2007

Development of Fluorescent Chemosensors Based on Energy Transfer in End-Capped Pi-Conjugated Systems

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DEVELOPMENT OF FLUORESCENT CHEMOSENSORS BASED ON ENERGY TRANSFER IN END-CAPPED \( \pi \)-CONJUGATED SYSTEMS

A Thesis

Submitted to the Graduate Faculty of the Louisiana State University and Agricultural and Mechanical College in partial fulfillment of the requirement for the degree of Master of Science

in

The Department of Chemistry

By
Huating Zhang
B.S., Shangxi Medical University, 2001
May, 2007
DEDICATION

To my parents,
Runlin Zhang, Yan’E Qian

To my husband,
Youjun Yang
ACKNOWLEDGMENTS

Mom and Dad, thank you giving me life, love, education. Thank you, all my sisters, for your unconditional supports all the time.

Next, I would like to thank my research advisor, Dr. Evgueni E. Nesterov, for affording me the opportunity to work in his group. Thank you for guiding me in my research and for always being there to help and support me. I would also like to thank the members (past and present) of the Nesterov Research Group.

Special thanks are extended to Dr. Garmo and Dr. Taylor for being my committee members.

I thank Hairong for help with MALDI-TOF and mostly importantly for your friendship. I’d also like to recognize Jieren Li for your encouragement all the time. I am very appreciated.

I’d also like to thank Dr. Crowe and Dr. Hammer for your excellent teaching.

Last, I want to thank my husband for help with everything.
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LIST OF ABBREVIATIONS

\( \text{B(OH)}_2 \)  Boronic acid
Br  bromide
Br\(_2\)  bromine
CDCl\(_3\)  Deuterated chloroform
CHCl\(_3\)  Chloroform
CN  nitrile
COOH  carboxylic acid
CP  Conjugated Polymer
CuI  Cupper (I) iodide
DCM  Dichloromethane
E-PAD  Electronic Paper Display
Et  Ethyl
h  hours
Hex  Hexyl
I  iodide
I\(_2\)  iodine
i-Pr\(_2\)NH  di-isopropylamine
K\(_2\)CO\(_3\)  potassium carbonate
KOH  potassium hydroxide
LED  Light Emitting Diode
MALDI-TOF  Matrix-Assisted Laser Desorption/Ionization Time-Of-Flight
Me  Methyl
MeMgI  Methyl Magnisium iodide
MeO  Methoxy
MeOH  Methanol
min  minutes
Na\(_2\)S\(_2\)O\(_4\)  Sodium hydrosulfite
Na\(_2\)SO\(_3\)  Sodium sulfite
NaIO\(_4\)  Sodium periodate
n-BuLi  \( n \)-butyllithium
NH\(_2\)  Amino
NMR  Nuclear Magnetic Resonance
NR\(_3\)  Triarylamine
OH  Hydroxyl
OLED  Organic Light Emitting Diode
P(t-Bu)\(_3\)  Triterrbutylphosphine
PAn  Polyaniline
Pd(PhCN)\(_2\)Cl\(_2\)  Bis(benzonitrile)palladium(II) chloride
Pd(PPh\(_3\))\(_4\)  Tetrakis(triphenylphosphine)palladium(0)
Ph  Phenyl
PPE  Poly(phenyleneethynylene)
<table>
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<th>Abbreviation</th>
<th>Definition</th>
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<tr>
<td>PPh$_3$</td>
<td>Triphenylphosphine</td>
</tr>
<tr>
<td>ppm</td>
<td>parts per million</td>
</tr>
<tr>
<td>PPy</td>
<td>Polypyrrole</td>
</tr>
<tr>
<td>PT</td>
<td>Polythiophene</td>
</tr>
<tr>
<td>PTSA</td>
<td>para-Toluenesulphonic acid</td>
</tr>
<tr>
<td>R</td>
<td>Alkyl</td>
</tr>
<tr>
<td>rt</td>
<td>room temperature</td>
</tr>
<tr>
<td>SH</td>
<td>thiol</td>
</tr>
<tr>
<td>TBDMS</td>
<td>Tertbutyldimethylsilyl</td>
</tr>
<tr>
<td>TIPS</td>
<td>Triisopropylsilyl</td>
</tr>
<tr>
<td>TMS</td>
<td>Trimethylsilyl</td>
</tr>
<tr>
<td>Ts</td>
<td>Tosylate</td>
</tr>
<tr>
<td>TsCl</td>
<td>Tosylate chloride</td>
</tr>
<tr>
<td>UV-Vis</td>
<td>Ultra violet-visible</td>
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ABSTRACT

A novel sensory platform based on conjugated polymer was developed, that consists of a monodispersed oligo(phenylene ethynylene) backbone, end-capped with a terminal alkene for further attachment to a solid surface at one terminus, and an anthracene based receptor group at the other terminus. Energy transfer from backbone to end-cap was observed by absorption spectroscopy and fluorescence spectroscopy. Other ongoing projects described herein include the synthesis of longer-chain analogues of the above platform, the synthesis of silica microspheres based conjugated polymer sensory platform and the synthesis of long wavelength (NIR) dye for in vivo amyloid screening studies.
I THE HISTORY OF CONJUGATED POLYMERS

The Nobel Prize in Chemistry in 2000 was awarded to Heeger, MacDiarmid and Shirakawa to acknowledge their discovery and development of conductive polymer, an oxidized polyacetylene (Figure 1), synthesized from polymerization of acetylene. They found that polyacetylene will become $1 \times 10^{10}$ times more conductive after oxidation by I$_2$, a process called doping. This metal-like property has drastically changed our conventional understanding towards plastic material, to which conductive polymer belongs.\textsuperscript{1}

\begin{center}
\textbf{Figure 1}. Structure of polyacetylene.
\end{center}

A variety of different conductive polymers were developed and have found wide practical applications in electronic and optical devices, light emitting diodes (LED), corrosion protection, photovoltaic cells and sensory devices, photodetectors, field-effect transistors, etc.\textsuperscript{2} A few representative examples such as poly(phenylene vinylene) (PPV), poly(phenylene ethynylene) (PPE), polythiophenes (PT), polypyrrole (PPy) and polyaniline (PAn) are shown in Figure 2.

\begin{center}
\textbf{Figure 2}. Structures of common conjugated polymers.
\end{center}
However, scientists currently show greater enthusiasm towards the less conductive, undoped form of conjugated polymers since conjugated polymer was found to display electroluminescence after voltage is applied. This property has rendered conjugated polymers as effective candidates for polymer light emitting diodes (PLED). Compared to their traditional inorganic LED analogs, PLED has significant advantages. First, ink-jet printing technology can be applied for processing plastic soluble polymers. Second, the devices can be flexible. The research toward the development of flexible large area display and Electronic Paper Display (E-PAD) are intensively sought-after. The electroluminescent property originates from the fact that conjugated polymers are semiconductors. Upon excitation, an electron of the valence band of conjugated polymer is excited to the conduction band. The resulting vacancy in the valence band is termed “hole”. This bound electron-hole pair, excited state of conjugated polymer, is called “exciton” and it generates fluorescence because the recombination of the electron and hole leads to the emission of a photon. By varying the structure of conjugated polymer, the wavelength of emission covers a wide range of the spectrum from ultra-violet, to visible, to near infrared.

