

Synthesis of Oligosubstituted Bullvalones: Shapeshifting Molecules Under Basic Conditions

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Dynamic chemical systems that adapt and evolve to generate novel characteristics are an emerging approach to the rapid discovery of molecules with customized properties.¹ For example, dynamic combinatorial libraries created from a set of functional molecules by reversible covalent bond formation provide a “smart” library of diverse compounds from a small number of building blocks. Under thermodynamic conditions, the population of these equilibrium mixtures will change in response to stimuli toward the lowest energy states, a concept that has been used to develop enzyme inhibitors² and receptors for guests.³

A major limitation of the existing implementations of dynamic combinatorial chemistry is the limited and relatively harsh conditions under which reversible covalent bond formation can occur. An ideal dynamic covalent chemical library would equilibrate under mild, reagent-free conditions in a wide variety of reaction media, allowing it to operate in diverse contexts from drug discovery to adaptive materials. We reasoned that this ideal would most easily be achieved in a “self-contained” dynamic combinatorial library where distinct spatial arrangements of key functional groups or recognition elements would arise from spontaneous intramolecular rearrangement processes. In this regard, an oligosubstituted bullvalene^{1b,4–6} would provide a unique and robust dynamic platform in which hundreds or thousands of constitutional isomers could be accessed by facile valence tautomerization reactions (Figure 1). Such a strategy, however, presents a daunting synthetic challenge and demands an innovative means of switching the dynamic interconversion on or off. We now document our progress toward both of these goals through the concise, scalable synthesis of an oligosubstituted bullvalene precursor in which dynamic behavior can be modulated by external control.

The bullvalene core consists of a bridged trisvinyl cyclopropane, a unique arrangement that allows for every carbon to interchange with each other through rapid strain-assisted Cope rearrangements (Figure 1).⁴ Our rational synthesis of oligosubstituted bullvalenes⁷ began with cycloheptadienone **1**.⁸ Titanium tetrachloride catalyzed Mukaiyama–Michael addition⁹ provided enone **2** in excellent yield. Radical bromination followed by direct oxidation of the resulting allylic bromide with *N*-methylmorpholine-*N*-oxide¹⁰ and deprotection of the *tert*-butyl ester afforded enedione **4** on a multigram scale.

After exploring several unproductive routes to the 10-carbon bullvalene core, we were pleased to develop a unique approach to the installation and catalytic cyclization of a sulfur ylide. Activation of acid **4** with *iso*-butyl chloroformate followed by coupling with sulfur ylide **5**,¹¹ derived from pentamethylenesulfide and ethyl bromoacetate, provided highly stabilized ylide **6**.¹² In a key step, **6** could be smoothly converted into tetracarbonyl cyclopropane **7** by a novel Lewis acid catalyzed intramolecular cyclopropanation. Optimization studies identified 0.01 M chlorobenzene and 15 mol % of Sc(OTf)₃ as ideal conditions, reliably providing the cyclopropane product in 70% yield. This step results in the formation of

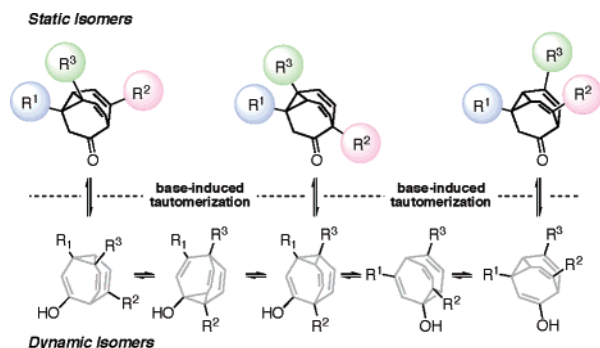
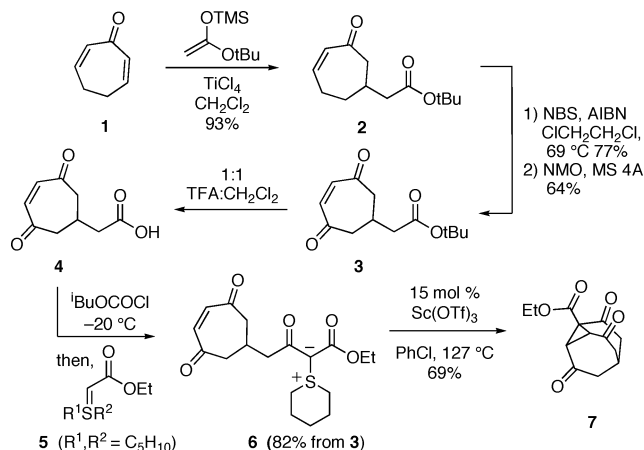


Figure 1. Dynamic interconversion of $>10^3$ bullvalone constitutional isomers via the intermediacy of base-generated hydroxybullvalenes.

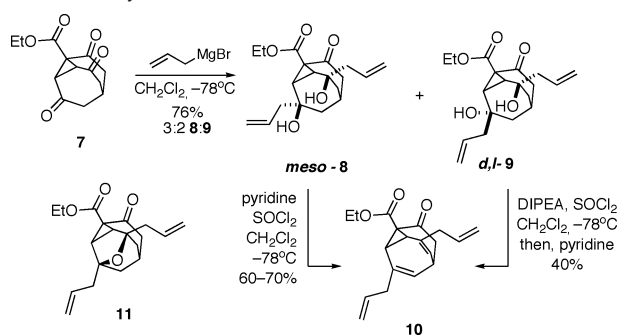
Scheme 1. Synthesis of Triketone **6**



two new seven-membered rings, a quaternary center, two carbon–carbon bonds, and a tetrasubstituted cyclopropane; the structure of **7** was confirmed by single-crystal X-ray analysis (see Supporting Information).

