Doctoral Dissertation

Highly Controlled and Precisely Tuned Syntheses of Advanced Functional Polymeric Materials

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PREFACE

The study in this thesis has been carried out under direction of Professor Kohji Yoshinaga at the Department of Materials Science, Graduate School of Engineering, Kyushu Institute of Technology. The study is concerned with "*Highly Controlled and Precisely Tuned Syntheses of Advanced Functional Polymeric Materials*''.

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CONTENTS

GENERAL INTRODUCTION

Polymeric materials are one of the best inventions of 20th century. Tremendous amount and kinds of polymers are being used for commodities like brush, containers, toys, and vehicles etc. In the meanwhile, the past three decades have seen increasing attention paid to synthetic polymers for biomedical applications including surgery and medicine. Especially in the research area of targeted drug/gene delivery, diagnostic agents and microsurgical instrument, well-defined macromolecules and/or nano-scale objects are topics of great interest since they can be utilized for carrying payloads, cell targeting, and in *vivo* imaging etc.

The properties of polymers are significantly influenced by their molecular structure. This structure-property relationship of polymers has been studied extensively for decades. However, in order to meet the world's changing needs for materials, significant challenges remain to be solved. Some of these challenges are synthesis of brand new sophisticated materials, synthesis of well defined materials with precisely tuned size, introduction of controlled multiple reaction sites on the polymer backbone for post-functionalization, quantitative conversions, easier purification methods, novel characterization techniques, environmental consciousness, and manufacturing cost, etc. One of the solutions of these challenges lies, we believe, in the use of efficient and orthogonal synthetic strategies for the preparation and modification of polymeric materials. Although the applications are very diverse, most of the polymer structures used today are still based on only classical vinyl monomers which are limited by the functional groups that can be used[1]. Hence the ability to design, construct, and functionalize macromolecules with highly tuned properties is becoming fundamental in the development of new materials[2].

CHAPTER 1

'Facile Syntheses of 4-Vinyl-1,2,3-Triazole Monomers and Polymers by Click Azide/Acetylene Coupling'

With the advent of 'Click' reactions, specifically Cu (I) catalyzed 1,3-dipolar cycloaddition of azides and alkynes, triazoles have found their way into many applications. They are used in the area of, for example, medicine[3], herbicides, dyes[4], adhesives for metals, and proton exchange membranes (PEM)[5].

In the first chapter, we report a new monomer family based on 4-vinyl-1,2,3-triazoles[6]. By employing the efficient Cu (I) catalyzed 'Click' reaction, which is extremely tolerant to the presence of functional groups and proceeds with high fidelity under benign conditions[7], a library of 4-vinyl-1,2,3-triazoles with various kinds of functional groups was prepared[6]. The vinyl triazole based monomers do not only significantly expand the variety of functional groups that can be incorporated but also combine the features found in different classical monomers such as aromaticity, polarity, and functionality inherent in styrenics, vinylpyridines, and acrylates. In addition to these attractive features, poly(vinyl triazole)s bring unique properties such as increased solubility. Four synthetic strategies including a Direct 'Click' reaction route using Trimethylsilyl (TMS) protected vinylacetylene and the corresponding organic azides, two Elimination type routes, and a Wittig type route were successfully established. It was found that all these routes offer efficient synthetic pathways for the preparation of vinyl triazoles[6].

CHAPTER 2

'Synthesis and Characterization of 1,2,3-Triazole Oligomers'

To exploit the unique properties of 1,2,3-triazole ring, a linear macromolecule which contains 1,2,3-triazoles along its backbone[8] in high density was synthesized and its properties were studied. By employing the efficient Cu (I) catalyzed 'Click' reaction, we established a facile synthetic route to 1,2,3-triazole oligomers/polymers. Furthermore, precise control of its chain length allowed us to investigate the effect of the molecular size onto its chemical and physical properties. In the second chapter, we discuss in great detail the synthesis of this 1,2,3-triazole oligomers/polymers.

CHAPTER 3

'Molecularly Defined ε-Caprolactone Oligomers and Polymers: Synthesis and Characterization'

Taking a hint from 1,2,3-triazole oligomer synthesis in the second chapter, we realized a method called 'Exponential Growth Strategy[9]' is a very powerful tool to synthesize a precisely size tuned organic oligomers/polymers. On the other hand, a wide range of biocompatible, biodegradable and resorbable synthetic polymers have been developed for bioengineering and biomedical applications in the past three decades[10]. Among those biocompatible and biodegradable compounds, Poly(ε-caprolactone) (PCL) is one of the most widely studied synthetic materials[11]. The leading role of PCL as a biomaterial is further evidenced by its approval by the USA's Food and Drug Administration (FDA) for use in the human body as a drug delivery device, a suture (sold under the brand name, Monocryl), and an adhesion barrier. And it is also being investigated as a scaffold for tissue engineering. While there is a growing academic and industrial interest in Poly(ε-caprolactone) and biodegradable polyesters in general, there have been almost no studies on the synthesis of well-defined oligomers based on Poly(ε-caprolactone), Poly(lactide), etc. This is unfortunate since the availability of precisely defined oligomers[12] would enable a wide range of structure-property studies in order to fully understand, predict and tune the degradation rate, crystal structure, self assembly, and performance of these materials in a variety of applications. Hence, in the third chapter, we report the development of a strategy for the synthesis of well-defined polyester oligomers/polymers and demonstrate the preparation of a series of Poly(ε-caprolactone) derivatives up to 64mer[13]. The physical and structural properties of these essentially single molecule species allow a fundamental insight into the physical and structural properties of the widely studied parent polymer.

CHAPTER 4

'Molecularly Defined (L)-Lactic Acid Oligomers and Polymers: Synthesis and Characterization'

Polymers obtained from Lactic acid are also currently used in a number of biomedical applications, such as sutures, stents, dialysis media and drug delivery devices. Poly(lactide) (PLA) is prepared from renewable resources, such as corn starch or sugarcane and is commercially available on a large scale from a variety of manufacturers. Traditionally, Poly(lactide) has been prepared via ring opening polymerization of cyclic Lactide dimers using a catalyst such as Stannous octanoate with significant effort in recent years being devoted to the development of both controlled polymerization processes[14] and self-assembly of Lactide derived materials[15]. As discussed above, while

there is a growing academic and industrial interest in Poly(lactide) (PLA) and other biodegradable polyesters like Poly(ε-caprolactone) (PCL), there have been almost no studies on the synthesis of well-defined oligomers/polymers based on Lactic acid[16]. As in the PCL's case, the preparation of these monodisperse oligomers/polymers would enable a wide range of structure-property studies in order to fully understand, predict and tune the degradation rate, crystal structure, self assembly, and performance of these materials in a lot of applications[17]. The availability and detailed study of dimers, tetramers, octamers, ... again offers an unprecedented opportunity to impact material design and at the same time develop a fundamental understanding of the parent polymer. In the fourth chapter, we report the development of a synthetic strategy for the synthesis of well-defined Poly((L)-lactide) oligomers/polymers up to 64mer and a fundamental insight into their structure-property relationship[13(c), 18].

CHAPTER 5

'Fabrication of Functionalized Nano-scale Polymer Objects for Multivalent Biological Interactions Using a Dendronized Poly((L)-lysine)'

Not only polyesters like PCL or PLA but also linear peptides are considered to be very promising materials for a variety of medical and biological applications. On the other hand, rigid-rod dendronized linear polymers that bear pendant dendron groups at every single repeating unit are also considered to be good candidates for a lot of applications including a catalyst of organic chemistry and an imaging material. And they can be suitable especially for drug delivery application since they can have multivalent and highly functionalized structures which enable facile drug attachment[19]. Thus, in the fifth chapter, we report the syntheses of precisely size tuned linear L-Lysine oligomers with Bis-MPA type dendrons on their each repeating unit so that we can functionalize the terminal hydroxyl groups on the dendrons with various type of biologically active groups afterwards. This kind of precisely size tuned dendronized linear Poly((L)-lysine) will give us a good access to an artificial mimic of viruses. Herein we report the syntheses of precisely size tuned dendronized linear Poly((L)-lysine)s up through 20-mer with Bis-MPA type G2-dendron and Tetramer with G4-dendron[20].

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CHAPTER 1

'Facile Syntheses of 4-Vinyl-1,2,3-Triazole Monomers and Polymers by Click Azide/Acetylene Coupling'

1-1. Introduction

Efficient and orthogonal chemistry is gaining significant attention in synthetic materials chemistry, due to the increasing importance of functionality and structural definition in all aspects of polymer research[1]. With the advent of 'Click' reactions, specifically the Cu(I)-catalyzed 1,3-dipolar cycloaddition of azides and alkynes[2], the 1,2,3-triazole sub-unit has become a very important and useful component of various small molecule and macromolecular systems, ranging from therapeutics, self-assembling systems, and responsive polymers[3] to proton exchange membranes (PEM)[4]. This current interest is driven by the quantitative nature of the reaction to synthesize 1,2,3-triazole ring, benign reaction conditions, and its compatibility with a wide range of functional groups. Significantly, little attention has been paid to the distinctive properties of the triazole nucleus with the vast majority of reports simply exploiting 'Click' chemistry and its associated triazole linkage as a connecting unit[5]. This neglect/oversight is unfortunate, since it does not address the potentially more interesting aspect of combining the synthetic robustness and efficiency with the unique chemical and physical properties of the triazole ring itself[6]. The ability to design functionalized macromolecules with new and/or improved physical properties is becoming fundamental to the development of new materials and 'Click' chemistry has the potential to significantly impact the range of functional polymers which are readily available[7]. Furthermore, the majority of polymer structures employed today is based on classical vinyl monomers, which limits the range of functional groups that can be used unfortunately[8]. Thus the availability of new highly functional monomer families means the potential to address many unmet needs. To alleviate this scarcity of new monomer families, 4-vinyl-1,2,3-triazoles have been designed to take advantage of the 1,2,3-triazole sub-unit and combine the features found in classical monomers, such as aromaticity, polarity, and structural diversity inherent in styrenics, vinylpyridines, and acrylates, respectively, into a single building block. By employing the highly-efficient Cu(I)-catalyzed azide/acetylene coupling reaction, the syntheses of triazole-based monomers and their resulting macromolecules will be reported in this chapter. Herein, we release four synthetic strategies based on direct 'Click' reactions of Trimethylsilyl (TMS)-protected vinylacetylene with the corresponding organic azides, elimination reactions, and Wittig reactions that offer efficient, high yielding and scalable synthetic pathways for the preparation of 4-vinyl-1,2,3-triazoles. And these pathways have enabled 4-vinlyl-1,2,3-triazoles' widespread adoption to various applications. As described above, 4-vinyl-1,2,3-triazoles, especially 1-Unsubstituted-4-vinyl-1,2,3-triazole has shown promise for application in PEM membranes recently[4]. But the only one synthetic route to 1-Unsubstituted-4-vinyl1,2,3-triazole known to date used potentially dangerous and expensive HN_3. In view of this fact, we also developed safe and less costly alternative routes to 1-Unsubstituted-4-vinyl-1,2,3-triazole that do not require the use of HN_3. To make the total system safer[9], the possibility of in-situ generation of organic azides and their rapid consumption via 'Click' reaction, which we call "*One-pot* 'Click' reaction" was explored, as well, with an encouraging result. This offers the benefit of no isolation of the organic azide species, which makes 4-vinyl-1,2,3-triazoles much more attractive from not only academic but also industrial point of view.

1-2. Experimental Section

Materials.

All the chemicals and solvents were purchased from Aldrich, of reagent grade, and used without further purification. Unless otherwise denoted below, all reactions were carried out under air. All the organic azides[5, 6(a)] and reversible addition fragmentation chain transfer (RAFT)[10] reagent were synthesized according to the well established protocols.

General Procedures/Characterization.

Analytical TLC was performed on commercial Merck Plates coated with silica gel GF254 (0.24 mm thick). Silica gel for flash chromatography was Merck Kieselgel 60 (230-400 mesh, ASTM). ^{1}H-NMR (400MHz and 200 MHz) and ^{13}C-NMR (100 MHz) measurements were performed on a Bruker AC 400 and 200 spectrometers at room temperature. Size exclusion chromatography (SEC) was carried out at room temperature on a Waters chromatograph connected to a Waters 410 differential refractometer and six Waters Styragel® columns (five HR-5 μm and one HMW-20 μm) using THF as eluent (flow rate: 1 mL/min). A Waters 410 differential refractometer and a 996 photodiode array detector were employed. The molecular weights of the polymers were calculated relative to linear polystyrene standards.

4-Trimethylsilyl-1-buten-3-yne (1).

To a two-neck flask equipped with a Dimroth condenser was added 200 mL of dry Triethylamine. This solution was degassed with argon for 30 minutes prior to the addition of Vinyl bromide (12.84 g, 120 mmol) and Trimethylsilylacetylene (7.86 g, 80 mmol). The reaction mixture was subjected to a single freeze-pump-thaw cycle before adding CuI (152 mg, 0.80 mmol) and $PdCl_2(PPh_3)_2$ (281 mg, 0.40 mmol). Then After two additional freeze-pump-thaw cycles, the reaction mixture was stirred overnight at room temperature. 200 mL of Diethyl ether was then added to this reaction mixture and the organic layer was washed with ice cold 1M $NaHSO_4$*aq.* (15x200 mL), satd. $NaHCO_3$*aq.* (1x200 mL), and brine (1x200 mL). The ethereal layer was dried over $MgSO_4$ and concentrated. The product (bp 52-53 °C/80 Torr) was distilled from the brown residue into a receiving flask cooled to -78 °C. Yield: 6.43 g (67%) of a colorless liquid. ^{1}H NMR (400 MHz $CDCl_3$): δ 5.83 (dd, J = 17.6, 11.1 Hz, CH_2=C**H**, 1H), 5.69 (dd, J = 17.6, 2.4 Hz, *cis* C**H**$_2$=CH, 1H), 5.49 (dd, J = 11.1, 2.4 Hz, *trans* C**H**$_2$=CH, 1H), 0.19 (s, C(C**H**$_3$)$_3$, 9H). ^{13}C NMR ($CDCl_3$): δ127.9, 117.2, 103.7, 95.0, -0.2. Anal. Calcd for ($C_7H_{12}Si$): C, 67.66; H, 9.73. Found: C, 67.60; H, 9.72.

General procedure A: synthesis of vinyl triazole derivatives via the *in situ* generation of Vinyl acetylene. Synthesis of 1-Octyl-4-vinyl-1,2,3-triazole (24) depicted.

To a vigorously stirred solution of **1** (0.5 g, 4.0 mmol) and 1-Azidooctane (0.94 g, 6.00 mmol) in 1:1 THF:H_2O was added Sodium L-ascorbate (0.080 g, 0.40 mmol), $CuSO_4$ (0.032 g, 0.20 mmol), and 6 mL of Tetrabutylammonium fluoride (1 M in THF). Reaction flask was fitted with a rubber septum and allowed to stir overnight. The solution was concentrated and then product was extracted into 50 ml of Dichloromethane (twice). The organic fractions were combined, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Crude product was then purified via flash column chromatography using 1:1 Hexanes:Ethyl acetate as eluent yielding 0.733g (88%) of **24** as a clear oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ7.49 (s, Ar**H**, 1H), 6.74 (dd, J = 17.8, 11.2 Hz,

CH_2=C**H**, 1H), 5.86 (dd, J = 17.8, 1.2 Hz, *cis* C**H**$_2$=CH, 1H), 5.32 (dd, J = 11.2, 1.4Hz, *trans* C**H**$_2$=CH, 1H), 4.33 (t, J = 7.2, NC**H**$_2$CH$_2$, 2H), 1.89 (m, NCH$_2$C**H**$_2$, 2H), 1.27 (m, NCH$_2$CH$_2$[C**H**$_2$]$_5$CH$_3$, 10H), 0.87 (t, J = 13.8 Hz, N[C**H**$_2$]$_7$CH$_3$ 3H). ^{13}C NMR ($CDCl_3$): δ146.65 (NCH=**C**, 1C) 126.09 (**C**H=CH$_2$, 1C), 120.29 (N**C**H=C, 1C), 116.13 (CH=**C**H$_2$, 1C), 50.63 (N**C**H$_2$, 1C), 32.01 (NCH$_2$**C**H$_2$, 1C), 30.63 (N[CH$_2$]$_2$**C**H$_2$, 1C), 29.35 (N[CH$_2$]$_3$**C**H$_2$, 1C), 29.27 (N[CH$_2$]$_4$**C**H$_2$, 1C), 26.78 (N[CH$_2$]$_5$**C**H$_2$, 1C), 22.91 (N[CH$_2$]$_6$**C**H$_2$, 1C), 14.45 (N[CH$_2$]$_7$**C**H$_3$, 1C). Mass Spec for $C_{12}H_{21}N_3$ Calculated: 207.17; Found $(M+H)^+$: 208.18.

Modified procedure A: '*One-pot*' synthesis of 1-Methyl-4-vinyl-1,2,3-triazole (31) is depicted.

To a 20 mL scintillation vial was added Sodium azide (1.95 g, 30.00 mmol), Diisopropylethylamine (2.06 g, 15.94 mmol), and $CuBr(PPh_3)_3$, and 1M (in THF) Tetrabutylammonium fluoride (12 mL, 12.00 mmol). This heterogeneous mixture was then transferred via Pasteur pipette to a large glass ampule (100 mL) containing Methyl iodide (1.42 g, 9.93 mmol) and **1** (1.00 g, 8.05 mmol) and submerged the ampule in liquid nitrogen. This glass ampule was then subjected to a single freeze-pump-thaw cycle, sealed, and allowed to react for 16 hours at 60 ^{o}C. Upon completion, the reaction mixture was concentrated under reduced pressure then partitioned into a separatory funnel containing 15 mL of deionized water and 15 mL of Dichloromethane. The aqueous layer was extracted thrice more with 15 mL CH_2Cl_2. The organic fractions were then combined, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Crude product was then purified via flash column chromatography using Ethyl acetate as eluent yielding 0.60 g (68%) of **31** as a clear oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ7.49 (s, Ar**H**, 1H), 6.65 (dd, J = 17.7, 11.2 Hz, C**H**=CH$_2$, 1H), 5.84 (d, J = 17.7 Hz, *trans* CH=C**H**$_2$, 1H), 5.31 (d, J = 11.2 Hz, *cis* CH=C**H**$_2$, 1H), 4.01 (s, NC**H**$_3$, 3H). ^{13}C NMR ($CDCl_3$): δ146.15 (Ar, NCH=**C**, 1C) 125.59 (**C**H=CH$_2$, 1C), 121.22 (N**C**H=C, 1C), 115.95 (CH=**C**H$_2$, 1C), 36.59 (N**C**H$_3$, 1C). Mass Spec for $C_5H_7N_3$ Calculated: 109.13; Found $(M+H)^+$: 110.07.

General procedure B: Synthesis of 1-Octyl-4-vinyl-1,2,3-triazole (24) depicted.

A 50 mL round bottom flask equipped with a magnetic stir bar was charged with 1-Azidoctane (1.01 g, 6.51 mmol), 3-Butyn-1-ol (**2**) (0.47 g, 6.69 mmol), and 10 mL of *t*-Butanol. In separate flasks, Sodium L-ascorbate (0.13 g, 0.64 mmol) and $CuSO_4$ (0.05 g, 0.32 mmol) were introduced to 5 mL of deionized water, respectively. Upon dissolution, these aqueous solutions were then added to the *t*-Butanol mixture. After 13 hours of vigorous stirring, the reaction mixture was poured into a separatory funnel containing 80 mL of deionized water and extracted 4 times with 80 mL of CH_2Cl_2. The organic fractions were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure. This crude mixture was then purified via flash column chromatography (Ethyl acetate) to yield 1.47 g (100%) of 2-(1-Octyl-1*H*-1,2,3-triazol-4-yl)ethanol (**52**) as a white solid. ^{1}H NMR (200 MHz, $CDCl_3$): δ7.36 (s, Ar**H**, 1H), 4.32 (t, J = 7.3 Hz, NC**H**$_2$, 2H), 3.95 (t, J = 5.9 Hz, OC**H**$_2$CH$_2$, 2H), 2.95 (t, J = 5.8 Hz, OCH$_2$C**H**$_2$, 2H), 1.89 (m, O**H**, NCH$_2$C**H**$_2$, 3H), 1.28 (m, NCH$_2$CH$_2$[C**H**$_2$]$_5$CH$_3$, 10H), 0.88 (m, N[CH$_2$]$_7$C**H**$_3$, 3H). ^{13}C NMR ($CDCl_3$): δ145.65 (NCH=**C**, 1C), 121.52 (N**C**H=C, 1C), 61.79 (O**C**H$_2$CH$_2$, 1C), 50.45 (N**C**H$_2$, 1C), 31.86 (N[CH$_2$]$_5$**C**H$_2$, 1C), 30.46 (NCH$_2$**C**H$_2$, 1C), 29.19 (N[CH$_2$]$_3$**C**H$_2$, 1C), 29.12 (N[CH$_2$]$_4$**C**H$_2$, 1C), 28.87 (OCH$_2$**C**H$_2$, 1C), 26.67 (N[CH$_2$]$_2$**C**H$_2$, 1C), 22.75 (N[CH$_2$]$_6$**C**H$_2$, 1C), 14.22 (N[CH$_2$]$_7$**C**H$_3$, 1C). Mass Spec for $C_{12}H_{23}N_3O$ Calculated: 225.18; Found (M): 225.18. Usually these hydroxyl compounds were utilized without further characterization except for ^{1}H-NMR.

To a 20 mL scintillation vial was added **52** (0.14 g, 0.64 mmol), Et_3N (0.19 g, 19.1 mmol), and 6 mL of CH_2Cl_2. After cooling the vial to 0 °C, Methanesulfonyl chloride (0.12 g, 1.03 mmol) was added dropwise and stirred at 0 °C

for 13 hours. Then the vial was heated to room temperature gradually and the reaction mixture was poured into a separatory funnel containing 10 mL of CH_2Cl_2 and washed with 1M HCl*aq.* and Brine. The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield 0.18 g (95%) of 2-(1-Octyl-1*H*-1,2,3-triazol-4-yl)ethyl methanesulfonate (**53**) as a white solid. ^{1}H NMR (200 MHz, $CDCl_3$): δ7.43 (s, Ar**H**, 1H), 4.53 (t, J = 6.4 Hz, OC**H**$_2$CH$_2$, 2H), 4.33 (t, J= 7.3 Hz, NC**H**$_2$, 2H), 3.19 (t, J = 6.4 Hz, OCH$_2$**C**H$_2$, 2H), 2.97 (s, C**H**$_3$S, 3H), 1.89 (m, NCH$_2$C**H**$_2$, 2H), 1.26 (m, NCH$_2$CH$_2$(C**H**$_2$)$_5$CH$_3$, 10H), 0.88 (m, N(CH$_2$)$_7$C**H**$_3$, 3H). Mesylated compounds were utilized without further characterization unless otherwise denoted.

A 5 mL round bottom flask equipped with a magnetic stir bar and a reflux condenser was charged with **53** (0.03 g, 0.11 mmol) and Glyme (1.00 g, 1.15 mL) to make a 0.1 M solution of **53**. To this mixture was added NaI (0.05 g, 0.34 mmol) followed by 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) (0.03 g, 0.23 mmol). After addition of all reagents, the reaction mixture was heated to reflux for a period of 30 minutes. Upon completion, the reaction mixture was partitioned between CH_2Cl_2 and water, and the aqueous layer was extracted three times with CH_2Cl_2. The organic fractions were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure. This crude mixture was then purified via flash column chromatography (1:1 Ethyl acetate:Hexanes) to yield 0.02 g (79%) of **24** as a clear oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ7.49 (s, Ar**H**, 1H), 6.74 (dd, J = 17.8, 11.2 Hz, CH$_2$=C**H**, 1H), 5.86 (dd, J = 17.8, 1.2 Hz, *cis* C**H**$_2$=CH, 1H), 5.32 (dd, J = 11.2, 1.4Hz, *trans* C**H**$_2$=CH, 1H), 4.33 (t, J = 7.2 Hz, NC**H**$_2$CH$_2$, 2H), 1.89 (m, NCH$_2$C**H**$_2$, 2H), 1.27 (m, NCH$_2$CH$_2$[C**H**$_2$]$_5$CH$_3$, 10H), 0.87 (t, J = 6.9 Hz, N[CH$_2$]$_7$C**H**$_3$ 3H). ^{13}C NMR ($CDCl_3$): δ146.65 (NCH=**C**, 1C), 126.09 (**C**H=CH$_2$, 1C), 120.29 (N**C**H=C, 1C), 116.13 (CH=**C**H$_2$, 1C), 50.63 (N**C**H$_2$, 1C), 32.01 (NCH$_2$**C**H$_2$, 1C), 30.63 (N[CH$_2$]$_2$**C**H$_2$, 1C), 29.35 (N[CH$_2$]$_3$**C**H$_2$, 1C), 29.27 (N[CH$_2$]$_4$**C**H$_2$, 1C), 26.78 (N[CH$_2$]$_5$**C**H$_2$, 1C), 22.91 (N[CH$_2$]$_6$**C**H$_2$, 1C), 14.45 (N[CH$_2$]$_7$**C**H$_3$, 1C). Mass Spec for $C_{12}H_{21}N_3$ Calculated: 207.17; Found $(M+H)^+$: 208.18.

Elimination reaction of 2-(1-Octyl-1*H*-1,2,3-triazol-4-yl)ethyl methanesulfonate (53) using *t*-BuOK.

A 5 mL round bottom flask equipped with a magnetic stir bar was charged with **53** (0.04 g, 0.12 mmol) and *t*-BuOH (3.09 g, 3.99 mL). To this mixture was added *t*-BuOK (0.06 g, 0.50 mmol) and 18-Crown-6 (0.13 g, 0.49 mmol). After addition of all the reagents, the mixture was heated to 50 °C for a period of 1 hour. Upon completion, the reaction mixture was partitioned between CH_2Cl_2 and water, and the aqueous layer was extracted three times with CH_2Cl_2. The organic fractions were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure. This crude mixture was then purified via flash column chromatography (1:1 Ethyl acetate:Hexanes) to yield 0.02 g (79%) of **24** as a clear oil.

General procedure B: Synthesis of 2-(2-(2-(4-Vinyl-1,2,3-triazole-1-yl))ethoxy)ethoxyethanol (7) depicted.

A 50 mL round bottom flask equipped with a magnetic stir bar was charged with 2-(2-(2-Azide)ethoxy)ethoxyethanol (0.50 g, 2.86 mmol), 3,4-Dihydro-2*H*-pyran (0.36 g, 4.28 mmol), CH_2Cl_2 (26.50 g, 20.08 mL) and Pyridinium *p*-toluenesulfonate (0.08 g, 0.33 mmol). After 4 hours of vigorous stirring, the reaction mixture was poured into a separatory funnel containing 80 mL of deionized water and extracted 4 times with 80 mL of Et_2O. The organic fractions were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure. This crude mixture was then purified via flash column chromatography (1:1 Ethyl acetate:Hexanes) to yield 0.50 g (71%) of protected azide (**3**) as a colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ4.64 (t, J = 3.3 Hz, OC**H**(CH$_2$)O, 1H),

3.94-3.37 (m, OC**H**$_2$, 14H), 1.95-1.47 (m, cyclic-C**H**$_2$, 6H). This protected azide was utilized without further characterization.

'Click reaction' with 3-Butyn-1-ol (**2**) followed by mesylation reaction and elimination reaction was conducted by using a similar method with the one depicted above for **24** to yield protected 4-Vinyl-1,2,3-triazole (**6**) as a slightly yellow oil (53% yield for 3 steps). ^{1}H NMR (200 MHz, $CDCl_3$): δ7.73 (s, ArH, 1H), 6.74 (dd, J = 17.8, 11.1 Hz, CH_2=C**H**, 1H), 5.86 (dd, J = 17.8, 1.5 Hz, *trans* C**H**$_2$=CH, 1H), 5.32 (dd, J = 11.1, 1.3Hz, *cis* C**H**$_2$=CH, 1H), 4.60 (b, OC**H**(CH_2)O, 1H), 4.52 (t, J = 5.2, cyclic-OC**H**$_2$CH_2, 2H), 3.89-3.43 (m, OC**H**$_2$, 12H), 1.95-1.47 (m, cyclic-C**H**$_2$, 6H). This compound was utilized without further characterization.

To a 20 mL scintillation vial were added THF (0.54 g, 0.06 mL), acetic acid (1.26 g, 1.20 mL), and 0.3 mL of H_2O. Then **6** (0.06 g, 0.19 mmol) was added and stirred at 50 °C for a period of 4 hours. Upon completion, the reaction mixture was concentrated under reduced pressure. This crude mixture was then purified via flash column chromatography (1:1 Ethyl acetate:Hexanes) to yield 0.04 g (91%) of **7** as a white solid. ^{1}H NMR (200 MHz, $CDCl_3$): δ7.70 (s, Ar**H**, 1H), 6.69 (dd, J = 17.8, 12.6 Hz, C**H**=CH_2, 1H), 5.85 (dd, J = 17.8, 1.4 Hz, *trans* CH=C**H**$_2$, 1H), 5.30 (dd, J = 12.6, 1.4 Hz, *cis* CH=C**H**$_2$, 1H), 4.50 (t, J = 5.2 Hz HOC**H**$_2$, 2H), 3.85 (t, J = 5.2 Hz, HOCH_2C**H**$_2$, 2H), 3.72-3.51 (m, OC**H**$_2$C**H**$_2$, 8H), 2.50 (s, O**H**). ^{13}C NMR ($CDCl_3$): δ146.51 (NCH=**C**, 1C), 125.89 (**C**H=CH_2, 1C), 121.72 (N**C**H=C, 1C), 116.11 (CH=**C**H_2, 1C), 72.61 (N**C**H_2, 1C), 70.80 (NCH_2**C**H_2, 1C), 70.40 (N(CH_2)$_2$O**C**H_2, 1C), 69.67 (N(CH_2)$_2$OCH_2**C**H_2, 1C), 61.90 (N[(CH_2)$_2$O]$_2$**C**H_2, 1C), 50.39 (CH_2**C**H_2OH, 1C). Mass Spec for $C_{10}H_{17}N_3O_3$ Calculated: 227.13; Found $(M+H)^+$: 228.13.

Modified procedure B: Synthesis of 1-Butyl-4-vinyl-1,2,3-triazole (11) via "*One-pot* 'Click' reaction" depicted.

A 50 mL round bottom flask equipped with a magnetic stir bar was charged with NaN_3 (4.25 g, 65.30 mmol), $CuSO_4$ (0.34 g, 2.16 mmol), Sodium L-ascorbate (1.46 g, 7.39 mmol), DMF (9.45 g, 10mL), and 10 mL of H_2O. Then 3-Butyn-1-ol (**2**) (1.54 g, 22.00 mmol) and 1-Bromobutane (3.62 g, 26.40 mmol) were added and heated to 60°C. After 15 hours of vigorous stirring, the reaction mixture was cooled to room temperature and conducted three series of (filtration through celite, washing the celite cake with MeOH, and concentration under reduced pressure). The resulting crude mixture was then purified via flash column chromatography (Ethyl acetate) to yield 1.75 g (47%) of 2-(1-Butyl-1*H*-1,2,3-triazol-4-yl)ethanol (**9**) as a clear oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ7.35 (s, Ar**H**, 1H), 4.15 (t, J = 7.1 Hz, NC**H**$_2$, 2H), 3.73 (b, OC**H**$_2$CH_2, 2H), 2.79 (b, OCH_2C**H**$_2$, 2H), 1.70 (t, J = 7.0 Hz, NCH_2C**H**$_2$, 2H), 1.17 (m, NCH_2CH_2C**H**$_2$CH_3, 2H), 0.76 (t, J = 7.1 Hz, N[CH_2]$_3$C**H**$_3$, 3H). ^{13}C NMR ($CDCl_3$): δ145.19 (NCH=**C**, 1C), 121.62 (N**C**H=C, 1C), 61.08 (O**C**H_2CH_2, 1C), 49.75 (N**C**H_2, 1C), 32.02 (NCH_2**C**H_2, 1C), 28.78 (OCH_2**C**H_2, 1C), 19.48 (N[CH_2]$_2$**C**H_2, 1C), 13.26 (N[CH_2]$_3$**C**H_3, 1C). Mass Spec for $C_8H_{15}N_3O$ Calculated: 169.24; Found $(M+H)^+$: 170.13.

Mesylation reaction followed by elimination reaction was conducted by using the similar method depicted above for **24** to yield **11** as a clear oil (58% yield for 2 steps). ^{1}H NMR (200 MHz, $CDCl_3$): δ7.48 (s, Ar**H**, 1H), 6.57 (dd, J = 17.8, 11.2 Hz, C**H**=CH_2, 1H), 5.85 (dd, J = 17.6, 1.2 Hz, *trans* CH=C**H**$_2$, 1H), 5.17 (d, J = 11.0 Hz, *cis* CH=C**H**$_2$, 1H), 4.19 (t, J = 7.2 Hz, NC**H**$_2$, 2H), 1.73 (m, NCH_2C**H**$_2$, 2H), 1.22 (m, NCH_2CH_2C**H**$_2$CH_3, 2H), 0.79 (t, J = 7.2 Hz, N[CH_2]$_3$C**H**$_3$, 3H). ^{13}C NMR ($CDCl_3$): δ146.08 (NCH=**C**, 1C), 125.67 (**C**H=CH_2, 1C), 120.22 (N**C**H=C, 1C), 115.53 (CH=**C**H_2, 1C), 49.82 (N**C**H_2, 1C), 32.10 (NCH_2**C**H_2, 1C), 19.49 (N[CH_2]$_2$**C**H_2, 1C), 13.29 (N[CH_2]$_3$**C**H_3, 1C). Mass Spec for $C_8H_{13}N_3$ Calculated: 151.23; Found $(M+H)^+$: 152.12.

Synthesis of But-3-ynyl methanesulfonate (8) (for General procedure C, below).

To a 250 mL round bottom flask charged with a magnetic stir bar and 90 mL of CH_2Cl_2, 3-Butyn-1-ol (**2**) (0.50 g, 7.13 mmol), and Triethylamine (2.17 g, 21.40 mmol) were added. After cooling this mixture in an ice bath, Methanesulfonyl chloride (1.06 g, 9.23 mmol) was added dropwise over 30 minutes. The reaction mixture was then allowed to warm to room temperature and was allowed to react overnight (16 hours). Upon completion, the reaction mixture was washed with 1M HCl*aq.* and brine. The organic extract was then dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield 1.02 g (96%) of **8** as an orange oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ4.23 (t, J = 6.6 Hz, OC**H**$_2$CH$_2$, 2H), 3.00 (S, C**H**$_3$S, 3H), 2.59 (dt, J = 6.6, 2.6 Hz, OCH$_2$C**H**$_2$CCH, 2H), 2.05 (t, J = 2.6 Hz, CH$_2$CC**H**, 1H). ^{13}C NMR ($CDCl_3$): δ78.83 (HC**C**CH$_2$, 1C), 71.03 (H**C**CCH$_2$, 1C), 67.36 (CH$_2$**C**H$_2$O, 1C), 37.50 (S**C**H$_3$, 1C), 19.63 (**C**H$_2$CH$_2$O, 1C). Mass Spec for $C_5H_8N_3O_3S$ Calculated: 148.02; Found $(M+H)^+$: 149.04.

General procedure C: Synthesis of 1-Octyl-4-vinyl-1,2,3-triazole (24) depicted.

A 250 mL round bottom flask equipped with a magnetic stir bar was charged with 1-Azidoctane (3.53 g, 20.30 mmol), **8** (3.05 g, 20.30 mmol), and 30 mL of *t*-Butanol. In separate flasks, Sodium L-ascorbate (1.20 g, 0.61 mol) and $CuSO_4$ (0.16 g, 0.1 mmol) was introduced to 15 mL of deionized water respectively. Upon dissolution, these aqueous mixtures were then added to the *t*-butanol mixture. After 16 hours of vigorous stirring, the reaction mixture was concentrated under reduced pressure. The resulting aqueous mixture was then extracted three times with CH_2Cl_2 (30 mL). The organic fractions were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure and was further purified via flash column chromatography (1:1 Ethyl acetate:Hexanes) to yield 5.61 g (86%) of **53** as a white solid. ^{1}H NMR (200 MHz, $CDCl_3$): δδ7.43 (s, Ar**H**, 1H), 4.53 (t, J = 6.4 Hz, OC**H**$_2$CH$_2$, 2H), 4.33 (t, J= 7.3 Hz, NC**H**$_2$, 2H), 3.19 (t, J = 6.4 Hz, OCH$_2$**C**H$_2$, 2H), 2.97 (s, C**H**$_3$S, 3H), 1.89 (m, NCH$_2$C**H**$_2$, 2H), 1.26 (m, NCH$_2$CH$_2$[C**H**$_2$]$_5$CH$_3$, 10H), 0.88 (m, N[CH$_2$]$_7$C**H**$_3$, 3H). Mesylated compounds were utilized without further characterization unless otherwise denoted.

The elimination reaction of **53** to yield **24** was conducted in exactly the same way with **procedure B** described above.

General procedure D: Synthesis of 1-Benzyl-4-vinyl-1,2,3-triazole (39) depicted.

A 100 mL round bottom flask equipped with a magnetic stir bar was charged with Benzyl azide (2.00 g, 14.27 mmol), 3-Butyn-2-ol (**16**) (1.02 g, 14.50 mmol), and 25.8 mL of *t*-Butanol. In separate flasks, Sodium L-ascorbate (0.85 g. 4.28 mmol) and $CuSO_4$ (0.23 g, 1.43 mmol) were introduced to 25.8 mL of deionized water respectively. Upon dissolution, these aqueous solutions were then added to the *t*-Butanol mixture. After overnight of vigorous stirring, the reaction mixture was poured into a separatory funnel containing 200 mL of deionized water and extracted 4 times with 200 mL of CH_2Cl_2. The organic fractions were dried over $MgSO_4$, filtered and concentrated under reduced pressure. This crude mixture was then purified via flash column chromatography (Ethyl acetate) to yield 2.67 g (85%) of 1-(1-Benzyl-1,2,3-triazol-4-yl)ethanol (**54**) as a white solid. ^{1}H NMR (200 MHz, $CDCl_3$): δ7.41 (s, Ar(triazole)**H**, 1H), 7.35-7.10 (m, Ar(benzene)**H**, 5H), 5.38 (s, NC**H**$_2$C, 2H), 4.97 (q, HOC**H**CH$_3$C, 1H), 4.40 (b, O**H**, 1H), 1.45 (d, C**H**$_3$, 1H). ^{13}C NMR ($CDCl_3$): δ153.08 (NCH=**C**, 1C), 134.73 (Ar, CH$_2$**C**, 1C), 129.04 (*m*-Ar, 2C), 128.64 (*p*-Ar, 1C), 128.08 (*o*-Ar, 2C), 120.48 (N**C**H=C, 1C), 62.72 (HO**C**HCH$_3$C, 1C), 54.03 (N**C**H$_2$, 1C), 23.21 (**C**H$_3$, 1C). Mass Spec for $C_{11}H_{13}N_3O$ Calculated: 203.11; Found $(M+H)^+$: 204.10.

A 50 mL round bottom flask equipped with a magnetic stir bar was charged with **54** (0.27 g, 1.35 mmol), *p*-Toluenesulfonic acid monohydrate (0.01 g, 0.04 mmol), 2,6-Di-*tert*-butyl-4-methylphenol (BHT) (about 0.0001g), and 4.5 mL of DMSO. This mixture was heated up to 140°C and stirred for 1.5 hours. The reaction mixture was poured into a separatory funnel containing 100 mL of satd. $NaHCO_3$*aq*. and was extracted 4 times with 100 mL of CH_2Cl_2. The organic fractions were dried over $MgSO_4$, filtered and concentrated under reduced pressure. This crude mixture was then purified via flash column chromatography (1:1 Ethyl acetate:Hexanes) to yield 0.08 g (34%) of 1-Benzyl-4-vinyl-1*H*-1,2,3-triazole (**39**) as a white solid. ^{1}H NMR (200 MHz, $CDCl_3$): δ7.39-7.24 (s, Ar**H**, 6H), 6.69 (dd, J = 17.8, 11.2 Hz, C**H**=CH_2, 1H), 5.85 (dd, J = 17.8, 1.2 Hz, *trans* CH=C**H**$_2$, 1H), 5.51 (s, NC**H**$_2$, 2H), 5.30 (dd, J = 11.2, 1.0 Hz, *cis* CH=C**H**$_2$, 1H). ^{13}C NMR ($CDCl_3$): δ146.98 (NCH=**C**, 1C), 134.80 (Ar, NCH_2**C**, 1C), 129.31 (*o*-Ar, 2C), 128.95 (**C**H=CH_2, 1C), 128.23 (*m*-Ar, 2C), 125.78 (*p*-Ar, 1C), 120.28 (CH=**C**H_2, 1C), 116.04 (N**C**H=C, 1C), 54.29 (N**C**H_2, 1C).Mass Spec for $C_{11}H_{11}N_3$ Calculated: 185.23; Found $(M+H)^+$: 186.10.

General procedure E: Synthesis of 1-(4-Methoxybenzyl)-4-vinyl-1,2,3-triazole (18) depicted.

A 500 mL round bottom flask equipped with a magnetic stir bar was charged with 4-Methoxybenzylazide (9.15 g, 56.08 mmol), Propargyl alcohol (**17**) (3.64 g, 6.69 mmol), and 100 mL of *t*-Butanol. In separate flasks, Sodium L-ascorbate (3.72 g, 18.79 mmol) and $CuSO_4$ (0.51 g, 3.21 mmol) were introduced to 50 mL of deionized water, respectively. Upon dissolution, these aqueous solutions were then added to the *t*-Butanol mixture. After 3 nights of vigorous stirring, the reaction mixture was poured into a separatory funnel containing 400 mL of deionized water and was extracted 4 times with 500 mL of CH_2Cl_2. The organic fractions were dried over $MgSO_4$, filtered and concentrated under reduced pressure. This crude mixture was then purified via gradient flash column chromatography (Ethyl acetate to MeOH) to yield 10.80 g (88%) of 1-(4-Methoxybenzyl)-4-hydroxymethyl-1,2,3-triazole (**54**) as a white solid. ^{1}H NMR (200 MHz, $CDCl_3$): δ7.41 (s, Ar(triazole)**H**, 1H), 7.23 (d, J = 6.6 Hz, Ar(benzene-*ortho*)**H** 2H), 6.89 (d, J = 6.6 Hz, Ar(benzene-*meta*)**H** 2H), 5.45 (s, NC**H**$_2$C, 2H), 4.75 (s, OC**H**$_2$C, 2H), 3.80 (s, OC**H**$_3$, 3H), 2.01 (s, O**H**, 1H). ^{13}C NMR ($CDCl_3$): δ160.06 (CH3O**C**, 1C) 148.28 (NCH=**C**, 1C), 129.87 (*o*-Ar, 2C), 126.63 (Ar, CCH_2**C**, 2C), 121.68 (N**C**H=C, 1C), 114.61 (*m*-Ar, 2C), 56.35 (O**C**H_2C, 1C), 55.49 (**C**H_3O, 1C), 53.86 (N**C**H_2, 1C). Mass Spec for $C_{11}H_{13}N_3O_2$ Calculated: 219.10; Found (M): 219.10.

A 50 mL round bottom flask equipped with a magnetic stir bar was charged with **54** (0.29 g, 1.34 mmol), Triphenylphosphine (0.38 g, 1.46 mmol), and 3.32 mL of CH_2Cl_2. This mixture was cooled to 0°C and *N*-Bromosuccinimide (0.28 g, 1.55 mmol) was added under argon atmosphere. After 3 hours of vigorous stirring, the reaction mixture was concentrated under reduced pressure. This crude mixture was then purified via flash column chromatography (Ethyl acetate) to yield 0.34 g (89%) of 1-(4-Methoxybenzyl)-4-bromomethyl-1,2,3-triazole (**55**) as a white solid. ^{1}H NMR (200 MHz, $CDCl_3$): δ7.44 (s, Ar(triazole)**H**, 1H), 7.24 (d, J = 9.0 Hz, Ar(benzene-*ortho*)**H** 2H), 6.91 (d, J = 9.0 Hz, Ar(benzene-*meta*)**H** 2H), 5.45 (s, NC**H**$_2$C, 2H), 4.54 (s, BrC**H**$_2$C, 2H), 3.81 (s, OC**H**$_3$, 3H). ^{13}C NMR ($CDCl_3$): δ160.22 (CH3O**C**, 1C) 145.04 (NCH=**C**, 1C), 129.98 (*o*-Ar, 2C), 126.31 (Ar, CH_2**C**, 1C), 122.67 (N**C**H=C, 1C), 114.74 (*m*-Ar, 2C), 55.54 (**C**H_3O, 1C), 54.08 (N**C**H_2, 1C), 21.83 (Br**C**H_2, 1C). Mass Spec for $C_{11}H_{12}BrN_3O$ Calculated: 281.02; Found (M): 281.02.

A 20 mL scintillation vial equipped with a magnetic stir bar was charged with **55** (0.34 g, 1.20 mmol), Triphenylphosphine (0.32 g, 1.20 mmol), and 2.31 mL of CH_2Cl_2. After 40 hours of vigorous stirring, the reaction mixture was concentrated under reduced pressure. Hexanes were added to this resulting crude mixture and rinsed the crude solid. Then, Hexanes were decanted off to yield 0.56 g (86%) of phosphineylide of **55** (**56**) as a pale yellow

solid. ^{1}H NMR (200 MHz, $CDCl_3$): δ8.29 (s, Ar(triazole)**H**, 1H), 7.80-7.48 (m, Ar(triphenylphosphine)**H** 15H), 7.04 (d, J = 8.6 Hz, Ar(benzene-*ortho*)**H** 2H), 7.04 (d, J = 8.6 Hz, Ar(benzene-*meta*)**H** 2H), 5.48 (d, J = 13.6 Hz, PC**H**$_2$C, 2H), 5.26 (s, NC**H**$_2$C, 2H), 3.75 (s, OC**H**$_3$, 3H). Mass Spec for $C_{29}H_{27}BrN_3OP$ Calculated: 543.11; Found (M): 464.19 (only cationic moiety). This compound was utilized without further characterization.

In a 20 mL scintillation vial equipped with a magnetic stir bar, **56** (0.25 g, 0.46 mmol) and 37% HCHO*aq.* (0.10 g, 1.21 mmol) were dissolved into 0.49 mL of H_2O. After the addition of 0.31 mL of Hexanes and 0.85 mL of CH_2Cl_2, 10M NaOH*aq.* (0.17 g) was also added dropwise to this mixture. After 14 hours of vigorous stirring, the reaction mixture was poured into a separatory funnel containing 10 mL of 1M HCl*aq.* and was extracted 4 times with 10 mL of CH_2Cl_2. The organic fractions were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure. This crude mixture was then purified via flash column chromatography (1:1 Ethyl acetate:Hexanes) to yield 0.08 g (84%) of **18** as a white solid. ^{1}H NMR (200 MHz, $CDCl_3$): δ7.40 (s, Ar(triazole)**H**, 1H), 7.23 (d, J = 6.8 Hz, Ar(benzene-*ortho*)**H** 2H), 6.90 (d, J = 6.8 Hz, Ar(benzene-*meta*)**H** 2H), 6.69 (dd, J = 18.0, 10.6 Hz, CH2=C**H** 1H), 5.85 (d, J = 18.0 Hz, *trans* CH=C**H**$_2$, 1H), 5.44 (s, NC**H**$_2$C, 2H), 5.31 (d, J = 10.6 Hz, *cis* CH=C**H**$_2$, 1H), 3.81 (s, OC**H**$_3$, 3H), 2.01 (s, O**H**, 1H). ^{13}C NMR ($CDCl_3$): δ160.10 (CH3O**C**, 1C) 146.87 (NCH=**C**, 1C), 129.82 (*o*-Ar, 2C), 126.75 (Ar, CH_2**C**, 2C), 125.84 (CH_2=**C**H, 1C), 120.05 (N**C**H=C, 1C), 116.19 (**C**H_2=CH, 1C), 114.65 (*m*-Ar, 2C), 55.51 (**C**H_3O, 1C), 53.82 (N**C**H_2, 1C). Mass Spec for $C_{12}H_{13}N_3O$ Calculated: 215.06; Found $(M+H)^+$: 216.11.

Synthesis of 1-Unsubstituted-4-vinyl-1,2,3-triazole (19) from 1-(4-Methoxybenzyl)-4-vinyl-1,2,3-triazole (18).

A 500 mL round bottom flask equipped with a magnetic stir bar and a reflux condenser was charged with 1-(4-Methoxybenzyl)-4-vinyl-1,2,3-triazole (**18**) (35.01 g, 0.16 mmol), 4-Methoxyphenol (MEHQ) as a radical inhibitor (0.001 g), and 165 g of *conc.* H_2SO_4*aq*. After 1 hour of vigorous stirring at refluxing condition, the reaction mixture was cooled to 0°C. By adding NaOH and deionized water, the pH of the reaction mixture was adjusted to about 3. Then the reaction mixture was poured into a separatory funnel and extracted 4 times with 300 mL of CH_2Cl_2. The organic fractions were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure. This crude mixture was then purified via flash column chromatography (1:1 Ethyl acetate:Hexanes) to yield 3.43 g (22%) of **19** as a clear oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ7.79 (s, Ar**H**, 1H), 6.79 (dd, J = 17.8, 11.2 Hz, C**H**=CH_2, 1H), 5.92 (dd, J = 17.8, 0.8 Hz, *trans* CH=C**H**$_2$, 1H), 5.47 (dd, J = 11.2, 0.8 Hz, *cis* CH=C**H**$_2$, 1H). ^{13}C NMR ($CDCl_3$): δ143.57 (NHCH=**C**, 1C), 127.50 (NH**C**H=C, 1C), 124.06 (**C**H=CH_2, 1C), 117.96 (CH=**C**H_2, 1C),. Mass Spec for $C_4H_5N_3$ Calculated: 95.05; Found (M): 95.07. (This 1-Unsubstituted-4-vinyl-1,2,3-triazole (**19**) tends to auto-polymerize easily thus storing in a freezer in the presence of radical inhibitor is required.)

Synthesis of 1-Unsubstituted-4-vinyl-1,2,3-triazole (19) from (4-Vinyl-1,2,3-triazol-1-yl)methyl pivalate (13-A) and (4-Vinyl-1,2,3-triazol-2-yl)methyl pivalate (13-B).

A 2 L round bottom flask equipped with a magnetic stir bar was charged with the mixture of (4-Vinyl-1,2,3-triazol-1-yl)methyl pivalate (**13-A**) (7.16 g, 34.20 mmol) and (4-Vinyl-1,2,3-triazol-2-yl)methyl pivalate (**13-B**) (8.95 g, 42.80 mmol), 2,6-Di-*tert*-butyl-4-methylphenol (BHT) as a radical inhibitor (0.003 g), 730 mL of MeOH, and 240 mL of deionized water. Then NaOH (6.57 g, 164.25 mmol) was added. After 30 minutes of vigorous stirring, the pH of the reaction mixture was adjusted to about 3 by adding 1M HCl*aq*. Then the reaction mixture was poured into a separatory funnel and extracted 4 times with 800 mL of CH_2Cl_2. The organic fractions were combined,

dried over $MgSO_4$, filtered and concentrated under reduced pressure. This crude mixture, which mainly includes **19** and 1-Hydroxymethyl-4-vinyl-1,2,3-triazole (**20**) (Calculated from ^{1}H-NMR, 2.45 g (25.70 mmol, 33% yield) of **19** and 3.12 g (24.90 mmol, 32% yield) of **20** were contained respectively), was used without further purification. ^{1}H NMR (200 MHz, $CDCl_3$) of **20**: δ7.73 (s, Ar**H**, 1H), 7.26 (b, O**H**), 6.73 (dd, J = 17.8, 11.2 Hz, C**H**=CH_2, 1H), 5.89 (dd, J = 17.8, 1.0 Hz, *trans* CH=C**H**$_2$, 1H), 5.79 (s, NC**H**$_2$OH), 5.47 (dd, J = 11.2, 1.0 Hz, *cis* CH=C**H**$_2$, 1H).

A 2 L round bottom flask equipped with a magnetic stir bar and was charged with this crude mixture (2.45 g (25.70 mmol) of **19** and 3.12 g (24.90 mmol) of **20**), Dess-Martin periodinane (17.75 g, 41.85 mmol) and 150 mL of CH_2Cl_2. After 21 hours of vigorous stirring, the reaction mixture was poured into a separatory funnel containing 300 mL of deionized water and 150 mL of CH_2Cl_2. Then by adding 1M HCl*aq.*, the pH of the aqueous layer was adjusted to about 3 and extracted 4 times with 300 mL of CH_2Cl_2. The organic fractions were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting crude mixture was purified via flash column chromatography (1:1 Ethyl acetate:Hexanes) to yield 4.45 g (93% from mixture of **19** and **20**) of **19** as a light yellow oil.

General procedure F: Synthesis of *α*-methylvinyl triazole derivatives. Synthesis of 1-Benzyl-4-(prop-1-en-2-yl)-1,2,3-triazole (49) is depicted.

A 100 mL round bottom flask equipped with a magnetic stir bar was charged with Benzyl azide (4.12 g, 30.91 mmol), 2-Methyl-3-butyn-2-ol (**21**) (2.60 g, 30.91 mmol), and 38 mL of *t*-Butanol. In separate flasks, Sodium L-ascorbate (0.18 g, 0.93 mmol) and $CuSO_4$ (0.05 g, 0.31 mmol) were introduced to 19 mL of deionized water, respectively. Upon dissolution, these aqueous solutions were then added to the *t*-Butanol mixture. After 20 hours of vigorous stirring at room temperature, the reaction mixture was poured into a separatory funnel containing 70 mL of deionized water and extracted 3 times with 70 mL of CH_2Cl_2. The organic fractions were combined, washed once with deionized water, dried over $MgSO_4$, filtered and concentrated under reduced pressure. This crude mixture was then purified via flash column chromatography (Ethyl acetate) to yield 4.75 g (71%) of 1-Benzyl-4-(2'-hydroxypropan-2'yl)-1,2,3-triazole (**57**) as a white solid. ^{1}H NMR (200 MHz, $CDCl_3$): δ7.37-7.20 (s, Ar**H**, 6H), 5.47 (s, NC**H**$_2$CH, 2H), 1.60 (s, C(C**H**$_3$)$_2$OH, 6H). These hydroxyl compounds were utilized without further characterization.

To a 100 mL round bottom flask equipped with a magnetic stir bar and reflux condenser was added **57** (4.70 g, 21.60 mmol) and Pyridine (45 g) at room temperature. After stirring for 5 minutes, $POCl_3$ (6.63 g, 43.20 mmol) was added dropwise over 5 minutes at 0°C. The reaction mixture was then heated to 120 °C and allowed to reflux for 2 hours. Upon completion, the reaction mixture was poured over ice-CH_2Cl_2 mixture. And the aqueous layer was washed with 1M HCl*aq.* and satd. $NaHCO_3$*aq*. The organic fraction was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. This crude mixture was then purified via flash column chromatography (Ethyl acetate) to yield 4.20 g (98%) of **49** as a white solid. ^{1}H NMR (200 MHz, $CDCl_3$): δ7.41 (s, Ar**H**(triazole), 1H), 7.37-7.22 (s, Ar**H**(benzene), 5H) 5.67 (s, *cis(to CH_3)* C**H**$_2$=CCH_3, 1H), 5.50 (s, NC**H**$_2$C, 2H), 5.06 (m, *trans(to CH_3)* C**H**$_2$=CCH_3, 1H), 2.09 (s, C**H**$_3$C=CH_2, 3H). ^{13}C NMR ($CDCl_3$): δ149.21 (NCH=**C**, 1C), 134.84 (NCH_2**C**, 1C), 133.56 (CH_3**C**=CH_2, 1C), 129.11 (*o*-Ar, 2C), 128.71 (*p*-Ar, 2C), 128.01 (*m*-Ar, 1C), 119.63 (N**C**H=C, 1C), 112.51 (CH_3C=**C**H_2, 1C), 54.07 (N**C**H_2, 1C), 20.65 (**C**H_3C=CH_2, 1C). Mass Spec for $C_{12}H_{13}N_3$ Calculated: 199.11; Found $(M+H)^+$: 200.12.

Elimination reaction of 1-Benzyl-4-(2'-hydroxypropan-2'yl)-1,2,3-triazole (57) using Methanesulfonyl chloride.

To a 50 mL round bottom flask charged with a magnetic stir bar, 11.7 mL of CH_2Cl_2, **57** (0.20 g, 0.93 mmol), and Triethylamine (0.28 g, 2.76 mmol) were added. After cooling this mixture in an ice bath, Methanesulfonyl chloride (0.16 g, 1.38 mmol) was added dropwise. The reaction mixture was then allowed to warm to room temperature and was allowed to react overnight (11 hours). Upon completion, the reaction mixture was washed with 1M HCl*aq.* and deionized water. The organic layer was then dried over $MgSO_4$, filtered, and concentrated under reduced pressure to yield 0.15 g (80%) of **49** as a white solid.

Modified procedure F: Synthesis of Methyl 3-(4-(prop-1-en-2-yl)-1,2,3-triazol-1-yl)propanoate (23) via "*One-pot* 'Click' reaction" is depicted.

A 100 mL round bottom flask equipped with a magnetic stir was charged (in the following order) with deionized water (7 mL), Sodium azide (1.77 g, 27.26 mmol), Sodium L-ascorbate (0.36 g, 1.81 mmol), and $CuSO_4$ (0.10 g, 0.63 mmol). After stirring until dissolution, Dimethylformamide (7 mL, to make a 1:1 H_2O:DMF volume ratio) was added followed by Methyl 3-bromopropanoate (1.05 g, 6.28 mmol), and 2-Methyl-3-butyn-2-ol (**21**) (0.81 g, 9.65 mmol). The resulting reaction mixture was allowed to stir at 70 °C overnight (16 hours). Upon completion, the reaction mixture was partitioned between CH_2Cl_2 and H_2O, and the aqueous layer was extracted three times with CH_2Cl_2. The organic fractions were combined, washed once with deionized water, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. This crude mixture was then purified via flash column chromatography (5:1 Ethyl acetate:MeOH) to yield 0.45 g (34%) of 3-(4'-(2''-Hydroxyprppan-2''-yl)-1',2',3'-triazol-1'yl)propanoate (**22**) as a clear oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ7.53 (s, Ar**H**, 1H), 4.62 (t, J = 6.5 Hz, NC**H**$_2$CH$_2$, 2H), 3.68 (s, COOC**H**$_3$, 3H), 2.95 (t, J = 6.5 Hz, NCH$_2$**C**H$_2$, 2H), 2.61 (s, O**H**, 1H), 1.60 (s, C(C**H**$_3$)$_2$OH, 6H). ^{13}C NMR ($CDCl_3$): δ170.91 (**C**OOCH$_3$, 1C), 155.59 (NCH=**C**, 1C), 120.31 (N**C**H=C, 1C), 68.02 (**C**(CH$_3$)$_2$OH, 1C), 51.93 (COO**C**H$_3$, 1C), 45.23 (N**C**H$_2$, 1C), 34.16 (NCH$_2$**C**H$_2$, 1C), 30.17 (C(**C**H$_3$)$_2$OH, 2C). Mass Spec for $C_9H_{15}N_3O_3$ Calculated: 213.11; Found $(M+H)^+$: 236.10.

A similar reaction condition described above for **49** was applied to **22** and gave **23** as a clear oil (90% yield). ^{1}H NMR (200 MHz, $CDCl_3$): δ7.57 (s, Ar**H**, 1H), 5.63 (dd, J = 1.5, 0.9 Hz, *cis(to CH$_3$)* C**H**$_2$=CCH$_3$, 1H), 5.01 (p, J = 1.6 Hz, *trans(to CH$_3$)* C**H**$_2$=CCH$_3$, 1H), 4.58 (t, J = 6.4 Hz, NC**H**$_2$CH$_2$, 3H), 3.63 (s, OC**H**$_3$, 3H), 2.91 (t, J = 6.4 Hz, NCH$_2$C**H**$_2$, 2H), 2.05 (dd, J = 1.0, 0.4 Hz, C**H**$_3$C=CH$_2$, 3H). ^{13}C NMR ($CDCl_3$): δ171.09 (**C**OOCH$_3$, 1C), 148.63 (NCH=**C**, 1C), 133.53 (CH$_3$**C**=CH$_2$, 1C), 120.68 (N**C**H=C, 1C), 112.45 (CH$_3$C=**C**H$_2$, 1C), 52.17 (O**C**H$_3$, 1C), 45.45 (N**C**H$_2$, 1C), 34.46 (NCH$_2$**C**H$_2$, 1C), 20.64 (**C**H$_3$C=CH$_2$, 1C). Mass Spec for $C_9H_{13}N_3O_2$ Calculated: 195.10; Found $(M+H)^+$: 196.11.

General procedure of polymerization of vinyl triazole derivatives. Polymerization of 1-Octyl-4-vinyl-1,2,3-triazole (24) depicted.

A mixture of RAFT chain transfer agent (Methyl 2-phenyl-2-(phenylcarbonothioylthio)acetate) (9.7mg, 0.032 mmol), AIBN (1.1 mg, 6.4 μmol), and triazole monomer **24** (2.00 g, 9.65 mmol) in 1 mL of Dimethylformamide was degassed by three successive freeze-pump-thaw cycles, sealed under vacuum, and stirred at 70 °C for 18 hours. The viscous crude polymerization mixture was then precipitated twice in cold Hexanes (-78 °C). The Hexanes were then decanted and the remaining pure polymer was redissolved in a minimum amount of Benzene. This mixture was

then frozen in liquid nitrogen and the solvent was removed in vacuo to yield homopolymer **30** as a pink solid (1.17 g, 58.5 %, M_n=44,900 g/mol, PDI = 1.08, T_g= 23 °C). ^{1}H NMR (200 MHz, $CDCl_3$): δ7.08 (m, Ar**H**), 4.17 (b, NC**H**$_2$), 2.63-2.05 (b, aliphatic H), 1.90-1.55 (m, aliphatic H and $NCH_2C\mathbf{H}_2$), 1.28 (b, $NCH_2CH_2[C\mathbf{H}_2]_5CH_3$), 0.87 (b, $N[CH_2]_7C\mathbf{H}_3$).

Characterization of Vinyl Triazole Derivatives:

Synthetic procedures utilized to obtain the molecules are indicated by the letters of General procedures above (A, B, C, or Modified-A, B, E). Yields of procedure A, B, and C were calculated based on the amount of organic azides or acetylenes used. And those of Modified-A, B, and E were based on the amount of organic halides or acetylenes used.

1-Pentyl-4-vinyl-1,2,3-triazole (32), via procedure C (73% overall yield (2 steps)).

^{1}H NMR (200 MHz, $CDCl_3$): δ7.50 (s, Ar**H**, 1H), 6.65 (dd, J = 17.6, 11.2 Hz, CH_2=C**H**, 1H), 5.82 (dd, J = 17.6, 1.0 Hz, *trans* C**H**$_2$=CH, 1H), 5.29 (dd, J = 11.2, 1.0 Hz, *cis* C**H**$_2$=CH, 1H), 4.36 (t, J = 7.2 Hz, NC**H**$_2$CH$_2$, 2H), 1.89 (m, $NCH_2C\mathbf{H}_2$, 2H), 1.40 (m, $NCH_2CH_2[C\mathbf{H}_2]_2CH_3$, 4H), 0.88 (t, J = 6.9 Hz, $N[CH_2]_4C\mathbf{H}_3$ 3H). ^{13}C NMR ($CDCl_3$): δ146.11 (NCH=**C**, 1C), 125.65 (**C**H=CH$_2$, 1C), 120.29 (N**C**H=C, 1C), 115.57 (CH=**C**H$_2$, 1C), 50.54 (N**C**H$_2$, 1C), 29.88 ($NCH_2\mathbf{C}H_2$, 1C), 28.42 ($N[CH_2]_2\mathbf{C}H_2$, 1C), 21.97 ($N[CH_2]_3\mathbf{C}H_2$, 1C), 13.78 ($N[CH_2]_4\mathbf{C}H_3$, 1C). Mass Spec for $C_9H_{15}N_3$ Calculated: 165.13; Found $(M+H)^+$: 166.14.

1-Hexyl-4-vinyl-1,2,3-triazole (33), via procedure C (74% overall yield (2 steps)).

^{1}H NMR (200 MHz, $CDCl_3$): δ7.50 (s, Ar**H**, 1H), 6.64 (dd, J = 17.6, 11.1 Hz, CH_2=C**H**, 1H), 5.82 (dd, J = 17.6, 1.2 Hz, *trans* C**H**$_2$=CH, 1H), 5.29 (dd, J = 11.1, 1.2 Hz, *trans* C**H**$_2$=CH, 1H), 4.32 (t, J = 7.2 Hz, NC**H**$_2$CH$_2$, 2H), 1.88 (m, $NCH_2C\mathbf{H}_2$, 2H), 1.30 (m, $NCH_2CH_2[C\mathbf{H}_2]_3CH_3$, 6H), 0.86 (t, J = 6.5 Hz, $N[CH_2]_5C\mathbf{H}_3$, 3H). ^{13}C NMR ($CDCl_3$): δ146.16 (NCH=**C**, 1C), 125.70 (**C**H=CH$_2$, 1C), 120.40 (N**C**H=C, 1C), 115.61 (CH=**C**H$_2$, 1C), 50.19 (N**C**H$_2$, 1C), 31.06 ($NCH_2\mathbf{C}H_2$, 1C), 30.19 ($N[CH_2]_2\mathbf{C}H_2$, 1C), 26.03 ($N[CH_2]_3\mathbf{C}H_2$, 1C), 22.33 ($N[CH_2]_4\mathbf{C}H_2$, 1C), 23.86 ($N[CH_2]_5\mathbf{C}H_3$, 1C). Mass Spec for $C_{10}H_{17}N_3$ Calculated: 179.14; Found $(M+H)^+$: 180.15.

1-Heptyl-4-vinyl-1,2,3-triazole (34), via procedure C (69% overall yield (2 steps)).

^{1}H NMR (200 MHz, $CDCl_3$): δ7.50 (s, Ar**H**, 1H), 6.65 (dd, J = 17.8, 11.4 Hz, CH_2=C**H**, 1H), 5.83 (dd, J = 17.8, 1.2 Hz, *trans* C**H**$_2$=CH, 1H), 5.30 (dd, J = 11.4, 1.0 Hz, *cis* C**H**$_2$=CH, 1H), 4.29 (t, J = 7.2 Hz, NC**H**$_2$CH$_2$, 2H), 1.85 (m, $NCH_2C\mathbf{H}_2$, 2H), 1.27 (m, $NCH_2CH_2[C\mathbf{H}_2]_4CH_3$, 8H), 0.83 (m, $N[CH_2]_6C\mathbf{H}_3$, 3H). ^{13}C NMR ($CDCl_3$): δ146.35 (NCH=**C**, 1C), 125.85 (**C**H=CH$_2$, 1C), 120.18 (N-**C**H=C, 1C), 115.82 (CH=**C**H$_2$, 1C), 50.36 (N**C**H$_2$, 1C), 31.63 ($NCH_2\mathbf{C}H_2$, 1C), 30.37 ($N[CH_2]_2\mathbf{C}H_2$, 1C), 28.72 ($N[CH_2]_3\mathbf{C}H_2$, 1C), 26.47 ($N[CH_2]_4\mathbf{C}H_2$, 1C), 22.58 ($N[CH_2]_5\mathbf{C}H_2$, 1C), 14.08 ($N[CH_2]_6\mathbf{C}H_3$, 1C). Mass Spec for $C_{11}H_{19}N_3$ Calculated: 193.16; Found $(M+H)^+$: 194.18.

1-Nonyl-4-vinyl-1,2,3-triazole (35), via procedure C (72% overall yield (2 steps)).

^{1}H NMR (200 MHz, $CDCl_3$): δ7.49 (s, Ar**H**, 1H), 6.64 (dd, J = 17.8, 11.2 Hz, CH_2=C**H**, 1H), 5.82 (dd, J = 17.8, 1.4 Hz, *trans* C**H**$_2$=CH, 1H), 5.28 (dd, J = 11.2, 1.2 Hz, *cis* C**H**$_2$=CH, 1H), 4.31 (t, NC**H**$_2$CH$_2$, J = 7.2 Hz, 2H), 1.88 (m, $NCH_2C\mathbf{H}_2$, 2H), 1.24 (m, $NCH_2CH_2[C\mathbf{H}_2]_6CH_3$, 12H), 0.86 (m, $N[CH_2]_8C\mathbf{H}_3$, 3H). ^{13}C NMR ($CDCl_3$): δ146.49 (NCH=**C**, 1C), 125.94 (**C**H=CH$_2$, 1C), 120.15 (N**C**H=C, 1C), 116.00 (CH=**C**H$_2$, 1C), 50.49 (N**C**H$_2$, 1C), 31.97

($NCH_2\mathbf{C}H_2$, 1C), 30.49 ($N[CH_2]_2\mathbf{C}H_2$, 1C), 29.50 ($N[CH_2]_3\mathbf{C}H_2$, 1C), 29.33 ($N[CH_2]_4\mathbf{C}H_2$, 1C), 29.17 ($N[CH_2]_5\mathbf{C}H_2$, 1C), 26.63 ($N[CH_2]_6\mathbf{C}H_2$, 1C), 22.80 ($N[CH_2]_7\mathbf{C}H_2$, 1C), 14.27 ($N[CH_2]_8\mathbf{C}H_3$, 1C). Mass Spec for $C_{13}H_{23}N_3$ Calculated: 221.19; Found $(M+H)^+$: 222.20.