![Figure 3](image_url)  
**Figure 3.** The basics of the electronic structure of a semiconducting polymer.
II APPLICATIONS OF CPs IN SENSORY SYSTEMS UTILIZING ENERGY TRANSFER

In recent years, conjugated polymer-based sensory systems have attracted attention due to their signal amplification effects after T. M. Swager proposed the concept of a molecular wire in 1995.\textsuperscript{4} Signal amplification originates from the transport properties of conjugated polymers. Transport properties refer to the fact that binding of the analyte to one or a minimal number of receptors in conjugated polymers is enough to result in a measurable macro-property disturbance. Electrical conductivity (resistivity) and fluorescence (based on fast energy migration) are two properties most readily monitored.

Electrical conductivity is very sensitive to the molecular structures and conformation changes of the conjugated polymers and can be precisely monitored by relatively simple instrumentation. For example, polypyrrole is 10 thousand times more conductive compared to its \textit{N}-methyl analog.\textsuperscript{5} The steric induced by the \textit{N}-methyl group cause the adjacent pyrrole rings not to be co-planar, and consequently this affects the delocalization of the electrons in the poly pyrrole backbone. The effective delocalization is also dependent on the conformational change of the backbone caused by binding to analytes. An example is polythiophene with a crown-ether macrocycle tethered to two adjacent thiophene units. In the presence of alkali metal ions, depending on the macrocycles present, different thiophene units adopt a planar geometry. Upon coordination with metal ions, adjacent thiophene units will no longer be co-planar. This twisted geometry leads to significant conductivity alternation.\textsuperscript{6}

The end group of a polymer is generally not taken into consideration. However, the end group of a rigid-rod conjugated polymer can play an important role in signal amplification. After excitation by light, the exciton rapidly migrates to an end group, which has a lower band-gap.
Scheme 1. The geometry change of polythiophene upon coordination with alkali metal ions.

Recombination of electrons and holes leads to longer wavelength emission. It was reported that the emission from the end capped group can be dominant. For example, an anthracene end-cap in the following conjugated polymer has a lower band-gap compared to its PPE backbone. Emission from the anthracene comprises 95% of total emission, which results from the fast energy migration from the polymer backbone to the low band-gap terminus (Figure 4).

Figure 4. The above poly(phenylene ethynylene) displays a dominant anthracene emission resulting from fast energy migration from the backbone.

There are two possible pathways for the energy migration in conjugated polymers: Förster energy transfer or Dexter Energy Transfer. Förster energy transfer can happen both intramolecularly and intermolecularly since it is a through-space energy transfer based on a dipole-induced dipole mechanism. The efficiency is proportional to $1/R^6$, where $R$ is the distance between the donor and acceptor. In solid state applications such as fluorescent polymer thin films, Förster energy transfer is the dominant process due to the decreased intermolecular...
distances. Dexter Energy Transfer occurs via an exchange mechanism, which can be seen as a simultaneous exchange of a pair of electrons occurring through interacting molecular orbitals. It requires strong electronic coupling between the donor and acceptor to compete with the Förster energy transfer process. The mechanistic difference between Förster and Dexter energy transfers is shown in Figure 5.

**Figure 5.** Mechanistic difference between Förster and Dexter energy transfer, where D is Donor, A is Acceptor, D* is the excited state of Donor and A* is the excited state of Acceptor.

Much research has been carried out to further address the energy migration mechanism in different situations. The aim of our research is to study the factors that have an effect on the photophysical properties of specially designed, conjugated polymer/oligomer and influence energy transfer pathways in these systems.
III EXPERIMENTAL DESIGN

The development of sensitive and selective templates for real-time detection of various analytes is of crucial importance for various fields including clinical, environmental and food applications, etc.\textsuperscript{11} Fluorescence-based techniques are desirable due to their high sensitivity. Recently, substantial progress has been made in the development of small-molecule fluorescent sensors for the selective detection of a wide array of analytes ranging from ions or small molecules to large biomolecules utilizing different chemical reactions, supramolecular interactions and other non-bonding interactions between the sensor and the analyte.\textsuperscript{12} The signaling processes are generally restricted to dilute solutions of sensors in various solvents. However, solution-based detection is harder to implement into practical devices. In contrast, solid-state fluorescent sensors can be conveniently applied in instrumentation. In addition, they are well-suited for vapor sensing.\textsuperscript{13} However, aggregation of the fluorescent sensors in the solid state usually leads to much diminished fluorescence.\textsuperscript{14} Furthermore, the analyte-sensor interaction is limited mostly to the film surface, since it is difficult for the analyte to diffuse into the solid film.\textsuperscript{15} Due to these reasons, small-molecule-based solid devices are challenging to be used in practical sensing applications. Compared to small-molecule sensors, conjugated polymers (CPs) have apparent advantages such as bright fluorescence in the solid state and analyte binding amplification resulting from their excitation transport properties.

From a practical viewpoint, it is preferable for a sensory signal to exhibit a new emission at a different wavelength rather than display fluorescence quenching or enhancement of the original signal to facilitate detection. Many CP-based fluorescent turn-on sensors have been reported to date, but most of them do not operate in solid state.\textsuperscript{15} Herein, we are designing a novel approach to building turn-on or color-changing solid-state fluorescent sensors, based on attenuation of
energy transfer in conjugated systems utilizing the self-assembled monolayer technique (Figure 6).

The core of the strategy lies in the design of the conjugated polymer system. The sensor is composed of a rigid-conjugated monodisperse oligomer core (oligophenylene ethynylene) end-capped with an anthracene based sensing group at one terminus, and a silicon-terminated linkage at the other end. The latter group can be used to covalently attach these molecules to a glass substrate through self-assembly (Scheme 3). The terminal sensing group is a $\pi$-conjugated moiety bearing a receptor for selective attachment or coordination binding with a specific analyte. Upon appropriate UV-Vis irradiation, the oligomer backbone will be selectively excited. In dilute solution, the exciton migration will occur intramolecularly both by through-bond (Dexter-type) and through-space (Förster-type) mechanisms. Efficiency will strongly depend on the relative position of the band-gap of the backbone and the HOMO-LUMO gap of the end group.

**Figure 6.** General design of a molecular sensor self-assembled on a solid support. Binding of an analyte results in lowering the band gap at the receptor terminus, thus directing energy migration towards the end group and enhancing its fluorescence.
In a particular case where they are approximately equal before binding the analyte, the energy transfer towards the end group is not favorable. Short wavelength fluorescence from the oligomer backbone will be predominant. Analyte binding will lower the energy gap of the termini. At this moment, exciton migration towards the end cap will be favorable and lead to a much enhanced fluorescence emission from the end group located at a longer wavelength compared to the emission from the backbone. One can also envision an opposite situation. Prior to analyte binding, the band gap at the terminus is relatively low, therefore leading to significant emission from the end-cap. Upon binding the analyte, the energy gap of the end-cap increases, energy migration becomes less favorable, and shorter-wavelength emission from the backbone will be enhanced. In any case, the analyte binding will lead to a fluorescence wavelength change, making quantitative analytical detection accurate and simple.

