5 mmol) was added and the reaction mixture was stirred at room temperature for 18 h. The reaction mixture was filtered and the filtrate was washed with 10% HCl (2 × 150 ml) and H_2O (2 × 100 ml). The organic layer was dried with $MgSO_4$ and concentrated *in vacuo* to yield a colorless oil (18.0 g, 97%). The ^{1}H NMR spectrum revealed that the resultant oil contained up to 10% TBDPSCl.

The resultant oil (11.0 g, 33.4 mmol) was dissolved in 550 ml of THF and cooled in an ice bath. $LiOH{\cdot}H_2O$ (5.6 g, 134 mmol) in 205 ml of H_2O was added dropwise over 15 min. The ice bath was removed and the reaction was allowed to stir for 10 min. Water (100 ml) was added and the THF was removed *in vacuo*. The aqueous phase was extracted with Et_2O (2 × 150 ml) to remove starting material, acidified using 1.0 M HCl, and then extracted with Et_2O (2 × 150 ml). The second ethereal phase was dried with $MgSO_4$ and concentrated *in vacuo* to yield a colorless oil (8.07 g, 77%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.8-7.6 (m, 4H), 7.5-7.3 (m, 6H), 4.39 (s, 2H), 1.24 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.2, 135.7, 132.4, 130.3, 128.1, 62.0, 26.9, 19.3; MS (EI) m/z 257 (M- *t*-butyl).

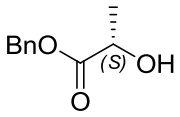


L-SiR$_3$. The product was a colorless solid (17.58 g, 92%). MP 73.5-75°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.2 (s, 1H), 7.8-7.6 (m, 4H), 7.5-7.3 (m, 6H), 4.33 (q, J = 6.78 Hz, 1H), 1.48 (d, J = 6.81 Hz, 3H), 1.24 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.2, 135.9, 135.8, 133.1, 132.5, 130.2, 128.0, 69.0, 27.0, 21.2, 19.3; MS (EI) *m/z* 271 (M-t-butyl).



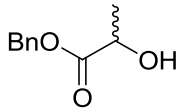
L$_R$-SiR$_3$ *rmsvii-96a/rmsviii-9a:* The product was a colorless solid (17.3 g, 90%). MP 69-70°C, ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.14 (s, 1H), 7.69- 7.64 (m, 4H), 7.5- 7.24 (m, 6H), 4.32 (q, J= 6.7 Hz, 1H), 1.34 (d, J= 6.9 Hz, 3H), 1.11 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.2, 135.7, 132.8, 132.2, 130.2, 130.1, 127.8, 127.7, 69.1, 26.8, 21.0, 19.2; MS (EI) m/z 271 (M-*t*-butyl).

2.7.2 General procedure for benzyl protection of α-hydroxy acids

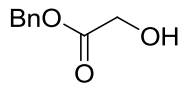


Bn-L *rmsv-32a:* 1,8-diazobicyclo[5.4.0]undec-7-ene (DBU) (85.3 g, 0.56 mol) was added dropwise to a stirring solution of 90% (S)-lactic acid (50.0 g, 0.56 mol) and methanol (230 ml) in an ice bath. The reaction mixture was stirred at RT for 30 min and then the solvent was removed by distillation under reduced pressure. DMF (230 ml) was added to the reaction mixture, followed by the dropwise addition of benzyl bromide (80.4 g, 0.47 mol). After 20 h, DMF was removed by vacuum distillation and the resulting residue was taken up in brine and EtOAc. The

layers were separated and the aqueous layer was extracted EtOAc (2 × 300 ml). The organic layers were combined and washed with 1.0 M HCl (3 × 250 ml), sat. $NaHCO_3$ (3 × 250 ml), and H_2O (2 × 250 ml). The organic layer was dried with $MgSO_4$ and concentrated *in vacuo*. The product was purified by vacuum distillation (85 °C at 0.15 mm Hg) to yield a colorless liquid (65.61 g, 78%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.5-7.3 (m, 5H), 5.19 (s, 2H), 4.30 (q, J= 6.90 Hz, 1H), 3.00 (s, 1H), 1.42 (d, J= 6.90 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.4, 135.2, 128.4, 128.1, 67.1, 66.8, 20.2, MS (GC) m/z 180 (M+).

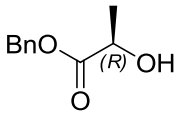


Bn-L$_{rac}$ *rmsv-17a:* The product was distilled under vacuum (78 °C at 0.1 mm Hg) to yield a colorless liquid (56.0 g, 67%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.4-7.3 (m, 5H), 5.19 (s, 2H), 4.30 (quartet, J= 6.90 Hz, 1H), 3.00 (s, 1H), 1.42 (d, J= 6.90 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.4, 135.2, 128.5, 128.4, 128.1, 67.1, 66.8, 20.2, MS (GC) m/z 180 (M+).



Bn-G *rmsv-102:* Glycolic acid (100 g, 1.31 mol) and DBU (202.5 g, 1.33 mol) were added to 1500 mL of dry benzene and allowed to stir for 30 min. Benzyl bromide (232.6 g, 1.36 mol) was added dropwise and the reaction mixture was refluxed for 10 h. The reaction mixture was filtered and concentrated to 1000 mL. The concentrate was extracted with 1.0 M HCl (2 x 400 mL) followed by H_2O (1 x 400 mL). The organic layer was dried with $MgSO_4$ and concentrated *in vacuo*. The product was distilled (70 °C, 0.06 mm Hg) to yield a colorless liquid (197.7 g, 91% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.4-7.3 (m, 5H), 5.20 (s, 2H), 4.18 (d, J= 5.66 Hz,

2H), 2.66 (t, J= 5.68 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.1, 135.0, 128.6, 128.5, 128.4, 67.2, 60.6; MS (GC) *m/z* 166 (M+).

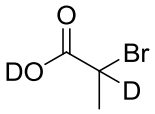


Bn-L$_R$ *rmsviii-77a/rmsviii-82a:* Benzyl alcohol (5.95 g, 55 mmol), **L$_R$-SiR$_3$** (16.5 g, 50 mmol), 1,3-dicyclohexylcarbodiimide (DCC) (11.35 g, 55 mmol) and DMAP (3.05 g, 25 mmol) were combined in 250 ml of methylene chloride (CH_2Cl_2) and stirred for 4 h at RT. The reaction mixture was filtered and concentrated *in vacuo*. The concentrate was chromatographed (silica, 2.5-5% EtOAc in hexanes) to yield a colorless oil (18.1 g, 86%). ^{1}H NMR (300MHz, $CDCl_3$) δ 7.65- 7.62 (m, 4H), 7.42-7.2 (m, 11H), 5.03 (d, J= 12.3 Hz, 1H), 4.96 (d, J= 12.3 Hz, 1H), 4.31 (q, J= 6.7 Hz, 1H), 1.37 (d, J= 6.9 Hz, 3H), 1.07 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.5, 135.9, 135.7, 135.6, 133.5, 133.1, 129.7, 128.4, 128.2, 127.6, 127.5, 68.9, 66.3, 26.8, 21.2, 19.2; HRMS (M+Na) calc mass 441.1862, mass found 441.1883.

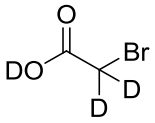
Di-protected **Bn-L$_R$-SiR$_3$** (18.0 g, 43 mmol) was added to 430 ml of dry THF under N_2. Acetic acid (4.4 ml, 77 mmol) was added followed by *t*-butyl ammonium fluoride (TBAF) (1.0 M, 64.5 ml, 64.5 mmol). After 1 h, the reaction mixture was added to 500 ml brine and 200 ml of Et_2O and the layers were separated. The aqueous layer was washed with Et_2O (1 x 200 ml). The organic layers were combined, dried with $MgSO_4$ and concentrated *in vacuo*. The concentrate was chromatographed (silica, 10-15% EtOAc in hexanes) to yield a colorless liquid (6.91 g, 89%). ^{1}H NMR (300MHz, $CDCl_3$) δ 7.36-7.32 (m, 5H), 5.19 (s, 2H), 4.35-4.26 (m, 1H), 2.88 (d, J= 4.8 Hz, 1H), 1.42 (d, J= 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.5, 135.2, 128.6, 128.5, 128.2, 67.3, 66.8, 20.3; HRMS (M+Na) calc mass 180.0786, mass found 180.0779.

2.7.3 Deuterated Building Blocks, Oligomers and Intermediates

Malonic acid based Synthesis:

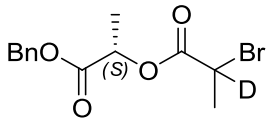


α-d-bromopropionic acid ($L_{d,rac}$-Br) *rmsvi-99:* Methyl malonic acid (20.0 g, 0.17 mol) was dissolved in 500 ml of dry Et_2O under N_2 and cooled to 0 °C. Bromine (8.7 ml, 0.17 mol) was added dropwise and upon completion of the addition the reaction mixture was concentrated by vacuum distillation. The pale orange colored solid was dried under vacuum overnight. Deuterium oxide (200 ml, 20 mol) was added and the reaction mixture was allowed to stir for 1 h. D_2O was removed by vacuum distillation and the product was dried under vacuum for 5 d. Decarboxylation was achieved by heating the reaction mixture at 150 °C for 1 h until gas bubbles were no longer observed. The red liquid was distilled under reduced pressure (105-110 °C) to yield a colorless liquid (25.9 g, 99%). ^{1}H NMR (300 MHz, DMSO) δ 1.93 (s, 3H); ^{13}C NMR (75 MHz, DMSO) δ 168.7, 58.5, 26.9; MS (EI) m/z 155 (M+).

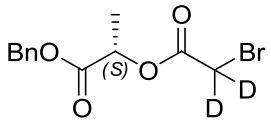


α-d,d-bromo acetic acid (G_{d2}-Br) *rmsvi-96:* Per-deuterated malonic acid (20 g, 0.18 mol) was dissolved in 500 ml of dry Et_2O under N_2 and cooled to 0 °C. Bromine (9.53 ml, 0.18 mol) was added dropwise and upon completion the reaction mixture was concentrated by vacuum distillation. The pale orange solid was dried under vacuum overnight. Decarboxylation was achieved by heating the reaction mixture at 140 °C for 2 h until gas bubbles were no longer

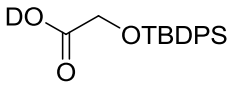
observed. The red liquid was distilled under reduced pressure (112 °C) to yield a colorless liquid (16.94 g, 65%). ^{13}C NMR (75 MHz, DMSO) δ 168.5, 27.5 (m); MS (EI) m/z 142 (M+).



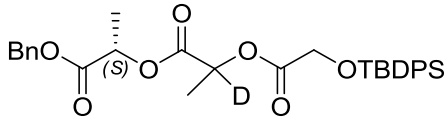
Bn-LL$_{d,rac}$-Br *rmsvii-18a:* The acid **L$_{d,rac}$-Br** (8.0 g, 51.6 mmol), **Bn-L** (10.8 g, 60 mmol) and DPTS (3.04 g, 10 mmol) were combined in 200 ml of dry CH_2Cl_2 under N_2. 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide (11.5 g, 60 mmol) was added and the reaction mixture was stirred at RT for 16 h. The reaction mixture was washed with water (2 x 300 ml) to remove the urea. The organic layer was dried with $MgSO_4$ and concentrated *in vacuo*. The concentrate was chromatographed (silica, CH_2Cl_2) to yield a colorless oil (14.52 g, 89%). ^{1}H NMR (300MHz, $CDCl_3$) δ 7.34-7.31 (m, 10H), 5.22-5.11 (m, 6H), 1.82-1.79 (m, 3H), 1.68-1.66 (m, 3H), 1.55-1.51 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.0, 169.9, 169.7, 169.4, 135.1, 128.6, 128.5, 128.4, 128.2, 128.1, 69.8, 69.7, 67.2, 21.4, 21.3, 16.7, 16.6; MS (EI) m/z 317 (M+).



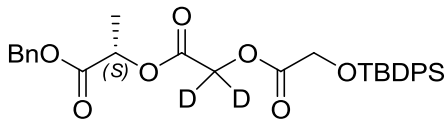
Bn-LG$_{d2}$-Br *rmsvii-12a:* Procedure as described above for **Bn-LL$_{d,rac}$-Br**. The crude was chromatographed (silica, CH_2Cl_2) to yield a colorless oil (13.64 g, 80%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36-7.31 (m, 5H), 5.24-5.13 (m, 3H), 1.52 (d, J= 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.8, 169.7, 135.2, 128.7, 128.6, 128.5, 128.2, 77.1 (t), 70.1, 67.3, 16.8; MS (EI) m/z 303 (M+).



D-G-SiR$_3$. Deuterium oxide was added to silyl-protected glycolic acid (**G-SiR$_3$**) and the mixture was allowed to stir for 1 h. D_2O was removed by vacuum distillation and the product was dried under vacuum overnight. The compound was used without further purification.



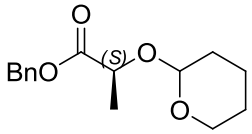
Bn-LL$_{d,rac}$G-SiR$_3$ *rmsvii-66a:* The bromo-dimer, **Bn-LL$_{d,rac}$-Br** (4.52 g, 14.3 mmol) was combined with **D-G-SiR$_3$** (5.0 g, 15.9 mmol), Cs_2CO_3(7.0 g, 21.5 mmol) and KI (0.24 g, 1.4 mmol) in 200 ml dry CH_3CN under N_2. The reaction mixture was stirred at RT for 24 h, quenched with D_2O and extracted with Et_2O (2 x 150 ml). The organic layers were dried with $MgSO_4$ and concentrated *in vacuo*. The concentrate was chromatographed (silica, 5% EtOAc in hexanes) to yield a colorless oil (3.74 g, 48%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.68-7.66 (m, 8H), 7.4-7.3 (m, 22H), 5.21-5.11 (m, 6H), 4.34 (d, J= 16.8 Hz, 1H), 4.32 (d, J=16.8 Hz, 1H), 4.28 (d, J= 16.8 Hz, 1H), 4.27 (d, J= 16.8 Hz, 1H), 1.51 (d, J= 7.2 Hz, 3H), 1.45 (d, J= 6.6 Hz, 3H), 1.43 (s, 6H), 1.073 (s, 9H), 1.069 (s, 9H); ^{13}C (150 MHz, $CDCl_3$) δ 170.6, 170.4, 170.0, 169.83, 169.82, 169.7, 135.58, 135.55, 135.54, 135.2, 135.1, 132.74, 132.71, 129.9, 128.6, 128.5, 128.4, 128.2, 127.8, 127.7, 69.3, 69.1, 68.3 (m), 67.2, 67.1, 62.0, 61.9, 26.6, 19.3, 16.76, 16.74, 16.71, 16.6; MS (EI) m/z 536 (M+).



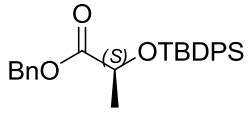
Bn-LG$_{d2}$G-SiR$_3$ *rmsvii-65a:* Procedure as described above for **Bn-LL$_{d,rac}$G-SiR$_3$**. The crude was chromatographed (silica, 5% EtOAc in hexanes) to yield a colorless oil (3.55 g, 46%). ^{1}H

NMR (600 MHz, $CDCl_3$) δ 7.7-7.65 (m, 4H), 7.41-7.3 (m, 11H), 5.20 (q, J= 6.9 Hz, 1H), 4.72 (d, J= 18 Hz, .05H), 4.64 (d, J= 14.4 Hz, .05H), 4.35 (d, J= 16.8 Hz, 1H), 4.32 (d, J= 17.4 Hz, 1H), 1.48 (d, J= 6.6 Hz, 3H), 1.06 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.5, 169.9, 166.8, 135.5, 135.1, 132.7, 132.6, 129.9, 128.6, 128.4, 128.2, 127.8, 69.4, 67.2, 61.9, 60.1 (m), 26.6, 19.3, 16.8; MS (ES) m/z 559 (M+Na).

Enolate mediated synthesis:

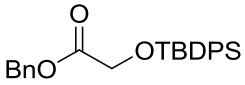


Bn-L-THP *rmsvi-6a:* **Bn-L** (10 g, 55.5 mmol) and dihydropyran (23.5 mL, 278 mmol) were combined in 250 mL of CH_2Cl_2 and chilled in an ice bath. *p*-Toluenesulfonic acid (0.1 g, 0.56 mmol) was added and the reaction mixture was stirred at room temperature for 2 h. The reaction mixture was added to a separation funnel and washed with sat $NaHCO_3$ and brine. The organic layer was dried with $MgSO_4$ and concentrated *in vacuo*. The concentrate was chromatographed (silica, 5% EtOAc in hexanes) to yield a colorless liquid (14.6 g, 100%). ^1H NMR ($CDCl_3$, 300 MHz) δ 7.35-7.29 (m, 10H), 5.14 (d, J= 12.0 Hz, 2H), 5.11 (d, J= 12.6 Hz, 2H), 4.70-4.66 (m, 2H), 4.47 (q, J= 6.9 Hz, 1H), 4.21 (q, J= 6.6 Hz, 1H), 3.85-3.77 (m, 4H), 3.6-3.4 (m, 4H), 1.9-1.35 (m, 18H).

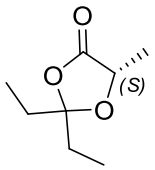


Bn-L-SiR$_3$ *rmsvi-39a:* This compound was prepared using the same silyl-protecting procedures as **L-SiR$_3$**. The crude was chromatographed (silica, 2.5% EtOAc in hexanes) to yield a colorless liquid (5.22 g, 90%). ^1H NMR ($CDCl_3$, 300 MHz) δ 7.67-7.62 (m, 4H), 7.39-7.19 (m, 11H), 5.01

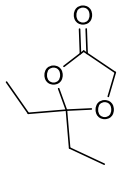
(d, J= 12.3 Hz, 1H), 4.95 (d, J= 12.3 Hz, 1H), 4.31 (q, J= 6.9 Hz, 1H), 1.36 (d, J= 6.9 Hz, 3H), 1.05 (s, 9H).



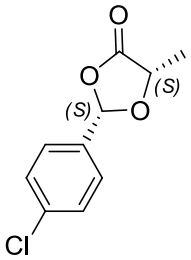
Bn-G-SiR$_3$ *rmsvi-40a:* See above. The crude was chromatographed (silica, 2.5% EtOAc in hexanes) to yield a colorless liquid (5.50 g, 90%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.68-7.62 (m, 4H), 7.40-7.26 (m, 11H), 5.11 (s, 2H), 4.27 (s, 2H), 1.06 (s, 9H).



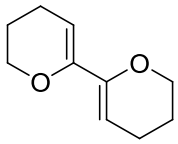
L-Dioxo *rmsvi-69a:* Lactic acid (solid, not aqueous solution) (23.7 g, 263 mmol) was added to 300 ml of dry THF and cooled to -78 °C. While cooling, BF_3•Et_2O (49 ml, 400 mmol) was added dropwise over 10 min followed by the dropwise addition of 3-pentanone (56 ml, 400 mmol) over 10 min. Once the additions were completed the reaction mixture was warmed to 0 °C. After 6 h, Et_3N (60 ml, 430 mmol) was added dropwise and the reaction mixture was poured into 250 ml of ice water. The aqueous layer was extracted with Et_2O (3 × 150 ml). The ethereal layers were dried with $MgSO_4$ and concentrated *in vacuo*. The concentrate was chromatographed (silica, 5% EtOAc in hexanes) to yield a colorless liquid (35.3 g, 85%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.43 (q, J= 6.7 Hz, 1H), 1.85-1.65 (m, 4H), 1.40 (d, J= 6.6 Hz, 3H), 0.93-0.86 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.0, 113.9, 70.8, 30.7, 30.0, 17.4, 7.4, 6.7; MS (EI) m/z 159 (M+1).



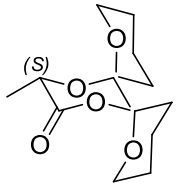
G-Dioxo *rmsvi-64a:* See **L-Dioxo**. The crude was chromatographed (silica, 5-10% EtOAc in hexanes) to yield a colorless liquid (21.2 g, 56%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.33 (s, 2H), 1.81 (q, J= 7.5 Hz, 2H), 1.80 (q, J= 7.5 Hz, 2H), 0.94 (t, J= 7.5 Hz, 6H).



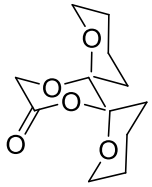
L-ChlorophenylDioxo *rmsviii-30a:* Lactic acid (7.65 g, 76 mmol, 90% in water) and trimethyl orthoformate (15.9 g, 150 mmol) were added to 100 mL of cyclohexane and heated to reflux with a Dean-Stark trap to remove water. After 45 min the reaction mixture was let cool to RT and remaining solvent was removed *in vacuo*. To the concentrate 50 mL of dry toluene was added and the mixture was cooled in an ice bath. Camphorsulfonic acid (0.35 g, 50 mmol) was added followed by the dropwise addition of *p*-chlorobenzaldehyde (7.03 g, 50 mmol) in 25 mL of toluene. The reaction mixture was allowed to stir at RT for 24 h and then quenched with 5% Na_2CO_3 solution. The reaction mixture was extracted with ether (2 × 50 mL), dried with $MgSO_4$ and concentrated *in vacuo*. The crude was chromatographed (silica, 5-10% EtOAc in hexanes) and recrystallized in hexanes to yield a colorless solid (2.2 g, 21%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.45-7.38 (m, 4H), 6.33 (d, J= 1.2 Hz (W-coupling), 1H), 4.51 (dq, J_1= 6.6 Hz, J_2= 1.2 Hz, 1H), 1.58 (d, J= 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.2, 136.6, 132.9, 128.9, 128.0, 102.1, 71.9, 16.3.



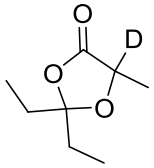
BisTHP[114] *rmsvi-34:* Dihydropyran (30 mL, 330 mmol) in 60 mL dry THF under N_2 was cooled to -78 °C. tBuLi (1.7 M in THF, 200 mL, 340 mmol) was added dropwise and the reaction mixture was allowed to stir for 1 h at 0 °C. This solution was then cannulated into a chilled solution of $PdCl_2(CH_3CN)_2$ (2.0 g, 7.7 mmol) and Cu(II)Cl (46.3 g, 343 mmol) in 300 mL THF. The reaction mixture was allowed to stir for 1 h in an ice bath. The reaction was quenched with sat NH_4Cl with NH_4OH and then extracted with ether (2 × 300 mL). The organic layers were dried with $MgSO_4$, concentrated *in vacuo* and chromatographed (silica, 5% ether in hexanes or neutral alumina, hexanes) to yield a colorless solid (14.97 g, 55%) ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.15 (t, J= 3.9 Hz, 2H), 4.03-4.10 (m, 4H), 2.12-2.07 (m, 4H), 1.85-1.77 (m, 4H).



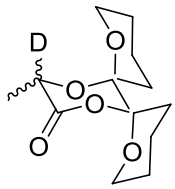
BisTHP-L *rmsvi-26b:* **Bis-THP** (0.45 g, 2.7 mmol) and lactic acid (recrystallized solid, 0.24 g, 2.7 mmol) were dried under vacuum for 1 h and then combined in 10 mL of dry toluene. HCl/Ether (1.0 M, 0.27 mL, 0.27 mmol) was added and the reaction mixture was allowed to stir at RT for 20 h. The reaction mixture was concentrated and chromatographed (silica, 2.5% EtOAc in hexanes) followed by recrystallization in hexanes to yield a colorless solid (0.39 g, 57%) ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.32 (q, J= 6.6 Hz, 1H), 4.0-3.5 (m, 4H), 2.0-1.6 (m, 12H), 1.52 (d, J= 7.8 Hz, 3H).



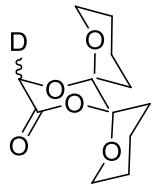
BisTHP-G *rmsvi-30:* See **BisTHP-L**. Recrystallization in hexanes and EtOAc yielded a colorless solid (1.81 g, 42%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.33 (d, J= 17.4 Hz, 1H), 4.21 (d, J= 17.7 Hz, 1H), 4.0-3.5 (m, 4H), 2.0-1.5 (m, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 167.3, 103.3, 95.0, 62.9, 62.3, 59.5, 28.3, 27.8, 24.5, 24.3, 17.9, 17.1.



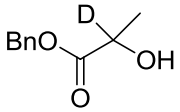
$L_{d,rac}$-Dioxo *rmsvi-79a:* Lithium hexamethyldisilazide (46.9 g, 280 mmol) was dissolved in 500 ml of dry THF and cooled to -78 °C. **L-Dioxo** (22.2 g, 140 mmol) was dissolved in 30 ml of THF and added dropwise. The reaction mixture was allowed to stir at -78 °C for 30 min and quenched with D_2O (11.2 g, 560 mmol). Once at RT, the reaction mixture was added to a brine solution and extracted with Et_2O (3 × 300 ml). The ethereal layers were dried with $MgSO_4$ and concentrated *in vacuo*. The concentrate was chromatographed (silica, 10% EtOAc in hexanes) to yield a colorless liquid (17.1 g, 77%) with > 85% deuterium incorporation. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.45 (q, J= 6.9 Hz, 0.14 H), 1.82-1.69 (m, 4H), 1.43-1.4 (m, 3H), 0.95-0.86 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.1, 114.1, 70.8, 70.5 (t), 30.8, 30.1, 17.4, 7.5, 6.8; HRMS (M+) calc mass 159.1005 mass found 159.1006.



BisTHP-L$_d$ *rmsvi-52a:* Diisopropylamine (0.32 mL, 2.3 mmol) was added to 10 mL of dry THF and cooled to -78 °C. *n*BuLi (1.6 M, 1.44 mL, 2.3 mmol) was added and the reaction mixture was allowed to stir for 20 min. **BisTHP-L** (0.5 g, 1.95 mmol) was added in 5 mL of THF. After 30 min, D_2O (5 mL) was added and the reaction mixture was allowed to warm to RT. More D_2O was added and the reaction mixture was extracted with ether, dried and concentrated *in vacuo*. The concentrate was chromatographed (silica, 5% EtOAc in hexanes) to yield a colorless liquid (0.42 g, 84%, ~70% d). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.47 (q, J= 69. Hz, 0.15H, equatorial), 4.32 (q, J= 6.9 Hz, 0.17H, axial), 4-3.5 (m, 4H), 2-1.5 (m, 15H).



BisTHP-G$_d$ *rmsvi-53a:* See **BisTHP-L$_d$**. The crude was chromatographed (silica, 5% EtOAc in hexanes) to yield a colorless solid (0.103 g, 21%, 90+% d). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.36-4.18 (m, 1H), 4.0-3.5 (m, 4H), 2-1.5 (m, 12H).



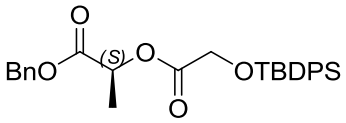
Bn-L$_{d,rac}$ *rmsvi-81a:* Dioxolanone **L$_{d,rac}$-Dioxo** (5.0 g, 31.4 mmol) was dissolved in benzyl alcohol (BnOH, 34 g, 314 mmol) with camphorsulfonic acid (3.48 g, 15 mmol) and heated at 85 °C for 6 h. After cooling, the mixture was taken up in CH_2Cl_2 and washed with saturated $NaHCO_3$ (2 × 100 ml) and brine (75 ml). The organic layer was dried with $MgSO_4$ and

concentrated *in vacuo*. The concentrate was chromatographed (silica, 15% EtOAc in hexanes) followed by removal of excess BnOH by vacuum distillation to yield a colorless oil (2.52 g, 44%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.38-7.31 (m, 5H), 5.19 (s, 2H), 3.08 (s, 1H), 1.41 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 175.5, 135.2, 128.6, 128.5, 128.2, 67.3, 66.5 (t), 20.3; HRMS (M+) calc mass 181.0849 found 181.0850.

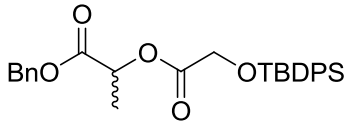
2.7.4 General procedure for DCC/DMAP coupling reactions

One equivalent of TBDPS-acid was combined with 1-1.2 equivalents of benzyl protected alcohol, 1.2 equivalents of DCC and 0.5 equivalents of DMAP. The reaction mixture was let stir at RT for 4 h under N_2 and then filtered to remove dicyclohexylurea. The filtrate was concentrated *in vacuo* and chromatographed.

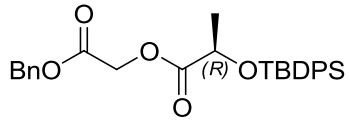
Dimer synthesis. Di-protected dimers were assembled by coupling orthogonally protected building blocks using the above general procedures. All products were purified by chromatography (silica, 2.5-5% EtOAc in hexanes).



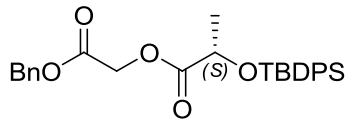
Bn-LG-SiR$_3$ *rmsvii-51a:* The product was a colorless oil (9.25 g, 87%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.7-7.6 (m, 4H), 7.4-7.3 (m, 11H), 5.2-5.1 (m, 3H), 4.34 (d, J= 16.8 Hz, 1H), 4.27 (d, J= 16.8 Hz, 1H), 1.29 (d, J= 7.2 Hz, 3H), 1.06 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.5, 170.2, 135.5, 135.2, 129.8, 128.5, 128.3, 128.1, 128.0, 127.8, 68.7, 66.9, 61.9, 26.6, 19.2, 16.8; MS (Q-Tof) m/z 499 (M+Na), 445, 399; HRMS (M+Na) calc mass 499.1917, found 499.1883; elemental analysis calc. C 70.56, H 6.77, found C 70.89, H 6.83.



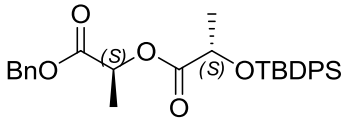
Bn-L$_{rac}$G-SiR$_3$ *rmsvii-52a:* The product was a colorless oil (8.76 g, 82%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.8- 7.6 (m, 4H), 7.5- 7.3 (m, 11H), 5.2- 5.1 (m, 3H), 4.37 (d, J= 16.5 Hz, 1H), 4.31 (d, J= 13.2 Hz, 1H), 1.45 (d, J= 7.2 Hz, 3H), 1.10 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.5, 170.2, 135.6, 135.3, 134.8, 132.7, 129.9, 128.6, 128.4, 128.0, 127.4, 68.7, 67.0, 62.0, 26.7, 19.3, 16.9; MS (ES) m/z 499.1 (M+Na).



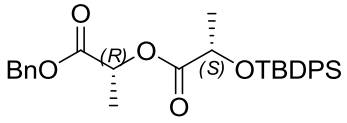
Bn-GL$_R$-SiR$_3$ *rmsviii-11a:* The product was a colorless oil (18.2 g, 84%).^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68-7.64 (m, 4H), 7.43-7.31 (m, 6H), 5.15 (s, 2H), 4.60 (d, J= 15.9 Hz, 1H), 4.44 (d, J= 15.9 Hz, 1H), 4.38 (q, J= 6.8 Hz, 1H), 1.39 (d, J= 6.9 Hz, 3H), 1.09 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.0, 167.3, 135.9, 135.7, 135.0, 133.4, 133.0, 19.8, 128.6, 128.5, 128.4, 127.7, 127.6, 68.7, 67.0, 60.6, 26.8, 21.3, 19.2; MS (EI) m/z 419 (M-*t*-butyl).



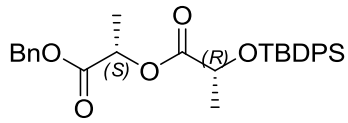
Bn-GL-SiR$_3$ *rmsiv-36a:* The product was a colorless oil (4.8 g, 79%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68-7.66 (m, 4H), 7.43-7.30 (m, 11H), 5.16 (s, 2H), 4.60 (d, J= 15.9 Hz, 1H), 4.44 (d, J= 15.9 Hz, 1H), 4.38 (q, J= 6.8 Hz, 1H), 1.39 (d, J= 6.9 Hz, 3H), 1.09 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.1, 167.3, 135.9, 135.7, 135.0, 134.8, 133.4, 132.9, 129.8, 129.6, 128.6, 128.5, 128.4, 127.7, 127.6, 127.5, 68.6, 67.0, 60.6, 26.8, 21.2, 19.2; HRMS (M+Na) calc mass 499.1917, found 499.1965.



Bn-LL-SiR$_3$ *rmsiv-63a:* The product was a colorless oil (16.6 g, 75%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.7-7.6 (m, 4H), 7.5-7.3 (m, 11H), 5.15 (d= 12 Hz, 1H), 5.09 (d, J= 12 Hz, 1H), 4.97 (q, J= 7.0 Hz, 1H), 4.30 (q, J= 6.6 Hz, 1H), 1.36 (d, J= 7.2 Hz, 3H), 1.32 (d, J= 7.8 Hz, 3H), 1.08 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.1, 170.3, 136.0, 135.7, 135.2, 133.4, 133.0, 130.0, 128.6, 128.4, 128.2, 127.6, 127.5, 68.5, 66.9, 26.8, 21.1, 19.2, 16.7; HRMS (M+Na) calc mass 513.207, found 513.203.

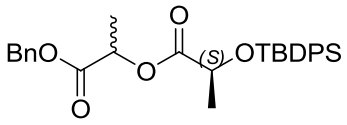


Bn-L$_R$L-SiR$_3$ *rmsviii-88a:* The product was a colorless oil (5.16 g, 76%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.67-7.63 (m, 4H), 7.41-7.30 (m, 11H), 5.14 (s, 2H), 5.00 (q, J= 7.2 Hz, 1H), 4.37 (q, J= 7.2 Hz, 1H), 1.41 (d, J= 7.2 Hz, 3H), 1.35 (d, J= 7.2 Hz, 3H), 1.08 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.0, 170.2, 135.9, 135.7, 135.3, 133.5, 133.1, 129.8, 128.6, 128.4, 128.1, 127.6, 68.9, 68.7, 66.9, 26.8, 21.3, 19.24, 16.8.



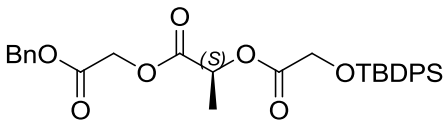
Bn-LL$_R$-SiR$_3$ *rmsviii-92a:* The product was a colorless oil (10.5 g, 72%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.67- 7.63 (m, 4H), 7.43- 7.30 (m, 11H), 5.14 (s, 2H), 5.00 (q, J= 7.0 Hz, 1H), 4.37 (q, J= 6.6 Hz, 1H), 1.42 (d, J= 7.2 Hz, 3H), 1.35 (d, J= 6.6 Hz, 3H), 1.08 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.0, 170.2, 135.8, 135.7, 135.3, 133.5, 133.0, 129.8, 128.5, 128.3, 128.1,

127.6, 127.5, 68.9, 68.7, 66.9, 26.8, 21.2, 19.2, 16.8; HRMS (M+Na) calc mass 513.2073, found 513.2075.



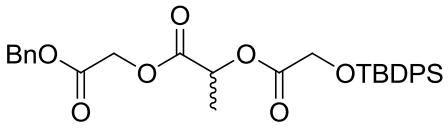
Bn-L$_{rac}$L-SiR$_3$ *rmsv-98a:*The product was a colorless oil (28.2 g, 72%) with an diastereometric excess of 20% in favor of the RS diastereomer. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.7-7.6 (m, 8H), 7.5-7.3 (m, 22H), 5.15 (d, J= 10.2 Hz, 1H), 5.14 (s, 2H), 5.09 (d, J= 12.6 Hz, 1H), 4.99 (quartet, J= 7.2 Hz, 1H), 4.97 (quartet, J= 6.9 Hz, 1H), 4.37 (quartet, J= 6.8 Hz, 1H), 4.30 (quartet, J= 6.6 Hz, 1H), 1.42 (d, J= 7.2 Hz, 3H), 1.36 (d, J= 6.6 Hz, 3H), 1.35 (d, J= 6.0 Hz, 3H), 1.32 (d, J= 7.2 Hz, 3H), 1.08 (s, 18H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.06, 173.04, 170.30, 170.23, 136.0, 135.9, 135.8, 135.7, 135.3, 135.2, 133.5, 133.4, 133.0, 129.8, 129.7, 128.6, 128.4, 128.3, 128.2, 128.1, 127.6, 127.5, 68.7, 68.52, 68.51, 67.0, 66.9, 26.8, 21.3, 21.1, 19.23, 19.20, 16.8, 16.7.

Trimer Synthesis. Di-protected L_xL_xG and $L_xL_xL_x$ families of trimers were prepared by coupling of **LG-SiR$_3$/L$_{rac}$G-SiR$_3$** or **LL-SiR$_3$/L$_{rac}$L-SiR$_3$** with the desired benzyl-protected alcohol using general DCC/DMAP coupling procedures unless otherwise stated. All products were purified by chromatography (silica, 5-10% EtOAc in hexanes).

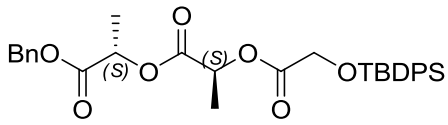


Bn-GLG-SiR$_3$ *rmsvii-58a:* The product was a colorless oil (6.39 g, 84%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.7-7.6 (m, 4H), 7.5-7.3 (m, 11H), 5.16 (s, 2H), 5.15 (q, J= 7.2 Hz, 1H), 4.77 (d, J= 15.6 Hz, 1H), 4.59 (d, J= 15.0 Hz, 1H), 4.33 (d, J= 16.2 Hz, 1H), 4.28 (d, J= 16.8 Hz, 1H), 1.46 (d, J= 7.8 Hz, 3H), 1.06 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.5, 169.9, 167.0, 135.6,

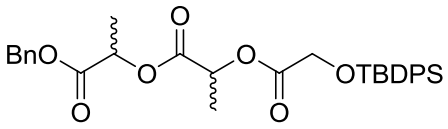
135.5, 134.9, 132.7, 129.9, 128.6, 128.5, 127.8, 127.7, 68.5, 67.2, 61.9, 60.9, 26.6, 19.2, 16.8; HRMS (M+Na) calc mass 557.197, found 557.196.



Bn-GL$_{rac}$G-SiR$_3$ *rmsvii-59a:* The product was a colorless oil (5.8 g, 83%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.7-7.6 (m, 4H), 7.5-7.3 (m, 11H), 5.16 (s, 2H), 5.15 (q, J= 7.2 Hz, 1H), 4.76 (d, J= 16.2 Hz, 1H), 4.59 (d, J= 16.8 Hz, 1H), 4.33 (d, J= 16.8 Hz, 1H), 4.28 (d, J= 16.8 Hz, 1H), 1.46 (d, J= 7.8 Hz, 3H), 1.06 (s, 9H), ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.5, 169.9, 167.0, 135.6, 135.5, 134.9, 132.7, 129.9, 128.6, 128.5, 127.8, 68.5, 67.2, 61.9, 61.0, 26.6, 19.2, 16.8; HRMS (M+Na) calc mass 557.197, found 557.192.

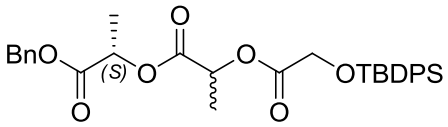


Bn-LLG-SiR$_3$ *rmsv-63a:*The product was a colorless oil (35.3 g, 84%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.7-7.6 (m, 4H), 7.5-7.3 (m, 11H), 5.21-5.1 (m, 4H), 4.34 (d, J= 17.4 Hz, 1H), 4.28 (d, J= 16.8 Hz, 1H), 1.51 (d, J= 7.2 Hz, 3H), 1.44 (d, J= 6.6 Hz, 3H), 1.07 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.6, 170.0, 169.8, 135.6, 135.5, 135.1, 134.8, 132.7, 129.9, 128.6, 128.5, 128.2, 127.8, 127.7, 69.1, 68.4, 67.1, 61.9, 26.6, 19.3, 16.8, 16.7; HRMS (M+Na) calc mass 571.212, found 571.213.

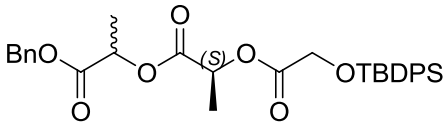


Bn-L$_{rac}$L$_{rac}$G-SiR$_3$ *rmsviii-82a:* The product was a colorless oil (6.74 g, 82%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.68-7.66 (m, 16H), 7.41-7.30 (m, 44H), 5.21-5.10 (m, 16H), 4.36-4.27 (m, 8H),

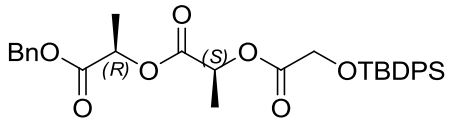
1.51 (d, J= 7.2 Hz, 3H), 1.45-1.43 (m, 21H), 1.07 (s, 36H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.6, 170.4, 170.0, 169.83, 169.82, 169.7, 135.6, 135.5, 135.2, 135.1, 132.7, 129.9, 128.6, 128.5, 128.4, 128.2, 127.8, 127.7, 69.3, 69.1, 68.7, 68.5, 67.14, 67.13, 61.98, 61.96, 26.6, 19.3, 16.8, 16.76, 16.74, 16.66; HRMS (M+Na) calc mass 571.2128, found 571.2093.



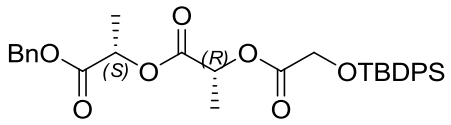
Bn-LL$_{rac}$G-SiR$_3$ *rmsv-63a:* The product was a colorless oil (33.6 g, 85%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.7-7.6 (m, 4H), 7.5-7.3 (m, 22H), 5.21-5.1 (m, 8H), 4.34 (d, J= 16.8 Hz, 1H), 4.32 (d, J= 16.8 Hz, 1H), 4.282 (d, J= 16.8 Hz, 1H), 2.281 (d, J= 17.4 Hz, 1H), 1.51 (d, J= 7.2 Hz, 3H), 1.45 (d, J= 7.2 Hz, 3H), 1.44 (d, J= 7.2 Hz, 3H), 1.43 (d, J=7.2 Hz, 3H), 1.07 (s, 18H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.6, 170.4, 170.0, 169.84, 169.82, 169.7, 135.57, 135.53, 135.14, 135.1, 132.7, 132.67, 129.9, 128.6, 128.57, 128.47, 1218.43, 128.24, 128.22, 127.8, 69.2, 69.1, 68.6, 68.4, 67.14, 67.13, 61.96, 61.93, 26.6, 19.2, 16.82, 16.75, 16.73, 16.65; HRMS (M+Na) calc mass 571.213, found 571.213.



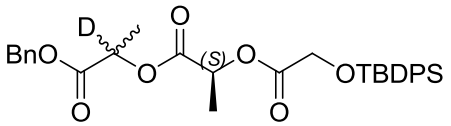
Bn-L$_{rac}$LG-SiR$_3$ *rmsviii-21a:* The product was a colorless oil (12.53 g, 88%) ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.7- 7.6 (m, 8H), 7.4-7.3 (m, 22H), 5.21-5.1 (m, 8H), 4.35 (d, J= 16.8 Hz, 1H), 4.32 (d, J= 16.8 Hz, 1H), 4.28 (d, J= 17.4 Hz, 4H), 1.51 (d, J= 7.2 Hz, 3H), 1.45 (d, J= 7.2 Hz, 3H), 1.44 (d, J= 7.8 Hz, 6H), 1.08 (s, 9H), 1.07 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.6, 170.4, 170.0, 169.83, 169.81, 169.68, 135.57, 135.53, 135.15, 135.1, 132.7, 132.6, 129.9, 128.6, 128.5, 128.4, 128.2, 127.8, 69.3, 69.1, 68.6, 68.4, 67.1, 62.0, 61.9, 26.6, 19.2, 16.8, 16.75, 16.74, 16.7; MS (EI) m/z 491 (M-tbutyl).



Bn-L$_R$LG-SiR$_3$ *rmsviii-87a:* The product was a colorless oil (4.79 g, 72%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.68-7.66 (m, 4H), 7.42-7.30 (m, 11H), 5.17 (q, J= 7.2 Hz, 1H), 5.169 (d, J= 12.0 Hz, 1H), 5.14 (q, J= 7.2 Hz, 1H), 5.12 (d, J= 12.6 Hz, 1H), 4.31 (d, J= 16.8 Hz, 1H), 4.27 (d, J= 16.8 Hz, 1H), 1.44 (d, J= 7.8 Hz, 3H), 1.43 (d, J= 7.2 Hz, 3H), 1.07 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.4, 169.8, 169.7, 135.6, 135.5, 135.2, 132.7, 129.9, 128.6, 128.4, 128.2, 127.8, 69.3, 68.3, 67.1, 62.0, 26.6, 19.2, 16.8, 16.7; HRMS (M+Na) calc mass 571.2128, found 571.2090.

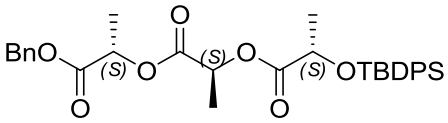


Bn-LL$_R$G-SiR$_3$ *rmsviii-61a:* Benzyl-protected dimer **Bn-LL$_R$** (4.8 g, 19 mmol), **G-SiR$_3$** (7.23 g, 23 mmol), DCC (4.75 g, 23 mmol) and DMAP (1.22 g, 10 mmol) were combined in 200 ml of CH_2Cl_2 and stirred at room temperature for 4 h under N_2. The reaction mixture was filtered and concentrated *in vacuo*. The concentrate was chromatographed (silica, 2.5-5% EtOAc in hexanes) to yield a colorless oil (7.34 g, 71%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.68- 7.65 (m, 4H), 7.43-7.30 (m, 11H), 5.19- 5.12 (m, 4H), 4.32 (d, J= 16.8 Hz, 1H), 4.28 (d, J= 16.8 Hz, 1H), 1.45 (d, J= 7.8 Hz, 3H), 1.43 (d, J= 7.2 Hz, 3H), 1.07 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.4, 169.8, 169.7, 135.6, 135.5, 135.1, 132.7, 129.9, 128.6, 128.4, 128.2, 127.8, 69.3, 68.7, 67.1, 61.9, 26.6, 19.3, 16.9, 16.7; HRMS (M+Na) calc mass 571.2128, found 571.2087.

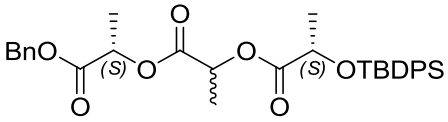


Bn-L$_{d,rac}$LG-SiR$_3$ *rmsvi-86a:* The product was a colorless oil (4.68 g, 71%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.68-7.65 (m, 8H), 7.42-7.29 (m, 22H), 5.17-5.10 (m, 6H), 4.33 (d, J= 16.8 Hz,

1H), 4.31 (d, J= 16.2 Hz, 1H), 4.272 (d, J= 16.2 Hz, 1H), 4.270 (d, J=16.8 Hz, 1H), 1.50 (s, 3H), 1.43 (s, 3H), 1.42 (d, J= 7.8 Hz, 6H), 1.063 (s, 9H), 1.060 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.6, 170.4, 170.0, 169.83, 169.8, 169.7, 135.6, 135.5, 135.1, 132.7, 129.9, 128.6, 128.2, 127.8, 69.1 (t), 68.6, 68.4, 67.1, 61.94, 61.92, 26.6, 19.2, 16.8, 16.64, 16.62, 16.61; MS (EI) m/z 493 (M-tbutyl).

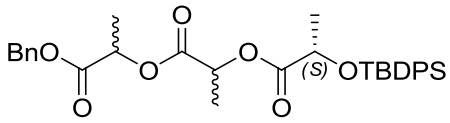


Bn-LLL-SiR$_3$ *rmsvi-3a:* The product was a colorless oil (23.6 g, 92%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.7-7.6 (m, 4H), 7.5-7.3 (m, 11H), 5.16 (d, J= 12.6 Hz, 1H), 5.15 (q, J= 7.2 Hz, 1H), 5.10 (d, J= 12.6 Hz, 1H), 4.92 (q, J= 7.0 Hz, 1H), 4.31 (q, J= 6.8 Hz, 1H), 1.48 (d, J= 7.2 Hz, 3H), 1.40 (d, J= 6.6 Hz, 3H), 1.32 (d, J= 7.2 Hz, 3H), 1.07 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.1, 170.0, 169.9, 136.0, 135.7, 135.1, 133.4, 133.0, 129.8, 129.7, 128.6, 128.5, 128.2, 127.6, 127.5, 69.0, 68.5, 68.2, 67.1, 26.8, 21.1, 19.2, 16.8, 16.5; HRMS (M+Na) calc mass 585.229, found 585.224.



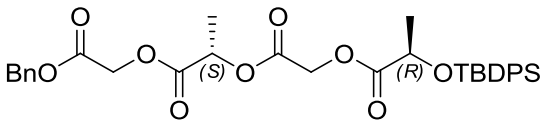
Bn-LL$_{rac}$L-SiR$_3$ *rmsvi-2a:* The product was a colorless oil (24.5 g, 97%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.7-7.6 (m, 8H), 7.5-7.3 (m, 22H), 5.2-5.1 (m, 6H), 4.98 (q, J= 7.0 Hz, 1H), 4.92 (q, J= 7.0 Hz, 1H), 4.36 (q, J=6.8 Hz, 1H), 4.31 (q, J= 7.0 Hz, 1H), 1.48 (d, J= 7.2 Hz, 3H), 1.42 (d, J= 7.2 Hz, 3H), 1.41 (d, J= 7.2 Hz, 3H), 1.40 (d, J= 7.2 Hz, 3H), 1.37 (d, J= 7.2 Hz, 3H), 1.32 (d, J= 6.6 Hz, 3H), 1.08 (s, 18H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.1, 172.9, 170.0, 169.9, 169.7, 136.0, 135.9, 135.7, 135.2, 135.1, 133.5, 133.4, 133.1, 133.0, 129.8, 129.7, 129.6, 128.6, 128.5,

128.4, 128.2, 127.7, 127.6, 127.5, 126.5, 125.7, 69.2, 69.1, 68.9, 68.8, 68.5, 68.2, 67.1, 67.0, 26.8, 21.3, 21.1, 19.3, 19.2, 16.8, 16.7, 16.5; HRMS (M+Na) Calc mass 585.229, found 585.227.



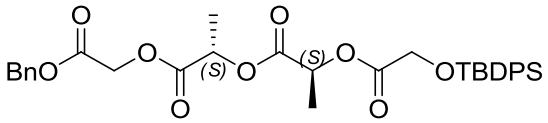
Bn-L$_{rac}$L$_{rac}$L-SiR$_3$ *rmsvi-1a:* The product was a colorless oil (16.8 g, 85%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.7-7.6 (m, 16H), 7.5-7.3 (m, 44H), 5.2-5.1 (m, 12H), 5.0-4.9 (m, 4H), 4.4-4.35 (m, 2H), 4.35-4.30 (m, 2H), 1.52-1.25 (m, 36H), 1.08 (36H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.1, 173.0, 172.9 (2), 170.1, 170.0, 169.87, 169.84, 169.76, 169.75, 169.72, 136.3, 136.0, 135.9, 135.7, 135.2, 135.1, 134.8, 133.5, 133.4, 133.1, 133.0, 129.8, 129.7, 128.6, 128.5, 128.4, 128.2, 127.7, 127.6, 127.5, 69.2, 69.1, 69.0, 68.92, 68.90, 68.8, 68.5, 68.4, 68.3, 68.2, 67.12, 67.10, 26.8, 21.3, 21.1, 19.23, 19.20, 16.76, 16.74, 16.72, 16.70, 16.6, 16.5; HRMS (M+Na) Calc mass 585.229, found 585.224.

Tetramer Synthesis. Di-protected GLGL$_R$ and GL$_x$L$_x$G family of tetramers were assembled from the corresponding orthogonally protected dimer units using general DCC/DMAP procedures. The **L$_x$L$_x$L$_x$G** family of tetramers was assembled from coupling of **Bn-L$_x$L$_x$L$_x$** and **G-SiR$_3$**. All products were purified by chromatography (silica, 5-10% EtOAc in hexanes).

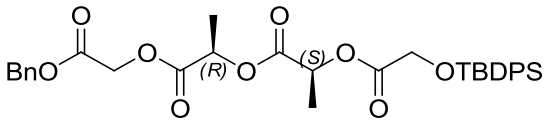


Bn-GLGL$_R$-SiR$_3$ *rmsviii-19a:* The product was a colorless oil (3.41 g, 87%).^{1}H NMR (600 MHz, $CDCl_3$) δ 7.66-7.64 (m, 4H), 7.4-7.31 (m, 11H), 5.21 (q, J= 7.2 Hz, 1H), 5.17 (s, 2H), 4.78 (d, J= 16.2 Hz, 1H), 4.60 (d, J= 16.2 Hz, 1H), 4.59 (d, J= 16.2 Hz, 1H), 4.36 (q, J= 7.2 Hz, 1H), 1.51 (q, J= 7.2 Hz, 1H), 1.39 (d, J= 7.2 Hz, 1H), 1.07 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ

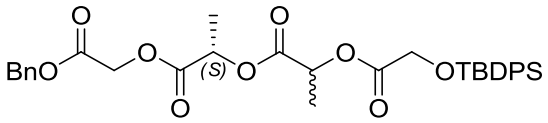
172.7, 169.5, 166.9, 166.8, 135.9, 135.7, 134.9, 133.4, 132.9, 129.8, 128.6, 128.5, 127.6, 69.0, 68.7, 67.2, 61.1, 60.3, 26.8, 21.3, 19.2, 16.8; MS (EI) m/z 549 (M-tbutyl).



Bn-GLLG-SiR$_3$ *rmsix-54a:* The product was a colorless oil (6.54 g, 83%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.67-7.65 (m, 4H), 7.43-7.32 (m, 11H), 5.22 (q, J= 7.2 Hz, 1H), 5.17 (s, 2H), 5.13 (q, J= 7.2 Hz, 1H), 4.78 (d, J= 16.2 Hz, 1H), 4.59 (d, J= 15.6 Hz, 1H), 4.35 (d, J= 16.2 Hz, 1H), 4.29 (d, J= 16.8 Hz, 1H), 1.55 (d, J= 7.2 Hz, 3H), 1.49 (d, J= 7.2 Hz, 3H), 1.07 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.6, 169.8, 169.7, 166.9, 135.6, 135.5, 134.8, 132.7, 132.6, 129.9, 128.6, 128.5, 127.8, 127.7, 68.8, 68.4, 67.3, 61.9, 61.1, 26.6, 19.2, 16.7(2).

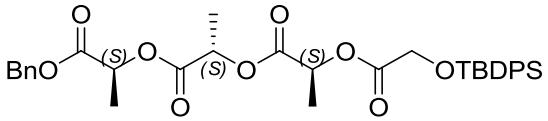


Bn-GL$_R$LG-SiR$_3$ *rmsix-57a:* The product was a colorless oil (4.87 g, 79%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.68-7.67 (m, 4H), 7.43-7.32 (m, 11H), 5.18 (q, J= 7.2 Hz, 1H), 5.17 (q, J= 7.0 Hz, 1H), 5.166 (s, 2H), 4.77 (d, J= 16.2 Hz, 1H), 4.60 (d, J= 15.6 Hz, 1H), 4.33 (d, J= 16.8 Hz, 1H), 4.28 (d, J= 16.8 Hz, 1H), 1.49 (d, J= 7.2 Hz, 3H), 1.46 (d, J= 7.2 Hz, 3H), 1.07 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.4, 169.7, 169.5, 167.0, 135.6, 135.5, 134.8, 132.7, 132.6, 129.9, 128.6, 128.5, 127.8, 69.0, 68.6, 67.3, 62.0, 61.0, 26.6, 19.2, 16.8, 16.7.