Having developed a scalable route to our advanced triketone intermediate, we focused on its chemoselective transformation into a versatile bullvalene scaffold. Cognizant of the need to append a variety of pendent groups to the advanced bullvalene precursor, we sought to introduce side chains that could be reliably processed under mild, tolerant reaction conditions and selected terminal olefins as ideally suited for late-stage elaboration. These olefins were incorporated by highly regioselective addition of allylmagnesium bromide to the two ketones *not* adjacent to the ester functionality in 76% yield as a separable 3:2 mixture of *meso* diastereomer **8** and *D,L*-**9**. After exploring numerous bis elimination protocols, we eventually found that premixing thionyl chloride and pyridine,¹³ followed by addition of the *meso* diol **8**, gave the best results for the elimination of the *meso* diastereomer, selectively producing the desired bis endocyclic elimination product **10** in 60–70% yield.

Scheme 2. Synthesis of Functionalized Bullvalone 10



Under these same conditions, the D,L -diastereomer afforded tetrahydrofuran product **11** as the major product. Upon further experimentation, we discovered that treatment of **9** with a solution of Hünig's base and thionyl chloride followed by addition of pyridine led to bullvalone **10**.

Although **10** is a divinylcyclopropane poised for interconversion via Cope rearrangements between two valence isomers, the presence of two electron-withdrawing groups on the cyclopropane apparently deters such processes, and it was isolated and characterized as a single, static isomer. Reduction of the ketone to the alcohol, however, resulted in significant broadening of the cyclopropyl and methine ^1H NMR peaks, indicative of a molecule that interconverts between two valence tautomers. This stabilizing effect greatly facilitates the synthesis of polysubstituted bullvalenes by rendering this late-stage intermediate amenable to chromatography and further transformation. For example, **10** was readily elaborated by chemoselective cross-metathesis reactions without rearrangement or affecting the endocyclic olefins (see the Supporting Information).

A goal of our research program is to develop a bullvalene precursor in which the dynamic interconversions can be turned on or off in response to an external stimulus. Doering has demonstrated that unsubstituted bullvalene undergoes rapid valence tautomerization under basic conditions.^{4e} In the absence of rearrangement, only the two protons adjacent to the ketone should be exchanged with a deuterium source. If rearrangement occurs, each proton on the bullvalene core of **10** could be exchanged, permitting up to seven deuterons to be incorporated. To test this, we performed an experiment^{4e} in which a 0.05 M solution of bullvalone **10** in 5:2 $\text{CD}_3\text{OD}/\text{CDCl}_3$ was treated with excess NaOCD_3 .¹⁴ After acidic quench, the crude reaction mixture was analyzed by mass spectrometry. Transesterification by CD_3O^- was revealed by a molecular peak at 287 m/z , and the major peak at 290 m/z corresponded to the incorporation of three deuterons along with evidence for the incorporation of up to seven (Figure 2). Further evidence of the base-induced dynamic interconversion was supplied by resubjecting the material thus obtained to NaOCH_3 . Upon quenching, mass spectrometric analysis revealed that the nondeuterated products gave the strongest signal, followed by decreasing intensities of deuterated products. The residual traces of deuterated material suggest the existence of a decomposition pathway that leads to nondynamic compounds. Studies to identify and suppress this pathway, tentatively assigned to the formation of a donor–acceptor cyclopropane and ring opening, are underway.

In summary, we have documented the concise synthesis of an oligosubstituted bullvalone suitable for further elaboration and have demonstrated that its shapeshifting properties can be induced under basic conditions. These studies provide the basis for future work including the development of more robust systems and the use of these adaptive molecules in diverse applications.

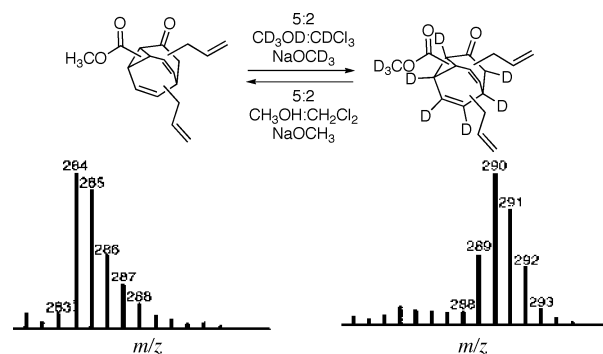


Figure 2. EI-MS of isomerized bullvalones. Right: base-mediated enolization and subsequent Cope rearrangements and tautomerizations introduce up to seven deuterons into the tetrasubstituted bullvalene core. Left: deuterons are washed out under basic protic conditions.

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Supporting Information Available: Experimental procedures, characterization data for all new compounds, and spectral evidence for dynamic interconversions of **10**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- We have also demonstrated that dynamic isomerization can be induced under milder conditions including NEt_3 in EtOH.

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