The molecular sensors will be combined into a solid-state sensor device through self-assembling. The self-assembling of alkanethiol on gold surfaces is well established. Detections of various analytes including metal ions, biologically important molecules, and vapors, based on such strategies were reported. However, gold usually leads to fluorescence quenching, thus forcing the use of less sensitive optical and electrochemical techniques as analyte binding transduction schemes. Recently, Reinhoudt et al. reported the self-assembling on a glass surface for sensing studies where fluorescence was not quenched by the glass support.
IV RESULTS AND DISCUSSION

Compound 1 was the initially designed target of our mono-dispersed oligomer sensing platform (Scheme 2). The anthracene end-cap is functionalized with an aldehyde group for chemosensing of cysteine and homosysteine\textsuperscript{18} Cysteine and homocysteine are the chemical stimuli which can result in the band-gap variation through reaction with an aldehyde to give a thiazolidine ring. Changes from an electron-withdrawing aldehyde group to an electron donating thiazolidine functionality increase the HOMO-LUMO gap of the end-cap so that the emission from the end-cap would decrease and that of the backbone should be enhanced. In addition to the fundamental significance of demonstrating the validity of this chemosensing platform, the choice of these particular analytes was also dictated by practical considerations. Cysteine and homocysteine are important biomolecules. Elevated levels of homocysteine are an indication of cardiovascular and Alzheimer’s disease. Deficiency of cysteine is related to various diseases such as slow growth, edema, lethargy, liver damage, muscle and fat loss etc. Therefore, development of a reliable practical methodology is of crucial importance for cysteine and homocysteine detection.

Scheme 2. Designed sensor 1 and its interaction with cysteine and homocysteine.
Scheme 3. An approach to chemical transformation of terminal alkenes for their self-assembly on a glass surface.

A. Synthetic Attempts toward 1.

A retrosynthetic analysis revealed that compound 1 might be assembled from three different fragments (Scheme 4) using palladium-catalyzed Sonogashira coupling (Scheme 5). The catalytic cycle of Sonogashira coupling is shown in Scheme 6.

My contribution focused on the synthesis of the Fragment A and Fragment B, and assembling the target molecule by coupling between the different fragments. Fragment C was synthesized by Dr. Evgueni Nesterov.

Scheme 4. Retrosynthetic analysis of compound 1.
Scheme 5. An example of Sonogashira Coupling catalyzed by Pd(0) catalyst.

**B  Synthesis of Fragment A**

10-Undecen-1-ol (2) reacted with TsCl in the presence of pyridine to afford 3 in 62% yield. Williamson alkylation of 4-iodophenol by tosylate 3 in the presence of K₂CO₃ furnishes 4 in 91% yield (Scheme 7). Sonogashira coupling between 4 and TMS-acetylene gives 5 in 99% yield. Desilylation of 5 by KOH in MeOH furnished the desired fragment A in 85%


yield. The ¹H NMR of fragment A is shown in Figure 7. The terminal alkyne proton has a resonance at 3.00 ppm. The three protons on the mono-substituted alkene group shows up at 5.0 ppm (2H) and 5.8 ppm (1H) respectively. The two protons on the methylene group next to the
Scheme 7. a) TsCl, Pyridine, 0°C for 2h, r.t. for 16 h, 63%, b) 4-iodophenol, K$_2$CO$_3$, 100°C, 50 h, 91%, c) TMS-acetylene, Pd(PPh$_3$)$_4$, CuI, i-Pr$_2$NH, 55°C, 30 h, 99%, d) KOH, r.t., 40 min, 85%.

Figure 7. $^1$H NMR spectrum of Fragment A in CDCl$_3$. The resonance of the alkyne proton is located at 3.00 ppm.
Scheme 8. Synthesis of Fragment B. a) Br₂, cat. I₂, 0°C, 17 h, b) n-BuLi, -78°C, 1 h, c) I₂, -78°C – r. t., overnight, d) TMS-acetylene, Pd(PPh₃)₄, Cul, i-Pr₂NH, 55°C, 24 h, e) KOH, r.t., 40 min.

The oxygen atom locate at 3.96 ppm. Aromatic protons show as two doublets at 6.8 ppm and 7.4 ppm. All the remaining protons from the alkyl chains locate in a range from 1.3 ppm to 2.1 ppm.

C Synthesis of Fragment B

para-Diethylbenzene 6 was brominated to afford 7 in 50% yield. Monolithiation with 1 equiv of n-BuLi followed by quenching with I₂ gave monoiodo compound 8 in 96% yield (Scheme 8). Sonogashira coupling between 8 and TMS-acetylene catalyzed by Pd(PPh₃)₄ and
CuI in the presence of diisopropylamine afforded 9 in 99% yield. To achieve a high yield, the reaction should be carried out at a relatively low (~55°C) temperature. Under these conditions, the coupling selectively occurred at the more reactive iodine center. A similar strategy was utilized throughout the rest of the synthesis to achieve highly regioselective mono-alkynylation by Sonogashira coupling. Half of 9 was lithiated, followed by iodination, to generate 10 in 95% yield. The other half of 9 was desilylated by KOH in MeOH to produce 11 in 99% yield. Sonogashira coupling between 10 and 11 furnished 12 in 98% yield. The same procedures were followed to synthesize tetramer 15 and octamer 18 (Scheme 8). The structure of compound 18 was confirmed via MALDI-TOF. The exact mass of 18 was calculated to be 1400.72 and [M+H]$^+$ was found to be 1401.41 (Figure 9). However, due to the fact that 18 is very sticky and has very poor solubility in common organic solvents, purification via standard chromatography was not successful and 18 could not be recovered. A byproduct—a result of homocoupling of two acetylene—has similar solubilities in different solvents compared to 18 and could not be removed. Still the impure sample of 18 was subjected to desilylation by KOH in MeOH to effect fragment B. Multiple attempts to use chromatography to purify fragment B resulted in a very small fraction of relatively pure sample. Most of the product was lost in the column since no solvents could elute it down. The $^1$H NMR spectra of fragment B is shown in Figure 10, and its UV-Vis and fluorescence spectra are shown in Figure 8. Fragment B displays a strong absorption in CHCl$_3$ with maximum at 370 nm, corresponding to the oligo(phenylene enthynylene) backbone. It is strongly fluorescent and displays an intense maximum at 415 nm with a shoulder peak at 440 nm due to aggregation.
Figure 8. Absorption and emission spectra of fragment B in CHCl₃.

D Attempts to Couple All Three Fragments

The more soluble tetramer 16 was used to prepare Compound 22, an analogue of

Figure 9. MALDI-TOF of compound 18. A molecular peak [M+H]⁺ is found at 1401.41.
Figure 10. $^1$H NMR of the Fragment B in CDCl$_3$. Singlet at 3.30 ppm corresponds to the terminal alkyne H.

Compound 1 (Scheme 9). Compound 19 was obtained in 56% yield. TMS on 19 was removed by treating with KOH in MeOH to yield 20 in 92% yield. This was followed by coupling with fragment A to furnish compound 21 in 53% yield. Ethylene glycol acetal protection of aldehyde was removed by a catalytic amount of PTSA to generate 22 in 51% yield (Scheme 9). The $^1$H NMR of 22 is shown in Figure 11. The aldehyde peak is located at 11.55 ppm. The terminal monosubstituted alkene peaks are located at 4.97 (2H) and 5.85 (1H) ppm. The presence of the resonances from both alkene and aldehyde confirmed the attainment of compound 22. Sensing studies in solutions are currently ongoing. They will be followed by preparations of solid-state devices through self-assembling on a glass surface.
Compound 20 (Figure 12A) shows a strong absorption at ca. 375 nm. The corresponding emission maximum is located at 408 nm, and an additional shoulder peak from aggregation is located at 430 nm. The absorption of fragment C (Figure 12B) has a strong absorption maxima corresponding to the vibronic transitions at 407 and 431 nm respectively. The emission of fragment C also shows a vibronic structure with maximum of 439 nm and a less intensive peak at