1-Decyl-4-vinyl-1,2,3-triazole (36), via procedure C (72% overall yield (2 steps)).

^{1}H NMR (200 MHz, $CDCl_3$): δ7.50 (s, Ar**H**, 1H), 6.64 (dd, J = 17.7, 11.2 Hz, CH_2=C**H**, 1H), 5.82 (dd, J = 17.7, 1.2 Hz, *trans* C$\mathbf{H}_2$=CH, 1H), 5.28 (dd, J = 11.2, 1.2 Hz, *cis* C$\mathbf{H}_2$=CH, 1H), 4.31 (t, NC$\mathbf{H}_2CH_2$, J = 7.3 Hz, 2H), 1.91 (t, $NCH_2C\mathbf{H}_2$, J = 7.0 Hz, 2H), 1.24 (m, $NCH_2CH_2[C\mathbf{H}_2]_7CH_3$, 14H), 0.86 (m, $N[CH_2]_9C\mathbf{H}_3$, 3H). ^{13}C NMR ($CDCl_3$): δ146.48 (NCH=**C**, 1C), 125.93 (**C**H=CH_2, 1C), 120.16 (N**C**H=C, 1C), 116.00 (CH=**C**H_2, 1C), 50.49 (N**C**H_2, 1C), 32.02 ($NCH_2\mathbf{C}H_2$, 1C), 30.49 ($N[CH_2]_2\mathbf{C}H_2$, 1C), 29.63 ($N[CH_2]_3\mathbf{C}H_2$, 1C), 29.55 ($N[CH_2]_4\mathbf{C}H_2$, 1C), 29.42 ($N[CH_2]_5\mathbf{C}H_2$, 1C), 29.17 ($N[CH_2]_6\mathbf{C}H_2$, 1C), 26.63 ($N[CH_2]_7\mathbf{C}H_2$, 1C), 22.83 ($N[CH_2]_8\mathbf{C}H_2$, 1C), 14.28 ($N[CH_2]_9\mathbf{C}H_3$, 1C). Mass Spec for $C_{14}H_{25}N_3$ Calculated: 235.21; Found $(M+H)^+$: 236.21.

1-Adamantyl-4-vinyl-1,2,3-triazole (37), via procedure A (85% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ7.58 (s, Ar**H**, 1H), 6.64 (dd, J = 18.0, 11.2 Hz, C**H**=CH_2, 1H), 5.83 (dd, J = 18.0, 1.6 Hz, *trans* C$\mathbf{H}_2$=CH, 1H), 5.28 (dd, J = 11.2, 1.2 Hz, *cis* C$\mathbf{H}_2$=CH, 1H), 2.24 (s, 9H), 1.79 (t, J = 2.0 Hz, $NC(C\mathbf{H}_2)_3$, 6H). ^{13}C NMR ($CDCl_3$): δ145.75 (NCH=**C**, 1C), 126.49 (**C**H=CH_2, 1C), 116.95 (N**C**H=C, 1C), 115.62 (CH=**C**H_2, 1C), 102.91 (N**C**$(CH_2)_3$, 1C), 43.31 ($N(\mathbf{C}H_2CH)_3$, 3C), 36.25 ($N(CH_2\mathbf{C}H)_3$, 3C), 29.77 ($N(CH_2CH\mathbf{C}H_2)_3$, 3C). Mass Spec for $C_{14}H_{19}N_3$ Calculated: 229.16; Found $(M+H)^+$: 230.17.

1-Phenyl-4-vinyl-1,2,3-triazole (38), via procedure A (85% yield), Modified-A (66% yield), and B (75% overall yield (3 steps)).

^{1}H NMR (200 MHz, $CDCl_3$): δ7.95 (s, Ar**H**(triazole), 1H), 7.74-7.41 (m, Ar**H**(benzene), 5H), 6.78 (dd, J = 17.6, 11.1 Hz, C**H**=CH_2, 1H), 6.00 (dd, J = 17.6, 1.3 Hz, *trans* C$\mathbf{H}_2$=CH, 1H), 5.40 (dd, J = 11.1, 1.3 Hz, *cis* C$\mathbf{H}_2$=CH, 1H). ^{13}C NMR ($CDCl_3$): δ148.65 (NCH=**C**, 1C), 137.15 (Ar(benzene), N**C**, 1C), 129.76 (*m*-Ar, 2C), 128,74 (*p*-Ar, 2C), 125.32 (**C**H=CH_2, 1C), 120.50 (*o*-Ar, 2C), 118.59 (N**C**H=C, 1C), 116.77 (CH=**C**H_2, 1C), 102.91 (N**C**$(CH_2)_3$, 1C), 43.31 ($N(\mathbf{C}H_2CH)_3$, 3C), 36.25 ($N(CH_2\mathbf{C}H)_3$, 3C), 29.77 ($N(CH_2CH\mathbf{C}H_2)_3$, 3C). Mass Spec for $C_{10}H_9N_3$ Calculated: 171.08; Found $(M+H)^+$: 172.18.

1-Benzyl-4-vinyl-1,2,3-triazole (39), via procedure A (86% yield) B (69% overall yield (3 steps)).

1-(4-Methoxybenzyl)-4-vinyl-1,2,3-triazole (18), via procedure B (62% overall yield (3 steps)) and C (86% overall yield (2 steps)).

2-((4-Vinyl-1,2,3-triazol-1-yl)methyl)pyridine (40), via procedure A (81% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ8.54 (s, Ar**H**(6-pyr), 1H), 7.63-7.66 (m, Ar**H**(4-pyr and triazole), 2H), 7.22 (m, Ar**H**(5-Pyr), 1H), 7.15 (d, J = 3.0 Hz, Ar**H**(3-Pyr), 1H), 6.67 (dd, J = 17.6, 11.2 Hz, C**H**=CH_2, 1H), 5.85 (dd, J = 17.6, 0.7 Hz, *trans* CH=C$\mathbf{H}_2$, 1H), 5.60 (s, NC$\mathbf{H}_2$Pyr, 2H), 5.28 (dd, J = 11.2, 0.7 Hz, *cis* CH=C$\mathbf{H}_2$, 1H). ^{13}C NMR ($CDCl_3$): δ154.34 (2-Pyr, 1C), 149.65 (6-Pyr, 1C), 146.71 (NCH=**C**, 1C), 137.44 (3-Pyr, 1C), 129.48 (**C**H=CH_2, 1C),

125.51 (4-Pyr, 1C), 121.04 (5-Pyr, 1C), 119.51 (CH=**C**H_2, 1C), 55.49 (N**C**H_2, 1C). Mass Spec for $C_{10}H_{10}N_4$ Calculated: 186.09; Found $(M+H)^+$: 187.10.

(4-Vinyl-1,2,3-triazol-1-yl)methyl pivalate (13-A), via procedure A (79% yield), B (52% overall yield (3 steps)), and C (21% overall yield (2 steps)).

^{1}H NMR (200 MHz, $CDCl_3$): δ7.75 (s, Ar**H**, 1H), 6.69 (dd, J = 17.8, 11.2 Hz, C**H**=CH_2, 1H), 6.21 (s, NC**H**$_2$O, 2H), 5.95 (dd, J = 17.6, 1.0 Hz, *trans* CH=C**H**$_2$, 1H), 5.37 (dd, J = 11.2, 1.2 Hz, *cis* CH=C**H**$_2$, 1H), 1.18 (s, CO(C**H**$_3$)$_3$, 9H). ^{13}C NMR ($CDCl_3$): δ178.10 (**C**=O, 1C), 146.95 (NCH=**C**, 1C), 125.24 (**C**H=CH_2, 1C), 121.82 (N**C**H=C, 1C), 117.12 (CH=**C**H_2, 1C), 69.80 (N**C**H_2O, 1C), 38.98 (C=O**C**$(CH_3)_3$, 1C), 26.99 (C(**C**$H_3)_3$, 3C). Mass Spec for $C_{10}H_{15}N_3O_2$ Calculated: 209.12; Found $(M+H)^+$: 210.12. Rf-value of TLC; 0.7 (1:1 ethyl acetate:hexanes)

(4-Vinyl-1,2,3-triazol-2-yl)methyl pivalate (13-B), via procedure B (9% overall yield (3 steps)) and C (27% overall yield (2 steps)).

^{1}H NMR (200 MHz, $CDCl_3$): δ7.73 (s, Ar**H**, 1H), 6.73 (dd, J = 17.8, 11.2 Hz, C**H**=CH_2, 1H), 6.23 (s, NC**H**$_2$O, 2H), 5.91 (dd, J = 17.8, 1.0 Hz, *trans* CH=C**H**$_2$, 1H), 5.46 (dd, J = 11.2, 0.9 Hz, *cis* CH=C**H**$_2$, 1H), 1.13 (s, CO(C**H**$_3$)$_3$, 9H). ^{13}C NMR ($CDCl_3$): δ177.16 (**C**=O, 1C), 148.39 (CH_2=CH**C**, 1C), 133.42 (N=**C**HC, 1C), 125.52 (**C**H=CH_2, 1C), 118.68 (CH=**C**H_2, 1C), 74.23 (N**C**H_2O, 1C), 39.04 (C=O**C**$(CH_3)_3$, 1C), 27.05 (C(**C**$H_3)_3$, 3C). Mass Spec for $C_{10}H_{15}N_3O_2$ Calculated: 209.12; Found $(M+H)^+$: 210.12. Rf-value of TLC; 0.9 (1:1 ethyl acetate:hexanes)

Methyl 3-(4-vinyl-1,2,3-triazol-1-yl)propanoate (15-A), via procedure A (79% yield), B (9% overall yield (3 steps)), and C (2% overall yield (2 steps)).

^{1}H NMR (400 MHz, $CDCl_3$): δ7.61 (s, Ar**H**, 1H), 6.69 (dd, J = 17.2, 11.2 Hz, C**H**=CH_2, 1H), 5.85 (dd, J = 17.2, 0.8 Hz, *trans* CH=C**H**$_2$, 1H), 5.32 (dd, J = 11.2, 1.2 Hz, *cis* CH=C**H**$_2$, 1H), 4.63 (t, J = 6.4 Hz, NC**H**$_2$$CH_2$, 2H), 3.69 (s, COOC**H**$_3$, 3H), 2.94 (t, J = 6.4 Hz, NCH_2C**H**$_2$, 2H). ^{13}C NMR ($CDCl_3$): δ171.37 (**C**=O, 1C), 146.59 (NCH=**C**, 1C) 125.86 (**C**H=CH_2, 1C), 121.49 (N**C**H=C, 1C), 116.44 (CH=**C**H_2, 1C), 52.50 (N**C**$H_2$$CH_2$, 1C), 45.74 (COO**C**$H_3$, 1C), 34.76 ($NCH_2$**C**$H_2$, 1C). Mass Spec for $C_8H_{11}N_3O_2$ Calculated: 181.09; Found $(M+H)^+$: 182.09. Rf-value of TLC; 0.2 (1:1 ethyl acetate:hexanes)

Methyl 3-(4-vinyl-1,2,3-triazol-2-yl)propanoate (15-B), via procedure B (11% overall yield (3 steps)), and C (20% overall yield (2 steps)).

^{1}H NMR (200 MHz, $CDCl_3$): δ7.61 (s, Ar**H**, 1H), 6.69 (dd, J = 17.8, 11.2 Hz, C**H**=CH_2, 1H), 5.85 (dd, J = 17.8, 1.4 Hz, *trans* CH=C**H**$_2$, 1H), 5.32 (dd, J = 11.2, 1.3 Hz, *cis* CH=C**H**$_2$, 1H), 4.62 (t, J = 6.4 Hz, NC**H**$_2$$CH_2$, 2H), 3.69 (s, COOC**H**$_3$, 3H), 2.96 (t, J = 6.4 Hz, NCH_2C**H**$_2$, 2H). ^{13}C NMR ($CDCl_3$): δ171.07 (**C**=O, 1C), 146.27 (CH_2=CH**C**, 1C) 125.52 (**C**H=CH_2, 1C), 121.20 (N=**C**HC, 1C), 116.14 (CH=**C**H_2, 1C), 52.19 (N**C**$H_2$$CH_2$, 1C), 45.42 (COO**C**$H_3$, 1C), 34.43 ($NCH_2$**C**$H_2$, 1C). Mass Spec for $C_8H_{11}N_3O_2$ Calculated: 181.09; Found (M): 181.09. Rf-value of TLC; 0.6 (1:1 ethyl acetate:hexanes)

Methyl 4-(4-vinyl-1,2,3-triazol-1-yl)butanoate (41), via procedure A (72% yield).

^{1}H NMR (200 MHz, $CDCl_3$): δ7.53(s, Ar**H**, 1H), 6.71 (dd, J = 17.6, 11.1 Hz, C**H**=CH_2, 1H), 5.88 (dd, J = 17.6, 1.2 Hz, *trans* CH=C**H**$_2$, 1H), 5.33 (dd, J = 11.1, 1.3 Hz, *cis* CH=C**H**$_2$, 1H), 4.42 (t, J = 6.6 Hz, NC**H**$_2$$CH_2$, 2H), 3.67

(s, $CO_2C\mathbf{H}_3$, 3H), 2.40-2.18 (m, $NCH_2C\mathbf{H}_2C\mathbf{H}_2CO$, 4H). ^{13}C NMR ($CDCl_3$): δ172.85 (**C**=O, 1C), 146.48 (NCH=**C**, 1C) 125.64 (**C**H=CH_2, 1C), 120.50 (N**C**H=C, 1C), 116.14 (CH=**C**H_2, 1C), 51.90 (N**C**H_2CH_2, 1C), 49.20 (COO**C**H_3, 1C), 30.46 ($NCH_2\mathbf{C}H_2$, 1C) 25.48 ($NCH_2CH_2\mathbf{C}H_2$, 1C).

Ethyl 4-(4-vinyl-1,2,3-triazol-1-yl)butanoate (42), via procedure A (92% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ7.54 (s, Ar**H**, 1H), 6.73 (dd, J = 17.2, 11.2 Hz, C**H**=CH_2, 1H), 5.83 (d, J = 17.2 Hz, *trans* CH=C$\mathbf{H}_2$, 1H), 5.35 (d, J = 11.2 Hz, *cis* CH=C$\mathbf{H}_2$, 1H), 4.44 (t, J = 6.8 Hz, NC$\mathbf{H}_2CH_2$, 2H), 4.15 (q, J = 7.2 Hz, $CO_2C\mathbf{H}_2CH_3$, 2H), 2.36 (t, J = 6.8 Hz, $NCH_2CH_2C\mathbf{H}_2$, 2H), 2.25 (m, $NCH_2C\mathbf{H}_2CH_2$, 2H), 1.27 (t, J = 7.2 Hz, $CO_2CH_2C\mathbf{H}_3$ 3H).

4-(4-Vinyl-1,2,3-triazol-1-yl)butanoic acid (43), via procedure A (Converted from 42 by hydrolysis; 99% yield).

^{1}H NMR (200 MHz, $CDCl_3$): δ11.19 (s, COO**H**, 1H), 7.57 (s, Ar**H**, 1H), 6.70 (dd, J = 17.6, 11.2 Hz, C**H**=CH_2, 1H), 5.86 (dd, J = 17.6, 1.2 Hz, *trans* CH=C$\mathbf{H}_2$, 1H), 5.35 (dd, J = 11.2, 1.2 Hz, *cis* CH=C$\mathbf{H}_2$, 1H), 4.45 (t, J = 6.7 Hz, NC$\mathbf{H}_2CH_2$, 2H), 2.42 (t, J = 7.0 Hz, $CH_2C\mathbf{H}_2COOH$, 2H), 2.24 (m, C$\mathbf{H}_2CH_2COOH$, 2H). ^{13}C NMR ($CDCl_3$): δ176.50 (**C**OOH, 1C), 146.25 (NCH=**C**, 1C), 125.10 (**C**H=CH_2, 1C), 120.73 (N**C**H=C, 1C), 116.75 (CH=**C**H_2, 1C), 49.30 (N**C**H_2, 1C), 30.49 (**C**H_2COOH, 1C), 25.26 ($NCH_2\mathbf{C}H_2CH_2$, 1C). Mass Spec for $C_8H_{11}N_3O_2$ Calculated: 181.09; Found $(M-H)^-$: 180.08. To make triazol-1-yl acid like this compound (**43**), usually higher overall yields were obtained by making triazol-1-yl ester like (**42**) first and then hydrolyzing it into a corresponding acid by using strong base such as NaOH than direct 'Click' reactions of acid-azides and acetylenes.

5-(4-Vinyl-1,2,3-triazol-1-yl)pentanoic acid (44), via procedure B (1% overall yield (3 steps)).

^{1}H NMR (200 MHz, $CDCl_3$): δ7.53 (s, Ar**H**, 1H), 6.72 (dd, J = 17.6, 11.2 Hz, C**H**=CH_2, 1H), 5.86 (dd, J = 17.6, 1.1 Hz, *trans* CH=C$\mathbf{H}_2$, 1H), 5.35 (dd, J = 11.2, 1.3 Hz, *cis* CH=C$\mathbf{H}_2$, 1H), 4.37 (t, J = 7.0 Hz, NC$\mathbf{H}_2CH_2$, 2H), 2.41 (t, J = 7.2 Hz, $CH_2C\mathbf{H}_2COOH$, 2H), 1.95 (m, $NCH_2C\mathbf{H}_2$, 2H), 1.63 (m, C$\mathbf{H}_2CH_2COOH$, 2H).

2-(4-Vinyl-1,2,3-triazol-1-yl)ethanol (45), via procedure A (58% yield).

^{1}H NMR (200 MHz, $CDCl_3$): δ7.63 (s, Ar**H**, 1H), 6.68 (dd, J = 17.8, 11.2 Hz, C**H**=CH_2, 1H), 5.82 (d, J = 17.8, 1.2 Hz, trans CH=C$\mathbf{H}_2$, 1H), 5.35 (dd, J = 11.2, 1.2 *cis* CH=C$\mathbf{H}_2$, 1H), 4.47 (t, J = 4.9 Hz NC$\mathbf{H}_2CH_2$, 2H), 4.08 (t, J = 4.9 Hz $CH_2C\mathbf{H}_2OH$, 2H), 2.73 (s, $CH_2CH_2O\mathbf{H}$, 1H). ^{13}C NMR ($CDCl_3$): δ145.81 (NCH=**C**, 1C), 125.21 (**C**H=CH_2, 1C), 121.75 (N**C**H=C, 1C), 116.16 (CH=**C**H_2, 1C), 60.79 (N**C**H_2, 1C), 52.89 ($NCH_2\mathbf{C}H_2$, 1C). Mass Spec for $C_6H_9N_3O$ Calculated: 139.16; Found $(M+H)^+$: 140.18.

2-(2-(4-Vinyl-1,2,3-triazol-1-yl))ethoxyethanol (46), via procedure A (56% yield), Modified-A (54% yield), and C (25% overall yield (2 steps)).

^{1}H NMR (200 MHz, $CDCl_3$): δ7.67 (s, Ar**H**, 1H), 6.73 (dd, J = 17.8, 11.2 Hz, C**H**=CH_2, 1H), 5.85 (dd, J = 17.8, 1.0 Hz, *trans* CH=C$\mathbf{H}_2$, 1H), 5.35 (dd, J = 11.2, 1.2 Hz, *cis* CH=C$\mathbf{H}_2$, 1H), 4.55 (t, J = 4.9 Hz, NC$\mathbf{H}_2CH_2$, 2H), 3.90 (t, J = 5.1 Hz, $NCH_2C\mathbf{H}_2O$, 2H), 3.73 (b O$C\mathbf{H}_2CH_2$, 2H), 3.59 (t, J = 4.3 Hz $OCH_2C\mathbf{H}_2OH$, 2H), 2.13 (s, $CH_2O\mathbf{H}$, 1H). ^{13}C NMR ($CDCl_3$): δ146.31 (NCH=**C**, 1C), 125.56 (**C**H=CH_2, 1C), 121.38 (N**C**H=C, 1C), 116.04 (CH=**C**H_2,

1C), 72.57 (N**C**H_2, 1C), 69.29 (NCH_2**C**H_2, 1C), 61.53 (O**C**H_2CH_2, 1C), 50.20 (CH_2**C**H_2OH, 1C). Mass Spec for $C_8H_{13}N_3O_2$ Calculated: 183.21; Found $(M+H)^+$: 184.11.

2-(2-(2-(4-Vinyl-1,2,3-triazole-1-yl))ethoxy)ethoxyethanol (7), via procedure Modified-A (28% yield).

1-Heptyl-4-(prop-1-en-2-yl)-1*H*-1,2,3-triazole (47), via procedure F (62% overall yield (2 steps)).

^{1}H NMR (200 MHz, $CDCl_3$): δ7.47 (s, Ar**H**, 1H), 5.68 (s, *cis(to CH_3)* C**H**$_2$=CCH_3, 1H), 5.51 (m, *trans(to CH_3)* C**H**$_2$=CCH_3, 1H), 4,32 (t, J = 7.3 Hz, NC**H**$_2$CH_2, 2H), 2.12 (s, C**H**$_3$C=CH_2, 3H). 1.88 (m, NCH_2C**H**$_2$, 2H), 1.30 (m, NCH_2CH_2[C**H**$_2$]$_4$CH_3, 8H), 0.86 (t, J = 6.5 Hz, NCH_2CH_2[CH_2]$_4$C**H**$_3$, 3H).

1-Octyl-4-(prop-1-en-2-yl)-1*H*-1,2,3-triazole (48), via procedure F (86% overall yield (2 steps)).

^{1}H NMR (200 MHz, $CDCl_3$): δ7.47 (s, Ar**H**, 1H), 5.61 (s, *cis(to CH_3)* C**H**$_2$=CCH_3, 1H), 4.99(m, *trans(to CH_3)* C**H**$_2$=CCH_3, 1H), 4,24 (t, J = 7.3 Hz, NC**H**$_2$CH_2, 2H), 2.04 (s, C**H**$_3$C=CH_2, 3H). 1.60 (m, NCH_2C**H**$_2$, 2H), 1.17 (m, NCH_2CH_2[C**H**$_2$]$_5$CH_3, 8H), 0.78 (t, J = 6.4 Hz, NCH_2CH_2[CH_2]$_4$C**H**$_3$, 3H). ^{13}C NMR ($CDCl_3$): δ148.57 (CH_3**C**=CH_2, 1C), 133.65 (NCH=**C**, 1C), 119.54 (N**C**HCC, 1C), 112.04 (NCCH_3=**C**H_2, 1C), 50.20 (N**C**H_2CH_2, 1C), 31.67 (NCH_2**C**H_2CH_2, 1C), 30.30-20.59, (CH_2CH_2(**C**H_2)$_5$CH_3, 5C), 25.44 (NC**C**H_3=CH_2, 1C), 14.02 ((CH_2)$_7$CH_3, 1C). Mass Spec for $C_{13}H_{23}N_3$ Calculated: 221.34; Found $(M+H)^+$: 222.19.

2-(4-(Prop-1-en-2-yl)-1*H*-1,2,3-triazol-1-yl)ethanol (50), via procedure F (7% overall yield (4 steps (including the protection and deprotection reactions of hydroxyl group with 3,4-Dihydro-2*H*-pyran))).

^{1}H NMR (200 MHz, $CDCl_3$): δ7.63 (s, Ar**H**, 1H), 5.73 (s, *cis(to CH_3)* C**H**$_2$=CH, 1H), 5.12 (m, *trans(to CH_3)* C**H**$_2$=CH, 1H), 4,69 (t, J = 5.8 Hz, NC**H**$_2$CH_2O, 2H), 3.92 (t, J = 5.8 Hz, NCH_2C**H**$_2$O, 2H), 2.13 (s, C**H**$_3$C=CH_2, 3H), 1.80 (b, O**H**, 1H).

2-(2-(2-(4-(Prop-1-en-2-yl)-1*H*-1,2,3-triazol-1-yl)ethoxy)ethoxy)ethanol (51), via procedure F (8% overall yield (4 steps (including the protection and deprotection reactions of hydroxyl group with 3,4-Dihydro-2*H*-pyran))).

^{1}H NMR (200 MHz, $CDCl_3$): δ7.68 (s, Ar**H**, 1H), 5.69 (s, *cis(to CH_3)* C**H**$_2$=CH, 1H), 5.09 (m, *trans(to CH_3)* C**H**$_2$=CH, 1H), 4,53 (t, J = 5.1 Hz, NC**H**$_2$CH_2O, 2H), 3.88 (t, J = 5.0 Hz, CH_2C**H**$_2$OH, 2H), 3.74-3.57 (m, NCH_2C**H**$_2$OC**H**$_2$C**H**$_2$OC**H**$_2$CH_2OH, 8H), 2.13 (s, C**H**$_3$C=CH_2, 3H), 1.78 (b, O**H**, 1H).

Characterization of mesylated derivatives utilized in General procedure B and C:

2-(1-Butyl-1,2,3-triazol-4-yl)ethyl methanesulfonate (10).

^{1}H NMR (200 MHz, $CDCl_3$): δ7.41 (s, Ar**H**, 1H), 4.43 (t, J = 6.5 Hz, OC**H**$_2$CH_2, 2H), 4.26 (t, J = 7.2 Hz, NC**H**$_2$CH_2, 2H), 3.09 (t, J = 6.4 Hz, OCH_2C**H**$_2$, 2H), 2.90 (s, C**H**$_3$S, 3H), 1.80 (m, NCH_2C**H**$_2$, 2H), 1.26 (m, NCH_2CH_2C**H**$_2$CH_3, 2H), 0.86 (t, J = 7.2 Hz, N[CH_2]$_3$C**H**$_3$, 3H). ^{13}C NMR ($CDCl_3$): δ142.54 (NCH=**C**, 1C), 122.01 (N**C**H=C, 1C), 68.83 (CH_2**C**H_2O, 1C), 49.98 (N**C**H_2, 1C), 37.25 (SOO**C**H_3, 1C), 32.19 (NCH_2**C**H_2, 1C), 26.02

(**C**H_2CH_2O, 1C), 19.61 (N[CH_2]$_2$**C**H_2, 1C), 13.41 (N[CH_2]$_3$**C**H_3, 1C). Mass Spec for $C_9H_{17}N_3O_3S$ Calculated: 247.10; Found $(M+H)^+$: 248.11.

2-(1-Pentyl-1,2,3-triazol-4-yl)ethyl methanesulfonate (58).

^{1}H NMR (200 MHz, $CDCl_3$): δ7.43 (s, Ar**H**, 1H), 4.51 (t, J = 6.5 Hz, OC**H**$_2$$CH_2$, 2H), 4.32 (t, J = 7.2 Hz, NC**H**$_2$$CH_2$, 2H), 3.09 (t, J = 6.5 Hz, OCH_2C**H**$_2$, 2H), 2.96 (s, C**H**$_3$S, 3H), 1.88 (m, NCH_2C**H**$_2$, 2H), 1.38 (m, NCH_2CH_2C**H**$_2$C**H**$_2$$CH_3$, 4H), 0.86 (t, J = 7.2 Hz, N[CH_2]$_4$C**H**$_3$, 3H). ^{13}C NMR ($CDCl_3$): δ142.59 (NCH=**C**, 1C), 122.06 (N**C**H=C, 1C), 68.84 (CH_2**C**H_2O, 1C), 50.32 (N**C**H_2, 1C), 37.29 (SOO**C**H_3, 1C), 29.98 (NCH_2**C**H_2, 1C), 28.53 (N[CH_2]$_2$**C**H_2, 1C), 26.04 (**C**H_2CH_2O, 1C), 22.05 (N[CH_2]$_3$**C**H_2, 1C), 13.84 (N[CH_2]$_4$**C**H_3, 1C). Mass Spec for $C_{10}H_{19}N_3O_3S$ Calculated: 261.11; Found $(M+H)^+$: 262.13.

2-(1-Hexyl-1,2,3-triazol-4-yl)ethyl methanesulfonate (59).

^{1}H NMR (200 MHz, $CDCl_3$): δ7.43 (s, Ar**H**, 1H), 4.52 (t, J = 6.4 Hz, OC**H**$_2$$CH_2$, 2H), 4.33 (t, J = 7.2 Hz, NC**H**$_2$$CH_2$, 2H), 3.18 (t, J = 6.4 Hz, OCH_2C**H**$_2$, 2H), 2.97 (s, C**H**$_3$S, 3H), 1.89 (m, NCH_2C**H**$_2$, 2H), 1.31 (m, NCH_2CH_2[C**H**$_2$]$_3$$CH_3$, 6H), 0.86 (t, J = 7.2 Hz, N[CH_2]$_5$C**H**$_3$, 3H). ^{13}C NMR ($CDCl_3$): δ142.78 (NCH=**C**, 1C), 122.08 (N**C**H=C, 1C), 68.95 (CH_2**C**H_2O, 1C), 50.55 (N**C**H_2, 1C), 37.51 (SOO**C**H_3, 1C), 31.29 (NCH_2**C**H_2, 1C), 30.43 (N[CH_2]$_2$**C**H_2, 1C), 26.30 (**C**H_2CH_2O, N[CH_2]$_3$**C**H_2, 2C), 22.58 (N[CH_2]$_4$**C**H_2, 1C), 14.11 (N[CH_2]$_5$**C**H_3, 1C). Mass Spec for $C_{11}H_{21}N_3O_3S$ Calculated: 275.13; Found $(M+H)^+$: 276.14.

2-(1-Heptyl-1,2,3-triazol-4-yl)ethyl methanesulfonate (60).

^{1}H NMR (200 MHz, $CDCl_3$): δ7.41 (s, Ar**H**, 1H), 4.43 (t, J = 6.4 Hz, OC**H**$_2$$CH_2$, 2H), 4.25 (t, J = 7.2 Hz, NC**H**$_2$$CH_2$, 2H), 3.10 (t, J = 6.4 Hz, OCH_2C**H**$_2$, 2H), 2.90 (s, C**H**$_3$S, 3H), 1.85(m, NCH_2C**H**$_2$, 2H), 1.31 (m, NCH_2CH_2[C**H**$_2$]$_4$$CH_3$, 8H), 0.86 (t, J = 7.2 Hz, N[CH_2]$_6$C**H**$_3$, 3H). ^{13}C NMR ($CDCl_3$): δ142.57 (NCH=**C**, 1C), 122.00 (N**C**H=C, 1C), 68.84 (CH_2**C**H_2O, 1C), 50.32 (N**C**H_2, 1C), 37.28 (SOO**C**H_3, 1C), 31.53 (NCH_2**C**H_2, 1C), 30.28 (N[CH_2]$_2$**C**H_2, 1C), 28.61 (N[CH_2]$_3$**C**H_2, 1C), 26.39 (N[CH_2]$_4$**C**H_2, 2C), 26.06 (**C**H_2CH_2O, 1C), 22.49 (N[CH_2]$_5$**C**H_2, 1C), 14.01 (N[CH_2]$_6$**C**H_3, 1C). Mass Spec for $C_{12}H_{23}N_3O_3S$ Calculated: 289.15; Found $(M+H)^+$: 290.15.

2-(1-Nonyl-1,2,3-triazol-4-yl)ethyl methanesulfonate (61).

^{1}H NMR (200 MHz, $CDCl_3$): δ7.42 (s, Ar**H**, 1H), 4.51 (t, J = 6.4 Hz, OC**H**$_2$$CH_2$, 2H), 4.31 (t, J = 7.2 Hz, NC**H**$_2$$CH_2$, 2H), 3.17 (t, J = 6.4 Hz, OCH_2C**H**$_2$, 2H), 2.96 (s, C**H**$_3$S, 3H), 1.85 (m, NCH_2C**H**$_2$, 2H), 1.24 (m, NCH_2CH_2[C**H**$_2$]$_6$$CH_3$, 12H), 0.86 (t, J = 6.3 Hz, N[CH_2]$_6$C**H**$_3$, 3H). ^{13}C NMR ($CDCl_3$): δ142.79 (NCH=**C**, 1C), 122.07 (N**C**H=C, 1C), 68.94 (CH_2**C**H_2O, 1C), 50.56 (N**C**H_2, 1C), 37.52 (SOO**C**H_3, 1C), 31.96 (NCH_2**C**H_2, 1C), 30.49 (N[CH_2]$_2$**C**H_2, 1C), 29.51 (N[CH_2]$_3$**C**H_2, 1C), 29.33 (N[CH_2]$_4$**C**H_2, 2C), 29.16 (N[CH_2]$_5$**C**H_2, 2C), 26.65 (N[CH_2]$_6$**C**H_2, 2C), 26.30 (**C**H_2CH_2O, 1C), 22.80 (N[CH_2]$_7$**C**H_2, 1C), 14.27 (N[CH_2]$_8$**C**H_3, 1C). Mass Spec for $C_{14}H_{27}N_3O_3S$ Calculated: 317.18; Found $(M+H)^+$: 318.18.

2-(1-Decyl-1,2,3-triazol-4-yl)ethyl methanesulfonate (62).

^{1}H NMR (200 MHz, $CDCl_3$): δ7.43 (s, Ar**H**, 1H), 4.52 (t, J = 6.4 Hz, OC**H**$_2$$CH_2$, 2H), 4.32 (t, J = 7.2 Hz, NC**H**$_2$$CH_2$, 2H), 3.18 (t, J = 6.4 Hz, OCH_2C**H**$_2$, 2H), 2.97 (s, C**H**$_3$S, 3H), 1.88 (m, NCH_2C**H**$_2$, 2H), 1.25 (m,

$NCH_2CH_2[CH_2]_7CH_3$, 14H), 0.87 (t, J = 6.4 Hz, $N[CH_2]_6CH_3$, 3H). ^{13}C NMR ($CDCl_3$): δ142.78 (NCH=**C**, 1C), 122.07 (N**C**H=C, 1C), 68.95 (CH_2CH_2O, 1C), 50.55 (NCH_2, 1C), 37.50 ($SOOCH_3$, 1C), 32.01 (NCH_2CH_2, 1C), 30.48 ($N[CH_2]_2CH_2$, 1C), 29.63 ($N[CH_2]_3CH_2$, 1C), 29.55 ($N[CH_2]_4CH_2$, 2C), 29.41 ($N[CH_2]_5CH_2$, 2C), 29.15 ($N[CH_2]_6CH_2$, 2C), 26.65 ($N[CH_2]_7CH_2$, 2C), 26.28 (CH_2CH_2O, 1C), 22.82 ($N[CH_2]_8CH_2$, 1C), 14.27 ($N[CH_2]_9CH_3$, 1C). Mass Spec for $C_{15}H_{29}N_3O_3S$ Calculated: 331.19; Found $(M+H)^+$: 332.20.

2-(1-Phenyl-1,2,3-triazol-4-yl)ethyl methanesulfonate (63).

^1H NMR (200 MHz, $CDCl_3$): δ7.43 (s, Ar**H**(triazole), 1H), 7.72-7.44 (m, Ar**H**(benzene), 5H), 4.60 (t, J = 6.3 Hz, OCH_2CH_2, 2H), 3.29 (t, J = 6.3 Hz, OCH_2CH_2, 2H), 3.00 (s, CH_3S, 3H). ^{13}C NMR ($CDCl_3$): δ143.67 (NCH=**C**, 1C), 137.15 (Ar(benzene), N**C**, 1C), 130.00 (*m*-Ar, 2C) 129.06 (*p*-Ar, 1C), 120.72 (*o*-Ar and N**C**H=C, 3C), 68.67 (CH_2CH_2O, 1C), 37.64 ($SOOCH_3$, 1C), 26.33 (CH_2CH_2O, 1C). Mass Spec for $C_{11}H_{13}N_3O_3S$ Calculated: 267.07; Found $(M+H)^+$: 268.08.

2-(1-Benzyl-1,2,3-triazol-4-yl)ethyl methanesulfonate (64).

^1H NMR (200 MHz, $CDCl_3$): δ7.41-7.23 (m, Ar**H**, 6H), 5.51 (s, $ArCH_2Ar$, 2H), 4.50 (t, J = 6.4 Hz, OCH_2CH_2, 2H), 3.15 (t, J = 6.4 Hz, OCH_2CH_2, 2H), 2.90 (s, CH_3S, 3H). ^{13}C NMR ($CDCl_3$): δ143.27 (NCH=**C**, 1C), 134.75 (Ar(benzene), NCH_2C, 1C), 129.30 (*m*-Ar, 2C), 128.96 (*p*-Ar, 1C), 128.20 (*o*-Ar, 2C), 122.26 (N**C**H=C, 1C), 68.77 (CH_2CH_2O, 1C), 54.34 ($ArCH_2Ar$, 1C), 37.43 ($SOOCH_3$, 1C), 26.21 (CH_2CH_2O, 1C). Mass Spec for $C_{12}H_{15}N_3O_3S$ Calculated: 281.08; Found $(M+H)^+$: 282.09.

2-(1-(4-Methoxybenzyl)-1*H*-1,2,3-triazol-4-yl)ethyl methanesulfonate (65).

^1H NMR (200 MHz, $CDCl_3$): δ7.32 (s, Ar**H**(triazole), 1H), 7.24 (dd, J = 6.7, 2.2 Hz, *o*-Ar**H**, 2H), 6.90 (dd, J = 6.6, 2.2 Hz, *m*-Ar**H**, 2H), 5.44 (s, $ArCH_2Ar$, 2H), 4.49 (t, J = 6.4 Hz, OCH_2CH_2, 2H), 3.85 (s, OCH_3, 3H), 3.14 (t, J = 6.4 Hz, OCH_2CH_2, 2H), 2.91 (s, CH_3S, 3H). ^{13}C NMR ($CDCl_3$): δ160.11 (Ar(benzene), CH_3O**C**, 1C), 143.18 (NCH=**C**, 1C), 129.30 (*o*-Ar, 2C), 126.70 (Ar(benzene), NCH_2C, 1C), 122.26 (N**C**H=C, 1C), 114.65 (*m*-Ar, 2C), 68.80 (CH_2CH_2O, 1C), 55.51 (CH_3O, 1C), 53.90 ($ArCH_2Ar$, 1C), 37.44 ($SOOCH_3$, 1C), 26.22 (CH_2CH_2O, 1C). Mass Spec for $C_{13}H_{17}N_3O_4S$ Calculated: 311.09; Found $(M+H)^+$: 312.10.

2-(1-((Pivaloyloxy)methyl)-1*H*-1,2,3-triazol-4-yl)ethyl methanesulfonate (66).

^1H NMR (200 MHz, $CDCl_3$): δ7.70 (s, Ar**H**, 1H), 6.21 (s, NCH_2O, 2H), 4.52 (t, J = 6.4 Hz, OCH_2CH_2, 2H), 3.19 (t, J = 6.4 Hz, OCH_2CH_2, 2H), 2.96 (s, CH_3S, 3H), 1.19 (s, $C(CH_3)_3$, 9H).

2-(1-(2-Methoxycarbonyl)ethyl)-1*H*-1,2,3-triazol-4-yl)ethyl methanesulfonate (67).

^1H NMR (200 MHz, $CDCl_3$): δ7.54 (s, Ar**H**, 1H), 4.63 (t, J = 6.4 Hz, NCH_2CH_2, 2H), 4.51 (t, J = 6.4 Hz, OCH_2CH_2, 2H), 3.70 (s, $COOCH_3$, 3H), 3.17 (t, J = 6.3 Hz, OCH_2CH_2, 2H), 2.97 (s, CH_3S, 3H), 2.97 (t, J = 6.4 Hz, NCH_2CH_2, 2H).

5-(4-(2-(Methylsulfonyloxy)ethyl)-1*H*-1,2,3-triazol-1-yl)pentanoic acid (68).

^{1}H NMR (200 MHz, $CDCl_3$): δ7.48 (s, Ar**H**, 1H), 4.49 (t, J = 6.4 Hz, NC**H**$_2$CH$_2$, 2H), 4.32 (t, J = 7.2 Hz, OC**H**$_2$CH$_2$, 2H), 3.16 (t, J = 6.4 Hz, OCH$_2$C**H**$_2$, 2H), 2.96 (s, C**H**$_3$S, 3H), 2.37 (t, J = 7.2 Hz, HO$_2$CC**H**$_2$, 2H), 1.92 (m, NCH$_2$C**H**$_2$, 2H), 1.64 (m, NCH$_2$CH$_2$C**H**$_2$, 2H).

2-(1-(2-(2-Hydroxyethyl)oxyethyl)-1*H*-1,2,3-triazol-4-yl)ethyl methanesulfonate (69).

^{1}H NMR (200 MHz, $CDCl_3$): δ7.67 (s, Ar**H**, 1H), 4.57-4.48 (m, SOC**H**$_2$CH$_2$ and NC**H**$_2$CH$_2$O, 4H), 3.85 (t, J = 4.8 Hz, NCH$_2$C**H**$_2$O, 2H), 3.72 (t, J = 4.3 Hz, OCH$_2$C**H**$_2$OH, 2H), 3.55 (t, J = 4.3 Hz, OC**H**$_2$CH$_2$OH, 2H), 3.18 (t, J = 6.1 Hz, SOCH$_2$C**H**$_2$, 2H), 2.97 (s, C**H**$_3$S, 3H), 2.30 (s, CH$_2$O**H**, 1H). Mass Spec for $C_{11}H_{21}N_3O_6S$ Calculated: 279.09; Found $(M+H)^+$: 280.10.

2-(1-(2-(2-(2-(Tetrahydro-2*H*-pyran-2-yloxy)ethoxy)ethoxy)ethyl)-1H-1,2,3-triazol-4-yl)ethyl methanesulfonate (70).

^{1}H NMR (200 MHz, $CDCl_3$): δ7.66 (s, Ar**H**, 1H), 4.61 (b, ring, OC**H**, 1H), 4.52 (t, J = 6.4 Hz, SOC**H**$_2$CH$_2$ and NC**H**$_2$CH$_2$O, 4H), 3.90-3.45 (m, NCH$_2$C**H**$_2$[OC**H**$_2$C**H**$_2$]$_2$O and OCH[CH$_2$]$_3$C**H**$_2$O-ring, 12H), 3.18 (t, J = 6.5 Hz, SOCH$_2$C**H**$_2$, 2H), 1.89-1.45 (m, OCH[C**H**$_2$]$_3$CH$_2$O-ring, 6H).

Characterization of hydroxyl derivatives utilized in General procedure B, D, E and F:

2-(1-Phenyl-1,2,3-triazol-4-yl)ethanol (71).

^{1}H NMR (200 MHz, $CDCl_3$): δ7.85 (s, Ar**H**(triazole), 1H), 7.73-7.37 (m, Ar**H**(benzene), 5H), 4.01 (t, J = 5.9 Hz, OC**H**$_2$CH$_2$, 2H), 3.29 (t, J = 5.9 Hz, OCH$_2$C**H**$_2$, 2H), 2.66 (s, O**H**, 1H). ^{13}C NMR ($CDCl_3$): δ146.40 (NCH=**C**, 1C), 137.22 (Ar(benzene), N**C**, 1C), 129.87 (*m*-Ar, 2C) 128.79 (*p*-Ar, 1C), 120.60 (*o*-Ar, 2C), 120.15 (N**C**H=C, 1C), 61.64 (CH$_2$**C**H$_2$O, 1C), 28.97 (**C**H$_2$CH$_2$O, 1C). Mass Spec for $C_{10}H_{11}N_3O$ Calculated: 189.09; Found $(M+Na)^+$: 212.08.

2-(1-Benzyl-1,2,3-triazol-4-yl)ethanol (72).

^{1}H NMR (200 MHz, $CDCl_3$): δ7.39-7.27 (m, Ar**H**, 6H), 5.50 (s, ArC**H**$_2$Ar, 2H), 3.93 (t, J = 6.0 Hz, OC**H**$_2$CH$_2$, 2H), 2.92 (t, J = 6.0 Hz, OCH$_2$C**H**$_2$, 2H), 2.60 (s, O**H**, 1H). ^{13}C NMR ($CDCl_3$): δ145.88 (NCH=**C**, 1C), 134.74 (Ar(benzene), NCH$_2$**C**, 1C), 129.05 (*m*-Ar, 2C), 128.66 (*p*-Ar, 1C), 128.04 (*o*-Ar, 2C), 121.76 (N**C**H=C, 1C), 61.32 (CH$_2$**C**H$_2$O, 1C), 54.02 (Ar**C**H$_2$Ar, 1C), 28.82 (**C**H$_2$CH$_2$O, 1C). Mass Spec for $C_{11}H_{13}N_3O$ Calculated: 203.11; Found $(M+Na)^+$: 226.10.

2-(1-(4-Methoxybenzyl)-1*H*-1,2,3-triazol-4-yl)ethanol (73).

^{1}H NMR (200 MHz, $CDCl_3$): δ7.26 (s, Ar**H**(triazole), 1H), 7.24 (d, J = 10.0 Hz, *o*-Ar**H**, 2H), 6.89 (d, J = 10.0 Hz, *m*-Ar**H**, 2H), 5.43 (s, ArC**H**$_2$Ar, 2H), 3.93 (t, J = 5.9 Hz, OC**H**$_2$CH$_2$, 2H), 3.81 (s, OC**H**$_3$, 3H), 2.91 (t, J = 5.8 Hz, OCH$_2$C**H**$_2$, 2H), 1.57 (s, O**H**, 1H). ^{13}C NMR ($CDCl_3$): δ160.08 (Ar(benzene), CH$_3$O**C**, 1C), 146.08 (NCH=**C**, 1C), 129.86 (*o*-Ar, 2C), 126.84 (Ar(benzene), NCH$_2$**C**, 1C), 121.39 (N**C**H=C, 1C), 114.64 (*m*-Ar, 2C), 61.77 (CH$_2$**C**H$_2$O, 1C), 55.52 (**C**H$_3$O, 1C), 53.83 (Ar**C**H$_2$Ar, 1C), 28.88 (**C**H$_2$CH$_2$O, 1C). Mass Spec for $C_{12}H_{15}N_3O_2$ Calculated: 233.12; Found (M): 233.12.

2-(1-((Pivaloyloxy)methyl)-1*H*-1,2,3-triazol-4-yl)ethanol (74).

^{1}H NMR (200 MHz, $CDCl_3$): δ7.65 (s, Ar**H**, 1H), 6.19 (s, NC**H**$_2$O, 2H), 3.93 (t, J = 6.0 Hz, OC**H**$_2$CH$_2$, 2H), 2.95 (t, J = 6.0 Hz, OCH$_2$C**H**$_2$, 2H), 2.63 (b, O**H**, 1H), 1.17 (s, C(C**H**$_3$)$_3$, 9H). ^{13}C NMR ($CDCl_3$): δ177.97 (**C**=O, 1C), 146.23 (NCH=**C**, 1C), 123.17 (N**C**H=C, 1C), 69.81 (N**C**H$_2$, 1C), 61.54 (CH$_2$**C**H$_2$O, 1C), 38.94 ((CH$_3$)$_3$**C**, 1C), 28.79 (**C**H$_2$CH$_2$O, 1C), 26.96 ((**C**H$_3$)$_3$C, 3C). Mass Spec for $C_{10}H_{17}N_3O_3$ Calculated: 227.13; Found (M+Na)$^+$: 250.12.

2-(1-(2-Methoxycarbonyl)ethyl)-1*H*-1,2,3-triazol-4-yl)ethanol (75).

^{1}H NMR (200 MHz, $CDCl_3$): δ7.48 (s, Ar**H**, 1H), 4.63 (t, J = 6.3 Hz, NC**H**$_2$CH$_2$, 2H), 3.94 (t, J = 6.4 Hz, OC**H**$_2$CH$_2$, 2H), 3.70 (s, COOC**H**$_3$, 3H), 2.95 (m, OCH$_2$C**H**$_2$ and NCH$_2$C**H**$_2$, 2H), 2.20 (b, O**H**, 1H).

5-(4-(2-Hydroxyethyl)-1*H*-1,2,3-triazol-1-yl)pentanoic acid (76).

^{1}H NMR (200 MHz, CD_3OD): δ7.78 (s, Ar**H**, 1H), 4.86 (s, O**H**, 2H), 4.39 (t, J = 6.9 Hz, NC**H**$_2$CH$_2$, 2H), 3.80 (t, J = 6.8 Hz, OC**H**$_2$CH$_2$, 2H), 2.90 (t, J = 6.8 Hz, OCH$_2$C**H**$_2$, 2H), 2.32 (t, J = 7.3 Hz, HO$_2$CC**H**$_2$, 2H), 1.92 (m, NCH$_2$C**H**$_2$, 2H), 1.60 (m, NCH$_2$CH$_2$C**H**$_2$, 2H). ^{13}C NMR (CD_3OD): δ178.06 (**C**=O, 1C), 146.35 (NCH=**C**, 1C), 124.07 (N**C**H=C, 1C), 62.25 (CH$_2$**C**H$_2$O, 1C), 51.10 (N**C**H$_2$CH$_2$, 1C), 35.00 (HO$_2$C**C**H$_2$, 1C), 30.91 (**C**H$_2$CH$_2$O, 1C), 30.06 (NCH$_2$**C**H$_2$, 3C), 23.34 (HO$_2$CCH$_2$**C**H$_2$, 1C). Mass Spec for $C_9H_{15}N_3O_3$ Calculated: 213.11; Found (M): 213.11.

2-(1-(2-(2-(2-(Tetrahydro-2*H*-pyran-2-yloxy)ethoxy)ethoxy)ethyl)-1H-1,2,3-triazol-4-yl)ethanol (77).

^{1}H NMR (200 MHz, $CDCl_3$): δ7.62 (s, Ar**H**, 1H), 4.63 (b, ring, OC**H**, 1H), 4.52 (t, J = 5.0 Hz, NC**H**$_2$CH$_2$, 2H), 3.95-3.45 (m, HOC**H**$_2$CH$_2$ and NCH$_2$C**H**$_2$[OC**H**$_2$C**H**$_2$]$_2$O and OCH[CH$_2$]$_3$C**H**$_2$O-ring, 14H), 2.94 (t, J = 5.9 Hz, HOCH$_2$C**H**$_2$, 2H), 1.84-1.46 (m, OCH[C**H**$_2$]$_3$CH$_2$O-ring, 6H).

2-(1-((Pivaloyloxy)methyl)-1*H*-1,2,3-triazol-4-yl)methanol (78).

^{1}H NMR (200 MHz, $CDCl_3$): δ7.79 (s, Ar**H**, 1H), 6.22 (s, NC**H**$_2$O, 2H), 4.81 (s, HOC**H**$_2$C, 2H), 2.17 (b, O**H**, 1H), 1.19 (s, C(C**H**$_3$)$_3$, 9H). ^{13}C NMR ($CDCl_3$): δ177.87 (**C**=O, 1C), 148.47 (NCH=**C**, 1C), 123.46 (N**C**H=C, 1C), 69.87 (N**C**H$_2$, 1C), 56.03 (C**C**H$_2$OH, 1C), 38.88 ((CH$_3$)$_3$**C**, 1C), 26.90 ((**C**H$_3$)$_3$C, 3C). Mass Spec for $C_9H_{15}N_3O_3$ Calculated: 213.11; Found (M+Na)$^+$: 236.10.

2-(1-Heptyl-1*H*-1,2,3-triazol-4-yl)propan-2-ol (79).

^{1}H NMR ((200 MHz, $CDCl_3$): δ7.42 (s, Ar**H**, 1H), 4.30 (t, J = 8.6 Hz, NC**H**$_2$CH$_2$, 2H), 1.88 (m, NCH$_2$C**H**$_2$, 2H), 1.61 (s, C(C**H**$_3$)$_2$OH, 6H), 1.27 (m, NCH$_2$CH$_2$(C**H**$_2$)$_4$CH$_3$, 8H), 0.83 (t, J = 6.6 Hz. NCH$_2$CH$_2$(CH$_2$)$_4$C**H**$_3$, 3H).

2-(1-Octyl-1*H*-1,2,3-triazol-4-yl)propan-2-ol (80).

^{1}H NMR ((200 MHz, $CDCl_3$): δ7.43 (s, Ar**H**, 1H), 4.31 (t, J = 8.6 Hz, NC**H**$_2$CH$_2$, 2H), 1.89 (m, NCH$_2$C**H**$_2$, 2H), 1.64 (s, C(C**H**$_3$)$_2$OH, 6H), 1.28 (m, NCH$_2$CH$_2$(C**H**$_2$)$_5$CH$_3$, 8H), 0.87 (t, J = 6.6 Hz. NCH$_2$CH$_2$(CH$_2$)$_4$C**H**$_3$, 3H).

2-(1-(2-(Tetrahydro-2H-pyran-2-yloxy)ethyl)-1*H*-1,2,3-triazol-4-yl)propan-2-ol (81).

^{1}H NMR ((200 MHz, $CDCl_3$): δ7.59 (s, Ar**H**, 1H), 4.56 (m, NC**H**$_2$CH$_2$O and OC**H**(ring), 3H), 4.14-3.45 (m, NCH$_2$C**H**$_2$O and OCH[CH$_2$]$_3$C**H**$_2$O-ring, 4H), 2.47 (b, O**H**, 1H), 1.74-1.45 (m, OCH[C**H**$_2$]$_3$CH$_2$O-ring, 6H), 1.63 (s, C(C**H**$_3$)$_2$OH, 6H). The dehydration reaction of this compound using $POCl_3$ and Pyridine gave **50** directly.

2-(1-(2-(2-(2-(Tetrahydro-2H-pyran-2-yloxy)ethoxy)ethoxy)ethyl)-1*H*-1,2,3-triazol-4-yl)propan-2-ol (82).

^{1}H NMR ((200 MHz, $CDCl_3$): δ7.67 (s, Ar**H**, 1H), 4.60 (m, OC**H**(ring), 1H), 4.60 (t, J = 5.0 Hz, NC**H**$_2$CH$_2$O, 2H), 3.89-3.42 (m, NCH$_2$C**H**$_2$O[C**H**$_2$C**H**$_2$O]$_2$C and OCH[CH$_2$]$_3$C**H**$_2$O-ring, 12H), 2.61 (b, O**H**, 1H), 1.85-1.45 (m, OCH[C**H**$_2$]$_3$CH$_2$O-ring, 6H), 1.62 (s, C(C**H**$_3$)$_2$OH, 6H). The dehydration reaction of this compound using $POCl_3$ and Pyridine gave **51** directly.

Characterization of polymers obtained from homopolymerization of vinyl triazoles:

***Poly*(1-pentyl-4-vinyl-1,2,3-triazole) (83).**

^{1}H NMR (200 MHz, $CDCl_3$): δ7.03 (m, Ar**H**), 4.08 (b, NC**H**$_2$), 2.38-2.07 (b, aliphatic H), 1.85-1.50 (b, aliphatic H and NCH$_2$C**H**$_2$), 1.20 (NCH$_2$CH$_2$[C**H**$_2$]$_2$CH$_3$), 0.78 (N[CH$_2$]$_4$C**H**$_3$).

***Poly*(1-hexyl-4-vinyl-1,2,3-triazole) (84).**

^{1}H NMR (200 MHz, $CDCl_3$): δ7.01 (m, Ar**H**), 4.04 (b, NC**H**$_2$), 2.36-2.02 (b, aliphatic H), 1.85-1.40 (b, aliphatic H and NCH$_2$C**H**$_2$), 1.15 (NCH$_2$CH$_2$[C**H**$_2$]$_3$CH$_3$), 0.71 (N[CH$_2$]$_5$C**H**$_3$).

***Poly*(1-heptyl-4-vinyl-1,2,3-triazole) (85).**

^{1}H NMR (200 MHz, $CDCl_3$): δ6.94 (m, Ar**H**), 4.03 (b, NC**H**$_2$), 2.30-1.99 (b, aliphatic H), 1.86-1.40 (b, aliphatic H and NCH$_2$C**H**$_2$), 1.12 (NCH$_2$CH$_2$[C**H**$_2$]$_4$CH$_3$), 0.69 (N[CH$_2$]$_6$C**H**$_3$).

***Poly*(1-nonyl-4-vinyl-1,2,3-triazole) (86).**

^{1}H NMR (200 MHz, $CDCl_3$): δ6.95 (m, Ar**H**), 4.02 (b, NC**H**$_2$), 2.28-1.97 (b, aliphatic H), 1.85-1.35 (b, aliphatic H and NCH$_2$C**H**$_2$), 1.10 (NCH$_2$CH$_2$[C**H**$_2$]$_6$CH$_3$), 0.71 (N[CH$_2$]$_8$C**H**$_3$).

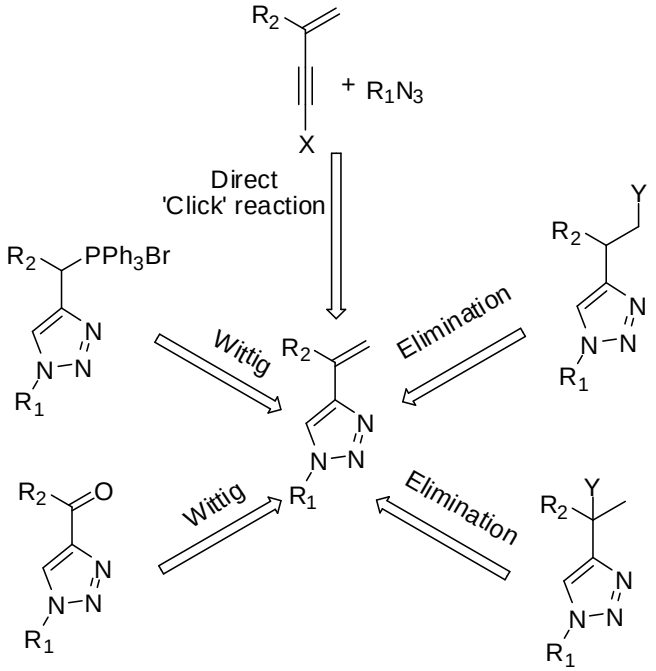
***Poly*(1-decyl-4-vinyl-1,2,3-triazole) (87).**

^{1}H NMR (200 MHz, $CDCl_3$): δ6.97 (m, Ar**H**), 4.02 (b, NC**H**$_2$), 2.29-1.97 (b, aliphatic H), 1.85-1.36 (b, aliphatic H and NCH$_2$C**H**$_2$), 1.09 (NCH$_2$CH$_2$[C**H**$_2$]$_7$CH$_3$), 0.71 (N[CH$_2$]$_9$C**H**$_3$).

1-3. Results and Discussion

1-3-1. Promising Routes/Strategies

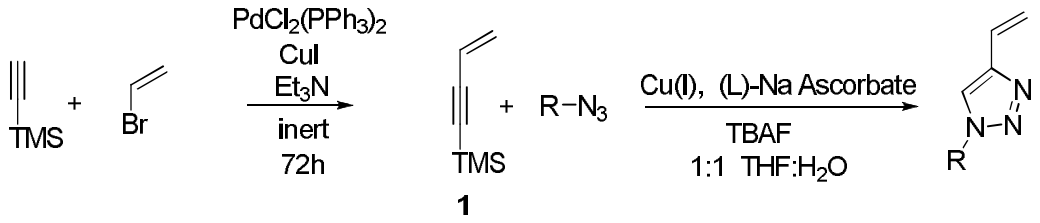
Initially, we thought that five routes depicted in Scheme 1 including a Direct 'Click' reaction route, two Wittig type routes, and two Elimination type routes are plausible routes to 4-vinyl-1,2,3-triazoles.



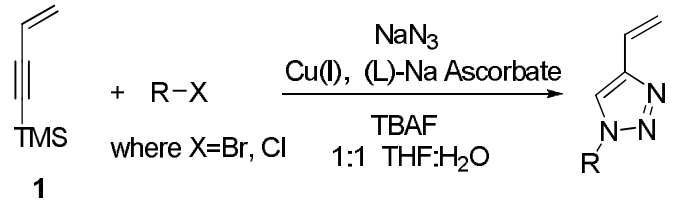
Scheme 1. Retrosynthetic analyses for the preparation of 4-vinyl-1,2,3-triazoles. (R_2 = H or Me)

1-3-2. Strategy 1 (Direct 'Click' reaction route)

First, we tried to establish a synthetic route using Direct 'Click' reaction depicted on the top of scheme 1. A couple of synthetic routes to 4-vinyl-1,2,3-triazoles which are similar to the Direct 'Click' reaction route had already been reported by other groups but unfortunately, thier procedures included harsh reaction conditions with strong base or acid, used expensive and uncommon reagents, or the reported yields were very low[4,12]. By optimizing the protocol, we have developed a synthetic preparation method of 4-vinyl-1,2,3-triazole monomers via Direct 'Click' reaction of 1-Trimethylsilyl-2-vinyl acetylene (**1**) and a variety of alkyl/aryl azides in a Tetrahydrofuran (THF) solution containing Tetrabutylammonium fluoride (TBAF) as a deprotection reagent of the Trimethylsilyl (TMS) protective group[5(c), 11] (Scheme 2; **Procedure A**). The *one-pot* approach using alkyl/aryl halides and NaN_3 mixture instead of isolated alkyl/aryl azides was also found to be practicable[11] (Scheme 3). And we found that this Direct 'Click' reaction route is compatible with various types of functional groups.



Scheme 2. Direct 'Click' reaction to synthesize 4-vinyl-1,2,3-triazoles (**Procedure A**).

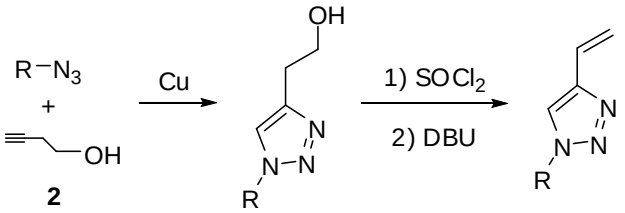


Scheme 3. *One-pot* direct synthesis of 4-vinyl-1,2,3-triazoles.

1-3-3. Strategy 2 (Elimination type route)

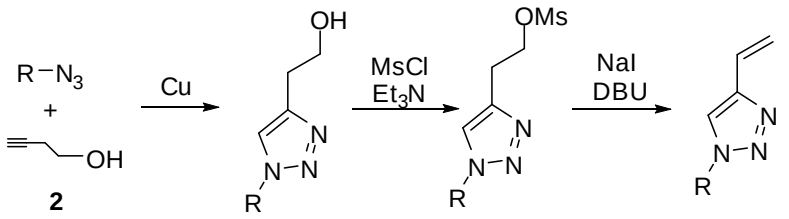
We also established Elimination type routes to 4-vinyl-1,2,3-triazoles.

A similar procedure with this Elimination type route via a thermal [3π+2π] Diels-Alder[12(f)] reaction with 3-Butyn-1-ol (**2**) followed by dehydration had been reported. But because of the poor yields and poor regio selectivities of their reactions especially at the dehydration step employing $SOCl_2$ under reflux conditions followed by 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), they never seemed to be practical (Scheme 4).



Scheme 4. First attempt of Elimination type reaction according to the previous report[12(f)] (We used 'Click' reaction instead of thermal Diels-Alder reaction.).

Through intensive and keen studies, we found that mesylation (or tosylation) of the 'Click' reaction product, 2-(1,2,3-triazol-4-yl)ethanols, using Methanesulfonyl chloride (MsCl) (or *p*-Toluenesulfonic chloride (TsCl)) followed by elimination using NaI and DBU gives 4-vinyl-1,2,3-triazoles with excellent yields[13] (Scheme 5; **Procedure B**).



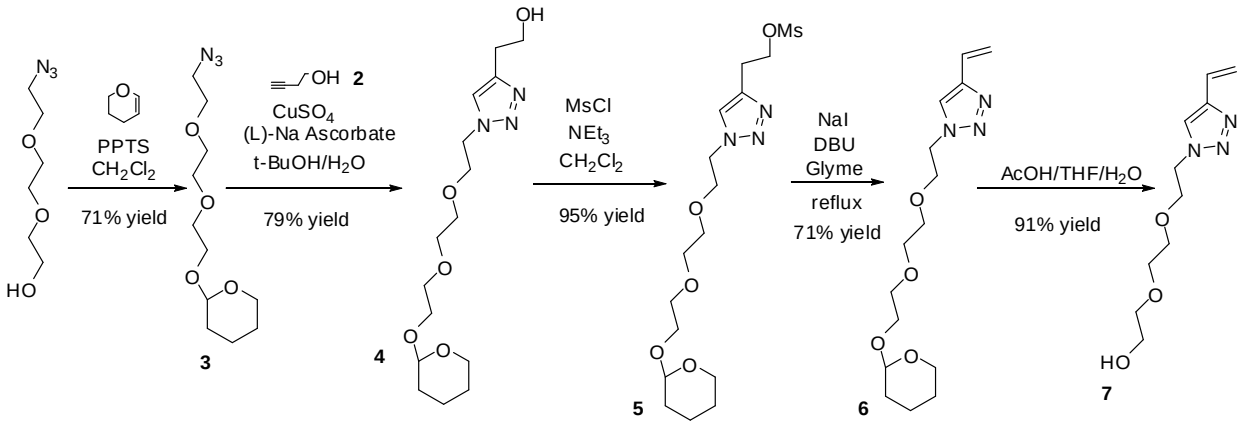
Scheme 5. Elimination type synthetic route to 4-vinyl-1,2,3-triazoles (**Procedure B**).

NaI and DBU were compatible as elimination reagents with a great variety of functional groups. Alternatively, Potassium *t*-butoxide (*t*-BuOK)[14] also worked very well as an elimination reagent with a little bit less tolerance to functional groups than NaI/DBU system (Table 1). And less costly method to this system is to use greater excess of Triethylamine (Et_3N) at the mesylation step and add only NaI without DBU afterwards.

R	NaI/ DBU	*t* - BuOK
C_8H_{17}	81%yield	79%yield
Benzyl	95%yield	86%yield

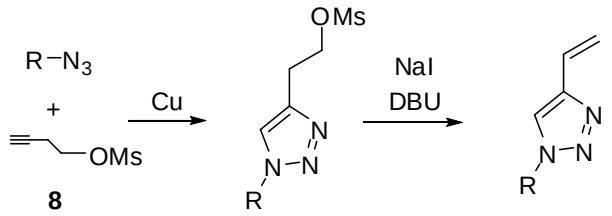
Table 1. Reagents for elimination reactions and their results.

Though **Procedure B** is tolerant of wide variety of functional groups, additional protection-deprotection steps are necessary when the organic halides/azides conatain alcohols, thiols or amines, as illustrated in synthesis of 2-(2-(2-(4-Vinyl-1,2,3-tiazole-1-yl))ethoxy)ethoxyethanol (**7**) (Scheme 6).



Scheme 6. Synthesis of 2-(2-(2-(4-Vinyl-1,2,3-tiazole-1-yl))ethoxy)ethoxyethanol (**7**) by **Procedure B**.

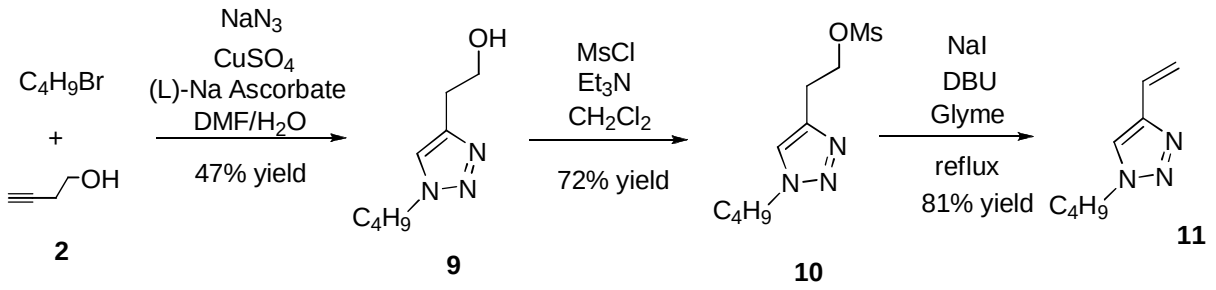
To avoid this bothering additional protection-deprotection steps in **Procedure B**, a similar but improved method (**Procedure C**) using 3-Butynyl methansulfonate (**8**) was developed (Scheme 7). In this method, the mesylation is performed prior to the 'Click' reaction.



Scheme 7. Synthetic route to 4-vinyl-1,2,3-triazoles (**Procedure C**).

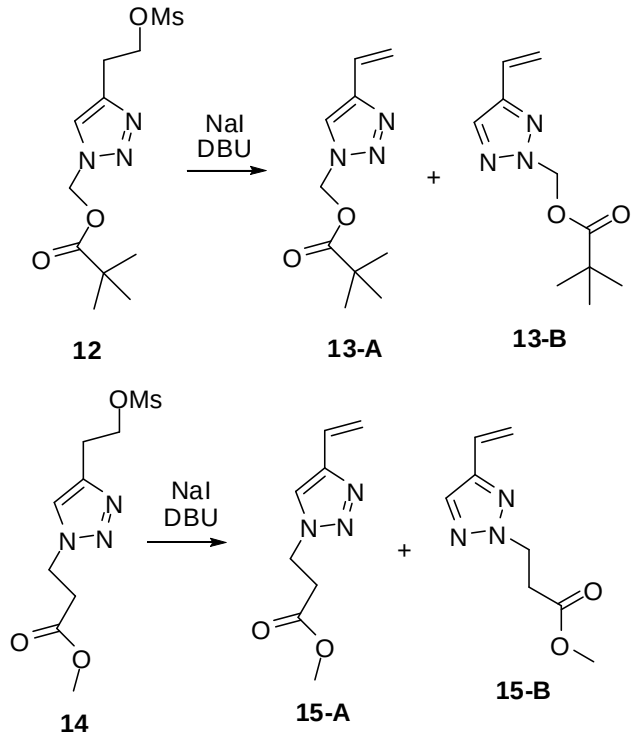
Even though many organic azides are stable at ambient conditions, some organic azides especially small molecular weight azides are known to be explosive, hazardous[9] and difficult to handle because of their low boiling points. So we explored the possibility of '*One-pot*' synthesis which requires no isolation of organic azide in this Elimination type route. We found that **Procedure B** is able to apply "*One-pot* 'Click' reaction" with moderate to good yield by using DMF/H_2O mixture as the solvent system. (Synthesis of 1-Butyl 4-vinyl-1,2,3-triazole (**11**) is depicted (Scheme 8)).