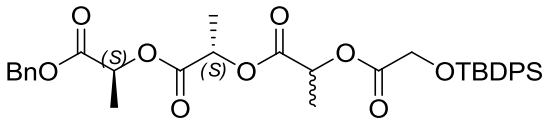


Bn-GLL$_{rac}$G-SiR$_3$ *rmsix-48a:* The product was a colorless oil (4.94 g, 63%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.68-7.65 (m, 8H), 7.43-7.31 (m, 22H), 5.22 (q, J= 7.2 Hz, 1H), 5.18 (q, J= 7.2

Hz, 1H), 5.17 (q, J= 6.6 Hz, 1H), 5.166 (s, 2H), 5.13 (q, J= 7.2 Hz, 1H), 4.774 (d, J= 15.6 Hz, 1H), 4.77 (d, J= 15.6 Hz, 1H), 4.60 (d, J= 16.2 Hz, 1H), 4.59 (d, J= 15.6 Hz, 1H), 4.34 (d, J= 16.8 Hz, 1H), 4.33 (d, J= 16.8 Hz, 1H), 4.285 (d, J= 16.8 Hz, 1H), 4.283 (d, J= 16.8 Hz, 1H), 1.54 (d, J= 7.2 Hz, 3H), 1.49 (d, J= 7.2 Hz, 3H), 1.489 (d, J= 7.2 Hz, 3H), 1.47 (d, J= 7.2 Hz, 3H), 1.068 (s, 9H), 1.067 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.6, 170.4, 169.8, 169.7(2), 169.5, 166.94, 166.9, 135.56, 135.53, 135.52, 134.86, 134.83, 132.7, 132.68, 132.66, 129.9, 128.64, 128.6, 128.47, 128.46, 127.8, 127.7, 69.0, 68.8, 68.6, 68.4, 67.3, 67.2, 61.97, 61.93, 61.05, 26.6, 19.2, 16.8, 16.7(3).

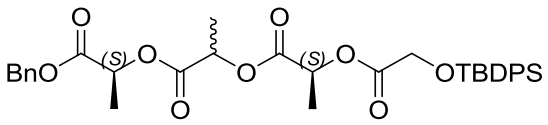


Bn-LLLG-SiR$_3$ *rmsix-17a:* The product was a colorless oil (2.53 g, 69%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.67-7.65 (m, 4H), 7.43-7.30 (m, 11H), 5.171 (d, J= 12.0 Hz, 1H), 5.168 (q, J= 7.2 Hz, 1H), 5.15 (q, J= 7.2 Hz, 1H), 5.12 (q, J= 7.2 Hz, 1H), 5.11 (d, J= 12.0 Hz, 1H), 4.34 (d, J= 16.8 Hz, 1H), 4.28 (d, J= 16.8 Hz, 1H), 1.507 (d, J= 7.2 Hz, 3H), 1.505 (d, J= 7.2 Hz, 3H), 1.49 (d, J= 7.2 Hz, 3H), 1.07 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.6, 169.94, 169.9, 169.7, 135.57, 135. 53, 135.1, 132.7, 132.6, 129.9, 128.5, 128.2, 127.8, 127.7, 69.2, 68.9, 68.4, 67.2, 61.9, 26.6, 19.2, 16.75, 16.73, 16.56.

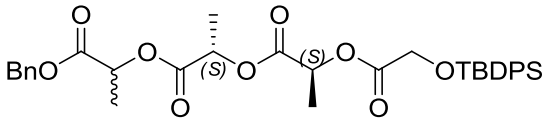


Bn-LLL$_{rac}$G-SiR$_3$ *rmsix-13a:* The product was a colorless oil (5.23 g, 91%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.68-7.66 (m, 8H), 7.43-7.30 (m, 22H), 5.19-5.10 (m, 10H), 4.34 (d, J= 16.8 Hz, 1H), 4.33 (d, J= 16.8 Hz, 1H), 4.285 (d, J= 16.2 Hz, 1H), 4.284 (d, J= 16.2 Hz, 1H), 1.51 (d, J= 7.2 Hz, 3H), 1.508 (d, J= 7.2 Hz, 6H), 1.50 (d, J= 7.2 Hz, 3H), 1.47 (d, J= 7.2 Hz, 3H), 1.45 (d,

J= 7.2 Hz, 3H), 1.071 (s, 9H), 1.068 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.6, 170.4, 169.95, 169.92, 169.9, 169.7, 169.6, 169.4, 135.56, 135. 52, 135.07, 135.04, 132.7, 132.6, 129.89, 129.87, 128.6, 128.5, 128.4, 128.22, 128.21, 127.8, 69.2, 68.91, 68.88, 68.7, 68.4, 67.17, 67.15, 61.95, 61.91, 26.6, 19.2, 16.85, 16.74, 16.71(2), 16.5(2).

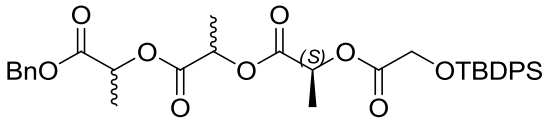


Bn-LL$_{rac}$LG-SiR$_3$ *rmsix-18a:* The product was a colorless oil (2.65 g, 72%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.66-7.65 (m, 8H), 7.43-7.30 (m, 22H), 5.20-5.10 (m, 10H), 4.34 (d, J= 16.8 Hz, 1H), 4.33 (d, J= 16.8 Hz, 1H), 4.283 (d, J= 16.2 Hz, 1H), 4.280 (d, J= 16.2 Hz, 1H), 1.508 (d, J= 7.2 Hz, 3H), 1.506 (d, J= 7.2 Hz, 3H), 1.496 (d, J= 7.2 Hz, 3H), 1.493 (d, J= 7.2 Hz, 3H), 1.46 (d, J= 7.2 Hz, 6H), 1.06 (s, 18H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.6, 170.4, 169.94, 169.9, 169.87, 169.7, 169.67, 169.4, 135.56, 135. 52, 135.15, 135.05, 132.7, 132.66, 129.90, 128.6, 128.58, 128.5, 128.4, 128.2, 127.8, 69.39, 69.37, 69.2, 68.9, 68.5, 68.4, 67.18, 67.12, 61.93, 26.6, 19.2, 16.80, 16.75, 16.72, 16.67, 16.65, 16.56.



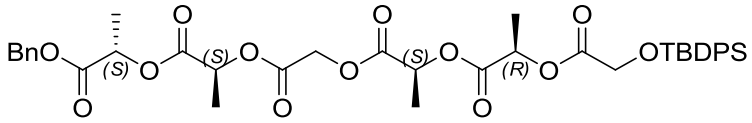
Bn-L$_{rac}$LL-SiR$_3$ *rmsix-10a:* The product was a colorless oil (3.61 g, 85%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.69-7.66 (m, 8H), 7.42-7.31 (m, 22H), 5.22 (q, J= 7.2 Hz, 1H), 5.20-5.10 (m, 9H), 4.354 (d, J= 16.8 Hz, 1H), 4.35 (d, J= 16.8 Hz, 1H), 4.29 (d, J= 16.2 Hz, 1H), 4.28 (d, J= 16.2 Hz, 1H), 1.514 (d, J= 7.2 Hz, 3H), 1.511 (d, J= 7.2 Hz, 6H), 1.50 (d, J= 7.2 Hz, 3H), 1.48 (d, J= 7.2 Hz, 3H), 1.47 (d, J= 7.2 Hz, 3H), 1.07 (s, 18H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.6, 170.56, 169.91, 169.9, 169.71, 169.67, 169.64, 169.45, 135.54, 135. 5, 135.08, 135.03, 132.7,

132.6, 129.90, 128.6, 128.57, 128.5, 128.4, 128.2, 127.8, 69.31, 69.2, 69.03, 68.9, 68.4, 68.36, 67.16, 67.14, 61.9, 26.6, 19.2, 16.73, 16.68, 16.54.



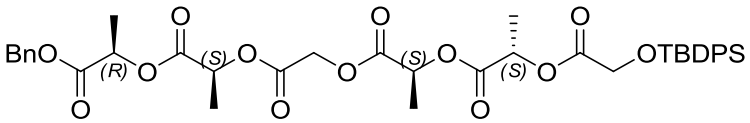
Bn-L$_{rac}$L$_{rac}$L-SiR$_3$ *rmsix-19a:* The product was a colorless oil (2.36 g, 72%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.68-7.66 (m, 16H), 7.43-7.30 (m, 44H), 5.23-5.10 (m, 20H), 4.348 (d, J= 16.2 Hz, 1H), 4.342 (d, J= 16.2 Hz, 1H), 4.33 (d, J= 16.2 Hz, 1H), 4.32 (d, J= 16.2 Hz, 1H), 4.29 (d, J= 16.2 Hz, 4H), 1.52-1.44 (m, 36H), 1.07 (s, 36H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.62, 170.57, 170.39, 170.35, 169.95, 169.92, 169.9, 169.86, 169.73, 169.68, 169.66, 169.46, 169.39, 169.35, 135.56, 135. 5, 135.15, 135.10, 135.07, 135.05, 132.7, 132.68, 132.64, 129.90, 128.6, 128.57, 128.5, 128.47, 128.45, 128.43, 128.2, 127.8, 69.38, 69.36, 69.32, 69.2, 69.04, 68.92, 68.88, 68.67, 68.52, 68.4, 68.37, 67.16, 67.12, 61.96, 61.93, 61.91, 26.61, 26.59, 19.2, 16.86, 16.79, 16.74, 16.73, 16.70, 16.66, 16.64, 16.56.

Hexamer Synthesis.



Bn-LLGLL$_R$G-SiR$_3$ *rmsviii-69a:* Benzyl-proteceted **Bn-LLG** (0.97 g, 3.11 mmol), **LL$_R$G-SiR$_3$** (1.3 g, 2.83 mmol), DPTS (0.17 g, 0.57 mmol) and EDCI (0.65 g, 3.4 mmol) were combined in 30 ml of dry CH_2Cl_2 under N_2. The reaction mixture was stirred at room temperature for 4 h and then washed with brine (2 x 50 ml) and $NaHCO_3$ (2 x 50 ml). The organic layer was dried with $MgSO_4$ and concentrated *in vacuo*. The concentrate was chromatographed (silica, 10% EtOAc in hexanes) to yield a colorless oil (1.76 g, 83%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.68- 7.66 (m,

4H), 7.43- 7.30 (m, 11H), 5.2- 5.1 (m, 6H), 4.84 (d, J= 15.6 Hz, 1H), 4.61 (d, J= 16.2 Hz, 1H), 4.32 (d, J= 16.2 Hz, 1H), 4.28 (d, J= 16.8 Hz, 1H), 1.512 (d, J= 7.2 Hz, 3H), 1.508 (d, J= 7.2 Hz, 3H), 1.499 (d, J= 7.2 Hz, 3H), 1.47 (d, J= 7.2 Hz, 3H), 1.07 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.4, 169.9, 169.7, 169.42, 169.4, 166.7, 135.6, 135.5, 135.0, 132.7, 132.6, 129.9, 128.6, 128.5, 128.2, 127.8, 69.3, 69.2, 68.9, 68.6, 67.2, 62.0, 60.7, 26.6, 19.2, 16.8, 16.73, 16.7, 16.6; HRMS (M+Na) calc mass 773.2605, found 773.2568.

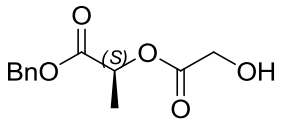


Bn-L$_R$LGLLG-SiR$_3$ *rmsviii-103a:* Benzyl-protected **Bn-L$_R$LG** (0.87 g, 2.7 mmol), **LLG-SiR$_3$** (1.26 g, 2.7 mmol), DPTS (0.16 g, 0.55 mmol) and EDCI (0.58 g, 3 mmol) were combined in 20 ml of dry CH_2Cl_2 under N_2. The reaction mixture was stirred at RT for 4 h and then washed with brine (2 x 50 ml) and $NaHCO_3$ (2 x 50 ml). The organic layer was dried with $MgSO_4$ and concentrated *in vacuo*. The concentrate was chromatographed (silica, 10% EtOAc in hexanes) to yield a colorless oil (1.76 g, 83%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.68-7.66 (m, 4H), 7.43-7.31 (m, 11H), 5.23 (q, J= 7.2 Hz, 2H), 5.18 (d, J= 12 Hz, 1H), 5.16 (q, J= 7.2 Hz, 1H), 5.13 (d, J= 12.6 Hz, 1H), 5.129 (q, J= 7.2 Hz, 1H), 4.81 (d, J= 16.2 Hz, 1H), 4.60 (d, J= 16.2 Hz, 1H), 4.34 (d, J= 16.8 Hz, 1H), 4.29 (d, J= 16.8 Hz, 1H), 1.57 (d, J= 7.2 Hz, 3H), 1.50 (d, J= 6.6 Hz, 3H), 1.49 (d, J= 7.2 Hz, 6H), 1.07 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.6, 169.8, 169.7, 169.6, 169.2, 166.3, 135.6, 135.5, 135.1, 132.7, 129.9, 128.6, 128.5, 128.2, 127.8, 69.5, 69.3, 68.8, 68.4, 67.2, 61.9, 60.7, 26.6, 19.2, 16.69, 16.67; HRMS (M+K) calc mass 789.2345, found 789.2358.

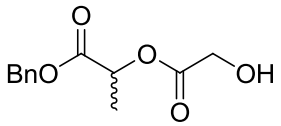
2.7.5 General Procedure for TBDPS deprotection

For primary alcohols, 1.5 equivalents of TBAF (1.0 M in THF) buffered by 8 equiv of acetic acid was added to the di-protected oligomer in dry THF. The reaction mixture was allowed to stir for 1.5 to 2 h and then poured into brine. The product was extracted using Et_2O, dried with $MgSO_4$ and concentrated *in vacuo*. The concentrate was chromatographed (silica, 15-30% EtOAc in hexanes) to yield a clear liquid. For secondary alcohols, 1.5 equiv of TBAF was buffered with 1.2-2 equivalents of acetic acid.

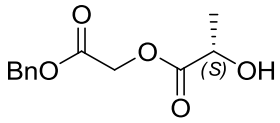
Dimers.



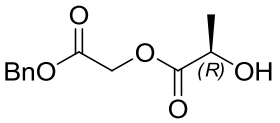
Bn-LG *rmsv-67a:* The product was a colorless liquid (18.1 g, 88%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.4-7.3 (m, 5H), 5.24 (quartet, J= 7.1 Hz, 1H), 5.17 (s, 2H), 4.27 (dd, J= 17.4 Hz, J= 5.4 Hz, 1H), 4.20 (dd, J= 17.4 Hz, J= 6.0 Hz, 1H), 2.26 (t, J= 5.6 Hz, 1H), 1.52 (d, J= 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.4, 170.1, 134.9, 128.4, 128.3, 128.0, 69.0, 67.0, 60.3, 16.6; MS (EI) m/z 238 (M+); elemental analysis calc. C 60.50, H 5.92, found C 60.11, H 6.05.



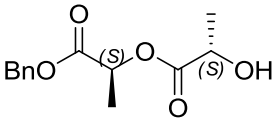
Bn-L$_{rac}$G *rmsvii-100a:* The product was a colorless liquid (2.20 g, 88%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.4-7.3 (m, 5H), 5.24 (quartet, J= 7.1 Hz, 1H), 5.17 (s, 2H), 4.27 (dd, J= 17.1 Hz, J= 5.4 HZ, 1H), 4.20 (dd, J= 17.4 HZ, J= 5.7 Hz, 1H), 2.26 (t, J= 5.6 Hz, 1H), 1.52 (d, J= 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.5, 170.0, 135.0, 128.4, 128.3, 128.0, 69.0, 67.0, 60.3, 16.6; MS (EI) m/z 238 (M+).



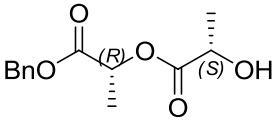
Bn-GL. The product was a colorless liquid (3.3 g, 67% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39-7.30 (m, 5H), 5.17 (s, 2H), 4.76 (d, J= 15.9 Hz, 1H), 4.66 (d, J= 15.9 Hz, 1H), 4.39 (q, J= 7.0 Hz, 1H), 1.44 (d, J= 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.9, 167.2, 134.7, 128.6, 67.3, 66.7, 61.1, 20.2; HRMS (M+Na) calc mass 261.0739, found 261.0738.



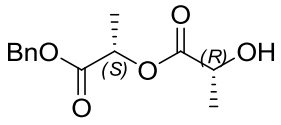
Bn-GL$_R$ *rmsix-56a:* The product was a colorless liquid (2.98 g, 85%). 1H NMR (600 MHz, CDCl3) d 7.37-7.32 (m, 5H), 5.18 (s, 2H), 4.77 (d, J= 16.2 Hz, 1H), 4.68 (d, J= 16.2 Hz, 1H), 4.4-4.36 (m, 1H), 2.76 (d, J= 5.4 Hz, 1H), 1.45 (d, J= 6.6 Hz, 3H); 13C NMR (150 MHz, CDCl3) d 175.0, 167.1, 134.8, 128.7, 128.4, 67.3, 66.7, 61.2, 20.3.



Bn-LL *rmsix-11a:* The product was a colorless liquid (4.14 g, 92%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.37-7.3 (m, 5H), 5.21 (q, J= 7.2 Hz, 1H), 5.18 (d, J= 11.4 Hz, 1H), 5.13 (d, J= 12 Hz, 1H), 4.32 (q, J= 7.0 Hz, 1H), 2.74 (s, 1H), 1.52 (d, J= 7.2 Hz, 3H), 1.42 (d, J= 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 175.1, 170.0, 135.0, 128.6, 128.5, 128.2, 69.4, 67.2, 66.7, 20.4, 16.8; HRMS (M+Na) calc mass 252.099, found 252.099.

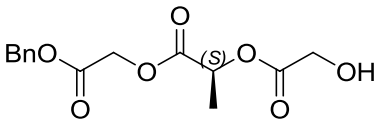


Bn-L$_R$L *rmsviii-91a:* The product was a colorless liquid (2.30 g, 90%).

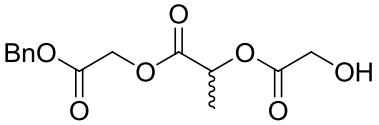


Bn-LL*R* *rmsviii-97a:* The product was a colorless liquid (2.46 g, 96%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.37- 7.31 (m, 5H), 5.19 (q, J= 7.0 Hz, 1H), 5.18 (d, J= 12.0 Hz, 1H), 5.15 (d, J= 12.6 Hz, 1H), 4.36 (dq, J= 6.0 Hz, J= 1.8 Hz, 1H), 2.81 (d, J= 5.4 Hz, 1H), 1.52 (d, J= 7.2 Hz, 3H), 1.42 (d, J= 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.9, 170.0, 135.1, 128.6, 128.5, 128.2, 69.5, 67.2, 66.7, 20.0, 16.8; HRMS (M+Na) calc mass 275.0895, found 275.0912.

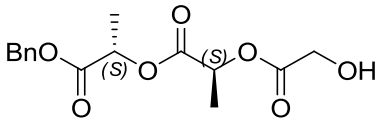
Trimers.



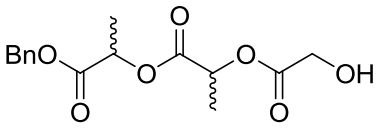
Bn-GLG *rmsvii-33a:* The product was a colorless liquid (6.37 g, 83%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.37-7.32 (m, 5H), 5.28 (q, J= 6.9 Hz, 1H), 5.18 (s, 2H), 4.79 (d, J= 15.6 Hz, 1H), 4.63 (d, J= 15.6 Hz, 1H), 4.27 (dd, J= 17.4 Hz, 3.6 Hz, 1H), 4.22 (dd, J= 17.4 Hz, 4.8 Hz, 1H), 2.29 (s, 1H), 1.55 (d, J= 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.6, 169.6, 166.9, 134.8, 128.7, 128.5, 69.2, 67.4, 61.1, 60.5, 16.8; HRMS (M+Na) calc mass 319.079, found 319.080.



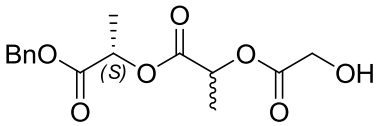
Bn-GL*rac*G *rmsvii-34a:* The product was a colorless liquid (6.81 g, 88%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.37-7.32 (m, 5H); 5.27 (q, J= 6.9 Hz, 1H), 5.17 (s, 2H), 4.79 (d, J= 15.6 Hz, 1H), 4.63 (d, J= 15.6 Hz, 1H), 4.26 (d, J= 17.4 Hz, 1H), 4.22 (d, J= 17.4 Hz, 1H), 2.41 (s, 1H), 1.55 (d, J= 6.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.6, 169.6, 166.9, 134.8, 128.7, 69.1, 67.3, 61.1, 60.5, 16.8; MS (EI) m/z 296 (M+).



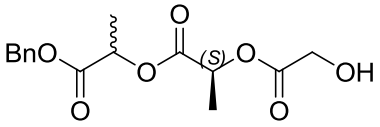
Bn-LLG *rmsvii-19a:* The product was a colorless liquid (7.72 g, 86%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36- 7.30 (m, 5H), 5.22-5.18 (m, 2H), 5.16 (d, J= 12 Hz, 1H), 5.12 (d, J= 12 Hz, 1H), 4.26 (d, J= 17.4 Hz, 1H), 4.20 (d, J= 17.4 Hz, 1H), 2.53 (s, 1H), 1.51 (d, J= 7.2 Hz, 3H), 1.50 (d, J= 7.8 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.6, 169.8, 169.6, 135.1, 128.6, 128.5, 128.2, 69.3, 69.1, 67.2, 60.4, 16.7, 16.6; HRMS (M+Na) calc mass 333.095, found 333.096.



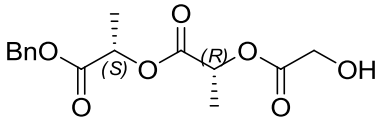
Bn-L$_{rac}$L$_{rac}$G *rmsix-33a:*The product was a colorless liquid (2.05 g, 82%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36-7.29 (m, 20H), 5.27 (q, J= 6.6 Hz, 2H), 5.21-5.12 (m, 14H), 4.27-4.18 (m, 8H), 2.60 (s, 4H), 1.52-1.48 (m, 24H); ^{13}C (600 MHz, $CDCl_3$) δ 172.6, 172.5, 169.9, 169.7, 169.6, 169.4, 135.1, 135.0, 128.6, 128.5, 128.4, 128.2, 69.5, 69.3, 69.2, 69.1, 67.2, 60.4, 16.78, 16.73, 16.68, 16.63; HRMS (M+Na) calc mass 333.0950, found 333.0966.



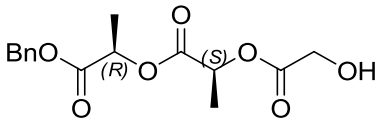
Bn-LL$_{rac}$G *rmsvii-20a:* The product was a colorless liquid (7.55 g, 81%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36-7.3 (m, 10H), 5.27 (q, J= 7.2 Hz, 1H), 5.22-5.11 (m, 7H), 4.27-4.19 (m, 4H), 2.49 (s, 2H), 1.513 (d, J= 6.6 Hz, 3H), 1.51 (d, J= 7.2 Hz, 6H), 1.49 (d, J= 7.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.7, 172.5, 169.9, 169.7, 169.6, 169.4, 135.1, 135.0, 128.6, 128.57, 128.51, 128.4, 128.23, 128.22, 69.4, 69.3, 69.2, 69.1, 67.2, 16.75, 16.73 (2), 16.6; HRMS (M+Na) calc mass 333.095, found 333.096.



Bn-L$_{rac}$LG *rmsviii-23a:* The product was a colorless liquid (4.93 g, 97%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36-7.30 (m, 10H), 5.28 (q, J= 7.2 Hz, 1H), 5.22-5.11 (m, 7H), 4.26 (d, J= 18.0 Hz, 1H), 4.24 (d, J= 17.4 Hz, 1H), 4.21 (d, J= 18.6 Hz, 1H), 4.20 (d, J= 17.4 Hz, 1H), 2.42 (s, 2H), 1.52 (d, J= 6.6 Hz, 3H), 1.51 (d, J= 7.2 Hz, 6H), 1.49 (d, J= 6.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.7, 172.5, 169.9, 169.7, 169.6, 169.4, 135.1, 135.0, 128.6, 128.5, 128.4, 128.3, 128.2, 69.5, 69.3, 69.2, 69.1, 67.2, 60.5, 16.8, 16.7 (2), 16.6; MS (EI) m/z 310 (M+).

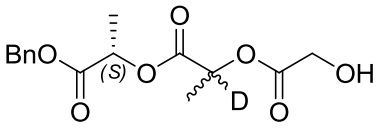


Bn-LL$_R$G *rmsviii-64a:* The product was a colorless liquid (1.40 g, 99%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36 (m, 5H), 5.27 (q, J= 7.2 Hz, 1H), 5.19 (d, J= 12.0 Hz, 1H), 5.16 (q, J= 7.2 Hz, 1H), 5.13 (d, J= 12.0 Hz, 1H), 4.24 (d, J= 17.4 Hz, 1H), 4.20 (d, J= 17.4 Hz, 1H), 2.54 (s, 1H), 1.51 (d, J= 7.2 Hz, 3H), 1.49 (d, J= 6.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.5, 169.7, 169.5, 135.1, 128.6, 128.5, 128.2, 69.5, 69.2, 67.2, 60.4, 16.75, 16.73; HRMS (M+Na) calc mass 333.0950, found 333.0935.

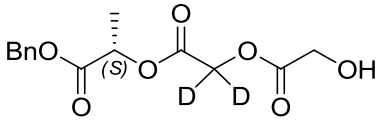


Bn-L$_R$LG *rmsviii-90a:* The product was a colorless liquid (1.84 g, 69%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36-7.31 (m, 5H), 5.27 (q, J= 7.2 Hz, 1H), 5.19 (d, J= 12.0 Hz, 1H), 5.16 (q, J= 7.2 Hz, 1H), 5.13 (d, J= 12.0 Hz, 1H), 4.24 (d, J= 16.8 Hz, 1H), 4.20 (d, J= 18.0 Hz, 1H), 2.50 (s, 1H), 1.51 (d, J= 7.2 Hz, 3H), 1.49 (d, J= 6.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.5,

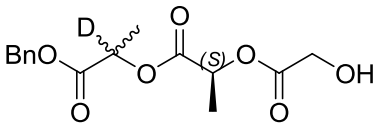
169.8, 169.5, 135.1, 128.6, 128.5, 128.3, 69.5, 69.3, 67.3, 60.5, 16.8, 16.78; HRMS (M+Na) calc mass 333.0950, found 333.0921.



Bn-LL$_{d,rac}$G *rmsvii-67a:* The product was a colorless liquid (1.67 g, 98%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.4-7.3 (m, 10H), 5.21-5.12 (m, 6H), 4.27 (d, J= 17.4 Hz, 1H), 4.26 (d, J=17.4 Hz, 1H), 4.21 (dd, J= 16.8 Hz, 6.6 Hz, 1H), 4.20 (dd, J= 16.8 Hz, 6.0 Hz, 1H), 2.26 (t, J= 6.0 Hz, 1H), 2.22 (t, J=6.0 Hz, 1H), 1.51 (d, J= 7.2 Hz, 3H), 1.45 (d, J= 6.6 Hz, 3H), 1.43 (s, 6H), 1.073 (s, 9H), 1.069 (s, 9H); ^{13}C (150 MHz, $CDCl_3$) δ 172.7, 172.5, 169.9, 169.7, 169.6, 169.4, 135.1, 135.0, 128.6, 128.5, 128.4, 128.3, 128.2, 69.5, 69.3, 69.0 (m), 67.2, 60.5, 16.8 (2), 16.7, 16.6; HRMS (M+) calc mass 311.1115, found 311.1107.

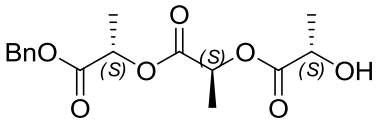


Bn-LG$_{d2}$G *rmsvii-68a:* The product was a colorless liquid (1.53 g, 92%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.34-7.31 (m, 5H), 5.22 (q, J=6.6 Hz, 1H), 5.18 (d, J= 12.6 Hz, 1H), 5.5 (d, J= 12.0 Hz, 1H), 4.28 (s, 2H), 2.25 (s, 1H), 1.51 (d, J= 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.6, 169.8, 166.7, 155.1, 128.6, 128.5, 128.2, 69.6, 67.3, 60.5 (m), 60.4, 16.8; HRMS (M+) calc mass 298. 1021, found 298.1019.

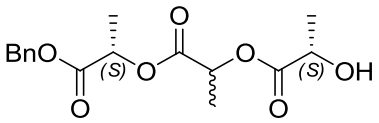


Bn-L$_{d,rac}$LG *rmsvi-91a:* The product was a colorless liquid (1.72 g, 71%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36-7.30 (m, 10H), 5.28 (q, J= 6.8 Hz, 1H), 5.23-5.12 (m, 5H), 4.27 (dd, J= 17.4 Hz,

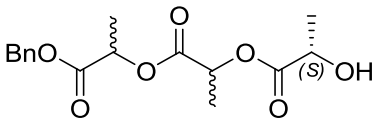
5.4 Hz 1H), 4.24 (dd, J= 19.8 Hz, 6.0 Hz, 1H), 4.21 (dd, J= 18.0 Hz, 6.0 Hz, 1H), 4.20 (dd, J= 17.4 Hz, 6.0 Hz, 1H), 2.29 (t, J= 5.7 Hz, 1H), 2.26 (t, J= 5.7 Hz, 1H), 1.52 (d, J= 7.2 Hz, 6H), 1.51 (s, 3H), 1.49 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.6, 172.4, 169.8, 169.7, 169.5, 135.0, 134.9, 128.5, 128.4, 128.3, 128.2, 69.2 (t), 69.1, 68.9, 67.1, 60.4, 16.7, 16.6, 16.57, 16.5; MS (EI) m/z 311 (M+).



Bn-LLL *rmsvii-81a:* The product was a colorless liquid (4.70 g, 74%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36-7.3 (m, 5H), 5.19 (q, J= 7.2 Hz, 2H), 5.17 (d, J= 12.6 Hz, 1H), 5.12 (d, J= 12 Hz, 1H), 4.33 (q, J= 7.0 Hz, 1H), 2.69 (s, 1H), 1.52 (d, J= 7.2 Hz, 3H), 1.51 (d, J= 7.2 Hz, 3H), 1.47 (d, J= 7.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 175.1, 169.9, 169.6, 135.1, 128.6, 128.5, 128.3, 69.3, 69.1, 67.2, 66.7, 20.5, 16.8, 16.6; HRMS (M+) calc mass 324.121, found 324.120.

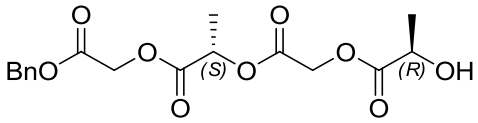


Bn-LL$_{rac}$L *rmsix-15a:* The product was a colorless liquid (2.86 g, 83%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36-7.3 (m, 10H), 5.23 (q, J= 7.0 Hz, 1H), 5.20-5.10 (m, 7H), 4.33 (q, J= 7.0 Hz, 1H), 2.71 (s, 2H), 1.52 (d, J= 7.2 Hz, 6H), 1.51 (d, J= 7.2 Hz, 3H), 1.49 (d, J= 6.7 Hz, 3H), 1.47 (d, J= 6.7 Hz, 3H), 1.43 (d, J= 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 175.1, 174.7, 169.9, 169.7, 169.6, 169.4, 135.1, 135.0, 128.6, 128.5, 128.4, 128.3, 69.4, 69.34, 69.30, 69.1, 67.2, 67.0, 20.5, 20.1, 16.8, 16.7; HRMS (M+) calc mass 325.128, found 325.127.

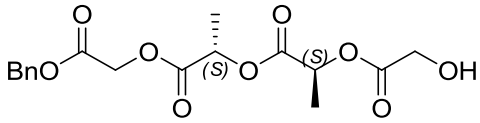


Bn-L$_{rac}$L$_{rac}$L *rmsix-16a:* The product was a colorless liquid (2.98 g, 86%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36-7.3 (m, 20H), 5.25-5.10 (m, 16H), 4.39-4.31(m, 4H), 2.71-2.69 (m, 4H), 1.54-1.40 (m, 36H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 175.1, 175.0, 174.9, 174.4, 169.9, 169.8, 169.73, 169.71, 169.6, 169.5, 169.39, 169.38, 135.1, 135.0, 128.6, 128.5, 128.4, 128.3, 69.4, 69.39, 69.34, 69.3, 69.27, 69.25, 69.1, 67.2, 66.7, 66.6, 20.5, 20.08, 20.03, 16.8, 16.7, 16.67, 16.65; HRMS (M+) calc mass 325.129, mass found 325.127.

Tetramers.

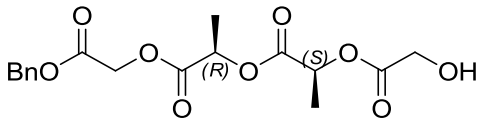


Bn-GLGL$_{R}$ *rmsviii-22a:* The product was a colorless liquid (1.37 g, 75%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.4-7.3 (m, 5H), 5.25 (q, J= 7.2 Hz, 1H), 5.17 (s, 2H), 4.795 (d, J= 16.2 Hz, 1H), 4.792 (d, J= 15.6 Hz, 1H), 4.75 (d, J= 15.6 Hz, 1H), 4.62 (d, J= 16.2 Hz, 1H), 4.40 (dq, J= 6.0 Hz, J= 6.6 Hz, 1H), 2.66 (dd, J= 3.0 Hz, J= 6.0 Hz, 1H), 1.55 (d, J= 7.2 Hz, 3H), 1.47 (d, J= 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.9, 169.4, 166.9, 166. 6, 134.8, 128.7, 128.5, 69.2, 67.3, 66.7, 61.1, 60.9, 20.3, 16.8; MS (EI) m/z 368 (M+).

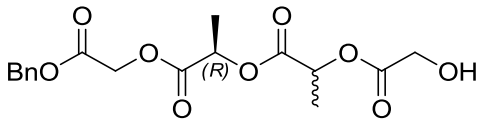


Bn-GLLG *rmsix-98a:* The product was a colorless liquid (3.77 g, 97%). ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.36-7.31 (m, 5H), 5.23 (q, J= 7.7 Hz, 1H), 5.22 (q, J= 7.0 Hz, 1H), 5.17 (s, 2H), 4.77 (d, J= 16.1 Hz, 1H), 4.60 (d, J= 16.1 Hz, 1H), 4.27 (d, J= 17.5 Hz, 1H), 4.21 (d, J= 17.5 Hz, 1H),

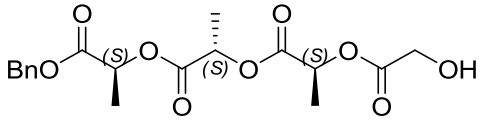
2.43 (s, 1H), 1.57 (d, J= 7.0 Hz, 3H), 1.55 (d, J= 7.0 Hz, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 172.7, 169.58, 169.53, 166.9, 134.8, 128.6, 128.5, 69.1, 69.0, 67.3, 61.1, 60.5, 16.7(2).



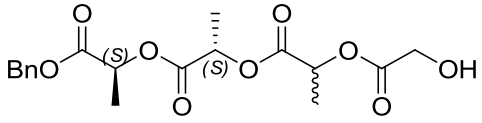
Bn-GL$_R$LG *rmsix-99a:* The product was a colorless liquid (2.65 g, 92%).^{1}H NMR (700 MHz, $CDCl_3$) δ 7.36-7.31 (m, 5H), 5.28 (q, J= 7.0 Hz, 1H), 5.20 (q, J= 7.0 Hz, 1H), 5.17 (s, 2H), 4.79 (d, J= 16.1 Hz, 1H), 4.61 (d, J= 16.1 Hz, 1H), 4.25 (d, J= 17.5 Hz, 1H), 4.21 (d, J= 17.5 Hz, 1H), 2.42 (s, 1H), 1.54 (d, J= 7.0 Hz, 3H), 1.53 (d, J= 7.0 Hz, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 172.5, 169.4, 169.3, 166.9, 134.8, 128.6, 128.5, 69.2, 67.3, 61.1, 60.5, 16.75, 16.69.



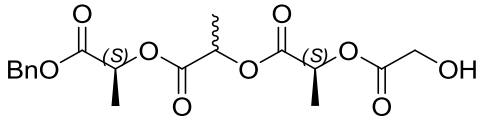
Bn-GLL$_{rac}$G *rmsix-100a:* The product was a colorless liquid (2.54 g, 92%). ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.36-7.31 (m, 10H), 5.28 (q, J= 7.0 Hz, 1H), 5.23 (q, J= 7.7 Hz, 1H), 5.22 (q, J= 7.0 Hz, 1H), 5.20 (q, J= 7.0 Hz, 1H), 5.17 (s, 4H), 4.79 (d, J= 16.1 Hz, 1H), 4.77 (d, J= 16.1 Hz, 1H), 4.61 (d, J= 16.1 Hz, 1H), 4.60 (d, J= 16.1 Hz, 1H), 4.27 (d, J= 17.5 Hz, 1H), 4.25 (d, J= 17.5 Hz, 1H), 4.21 (d, J= 16.8 Hz, 2H), 2.42 (s, 2H), 1.57 (d, J= 7.0 Hz, 3H), 1.55 (d, J= 7.0 Hz, 3H) 1.54 (d, J= 7.0 Hz, 3H), 1.53 (d, J= 7.0 Hz, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 172.7, 172.5, 169.57, 169.53, 169.4, 169.3, 166.92, 166.89, 134.81, 134.78, 128.6, 128.5, 128.4, 69.18, 69.12, 69.0, 67.31, 67.28, 61.1, 60.5, 60.4, 16.75, 16.69.



Bn-LLLG *rmsx-20a:* The product was a colorless liquid (1.40 g, 92%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36-7.30 (m, 5H), 5.21 (q, J= 7.2 Hz, 1H), 5.17 (q, J= 6.8 Hz, 1H), 5.169 (d, J= 12.6 Hz, 1H), 5.16 (q, J= 6.8 Hz, 1H), 5.11 (d, J= 12.0 Hz, 1H), 4.26 (d, J= 17.4 Hz, 1H), 4.21 (d, J= 17.4 Hz, 1H), 2.46 (s, 1H), 1.57 (d, J= 6.6 Hz, 3H), 1.52 (d, J= 7.2 Hz, 3H), 1.50 (d, J= 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.7, 169.9, 169.7, 169.6, 135.0, 128.6, 128.5, 128.2, 69.3, 69.1, 69.08, 67.2, 60.5, 16.71(2), 16.55.

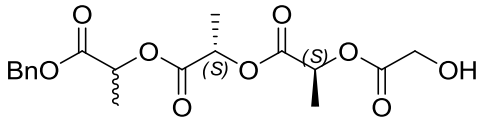


Bn-LLL$_{rac}$G *rmsix-20a:* The product was a colorless liquid (1.80 g, 89%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36-7.30 (m, 10H), 5.28 (q, J= 7.2 Hz, 1H), 5.25-5.10 (m, 9H), 4.27 (d, J= 17.4 Hz, 1H), 4.25 (d, J= 17.4 Hz, 1H), 4.22 (d, J= 17.4 Hz, 1H), 4.21 (d, J= 17.4 Hz, 1H), 2.46 (s, 2H), 1.58 (d, J= 6.6 Hz, 3H), 1.54 (d, J= 7.2 Hz, 3H), 1.52 (d, J= 7.2 Hz, 3H), 1.508 (d, J= 7.2 Hz, 3H), 1.502 (d, J= 7.2 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.7, 172.55, 169.91, 169.89, 169.65, 169.52, 169.4, 169.3, 135.0, 128.6, 128.5, 128.2, 69.27, 69.25, 69.15, 69.1, 67.21, 67.2, 60.5, 16.79, 16.73(3), 16.59, 16.57.

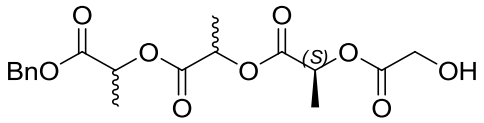


Bn-LL$_{rac}$LG *rmsx-21a:* The product was a colorless liquid (1.35 g, 86%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36-7.30 (m, 10H), 5.27 (q, J= 7.2 Hz, 1H), 5.22 (q, J= 7.2 Hz, 1H), 5.20-5.10 (m, 8H), 4.27 (dd, J_1= 17.4 Hz, J_2= 4.8 Hz, 1H), 4.25 (dd, J_1= 17.4 Hz, J_2= 5.4 Hz, 1H), 4.21 (dd, J_1=

17.4 Hz, J_2= 6.0 Hz, 1H), 4.20 (dd, J_1= 17.4 Hz, J_2= 6.0 Hz, 1H), 2.40 (t, J= 6.0 Hz, 2H), 1.57 (d, J= 7.2 Hz, 3H), 1.54 (d, J= 7.2 Hz, 3H), 1.52 (d, J= 7.2 Hz, 3H), 1.50 (d, J= 7.2 Hz, 3H), 1.499 (d, J= 7.2 Hz, 3H), 1.494 (d, J= 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.7, 172.5, 169.88, 169.80, 169.64, 169.5, 169.3, 169.2, 135.0, 128.6, 128.5, 128.2, 69.46, 69.40, 69.27, 69.12, 67.21, 67.16, 60.5, 16.74, 16.72, 16.68, 16.67, 16.56.

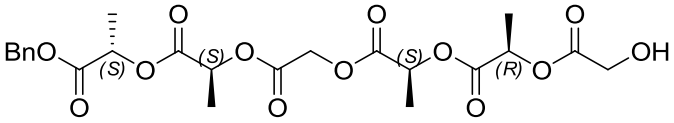


Bn-L$_{rac}$LLG *rmsix-20a:* The product was a colorless liquid (2.71 g, 88%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36-7.30 (m, 10H), 5.25-5.10 (m, 10H), 4.27 (d, J= 17.4 Hz, 2H), 4.22 (d, J= 17.4 Hz, 2H), 2.40 (s, 2H), 1.58 (d, J= 7.2 Hz, 3H), 1.56 (d, J= 7.2 Hz, 3H), 1.52 (d, J= 7.2 Hz, 3H), 1.515 (d, J= 7.2 Hz, 3H), 1.50 (d, J= 7.2 Hz, 3H), 1.48 (d, J= 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.7, 172.66, 169.89, 169.75, 169.66, 169.5, 169.45, 169.3, 135.0, 128.6, 128.5, 128.2, 69.38, 69.27, 69.17, 69.14, 69.10, 67.2, 60.5, 16.74 (3), 16.68(2), 16.57.

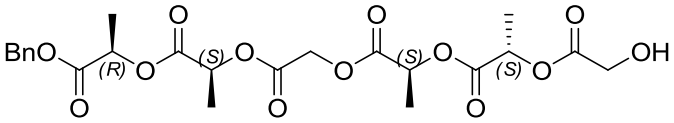


Bn-L$_{rac}$L$_{rac}$LG *rmsx-17a:* The product was a colorless liquid (1.20 g, 87%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36-7.30 (m, 20H), 5.30-5.10 (m, 20H), 4.30-4.19 (m, 8H), 2.37-2.34 (m, 4H), 1.60-1.45 (m, 36H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.71, 172.66, 172.54, 172.48, 169.91, 169.89, 169.81, 169.74, 169.64, 169.51, 169.43, 169.30, 169.17, 135.11, 135.06, 135.05, 135.02, 128.60, 128.58, 128.51, 128.50, 128.48, 128.45, 128.23, 128.22, 69.47, 69.40, 69.39, 69.29, 69.25, 69.17, 69.15, 69.11, 67.22, 67.20, 67.17, 60.46, 16.79, 16.75, 16.73, 16.70, 16.68, 16.59, 16.57.

Hexamers.



Bn-LLGLL*R*G *rmsviii-71a:* The product was a colorless liquid (1.01 g, 92%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36- 7.30 (m, 5H), 5.28 (q, J= 7.0 Hz, 1H), 5.20 (q, J= 6.8 Hz, 1H), 5.18 (q, J= 7.0 Hz, 1H), 5.162 (d, J= 12.6 Hz, 1H), 5.160 (q, J= 7.2 Hz, 1H), 5.12 (d, J= 12.0 Hz, 1H), 4.87 (d, J= 16.2 Hz, 1H), 4.62 (d, J= 16.2 Hz, 1H), 4.25 (d, J= 17.4 Hz, 1H), 4.21 (d, J= 17.4 Hz, 1H), 2.40 (s, 1H), 1.56 (d, J= 7.2 Hz, 3H), 1.55 (d, J= 7.2 Hz, 3H), 1.51 (d, J= 7.2 Hz, 3H), 1.50 (d, J= 7.2 Hz, 3H); ^{13}C NMR (600 MHz, $CDCl_3$) δ 172.5, 169.9, 169.42, 169.4, 169.3, 166.5, 135.0, 128.6, 128.5, 128.2, 69.3, 69.2 (2), 69.1, 67.2, 60.8, 60.4, 16.74, 16.7 (2), 16.6; HRMS (M+Na) calc mass 535.1428, found 535.1451.

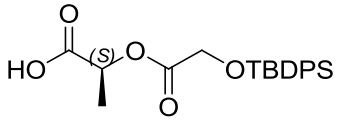


Bn-L*R*LGLLG *rmsix-3a:* The product was a colorless liquid (1.05 g, 96%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.35-7.30 (m, 5H), 5.24-5.19 (m, 3H), 5.17 (d, J= 12.6 Hz, 1H), 5.15 (q, J= 7.2 Hz, 1H), 5.12 (d, J= 12.6 Hz, 1H), 4.80 (d, J= 16.2 Hz, 1H), 4.61 (d, J= 15.6 Hz, 1H), 4.25 (d, J= 17.4 Hz, 1H), 4.20 (d, J= 17.4 Hz, 1H), 2.56 (s, 1H), 1.57 (d, J= 7.8 Hz, 3H), 1.56 (d, J= 7.2 Hz, 3H), 1.49 (d, J= 7.2 Hz, 3H), 1.48 (d, J= 6.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.6, 169.7, 169.6, 169.4, 169.2, 166.3, 135.1, 128.5, 128.4, 128.2, 69.4, 69.3, 69.0, 68.9, 67.1, 60.7, 60.4, 16.7; HRMS (M+Na) calc mass 535.1428, found 535.1420.

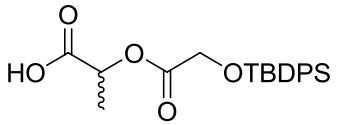
2.7.6 General procedures for benzyl deprotections

The benzyl protected oligomer was combined with 10% Pd/C (5% w/w) in dry EtOAc. The reaction mixture was stirred 16- 18 h under 1 atm of hydrogen, filtered through celite and concentrated *in vacuo*. No further purification was necessary unless stated.

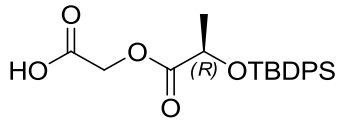
Silyl-protected dimers.



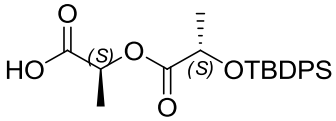
LG-SiR$_3$ *rmsv-56a:* The crude was chromatographed (silica, 15% EtOAc in hexanes) to yield a colorless oil (30.6 g, 95%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.7-7.6 (m, 4H), 7.5-7.3 (m, 6H), 5.14 (quartet, J= 7.1 Hz, 1H), 4.36 (d, J= 16.8 Hz, 1H), 4.29 (d, J=16.8 Hz, 1H), 1.48 (d, J= 7.2 Hz, 3H), 1.07 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.3, 170.6, 135.6, 135.5, 132.7, 132.6, 129.9, 127.8, 68.2, 61.9, 26.6, 19.3, 16.7; MS (EI) m/z 329 (M-*t*butyl).



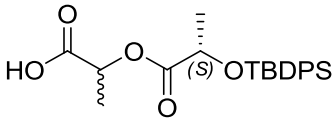
L$_{rac}$G-SiR$_3$ *rmsv-55a:* The crude was chromatographed (silica, 15% EtOAc in hexanes) to yield a colorless oil (28.8 g, 90%). ^{1}H NMR(300 MHz, $CDCl_3$) δ 7.7-7.6 (m, 4H), 7.5-7.3 (m, 6H), 5.13 (quartet, J= 7.0 Hz, 1H), 4.35 (d, J= 16.8 Hz, 1H), 4.29 (d, J=17.1 Hz, 1H), 1.48 (d, J= 7.5 Hz, 3H), 1.07 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.3, 170.6, 135.6, 135.5, 132.7, 132.6, 129.9, 127.9, 68.3, 61.9, 26.7, 19.3, 16.7; MS (EI) m/z 329 (M-*t*-butyl).



GL_R-SiR_3 *rmsviii-16a:* The crude was chromatographed (silica, 15% EtOAc in hexanes) to yield a colorless oil (2.85 g, 50%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.67-7.64 (m, 4H), 7.42-7.33 (m, 6H), 4.58 (d, J= 16.2 Hz, 1H), 4.48 (d, J= 16.8 Hz, 1H), 4.38 (q, J= 6.6 Hz, 1H), 1.40 (d, J= 7.2 Hz, 3H), 1.08 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.1, 173.0, 135.9, 135.7, 133.4, 132.9, 129.9, 129.8, 127.9, 127.7, 127.6, 68.6, 60.0, 26.8, 21.2, 19.2; MS (EI) m/z 329 (M-*t*-butyl).



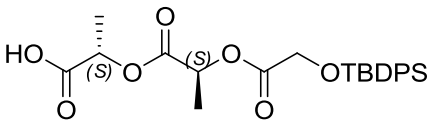
LL-SiR_3 *rmsv-101a:* Chromatography using 15% ethyl acetate in heaxanes yielded a colorless oil (18.6 g, 90%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.0 (s, 1H), 7.7-7.6 (m, 4H), 7.5-7.3 (m, 6H), 4.94 (q, J= 7.0 Hz, 1H), 4.33 (q, J= 6.6 Hz, 1H) 1.40 (d, J= 6.9 Hz, 3H), 1.37 (d, J= 7.2 Hz, 3H), 1.08 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.5, 173.1, 136.0, 135.8, 133.4, 133.0, 129.8, 127.7, 127.6, 68.5, 68.1, 26.8, 21.1, 19.2, 16.6; HRMS (M+Na) Calc mass 423.160, found 423.160.



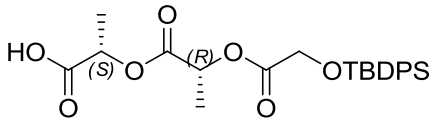
L_{rac}L-SiR_3 *rmsv-100a:*Chromatography using 15% ethyl acetate in hexanes yielded a colorless oil (18.5 g, 87%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.8 (s, 2H), 7.7-7.6 (m, 8H), 7.5-7.3 (m, 12H), 5.1-4.9 (m, 2H) 4.40 (q, J= 6.8 Hz, 1H), 4.38 (q, J= 6.8 Hz, 1H) 1.45 (d, J= 6.9 Hz, 3H), 1.41 (d, J= 6.6 Hz, 3H), 1.39 (d, J=6.9 Hz, 3H), 1.37 (d, J= 6.6 Hz, 3H), 1.09 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.5, 176.4, 173.1, 173.0, 136.0, 136.0, 135.9, 135.8, 135.7, 133.5, 133.4,

133.0, 132.9, 129.9, 129.8, 127.6, 127.5, 68.8, 68.5, 68.2, 68.1, 26.8, 21.3,, 21.0, 19.3, 19.2, 16.6, 16.5; HRMS (M+Na) Calc mass 423.160, found 423.159.

Silyl-protected trimers.



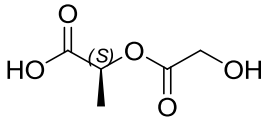
LLG-SiR$_3$ *rmsviii-63a:*The crude was chromatographed (silica, 15% EtOAc in hexanes) to yield a colorless oil (2.32 g, 93%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.68-7.56 (m, 4H), 7.43-7.36 (m, 6H), 5.16 (q, J= 7.2 Hz, 1H), 5.12 (q, J= 7.2 Hz, 1H), 4.34 (d, J= 16.8 Hz, 1H), 4.29 (d, J= 16.8 Hz, 1H), 1.54 (d, J= 7.2 Hz, 3H), 1.48 (d, J= 7.2 Hz, 3H), 1.07 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 175.8, 170.7, 169.8, 135.6, 135.5, 132.7, 132.6, 129.9, 127.8, 127.7, 68.6, 68.4, 62.0, 26.6, 19.2, 16.67, 16.64; HRMS (M+Na) calc mass 481.1659, found 481.1616.



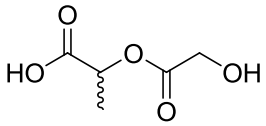
LL$_R$G-SiR$_3$ *rmsviii-62a:* The crude was chromatographed (silica, 15% EtOAc in hexanes) to yield a colorless oil (1.46 g, 87%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.68-7.66 (m, 4H), 7.43- 7.35 (m, 6H), 5.17 (q, J=7.2 Hz, 1H), 5.12 (q, J= 7.0 Hz, 1H), 4.33 (d, J= 16.8 Hz, 1H), 4.29 (d, J= 16.8 Hz, 1H), 1.48 (d, J= 7.8 Hz, 3H), 1.46 (d, J= 7.2 Hz, 3H), 1.07 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 175.2, 170.6, 169.7, 135.6, 135.5, 132.6, 129.9, 127.8, 68.8, 68.7, 62.0, 26.6, 19.3, 16.8, 16.6; HRMS (M+Na) calc mass 481.1659, found 481.1678.

Segmers.

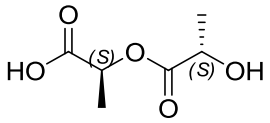
Dimers.



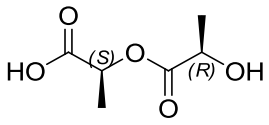
LG *rmsvii-8a:* The filtrate was concentrated *in vacuo* to yield a colorless oil (4.35 g, 100%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.18 (quartet, J= 7.1 Hz, 1H, CH), 4.29 (d, J= 17.4 Hz, 1H, CH_2), 4.22 (d, J= 17.4 Hz, 1H, CH_2), 1.49 (d, J= 6.9 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.4 (C=O), 172.6 (C=O), 68.9, 60.2, 16.6; MS (EI) m/z 131 (M- H_2O), 117; HRMS (M-H_2O) calc mass 131.0344, found 131.0348.



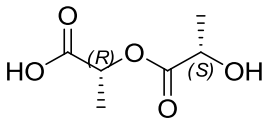
L$_{rac}$G *rmsvii-36a:* The filtrate was concentrated *in vacuo* to yield a colorless oil (4.35 g, 100%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.17 (quartet, J= 7.1 Hz, 1H), 4.29 (d, J= 17.4 Hz, 1H), 4.22 (d, J= 17.4 Hz, 1H), 1.52 (d, J= 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.5, 172.8, 69.0, 60.4, 16.7; MS (EI) m/z 149 (M+).



LL *rmsvii-88a:*The filtrate was concentrated to yield a colorless oil (1.75 g, 100%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.17 (q, J= 7.2 Hz, 1H), 4.36 (q, J= 7.2 Hz, 1H), 1.54 (d, J= 6.8 Hz, 3H), 1.46 (d, J= 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.1, 69.0, 66.8, 20.3, 16.7.

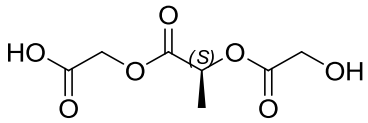


LL$_R$ *rmsviii-85a:* The filtrate was concentrated to yield a colorless oil (1.27 g, 99%). 1H NMR (300 MHz, CDCl3) d 1H NMR (300 MHz, CDCl3) d 5.14 (q, J= 7.2 Hz,1H), 4.40 (q, J= 7.2 Hz, 1H), 1.53 (d, J= 7.2 Hz, 3H), 1.43 (d, J= 6.9 Hz, 3H); 13C NMR (75 MHz, CDCl3) d 174.9, 174.5, 69.2, 66.7, 19.8, 16.7.

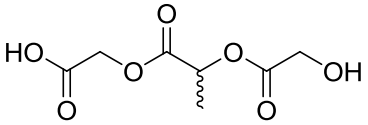


L$_R$L *rmsviii-98a:*The filtrate was concentrated to yield a colorless oil (1.23 g, 96%).

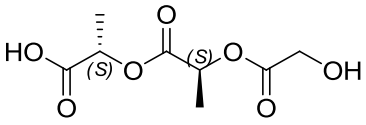
Trimers.