Scheme 9. Synthesis of a tetramer analog (22) of compound 1. a) Pd(PPh₃)₄, Cul, Toluene:i-Pr₂NH(7:3), 55°C, 24h, b) PTSA, rt, 12 h.
466 nm. It is interesting to point out that the absorption of fragment C (acceptor) and emission of compound 20 (donor) overlap very well (Figure 12C). This indicates that the energy transfer from the oligomer backbone to the anthracene moiety through the through-space dipole-induced dipole Förster mechanism will prevail in compound 21. Indeed, the emission of 21 mostly comes from the anthracene end group (Figure 12D). The excitation wavelength was chosen to be 350 nm, which excites the backbone efficiently but not the anthracene unit. The absorption spectrum of 21 appears to be a superposition of absorption spectra of its constituents, fragment C and compound 20 (Figure 12D). This can be attributed to the weak electronic interactions between the tetramer core and the end group in 21. With these weak electronic couplings, we can assume that the Förster through-space energy transfer mechanism seems to be predominant for compound 21. The absorption and emission of the aldehyde-terminated compound 22 displays a significant red shift compared to 21 (Figure 13). This is due to the incorporation of the electron withdrawing carbonyl group onto the end-cap. As in the previous case, the efficiency of energy transfer is very high, resulting in predominance of the end-group emission. With the apparent smaller spectral overlap in this case, there is a good probability for the Dexter through-bond mechanism to contribute significantly into energy transfer. However, more studies are required to fully support this conclusion.

Encouraged by the successful synthesis of 22, I tried the synthesis using the less soluble octamer (18). However, iodination of 18 to its more reactive iodide analog was unsuccessful under the same condition. I changed the catalyst from Pd(PPh₃)₄ to a more reactive system, Pd(PhCN)₂Cl₂ with P(t-Bu)₃.²⁰ Considering the large molecular weight, extended reaction time was applied when coupling with Fragment A. As a result, compound 23 is obtained in a form of a sticky yellow residue. Desilylation of 23 generated 24 smoothly. However, further attempts to
couple 24 with fragment C were not successful (Scheme 10). 1H NMR spectrum of 24 is shown in Figure 14.

Figure 11. 1H NMR of 22 in CDCl₃. Peak at 11.55 ppm is the resonance of the aldehyde proton. Resonances of the terminal alkene protons are located at 4.97 ppm and 5.85 ppm.

Figure 12. A) Absorption and emission of 20 in CHCl₃, B) Absorption and emission of fragment C in CHCl₃, C) Overlay of the emission of 20 and absorption of fragment C in CHCl₃, D) Absorption and emission of 21 in CHCl₃ showing that the emission is mainly from terminal anthracene moiety.
**Figure 13.** Absorption and emission of 22 in CHCl$_3$.

**Scheme 10.** Synthetic attempts toward 1. a) Pd(PhCN)$_2$Cl$_2$, P(t-Bu)$_3$, i-Pr$_2$NH, Cul, 65°C, 48 h, b) KOH/MeOH, rt, 1 h.
Figure 14. $^1$H NMR spectrum of 24 in CDCl$_3$. The alkyne proton appears at 3.32 ppm. Terminal alkene protons are located at ca. 5.00 ppm and 5.83 ppm. The peak at 5.30 ppm is from DCM, which is trapped in the gel-like 24 and cannot be removed. The $^1$H NMR spectrum was collected at elevated temperature to improve 24’s solubility in CDCl$_3$.

We found that the absorption and emission spectra of 24 red are shifted by ca. 15 nm. This is in a good agreement with the fact that 24 has extended $\pi$-electron conjugation (Figure 15).

Figure 15. Comparison of the absorption (solid lines) and emission (dashed lines) of 24 and 20 in CHCl$_3$.  

$\lambda_{ex}=350$ nm in CHCl$_3$.
E Attempt with the Hexyl Substituted Derivative

It is well-known that long alkyl chains increase the solubility of compounds in common organic solvents. To increase the solubility of oligomers in organic solvents and further facilitate the coupling of different fragments, we tried to use $p$-dihexylbenzene instead of the diethyl counterpart (Scheme 11). The same procedures as for the synthesis with diethylbenzene described above were used. After the tetramer 35 was synthesized, I transferred the project to

**Scheme 11.** Toward the synthesis of $n$-Hexyl substituted oligomers.
another student in my group. The $^1$H NMR spectrum of 35 is shown in Figure 16. Hexyl groups indeed increased the solubility of the compounds and made them very soluble even in such a non-polar solvent as hexane. Importantly, the use of the longer hexyl side chain did not seem to affect electronic conjugation in the oligomers. Figure 17 shows that the ethyl and hexyl analogs (20 and 35) have very close absorption and emission spectra in CHCl₃.

**F Synthesis of Silica Supported Conjugated Polymer**

An alternative approach to the oligomer self-assembly-based one described above was to synthesize the end-capped conjugated polymer chains starting from the low molecular weight precursor pre-attached to the solid support. This approach seemed to allow avoiding problems

![Figure 16](image_url)

**Figure 16.** $^1$H NMR of 35 in CDCl₃. Terminal TMS (9H) is located at 0.29 ppm, and the terminal alkene (3Hs) is at 4.99 ppm and 5.84 ppm.
Figure 17. Overlay of the absorption (solid lines) and emission (dashed lines, excited at 350 nm) spectra of 20 and 36 clearly shows that alkyl substituents on the phenylene group do not exhibit a strong influence on the photophysical properties of the oligomer backbone.

with low solubility of oligomers. So we attempted it as well, using 0.33 µm silica microspheres. Compound 37 reacted with commercially available 3-(trimethoxysilyl)propylamine (38) to yield the amide 39 in 72% yield (Scheme 12). Special precaution should be taken for column purification of 39 since it readily reacts with silica gel unless column is pre-treated with triethylamine. Compound 39 was attached to the surface of silica particles to generate 40, which has a terminal aryl iodide functionality. This could serve to initiate a Sonogashira-Coupling based polymerization of monomer 41. After carrying out the polymerization reaction for 24 h, a solution of end-capping reagent (fragment C) was added to the resulting mixture. This afforded highly fluorescent microparticles 43 bearing short conjugated polymer chains. GPC studies of the solution fraction 42 found the number averaged molecular weight $M_n \approx 1800$, which corresponds to a chain of ca. 10 repeating units, with a polydispersity of 1.65. The overlay of the emission spectra of the solution fraction and the silica particle clearly showed that the backbone emission of 42 has almost the same emission maximum as the particle fraction. This also
confirms that the GPC data were also valid in estimating the short polymer chains attached to the silica particles. The project was then transferred to my labmate and further studies are ongoing.

![Graph](image)

**Figure 18.** Comparison of the UV-Vis and fluorescence spectra of solution fraction and the silica particle fraction.

### G Synthesis of a Monomer for a Water Soluble Boronic Acid Functionalized Conjugated Polymer

My task was to synthesize monomer 48 which will be used to prepare a water soluble polymer (45) with pendant boronic acid groups for ultra-sensitive vicinal glycol detection (Scheme 13). para-Xylene (49) was brominated to afford 50 in a 70% yield. Benzylic bromination of 50 with NBS gave 51 in 73% yield. Nucleophilic substitution of the benzylic bromide by Na₂SO₃ leads to 52 in 77% yield. However, 52 did not couple with TMS-acetylene to yield the desired monomer 48. It is likely that the benzylic sulfonate groups hinder the Sonogashira coupling. In an alternative approach, coupling between 51 and TMS-acetylene did not yield the desired bis-acetylene, but the tetrasubstituted product 53 (Scheme 14). We are currently exploring the coupling between 50 and TIPS acetylene. TIPS is chosen to replace TMS due to its better robustness. Compound 54 was obtained in almost 99% yield. I am currently working on the NBS bromination of the compound 54. Once 55 has been obtained, Na₂SO₃ will be used to displace the benzylic bromides to furnish 56. Further desilylation will generate desired monomer 48 (Scheme 15).
Scheme 12. Synthesis of a silica microsphere supported conjugated polymer system. a) DCM, 0°C, 1 h, b) Toluene, reflux, 4 h, c) KOH, MeOH, rt, 1 h, d) Pd(PPh₃)₄, CuI, i-Pr₂NH, 60°C, 24 h.
Scheme 13. Retrosynthetic analysis of polymer 45.