However **Procedure C** could not apply "*One-pot* 'Click' reaction" likely due to the side reaction where azide anion attacks the mesyloxyl group on But-3-ynyl methansulfonate (**8**) ,which converts it into easily polymerizable But-3-ynyl azide.



Scheme 8. Synthesis of 1-Butyl-4-vinyl-1,2,3-triazole (**11**) by **Procedure B** using "*One-pot* 'Click' reaction".

Though this Elimination type reaction (**Procedure B and C**) gave an excellent approach to various 4-vinyl-1,2,3-triazoles, only when ester group is on the substituent R at *N-1*, somehow two types of the products were obtained. From all their data (^1H, ^{13}C-NMR and Mass Spec.) including the data of 4-vinyl-1,2,3-triazoles made by **Procedure A** and the previous reports[15] related to this issue, we are assuming that these two types of products are 1-substituted-4-vinyl-1,2,3-triazoles (product) and 2-substituted-4-vinyl-1,2,3-triazoles (Scheme 9, Table 2, and Figure 1 for NMRs). But there still is a possibility that they are a combination of 1-substituted-4-vinyl-1,2,3-triazoles and 1-substituted-5-vinyl-1,2,3-triazoles, and further and detailed investigation of this reaction mechanism including single crystal X-ray analysis is currently underway.



Scheme 9. Two products obtained by elimination reactions of 2-(1-"ester"-1,2,3-triazol-4-yl)ethyl methanesulfonates.

	13		15	
Reaction Condition	13-A	13-B	15-A	15-B
reflux * 0.5h	58% yield	10% yield	6% yield	38% yield
50°C * 3h	4% yield	43% yield	25% yield	29% yield
25°C * 1d	2% yield	28% yield	12% yield	38% yield

Table 2. Results of elimination reactions of 2-(1-"ester"-1,2,3-triazol-4-yl)ethyl methanesulfonates using 1,2-Dimethoxyethane as the solvent. Products' ratios and yields were found to vary by reaction conditions.

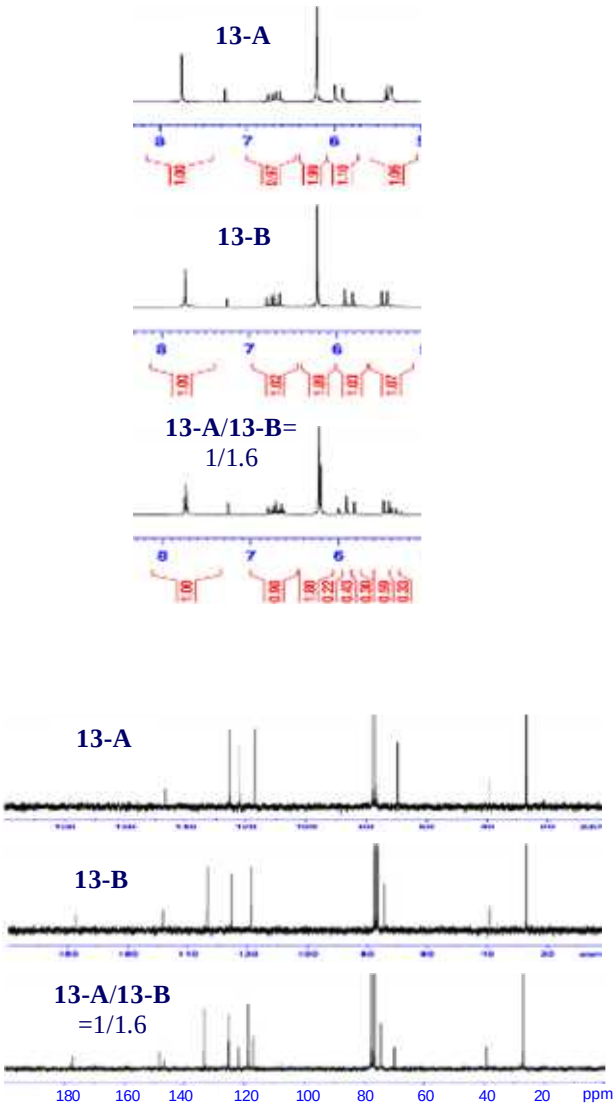
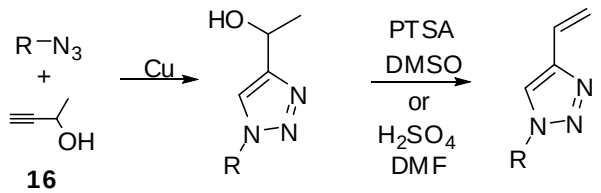


Figure 1. ^{1}H and ^{13}C-NMR of **13-A**, **13-B**, and their mixture.

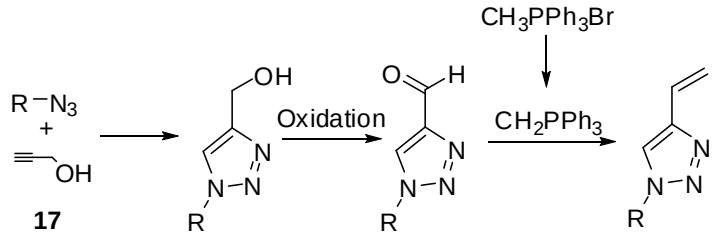
Also, we successfully developed a synthetic route using 3-Butyn-2-ol (**16**) as an acetylene source which is less expensive than 3-Butyn-1-ol (**2**). For the elimination reaction, we could use either *p*-Toluenesulfonic acid[16] or Sulfuric acid as an elimination reagent and yielded the product in good to moderate yields (Scheme 10).



Scheme 10. Synthetic route to 4-vinyl-1,2,3-triazoles (**Procedure D**) using 3-Butyn-2-ol (**16**).

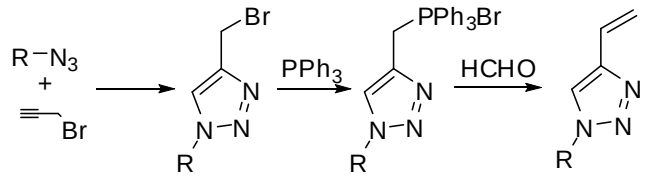
1-3-4. Strategy 3 (Wittig type route)

As further alternative routes, we investigated the practicability of a synthetic approach using Wittig reaction. After the 'Click' reaction of organic azides with Propargyl alchol (**17**), the oxidation reaction was performed using Swern Oxidation or Dess-Martin Oxidation, which were found to be much more efficient than the similar oxidation reaction using MnO_2 reported by other group[12(c)]. Unfortunatelly, the following Wittig reaction using Methyltriphenylphosphonium bromide proved to afford only low yields (Scheme 11) in spite of our through and intensive effort. And even CH_2Br_2-Zn-$TiCl_4$, which is known as a better reagent for Wittig reaction than phosphonium ylides[17], did not work, either.



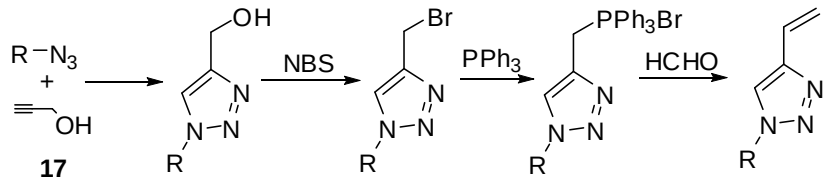
Scheme 11. First attempt of Wittig type route.

'Click' reaction using Propargyl aldehyde instead of Propargyl alcohol also seemed to be promising[4, 12(a), 12(b)] but mainly because of Propargyl aldehyde's high volatility, the yield turned out to be low and its handling was rather difficult. Based on these insights, we changed the strategy of this Wiitig route and tried to use triazoles as phosphine-ylides (Scheme 12).



Scheme 12. Wittig type reaction using Propargyl bromide.

In this case, somehow the yield of the 'Click' reaction was found to be low, so again we changed the acetylene compound back to Propargyl alcohol (**17**) and brominated it in a subsequent step by using *N*-Bromosuccinimide. Although larger numbers of synthetic steps were required, the overall yield of this procedure was found to be much better than that of Scheme 12 (Scheme 13; **Procedure E**).



Scheme 13. Synthetic route for 4-vinyl-1,2,3-triazoles (**Procedure E**).

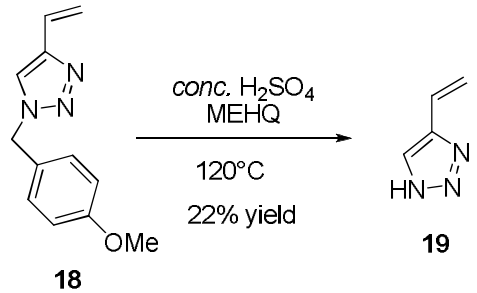
1-3-5. Synthesis of 1-Unsubstituted-4-vinyl-1,2,3-triazole (19)

Applying the synthetic routes described above to 1-Unsubstituted-4-vinyl-1,2,3-triazole (**19**)[4, 12(a), 12(b)] directly is not desirable because one of the reagents, HN_3 is extremely explosive and hazardous. To the best of our knowledge, only one group had successfully prepared the homo polymer of 1-Unsubstituted-4-vinyl-1,2,3-triazole (**19**) other than us. Two methods were proposed by that group and one is a route using dangerous HN_3 to make the monomer[4] and another route avoided making 1-Unsubstituted-4-vinyl-1,2,3-triazole (**19**) by deprotecting a protective group of nitrogen at *N-1* at the post polymerization step[12(c)]. Here we report the first synthetic routes to 1-Unsubstituted-4-vinyl-1,2,3-triazole monomer (**19**) without using HN_3.

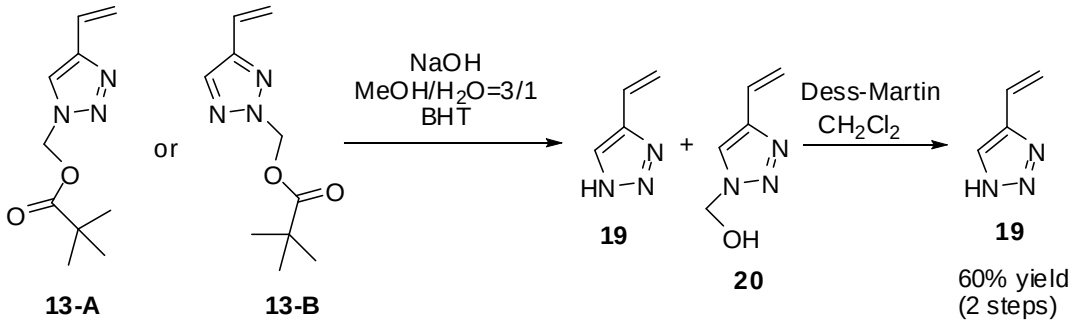
First we tried to use benzyl (Bn) or *p*-methoxybenzyl group as the protective group of *N-1* nitrogen and thought that deprotecting them by hydrogenation would work. Even though we tried a lot of reaction conditions and various types of palladium catalysts, we were unable to synthesize 1-Unsubstituted-4-vinyl-1,2,3-triazole (**19**) successfully.

But both deprotection of 1-*p*-Methoxybenzyl-4-vinyl-1,2,3-triazole (**18**) using concentrated H_2SO_4[12(c),18] and deprotection of 1 or 2-Pivaloyloxymethyl-4-vinyl-1,2,3-triazole (**13-A** or **B**)[19] using NaOH followed by additional oxidative cleavage step of hydroxymethyl group were found to give essentially pure 1-Unsubstituted-4-vinyl-1,2,3-triazole (**19**) in good yield (Scheme 14 and 15). Also, in this case, both **13-A** and **B** was found to give the same product **19**.

To store 1-Unsubstituted-4-vinyl-1,2,3-triazole (**19**), it requires radical inhibitor like 2,6-Di-*tert*-butyl-4-methylphenol (BHT) or 4-Methoxyphenol (MEHQ) to prevent automatic undesirable polymerization at ambient condition.



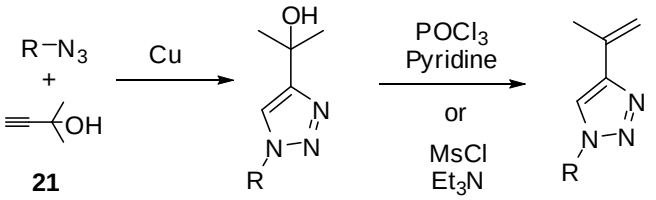
Scheme 14. Deprotection 1-*p*-Methoxybenzyl-4-vinyl-1,2,3-triazole (**18**). (Applying Trifluoroacetic acid instead of H_2SO_4 did not work[12(c)].)



Scheme 15. Deprotection of pivaloyloxymethyl group from **13-A** or **B** followed by oxidative cleavage of hydroxymethyl group.

1-3-6. Synthesis of α–Methyl-4-vinyl-1,2,3-triazoles

Since the difference of polymerization properties of Styrene and α-Methylstyrene has significant implications from both an academic and industrial point of view, we also tried to synthesize α-methyl-4-vinyl-1,2,3-triazoles. A procedure similar to **Procedure D** using 2-Methyl-3-butyn-2-ol (**21**) was found to be very effective (Scheme 16; **Procedure F** and Table 3). In addition, we found that 2-Methyl-3-butyn-2-ol (**21**) can also act as the solvent for its own 'Click' reaction.



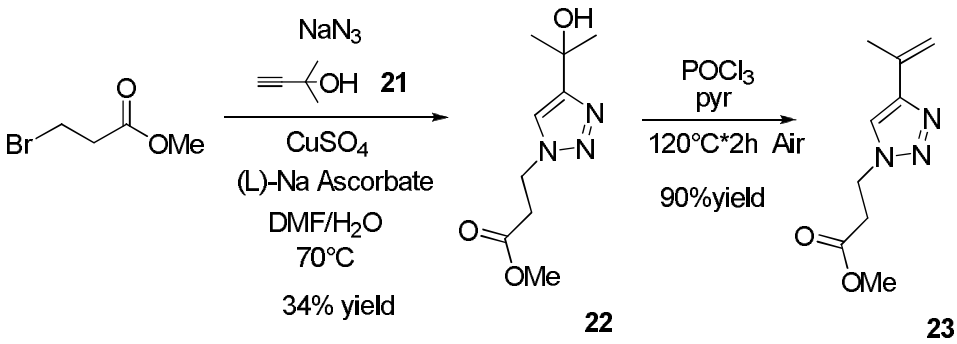
Scheme 16. Synthetic route to α-methyl-4-vinyl-1,2,3-triazoles (**Procedure F**).

R	$POCl_3$/Pyridine	MsCl/Et_3N
C_7H_{15}	76% yield	73% yield
Benzyl	98% yield	80% yield

Table 3. The results of elimination reactions to synthesize α-methyl-4-vinyl-1,2,3-triazoles.

When we tried to mesylate 2-Methyl-(1,2,3-triazol-4-yl)-ethan-2-ol, most of the mesylated compound turned into vinyl compound automatically under this reaction condition mainly due to the low stability of the mesylated compound. Furthermore we failed in an attempt to mesylate 2-Methyl-3-butyn-2-ol (**21**), mainly because of the extremely low stability of 2-Methyl-3-butynyl methansulfonate and very high reactivity of the subsequent de-mesylated product, 2-Methyl-1-buten-3-yne.

Again, we explored the possibility of "*One-pot* 'Click' reaction" here which requires no isolation of organic azides. And we successfully synthesized α-methyl-4-vinyl-1,2,3-triazoles using DMF/H_2O mixture as the solvent. (Synthesis of 3-(4-(Prop-1-en-2-yl)-1,2,3-triazole)-1-yl propanoate (**23**) is depicted (Scheme 17).).



Scheme 17. Synthesis of 3-(4-(Prop-1-en-2-yl)-1,2,3-triazole)-1-yl propanoate (**23**) via "*One-pot* 'Click' reaction".

In Table 4, 5, Figure 2, and 3, we summarize the data and show the list of 4-vinyl-1,2,3-triazoles and α-methyl-4-vinyl-1,2,3-triazoles we have synhtesized.

R	Compound number	Procedure	R	Compound number	Procedure
Methyl	**31**	**A***	2-Methylpyridyl	**40**	**A**
Butyl	**11**	**B***	Pivaloyloxymethyl	**13-A**	**A,B,C**
Pentyl	**32**	**C**	-$(CH_2)_2CO_2Me$	**15-A**	**A,B,C**
Hexyl	**33**	**C**	-$(CH_2)_3CO_2Me$	**41**	**A**
Heptyl	**34**	**C**	-$(CH_2)_3CO_2Et$	**42**	**A**
Octyl	**24**	**A,B,C**	-$(CH_2)_3CO_2H$	**43**	**A**$^{\text{Ŧ}}$
Nonyl	**35**	**C**	-$(CH_2)_4CO_2H$	**44**	**B**
Decyl	**36**	**C**	-CH_2CH_2OH	**45**	**A**
Adamentyl	**37**	**A**	-$(CH_2CH_2O)_2H$	**46**	**A,A*,C**
Phenyl	**38**	**A*,B**	-$(CH_2CH_2O)_3H$	**7**	**A*,B**
Benzyl	**39**	**A,B,D**	-H	**19**	**P**
p-Methoxybenzyl	**18**	**B,C,E**			

*; Modified procedure, details are in the experimental section.

[Ŧ]; Converted from compound **42**

P; Converted from **18**, **13-A**, or **13-B**

Table 4. The list of 4-vinyl-1,2,3-triazoles.

R	Compound number	Procedure
Heptyl	**47**	**F**
Octyl	**48**	**F**
Benzyl	**49**	**F**
$-(CH_2)_2CO_2Me$	**23**	**F**[*]
$-CH_2CH_2OH$	**50**	**F**
$-(CH_2CH_2O)_3H$	**51**	**F**

[*]; Modified procedure, details are in the experimental section.

Table 5. The list of α-methyl-4-vinyl-1,2,3-triazoles.

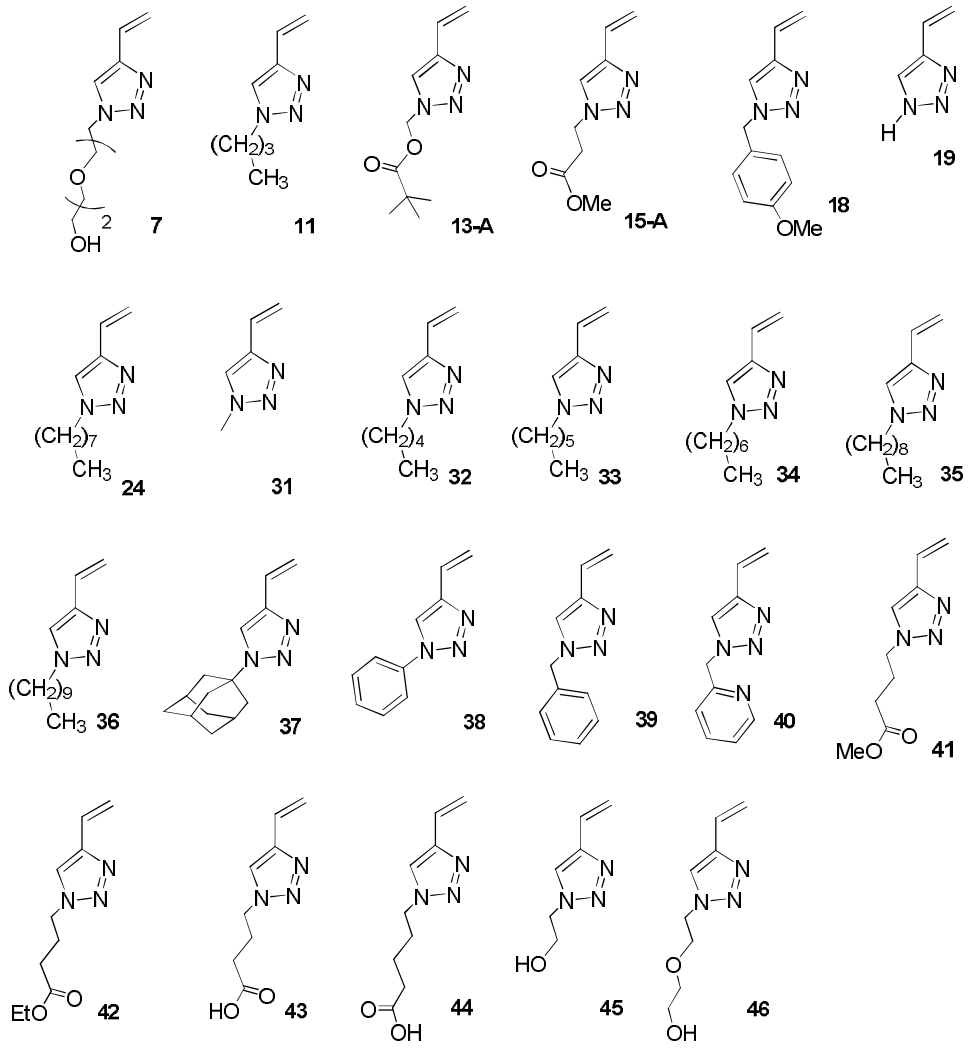


Figure 2. Range of 4-vinyl-1,2,3-triazole monomers prepared.

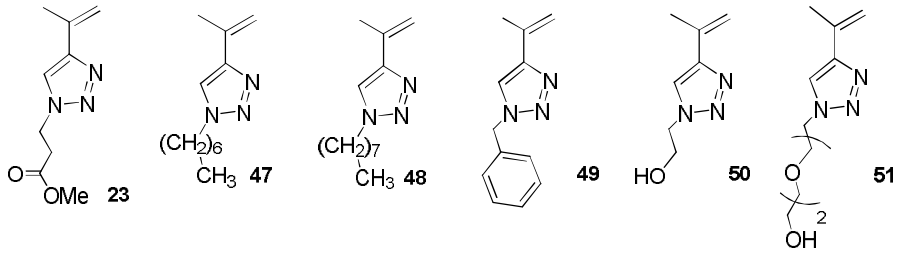


Figure 3. Range of α-methyl-4-vinyl-1,2,3-triazole monomers prepared.

X-ray crystallography confirmed the 1,4-substitution pattern on the triazole ring as well as the introduction of the α-methyl group. Examples of single crystal structures for the 1-hydroxyethyl derivative, **45**, and α-methyl 1-benzyl derivative, **49**, are shown in Figure 4.

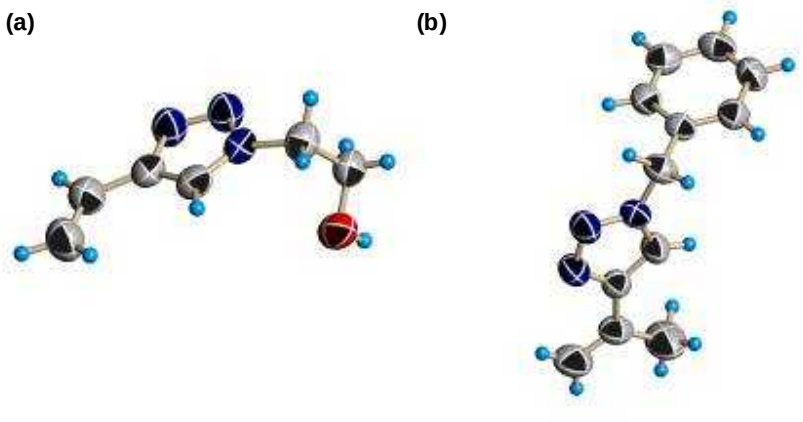


Figure 4. X-ray crystal structures for the triazole monomers, (a) 1-(2'-Hydroxyethyl)-4-vinyl-1,2,3-triazole, **45**, and (b) 1-Benzyl-4-(prop-1'-en-2'-yl)-1,2,3-triazole, **49**.

1-3-7. Polymerization

As we have already reported[11], polymerization of these 4-vinyl-1,2,3-triazole monomers to give both homopolymers and copolymers under reversible addition fragmentation chain transfer (RAFT) conditions[10] proceeded with a high degree of control over molecular weight and polydispersity. Figure 5 and Table 6 show the SEC result of polymerization of **24** and Figure 6 shows the kinetic data of polymerization of 1-Pentyl-4-vinyl-1,2,3-triazole (**25**), 1-Hexyl-4-vinyl-1,2,3-triazole (**26**), 1-Heptyl-4-vinyl-1,2,3-triazole (**27**), 1-Nonyl-4-vinyl-1,2,3-triazole (**28**), and 1-Decyl-4-vinyl-1,2,3-triazole (**29**).

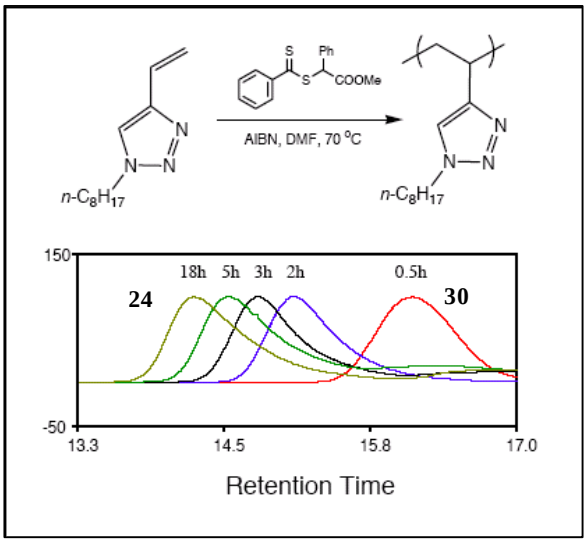


Figure 5. Polymerization of 1-Octyl-4- vinyl-1,2,3-triazole (**24**) and its SEC chromatogram.

Time (hr)	Conv. (NMR)	M_w	M_w/M_n
0.5	11%	6,200	1.05
2	23%	19,400	1.03
3	32%	24,800	1.04
5	39%	32,500	1.05
18	61%	44,900	1.08

Table 6. Polymerization of 1-Octyl-4-vinyl-1,2,3-triazole (**24**) and its SEC chromatogram.

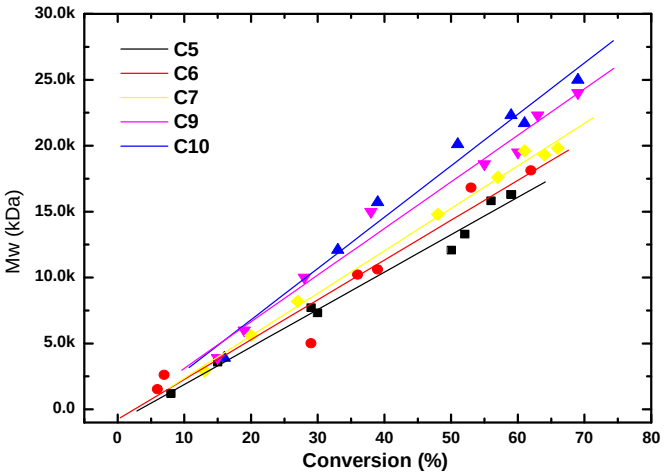
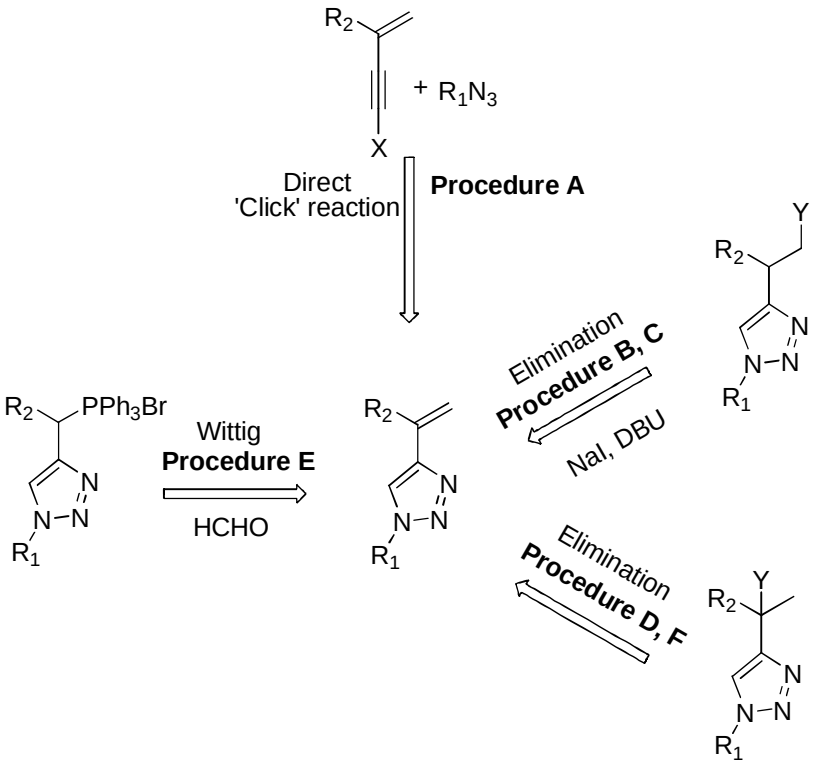


Figure 6. Kinetic data of polymerization of 4-vinyl-1,2,3-triazoles (**25, 26, 27, 28, 29**).

1-4. Summary

We have achieved four elegant synthetic routes to 4-vinyl-1,2,3-triazoles (**Procedure A** to **E**) and an excellent route to α-methyl-4-vinyl-1,2,3-triazoles (**Procedure F**), as well (Scheme 18).



Scheme 18. Developed synthetic routes to 4-vinyl-1,2,3-triazoles. (R_2 = H or Me)

Also "*One-pot* 'Click' reactions" were found to be applicable to these synthetic routes so that isolations of potentially hazardous organic azides are not necessary.

Furthermore, we successfully demonstrated synthetic routes to 1-Unsubstituted 4-vinyl-1,2,3-triazole without using dangerous HN_3 for the first time.

Currently, preparation of all the similar types of monomers (i.e. 4-vinyl, α-methyl-4-vinyl, 5-vinyl, α-methyl-5-vinyl, *N*-vinyl, and α-methyl-*N*-vinyl-1,2,3-triazoles) and the study of their homo and co-polymerizations are underway.

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CHAPTER 2

'Synthesis and Characterization of 1,2,3-Triazole Oligomers'

2-1. Introduction

As described in Chapter 1, with the development of 'Click' reactions, especially Cu (I) catalyzed 1,3-dipolar cycloaddition of azides and alkynes, triazoles have found their way into many applications. They are playing important roles in for example medicine[1], herbicides, dyes[2] and proton exchange membranes (PEM)[3]. We reported a new monomer family based on 4-vinyl-1,2,3-triazoles[4] and this monomer can provide a linear macromolecule contains 1,2,3-triazole ring as its branches in high density. On the other hand, for exploiting the unique properties of 1,2,3-triazole ring, a linear macromolecule which contains 1,2,3-triazoles along its backbone seems to be one of the best systems to study. It is anticipated that this linear macromolecule containing 1,2,3-triazoles along its backbone can be a good substitute for Polyethylene glycol and Polyethylenimine. Also, precise control of its chain length can allow us to investigate the effect of the molecular size onto the macromolecule's chemical and physical properties. By employing the combination of a method called 'Exponential Growth Strategy[5]'', which repeats deprotection of protective groups and coupling reaction to lengthen the molecular chain, and this Cu (I) catalyzed 'Click' reaction, we could achieve a facile synthetic route to precisely size tuned 1,2,3-triazole oligomers.

In this chapter, we discuss in great detail about the syntheses of oligomers containing 1,2,3-triazoles along their backbones and present their interesting properties. Also we discuss about the direct oligomerization/polymerization by using 'Click' reaction[6]. The facile syntheses of these 1,2,3-triazole oligomers combined with their unique properties may make them ideal candidates for future advances in the field of functional chemicals as well as maclomolecule chemistry.

2-2. Experimental Section

Materials.

All the chemicals and solvents were purchased from Aldrich, of reagent grade, and used without further purification. Unless otherwise denoted, all reactions were carried out under air. All the organic azides[7] were synthesized according to the well established protocols.

General Procedures/Characterization.

Analytical TLC was performed on commercial Merck Plates coated with silica gel GF254 (0.24 mm thick). Silica gel for flash chromatography was Merck Kieselgel 60 (230-400 mesh, ASTM). ^{1}H-NMR (200 MHz) and ^{13}C-NMR measurements were performed on a Bruker AC 500 and 200 spectrometers at room temperature. Size exclusion chromatography (SEC) was carried out at room temperature on a Waters chromatograph connected to a Waters 410 differential refractometer and six Waters Styragel® columns (five HR-5 μm and one HMW-20 μm) using THF as eluent (flow rate: 1 mL/min). A Waters 410 differential refractometer and a 996 photodiode array detector were employed. The molecular weights of the polymers were calculated relative to linear polystyrene standards. ThermoGravimetric Analysis was conducted using METTLER TGA/sDTA851e under N_2 atmosphere. Differential

Scanning Calorimetry (DSC) measurements were performed with a TA Instruments DSC 2920 and a ramp rate of 5 degrees per minute with data usually collected during the third cycle in the selected temperature ranges. Calibrations were made using indium as a standard for both temperature transitions and the heats of fusion. Melting transition temperatures (T_m) were determined as the peak maxima of the transition. Small Angle X-ray Scattering (Intermediate-SAXS (X-ray Source; 18 kW Rigaku rotationg anode generator, Wavelength; 1.54 Å, Sample to Detector Dintance; 75.8 cm, Interface; SPEC)) was carried out using quartz capillary cell.

General procedure of azidation: synthesis of 1-Azido-5-trimethylsilyl-4-pentyne (1) depicted.

To a 100 mL round bottom flask equipped with a magnetic stir bar was charged with Sodium azide (1.01 g, 6.51 mmol), DMF (26.3 mL), 1-Chloro-5-trimethylsilyl-4-pentyne (12.02g, 68.77 mmol) in this order. After 23 hours of vigorous stirring, the reaction mixture was poured into a separatory funnel containing 100 mL of deionized water and extracted 3 times with 100 mL of Hexanes. The organic fractions were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure. This crude mixture was then purified via flash column chromatography (1:9 Ethyl acetate:Hexanes) to yield 10.41 g (84%) of 1-Azido-5-trimethylsilyl-4-pentyne (**1**) as a colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ7.36 (s, Ar**H**, 1H), 3.41 (t, J = 6.6 Hz, $N_3C\mathbf{H}_2$, 2H), 2.31 (t, J = 6.8 Hz, $SiCCC\mathbf{H}_2CH_2$, 2H), 1.78 (m, $CH_2C\mathbf{H}_2CH_2$, 2H), 0.15 (s, $(C\mathbf{H}_3)_3Si$, 9H). ^{13}C NMR ($CDCl_3$): δ105.44 (Si**C**C, 1C), 86.03 (SiC**C**, 1C), 50.37 ($\mathbf{C}H_2N_3$, 1C), 27.95 ($N_3CH_2\mathbf{C}H_2$, 1C), 17.34 ($SiCC\mathbf{C}H_2$, 1C), 0.27 ($(\mathbf{C}H_3)_3Si$, 3C). Mass Spec for $C_8H_{15}N_3Si$ Calculated: 181.10; Found $(M+H)^+$: 182.11.

General procedure of 'Click' reaction: synthesis of 4-(3-Chloropropyl)-1-(5-(trimethylsilyl)pent-4-ynyl)-1*H*-1,2,3-triazole (2) depicted. (Named; Monomer)

A 500 mL round bottom flask equipped with a magnetic stir bar was charged with 1-Azido-5-trimethylsilyl-4-pentyne (**1**) (9.50 g, 52.38 mmol), 5-Chloro-1-pentyne (5.91 g, 57.62 mmol), and 100 mL of *t*-Butanol. In separate flasks, Sodium L-ascorbate (3.11 g, 15.71 mmol) and $CuSO_4$ (0.84 g, 5.24 mmol) were introduced to 50 mL of deionized water, respectively. Upon dissolution, these aqueous solutions were then added to the *t*-Butanol mixture. After 13 hours of vigorous stirring, the most of *t*-Butanol was removed by reducing the pressure and the residue mixture was poured into a separatory funnel containing 80 mL of deionized water and 100mL of Ethyl acetate. After the separation, the organic layer was washed twice with 100 mL of deionized water. The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. This crude mixture was then purified via flash column chromatography (1:1 Ethyl acetate:Hexanes) to yield 10.81 g (73%) of 4-(3-Chloropropyl)-1-(5-(trimethylsilyl)pent-4-ynyl)-1*H*-1,2,3-triazole (**2**) as a white crystal. ^{1}H NMR (200 MHz, $CDCl_3$): δ7.34 (s, Ar**H**, 1H), 4.43 (t, J = 6.7 Hz, $NC\mathbf{H}_2$, 2H), 3.56 (t, J = 6.4 Hz, $ClC\mathbf{H}_2$, 2H), 2.87 (t, J = 7.3Hz, $ClCH_2CH_2C\mathbf{H}_2C$, 2H), 2.18 (m, $C\mathbf{H}_2$, 6H), 0.15 (s, $(C\mathbf{H}_3)_3Si$, 9H). ^{13}C NMR ($CDCl_3$): δ146.40 (NCH=**C**, 1C), 121.68 (N**C**H=C, 1C), 104.74 (Si**C**C, 1C), 86.81 (SiC**C**, 1C), 48.83 ($N\mathbf{C}H_2$, 1C), 44.37 ($Cl\mathbf{C}H_2$, 1C), 32.04 ($NCH_2\mathbf{C}H_2$, 1C), 28.96 ($\mathbf{C}H_2$, 1C), 22.82 ($\mathbf{C}H_2$, 1C), 17.17 ($SiCC\mathbf{C}H_2CH_2$, 1C), 0.25 ($(\mathbf{C}H_3)_3Si$, 3C). Mass Spec for $C_{13}H_{22}ClN_3Si$ Calculated: 283.13; Found $(M+H)^+$: 284.13.

Synthesis of 4-(3-Azidopropyl)-1-(5-(trimethylsilyl)pent-4-ynyl)-1H-1,2,3-triazole (3). (Named; Monomer-N_3-TMS)

A similar azidation reaction condition described above for the synthesis of **1** was applied to **2** except that most of DMF was removed under vacuum at 60 ^{o}C before extraction. After the purification via flash column chromatography (2:1 Ethyl acetate:Hexanes), **3** was obtained as a clear oil (79% yield). ^{1}H NMR (200 MHz, $CDCl_3$): δ7.33 (s, Ar**H**, 1H), 4.44 (t, J = 6.7 Hz, N(Ar)C**H**$_2$, 2H), 3.34 (t, J = 6.7 Hz, N_3C**H**$_2$, 2H), 2.76 (t, J = 7.3Hz, $N_3CH_2CH_2$C**H**$_2$C, 2H), 2.12 (m, C**H**$_2$, 6H), 0.15 (s, (C**H**$_3$)$_3$Si, 9H). ^{13}C NMR ($CDCl_3$): δ146.64 (NCH=**C**, 1C), 121.51 (N**C**H=C, 1C), 104.74 (Si**C**C, 1C), 86.82 (SiC**C**, 1C), 50.83 (N_3**C**H$_2$, 1C), 48.84 (N(Ar)**C**H$_2$, 1C), 28.97 (**C**H$_2$, 1C), 28.72 (**C**H$_2$, 1C), 22.81 (**C**H$_2$, 1C), 17.18 (SiCC**C**H$_2$CH$_2$, 1C), 0.25 ((**C**H$_3$)$_3$Si, 3C). Mass Spec for $C_{13}H_{22}N_6Si$ Calculated: 290.17; Found $(M+H)^+$: 291.17.

General procedure of TMS deprotection: Synthesis of 4-(3-chloropropyl)-1-(pent-4-ynyl)-1*H*-1,2,3-triazole (4) depicted. (Named; Monomer-Cl-H)

A 100 mL round bottom flask equipped with a magnetic stir bar was charged with 4-(3-Chloropropyl)-1-(5-(trimethylsilyl)pent-4-ynyl)-1*H*-1,2,3-triazole (**2**) (4.34 g, 15.30 mmol) and 15 mL of THF. Upon dissolution, a mixture of 1.88 g (31.37 mmol) of Acetic acid and 28.33 g (31.37 mmol) of Tetrabutylammonium fluoride (TBAF) 1.0 M solution in THF was added. After 19 hours of vigorous stirring, the reaction mixture was poured into a separatory funnel containing 200 mL of deionized water and 200mL of Ethyl acetate. After the separation, the organic layer was washed once with 200 mL of satd. $NaHCO_3$*aq*., twice with 300ml of 5 wt% Citric acid*aq*., and twice with 200 mL of deionized water. The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. This crude mixture was then purified via flash column chromatography (5:1 Ethyl acetate:Hexanes), to yield 2.78 g (86%) of 4-(3-Chloropropyl)-1-(pent-4-ynyl)-1*H*-1,2,3-triazole (**4**) as a colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ7.36 (s, Ar**H**, 1H), 4.45 (t, J = 6.6 Hz, N(Ar)C**H**$_2$, 2H), 3.56 (t, J = 6.3 Hz, ClC**H**$_2$, 2H), 2.87 (t, J = 7.4Hz, $ClCH_2CH_2$C**H**$_2$C, 2H), 2.12 (m, C**H**$_2$, CC**H**, 7H). ^{13}C NMR ($CDCl_3$): δ146.45 (NCH=**C**, 1C), 121.69 (N**C**H=C, 1C), 82.21 (HC**C**CH$_2$, 1C), 70.27 (H**C**CCH$_2$, 1C), 48.69 (N(Ar)**C**H$_2$, 1C), 44.37 (Cl**C**H$_2$, 1C), 32.04 (**C**H$_2$, 1C), 28.86 (**C**H$_2$, 1C), 22.81 (**C**H$_2$, 1C), 15.74 (HCC**C**H$_2$CH$_2$, 1C). Mass Spec for $C_{10}H_{14}ClN_3$ Calculated: 211.09; Found $(M+H)^+$: 212.09.

Trimer (5).

A similar 'Click' reaction condition described above for the synthesis of **2** was applied to **3** and **4**. After the purification via gradient flash column chromatography (2:1 Ethyl acetate:Hexanes to 1:2 MeOH:Ethyl acetate), **5** was obtained as a white solid (80% yield). ^{1}H NMR (200 MHz, $CDCl_3$): δ7.41 (s, Ar**H**, 1H), 7.40 (s, Ar**H**, 1H), 7.36 (s, Ar**H**, 1H), 4.39 (m, NC**H**$_2$, 6H), 3.53 (t, J = 6.4 Hz, ClC**H**$_2$, 2H), 2.83 (t, J = 7.3Hz, $ClCH_2CH_2$C**H**$_2$C, 2H), 2.66 (t, J = 7.1Hz, NCH_2CH_2C**H**$_2$C, 4H), 2.18 (m, C**H**$_2$, 10H), 0.11 (s, (C**H**$_3$)$_3$Si, 9H). ^{13}C NMR ($CDCl_3$): δ146.42 (NCH=**C**, 1C), 146.03 (NCH=**C**, 1C), 145.95 (NCH=**C**, 1C), 121.78 (N**C**H=C, 2C), 121.53 (N**C**H=C, 1C), 104.62 (Si**C**C, 1C), 86.66 (SiC**C**, 1C), 49.13 (N**C**H$_2$CH$_2$CH$_2$C(Ar), 2C), 48.83 (N**C**H$_2$CH$_2$CH$_2$CCSi, 1C), 44.31 (Cl**C**H$_2$, 1C), 31.98 (**C**H$_2$, 1C), 29.86 (**C**H$_2$, 2C), 28.90 (**C**H$_2$, 1C), 22.77 (**C**H$_2$, 1C), 22.28 (**C**H$_2$, 2C), 17.11 (SiCC**C**H$_2$CH$_2$, 1C), 0.16 ((**C**H$_3$)$_3$Si, 3C). Mass Spec for $C_{23}H_{36}ClN_9Si$ Calculated: 501.26; Found $(M+H)^+$: 502.26

Trimer-N_3-TMS (6).

A similar azidation reaction condition described above for the synthesis of **1** was applied to **2** except that most of DMF was removed under vacuum at 60 ^{o}C before extraction. After the purification via gradient flash column

chromatography (1:5 Ethyl acetate:Hexanes to 1:2 Ethyl acetate:Hexanes), **6** was obtained as a white solid (87% yield). ^{1}H NMR (200 MHz, $CDCl_3$): δ7.41 (s, Ar**H**, 1H), 7.39 (s, Ar**H**, 1H), 7.35 (s, Ar**H**, 1H), 4.37 (m, N(Ar)C**H**$_2$, 6H), 3.30 (t, J = 6.8 Hz, N_3C**H**$_2$, 2H), 2.75 (t, J = 7.4Hz, $N_3CH_2CH_2C$**H**$_2$C, 2H), 2.66 (t, J = 7.2Hz, N(Ar)CH_2CH_2C**H**$_2$C, 4H), 2.10 (m, C**H**$_2$, 10H), 0.11 (s, (C**H**$_3$)$_3$Si, 9H). ^{13}C NMR ($CDCl_3$): δ146.63 (NCH=**C**, 1C), 146.02 (NCH=**C**, 1C), 145.94 (NCH=**C**, 1C), 121.79 (N**C**H=C, 1C), 121.75 (N**C**H=C, 1C), 121.39 (N**C**H=C, 1C), 104.61 (Si**C**C, 1C), 86.65 (SiC**C**, 1C), 50.72 (N_3**C**H$_2$, 1C), 49.13 (N**C**H$_2$CH$_2$CH$_2$C(Ar), 1C), 49.10 (N**C**H$_2$CH$_2$CH$_2$C(Ar), 1C), 48.82 (N**C**H$_2$CH$_2$CH$_2$CCSi, 1C), 29.85 (**C**H$_2$, 2C), 28.89 (**C**H$_2$, 1C), 28.60 (**C**H$_2$, 1C), 22.72 (**C**H$_2$, 1C), 22.26 (**C**H$_2$, 2C), 17.09 (SiCC**C**H$_2$CH$_2$, 1C), 0.15 ((**C**H$_3$)$_3$Si, 3C). Mass Spec for $C_{23}H_{36}N_{12}Si$ Calculated: 508.30; Found $(M+H)^+$: 509.31

Trimer-Cl-H (7).

A similar TMS deprotection reaction condition described above for the synthesis of **4** was applied to **5**. Crude mixture was used for the next reaction without further purification (95% yield). ^{1}H NMR (200 MHz, $CDCl_3$): δ7.41 (s, Ar**H**, 1H), 7.40 (s, Ar**H**, 1H), 7.38 (s, Ar**H**, 1H), 4.40 (m, NC**H**$_2$, 6H), 3.54 (t, J = 6.4 Hz, ClC**H**$_2$, 2H), 2.84 (t, J = 7.3Hz, $ClCH_2CH_2C$**H**$_2$C, 2H), 2.67 (t, J = 7.1Hz, NCH_2CH_2C**H**$_2$C, 4H), 2.18 (m, C**H**$_2$, CH_2CC**H**, 11H). ^{13}C NMR ($CDCl_3$): δ146.47 (NCH=**C**, 1C), 146.06 (NCH=**C**, 1C), 146.00 (NCH=**C**, 1C), 121.90 (N**C**H=C, 1C), 121.83 (N**C**H=C, 1C), 121.54 (N**C**H=C, 1C), 82.12 (HC**C**CH$_2$, 1C), 70.29 (H**C**CCH$_2$, 1C), 49.15 (N**C**H$_2$CH$_2$CH$_2$C(Ar), 2C), 48.70 (N**C**H$_2$CH$_2$CH$_2$CCH, 1C), 44.35 (Cl**C**H$_2$, 1C), 32.00 (**C**H$_2$, 1C), 29.87 (**C**H$_2$, 2C), 28.78 (**C**H$_2$, 1C), 22.81 (**C**H$_2$, 1C), 22.31 (**C**H$_2$, 1C), 22.28 (**C**H$_2$, 1C), 15.69 (HCC**C**H$_2$CH$_2$, 1C). Mass Spec for $C_{20}H_{28}ClN_9$ Calculated: 429.22; Found $(M+H)^+$: 430.22

7mer (8).

A similar 'Click' reaction condition described above for the synthesis of **2** was applied to **6** and **7**. After the purification via crystallization from $CHCl_3$/Acetone, **8** was obtained as a white solid (77% yield). ^{1}H NMR (200 MHz, $CDCl_3$): δ7.42 (m, Ar**H**, 7H), 4.41 (m, NC**H**$_2$, 14H), 3.58 (t, J = 6.4 Hz, ClC**H**$_2$, 2H), 2.88 (t, J = 7.2Hz, $ClCH_2CH_2C$**H**$_2$C, 2H), 2.71 (t, J = 6.9Hz, NCH_2CH_2C**H**$_2$C, 12H), 2.20 (m, C**H**$_2$, 18H), 0.16 (s, (C**H**$_3$)$_3$Si, 9H). ^{13}C NMR ($CDCl_3$): δ146.58 (NCH=**C**, 1C), 146.15 (NCH=**C**, 6C), 121.94 (N**C**H=C, 6C), 121.64 (N**C**H=C, 1C), 104.62 (Si**C**C, 1C), 86.66 (SiC**C**, 1C), 49.29 (N**C**H$_2$CH$_2$CH$_2$C(Ar), 6C), 48.98 (N**C**H$_2$CH$_2$CH$_2$CCSi, 1C), 44.45 (Cl**C**H$_2$, 1C), 32.11 (**C**H$_2$, 1C), 29.98 (**C**H$_2$, 6C), 29.04 (**C**H$_2$, 1C), 22.92 (**C**H$_2$, 1C), 22.42 (**C**H$_2$, 6C), 17.25 (SiCC**C**H$_2$CH$_2$, 1C), 0.30 ((**C**H$_3$)$_3$Si, 3C). Mass Spec for $C_{43}H_{64}ClN_{21}Si$ Calculated: 937.51; Found $(M+H)^+$: 938.51

Synthesis of triazole oligomer (12) via direct 'Click' reaction

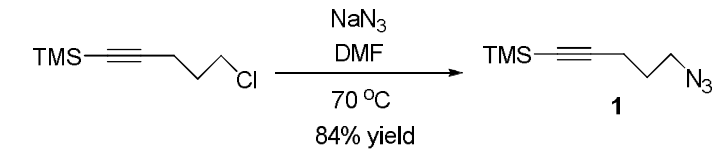
A similar 'Click' reaction condition described above for the synthesis of **2** was applied to the mixture of **9**, **10**, and **11**. Details are described in the main body below.

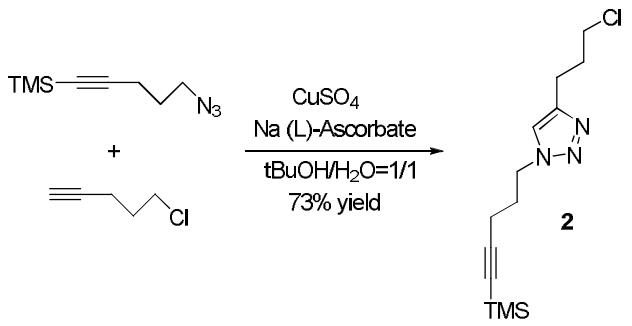
2-3. Results and Discussion

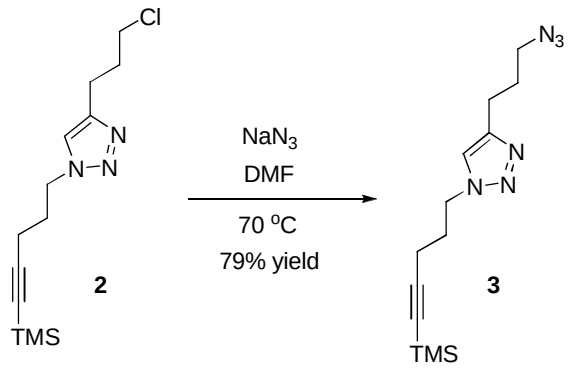
2-3-1. Synthesis

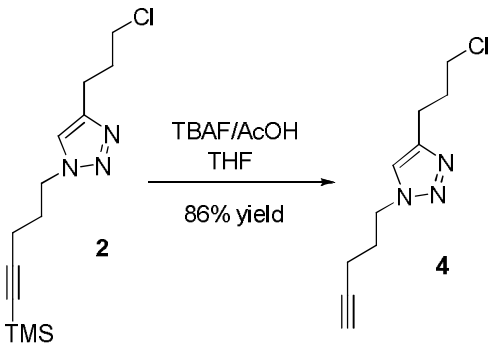
Azide syntheses and 'Click' reactions were basically conducted by following previous reports[7].

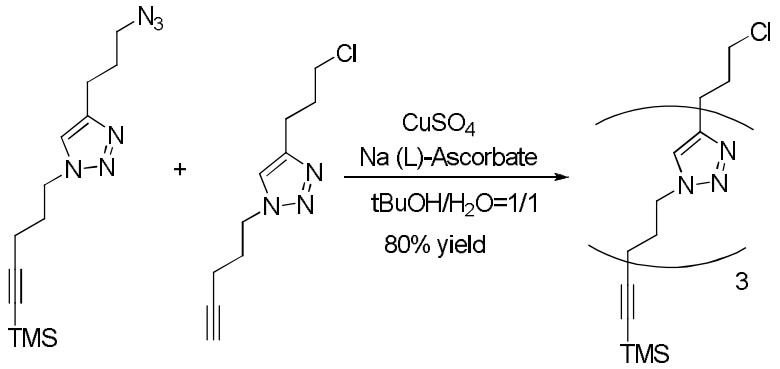
To make the work up of the 'Click' reactions easier, first, we tried to apply Cu/C as the heterogeneous catalyst[8], but even though we tried various types of solvents and reaction conditions, unfavorable TMS deprotection reaction was inevitable. So we decided to use the classical 'Click' reaction catalyst system, $CuSO_4$/Na (L)-Ascorbate as depicted in Scheme 1. And we successfully synthesized triazole oligomers up to 7mer (**8**).



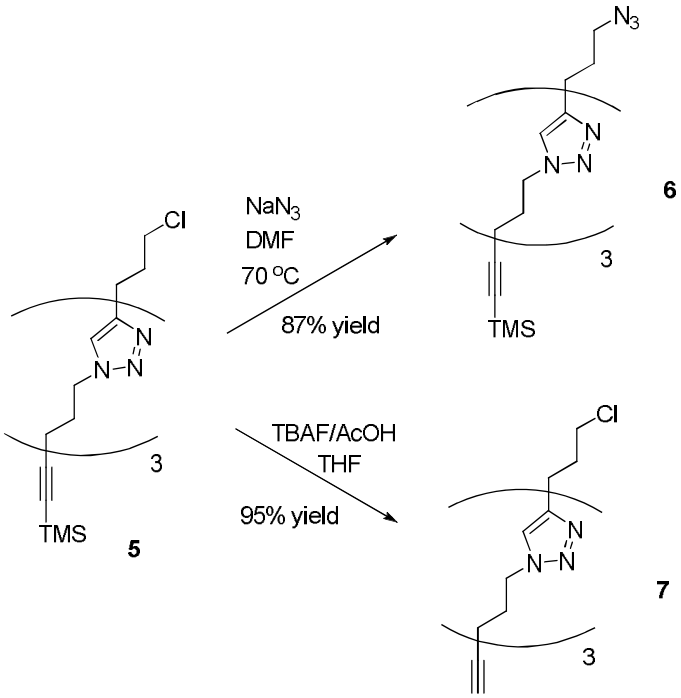




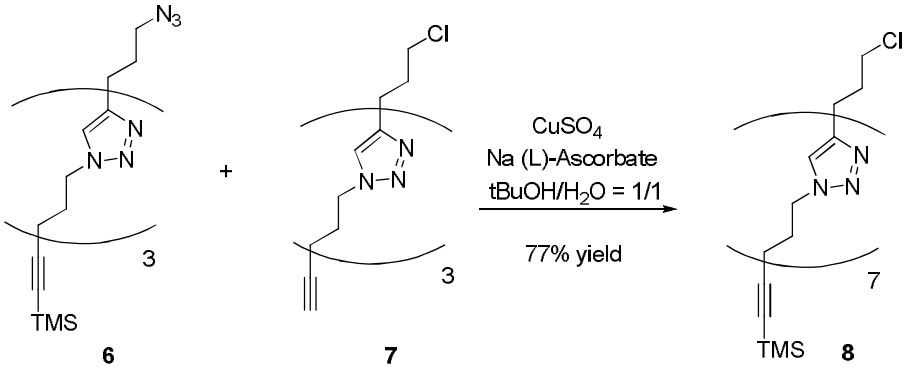



N3
Cl
CuSO4
Na (L)-Ascorbate
tBuOH/H2O=1/1
80% yield
TMS
3

3 **4** **5**


N3
Cl
NaN3
DMF
70 °C
87% yield
TBAF/AcOH
THF
95% yield
TMS
3

5 **6** **7**


N3
Cl
CuSO4
Na (L)-Ascorbate
tBuOH/H2O = 1/1
77% yield
TMS
3
7

6 **7** **8**

Scheme 1. Synthesis of 1,2,3-triazole oligomers (up to 7mer (**8**)).

As the number of the triazole ring becomes bigger, the polarity of the molecule increased dramatically and in case of 7mer (**8**), a lot of common solvents including H_2O, MeOH, CH_3CN, THF, Acetone, EtOAc, Toluene, Hexanes, Et_2O could not dissolve it. Even DMF, NMP, and DMSO barely dissolved it very little. This phenomenon is quite unexpected if we think about the good solubility of previously reported dendritic triazoles[9] and poly-4-vinyl-1,2,3-triazoles[4]. The GPC data using THF as eluent shows that again 7mer is not soluble into THF at all (Figure 1).

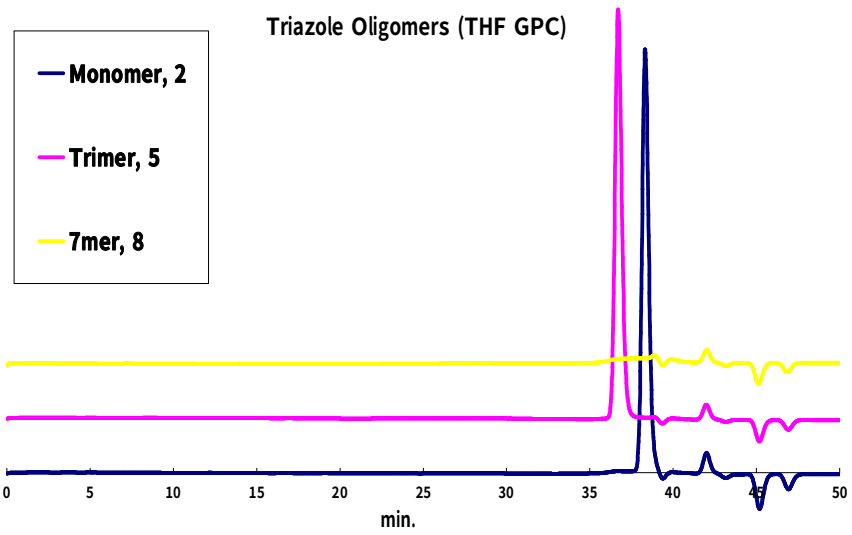
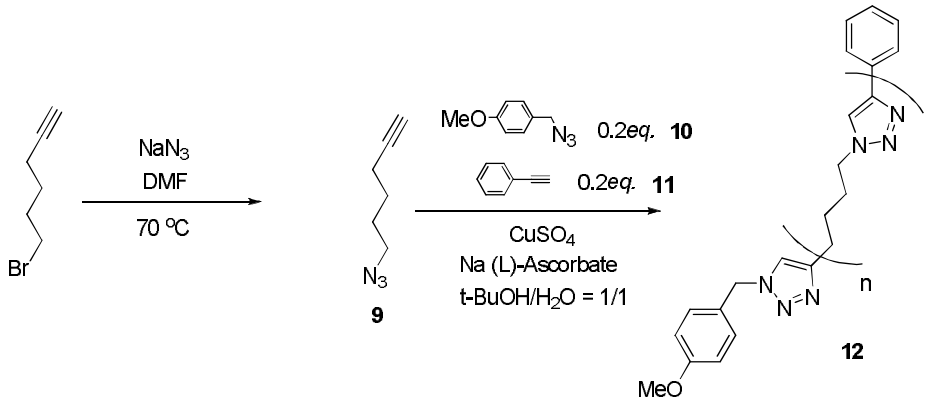


Figure 1. SEC results of the oligomers (**2**, **5**, **8**) using THF as eluent.

To investigate this phenomenon more in detail, we also conducted direct automatic oligomerization/polymerization reaction using 'Click' reaction (Scheme 2).



Scheme 2. Direct automatic synthesis of 1,2,3-triazole oligomers/polymers (**12**).

After the oligomerization reaction, a lot of greenish brown rubbery agglomerate was obtained (about 90 wt% of the theoretical yield) and it was found to be insoluble into almost all of the common solvents including DMF and NMP. We purified the soluble part (in total, about 10 wt% of the theoretical yield) using gradient flash column chromatography (Ethyl acetate to 1:4 MeOH:Ethyl acetate).

In Table 1, we summarize the result of the column chromatography and from this result, linear triazole oligomers found to become more and more polar as the number of the triazoles becomes bigger. Also we confirmed that solubility into solvents decreases significantly also as the number of the triazoles becomes bigger.

Fraction #[(a)]	4-8	29-38	39-52	82	83	84-88	89-92
Rf Value on TLC (EtOAc)	0.9	0.4	0.3	0.1	almost 0	0	0
Rf Value on TLC (MeOH/EtOAc=1/9)	0.9	0.6	0.5	0.3	0.2	0.1	0
Mw (from GPC)	200	400	400	600	700	1000	1900
Solubility into THF	Good	Good	Good	A little	A little	Little	Little

(a) Fraction number of the column chromatography counted from the beginning.

Table 1. Column chromatography results of the direct automatic oligomerization product.

n	0	1	2	3	4	5	6	7	13
FW	265	388	512	635	758	881	1004	1128	1867

Table 2. Theoretical molecular weight of the each oligomer.

And if we compare the results of Table 1 and Table 2, in this system, oligomers having more than 10 triazole units are very difficult to dissolve into organic solvents.

2-3-2. Analytical Studies of Oligomers

We also characterized oligomers synthesized in Scheme 1 using TGA, DSC, and SAXS.

Figure 2 shows the TGA data of the oligomers. From the amount of the weight loss of the curves, the 1st steep declination is attributed to the decomposition of TMS-acetylene moiety and chloropropyl moiety, and the 2nd steep declination is attributed to the decomposition of triazole ring moiety.

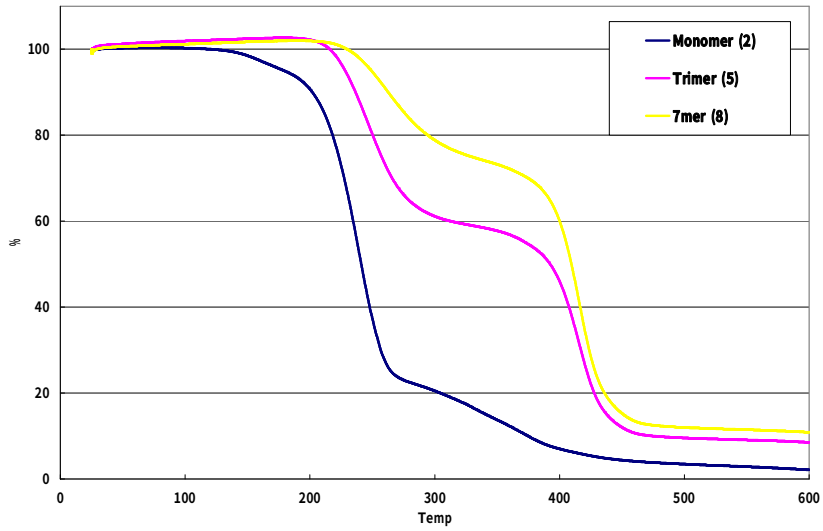
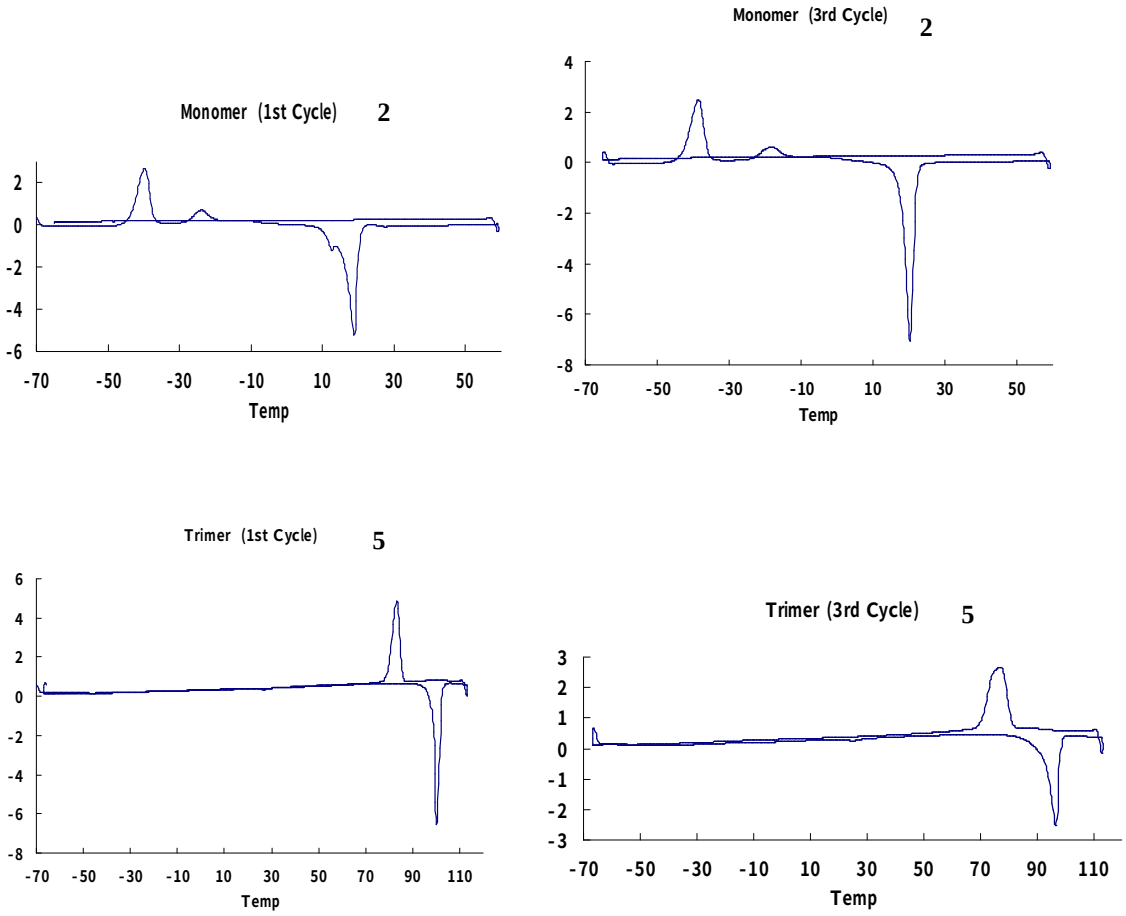


Figure 2. TGA results of the oligomers (**2**, **5**, **8**).

And Figure 3 shows DSC data of the oligomers.



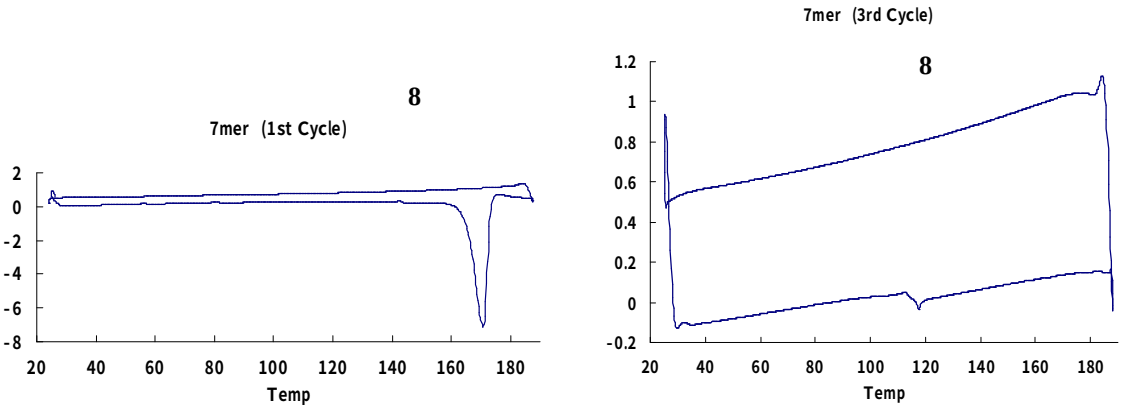


Figure 3. DSC data of oligomers (**2**, **5**, **8**).