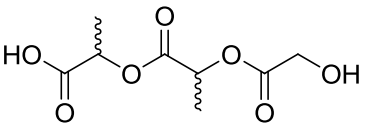
GLG *rmsvii-7a:* The filtrate was concentrated *in vacuo* to yield a colorless oil (4.33 g, 100%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.28 (q, J= 7.2 Hz, 1H), 4.77 (d, J= 15.6 Hz, 1H), 4.65 (d, J= 16.8 Hz, 1H), 4.29 (d, J= 18 Hz, 1H), 4.24 (d, J= 17.4 Hz, 1H), 1.57 (d, J= 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.8, 171.3, 169.7, 69.1, 60.7, 60.4, 16.7; MS (EI) m/z 207 (M+).



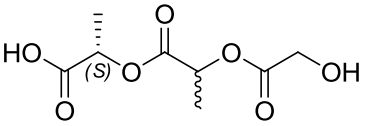
GL$_{rac}$G *rmsvii-38a:* The filtrate was concentrated *in vacuo* to yield a colorless oil (4.63 g, 100%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.27 (q, J= 6.9 Hz, 1H), 4.76 (d, J= 16.2 Hz, 1H), 4.64 (d, J= 16.8 Hz, 1H), 4.29 (d, J= 17.4 Hz, 1H), 4.24 (d, J= 17.4 Hz, 1H), 1.56 (d, J= 6.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.8, 171.3, 169.7, 69.1, 60.7, 60.4, 16.7; MS (EI) m/z 207 (M+).



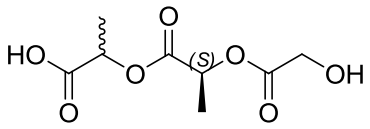
LLG *rmsvii-27a:* The filtrate was concentrated *in vacuo* to yield a colorless oil (4.90 g, 97%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.22 (q, J= 7.2 Hz, 1H), 5.17 (q, J= 7.2 Hz, 1H), 4.28 (d, J= 16.8 Hz, 1H), 4.23 (d, J= 17.4 Hz, 1H), 1.56 (d, J= 7.2 Hz, 3H), 1.55 (d, J= 7.1 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 175.0, 172.8, 169.7, 69.2, 68.9, 60.4, 16.66, 16.63; MS (EI) m/z 203 (M-H_2O).



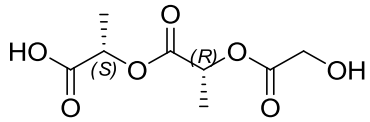
$L_{rac}L_{rac}$G *rmsviii-94a:* The filtrate was concentrated *in vacuo* to yield a colorless oil (0.70 g, 99%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.27-5.10 (m, 8H), 4.30-4.21 (m, 8H), 1.56-1.51 (m, 24H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.3, 174.1, 172.8, 169.8, 169.7, 69.3, 69.2, 69.0, 60.42, 60.39, 16.66, 16.63; HRMS (M+Na) calc mass 243.0481, found 243.0484.



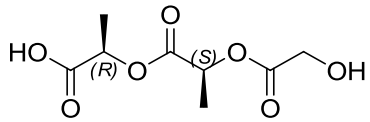
LL$_{rac}$G *rmsvii-28a:*The filtrate was concentrated *in vacuo* to yield a colorless oil (4.60 g, 90%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.27 (q, J= 7.2 Hz, 1H), 5.23 (q, J= 7.2 Hz, 1H), 5.18 (q, J= 7.2 Hz, 1H), 5.15 (q, J= 7.2 Hz, 1H), 4.29 (d, J= 18.0 Hz, 1H), 4.28 (d, J= 18.0 Hz, 1H), 4.24 (d, J= 17.4 Hz, 1H), 4.23 (d, J= 16.8 Hz, 1H), 1.57 (d, J= 7.2 Hz, 3H), 1.56 (d, J= 6.6 Hz, 3H), 1.54 (d, J= 7.2 Hz, 3H), 1.53 (d, J= 6.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 175.1, 174.8, 172.9, 172.8, 169.7, 169.6, 69.3, 69.2, 69.0, 68.9, 60.4, 16.7, 16.6 (2), 16.5; MS (EI) m/z 203 (M-H_2O).



L_{rac}LG *rmsviii-25a:*The filtrate was concentrated *in vacuo* to yield a colorless oil (3.22 g, 97%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.26 (q, J= 7.2 Hz, 1H), 5.22 (q, J= 7.2 Hz, 1H), 5.17 (q, J= 7.2 Hz, 1H), 5.13 (q, J= 7.2 Hz, 1H), 4.29 (d, J= 17.4 Hz, 1H), 4.28 (d, J= 17.4 Hz, 1H), 4.24 (d, J= 17.4 Hz, 1H), 4.23 (d, J= 17.4 Hz, 1H), 1.57 (d, J= 7.2 Hz, 3H), 1.55 (d, J= 6.6 Hz, 1H), 1.54 (d, J= 6.6 Hz, 1H), 1.53 (d, J= 7.2 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 175.1, 174.9, 172.9, 172.8, 169.7, 169.6, 69.3, 69.2, 69.1, 68.9, 60.5, 60.4, 16.72, 16.7 (2), 16.6; MS (EI) m/z 221 (M+).

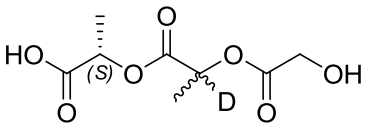


LL$_R$G *rmsviii-67a:*The filtrate was concentrated *in vacuo* to yield a colorless oil (0.91 g, 99%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.26 (q, J= 7.0 Hz, 1H), 5.14 (q, J= 7.0 Hz, 1H), 4.29 (d, J= 17.4 Hz, 1H), 4.24 (d, J= 17.4 Hz, 1H), 1.54 (d, J= 7.2 Hz, 3H), 1.53 (d, J= 6.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.6, 173.0, 169,6, 69.3, 69.2, 60.4, 16.7; HRMS (M+Na) calc mass 243.0481, found 243.0488.

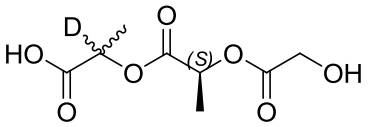


L$_R$LG *rmsviii-93a:* The filtrate was concentrated *in vacuo* to yield a colorless oil (0.59 g, 97%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.23 (q, J= 7.2 Hz, 1H), 5.13 (q, J= 7.2 Hz, 1H), 4.28 (d, J= 17.4 Hz, 1H), 4.23 (d, J= 17.4 Hz, 1H), 1.53 (d, J= 6.6 Hz, 3H), 1.52 (d, J= 7.2 Hz, 3H); ^{13}C NMR

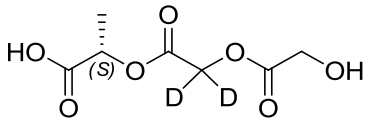
(150 MHz, $CDCl_3$) δ 174.4, 173.0, 169.7, 69.3, 69.2, 60.4, 16.7; HRMS (M+Na) calc mass 243.0481, found 243.0487.



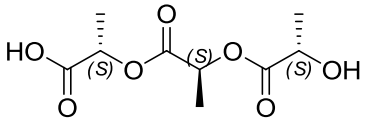
$LL_{d,rac}G$ *rmsvii-70a:*The filtrate was concentrated *in vacuo* to yield a colorless oil (1.0 g, 94%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.17 (q, J= 7.2 Hz, 1H), 5.13 (q, J= 7.2 Hz, 1H), 4.282 (d, J= 16.8 Hz, 1H), 4.276 (d, J= 16.8 Hz, 1H), 4.23 (d, J= 17.4 Hz, 2H), 1.55 (s, 3H), 1.54 (d, J= 7.2 Hz, 3H), 1.53 (s, 3H), 1.52 (d, J= 6.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.7, 174.5, 172.9, 172.8, 169.8, 169.7, 69.4, 69.2, 69.1, 68.9, 68.8, 68.7, 60.4, 60.3, 16.6, 16.5; MS (EI) m/z 204 (M-H_2O).



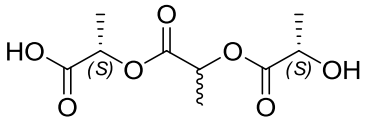
$L_{d,rac}LG$ *rmsvii-10a:* The filtrate was concentrated *in vacuo* to yield a colorless oil (1.05 g, 99%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.2-5.1 (m, 2H), 4.4-4.1 (m, 4H), 1.6-1.3 (m, 12H); MS (EI) m/z 204 (M-H_2O).



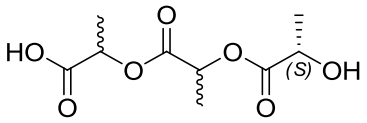
$LG_{d2}G$ *rmsvii-69a:* The filtrate was concentrated *in vacuo* to yield a colorless oil (0.95 g, 98%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.19 (q, J= 7.2 Hz, 1H), 4.3 (s, 2H), 1.55 (d, J= 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.5, 172.9, 166.8, 69.2, 60.5 (t), 60.4, 16.7; MS (EI) m/z 206 (M+).



LLL *rmsvii-90a:* The filtrate was concentrated to yield a colorless solid (2.85 g, 86%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.19 (q, J= 7.2 Hz, 1H), 5.15 (q, J= 7.2 Hz, 1H), 4.36 (q, J= 6.6 Hz, 1H), 1.57 (d, J= 7.2 Hz, 3H), 1.54 (d, J= 7.2 Hz, 3H), 1.47 (d, J= 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 175.3, 175.2, 169.6, 69.1, 68.9, 66.7, 20.4, 16.6; MS (EI) m/z 235 (M+).



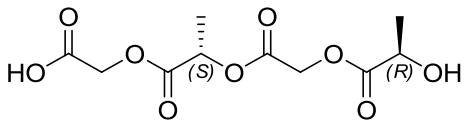
LL$_{rac}$L *rmsvii-94a:*The filtrate was concentrated to yield a colorless oil (3.50 g, 98%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.21 (q, J= 7.2 Hz, 1H), 5.19 (q, J= 7.2 Hz, 1H, i), 5.15 (q, J= 7.2 Hz, 1H, i), 5.13 (q, J= 7.2 Hz, 1H), 4.38 (q, J= 6.6 Hz, 1H), 4.36 (q, J= 7.2 Hz, 1H, i), 1.56 (d, J= 7.2 Hz, 3H, i), 1.542 (d, J= 7.2 Hz, 3H), 1.539 (d, J= 7.2 Hz, 3H, i), 1.52 (d, J= 7.2 Hz, 3H), 1.47 (d, J= 7.2 Hz, 3H, i), 1.44 (d, J=6.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 175.3, 175.2, 169.6, 69.1, 68.9, 66.7, 20.4, 16.6; MS (EI) m/z 235 (M+).



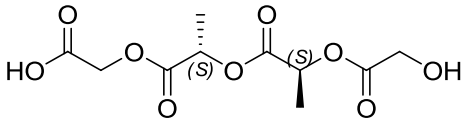
L$_{rac}$L$_{rac}$L *rmsvii-95a:* The filtrate was concentrated to yield a colorless oil (2.27 g, 100%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.23 (q, J= 7.2 Hz, 1H), 5.21 (q, J= 7.2 Hz, 1H), 5.20 (q, J= 7.2 Hz, 1H), 5.19 (q, J= 7.2 Hz, 1H, i), 5.18 (q, J= 7.2 Hz, 1H), 5.17 (q, J= 7.2 Hz, 1H, i), 5.133 (q, J= 7.2 Hz, 1H), 5.130 (q, J= 7.2 Hz, 1H), 4.39 (q, J= 7.2 Hz, 1H), 4.38 (q, J= 6.6 Hz, 2H), 4.36 (q, J= 7.2 Hz, 1H, i), 1.569 (d, J= 7.8 Hz, 3H), 1.567 (d, J= 7.2 Hz, 3H, i), 1.54 (d, J= 7.2 Hz, 9H), 1.52 (d, J= 7.2 Hz, 6H), 1.517 (d, J= 7.32 Hz, 3H), 1.47 (d, J= 7.2 Hz, 3H, i), 1.46 (d, J= 7.2 Hz,

3H), 1.44 (d, J=6.6 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 175.2, 175.1, 175.0, 174.96, 174.95, 174.89, 174.87, 169.69, 169.65, 169.58, 169.5, 69.4, 69.3, 69.1, 69.0, 68.9, 68.8, 66.75, 66.73, 20.39, 20.37, 19.94, 19.93, 16.68, 16.65, 16.64.

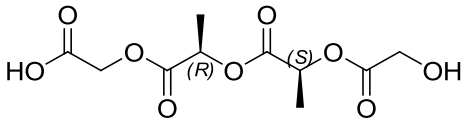
Tetramers.



GLGL$_R$ *rmsviii-24a:* The filtrate was concentrated in vacuo to yield a colorless oil (0.84 g, 93%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.26 (q, J= 7.2 Hz, 1H), 4.80 (d, J= 15.6 Hz, 1H), 4.78 (d, J= 15.6 Hz, 1H), 4.75 (d, J= 15.6 Hz, 1H), 4.64 (d, J= 16.2 Hz, 1H), 4.41 (q, J= 7.2 Hz, 1H), 1.57 (d, J= 7.2 Hz, 3H), 1.47 (d, J= 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.9, 171.5, 169.4, 166.7, 69.2, 66.8, 60.9, 60.7, 20.2, 16.7; MS (EI) m/z 279 (M+).

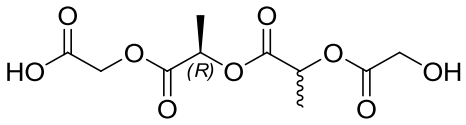


GLLG *rsmx-1a:* The product was a colorless oil (2.76 g, 99%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.24 (q, J= 7.2 Hz, 1H), 5.21 (q, J= 7.2 Hz, 1H), 4.73 (d, J= 16.8 Hz, 1H), 4.62 (d, J= 16.2 Hz, 1H), 4.23 (d, J= 17.4 Hz, 1H), 4.22 (d, J= 17.4 Hz, 1H), 1.56 (d, J= 7.2 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.8, 171.3, 169.8, 169.5, 69.17, 69.11, 60.8, 60.4, 16.7(2).

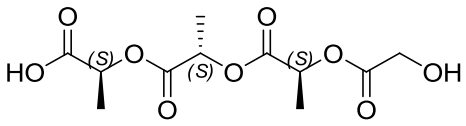


GL$_R$LG *rmsx-2a:* The product was a colorless oil (1.94 g, 100%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.27 (q, J= 7.2 Hz, 1H), 5.21 (q, J= 7.2 Hz, 1H), 4.75 (d, J= 16.8 Hz, 1H), 4.63 (d, J= 16.2 Hz, 1H), 4.27 (d, J= 17.4 Hz, 1H), 4.23 (d, J= 17.4 Hz, 1H), 1.55 (d, J= 7.2 Hz, 3H), 1.53 (d, J= 6.6

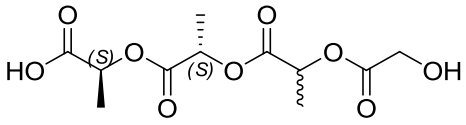
Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.7, 171.3, 169.6, 169.4, 69.3, 69.2, 60.9, 60.4, 16.67, 16.65.



GLL$_{rac}$G *rmsx-3a:* The product was a colorless oil (1.87 g, 100%).^{1}H NMR (600 MHz, $CDCl_3$) δ 5.3-5.1 (m, 4H), 4.74 (d, J= 16.2 Hz, 1H), 4.73 (d, J= 16.2 Hz, 1H), 4.62 (d, J= 16.2 Hz, 2H), 4.28 (d, J= 17.4 Hz, 1H), 4.27 (d, J= 17.4 Hz, 1H), 4.22 (d, J= 17.4 Hz, 2H), 1.56 (d, J= 7.2 Hz, 6H), 1.55 (d, J= 7.2 Hz, 3H), 1.53 (d, J= 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.78, 172.71, 171.2, 169.76, 169.44, 169.55, 169.47, 69.3, 69.18, 69.15, 69.11, 60.96, 60.85, 60.36, 60.34, 16.65(4).

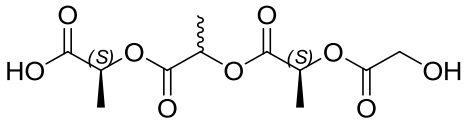


LLLG *rmsx-22a:* The product was a colorless oil (0.82 g, 80%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.22 (q, J= 7.2 Hz, 1H), 5.18 (q, J= 7.2 Hz, 1H), 5.13 (d, J= 7.2 Hz, 1H), 4.27 (d, J= 17.4 Hz, 1H), 4.22 (d, J= 17.4 Hz, 1H), 1.57 (d, J= 7.2 Hz, 3H), 1.56 (d, J= 7.2 Hz, 3H), 1.53 (d, J= 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 175.1, 172.8, 169.8, 169.6, 69.17, 69.15, 68.94, 60.4, 16.7, 16.62, 16.58.

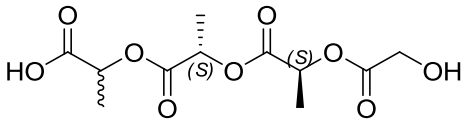


LLL$_{rac}$G *rmsix-23a:* The product was a colorless oil (1.85 g, 97%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.27 (q, J= 7.2 Hz, 1H), 5.21 (q, J= 7.2 Hz, 1H), 5.18 (q, J= 6.6 Hz, 1H), 5.15 (q, J= 7.2 Hz, 2H), 5.13 (d, J= 6.6 Hz, 1H), 4.28 (d, J= 17.4 Hz, 1H), 4.26 (d, J= 17.4 Hz, 1H), 4.224 (d, J=

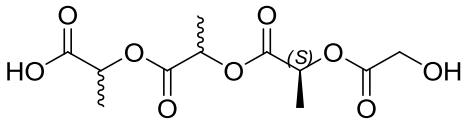
17.4 Hz, 1H), 4.222 (d, J= 17.4 Hz, 1H), 1.569 (d, J= 7.2 Hz, 3H), 1.565 (d, J= 7.2 Hz, 3H), 1.545 (d, J= 7.2 Hz, 3H), 1.538 (d, J= 7.2 Hz, 3H), 1.531 (d, J= 7.2 Hz, 3H), 1.529 (d, J= 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.74, 174.66, 172.80, 172.65, 169.83, 169.64, 169.60, 169.41, 69.27, 69.23, 69.18, 69.01, 68.95, 60.45, 60.44, 16.79, 16.75, 16.66, 16.62.



LL$_{rac}$LG *rmsx-23a:* The product was a colorless oil (0.70 g, 70%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.26 (q, J= 7.2 Hz, 1H), 5.22 (q, J= 7.2 Hz, 1H), 5.181 (q, J= 7.2 Hz, 1H), 5.178 (q, J= 7.2 Hz, 1H), 5.14 (d, J= 7.2 Hz, 1H), 5.12 (q, J= 7.2 Hz, 1H), 4.275 (d, J= 17.4 Hz, 1H), 4.268 (d, J= 17.4 Hz, 1H), 4.22 (d, J= 17.4 Hz, 2H), 1.569 (d, J= 7.2 Hz, 3H), 1.564 (d, J= 7.2 Hz, 3H), 1.536 (d, J= 7.2 Hz, 3H), 1.530 (d, J= 7.2 Hz, 3H), 1.52 (d, J= 7.2 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.88, 174.68, 172.77, 172.66, 169.77, 169.55, 169.52, 169.33, 69.44, 69.21, 69.16, 69.13, 68.94, 60.5, 60.41, 60.38, 16.70, 16.68, 16.63, 16.60, 16.58.

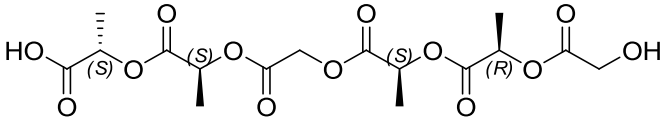


L$_{rac}$LLG *rmsix-22a:* The product was a colorless oil (1.22 g, 100%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.25-5.10 (m, 6H), 4.28 (d, J= 17.4 Hz, 2H), 4.222 (d, J= 17.4 Hz, 1H), 4.220 (d, J= 17.4 Hz, 1H), 1.565 (d, J= 7.2 Hz, 3H), 1.562 (d, J= 7.2 Hz, 3H), 1.558 (d, J= 6.6 Hz, 3H), 1.537 (d, J= 6.6 Hz, 3H), 1.527 (d, J= 7.2 Hz, 3H), 1.51 (d, J= 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.81, 174.49, 172.45, 172.69, 169.79, 169.68, 169.56, 169.34, 69.20, 69.13, 69.09, 69.01, 68.87, 60.39, 60.37, 16.70, 16.62, 16.57.

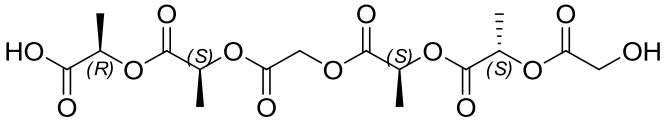


$L_{rac}L_{rac}LG$ *rmsx-18a:* The product was a colorless oil (0.78 g, 93%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.3-5.1 (m, 12H), 4.28 (d, J= 17.4 Hz, 2H), 4.27 (d, J= 17.4 Hz, 2H), 4.22 (d, J= 17.4 Hz, 5H), 1.58-1.50 (m, 36H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.84, 174.70, 174.63, 174.61, 172.72, 172.64, 169.65, 169.64, 169.59, 169.55, 169.51, 169.35, 169.33, 169.32, 69.45, 69.26, 69.21, 69.16, 69.13, 60.5, 60.39, 16.75, 16.71, 16.69, 16.64, 16.61, 16.59.

Hexamers.



$LLGLL_RG$ *rmsviii-73a:* The filtrate was concentrated *in vacuo* to yield a colorless oil (0.68 g, 92%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.26 (q, J= 7.0 Hz, 1H), 5.22 (q, J= 7.0 Hz, 1H), 5.17 (q, J= 7.0 Hz, 1H), 5.16 (q, J= 7.0 Hz, 1H), 4.84 (d, J= 16.2 Hz, 1H), 4.67 (d, J= 15.6 Hz, 1H), 4.27 (d, J= 17.4 Hz, 1H), 4.22 (d, J= 17.4 Hz, 1H), 1.56 (d, J= 7.2 Hz, 3H), 1.55 (d, J= 7.2 Hz, 1H), 1.54 (d, J= 6.6 Hz, 3H), 1.53 (d, J= 6.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.3, 172.9, 169.5, 169.4, 169.3, 166.6, 69.4, 69.3, 69.1, 69.0, 60.0, 60.4, 16.7 (2), 16.6 (2); HRMS (M+Na) calc mass 445.0958, found 445.0998.

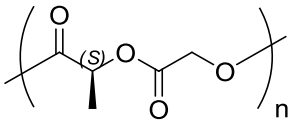


L_RLGLLG *rmsix-6a:* The filtrate was concentrated *in vacuo* to yield a colorless oil (0.61 g, 78%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.26-5.21 (m, 3H), 5.13 (q, J= 6.6 Hz, 1H), 4.82 (d, J= 15.7 Hz, 1H), 4.64 (d, J= 16.2 Hz, 1H), 4.27 (d, J= 16.8 Hz, 1H), 4.22 (d, J= 16.8 Hz, 1H), 1.58 (d, J=

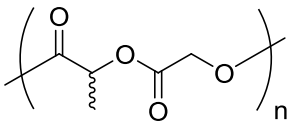
7.2 Hz, 3H), 1.57 (d, J= 6.6 Hz, 3H), 1.53 (d, J= 7.7 Hz, 3H), 1.52 (d, J= 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.1, 172.7, 169.6, 169.4, 169.3, 166.4, 69.4, 69.2, 69.1, 60.8, 60.5, 16.69 (2), 16.66, 16.64; HRMS (M+Na) calc mass 445.0958, found 445.0930.

2.7.7 General procedures for DCC/DMAP polymerizations

The segmer and 0.08 equivalents of DMAP were dissolved in a mixture of CH_2Cl_2 and EtOAc and cooled to 0°C. Slowly, 1.5 equiv of DCC were added and the reaction mixture was stirred at RT for 24 h. The polymers were precipitated twice in MeOH and dried under vacuum.



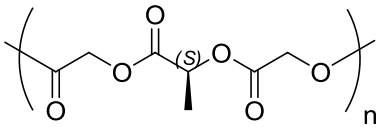
Poly LG *rmsiv-72a:* A white powder was collected (0.18 g, 42%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.23 (q, J= 7.0 Hz, 1H), 4.86 (d, J= 16.2 Hz, 1H), 4.63 (d, J= 15.6 Hz, 1H), 1.57 (t, J= 6.6 Hz, 3H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.3, 166.4, 69.2, 60.8, 16.7; SEC (THF): M_n – 15.6 kDa, M_w – 26.9 kDa, PDI – 1.7.



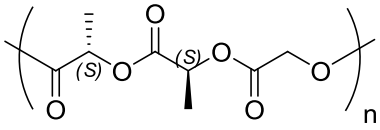
Poly L_{rac}G *rmsv-3a:* A white powder was collected (0.156 g, 28%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.242 (quartet, J= 7.2 Hz, 2H), 5.237 (quartet, J= 7.2 Hz, 2H), 5.235 (quartet, J= 7.2 Hz, 2H), 5.230 (quartet, J= 7.2 Hz, 2H), 4.857 (d, J= 15.6 Hz, 2H), 4.855 (d, J= 16.2 Hz, 2H), 4.813 (d, J= 16.2 Hz, 1H), 4.809 (d, J= 16.2 Hz, 1H), 4.808 (d, J= 16.2 Hz, 1H), 4.804 (d, J= 16.2 Hz, 1H), 4.684 (d, J= 15.6 Hz, 1H), 4.681 (d, J= 16.2 Hz, 2H), 4.678 (d, J= 16.2 Hz, 1H), 4.63 (d, J= 15.6 Hz, 4H), 1.568 (d, J= 7.2 Hz, 6H), 1.565 (d, J= 7.2 Hz, 6H), 1.563 (d, J= 7.2 Hz,

6H), 1.56 (d, J= 7.2 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.33, 169.27, 169.24, 169.19, 166.40, 166.37, 166.36, 166.33, 69.18, 69.16, 69.14, 69.13, 60.81, 16.74, 16.73, 16.72, 16.70; SEC (THF): M_n – 9.25 kDa, M_w – 12.9 kDa, PDI – 1.4.

Poly (LG/L*rac*G) (60/40) *rmsv-71a:* The **LG** dimer (0.40 g, 2.7 mmol) and **L*rac*G** dimer (0.60 g, 4.05 mmol) were added to 1.0 ml of ethyl acetate and 2.0 ml of methylene chloride. DMAP (0.066 g, 0.54 mmol) was added and the reaction mixture was cooled to 0°C. DCC (2.09 g, 10.1 mmol) was added slowly over 5 minutes and the reaction mixture was allowed to stir for 23 h at room temperature. The mixture was taken up in methylene chloride and precipitated in methanol. A white powder was collected (0.17 g, 20%). SEC (THF) M_n – 9.5 kDa, M_w – 11.5 kDa, PDI – 1.2.



Poly GLG *rmsv-11a:* A white powder was collected (0.28 g, 80%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.25 (q, J= 7.2 Hz, 1H), 4.86 (d, J= 16.0 Hz, 1H), 4.80 (d, J= 16.2 Hz, 1H), 4.72 (d, J= 16.2 Hz, 1H), 4.69 (d, J= 16.2 Hz, 1H), 1.57 (d, J= 7.2 Hz, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 169.2, 166.4, 166.3, 69.2, 60.9, 60.7, 16.7; GPC (THF): M_n – 12.4 kDa, M_w – 19.2 kDa, PDI – 1.6.

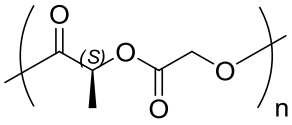


Poly LLG *rmsiv-96a:* A white powder was collected (0.20 g, 41%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.21 (q, J= 7.2 Hz, 1H), 5.18 (q, J= 7.2 Hz, 1H), 4.85 (d, J= 16.2 Hz, 1H), 4.60 (d, J= 16.2 Hz, 1H), 1.57 (d, J= 7.2 Hz, 3H), 1.56 (d, J= 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ

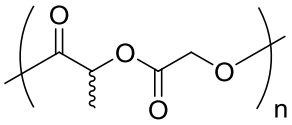
169.5, 169.3, 166.5, 69.2, 69.0, 60.8, 16.7, 16.6; GPC: M_n – 12.9 kDa, M_w – 20.1 kDa, PDI – 1.6.

2.7.8 General procedures for DIC/DPTS polymerizations

Polymerization was adapted from Stupp and coworkers.[99] The oligomer and 0.2 equivalents of DPTS were dissolved in CH_2Cl_2 and chilled to 0°C. DIC (1.5 equiv) was added dropwise by syringe and the reaction mixture was stirred at RT for 3 h. The polymers were precipitated twice in MeOH and dried under vacuum.

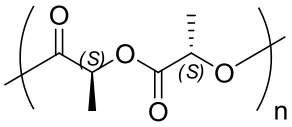


Poly LG *rmsvii-41b:* A white solid was collected (2.14 g, 63%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.23 (q, J= 7.2 Hz, 1H), 4.86 (d, J= 15.6 Hz, 1H), 4.63 (d, J= 16.2 Hz, 1H), 1.57 (d, J= 7.2 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.4, 166.4, 69.2, 60.8, 16.7; SEC (THF): M_n – 27.4 kDa, M_w – 36.3 kDa, PDI – 1.3; SEC ($CHCl_3$): M_n – 33.3 kDa, M_w – 44.0 kDa, PDI – 1.3; SEC-MALLS ($CHCl_3$): M_n – 13.4 kDa, M_w – 14.5 kDa, PDI – 1.08; Thermal (DSC): *ppt:* T_g – 57 °C, *annealed film (85 °C, 3 h)*: T_g – 49 °C.

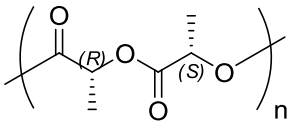


Poly L$_{rac}$G *rmsviii-14b:* A white solid was collected (0.62 g, 52%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.26-5.21 (m, 4H), 4.86 (d, J= 15.6 Hz, 1H), 4.85 (d, J= 16.2 Hz, 1H), 4.814 (d, J= 16.2 Hz, 1H), 4.809 (d, J= 16.8 Hz, 1H), 4.808 (d, J= 16.2 Hz, 1H), 4.804 (d, J= 15.6 Hz, 1H), 4.684 (d, J= 16.2 Hz, 1H), 4.680 (d, J=15.6 Hz, 2H), 4.677 (d, J= 16.2 Hz, 1H), 4.63 (d, J= 15.6 Hz, 1H),

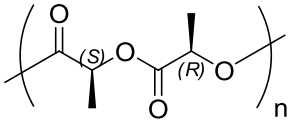
1.567 (d, J= 7.2 Hz, 3H), 1.564 (d, J= 7.2 Hz, 3H), 1.562 (d, J= 6.6 Hz, 1H), 1.558 (d, J= 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.38, 169.31, 169.28, 169.22, 166.44, 166.40(2), 166.36, 69.19, 69.17, 69.15, 60.8, 16.77, 16.76, 16.74; SEC (THF): M_n – 28.8 kDa, M_w – 37.1 kDa, PDI – 1.3; SEC ($CHCl_3$): M_n – 34.3 kDa, M_w – 47.2, PDI – 1.4; Thermal (DSC): *ppt:* T_g – 55 °C, *annealed film (85 °C, 3 h)*: T_g – 48 °C.



Poly LL *rmsvii-93b:* A white solid was collected (0.39 g, 28%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.14 (q, J= 7.2 Hz, 1H), 1.56 (d, J= 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.6, 69.0, 16.6; SEC (THF): M_n – 22.2 kDa, M_w – 30.6 kDa, PDI – 1.4; Thermal (DSC): *ppt:* T_g – 61 °C, $T_{crystal}$ – 110 °C, T_{m1} – 156 °C, T_{m2} – 163.5 °C.

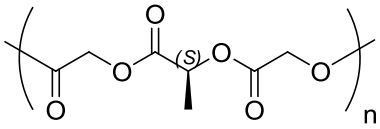


Poly L$_R$L *rmsviii-100b:* A white solid was collected (0.46 g, 43%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.13 (q, J= 7.2 Hz, 1H), 1.52 (d, J= 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.2, 69.2, 16.6; SEC (THF): M_n – 7.9 kDa, M_w – 12.1 kDa, PDI – 1.5; Thermal (DSC): *ppt:* T_g – 46 °C, T_m – 138 °C.

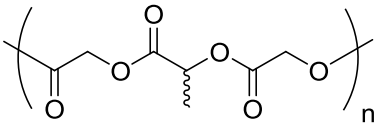


Poly LL$_R$ *rmsviii-89b:* A white solid was collected (0.40 g, 36%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.13 (q, J= 7.2 Hz, 1H), 1.52 (d, J= 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.2, 69.3,

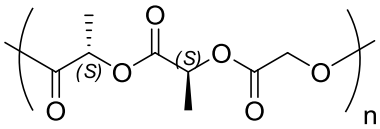
16.6; SEC (THF): M_n – 14.8 kDa, M_w – 19.7 kDa, PDI – 1.3; Thermal (DSC): *ppt:* T_g – 46 °C, $T_{crystal}$ – 110 °C, T_m – 148 °C.



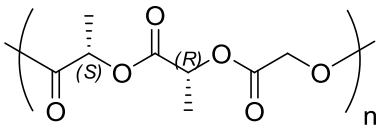
Poly GLG *rmsviii-5b:* A white solid was collected (0.85 g, 78%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.24 (q, J= 7.2 Hz, 1H), 4.86 (d, J= 16.2 Hz, 1H), 4.80 (d, J- 15.6 Hz, 1H), 4.72 (d, J= 15.6 Hz, 1H), 4.69 (d, J= 15.6 Hz, 1H), 1.57 (d, J= 7.2 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.3, 166.5, 166.4, 69.2, 60.9, 60.7, 16.7; SEC (THF): M_n – 26.2 kDa, M_w – 36.2 kDa, PDI – 1.2; SEC ($CHCl_3$): M_n – 36.2 kDa, M_w – 49.7 kDa, PDI – 1.4; SEC-MALLS ($CHCl_3$): M_n – 19.4 kDa, M_w – 21.3 kDa, PDI – 1.10; Thermal (DSC): *ppt:* T_g – 50 °C, *annealed film (85 °C, 3 h)*: T_g – 43 °C.



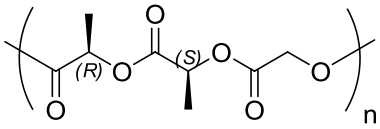
Poly GL$_{rac}$G *rmsviii-18b:* A white solid was collected (0.56 g, 60%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.24 (q, J= 7.2 Hz, 2H), 4.86 (d, J= 16.2 Hz, 1H), 4.84 (d, J= 16.2 Hz, 1H), 4.80 (d, J= 16.2 Hz, 1H), 4.78 (d, J= 16.2 Hz, 1H), 4.73 (d, J= 16.2, 1H), 4.72 (d, 16.8 Hz, 1H), 4.70 (d, J= 16.2 Hz, 1H), 4.68 (d, J= 15.6 Hz, 1H), 1.57 (d, J= 7.2 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.3 (2), 166.46, 166.44, 166.35 (2), 69.2, 60.9, 60.7, 16.7; SEC (THF): M_n – 21.4 kDa, M_w – 26.6 kDa, PDI – 1.3; SEC ($CHCl_3$): M_n – 27.5 kDa, M_w – 38.6 kDa, PDI – 1.4; Thermal (DSC): *ppt:* T_g – 50 °C.



Poly LLG *rmsvii-29b:* White fibers were collected (3.0 g, 70%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.21 (q, J= 7.2 Hz, 1H), 5.18 (q, J= 7.2 Hz, 1H), 4.85 (d, J= 16.2 Hz, 1H), 4.60 (d, J= 16.2 Hz, 1H), 1.57 (d, J= 7.2 Hz, 3H), 1.56 (d, J= 6.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.5, 169.4, 166.5, 69.2, 69.0, 60.8, 16.7, 16.6; SEC (THF): M_n – 41.2 kDa, M_w – 50.5 kDa, PDI – 1.2; SEC ($CHCl_3$): M_n – 41.8 kDa, M_w – 53.7 kDa, PDI – 1.3; SEC-MALLS ($CHCl_3$): M_n – 23.1 kDa, M_w – 25.3 kDa, PDI – 1.10; Thermal (DSC): *ppt:* T_g – 57 °C, *annealed film (85 °C, 3 h)*: T_g – 50 °C, T_m – 114 °C.

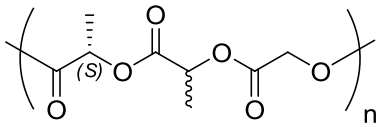


Poly LL*R*G *rmsviii-68b:* White fibers were collected (0.56 g, 71%). ^{1}H NMR (700 MHz, $CDCl_3$) δ 5.22 (q, J= 7.0 Hz, 1H), 5.18 (q, J= 7.0 MHz, 1H), 4.81 (d, J= 16.1 Hz, 1H), 4.65 (d, J= 16.1 Hz, 1H), 1.56 (d, J= 7.0 Hz, 3H), 1.53 (d, J= 7.7 Hz, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 169.23, 169.15, 166.4, 69.4, 69.2, 60.8, 16.74, 16.70; SEC (THF): M_n – 29.0 kDa, M_w – 39 kDa, PDI – 1.4; SEC ($CHCl_3$): M_n – 42.3 kDa, M_w – 55.8 kDa, PDI – 1.3; Thermal (DSC): *ppt:* T_g – 48 °C, T_{m1} – 151 °C, T_{m2} – 158 °C, *annealed film (85 °C, 3 h)*: T_g – 48 °C, T_m – 155 °C.

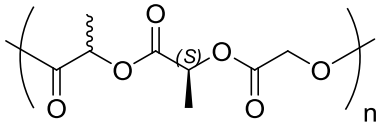


Poly L*R*LG *rmsviii-95b:* White fibers were collected (0.30 g, 59%). ^{1}H NMR (700 MHz, $CDCl_3$) δ 5.22 (q, J= 7.0 Hz, 1H), 5.19 (q, J= 7.0 Hz, 1H), 4.81 (d, J= 16.1 Hz, 1H), 4.65 (d, J= 16.1 Hz, 1H), 1.56 (d, J= 7.0 Hz, 3H), 1.53 (d, J= 7.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.2,

169.1, 166.4, 69.4, 69.2, 60.8, 16.74, 16.71; SEC (THF): M_n – 30.6 kDa, M_w – 43.1 kDa, PDI – 1.4; SEC ($CHCl_3$): M_n – 39.8 kDa, M_w – 54.7 kDa, PDI – 1.4; Thermal (DSC): *ppt:* T_g – 50 °C, T_m – 154°C.

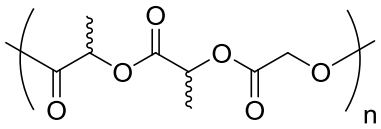


Poly LL$_{rac}$G *rmsvii-30b:* A white solid was collected (2.03 g, 50%). ^{1}H NMR (700 MHz, $CDCl_3$) δ 5.24- 5.16 (m, 8H) [possible interpretation: 5.22 (q, J= 7.0 Hz, 1H), 5.218 (q, J= 7.0 Hz, 2H), 5.212 (q, J= 7.0 Hz, 1H), 5.187 (q, J= 7.0 Hz, 1H), 5.185 (q, J= 7.0 Hz, 1H), 5.177 (q, J= 7.0 Hz, 1H), 5.175 (q, J= 7.0 Hz, 1H)], 4.87 (d, J= 16.1 Hz, 1H), 4.85 (d, J= 16.1 Hz, 3H), 4.813 (d, J= 16.1 Hz, 3H), 4.811 (d, J= 16.1 Hz, 1H), 4.808 (d, J= 16.1 Hz, 3H), 4.806 (d, J= 16.1 Hz, 1H), 4.652 (d, J= 16.1 Hz, 1H), 4.650 (d, J= 16.1 Hz, 1H), 4.63 (d, J= 16.1 Hz, 2H), 4.62 (d, J= 16.1 Hz, 2H), 4.60 (d, J= 16.1 Hz, 2H), 1.572 (d, J= 7.0 Hz, 3H), 1.569 (d, J= 7.0 Hz, 3H), 1.562 (d, J= 7.0 Hz, 3H), 1.560 (d, J= 7.0 Hz, 3H), 1.559 (d, J= 7.0 Hz, 3H), 1.556 (d, J= 7.0 Hz, 3H), 1.53 (d, J= 7.0 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.5, 169.4, 169.35 (m), 169.31, 169.30, 169.2, 169.18, 169.15, 169.12, 169.1, 166.52, 166.48, 166.34, 166.29, 69.3, 69.2, 69.1, 69.0, 68.9, 60.76, 60.74, 16.72, 16.65, 16.63, 16.61; SEC (THF): M_n – 17.8 kDa, M_w – 25.1 kDa, PDI – 1.4; SEC ($CHCl_3$): M_n – 19.3 kDa, M_w – 30.1 kDa, PDI – 1.6; Thermal (DSC): *ppt:* T_g – 53 °C, *annealed film (85 °C, 3 h)*: T_g – 48 °C.

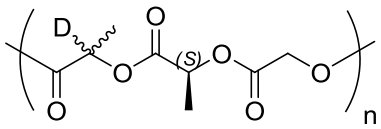


Poly L$_{rac}$LG *rmsviii-27b:* A white solid was collected (2.31 g, 83%). ^{1}H NMR (700 MHz, $CDCl_3$) δ 5.24-5.14 (m, 8H), 4.86 (d, J=16.1 Hz, 4H), 4.826 (d, J= 16.1 Hz, 1H), 4.824 (d, J= 16.1 Hz, 1H), 4.822 (d, J=16.1 Hz, 1H), 4.81 (d, J= 16.1 Hz, 1H), 4.79 (d, J= 15.4 Hz, 1H), 4.789

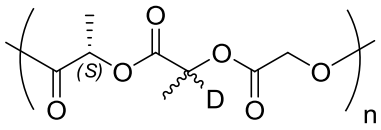
(d, J= 16.1 Hz, 1H), 4.69 (d, J= 16.1 Hz, 4H), 4.654 (d, J= 16.1 Hz, 2H), 4.652 (d, J= 16.1 Hz, 1H), 4.620 (d, J= 16.1 Hz, 1H), 4.618 (d, J= 16.1 Hz, 2H), 4.616 (d, J= 16.1 Hz, 1H), 4.604 (d, J= 16.1 Hz, 1H), 4.603 (d, J= 16.1 Hz, 2H), 4.601 (d, J= 16.1 Hz, 1H), 1.576 (d, J= 7.0 Hz, 3H), 1.573 (d, J= 7.0 Hz, 3H), 1.561 (d, J= 1.561 Hz, 3H), 1.560 (d, J= 6.3 Hz, 3H), 1.558 (d, J= 7.0 Hz, 3H), 1.556 (d, J= 7.0 Hz, 3H), 1.553 (d, J= 6.3 Hz, 3H), 1.534 (d, J= 7.7 Hz, 3H), 1.532 (d, J= 7.0 Hz, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 169.51, 169.50, 169.48, 169.46, 169.37, 169.32, 169.23, 169.21, 169.19, 169.18, 169.16, 169.14, 169.13, 166.50, 166.48, 166.35, 166.33, 69.34, 69.29, 69.16, 68.97, 60.76, 60.74, 16.72, 16.70, 16.67, 16.65, 16.64; SEC (THF): M_n – 27.4 kDa, M_w – 38.9 kDa, PDI – 1.4; SEC ($CHCl_3$): M_n – 40.5 kDa, M_w – 54.7 kDa, PDI – 1.4; SEC-MALLS ($CHCl_3$): M_n – 25.3 kDa, M_w – 28.5 kDa, PDI – 1.12; Thermal (DSC): *ppt:* T_g – 51 °C, *annealed film (85 °C, 3 h)*: T_g – 48 °C.



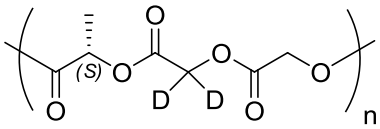
Poly $L_{rac}L_{rac}G$ *rmsix-35b:* A white solid was collected (0.92 g, 80%). ^{1}H NMR (700 MHz, $CDCl_3$) δ 5.24 – 5.16 (m, 8H), 4.85 (d, J= 16.1 Hz, 1H), 4.818 (d, J= 16.1 Hz, 1H), 4.808 (d, J= 16.1 Hz, 1H), 4.805 (d, J= 15.4 Hz, 1H), 4.78 (d, J= 16.8 Hz, 1H), 4.686 (d, J= 15.4 Hz, 1H), 4.65 (d, J= 14.0 Hz, 1H), 4.63 (d, J= 16.1 Hz, 1H), 4.61 (d, J= 16.1 Hz, 1H), 4.60 (d, J= 16.8 Hz, 1H), 1.58-1.52 (m, 24H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 169.49, 169.45, 169.36, 169.3, 169.27, 169.26, 169.18, 169.17, 169.14, 169.12, 169.1, 166.52, 166.48, 166.47, 166.42, 166.34, 166.3, 69.35, 69.29, 69.16, 69.12, 69.11, 69.01, 68.97, 60.77, 60.74, 16.72, 16.69, 16.67, 16.65, 16.63, 16.61; SEC (THF): M_n – 42.0 kDa, M_w – 61.7 kDa, PDI – 1.5; SEC ($CHCl_3$): M_n – 53.2 kDa, M_w – 71.6 kDa, PDI – 1.4; Thermal (DSC): *ppt:* T_g – 52 °C, *annealed film*: T_g – 47 °C.



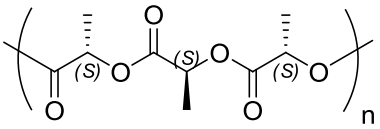
Poly $L_{d,rac}LG$ *rmsvii-15b:* A white solid was collected (0.64 g, 99%). ^{1}H NMR (700 MHz, $CDCl_3$) δ 5.25-5.15 (m, 4H), 4.86 (d, J= 16.1 Hz, 4H), 4.824 (d, J= 16.1 Hz, 1H), 4.822 (d, J= 16.1 Hz, 2H), 4.821 (d, J= 16.1 Hz, 1H), 4.81 (d, J= 16.1 Hz, 4H), 4.788 (d, J= 16.1 Hz, 2H), 4.786 (d, J= 16.1 Hz, 2H), 4.69 (d, J= 16.1 Hz, 4H), 4.652 (d, J= 16.1 Hz, 2H), 4.649 (d, J= 16.1 Hz, 2H), 4.618 (d, J= 16.1 Hz, 1H), 4.616 (d, J= 16.1 Hz, 2H), 4.614 (d, J= 16.1 Hz, 1H), 4.603 (d, J= 16.1 Hz, 1H), 4.601 (d, J= 16.1 Hz, 2H), 4.599 (d, J= 16.1 Hz, 1H). 1.58-1.53 (m, 24H); ^{13}C NMR (150 MHz, $CDCl_3$) d 169.50, 169.48, 169.46, 169.45, 169.36, 169.31, 169.2, 169.18, 169.16, 169.14, 169.12, 166.47 (2), 166.34, 166. 31, 69.34, 69.29, 69.16 (2), 69-68 (m), 60.75, 60.73, 16.71, 16.67, 16.63, 16.57, 16.55; SEC (THF) M_n – 32.8 kDa, M_w – 41.2 kDa, PDI – 1.3; SEC ($CHCl_3$): M_n – 31.7 kDa, M_w – 47.4 kDa, PDI – 1.5.



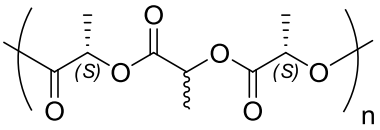
Poly $LL_{d,rac}G$ *rmsviii-13b:*A white solid was collected (0.55 g, 62%). ^{1}H NMR (700 MHz, $CDCl_3$) δ 5.23-5.15 (m, 4H), 4.85 (d, J= 16.1 Hz, 8H), 4.81 (d, J= 16.1 Hz, 4H), 4.807 (d, J= 16.1 Hz, 4H), 4.651 (d, J= 16.1 Hz, 2H), 4.649 (d, J= 16.1 Hz, 2H), 4.632 (d, J= 16.1 Hz, 4H), 4.615 (d, J= 16.1 Hz, 2H), 4.614 (d, J= 16.1 Hz, 2H), 4.602 (d, J= 16.1 Hz, 4H), 1.58-1.53 (m, 24H); ^{13}C NMR (150MHz, $CDCl_3$) δ 169.5, 169.39, 169.37, 169.34, 169.32, 169.31, 169.21, 169.19, 169.16, 169.13, 169.11, 166.54, 166.50, 166.35, 166.31, 69.17, 69.10, 69.0, 68.98, 60.77, 60.75, 16.70, 16.69, 16.66, 16.63, 16.53, 16.51; SEC (THF) M_n – 29.6 kDa, M_w – 40.1 kDa, PDI – 1.4; SEC ($CHCl_3$): M_n – 33.7 kDa, M_w – 48.4 kDa, PDI – 1.4.



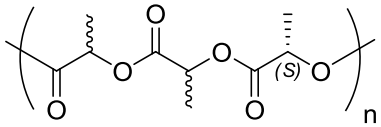
Poly GLG_{d2} *rmsvii-72b:* A white solid was collected (0.44 g, 52%). ^{1}H (600 MHz, $CDCl_3$) δ 5.25 (q, J= 7.2Hz, 1H), 4.86 (d, J= 16.2 Hz, 1H), 4.68 (d, J= 16.2 Hz, 1H), 1.57 (d, J= 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.3, 166.5, 166.4, 69.2, 60.7, 16.7; SEC (THF) M_n – 15.2 kDa, M_w – 21.6 kDa, PDI – 1.4; SEC ($CHCl_3$): M_n – 25.3 kDa, M_w – 38.4 kDa, PDI – 1.5.



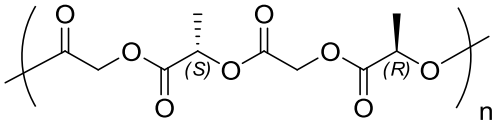
Poly LLL *rmsvii-91b:* A white solid was collected (0.97 g, 42%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.15 (q, J= 7.2 Hz, 1H), 1.56 (d, J= 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.6, 69.0, 16.6; SEC (THF): M_n – 24.0 kDa, M_w – 31.6 kDa, PDI – 1.3; Thermal (DSC): *ppt:* T_g – 59 °C, $T_{crystal}$ – 108.5 °C, T_m1 – 156 °C, T_m2 – 163 °C, *annealed film (85 °C, 24 h)*: T_g – 55°C, T_m – 164 °C.



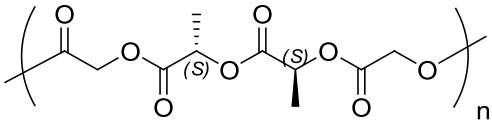
Poly $LL_{rac}L$ *rmsviii-3b:* A white solid was collected (1.52 g, 49%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.21-5.10 (m, 1H), 1.58-1.5 (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.64, 169.60, 169.59, 169.57, 169.53, 169.44, 169.43, 169.36, 169.26, 169.22, 169.19, 69.42, 69.39, 69.09, 69.07, 69.00, 68.98, 68.95, 16.73, 16.69, 16.63, 16.60, 16.57; SEC (THF): M_n – 15.3 kDa, M_w – 20.1 kDa, PDI – 1.3; Thermal (DSC): *ppt:* T_g – 52 °C, *annealed film:* T_{g1} – 50 °C, T_{g2} – 52 °C.



Poly $L_{rac}L_{rac}L$ *rmsviii-4b:* A white solid was collected (1.28 g, 63%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.21-5.10 (m, 1H), 1.58-1.5 (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.64, 169.59, 169.45, 169.40, 169.37, 169.33, 169.24, 169.22, 169.18, 169.11, 69.39, 69.30, 69.28, 69.17, 69.07, 69.00, 68.97, 16.73, 16.70, 16.66, 16.63, 16.59, 16.57; SEC (THF): M_n – 27.9 kDa, M_w – 37.4 kDa, PDI – 1.3; Thermal (DSC): *ppt:* T_g – 50 °C, $T_{crystal}$ – 77 °C, T_m – 124 °C, *annealed film:* $T_{g\,1}$– 50 °C, T_{g2} – 52 °C.

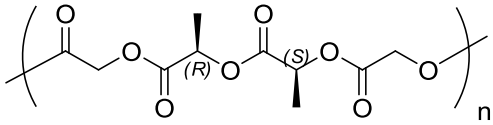


Poly $GLGL_R$ *rmsviii-26b:* A white powder was collected (0.49 g, 65%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.24 (q, J= 7.2 Hz, 1H), 4.81 (d, J= 16.2 Hz, 1H), 4.69 (d, J= 15.6 Hz, 1H), 1.56 (d, J= 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.2, 166.4, 69.2, 60.8, 16.8; SEC (THF): M_n – 12.3 kDa, M_w – 17.9 kDa, PDI – 1.5; SEC ($CHCl_3$): M_n – 12.1 kDa, M_w – 17.0 kDa, PDI – 1.4; Thermal (DSC): *ppt:* T_g – 50 °C.

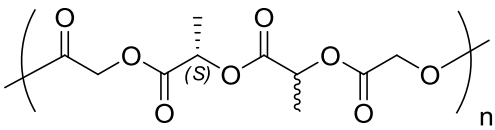


Poly GLLG *rmsx-4b:* A white solid was collected (2.13 g, 88%). ^{1}H NMR (700 MHz, $CDCl_3$) δ 5.21 (q, J= 7.7 Hz, 1H), 5.18 (q, J= 7.0 Hz, 1H), 4.855 (d, J= 16.1 Hz, 1H), 4.806 (d, J= 16.1 Hz, 1H), 4.699 (d, J= 16.1 Hz, 1H), 4.661 (d, J= 16.1 Hz, 1H), 1.569 (d, J= 7.0 Hz, 3H), 1.559 (d, J= 7.0 Hz, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 169.42, 169.33, 166.45, 166.42, 69.27, 69.0, 60.84,

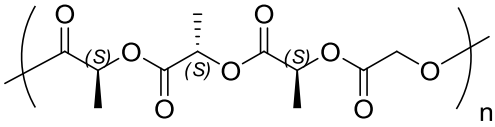
60.65, 16.66, 16.60; SEC (THF): M_n – 13.0 kDa, M_w – 21.1 kDa, PDI – 1.6; Thermal (DSC): *ppt:* T_g – 46 °C.



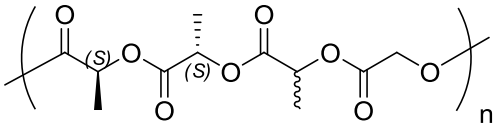
Poly GL$_R$LG *rmsx-5b:* A white solid was collected (1.48 g, 87%). ^{1}H NMR (700 MHz, $CDCl_3$) δ 5.23 (q, J= 7.0 Hz, 1H), 5.20 (q, J= 7.0 Hz, 1H), 4.843 (d, J= 16.1 Hz, 1H), 4.759 (d, J= 16.1 Hz, 1H), 4.732 (d, J= 16.8 Hz, 1H), 4.702 (d, J= 16.1 Hz, 1H), 1.555 (d, J= 7.0 Hz, 3H), 1.534 (d, J= 7.0 Hz, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 169.24, 169.14, 166.45, 166.28, 69.39, 69.15, 60.82, 60.68, 16.69, 16.65; SEC (THF): M_n – 13.3 kDa, M_w – 22.3 kDa, PDI – 1.7; Thermal (DSC): *ppt:* T_g – 44 °C.



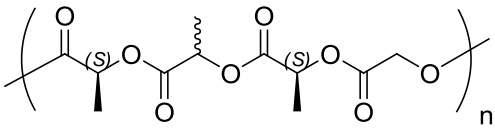
Poly GLL$_{rac}$G *rmsx-6b:* A white solid was collected (1.07 g, 68%). ^{1}H NMR (700 MHz, $CDCl_3$) δ 5.24-5.14 (m, 8H), 4.859 (d, J= 16.1 Hz, 1H), 4.856 (d, J= 16.1 Hz, 1H), 4.840 (d, J= 15.4 Hz, 1H), 4.838 (d, J= 14.7 Hz, 1H), 4.806 (d, J= 16.1 Hz, 1H), 4.802 (d, J= 16.1 Hz, 1H), 4.758 (d, J= 16.1 Hz, 2H), 4.731 (d, J= 16.8 Hz, 2H), 4.699 (d, J= 16.8 Hz, 3H), 4.686 (d, J= 16.8 Hz, 1H), 4.675 (d, J= 16.8 Hz, 1H), 4.662 (d, J= 16.8 Hz, 1H), 1.58-1.53 (m, 48H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 169.41, 169.31, 169.24, 169.14, 166.49, 166.44, 144.42, 166.26, 69.4, 69.27, 69.16, 69.00, 60.84, 60.82, 60.67, 16.69, 16.66, 16.65, 16.61; SEC (THF): M_n – 7.9 kDa, M_w – 13.3 kDa, PDI – 1.7; Thermal (DSC): *ppt:* T_g – 45 °C.