**Synthesis of Long Wavelength (Near-Infrared) Dye**

Compound 60 is synthesized following a literature procedure.\textsuperscript{21} It is further protected with TBDMS to yield 61 in 55% yield. Stirring with malononitrile in the presence of TiCl\(_4\) in anhydrous pyridine yields trace amounts of 62. Reaction optimization is ongoing and deprotection of 62 by fluoride will furnish the expected long wavelength dye (Scheme 16).

**Scheme 14.** Attempts to synthesize monomer 47. a) Br\(_2\), I\(_2\), 0\(^\circ\)C, 24 hr, b) NBS, CCl\(_4\), reflux, 24 h, c) Na\(_2\)SO\(_3\), EtOH/H\(_2\)O, TBAB, reflux, d) TMS-acetylene, Pd(PPh\(_3\))\(_4\), CuI, i-Pr\(_2\)NH, 60\(^\circ\)C, 24 h, e) TIPS-acetylene, Pd(PPh\(_3\))\(_4\), CuI, i-Pr\(_2\)NH, 85\(^\circ\)C, 22 h, f) KOH, rt, 1h.
Scheme 15. New route for the synthesis of monomer 47.

Scheme 16. Synthesis of long wavelength dye. a) MeMgI, rt, 6 h, b) H⁺, c) NaOH, 0°C, 1.5 h, d) Na₂S₂O₄, rt, 30 min, e) HCl, reflux, 1.5 h, f) NaIO₄, rt, 30 min, g) TBDMSCl, imidazole, rt, 24 h, h) CH₂(CN)₂, pyridine, TiCl₄, 0°C, 15 h.
V CONCLUSION

The synthesis of a monodispersed oligo(phenylene ethynylene) backbone, end-capped with a terminal alkene for further attachment to a solid surface at one terminus, and an anthracene based receptor group at the other terminus, was successfully accomplished. Efficient energy transfer from backbone to end-cap was observed by absorption spectroscopy and fluorescence spectroscopy in agreement with the initial experimental design. The synthesis of a longer-chain analogue of the above platform, silica microspheres based conjugated polymer sensory platform and the synthesis of long wavelength (NIR) dye for *in vivo* amyloid screening were described.
VI EXPERIMENTAL

Compound 3. 10-Undecen-1-ol (5.0 g, 29.4 mmol) was added in a 300 ml three-neck round bottom flask and dissolved in pyridine (20 mL). A solution of TsCl (8.4 g, 44.0 mmol) in pyridine (20 mL) was added dropwise with constant stirring at the ice bath temperature. Mixture was maintained at 0°C under N₂ atmosphere for 2 h before it was warmed up to rt. The mixture was stirred for another 19 h followed by addition of H₂O (150 mL). Then, the reaction mixture was stirred for another 1 h before extraction with EtOAc (3 × 75 mL). Combined organic layers were washed with 1% HCl (5 × 50 mL) and distilled water (5 × 50mL), and dried over Na₂SO₄. Solid was removed by suction filtration. The resulting solution was concentrated under reduced pressure to give compound 3 (6.0 g) in 63 % yield. Data for compound 3: ¹H NMR (CDCl₃, 400 MHz) δ 7.79 (d, J = 8.4 Hz, 2H), 7.34 (d, J = 8.4 Hz, 2H), 5.84-7.77 (m, 1H), 4.99 (d, J = 17.1 Hz, 1H), 4.93 (d, J = 10.2 Hz, 1H), 4.02 (t, J = 6.53 Hz, 2H), 2.04-1.20 (m).

Compound 4. A 250 ml round bottom flask was charged with 4-iodophenol (2.0 g, 9.3 mmol), compound 3 (6 g, 18.5 mmol), K₂CO₃ (2.6 g, 18.5 mmol) and KI (30.7 mg, 1.9 mmol). Methylethylketone (100 mL) was added. The reaction mixture was refluxed for 50 h under N₂ atmosphere. Inorganic salts were removed by suction filtration. The organic solvent was removed under reduced pressure. The residue was dissolved in DCM and washed with 10% NaOH solution and distilled water. The organic layer was separated and dried over MgSO₄. The resulting organic solution was concentrated under reduced pressure to give crude product, which was subjected to column chromatography (silica gel, Hexane) to give compound 4 (3.4 g) in 91% yield. Data for compound 4: ¹H NMR (CDCl₃, 250 MHz) δ 7.54 (d, J = 8.9 Hz, 2H), 6.68 (d, J = 8.9 Hz, 2H), 5.92-5.73 (m, 1H), 5.05-4.91 (m, 2H), 3.91 (t, J = 6.5 Hz, 2H), 2.10-1.25 (m).
Compound 5. A mixture of compound 4 (3.2 g, 8.5 mmol), TMS-acetylene (1.7 g, 16.9 mmol), Pd(PPh3)4 (147 mg, 0.13 mmol) and CuI (24.4 mg, 0.13 mmol) were charged in a sealed flask and dissolved in 70 mL of Toluene:i-Pr2NH (v/v 7:3). The mixture was stirred at 55°C for 30 h. The resulting mixture was passed through a short column (silica gel) to remove metal catalyst and inorganic salts. Concentration under reduced pressure affords compound 5 (2.9 g) in 99% yield. Data for compound 5: \( ^1H \) NMR (CDCl3, 250 MHz) \( \delta \) 7.39 (d, \( J = 8.7 \) Hz, 2H), 6.81 (d, \( J = 8.7 \) Hz, 2H), 5.90-5.73 (m, 1H), 5.50-4.92 (m, 2H), 3.95 (t, \( J = 6.5 \) Hz, 2H), 2.10-1.32 (m), 0.24 (s, 9H).

Fragment A. Compound 5 (2.9 g, 8.2 mmol) was dissolved in THF (175 mL) and added dropwise into a solution of KOH (2.4 g, 42.3 mmol) in MeOH (200 mL) with constant stirring. The resulting mixture was stirred for an additional 40 min at rt. The solution was poured into water (300 mL) and extracted with ether. The combined ether layers were washed successively with water (200 mL), saturated NH4Cl solution (100 mL), brine (100 mL) and water (3 × 100 mL), and dried over Na2SO4. Solution was concentrated under reduced pressure and the residue was subjected to column chromatography (silica gel, Hexane) to give fragment A (1.9 g) in 85%. Data for fragment A: \( ^1H \) NMR (CDCl3, 250 MHz) \( \delta \) 7.42 (d, \( J = 8.5 \) Hz, 2H), 6.83 (d, \( J = 8.5 \) Hz, 2H), 5.90-5.73 (m, 1H), 5.50-4.92 (m, 2H), 3.96 (t, \( J = 6.5 \) Hz, 2H), 2.99 (s, 1H), 2.13-1.20 (m).