From these DSC data, we found that Monomer (**2**) has its melting point at 20 ^{o}C, Trimer (**5**) has one at 100 ^{o}C, and 7mer (**8**) has one at 171 ^{o}C. But at the same time, it was found from the NMR analysis of the samples after DSC measurements that Trimer (**5**) and 7mer (**8**) had sarted decomposing while they were heated during their DSC measurements. So both Trimer (**5**) and 7mer (**8**) start decomposing at 115 ^{o}C or less and 200 ^{o}C or less, respectively. We can see this phenomenon from the comparison of the DSC charts of 1st Cycles and 3rd Cycles, too. (In the 3rd cycles, the melting peaks become smaller and broader significantly.)

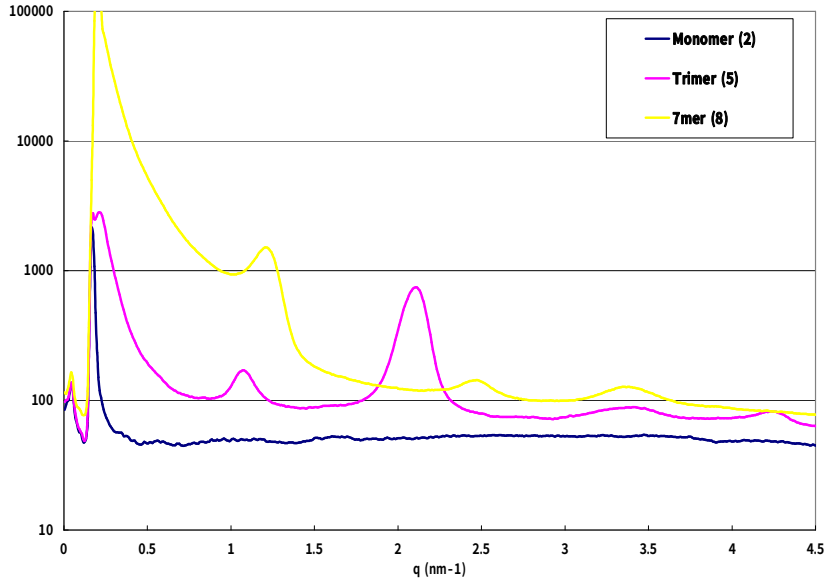


Figure 4. SAXS spectra of 1,2,3-triazole oligomers (**2**, **5**, **8**) at room temperature.

Also from the Intermediate-SAXS data (Figure 4), we found that Trimer (**5**) and 7mer (**8**) has a regular lamellae structure. And distance Ds were 6 nm and 5 nm, respectively. In case of Trimer (**5**), the distance D was almost double of the theoretical molecular length (assumed it was linear), and in case of 7mer (**8**), it was almost the same with its molecular length (Table 3).

	Monomer (**2**)	Trimer (**5**)	7mer (**8**)
Distance D	-	6nm	5nm
Calculated Molecular length*	2nm (If linear)	3nm (If linear)	6nm (If linear)

* Molecular length was calculated using ChemSketch (Advanced Chemistry Development, Inc.) and the distance D was calculated with the equation ($D = 2\pi/q$) based on the SAXS results.

Table 3. Distance D from SAXS measurements and the theoretical molecular length of the oligomers.

2-4. Summary

We have successful synthesized triazole oligomers up to 7mer. And a lot of unique properties including crystallinity and solubility were unveiled.

Currently, preparation of similar oligomers with longer spacers and functional groups to increase their solubilities into organic solvents and their further analytical studies are underway.

2-5. References

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CHAPTER 3

'Molecularly Defined ε-Caprolactone Oligomers and Polymers: Synthesis and Characterization'

3-1. Introduction

In Chapter 2, we found that a method called 'Exponential Growth Strategy[1]', which repeats deprotection of protective groups and coupling reaction to lengthen the molecular chain, is a very powerful tool to synthesize precisely size tuned organic oligomers/polymers. On the other hand, the past three decades have seen increasing attention paid to synthetic polymers for biomedical applications including surgery and medicine[2]. Especially in the research area of targeted drug/gene delivery and diagnostic agents, well-defined macromolecules and/or nano-scale objects are topics of great interest since they can be utilized for carrying payloads, cell targeting, and in *vivo* imaging etc.

One of the most promising polymer backbones for such applications is polyesters as they are readily hydrolyzed to constituent hydroxy acids which are eliminated by general metabolic pathways[3].

There are numerous reports on functional polyesters prepared either by condensation or ring-opening polymerization techniques[4] with significant focus on the polymers/monomers' functionalization. And there are a lot of reports on the syntheses of finely size tuned molecular wires and rods[5] by stepwise synthetic procedures. However, to the best of our knowledge, only very limited numbers of successful synthetic techniques have been reported to prepare precisely size tuned polymers or mono-disperse oligomers based on polyesters except for some recently issued patents[6] and a literature using a separation technique by preparative HPLC of the polydisperse oligomers[6(k), (l)]. This is unfortunate since the availability of precisely defined oligomers would enable a wide range of structure-property studies in order to fully understand, predict and tune the degradation rate, crystal structure, self assembly and performance of these materials in a variety of applications.

Herein, we report the development of a synthetic strategy for the synthesis of well-defined polyester oligomers and demonstrate the preparation of a series of Poly(ε-caprolactone) derivatives up to the 64mer. The physical and structural properties of these essentially single molecule species allow a fundamental insight into the physical and structural properties of the widely studied parent polymer.

3-2. Experimental Section

Materials.

4-(Dimethylamino)pyridinium *p*-toluenesulfonate (DPTS) was synthesized according to the previously reported procedure[7]. All the other chemicals and solvents were purchased from Aldrich, of reagent grade, and used without further purification. All reactions but silylation and hydrogenation were carried out under ambient conditions, i.e. non-inert atmospheres.

General Procedures/Characterization.

Analytical TLC was performed on commercial Merck Plates coated with silica gel GF254 (0.24 mm thick). Silica gel for flash column chromatography was Merck Kieselgel 60 (230-400 mesh, ASTM). ^{1}H-NMR (200 MHz) and ^{13}C-NMR measurements were performed on a Bruker AC 200 spectrometer at room temperature. Matrix Assisted Laser Desorption/Ionization (MALDI-TOF-MS) was carried out at room temperature on DYNAMO THERMO BIOANALYSIS using Dithranol in THF as the matrix and Sodium trifluoroacetate (NaOTf) in THF as the cationating agent. Size exclusion chromatography (SEC) was carried out at room temperature on a Waters Alliance HPLC System (Waters 2695 Separation Module) connected to Waters Styragel® HR columns (0.5, 2, 4, and % INT'L HAZA) using THF as eluent (flow rate: 1 mL/min). A Waters 2414 differential refractometer and a 2996 photodiode array detector were employed. Preparative GPC was carried out at room temperature on a Waters 1525 Binary HPLC connected to a Waters 2414 differential refractometer and Waters Styragel® columns (Ultrastyragel 100 Å, 10^{-3} Å and 10^{-4} Å THF 19*300 INT'L HAZA) using THF as eluent (flow rate: 6 mL/min). The molecular weights of the polymers were calculated relative to linear polystyrene standards. ThermoGravimetric Analysis was conducted using METTLER TGA/sDTA851e under N_2 atmosphere. Differential Scanning Calorimetry (DSC) measurements were performed with a TA Instruments DSC 2920 and a ramp rate of 5 degrees per minute with data usually collected during the third cycle in the selected temperature ranges. Calibrations were made using indium as a standard for both temperature transitions and the heats of fusion. Melting transition temperatures (T_m) were determined as the peak maxima of the transition. Small Angle X-ray Scattering (Ultra-SAXS (X-ray Source; Fine focus (0.2 mm) Rigaku rotationg anode generator, Wavelength; 1.54 Å, Sample to Detector Distance; 172.5 cm, Interface; Bruker SAXS software and SPEC) and Intermediate-SAXS (X-ray Source; 18kW Rigaku rotationg anode generator, Wavelength; 1.54 Å, Sample to Detector Dintance; 75.8 cm, Interface; SPEC)) were carried out using quartz capillary cell. Tapping mode AFM experiments were carried out using a Multimode Nanoscope III system equipped with a J-type vertical engage scanner (Digital Instruments, Santa Barbara, CA). The measurements were performed under ambient atmosphere using commercial Si cantilevers with a nominal spring constant and resonance frequency respectively equal to 48 N/m and 190 kHz (ACL, Applied Nanostructures, Santa Clara, CA).

6-Hydroxycaproic acid (1).

A 2 L round bottom flask was charged with 30.35 g (0.266 mol) of ε-Caprolactone, 1 L of H_2O, and 21.25 g (0.531 mol) of NaOH. This reaction mixture was stirred overnight at room temperature. Then the pH was adjusted to about 2 with 1M HCl*aq*. The compound **1** was then extracted by using a convertible liquid/liquid continuous extractor with 1.5 L of Diethyl ether for 4 days. The ethereal layer was dried over $MgSO_4$ and concentrated. Yield: 34.49 g (98%) of white solid. ^{1}H NMR (200 MHz, Acetone-d_6): δ3.70 (b, CH_2O**H,** CH_2CO_2**H**, 2H), 3.54 (t, J = 6.2 Hz, C**H**$_2$OH, 2H), 2.28 (t, J = 7.2 Hz, C**H**$_2$$CO_2$H, 2H), 1.57 (m, HOC$H_2$[C**H**$_2$]$_3$$CH_2CO_2$H, 6H). ^{13}C NMR (Acetone-d_6): δ175.36 (**C**O, 1C), 62.35 (HO**C**H_2, 1C), 34.32 (CH_2**C**H_2CO_2, 1C), 33.25 (HOCH_2**C**H_2, 1C), 26.21 (HO[CH_2]$_3$**C**H_2, 1C), 25.53 (HO[CH_2]$_2$**C**H_2, 1C).

6-(*tert*-Butyldimethyl)siloxycaproic acid (2).

17.30 g (114.78 mmol) of *tert*-Butyldimethylsilyl chloride was added to a DMF (90 g) solution of **1** (13.77 g (104.14 mmol)) and Imidazole (15.93 g (233.93 mmol)). This reaction mixture was stirred overnight at 50°C under Argon atmosphere. The resulting mixture was poured into a separatory funnel containing 400 mL of brine and

extracted 4 times with 400 mL of Diethyl ether. The organic fractions were combined, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Crude product was then purified via flash column chromatography using 1:1 Hexanes:Ethyl acetate as eluent yielding 20.52 g (80% yield) of **2** as a clear colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ3.61 (t, J = 6.3 Hz, C**H**$_2$OSi, 2H), 2.36 (t, J = 7.4 Hz, C**H**$_2$CO$_2$H, 2H), 1.55 (m, SiOCH$_2$[C**H**$_2$]$_3$CH$_2$CO$_2$H, 6H), 0.89 (s, (C**H**$_3$)$_3$CSi, 9H), 0.04 (s, (C**H**$_3$)$_2$Si, 6H). ^{13}C NMR ($CDCl_3$): δ180.02 (**C**O$_2$H, 1C), 63.14 (SiO**C**H$_2$, 1C), 34.26 (CH$_2$**C**H$_2$CO$_2$, 1C), 32.60 (SiOCH$_2$**C**H$_2$CH$_2$, 1C), 26.16 ((**C**H$_3$)$_3$CSi, 3C), 25.53 (SiO[CH$_2$]$_3$**C**H$_2$, 1C), 24.70 (SiO[CH$_2$]$_2$**C**H$_2$, 1C), 18.55 ((CH$_3$)$_3$**C**Si, 1C), -5.10 ((**C**H$_3$)$_2$Si, 2C).

Benzyl 6-hydroxyhexanoate (3).

9.25 g (70.01 mmol) of **1** in Acetone (100 g) was added dropwise to a CH_2Cl_2 (90 g) solution of Benzyl alcohol (BnOH) (78.43 g (725.26 mmol)), 1,3-Dicyclohexylcarbodiimide (DCC) (15.76 g (76.38 mmol)), and 4-(Dimethylamino)pyridine (DMAP) (9.30 g (76.12 mmol)). This reaction mixture was stirred overnight at room temperature. The resulting mixture was concentrated under reduced pressure and added 200 mL of Diethyl ether and then filtered. The filtrate was poured into a separatory funnel and washed with 200 mL of satd. $CuSO_4$*aq*. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Crude product was then purified via flash column chromatography using 1:1 Hexanes:Ethyl acetate as eluent yielding 11.90 g (76% yield) of **2** as a clear colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ7.38 (m, Ar, 5H), 5.12 (s, CO$_2$C**H**$_2$Ph, 2H), 3.63 (t, J = 6.3 Hz, C**H**$_2$OH, 2H), 1.58 (m, HOCH$_2$[C**H**$_2$]$_3$CH$_2$CO$_2$CH$_2$, 6H). ^{13}C NMR ($CDCl_3$): δ173.74 (**C**O, 1C), 136.21 (Ar, CH$_2$-**C**, 1C) 128.75 (Ar-*meta*, 2C), 128.41 (Ar-*orhto*, *para*, 3C), 66.35 (CO$_2$**C**H$_2$Ph, 1C), 62.82 (HO**C**H$_2$, 1C), 34.39 (CH$_2$**C**H$_2$CO$_2$, 1C), 32.48 (HOCH$_2$**C**H$_2$, 1C), 25.43 (HO[CH$_2$]$_3$**C**H$_2$, 1C), 24.81 (HO[CH$_2$]$_2$**C**H$_2$, 1C).

General procedure of coupling reaciton: Synthesis of the Dimer (4) depicted.

Dissolve **2** (20.50 g (83.19 mmol)), **3** (17.74 g (79.81 mmol)), 1,3-Dicyclohexylcarbodiimide (DCC) (19.29 g (93.49 mmol)), and 4-(Dimethylamino)pyridine (DMAP) (11.17 g (91.43 mmol)) into CH_2Cl_2 (200 g) and stirred overnight at room temperature. The resulting mixture was filetered. The filtrate was poured into a separatory funnel and washed with 200 mL of satd. $CuSO_4$*aq*. and 200 mL of H_2O. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Crude product was then purified via flash column chromatography using 3:1 Hexanes:Ethyl acetate as eluent yielding 26.60 g (71% yield) of **4** as a clear colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ7.33 (m, Ar, 5H), 5.10 (s, CO$_2$C**H**$_2$Ph, 2H), 4.03 (t, J = 6.5 Hz, CO$_2$C**H**$_2$CH$_2$, 2H), 3.58 (t, J = 6.3 Hz, C**H**$_2$OSi, 2H), 2.31 (t, t, J = 7.6 Hz, 7.6 Hz, CH$_2$C**H**$_2$CO$_2$, CH$_2$C**H**$_2$CO$_2$, 4H), 1.50 (m, SiOCH$_2$[C**H**$_2$]$_3$CH$_2$CO$_2$CH$_2$[C**H**$_2$]$_3$CH$_2$CO$_2$CH$_2$Ph, 12H), 0.88 (s, (C**H**$_3$)$_3$CSi, 9H), 0.04 (s, (C**H**$_3$)$_2$Si, 6H). ^{13}C NMR ($CDCl_3$): δ173.82 (**C**O, 1C), 173.35 (**C**O, 1C), 136.15 (Ar, CH$_2$-**C**, 1C) 128.64 (Ar-*meta*, 2C), 128.29 (Ar-*orhto*, *para*, 3C), 66.22 (CO$_2$**C**H$_2$Ph, 1C), 64.10 (CO$_2$**C**H$_2$CH$_2$, 1C), 63.04 (SiO**C**H$_2$, 1C), 34.40 (CH$_2$**C**H$_2$CO$_2$, 1C), 34.20 (CH$_2$**C**H$_2$CO$_2$, 1C), 32.56 (SiOCH$_2$**C**H$_2$CH$_2$, 1C), 28.43 (CO$_2$CH$_2$**C**H$_2$CH$_2$, 1C), 26.06 ((**C**H$_3$)$_3$CSi, 3C), 25.61 (CH$_2$**C**H$_2$CH$_2$, 1C), 25.55 (CH$_2$**C**H$_2$CH$_2$, 1C), 24.90 (CH$_2$**C**H$_2$CH$_2$, 1C), 24.66 (CH$_2$**C**H$_2$CH$_2$, 1C), 18.43 ((CH$_3$)$_3$**C**Si, 1C), -5.18 ((**C**H$_3$)$_2$Si, 2C). Mass Spec for $C_{25}H_{42}O_5Si$ Calculated: 450.28; Found $(M+Na)^+$: 473.26.

General procedure of deprotection of Benzyl ester (hydrogenation): Synthesis of the Acid-Terminated-Dimer (5) depicted.

0.87 g of Palladium on activated carbon (10wt%) was added to a solution of **4** (8.28 g (18.37 mmol)) in Ethyl acetate (87 g) and then stirred overnight under H_2 at room temperature. The resulting mixture was filtered through celite and the cake was washed with 100 mL of hot MeOH. The filtrate was concentrated under reduced pressure. And then conducted three sets of 'adding 100 g of CH_2Cl_2 and concentration under reduced pressure'. Yield; 13.12 g (100%) as a clear colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ4.05 (t, J = 6.5 Hz, $CO_2C\mathbf{H}_2CH_2$, 2H), 3.59 (t, J = 6.3 Hz, $C\mathbf{H}_2OSi$, 2H), 2.32 (t, t, J = 7.2 Hz, 7.2 Hz, $CH_2C\mathbf{H}_2CO_2$, $CH_2C\mathbf{H}_2CO_2$, 4H), 1.50 (m, $SiOCH_2[C\mathbf{H}_2]_3CH_2CO_2CH_2[C\mathbf{H}_2]_3CH_2CO_2\mathbf{H}$, 13H) 0.87 (s, $(C\mathbf{H}_3)_3CSi$, 9H), 0.02 (s, $(C\mathbf{H}_3)_2Si$, 6H). ^{13}C NMR ($CDCl_3$): δ179.68 ($\mathbf{C}O_2H$, 1C), 174.10 ($\mathbf{C}O_2CH_2$, 1C), 64.21 ($CO_2\mathbf{C}H_2CH_2$, 1C), 63.20 ($SiO\mathbf{C}H_2$, 1C), 34.51 ($CH_2\mathbf{C}H_2CO_2$, 1C), 34.05 ($CH_2\mathbf{C}H_2CO_2$, 1C), 32.61 ($SiOCH_2\mathbf{C}H_2CH_2$, 1C), 28.48 ($CO_2CH_2\mathbf{C}H_2CH_2$, 1C), 26.14 ($(\mathbf{C}H_3)_3CSi$, 3C), 25.61 ($CH_2\mathbf{C}H_2CH_2$, 2C), 24.98 ($CH_2\mathbf{C}H_2CH_2$, 1C), 24.46 ($CH_2\mathbf{C}H_2CH_2$, 1C), 18.53 ($(CH_3)_3\mathbf{C}Si$, 1C), -5.11 ($(\mathbf{C}H_3)_2Si$, 2C).

General procedure of deprotection of TBDMS (desilylation): Synthesis of the Hydroxyl-Terminated-Dimer (6) depicted.

A mixture of 4.41 g (73.41 mmol) of Acetic acid and 66.29 g (73.41 mmol) of Tetrabutylammonium fluoride (TBAF) 1.0 M solution in THF was added to a solution of **4** (16.55 g (36.72 mmol)) in THF (66 g). The reaction mixture was stirred overnight at 50°C. The resulting mixture was poured into a separatory funnel containing 300 mL of CH_2Cl_2 and 300 mL of H_2O and separated. The organic layer was washed with satd. $NaHCO_3$*aq.* (2x200 mL), 5wt% Citric acid*aq.* (2x200 mL), and H_2O (1x200 mL). The organic layer was then dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Crude product was then purified via flash column chromatography using 1:1 Hexanes:Ethyl acetate as eluent yielding 11.45 g (93% yield) of **6** as a clear colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ7.34 (s, Ar, 5H), 5.11 (s, $CO_2C\mathbf{H}_2Ph$, 2H), 4.05 (t, J = 6.4 Hz, $CO_2C\mathbf{H}_2CH_2$, 2H), 3.60 (t, J = 6.4 Hz, $C\mathbf{H}_2OH$, 2H), 2,99 (b, O**H**, 1H), 2.33 (t, t, J = 7.3 Hz, 7.3 Hz, $CH_2C\mathbf{H}_2CO_2$, $CH_2C\mathbf{H}_2CO_2$, 4H), 1.50 (m, $HOCH_2[C\mathbf{H}_2]_3CH_2CO_2CH_2[C\mathbf{H}_2]_3CH_2CO_2CH_2Ph$, 12H). ^{13}C NMR ($CDCl_3$): δ173.69 (**C**O, 1C), 173.22 (**C**O, 1C), 135.86 (Ar, CH_2-**C**, 1C) 128.38 (Ar-*meta*, 2C), 128.00 (Ar-*orhto*, *para*, 3C), 65.97 ($CO_2\mathbf{C}H_2Ph$, 1C), 63.94 ($CO_2\mathbf{C}H_2CH_2$, 1C), 62.05 ($HO\mathbf{C}H_2$, 1C), 34.06 ($CH_2\mathbf{C}H_2CO_2$, 1C), 33.92 ($CH_2\mathbf{C}H_2CO_2$, 1C), 32.12 ($HOCH_2\mathbf{C}H_2CH_2$, 1C), 28.13 ($CO_2CH_2\mathbf{C}H_2CH_2$, 1C), 25.33 ($CH_2\mathbf{C}H_2CH_2$, 1C), 25.18 ($CH_2\mathbf{C}H_2CH_2$, 1C), 24.56 ($CH_2\mathbf{C}H_2CH_2$, 1C), 24.37 ($CH_2\mathbf{C}H_2CH_2$, 1C).

Tetramer (7).

The procedure described above for coupling was applied to **5** and **6**. Crude product was then purified via flash column chromatography using 2:1 Hexanes:Ethyl acetate as eluent yielding **7** as a clear colorless oil. (89% yield) ^{1}H NMR (200 MHz, $CDCl_3$): δ7.34 (s, Ar, 5H), 5.10 (s, $CO_2C\mathbf{H}_2Ph$, 2H), 4.04 (t, J = 6.6 Hz, $CO_2C\mathbf{H}_2CH_2$, 6H), 3.58 (t, J = 6.3 Hz, $C\mathbf{H}_2OSi$, 2H), 2.33 (t, t, J = 7.4 Hz, 7.4 Hz, $CH_2C\mathbf{H}_2CO_2$, $CH_2C\mathbf{H}_2CO_2$, 8H), 1.50 (m, $CH_2C\mathbf{H}_2CH_2$, 24H), 0.88 (s, $(C\mathbf{H}_3)_3CSi$, 9H), 0.03 (s, $(C\mathbf{H}_3)_2Si$, 6H). ^{13}C NMR ($CDCl_3$): δ173.70 (**C**O, 1C), 173.46 (**C**O, 2C), 173.21 (**C**O, 1C), 136.08 (Ar, CH_2-**C**, 1C) 128.55 (Ar-*meta*, 2C), 128.19 (Ar-*orhto*, *para*, 3C), 66.11 ($CO_2\mathbf{C}H_2Ph$, 1C), 64.08 ($CO_2\mathbf{C}H_2CH_2$, 3C), 62.94 ($SiO\mathbf{C}H_2$, 1C), 34.31 ($CH_2\mathbf{C}H_2CO_2CH_2Ph$, 1C), 34.10 ($CH_2\mathbf{C}H_2CO_2CH_2CH_2$, 3C), 32.47 ($SiOCH_2\mathbf{C}H_2CH_2$, 1C), 28.35 ($CO_2CH_2\mathbf{C}H_2CH_2$, 3C), 25.98 ($(\mathbf{C}H_3)_3CSi$, 3C), 25.53 ($CH_2\mathbf{C}H_2CH_2$, 4C), 24.81 ($CH_2\mathbf{C}H_2CH_2$, 1C), 24.58 ($CH_2\mathbf{C}H_2CH_2$, 3C), 18.34 ($(CH_3)_3\mathbf{C}Si$, 1C), -5.26 ($(\mathbf{C}H_3)_2Si$, 2C). Mass Spec for $C_{37}H_{62}O_9Si$ Calculated: 678.42; Found $(M+Na)^+$: 701.41.

Acid-Terminated-Tetramer (8).

The procedure described above for deprotection of Benzyl ester (hydrogenation) was applied to Tetramer (**7**) gave Acid-Terminated-Tetramer (**8**) as a clear colorless oil. (100% yield) ^{1}H NMR (200 MHz, $CDCl_3$): δ11.00 (b, O**H**, 1H), 4.04 (t, J = 6.5 Hz, $CO_2C\mathbf{H}_2CH_2$, 6H), 3.56 (t, J = 6.3 Hz, $C\mathbf{H}_2OSi$, 2H), 2.31 (m, $CH_2C\mathbf{H}_2CO_2$, 8H), 1.50 (m, $CH_2C\mathbf{H}_2CH_2$, 24H), 0.84 (s, $(C\mathbf{H}_3)_3CSi$, 9H), 0.00 (s, $(C\mathbf{H}_3)_2Si$, 6H). ^{13}C NMR ($CDCl_3$): δ179.12 (**C**O_2H, 1C), 174.01 (**C**O_2CH_2, 1C), 173.80 (**C**O_2CH_2, 2C), 64.21 ($CO_2\mathbf{C}H_2CH_2$, 3C), 63.10 (SiO**C**H_2, 1C), 34.44 ($CH_2\mathbf{C}H_2CO_2H$, 1C), 34.24 ($CH_2\mathbf{C}H_2CO_2CH_2CH_2$, 2C), 33.95 ($CH_2\mathbf{C}H_2CO_2CH_2CH_2$, 1C), 32.54 ($SiOCH_2\mathbf{C}H_2CH_2$, 1C), 28.43 ($CO_2CH_2\mathbf{C}H_2CH_2$, 3C), 26.07 (($\mathbf{C}H_3)_3CSi$, 3C), 25.56 ($CH_2\mathbf{C}H_2CH_2$, 3C), 24.91 ($CH_2\mathbf{C}H_2CH_2$, 1C), 24.68 ($CH_2\mathbf{C}H_2CH_2$, 3C), 24.40 ($CH_2\mathbf{C}H_2CH_2$, 1C), 18.46 (($CH_3)_3\mathbf{C}Si$, 1C), -5.18 (($\mathbf{C}H_3)_2Si$, 2C).

Hydroxyl-Terminated-Tetramer (9).

The procedure described above for deprotection of TBDMS (desilylation) was applied to Tetramer (**7**). Crude product was then purified via flash column chromatography using 1:1 Hexanes:Ethyl acetate as eluent yielding **9** as a clear colorless oil. (96% yield) ^{1}H NMR (200 MHz, $CDCl_3$): δ7.35 (s, Ar, 5H), 5.11 (s, $CO_2C\mathbf{H}_2Ph$, 2H), 4.05 (t, J = 6.5 Hz, $CO_2C\mathbf{H}_2CH_2$, 6H), 3.62 (t, J = 6.4 Hz, $C\mathbf{H}_2OH$, 2H), 2.37 (t, J = 7.4 Hz, $CH_2C\mathbf{H}_2CO_2CH_2Ph$, 2H), 2.31 (t, J = 7.2 Hz, $CH_2C\mathbf{H}_2CO_2CH_2CH_2$, 6H), 1.50 (m, $CH_2C\mathbf{H}_2CH_2$, 24H). ^{13}C NMR ($CDCl_3$): δ173.75 (**C**O, 1C), 173.56 (**C**O, 2C), 173.29 (**C**O, 1C), 135.99 (Ar, CH_2-**C**, 1C) 128.51 (Ar-*meta*, 2C), 128.14 (Ar-*orhto*, *para*, 3C), 66.10 ($CO_2\mathbf{C}H_2Ph$, 1C), 64.09 ($CO_2\mathbf{C}H_2CH_2$, 3C), 62.33 (HO**C**H_2, 1C), 34.06 ($CH_2\mathbf{C}H_2CO_2CH_2$, 4C), 32.28 ($HOCH_2\mathbf{C}H_2CH_2$, 1C), 28.28 ($CO_2CH_2\mathbf{C}H_2CH_2$, 3C), 25.47 ($CH_2\mathbf{C}H_2CH_2$, 3C), 25.30 ($CH_2\mathbf{C}H_2CH_2$, 1C), 24.68 ($CH_2\mathbf{C}H_2CH_2$, 1C), 24.52 ($CH_2\mathbf{C}H_2CH_2$, 3C).

Octamer (10).

The procedure described above for coupling was applied to **8** and **9**. Crude product was then purified via flash column chromatography using 15:1 CH_2Cl_2:MeOH and 2:1 Hexanes:Ethyl acetate as eluents yielding **10** as a white solid. (84% yield) ^{1}H NMR (200 MHz, $CDCl_3$): δ7.34 (s, Ar, 5H), 5.11 (s, $CO_2C\mathbf{H}_2Ph$, 2H), 4.05 (t, J = 6.6 Hz, $CO_2C\mathbf{H}_2CH_2$, 14H), 3.59 (t, J = 6.3 Hz, $C\mathbf{H}_2OSi$, 2H), 2.36 (t, J = 7.4 Hz, $CH_2C\mathbf{H}_2CO_2CH_2Ph$, 2H), 2.30 (t, J = 7.4 Hz, $CH_2C\mathbf{H}_2CO_2CH_2CH_2$, 14H), 1.50 (m, $CH_2C\mathbf{H}_2CH_2$, 48H), 0.88 (s, $(C\mathbf{H}_3)_3CSi$, 9H), 0.03 (s, $(C\mathbf{H}_3)_2Si$, 6H). ^{13}C NMR ($CDCl_3$): δ174.00 (**C**O, 1C), 173.75 (**C**O, 7C), 173.50 (**C**O, 1C), 137.00 (Ar, CH_2-**C**, 1C) 128.75 (Ar-*meta*, 2C), 128.39 (Ar-*orhto*, *para*, 3C), 66.35 ($CO_2\mathbf{C}H_2Ph$, 1C), 64.33 ($CO_2\mathbf{C}H_2CH_2$, 7C), 63.16 (SiO**C**H_2, 1C), 34.52 ($CH_2\mathbf{C}H_2CO_2CH_2Ph$, 1C), 34.31 ($CH_2\mathbf{C}H_2CO_2CH_2CH_2$, 7C), 32.66 ($SiOCH_2\mathbf{C}H_2CH_2$, 1C), 28.35 ($CO_2CH_2\mathbf{C}H_2CH_2$, 7C), 26.15 (($\mathbf{C}H_3)_3CSi$, 3C), 25.72 ($CH_2\mathbf{C}H_2CH_2$, 8C), 25.00 ($CH_2\mathbf{C}H_2CH_2$, 1C), 24.76 ($CH_2\mathbf{C}H_2CH_2$, 7C), 18.54 (($CH_3)_3\mathbf{C}Si$, 1C), -5.09 (($\mathbf{C}H_3)_2Si$, 2C). Mass Spec for $C_{61}H_{102}O_{17}Si$ Calculated: 1134.69; Found $(M+Na)^+$: 1157.70.

Acid-Terminated-Octamer (11).

The procedure described above for deprotection of Benzyl ester (hydrogenation) was applied to Octamer (**10**). Crude product was then purified via flash column chromatography using 1:1 Hexanes:Ethyl acetate as eluent yielding **11** as a white solid. (96% yield) ^{1}H NMR (200 MHz, $CDCl_3$): δ4.04 (t, J = 6.6 Hz, $CO_2C\mathbf{H}_2CH_2$, 14H), 3.58 (t, J = 6.3 Hz, $C\mathbf{H}_2OSi$, 2H), 2.31 (m, $CH_2C\mathbf{H}_2CO_2$, 16H), 1.50 (m, $CH_2C\mathbf{H}_2CH_2$, 48H), 0.87 (s, $(C\mathbf{H}_3)_3CSi$, 9H), 0.02 (s, $(C\mathbf{H}_3)_2Si$, 6H). ^{13}C NMR ($CDCl_3$): δ178.34 (**C**O_2H, 1C), 174.04 (**C**O_2CH_2, 1C), 173.86 (**C**O_2CH_2, 5C),

173.79 (**C**O_2CH_2, 1C), 64.26 (CO_2**C**H_2CH_2, 7C), 63.15 (SiO**C**H_2, 1C), 34.50 (CH_2**C**H_2CO_2H, 1C), 34.29 (CH_2**C**$H_2CO_2CH_2CH_2$, 6C), 33.86 (CH_2**C**$H_2CO_2CH_2CH_2$, 1C), 32.62 (SiOCH_2**C**H_2CH_2, 1C), 28.50 (CO_2CH_2**C**H_2CH_2, 7C), 26.13 ((**C**$H_3)_3$CSi, 3C), 25.69 (CH_2**C**H_2CH_2, 7C), 24.97 (CH_2**C**H_2CH_2, 1C), 24.74 (CH_2**C**H_2CH_2, 7C), 24.47 (CH_2**C**H_2CH_2, 1C), 18.52 ($(CH_3)_3$**C**Si, 1C), -5.11 ((**C**$H_3)_2$Si, 2C).

Hydroxyl-Terminated-Octamer (12).

The procedure described above for deprotection of TBDMS (desilylation) was applied to Octamer (**10**). Crude product was then purified via flash column chromatography using 1:1 Hexanes:Ethyl acetate as eluent yielding **12** as a white solid. (97% yield) ^{1}H NMR (200 MHz, $CDCl_3$): δ7.35 (s, Ar, 5H), 5.09 (s, CO_2C**H**$_2$Ph, 2H), 4.04 (t, J = 6.6 Hz, CO_2C**H**$_2CH_2$, 14H), 3.62 (t, J = 6.4 Hz, C**H**$_2$OH, 2H), 2.35 (t, J = 7.2 Hz, CH_2C**H**$_2CO_2CH_2$Ph, 2H), 2.29 (t, J = 7.5 Hz, CH_2C**H**$_2CO_2CH_2CH_2$, 14H), 1.50 (m, CH_2C**H**$_2CH_2$, 48H). ^{13}C NMR ($CDCl_3$): δ173.92 (**C**O, 1C), 173.73 (**C**O, 7C), 173.48 (**C**O, 1C), 136.14 (Ar, CH_2-**C**, 1C) 128.71 (Ar-*meta*, 2C), 128.34 (Ar-*orhto*, *para*, 3C), 66.31 (CO_2**C**H_2Ph, 1C), 64.09 (CO_2**C**H_2CH_2, 7C), 62.72 (HO**C**H_2, 1C), 34.37 (CH_2**C**$H_2CO_2CH_2$, 7C), 34.26 (CH_2**C**$H_2CO_2CH_2$, 1C), 32.47 (HOCH_2**C**H_2CH_2, 1C), 28.48 (CO_2CH_2**C**H_2CH_2, 7C), 25.67 (CH_2**C**H_2CH_2, 7C), 25.45 (CH_2**C**H_2CH_2, 1C), 24.83 (CH_2**C**H_2CH_2, 1C), 24.71 (CH_2**C**H_2CH_2, 7C).

16mer (13).

The procedure described above for coupling was applied to **11** and **12**. Crude product was then purified via flash column chromatography using 15:1 CH_2Cl_2:MeOH as eluent yielding **13** as a white solid. (74% yield) ^{1}H NMR (200 MHz, $CDCl_3$): δ7.34 (s, Ar, 5H), 5.10 (s, CO_2C**H**$_2$Ph, 2H), 4.04 (t, J = 6.6 Hz, CO_2C**H**$_2CH_2$, 30H), 3.58 (t, J = 6.3 Hz, C**H**$_2$OSi, 2H), 2.36 (t, J = 7.4 Hz, CH_2C**H**$_2CO_2CH_2$Ph, 2H), 2.30 (t, J = 7.3 Hz, CH_2C**H**$_2CO_2CH_2CH_2$, 30H), 1.50 (m, CH_2C**H**$_2CH_2$, 96H), 0.87 (s, (C**H**$_3)_3$CSi, 9H), 0.02 (s, (C**H**$_3)_2$Si, 6H). ^{13}C NMR ($CDCl_3$): δ173.99 (**C**O, 1C), 173.73 (**C**O, 14C), 173.49 (**C**O, 1C), 136.18 (Ar, CH_2-**C**, 1C) 128.73 (Ar-*meta*, 2C), 128.37 (Ar-*orhto*, *para*, 3C), 66.33 (CO_2**C**H_2Ph, 1C), 64.31 (CO_2**C**H_2CH_2, 15C), 63.15 (SiO**C**H_2, 1C), 34.50 (CH_2**C**$H_2CO_2CH_2$Ph, 1C), 34.28 (CH_2**C**$H_2CO_2CH_2CH_2$, 15C), 32.64 (SiOCH_2**C**H_2CH_2, 1C), 28.51 (CO_2CH_2**C**H_2CH_2, 15C), 26.13 ((**C**$H_3)_3$CSi, 3C), 25.69 (CH_2**C**H_2CH_2, 16C), 24.97 (CH_2**C**H_2CH_2, 1C), 24.74 (CH_2**C**H_2CH_2, 15C), 18.52 ($(CH_3)_3$**C**Si, 1C), -5.11 ((**C**$H_3)_2$Si, 2C). Mass Spec for $C_{109}H_{182}O_{33}Si$ Calculated: 2047.23; Found $(M+Na)^+$: 2070.25.

Acid-Terminated-16mer (14).

The procedure described above for deprotection of Benzyl ester (hydrogenation) was applied to 16mer (**13**) and the cake on celite was washed with not only hot MeOH but also with Ethyl acetate. Crude product was then purified via flash column chromatography using gradient eluent (from 1:2 Hexanes:Ethyl acetate to MeOH only) yielding **14** as a white solid. (95% yield) ^{1}H NMR (200 MHz, $CDCl_3$): δ7.80 (b, CO_2**H**, 1H), 4.04 (t, J = 6.5 Hz, CO_2C**H**$_2CH_2$, 30H), 3.55 (t, J = 6.3 Hz, C**H**$_2$OSi, 2H), 2.26 (t, J = 7.4 Hz, CH_2C**H**$_2CO_2$, 32H), 1.50 (m, CH_2C**H**$_2CH_2$, 96H), 0.83 (s, (C**H**$_3)_3$CSi, 9H), -0.02 (s, (C**H**$_3)_2$Si, 6H). ^{13}C NMR ($CDCl_3$): δ178.91 (**C**O_2H, 1C), 173.89 (**C**O_2CH_2, 1C), 173.65 (**C**O_2CH_2, 14C), 64.22 (CO_2**C**H_2CH_2, 15C), 63.04 (SiO**C**H_2, 1C), 34.39 (CH_2**C**H_2CO_2H, 1C), 34.18 (CH_2**C**$H_2CO_2CH_2CH_2$, 15C), 32.52 (SiOCH_2**C**H_2CH_2, 1C), 28.41 (CO_2CH_2**C**H_2CH_2, 15C), 26.04 ((**C**$H_3)_3$CSi, 3C), 25.59 (CH_2**C**H_2CH_2, 16C), 24.87 (CH_2**C**H_2CH_2, 1C), 24.64 (CH_2**C**H_2CH_2, 15C), 18.41 ($(CH_3)_3$**C**Si, 1C), -5.20 ((**C**$H_3)_2$Si, 2C).

Hydroxyl-Terminated-16mer (15).

The procedure described above for deprotection of TBDMS (desilylation) was applied to 16mer (**13**). Crude product was then purified via flash column chromatography using 1:2 Hexanes:Ethyl acetate as eluent yielding **15** as a white solid. (96% yield) ^{1}H NMR (200 MHz, $CDCl_3$): δ7.31 (s, Ar, 5H), 5.05 (s, $CO_2C\mathbf{H}_2Ph$, 2H), 4.00 (t, J = 6.5 Hz, $CO_2C\mathbf{H}_2CH_2$, 30H), 3.58 (b, $C\mathbf{H}_2OH$, 2H), 2.31 (t, J = 7.4 Hz, $CH_2C\mathbf{H}_2CO_2CH_2Ph$, 2H), 2.25 (t, J = 7.5 Hz, $CH_2C\mathbf{H}_2CO_2CH_2CH_2$, 30H), 1.50 (m, $CH_2C\mathbf{H}_2CH_2$, 96H). ^{13}C NMR ($CDCl_3$): δ173.78 (**C**O, 1C), 173.59 (**C**O, 14C), 173.34 (**C**O, 1C), 136.07 (Ar, CH_2-**C**, 1C) 128.60 (Ar-*meta*, 2C), 128.24 (Ar-*orhto*, *para*, 3C), 66.18 ($CO_2\mathbf{C}H_2Ph$, 1C), 64.18 ($CO_2\mathbf{C}H_2CH_2$, 15C), 62.53 ($HO\mathbf{C}H_2$, 1C), 34.16 ($CH_2\mathbf{C}H_2CO_2CH_2$, 16C), 32.38 ($HOCH_2\mathbf{C}H_2CH_2$, 1C), 28.38 ($CO_2CH_2\mathbf{C}H_2CH_2$, 15C), 25.57 ($CH_2\mathbf{C}H_2CH_2$, 15C), 25.38 ($CH_2\mathbf{C}H_2CH_2$, 1C), 24.62 ($CH_2\mathbf{C}H_2CH_2$, 16C).

32mer (16).

The procedure described above for coupling was applied to **14** and **15** but instead of 4-(Dimethylamino)pyridine (DMAP), same mole ratio (0.2 *eq*. to **14** and **15**) of 4-(Dimethylamino)pyridinium *p*-toluenesulfonate (DPTS) was used. Crude product was then purified via flash column chromatography (1:2 Hexanes:Ethyl acetate as eluent) and Preparative GPC (THF) yielding **16** as a white solid. (75% yield) ^{1}H NMR (200 MHz, $CDCl_3$): δ7.29 (s, Ar, 5H), 5.06 (s, $CO_2C\mathbf{H}_2Ph$, 2H), 4.00 (t, J = 6.4 Hz, $CO_2C\mathbf{H}_2CH_2$, 62H), 3.55 (t, J = 6.3 Hz, $C\mathbf{H}_2OSi$, 2H), 2.25 (t, J = 7.2 Hz, $CH_2C\mathbf{H}_2CO_2$, 64H), 1.50 (m, $CH_2C\mathbf{H}_2CH_2$, 192H), 0.82 (s, $(C\mathbf{H}_3)_3CSi$, 9H), -0.03 (s, $(C\mathbf{H}_3)_2Si$, 6H). ^{13}C NMR ($CDCl_3$): δ173.83 (**C**O, 1C), 173.58 (**C**O, 30C), 173.34 (**C**O, 1C), 136.09 (Ar, CH_2-**C**, 1C) 128.61 (Ar-*meta*, 2C), 128.25 (Ar-*orhto*, *para*, 3C), 66.19 ($CO_2\mathbf{C}H_2Ph$, 1C), 64.19 ($CO_2\mathbf{C}H_2CH_2$, 31C), 63.02 ($SiO\mathbf{C}H_2$, 1C), 34.38 ($CH_2\mathbf{C}H_2CO_2CH_2Ph$, 1C), 34.17 ($CH_2\mathbf{C}H_2CO_2CH_2CH_2$, 31C), 32.52 ($SiOCH_2\mathbf{C}H_2CH_2$, 1C), 28.40 ($CO_2CH_2\mathbf{C}H_2CH_2$, 31C), 26.03 ($(\mathbf{C}H_3)_3CSi$, 3C), 25.59 ($CH_2\mathbf{C}H_2CH_2$, 32C), 24.87 ($CH_2\mathbf{C}H_2CH_2$, 1C), 24.63 ($CH_2\mathbf{C}H_2CH_2$, 31C), 18.40 ($(CH_3)_3\mathbf{C}Si$, 1C), -5.21 ($(\mathbf{C}H_3)_2Si$, 2C). Mass Spec for $C_{205}H_{342}O_{65}Si$ Calculated: 3872.32 (Exact Mass), 3874.33 (Most Frequent m/z); Found $(M+2Na)^{+2}$: 1960.17.

Acid-Terminated-32mer (17).

The procedure described above for deprotection of Benzyl ester (hydrogenation) was applied to 32mer (**16**) and the cake on celite was washed with Ethyl acetate instead of hot MeOH. It yielded **17** as a white solid. (100% yield) ^{1}H NMR (200 MHz, $CDCl_3$): δ4.04 (t, J = 6.5 Hz, $CO_2C\mathbf{H}_2CH_2$, 62H), 3.55 (t, J = 6.2 Hz, $C\mathbf{H}_2OSi$, 2H), 2.26 (t, J = 7.4 Hz, $CH_2C\mathbf{H}_2CO_2$, 64H), 1.50 (m, $CH_2C\mathbf{H}_2CH_2$, 192H), 0.83 (s, $(C\mathbf{H}_3)_3CSi$, 9H), -0.01 (s, $(C\mathbf{H}_3)_2Si$, 6H). ^{13}C NMR ($CDCl_3$): δ176.74 ($\mathbf{C}O_2H$, 1C), 173.89 ($\mathbf{C}O_2CH_2$, 1C), 173.73 ($\mathbf{C}O_2CH_2$, 30C), 173.63 ($\mathbf{C}O_2CH_2$, 1C), 64.22 ($CO_2\mathbf{C}H_2CH_2$, 31C), 63.05 ($SiO\mathbf{C}H_2$, 1C), 34.41 ($CH_2\mathbf{C}H_2CO_2H$, 1C), 34.20 ($CH_2\mathbf{C}H_2CO_2CH_2CH_2$, 31C), 32.54 ($SiOCH_2\mathbf{C}H_2CH_2$, 1C), 28.42 ($CO_2CH_2\mathbf{C}H_2CH_2$, 31C), 26.05 ($(\mathbf{C}H_3)_3CSi$, 3C), 25.61 ($CH_2\mathbf{C}H_2CH_2$, 32C), 24.89 ($CH_2\mathbf{C}H_2CH_2$, 1C), 24.66 ($CH_2\mathbf{C}H_2CH_2$, 31C), 18.42 ($(CH_3)_3\mathbf{C}Si$, 1C), -5.19 ($(\mathbf{C}H_3)_2Si$, 2C).

Hydroxyl-Terminated-32mer (18).

The procedure described above for deprotection of TBDMS (desilylation) was applied to 32mer (**16**). Crude product was then purified via flash column chromatography using 1:2 Hexanes:Ethyl acetate as eluent yielding **18** as a white solid. (90% yield) ^{1}H NMR (200 MHz, $CDCl_3$): δ7.31 (s, Ar, 5H), 5.05 (s, $CO_2C\mathbf{H}_2Ph$, 2H), 4.00 (t, J = 6.5 Hz, $CO_2C\mathbf{H}_2CH_2$, 30H), 3.58 (b, $C\mathbf{H}_2OH$, 2H), 2.31 (t, J = 7.4 Hz, $CH_2C\mathbf{H}_2CO_2CH_2Ph$, 2H), 2.25 (t, J = 7.5 Hz, $CH_2C\mathbf{H}_2CO_2CH_2CH_2$, 62H), 1.50 (m, $CH_2C\mathbf{H}_2CH_2$, 192H). ^{13}C NMR ($CDCl_3$): δ173.78 (**C**O, 1C), 173.59 (**C**O,

14C), 173.34 (**C**O, 1C), 136.07 (Ar, CH_2-**C**, 1C) 128.60 (Ar-*meta*, 2C), 128.24 (Ar-*orhto*, *para*, 3C), 66.18 (CO_2**C**H_2Ph, 1C), 64.18 (CO_2**C**H_2CH_2, 15C), 62.53 (HO**C**H_2, 1C), 34.16 (CH_2**C**$H_2CO_2CH_2$, 16C), 32.38 ($HOCH_2$**C**H_2CH_2, 1C), 28.38 (CO_2CH_2**C**H_2CH_2, 15C), 25.57 (CH_2**C**H_2CH_2, 15C), 25.38 (CH_2**C**H_2CH_2, 1C), 24.62 (CH_2**C**H_2CH_2, 16C).

64mer (19).

The procedure described above for coupling was applied to **17** and **18** but instead of 4-(Dimethylamino)pyridine (DMAP), same mole ratio (0.2 *eq.* to **17** and **18**) of 4-(Dimethylamino)pyridinium *p*-toluenesulfonate (DPTS) was used. Crude product was then purified via flash column chromatography (1:2 Hexanes:Ethyl acetate as eluent) and Preparative GPC yielding **19** as a white solid. (65% yield) ^{1}H NMR (200 MHz, $CDCl_3$): δ7.29 (s, Ar, 5H), 5.06 (s, CO_2C**H**$_2$Ph, 2H), 4.01 (t, J = 6.5 Hz, CO_2C**H**$_2CH_2$, 126H), 3.55 (t, J = 6.2 Hz, C**H**$_2$OSi, 2H), 2.26 (t, J = 7.3 Hz, CH_2C**H**$_2CO_2$, 128H), 1.50 (m, CH_2C**H**$_2CH_2$, 384H), 0.83 (s, (C**H**$_3)_3$CSi, 9H), -0.02 (s, (C**H**$_3)_2$Si, 6H). ^{13}C NMR ($CDCl_3$): δ173.50 (**C**O, 64C), 136.05 (Ar, CH_2-**C**, 1C) 128.54 (Ar-*meta*, 2C), 128.18 (Ar-*orhto*, *para*, 3C), 66.12 (CO_2**C**H_2Ph, 1C), 64.11 (CO_2**C**H_2CH_2, 63C), 62.95 (SiO**C**H_2, 1C), 34.10 (CH_2**C**H_2CO_2 64C), 32.45 ($SiOCH_2$**C**H_2CH_2, 1C), 28.34 (CO_2CH_2**C**H_2CH_2, 63C), 25.97 ((**C**$H_3)_3$CSi, 3C), 25.53 (CH_2**C**H_2CH_2, 64C), 24.57 (CH_2**C**H_2CH_2, 64C), 18.33 ($(CH_3)_3$**C**Si, 1C), -5.27 ((**C**$H_3)_2$Si, 2C). Mass Spec for $C_{397}H_{662}O_{129}Si$ Calculated: 7522.50 (Exact Mass), 7526.51 (Most Frequent m/z); Found $(M+3Na)^{+3}$: 2531.76.

Dimer-DCC-Adduct (20).

^{1}H NMR (200 MHz, $CDCl_3$): δ7.00 (b, N**H**, 1H), 4.01 (t, J = 6.6 Hz, CO_2C**H**$_2CH_2$, 2H), 3.90 (b, NC**H**$(CH_2)_2$, 1H), 3.66 (b, NC**H**$(CH_2)_2$, 1H), 3.56 (t, J = 6.4 Hz, C**H**$_2$OSi, 2H), 2.37 (t, J = 7.4 Hz, CH_2C**H**$_2CO_2$, 2H), 2.25 (t, J = 7.4 Hz, CH_2C**H**$_2$CON, 2H), 1.50 (m, C**H**$_2$, 32H), 0.84 (s, (C**H**$_3)_3$CSi, 9H), -0.01 (s, (C**H**$_3)_2$Si, 6H). ^{13}C NMR ($CDCl_3$): δ173.98 (CH_2**C**O_2, 1C), 173.50 (CH_2**C**ON, 1C), 154.20 (N**C**ON, 1C), 64.21 (CO_2**C**H_2CH_2, 1C), 63.10 (SiO**C**H_2, 1C), 56.00 (N**C**H, 1C), 49.91 (NH**C**H, 1C), 35.68 (CH_2**C**H_2CON, 1C), 34.47 (CH_2**C**H_2CO_2, 1C), 32.87 (NHCH(**C**$H_2CH_2)_2$, 2C), 32.61 ($SiOCH_2$**C**H_2CH_2, 1C), 31.04 (NCH(**C**$H_2CH_2)_2$, 2C), 28.65 (CO_2CH_2**C**H_2CH_2, 1C), 26.10 ((**C**$H_3)_3$CSi, 3C), 26.46-24.88 (CH_2**C**H_2CH_2, 10C), 18.48 ($(CH_3)_3$**C**Si, 1C), -5.14 ((**C**$H_3)_2$Si, 2C). Mass Spec for $C_{31}H_{58}O_5N_2Si$ Calculated: 566.41; Found $(M+Na)^+$: 589.42.

Acid-Hydroxyl-Terminated-32mer (21).

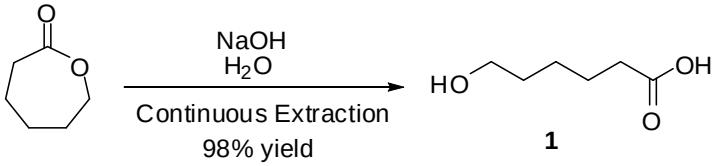
The procedure described above for deprotection of Benzyl ester (hydrogenation) was applied to Hydroxyl-Terminated-32mer (**18**) but instead of Ethyl acetate, THF was used as solvent and the cake on celite was washed with THF and $CHCl_3$. The both-end-deprotected 32mer (**20**) was yielded as a white solid. (56% yield) ^{1}H NMR (200 MHz, $CDCl_3$): δ4.02 (t, J = 6.5 Hz, CO_2C**H**$_2CH_2$, 62H), 3.60 (b, C**H**$_2$O**H**, 3H), 2.26 (t, J = 7.3 Hz, CH_2C**H**$_2CO_2$, 64H), 1.50 (m, CH_2C**H**$_2CH_2$, 192H). ^{13}C NMR ($CDCl_3$): δ176.56 (**C**O_2H, 1C), 173.67 (**C**O_2CH_2, 31C), 64.25 (CO_2**C**H_2CH_2, 31C), 62.63 (HO**C**H_2, 1C), 34.22 (CH_2**C**$H_2CO_2CH_2CH_2$, 31C), 33.68 (CH_2**C**H_2CO_2H, 1C),32.40 ($HOCH_2$**C**H_2CH_2, 1C), 28.44 (CO_2CH_2**C**H_2CH_2, 31C), 25.62 (CH_2**C**H_2CH_2, 32C), 24.67 (CH_2**C**H_2CH_2, 32C). Mass Spec for $C_{192}H_{322}O_{65}$ Calculated: 3668.19 (Exact Mass), 3670.57 (Most Frequent m/z); Found $(M+2Na)^{+2}$: 1857.24.

3-3. Results and Discussion

3-3-1. Monomer Synthesis

Initially, the synthesis of the monomer (6-Hydroxycaproic acid) (**1**) was undertaken by using solid phase acid catalysts such as Amberlite (IR-120H) or Dowex (50Wx2-100) but they gave only mixtures of the monomer and oligomers. On the other hand, NaOH as a strong base catalyst was found to be very efficient for ring opening hydrolysis of ε-Caprolacton (Scheme 1).

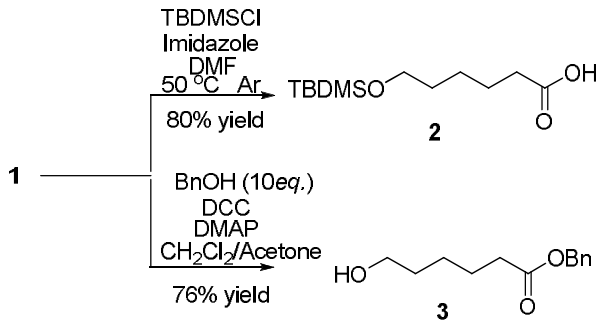
Furthermore, we found that continuous extraction using a convertible liquid/liquid continuous extractor after adjusting the pH to about 2 gave us 98% yield of pure **1** though normal extraction using a separatory funnel yielded only 57% of **1** even after extraction with Diethyl ether (4 times) and CH_2Cl_2 (4 times) because of the high solubility of **1** in H_2O.



Scheme 1. Synthetic route to 6-Hydroxycaproic acid (**1**).

The hydroxyl group of **1** was protected with *t*-Butyldimethylsilyl (TBDMS) ether[8, 9] yielding **2** (80%) and its carboxylic acid group was protected with Benzyl (Bn) ester yielding **3** (76%) (Scheme 2).

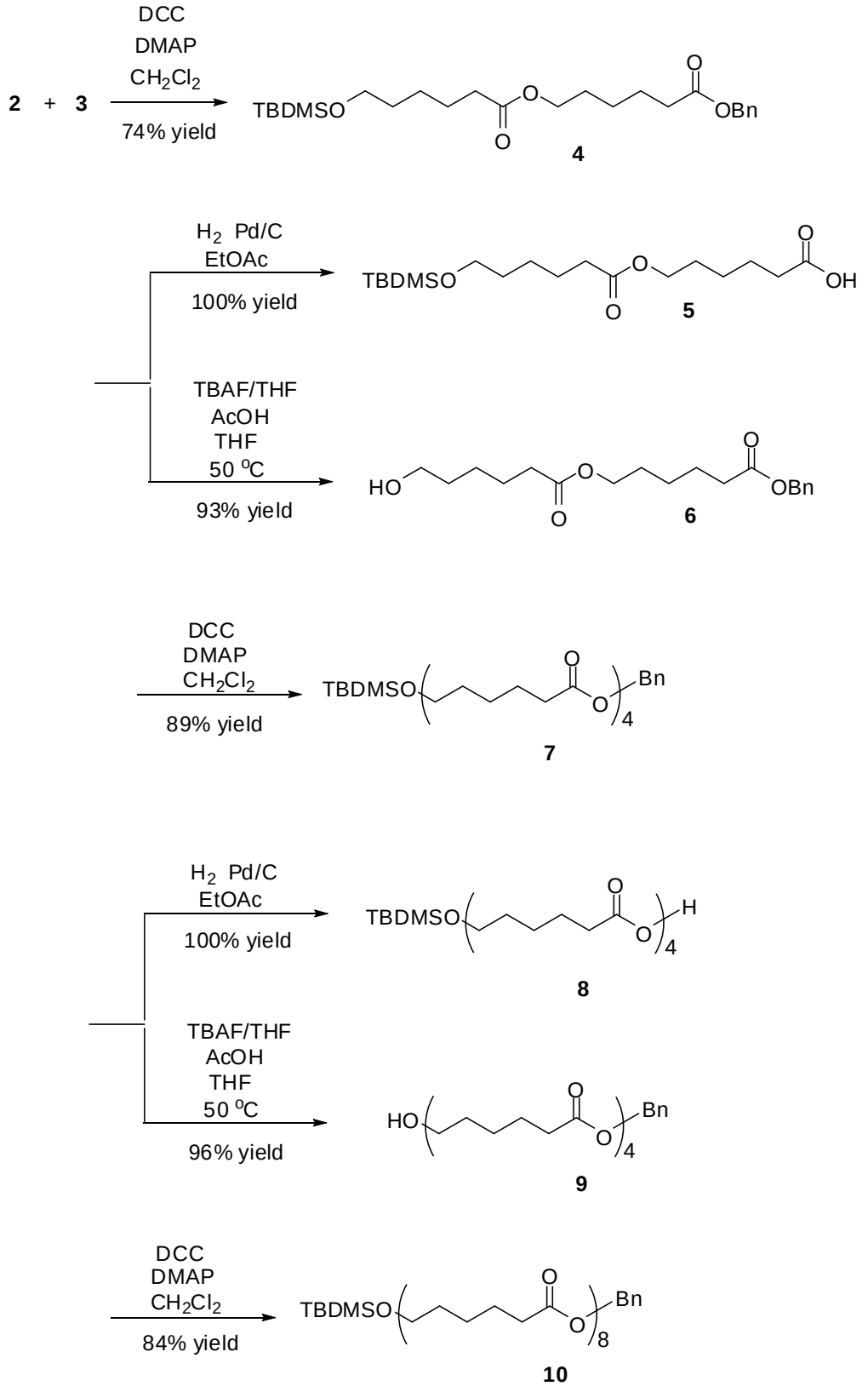
To minimize the formation of byproducts in the synthesis of the benzyl ester derivative (**3**), the starting material (**1**) was added dropwise to the reaction mixture containing excess amount of BnOH and the coupling reagents.

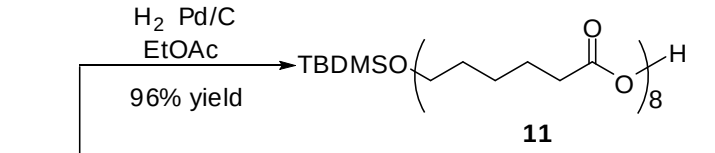


Scheme 2. Attachment of protective groups onto 6-Hydroxycaproic acid (**1**).

3-3-2. Oligomer/Polymer Synthesis

All the coupling and deprotection reactions to synthesize up to 64mer (**19**) were straightforward and resulted in high yields (usually over 95% yields for deprotection reactions and 70-90% yields for coupling reactions) (Scheme 3 and Figure 1).





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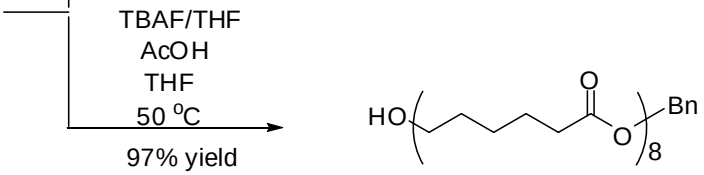

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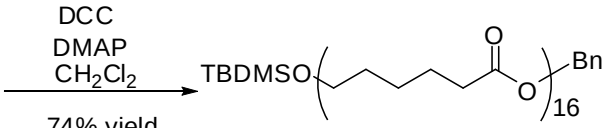

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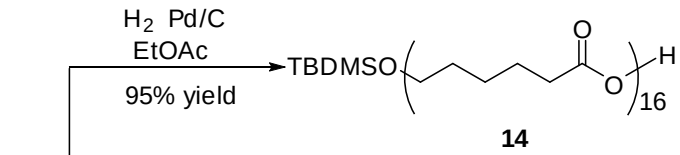

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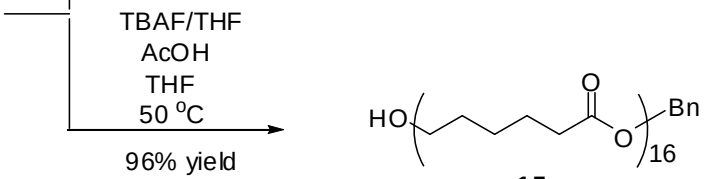

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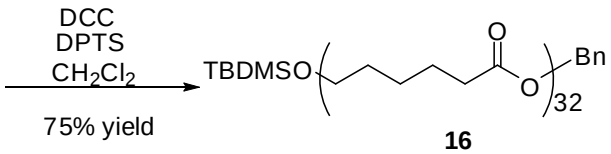

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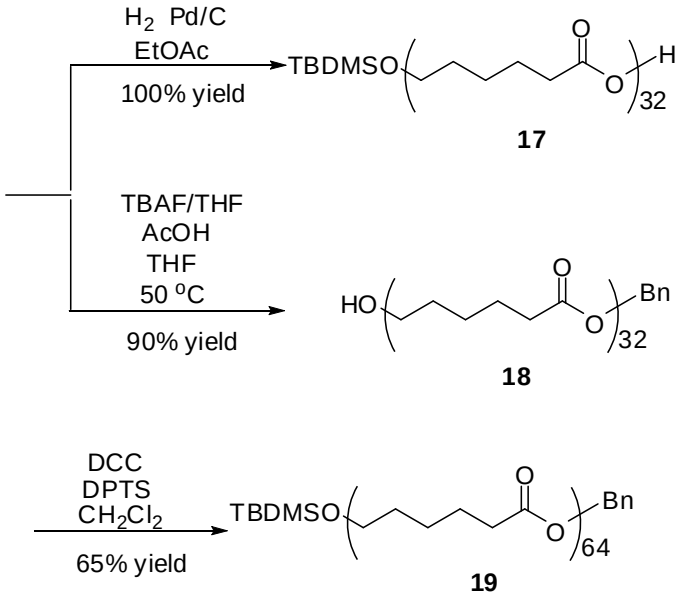


Scheme 3. Synthetic route to ε-Caprolactone 64mer (**19**).

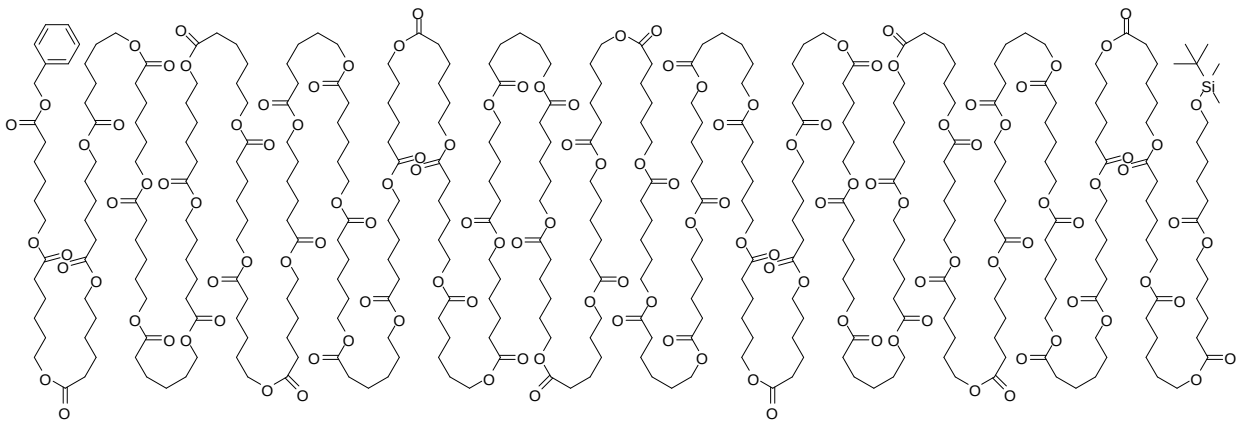
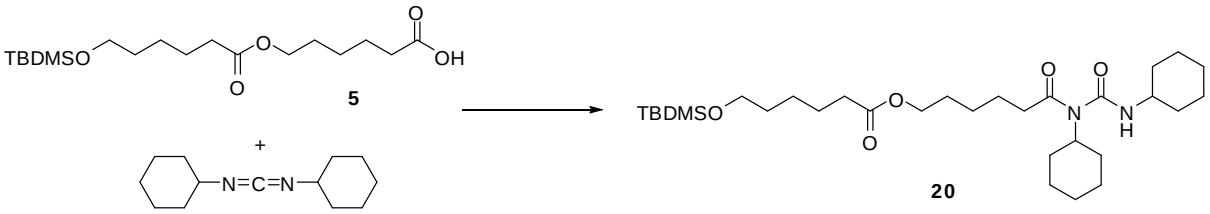


Figure 1. ε-Caprolactone 64mer (**19**) (Molecular Formula: $C_{397}H_{662}O_{129}Si$, MW = 7522.50).

As previously reported[7], carbodiimide esterifications are always slightly accompanied by a side reaction which converts carboxylic acids to unreactive N-acylureas (DCC-Adducts). In our case also, this kind of side reactions were observed (Scheme 4; Dimer-DCC-Adduct (**20**) is depicted).



Scheme 4. Formation of DCC-Adduct.

In case of higher molecular weight polymer syntheses (especially in cases of 32mer and 64mer syntheses), this side reaction was rather problematic because it was extremely difficult to separate DCC-Adducts from our products by means of normal flash column chromatography. And it surely affects the yields of the steps ahead.

But fortunately, use of 4-(Dimethylamino)pyridinium *p*-toluenesulfonate (DPTS) instead of DMAP suppressed this side reaction dramatically. Also, in case of higher molecular weight polymer syntheses (i.e. 32mer or 64mer syntheses), the difference of the molecular weights of the target molecules and undesired DCC-Adducts are quite large so preparative GPC was found to be a good additional tool to get rid of the DCC-Adducts.

3-3-3. Analytical Studies of Oligomers/Polymers

ε-Caprolactone oligomers/polymers' purities and molecular weights were evaluated by means of ^{1}H, ^{13}C-NMR, Mass Spectroscopy (ESI^{+}/TOF) combined with Matrix Assisted Laser Desorption/Ionization (MALDI) and Size Exclusion Chromatography (SEC).

Because of the high molecular weights of 32mer and 64mer, these two polymers' exact molecular weights were calculated using their doubly and triply charged peaks of the ESI^{+}/TOF results, respectively. ESI^{+}/TOF result of 16mer (**13**) is depicted in Figure 2 as an example.

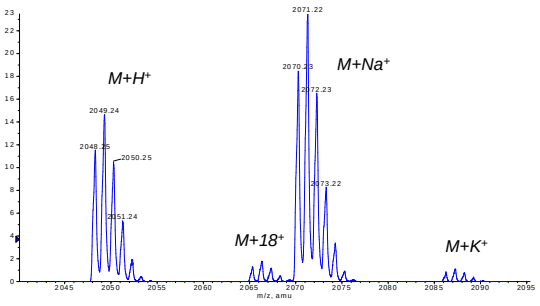


Figure 2. Mass Spec. (ESI^{+}/TOF) result of 16mer (**13**).

Both MALDI and SEC results (Figure 3, 4, and 5) also showed all the oligomers/polymers are well monodisperse and pure.

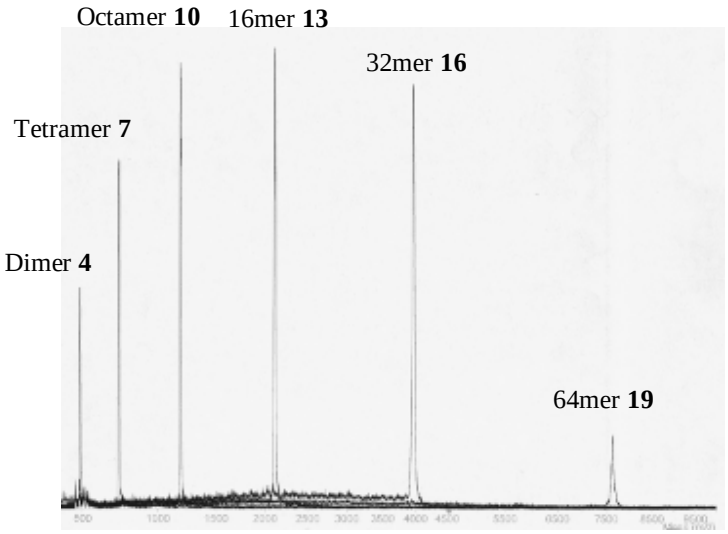


Figure 3. MALDI result (Matrix; Dithranol, Cationating reagent; NaOTf).