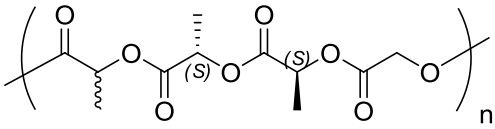
Poly LLLG *rmsx-25b:* A white fibers were collected (0.62 g, 85%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.19 (q, J= 7.2 Hz, 1H), 5.17 (q, J= 7.2 Hz, 1H), 5.15 (q, J= 7.2 Hz, 1H), 4.86 (d, J= 16.2 Hz, 1H), 4.59 (d, J= 15.6 Hz, 1H), 1.57 (d, J= 6.6 Hz, 3H), 1.56 (d, J= 7.2 Hz, 3H), 1.55 (d, J= 6.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.5 (2), 169.45, 166.5, 69.19, 69.08, 68.93, 60.77, 16.7, 16.65, 16.58; SEC (THF): M_n – 55.0 kDa, M_w – 82.4 kDa, PDI – 1.5; Thermal (DSC): *ppt:* T_g – 58 °C, *annealed film (85 °C for 24 h):* T_g – 56 °C.



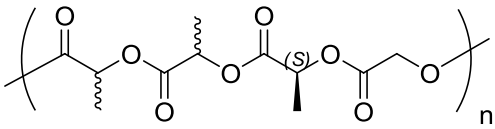
Poly LLL$_{rac}$G *rmsix-25b:* A white solid was collected (0.99 g, 58%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.23-5.10 (m, 12H) [J-Resolved spectra (600 MHz, $CDCl_3$) δ 5.207 (3H), 5.196 (2H), 5.184 (1H), 5.163 (2H), 5.15 (2H), 5.131 (2H)], 4.855 (d, J= 16.2 Hz, 1H), 4.851 (d, J= 16.2 Hz, 1H), 4.809 (d, J= 16.2 Hz, 1H), 4.805 (d, J= 16.2 Hz, 1H), 4.618 (d, J= 16.2 Hz, 1H), 4.616 (d, J=16.2 Hz, 1H), 4.590 (d, J= 17.4 Hz, 1H), 4.588 (d, J= 16.8 Hz, 1H), 1.58-1.51 (m, 36 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.51, 169.49, 169.44, 169.37, 16935, 169.29, 169.25, 169.16, 166.51, 166.48, 166.30, 166.28, 69.39, 69.16, 69.10, 69.06, 68.96, 68.94, 68.93, 68.92, 60.74, 60.71, 16.75, 16.69, 16.68, 16.67, 16.64, 16.56, 16.54; SEC (THF): M_n – 8.5 kDa, M_w – 11.5 kDa, PDI – 1.4; Thermal (DSC): *ppt:* T_g – 51 °C, *annealed film (85 °C for 24 h):* T_{g1} – 50 °C, T_{g2} – 53 °C.



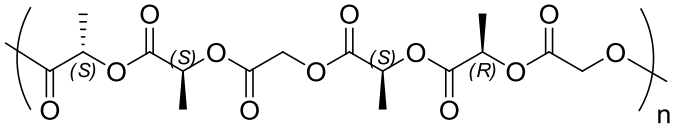
Poly LL$_{rac}$LG *rmsx-26b:* A white solid was collected (0.44 g, 71%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.23-5.10 (m, 12H) [J-Resolved spectra (600 MHz, $CDCl_3$) δ 5.207 (3H), 5.196 (1H), 5.175 (2H), 5.167 (2H), 5.154 (1H), 5.142 (3H)], 4.858 (d, J= 16.2 Hz, 2H), 4.831 (d, J= 16.2 Hz, 1H), 4.825 (d, J= 16.2 Hz, 1H), 4.628 (d, J= 16.2 Hz, 1H), 4.608 (d, J=16.2 Hz, 1H), 4.606 (d, J= 17.4 Hz, 1H), 4.589 (d, J= 16.8 Hz, 1H), 1.58-1.51 (m, 36 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.51, 169.47, 169.45, 169.38, 16934, 169.16, 169.14, 166.54, 166.49, 166.34, 166.28, 69.46, 69.44, 69.23, 69.17, 69.14, 69.05, 69.02, 68.92, 60.75, 16.69, 16.67, 16.65, 16.61, 16.57; SEC (THF): M_n – 32.9 kDa, M_w – 51.5 kDa, PDI – 1.6; Thermal (DSC): *ppt:* T_g – 54 °C, *annealed film (85 °C for 24 h):* T_{g1} – 50 °C, T_{g2} – 53 °C.



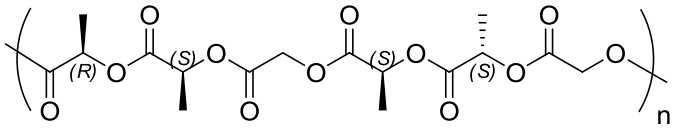
Poly L$_{rac}$LLG *rmsix-24b:* A white solid was collected (0.67 g, 61%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.23-5.10 (m, 12H) [J-Resolved spectra (600 MHz, $CDCl_3$) δ 5.202 (4H), 5.187 (1H), 5.179 (2H), 5.170 (2H), 5.160 (1H), 5.151 (2H)], 4.860 (d, J= 15.6 Hz, 1H), 4.856 (d, J= 16.2 Hz, 1H), 4.790 (d, J= 16.2 Hz, 1H), 4.785 (d, J= 16.2 Hz, 1H), 4.687 (d, J= 16.2 Hz, 1H), 4.677 (d, J=16.2 Hz, 1H), 4.591 (d, J= 17.4 Hz, 1H), 4.588 (d, J= 16.8 Hz, 1H), 1.58-1.51 (m, 36 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.51, 169.44, 169.38, 169.24, 169.17, 169.16, 166.49, 166.46, 166.42, 69.15, 69.06, 68.91, 60.76, 16.73, 16.68, 16.65, 16.57; SEC (THF): M_n – 11.7 kDa, M_w – 16.2 kDa, PDI – 1.4; Thermal (DSC): *ppt:* T_g – 51 °C, *annealed film (85 °C for 24 h):* T_{g1} – 50 °C, T_{g2} – 53 °C.



Poly $L_{rac}L_{rac}LG$ *rmsx-19b:* A white solid was collected (0.48 g, 68%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.24-5.10 (m, 3H), 4.90-4.75 (m, 1H), 4.71-4.55 (m, 1H), 1.58-1.51 (m, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.52, 169.47, 169.41, 169.39, 169.35, 169.27, 169.26, 169.24, 169.17, 169.15, 169.09, 166.55, 166.51, 166.46, 166.42, 166.34, 166.31, 166.29, 69.47, 69.44, 69.43, 69.38, 69.31, 69.24, 69.15, 69.12, 69.10, 69.07, 69.04, 69.02, 68.97, 68.92, 60.76, 60.74, 60.72, 16.76, 16.74, 16.72, 16.70, 16.66, 16.62, 16.57; SEC (THF): M_n – 32.3 kDa, M_w – 58.9 kDa, PDI – 1.8; Thermal (DSC): *ppt:* T_g – 53 °C, *annealed film (85 °C for 24 h):* T_{g1} – 49 °C, T_{g2} – 52 °C.



Poly LLGLL_RG *rmsviii-75b:* A white solid was collected (0.43 g, 70%). ^{1}H NMR (700 MHz, $CDCl_3$) δ 5.22 (q, J= 7.0 Hz, 1H), 5.215 (q, J= 7.2 Hz, 1H), 5.18 (q, J= 7.0 Hz, 2H), 4.85 (d, J= 16.1 Hz, 1H), 4.81 (d, J= 16.1 Hz, 1H), 4.63 (d, J= 16.1 Hz, 1H), 4.61 (d, J= 16.1 Hz, 1H), 1.57 (d, J= 7.0 Hz, 3H), 1.56 (d, J= 7.7 Hz, 6H), 1.53 (d, J= 7.0 Hz, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 169.36 (2), 169.32, 169.1, 166.5, 166.3, 69.4, 69.2, 69.1, 60.77, 60.75, 16.74, 16.70, 16.66, 16.62; SEC (THF): M_n – 30.0 kDa, M_w – 42.0 kDa, PDI – 1.4; SEC ($CHCl_3$): M_n – 32.0 kDa, M_w – 47.4 kDa, PDI – 1.5; Thermal (DSC): *ppt:* T_g – 52 °C, *annealed film (85 °C, 3 h)*: T_g – 48 °C.



Poly L$_R$LGLLG *rmsix-9b:*A white solid was collected (0.36 g, 63%). ^{1}H NMR (700 MHz, $CDCl_3$) δ 5.221 (q, J= 7.0 Hz, 1H), 5.212 (q, J= 7.0 Hz, 1H), 5.187 (q, J= 7.0 Hz, 1H), 5.182 (q, J= 7.0 Hz, 1H), 4.818 (d, J= 16.1 Hz, 1H), 4.785 (d, J= 16.1 Hz, 1H), 4.686 (d, J= 16.1 Hz, 1H), 4.613 (d, J= 16.8 Hz, 1H), 1.571 (d, J= 7.0 Hz, 3H), 1.554 (d, J= 7.0 Hz, 3H), 1.548 (d, J= 7.0 Hz, 3H), 1.528 (d, J= 7.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.5, 169.3, 169.2, 169.1, 166.5, 166.3, 69.3, 69.2 (2), 69.0, 60.8, 16.71 (2), 16.68, 16.65; GPC (THF): M_n – 30.1 kDa, M_w – 41.2 kDa, PDI 1.4; GPC ($CHCl_3$): M_n – 39.8 kDa, M_w – 52.7 kDa, PDI – 1.3; Thermal (DSC): *ppt:* T_g – 52 °C, *annealed film (85 °C, 3 h)*: T_g – 48 °C.

3.0 UNIFORM FUNCTIONALITY – INCORPORATION OF PENDANT HYDROXYL GROUPS IN PLGA RSCS

Sections 3.1 – 3.3 of this chapter are the pre-peer reviewed version of the following article: Stayshich, R. M.; Weiss, R. M.; Li, J.; Meyer, T. Y.; "Periodic Incorporation of Pendant Hydroxyl Groups in Repeating Sequence PLGA Copolymer" *Macromol. Rapid Commun.* **2011**, *32*, 220-225.

3.1 ABSTRACT

A series of repeating sequence poly(lactic-*co*-glycolic acid) copolymers (RSC PLGAs) has been prepared with the precise incorporation of a pendant benzyl-ether substituted monomer derived from serine. Copolymers were synthesized from the assembly of sequence-specific, stereopure dimeric and trimeric segmers of lactic, glycolic and (*S)*-3-benzyloxy-2-hydroxypropionic acids with controlled and varied tacticities. Deprotection of the hydroxyl groups was accomplished by catalytic hydrogenolysis to yield highly functionalized, hydrophilic polyesters. The ^{1}H and ^{13}C NMR spectra for all of the copolymers were consistent with sequence and stereochemical retention and lacked the signal broadening that is inherent with more random copolymers.

3.2 INTRODUCTION

The creation of polymers with a high degree of sequence- and/or stereo-control represents an exciting new frontier in materials science.[1,8,13,19,30,56,130-132] The potential value of sequence in synthetic polymers can be seen in Nature's example: exact sequences of a limited number of monomeric building blocks combine to produce complex macromolecules whose function matches precisely to need. Further encouragement in the pursuit of sequence control can be found in the amazing benefits that have been derived from the significant but limited microstructure control that has been accomplished in conventional polymer architectures e.g. block copolymers and isotactic polypropylenes.[133-136]

We report herein the synthesis and characterization of repeating sequence copolymers (RSCs) of (*S*)-lactic, (*R*)-lactic, glycolic and (*S*)-2,3-dihydroxypropionic acids and their post-polymerization functionalization. Our strategy for producing these RSCs involves the assembly by condensation polymerization of pre-formed segmers comprising exact sequences of the monomers. Our group is generally interested in the synthesis and study of repeating sequence copolymers and has been active in examining the possible benefits of sequence in the design of materials. Previously, we have reported the preparation of the closely related RSCs of lactic and glycolic acids and described in detail the NMR analysis of the microstructures of these copolymers.[1] We have also synthesized and examined the role of sequence in the properties of fluorescent copolymers bearing sequences of fluorene and methylene units.[56]

Although the idea of incorporating a monomer bearing a reactive side chain into PLA systems is not a new one, the typical ring-opening approach does not offer the advantages of copolymer uniformity and monomer generality that are inherent in the condensation-based synthesis that we use in the production of RSCs described in this paper. Researchers in the field

of biomaterials have recognized and in many cases realized the benefits of being able to post-modify a biodegradable and bioassimilable polymer with side chains that tailor the polymers for use in specific tissue engineering and drug delivery applications.[14,137-141] In the case of PLAs, the typical synthesis of the side-chain bearing polymers is accomplished by the ring-opening polymerization (ROP) of the cyclic lactide monomer with lactide/glycolide derivatives, esteramides, or *N*-carboxyanhydrides.[142-145] These polymerizations, however, produce random copolymers whose microstructure is governed only loosely by the reactivity ratios of the monomers. For some applications the likely non-uniform distribution of the functional groups could interfere with polymer application e.g. RGD groups added to promote cell adhesion could be concentrated in some areas of a scaffold and absent in others. RSCs, produced using a condensation strategy will, in contrast, give a more evenly distributed functionality. Generality is also an important benefit of our condensation strategy. Although the serine-derived comonomer described in this paper can be introduced using ROP,[143,144,146] ROP monomers are generally a limited pool and small changes in substituents can limit activity and degree of incorporation.[147] Comonomer choice for the condensation approach described herein, in contrast, is limited only by stability of the monomer to the deprotection and mild coupling conditions used. It is of course true that there are potential drawbacks to using a condensation approach including lower molecular weights, a more difficult synthesis, and poor control of molecular weight. Although these are valid concerns and will have an impact on the ultimate utility of RSCs for specific applications, we believe the potential advantages of exact tailoring of sequence to function justify the synthesis and examination of RSC properties relative to their random analogues.

3.3 RESULTS AND DISCUSSION

3.3.1 Naming conventions

Compounds, segmers and polymers are named using the abbreviations listed in Table 12 such that a polymer of the segmer **LS*(Bn)G** will be named **poly LS*(Bn)G**. Similar to peptides, the monomers comprising a segmer are listed in sequence order from the *C*-side to the *O*-side; terminal protecting groups are specified when present. The dihydroxypropionic acid monomer is abbreviated with the symbol S* due to the near homology of the monomer with the amino acid serine.

Table 12. Naming Convention for Segmers and Polymers

Symbol	Definition
L	L-Lactic acid unit (*S* configuration)
L_R	D-Lactic acid unit (*R* configuration)
G	Glycolic acid unit
S*(Bn)	*S*-3-Benzyloxy-2-hydroxypropionic acid unit
S*(OH)	*S*-2,3-dihydroxypropionic acid unit
Bn	Terminal benzyl protecting group
SiR_3	Terminal silyl protecting group (*tert*-butyldiphenylsilyl group-TBDPS)

3.3.2 Synthesis

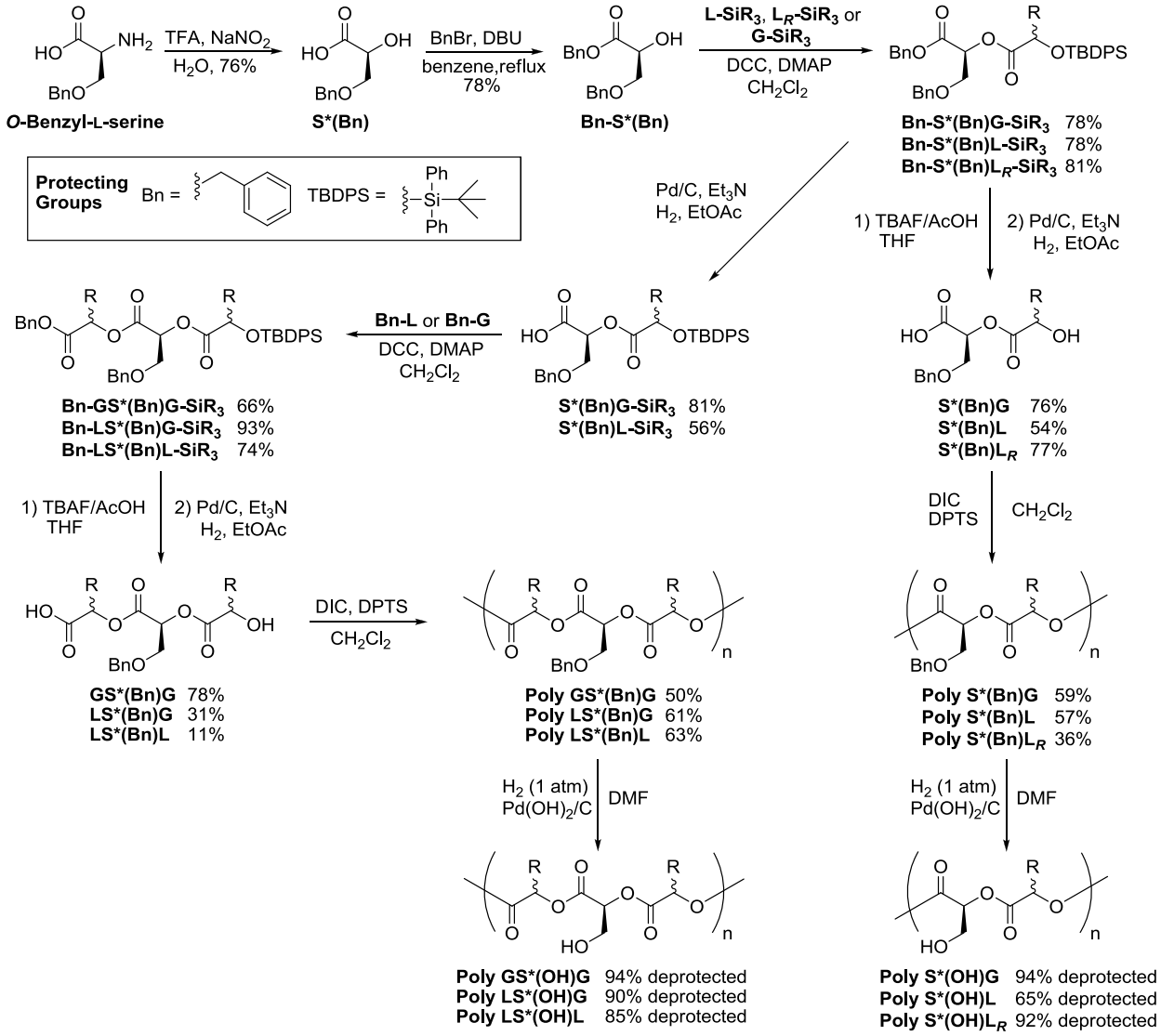
Segmers were assembled in a convergent fashion by reacting partly protected subunits to form completely protected products which, after subsequent deprotection of both termini, yielded the desired segmers as α-hydroxy carboxylic acids. In contrast with our earlier work which focused

on simple PLGAs,[1] in this investigation we have incorporated pendant functionality from the serine-derived **S*(Bn)** monomer. Following procedures developed by the Kelly and Weck groups,[143,146,148] **S*(Bn)** was prepared by diazotization and hydrolysis of the commercially available *O*-benzyl-L-serine in 76% yield (Scheme 8). Protection of the carboxylic acid was accomplished by treatment of **S*(Bn)** with benzyl bromide in the presence of a sterically hindered base to give **Bn-S*(Bn)** in a 78% yield. The di-protected monomer was coupled with a series of silyl-protected lactic and glycolic acids to give dimers **Bn-S*(Bn)G-SiR$_3$**, **Bn-S*(Bn)L-SiR$_3$**, and **Bn-S*(Bn)L$_R$-SiR$_3$** in 78-81% yields. Trimeric segmers were accessed by selective deprotection of the terminal benzyl group using catalytic hydrogenation to give **S*(Bn)G-SiR$_3$** and **S*(Bn)L-SiR$_3$** in 81 and 56% yields, respectively.[149] Coupling with benzyl-lactate (**Bn-L**) or benzyl-glycolate (**Bn-G**) gave trimers **Bn-GS*(Bn)G-SiR$_3$**, **Bn-LS*(Bn)G-SiR$_3$**, and **Bn-LS*(Bn)L-SiR$_3$** in yields of 66-93%. Subsequent removal of the terminal protecting groups gave segmers **S*(Bn)G**, **S*(Bn)L**, **S*(Bn)L$_R$**, **GS*(Bn)G**, **LS*(Bn)G**, and **LS*(Bn)L** in yields of 50-75% in most cases. These segmers exhibit lower stabilities than observed in the simple PLGA RSCs; small differences in deprotection/isolation conditions gave lower yields for some preparations.

Polymerization of the segmers was accomplished utilizing mild esterification reagents 1,3 diisopropylcarbodiimide (DIC) and 4-(dimethylamino)pyridinium *p*-toluenesulfonate (DPTS) as we have previously reported for PLGA RSC synthesis.[1] After 3 h, the number average molecular weight (M_n) of the polymers, as determined by size exclusion chromatography (SEC), ranged from 9.3 to 42.2 kDa in THF and 36.7 to 88.2 kDa in DMF (Table 13). M_ns, although modest in some cases, are comparable to similarly functionalized random copolymers synthesized from cyclic dimers.[143,146,150] The glass transition temperatures (T_g) of the protected polymers ranged

between 21 and 36 °C (Table 13), which are slightly higher than the T_gs reported for random functionalized copolymers with similar monomer ratios. [143,146,150]

Removal of the benzyl functional group was challenging. Under the majority of common catalytic hydrogenolysis conditions including 1, 3 or 6 atm of hydrogen, a range of catalysts (Pd/C, $Pd(OH)_2/C$, or $PdCl_2$/Pd black) and a variety of solvents (ethyl acetate, methylene chloride, acetic acid or THF), no deprotection was observed.[143,145,146,150,151] Only in DMF was the deprotection viable.[152] We hypothesize that DMF promotes the hydrogenolysis by optimal solvation of both the relatively non-polar benzyl-protected polymer and the considerably more polar poly(hydroxyl) product and/or by providing the minimum activation enthalpy between the benzyl-protected polymers and the more polar transition state. Deprotection reactions gave nearly quantitative yields with deprotection rates generally >85% except in the case of **poly S*(OH)L**.



Scheme 8. Functional PLGA RSC synthesis

Table 13. Protected and deprotected PLGA RSC characterization data

		THF		DMF		
Polymer	Yield %[a]	M_n (kDa)[b]	PDI[b]	M_n (kDa)[c]	PDI[c]	Tg (°C)[d]
S*(Bn)G	59	31.4	1.7	60.2	1.3	32.1
S*(Bn)L	57	10.0	1.7	36.8	1.2	30.0
S*(Bn)LR	36	9.3	1.6	39.1	1.2	21.3
GS*(Bn)G	50	10.2	1.5	40.1	1.2	30.0
LS*(Bn)G	61	42.2	2.6	88.2	2.1	36.1
LS*(Bn)L	63	21.3	1.7	50.8	1.3	29.0
S*(OH)G	94[e]	-[f]	-[f]	19.9	1.1	-
S*(OH)L	65[e]	-[f]	-[f]	17.7	1.1	-
S*(OH)LR	92[e]	-[f]	-[f]	24.1	1.1	-
GS*(OH)G	94[e]	-[f]	-[f]	19.8	1.1	-
LS*(OH)G	90[e]	-[f]	-[f]	19.9	1.1	-
LS*(OH)L	85[e]	-[f]	-[f]	47.5	1.2	-

[a]Isolated as ppt; [b]Determined by SEC (THF, 30 °C) relative to PS standards; [c]Determined by SEC (DMF, 50 °C) relative to PS standards; [d] Determined by DSC, transitions were measured in second heating cycle; [e]Percentage deprotection as determined by ^{1}H NMR spectroscopy [f] Polymer was not sufficiently soluble in THF for SEC analysis.

3.3.3 Microstructural Analysis.

Consistent with our observations in PLGA RSCs, the RSC polymers bearing both the protected and deprotected pendant alcohol groups exhibit sharp NMR resonances that are highly sequence dependent. The ^{1}H NMR spectra for **poly S*(Bn)G** and **poly S*(OH)G** are shown in Figure 33. It should be noted that due to the extreme differences in solubilities, the NMR data for the benzyl-protected polymers were obtained in $CDCl_3$ while those of the hydrophilic deprotected polymers were obtained in d_6-DMSO. Of particular note is the lack of peak broadening that is typically observed in random copolymers. Even for the case of **poly LS*(Bn)G** which exhibits an SEC molecular weight of >40 kDa in THF and >80 kDa in DMF (relative to PS standards), the resonances are surprisingly narrow and well-resolved.

The NMR data for the protected copolymers establishes that there is a nearly complete preservation of sequence and stereochemistry in the synthesis and that differences in tacticity are readily visible. In the case of simple PLGAs, we had previously reported the unique sensitivity of the diastereotopic methylene protons of the G monomers to the stereochemical environment.[1] In RSCs bearing S*(Bn) units we find that the two diastereotopic methylene groups in the pendant side chain are similarly sensitive to tacticity. There is, for example, a dramatic difference in the ^{1}H NMR spectra for the isotactic **poly S*(Bn)L** and the syndiotactic **poly S*(Bn)L$_R$** (Figure 34)**.** The chemical shifts of the geminal protons of the two sets of diastereotopic methylene groups are well separated in the case of the syndiotactic polymer (Δ > 0.11 ppm) whereas the resonances for the geminal protons of the isotactic polymer are not cleanly resolved. The sensitivity of the chemical shifts of these diastereotopic protons (and those of the G groups when present) makes it possible to conclude that scrambling and/or epimerization are not significant in these polymers.

The NMR data for the deprotected copolymers also shows dependence on both structure and stereochemistry although the remaining diastereotopic methylene protons of the S*(OH) group are not as sensitive to environment. It is not clear if the decreased sensitivity is due to a diminishment of sequence/stereochemical control of conformation by the smaller alcohol group relative to the benzyl or if this effect is primarily due to stronger solvation, with a resulting "denaturation", by the DMSO solvent. The incomplete deprotection of the polymers can be seen not only in the presence of resonances for the remaining benzyl groups but also in the appearance of signals for multiple "sequences" in the same polymer e.g. …**S*(OH)GS*(Bn)GS*(OH)GS*(OH)G**…

The ^{13}C NMR spectra also verify the retention of sequence and stereochemistry in the polymer synthesis. Curiously, the chemical shift range for the C=O peak of the S* units falls into the range of chemical shifts associated with G units (δ166-7) rather than in the L range (δ169-71).

3.3.4 Conclusion

We have prepared a series of copolymers of glycolic, lactic and benzyl-protected 2,3-dihydroxypropionic- acids. Deprotection by hydrogenolysis produced hydrophilic PLGA-type copolymers bearing evenly distributed pendant alcohol groups. Future work will focus on chemical modification by attachment of drugs or cell adhesion/growth functionalities

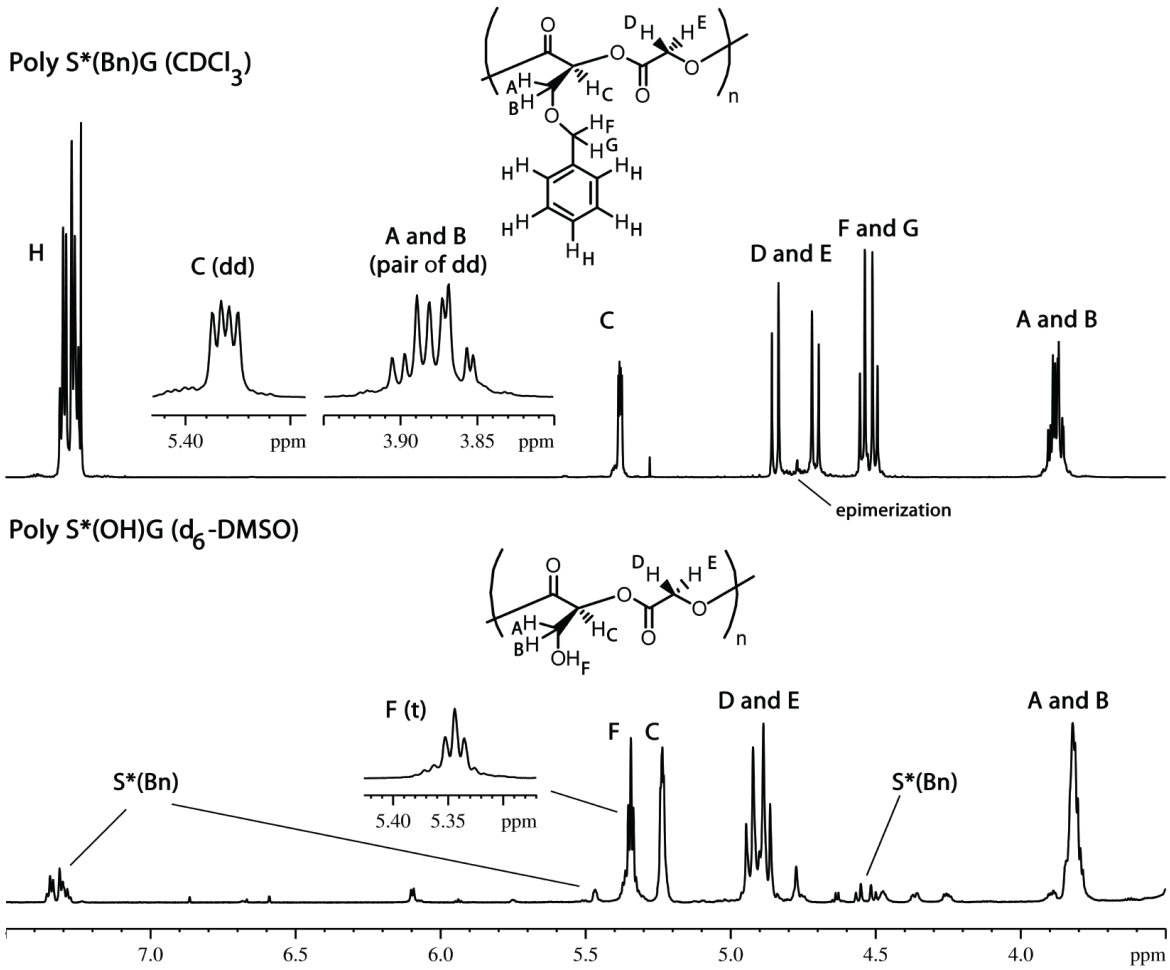


Figure 33. ^{1}H NMR spectra of **poly S*(Bn)G** in $CDCl_3$ (top) and **poly S*(OH)G** in d_6-DMSO (bottom, 94% deprotected) at 700 MHz.

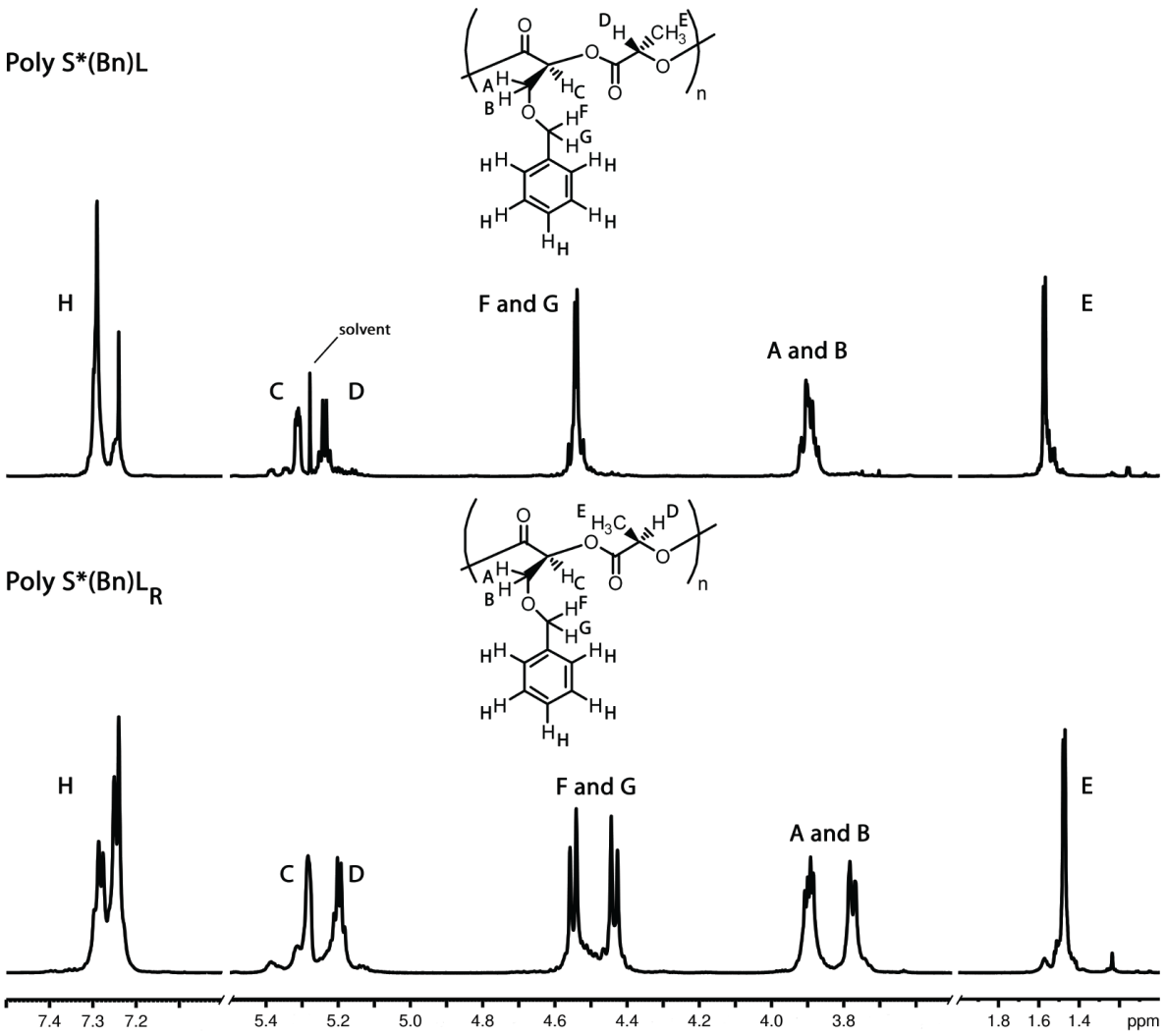


Figure 34. ^{1}H NMR spectra of **poly S*(Bn)L** (top) and **poly S*(Bn)L$_R$** at 700 MHz in $CDCl_3$.

3.4 EXTENDED RSC ASSEMBLY AND CHARACTERIZATION

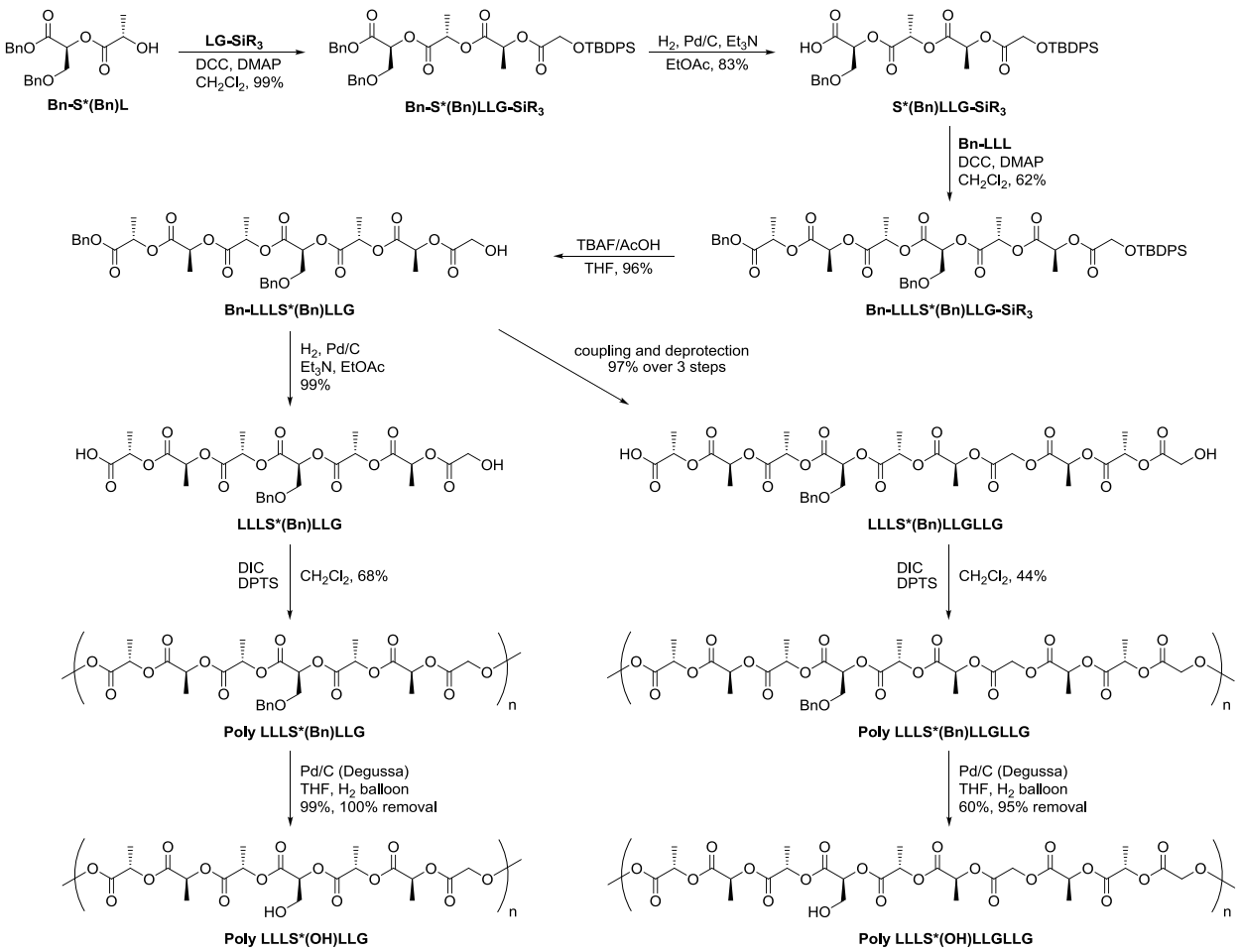
Following the publication of the manuscript focused on highly functionalized dimeric and trimeric PLGA RSCs,[153] heptameric and decameric RSCs were assembled to investigate the effect of functionality and sequence length on solubility and thermal properties. Starting from dimers **Bn-S*(Bn)L** and **GL-SiR$_3$**, tetramer **Bn-S*(Bn)LLG-SiR$_3$** was prepared in 99% yield (Scheme 9). Removal of the benzyl ester by hydrogenolysis followed by subsequent coupling of **Bn-LLL** gave heptamer **Bn-LLLS*(Bn)LLG-SiR$_3$** in 51% yield over 2 steps. Decamer **Bn-LLLS*(Bn)LLGLLG-SiR$_3$** was assembled in 2 steps from the heptamer by silyl-deprotection then coupling with **LLG-SiR$_3$** in 95% yield over those 2 steps. Deprotection of the terminal protecting groups gave segmers **LLLS*(Bn)LLG** and **LLLS*(Bn)LLGLLG** in 95% and 98% yields respectively.

Polymerization utilizing the standard DIC/DPTS conditions gave **poly LLLS*(Bn)LLG** and **poly LLLS*(Bn)LLGLLG** in 68% and 44% yields respectively. The M_ns for both polymers approached 41.0 kDa in THF (Table 14). Microstructural analysis by ^{1}H and ^{13}C NMR spectroscopy confirmed sequence fidelity even at the heptamer and decamer segmer length. The T_g for both polymers was much higher than the dimeric and trimeric RSCs at 50.0 °C and 52.0 °C respectively.

Table 14. Protected and deprotected heptamer and decamer RSC characterization data

Polymer	Yield %[a]	Mn (kDa)[b] THF	PDI[b]	Tg (°C)[c]
LLLS*(Bn)LLG	68	40.9	1.2	50.0
LLLS*(Bn)LLGLLG	44	41.5	1.6	52.0
LLLS*(OH)LLG	100[d]	39.9	1.2	53.0
LLLS*(OH)LLGLLG	95[d]	35.4	1.3	-

[a]Isolated as ppt; [b]Determined by SEC (THF, 30 °C) relative to PS standards; [c]Determined by DSC, transitions were measured in second heating cycle; [d]Percentage deprotection as determined by ^{1}H NMR spectroscopy.



Scheme 9. Synthesis of heptameric and decameric PLGA RSCs

While not available during the preparation of the manuscript, removal of the pendant benzyl ether was possible under standard hydrogenolysis conditions, 1 atm. hydrogen and THF, utilizing Degussa (E101 NE/W, wet) Pd/C (10% w/w Pd), avoiding the use of DMF.[145,153,154] Deprotection gave **poly LLLS*(OH)LLG** in nearly quantitative yield with complete removal of the benzyl group. The yield for **poly LLLS*(OH)LLGLLG** was less (60%) but > 95% of the benzyl groups had been removed. Further optimization could improve both yields. Due to the sequence length, increased L content and decreased functional comonomer loadings (15% and 10%), the resulting hydroxyl RSCs were soluble in organic solvents, i.e. THF and $CDCl_3$. While the M_ns of the dimer and trimer derived hydroxyl RSCs varied greatly from the benzyl RSCs, the heptamer and decamer hydroxyl RSCs were similar to that of the benzyl protected derivatives (Figure 35). The difference in M_ns could be attributed to the benzyl protecting group having more influence on the R_g at high comonomer loadings. While degradation of the polymer is possible in DMF, there were no visible degradation byproducts in the ^1H and ^{13}C NMR spectra of **poly LLLS*(OH)LLG** and **LLLS*(OH)LLGLLG**. The T_g for **poly LLLS*(OH)LLG** increased by 1 °C, 53 °C, from the benzyl protected analog.

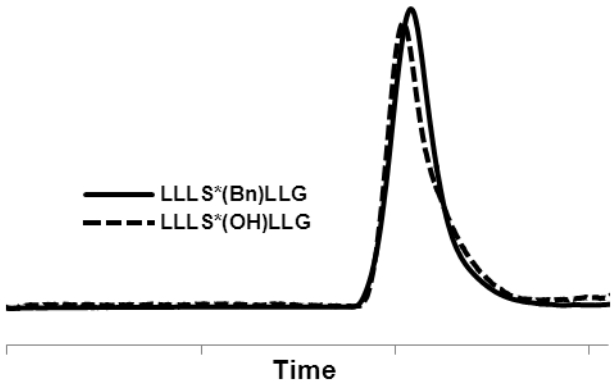
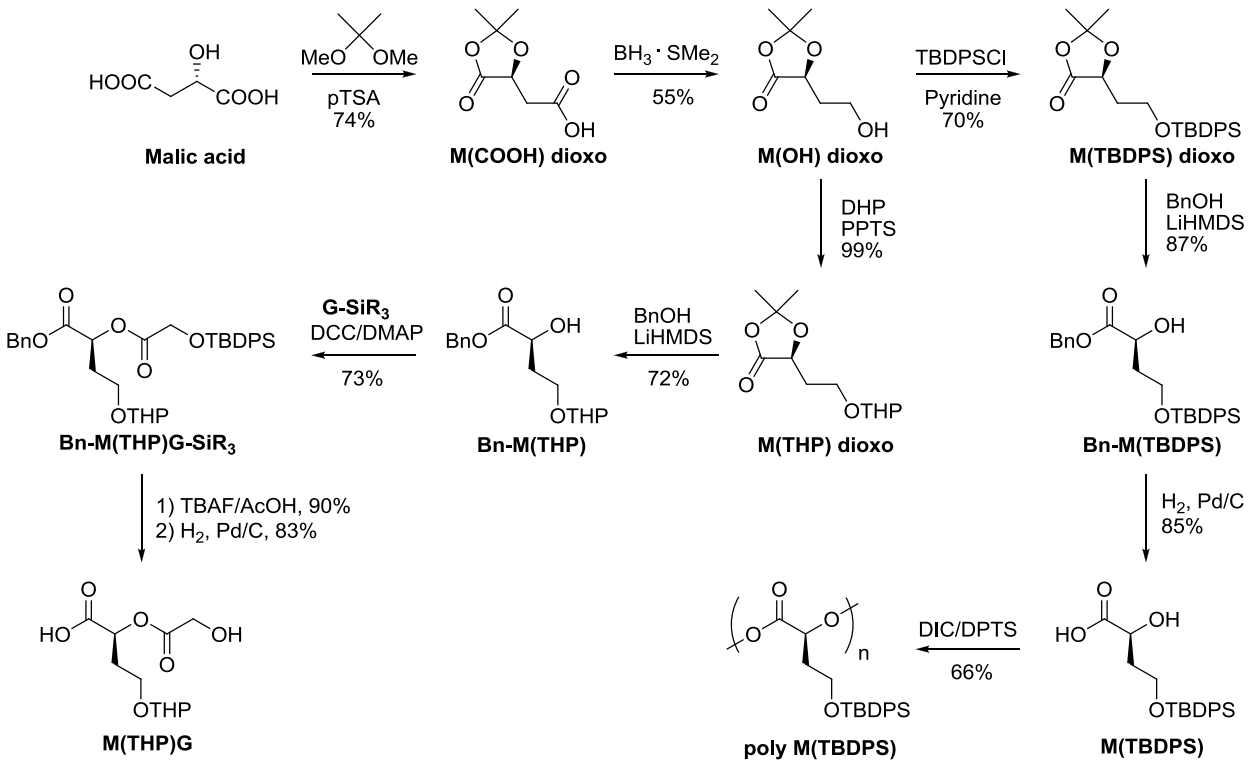


Figure 35. SEC trace of **poly LLLS*(Bn)LLG** and **poly LLLS*(OH)LLG** in THF

3.5 MALIC ACID DERIVED MONOMERS

3.5.1 RSC Assembly and Characterization

Malic acid is an attractive multifunctional monomer that, unlike the serine derived S*(Bn), is more amenable to synthetic variation and functional group manipulation. Following procedures by Denmark and Yang,[155] L- malic acid was treated with 2,2-dimethoxypropane and pTSA to give dimethyl dioxolanone **M(COOH) dioxo** in 74% yield (Scheme 10). Although this pendant carboxylic acid has been utilized, after addition of a protecting group, to prepare functionalized α-hydroxy based cyclic diesters and β-malolactonates for ROP,[156-158] differentiation between protected esters necessary in SAP is difficult. The carboxylic acid was reduced to an alcohol using BH_3•SMe_3 to give **M(OH) dioxo** in 55% yield followed by protection utilizing TBDPSCl with pyridine to give **M(TBDPS) dioxo** in 70% yield and the near quantitative THP protection with dihydropyran and pyridinium *p*-toluenesulfonate to give **M(THP) dioxo**. Both dioxolanones were ring-opened by benzyl alcohol treated with LiHMDS to give di-protected monomers **Bn-M(TBDPS)** and **Bn-M(THP)** in 87% and 72% yields respectively. Removal of the benzyl group gave segmer **M(TBDPS)** in 85% while **M(THP)G** was assembled in 55% yield overall following coupling and deprotection reactions. **Poly M(TBDPS)** was prepared using standard DIC/DPTS conditions in 66% yield with an M_n of 11.0 kDa and PDI of 2.0. **Poly M(THP)G** was not prepared, the THP decomposed due to exposure to the slightly acidic DPTS. Deprotection of **poly M(TBDPS)** was not attempted.



Scheme 10. Malic acid derived intermediates and polymer.

3.5.1.1 Conclusion

Although these initial attempts at malic acid derived functional PLGA RSCs were limited, the synthetic methodology presented is rather elegant and could provide a means to incorporate different functionalities. Further development and protecting group selection could enable more advanced functionalized RSCs.

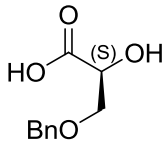
3.6 EXPERIMENTAL SECTION

Materials. *O*-Benzyl-L-Serine was purchased from AAPPTec and used without further purification. L-Malic acid was purchased from Acros and used without further purification. Segmers and RSCs were assembled according to previously detailed General Procedures reported in Section 2.7. Ethyl acetate and methylene chloride were distilled under nitrogen from calcium hydride. All other reagents were purchased and used without further purification. Column chromatography was performed using EMD 60 Å, 40-63 μm standard grade silica.

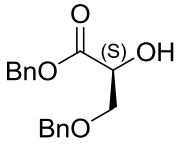
Characterization. ^{1}H (300, 400, 600 and 700 MHz) and ^{13}C (75, 100, 150 and 175 MHz) NMR spectra were recorded with Bruker spectrometers in $CDCl_3$ or d_6-DMSO and calibrated to the residual solvent peaks. 2D NMR HMBC and HETCOR experiments were recorded with a Bruker 700 MHz NMR spectrometer equipped with a 5 mm gradient probe using corresponding gradient pulse sequences. Molecular weights and polydispersities in THF were acquired on a Waters GPC with Jordi 500 Å, 1000 Å and 10000 Å divinylbenzene (DVB) columns at 30 °C and refractive index detector (Waters) calibrated to polystyrene standards. Molecular weights and polydispersities in DMF were acquired on a Waters GPC with Polymer Standard Service (PSS) 105 Å, 103 Å and 102 Å columns at 50 °C and refrective index detector (Waters 2410) calibrated to polystyrene standards. Differential scanning calorimetry (DSC) measurements were performed with a Perkin Elmer Pyris 6 DSC. Standard data were collected with a heating and cooling rate of 10°C/min and data was collected from the second cycle.

3.6.1 Serine Based RSCs

The following experimental section is a detail of my contributions for the publication.[153]



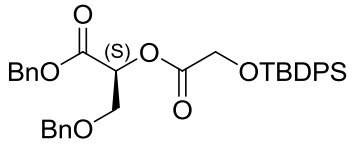
3-Benzyloxy-2-hydroxypropionic acid, S*(Bn) *rmsx-15a:* The α-hydroxy acid was prepared according to procedures reported by Deechongkit and Weck.[143,148] *O*-benzyl-L-serine (10.0 g, 51.0 mmol) was dissolved in 0.7 M aqueous solution of trifluoroacetic acid (100 ml) and cooled on ice. $NaNO_2$ (5.30 g, 76.8 mmol) in water (50 ml) was added slowly over 1.5 h and the reaction mixture was stirred for 3 h at RT. NaCl (10 g) was added and the mixture was extracted with EtOAc (3 x 100 ml). The organic layer was dried with $MgSO_4$ and concentrated *in vacuo*. The resulting residue was placed under vacuum overnight to yield a slightly yellow solid (9.49 g, 95%) without further purification. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.35−7.27 (m, 5H), 4.60 (d, J= 12.6 Hz, 1H), 4.57 (d, J= 12.0 Hz, 1H), 4.36 (dd, J_1=J_2= 4.2 Hz, 1H), 3.81 (dd, J_1 = 9.6 Hz, J_2= 4.2 Hz, 1H), 3.76 (dd, J_1= 10.2 Hz, J_2= 4.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.2, 137.1, 128.5, 128.1, 127.8, 73.7, 70.8, 70.3; MS (ES) m/z: 219 (M+Na).



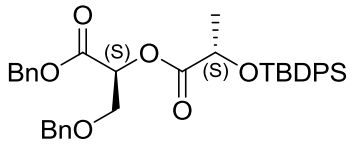
Bn-S*(Bn) *rmsx-16a:* In 150 ml of dry benzene under N_2, **S*(Bn)** (9.48 g, 48.0 mmol) and 1,8-diazobicyclo[5.4.0]undec-7-ene (8.04 g, 53 mmol) were combined and let stir for 15 min. Benzyl bromide (9.03 g, 53 mmol) was added slowly and the reaction mixture was refluxed for 16 h (overnight). After cooling, the mixture was filtered and washed with 1.0 M HCl (2 x 100 ml) followed by brine (1 x 100 ml). The organic layer was dried with $MgSO_4$ and concentrated *in vacuo*. The concentrate was chromatographed (silica, 10% EtOAc in hexanes) to yield a colorless liquid (10.72 g, 78%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.33-7.23 (m, 10 H*)*, 5.23 (d, J=

12.6 Hz, 1H), 5.20 (d, J= 12.6 Hz, 1H), 4.56 (d, J= 12.0 Hz, 1H), 4.48 (d, J= 12 Hz, 1H), 4.35 (ddd, J_1= 3.0 Hz, J_2= 3.6 Hz, J_3= 6.6 Hz, 1H), 3.78 (dd, J_1= 10.2 Hz, J_2= 3.6 Hz, 1H), 3.74 (dd, J_1= 9.6 Hz, J_2= 3.0 Hz, 1H), 3.10 (d, J= 7.2 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.5, 137.7, 135.1, 128.6, 128.5, 128.4, 128.3, 127.7, 127.6, 73.5, 71.3, 70.9, 67.4; ES-TOF HRMS (M+Na) calc mass 309.1103, found 309.1106.

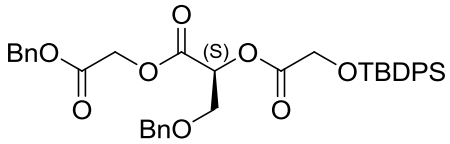
General procedure for DCC/DMAP coupling reactions. 1-1.2 equivalents of TBDPS-acid was combined with 1-1.2 equivalents of benzyl protected alcohol, 1.2 equivalents of DCC and 0.5 equivalents of DMAP. The reaction mixture was let stir at RT for 4 h under N_2 and then filtered to remove dicyclohexylurea. The filtrate was concentrated *in vacuo* and chromatographed (silica, 5-10% EtOAc in hexanes for dimers and 10-15% for trimers).



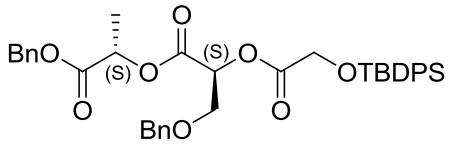
Bn-S*(Bn)G-SiR$_3$ *rmsix-74a:* The product was a colorless liquid (9.58 g, 78%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.65-7.61 (m, 4H), 7.37-7.13 (m, 16H), 5.27 (dd, J_1= 5.4 Hz, J_2= 3.0 Hz, 1H), 5.13 (d, J= 12.0 Hz, 1H), 5.10 (d, J= 12.0 Hz, 1H), 4.46 (d, J= 12.0 Hz, 1H), 4.37 (d, J= 12.0 Hz, 1H), 4.34 (d, J= 16.8 Hz, 1H), 4.28 (d, J= 16.8 Hz, 1H), 3.80 (dd, J_1= 10.8 Hz, J_2= 4.8 Hz, 1H), 3.67 (dd, J_1= 10.8 Hz, J_2= 3.0 Hz, 1H), 1.02 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.6, 167.5, 137.3, 135.6, 135.5, 135.2, 135.1, 134.8, 132.7, 132.6, 129.9, 129.6, 128.5, 128.4, 128.1, 127.8, 127.78, 127.76, 127.7, 127.6, 73.4, 72.2, 68.7, 67.2, 62.0, 26.6, 19.3; ES-TOF HRMS (M+Na) calc mass 605.2335, found 605.2318.