Compound 8. A solution of \( n \)-BuLi (145 mL of 1.6 M solution in Hexane, 0.23 mol) was added dropwise to a solution of compound 7 (63 g, 0.23 mol) in THF (900 ml) with constant stirring at the dry ice/Acetone bath temperature. After addition was complete, the resulting mixture was stirred for another 3 h followed by addition of a solution of I2 (71.3 g, 0.28 mol) in THF (250 mL). The resulting mixture was stirred for another 1 h at -78°C and allowed to warm to rt overnight. The solution was concentrated to 30% of the initial volume, and 20% Na2S2O3
solution in H$_2$O was added till the mixture turned yellow. Water (300 mL) was added, and the reaction mixture was extracted with DCM. Organic layers were washed successively with dilute Na$_2$S$_2$O$_3$, brine, and water before drying over Na$_2$SO$_4$. Solvents were removed under reduced pressure. Compound 8 (70 g) was obtained after recrystallization from EtOH. Data for compound 8: $^1$H NMR (Acetone-$d_6$, 250 MHz) $\delta$ 7.77 (s, 1H), 7.48 (s, 1H), 2.84-2.68 (m, 4), 1.22-1.15 (m, 6H).

Compound 9 was prepared following the synthetic procedure for compound 5. The following amounts of reagents were used: compound 8 (35.7 g, 0.11 mol), TMS-acetylene (10.3 g, 0.11 mol), Pd(PPh$_3$)$_4$ (1.8 g, 1.6 mmol) and CuI (0.31 g, 1.6 mmol) in 400 mL of Toluene:i-Pr$_2$NH (v/v 7:3). The crude product was purified by column chromatography (silica gel, Hexane) to give compound 9 (32 g) in 98% yield. Data for compound 9: $^1$H NMR (CDCl$_3$, 250 MHz) $\delta$ 7.36 (s, 1H), 7.26 (s, 1H), 2.77-2.64 (m, 4H), 1.25-1.18 (m, 6H), 0.25 (s, 9H).

Compound 10 was iodinated following the synthetic procedure for compound 8. The following amounts of reagents were used: compound 9 (16.22 g, 52.5 mmol), n-BuLi (40 mL of 1.6 M solution in Hexane, 64 mmol), I$_2$ (18 g, 69.8 mmol). Crude product was purified by column chromatography (silica gel, Hexane) to give compound 10 (17.7 g) in 95% yield. Data for compound 10: $^1$H NMR (CDCl$_3$, 250 MHz) $\delta$ 7.65 (s, 1H), 7.26 (s, 1H), 2.72-2.64 (m, 4H), 1.25-1.15 (m, 6H), 0.26 (s, 9H).

Compound 11 was prepared following the synthetic procedure for the fragment A. The following amounts of reagents were used: compound 9 (16.22 g, 52.5 mmol), KOH (9.9 g, 0.16 mol). The product was purified by column chromatography (silica gel, Hexane) to give
compound 11 (12.3 g) in 99% yield. Data for compound 11: \(^1\)H NMR (CDCl\(_3\), 250 MHz) \(\delta\) 7.38 (s, 1H), 7.30 (s, 1H), 3.26 (s, 1H), 2.80-2.65 (m, 4H), 1.25-1.18 (m, 6H).

Compound 12 was prepared following the synthetic procedure for compound 5. The following amounts of reagents were used: compound 11 (12.4 g, 52.5 mmol), compound 10 (17.0 g, 47.7 mmol), Pd(PPh\(_3\))\(_4\) (0.83 g, 0.72 mmol) and CuI (0.14 g, 0.72 mmol) in 300 mL of Toluene:i-Pr\(_2\)NH (v/v 7:3). The product was purified by column chromatography (silica gel, Hexane) to give compound 12 (21.6 g) in 98% yield. Data for compound 12: \(^1\)H NMR (CDCl\(_3\), 250 MHz) \(\delta\) 7.42 (s, 1H), 7.36 (s, 1H), 7.34 (s, 1H), 7.33 (s, 1H), 2.90-2.65 (m, 8H), 1.34-1.19 (m, 12H), 0.27 (s, 9H).

Compound 13 was prepared following the synthetic procedure for compound 8. The following amounts of reagents were used: compound 12 (10 g, 21.5 mmol), \(n\)-BuLi (16.1 mL of 1.6 M solution in Hexane, 25.8 mmol) and I\(_2\) (7.3 g, 28.6 mmol). The product was purified by column chromatography (silica gel, Hexane) to give compound 13 (8.9 g) in 81% yield. Data for compound 13: \(^1\)H NMR (Acetone-\(d_6\), 250 MHz) \(\delta\) 7.80 (s, 1H), 7.45 (s, 1H), 7.43 (s, 1H), 7.35 (s, 1H), 2.90-2.65 (m, 8H), 1.30-1.19 (m, 12H), 0.26 (s, 9H).

Compound 14 was prepared following the synthetic procedure for the fragment A. The following amounts of reagents were used: compound 12 (10.3 g, 22.2 mmol), KOH (3.7 g, 66.7 mmol). The product was purified by column chromatography (silica gel, Hexane) to give compound 14 (7.5 g) in 86% yield. Data for compound 14: \(^1\)H NMR (Acetone-\(d_6\), 250 MHz) \(\delta\) 7.53 (s, 1H), 7.48 (s, 1H), 7.45 (s, 1H), 7.40 (s, 1H), 3.96 (s, 1H), 2.90-2.73 (m, 8H), 1.31-1.20 (m, 12H).
Compound 15 was prepared following the synthetic procedure for compound 5. The following amounts of reagents were used: compound 13 (7.5 g, 14.6 mmol), compound 14 (6.3 g, 16.1 mmol), Pd(PPh₃)₄ (0.3 g, 0.22 mmol) and CuI (0.042 g, 0.22 mmol) in 100 mL of Toluene:i-Pr₂NH (v/v 7:3). The product was purified by column chromatography (silica gel, Hexane:CHCl₃ 95:5) to give compound 15 (9.8 g) in 86% yield. Data for compound 15: ¹H NMR (CDCl₃, 300 MHz) δ 7.42-7.33 (m, 8H), 2.92-2.72 (m, 16H), 1.35-1.22 (m, 24H), 0.27 (s, 9H).

Compound 16 was prepared following the synthetic procedure for compound 8. The following amounts of reagents were used: compound 15 (4.6 g, 5.9 mmol), ICH₂CH₂I (2.3 g, 8.3 mmol) as a replacement for I₂, n-BuLi (5.1 mL of 1.6 M solution in Hexane, 8.2 mmol). The product was purified by column chromatography (silica gel, Hexane:CHCl₃=50:50) to give compound 16 (3.8 g) in 77% yield. Data for compound 16: ¹H NMR (CDCl₃, 300 MHz) δ 7.71 (s, 1H), 7.40-7.26 (m, 7H), 2.92-2.69 (m, 16H), 1.34-1.20 (m, 24H), 0.27 (s, 9H).

Compound 17 was prepared following the synthetic procedure for the fragment A. The following amounts of reagents were used: compound 15 (5.2 g, 6.6 mmol), KOH (1.3 g, 24 mmol). The product was purified by column chromatography (silica gel, Hexane:CHCl₃=1:1) to give compound 17 (4.6 g) in 99% yield. Data for compound 17: ¹H NMR (CDCl₃, 250 MHz) δ 7.43-7.36 (m, 8H), 3.32 (s, 1H), 2.92-2.69 (m, 16H), 1.56-1.24 (m, 24H).