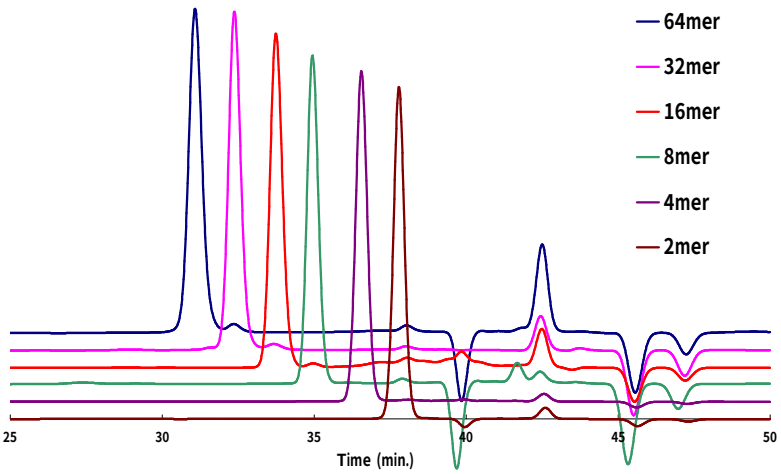


Figure 4. SEC results of ε-Caprolactone oligomers/polymers.

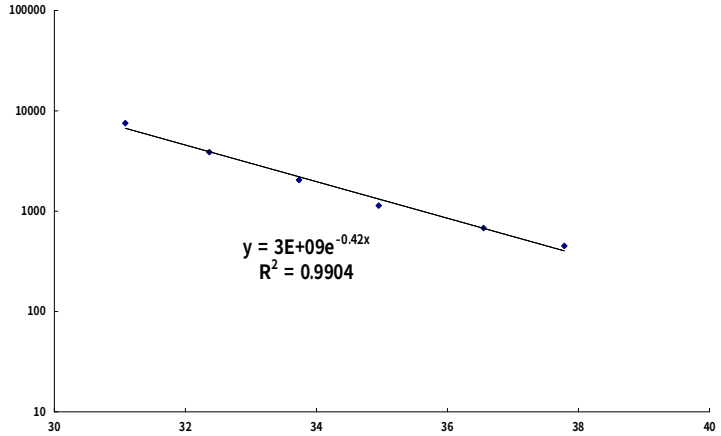
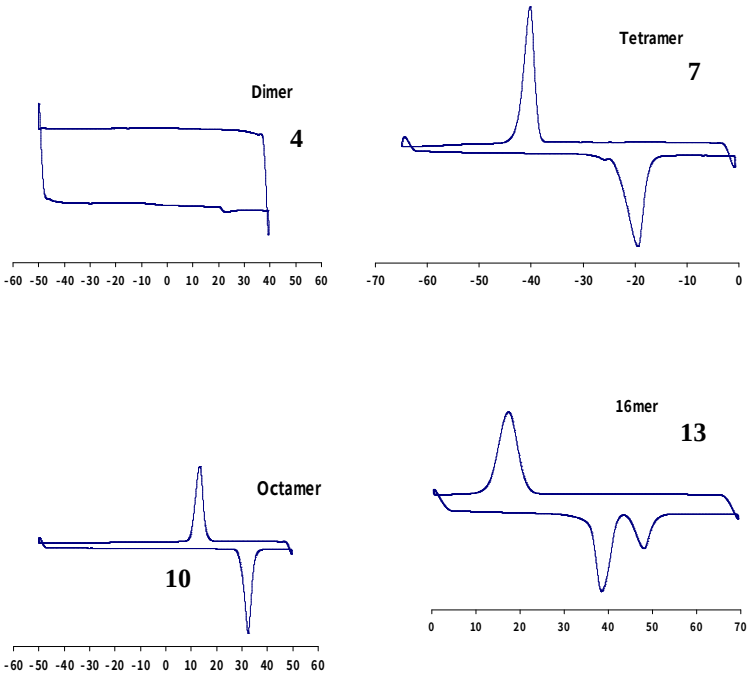


Figure 5. Plot of the molecular weights (logarithmic) of ε-Caprolactone oligomers/polymers against retention time of SEC measurement.

DSC measurements (Figure 6) showed melting transitions for the tetramer and bigger oligomers. The melting points increased with molecular weights and reached 57 °C for the 64mer (**19**) which is comparable to the melting point of high molecular weight Poly(ε-caprolactone) (PCL) (see below). Two melting peaks appeared for 16mer (**13**) and bigger oligomers indicate the presence of two crystalline sizes, which means that at the first melting peak, crystallization into larger structures takes place while the larger crystal melts completely at the second melting point. This kind of behavior has previously been reported on semi-crystalline aliphatic polycarbonates, too[10]. The peaks of the 32mer (**16**) and 64mer (**19**) merged and formed a single bimodal peak.



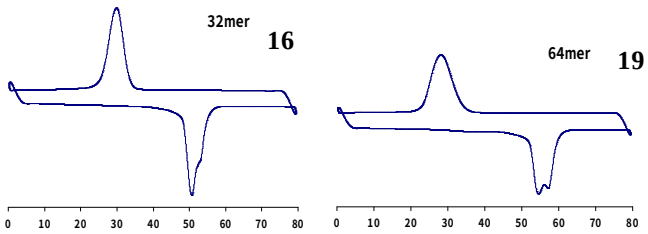


Figure 6. DSC data of end-protected ε-Caprolactone oligomers.

SAXS measurements at room temperature (Figure 7(a), 7(b) and Table 1) indicate the presence of lamellae structure in cases of Octamer (**10**) through 64mer (**19**). And their distance (D)s were very close to the theoretical molecular lengths for Octamer (**10**) and 16mer (**13**), indicates that the chains are fully extended in each lamellae layer in these two cases. On the other hand, 32mer (**16**) and 64mer (**19**) showed regular features of almost one half and one quarter of their respective theoretical lengths, suggesting that a 32mer (**16**) chain is folded once at the center and that a 64mer (**19**) cahin is folded twice or three times in each lamellae layer (Figure 8).

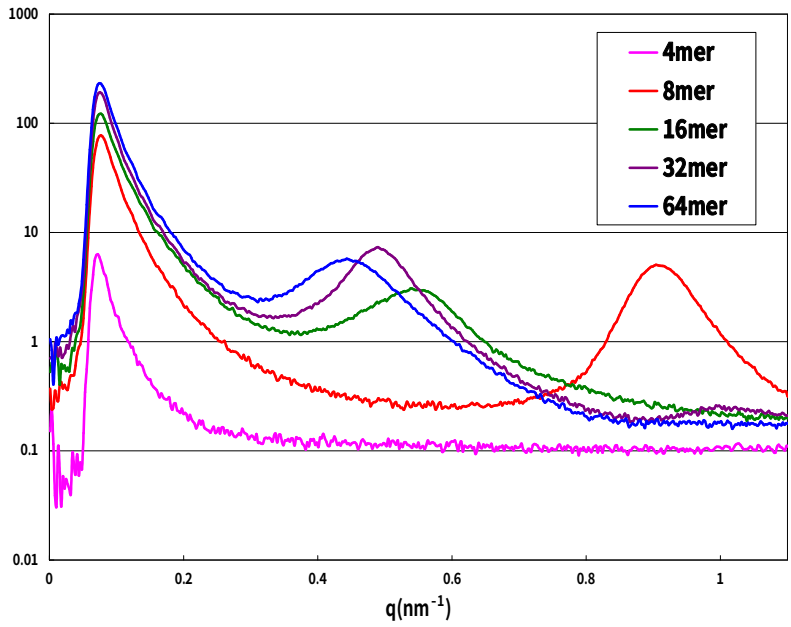


Figure 7(a). Ultra-SAXS spectra of Tetramer (**7**) through 64mer (**19**) at room temperature.

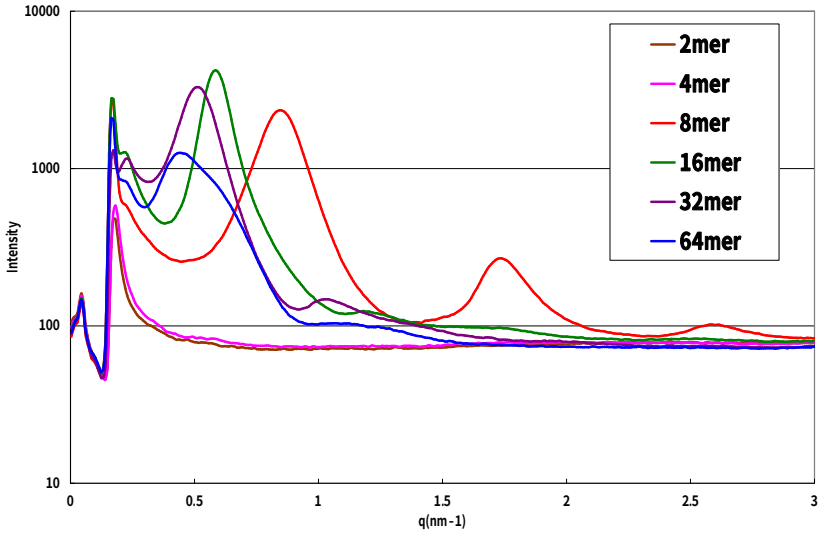
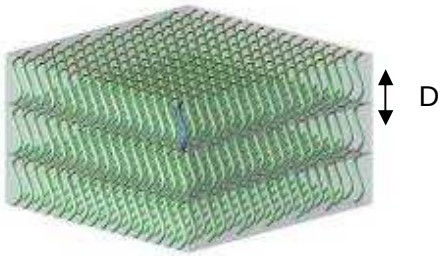


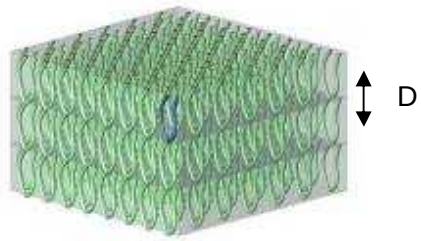
Figure 7(b). Intermediate-SAXS spectra of Dimer (**4**) through 64mer (**19**) at room temperature.

	Dimer	Tetramer	Octamer	16mer	32mer	64mer
Calculated Molecular	2nm	4nm	7nm	12nm	23nm	46nm
D	-	-	7nm	11nm	13nm	14nm

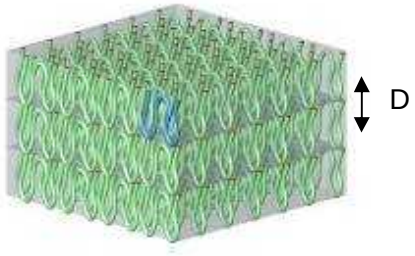
Table 1. Calculated molecular lengths of oligomers/polymers using ChemSketch (Advanced Chemistry Development, Inc.) and distance D calculated using the equation ($D = 2\pi / q$) based on the SAXS results (Figure 7(a) and 7(b)).



Octamer (**10**) and 16mer (**13**)



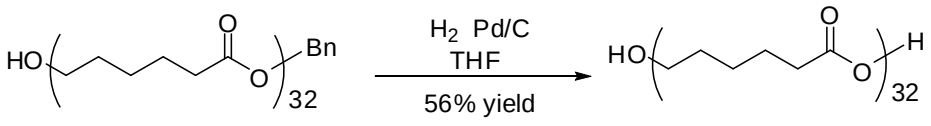
32mer (**16**)



64mer (**19**)

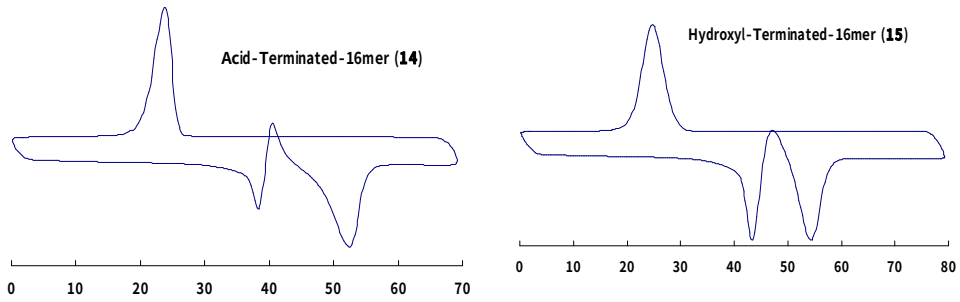
Figure 8. Proposed crystal structure of Octamer (**10**) through 64mer (**19**).

Also, we synthesized both-ends-deprotected 32mer (**21**) (Scheme 5) and conducted analytical experiments of deprotected samples of 16mers (**14**, **15**) and 32mers (**17**, **18**, **21**) together with commercially available Poly(ε-caprolactone) (Mw=14000, Mn=10000 from Aldrich).



18 **21**

Scheme 5. Synthesis of both-ends-deprotected 32mer (Acid-Hydroxyl-Terminated-32mer) (**21**).



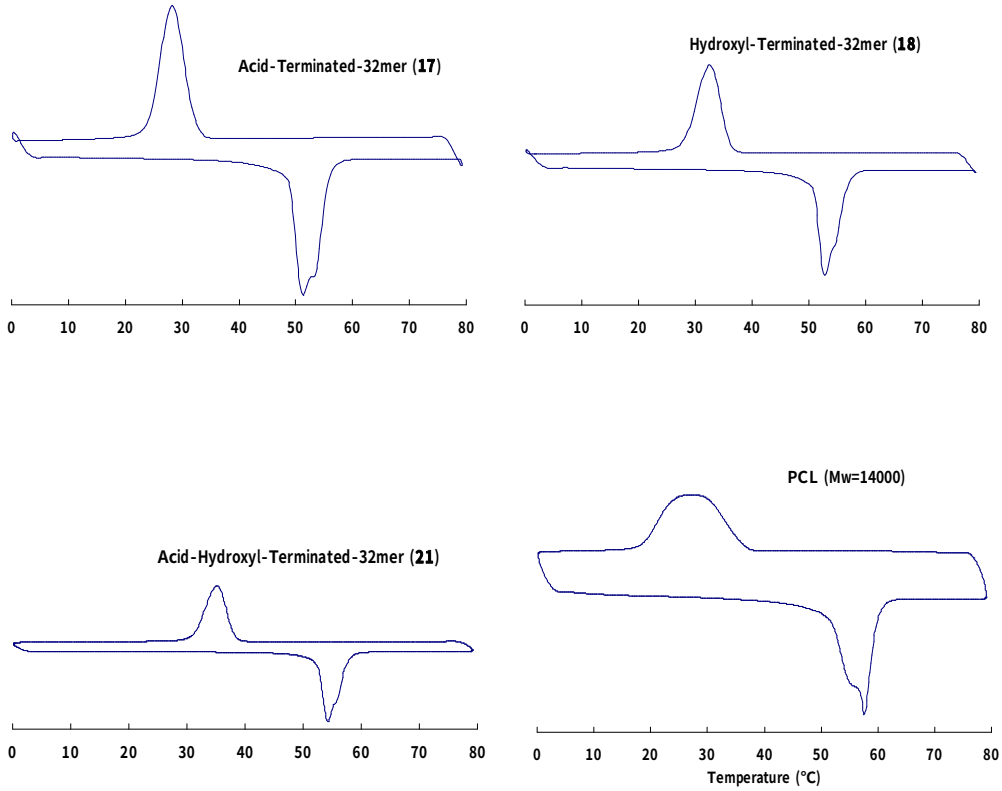


Figure 9. DSC data of ends-deprotected ε-Caprolactone oligomers and Poly(ε-caprolactone).

From DSC data (Figure 9), ends-deprotected 16mers again gave bimodal melting peaks and we found that melting points became slightly higher in the order of Oligomer < Acid-Terminated-Oligomer < Hydroxyl-Terminated-Oligomer < Acid-Hydroxyl-Terminated-Oligomer, and 51 ℃ for 32mer (**16**) became 54 ℃ for Acid-Hydroxyl-Terminated-32mer (**21**). This suggests that hydrogen bonding contributes to some extent to the increase of the thermal stability of crystals.

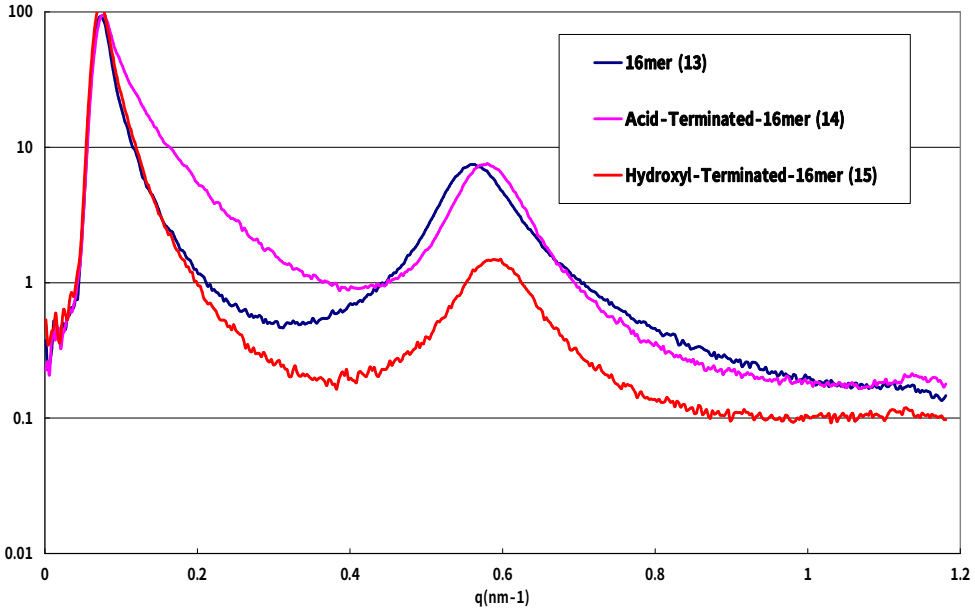


Figure 10. Ultra-SAXS spectra of 16mers at room temperature.

	16mer (**13**)	Acid-Terminated-16mer (**14**)	Hydroxyl-Teminated-16mer (**15**)
Calculated Molecular Length	12nm	12nm	12nm
D	11nm	11nm	11nm

Table 2. Calculated molecular lengths of 16mers using ChemSketch (Advanced Chemistry Development, Inc.) and distance Ds calculated using the equation ($D = 2\pi / q$) based on the SAXS results.

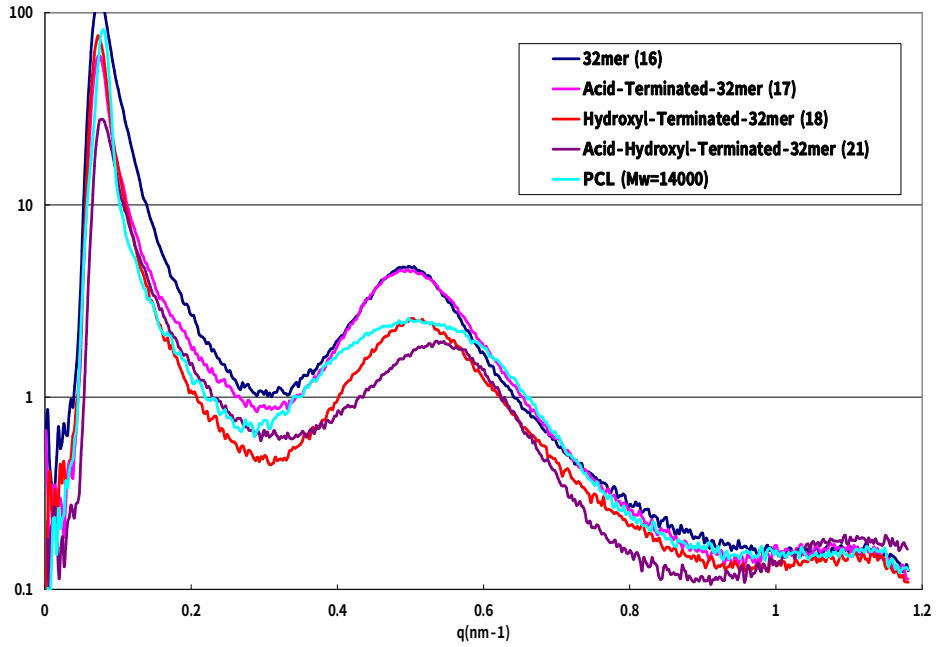


Figure 11. Ultra-SAXS spectra of 32mers and commercial PCL at room temperature.

	32mer (**16**)	Acid-Terminated-32mer (**17**)	Hydroxyl-Teminated-32mer (**18**)	Acid-Hydroxyl-Terminated-32mer (**21**)	PCL
Calculated Molecular Length	23nm	23nm	23nm	22nm	82nm
D	13nm	12nm	12nm	12nm	13nm

Table 3. Calculated molecular lengths of 32mers and commercial PCL using ChemSketch (Advanced Chemistry Development, Inc.) and distance Ds calculated using the equation ($D = 2\pi / q$) based on the SAXS results.

From SAXS data of ends-deprotected-16mers and 32mers (Figure 10, 11, Table 2, 3), in both cases, lamellae thicknesses (D) did not change regardless of their chain ends. And higher molecular weight Poly(ε-caprolactone) (PCL) was found to have lamellae structure with a layer thickness of 12 nm which is very similar to those of both-end-protected 16mer (**13**) through 64mer (**19**). This indicates a interesting fact that even in case of very long (high molecular weight) Poly(ε-caprolactone), it consists a lamellae structure with the thickness of about 16 caprolactone repeating units at room temperature.

Also, SAXS equipped with a heating stage was used to investigate if the first melting point of the DSC spectra especially for 16mer really means the formation of larger crystal structures or not. The data of 16mer (**13**) in Figure 12 and Table 4 show significant increase in feature size as the temperature increases. And the distance D at 49 ^{o}C became roughly 1.5 times bigger than that at 25 ^{o}C, which confirmed the formation of bigger crystals after the first melting peak.

One of the explanations for this behavior is, we theorize that there happened a half space shift between neighboring molecules as the temperature increased (Figure 13).

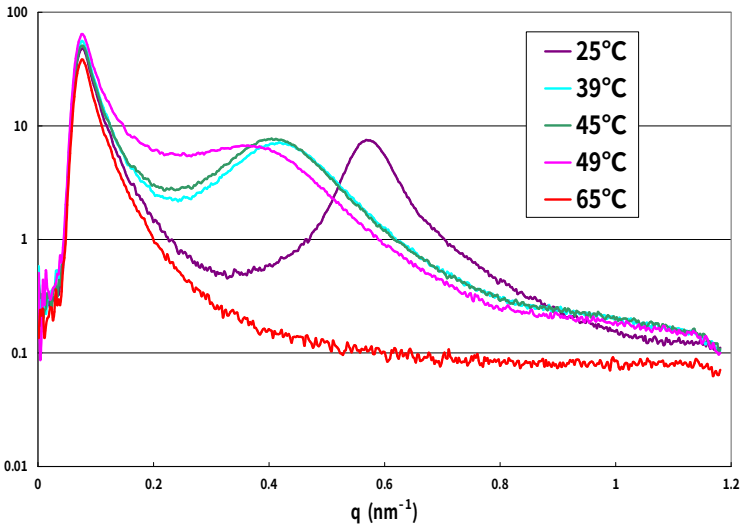


Figure 12. SAXS spectra of 16mer (**13**) at various temperature.

16mer	25°C	39°C	45°C	49°C	65°C
D	11nm	15nm	15nm	17nm	-

Calculated Molecular Length = 12nm

Table 4. Distance D calculated using the equation (D = 2π / q) based on the SAXS results of 16mer (**13**).

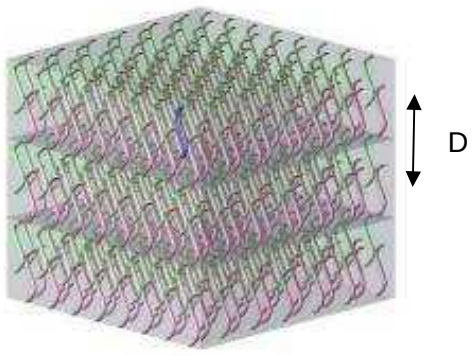


Figure 13. Proposed crystal structure of 16mer (**13**) at around 40 °C to 50 °C. (For clarification, we used different colors but all of them stand for the same molecule.)

Also from TGA data, we found that longer chain length give higher decomposition temperature and protective groups on the chain ends give slightly higher decomposition temperature, too (Figure 14, 15). Of particular note was the observation that all of the 32mer samples, irrespective of the end groups, were significantly more stable than the

commercial Poly(ε-caprolactone) (MW = 14,000, PDI. = 1.1). The onset of decomposition was lower for the polydisperse commercial sample (poorly defined end groups) being ca. 100°C less stable than the monodisperse derivatives. Interestingly, the 32mer with the lowest thermal stability was the hydroxyl-terminated derivative (**18**) followed by both the acid-terminated oligomer (**17**) and the doubly deprotected, acid-hydroxyl-terminated-32-mer (**21**) (Figure 15). From these results, it is apparent that the presence of a hydroxyl chain end leads to decreased thermal stability, presumably due to the occurrence of chain backbiting and associated depolymerization. The presence of a terminal carboxylic acid group is also destabilizing but to a decreased degree when compared to a hydroxyl group while the polydisperse nature together with possible impurities in the commercial PCL dramatically decreasing its thermal stability. This may indicate that there is a high possibility that end-capping might also change the biodegradability of the material.

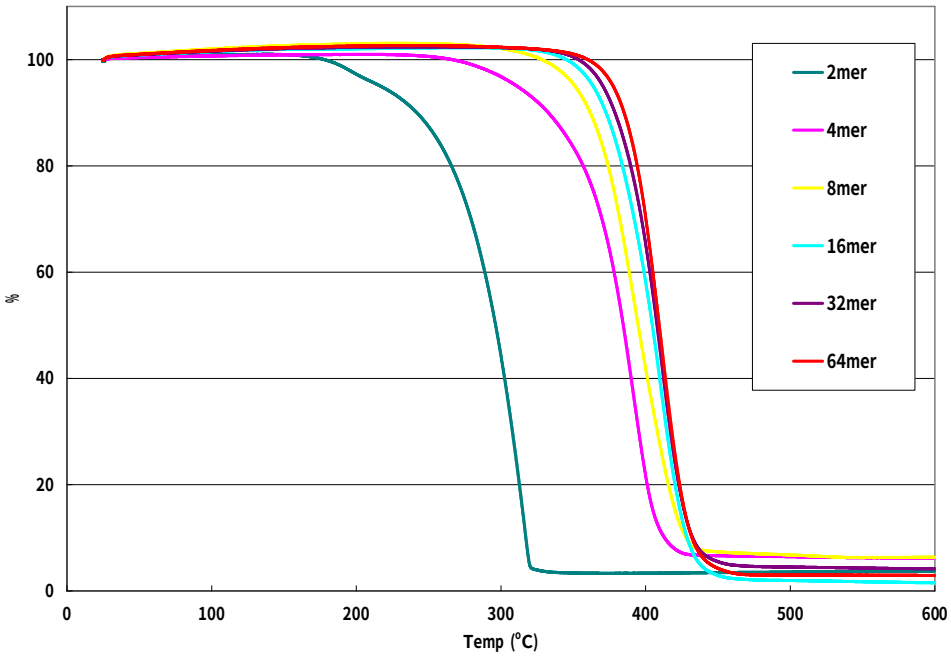


Figure 14. TGA data of Dimer (**4**) through 64mer (**19**).

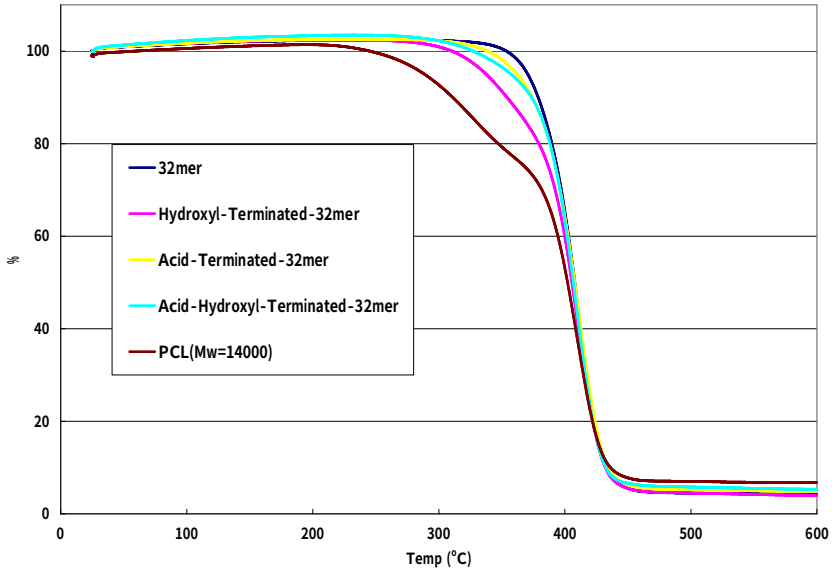


Figure 15. TGA data of 32mer (**16**), ends-deprotected 32mers (**17**, **18**, **21**), and commercial PCL.

A similar strong dependence of crystal shape on molecular weight and polydispersity of the sample was observed by atomic force microscopy (AFM). Analysis of the oligomers showed a systematic increase in crystallite size with monomer length for thin films under both normal spin casting conditions and after identical thermal annealing profiles. As can be seen in Figure 16, the size of the crystallites increases from ca. 30 microns for the 32mer (**16**) to over 100 microns for the 64mer (**19**). Interestingly enough, increasing the molecular weight from 7,318 for the 64mer to a MW of 14,000 for the commercial PCL sample gave significantly different results with a multitude of small, ca. 10 micron, crystallites being formed. This study again demonstrates the significant difference in physical properties and behavior between the well-defined oligomers and low polydispersity, commercial PCL materials of comparable molecular weight, and a systematic, in-depth examinination of the thin film properties of these materials is in progress.

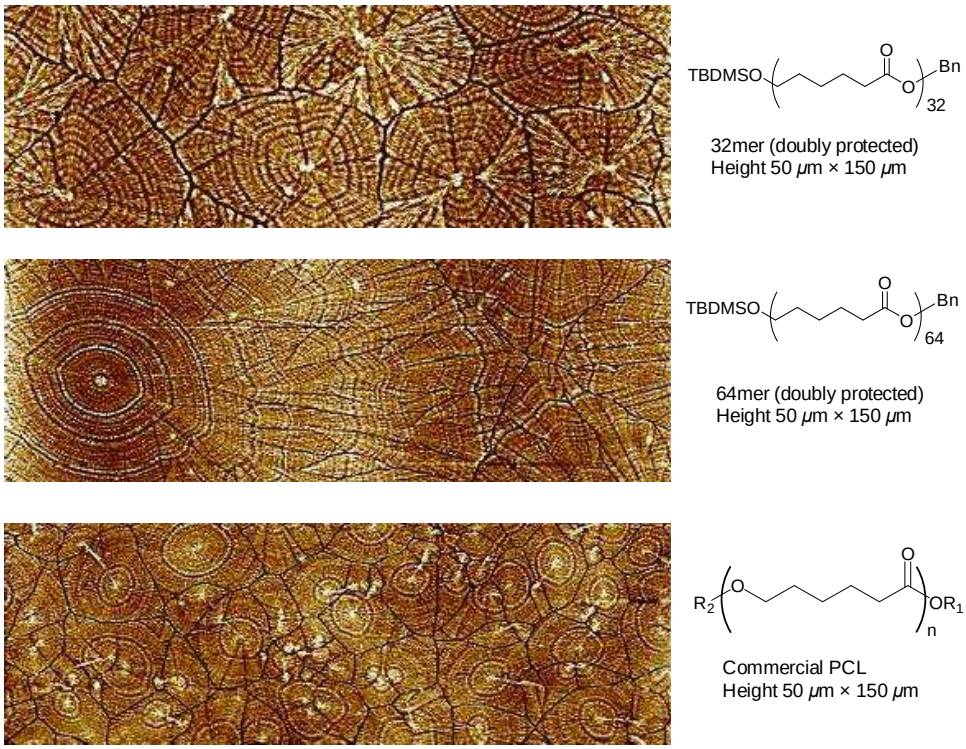


Figure 16. Sequence of TM-AFM images for crystallized thin films of the 32mer (**16**), 64mer (**19**), and a commercial PCL sample of MW = 14,000. Scan size is 50 microns x 150 microns.

3-4. Summary

We have reported the synthesis of ε-Caprolactone oligomers/polymers up to 64mer by using an iterative divergent-convergent approach which is called 'Exponential Growth Strategy[1]'. All the syntheses are straightforward and gave excellent yields.

The obtained high molecular weight oligomers/polymers are semi-crystalline and the melting point increased as the chain length became long. The thermal analysis showed bimodal melting peaks and SAXS measurements confirmed an increase in crystal feature size by crystalline growth during heating. SAXS data also suggested that the polymer chains fold and form crystalline lamellae structure that is of 16 repeating units in thickness. These oligomers will allow further insight into the crystallization behavior and biodegradability of polyesters includes Poly(ε-caprolactone) etc. Furthermore, syntheses of functionalized ε-Caprolactone oligomers/polymers at the position of C-$2^{4(p)}$ or C-$4^{4(o)}$ with biologically active groups using 'Click' chemistry[11] are underway.

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CHAPTER 4

'Molecularly Defined (L)-Lactic Acid Oligomers and Polymers: Synthesis and Characterization'

4-1. Introduction

As we discussed in Chapter 2 and 3, a method called 'Exponential Growth Strategy[1]' has been found to be a very powerful tool to synthesize precisely size tuned organic oligomers/polymers. On the other hand, the last 30 years, a lot of attention has been paid onto synthetic polymers for biomedical applications including surgery and medicine[2]. Especially in the research area of targeted drug/gene delivery and diagnostic agents, well-defined macromolecules and/or nano-scale objects are topics of great interest since they can be utilized for carrying payloads, cell targeting, and in *vivo* imaging.

As well as these, the demand for biodegradable polymers are nowadays becoming higher and higher. As well known, two factors have been making biodegradable polymers attractive. One factor is the environmental and economical concerns associated with waste disposal. And another is the rising cost of petroleum production resulting from the depletion of the most common natural resources in the world.

One of the most promising polymers which may be a substitute for the fossil fuel-based polymers is Poly((L)-lactic acid) or Poly(lactide) as it is readily hydrolyzed to constituent hydroxyl acids which are eliminated by general metabolic pathways[3]. And polymers obtained from Lactic acid have already started being used in a number of biomedical applications, such as sutures, stents, dialysis media and drug delivery devices. Also, (L)-Lactic acid oligomers are known for their antitumor activities.

Traditionally, Poly(lactide) has been prepared via ring opening polymerization of cyclic lactide dimers using a catalyst such as Stannous octanoate but now it can be prepared from renewable resources, such as corn starch or sugarcane and is commercially available on a large scale from a variety of manufacturers. There are numerous reports of functional polyesters prepared from monomers by both condensation and ring-opening polymerization techniques[4] including Poly(lactide)s and their derivatives. And also there are a lot of reports on the syntheses of finely size tuned molecules[5] by stepwise procedures. However, to the best of our knowledge, only very limited number of successful synthetic techniques have been reported to prepare precisely size tuned monodisperse oligomers/polymers based on polyesters except for some recently issued patents and a literatures using a separation technique by preparative HPLC of the polydisperse oligomers[6]. Syntheses of these well defined polymers allow their physical and chemical properties to be precisely controlled, which is an essential strategy for further advances in these fields.

Herein, we report strategies for preparing mono-disperse (L)-Lactic acid oligomers/polymers up through 64mer and the detailed studies of the crystallinity and thermal properties of these monodisperse oligomers/polymers.

4-2. Experimental Section

Materials.

4-(Dimethylamino)pyridinium *p*-toluenesulfonate (DPTS) was synthesized according to the previously reported procedure[7]. All the other chemicals and solvents were purchased from Aldrich, of reagent grade, and used without further purification. All reactions were carried out under ambient conditions unless specified.

General Procedures/Characterization.

Freeze drying was conducted using LABCONCO 1 Liter Benchtop Freeze Dry Systems. Analytical TLC was performed on commercial Merck Plates coated with silica gel GF254 (0.24 mm thick). Silica gel for flash column chromatography was Merck Kieselgel 60 (230-400 mesh, ASTM). ^{1}H-NMR and ^{13}C-NMR measurements were performed on a Bruker AC 500 and/or AC 200 spectrometer at room temperature. $CDCl_3$ was used as NMR solvent if not otherwise specified. Matrix Assisted Laser Desorption/Ionization (MALDI-TOF-MS) was carried out at room temperature on DYNAMO THERMO BIOANALYSIS using Dithranol in THF as the matrix and Sodium trifluoroacetate in THF as the cationating agent. Size exclusion chromatography (SEC) was carried out at room temperature on a Waters Alliance HPLC System (Waters 2695 Separation Module) connected to Waters Styragel® HR columns (0.5, 2, 4, and 5 INT'L HAZA) using THF as eluent (flow rate: 1 mL/min). A Waters 2414 differential refractometer and a 2996 photodiode array detector were employed. The molecular weights of the polymers were calculated relative to linear polystyrene standards. ThermoGravimetric Analysis was conducted using METTLER TGA/sDTA851e under N_2 atmosphere. Differential Scanning Calorimetry (DSC) measurements were performed with a TA Instruments DSC 2920 and a ramp rate of 5 degrees per minute with data usually collected during the third cycle in the selected temperature ranges if not otherwise specified. Calibrations were made using indium as a standard for both temperature transitions and the heats of fusion. Melting transition temperatures (T_m) were determined as the peak maxima of the transition. Small Angle X-ray Scattering measurements were carried out in quartz capillary cells using Ultra-SAXS (X-ray Source; Fine focus (0.2 mm) Rigaku rotationg anode generator, Wavelength; 1.54 Å, Sample to Detector Distance; 172.5 cm, Interface; Bruker SAXS software and SPEC) and Intermediate-SAXS (X-ray Source; 18 kW Rigaku rotationg anode generator, Wavelength; 1.54 Å, Sample to Detector Dintance; 75.8 cm, Interface; SPEC). Also, WAXS (Four Circle Wide Angle X-ray Spectrometer: X-ray Source; 18 kW Rigaku rotationg anode generator, Wavelength; 1.54 Å, Monochromator; OSMIC Confocal Maxflux focusing multilayer mirror, Detector; MAR345 Image Plate Area Detector, Goniometer; Large Huber 4-circle, Typical range of length scale probed; 2 Å-20 Å, Software for data collection; SPEC, Software for data processing; CPLOT and Fit2D) was used. UV-VIS measurements were performed in quartz cells (inside dimension; 1 cm) using PERKIN ELMER Lambda20. Optical rotation and chirality were evaluated using JASCO Digital Polaqrimeter DIP-1000 (Cell length; 100 mm, Light source; Na 589 nm) and OLIS RSM Circular Dichroism Spectrometer at room temperature, respectively. Single Crystal Diffraction measurements were conducted using Bruker 3-axis platform diffractometer (X-ray Source and Optics; Sealed 2.4 kW Mo tube, graphite monochromator, Detector; SMART 1000 CCD detector, Cryostream System; OXFORD-600, operating temperature from 90 to 300 K, Software; Windows version SMART, Saint, SHELXTL, Cambridge Structure Database, Microscope: Nikon SMZ-U, magnification range 7X -75X, Sample Requirement; Typically 0.1-0.3 mm single crystal).

Benzyl (L)-lactate (2).

A 500 mL round bottom flask was charged with 20.57 g (0.18 mol) of Sodium L-lactate (**1**), 30.85g (0.18 mol) of Benzyl bromide, 0.10 g of 15-Crown-5, and 170 mL of DMF. This reaction mixture was stirred overnight at 100 ^{o}C. After the reaction, most of DMF was removed by reducing the pressure at 80 ^{o}C. Crude product was then purified via flash column chromatography using 1:1 Hexanes:Ethyl acetate as eluent yielding 29.98 g (91% yield) of **2** as a clear slightly yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ7.37 (m, Ar, 5H), 5.22 (s, $CO_2C\mathbf{H}_2Ph$, 2H), 4.32 (m, $C\mathbf{H}_2OH$, 2H), 2.84 (b, **H**O, 1H), 1.43 (d, J = 7.0 Hz, $C\mathbf{H}_3$, 3H). ^{13}C NMR ($CDCl_3$): δ175.75 (**C**O, 1C), 135.44 (Ar, CH_2-**C**, 1C) 128.87 (Ar-*meta*, 2C), 128.76 (Ar-*para*, 1C), 128.44 (Ar-*orhto*, 2C), 67.52 (HO**C**H(CH_3)CO, 1C), 67.06 ($CO_2\mathbf{C}H_2Ph$, 1C), 20.58 (**C**H_3, 1C). Mass Spec for $C_{10}H_{12}O_3$ Calculated: 180.08; Found $(M+Na)^+$: 203.07.

Monomer ((*S*)-Benzyl 2-(*tert*-butyldimethylsilyloxy)propanoate) (6).

50.07 g (0.33 mol) of *tert*-Butyldimethylsilyl chloride was added to a DMF (50 mL) solution of **2** (28.73 g (0.16 mol)) and Imidazole (43.90 g (0.64 mol)). This reaction mixture was stirred overnight at room temperature under Argon atmosphere. The resulting mixture was poured into a separatory funnel containing 300 mL of satd. $NaHCO_3$*aq.* and extracted 4 times with 300 mL of Hexanes. The organic fractions were combined, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Crude product was then purified via flash column chromatography using 5:1 Hexanes:Ethyl acetate as eluent yielding 45.31 g (97% yield) of **6** as a clear colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ7.35 (b, Ar, 5H), 5.16 (m, $C\mathbf{H}_2Ph$, 2H), 4.38 (q, J = 6.7 Hz, SiOC**H**(CH_3)CO, 1H), 1.43 (d, J = 6.8 Hz, SiOCH(C**H**$_3$)CO, 3H), 0.92 (s, ($C\mathbf{H}_3)_3CSi$, 9H), 0.10 (s, ($C\mathbf{H}_3)_2Si$, 3H), 0.08 (s, ($C\mathbf{H}_3)_2Si$, 3H). ^{13}C NMR ($CDCl_3$): δ173.97 (**C**O_2CH_2Ph, 1C), 135.93 (Ar, CH_2-**C**, 1C), 128.66 (Ar-*meta*, 2C), 128.41 (Ar-*orhto*, *para*, 3C), 68.60 (SiO**C**H(CH_3)CO, 1C), 66.61 ($CO_2\mathbf{C}H_2Ph$, 1C), 25.86 ((**C**$H_3)_3CSi$, 3C), 21.46 (SiOCH(**C**H_3)CO, 1C), 18.43 (($CH_3)_3$**C**Si, 1C), -4.79 ((**C**$H_3)_2Si$, 1C), -5.14 ((**C**$H_3)_2Si$, 1C). Mass Spec for $C_{16}H_{26}O_3Si$ Calculated: 294.17; Found $(M+Na)^+$: 317.16. $[\alpha]^{23}_D$ = -28^{o} (c = 1.11 cg/mL $CHCl_3$)

Dimer-OH-CO_2H ((*S*)-2-((*S*)-2-Hydroxypropanoyloxy)propanoic acid) (10).

A suspension of 20.16 g (0.14 mol) of (3*S*,6*S*)-3,6-Dimethyl-1,4-dioxane-2,5-dione (**9**) in water (114.75 g) was stirred at 40 ^{o}C for 4 hours to make it homogeneous. After the reaction, it was dried by conducting freeze drying yielding 20.40 g (90% yield) of **10** as a clear colorless oil together with 1.00 g of starting material (**9**) and 0.79 g of (L)- lactic acid (**3**). ^{1}H NMR (200 MHz, MeOD-d_4): δ5.22 (b, O**H**, 2H), 5.07 (q, J = 7.0 Hz, $CO_2C\mathbf{H}(CH_3)CO_2H$, 1H), 4.32 (q, J = 7.0 Hz, HOC**H**(CH_3)CO_2, 1H), 1.49 (d, J = 7.0 Hz, $CO_2CH(C\mathbf{H}_3)CO_2H$, 3H), 1.43 (d, J = 7.0 Hz, HOCH(C**H**$_3$)CO_2, 3H). ^{13}C NMR (MeOD-d_4): δ175.74 (**C**O_2H, 1C), 173.99 (**C**O_2C, 1C), 70.17 ($CO_2\mathbf{C}H(CH_3)CO_2H$, 1C) 67.57 (HO**C**H($CH_3$)$CO_2$, 1C), 20.57 (HOCH(**C**$H_3$)$CO_2$, 1C) 17.28 ($CO_2CH(\mathbf{C}H_3)CO_2H$, 1C). Mass Spec for $C_6H_{10}O_5$ Calculated: 162.05; Found $(M+Na)^+$: 185.03.

Dimer-OH ((*S*)-Benzyl 2-((*S*)-2-hydroxypropanoyloxy)propanoate) (11).

A 1 L round bottom flask was charged with 20.30 g (0.13 mol) of **10**, 38.46 g (0.22 mol) of Benzyl bromide, 44.63 g (0.44 mol) of Triethylamine, and 221 mL of CH_2Cl_2. This reaction mixture was stirred overnight at room temperature. After the reaction, most of CH_2Cl_2 and Triethylamine were removed by reducing the pressure. Then CH_2Cl_2 was added and removed again in vacuo. Again CH_2Cl_2 was added together with saturated NH_4Cl*aq.* and separated. The organic layer was then dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Crude product was then purified via flash column chromatography using 1:1 Hexanes:Ethyl acetate as eluent yielding

21.11 g (67% yield) of **11** as a colorless clear oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ7.35 (m, Ar, 5H), 5.21 (m, $CO_2CH(CH_3)CO_2CH_2Ph$, 3H), 4.34 (m, $HOCH(CH_3)CO_2CH(CH_3)CO_2Ph$, 1H), 2.72 (d, J = 6.0 Hz, **H**O, 1H), 1.54 (d, J = 7.0 Hz, $CO_2CH(CH_3)CO_2CH_2Ph$, 3H), 1.43 (d, J = 7.0 Hz, $HOCH(CH_3)CO_2$, 3H). ^{13}C NMR ($CDCl_3$): δ175.33 (**C**O_2C, 1C), 170.22 (**C**O_2C, 1C), 135.30 (Ar, CH_2-**C**, 1C) 128.86 (Ar-*meta*, 2C), 128.77 (Ar-*orhto*, 1C), 128.47 (Ar-*para*, 2C), 69.63 (CO_2**C**$H(CH_3)CO_2CH_2Ph$, 1C), 67.48 ($CO_2CH(CH_3)CO_2$**C**H_2Ph, 1C), 66.93 (HO**C**$H(CH_3)CO_2$, 1C), 20.65 ($HOCH($**C**$H_3)CO_2$, 1C) 17.04 ($CO_2CH($**C**$H_3)CO_2CH_2Ph$, 1C). Mass Spec for $C_{13}H_{16}O_5$ Calculated: 252.10; Found $(M+Na)^+$: 275.09.

Dimer ((*S*)-Denzyl 2-((*S*)-2-(*tert*-butyldimethylsilyloxy)propanoyloxy)propanoate) (5).

25.67 g (0.17 mol) of *tert*-Butyldimethylsilyl chloride was added to a DMF (25 mL) solution of **11** (21.08 g (0.08 mol)) and Imidazole (22.65 g (0.33 mol)). This reaction mixture was stirred overnight at room temperature under Argon atmosphere. The resulting mixture was poured into a separatory funnel containing 150 mL of satd. $NaHCO_3$*aq.* and extracted 4 times with 150 mL of Hexanes. The organic fractions were combined, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Crude product was then purified via flash column chromatography using 5:1 Hexanes:Ethyl acetate as eluent yielding 24.93 g (81% yield) of **5** as a clear colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ7.34 (b, Ar, 5H), 5.16 (m, CO_2C**H**$(CH_3)CO_2C$**H**$_2Ph$, 3H), 4.38 (q, J = 6.8 Hz, SiOC**H**$(CH_3)CO$, 1H), 1.43 (d, J = 6.8 Hz, $SiOCH(C$**H**$_3)CO$, 3H), 0.90 (s, $(C$**H**$_3)_3CSi$, 9H), 0.10 (s, $(C$**H**$_3)_2Si$, 3H), 0.08 (s, $(C$**H**$_3)_2Si$, 3H). ^{13}C NMR ($CDCl_3$): δ173.56 (**C**O_2C, 1C), 170.45 (**C**O_2C, 1C), 135.44 (Ar, CH_2-**C**, 1C), 128.72 (Ar-*meta*, 2C), 128.54 (Ar-*para*, 1C), 128.34 (Ar-*orhto*, 2C), 68.95 (CO_2**C**$H(CH_3)CO_2CH_2Ph$, 1C), 68.21 (SiO**C**$H(CH_3)CO_2$, 1C), 67.14 (CO_2**C**H_2Ph, 1C), 25.84 ($($**C**$H_3)_3CSi$, 3C), 21.32 ($SiOCH($**C**$H_3)CO$, 1C), 18.41 ($(CH_3)_3$**C**Si, 1C), 17.01 ($CO_2CH($**C**$H_3)CO_2CH_2Ph$, 1C), -4.78 ($($**C**$H_3)_2Si$, 1C), -5.14 ($($**C**$H_3)_2Si$, 1C). Mass Spec for $C_{19}H_{30}O_5Si$ Calculated: 366.19; Found $(M+Na)^+$: 389.17.

General procedure of deprotection of benzyl ester (hydrogenation): Synthesis of Dimer-CO_2H ((*S*)-2-((*S*)-2-(*tert*-Butyldimethylsilyloxy)propanoyloxy)propanoic acid) (12) depicted.

1.39 g of Palladium on activated carbon (10wt%) was added to a solution of Dimer (**5**) (12.09 g (32.99 mmol)) in Ethyl acetate (122.40 g) and then stirred overnight at room temperature under Hydrogen. The resulting mixture was filtered through celite and the cake was washed with 100 mL of Ethyl acetate. The filtrate was concentrated under reduced pressure yielding 9.12 g (100% yield) of **12** as a clear colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ11.76 (b, CO_2H, 1H), 5.11 (q, J = 7.1 Hz, CO_2C**H**$(CH_3)CO_2H$, 1H), 4.38 (q, J = 6.8 Hz, SiOC**H**$(CH_3)CO$, 1H), 1.52 (d, J = 7.2 Hz, $SiOCH(CH_3)CO_2CH(C$**H**$_3)CO_2H$, 3H), 1.42 (d, J = 6.8 Hz, $SiOCH(C$**H**$_3)CO_2CH(CH_3)CO_2H$, 3H), 0.88 (s, $(C$**H**$_3)_3CSi$, 9H), 0.08 (s, $(C$**H**$_3)_2Si$, 3H), 0.06 (s, $(C$**H**$_3)_2Si$, 3H). ^{13}C NMR ($CDCl_3$): δ176.70 (**C**O_2H, 1C), 173.68 (**C**O_2C, 1C), 68.56 (CO_2**C**$H(CH_3)CO_2H$, 1C), 68.25 (SiO**C**$H(CH_3)CO_2$, 1C), 25.83 ($($**C**$H_3)_3CSi$, 3C), 21.29 ($SiOCH($**C**$H_3)CO$, 1C), 18.42 ($(CH_3)_3$**C**Si, 1C), 16.88 ($CO_2CH($**C**$H_3)CO_2H$, 1C), -4.81 ($($**C**$H_3)_2Si$, 1C), -5.20 ($($**C**$H_3)_2Si$, 1C). Mass Spec for $C_{12}H_{24}O_5Si$ Calculated: 276.14; Found $(M+Na)^+$: 299.12.

General procedure of deprotection of TBDMS (desilylation): Synthesis of Dimer-OH (11) depicted.

25.20 g (419.65 mmol) of Acetic acid was added to a solution of Dimer (**5**) (12.09 g (32.99 mmol)) in THF (58.85 g). And 65.82 g (72.89 mmol) of Tetrabutylammonium fluoride (TBAF) 1.0 M solution in THF was then added gradually. The reaction mixture was stirred overnight at room temperature. The resulting mixture was poured into a

separatory funnel containing 300 mL of Ethyl acetate and 300 mL of H_2O and then separated. The organic layer was washed with satd. $NaHCO_3$*aq*. (2x200 mL), 5wt% Citric acid*aq*. (2x200 mL), and H_2O (1x200 mL). The organic layer was then dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Crude product was then purified via flash column chromatography using 1:1 Hexanes:Ethyl acetate as eluent yielding 7.44 g (89% yield) of **11** as a clear colorless oil.

General procedure of coupling reaciton: Synthesis of Tetramer (13) depicted.

Dissolve **11** (After deprotection of TBDMS) (7.43 g (29.45 mmol)), **12** (8.66 g (31.33 mmol)), 1,3-Dicyclohexylcarbodiimide (DCC) (7.63 g (36.98 mmol)), and 4-(Dimethylamino)pyridinium *p*-toluenesulfonate (DPTS)[7] (1.74 g (5.92 mmol)) in CH_2Cl_2 (50 mL) and stirred overnight at room temperature. The resulting mixture was filetered. The filtrate was then poured into a separatory funnel and washed with 100 mL of satd. $CuSO_4$*aq*. and 100 mL of H_2O. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Crude product was then purified via gradient flash column chromatography (20:1 Hexanes:Ethyl acetate to 4:1 Hexanes:Ethyl acetate) yielding 13.99 g (93% yield) of **13** as a colorless crystal. ^{1}H NMR (200 MHz, $CDCl_3$): δ7.32 (b, Ar, 5H), 5.15 (m, $CH(CH_3)CO_2[CH(CH_3)CO_2]_3CH_2Ph$, 5H), 4.38 (q, J = 6.8 Hz, $SiOCH(CH_3)CO$, 1H), 1.57 (d, J = 6.8 Hz, $CH(CH_3)CO_2CH_2Ph$, 3H), 1.51 (m, $CH(CH_3)CO_2[CH(CH_3)CO_2]_2CH(CH_3)CO_2CH_2Ph$, 6H), 1.44 (d, J = 6.8 Hz, $SiOCH(CH_3)CO$, 3H), 0.90 (s, $(CH_3)_3CSi$, 9H), 0.10 (s, $(CH_3)_2Si$, 3H), 0.08 (s, $(CH_3)_2Si$, 3H). ^{13}C NMR ($CDCl_3$): δ173.61 (CO_2C, 1C), 170.08 (CO_2C, 2C), 169.76 (CO_2C, 1C), 135.25 (Ar, CH_2-**C**, 1C), 128.73 (Ar-*meta*, 2C), 128.62 (Ar-*para*, 1C), 128.36 (Ar-*orhto*, 2C), 69.35 ($CO_2CH(CH_3)CO_2$, 1C), 68.94 ($CO_2CH(CH_3)CO_2$, 1C), 68.66 ($CO_2CH(CH_3)CO_2$, 1C), 68.11 ($SiOCH(CH_3)CO_2$, 1C), 67.28 (CO_2CH_2Ph, 1C), 25.82 ($(CH_3)_3CSi$, 3C), 21.34 ($SiOCH(CH_3)CO$, 1C), 18.38 ($(CH_3)_3CSi$, 1C), 16.85 ($CO_2CH(CH_3)CO_2$, 2C), 16.71 ($CO_2CH(CH_3)CO_2$, 1C), -4.78 ($(CH_3)_2Si$, 1C), -5.17 ($(CH_3)_2Si$, 1C). Mass Spec for $C_{25}H_{38}O_9Si$ Calculated: 510.23; Found $(M+Na)^+$: 533.21.

Tetramer-CO_2H (14).

The monoprotected, acid-functionalized Tetramer-CO_2H (**14**) was prepared using the general procedure described above for deprotection of Benzyl ester (hydrogenation), starting from Tetramer (**13**). The crude product was then purified via gradient flash column chromatography (2:1 Hexanes:Ethyl acetate to 2:1 Ethyl acetate:MeOH) yielding a colorless oil. (93% yield) ^{1}H NMR (200 MHz, $CDCl_3$): δ11.70 (b, CO_2H, 1H), 5.15 (m, $CH(CH_3)CO_2[CH(CH_3)CO_2]_3H$, 3H), 4.37 (q, J = 6.8 Hz, $SiOCH(CH_3)CO$, 1H), 1.47 (m, $SiO[CH(CH_3)CO_2]_4H$, 12H), 0.87 (s, $(CH_3)_3CSi$, 9H), 0.07 (s, $(CH_3)_2Si$, 3H), 0.05 (s, $(CH_3)_2Si$, 3H). ^{13}C NMR ($CDCl_3$): δ176.00 (CO_2H, 1C), 173.76 (CO_2C, 1C), 170.20 (CO_2C, 2C), 169.90 (CO_2C, 1C), 69.59 ($CO_2CH(CH_3)CO_2$, 1C), 69.08 ($CO_2CH(CH_3)CO_2$, 1C), 68.74 ($CO_2CH(CH_3)CO_2$, 1C), 68.13 ($SiOCH(CH_3)CO_2$, 1C), 25.82 ($(CH_3)_3CSi$, 3C), 21.34 ($SiOCH(CH_3)CO$, 1C), 18.38 ($(CH_3)_3CSi$, 1C), 16.83 ($CO_2CH(CH_3)CO_2$, 2C), 16.69 ($CO_2CH(CH_3)CO_2$, 1C), -4.79 ($(CH_3)_2Si$, 1C), -5.18 ($(CH_3)_2Si$, 1C). Mass Spec for $C_{18}H_{32}O_9Si$ Calculated: 420.18; Found $(M+Na)^+$: 443.17.

Tetramer-OH (15).

The monoprotected, hydroxyl-functionalized Tetramer-OH (**15**) was prepared using the general procedure described above for deprotection of TBDMS (desilylation), starting from Tetramer (**13**). The crude product was then purified via gradient flash column chromatography (1:1 Hexanes:Ethyl acetate to Ethyl acetate) yielding **15** as a colorless oil. (88% yield) ^{1}H NMR (200 MHz, $CDCl_3$): δ7.34 (b, Ar, 5H), 5.18 (m,

$CH(CH_3)CO_2[CH(CH_3)CO_2]_3CH_2Ph$, 5H), 4.36 (m, $SiOCH(CH_3)CO$, 1H), 3.10 (b, OH, 1H), 1.50 (m, $CH(CH_3)CO_2$, 12H). ^{13}C NMR ($CDCl_3$): δ175.06 (CO_2C, 1C), 169.96 (CO_2C, 1C), 169.80 (CO_2C, 1C), 169.61 (CO_2C, 1C), 135.16 (Ar, CH_2-C, 1C), 128.66 (Ar-*meta*, 2C), 128.56 (Ar-*para*, 1C), 128.30 (Ar-*orhto*, 2C), 69.35 ($CO_2CH(CH_3)CO_2$, 1C), 69.08 ($CO_2CH(CH_3)CO_2$, 1C), 69.00 ($CO_2CH(CH_3)CO_2$, 1C), 67.24 (CO_2CH_2Ph, 1C), 66.73 ($HOCH(CH_3)CO_2$, 1C), 20.48 ($HOCH(CH_3)CO$, 1C), 16.77 ($CO_2CH(CH_3)CO_2$, 2C), 16.62 ($CO_2CH(CH_3)CO_2$, 1C). Mass Spec for $C_{19}H_{24}O_9$ Calculated: 396.14; Found $(M+Na)^+$: 419.13.

Octamer (16).

The doubly protected Octamer (**16**) was prepared using the general procedure described above for coupling, from the tetramers, **14** and **15**. The crude product was then purified via gradient flash column chromatography (4:1 Hexanes:Ethyl acetate to 1:1 Hexanes:Ethyl acetate) yielding **16** as a colorless sticky oil. (92% yield) ^1H NMR (200 MHz, $CDCl_3$): δ7.33 (b, Ar, 5H), 5.17 (m, $CH(CH_3)CO_2[CH(CH_3)CO_2]_7CH_2Ph$, 9H), 4.38 (q, J = 6.8 Hz, $SiOCH(CH_3)CO$, 1H), 1.55 (m, $CH(CH_3)CO_2$, 24H), 0.90 (s, $(CH_3)_3CSi$, 9H), 0.10 (s, $(CH_3)_2Si$, 3H), 0.08 (s, $(CH_3)_2Si$, 3H). ^{13}C NMR ($CDCl_3$): δ173.69 (CO_2C, 1C), 170.16 (CO_2C, 2C), 170.06 (CO_2C, 1C), 169.89 (CO_2C, 1C), 169.81 (CO_2C, 1C), 169.77 (CO_2C, 2C), 169.70 (CO_2C, 1C), 135.26 (Ar, CH_2-C, 1C), 128.80 (Ar-*meta*, 2C), 128.70 (Ar-*para*, 1C), 128.42 (Ar-*orhto*, 2C), 69.45 ($CO_2CH(CH_3)CO_2$, 1C), 69.17 ($CO_2CH(CH_3)CO_2$, 4C), 68.98 ($CO_2CH(CH_3)CO_2$, 1C), 68.71 ($CO_2CH(CH_3)CO_2$, 1C), 68.17 ($SiOCH(CH_3)CO_2$, 1C), 67.38 (CO_2CH_2Ph, 1C), 25.87 ($(CH_3)_3CSi$, 3C), 21.39 ($SiOCH(CH_3)CO$, 1C), 18.44 ($(CH_3)_3CSi$, 1C), 16.92 ($CO_2CH(CH_3)CO_2$, 2C), 16.81 ($CO_2CH(CH_3)CO_2$, 4C), 16.74 ($CO_2CH(CH_3)CO_2$, 1C), -4.74 ($(CH_3)_2Si$, 1C), -5.12 ($(CH_3)_2Si$, 1C). Mass Spec for $C_{37}H_{54}O_{17}Si$ Calculated: 798.31; Found $(M+Na)^+$: 821.30.

Octamer-CO_2H (17).

The monoprotected, acid-functionalized Octamer-CO_2H (**17**) was prepared using the general procedure described above for deprotection of Benzyl ester (hydrogenation), starting from Octamer (**16**). The crude product was then purified via gradient flash column chromatography (1:1 Hexanes:Ethyl acetate to 2:1 Ethyl acetate:MeOH) yielding a colorless sticky oil. (94% yield) ^1H NMR (200 MHz, $CDCl_3$): δ6.20 (b, CO_2H, 1H), 5.15 (m, $CH(CH_3)CO_2[CH(CH_3)CO_2]_7H$, 7H), 4.39 (q, J = 6.8 Hz, $SiOCH(CH_3)CO$, 1H), 1.50 (m, $SiO[CH(CH_3)CO_2]_8H$, 24H), 0.89 (s, $(CH_3)_3CSi$, 9H), 0.10 (s, $(CH_3)_2Si$, 3H), 0.07 (s, $(CH_3)_2Si$, 3H). ^{13}C NMR ($CDCl_3$): δ173.85-169.82 (CO_2, 8C), 69.13-68.73 ($CO_2CH(CH_3)CO_2$, 7C), 68.19 ($SiOCH(CH_3)CO_2$, 1C), 25.89 ($(CH_3)_3CSi$, 3C), 21.41 ($SiOCH(CH_3)CO$, 1C), 18.47 ($(CH_3)_3CSi$, 1C), 16.93-16.83 ($CO_2CH(CH_3)CO_2$, 7C), -4.72 ($(CH_3)_2Si$, 1C), -5.10 ($(CH_3)_2Si$, 1C). Mass Spec for $C_{30}H_{48}O_{17}Si$ Calculated: 708.27; Found $(M+Na)^+$: 731.25.

Octamer-OH (18).

The monoprotected, hydroxyl-functionalized Octamer-OH (**18**) was prepared using the general procedure described above for deprotection of TBDMS (desilylation), starting from Octamer (**16**). The crude product was then purified via flash column chromatography using 1:1 Hexanes:Ethyl acetate as eluent yielding **18** as a white solid. (88% yield) ^1H NMR (200 MHz, $CDCl_3$): δ7.33 (m, Ar, 5H), 5.18 (m, $CH(CH_3)CO_2[CH(CH_3)CO_2]_7CH_2Ph$, 9H), 4.33 (m, $SiOCH(CH_3)CO$, 1H), 2.78 (b, OH, 1H), 1.50 (m, $CH(CH_3)CO_2$, 24H). ^{13}C NMR ($CDCl_3$): δ175.27-169.70 (CO_2, 8C), 135.25 (Ar, CH_2-C, 1C), 128.79 (Ar-*meta*, 2C), 128.69 (Ar-*para*, 1C), 128.41 (Ar-*orhto*, 2C), 69.45-

69.19 (CO_2**C**H(CH_3)CO_2, 7C), 67.38 (CO_2**C**H_2Ph, 1C), 66.86 (HO**C**H(CH_3)CO_2, 1C), 20.67 (HOCH(**C**H_3)CO, 1C), 16.90-16.73 (CO_2CH(**C**H_3)CO_2, 7C). Mass Spec for $C_{31}H_{40}O_{17}$ Calculated: 684.23; Found $(M+Na)^+$: 707.22.

16mer (19).

The doubly protected 16mer (**19**) was prepared using the general procedure described above for coupling, from the Octamers, **17** and **18**. The crude product was then purified via gradient flash column chromatography (4:1 Hexanes:Ethyl acetate to Ethyl acetate) and precipitation from CH_2Cl_2/Hexanes. **19** was obtained as a white solid. (77% yield) ^{1}H NMR (200 MHz, $CDCl_3$): δ7.34 (b, Ar, 5H), 5.17 (m, CH(CH_3)CO_2[C**H**(CH_3)CO_2]$_{15}$C**H**$_2$Ph, 17H), 4.38 (q, J = 6.8 Hz, SiOC**H**(CH_3)CO, 1H), 1.54 (m, CH(C**H**$_3$)CO_2, 48H), 0.90 (s, (C**H**$_3$)$_3$CSi, 9H), 0.10 (s, (C**H**$_3$)$_2$Si, 3H), 0.08 (s, (C**H**$_3$)$_2$Si, 3H). ^{13}C NMR ($CDCl_3$): δ173.73-169.80 (**C**O_2, 16C), 135.27 (Ar, CH_2-**C**, 1C), 128.82 (Ar-*meta*, 2C), 128.74 (Ar-*para*, 1C), 128.45 (Ar-*orhto*, 2C), 69.48-68.74 (CO_2**C**H(CH_3)CO_2, 15C), 68.20 (SiO**C**H(CH_3)CO_2, 1C), 67.42 (CO_2**C**H_2Ph, 1C), 25.89 ((**C**H_3)$_3$CSi, 3C), 21.42 (SiOCH(**C**H_3)CO, 1C), 18.47 ((CH_3)$_3$**C**Si, 1C), 16.84 (CO_2CH(**C**H_3)CO_2, 15C), -4.71 ((**C**H_3)$_2$Si, 1C), -5.12 ((**C**H_3)$_2$Si, 1C). Mass Spec for $C_{61}H_{86}O_{33}Si$ Calculated: 1374.48; Found $(M+Na)^+$: 1397.45.

16mer-CO_2H (20).

The monoprotected, acid-functionalized 16mer-CO_2H (**20**) was prepared using the general procedure described above for deprotection of Benzyl ester (hydrogenation), starting from 16mer (**19**). The crude product was then purified via gradient flash column chromatography (1:1 Hexanes:Ethyl acetate to 2:1 Ethyl acetate:MeOH) yielding **20** as a colorless solid. (98% yield) ^{1}H NMR (200 MHz, $CDCl_3$): δ5.14 (m, CH(CH_3)CO_2[C**H**(CH_3)CO_2]$_{15}$H, 15H), 4.92 (b, CO_2**H**, 1H), 4.38 (q, J = 6.8 Hz, SiOC**H**(CH_3)CO, 1H), 1.52 (m, SiO[CH(C**H**$_3$)CO_2]$_{16}$H, 48H), 0.89 (s, (C**H**$_3$)$_3$CSi, 9H), 0.09 (s, (C**H**$_3$)$_2$Si, 3H), 0.07 (s, (C**H**$_3$)$_2$Si, 3H). ^{13}C NMR ($CDCl_3$): δ173.71-169.79 (**C**O_2, 16C), 69.69-68.71 (CO_2**C**H(CH_3)CO_2, 15C), 68.17 (SiO**C**H(CH_3)CO_2, 1C), 25.86 ((**C**H_3)$_3$CSi, 3C), 21.38 (SiOCH(**C**H_3)CO, 1C), 18.44 ((CH_3)$_3$**C**Si, 1C), 16.91-16.81 (CO_2CH(**C**H_3)CO_2, 15C), -4.75 ((**C**H_3)$_2$Si, 1C), -5.13 ((**C**H_3)$_2$Si, 1C). Mass Spec for $C_{54}H_{80}O_{33}Si$ Calculated: 1284.44; Found $(M+Na)^+$: 1307.43.

16mer-OH (21).

