Synthesis of Conformationally Constrained Diarylether Paracyclophanes

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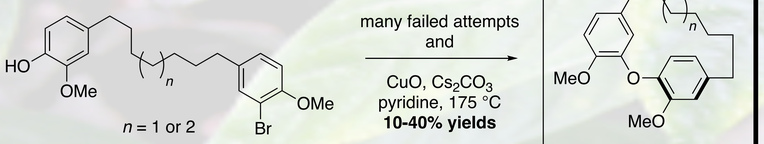
Abstract

The syntheses of a series of macrocyclic diarylether paracyclophanes with varying length in the bridging chain are reported. Several naturally occurring biologically active cyclophanes have been described in the literature, and many of these are chiral by virtue of restricted bond rotation opposed to the presence of stereocenters. We report the first systematic study of the relationship between the bridging chain length and the barrier to racemization of these important compounds. Progress toward the synthesis of a library of diarylether paracyclophanes with varying tether lengths is described, as well as stereochemical implications.

7 & 8 Carbon Tether Cyclophanes



- Completed the synthesis of two cyclophanes
- Eight carbon tether is first ever reported
- Characterized each by ^{1}H-NMR

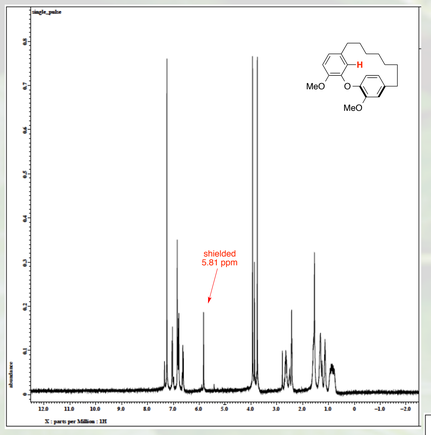


Figure 1. Seven carbon tethered cyclophane. Hydrogen is more shielded because of its close proximity to the electron rich π orbitals of the aromatic ring.

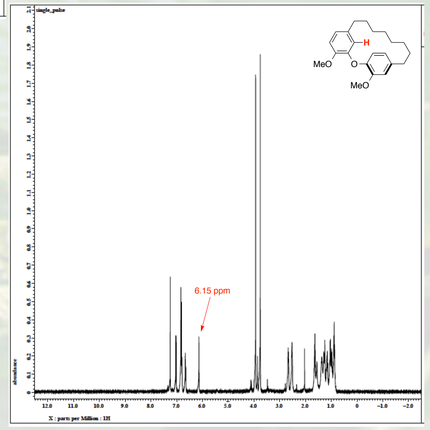
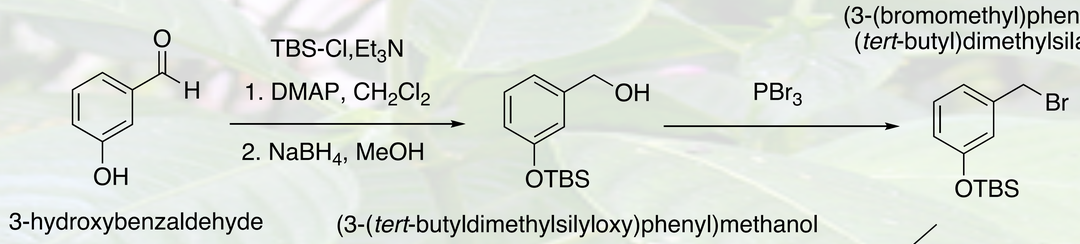


Figure 2. Eight carbon tethered cyclophane. Hydrogen is less shielded due to the increased distance from the aromatic electrons.

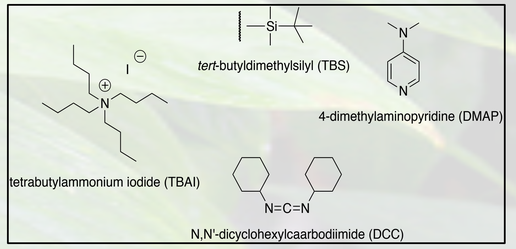
Tether Ring Synthesis



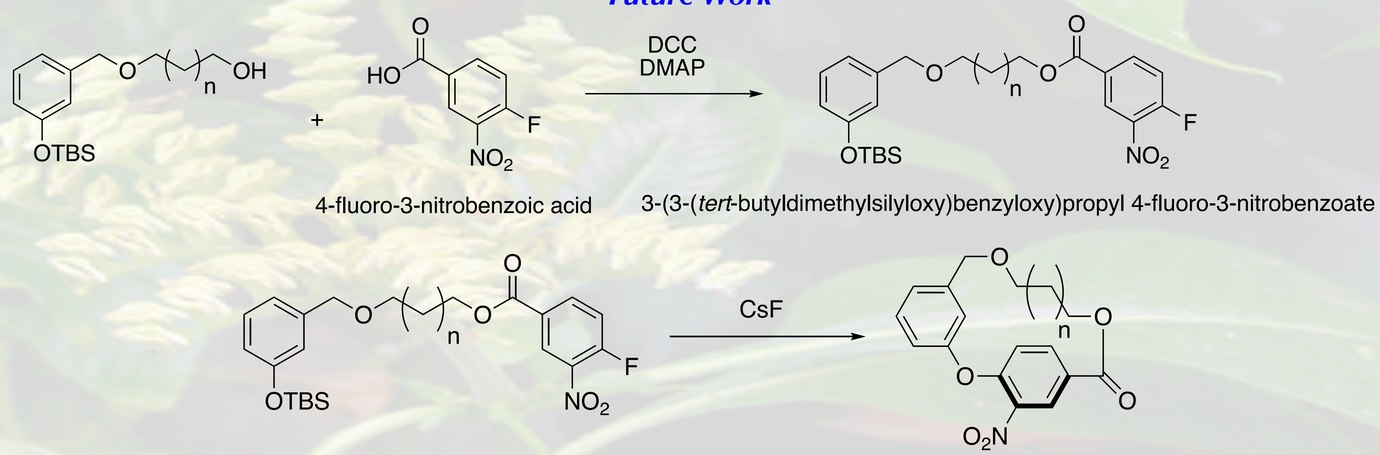
3-hydroxybenzaldehyde

(3-(*tert*-butyldimethylsilyloxy)phenyl)methanol

3-(3-(*tert*-butyldimethylsilyloxy)benzyloxy)propan-1-ol



Future Work



4-fluoro-3-nitrobenzoic acid

3-(3-(*tert*-butyldimethylsilyloxy)benzyloxy)propyl 4-fluoro-3-nitrobenzoate

Conclusion

We successfully synthesized two cyclophanes with saturated carbon tethers. Based on the NMR spectra we can infer that these compounds are still chiral and are conformationally constrained. We are using a different approach in our synthesis of these cyclophanes. Rather than using a Ullmann coupling reaction, which requires high heat, we designed our strategy so that we can close the cyclophane ring by a nucleophilic aromatic substitution reaction. Future research will focus on synthesizing a library of various conformationally constrained diarylethers and screening them for activity against NF-κB in collaboration with Dr. David Blake in Biology.

Acknowledgements

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