Compound 18 was prepared following the synthetic procedure for compound 5. The following amounts of reagents were used: compound 16 (2.0 g, 2.3 mmol), compound 17 (2.0 g, 2.6 mmol), Pd(PPh₃)₄ (0.040 g, 0.04 mmol) and CuI (0.007 g, 0.04 mmol) in 60 mL of Toluene:i-Pr₂NH (v/v 7:3). An attempt to purify the product by column chromatography (silica gel, CHCl₃)
gave crude compound 18 (100 mg). Data for compound 18: $^1$H NMR (CDCl$_3$, 250 MHz) $\delta$ 7.46-7.37 (m, 16H), 2.93-2.66 (m, 32H), 1.37-1.14 (m, 48H), 0.31 (s, 9H).

Fragment B was prepared following the synthetic procedure for the fragment A. The following amounts of reagents were used: compound 18 (88 mg, 0.062 mmol), KOH (10 mg, 0.2 mmol). An attempt to purify the product by column chromatography (silica gel, CHCl$_3$) gave crude fragment B (40 mg). Data for fragment B: $^1$H NMR (CDCl$_3$, 250 MHz) $\delta$ 7.43-7.35 (m, 16H), 3.31 (s, 1H), 2.93-2.68 (m, 32H), 1.33-1.21 (m, 48H).

Compound 19 was prepared following the synthetic procedure for compound 5. The following amounts of reagents were used: compound 16 (0.8 g, 0.97 mmol), fragment A (0.3 g, 1.1 mmol), Pd(PPh$_3)_4$ (0.017 g, 0.015 mmol) and CuI (0.003 g, 0.015 mmol) in 20 mL of Toluene:i-Pr$_2$NH (v/v 7:3). The product was purified by column chromatography (silica gel, Hexane:CHCl$_3$ 90:10) to give compound 19 (500 mg) in 56% yield. Data for compound 19: $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 7.48-7.34 (m, 18H), 6.88 (d, $J$ = 8.4 Hz, 2H), 5.88-7.58 (m, 1H), 5.03-4.93 (m, 2H), 3.98 (t, $J$ = 6.4 Hz, 2H), 2.92-2.79 (m), 2.07-0.87 (m), 0.28 (s, 9H).

Compound 20 was prepared following the synthetic procedure for the fragment A. The following amounts of reagents were used: compound 19 (500 mg, 0.52 mmol), KOH (87 mg, 1.6 mmol). The product was purified by column chromatography (silica gel, Hexane:CHCl$_3$=80:20) to give compound 20 (427 mg) in 92% yield. Data for compound 20: $^1$H NMR (CDCl$_3$, 250 MHz) $\delta$ 7.49-7.39 (m, 18H), 6.89 (d, $J$ = 8.4 Hz, 2H), 5.92-5.75 (m, 1H), 5.08-4.92 (m, 2H), 3.97 (t, $J$ = 6.5 Hz, 2H), 3.33 (s, 1H), 2.91-2.85 (m), 2.10-0.87 (m).

Compound 21 was prepared following the synthetic procedure for compound 5. The following amounts of reagents were used: compound 20 (0.053 g, 0.06 mmol), the fragment C
(0.029 g, 0.06 mmol), Pd(PH3)4 (2 mg, 0.002 mmol) and Cul (0.35 mg, 0.002 mmol) in 6 mL of Toluene:i-Pr2NH (v/v 7:3). The product was purified by column chromatography (silica gel, Hexane:EtOAc=80:20) to give compound 21 (39.6 mg) in 53% yield. Data for compound 9: 1H NMR (CDCl3, 250 MHz) δ 8.76 (d, J = 8.8 Hz, 2H), 8.61 (d, J = 8.1 Hz, 2H), 7.81-7.34 (m, 21H), 7.13 (s, 1H), 6.90 (d, J = 8.8 Hz, 2H), 5.89-5.80 (m, 1H), 5.05-4.94 (m, 2H), 4.56 (t, J = 6.5 Hz, 2H), 4.34 (m, 4H), 4.00 (t, J = 6.5 Hz, 2H), 2.93-2.87 (m), 1.82-0.88 (m).

Compound 22. The mixture of compound 21 (39.6 mg, 0.032 mmol) and PTSA (10 mg, 0.015 mmol) are dissolved in a mixture of acetone (5 mL) and CHCl3 (5mL) and stirred at rt for 24 h. Five drops of conc. aqueous NaHCO3 were added before drying over Na2SO4. Organic solvents were removed under reduced pressure. Resulting crude product was subjected to column chromatography (silica gel, Hexane:CHCl3=50:50) to give compound 22 (20 mg) in 51% yield. Data for compound 22: 1H NMR (CDCl3, 250 MHz) δ 11.77 (s, 1H), 8.99 (d, J = 8.8 Hz, 2H), 8.79 (d, J = 8.2 Hz, 2H), 7.83-7.35 (m, 22H), 6.89 (d, J = 8.1 Hz, 2H), 5.92-5.83 (m, 1H), 5.03-4.90 (m, 2H), 3.99 (t, J = 6.4 Hz, 2H), 2.88 (m), 2.12-0.86 (m).

Compound 23 was prepared following the synthetic procedure for compound 5. The following amounts of reagents were used: compound 18 (380 mg, 0.27 mmol), the fragment A (88 mg, 0.33 mmol), Pd(PhCN)2Cl2 (3.1 mg, 0.015 mmol) as a replacement for Pd(PH3)4, P(t-Bu)3 (0.2 ml of 0.1 M solution in dioxane) and Cul (1 mg, 0.008mmol) in 5 mL of Dioxane:i-Pr2NH (v/v 98:2). An attempt to purify the product by column chromatography (silica gel, EtOAc) gave crude compound 23 (77 mg). Data for compound 23: 1H NMR (CDCl3, 250 MHz) δ 7.41-7.34 (m, 18H), 6.88-6.80 (m, 2H), 5.89-5.72 (m, 1H), 5.06-4.93 (m, 2H), 3.96 (t, J = 6.4 Hz, 2H), 2.97-2.60 (m), 2.10-0.83 (m), 0.28 (s, 9H).
Compound 24 was prepared following the synthetic procedure for the fragment A. The following amounts of reagents were used: compound 23 (77 mg, 0.05 mmol), KOH (10.5 mg, 0.19 mmol). The product was purified by column chromatography (silica gel, Hexane:EtOAc=95:5) to give compound 24 (59 mg) in 80% yield. Data for compound 24: $^1$H NMR (CDCl$_3$, 250 MHz) $\delta$ 7.48-7.36 (m, 18H), 6.88 (d, $J$ = 8.2 Hz, 2H), 5.88-5.77 (m, 1H), 5.03-4.92 (m, 2H), 3.98 (t, $J$ = 6.5 Hz, 2H), 3.32 (s, 1H), 2.93-2.76 (m), 2.06-2.01 (m), 1.82-1.76 (m), 1.43-0.85 (m).

Compound 26-34 were synthesized following the literature procedures.$^{22}$

Compound 35 was prepared following the synthetic procedure for compound 5. The following amounts of reagents were used: compound 34 (0.10 g, 0.08 mmol), the fragment A (0.05 g, 0.17 mmol), Pd(PPh$_3$)$_4$ (0.9 mg, 0.002 mmol) and CuI (0.45 mg, 0.002 mmol) in 5 mL of Toluene:i-Pr$_2$NH (v/v 7:3). The product was purified by column chromatography (silica gel, Hexane:EtOAc=80:20) to give compound 35 (88 mg) in 78% yield. Data for compound 9: $^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 7.49-7.33 (m, 10H), 6.90 (d, $J$ = 8.9 Hz, 2H), 5.88-5.78 (m, 1H), 5.05-4.94 (m, 2H), 3.99 (t, $J$ = 6.5 Hz, 2H), 2.90-2.65 (m), 2.09-0.87 (m), 0.30 (s, 9H).