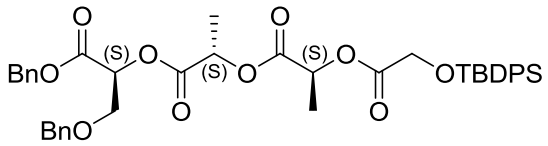
Bn-S*(Bn)L-SiR$_3$ *rmsx-27a:* The product was a colorless liquid (5.79 g, 92%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.74-7.60 (m, 4H), 7.39-7.17 (m, 16H), 5.16 (d, J= 12.0 Hz, 1H), 5.13 (dd, J_1= 4.8 Hz, J_2= 3.0 Hz, 1H), 5.11 (d, J= 12.0 Hz, 1H), 4.47 (d, J= 12.0 Hz, 1H), 4.38 (d, J= 12.0 Hz, 1H), 4.36 (q, J= 6.6 Hz, 1H), 3.79 (dd, J_1= 10.8 Hz, J_2= 4.8 Hz, 1H), 3.52 (dd, J_1= 10.8 Hz, J_2= 3.0 Hz, 1H), 1.38 (d, J= 6.6 Hz, 3H). 1.07 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.1, 167.5, 137.4, 135.9, 135.8, 135.1, 133.4, 133.1, 129.8, 128.7, 128.5, 128.4, 128.3, 127.7, 127.6, 127.5, 73.3, 72.0, 68.6, 68.5, 67.2, 26.8, 21.2, 19.2; ES-TOF HRMS (M+Na) calc mass 619.2492, found 619.2464.



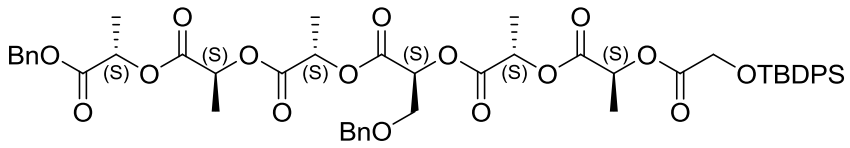
Bn-GS*(Bn)G-SiR$_3$ *rmsix-78a:* The product was a colorless oil (1.71 g, 66%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69-7.66 (m, 4H), 7.43-7.22 (m, 16 H), 5.38 (dd, J_1= 5.6 Hz, J_2= 3.2 Hz, 1H), 5.16 (s, 2H), 4.73 (d, J= 16.0 Hz, 1H), 4.64 (d, J= 16 Hz, 1H), 4.52 (d, J= 12.0 Hz, 1H), 4.47 (d, J= 12.0 Hz, 1H), 4.40 (d, J= 16.8 Hz, 1H), 4.33 (d, J= 16.8 Hz, 1H), 3.84 (dd, J_1= 11.2 Hz, J_2= 5.6 Hz, 1H), 3.80 (dd, J_1= 11.6 Hz, J_2= 3.2 Hz, 1H), 1.07 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 167.1, 166.8, 137.4, 135.6, 135.5, 134.9, 132.7, 129.9, 128.6, 128.5, 128.4, 127.8, 127.7, 73.5, 71.9, 68.6, 67.2, 61.9, 61.3, 26.6, 19.3; ES-TOF HRMS (M+Na): calc mass 663.2390, found 663.2366.



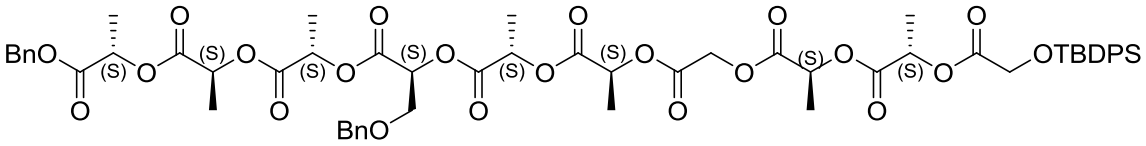
Bn-LS*(Bn)G-SiR$_3$ *rmsix-77a:* The product was a colorless oil (2.46 g, 93%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69-7.66 (m, 4H), 7.43-7.22 (m, 16H), 5.32 (dd, J_1= 6.4 Hz, J_2= 2.8 Hz, 1H), 5.22 (q, J= 7.1 Hz, 1H), 5.14 (d, J= 12.4 Hz, 1H), 5.11 (d, J= 12.4 Hz, 1H), 4.49 (d, J= 12.4 Hz, 1H), 4.45 (d, J= 12.4 Hz, 1H), 4.39 (d, J= 16.8 Hz, 1H), 4.32 (d, J= 16.8 Hz, 1H), 3.83 (dd, J_1= 11.2 Hz, J_2= 2.8 Hz, 1H), 3.77 (dd, J_1= 11.2 Hz, J_2= 6.8 Hz, 1H), 1.51 (d, J= 7.2 Hz, 3H), 1.07 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 169.8, 167.0, 137.5, 135.6, 135.5, 135.1, 132.7, 132.6, 129.9, 128.6, 128.5, 128.3, 128.2, 127.9, 127.8, 127.7, 127.6, 73.4, 72.1, 69.5, 68.7, 67.2, 61.9, 26.6, 19.3, 16.8; ES-TOF HRMS (M+Na): calc mass 677.2547, found 677.2505.



Bn-S*(Bn)LLG-SiR$_3$ *rmsx-30a:* The product was a viscous colorless oil (5.87 g, 99%). ^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.73-7.71 (m, 4H), 7.47-7.28 (m, 16H), 5.36 (dd, J_1= 4.2 Hz, J_2= 2.1 Hz, 1H), 5.27 (q, J= 7.0 Hz, 1H), 5.25 (d, J= 12.6 Hz, 1H), 5.19 (d, J= 11.2 Hz, 1H), 4.63 (d, J= 12.6 Hz, 1H), 4.53 (d, J= 12.6 Hz, 1H), 4.39 (d, J= 16.8 Hz, 1H), 4.33 (d, J= 16.8 Hz, 1H), 3.98 (dd, J_1= 11.2 Hz, J_2= 4.9 Hz, 1H), 3.85 (dd, J_1= 11.2 Hz, J_2= 2.1 Hz, 1H), 1.60 (d, J= 7.0 Hz, 3H), 1.54 (d, J= 7.0 Hz, 3H), 1.12 (s, 9H); ^{13}C NMR ($CDCl_3$, 175 MHz) δ 170.6, 169.9, 169.7, 137.3, 135.6, 135.5, 134.7, 132.7, 129.9, 128.6, 128.5, 128.4, 128.3, 127.8, 127.7, 127.6, 73.4, 72.7, 68.9, 68.5, 68.4, 67.4, 61.9, 26.6, 19.2, 16.7, 16.6.



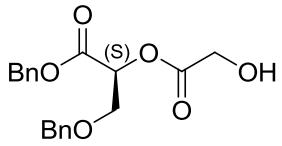
Bn-LLLS*(Bn)LLG-SiR$_3$ *rmsx-32a:* Benzyl protected trimer, **Bn-LLL** (2.30 g, 6.4 mmol) and **S*(Bn)LLG-SiR$_3$** (4.0 g, 6.28 mmol) were combined in 31 mL of dry CH_2Cl_2 under nitrogen. DPTS (0.37 g, 1.26 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI) (1.25 g, 6.5 mmol) were added and the reaction mixture was allowed to stir at RT for 4 h. The reaction mixture was washed with sat $NaHCO_3$ (1 × 30 mL), 1.0 M HCl (1 × 30 mL) and brine (1 × 30 mL). The organic layer was dried with $MgSO_4$ and concentrated *in vacuo*. The concentrate was chromatographed (silica, 5-20% EtOAc in hexanes) to yield a viscous colorless oil (3.66 g, 62%). ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.68-7.65 (m, 4H), 7.41-7.30 (m, 16H), 5.33 (dd, J_1= 5.4 Hz, J_2= 3.0 Hz, 1H), 5.24 (q, J= 7.2 Hz, 1H), 5.177 (q, J= 6.6 Hz, 1H), 5.171 (d, J= 12.0 Hz, 1H), 5.16 (q, J= 7.2 Hz, 1H), 5.124 (q, J= 7.2 Hz, 1H), 5.12 (q, J= 6.6 Hz, 1H), 5.11 (d, J= 12.6 Hz, 1H), 4.59 (d, J= 12.0 Hz, 1H), 4.56 (d, J= 12.0 Hz, 1H), 4.34 (d, J= 16.8 Hz, 1H), 4.28 (d, J= 16.8 Hz, 1H), 3.93 (dd, J_1= 11.4 Hz, J_2= 3.0 Hz, 1H), 3.91 (dd, J_1= 11.4 Hz, J_2= 6.0 Hz, 1H), 1.59 (d, J= 7.2 Hz, 3H), 1.56 (d, J= 6.6 Hz, 3H), 1.50 (d, J= 7.2 Hz, 3H), 1.49 (d, J= 6.6 Hz, 3H), 1.48 (d, J= 6.6 Hz, 3H), 1.07 (s, 9H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 170.6, 170.0, 169.8, 169.7, 169.5, 169.3, 166.8, 137.5, 135.6, 135.5, 135.0, 132.7, 132.6, 129.9, 128.6, 128.5, 128.4, 128.2, 127.8, 127.7, 127.6, 73.4, 72.5, 69.3, 69.2, 68.9, 68.8, 68.4, 67.2, 61.9, 26.6, 19.2, 16.7, 16.5.



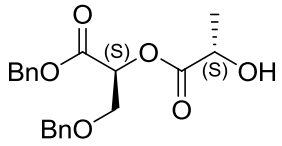
Bn-LLLS*(Bn)LLGLLG-SiR$_3$ *rmsx-36a:* Silyl protected trimer **LLG-SiR$_3$** (0.5 g, 0.91 mmol) and **Bn-LLLS*(Bn)LLG** (0.64 g, 0.91 mmol) were combined in 5 mL dry CH_2Cl_2 under

nitrogen. DPTS (53.0 mg, 0.18 mmol) and EDCI (0.19 g, 1.0 mmol) were added and the reaction mixture was allowed to stir at RT for 4 h. The reaction mixture was worked up similar to **Bn-LLLS*(Bn)LLG-SiR$_3$** and chromatographed (silica, 20-30% EtOAc in hexanes) to yield a viscous colorless oil (1.02 g, 99%). ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.68-7.65 (m, 4H), 7.41-7.30 (m, 16H), 5.33 (dd, J_1= 6.0 Hz, J_2= 3.0 Hz, 1H), 5.23 (q, J= 6.6 Hz, 1H), 5.21 (q, J= 7.2 Hz, 1H), 5.181 (q, J= 7.2 Hz, 1H), 5.171 (d, J= 12.0 Hz, 1H), 5.169 (q, J= 7.8 Hz, 2H), 5.16 (q, J= 6.6 Hz, 1H), 5.124 (q, J= 7.2 Hz, 1H), 5.12 (q, J= 7.2 Hz, 1H), 5.11 (d, J= 12.0 Hz, 1H), 4.85 (d, J= 15.6 Hz, 1H), 4.69 (d, J= 16.2 Hz, 1H), 4.58 (d, J= 12.0 Hz, 1H), 4.56 (d, J= 12.0 Hz, 1H), 4.34 (d, J= 16.8 Hz, 1H), 4.28 (d, J= 16.8 Hz, 1H), 3.93 (dd, J_1= 11.4 Hz, J_2= 3.0 Hz, 1H), 3.90 (dd, J_1= 11.4 Hz, J_2= 5.4 Hz, 1H), 1.58 (d, J= 7.2 Hz, 3H), 1.57 (d, J= 7.2 Hz, 3H), 1.56 (d, J= 6.6 Hz, 3H), 1.54 (d, J= 7.2 Hz, 3H), 1.50 (d, J= 7.2 Hz, 3H), 1.49 (d, J= 7.2 Hz, 6H), 1.06 (s, 9H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 170.6, 169.87, 169.82, 169.6, 169.5(2), 169.3, 169.2, 166.8, 166.5, 137.5, 135.6, 135.5, 135.0, 132.7, 132.6, 129.9, 129.8, 128.6, 128.5, 128.4, 128.2, 127.8, 127.7, 127.6, 73.4, 72.5, 69.3, 69.2, 69.1, 69.0, 68.8, 68.4, 67.2, 61.9, 60.7, 26.6, 19.2, 16.73, 16.70(4), 16.6, 16.5.

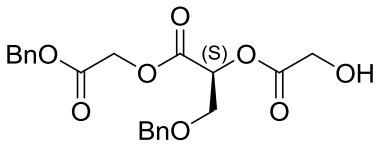
General Procedure for Silyl-deprotection. For primary alcohols, 1.5 equivalents of tetra-n-butylammonium floride (TBAF) (1.0 M in THF) buffered by 8 equiv of acetic acid was added to the di-protected oligomer in dry THF. The reaction mixture was allowed to stir for 1 h and then poured into brine. The product was extracted using Et_2O, dried with $MgSO_4$ and concentrated *in vacuo*. The concentrate was chromatographed (silica, 15-40% EtOAc in hexanes). For secondary alcohols, 1.5 equiv of TBAF was buffered with 1.8 equivalents of acetic acid.



Bn-S*(Bn)G *rmsix-71a:* The product was a colorless liquid (2.26 g, 87%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.22 (m, 10H), 5.39 (dd, J_1= 4.8 Hz, J_2= 2.4 Hz, 1H), 5.21 (d, J= 12.4 Hz, 1H), 5.17 (d, J= 12.4 Hz, 1H), 4.56 (d, J= 12.4 Hz, 1H), 4.48 (d, J= 12.0 Hz, 1H), 4.32 (dd, J_1= 17.2 Hz, J_2= 4.8 Hz, 1H), 4.26 (dd, J_1= 17.2 Hz, J_2= 5.2 Hz, 1H), 3.91 (dd, J_1= 10.8 Hz, J_2= 5.2 Hz, 1H), 3.80 (dd, J_1= 10.8, J_2= 2.4 Hz, 1H), 2.44 (t, J= 5.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7, 167.2, 137.1, 134.9, 128.6, 128.5, 128.4, 128.2, 127.9, 127.7, 73.5, 72.7, 68.4, 67.5, 60.5; ES-TOF HRMS (M+Na) calc mass 367.1158, found 367.1133.

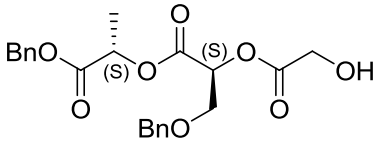


Bn-S*(Bn)L *rmsx-28a:* The product was a colorless liquid (2.93 g, 89%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.28 (m, 10H), 5.41 (dd, J_1= 5.2 Hz, J_2= 2.4 Hz, 1H), 5.26 (d, J= 12.0 Hz, 1H), 5.20 (d, J= 12.4 Hz, 1H), 4.63 (d, J= 12.4 Hz, 1H), 4.55(d, J= 12.0 Hz, 1H), 4.32 (q, J= 7.2 Hz, 1H), 3.98 (dd, J_1= 11.2 Hz, J_2= 5.6 Hz, 1H), 3.86 (dd, J_1= 11.2 Hz, J_2= 2.8 Hz, 1H), 2.77 (br s, 1H), 1.50 (d, J= 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.3, 167.4, 137.5, 135.1, 128.8, 128.7, 128.6, 128.5, 128.4, 128.1, 127.8, 73.6, 73.0, 68.7, 67.7, 66.9, 20.7; HRMS (M+Na) calc mass 381.1314, found 381.1300.

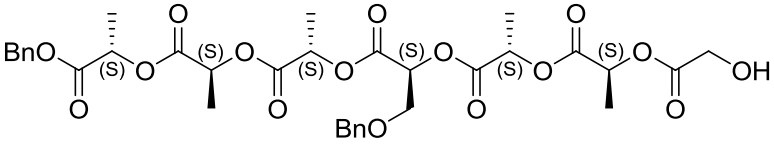


Bn-GS*(Bn)G *rmsix-80a:* The product was a colorless liquid (0.92 g, 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.28 (m, 10H), 5.45 (dd, J_1= 5.2 Hz, J_2= 3.2 Hz, 1H), 5.18 (d, J= 12.4 Hz,

1H), 5.15 (d, J= 12.0 Hz, 1H), 4.75 (d, J= 15.6 Hz, 1H), 4.67 (d, J= 15.6 Hz, 1H), 4.57 (d, J= 12.4 Hz, 1H), 4.52 (d, J= 12.0 Hz, 1H), 4.31 (d, J= 17.2 Hz, 1H), 4.25 (d, J= 17.6 Hz, 1H), 3.90 (dd, J_1= 11.2 Hz, J_2= 5.6 Hz, 1H), 3.86 (dd, J_1= 11.2 Hz, J_2= 3.6 Hz, 1H), 2.45 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 166.8, 166.7, 137.2, 134.8, 128.6, 128.5, 127.9, 127.7, 73.5, 72.5, 68.3, 67.3, 61.4, 60.5; ES-TOF HRMS (M+Na) calc mass 425.1212, found 425.1211.

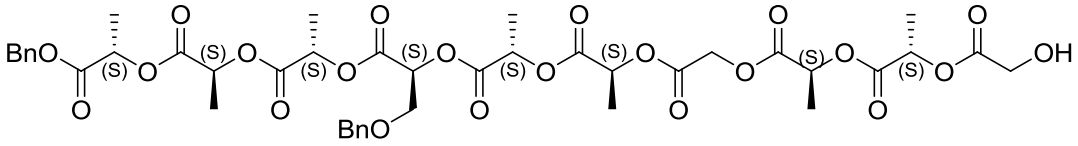


Bn-LS*(Bn)G *rmsix-79a:* The product was a colorless (0.54 g, 37%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.27 (m, 10H), 5.39 (dd, J_1= 6.8 Hz, J_2= 2.8 Hz, 1H), 5.23 (q, J= 7.2 Hz, 1H), 5.13 (s, 2H), 4.52 (s, 2H), 4.30 (dd, J_1= 17.4 Hz, J_2= 5.2 Hz, 1H), 4.24 (dd, J_1= 17.4 Hz, J_2= 5.8 Hz, 1H), 3.89 (dd, J_1= 11.2 Hz, J_2= 3.2 Hz, 1H), 3.83 (dd, J_1= 11.2 Hz, J_2= 6.4 Hz, 1H), 2.35 (t, J= 5.8 Hz, 1H), 1.52 (d, J= 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7, 169.7, 166.8, 137.3, 135.0, 128.6, 128.5, 128.4, 128.3, 127.9, 127.7, 73.5, 72.6, 69.7, 68.5, 67.3, 60.5, 16.8.



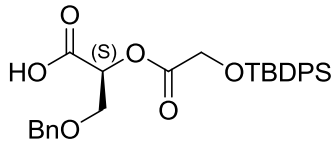
Bn-LLLS*(Bn)LLG *rmsx-33a:* The product was a colorless oil (2.51 g, 96%). ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.36-7.27 (m, 10H), 5.34 (dd, J_1= 6.0 Hz, J_2= 3.0 Hz, 1H), 5.26 (q, J= 7.2 Hz, 1H), 5.22 (q, J= 7.2 Hz, 1H), 5.18 (q, J= 72 Hz, 1H), 5.17 (d, J= 12.0 Hz, 1H), 5.16 (q, J= 7.2 Hz, 1H), 5.12 (q, J= 7.2 Hz,1H), 5.11 (d, J= 12.0 Hz, 1H), 4.58 (d, J= 12.0 Hz, 1H), 4.56 (d, J= 12.0 Hz, 1H), 4.26 (dd, J_1= 17.4 Hz, J_2= 4.8 Hz, 1H), 4.21 (dd, J_1= 17.4 Hz, J_2= 5.4 Hz, 1H), 3.93 (dd, J_1= 11.4 Hz, J_2= 3.6 Hz, 1H), 3.90 (dd, J_1= 11.4, J_2= 5.4 Hz, 1H), 2.28 (t, J= 6.0 Hz, 1H), 1.60 (d, J= 6.6 Hz, 3H), 1.562 (d, J= 6.6 Hz, 3H), 1.561 (d, J= 6.6 Hz, 3H), 1.50 (d, J= 7.2

Hz, 3H), 1.49 (d, J= 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 172.7, 169.9, 169.5(3), 169.3, 166.7, 137.4, 135.0, 128.6, 128.5, 128.4, 128.2, 127.8, 127.7, 73.4, 72.5, 69.4, 69.3, 69.1, 69.0, 68.4, 67.2, 60.5, 16.73, 16.71(2), 16.7, 16.5.

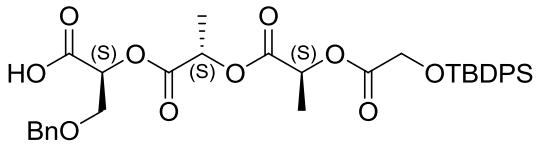


Bn-LLLS*(Bn)LLGLLG *rmsx-38a:* The product was a colorless oil (0.71 g, 99%). ^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.35-7.26 (m, 10H), 5.32 (dd, J_1= 4.9 Hz, J_2= 2.8 Hz, 1H), 5.25-5.10 (m, 9H), 4.85 (d, J= 16.1 Hz, 1H), 4.61 (d, J= 16.1 Hz, 1H), 4.58 (d, J= 12.6 Hz, 1H), 4.55 (d, J= 12.6 Hz, 1H), 4.26 (d, J= 17.5 Hz, 1H), 4.21 (d, J= 17.5 Hz, 1H), 3.92 (dd, J_1= 11.2 Hz, J_2= 2.1 Hz, 1H), 3.90 (dd, J_1= 11.2, J_2= 6.3 Hz, 1H), 1.58 (d, J= 7.0 Hz, 6H), 1.57 (d, J= 7.0 Hz, 3H), 1.56 (d, J= 7.0 Hz, 3H), 1.55 (d, J= 7.0 Hz, 3H), 1.491 (d, J= 7.0 Hz, 3H), 1.486 (d, J= 70 Hz, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 172.7, 169.9, 169.6, 169.5(2), 169.4, 169.33, 169.3, 166.7, 166.5, 137.4, 135.0, 128.6, 128.5, 128.4, 128.2, 127.8, 127.7, 73.4, 72.5, 69.3, 69.24, 69.2, 69.1, 69.0, 68.9, 68.4, 67.2, 60.8, 60.4, 60.3, 16.71, 16.7, 16.6 16.5.

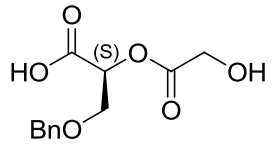
General procedures for oligomer benzyl deprotections. The benzyl protected oligomer was combined with 10% Pd/C (5% w/w) and 0.5 equivalents of triethylamine in dry EtOAc.[149] The reaction mixture was stirred 5 - 18 h under 1 atm of hydrogen and filtered through celite. The filtrate was washed with 1.0 M HCl diluted in brine follwed by a brine wash. The organic layer was dried with $MgSO_4$, filtered and concentrated *in vacuo*. No further purification was used unless stated.



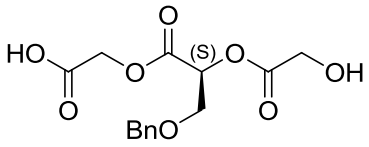
S*(Bn)G-SiR$_3$ *rmsix-75a:* The concentrate was chromatographed (silica, 10-20% EtOAc in hexanes) to yield a colorless oil (6.60 g, 81%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.59 (s, 1H), 7.7-7.68 (m, 4H), 7.43-7.23 (m, 11H), 5.31 (dd, J_1= 5.2 Hz, J_2= 2.8 Hz, 1H), 4.57 (d, J= 12.4 Hz, 1H), 4.51 (d, J= 12.4 Hz, 1H), 4.43 (d, J= 16.8 Hz, 1H), 4.35 (d, J= 16.8 Hz, 1H), 3.88 (dd, J_1= 11.2 Hz, J_2= 5.2 Hz, 1H), 3.76 (dd, J_1= 10.8 Hz, J_2= 2.8 Hz, 1H), 1.09 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.2, 170.6, 137.1, 135.6, 135.5, 132.6, 132.5, 129.9, 128.4, 127.9, 127.8, 127.7, 73.7, 71.6, 68.3, 61.9, 26.6, 19.2; ES-TOF HRMS (M+Na) calc mass 515.1866, found 515.1882.



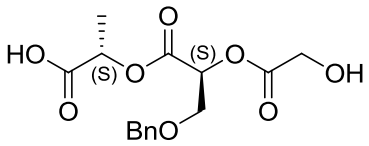
S*(Bn)LLG-SiR$_3$ *rmsx-31a:* The concentrate was chromatographed (silica, 15-25% EtOAc in hexanes) to yield a colorless oil (4.12 g, 83%). ^{1}H NMR ($CDCl_3$, 600 MHz) δ 10.7 (s, 1H), 7.69-7.66 (m, 4H), 7.43-7.26 (m, 11H), 5.30 (dd, J_1= 4.8 Hz, J_2= 3.0 Hz, 1H), 5.24 (q, J= 7.2 Hz, 1H), 5.13 (q, J= 6.6 Hz, 1H), 4.62 (d, J= 12.0 Hz, 1H), 4.55 (d, J= 12.6 Hz, 1H), 4.35 (d, J= 16.8 Hz, 1H), 4.29 (d, J= 17.4 Hz, 1H), 3.94 (dd, J_1= 10.8 Hz, J_2= 4.8 Hz, 1H), 3.82 (dd, J_1= 10.8 Hz, J_2= 2.4 Hz, 1H), 1.59 (d, J= 7.2 Hz, 3H), 1.49 (d, J= 72 Hz, 3H), 1.08 (s, 9H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 172.8, 170.7, 169.9, 169.6, 137.1, 135.6, 135.5, 132.7, 132.6, 129.9, 128.5, 127.9, 127.8, 127.7, 73.5, 72.1, 68.9, 68.5, 68.2, 61.9, 26.6, 19.2, 16.7, 16.6.



S*(Bn)G *rmsix-72a:* The concentrate was a colorless oil (0.64 g, 87%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.27 (m, 5H), 5.34 (dd, J_1= 5.2 Hz, J_2= 2.8 Hz, 1H), 4.59 (d, J= 12.4 Hz, 1H), 4.54 (d, J= 12.4 Hz, 1H), 4.32 (d, J= 17.6 Hz, 1H), 4.25 (d, J= 17.6 Hz, 1H), 3.90 (dd, J_1= 11.2 Hz, J_2= 5.2 Hz, 1H), 3.81 (dd, J_1= 11.2 Hz, J_2= 2.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7, 171.5, 136.9, 128.5, 128.1, 127.8, 73.6, 72.3, 68.2, 60.4.

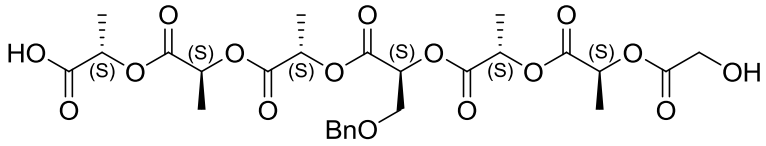


GS*(Bn)G *rmsix-82a:* The concentrate was a colorless oil (0.57 g, 85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.27 (m, 5H), 5.43 (dd, J_1= 5.2 Hz, J_2= 2.8 Hz, 1H), 4.71 (d, J= 16.4 Hz, 1H), 4.66 (d, J= 16.0 Hz, 1H), 4.59 (d, J= 12.0 Hz, 1H), 4.53 (d, J= 12.0 Hz, 1H), 4.33 (d, J= 17.6 Hz, 1H), 4.26 (d, J= 17.2 Hz, 1H), 3.93 (dd, J_1= 10.8 Hz, J_2= 5.2 Hz, 1H), 3.86 (dd, J_1= 11.2 Hz, J_2= 3.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7, 170.8, 166.9, 136.9, 128.5, 128.0, 127.8, 73.6, 72.4, 68.2, 60.9, 60.4.

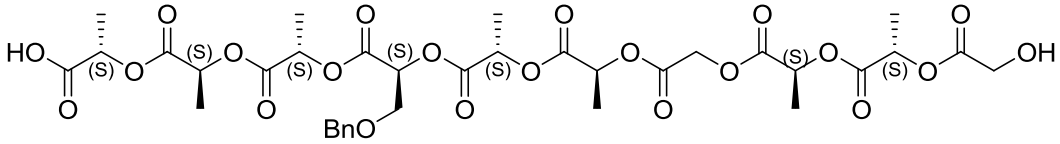


LS*(Bn)G *rmsix-83a:* The concentrate was a colorless oil (0.33 g, 85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.26 (m, 5H), 5.40 (dd, J_1= 5.6 Hz, J_2= 3.2 Hz, 1H), 5.24 (q, J= 7.2 Hz, 1H), 4.59 (d, J= 12.0 Hz, 1H), 4.56 (d, J= 12.0 Hz, 1H), 4.33 (d, J= 17.6 Hz, 1H), 4.26 (d, J= 17.2 Hz, 1H), 3.93 (dd, J_1= 11.2 Hz, J_2= 6.0 Hz, 1H), 3.89 (dd, J_1= 10.8 Hz, J_2= 3.2 Hz, 1H), 1.55 (d, J= 6.8

Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.3, 172.8, 166.8, 137.0, 128.5, 128.0, 127.8, 73.6, 72.5, 69.3, 68.4, 60.5, 16.7.



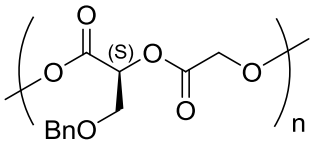
LLLS*(Bn)LLG *rmsx-39a:* The concentrate was a colorless oil (0.86 g, 99%). ^{1}H NMR ($CDCl_3$, 600MHz) δ 7.31-7.26 (m, 5H), 5.34 (dd, J_1= J_2= 4.2 Hz, 1H), 5.25 (q, J= 7.2 Hz, 1H), 5.22 (q, J= 6.6 Hz, 1H), 5.19 (q, J= 7.2 Hz, 1H), 5.14 (q, J= 7.2 Hz, 1H), 5.13 (q, J= 7.2 Hz, 1H), 4.59 (d, J= 12.0 Hz, 1H), 4.56 (d, J= 12.0 Hz, 1H), 4.26 (d, J= 17.4 Hz, 1H), 4.21 (d, J= 17.4 Hz, 1H), 3.93-3.89 (m, 2H), 1.59 (d, J= 6.6 Hz, 3H), 1.56 (d, J= 7.2 Hz, 3H), 1.55 (d, J= 7.2 Hz, 3H), 1.54 (d, J= 7.2 Hz, 3H), 1.53 (d, J= 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 174.6, 172.7, 169.53, 169.51, 169.3, 166.8, 137.4, 128.4, 127.8, 127.7, 73.5, 72.5, 69.4, 69.2, 69.1, 69.0, 68.4, 60.5, 16.74, 16.71, 16.69, 16.63, 16.53.



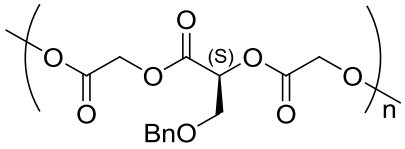
LLLS*(Bn)LLGLLG *rmsx-41a:* The concentrate was a colorless oil (0.57 g, 99%). ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.33- 7.25 (m, 5H), 5.33 (dd, J_1= 4.8 Hz, J_2= 3.6 Hz, 1H), 5.232 (q, J= 7.2 Hz, 1H), 5.23 (q, J= 7.2 Hz, 1H), 5.21 (q, J= 7.2 Hz, 1H), 5.18 (q, J= 6.6 Hz, 1H), 5.17 (q, J= 7.2 Hz, 1H), 5.13 (q, J= 7.2 Hz, 1H), 5.10 (q, J= 6.6 Hz, 1H), 4.84 (d, J= 16.2 Hz, 1H), 4.62 (d, J= 15.6 Hz, 1H), 4.58 (d, J= 12.0 Hz, 1H), 4.55 (d, J= 12.0 Hz, 1H), 4.26 (d, J= 17.4 Hz, 1H), 4.21 (d, J= 17.4 Hz, 1H), 3.93-3.88 (m, 2H), 1.58 (d, J= 6.6 Hz, 6H), 1.57 (d, J= 7.2 Hz, 6H), 1.54 (d, J= 7.8 Hz, 3H), 1.53 (d, J= 7.2 Hz, 3H), 1.51 (d, J= 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ

174.5, 172.8, 169.6, 169.55, 169.5, 169.4(2), 166.8, 166.5, 137.4, 128.4, 127.8, 127.7, 73.4, 72.5, 69.4, 69.2, 69.16, 69.1, 69.0, 68.4, 60.8, 60.4, 16.7(2), 16.68(3), 16.6, 16.5.

General procedure for DIC/DPTS polymerizations. The oligomer and 0.2 equivalents of DPTS were dissolved in dry CH_2Cl_2 and chilled to 0 °C. DIC (1.5 equiv) was added dropwise by syringe and the reaction mixture was stirred at RT for 3 h. The polymers were precipitated twice in MeOH and dried under vacuum.

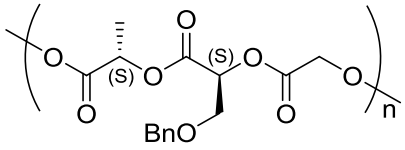


Poly S*(Bn)G *rmsix-73b:* The polymer was a colorless solid (0.33 g, 59%). ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.31-7.25 (m, 5H), 5.38 (dd, J_1= 5.6 Hz, J_2= 2.8 Hz, 1H), 4.85 (d, J= 16.1 Hz, 1H), 4.71 (d, J= 16.1 Hz, 1H), 4.55 (d, J= 11.9 Hz, 1H), 4.50 (d, J= 11.9 Hz, 1H), 3.89 (dd, J_1= 11.2 Hz, J_2= 5.6 Hz, 1H), 3.86 (dd, J_1= 11.2 Hz, J_2= 2.8 Hz, 1H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 166.5, 166. 2, 137.2, 128.4, 127.9, 127.8, 127.7, 73.5, 72.5, 68.3, 61.0; SEC (THF): M_n – 31.4 kDa, M_w – 53.9 kDa, PDI – 1.7; SEC (DMF): M_n – 60.2 kDa, M_w – 87.1 kDa, PDI – 1.3; Thermal (DSC): *ppt:* T_g – 32.1 °C.

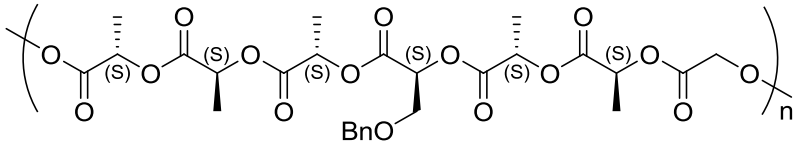


Poly GS*(Bn)G *rmsix-84b:* The polymer was a colorless solid (0.26 g, 50%). ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.33-7.24 (m, 5H), 5.39 (dd, J_1= 4.9 Hz, J_2= 2.1 Hz, 1H), 4.80 (d, J= 16.1 Hz, 1H), 4.79 (d, J= 16.1 Hz, 1H), 4.74 (d, J= 16.1 Hz, 1H), 4.71 (d, J= 16.1 Hz, 1H), 4.56 (d, J= 11.9 Hz, 1H), 4.52 (d, J= 11.9 Hz, 1H), 3.91 (dd, J_1= 11.2 Hz, J_2= 5.6 Hz, 1H), 3.86 (dd, J_1= 11.2

Hz, J_2= 2.8 Hz, 1H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 166.5, 166.4, 166.2, 137.2, 128.5, 127.9, 127.7, 73.5, 72.5, 68.2, 60.9, 60.8; SEC (THF): M_n – 10.2 kDa, M_w – 15.9 kDa, PDI – 1.5; SEC (DMF): M_n – 40.6 kDa, M_w – 48.2 kDa, PDI – 1.2; Thermal (DSC): *ppt:* T_g – 30.0 °C.

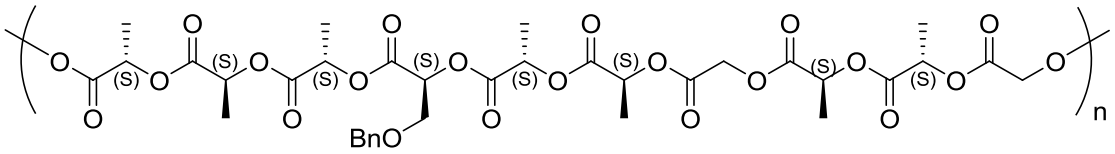


Poly LS*(Bn)G *rmsix-86a:* The polymer was a colorless solid (0.17 g, 61%). ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.32-7.25 (m, 5H), 5.33 (dd, J_1= 4.9 Hz, J_2= 2.8 Hz, 1H), 5.23 (q, J= 7.1 Hz, 1H), 4.84 (d, J= 16.1 Hz, 1H), 4.63 (d, J= 16.1 Hz, 1H), 4.56 (d, J= 12.6 Hz, 1H), 4.53 (d, J= 11.9 Hz, 1H), 3.91 (dd, J_1= 11.9 Hz, J_2= 3.5 Hz, 1H), 3.88 (dd, J_1= 10.5 Hz, J_2= 5.6 Hz, 1H), 1.55 (d, J= 7.7 Hz, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 169.2, 166.6, 166.5, 137.3, 128.4, 127.9, 127.7, 73.5, 72.6, 69.4, 68.4, 60.7, 16.8; SEC (THF): M_n – 42.2 kDa, M_w – 111.0 kDa, PDI – 2.6; SEC (DMF): M_n – 88.2 kDa, M_w – 188.3 kDa, PDI – 2.1; Thermal (DSC): *ppt:* T_g – 36.1 °C.



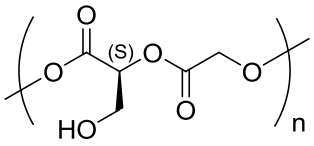
Poly LLLS*(Bn)LLG *rmsx-35b:* The polymer was a colorless solid (0.23 g, 68%). ^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.30-7.26 (m, 5H), 5.32 (dd, J_1= 5.6 Hz, J_2= 2.8 Hz, 1H), 5.23 (q, J= 7.0 Hz, 1H), 5.182 (q, J= 7.0 Hz, 1H), 5.177 (q, J= 7.0 Hz, 1H), 5.16 (q, J= 7.0 Hz, 1H), 5.13 (q, J= 7.0 Hz, 1H), 4.86 (d, J= 16.1 Hz, 1H), 4.582 (d, J= 16.1 Hz, 1H), 4.581 (d, J= 11.9 Hz, 1H), 4.56 (d, J= 12.6 Hz, 1H), 3.92 (dd, J_1= 11.9 Hz, J_2= 3.5 Hz, 1H), 3.90 (dd, J_1= 11.2 Hz, J_2= 6.3 Hz, 1H), 1.58 (d, J= 7.0 Hz, 3H), 1.56 (d, J= 7.0 Hz, 3H), 1.55 (d, J= 7.0 Hz, 3H), 1.54 (d, J= 7.0 Hz, 6H); ^{13}C NMR ($CDCl_3$, 175 MHz) δ 169.55(2), 169.54, 169.34, 169.32, 166.8, 166.5, 137.4,

128.4, 127.8, 127.7, 73.4, 72.5, 69.3, 69.2, 69.0, 68.96, 68.91, 68.4, 60.8, 16.7, 16.6, 16.56; SEC (THF): M_n – 40.9 kDa, M_w – 47.7 kDa, PDI – 1.2; Thermal (DSC): *ppt:* T_g – 50.0 °C.

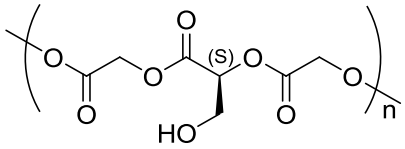


Poly LLLS*(Bn)LLGLLG *rmsx-42b:* The polymer was a colorless solid (0.24 g, 44%). ^{1}H NMR ($CDCl_3$, 700 MHz) δ 7.33-7.26 (m, 5H), 5.32 (dd, J_1= 6.3 MHz, J_2= 3.5 Hz, 1H), 5.23 (q, J= 7.0 Hz, 1H), 5.20 (q, J= 7.0 Hz, 1H), 5.18 (q, J= 7.0 Hz, 1H), 5.17 (q, J= 7.0 Hz, 1H), 5.167 (q, J= 7.0 Hz, 2H), 5.13 (q, J= 7.0 Hz, 1H), 4.858 (d, J= 16.1 Hz, 1H), 4.855 (d, J= 16.1 Hz, 1H), 4.593 (d, J= 16.1 Hz, 1H), 4.59 (d, J= 16.8 Hz, 1H), 4.58 (d, J= 11.9 Hz, 1H), 4.56 (d, J= 11.9 Hz, 1H), 3.92 (dd, J_1= 11.2 Hz, J_2= 3.5 Hz, 1H), 3.90 (dd, J_1= 11.2 Hz, J_2= 5.6 Hz, 1H), 1.58 (d, J= 7.0 Hz, 3H), 1.57 (d, J= 7.0 Hz, 3H), 1.56 (d, J= 7.0 Hz, 3H), 1.557 (d, J= 7.0 Hz, 3H), 1.555 (d, J= 7.0 Hz, 3H), 1.54 (d, J= 7.0 Hz, 6H); ^{13}C NMR ($CDCl_3$, 175 MHz) δ 169.55(2), 169.53, 169.4, 169.33, 169.32, 166.8, 166.5(2), 137.4, 128.4, 127.8, 127.7, 73.4, 72.5, 69.3, 69.19, 69.18, 69.0, 68.98, 68.96, 68.91, 68.4, 60.8, 60.7, 16.69(4), 16.64, 16.63, 16.56; SEC (THF): M_n – 41.5 kDa, M_w – 64.7 kDa, PDI – 1.6; Thermal (DSC): *ppt:* T_g – 52.0 °C.

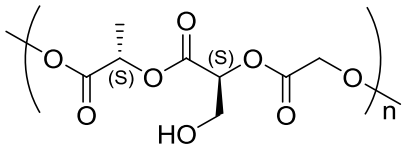
Polymer benzyl deprotection method A. The polymers were dissolved in 0.5 ml DMF and 50% w/w 10% $Pd(OH)_2$/C (wet) was added. The reaction mixture was placed under 1 atm H_2 and let stir for 5 h. After filtering, the reaction mixture was concentrated under vacuum for 18 h.



Poly S*(OH)G *rmsx-10a:* The polymer was a white powder (6.3 mg, 95% yield, 94% deprotected). ^{1}H NMR (700 MHz, DMSO) δ 5.34 (t, J= 6.3 Hz, 1H), 5.24 (dd, J_1= 4.9 Hz, J_2= 2.8 Hz, 1H), 4.94 (d, J= 16.8 Hz, 1H), 4.88 (d, J= 16.1 Hz, 1H), 3.85-3.78 (m, 2H); ^{13}C NMR (175 MHz, DMSO) δ 167.8, 167.54, 167.5, 167.48, 167.44, 167.41, 167.37, 167.17, 167.13, 74.7, 68.7, 61.5, 61.3, 61.0, 60.9; SEC (DMF): M_n – 19.9 kDa, M_w – 21.7 kDa, PDI - 1.1.

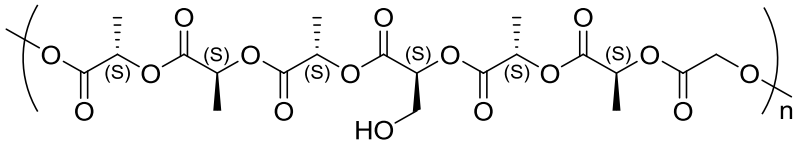


Poly GS*(OH)G *rmsx-11a:* The polymer was an off-white powder (7 mg, 100% yield, 94% deprotected). ^{1}H NMR (700 MHz, DMSO) δ 5.33 (t, J= 6.3 Hz, 1H), 5.24 (dd, J_1= J_2= 11.2 Hz, 1H), 4.94 (d, J= 16.1 Hz, 1H), 4.91 (s, 2H), 4.89 (d, J= 16.1 Hz, 1H), 3.82-3.81 (m, 2H); ^{13}C NMR (100 MHz, DMSO) δ 167.6, 167.5, 167.4, 167.2, 167.1, 74.7, 68.7, 66.6, 61.42, 61.40, 61.3, 61.2, 61.0, 60.92, 60.9; SEC (DMF): M_n – 19.8 kDa, M_w – 22.1 kDa, PDI - 1.1.

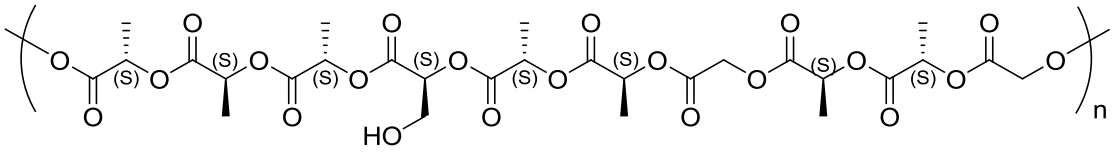


Poly LS*(OH)G *rmsx-12a:* The polymer was an off-white powder (8 mg, 100% yield, 90% deprotected). ^{1}H NMR (700 MHz, DMSO) δ 5.28-5.24 (m, 2H), 5.18 (dd, J_1= 6.3 Hz, J_2= 2.8 Hz, 1H), 4.93 (d, J= 16.8 Hz, 1H), 4.85 (d, J= 15.6 Hz, 1H), 3.86-3.83 (m, 1H), 3.77-3.74 (m, 1H), 1.49 (d, J= 7.0 Hz, 3H); ^{13}C NMR (150 MHz, DMSO) δ 169.2, 166.86, 166.82, 166.81, 166.79, 74.3, 68.9, 68.2, 60.7, 60.4, 16.6; SEC (DMF): M_n – 19.9 kDa, M_w – 22.1 kDa, PDI - 1.1.

Polymer benzyl deprotection method B. Following procedures developed by Hennink and coworkers,[154] polymers were dissolved in dry THF and 10% (w/w Pd) 10% Pd/C (Aldrich, Degussa type E101 NE/W, wet) was added. The reaction was allowed to stir under 1.0 atm of hydrogen for 16-20 h, filtered over celite and concentrated under vacuum. Further purification was accomplished by dissolving polymer in CH_2Cl_2 filtering through syringe filter and precipitating in cold ether to yield a colorless solid.



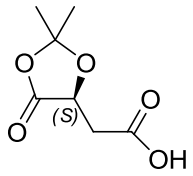
Poly LLLS*(OH)LLG rmsx-37a: The product was a colorless powder (16 mg, 99%, 100% deprotected, > 97% deprotection on average). ^{1}H NMR (700 MHz, $CDCl_3$) δ 5.26 (q, J= 7.7 Hz, 1H), 5.22-5.14 (m, 5H), 4.85 (d, J= 16.1 Hz, 1H), 4.59 (d, J= 16.1 Hz, 1H), 4.21-4.17 (m, 1H), 3.95-3.91 (m, 1H), 3.03 (t, J= 7.7 Hz, 1H), 1.6-1.5 (m, 15H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 170.7, 169.7, 169.5, 169.4 (2), 167.1, 166.6, 73.9, 69.5, 69.2, 69.15, 69.13, 69.1, 62.2, 60.8, 16.7, 16.6, 16.57, 16.52,16.5; SEC (THF): M_n – 39.9 kDa, M_w – 49.0 kDa, PDI – 1.2; Thermal (DSC): *ppt:* 53 °C.



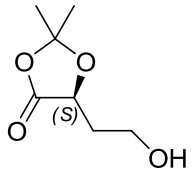
Poly LLLS*(OH)LLGLLG rmsx-46b: The product was a white powder (16 mg, 60%, > 95% deprotected). ^{1}H NMR (700 MHz, $CDCl_3$) δ 5.26 (q, J= 7.7 Hz, 1H), 5.23-5.15 (m, 6H), 4.86 (d, J= 16.1 Hz, 1H), 4.84 (d, J= 15.4 Hz, 1H), 4.60 (d, J= 16.1 Hz, 1H), 4.59 (d, J= 16.1 Hz, 1H), 4.21-4.17 (m, 1H), 3.96-3.92 (m, 1H), 3.00 (t, J= 7.4 Hz, 1H), 1.6-1.5 (m, 21H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 170.7, 169.7, 169.5, 169.4 (3), 169.3, 167.1, 166.6, 166.5, 73.9, 69.5, 69.23,

69.21, 69.15, 69.1, 69.0, 62.2, 60.8, 60.78, 16.7, 16.67, 16.66, 16.64, 16.58, 16.54; SEC (THF): M_n – 35.4 kDa, M_w – 45.0 kDa, PDI – 1.3.

3.6.2 Towards L-Malic Acid derived RSCs

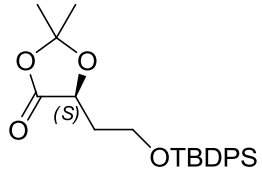


M(COOH) dioxo[155] *rmsviii-39a:* Malic acid (40.2 g, 300 mmol) was dissolved in 2,2-dimethoxypropane (150 mL, 1.2 mol) under N_2. *p*-Toluenesulfonic acid monohydrate (570 mg, 3.0 mmol) was added and the reaction mixture was allowed to stir for 3 h. Water (200 mL) and $NaHCO_3$ (252 mg, 3.0 mmol) were added and the aqueous layer was extracted with CH_2Cl_2 (5 × 200 mL). The organic layers were dried with $MgSO_4$ and concentrated *in vacuo*. The solid concentrate was dissolved in ether (250 mL) and hexanes (300 mL) were added. After sitting for 1 h, the mixture was filtered to yield a colorless solid. This procedure was repeated twice more to yield a total of 38.6 g (74%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 10.94 (s, 1H), 4.69 (dd, J_1= 6.6 Hz, J_2= 3.9 Hz, 1H), 2.98 (dd, J_1= 17.4 Hz, J_2= 3.9 Hz, 1H), 2.83 (dd, J_1= 17.1 Hz, J_2= 6.3 Hz, 1H), 1.60 (s, 3H), 1.55 (s, 3H); ^{13}C ($CDCl_3$, 75 MHz) δ 175.3, 171.9, 111.4, 70.3, 35.9, 26.7, 25.8.

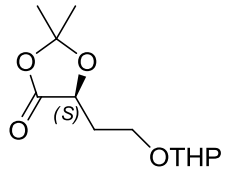


M(OH) dioxo[155] *rmsviii-43a:* The malic acid dioxolanone, **M(COOH) dioxo** (10 g, 57.4 mmol) was dissolved in 50 mL of dry THF under N_2 and cooled in an ice bath. BH_3•$S(CH_3)_2$ (18.0 mL, 190 mmol) in 100 mL (2.0 M) THF was added dropwise over 2 h. After addition the reaction

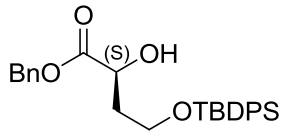
mixture was let stir at RT for 20 h and the reaction was quenched with the dropwise addition of 60 mL of MeOH. The reaction mixture was concentrated *in vacuo*, taken up in CH_2Cl_2 (50 mL), washed with sat $NaHCO_3$ and dried with $MgSO_4$. The organic layer was concentrated *in vacuo* to yield a colorless liquid (5.09 g, 55%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.56 (dd, J_1=7.2 Hz, J_2= 5.1 Hz, 1H), 3.88-3.78 (m, 2H), 2.19-2.09 (m, 1H), 2.05-1.94 (m, 1H), 1.62 (s, 3H), 1.54 (s, 3H).



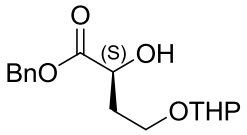
M(TBDPS) dioxo[155] *rmsviii-47b:* *tert*-Butyldiphenylsilyl chloride (10.3 g, 37.5 mmol, TBDPSCl) was dissolved in 20 mL dry CH_2Cl_2 under N_2. Pyridine (6 mL, 75 mmol) was added dropwise and the reaction mixture was allowed to stir for 10 min. **M(OH) dioxo** (4 g, 25 mmol) in 15 mL CH_2Cl_2 was added dropwise and reaction mixture was allowed to stir for 4 h. The reaction mixture was poured into 150 mL of brine and separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The organic layers were combined, dried with $MgSO_4$ and concentrated *in vacuo*. The concentrate was chromatographed (silica, 0-5% EtOAc in hexanes) to yield a colorless oil. The oil was vacuum distilled to remove the silanol byproduct (140-150 °C, 50 mmHg). The remaining oil (7.0 g, 70%) contained 90% product and 10% silanol and was used without further purification. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.72-7.68 (m, 4H), 7.43-7.40 (m, 6H), 4.65 (dd, J_1= 8.4 Hz, J_2= 4.2 Hz, 1H), 3.94-3.84 (m, 1H), 3.83-3.76 (m, 1H), 2.23-2.12 (m, 1H), 1.98-1.88 (m, 1H), 1.60 (s, 3H), 1.57 (s, 3H), 1.07 (s, 9H).



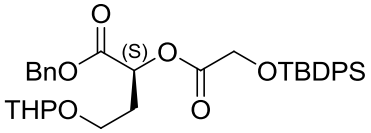
M(THP) dioxo[115] *rmsix-30a:* Hydroxyl dioxolanone **M(OH) dioxo** (2.0 g, 12.5 mmol) was combined with dihydropyran (1.6 mL, 18.8 mmol) and pyridinium *p*-toluenesulfonate (0.31 g, 1.25 mmol, PPTS) in 100 mL of CH_2Cl_2 and was allowed to stir at RT for 3.5 h. Ether (200 mL) was added and the mixture was washed with sat $NaHCO_3$ (2 × 100 mL). The organic layer was dried with $MgSO_4$ and concentrated *in vacuo* to yield a slightly yellow liquid (3.0 g, 99%). ^{1}H NMR ($CDCl_3$, 600 MHz) δ 4.61-4.57 (m, 2H), 4.54-4.51 (m, 2H), 3.9-3.8 (m, 4H), 3.6-3.48 (m, 4H), 2.18-2.14 (m, 2H), 2.03-1.96 (m, 2H), 1.8-1.75 (m, 2H), 1.7-1.6 (m, 2H), 1.6-1.4 (m, 20H).



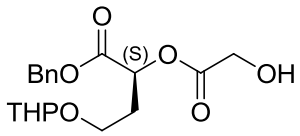
Bn-M(TBDPS) *rmsviii-51a:* **M(TBDPS) dioxo** (5.55 g, 12.5 mmol) and benzyl alcohol (13.5 g, 125 mmol) were combined in 50 mL of dry toluene and cooled in an ice bath. Lithium hexamethyldisalazide (10.5 g, 62.5 mmol) in 63 mL THF (1.0 M) was added dropwise and the reaction mixture was allowed to stir for 1.5 h at RT. The reaction was quenched with sat NH_4Cl and extracted with EtOAc. The organic layers were dried with $MgSO_4$, concentrated *in vacuo* and chromatographed (silica, 0-5% EtOAc in hexanes) to yield a colorless liquid (4.86 g, 87%). ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.67-7.65 (m, 4H), 7.43-7.32 (m, 11H), 5.21 (d, J= 12.6 Hz, 1H), 5.16 (d, J= 12.0 Hz, 1H), 4.51-4.45 (m, 1H), 3.84 (d, J= 6.0 Hz, 1H), 3.83 (d, J= 5.4 Hz, 1H), 3.26 (d, J= 5.4 Hz, 1H), 2.13-2.08 (m, 1H), 1.93-1.87 (m, 1H), 1.05 (s, 9H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 174.8, 135.5, 135.3, 133.2, 133.1, 129.7, 128.6, 128.4, 128.2, 127.7, 68.8, 67.1, 60.6, 36.2, 26.8, 19.1.



Bn-M(THP) *rmsix-36b:* Similar to **Bn-M(TBDPS)**. The product was a colorless liquid (2.45 g, 72 %). ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.40-7.34 (m, 10H), 5.27-5.19 (m, 4H), 4.74-4.72 (m, 1H), 4.58-4.57 (m, 1H), 4.43 (dd, J_1= 9.0 Hz, J_2= 60 Hz, 1H), 3.99-3.83 (m, 4H), 3.62-3.50 (m, 4H), 3.23 (s, 2H), 2.18-2.14 (m, 2H), 2.05-1.95 (m, 2H), 1.81-1.78 (m, 2H), 1.73-1.65 (m, 2H), 1.58-1.52 (m, 8H).

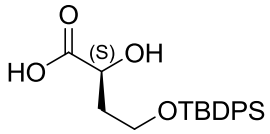


Bn-M(THP)G-SiR$_3$ *rmsix-37a:* The dimer was prepared under standard DCC/DMAP coupling conditions. The product was chromatographed (silica, 5-7.5% EtOAc in hexanes) to yield a colorless liquid (1.47 g, 73%). ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.67-7.65 (m, 8H), 7.42-7.32 (m, 22H), 5.25 (dd, J_1= 78 Hz, J_2= 6.0 Hz, 2H), 5.18-5.12 (m, 4H), 4.5-4.45 (m, 2H), 4.36-4.27 (m, 4H), 3.79-3.68 (m, 4H), 3.42-3.34 (m, 4H), 2.14-2.03 (m, 4H), 1.76-1.71 (m, 2H), 1.64-1.60 (m, 2H), 1.54-1.49 (m, 8H), 1.05 (s, 18H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 170.61, 170.58, 169.7, 169.66, 135.52, 135.5, 135.2, 132.6, 129.9, 128.5, 128.3, 128.1, 128.0, 127.8, 127.7, 98.8, 98.6, 69.6, 69.5, 67.0, 66.9, 62.5, 62.3, 62.0, 61.9, 31.3, 31.2, 30.9, 30.4, 26.6, 26.5, 25.3, 19.3, 19.2, 19.16.