The monoprotected, hydroxyl-functionalized 16mer-OH (**21**) was prepared using the general procedure described above for deprotection of TBDMS (desilylation), starting from 16mer (**19**). The crude product was then purified via flash column chromatography using 1:1 Hexanes:Ethyl acetate as eluent yielding **21** as a colorless sticky oil. (87% yield) ^{1}H NMR (200 MHz, $CDCl_3$): δ7.33 (m, Ar, 5H), 5.17 (m, CH(CH_3)CO_2[C**H**(CH_3)CO_2]$_{15}$C**H**$_2$Ph, 17H), 4.34 (m, SiOC**H**(CH_3)CO, 1H), 2.74 (b, O**H**, 1H), 1.55 (m, CH(C**H**$_3$)CO_2, 48H). ^{13}C NMR ($CDCl_3$): δ175.28-169.70 (**C**O_2, 16C), 135.25 (Ar, CH_2-**C**, 1C), 128.80 (Ar-*meta*, 2C), 128.70 (Ar-*para*, 1C), 128.42 (Ar-*orhto*, 2C), 69.46-69.19 (CO_2**C**H(CH_3)CO_2, 15C), 67.39 (CO_2**C**H_2Ph, 1C), 66.87 (HO**C**H(CH_3)CO_2, 1C), 20.68 (HOCH(**C**H_3)CO, 1C), 16.91-16.81 (CO_2CH(**C**H_3)CO_2, 15C). Mass Spec for $C_{55}H_{72}O_{33}$ Calculated: 1284.44; Found $(M+Na)^+$: 1307.43.

32mer (22).

The doubly protected 32mer (**22**) was prepared using the general procedure described above for coupling, from the 16mers, **20** and **21**, but instead of 1,3-Dicyclohexylcarbodiimide (DCC), 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) was used (1.3 *eq.* to **21**). The crude product was then purified via gradient

flash column chromatography (10:1 CH_2Cl_2:Ethyl acetate to 5:1 CH_2Cl_2:Ethyl acetate) yielding **22** as a white solid. (74% yield) ^{1}H NMR (200 MHz, $CDCl_3$): δ7.34 (b, Ar, 5H), 5.15 (m, $CH(CH_3)CO_2[CH(CH_3)CO_2]_{31}CH_2Ph$, 33H), 4.39 (q, J = 6.8 Hz, $SiOCH(CH_3)CO$, 1H), 1.57 (m, $CH(CH_3)CO_2$, 96H), 0.90 (s, $(CH_3)_3CSi$, 9H), 0.10 (s, $(CH_3)_2Si$, 3H), 0.08 (s, $(CH_3)_2Si$, 3H). ^{13}C NMR ($CDCl_3$): δ173.72-169.79 (CO_2, 32C), 135.26 (Ar, CH_2-**C**, 1C), 128.81 (Ar-*meta*, 2C), 128.72 (Ar-*para*, 1C), 128.44 (Ar-*orhto*, 2C), 69.47-68.72 ($CO_2CH(CH_3)CO_2$, 31C), 68.19 ($SiOCH(CH_3)CO_2$, 1C), 67.41 (CO_2CH_2Ph, 1C), 25.88 (($CH_3)_3CSi$, 3C), 21.40 ($SiOCH(CH_3)CO$, 1C), 18.46 (($CH_3)_3CSi$, 1C), 16.93-16.83 ($CO_2CH(CH_3)CO_2$, 31C), -4.71 (($CH_3)_2Si$, 1C), -5.12 (($CH_3)_2Si$, 1C). Mass Spec for $C_{109}H_{150}O_{65}Si$ Calculated: 2526.82; Found $(M+2Na)^{+2}$: 1286.89. $[\alpha]^{23}_D = -140^o$ (c = 1.09 cg/mL $CHCl_3$)

32mer- CO_2H (23).

The monoprotected, acid-functionalized 32mer-CO_2H (**23**) was prepared using the general procedure described above for deprotection of Benzyl ester (hydrogenation), starting from 32mer (**22**) yielding **23** as a white solid. (96% yield) ^{1}H NMR (200 MHz, $CDCl_3$): δ5.50 (b, CO_2H, 1H), 5.14 (q, J = 7.0 Hz, $CH(CH_3)CO_2[CH(CH_3)CO_2]_{31}H$, 31H), 4.38 (q, J = 6.8 Hz, $SiOCH(CH_3)CO$, 1H), 1.52 (m, $SiO[CH(CH_3)CO_2]_{32}H$, 96H), 0.89 (s, $(CH_3)_3CSi$, 9H), 0.09 (s, $(CH_3)_2Si$, 3H), 0.07 (s, $(CH_3)_2Si$, 3H). ^{13}C NMR ($CDCl_3$): δ174.10-169.68 (CO_2, 32C), 69.19-68.73 ($CO_2CH(CH_3)CO_2$, 31C), 68.18 ($SiOCH(CH_3)CO_2$, 1C), 25.87 (($CH_3)_3CSi$, 3C), 21.38 ($SiOCH(CH_3)CO$, 1C), 18.44 (($CH_3)_3CSi$, 1C), 16.81 ($CO_2CH(CH_3)CO_2$, 15C), -4.74 (($CH_3)_2Si$, 1C), -5.13 (($CH_3)_2Si$, 1C). Mass Spec for $C_{102}H_{144}O_{65}Si$ Calculated: 2436.77; Found $(M+Na)^+$: 2459.65.

32mer-OH (24).

The monoprotected, hydroxyl-functionalized 32mer-OH (**24**) was prepared using the general procedure described above for deprotection of TBDMS (desilylation), starting from 32mer (**22**). The crude product was then purified via gradient flash column chromatography (5:1 CH_2Cl_2:Ethyl acetate to 2:1 CH_2Cl_2:Ethyl acetate) yielding **24** as a white solid. (75% yield) ^{1}H NMR (200 MHz, $CDCl_3$): δ7.33 (m, Ar, 5H), 5.18 (m, $CH(CH_3)CO_2[CH(CH_3)CO_2]_{31}CH_2Ph$, 17H), 4.34 (m, $SiOCH(CH_3)CO$, 1H), 2.71 (b, OH, 1H), 1.56 (m, $CH(CH_3)CO_2$, 96H). ^{13}C NMR ($CDCl_3$): δ175.29-169.71 (CO_2, 32C), 135.25 (Ar, CH_2-**C**, 1C), 128.80 (Ar-*meta*, 2C), 128.71 (Ar-*para*, 1C), 128.43 (Ar-*orhto*, 2C), 69.45-69.19 ($CO_2CH(CH_3)CO_2$, 31C), 67.39 (CO_2CH_2Ph, 1C), 66.87 ($HOCH(CH_3)CO_2$, 1C), 20.69 ($HOCH(CH_3)CO$, 1C), 16.92-16.82 ($CO_2CH(CH_3)CO_2$, 31C). Mass Spec for $C_{103}H_{136}O_{65}$ Calculated: 2412.73; Found $(M+H)^+$: 2413.63.

64mer (25).

The doubly protected 64mer (**25**) was prepared using the general procedure described above for coupling, from the 16mers, **23** and **24**, but instead of 1,3-Dicyclohexylcarbodiimide (DCC), 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) was used (1.3 *eq*. to **24**). The crude product was then purified via flash column chromatography (5:1 CH_2Cl_2:Ethyl acetate) yielding **25** as a white solid. (70% yield) ^{1}H NMR (200 MHz, $CDCl_3$): δ7.34 (b, Ar, 5H), 5.15 (m, $CH(CH_3)CO_2[CH(CH_3)CO_2]_{63}CH_2Ph$, 65H), 4.39 (q, J = 6.8 Hz, $SiOCH(CH_3)CO$, 1H), 1.55 (m, $CH(CH_3)CO_2$, 192H), 0.89 (s, $(CH_3)_3CSi$, 9H), 0.10 (s, $(CH_3)_2Si$, 3H), 0.08 (s, $(CH_3)_2Si$, 3H). ^{13}C NMR ($CDCl_3$): δ173.74-169.79 (CO_2, 64C), 135.26 (Ar, CH_2-**C**, 1C), 128.81 (Ar-*meta*, 2C), 128.73 (Ar-*para*, 1C), 128.44 (Ar-*orhto*, 2C), 69.47-68.73 ($CO_2CH(CH_3)CO_2$, 63C), 68.19 ($SiOCH(CH_3)CO_2$, 1C), 67.41 (CO_2CH_2Ph, 1C), 25.88 (($CH_3)_3CSi$, 3C), 21.40 ($SiOCH(CH_3)CO$, 1C), 18.46 (($CH_3)_3CSi$, 1C), 16.83

($CO_2CH(\mathbf{C}H_3)CO_2$, 63C), -4.72 (($\mathbf{C}H_3)_2Si$, 1C), -5.12 (($\mathbf{C}H_3)_2Si$, 1C). Mass Spec for $C_{205}H_{278}O_{129}Si$ Calculated: 4831.50; Found $(M+2Na)^{+2}$: 2438.68.

16mer-OH-CO_2H (26).

The doubly deprotected, acid-hydroxyl-functionalized 16mer-OH-CO_2H (**26**) was prepared using the general procedure described above for deprotection of Benzyl ester (hydrogenation), starting from 16mer-OH (**21**). 16mer-OH-CO_2H (**26**) was obtained as a colorless solid. (99% yield) ^{1}H NMR (200 MHz, $CDCl_3$): δ5.15 (m, $CH(CH_3)CO_2[C\mathbf{H}(CH_3)CO_2]_{15}H$, 15H), 4.41 (b, O**H**, 2H), 4.37 (q, J = 6.9 Hz, HOC**H**(CH_3)CO, 1H), 1.54 (m, $HO[CH(C\mathbf{H}_3)CO_2]_{16}H$, 48H). ^{13}C NMR ($CDCl_3$): δ175.34-169.73 (**C**$O_2$, 16C), 69.22-68.98 ($CO_2\mathbf{C}H(CH_3)CO_2$, 15C), 66.92 (HO**C**$H(CH_3)CO_2$, 1C), 20.66 (HOCH(**C**$H_3$)CO, 1C), 16.83 ($CO_2CH(\mathbf{C}H_3)CO_2$, 15C). Mass Spec for $C_{48}H_{66}O_{33}$ Calculated: 1170.35; Found $(M+Na)^+$: 1193.33.

32mer-OH-CO_2H (27).

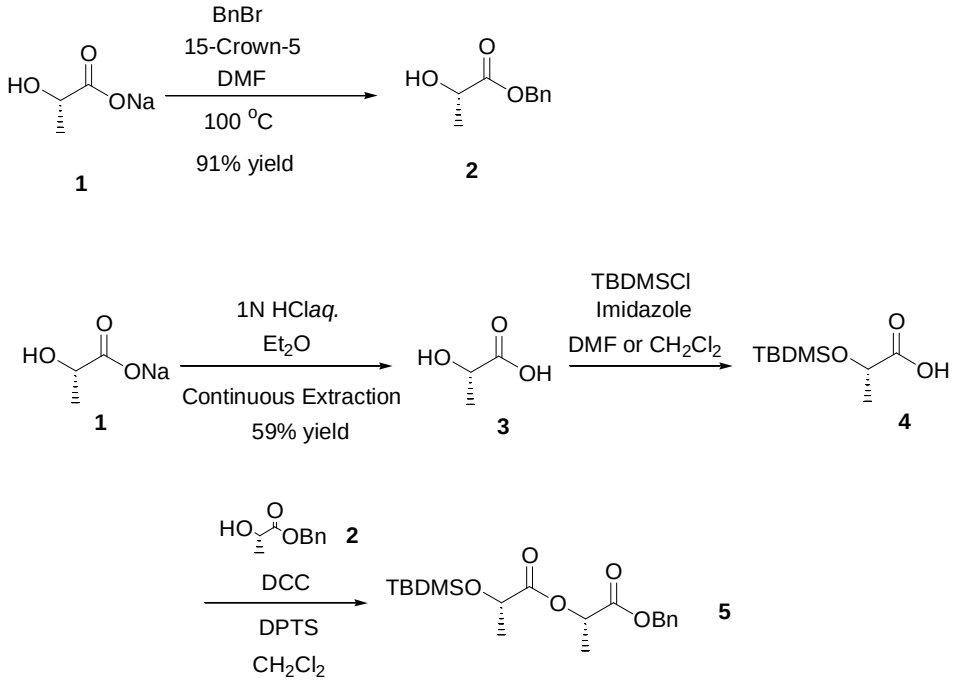
The doubly deprotected, acid-hydroxyl-functionalized 32mer-OH-CO_2H (**27**) was prepared using the general procedure described above for deprotection of Benzyl ester (hydrogenation), starting from 32mer-OH (**24**). 32mer-OH-CO_2H (**27**) was obtained as a white solid. (100% yield) ^{1}H NMR (200 MHz, $CDCl_3$): δ5.15 (m, $CH(CH_3)CO_2[C\mathbf{H}(CH_3)CO_2]_{31}H$, 31H), 4.70 (b, O**H**, 2H), 4.37 (q, J = 7.0 Hz, HOC**H**(CH_3)CO, 1H), 1.56 (m, $HO[CH(C\mathbf{H}_3)CO_2]_{32}H$, 96H). ^{13}C NMR ($CDCl_3$): δ175.26-169.69 (**C**$O_2$, 32C), 69.17 ($CO_2\mathbf{C}H(CH_3)CO_2$, 31C), 66.86 (HO**C**$H(CH_3)CO_2$, 1C), 20.61 (HOCH(**C**$H_3$)CO, 1C), 16.78 ($CO_2CH(\mathbf{C}H_3)CO_2$, 31C). Mass Spec for $C_{96}H_{130}O_{65}$ Calculated: 2322.69; Found $(M+2Na)^{+2}$: 1184.35.

4-3. Results and Discussion

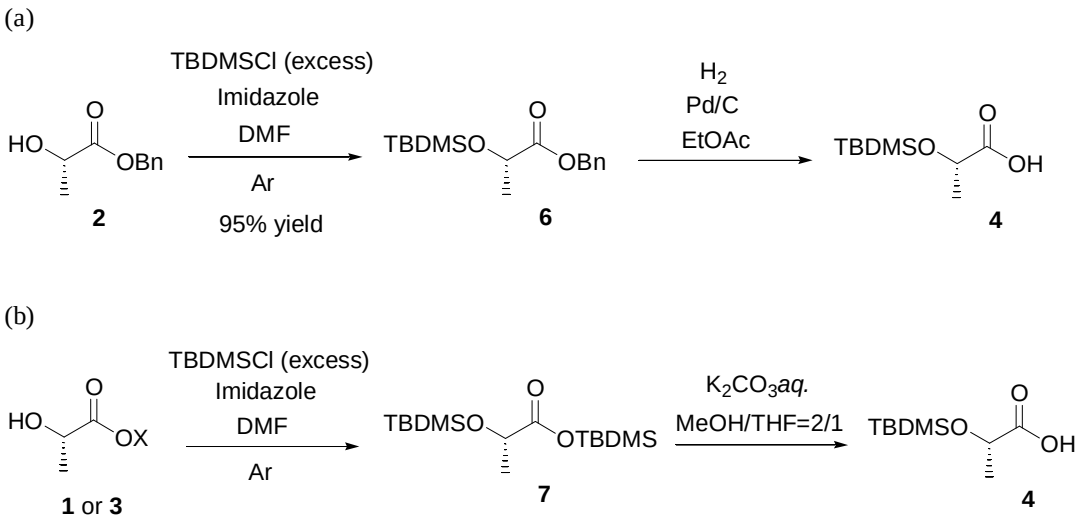
4-3-1. Synthesis

By careful selection of orthogonal protective groups, the syntheses were conducted using *t*-Butyldimethylsilyl (TBDMS) ether[8] as the protective group of the hydroxyl group and Benzyl (Bn) ester as the protective group of the carboxylic acid group. First, we tried to synthesize Dimer (**5**) by coupling one-end-protected Monomers, **2** and **4** (Scheme 1). Though it was easy to synthesize **2** and **6** via several routes including the routes depicted in Scheme 1 and 2, somehow the synthesis of **4** found to be very difficult. Actually, despite of our keen and intensive screening search, no attempts to synthesize **4** was successful (Scheme 2 (a) and (b)). We think that this difficulty was due to the low stability of **4** in the reaction conditions and all the yields of the steps making **4** were low and/or resulted in complex reaction mixtures.

Then we tried to synthesize Dimer (**5**) without making **4** based on the reactions described in Japanese patents (Scheme 3 (a) and (b))[6(a)-(c), (f), (g)]. But the three sequential reactions (Scheme 3 (a)) were very sensitive to a subtle difference of the reaction conditions and we finally found that the Cyclic-dimer-method (Scheme 3 (b)) was much more reliable than the previous Monomer-method (Scheme 3 (a)). Thus, we synthesized Dimer (**5**) in larger scale using the Cyclic-dimer-method (Scheme 3 (b)).

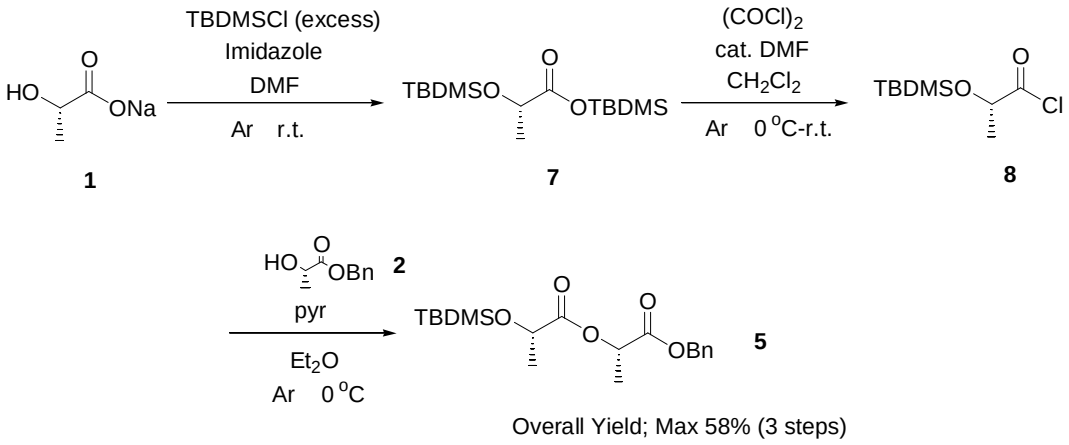


Scheme 1. Initial synthetic approach to Dimer (**5**).

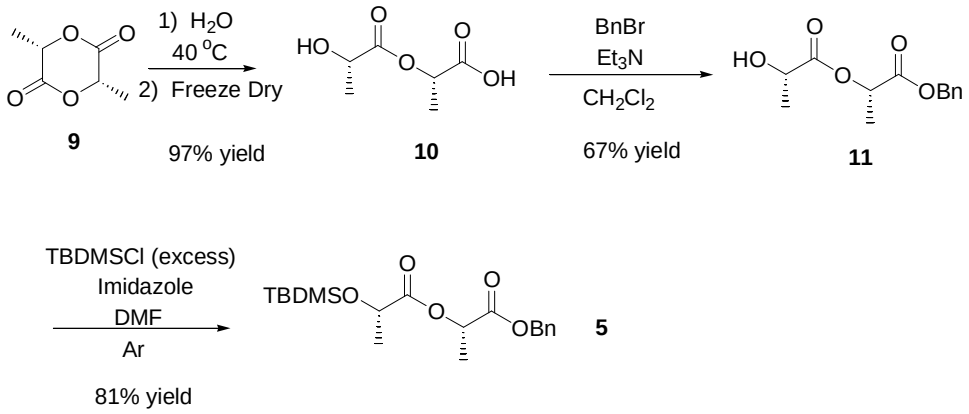


Scheme 2. Other attempts to synthesize **4**.

(a)



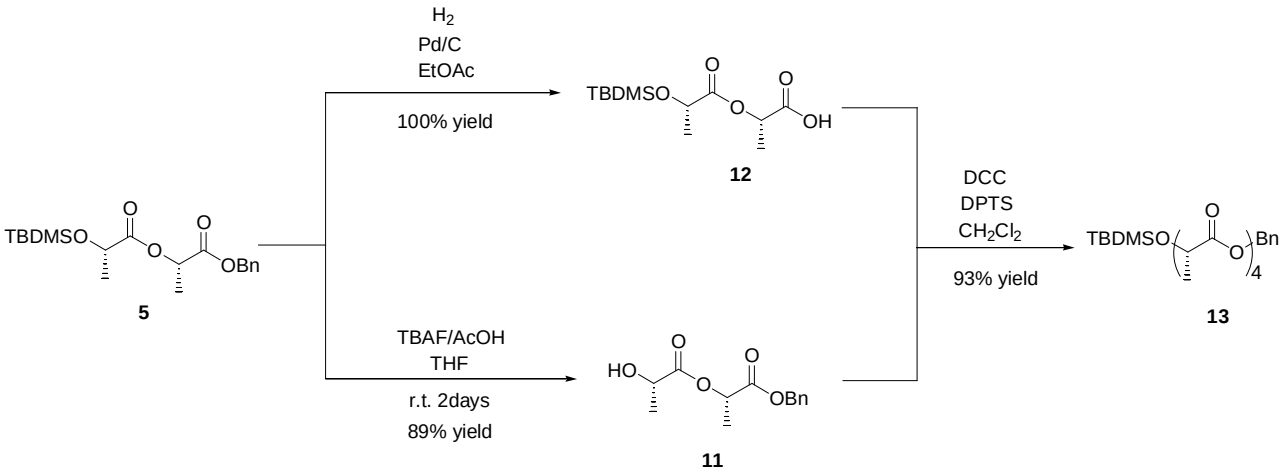
(b)

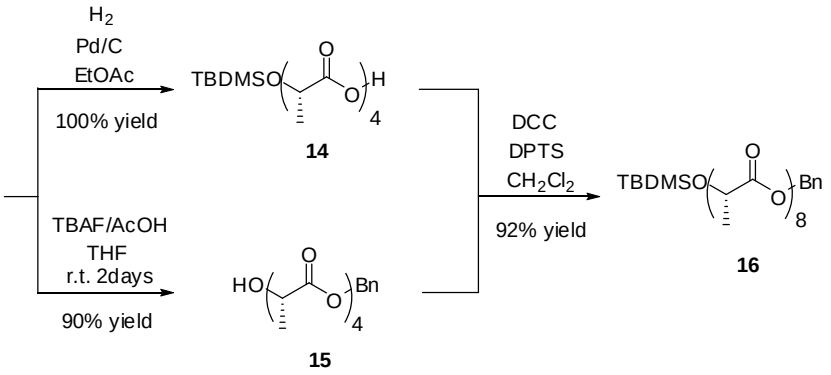


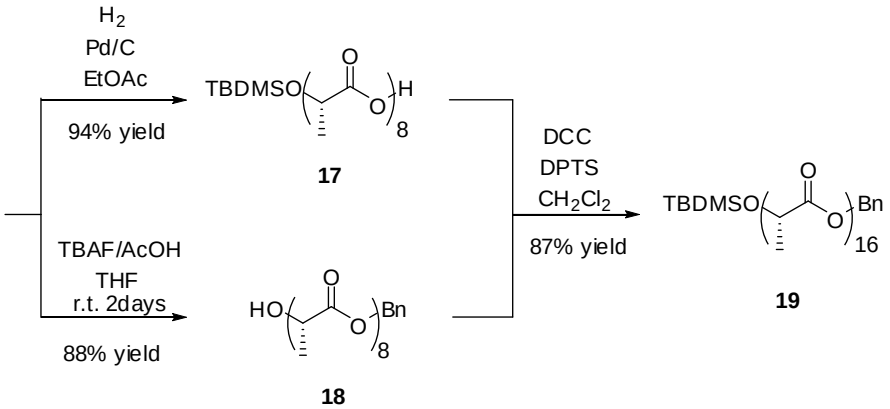
Scheme 3 . Successful synthetic routes to Dimer (**5**).

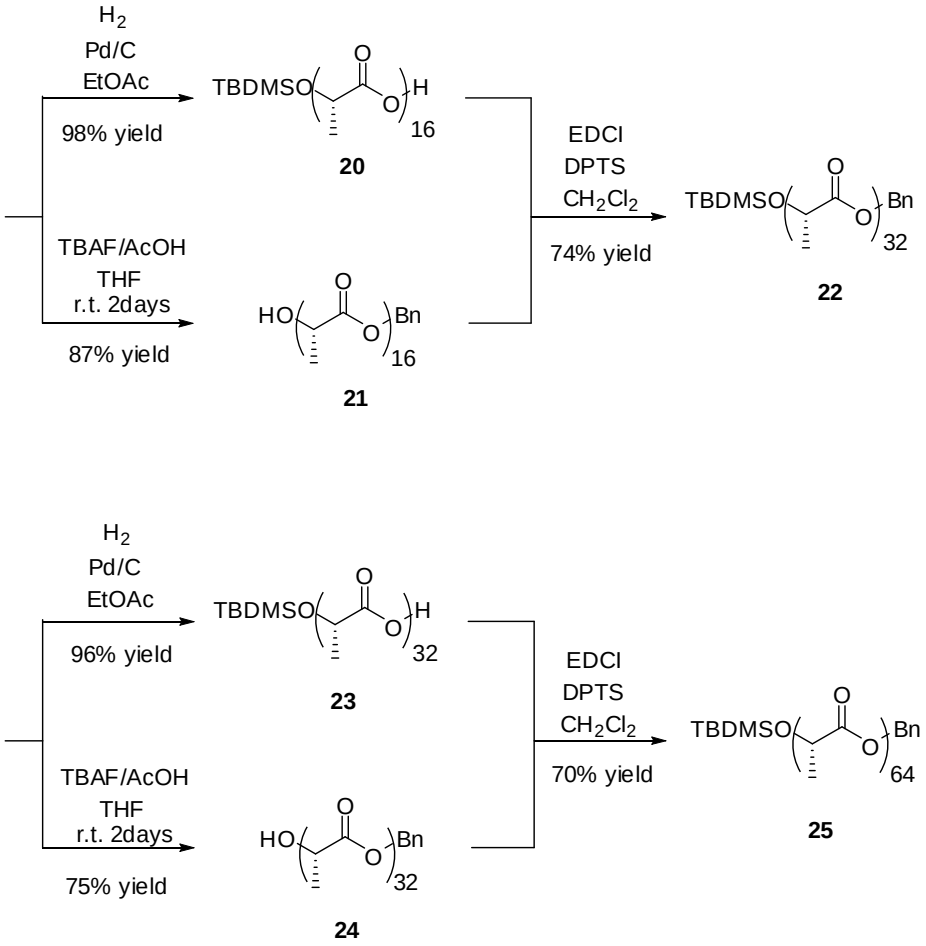
Once Dimer (**5**) was synthesized successfully, following coupling and deprotection reactions according to the 'Exponential Growth Strategy[1]' were straightforward and resulted in high yields (usually over 90% yields for deprotection reactions and 70-90% yields for coupling reactions) (Scheme 4, 5). 1,3-Dicyclohexylcarbodiimide (DCC) was used as the coupling reagent for the syntheses up to 16mer (**19**) and 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) was used to prepare 32mer (**22**) and 64mer (**25**). Benzyl ester (Bn) was deprotected using hydrogenation and TBDMS was deprotected by using a mixture of Tetrabutylammonium fluoride (TBAF) and Acetic acid.

Also, to obtain purer Dimer-OH (**11**), instead of using **11** from Scheme 3 (b) directly, hydroxyl group of **11** was protected first to make Dimer (**5**) (Scheme 3 (b)). And after its purification, TBDMS was removed again to yield purer Dimer-OH (**11**) (Scheme 4). Figure 1 shows a drawing of 64mer (**25**) whose molecular weight is 4834.

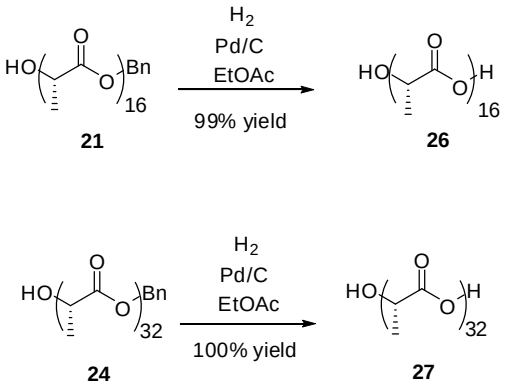

H2
Pd/C
EtOAc
100% yield
TBDMSO
OH
12
5
OBn
DCC
DPTS
CH2Cl2
93% yield
13
TBAF/AcOH
THF
r.t. 2days
89% yield
HO
11


H2
Pd/C
EtOAc
100% yield
14
DCC
DPTS
CH2Cl2
92% yield
16
TBAF/AcOH
THF
r.t. 2days
90% yield
15


H2
Pd/C
EtOAc
94% yield
17
DCC
DPTS
CH2Cl2
87% yield
19
TBAF/AcOH
THF
r.t. 2days
88% yield
18



Scheme 4. Synthetic route to (L)-Lactic acid 64mer (**25**).



Scheme 5. Syntheses of both-ends-deprotected (L)-Lactic acid 16mer (**26**) and 32mer (**27**).

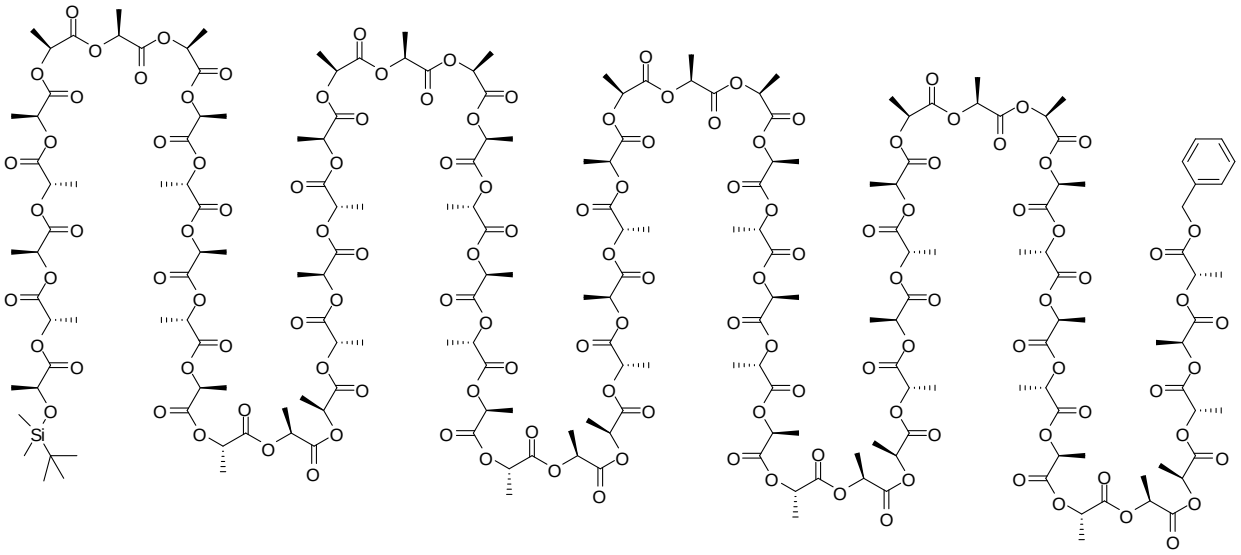


Figure 1. (L)-Lactic acid 64mer (**25**) (Molecular Formula: $C_{205}H_{278}O_{129}Si$, MW = 4834.41).

As previously reported[7] and discussed in Chapter 3, carbodiimide esterifications are always slightly accompanied by a side reaction which converts carboxylic acids into unreactive N-acylureas (DCC-Adducts). In our case also, this kind of side reactions were observed (Scheme 6; Dimer-DCC-Adduct (**28**) is depicted), and to get rid of this type of unfavorable impurities, we purified each product carefully by using flash column chromatography. But in case of higher molecular weight polymer syntheses (especially 32mer (**22**) and 64mer (**25**)), this side reaction turned out to be more problematic because it became extremely difficult to separate DCC-Adducts from our products by means of flash column chromatography and would surely affect the yields of the steps ahead. Thus, we conducted the coupling reactions using EDCI instead of DCC and successfully suppressed the contamination of EDCI-Adducts into our products. Also, especially in case of higher molecular weight polymer syntheses, the difference of the molecular weights of the target molecules and undesired EDCI(DCC)-Adducts are quite large, so preparative GPC was found to be another good additional tool to get rid of the EDCI(DCC)-Adducts.

Scheme 6. Formation of Dimer-DCC-Adduct (**28**).

4-3-2. Analytical Studies of Oligomers/Polymers

Oligomers/polymers' purities and molecular weights were evaluated by means of ^{1}H, ^{13}C-NMR, Mass Spectroscopy (ESI^{+}/TOF) combined with Matrix Assisted Laser Desorption/Ionization (MALDI) and Size Exclusion Chromatography (SEC). Figure 2, 3, and Table 1 show the SEC results of the doubly protected Monomer (**6**) through 64mer (**25**) and revealed high purity of each oligomer/polymer and the absence of significant defect structures.

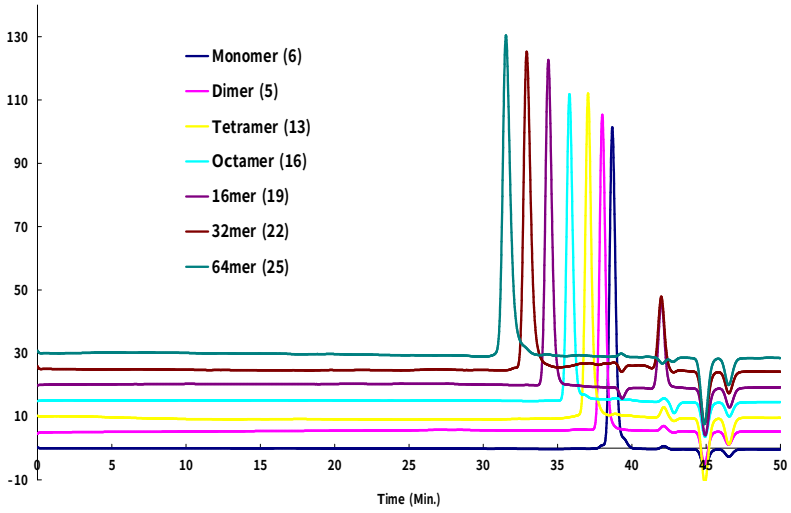


Figure 2. SEC results of the oligomers/polymers.

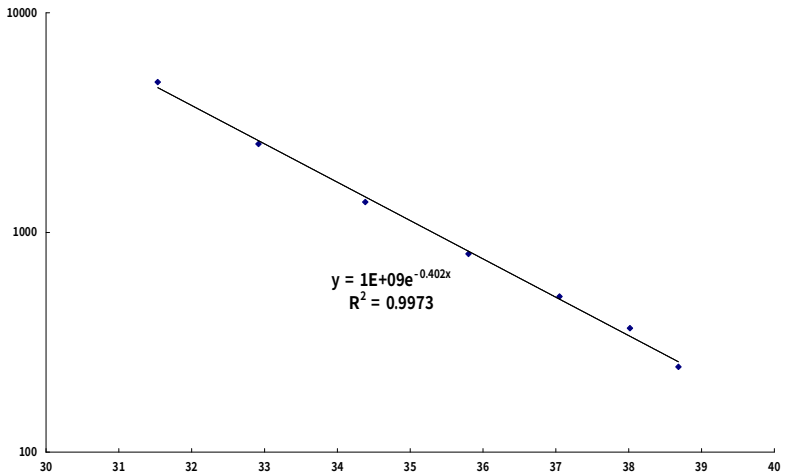


Figure 3. Plot of the molecular weights (logarithmic) of the oligomers/polymers against retention time of SEC measurements.

	Monomer, **6**	Dimer, **5**	Tetramer, **13**	Octamer, **16**	16mer, **19**	32mer, **22**	64mer, **25**
MW (Theoretical)	294	367	511	799	1375	2528	4834
Mw (from GPC)	300	400	600	1200	2300	4600	9100
PDI (from GPC)	1.01	1.01	1.01	1.01	1.01	1.02	1.03

Table 1. Calculated theoretical molecular weights and the actual data from SEC measurements.

MALDI and ESI^+/TOF results showed again the high purity and characteristic of each oligomer/polymer in greater detail.

From MALDI results (Figure 4), up to Octamer (**16**), each oligomer was found to be truly monodisperse, but from 16mer (**19**), especially (N-1)mer and (N-2)mer (which means 15mer and 14mer in case that 16mer is (N)mer) appeared slightly. And in case of 64mer (**25**), much smaller molecular weight oligomers including 61mer, 60mer, and 59mer etc were observed to some extent. These phenomena are due to the very small amount of BnOH generated in the reaction to synthesize Dimer-OH (**11**) in Scheme 3 (b), and Monomer-OH-CO_2H (**3**) generated in the very first reaction making Dimer-OH-CO_2H (**10**) (Scheme 3 (b)) which were rather difficult to separate from the desired products, respectively.

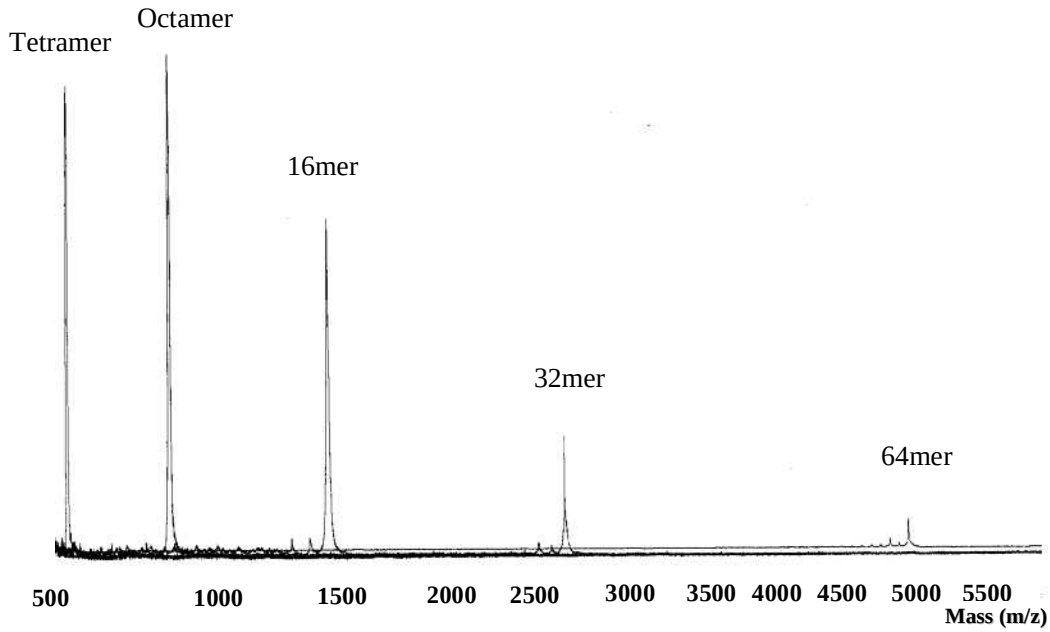
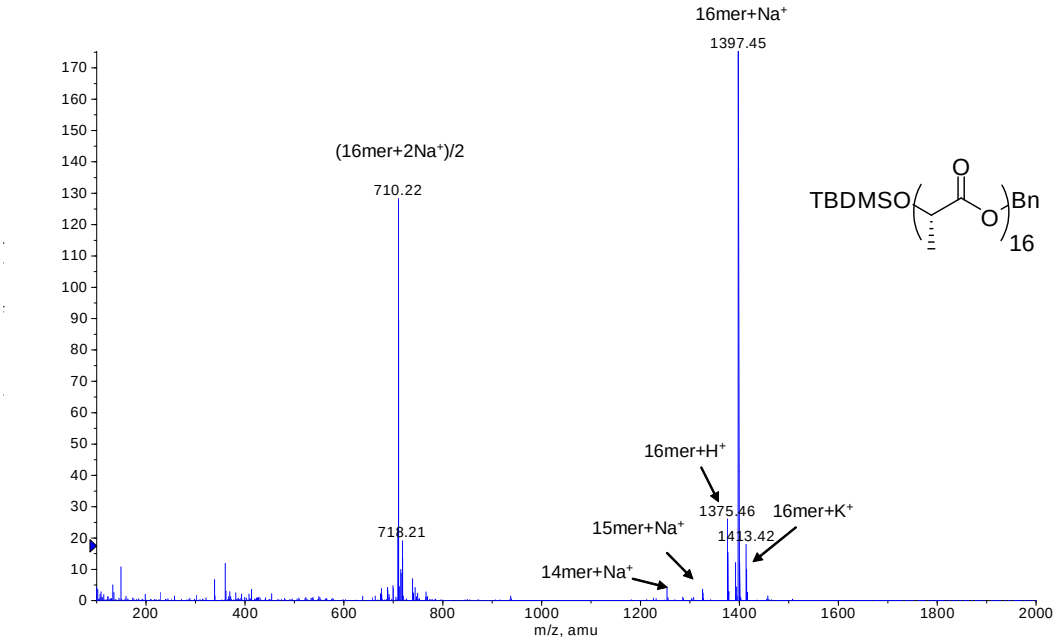


Figure 4. MALDI results (Matrix; Dithranol, Cationating reagent; Sodium trifluoroacetate).

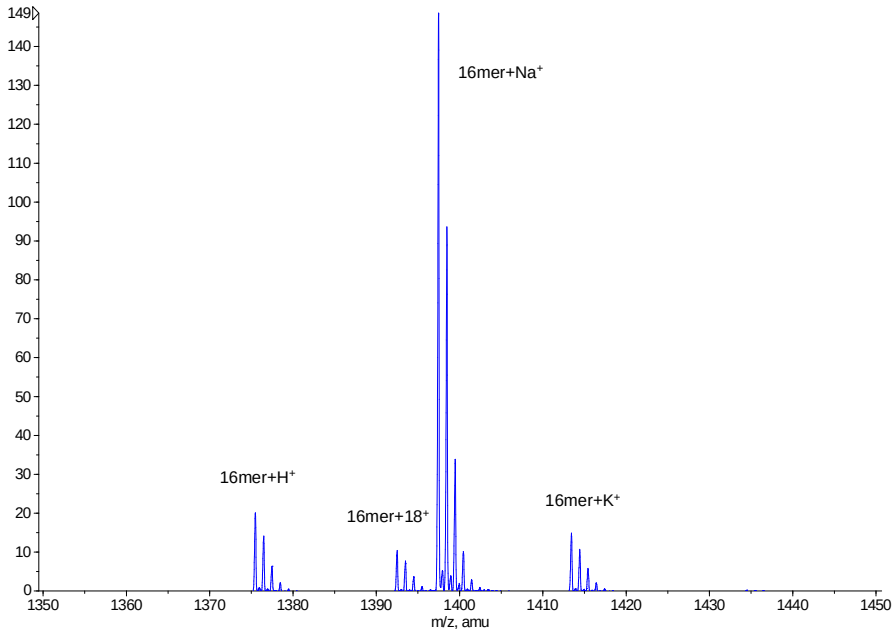
ESI^+/TOF measurements suggested similar results. Because of the high molecular weights of 32mer (**22**) and 64mer (**25**), these two polymers' exact molecular weights were calculated from their doubly and triply charged peaks of the ESI^+/TOF results, respectively. ESI^+/TOF results of 16mer (**19**) and 32mer (**22**) are depicted (Figure 5 (a), (b),

and (c)). From these data, it can be safely said that up to 16mer (**19**), oligomers are almost truly monodisperse. And 32mer (**22**) and 64mer (**25**) are almost perfectly monodisperse.

(a)



(b)



(c)

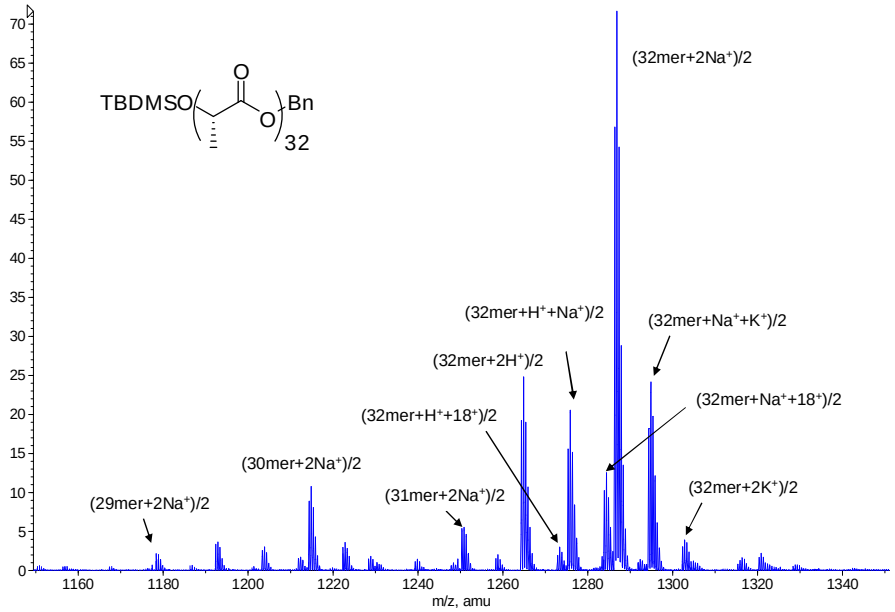


Figure 5. ESI$^+$/TOF result of 16mer (**19**) ((a) and (b)), and 32mer (**22**) (The area of doubly charged peaks is depicted.) ((c)).

SAXS measurements at room temperature (Figure 6(a), (b), and Table 2) indicated the presence of lamellae structure in cases of 16mer (**19**) through 64mer (**25**). And their distance (D)s were very close to the theoretical molecular lengths in cases of 16mer (**19**) and 32mer (**22**) indicating that the molecular chains are fully extended in their each lamellae layer. On the other hand, 64mer (**25**) showed regular features of almost one half of its theoretical molecular length, suggesting that 64mer (**25**) is folded once at the center of each long molecule chain in a lamellae layer (Figure 7).

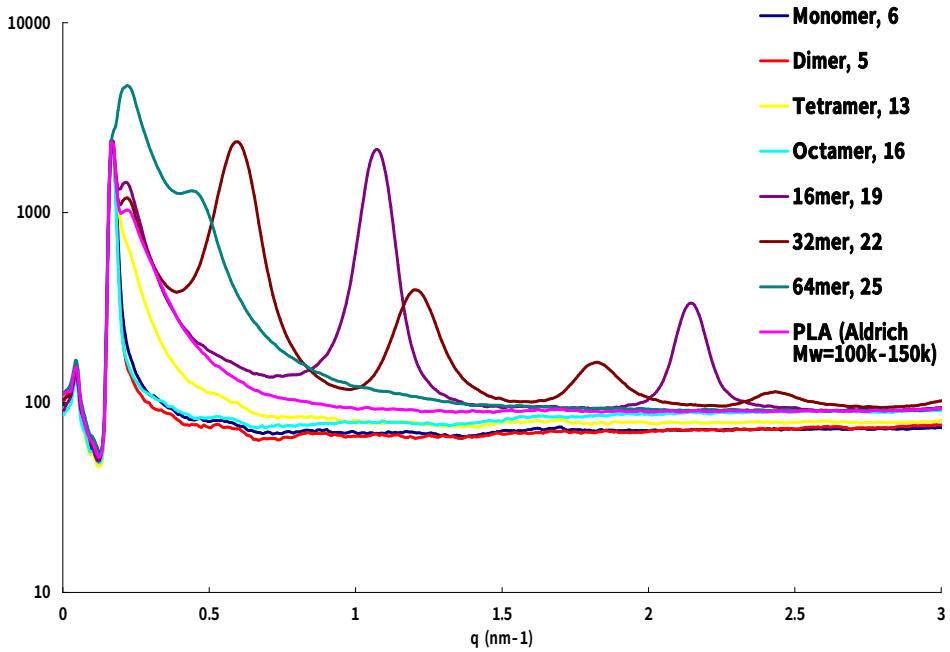


Figure 6(a). Intermediate-SAXS spectra of synthesized oligomers/polymers and commercially available Poly((L)-lactide) purchased from Aldrich.

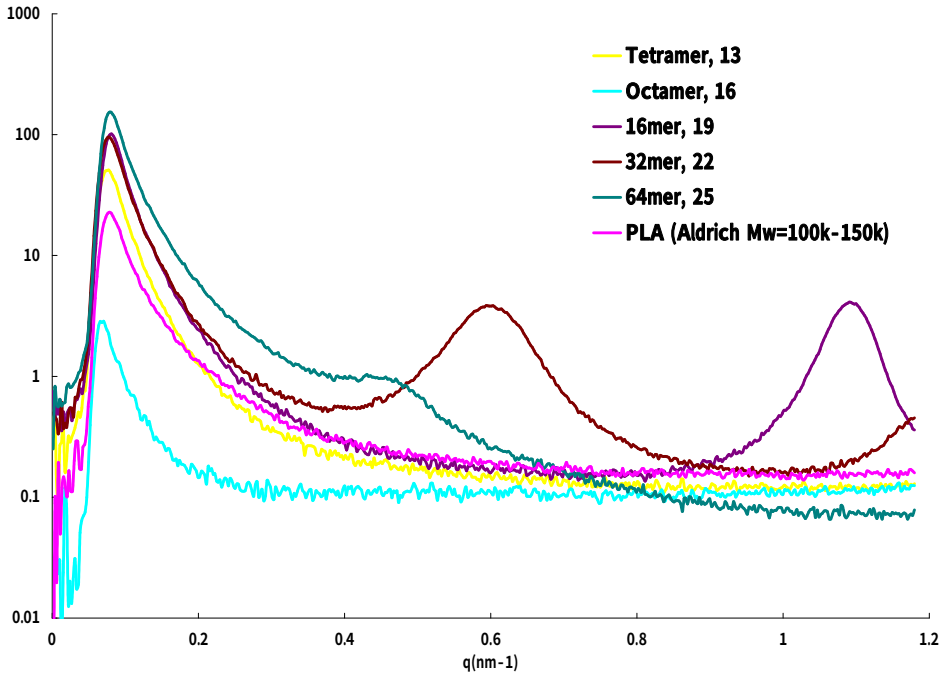
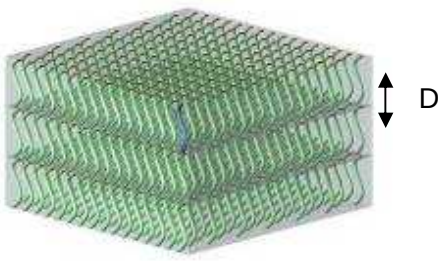


Figure 6(b). Ultra-SAXS spectra of synthesized oligomers and commercially available Poly((L)-lactide) purchased from Aldrich.

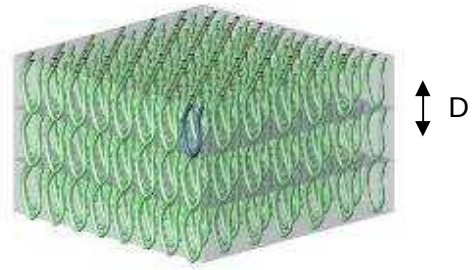
* Poly((L)-lactide) from Aldrich did not show any evidence of crystal structure even after annealing it at 120 ℃ for 2h.

	Monomer, 6	Dimer, 5	Tetramer, 13	Octamer, 16	16mer, 19	32mer, 22	64mer, 25
Calculated Molecular length	1nm	2nm	2nm	4nm	7nm	12nm	23nm
Distance (D)	-	-	-	-	6nm	10nm	14nm

Table 2. Calculated molecular lengths of synthesized oligomers/polymers using ChemSketch (Advanced Chemistry Development, Inc.) and distance D calculated by using the equation ($D = 2\pi / q$) based on the SAXS results (Figure 6(a) and 6(b)).



16mer (**19**) and 32mer (**22**)



64mer (**25**)

Figure 7. Proposed crystal structure of 16mer (**19**) through 64mer (**25**).

The discrepancy between the distance (D) and half of the calculated molecular length of 64mer (**25**) can be some computing error or an evidence of the existence of nonintegral folding chain (NIF) crystal found especially in case of Poly(ethylene oxide)[1(d), 9]. Also it is known that lamellae thickness varies a little bit depends on its crystallization conditions in many cases[10, 11].

And Figure 8(a), 8(b) and Table 3(a), 3(b) show SAXS data of deprotected 16mers and 32mers, **20**, **21**, **26**, **23**, **24**, and **27**.

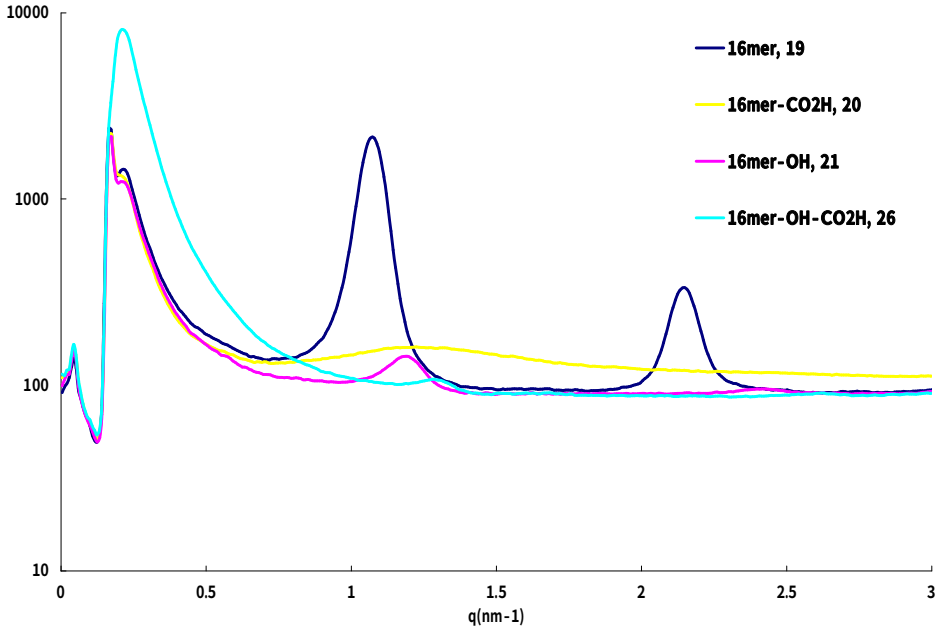


Figure 8(a). Intermediate-SAXS spectra of 16mers, **19**, **20**, **21**, and **26**.

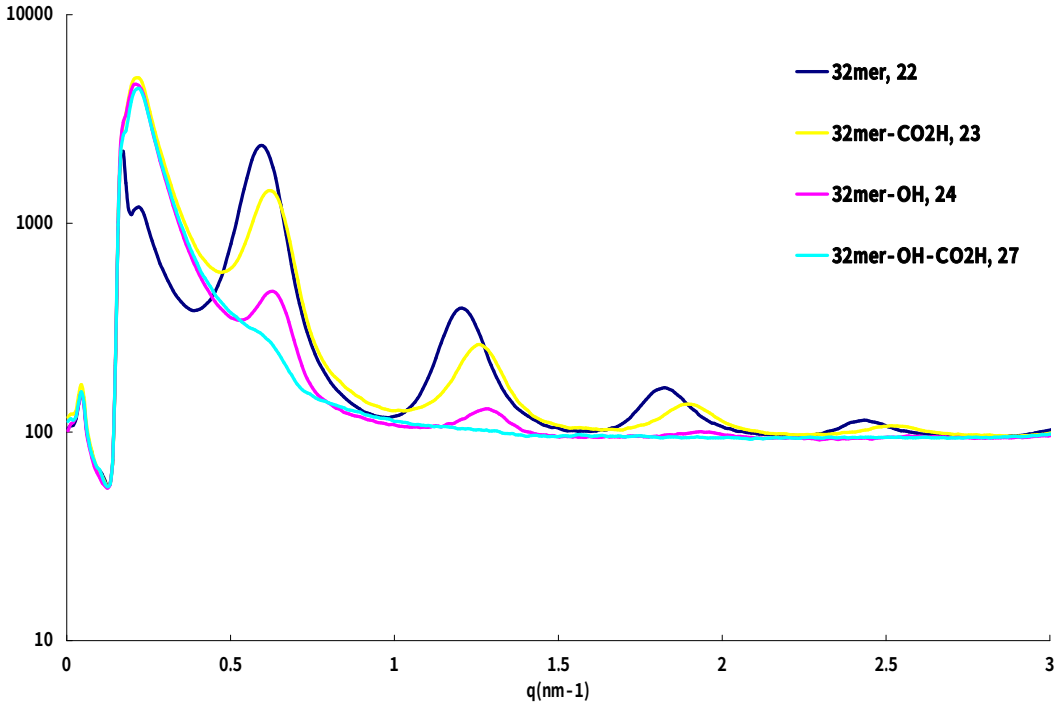


Figure 8(b). Intermediate-SAXS spectra of 32mers, **22**, **23**, **24**, and **27**.

	16mer, **19**	16mer-CO2H, **20**	16mer-OH, **21**	16mer-OH-CO2H, **26**
Distance (D)	6nm	5nm	5nm	5nm
Calculated Molecular length	7nm	6nm	6nm	6nm

Table 3(a). Calculated molecular lengths of 16mers using ChemSketch (Advanced Chemistry Development, Inc.) and distance D calculated by using the equation ($D = 2\pi / q$) based on the SAXS results (Figure 8(a)).

	32mer, **22**	32mer-CO2H, **23**	32mer-OH, **24**	32mer-OH-CO2H, **27**
Distance (D)	10nm	10nm	10nm	10nm
Calculated Molecular length	12nm	11nm	12nm	11nm

Table 3(b). Calculated molecular lengths of 32mers using ChemSketch (Advanced Chemistry Development, Inc.) and distance D calculated using the equation ($D = 2\pi / q$) based on the SAXS results (Figure 8(b)).

From these results, we found that in cases of deprotected 16mers and 32mers, every molecule is again stretched and aligned regularly in each lamellae layer but the crystallinity apparently decreases as the molecule loses its protective groups.

We are now assuming that the reason why the crystallinity decreases is because the arrangement of the lamellae layers becomes less organized as drawn in Figure 9.

Also in case of a longer oligomer, 64mer (**25**), a similar disorganization might have happened (Figure 6(a) and (b)).

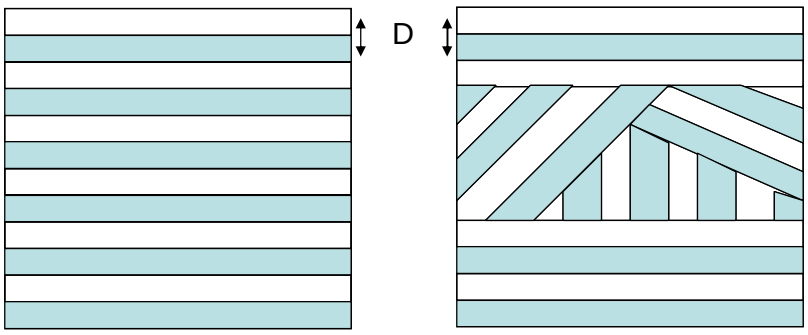


Figure 9. Left; Organized lamellae layers (Protected 16mer (**19**) and 32mer (**22**) etc.)
Right; Disorganized lamellae layers (Deprotected 16mers and 32mes and maybe 64mer (**25**))

Since Tetramer (**13**) is obtained as a crystalline small molecule, we conducted its single crystal diffraction measurement (Figure 10).

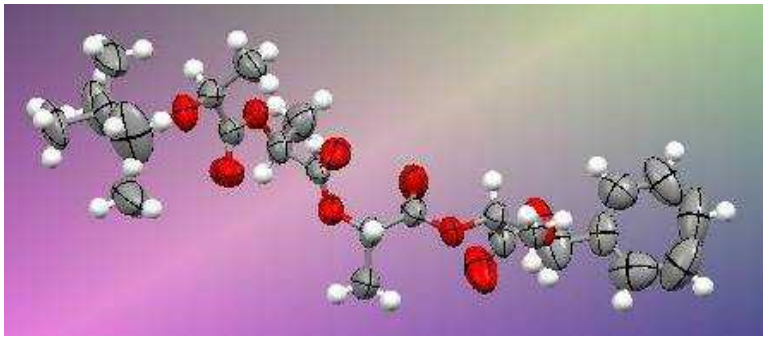


Figure 10. Single Crystal Diffraction of Tetramer (**13**).

From this single crystal diffraction result, no racemization was found and its *S* configurations were retained during the coupling reaction using DCC which is said to cause racemization in many peptide syntheses[11]. This result is also indirectly supported by optical rotation (Table 4) and circular dichroism measurements (Figure 11). The absolute figure of α value of 32mer (**22**) was much bigger than that of Monomer (**6**). And the peak height at 205 nm to 230 nm in the CD spectrum became higher as the molecular length became longer. And homonuclear decoupled ^{1}H-NMR measurements of carboxylic acid terminated oligomers confirmed this phenomenon, too (Figure 12, 13). To avoid the overlapping of Bn peak, we chose carboxylic acid terminated oligomers for this homonuclear decoupled ^{1}H-NMR measurements.

	Monomer, 6	32mer, 22
$[\alpha]^{23}_{D}$ ($CHCl_3$)	-28	-140

Table 4. Optical rotations of Monomer (**6**) and 32mer (**22**).

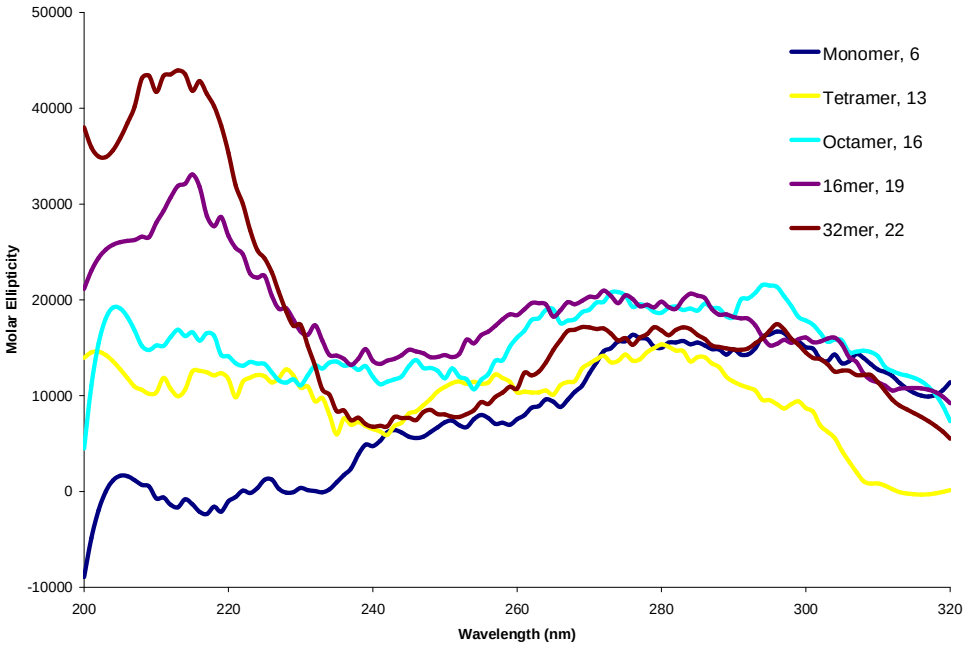


Figure 11. Circular Dichroism (CD) spectra of oligomers (**6**, **13**, **16**, **19**, and **20**).

The homonuclear decoupled ^{1}H-NMR spectra were acquired as approximately 1% solution in $CDCl_3$ or CD_2Cl_2 (In our case, CD_2Cl_2 somehow gave better peak resolutions than $CDCl_3$) with the methyl protons decoupled from the methine protons during the acquisition time. Figure 12 and 13 show NMR charts of their methine proton regions except for the methine proton just next to TBDMSO group.

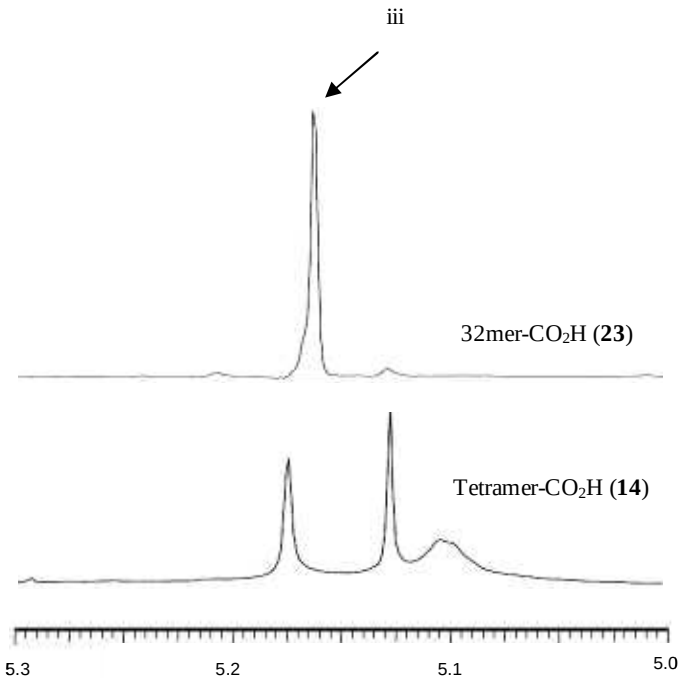


Figure 12. Homonuclear decoupled ^{1}H-NMR spectra using $CDCl_3$ as the solvent. The iii stands for three isotactic pairs, which means stereogenic sequence of –*SSSS*-. Since we used (L)-lactide as the initial raw material, –*RRRR*- is almost impossible to be involved.

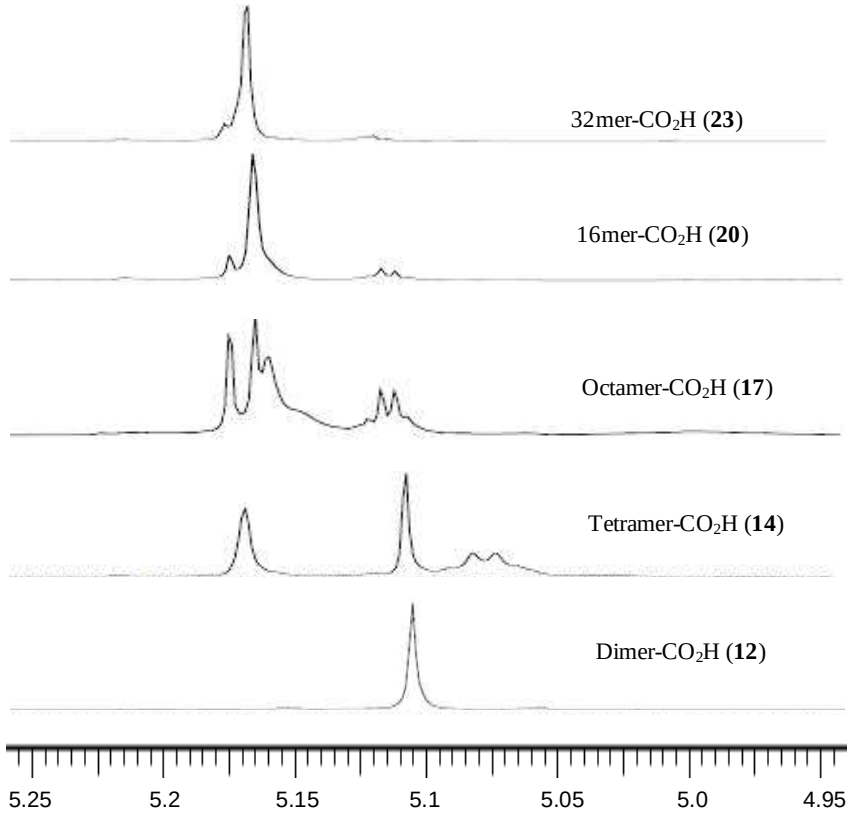


Figure 13. Homonuclear decoupled ^{1}H-NMR spectra using CD_2Cl_2 as the solvent.

Compared these NMR data with previous reports[12], we concluded that all the stereo configurations were retained during the coupling reactions using DCC (EDCI) since, the higher molecular oligomer 32mer-CO_2H (**23**) showed only one singlet peak exclusively with small peaks derived from methine protons near chain ends and spinning-side-bands (Figure 12, 13).

WAXS results also gave us a lot of insight into the small crystal strucuture inside a lamellae lyaer (Figure 14). As described above, Tetramer (**13**) was a crystalline small molecule, and Octamer (**16**) was found to be an amorphous material (liquid). In cases of 16mer (**19**), 32mer (**22**), and 64mer (**25**), there apparently exists some crystalline structure inside each lamellae layer because there found peaks on WAXS graphs, as well (Figure 14). But at the same time, the peaks of these three materials were rather broader and the reason for this phenomenon might be some disorder of the crystals. And we theorize that this disorder is due to twisted and/or reversed orientation of each molecule as drawn in Figure 15.

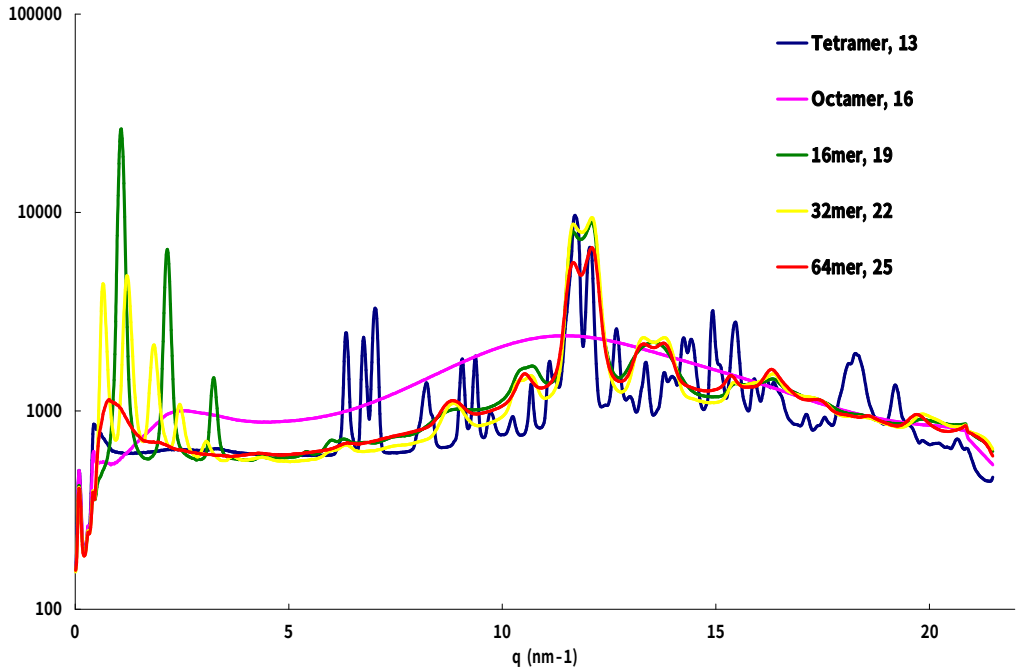


Figure 14. WAXS spectra of Tetramer (**13**) up through 64mer (**25**).