Compound 39. Compound 37 (164 mg, 0.615 mmol) and compound 38 (0.23 ml, 1.3 mmol) were dissolved in DCM (4mL) at 0ºC. The mixture was stirred for 1 h and solvents was evaporated under reduced pressure. The residue was subjected to column chromatography (silica gel, CHCl$_3$:MeOH 98:2) to give compound 39 (181 mg) in 72% yield. Data for compound 9: $^1$H NMR (CDCl$_3$, 250 MHz) $\delta$ 7.80 (d, $J$ = 8.3 Hz, 2H), 7.62 (d, $J$ = 8.3 Hz, 2H), 6.49 (s, 1H), 3.47 (q, $J$ = 7.5 Hz, 2H), 1.77 (m, 2H), 0.74 (t, $J$ = 8.7 Hz, 2H).
Compound 40. Compound 39 (90 mg, 0.22 mmol) and silica microspheres (254 mg, 0.33 µm, Bang Laboratories, Inc.) were mixed with toluene (10 mL) and refluxed for 4 h. The surface modified silica particle were collected via centrifugation and washed a few times with acetone after sonication.

Compound 41 was prepared following the synthetic procedure for the fragment A. The following amounts of reagents were used: compound 10 (750 mg, 2.1 mmol), KOH (0.35 g, 6.3 mmol). The product was purified by column chromatography (silica gel, Hexane) to give compound 41 (596 mg) in quantitative yield. Data for compound 9: $^1$H NMR (CDCl$_3$, 250 MHz) δ

Compound 42 was prepared following the synthetic procedure for compound 5. The following amounts of reagents were used: compound 41 (85 mg, 0.3 mmol), compound 40 (50 mg), Pd(PPh$_3$)$_4$ (1 mg, 0.001 mmol) and CuI (0.2 mg, 0.001 mmol) in 5 mL of Toluene:i-Pr$_2$NH (v/v 7:3). The reaction was carried out at 60ºC for 24 h. The fragment C was added thereafter and resulting mixture was stirred for 36 h. After centrifugation, compound 43 was obtained as a solution fraction.

Compound 51. A mixture of compound 50 (20 g, 77 mmol), NBS (28.3 g, 0.16 mol) and benzoyl peroxide (0.010 g) in benzene (380 mL) was refluxed for 8 h. The solvent was removed under reduced pressure. The pure product (23 g) was purified by recrystallization in 73% yield. Data for compound 51: $^1$H NMR (CDCl$_3$, 250 MHz) δ 7.67 (s, 2H), 4.52 (s, 4H).

Compound 52. Compound 51 (2.0 g, 4.7 mmol), Na$_2$SO$_3$ (1.5 g, 11.9 mmol) and TBAB (0.10 g, 0.28 mmol) were mixed in water (50 mL) and ethanol (50 mL) and refluxed for 72 hrs. The solvents were removed under reduced pressure and the crude product was recrystallized
from water (20 mL) to give compound 52 (1.7 g) in 77% yield. Data for compound 52: \(^1\)H NMR (D\(_2\)O, 250 MHz) \(\delta 7.62\) (s, 2H), 4.21 (s, 4H).

Compound 53 was prepared following the synthetic procedure for compound 5. The following amounts of reagents were used: compound 51 (0.513 g, 1.94 mmol), TIPS-acetylene (862 mg, 4.7 mmol), Pd(PPh\(_3\))\(_4\) (65.4 mg, 0.06 mmol) and CuI (10.8 mg, 0.06 mmol) in 8 mL of Toluene:i-Pr\(_2\)NH (v/v 7:3). The reaction was carried out at 85\(^\circ\)C. The product was purified by column chromatography (silica gel, Hexane) to give compound 53 (0.90 g) in 99% yield. Data for compound 53: \(^1\)H NMR (Acetone-\(d_6\), 250 MHz) \(\delta 7.39\) (s, 2H), 2.83 (s, 6H), 2.40 (s, 6H), 1.16 (s, 36H).

Compound 60 was synthesized following the literature procedures.\(^{21}\)

Compound 61. Compound 60 (200 mg, 0.65 mmol), TBDMSCI (196 mg, 1.3 mmol) and imidazole (110 mg, 1.6 mmol) were dissolved in DMF (12 mL) and stirred for 24 h under N\(_2\) atmosphere at rt. Mixture was poured into water (100 mL) and extracted with CHCl\(_3\) (3\(\times\)100 mL). The organic layer was washed with water and brine and dried over Na\(_2\)SO\(_4\). Solvents were removed under reduced pressure and the residue was subjected to column chromatography (silica gel, Hexane:EtOAc=50:50) to give compound 61 (151 mg) in 55% yield. Data for compound 61: \(^1\)H NMR (Acetone-\(d_6\), 300 MHz) \(\delta 7.67\) (s, 1H), 7.58 (d, \(J = 8.5\) Hz, 1H), 7.20 (s, 1H), 6.97 (d, \(J = 8.5\) Hz, 1H), 1.91 (s, 6H), 1.03 (s, 9H), 0.32 (s, 6H).
REFERENCES


Figure A1. $^1$H NMR of Compound 3.
Figure A2. $^1$H NMR of Compound 4.
Figure A3. $^1$H NMR of Compound 5.
Figure A4. $^1$H NMR of the fragment A.
Figure A5. $^1$H NMR of Compound 7.
Figure A6. $^1$H NMR of Compound 8.
Figure A7. $^1$H NMR of Compound 9.
Figure A8. $^1$H NMR of Compound 10.
Figure A9. $^1$H NMR of Compound 11.
Figure A10. $^1$H NMR of Compound 12.
Figure A11. $^{1}$H NMR of Compound 13.
Figure A12. $^1$H NMR of Compound 14.
Figure A13. $^1$H NMR of Compound 15.
Figure A14. $^1$H NMR of Compound 16.
Figure A15. $^1$H NMR of Compound 17.
Figure A16. $^1$H NMR of Compound 18.
Figure A17. $^1$H NMR of the fragment B.
Figure A18. $^1$H NMR of Compound 19.
Figure A19. $^1$H NMR of Compound 20.
Figure A20. $^1$H NMR of Compound 21.
Figure A21. $^1$H NMR of Compound 22.
Figure A22. $^1$H NMR of Compound 23.
Figure A23. $^1$H NMR of Compound 24.
Figure A24. $^1$H NMR of Compound 26.
Figure A25. $^1$H NMR of Compound 27.
Figure A26. $^1$H NMR of Compound 28.
Figure A27. $^1$H NMR of Compound 29.
Figure A28. $^1$H NMR of Compound 30.
Figure A29. $^1$H NMR of Compound 31.
Figure A30. $^1$H NMR of Compound 32.
Figure A31. $^1$H NMR of Compound 33.
Figure A32. $^1$H NMR of Compound 34.
Figure A33. $^1$H NMR of Compound 39.
Figure A34. $^1$H NMR of Compound 41.
Figure A35. $^1$H NMR of Compound 50.
Figure A36. $^1$H NMR of Compound 51.
Figure A37. $^1$H NMR of Compound 52.
Figure A38. $^1$H NMR of Compound 53.
Figure A39. $^1$H NMR of Compound 54.
Figure A40. $^1$H NMR of Compound 60.
Figure A41. $^1$H NMR of Compound 61.
VITA

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