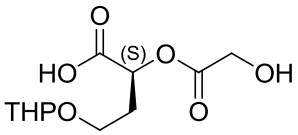


Bn-M(THP)G *rmsix-40a:* Silyl deprotection was conducted under standard conditions. The product was chromatographed (silica, 25-40% EtOAc in hexanes) to yield a colorless liquid

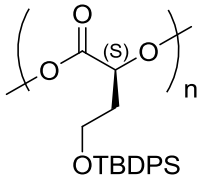
(1.60 g, 90%). ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.37-7.32 (m, 10H), 5.36-5.33 (m, 2H), 5.19-5.14 (m, 4H), 4.52-4.50 (m, 2H), 4.30-4.20 (m, 4H), 3.86-3.71 (m, 4H), 3.49-3.39 (m, 4H), 2.32-2.28 (m, 2H), 2.24-2.10 (m, 4H), 1.78-1.72 (m, 2H), 1.67-1.62 (m, 2H), 1.56-1.45 (m, 8H).



M(TBDPS) *rmsviii-52a:* Benzyl deprotection was accomplished using standard hydrogenolysis conditions. The product was a colorless oil (0.68 g, 85%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.65-7.62 (m, 4H), 7.45-7.39 (m, 11H), 4.48-4.45 (m, 1H), 3.90 (d, J= 4.5 Hz, 1H), 3.89 (d, J= 4.8 Hz, 1H), 2.2-2.12 (m, 1H), 2.03-1.95 (m, 1H), 1.04 (s, 9H).



M(THP)G *rmsix-41a:* Benzyl deprotection was accomplished using standard hydrogenolysis conditions. The product was a colorless oil (0.93 g, 83%).



Poly M(TBDPS) *rmsviii-54a:* Polymer prepared under standard DIC/DPTS conditions. The polymer was a fine colorless powder (0.40 g, 66%). ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.62-7.58 (m, 4H), 7.30-7.25 (m, 11H), 5.5-5.48 (m, 1H), 3.73-3.71 (m, 2H), 2.37-2.34 (m, 1H), 1.97-1.92 (m, 1H), 0.93 (s, 9H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 169.6, 135.5, 135.4, 133.4, 133.1, 129.6, 129.5, 127.7, 127.6, 69.4, 58.9, 33.8, 26.8, 19.1; SEC (THF): M_n – 11.0 kDa, M_w – 20.0 kDa, PDI – 2.0.

Poly M(THP) *rmsix-42:* Polymer decomposed under standard DIC/DPTS conditions. The decomposition was likely due to the interaction of DPTS with THP leading to deprotection of the segmer.

APPENDIX A: Chapter 2

A.1 FULL MALDI-TOF SPECTRA

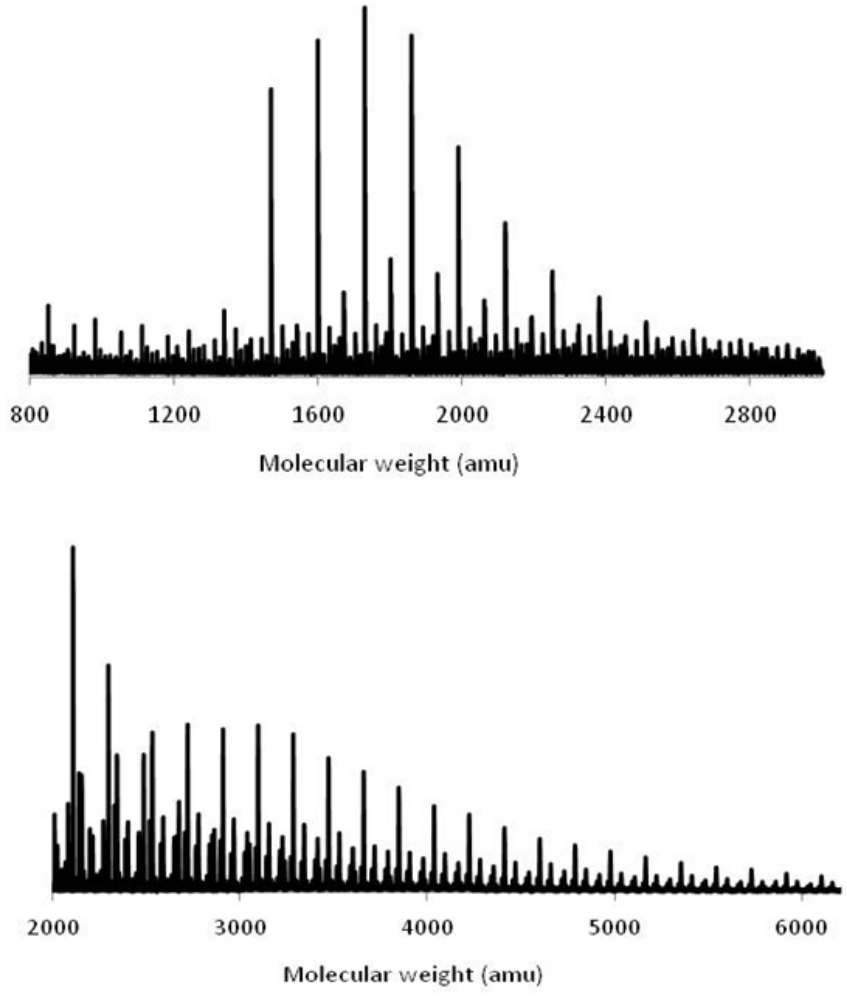


Figure 36. MALDI-TOF spectra for **poly LG** (top) and **GLG** (bottom).

A.2 ^{1}H AND ^{13}C NMR SPECTRA OF PLGA RSCS

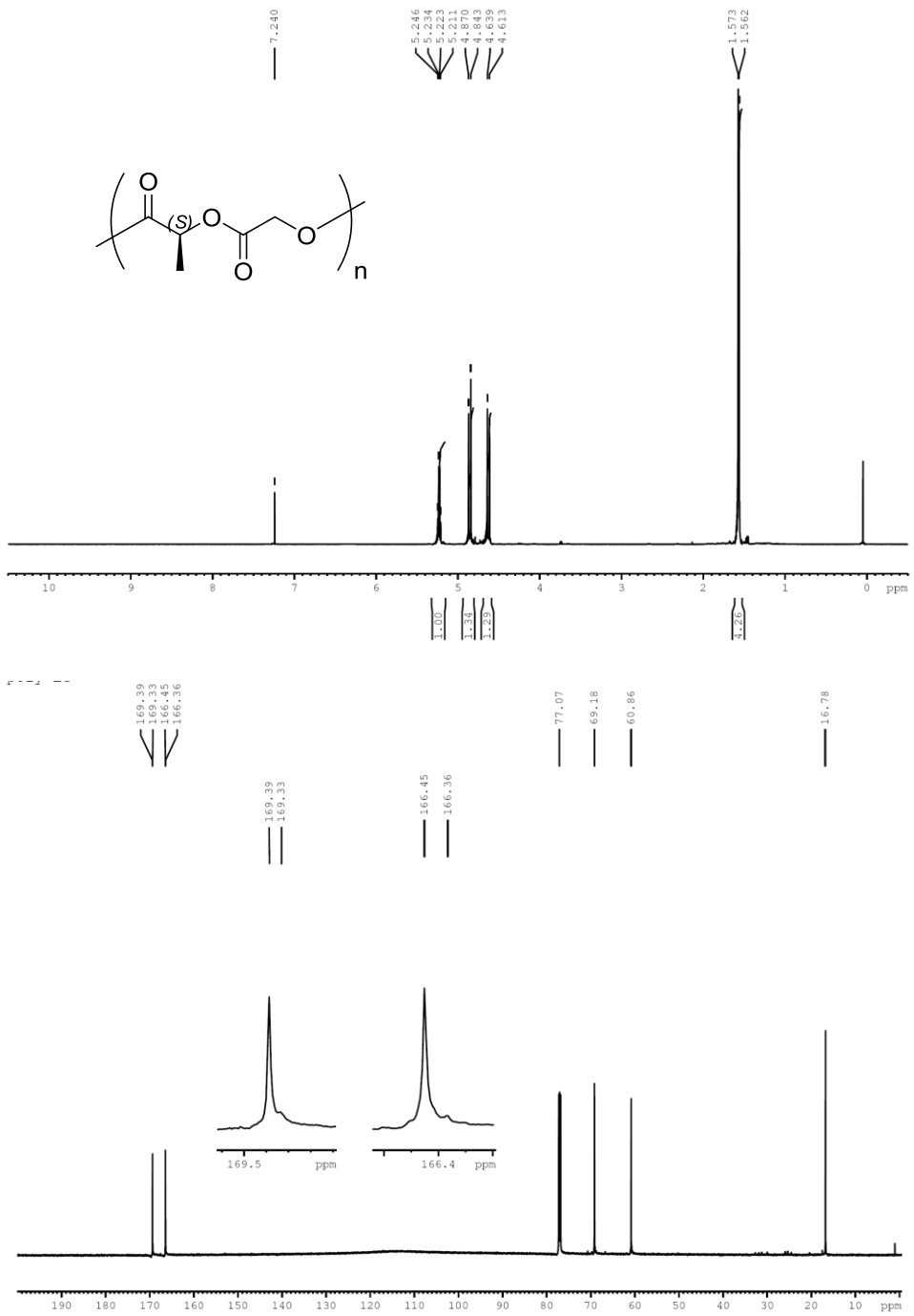


Figure 37. ^{1}H NMR (600 MHz, top) and ^{13}C NMR (125 MHz, bottom) spectra for **poly LG**

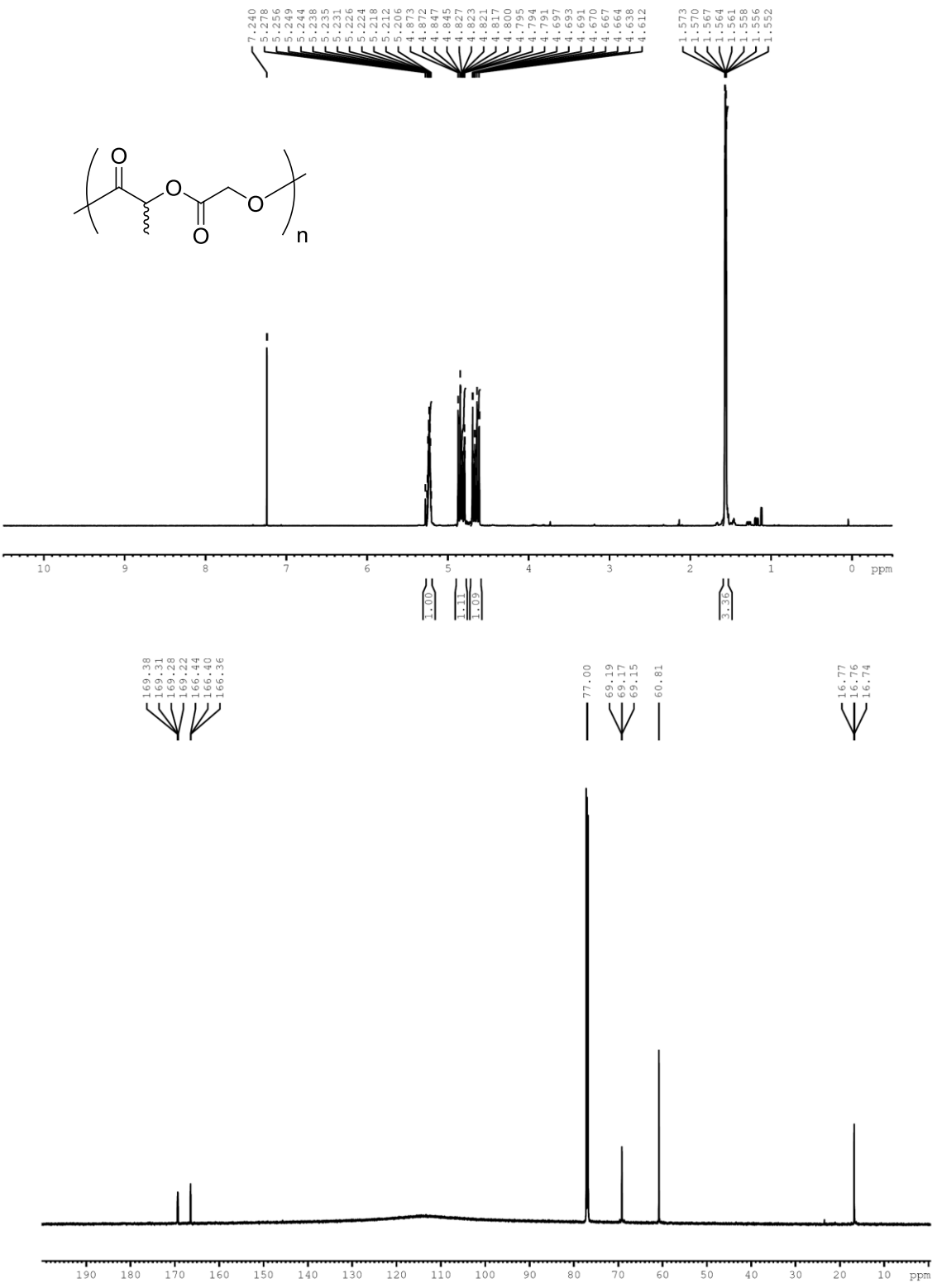


Figure 38. ^{1}H NMR (700 MHz, top) and ^{13}C NMR (175 MHz, bottom) spectra for **poly L$_{rac}$G**

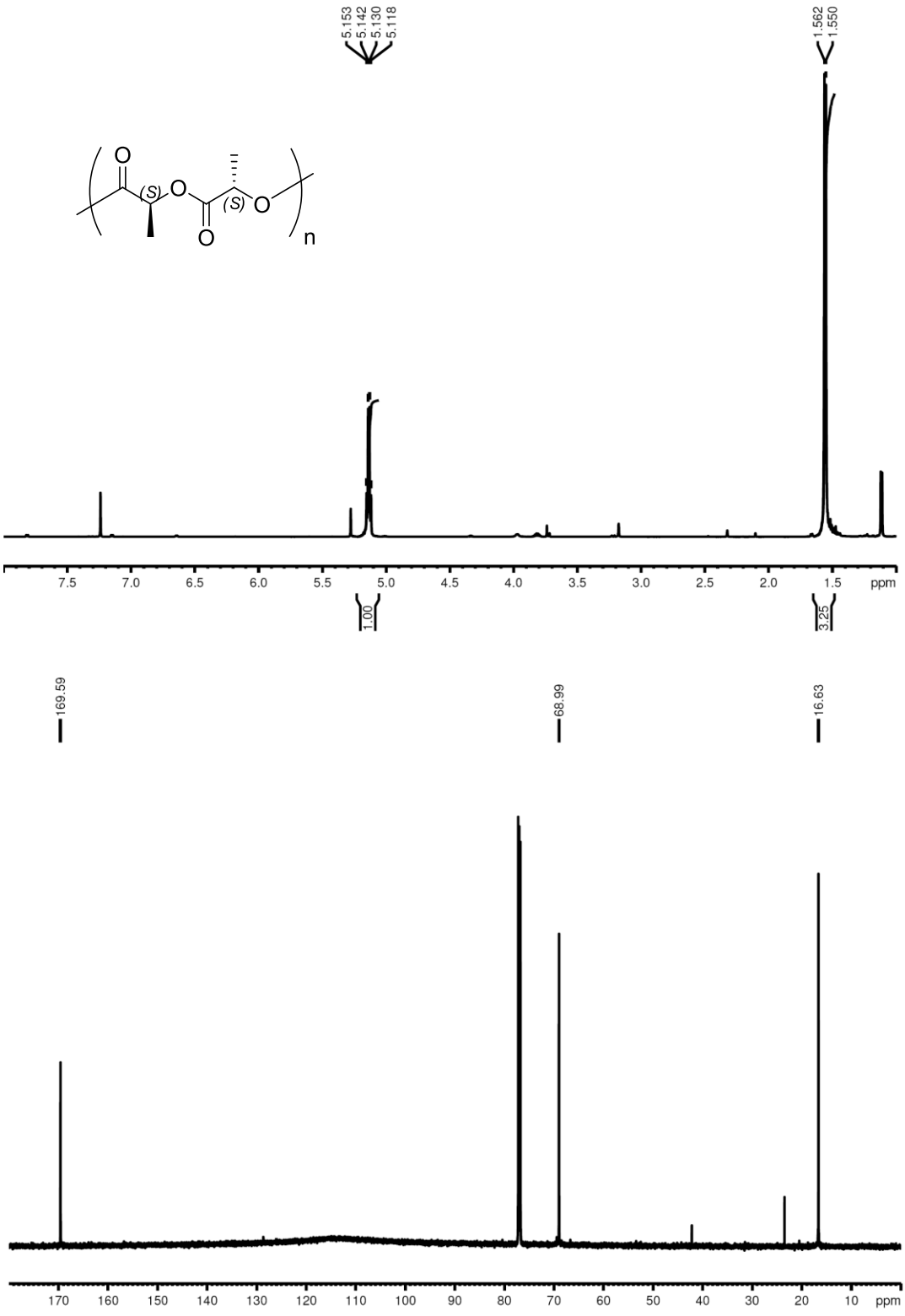


Figure 39. ^{1}H NMR (600 MHz, top) and ^{13}C NMR (125 MHz, bottom) spectra for **poly LL**

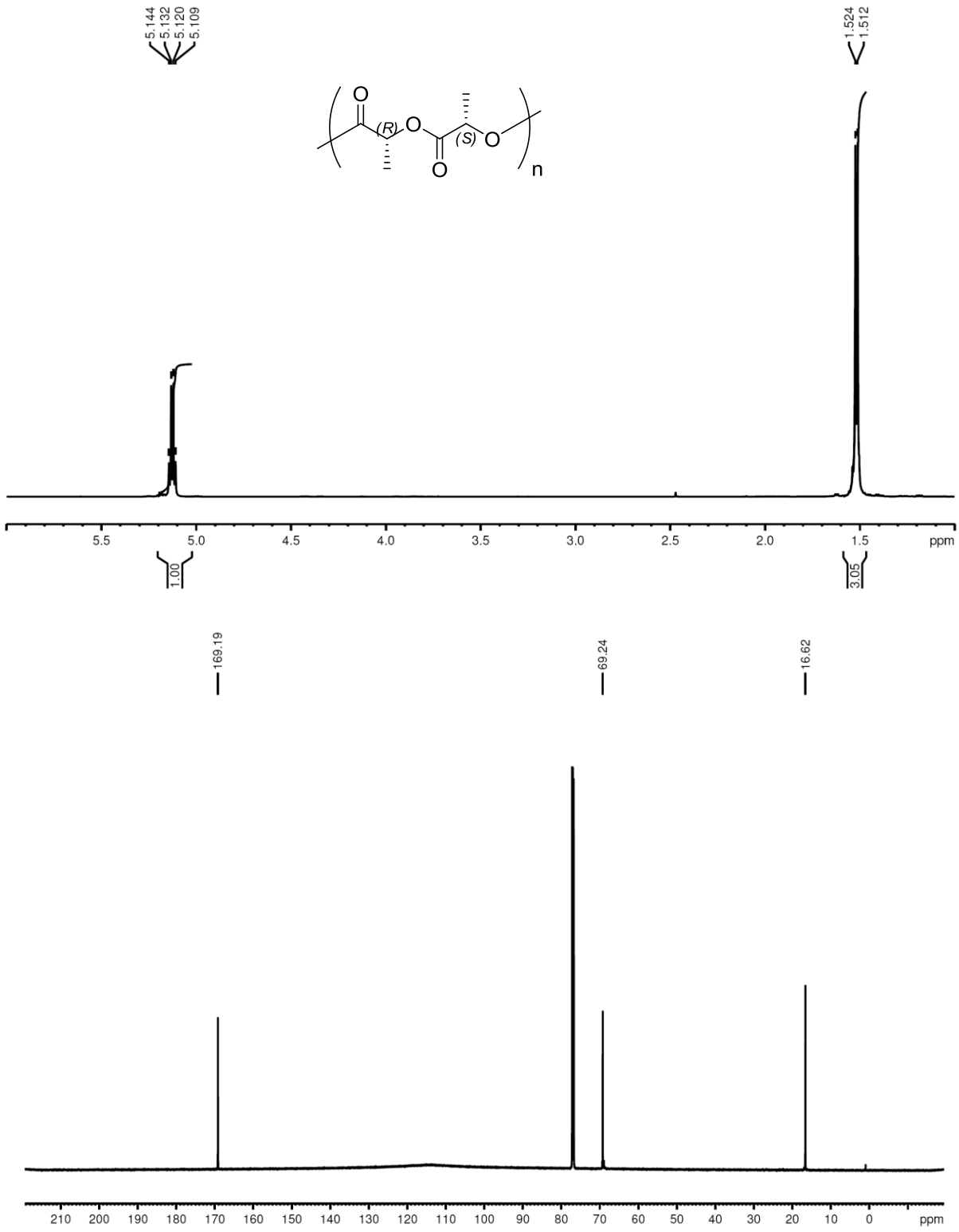


Figure 40. ^{1}H NMR (600 MHz, top) and ^{13}C NMR (125 MHz, bottom) spectra for **poly L_RL**

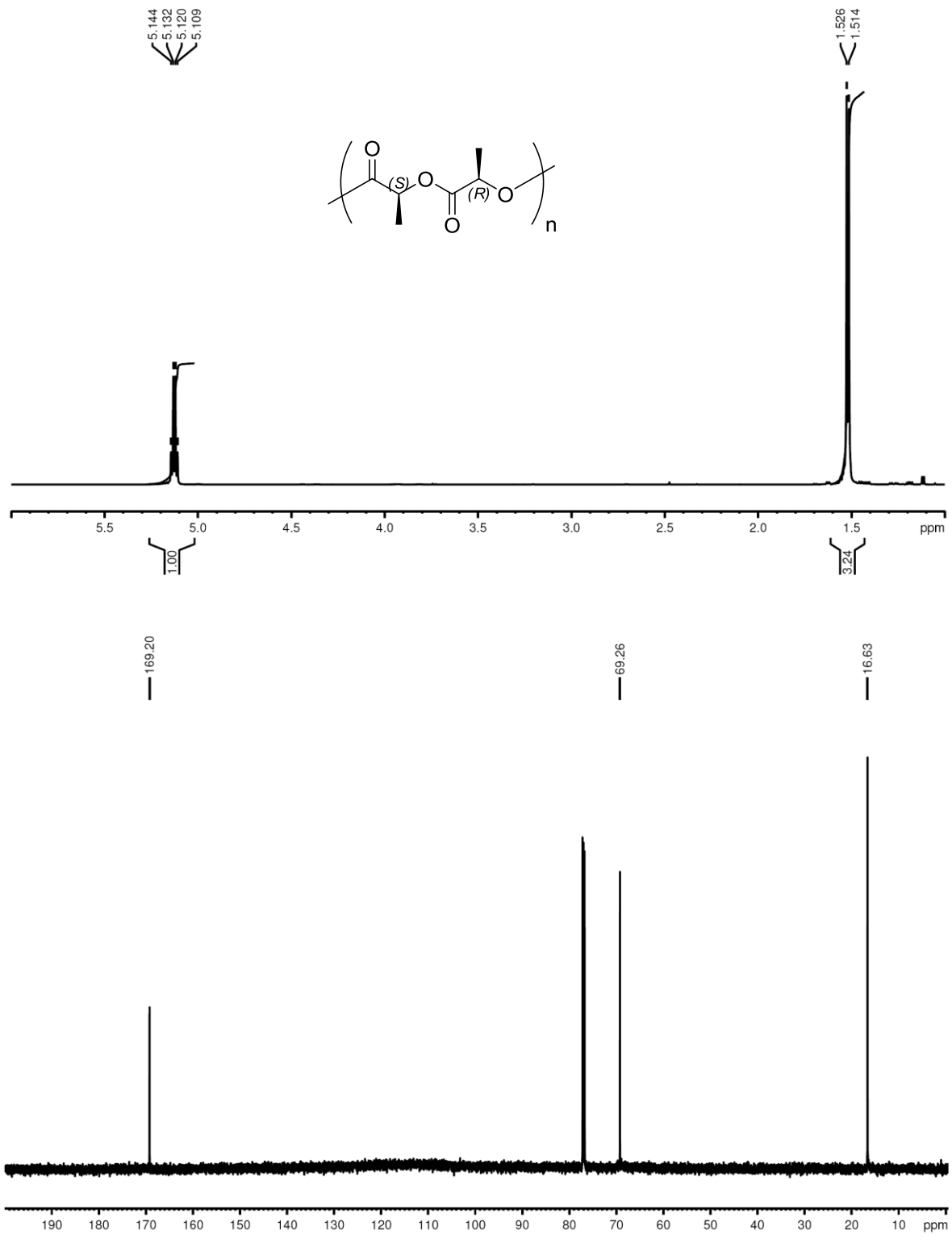


Figure 41. ^{1}H NMR (600 MHz, top) and ^{13}C NMR (125 MHz, bottom) spectra for **poly LL$_{R}$**

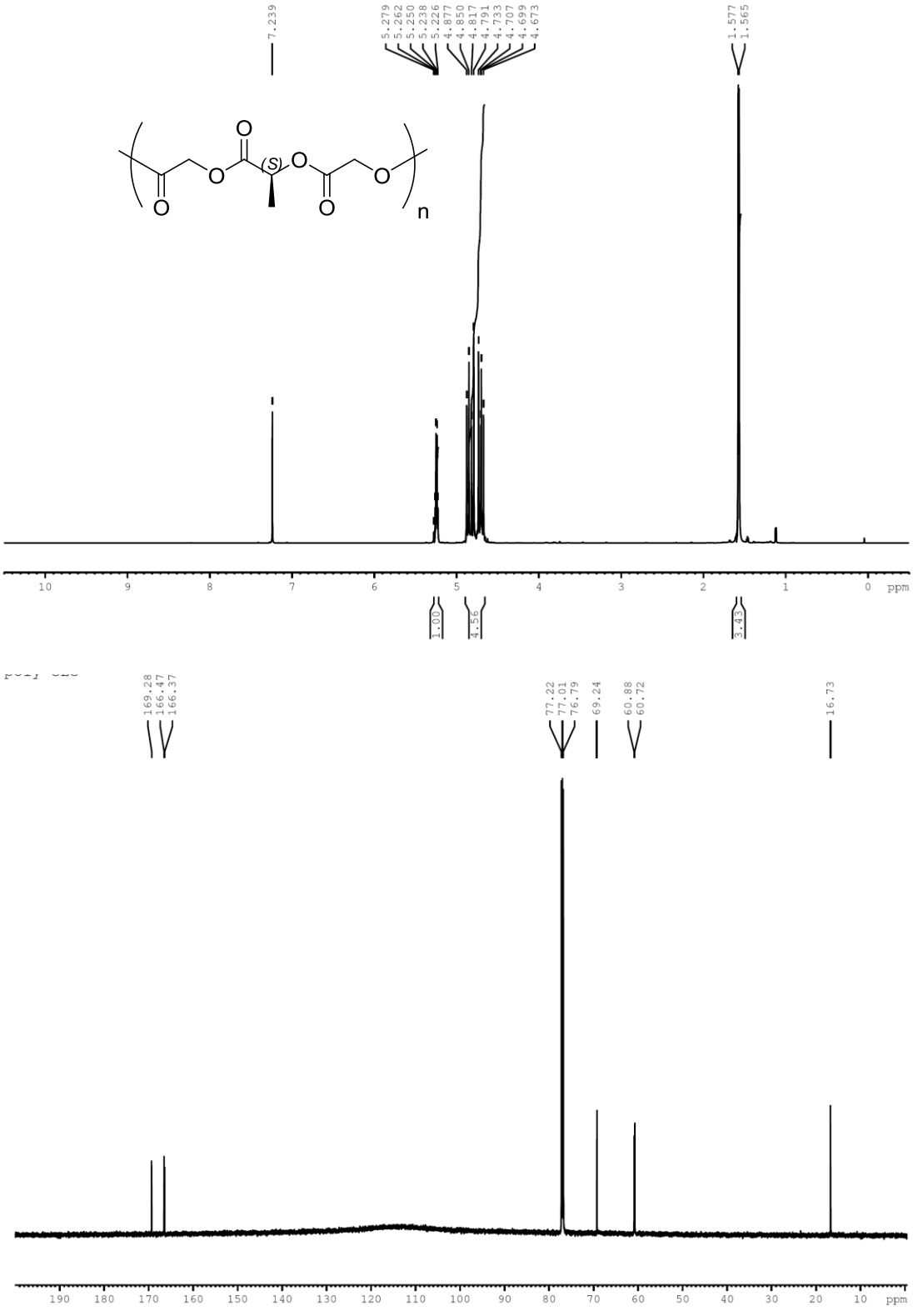


Figure 42. ^{1}H NMR (600 MHz, top) and ^{13}C NMR (125 MHz, bottom) spectra for **poly GLG**

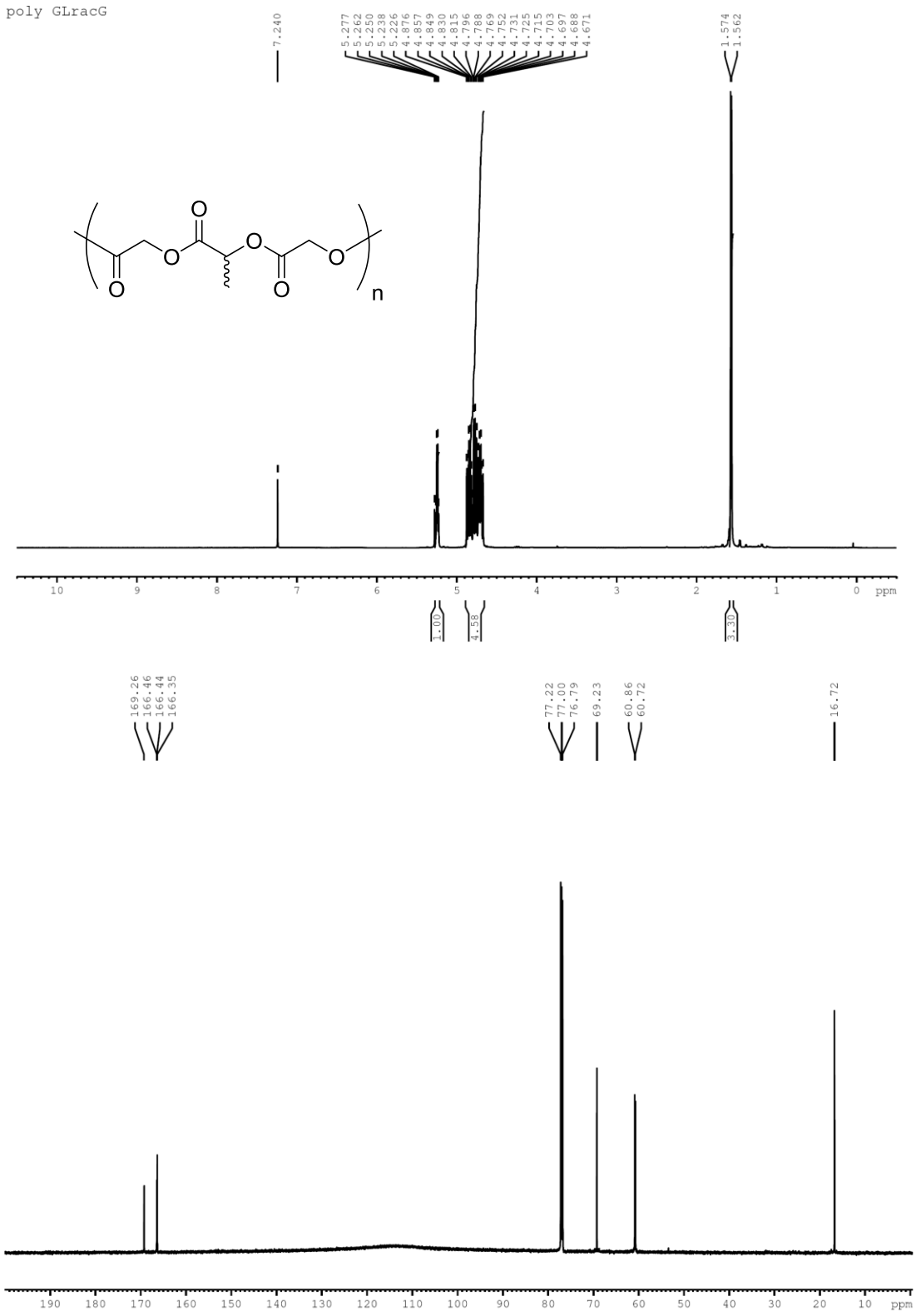


Figure 43. ^{1}H NMR (600 Hz, top) and ^{13}C NMR (125 MHz, bottom) spectra for **poly GL$_{rac}$G**

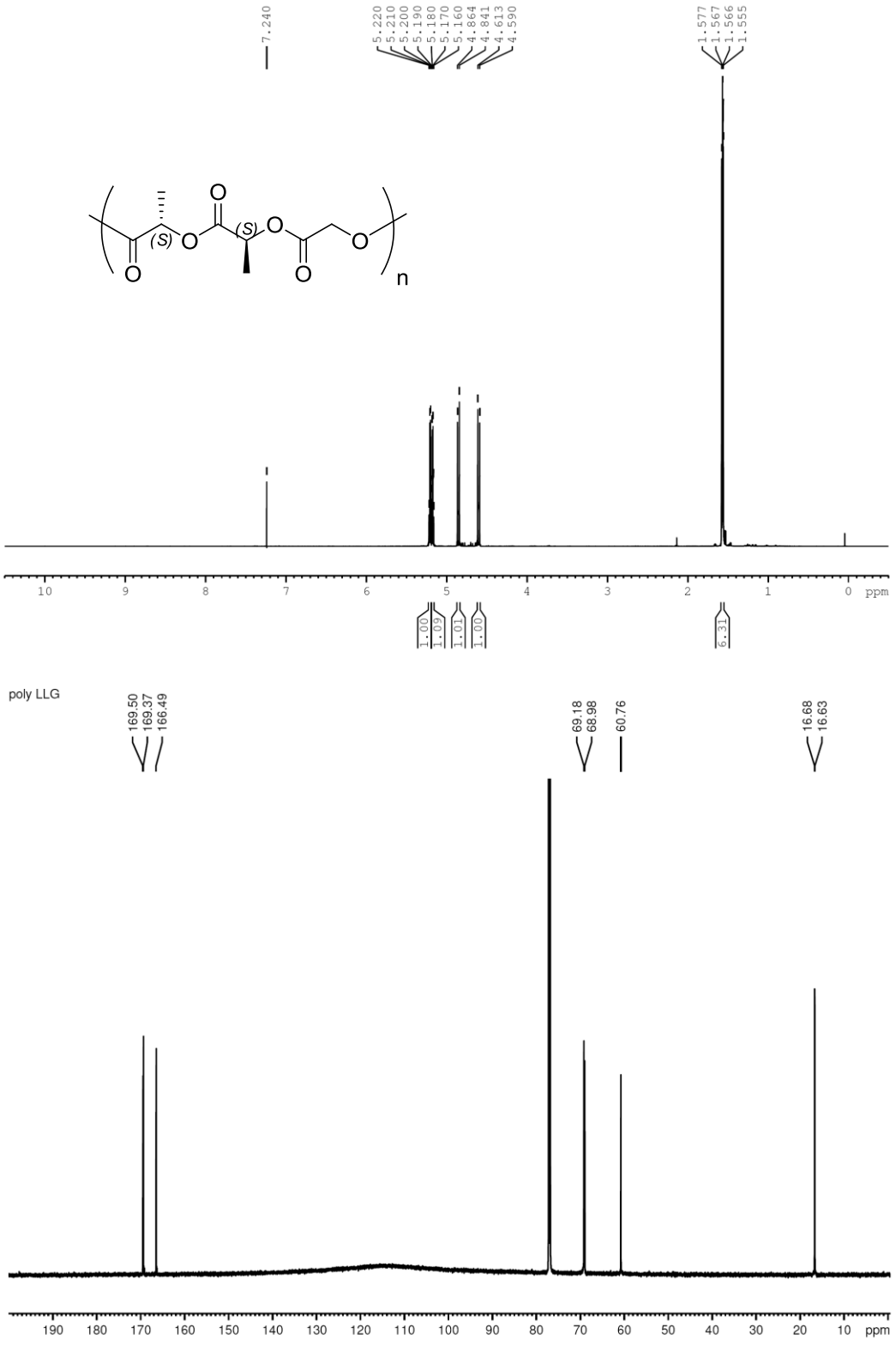


Figure 44. ^{1}H NMR (700 MHz, top) and ^{13}C NMR (175 MHz, bottom) spectra for **poly LLG**

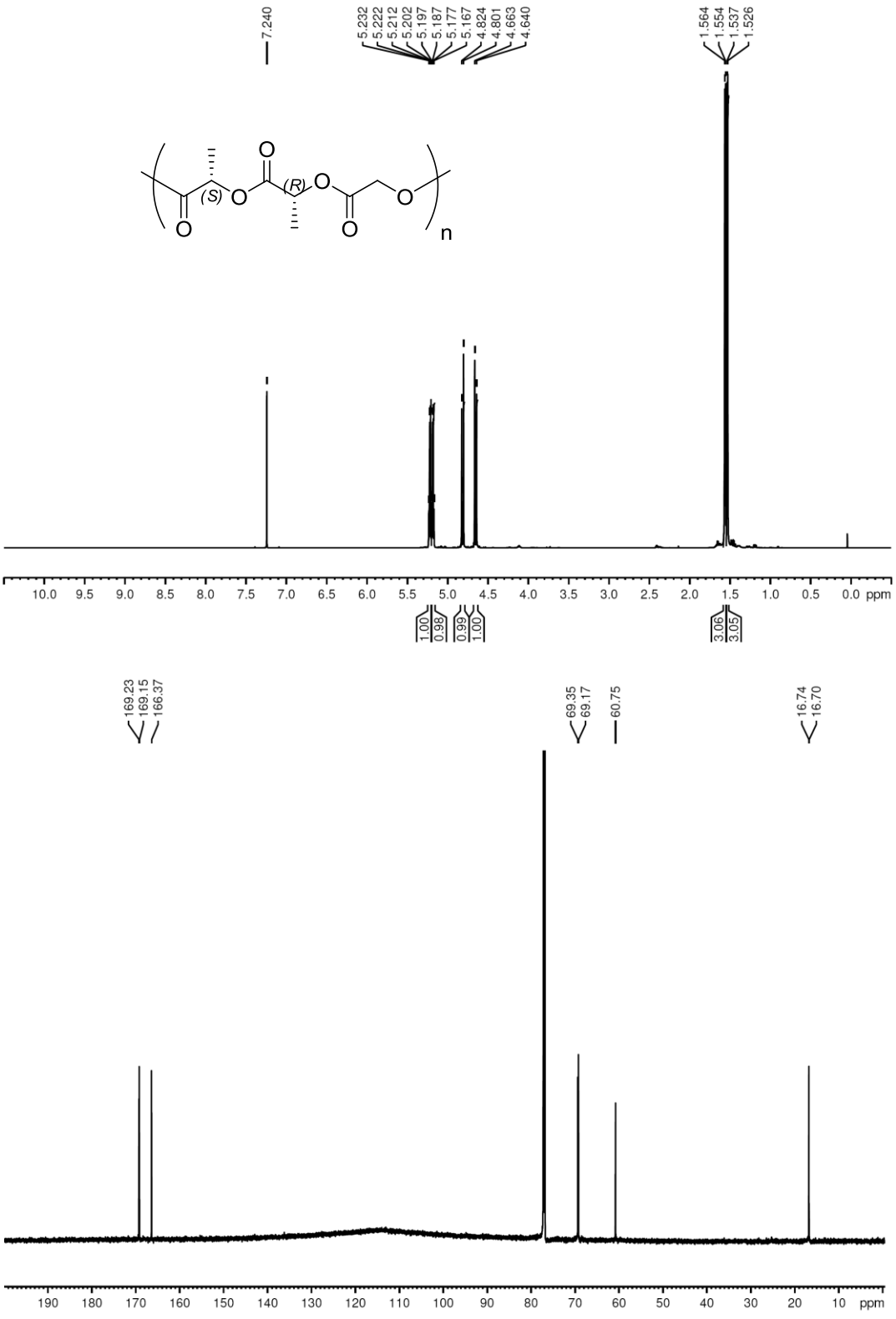


Figure 45. ^{1}H NMR (700 MHz, top) and ^{13}C NMR (175 MHz, bottom) spectra for **poly LL$_R$G**

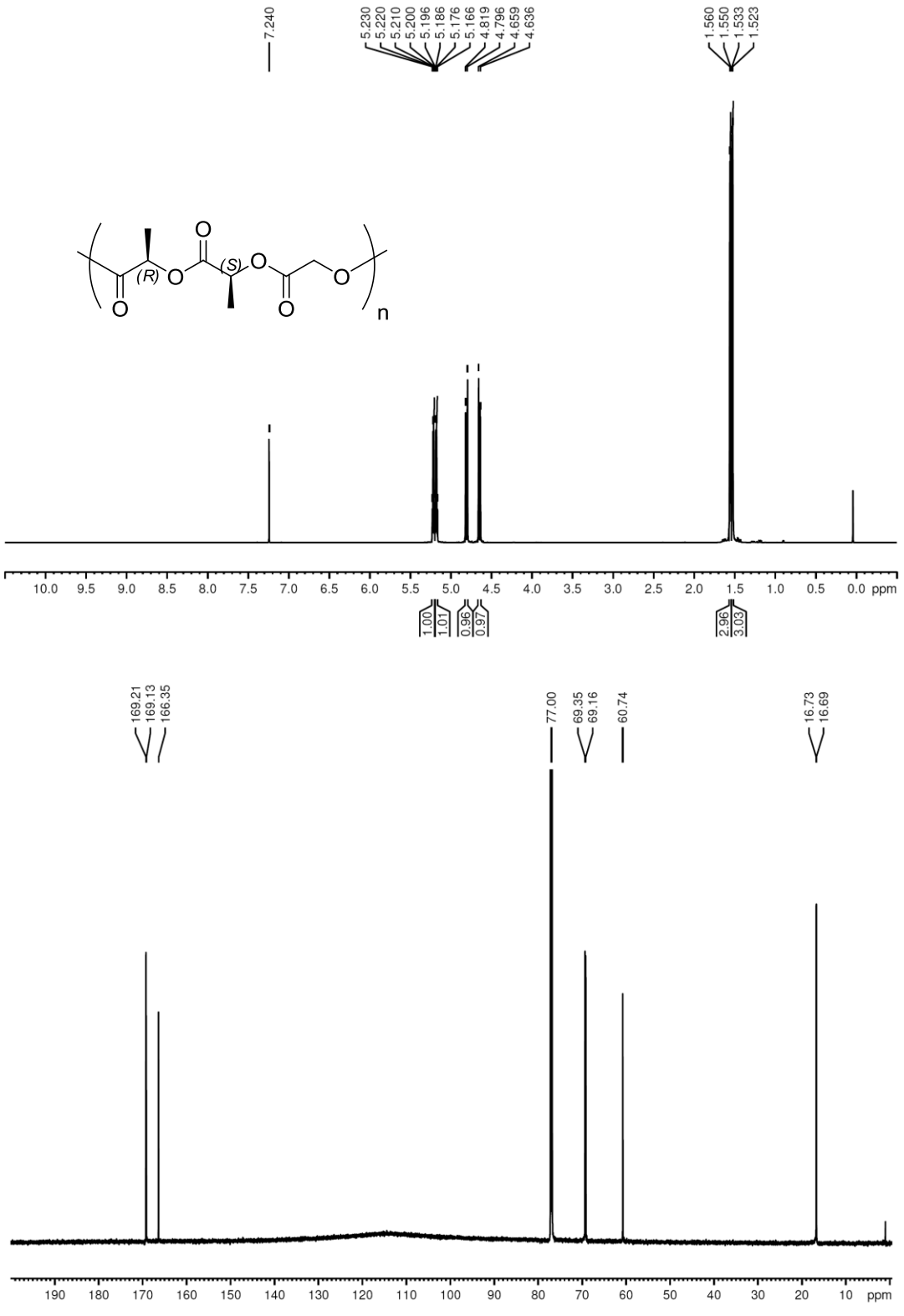


Figure 46. ^{1}H NMR (700 MHz, top) and ^{13}C NMR (175 MHz, bottom) spectra for **poly L$_R$LG**

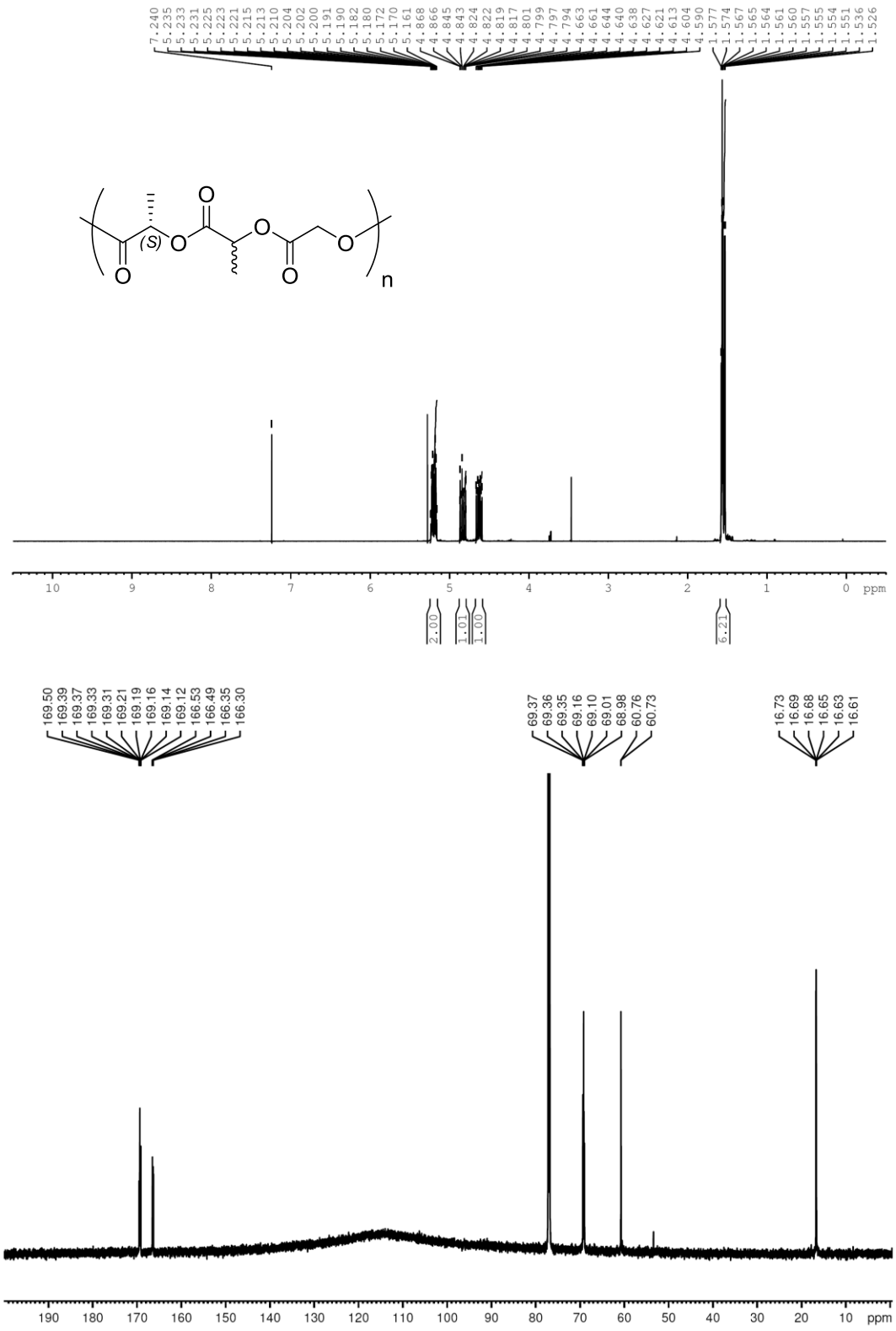


Figure 47. ^{1}H NMR (700 MHz, top) and ^{13}C NMR (175 MHz, bottom) spectra for **poly LL$_{rac}$G**

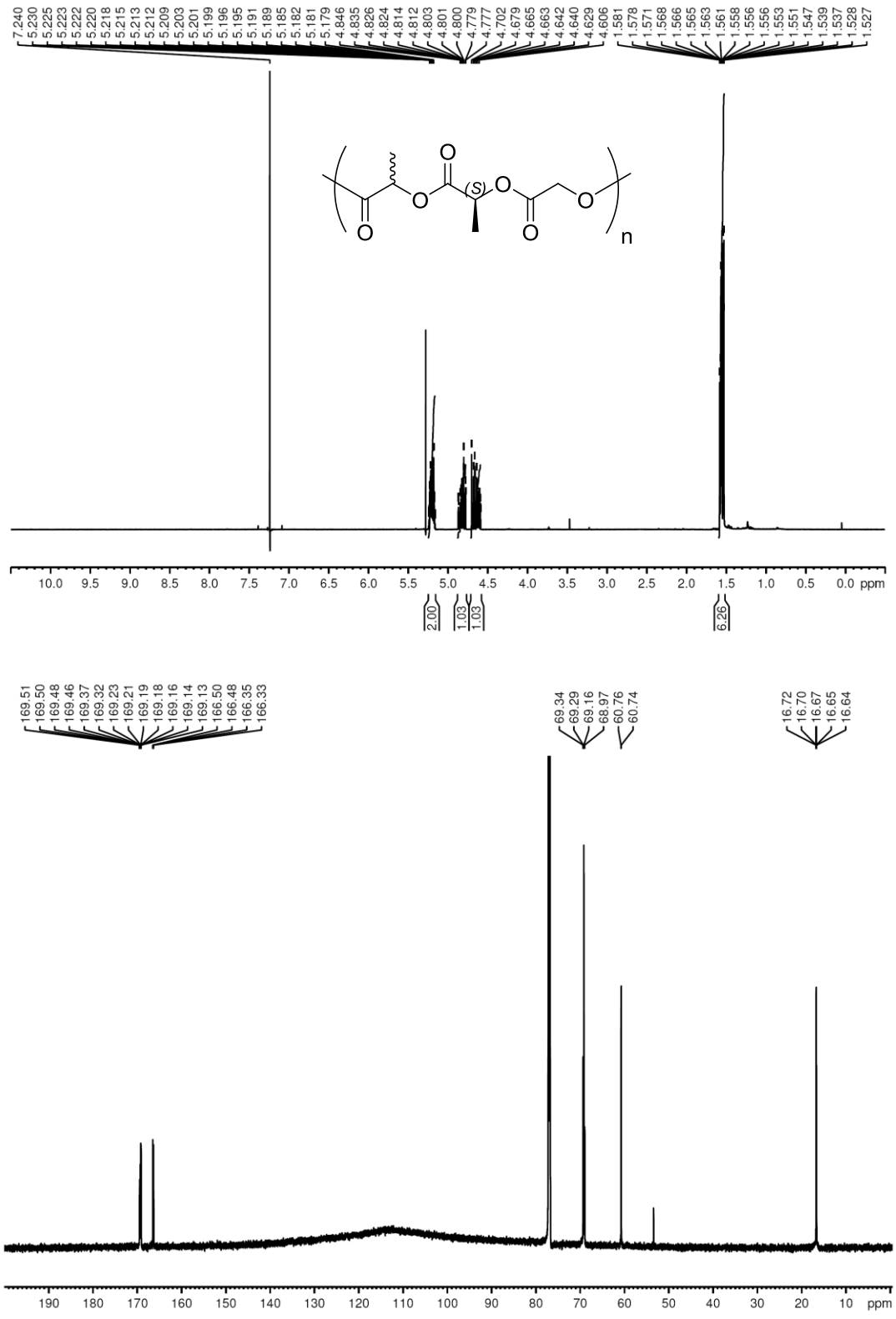


Figure 48. ^{1}H NMR (700 MHz, top) and ^{13}C NMR (175 MHz, bottom) spectra for **poly L$_{rac}$LG**

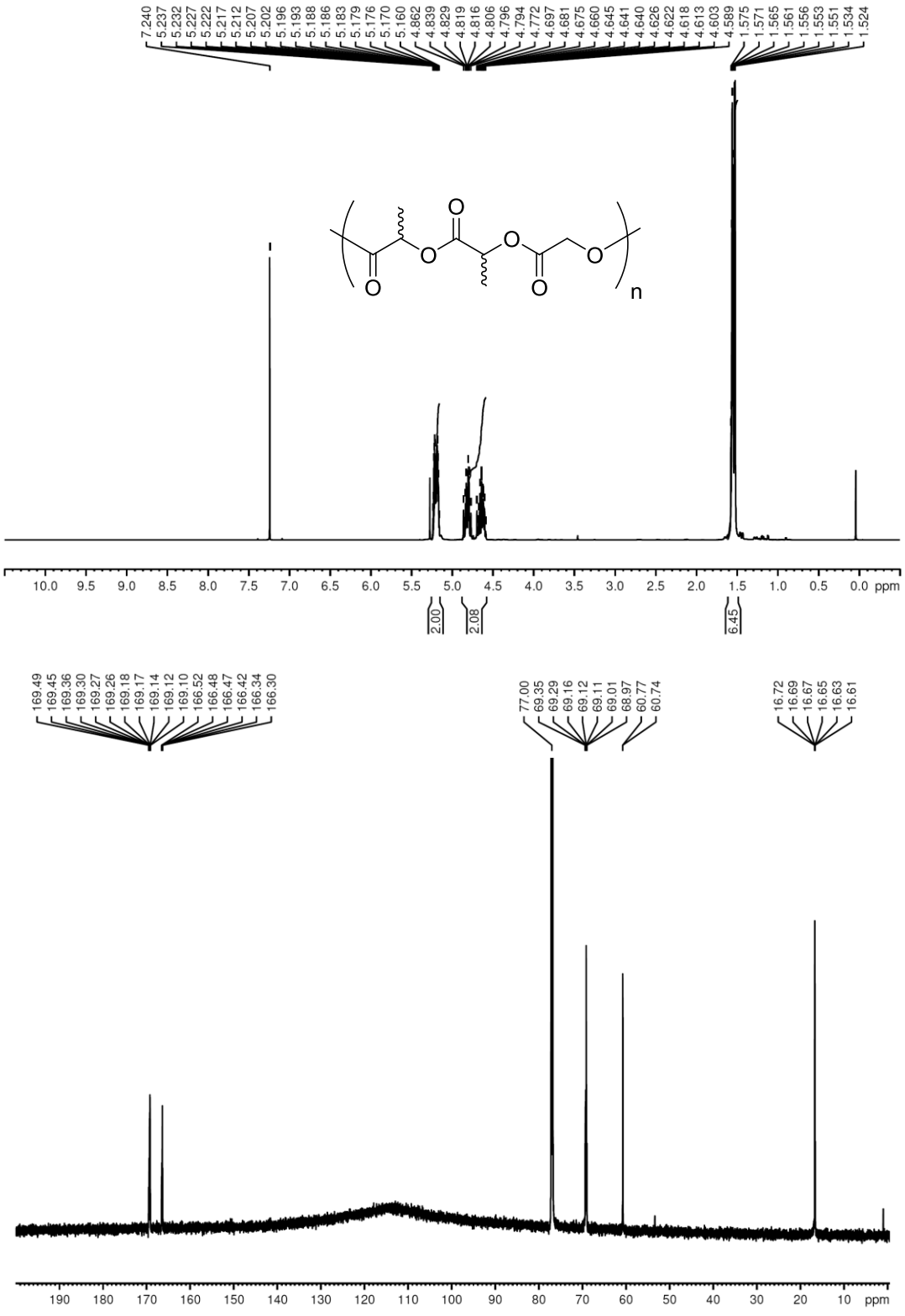


Figure 49. ^{1}H NMR (700 MHz, top) and ^{13}C NMR (175 MHz, bottom) spectra for **poly $L_{rac}L_{rac}G$**