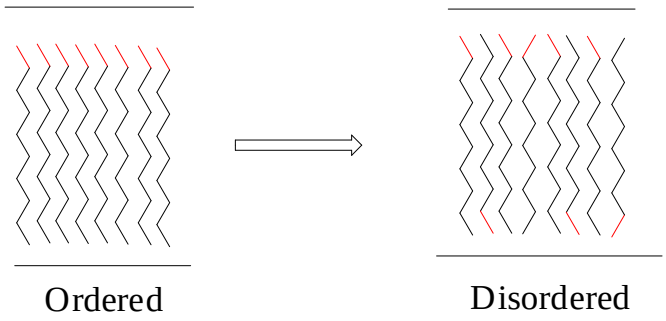


Figure 15. Proposed model of the regularity and order of crystal structure in each lamellae layer. For clarification, molecules are drawn stretched, but in case of 64mer (**25**), each molecule may be folded once as discussed above.

We also conducted DSC (under N_2) and TGA (under N_2) measurements to investigate these oligomers/polymers' thermal properties. As previously reported[13], DSC results of Lactic acid oligomers/polymers are very complicated. Figure 16 shows melting transitions for the 16mer (**19**) and higher oligomers. The melting points increased with molecular weights and reached 164 ℃ for the 64mer (**25**) which is comparable to the melting point of much higher molecular weight PLA (173 ℃).

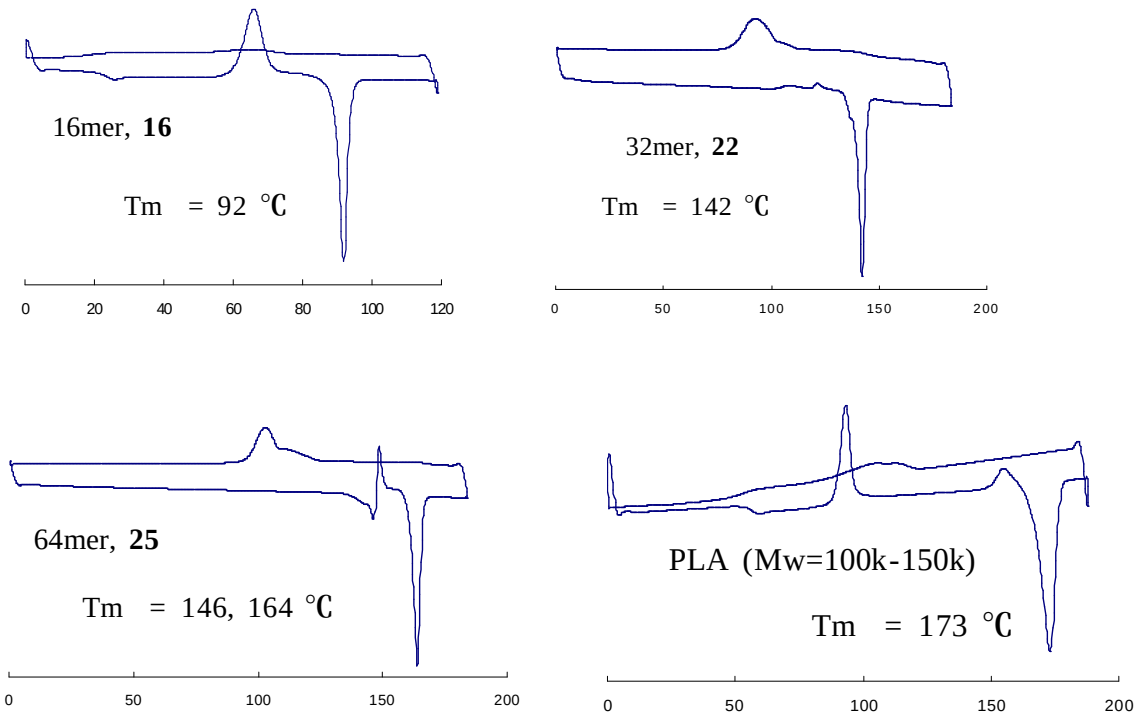
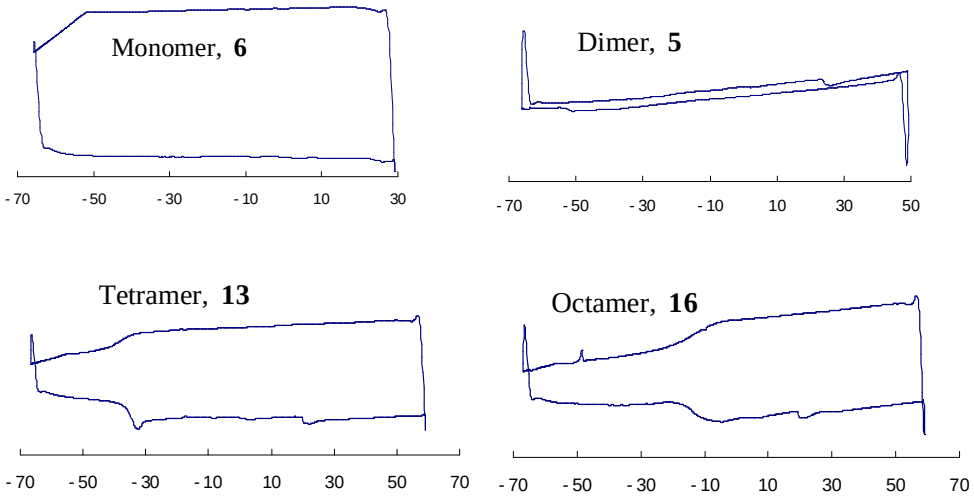


Figure 16. DSC data of ends-protected 16mer (**19**), 32mer (**22**), 64mer (**25**), and commercially available high molecular weight PLA. (5 ℃/min.)

Though Monomer (**6**), Dimer (**5**), and Octamer (**16**) did not show any melting peaks, Tetramer (**13**), a crystalline small molecule, gave a sharp melting peak at 38 ℃ in the 1st cycle when we tried to heat it up at the heating rate of 3 ℃/min (Figure 17). But once it was melt, it did not crystallize during the cooling process down to -70 ℃ (3 ℃/min.) and from the 2nd cycle, it did not show melting peak anymore. This indicates that it takes quite a long time to crystallize Tetramer (**13**). In fact, it took more than 24 hours to crystallize it in the freezer at -20 ℃.



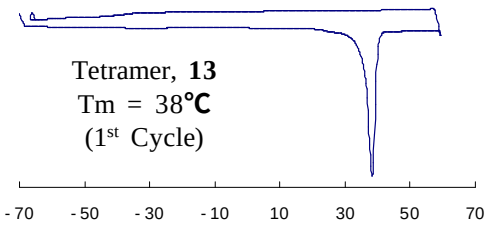


Figure 17. DSC data of end-protected Monomer (**6**), Dimer (**5**), Tetramer (**13**), and Octamer (**16**). If not otherwise specified, heating and cooling rate was 3 ℃/min. and the 3rd cycle results are shown. Only for Tetramer (**13**), the 1st cycle result is also shown. (3 ℃/min.)

Figure 18 shows the DSC data of 16mers. In case of 16mer (**19**), there observed a melting peak at 92 ℃ (5 ℃/min.). And in cases of 16mer-OH (**21**) and 16mer-OH-CO_2H (**26**), melting peaks were observed only in the 1st cycle when they were heated and cooled at the rate of 5 ℃/min. But when we heated and cooled them at 3 ℃/min., melting peaks were observed even in the 3rd cycles. And in case of 16mer-CO_2H (**20**), there observed no melting peak even though it was heated and cooled at 3 ℃/min.

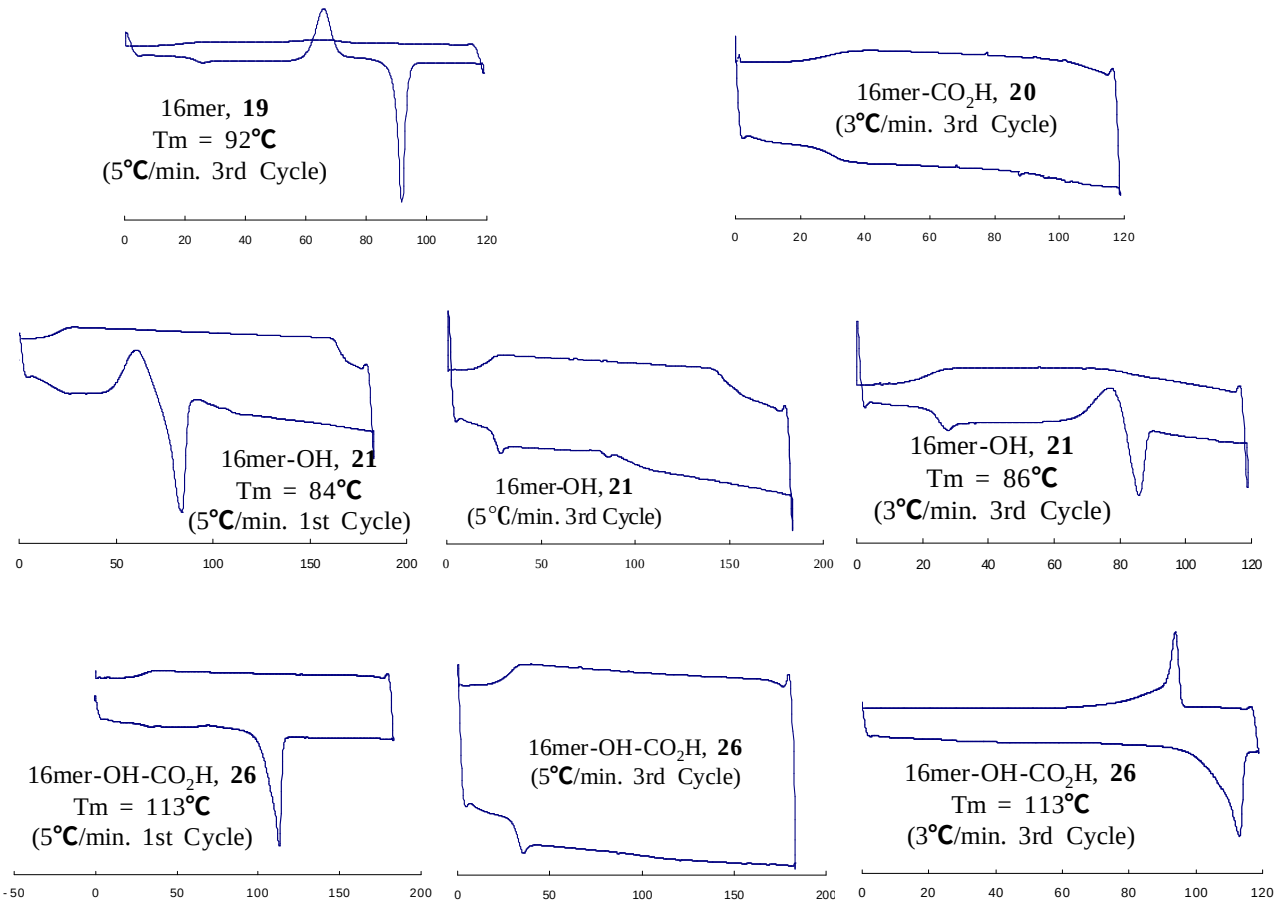


Figure 18. DSC data of 16mers.

Figure 19 shows the DSC data of 32mers. Different from 16mers, all the 32mers showed melting peaks in the 3rd cycles at the heating and cooling rate of 5 ℃/min. And from those data, the effect of the chain end groups was found to be minimal with little, if any, on the difference in melting temperature observed with variation in the chain ends.

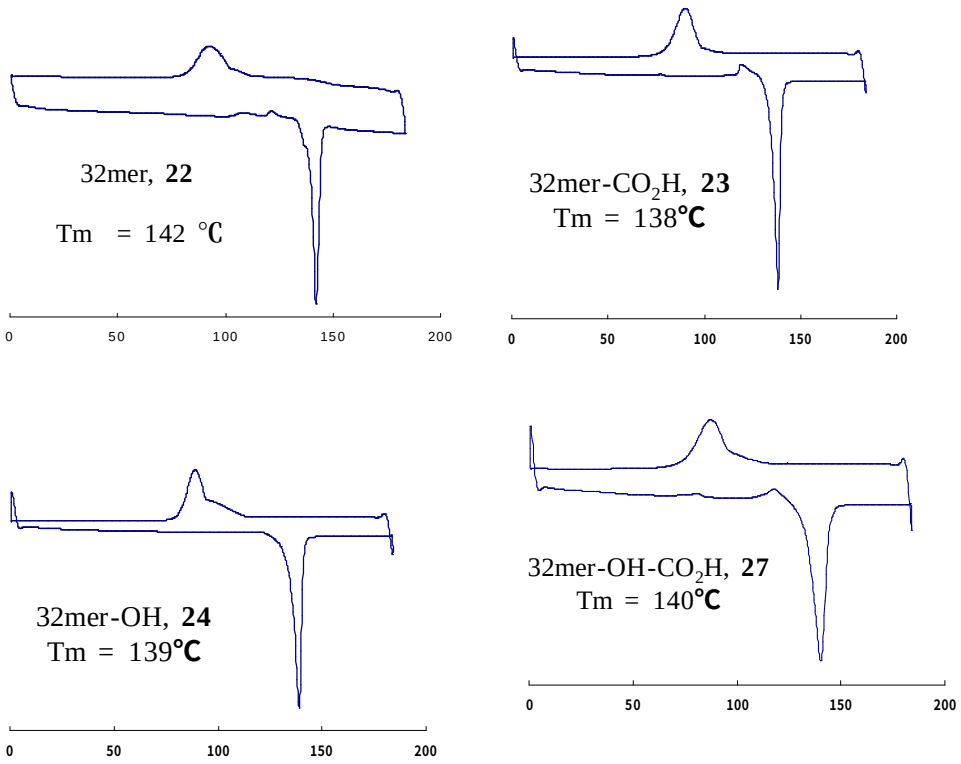


Figure 19. DSC data of 32mers. (5 ℃/min. 3rd cycle)

Table 5 gives a summary of the melting points of the oligomers obtained in the DSC measurements.

	Monomer, **6**	Dimer, **5**	Tetramer, **13**	Octamer, **16**	16mer, **19**	32mer, **22**	64mer, **25**	Commercial PLA
Tm (℃)	-	-	38 (Only 1st Cycle)	-	92	142	164 (146)	173

	16mer, **19** (5℃/min)	16mer-CO_2H, **20** (3℃/min)	16mer-OH, **21** (5℃/min)	16mer-OH, **21** (3℃/min)	16mer-OH-CO_2H, **26** (5℃/min)	16mer-OH-CO_2H, **26** (3℃/min)
Tm (℃)	92	-	84 (Only 1st Cycle)	86	113 (Only 1st Cycle)	113

	32mer, **22**	32mer-CO_2H, **23**	32mer-OH, **24**	32mer-OH-CO2H, **27**
Tm (℃)	142	138	139	140

Table 5. Summary of the melting points of (L)-Lactic acid oligomers/polymers from the DSC measurements.

On top of these insight described above, there found Tgs, small amount of endothermic and exothermic peaks during DSC measurements and they are about to be characterized fully soon.

Analysis of the decomposition of the (L)-Lactic acid oligomers with increasing molecular weight also proved to be very instructive. As shown in the TGA results (Figure 20), there is a well-defined increase in thermal stability from Monomer (**6**) which begins to decompose at 60 ℃, Dimer (**5**) (100 ℃), and finally to 64mer (**25**) where decomposition is initiated at 300 ºC. Dramatic increase in the thermal stability is observed when the molecular weight was doubled between Monomer (**6**) and 16mer (**19**), however the increase from **19** to 64mer (**25**) was significantly less even though the length of the polymer chain is increased 4 times. In all the cases, the chain ends were the same, with a single TBDMS protected hydroxyl group and a single Benzyl ester protected carboxylic acid group. The strong correlation between the oligomer's length and its thermal decomposition profile prompted an examination of the effect of chain end functionality and a direct comparison with a commercially available Poly((L)-lactide) (PLA) sample. Of particular note was the observation that all of the 32mer samples, irrespective of the end groups, were significantly more stable than the commercial PLA (MW = 100,000-150,000) and in each case the onset temperature of decomposition was higher than that of commercial PLA. Interestingly, the 32mer with the lowest thermal stabilities was the hydroxyl-terminated derivative, 32mer-OH (**24**) and the doubly deprotected, hydroxyl-carboxylic acid derivative, 32mer-OH-CO_2H (**27**) (Figure 21). From these results, it is apparent that the presence of a hydroxyl chain end leads to decreased thermal stability, presumably due to the occurrence of chain backbiting and associated depolymerization. The presence of a terminal carboxylic acid group is also destabilizing but to a decreased degree when compared to the hydroxyl group. The same phenomenon was observed for PCL as discussed in Chapter 3.

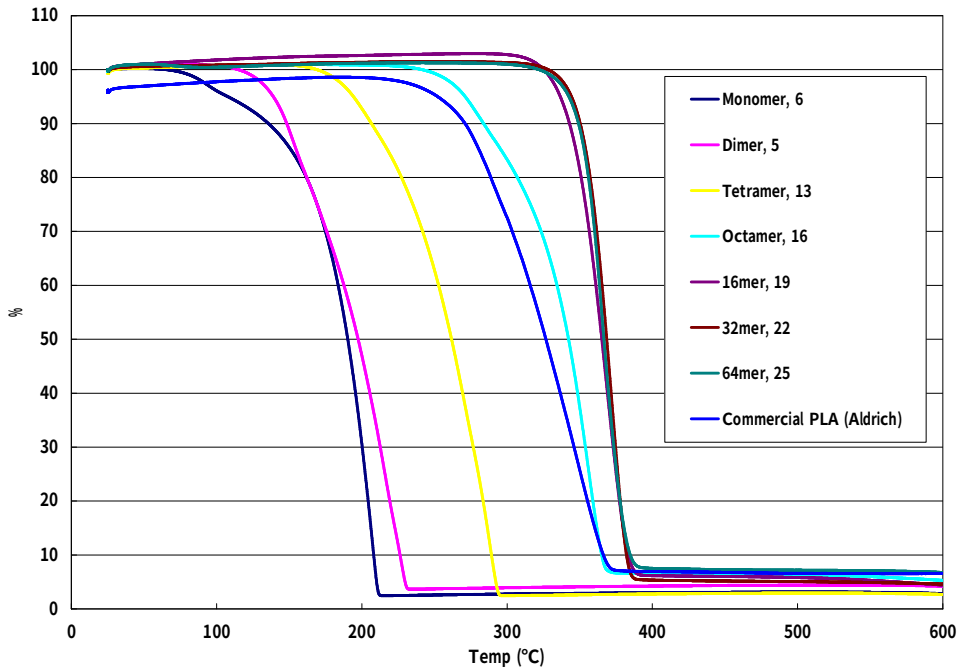


Figure 20. TGA data of Monomer (**6**) through 64mer (**25**) together with commercial PLA (MW = 100k-150k).

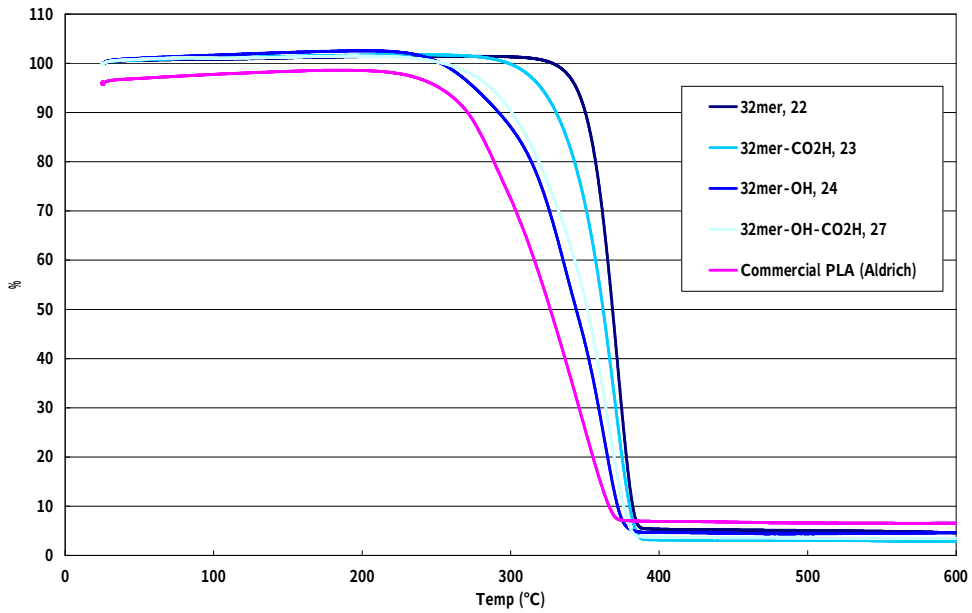


Figure 21. TGA data of 32mer (**22**), ends-deprotected 32mers, **23**, **24**, and **27**, and commercial PLA (MW = 100k-150k).

4-4. Summary

A synthetic strategy for the preparation of well-defined (L)-Lactic acid oligomers up through 64mer was developed using a method called 'Exponential Growth Strategy[1]'. By the selection of orthogonal protective groups, *t*-Butyldimethylsilyl ether and Benzyl ester, high yields of the oligomers were obtained and the effect of both oligomer length and chain end functionality onto the physical and chemical properties of parent polymer, Poly((L)-lactide), was examined. Characterization of each oligomer by a combination of spectroscopic and chromatographic techniques revealed very high purity of each oligomer and the absence of significant defect structures. A direct correlation between oligomer length and thermal properties was observed with novel semi-crystalline behavior being observed for each of the oligomers above 16mer. A similar relationship between oligomer length and crystal structure was observed by SAXS measurements which showed formation of lamellae crystals that increased in thickness with oligomer length in cases of the 16mer and 32mer. Interestingly, for the 64mer, chain folding was observed with a unit length of approximately 32 Lactic acid units. Also, all the stereo configuration of the each Lactic acid unit revealed to be retained during the coupling reactions using DCC or EDCI. The availability of well-defined oligomers of (L)-Lactic acid will allow new insight into the fundamental physical and biomaterial properties of this widely studied and commercially important parent polymer. Furthermore, this sophisticated method of synthesizing well-defined (L)-Lactic acid oligomers/polymrs together with ε-Caprolactone oligomers/polymers (Chapter 3)[14] allow us to synthesize truly monodisperse copolymer[15] of PLA and PCL in various combination, order, and chain length ratios.

4-5. References

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CHAPTER 5

'Fabrication of Functionalized Nano-scale Polymer Objects for Multivalent Biological Interactions Using a Dendronized Poly((L)-lysine)'

5-1. Introduction

Throughout Chapter 2, 3, and 4, we concluded that the 'Exponential Growth Strategy[1]' is a very powerful tool to synthesize precisely size tuned linear polymers[2]. Also, rigid-rod dendronized linear polymers that bear pendant dendron groups at every single repeating unit are considered to be good candidates for variety of applications including a catalyst of organic cheistry and an imaging material. And they can be suitable especially for drug delivery application since they have multivalent and highly functionalized structures which enable facile drug attachment. Such rodlike dendronized linear polymers were first described in a patent by Tomalia in the late 1980s[3], and Hawker and Fréchet reported the synthesis of a styrenic polymer containing Fréchet-type dendrons[4]. In 2006, again Fréchet reported the synthesis of dendronized Poly((L)-lysine)[5]. In case of Bis-MPA type dendrons, it is easy to functionalize the terminal hydroxyl groups with various type of biologically active groups and we have considered that synthesizing a precisely size tuned (between 10 nm and 1 μm) dendronized linear polymer like Poly((L)-lysine) will give us a good access to an artificial mimic of viruses. Herein we report the syntheses of precisely size tuned dendronized linear Poly((L)-lysine)s up through 20mer with Bis-MPA type G2 (the 2nd Generation)-dendron and Tetramer with G4-dendron.

5-2. Experimental Section

Materials.

4-(Dimethylamino)pyridinium *p*-toluenesulfonate (DPTS)[6] and Bis(2-nitrophenyl) methanol[7] were synthesized according to the previously reported procedures. Bis-MPA type dendrons like Acetonide-G2-OH dendron (**6**) were also synthesized according to the previously established protocol[8]. And by repeating the same protocol, up to the 4th generation derivative, Acetonide-G4-OH dendron (**27**) was synthesized, too. Fmoc-Lys(Boc)-OH (**1**), H-Val-2-ClTrt resin, and Fmoc-$(Lys(Dde))_8$-Val-2-ClTrt resin were purchased from AnaSpec Inc. and used without further purification. All the other chemicals and solvents were purchased from Aldrich, of reagent grade, and used without further purification if not otherwise specified. All the reactions were carried out under ambient conditions, i.e. non-inert atmospheres.

General Procedures/Characterization.

Shaking of the samples were conducted using IKA VIBRAX (VXR basic) at the vibration rate of 42 Hz. Analytical TLC was performed on commercial Merck Plates coated with silica gel GF254 (0.24 mm thick). Silica gel for flash column chromatography was Merck Kieselgel 60 (230-400 mesh, ASTM). ^{1}H-NMR and ^{13}C-NMR measurements were performed on a Bruker AC 500 and/or AC 200 spectrometer at room temperature. $CDCl_3$ was used as NMR solvent if not otherwise specified. Matrix Assisted Laser Desorption/Ionization (MALDI-TOF-MS) was carried out at room temperature on DYNAMO THERMO BIOANALYSIS using Dithranol in THF as the

matrix and Sodium trifluoroacetate in THF as the cationating agent. Size exclusion chromatography (SEC) was carried out at room temperature on a Waters Alliance HPLC System (Waters 2695 Separation Module) connected to Waters Styragel® HR columns (0.5, 2, 4, and 5 INT'L HAZA) using THF as eluent (flow rate: 1 mL/min). A Waters 2414 differential refractometer and a 2996 photodiode array detector were employed. The molecular weights of the polymers were calculated relative to linear polystyrene standards.

Fmoc-Lys(Boc)-OBn (2).

A 1 L round bottom flask was charged with 9.99 g (21.32 mmol) of Fmoc-Lys(Boc)-OH (**1**), 3.46 g (32.01 mmol) of Benzyl alcohol, 4.93 g of *N,N'*-Dicyclohexylcarbodiimide (DCC), 0.27 g (2.18 mmol) of 4-(Dimethylamino)pyridine (DMAP), and 377 mL of CH_2Cl_2. This reaction mixture was stirred overnight at room temperature. The resulting mixture was poured into a separatory funnel and washed with 200 mL of satd. $CuSO_4$*aq.* and 200 mL of satd. NaCl*aq*. The organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Crude product was then purified via flash column chromatography using 10:1 CH_2Cl_2:MeOH as eluent yielding 10.36 g (87% yield) of **2** as a clear colorless viscous oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ7.78-7.26 (m, Ar**H**, 13H), 5.41 (b, Fmoc-N**H**, 1H), 5.18 (b, $CO_2C\mathbf{H}_2Ph$, 2H), 4.37 (b, $CO_2C\mathbf{H}_2C\mathbf{H}$(in Fluorenylmethoxycarbonyl), 3H), 4.21 (t, J = 7.0 Hz, $CH_2C\mathbf{H}(NH(Fmoc))CO_2Bn$, 1H), 3.06 (b, $BocNHC\mathbf{H}_2$, 2H) 1.95-1.10 (b, $BocNHCH_2(C\mathbf{H}_2)_3CH(NH(Fmoc))CO_2$, 6H), 1.44 (s, $(C\mathbf{H}_3)_3CO$, 9H). ^{13}C NMR ($CDCl_3$): δ173.49 ($CH\mathbf{C}O_2Bn$, 1C), 156.25 ($CH_2O\mathbf{C}ONH$(in Fluorenylmethoxycarbonyl), 1C), 156.17 ($(CH_3)_3\mathbf{C}ONH$, 1C), 144.11 (Ar(Fmoc), CH_2CH-**C**, 1C), 143.94 (Ar(Fmoc), CH_2CH-**C**, 1C), 141.49 (Ar(Fmoc), **C**(Ar)-**C**(Ar'), 2C), 135.45 (Ar(Bn), CH_2-**C**, 1C) 128.85-125.29 (Ar(Fmoc, Bn), 11C), 120.16 (Ar(Fmoc), CH_2CH-C**C**H, 2C), 83.38 ($(CH_3)_3\mathbf{C}O$, 1C), 67.30 ($CO_2\mathbf{C}H_2$, (Fmoc, Bn), 2C), 54.00 ($CH_2\mathbf{C}H(NH(Fmoc)CO_2Bn$, 1C), 47.36 (Ar**C**$HCH_2OCONH$(in Fluorenylmethoxycarbonyl), 1C), 32.79 ($BocNH\mathbf{C}H_2CH_2CH_2CH_2$, 1C), 32.33 ($BocNHCH_2CH_2CH_2\mathbf{C}H_2$, 1C), 29.77 ($BocNHCH_2\mathbf{C}H_2CH_2CH_2$, 1C), 28.61 ($(\mathbf{C}H_3)_3CO$, 3C), 22.48 ($BocNHCH_2CH_2\mathbf{C}H_2CH_2$, 1C). Mass Spec for $C_{33}H_{38}N_2O_6$ Calculated: 558.27; Found $(M+Na)^+$: 581.26.

Fmoc-Lys(NH_3Cl)-OBn (3).

1.31 g (3.51 mmol) of 2M HCl/Et_2O was added to a CH_2Cl_2 (1.1 mL) solution of **2** (0.09 g (0.17 mmol)). This reaction mixture was stirred overnight at room temperature. The resulting mixture was concentrated under reduced pressure. Then, three sets of 'adding 5 mL of THF and concentrating under reduced pressure' were conducted to get rid of the residue of HCl. Crude product was washed with 20 mL of Hexanes and 20 mL of Et_2O, respectively yielding 0.08 g (93% yield) of **3** as a white powder. ^{1}H NMR (200 MHz, CD_3OD): δ8.00-7.00 (m, Ar**H**, 13H), 5.14 (b, Fmoc-N**H**, $CO_2C\mathbf{H}_2Ph$, 3H), 4.45-4.00 (m, $CO_2C\mathbf{H}_2C\mathbf{H}$(in Fluorenylmethoxycarbonyl) , $CH_2C\mathbf{H}(NH(Fmoc))CO_2Bn$, 4H), 2.87 (t, J = 7.5 Hz, $ClNH_3C\mathbf{H}_2$, 2H) 2.10-1.00 (b, $ClH_3NCH_2(C\mathbf{H}_2)_3CH(NH(Fmoc))CO_2$, 6H). ^{13}C NMR ($CD_3OD$): δ173.79 ($CH\mathbf{C}O_2Bn$, 1C), 158.84 ($CH_2O\mathbf{C}ONH$(in Fluorenylmethoxycarbonyl), 1C), 145.40 (Ar(Fmoc), CH_2CH-**C**, 1C), 145.22 (Ar(Fmoc), CH_2CH-**C**, 1C), 142.70 (Ar(Fmoc), **C**(Ar)-**C**(Ar'), 2C), 137.33 (Ar(Bn), CH_2-**C**, 1C) 130.44-125.11 (Ar(Fmoc, Bn), 11C), 121.07 (Ar(Fmoc), CH_2CH-C**C**H, 2C), 68.06 ($CO_2\mathbf{C}H_2$, (Fmoc, Bn), 2C), 55.03 ($CH_2\mathbf{C}H(NH(Fmoc)CO_2Bn$, 1C), 48.47 (Ar**C**$HCH_2OCONH$(in Fluorenylmethoxycarbonyl), 1C), 40.64 ($ClH_3N\mathbf{C}H_2CH_2CH_2CH_2$, 1C), 32.00 ($ClH_3NCH_2CH_2CH_2\mathbf{C}H_2$, 1C), 28.02 ($ClH_3NCH_2\mathbf{C}H_2CH_2CH_2$, 1C), 23.86 ($ClH_3NCH_2CH_2\mathbf{C}H_2CH_2$, 1C). Mass Spec for $C_{28}H_{31}ClN_2O_4$ Calculated: 494.20; Found $(M-Cl)^+$: 459.22.

General procedure of attachment of dendrons: Synthesis of Fmoc-Lys(Acetonide-G2)-OBn (7) depicted.

0.09 g (0.20 mmol) of Acetonide-G2-OH Dendron (**6**), 0.06 g (0.28 mmol) of DCC, 0.03 g (0.35 mmol) of Pyridine (pyr), and 0.03 g (0.23 mmol) of 1-Hydroxybenzotriazole hydrate (HOBT) were added to a THF/CH_2Cl_2 (1.9 mL/0.5 mL) solution of **3** (0.10 g (0.21 mmol)). This reaction mixture was stirred overnight at room temperature. The resulting mixture was filtered and poured into a separatory funnel containing 15 mL CH_2Cl_2 and 15 mL of H_2O. The organic layer was washed with 20 mL of satd. $CuSO_4$*aq*. and 20 mL of satd. NaCl*aq*. and concentrated under reduced pressure. Crude product was then purified via flash column chromatography using 1:2 Hexanes:Ethyl acetate as eluent yielding 10.36 g (65% yield) of **7** as a clear sticky oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ7.79-7.26 (m, Ar**H**, 13H), 6.52 (b, Acetonide-G2-N**H**CH_2, 1H), 5.41 (b, Fmoc-N**H**, 1H), 5.18 (b, $CO_2C\mathbf{H}_2$Ph, 2H), 4.50-3.50 (m, $CO_2C\mathbf{H}_2C\mathbf{H}$(in Fluorenylmethoxycarbonyl), $CH_2C\mathbf{H}$(NH(Fmoc))CO_2Bn, $COC(CH_3)(C\mathbf{H}_2O)_2$(in Acetonide-G2), 16H), 3.21 (b, Acetonide-G2-NHC$\mathbf{H}_2$, 2H), 2.10-0.80 (b, Acetonide-G2-$NHCH_2(C\mathbf{H}_2)_3CH(NH(Fmoc))CO_2$, 6H), 1.43, 1.41 (ss, $(C\mathbf{H}_3)_2C(OCH_2)_2$(in Acetonide-G2), 12H), 1.25 (s, $NHCOC(C\mathbf{H}_3)(CH_2OCO)_2$, 3H), 1.08 (s, $(CH_3)_2C(OCH_2)_2(C\mathbf{H}_3)CCO_2CH_2C$, 6H). ^{13}C NMR ($CDCl_3$): δ173.84 ($CH\mathbf{C}O_2$Bn, 1C), 172.71 ($O\mathbf{C}OC(CH_3)(CH_2O)_2C(CH_3)_2$, 2C), 172.45 ($NH\mathbf{C}OC(CH_3)(CH_2O)_2$, 1C), 156.27 ($CH_2O\mathbf{C}$ONH(in Fluorenylmethoxycarbonyl), 1C), 144.06 (Ar(Fmoc), CH_2CH-**C**, 1C), 143.94 (Ar(Fmoc), CH_2CH-**C**, 1C), 141.46 (Ar(Fmoc), **C**(Ar)-**C**(Ar'), 2C), 135.46 (Ar(Bn), CH_2-**C**, 1C) 128.80-125.24 (Ar(Fmoc, Bn), 11C), 120.15 (Ar(Fmoc), CH_2CH-C**C**H, 2C), 98.45 ($(CH_3)_2\mathbf{C}(OCH_2)_2C$, 2C), 67.34, 67.21 ($CO_2\mathbf{C}H_2$, (Fmoc, Bn), 2C), 66.51 ($(CO_2\mathbf{C}H_2)_2C(CH_3)CONH$, 2C), 66.33 ($(CH_3)_2C(O\mathbf{C}H_2)_2(CH_3)CCO_2CH_2C$, 4C), 54.06 ($CH_2\mathbf{C}H$(NH(Fmoc))$CO_2$Bn, 1C), 47.33 (Ar**C**H$CH_2$OCONH(in Fluorenylmethoxycarbonyl), 1C), 46.80 ($(CO_2CH_2)_2(CH_3)\mathbf{C}CONH$, 1C), 42.41 ($(CH_3)_2C(OCH_2)_2(CH_3)\mathbf{C}CO_2CH_2C$, 2C), 39.31 (G2-NH$\mathbf{C}H_2CH_2CH_2CH_2$, 1C), 32.06 (G2-$NHCH_2CH_2CH_2\mathbf{C}H_2$, 1C), 29.17 (G2-$NHCH_2\mathbf{C}H_2CH_2CH_2$, 1C), 26.42 ($(\mathbf{C}H_3)_2C(OCH_2)_2(CH_3)CCO_2CH_2C$, 4C), 22.64 (G2-$NHCH_2CH_2\mathbf{C}H_2CH_2$, 1C), 18.47 ($(CH_3)_2C(OCH_2)_2(\mathbf{C}H_3)CCO_2CH_2C$, 2C), 17.95 ($(CO_2CH_2)_2(\mathbf{C}H_3)CCONH$, 1C). Mass Spec for $C_{49}H_{62}N_2O_{13}$ Calculated: 886.43; Found $(M+H)^+$: 887.41.

General procedure of acetonide deprotection reaction (A): Synthesis of Fmoc-$(Lys(HO\text{-}G1))_4$-OBn (9) depicted.

0.3 g (0.3 mmol) of 1M HCl*aq*. was allowed to drip into a THF (0.7 mL) solution of Fmoc-Lys(Acetonide-G1)-OBn (**8**) (0.02 g (0.03 mmol)). This reaction mixture was stirred overnight at room temperature. The resulting mixture was poured into a separatory funnel containing 10 mL of CH_2Cl_2 and 10 mL of H_2O, and extracted with CH_2Cl_2 twice. The organic layer was combined and concentrated under reduced pressure. Crude product was then purified via flash column chromatography using 1:10 Hexanes:Ethyl acetate as eluent yielding 0.01 g (60% yield) of **9** as a clear sticky oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ7.79-7.10 (m, Ar**H**, 13H), 6.93 (b, HO-G1-N**H**CH_2, 1H), 5.61 (b, Fmoc-N**H**, 1H), 5.17 (b, $CO_2C\mathbf{H}_2$Ph, 2H), 4.50-4.00 (m, $CO_2C\mathbf{H}_2C\mathbf{H}$(in Fluorenylmethoxycarbonyl), $CH_2C\mathbf{H}$(NH(Fmoc))CO_2Bn, 4H), 3.71 (b, $(HOC\mathbf{H}_2)_2$(CH3)CCONH, 4H), 3.24 (b, **H**O-G1-NHC$\mathbf{H}_2$, 4H), 2.10-0.40 (b, HO-G1-$NHCH_2(C\mathbf{H}_2)_3CH(NH(Fmoc))CO_2$, 6H), 1.25 (s, $NHCOC(C\mathbf{H}_3)(CH_2OH)_2$(in HO-G1), 3H).

General procedure of the deprotection reaction of Bn: Synthesis of Fmoc-Lys(Acetonide-G2)-OH (10) depicted.

0.04 g (0.04 mmol) of Fmoc-Lys(Acetonide-G2)-OBn (**7**), 0.007 g of Palladium (10wt%) on activated carbon (Pd/C), and 0.5 mL of Ethyl acetate were charged into a 5 mL round bottom flask and stirred overnight under H_2 at room temperature. The resulting mixture was filtered through celite and the cake was washed with 10 mL of Ethyl acetate and 10 mL of hot MeOH. The filtrate was concentrated under reduced pressure yielding 0.02 g (67% yield) of **10** together with 0.005g (20% yield) of H_2N-Lys(Acetonide G2)-OH as a pale yellow sticky oil. ^{1}H NMR (200 MHz, $CDCl_3$) of **10**: δ7.793-7.21 (m, Ar**H**, 8H), 6.52 (b, Acetonide-G2-N**H**CH_2, 1H), 5.65 (b, Fmoc-N**H**, 1H), 4.50-3.50 (m, CO_2CH_2CH(in Fluorenylmethoxycarbonyl), CH_2CH(NH(Fmoc))CO_2H, $COC(CH_3)(CH_2O)_2$(in Acetonide-G2), 16H), 3.27 (b, Acetonide-G2-NHC**H**$_2$, 2H), 2.10-0.80 (b, Acetonide-G2-NHCH$_2$(C**H**$_2$)$_3$CH(NH(Fmoc))CO_2, 6H), 1.44, 1.37 (ss, (C**H**$_3$)$_2$C(OCH$_2$)$_2$(in Acetonide-G2), 12H), 1.22 (s, NHCOC(C**H**$_3$)(CH$_2$OCO)$_2$, 3H), 1.05 (s, (CH$_3$)$_2$C(OCH$_2$)$_2$(C**H**$_3$)CCO$_2$CH$_2$C, 6H).

General procedure of the deprotection reaction of Fmoc (A): Synthesis of H_2N-Lys(Acetonide-G2)-OBn (11) depicted.

0.02 g (0.02 mmol) of Fmoc-Lys(Acetonide-G2)-OBn (**7**) and 0.13 g of Et_2NH were dissolved into 0.15 mL of THF and stirred at room temperature for 3 hours. The resulting mixture was concentrated under reduced pressure. Then, three sets of 'adding 5 mL of THF and concentrating under reduced pressure' were conducted to get rid of the residue of Et_2NH. 0.01 g (92% yield) of **11** was obtained as a light yellow sticky oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ7.35 (b, Ar**H**, 5H), 7.08 (b, CH_2CH(N**H**$_2$)CO_2Bn, 2H), 6.54 (b, Acetonide-G2-N**H**CH_2, 1H), 5.14 (b, CO_2CH_2Ph, 2H), 4.39-3.58 (m, CH_2CH(NH$_2$)CO_2Bn, $COC(CH_3)(CH_2O)_2$(in Acetonide-G2), 13H), 3.21 (b, Acetonide-G2-NHC**H**$_2$, 2H), 2.00-0.80 (b, Acetonide-G2-NHCH$_2$(C**H**$_2$)$_3$CH(NH$_2$)CO_2, 6H), 1.42, 1.35 (ss, (C**H**$_3$)$_2$C(OCH$_2$)$_2$(in Acetonide-G2), 12H), 1.26 (s, NHCOC(C**H**$_3$)(CH$_2$OCO)$_2$, 3H), 1.10 (s, (CH$_3$)$_2$C(OCH$_2$)$_2$(C**H**$_3$)CCO$_2$CH$_2$C, 6H).

General procedure of the amide coupling reaction: Synthesis of Fmoc-(Lys(Acetonide-G2))$_2$-OBn (12) depicted.

0.02 g (0.02 mmol) of Fmoc-Lys(Acetonide-G2)-OH (**10**), 0.02 g (0.02 mmol) of H_2N-Lys(Acetonide-G2)-OH (**11**), 0.005 g (0.03 mmol) of DCC, and 0.002 g (0.02 mmol) of HOBT were dissolved into CH_2Cl_2/THF (0.13 mL/0.05 mL) and stirred overnight at room temperature. The resulting mixture was filtered and poured into a separatory funnel containing 10 mL CH_2Cl_2 and 10 mL of H_2O. The organic layer was washed with 5 mL of satd. $CuSO_4$*aq.* and 5 mL of satd. NaCl*aq.*, then concentrated under reduced pressure. Crude product was purified via flash column chromatography using 1:1 Hexanes:Ethyl acetate as eluent yielding 0.025 g (87% yield) of **12** as a pale yellow sticky oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ7.78-7.23 (m, Ar**H**, 13H), 7.07 (b, CH_2CH(NH(Fmoc))CON**H**CH, 1H), 6.62 (b, Acetonide-G2-N**H**CH_2, 2H), 5.82 (b, Fmoc-N**H**, 1H), 5.12 (b, CO_2CH_2Ph, 2H), 4.60-3.50 (m, CO_2CH_2CH(in Fluorenylmethoxycarbonyl), CH_2CH_2CH(NH(Fmoc))CONH, CH_2CH_2CH(NH)CO_2Bn, $COC(CH_3)(CH_2O)_2$(in Acetonide-G2), 29H), 3.21 (b, Acetonide-G2-NHC**H**$_2$, 4H), 2.00-0.80 (b, Acetonide-G2-NHCH$_2$(C**H**$_2$)$_3$CH(NH(Fmoc))CONH, Acetonide-G2-NHCH$_2$(C**H**$_2$)$_3$CH(NH)CO_2, 12H), 1.40, 1.38, 1.33, 1.31 (ssss, (C**H**$_3$)$_2$C(OCH$_2$)$_2$(in Acetonide-G2), 24H), 1.22, 1.20 (ss, NHCOC(C**H**$_3$)(CH$_2$OCO)$_2$, 6H), 1.07 (s, (CH$_3$)$_2$C(OCH$_2$)$_2$(C**H**$_3$)CCO$_2$CH$_2$C, 12H). ^{13}C NMR ($CDCl_3$): δ173.84, 172.74, 172.18, 172.06, 156.40 (**C**O$_2$, 9C), 143.94 (Ar(Fmoc), CH$_2$CH-**C**, 2C), 141.37 (Ar(Fmoc), **C**(Ar)-**C**(Ar'), 2C), 135.41 (Ar(Bn), CH$_2$-**C**, 1C) 128.73-125.25 (Ar(Fmoc, Bn), 11C), 120.10 (Ar(Fmoc), CH$_2$CH-C**C**H, 2C), 98.38 ((CH$_3$)$_2$**C**(OCH$_2$)$_2$C, 4C), 67.23 (CO$_2$**C**H$_2$, (Fmoc, Bn), 2C), 66.22 ((CH$_3$)$_2$C(O**C**H$_2$)$_2$(CH$_3$)CCO$_2$CH$_2$C, (CO$_2$**C**H$_2$)$_2$C(CH$_3$)CONH, 12C), 54.71,

52.35 (CH_2**C**H(NH)CO, 2C), 49.15 (Ar**C**HCH_2OCONH(in Fluorenylmethoxycarbonyl), 1C), 47.21, 46.69 (($CO_2CH_2)_2(CH_3)$**C**CONH, 2C), 42.33 (($CH_3)_2C(OCH_2)_2(CH_3)$**C**CO_2CH_2C, 4C), 39.05 (G2-NH**C**$H_2CH_2CH_2CH_2$, 2C), 34.07-21.33 (G2-NHCH_2**C**H_2**C**H_2**C**H_2, (**C**$H_3)_2C(OCH_2)_2(CH_3)CCO_2CH_2C$, 14C), 18.52 (($CH_3)_2C(OCH_2)_2$(**C**$H_3$)$CCO_2CH_2C$, 4C), 17.95 (($CO_2CH_2)_2$(**C**$H_3$)CCONH, 2C).

General procedure of the deprotection reaction of Fmoc (B): Synthesis of H_2N-Lys(Acetonide-G2)$_2$-OBn (14) depicted.

0.20 g (0.14 mmol) of Fmoc-(Lys(Acetonide-G2))$_2$-OBn (**12**) and 1.15 g (3.45 mmol) of 4-(Dimethylamino)pyridine on Polystyrene resin (DMAP/PS; 3.0 mmol/g) were added into 4.5 mL of THF and stirred overnight at room temperature. The resulting mixture was filtered and the filtrate was concentrated under reduced pressure. Crude product was then purified via flash column chromatography using gradient eluent (from Ethyl acetate only to 2:1 Ethyl acetate:MeOH) yielding **14** as a pale yellow sticky oil. (91% yield) ^{1}H NMR (200 MHz, $CDCl_3$): δ7.83 (b, CH_2CH(NH_2)CON**H**CH, 1H), 7.34 (b, Ar**H**, 5H), 6.64 (b, Acetonide-G2-N**H**CH_2, 2H), 5.15 (b, CO_2CH_2Ph, 2H), 4.60-3.40 (m, CO_2CH_2C**H**(in Fluorenylmethoxycarbonyl), CH_2CH_2C**H**(NH_2)CONH, CH_2CH_2C**H**(NH)CO_2Bn, COC(CH_3)(CH_2O)$_2$(in Acetonide-G2), 29H), 3.20 (b, Acetonide-G2-NHCH_2, 4H), 2.00-0.80 (b, Acetonide-G2-NHCH_2(CH_2)$_3$CH(NH(Fmoc))CONH, Acetonide-G2-NHCH_2(CH_2)$_3$CH(NH)CO_2, 12H), 1.43, 1.42, 1.35, 1.34 (ssss, (CH_3)$_2$C(OCH_2)$_2$(in Acetonide-G2), 24H), 1.27, 1.26 (ss, NHCOC(CH_3)(CH_2OCO)$_2$, 6H), 1.10 (s, ($CH_3)_2C(OCH_2)_2$(CH_3)CCO_2CH_2C, 12H).

General procedure of attachment of Lysine derivatives to SPPS support: Synthesis of H_2N-(Lys(Acetonide-G2))$_4$-Val-2-ClTrt resin depicted.

0.10 g (0.075 mmol) of H-Val-2-ClTrt resin was swollen in 0.5 mL of DMF for 1.5 hours. 0.74 g (0.30 mmol) of Fmoc-(Lys(Acetonide-G2))$_4$-OH (**16**), 0.06 g (ca. 0.3 mmol) of HOBT, 0.12 g (0.32 mmol) of *O*-Benzotriazole-1-yl-*N*,*N*,*N*',*N*'-tetramethyluronium hexafluorophospohate (HBTU), and 0.04 g (0.31 mmol) of *N*,*N*'-Diisopropylcarbodiimide (DIPCDI) were dissolved into 3.0 mL of DMF and stirred for 30 minutes at room temperature. This mixture was then added to the swollen resin/DMF slurry and shaken for 4 hours. After the reaction, the resulting mixture was filtered under vacuum and the resin was washed with 2 mL of DMF twice to obtain Fmoc-(Lys(Acetonide-G2))$_4$-Val-2-ClTrt resin. The absence of primary amine was checked by using Kaiser's Test (Yellow)[9].

5 mL of 20 vol% Piperidine/DMF was then added to this Fmoc-(Lys(Acetonide-G2))$_4$-Val-2-ClTrt resin and shaken for total 20 minutes (5 minutes * 4 times). After the shaking, the reaction mixuture was filtered under vacuum and the resin was washed with 3 mL of DMF twice and with CH_2Cl_2:DMF (1:1) once to obtain H_2N-(Lys(Acetonide-G2))$_4$-Val-2-ClTrt resin. The presence of primary amine was checked by using Kaiser's Test (Bluish purple)[9].

General two procedures (A and B) of cleavage of oligopeptides from 2-ClTrt resin support: Cleavage of Fmoc-(Lys(Acetonide-G2))$_{20}$-Val-OH (17) depicted.

(A) AcOH/TFE/CH_2Cl_2 system

1 mL of Acetic acid (AcOH), 1 mL of 2,2,2-Trifluoroethanol (TFE), and 3 mL of CH_2Cl_2 were added to 0.252 g of Fmoc-(Lys(Acetonide-G2))$_{20}$-Val-2-ClTrt resin (swollen with DMF) and the mixture was shaken for 3 hours at room

temperature. After the reaction, the resulting mixture was filtered under vacuum and the resin was washed with 20 mL of TFE/ CH_2Cl_2 (1:1). Then, three sets of 'adding 30 mL of Hexanes and concentrating under reduced pressure' were conducted to get rid of all the volatile components from the combined filtrate. 0.11 g of Fmoc-(Lys(Acetonide-G2))$_{20}$-Val-OH (**17**) was obtained as a light yellow sticky oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ7.90-7.26 (m, Ar**H**, 8H), 7.23-5.70 (b, N**H**, 41H), 4.60-3.40 (m, $CO_2C\mathbf{H}_2C\mathbf{H}$(in Fluorenylmethoxycarbonyl), $CH_2CH_2C\mathbf{H}$(NH)CO, $COC(CH_3)(C\mathbf{H}_2O)_2$(in Acetonide-G2), 264H), 3.15 (b, Acetonide-G2-NHC$\mathbf{H}_2$, 40H), 2.40-0.80 (b, Acetonide-G2-$NHCH_2(C\mathbf{H}_2)_3CH$(NH)CONH, 127H), 1.38, 1.30 (ss, $(C\mathbf{H}_3)_2C(OCH_2)_2$(in Acetonide-G2), 240H), 1.23 (s, $NHCOC(C\mathbf{H}_3)(CH_2OCO)_2$, 60H), 1.08 (s, $(CH_3)_2C(OCH_2)_2(C\mathbf{H}_3)CCO_2CH_2C$, 120H). Mass Spec for $C_{560}H_{901}O_{204}N_{41}$ Calculated: 11472.59; Found $(M+4H)^{+4}$: 2868.87.

(B) HFIP/CH_2Cl_2 system

1 mL of 1,1,1,3,3,3-Hexafluoro-2-propanol (HFIP) and 4 mL of CH_2Cl_2 were added to 0.275 g of Fmoc-(Lys(Acetonide-G2))$_{20}$-Val-2-ClTrt resin (swollen with DMF) and the mixture was shaken for 30 minutes at room temperature. After the reaction, the resulting mixture was filtered under vacuum and the resin was washed with 5 mL of HFIP/CH_2Cl_2 (1:4). Then, three sets of 'adding 30 mL of Et_2O and concentrating under reduced pressure' were conducted to get rid of all the volatile components from the combined filtrate. 0.15 g of Fmoc-(Lys(Acetonide-G2))$_{20}$-Val-OH (**17**) was obtained as a light yellow sticky oil.

General procedure of acetonide deprotection reaction (B): Synthesis of Fmoc-(Lys(HO-G2))$_4$-OBn (18) depicted.

4.3 g of Dowex 50Wx2-100 was added to a MeOH (27.4 mL) solution of Fmoc-(Lys(Acetonide-G2))$_4$-OBn (**15**) (0.61 g (0.99 mmol)). This reaction slurry was gently stirred at room temperature for 22 hours. The resulting slurry was filtered and the resin was washed with 30 mL of MeOH. The combined filtrate was concentrated under reduced pressure yielding 0.52 g (90% yield) of **18** as a light yellow sticky oil. From the Mass Spec data and ^{1}H NMR measurement, it was found that small amount (ca. 0.5 mol%) of Benzyl ester has changed into Methyl ester. ^{1}H NMR (200 MHz, Acetone-d6): δ7.90-7.20 (m, Ar**H**, 13H), 5.14 (b, $CO_2C\mathbf{H}_2Ph$, 2H), 4.50-3.50 (m, $CO_2C\mathbf{H}_2C\mathbf{H}$(in Fluorenylmethoxycarbonyl), $CH_2CH_2C\mathbf{H}$(NH)CO, $COC(CH_3)(C\mathbf{H}_2O)_2$(in HO-G2), 55H), 3.21 (b, HO-G2-NHC$\mathbf{H}_2$, 8H), 2.00-0.80 (b, HO-G2-$NHCH_2(C\mathbf{H}_2)_3CH$(NH)CONH, 24H), 1.30 (b, $NHCOC(C\mathbf{H}_3)(CH_2OCO)_2$, 12H), 1.08 (b, $(HOCH_2)_2(C\mathbf{H}_3)CCO_2CH_2C$, 24H). Mass Spec for $C_{106}H_{162}O_{43}N_8$ Calculated: 2236.45; Found $(M+2Na)^{+2}$: 1141.01.

General procedure of the deprotection reaction of Dde, (*N*-1-(4,4-dimethyl-2,6-dioxocyclohexylidene)ethy1 group): Synthesis of Fmoc-(Lys(NH_2))$_8$-Val-2-ClTrt resin depicted.

0.4 g of Fmoc-(Lys(Dde))$_8$-Val-2-ClTrt resin was added to CH_2Cl_2 (0.31 mL), NMP (1.4 mL) solution of $NH_2OH \cdot HCl$ (0.34 g (0.49 mmol)), and Imidazole (0.25 g (0.37 mmol)). This reaction slurry was shaken overnight at room temperature. The resulting slurry was filtered and four sets of 'adding 5 mL of DMF, shaking for 10 minutes, and filtering' were conducted. The resin was then dried overnight under vacuum at room temperature to get 0.325 g of the product.

Syntheses of esters of Fmoc-Lys(Boc)-OH (1) using *N*-Hydroxysuccinimide (HOSu) and 2-Nitrobenzyl alcohol.

The procedure described above for the synthesis of the Benzyl ester (**2**) was applied to the syntheses of the activated ester, Fmoc-Lys(Boc)-OSu, (100% yield) and the UV-labile ester, Fmoc-Lys(Boc)-O-(2-NO_2)Bn, (73% yield), respectively. (In case of Fmoc-Lys(Boc)-OSu synthesis, DPTS was used instead of DMAP.)

Fmoc-Lys(Boc)-O-(2-NO_2)Bn; ^{1}H NMR (200 MHz, $CDCl_3$): δ8.15-7.26 (m, Ar**H**, 12H), 5.58 (b, CO_2CH_2Ar, 2H), 5.41 (b, Fmoc-N**H**, 1H), 4.40 (b, CO_2CH_2CH(in Fluorenylmethoxycarbonyl), 3H), 4.21 (t, J = 7.0 Hz, CH_2CH(NH(Fmoc))CO_2Ar, 1H), 3.12 (b, BocNHC**H**$_2$, 2H) 1.95-1.10 (b, BocNHCH_2(CH_2)$_3$CH(NH(Fmoc))CO_2, 6H), 1.44 (s, (CH_3)$_3$CO, 9H).

Coupling reaction of the activated ester, Fmoc-Lys(Boc)-OSu, and H_2N-Lys(Boc)-OH to synthesize Fmoc-(Lys(Boc))$_2$-OH (31).

0.80 g (0.35 mmol) of H_2N-Lys(Boc)-OH was dissolved into 6.5 mL of MeOH. 0.20 g (0.35 mmol) of Fmoc-Lys(Boc)-OSu and 0.8 mL of CH_2Cl_2 were then added to the MeOH solution above and stirred overnight at room temperature. The resulting mixture was partly concentrated by reducing the pressure and poured into a separatory funnel containing 20 mL of CH_2Cl_2 and 20 mL of H_2O and then the two phases were separated. The organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Crude product was then purified via flash column chromatography using Ethyl acetate as eluent yielding 0.03 g (14% yield) of **31** as a white powder. **31** was also able to be prepared by deprotecting Bn ester from **29**. ^{1}H NMR (200 MHz, $CDCl_3$): δ7.80-7.26 (m, Ar**H**, 13H), 6.15 (b, N**H**, 2H), 4.35 (b, CO_2CH_2CH(in Fluorenylmethoxycarbonyl), CH_2CH(NH)CO, 5H), 3.45 (b, N**H**, 1H), 3.05 (b, BocNHC**H**$_2$, 4H), 2.00-1.00 (b, BocNHCH_2(CH_2)$_3$CH(NH)CO, 12H), 1.46 (s, (CH_3)$_3$CO, 18H).

Fmoc-Lys(Acetonide-G1)-OBn (8).

The procedure described above for attachment of dendrons was applied to **3** and anhydride of Acetonide-G1-OH (**4**) to yield Fmoc-Lys(Acetonide-G1)-OBn (**8**). ^{1}H NMR (200 MHz, $CDCl_3$): δ7.79-7.20 (m, Ar**H**, 13H), 7.08 (b, Acetonide-G1-N**H**CH_2, 1H), 5.59 (b, Fmoc-N**H**, 1H), 5.18 (b, CO_2CH_2Ph, 2H), 4.50-3.50 (m, CO_2CH_2CH(in Fluorenylmethoxycarbonyl), CH_2CH(NH(Fmoc))CO_2Bn, $COC(CH_3)(CH_2O)_2$(in Acetonide-G1), 8H), 3.27 (b, Acetonide-G1-NHC**H**$_2$, 2H), 2.00-0.70 (b, Acetonide-G2-NHCH_2(CH_2)$_3$CH(NH(Fmoc))CO_2, 6H), 1.43, 1.39 (ss, (CH_3)$_2$C(OCH_2)$_2$(in Acetonide-G1), 6H), 0.99 (NHCOC(CH_3)(CH_2OCO)$_2$C(CH_3)$_2$, 3H).

Fmoc-(Lys(Acetonide-G2))$_2$-OH (13).

The procedure described above for deprotection of Bn was applied to **12** to yield Fmoc-(Lys(Acetonide-G2))$_2$-OH (**13**). ^{1}H NMR (200 MHz, $CDCl_3$): δ7.78-7.21 (m, Ar**H**, 8H), 7.13 (b, CH_2CH(NH(Fmoc))CON**H**CH, 1H), 6.76 (b, Acetonide-G2-N**H**CH_2, 2H), 5.96 (b, Fmoc-N**H**, 1H), 4.60-3.50 (m, CO_2CH_2CH(in Fluorenylmethoxycarbonyl), CH_2CH_2CH(NH(Fmoc))CONH, CH_2CH_2CH(NH)CO_2H, $COC(CH_3)(CH_2O)_2$(in Acetonide-G2), 29H), 3.20 (b, Acetonide-G2-NHC**H**$_2$, 4H), 2.00-0.80 (b, Acetonide-G2-NHCH_2(CH_2)$_3$CH(NH(Fmoc))CONH, Acetonide-G2-NHCH_2(CH_2)$_3$CH(NH)CO_2, 12H), 1.40, 1.33 (ss, (CH_3)$_2$C(OCH_2)$_2$(in Acetonide-G2), 24H), 1.24 (s, NHCOC(CH_3)(CH_2OCO)$_2$, 6H), 1.08 (s, (CH_3)$_2$C(OCH_2)$_2$(CH_3)CCO_2CH_2C, 12H).

Fmoc-(Lys(Acetonide-G2))$_4$-OBn (15).

The procedure described above for amide coupling reaction was applied to **13** and **14** to yield Fmoc-(Lys(Acetonide-G2))$_4$-OBn (**15**). ^{1}H NMR (200 MHz, $CDCl_3$): δ7.77-7.23 (m, Ar**H**, 13H), 7.10 (b,

$CH_2CH(NH)CONHCH$, 3H), 6.76 (b, Acetonide-G2-N**H**CH_2, 4H), 6.27 (b, Fmoc-N**H**, 1H), 5.13 (b, CO_2CH_2Ph, 2H), 4.50-3.50 (m, CO_2CH_2CH(in Fluorenylmethoxycarbonyl), $CH_2CH_2CH(NH)CO$, $COC(CH_3)(CH_2O)_2$(in Acetonide-G2), 55H), 3.20 (b, Acetonide-G2-NHC**H**$_2$, 8H), 2.00-0.80 (b, Acetonide-G2-$NHCH_2(CH_2)_3CH(NH)CONH$, 24H), 1.41, 1.33 (ss, $(CH_3)_2C(OCH_2)_2$(in Acetonide-G2), 48H), 1.25 (s, $NHCOC(CH_3)(CH_2OCO)_2$, 12H), 1.09 (s, $(CH_3)_2C(OCH_2)_2(CH_3)CCO_2CH_2C$, 24H). Mass Spec for $C_{130}H_{194}O_{43}N_8$ Calculated: 2557.02; Found $(M+2H)^{+2}$: 1279.15.

Fmoc-(Lys(Acetonide-G2))$_4$-OH (16).

The procedure described above for deprotection of Bn was applied to **15** to yield Fmoc-(Lys(Acetonide-G2))$_4$-OH (**16**). ^{1}H NMR (200 MHz, $CDCl_3$): δ7.77-7.23 (m, Ar**H**, 8H), 7.23-6.60 (b, N**H**, 8H), 4.50-3.50 (m, CO_2CH_2CH(in Fluorenylmethoxycarbonyl), $CH_2CH_2CH(NH)CO$, $COC(CH_3)(CH_2O)_2$(in Acetonide-G2), 55H), 3.14 (b, Acetonide-G2-NHC**H**$_2$, 8H), 2.00-0.80 (b, Acetonide-G2-$NHCH_2(CH_2)_3CH(NH)CONH$, 24H), 1.40, 1.32 (ss, $(CH_3)_2C(OCH_2)_2$(in Acetonide-G2), 48H), 1.25 (s, $NHCOC(CH_3)(CH_2OCO)_2$, 12H), 1.08 (s, $(CH_3)_2C(OCH_2)_2(CH_3)CCO_2CH_2C$, 24H).

Fmoc-(Lys(Acetonide-G3))$_4$-OBn (19).

The procedure described above for attachment of dendrons was applied to **18** and anhydride of Acetonide-G1-OH (**4**) to yield Fmoc-(Lys(Acetonide-G3))$_4$-OBn (**19**). ^{1}H NMR (200 MHz, $CDCl_3$): δ7.78-7.21 (m, Ar**H**, 13H), 7.04-6.15 (b, N**H**, 8H), 5.11 (b, CO_2CH_2Ph, 2H), 4.60-3.40 (m, CO_2CH_2CH(in Fluorenylmethoxycarbonyl), $CH_2CH_2CH(NH)CO$, $COC(CH_3)(CH_2O)_2$(in Acetonide-G3), 119H), 3.19 (b, Acetonide-G3-NHC**H**$_2$, 8H), 2.00-0.70 (b, Acetonide-G3-$NHCH_2(CH_2)_3CH(NH)CO$, 24H), 1.37, 1.31 (bb, $(CH_3)_2C(OCH_2)_2$(in Acetonide-G3), 96H), 1.23 (b, $NHCOC(CH_3)(CH_2OCO)_2$, 12H), 1.09 (s, $((CH_3)_2C(OCH_2)_2(CH_3)CCO_2CH_2)_2C(CH_3)CO$, 72H). Mass Spec for $C_{234}H_{354}O_{91}N_8$ Calculated: 4735.43; Found $(M+3Na)^{+3}$: 1601.13.

Fmoc-(Lys(HO-G3))$_4$-OBn (20).

The procedure described above for acetonide deprotection reaction (B) was applied to **19** to yield Fmoc-(Lys(HO-G3))$_4$-OBn (**20**). ^{1}H NMR (200 MHz, $CDCl_3$): δ7.90-7.25 (m, Ar**H**, 13H), 7.04-6.15 (b, N**H**, 8H), 5.16 (b, CO_2CH_2Ph, 2H), 4.60-350 (m, CO_2CH_2CH(in Fluorenylmethoxycarbonyl), $CH_2CH_2CH(NH)CO$, $COC(CH_3)(CH_2O)_2$(in HO-G3), 119H), 3.21 (b, HO-G3-NHC**H**$_2$, 8H), 2.40-0.70 (b, HO-G3-$NHCH_2(CH_2)_3CH(NH)CO$, 24H), 1.25 (b, $NHCOC(CH_3)(CH_2OCO)_2$, 12H), 1.09 (s, $((HOCH_2)_2(CH_3)CCO_2CH_2)_2C(CH_3)CO$, 72H). Mass Spec for $C_{186}H_{290}O_{91}N_8$ Calculated: 4094.39; Found $(M+3H)^{+3}$: 1365.60.

Fmoc-(Lys(Acetonide-G4))$_4$-OBn (21).

The procedure described above for attachment of dendrons was applied to **20** and anhydride of Acetonide-G1-OH (**4**) to yield Fmoc-(Lys(Acetonide-G4))$_4$-OBn (**21**). ^{1}H NMR (200 MHz, $CDCl_3$): δ7.78-7.21 (m, Ar**H**, 13H), 7.20-6.40 (b, N**H**, 8H), 5.10 (b, CO_2CH_2Ph, 2H), 4.50-3.40 (m, CO_2CH_2CH(in Fluorenylmethoxycarbonyl), $CH_2CH_2CH(NH)CO$, $COC(CH_3)(CH_2O)_2$(in Acetonide-G4), 247H), 3.19 (b, Acetonide-G4-NHC**H**$_2$, 8H), 2.00-0.70 (b, Acetonide-G4-$NHCH_2(CH_2)_3CH(NH)CO$, 24H), 1.37, 1.31 (ss, $(CH_3)_2C(OCH_2)_2$(in Acetonide-G4), 192H), 1.23

(s, NHCOC(C**H**$_3$)(CH$_2$OCO)$_2$, 12H), 1.09 (s, (((CH$_3$)$_2$C(OCH$_2$)$_2$(C**H**$_3$)CCO$_2$CH$_2$)$_2$(C**H**$_3$)CCO$_2$CH$_2$)$_2$(C**H**$_3$)CCO, 168H). Mass Spec for $C_{442}H_{674}O_{187}N_8$ Calculated: 9092.24; Found $(M+4Na)^{+4}$: 2295.73.

Fmoc-(Lys(HO-G4))$_4$-OBn (22).

The procedure described above for acetonide deprotection reaction (B) was applied to **21** to yield Fmoc-(Lys(HO-G4))$_4$-OBn (**22**). ^{1}H NMR (200 MHz, CD$_3$OD): δ7.88-7.21 (m, Ar**H**, 13H), 5.15 (b, CO$_2$C**H**$_2$Ph, 2H), 4.50-3.40 (m, CO$_2$C**H**$_2$C**H**(in Fluorenylmethoxycarbonyl), CH$_2$CH$_2$C**H**(NH)CO, COC(CH$_3$)(C**H**$_2$O)$_2$(in HO-G4), 247H), 3.25 (b, HO-G4-NHC**H**$_2$, 8H), 2.30-0.70 (b, HO-G4-NHCH$_2$(C**H**$_2$)$_3$CH(NH)CO, 24H), 1.27, 1.16 (ss, NHCOC(C**H**$_3$)(CH$_2$OCO)$_2$, (((CH$_3$)$_2$C(OCH$_2$)$_2$(C**H**$_3$)CCO$_2$CH$_2$)$_2$(C**H**$_3$)CCO$_2$CH$_2$)$_2$(C**H**$_3$)CCO, 180H). Mass Spec for $C_{346}H_{546}O_{187}N_8$ Calculated: 7810.18; Found $(M+4Na)^{+4}$: 1974.88.

Acetonide-G4-OBn (26).

^{1}H NMR (500 MHz, CDCl$_3$): δ7.35 (b, Ar**H**, 5H), 5.15 (s, CO$_2$C**H**$_2$Ph, 2H), 4.50-3.50 (m, COC(CH$_3$)(C**H**$_2$O)$_2$, 60H), 1.40, 1.33 (ss, (C**H**$_3$)$_2$C(OCH$_2$)$_2$(in Acetonide-G4), 48H), 1.29-1.13 (m, ((((CH$_3$)$_2$C(OCH$_2$)$_2$(C**H**$_3$)CCO$_2$CH$_2$)$_2$(C**H**$_3$)CCO$_2$CH$_2$)$_2$(C**H**$_3$)CCO$_2$CH$_2$)$_2$(C**H**$_3$)CCO$_2$Bn, 45H). ^{13}C NMR (CDCl$_3$): δ173.67, 171.99, 171.59 (**C**O$_2$, 15C), 135.63 (Ar, CH$_2$-**C**, 1C), 128.89, 128.71, 128.57 (Ar, **C**H, 5C), 98.30 ((CH$_3$)$_2$**C**(OCH$_2$)$_2$, 8C), 67.38 (O**C**H$_2$Ph, 1C), 66.62, 66.16, 66.11, 65.71, 65.03 ((O**C**H$_2$)$_2$C(CH$_3$)CO$_2$, 30C), 47.03, 46.96, 46.87, 42.23 ((OCH$_2$)$_2$**C**(CH$_3$)CO$_2$, 15C), 25.29, 22.36 ((**C**H$_3$)$_2$C(OCH$_2$)$_2$C(CH$_3$)CO$_2$, 16C), 18.72, 17.87, 17.67, 17.59 ((OCH$_2$)$_2$C(**C**H$_3$)CO$_2$, 15C). Mass Spec for $C_{106}H_{160}O_{46}$ Calculated: 2169.02; Found $(M+Na+K)^{+2}$: 1116.02.

Acetonide-G4-OH (27).

The procedure described above for deprotection of Bn was applied to **26** to yield Acetonide-G4-OH (**27**). ^{1}H NMR (200 MHz, CDCl$_3$): δ4.40-3.50 (m, COC(CH$_3$)(C**H**$_2$O)$_2$, 60H), 1.41, 1.35 (ss, (C**H**$_3$)$_2$C(OCH$_2$)$_2$(in Acetonide-G4), 48H), 1.30-1.13 (m, ((((CH$_3$)$_2$C(OCH$_2$)$_2$(C**H**$_3$)CCO$_2$CH$_2$)$_2$(C**H**$_3$)CCO$_2$CH$_2$)$_2$(C**H**$_3$)CCO$_2$CH$_2$)$_2$(C**H**$_3$)CCO$_2$Bn, 45H). ^{13}C NMR (CDCl$_3$): δ173.65, 173.37, 171.87, 171.56 (**C**O$_2$, 15C), 98.23 ((CH$_3$)$_2$**C**(OCH$_2$)$_2$, 8C), 66.82, 66.16, 66.01, 65.76, 65.01 ((O**C**H$_2$)$_2$C(CH$_3$)CO$_2$, 30C), 46.92, 46.75, 46.13, 42.14 ((OCH$_2$)$_2$**C**(CH$_3$)CO$_2$, 15C), 25.46, 21.88 ((**C**H$_3$)$_2$C(OCH$_2$)$_2$C(CH$_3$)CO$_2$, 16C), 18.52, 17.74, 17.61 ((OCH$_2$)$_2$C(**C**H$_3$)CO$_2$, 15C). Mass Spec for $C_{99}H_{154}O_{46}$ Calculated: 2079.97; Found $(M+2H)^{2+}$: 1040.94.

H$_2$N-Lys(Boc)-OBn (28).

The procedure described above for deprotection reaction of Fmoc (A) was applied to **2** to yield H$_2$N-Lys(Boc)-OBn (**28**). ^{1}H NMR (500 MHz, CDCl$_3$): δ7.32 (b, Ar, 5H), 5.12 (s, C**H**$_2$Ph, 2H), 4.63 (b, CH$_2$N**H**CO$_2$, 1H), 4.29 (dd, J = 7.5, 2.0 Hz, CH$_2$C**H**(NH$_2$)CO$_2$, 1H), 3.04 (b, NHC**H**$_2$CH$_2$, 2H), 1.80-1.30 (NHCH$_2$C**H**$_2$C**H**$_2$C**H**$_2$CH(NH$_2$)CO$_2$, 6H), 1.40 (s, (C**H**$_3$)$_3$COCO, 9H). ^{13}C NMR (CDCl$_3$): δ175.94 (**C**O$_2$Bn, 1C), 156.05 (O**C**ONH, 1C), 135.84 (Ar, CH$_2$-**C**, 1C), 128.69, 128.46, 128.40 (Ar, **C**H, 5C), 79.07 ((CH$_3$)$_3$**C**OCO, 1C), 66.69 (O**C**H$_2$Ph, 1C), 54.48 (CH$_2$**C**H(NH$_2$)CO$_2$, 1C), 40.40 (CONH**C**H$_2$CH$_2$CH$_2$CH$_2$CH(NH$_2$)CO$_2$, 1C), 34.54 (CONHCH$_2$CH$_2$CH$_2$**C**H$_2$CH(NH$_2$)CO$_2$, 1C), 29.87 (CONHCH$_2$**C**H$_2$CH$_2$CH$_2$CH(NH$_2$)CO$_2$, 1C), 28.52 ((**C**H$_3$)$_3$COCO, 9C), 22.91 (CONHCH$_2$CH$_2$**C**H$_2$CH$_2$CH(NH$_2$)CO$_2$, 1C). Mass Spec for $C_{18}H_{28}O_4N_2$ Calculated: 336.20; Found $(M+H)^+$: 337.20.

Fmoc-(Lys(Boc))$_2$-OBn (29).

The procedure described above for amide coupling reaction was applied to **1** and **28** to yield Fmoc-(Lys(Boc))$_2$-OBn (**29**). ^{1}H NMR (200 MHz, $CDCl_3$): δ7.70-7.26 (m, Ar**H**, 13H), 6.66 (b, Boc-N**H**, 2H), 5.60 (b, Fmoc-N**H**, 1H), 5.15 (m, $CO_2C\mathbf{H}_2Ph$, 2H), 4.65 (b, $CO_2C\mathbf{H}_2C\mathbf{H}$(in Fluorenylmethoxycarbonyl), 3H), 4.50-4.10 (m, $CH_2C\mathbf{H}$(NH)CO, 2H), 4.06 (b, CH(NH(Fmoc))CON**H**CH, 1H), 3.05 (b, BocNHC$\mathbf{H}_2$, 4H), 2.00-1.00 (b, BocNHCH$_2$(C$\mathbf{H}_2$)$_3$CH(NH)CO, 12H), 1.43, 1.41 (ss, (C$\mathbf{H}_3$)$_3$CO, 18H). ^{13}C NMR ($CDCl_3$): δ172.12, 171.96 (CH(NH(Fmoc))**C**ONH, CH**C**O_2Bn, 2C), 156.38, 156.33 (CH_2NH**C**OBoc, 2C), 144.06, 143.96 (Ar(Fmoc), CH_2CH-**C**, 1C), 141.48 (Ar(Fmoc), **C**(Ar)-**C**(Ar'), 2C), 135.45 (Ar(Bn), CH_2-**C**, 1C) 128.82-125.31 (Ar(Fmoc, Bn), 11C), 120.16 (Ar(Fmoc), CH_2CH-C**C**H, 2C), 79.33 ((CH$_3$)$_3$**C**O, 1C), 67.41, 67.34 ($CO_2\mathbf{C}H_2$, (Fmoc, Bn), 2C), 54.84, 52.38 ($CH_2\mathbf{C}$H(NH)CO, 2C), 47.32 (Ar**C**HCH$_2$OCONH(in Fluorenylmethoxycarbonyl), 1C), 40.10 (BocNH**C**H$_2$CH$_2$CH$_2$CH$_2$, 2C), 35.12-22.49 (BocNHCH$_2$**C**H$_2$**C**H$_2$**C**H$_2$, 6C), 28.63 ((**C**H$_3$)$_3$CO, 6C). Mass Spec for $C_{44}H_{58}N_4O_9$ Calculated: 786.42; Found $(M+Na)^+$: 809.44.

H_2N-(Lys(Boc))$_2$-OBn (30).

The procedure described above for deprotection reaction of Fmoc (B) was applied to **29** to yield H_2N-(Lys(Boc))$_2$-OBn (**30**). ^{1}H NMR (500 MHz, $CDCl_3$): δ7.72 (b, N$\mathbf{H}_2$, 2H), 7.33 (m, Ar**H**, 5H), 5.15 (dd, J = 24.5, 12.0 Hz, $CO_2C\mathbf{H}_2Ph$, 2H), 4.60 (m, $CH_2C\mathbf{H}$(NH)CO, 2H), 3.35 (b, N**H**, 1H), 3.05 (b, BocNHC$\mathbf{H}_2$, 4H), 2.00-1.00 (b, BocNHCH$_2$(C$\mathbf{H}_2$)$_3$CH(NH)CO, 12H), 1.41 (s, (C$\mathbf{H}_3$)$_3$CO, 18H). ^{13}C NMR ($CDCl_3$): δ175.22 (CH(NH_2)**C**ONH, 1C), 172.42 (CH**C**O_2Bn, 1C), 156.27, 156.20 (CH_2NH**C**OBoc, 2C), 135.58 (Ar, CH_2-**C**, 1C) 128.90-128.47 (Ar, 5C), 79.21 ((CH$_3$)$_3$**C**O, 1C), 67.20 ($CO_2\mathbf{C}H_2$, 1C), 55.17, ($CH_2\mathbf{C}$H(NH_2)CO, 1C), 51.80 ($CH_2\mathbf{C}$H(NH)CO_2Bn, 1C), 40.40 (BocNH**C**H$_2$CH$_2$CH$_2$CH$_2$, 2C), 3480-22.69 (BocNHCH$_2$**C**H$_2$**C**H$_2$**C**H$_2$, 6C), 28.60 ((**C**H$_3$)$_3$CO, 6C). Mass Spec for $C_{29}H_{48}N_4O_7$ Calculated: 564.35; Found $(M+H)^+$: 565.37.

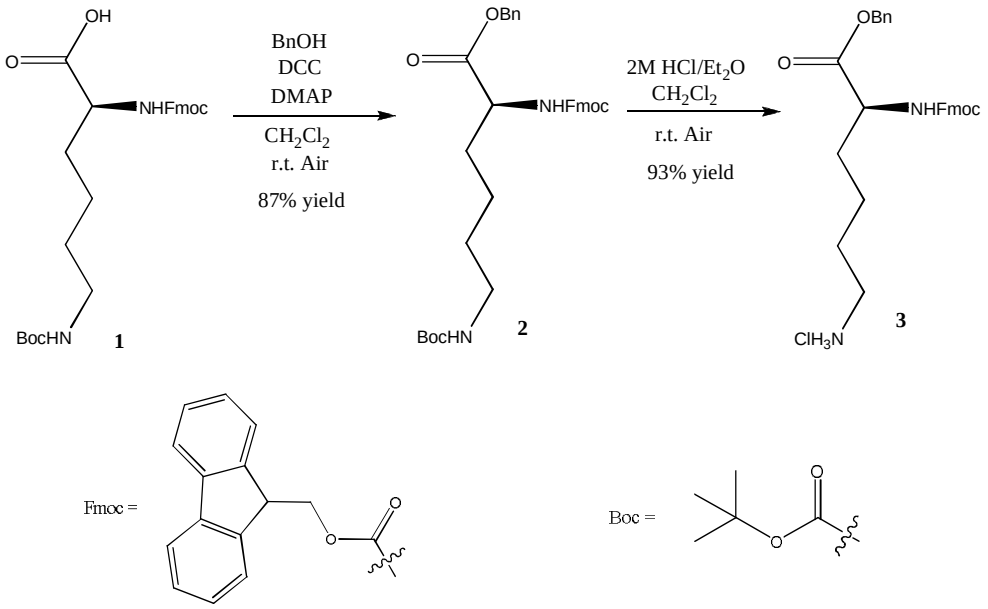
Dimer of Lys(Boc) (32).

^{1}H NMR (500 MHz, DMF-d_7): δ7.97, 6.66 (b, N**H**, 4H), 3.92 (b, C**H**(NH)CO, 2H), 3.04 (b, BocNHC$\mathbf{H}_2$, 4H), 2.00-1.00 (b, BocNHCH$_2$(C$\mathbf{H}_2$)$_3$CH(NH)CO, 12H), 1.40 (s, (C$\mathbf{H}_3$)$_3$CO, 18H). Mass Spec for $C_{22}H_{40}N_4O_6$ Calculated: 456.59; Found $(M+Na)^+$: 479.30.

5-3. Results and Discussion

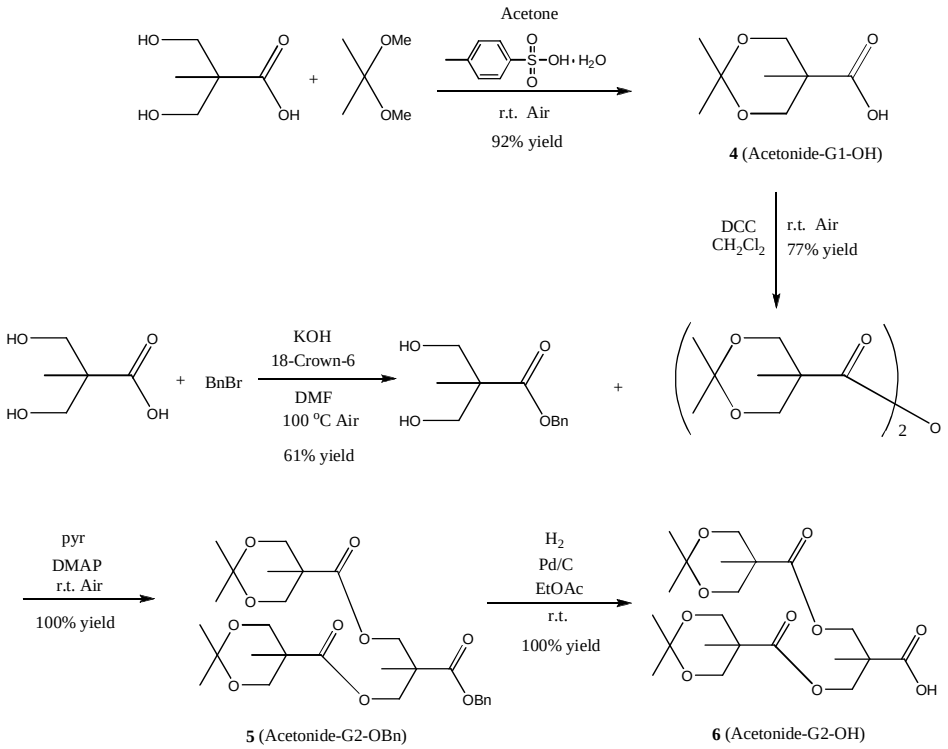
5-3-1. Monomer Synthesis

Fmoc-Lys(Boc)-OH (**1**) was used as the very raw material of this study. Its carboxylic acid group was protected with Benzyl (Bn) ester yielding **2** (87%). And its *tert*-Butoxycarbonyl (Boc) group was cleaved by using 2M HCl/Et_2O to yield **3** (Scheme 1).



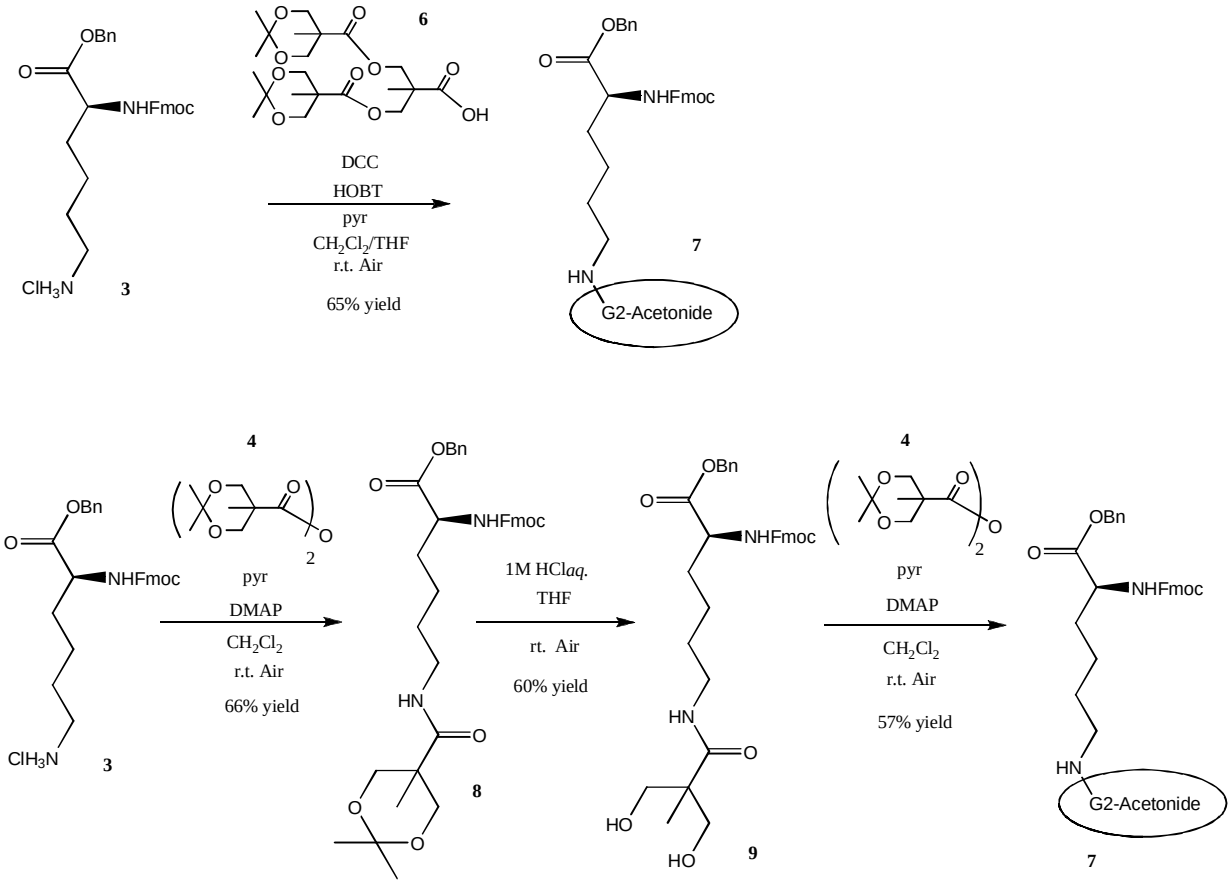
Scheme 1. Protection of calboxylic acid of Fmoc-Lys(Boc)-OH (**1**) with Bn ester and deprotection of Boc group. DCC: *N,N'*-Dicyclohexylcarbodiimide, DMAP: 4-(Dimethylamino)pyridine

Also Bis-MPA type Acetonide-G2-OH dendron (**6**) was synthesized as described elsewhere (Scheme 2) [8].



Scheme 2. Synthesis of Acetonide-G2-OH (**6**).

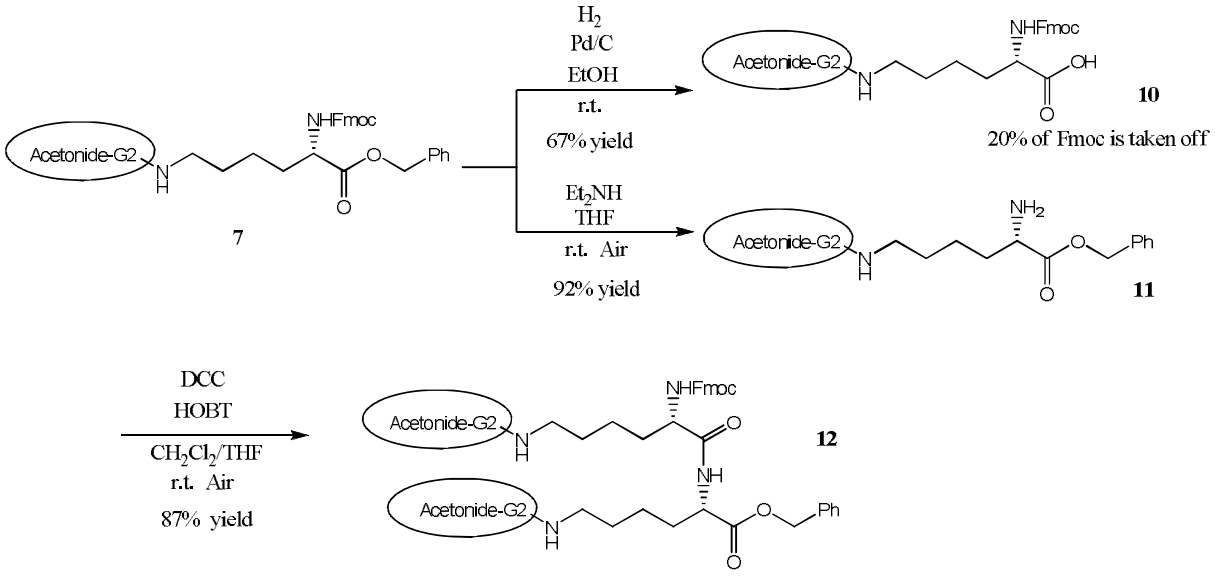
Acetonide-G2-OH (**6**) was then attached to the nitrogen (N_ε) of **3** yielding Fmoc-Lys(Acetonide-G2)-OBn (**7**) by using *N*,*N*'-Dicyclohexylcarbodiimide (DCC), 1-Hydroxybenzotriazole hydrate (HOBT), and Pyridine (pyr) as coupling reagents. Alternatively, stepwise procedure was also favorable as depicted in Scheme 3.



Scheme 3. Direct and stepwise syntheses of the Monomer, Fmoc-Lys(Acetonide-G2)-OBn (**7**).

5-3-2. Oligomer Synthesis

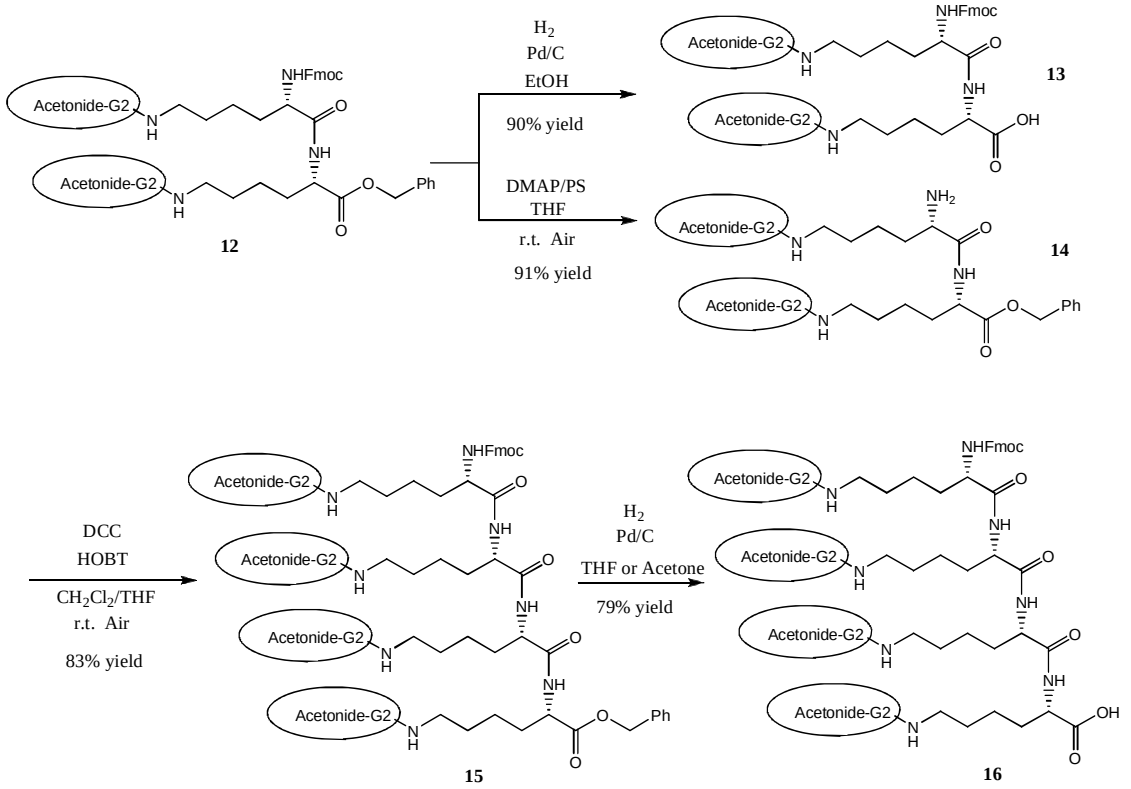
Once, the Monomer, Fmoc-Lys(Acetonide-G2)-OBn (**7**) was prepared, according to the "Exponential Growth Strategy[1]", deprotection of the both protective groups, Fmoc and Bn, was executed. Bn ester was deprotected by hydrogenation using Pd/C as the catalyst. Even though the deprotection of Bn itself proceeded smoothly, to our annoyance, some of the Fmoc was deprotected during the Bn deprotection, too. After the optimization of the reaction condition including the solvent system, the isolated yield reached 67% together with around 20% of De-Fmoc-byproduct. None of other reductive deprotection method using Cyclohexene, Cyclohexadiene, or Formic acid gave better result than this hydrogenation using Pd/C. On the other hand, Fmoc is known to be readily deprotected by cyclic amines like Piperidine or Morpholine. In our case also, these amine deprotected Fmoc well, but to make the purification easier, we decided to choose Et_2NH (bp = 55 ℃) as the Fmoc deprotection reagent since the amine's residue is easily gotten rid of simply by means of evaporation. The De-Fmoc-Monomer, H_2N-Lys(Acetonide-G2)-OBn (**11**) and the De-Bn-Monomer, Fmoc-Lys(Acetonide-G2)-OH (**10**) were then coupled together (amide coupling) using DCC and HOBT to make the Dimer, Fmoc-Lys(Acetonide-G2)$_2$-OBn (**12**) as depicted in Scheme 4.



Scheme 4. Synthesis of the Dimer, Fmoc-Lys(Acetonide-G2)$_2$-OBn (**12**).

The following deprotection of Bn ester was carried out by employing the same hydrogenation reaction with the de-benzylation of the Monomer (**7**). Surprisingly enough, in case of the de-benzylation of the Dimer (**12**), Fmoc was almost completely intact. On the other hand, to deprotect Fmoc of the Dimer (**12**) we chose 4-(Dimethylamino)pyridine (DMAP) on Polystyrene (PS) instead of Et_2N because different from the case of Monomer (**7**), Et_2NH, Piperidine, or Morpholine deprotected not only Fmoc but also almost half of Bn, as well, during each of these Fmoc deprotection reactions. Through our intensive screening of the De-Fmoc reagent, we found that DMAP/PS gives the De-Fmoc-Dimer, H_2N-(Lys(Acetonide-G2))$_2$-OBn (**14**) very cleanly even though the reaction rate was a little bit slower than in case of the reaction using Et_2NH etc. After both of those deprotection reactions, the two Dimers, **13** and **14**, were coupled together using DCC and HOBT to make Tetramer, Fmoc-(Lys(Acetonide-G2))$_4$-OBn (**15**) as depicted in Scheme 5.

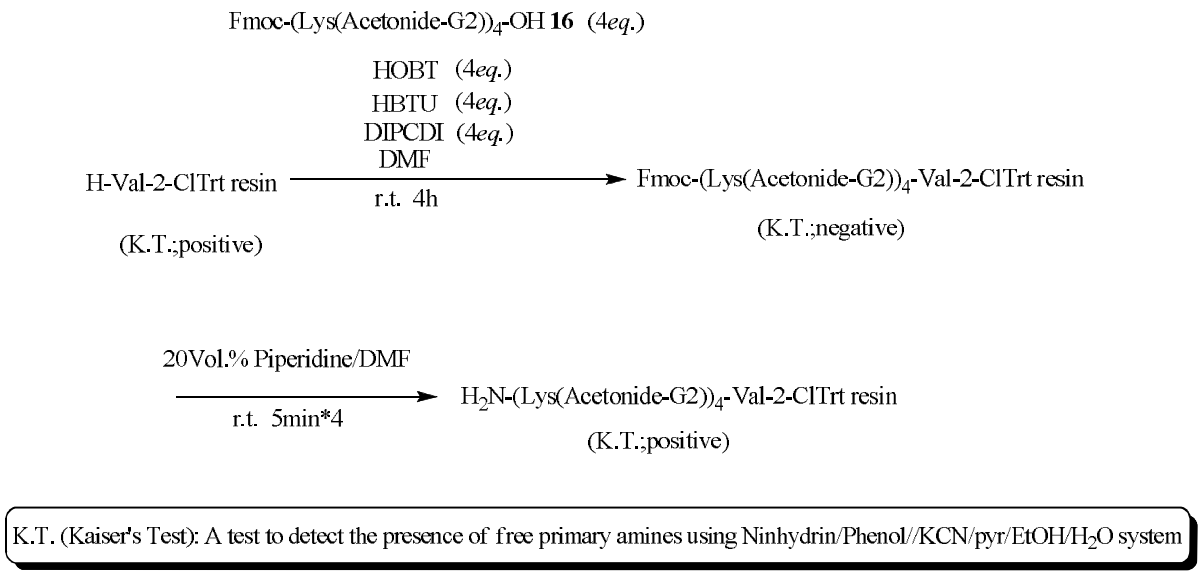
Interestingly, similar to the deprotection reaction of Bn from the Monomer, Fmoc-Lys(Acetonide-G2)-OBn (**7**), when we tried to deprotect the Bn ester from the Tetramer, Fmoc-(Lys(Acetonide-G2))$_4$-OBn (**15**) in EtOH as the solvent, unfavorable deprotection of Fmoc occurred to some extent. Furthermore, most of the acetonides on the dendron moieties were deprotected. Through the keen and intensive study, we found that THF and Acetone are the two best solvent candidates for the deprotection of Bn ester from the Tetramer (**15**) to yield Fmoc-(Lys(Acetonide-G2))$_4$-OH (**16**) (Scheme 5).



Schem 5. Synthesis of the De-Bn-Tetramer, Fmoc-(Lys(Acetonide-G2))$_4$-OH (**16**).

5-3-3. Solid Phase Peptide Synthesis (SPPS)

To synthesize Octamer and longer oligomers, we decided to apply Solid Phase Peptide Synthesis (SPPS) in order to avoid further loss of the yield caused by the nonorthognality of the protective groups. We used L-Valine preloaded acid labile 2-Chlorotrityl chloride modified Polystyrene (PS) resin, H-Val-2-ClTrt resin, as the initial SPPS support, which will enable us to cleave the peptide easily after the syntheses. As depicted in Scheme 6 and Figure 1, the attachment of the Tetramer, Fmoc-(Lys(Acetonide-G2))$_4$-OH (**16**) onto the resin was conducted using HOBT/HBTU/DIPCDI/DMF as the coupling reagent system.



Scheme 6. Attachment of Fmoc-(Lys(Acetonide-G2))$_4$-OH (**16**) onto the resin and the first Fmoc deprotection reaction using Piperidine.

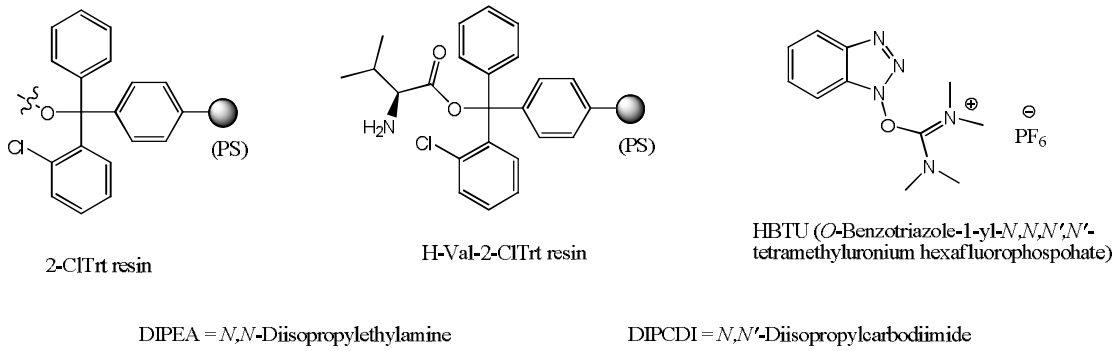
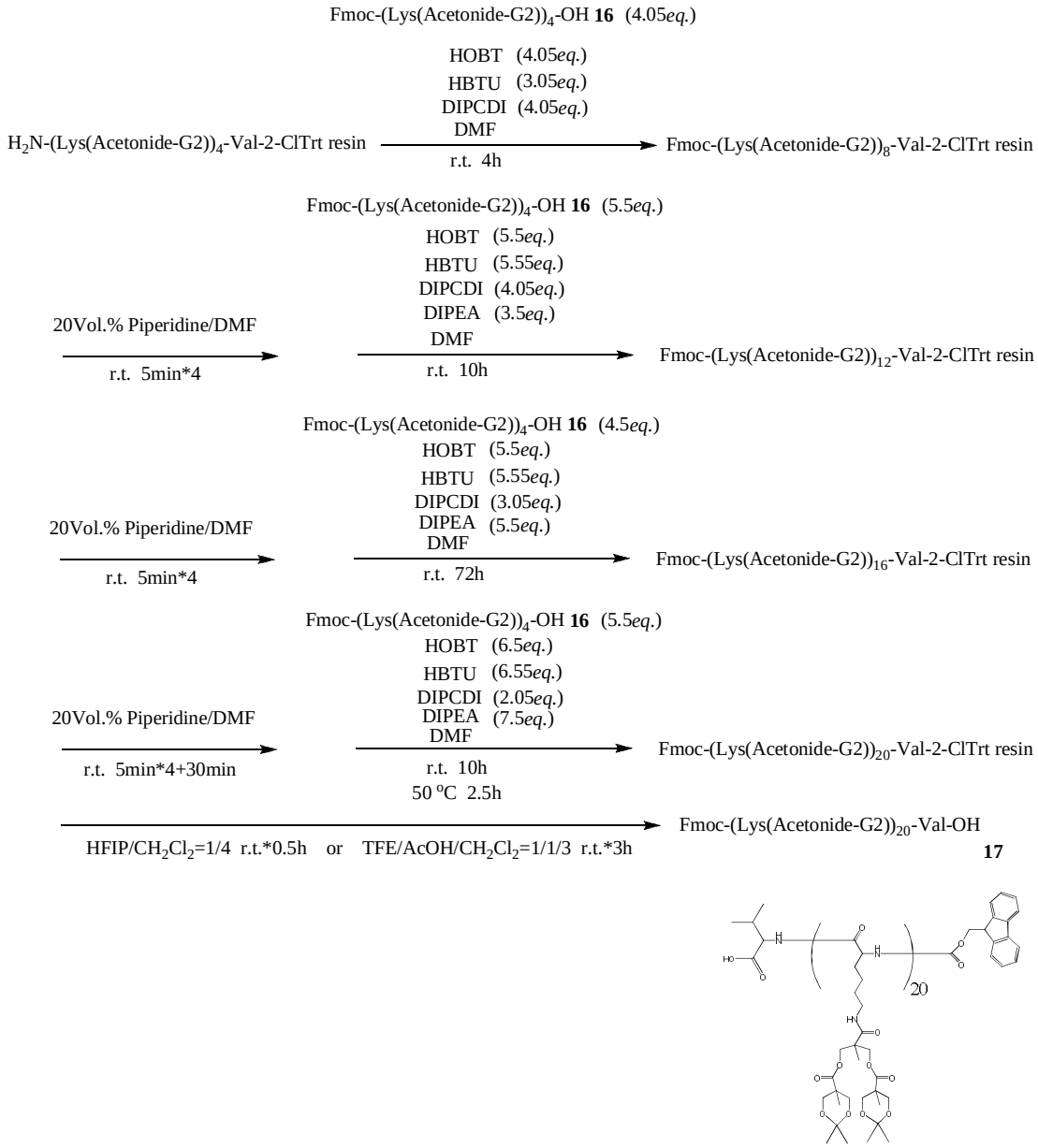


Figure 1. Reagents for SPPS.

Following synthetic procedure is shown in Scheme 7. After each coupling and De-Fmoc reaction, Kaiser's Test (K.T.)[9] was applied to confirm the presence/absence of the free primary amino groups. Most of the syntheses required excess amount of reagents and/or longer reaction time and/or repeating treatments to push the reaction completely. Nevertheless, sometimes the reactions were found to be not perfect and Kaiser's Test results of coupling reactions to make 12mer or longer oligomers turned out to be a little bit positive (Indicates the presence of free primary amino groups). After the coupling reaction to make 20mer, resultant oligopeptide (20mer + Val) was detached from the resin by an acid mediated cleavage system using 1,1,1,3,3,3-Hexafluoro-2-propanol (HFIP)[10(a)], or

a mixture of 2,2,2-Trifluoroethanol (TFE) and Acetic acid[10(b)-(d)]. Finally, we could get 20mer, Fmoc-(Lys(Acetonide-G2))$_{20}$-Val-OH (**17**) together with small amount of 16mer, 12mer, and Octamer as impurities. If we deprotected the acetonides from **17**, total 80 hydroxyl groups will appear on its surface. This also means that if we brought some biologically active functional group which can attach onto hydroxyl group, we could attach up to 80 biological active groups on this molecule.



Scheme 7. Solid Phase Synthesis of Fmoc-(Lys(Acetonide-G2))$_{20}$-Val-OH (**17**).

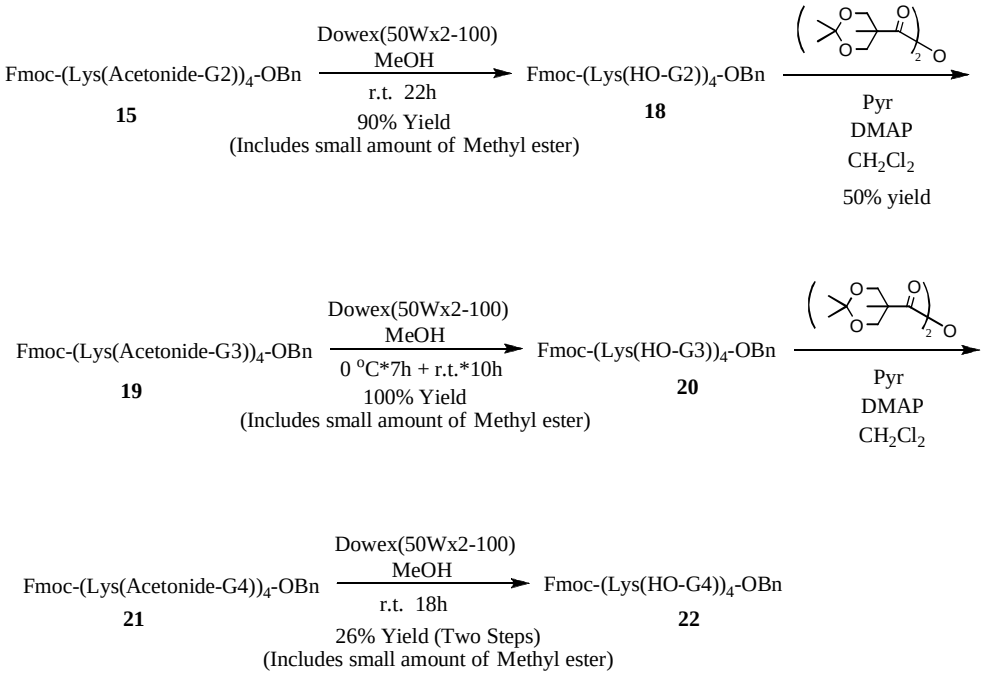
Although Solid Phase Peptide Synthesis has been applied as the major approach in peptide syntheses[11] for decades, solution phase synthesis still retains its value especially in large scale syntheses[12]. Here, it was found that the combination of the two strategies gave us the best route. So, Tetramers, **15** and **16**, were synthesized in solution

phase (Scheme 1-5) while for longer chains, the syntheses were conducted on solid phase supports using the Tetramer, Fmoc-(Lys(Acetonide-G2))$_4$-OH (**16**) as a 'Monomer Unit' of the well-known Fmoc-batch-SPPS method.

This combination dramatically reduced the total number of steps necessary to obtain for example 20mer from Monomer compared to the traditional linear synthetic approach adopted mostly in Solid Phase Peptide Snthesis (it requires total 40 steps)[13]. Also this strategy gives us products well separated in mass from failure sequences and undesired byproducts whereas linear synthesis produces a near-continuum of mass[13].

5-3-4. Divergent Growth of Bis-MPA Dendron

We also successfully synthesized higher generation dendron derivatives like Fmoc-(Lys(Acetonide-G4))$_4$-OBn (**21**) and Fmoc-(Lys(HO-G4))$_4$-OBn (**22**) by growing the dendron moiety divergently. To get around the problem of unfavorable hydrolysis of the Bis-MPA dendrons and transesterification of the benzyl ester moiety during the acetonide deprotection reactions, we selected a cation exchange resin Dowex (50Wx2-100) as the acid catalyst for de-acetonide reaction and conducted the reaction at lower temperature like r.t. or 0 ^oC for a very precise period of time (Scheme 8).



Scheme 8. Stepwise synthesis of the Generation-4-Tetramer, Fmoc-(Lys(HO-G4))$_4$-OBn (**22**).

As an example, the molecular structure of synthesized Fmoc-(Lys(HO-G4))$_4$-OBn (**22**) is shown in Figure 2. Even though this Tetramer is still too short to call it a virus mimic, this molecule has 64 hydroxyl groups on its surface and, again, if we brought some biologically active functional group which can attach onto a hydroxyl group, we could attach up to 64 biological active groups on this G4-Tetramer.

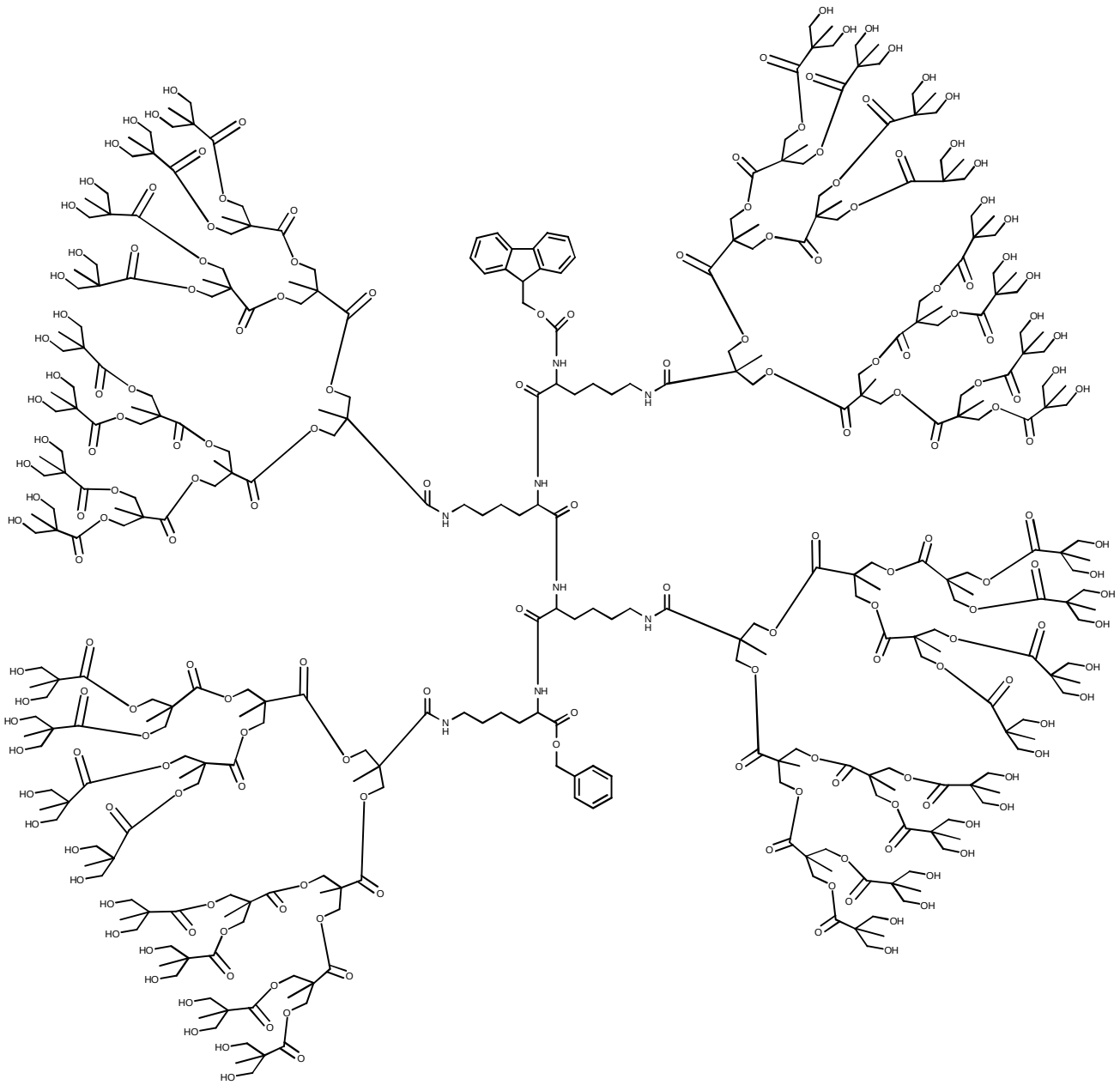
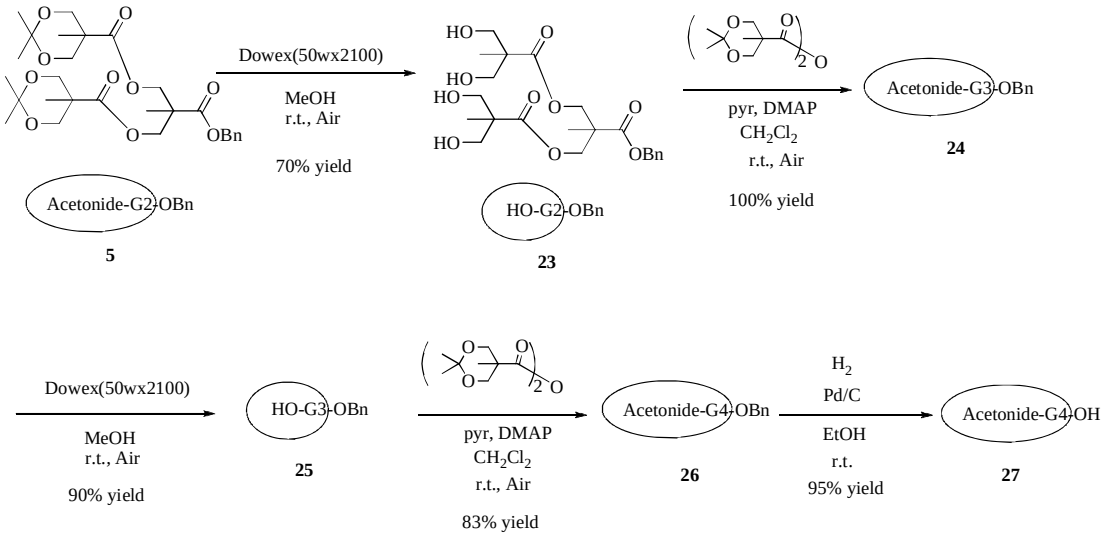


Figure 2. Fmoc-(Lys(HO-G4))$_4$-OBn (**22**).

5-3-5. Various Approaches

Instead of applying this stepwise approach, since Acetonide-G4-OH dendron (**27**) itself is possible to be synthesized (Scheme 9), it seemed to be easier to graft Acetonide-G4-OH (**27**) onto the Fmoc-(Lys-NH_2)$_n$-OBn directly. And plausible routes including "Direct graft to approach", "Stepwise graft from approach", and "Macromonomer approach"are shown in Figure 3. Et_2NH was found to be a good reagent for the deprotection of Fmoc from the Monomer, Fmoc-(Lys(BOC))-OBn (**2**) and DMAP/PS for the Fmoc deprotection from the Dimer, Fmoc-(Lys(BOC))$_2$-OBn (**29**). But debenzylation of the Dimer, Fmoc-(Lys(BOC))$_2$-OBn (**29**) was found to be very problematic and in spite of our through screening of the solvents and reaction conditions, and almost 40% of Fmoc was popped off even in case of the best reaction condition using THF as the solvent. On top of these problems, the solubility of the Dimers, Fmoc-(Lys(BOC))$_2$-OBn (**29**), H_2N-(Lys(BOC))$_2$-OBn (**30**), and Fmoc-(Lys(BOC))$_2$-OH (**31**) into most of the organic solvents was extremely lower compared to that of Monomers. Thus, we ceased proceeding further on this route (Scheme 10).



Schem 9. Synthesis of a higher generation dendron, Acetonide-G4-OH (**27**).

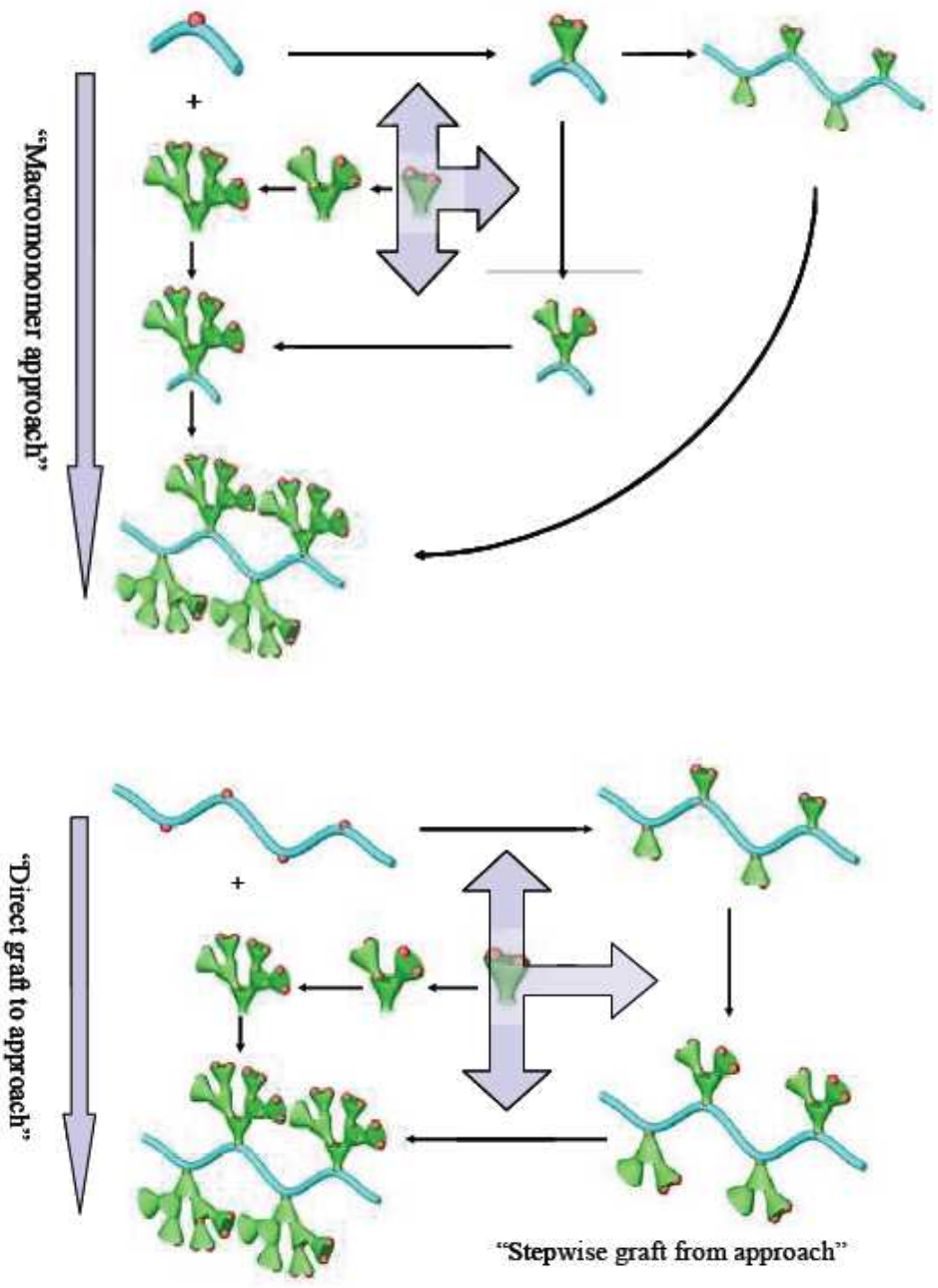
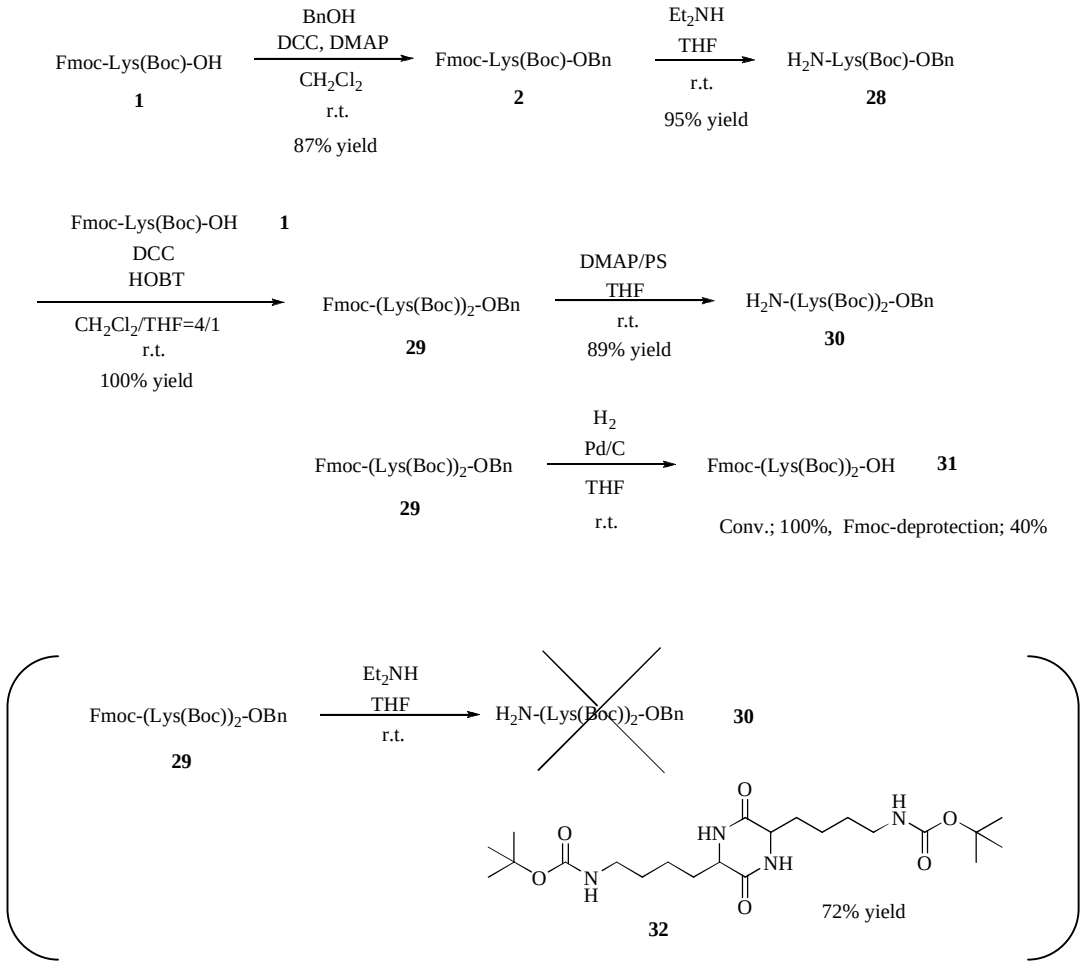


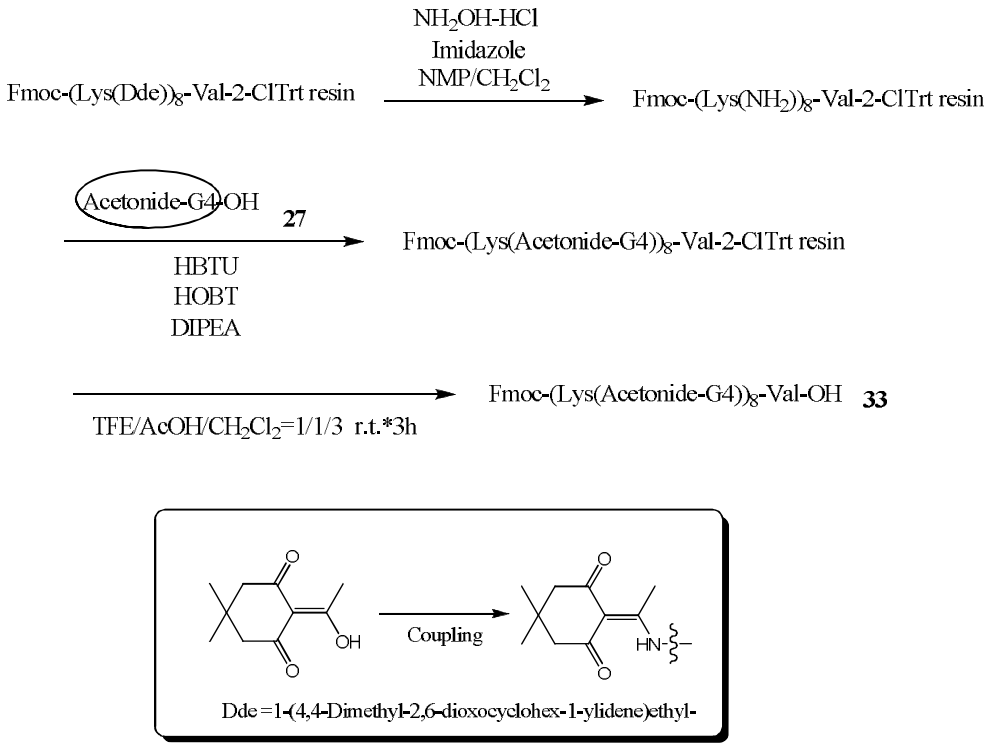
Figure 3. Various synthetic approaches to dendronized linear macromolecules.



Scheme 10. Synthetic trial of linear oligomers of (L)-Lysine with Boc group remained.

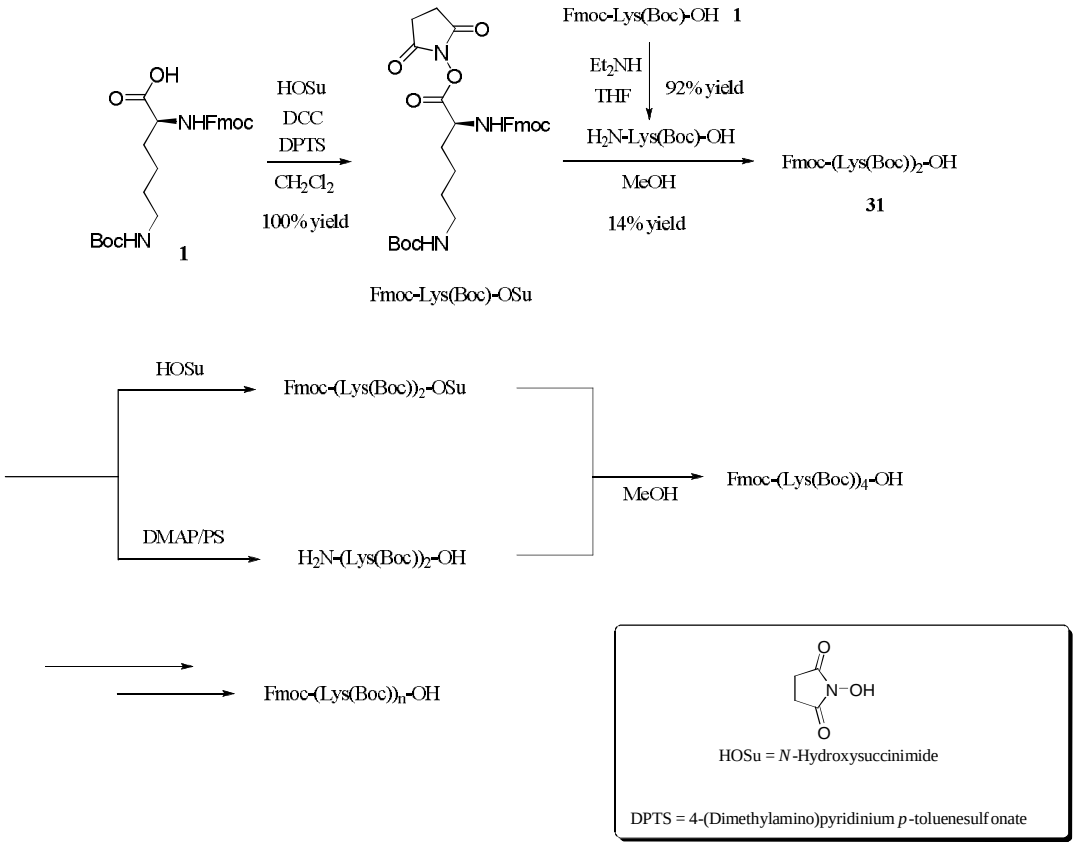
Also, we asked AnaSpec Inc. to synthesize spcially for us the (L)-Lysine-octamer with Valine on PS resin, Fmoc-(Lys(Dde))$_8$-Val-2-ClTrt resin, and tried to introduce Acetonide-G4-OH (**27**) to it. Dde stands for *N*-1-(4,4-dimethyl-2,6-dioxocyclohexylidene)ethy1 group and it can be used orthogonally with both Fmoc and Boc. And Dde is readily cleaved whenever it needs to be simply by exposing the compound to 2vol.% of Hydrazine in DMF or $NH_2OH \cdot HCl$/Imidazole in NMP[14].

But mainly because of the steric bulkiness of larger dendrons (G4), the complete coupling of the backbone was found to be difficult as reported previously[5] and the Kaiser's test result was remained positive despite an intensive effort to attach the Acetonide-G4-OH dendron (**27**) to the Octamer on the resin. The yield of the Fmoc-(Lys(Acetonide-G4))$_8$-Val-OH (**33**) came up with less than 10% of the theoretical yield and finally we gave up this direct-G4-graft approach (Scheme 11).

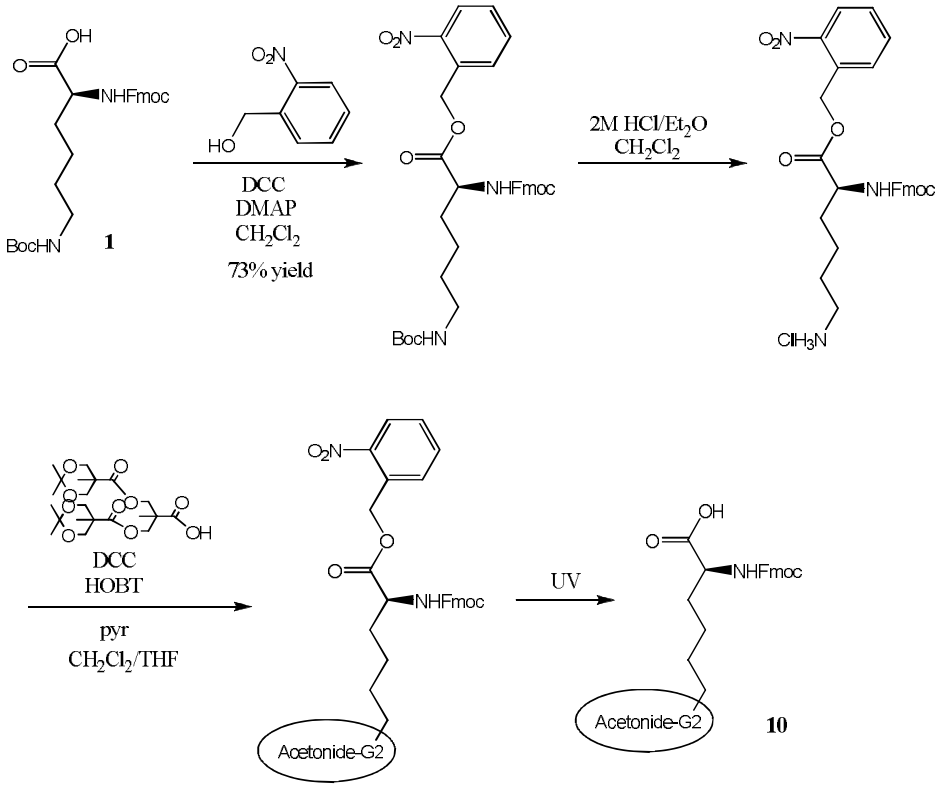


Scheme 11. Synthetic trial of Fmoc-(Lys(Acetonide-G4))$_8$-Val-OH (**33**) using Dde derivative on PS resin.

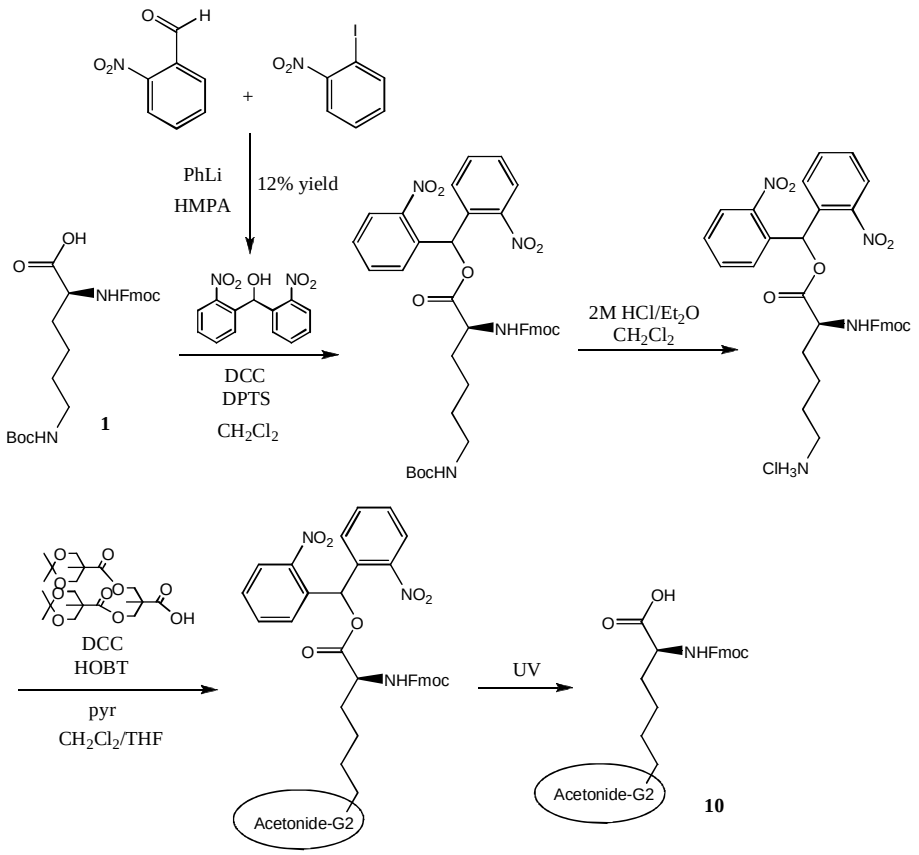
To avoid the nonorthogonality of the protective groups, then we tried to apply an activated ester method using *N*-Hydroxysuccinimide (HOSu)[15], and a photolytic ester method using a UV-labile group like 2-Nitrobenzyl alcohol or Bis(2-nitrophenyl) methanol[7]. But unfortunately, none of them gave satisfactory result (Scheme 12, 13, 14), either. For example, in case of HOSu route, because of the low solubility of the oligomers, yields of the Dimer (**31**) turned out to be very low.



Scheme 12. The activated-ester-method using *N*-Hydroxysuccinimide (HOSu).



Scheme 13. A photolytic ester method using a UV-labile group, 2-Nitrobenzyl alcohol.



Scheme 14. Another photolytic ester method using a UV-labile group, Bis(2-nitrophenyl) methanol[7].

5-4. Summary

We have synthesized dendronized linear Poly((L)-lysine)s up through 20mer with Bis-MPA type G2-dendron and Tetramer with G4-dendron by taking advantage of the combination of Solid Phase Peptide Synthesis (SPPS) and solution phase synthesis ('Exponential Growth Strategy[1]') which retains its value especially in larger scale syntheses.

Currently, further search for improved methodologies and study of the attachment of a biologically active group onto the multivalent hydroxyl groups of the dendrons along the backbone are underway.

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