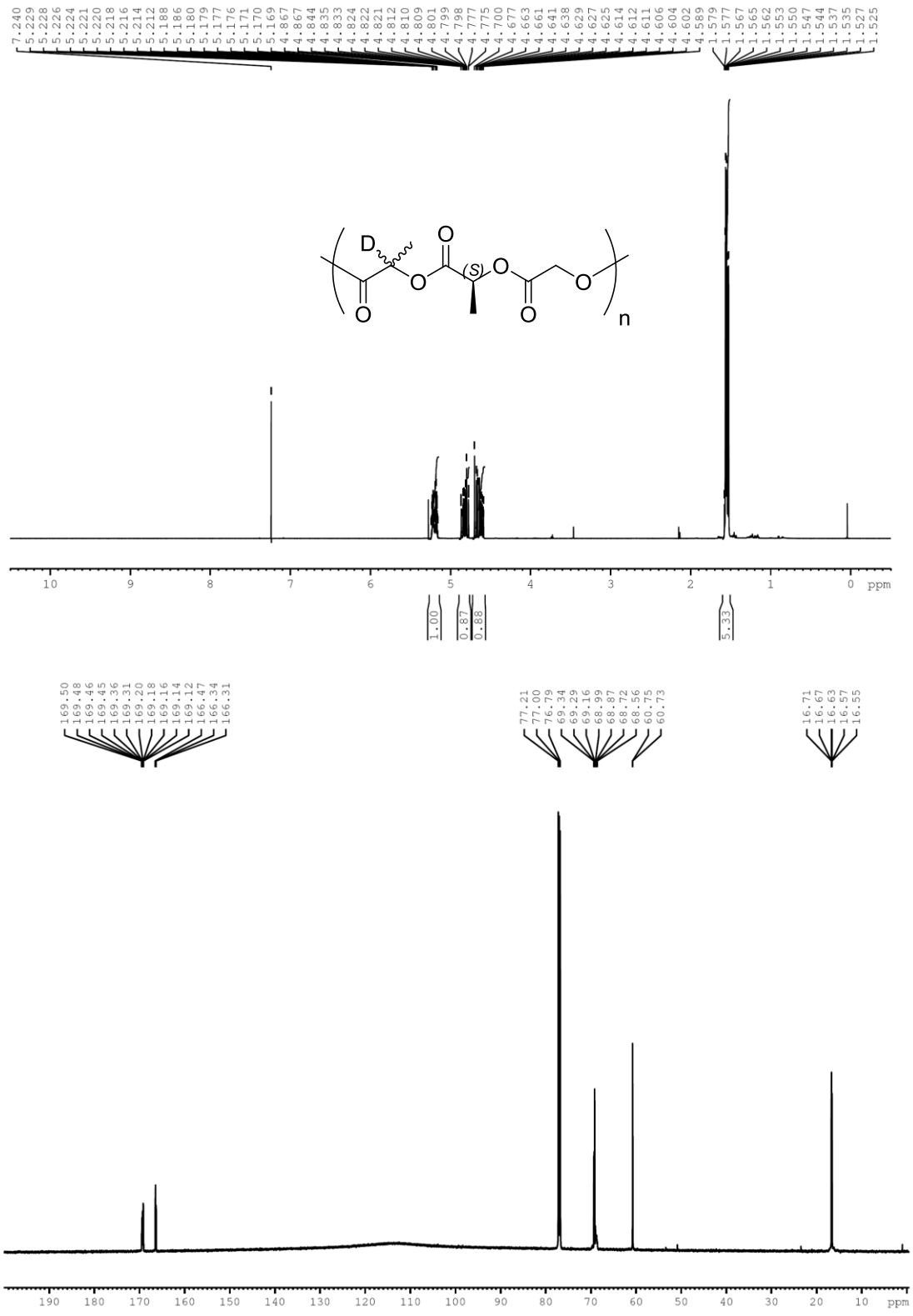


Figure 50. ^{1}H NMR (700 MHz, top) and ^{13}C NMR (125 MHz, bottom) spectra for **poly $L_{d,rac}$LG**

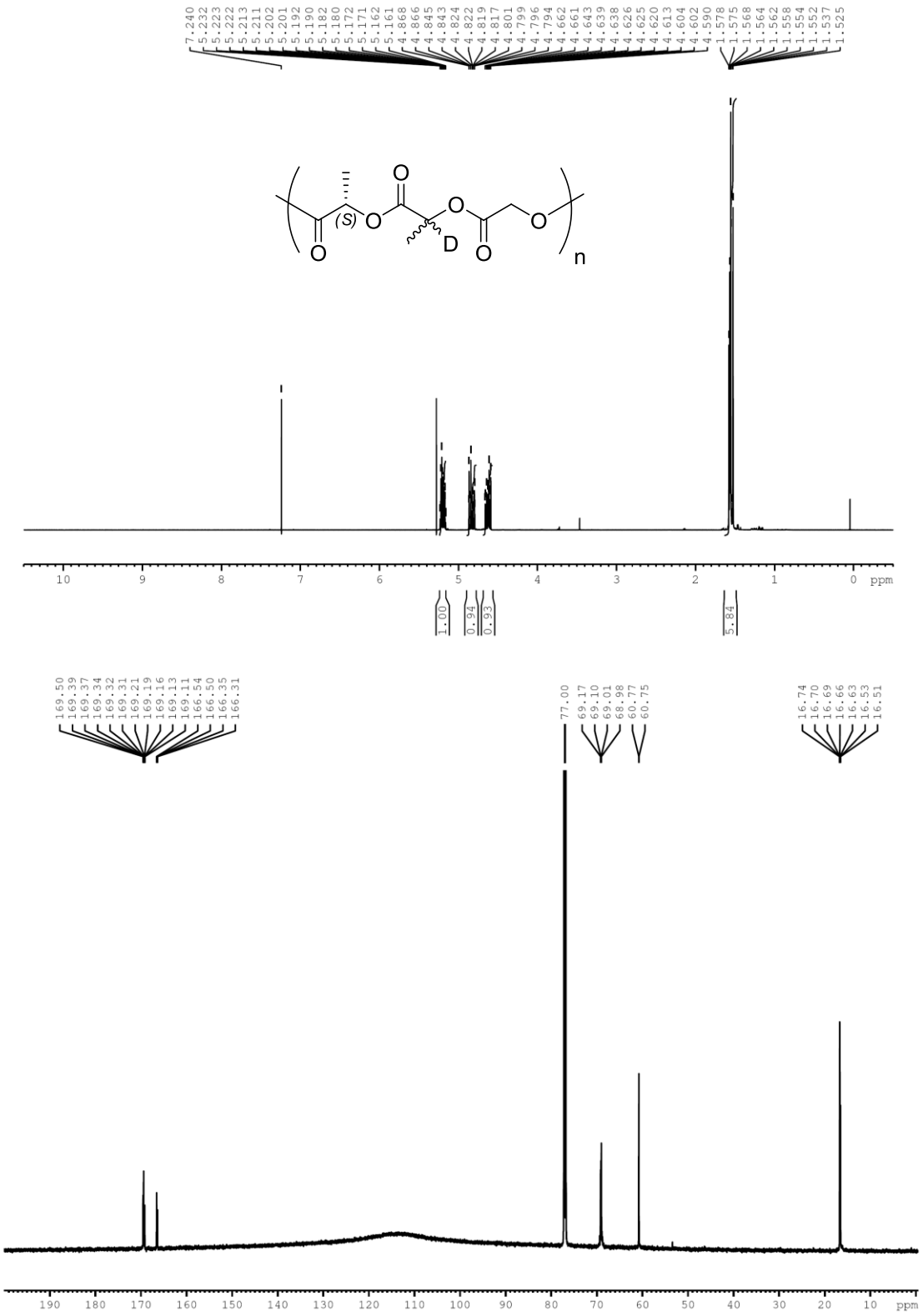


Figure 51. ^{1}H NMR (700 MHz, top) and ^{13}C NMR (125 MHz, bottom) spectra for **poly LL$_{\mathbf{d,}rac}$G**

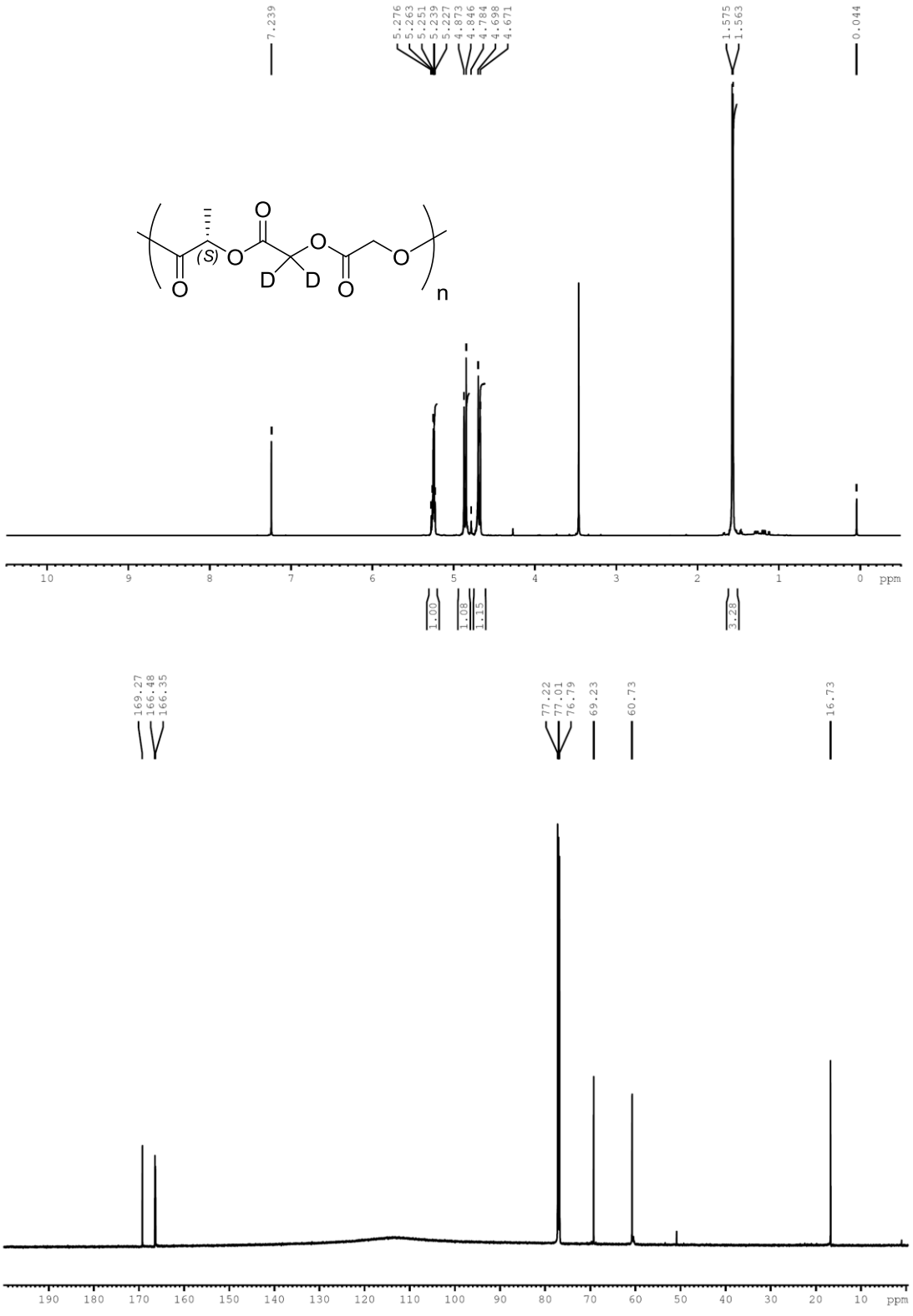


Figure 52. ^{1}H NMR (600 MHz, top) and ^{13}C NMR (125 MHz, bottom) spectra for **poly LG$_{d2}$G**

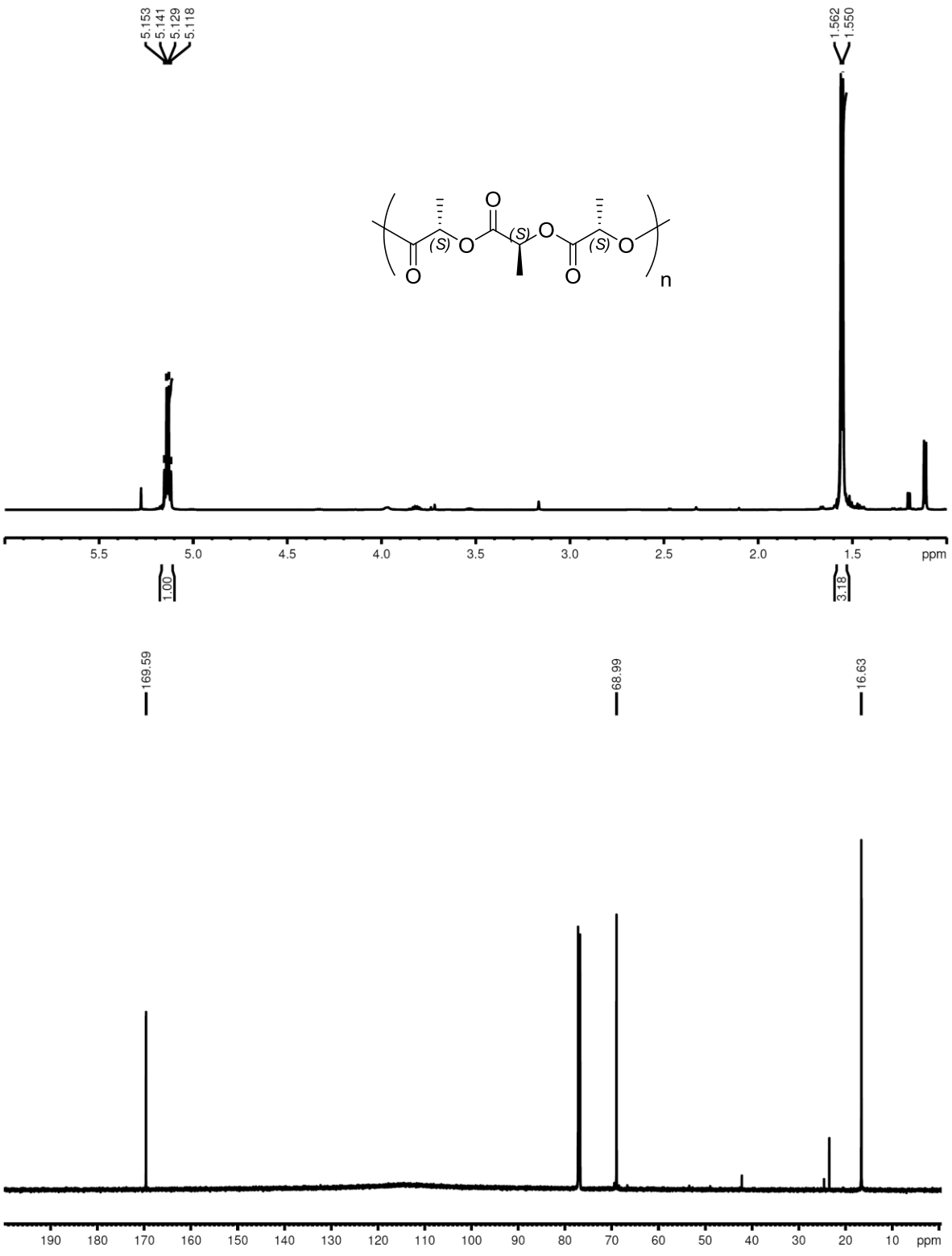


Figure 53. ^{1}H NMR (600 MHz, top) and ^{13}C NMR (125 MHz, bottom) spectra for **poly LLL**

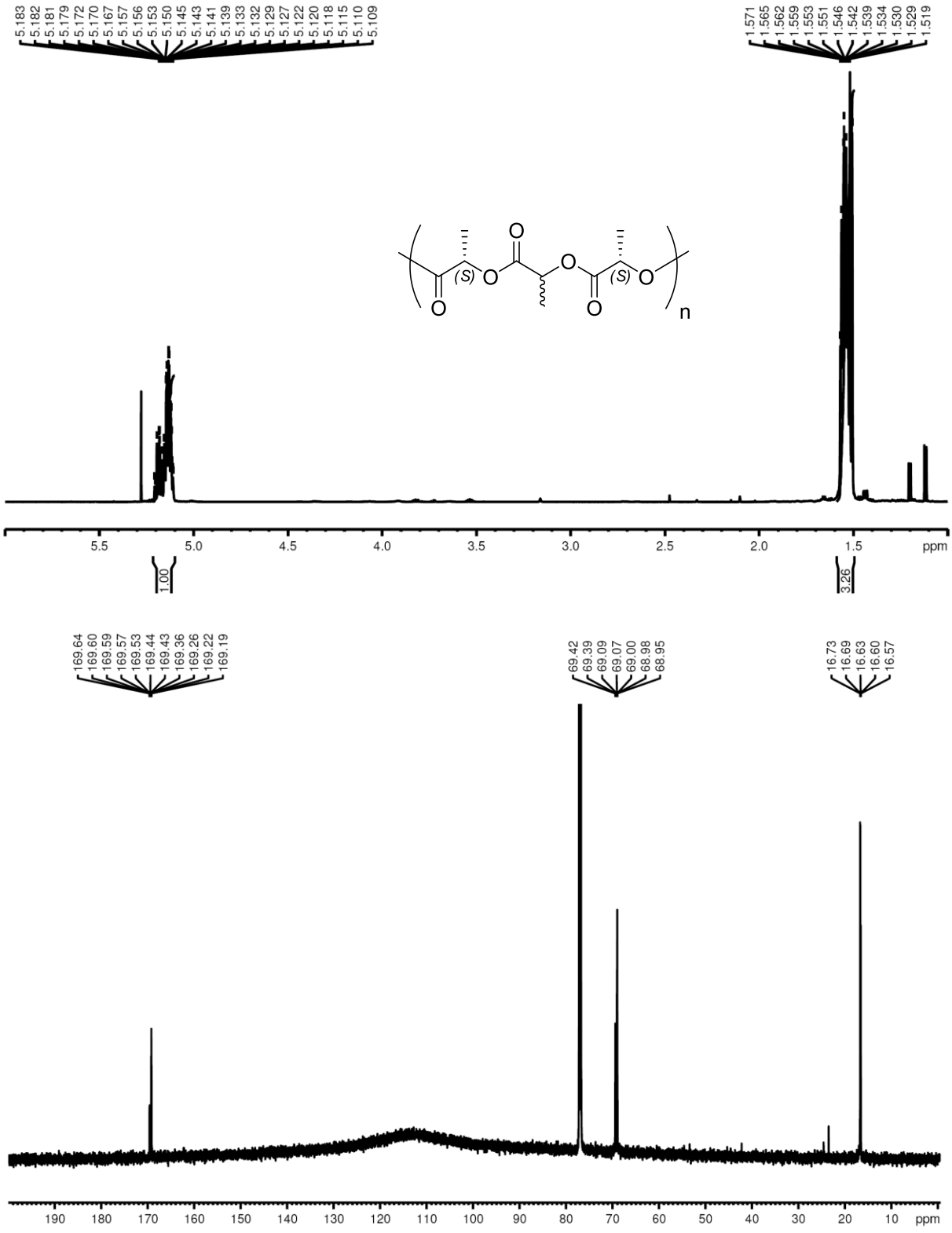


Figure 54. ^{1}H NMR (600 MHz, top) and ^{13}C NMR (125 MHz, bottom) spectra for **poly LL$_{rac}$L**

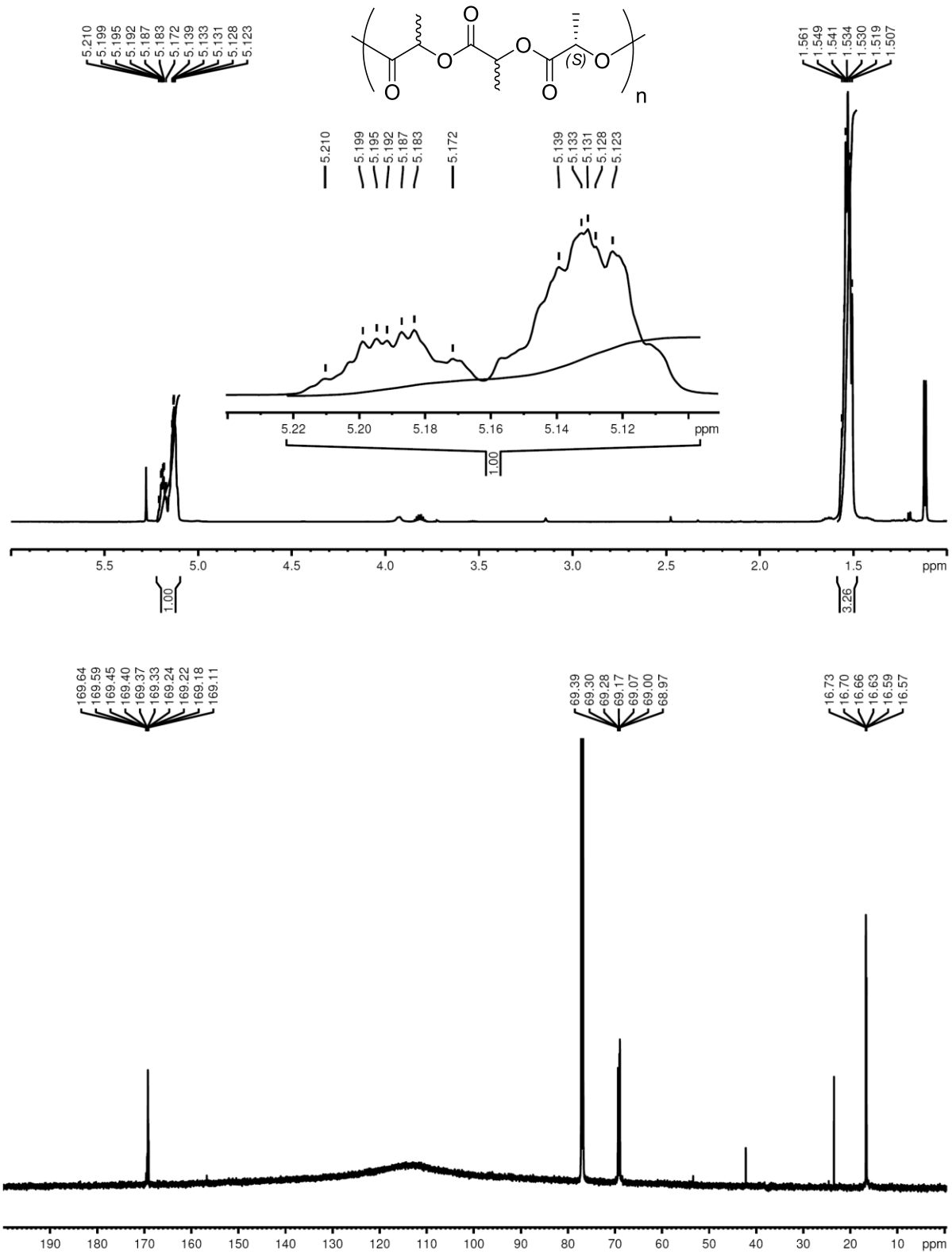


Figure 55. ^{1}H NMR (600 MHz, top) and ^{13}C NMR (125 MHz, bottom) spectra for **poly L$_{rac}$L$_{rac}$L**

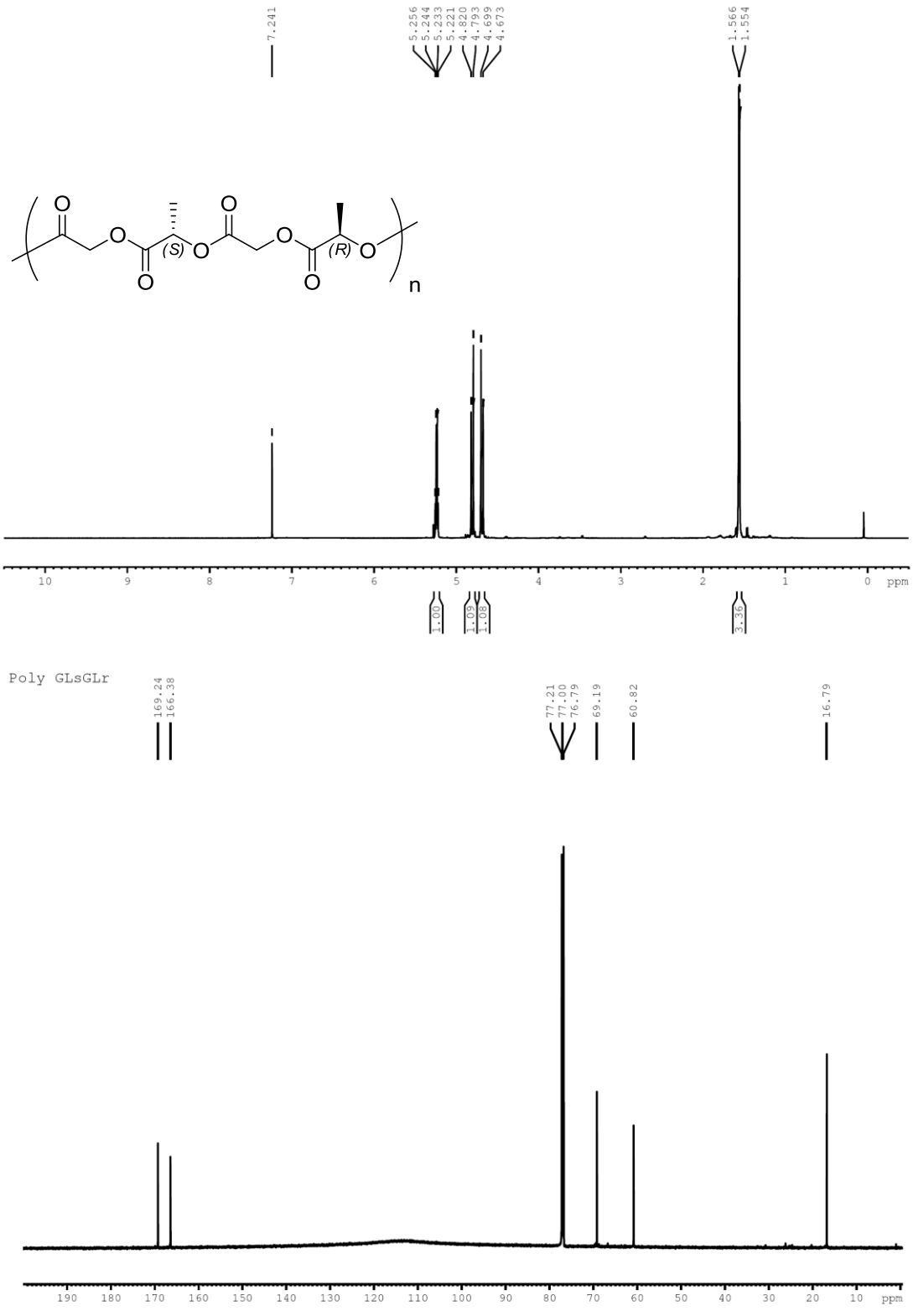


Figure 56. ^{1}H NMR (600 MHz, top) and ^{13}C NMR (125 MHz, bottom) spectra for **poly GLGL$_{R}$**

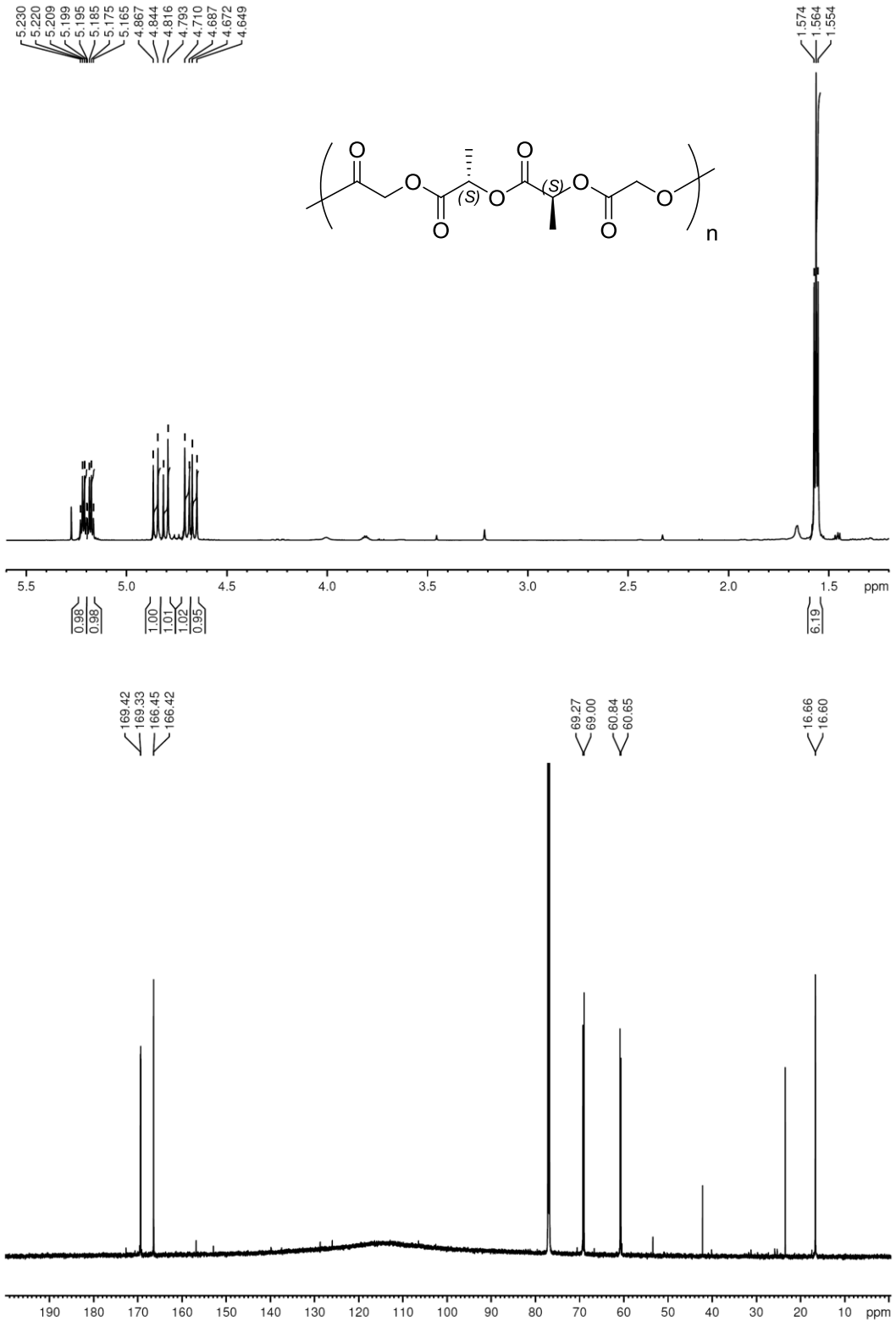


Figure 57. ^{1}H NMR (700 MHz, top) and ^{13}C NMR (175 MHz, bottom) spectra for **poly GLLG**

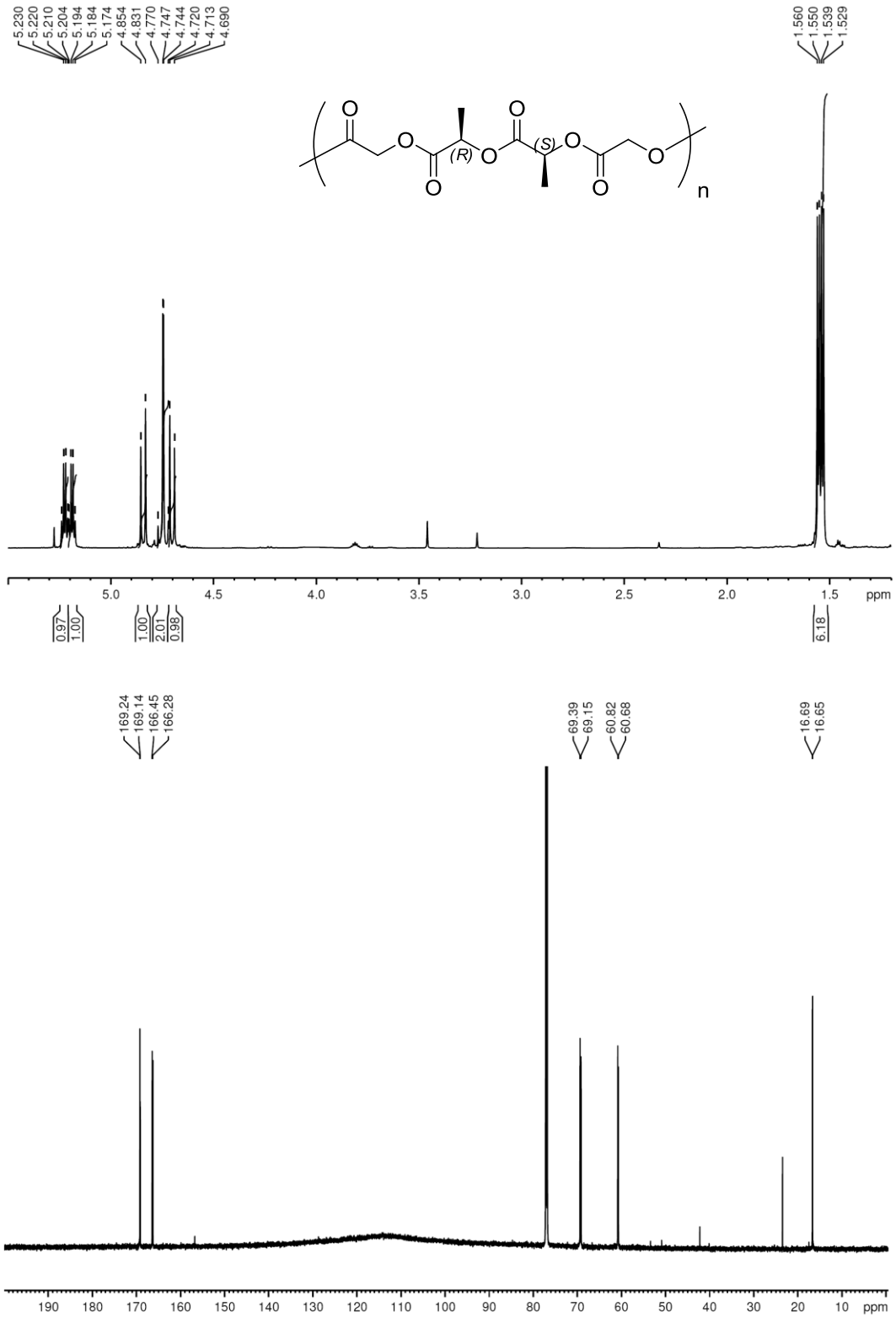


Figure 58. ^{1}H NMR (700 MHz, top) and ^{13}C NMR (175 MHz, bottom) spectra for **poly GL$_R$LG**

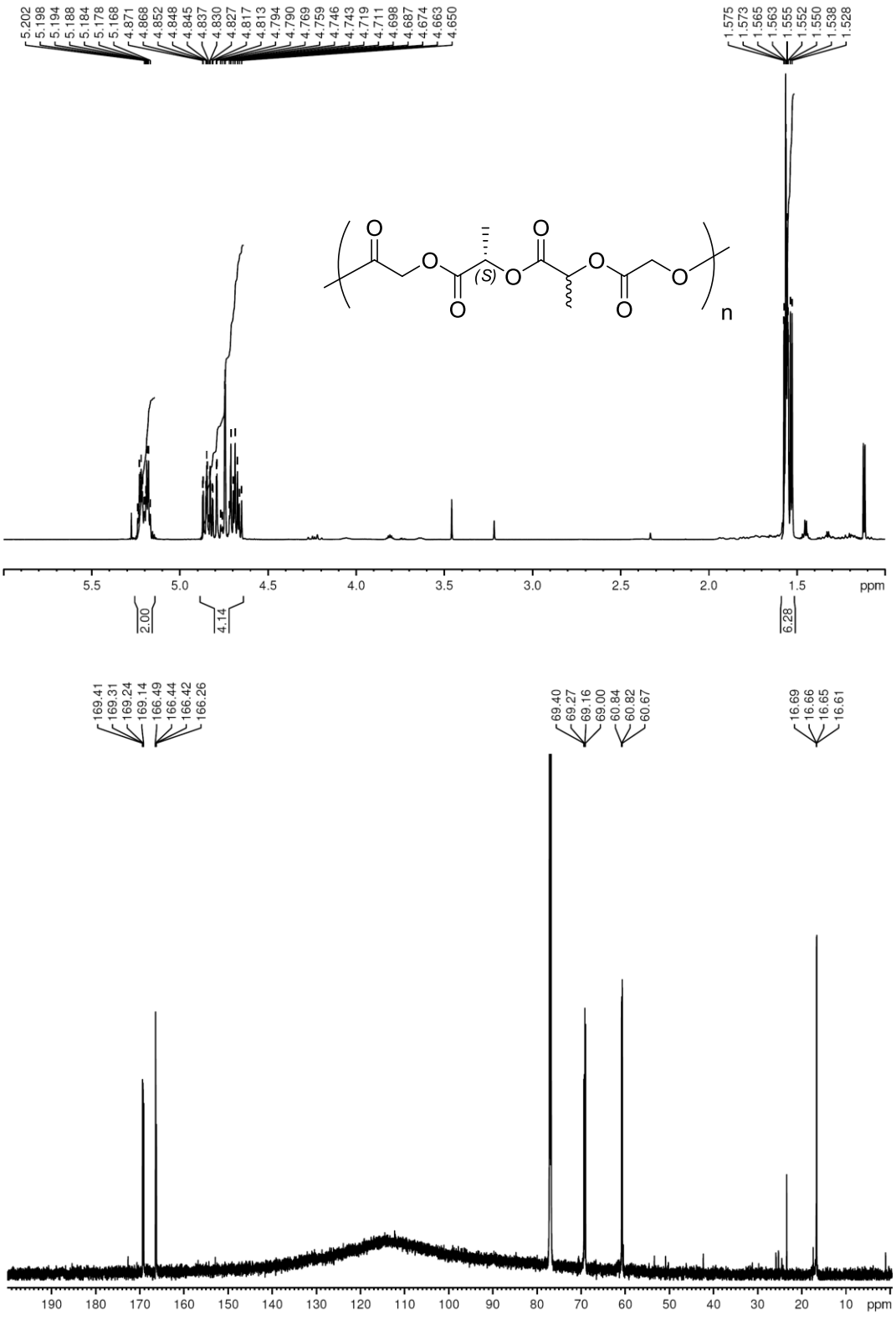


Figure 59. ^{1}H NMR (700 MHz, top) and ^{13}C NMR (175 MHz, bottom) spectra for **poly GLL$_{rac}$G**

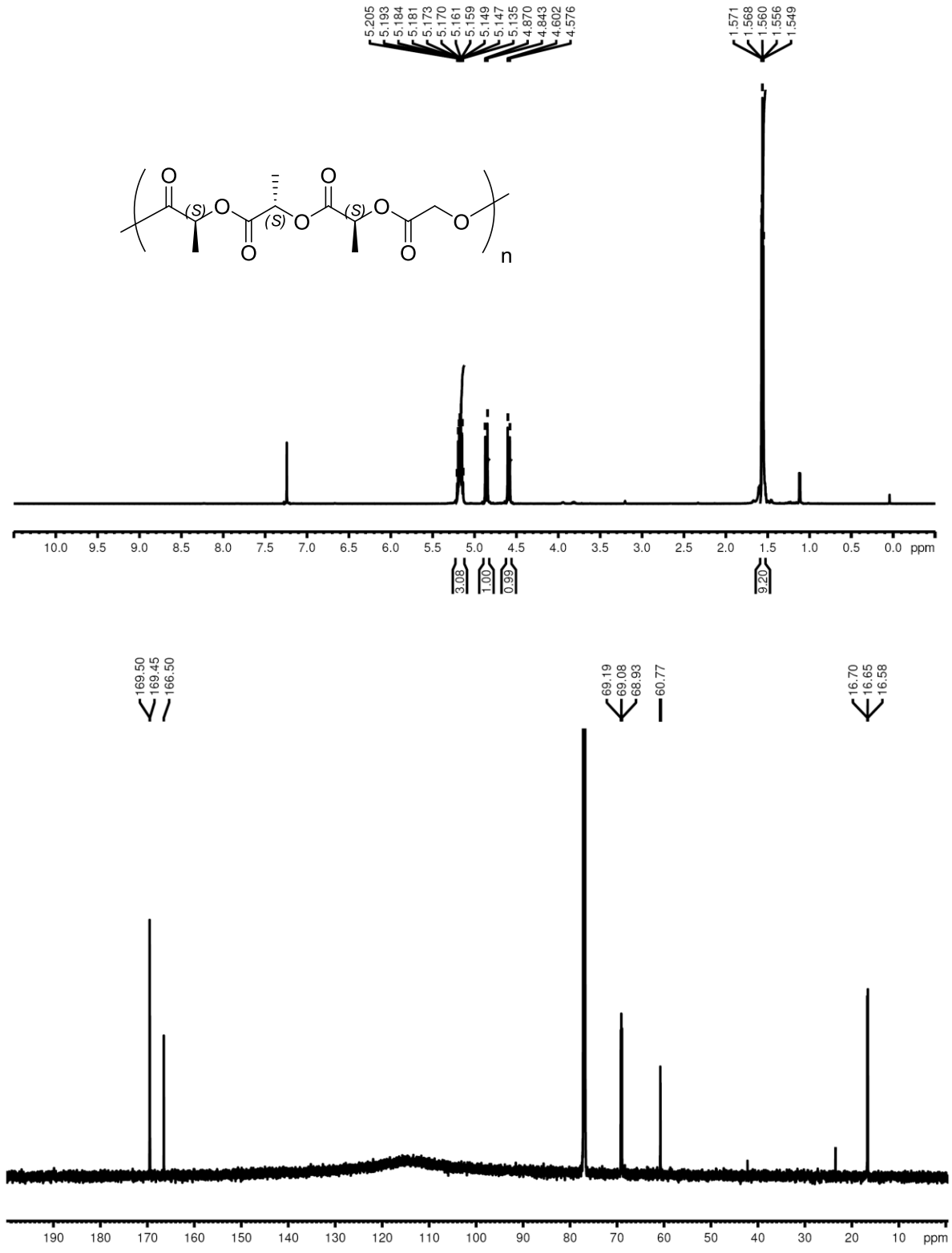


Figure 60. ^{1}H NMR (600 MHz, top) and ^{13}C NMR (125 MHz, bottom) spectra for **poly LLLG**

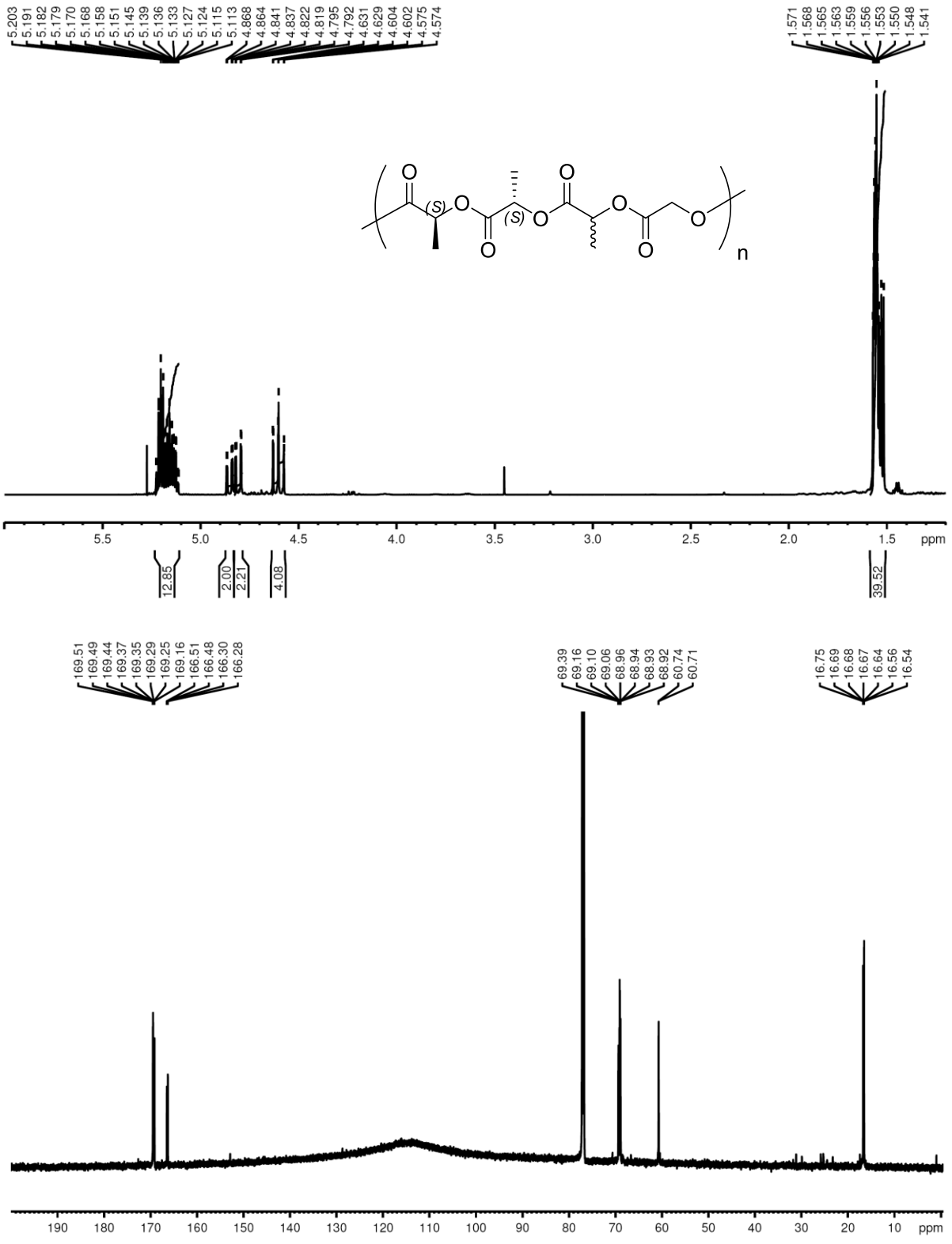


Figure 61. ^{1}H NMR (600 MHz, top) and ^{13}C NMR (125 MHz, bottom) spectra for **poly LLL$_{rac}$G**

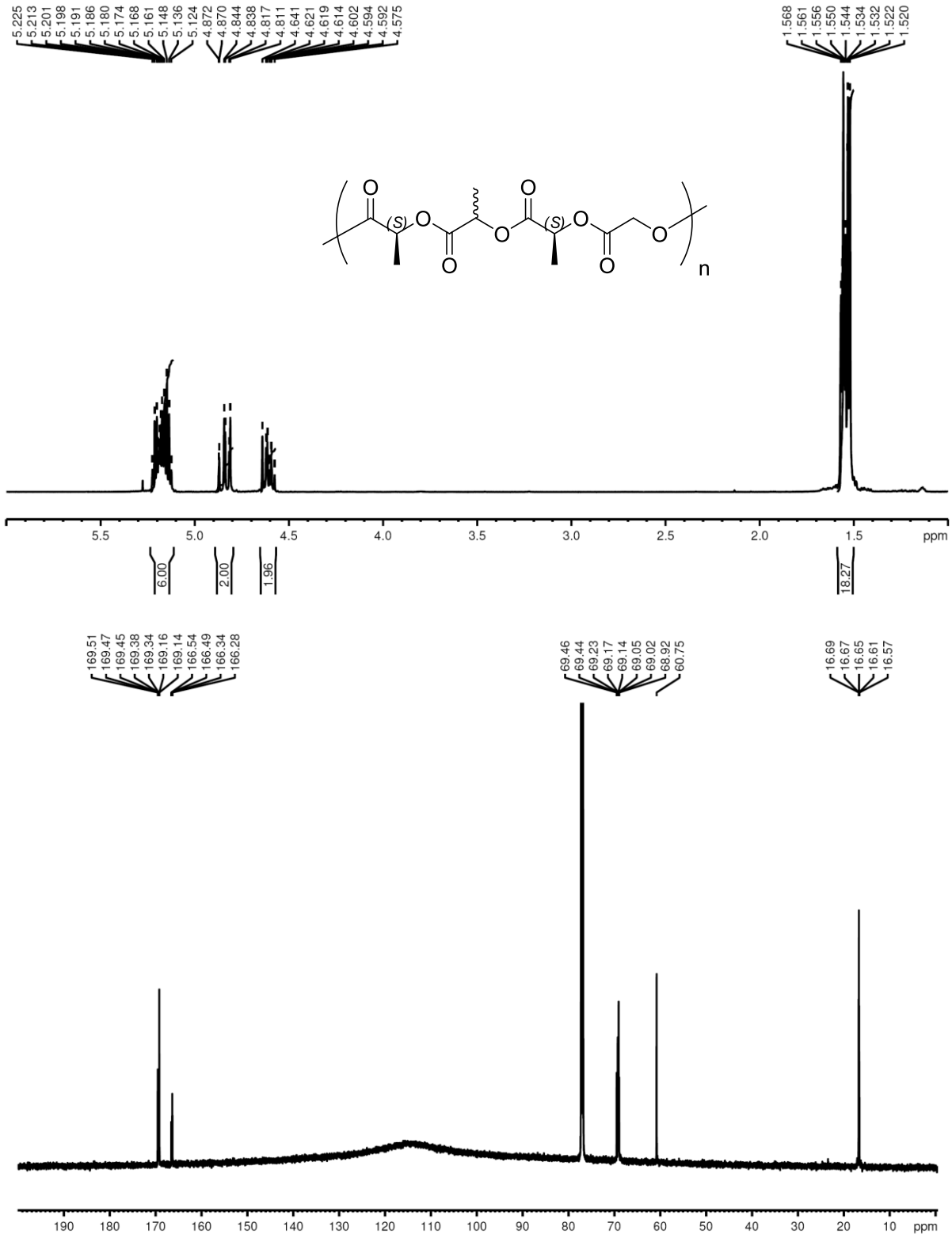


Figure 62. ^{1}H NMR (600 MHz, top) and ^{13}C NMR (125 MHz, bottom) spectra for **poly LL$_{rac}$LG**

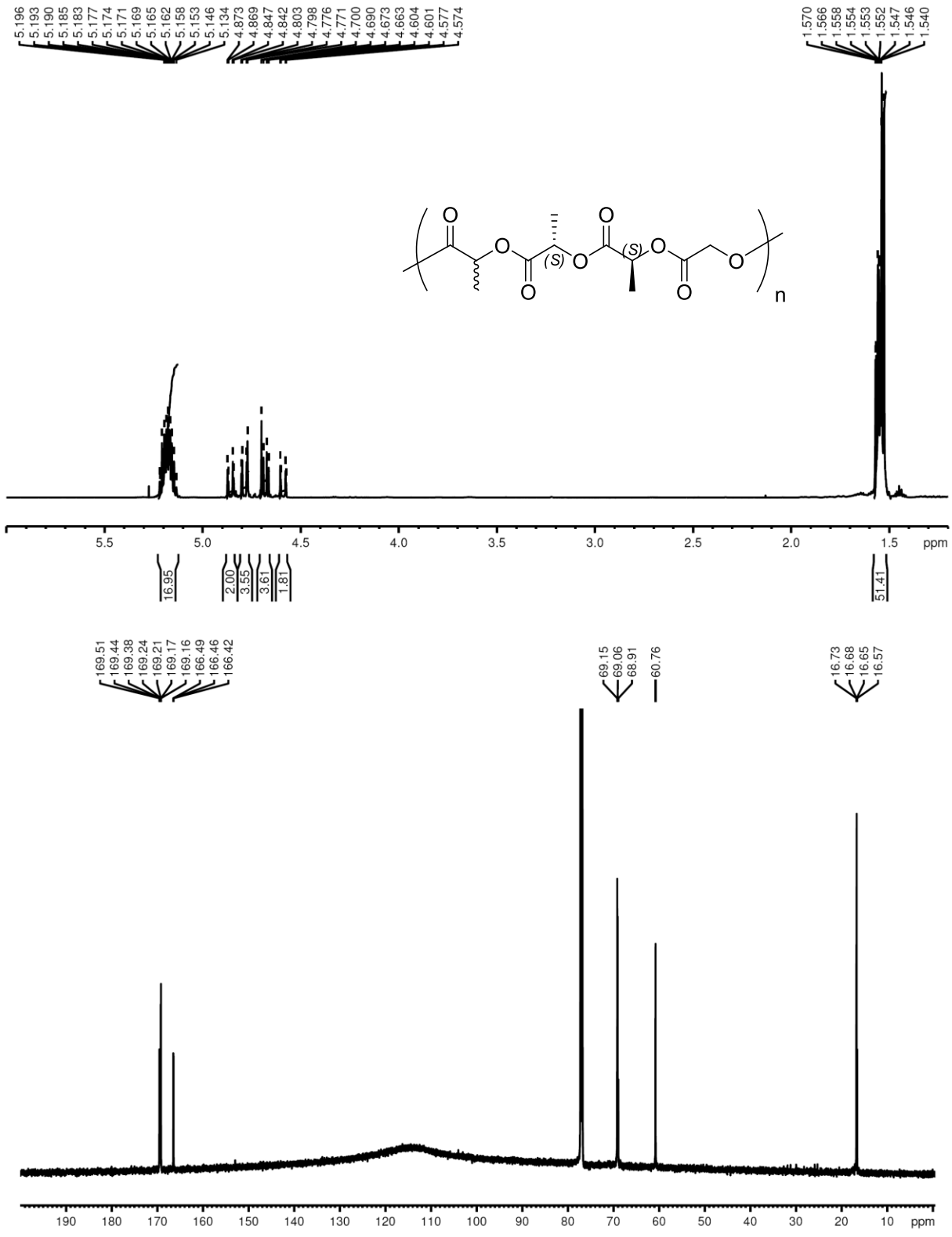


Figure 63. ^{1}H NMR (600 MHz, top) and ^{13}C NMR (125 MHz, bottom) spectra for **poly L$_{rac}$LLG**

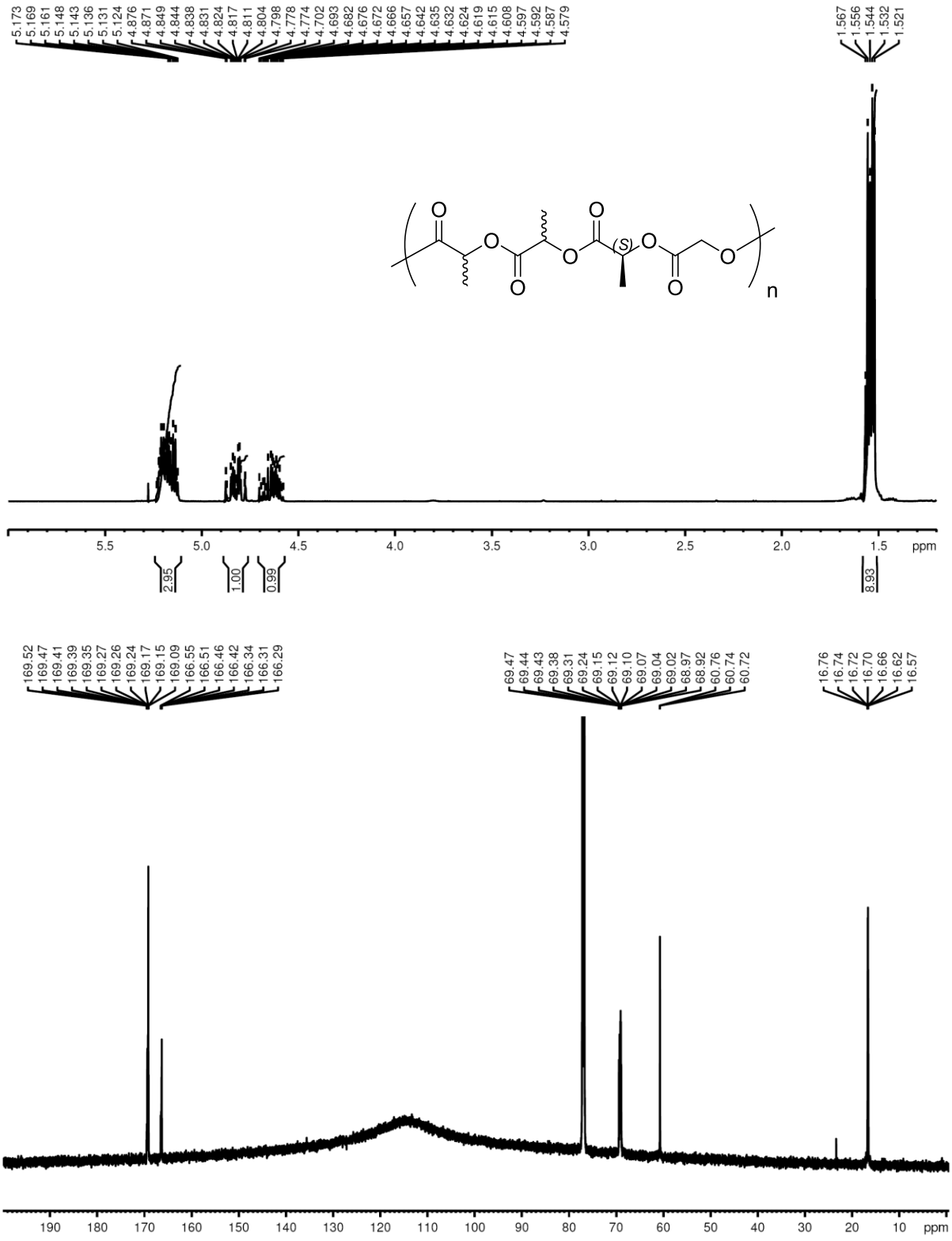


Figure 64. ^{1}H NMR (600 MHz, top) and ^{13}C NMR (125 MHz, bottom) spectra for **poly $L_{rac}L_{rac}LG$**

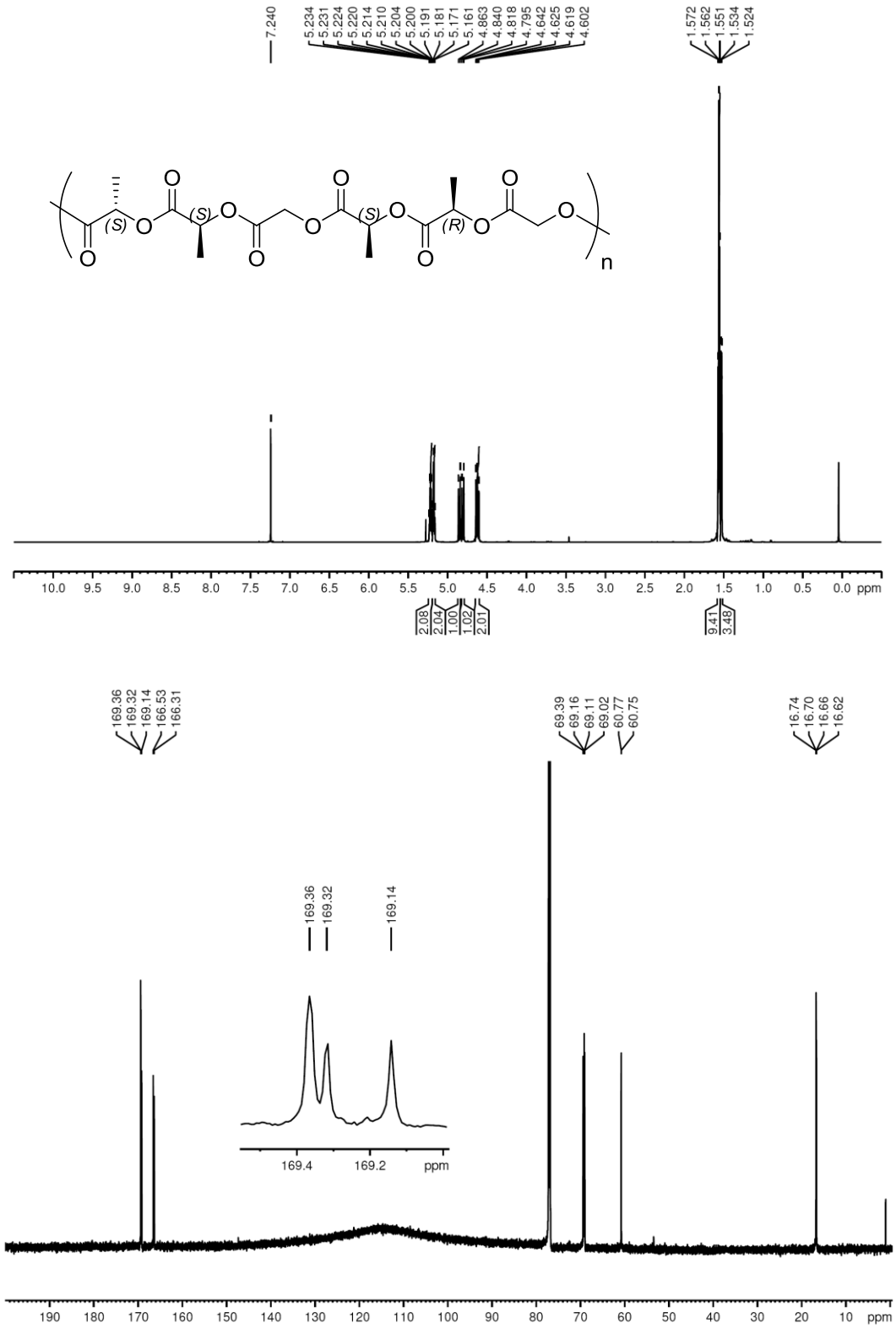


Figure 65. ^{1}H NMR (700 MHz, top) and ^{13}C NMR (175 MHz, bottom) spectra for **poly LLGLL$_R$G**

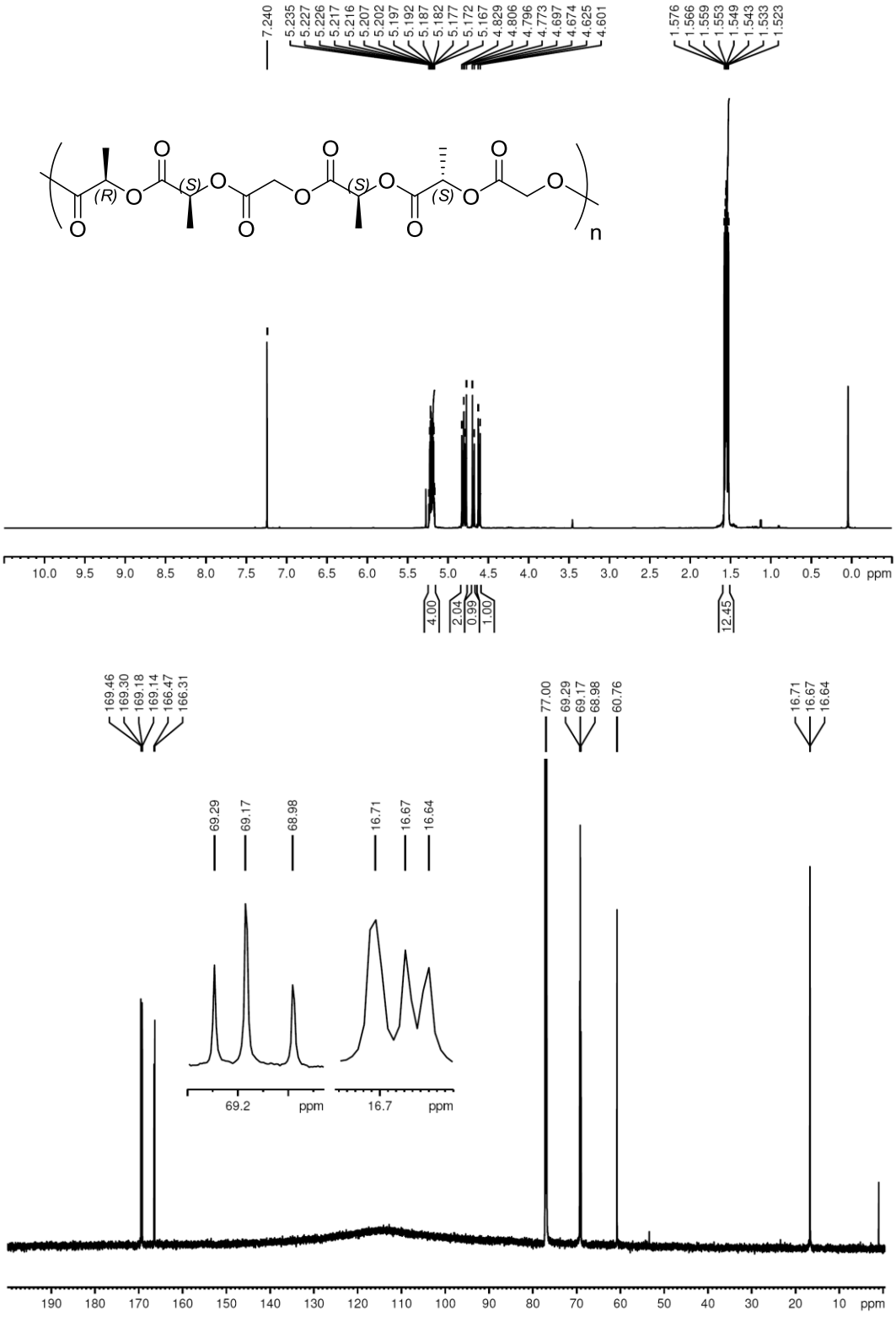


Figure 66. ^{1}H NMR (700 MHz, top) and ^{13}C NMR (175 MHz, bottom) spectra for **poly L$_R$LGLLG**

A.3 SELECTED DIFFERENTIAL SCANNING CALORIMOGRAMS

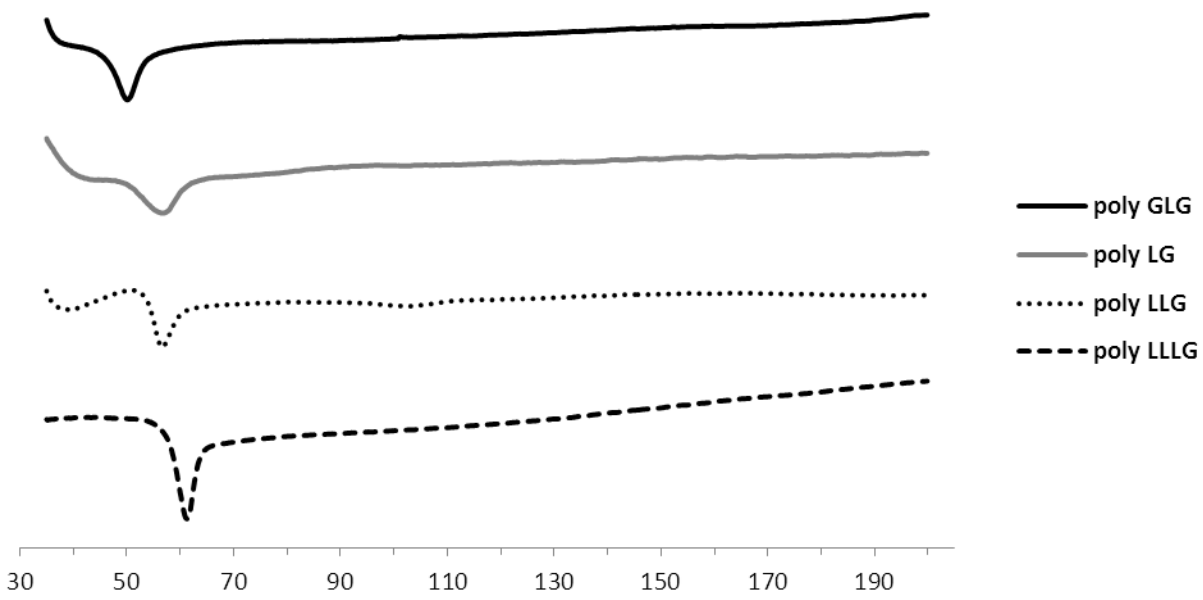


Figure 67. DSC traces for **poly GLG**, **LG**, **LLG** and **LLLG**. Data is from second heating cycle.

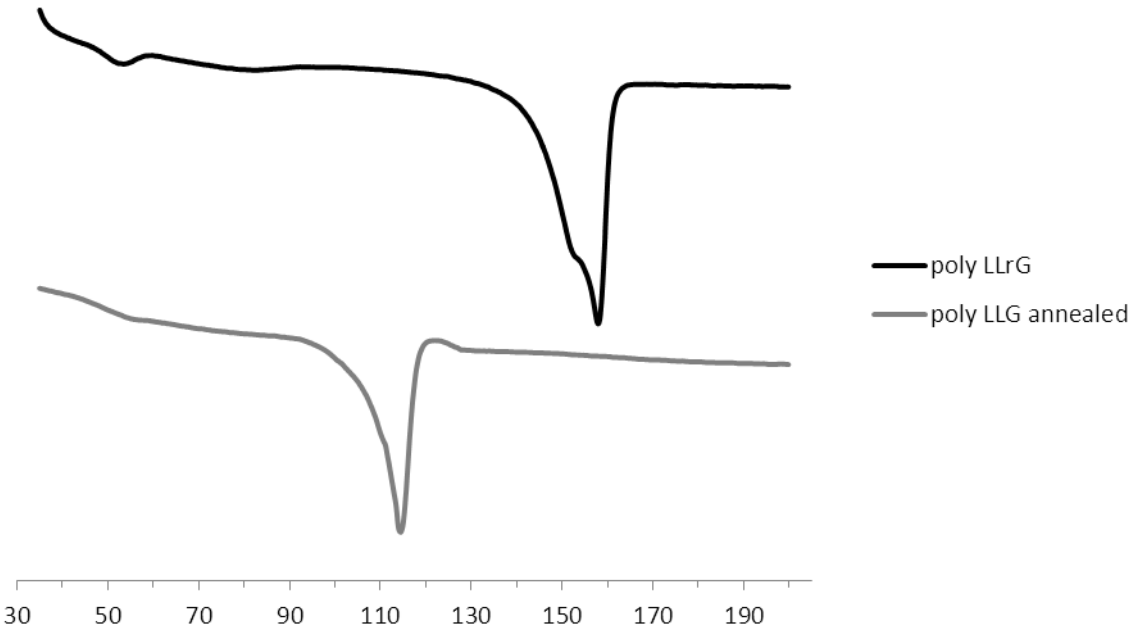


Figure 68. DSC trace for **poly LL$_R$G** (without annealing) and **LLG** annealed for 3 h at 85 °C. Data is from first heating cycle.

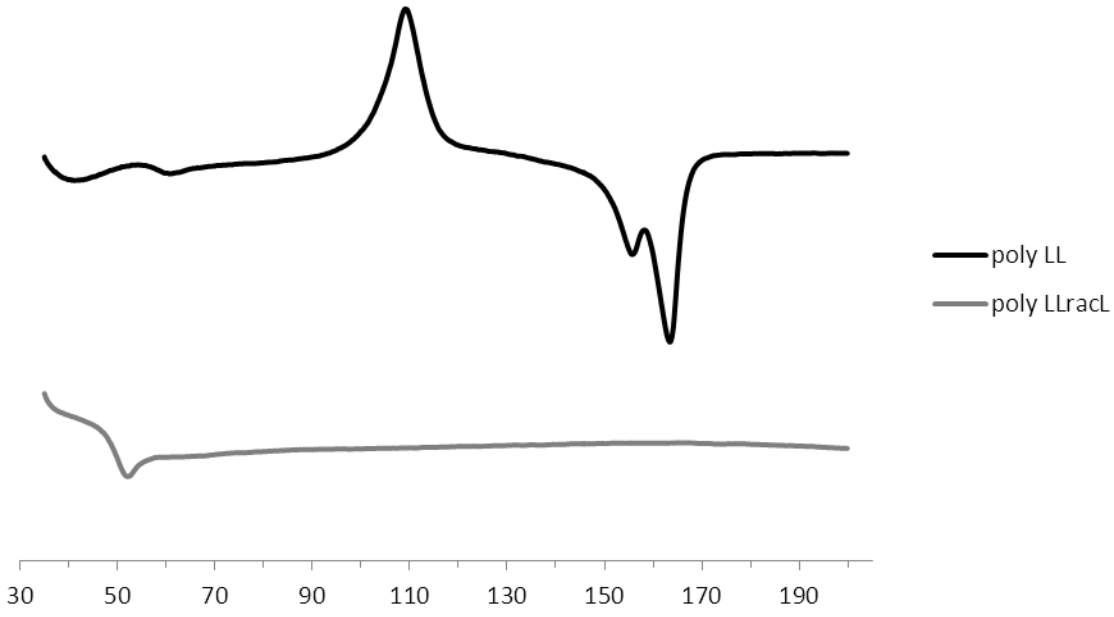


Figure 69. DSC traces for **poly LL** and **LL$_{rac}$L**. Data is from second heating cycle.

APPENDIX B: Chapter 3

B.1 ^{1}H AND ^{13}C NMR SPECTRA FOR FUNCTIONALIZED PLGA RSCS

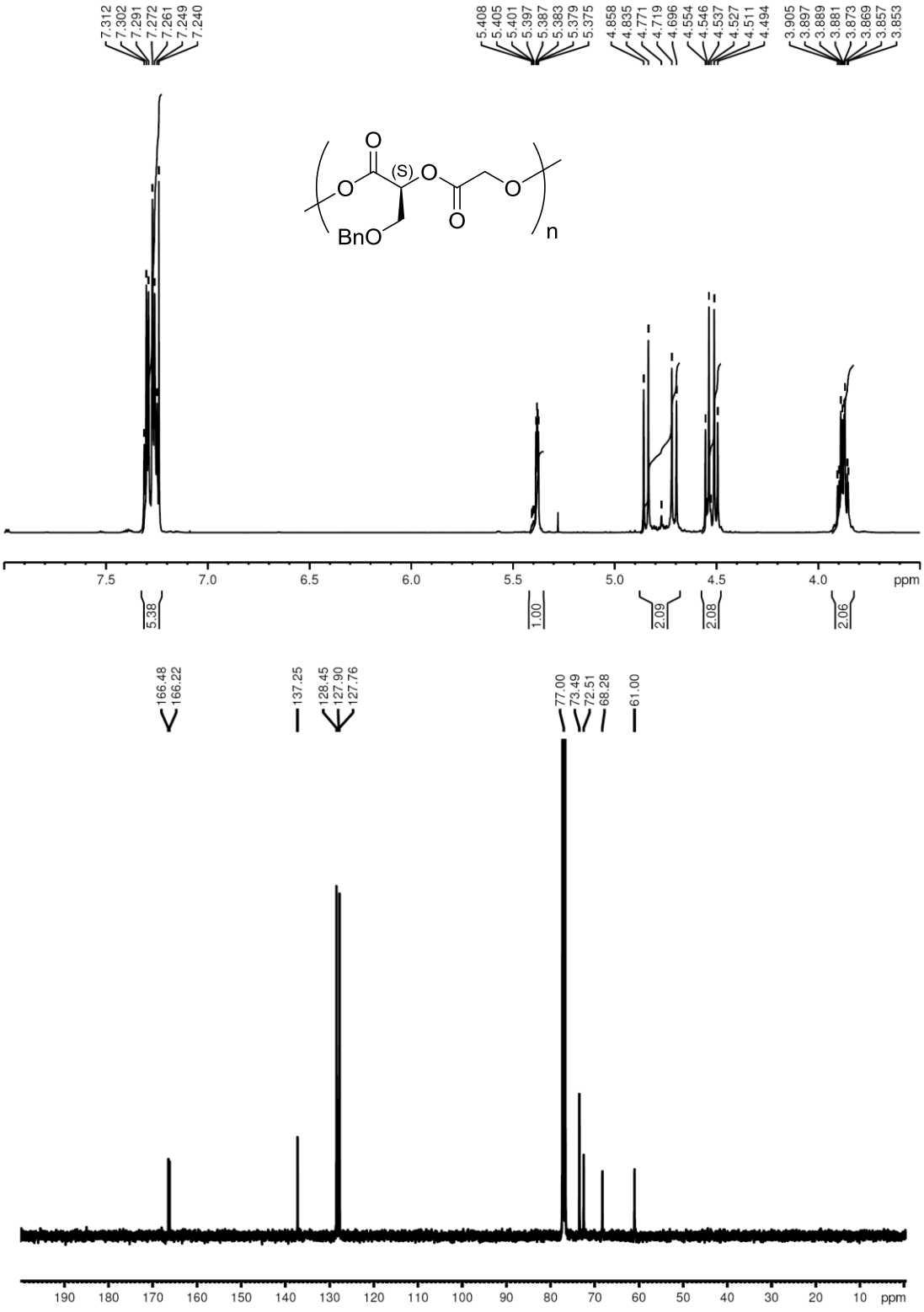


Figure 70. ^{1}H NMR (700 MHz, top) and ^{13}C NMR (100 MHz, bottom) spectra for **poly S*(Bn)G**

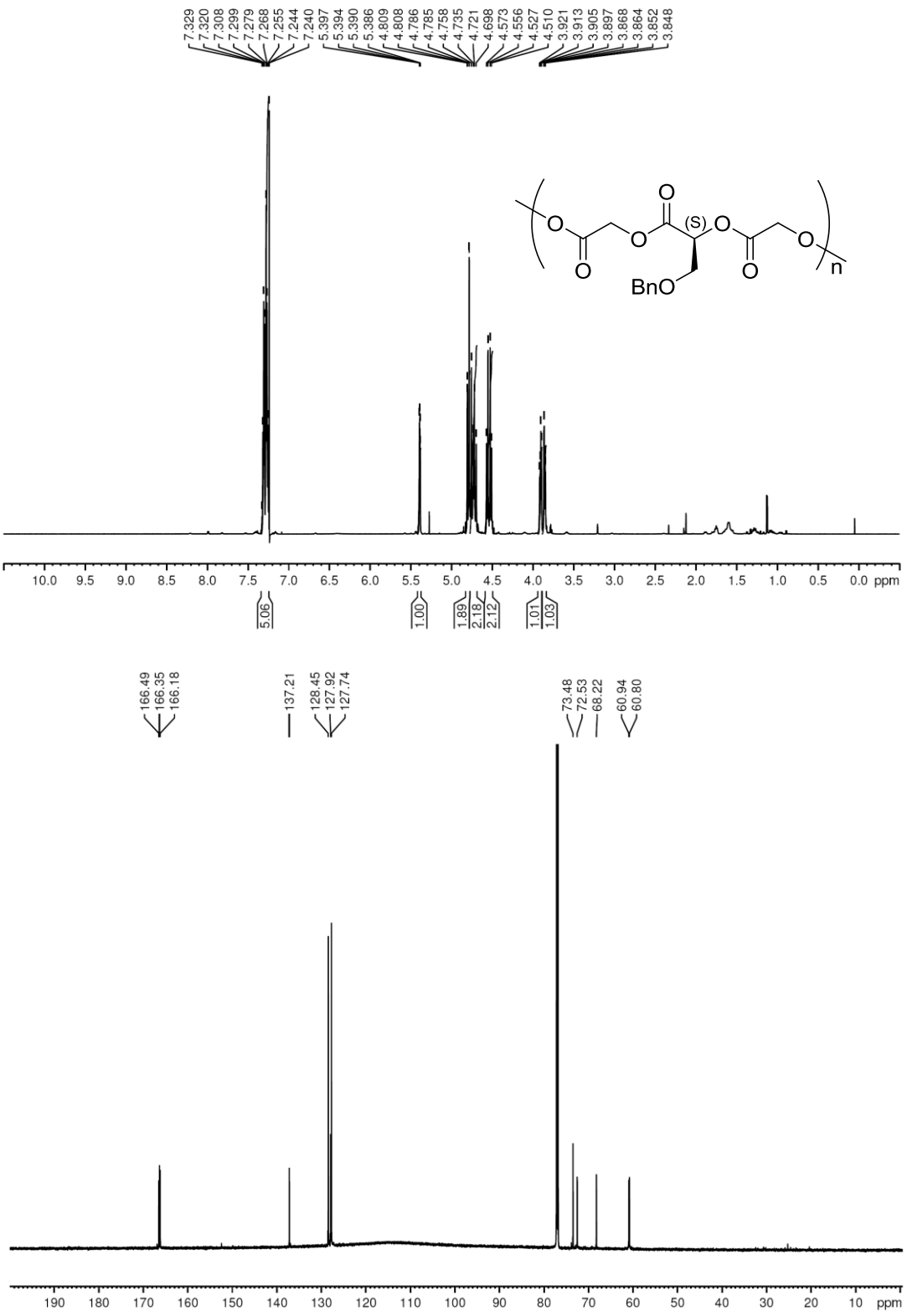


Figure 71. ^{1}H NMR (700 MHz, top) and ^{13}C NMR (175 MHz, bottom) spectra for **poly GS*(Bn)G**

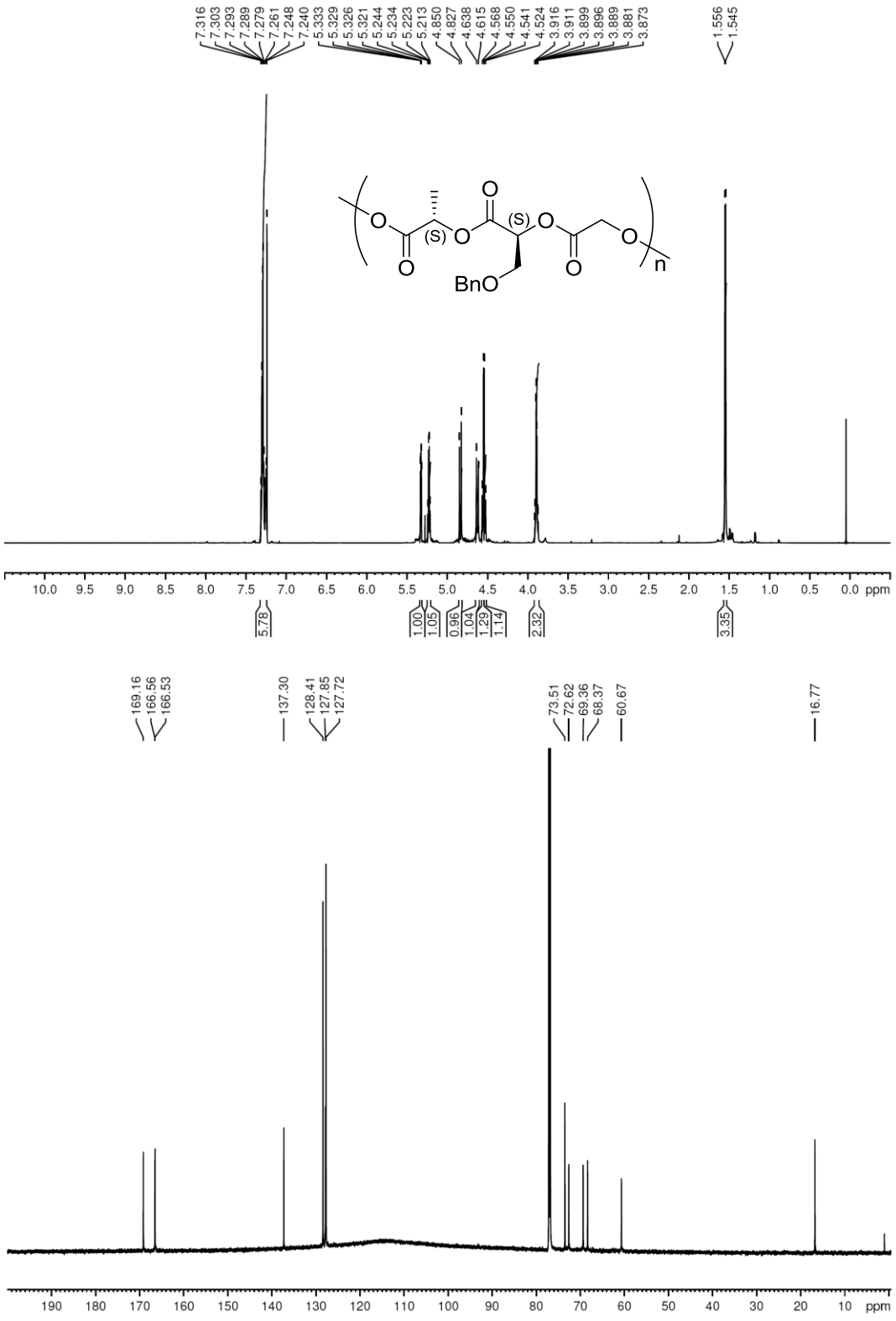


Figure 72. ^{1}H NMR (700 MHz, top) and ^{13}C NMR (175 MHz, bottom) spectra for **poly LS*(Bn)G**

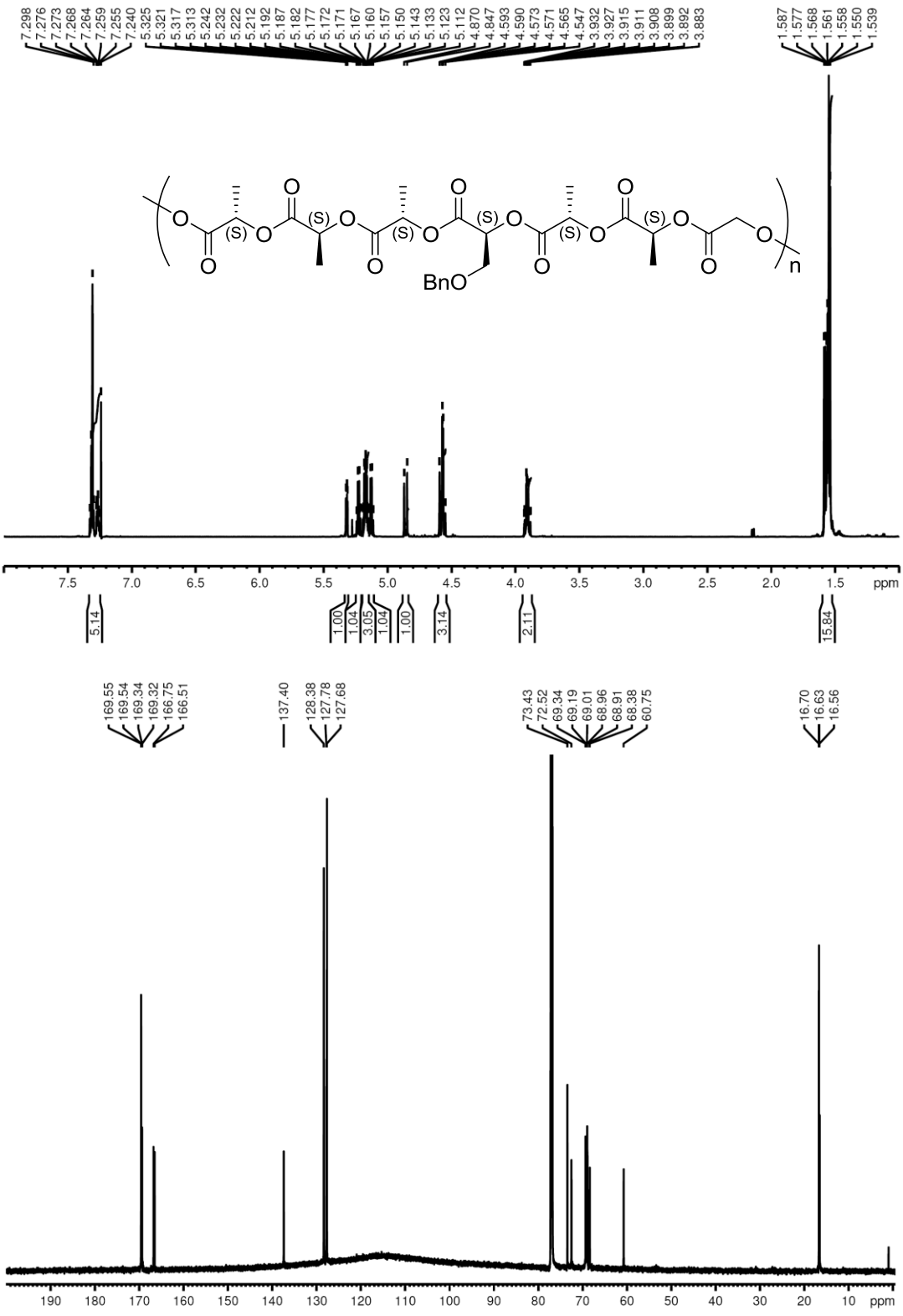


Figure 73. [1]H NMR (700 MHz, top) and [13]C NMR (175 MHz, bottom) spectra for **poly LLLS*(Bn)LLG**

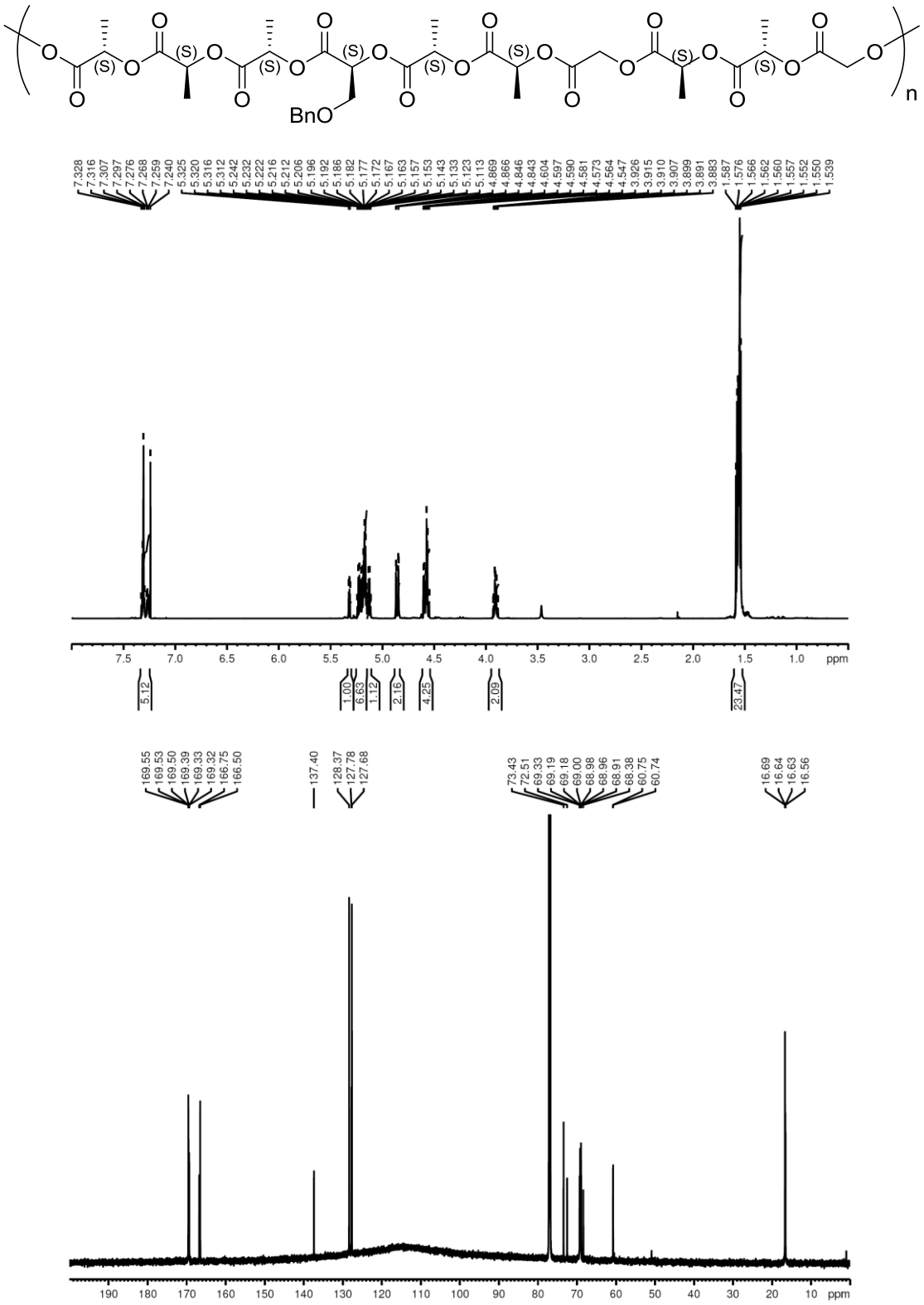


Figure 74. [1]H NMR (700 MHz, top) and [13]C NMR (175 MHz, bottom) spectra for **poly LLLS*(Bn)LLGLLG**

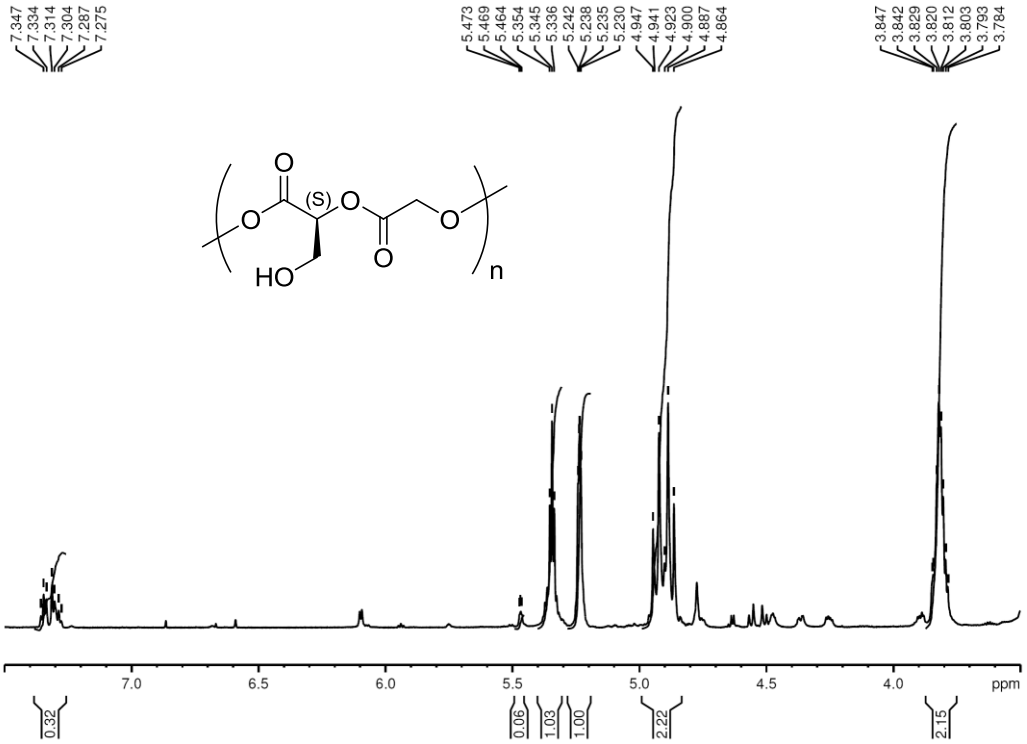


Figure 75. [1]H NMR (700 MHz) spectra for **poly S*(OH)G**

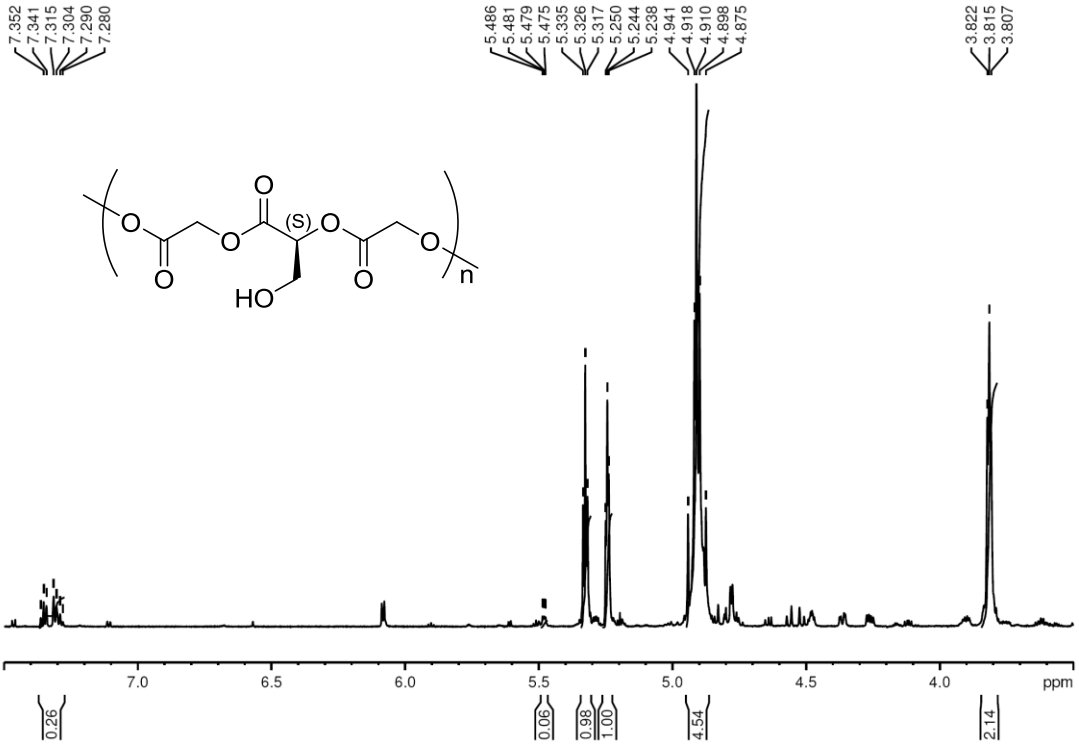


Figure 76. [1]H NMR (700 MHz) spectra for **poly GS*(OH)G**

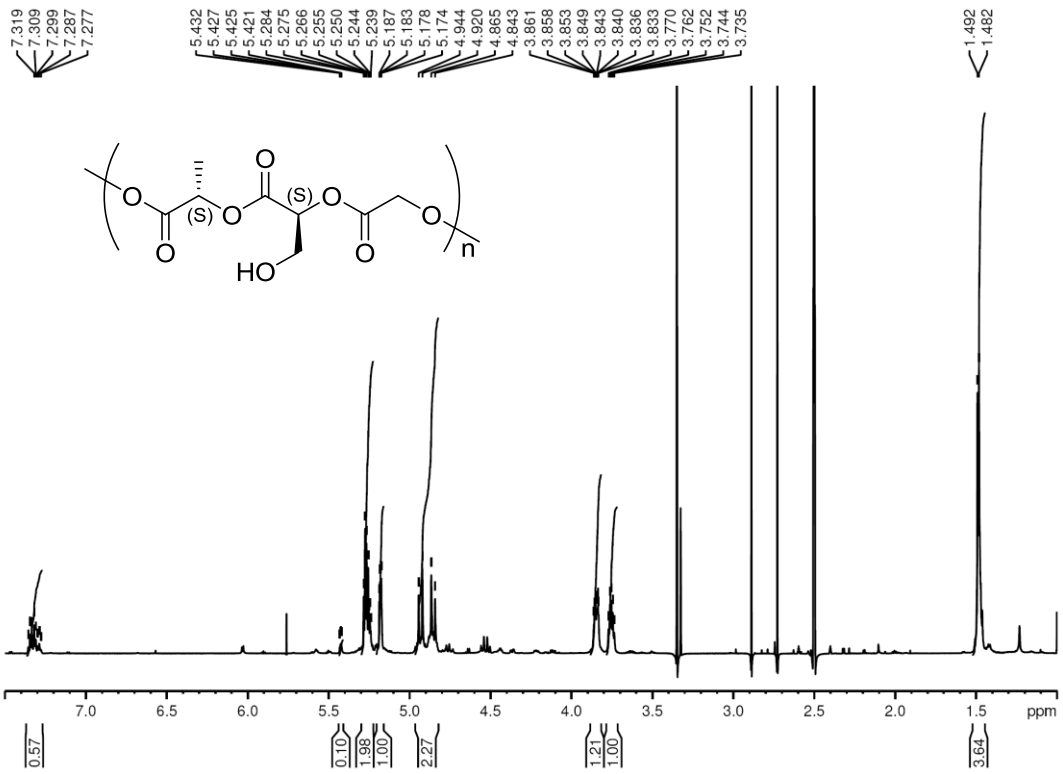


Figure 77. ^{1}H NMR (700 MHz, top) and ^{13}C NMR (175 MHz, bottom) spectra for **poly LS*(OH)G**

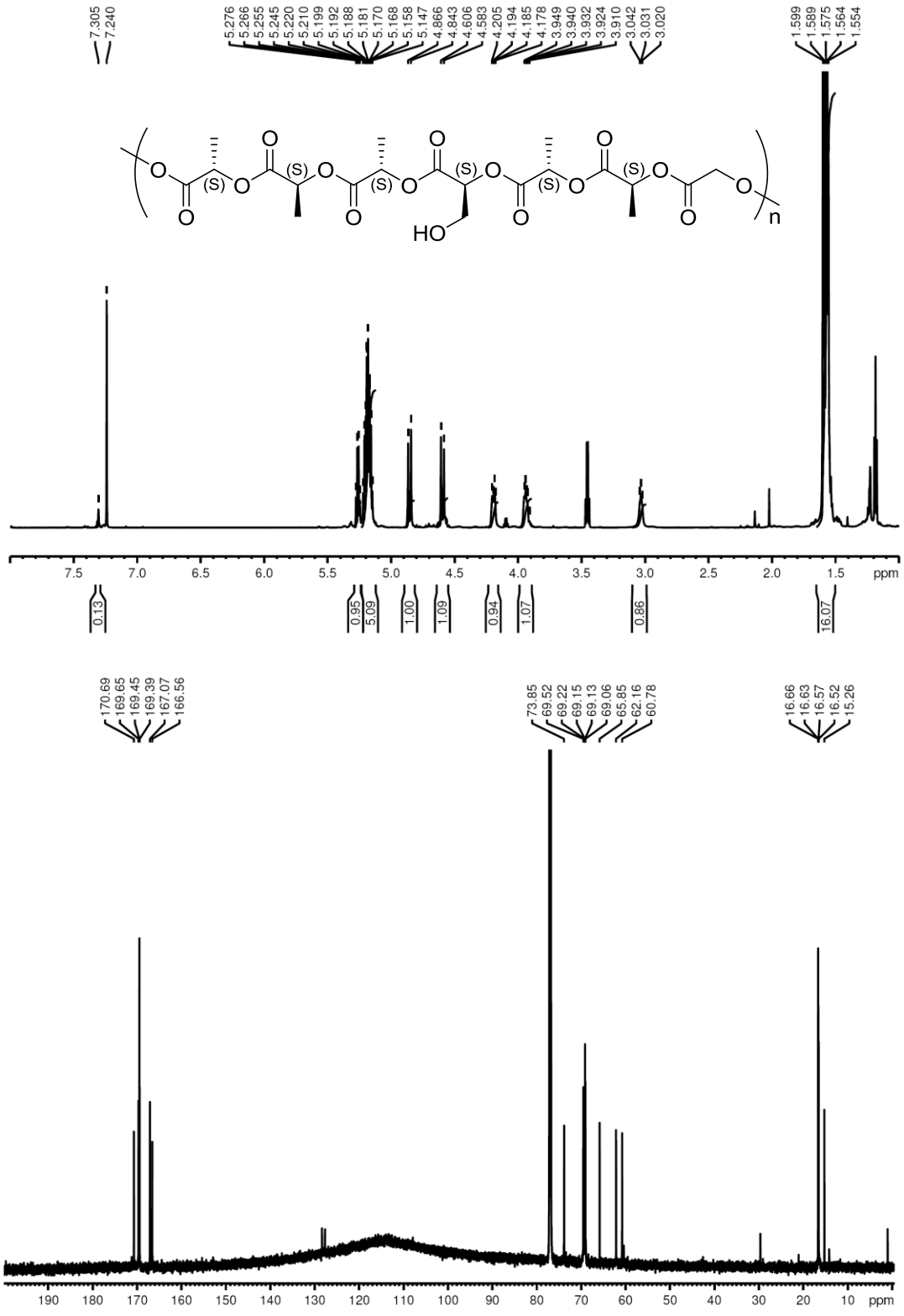


Figure 78. [1]H NMR (700 MHz, top) and [13]C NMR (175 MHz, bottom) spectra for **poly LLLS*(OH)LLG**

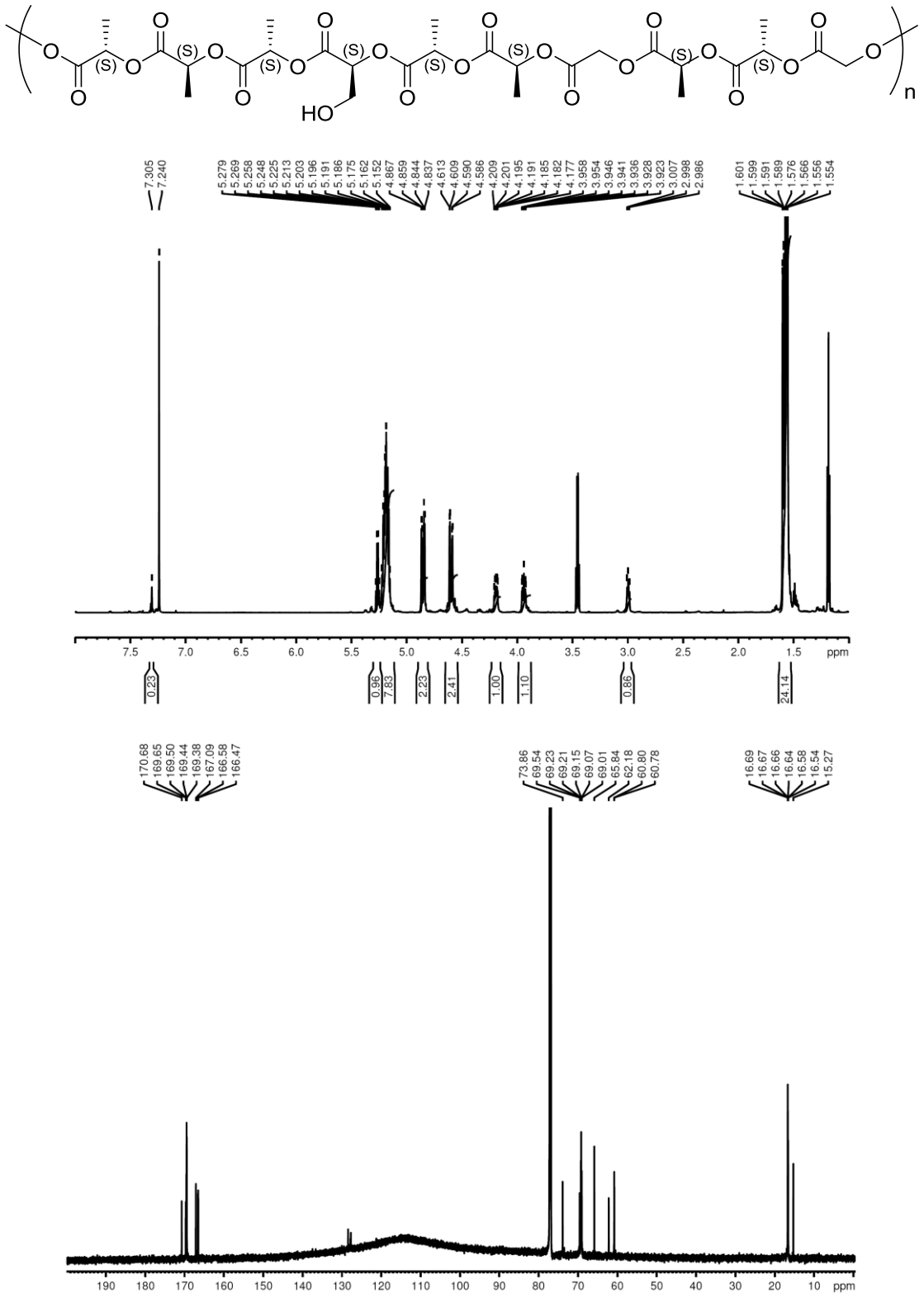


Figure 79. ^{1}H NMR (700 MHz, top) and ^{13}C NMR (175 MHz, bottom) spectra for **poly LLLS*(OH)LLGLLG**

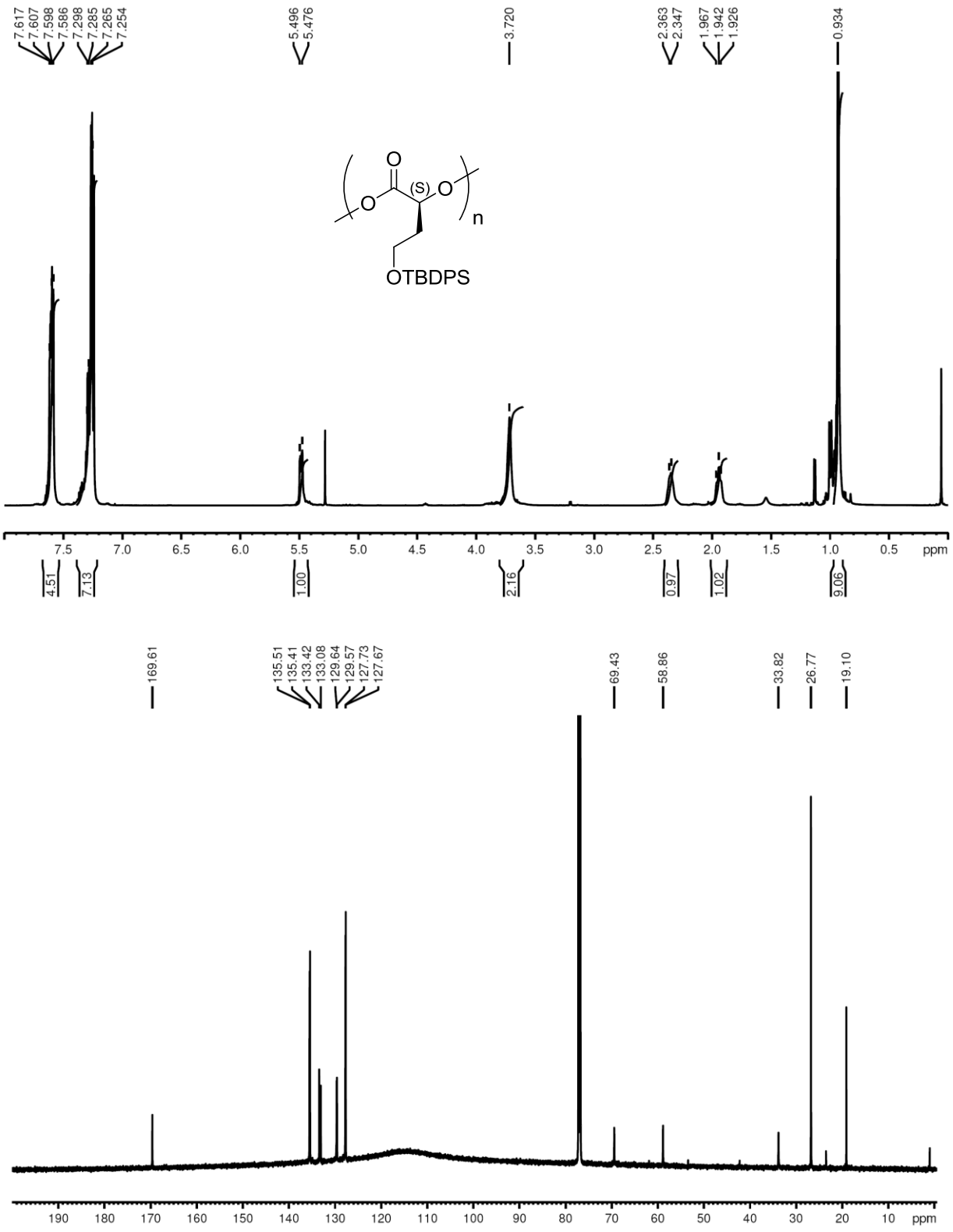


Figure 80. ^{1}H NMR (600 MHz, top) and ^{13}C NMR (125 MHz, bottom) spectra for **poly M(TBDPS)**

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