

## An Approach to Controlled Oligomerization via Iterative Diels–Alder Cycloadditions on Solid Supports†

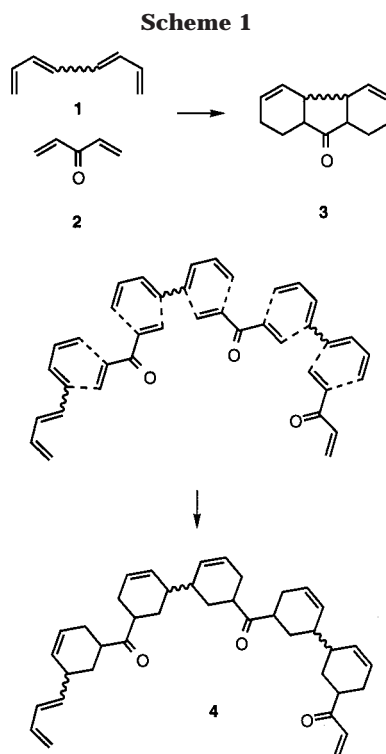
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The techniques of solid-phase organic synthesis have recently been applied to the generation of libraries of small organic molecules via combinatorial chemistry for drug discovery.<sup>1</sup> In addition to providing a facile entry into molecular diversity, solid-phase synthesis can address problems in organic chemistry that cannot be solved via solution chemistry.<sup>2</sup> We have recently described the application of the tandem Diels–Alder cycloaddition to the synthesis of polycyclic ring systems with exceedingly high levels of stereochemical control.<sup>3</sup> This 1:1 dimerization of a bis-diene and a bis-dienophile, as shown in Scheme 1, leads to the stereoselective formation of the tricyclic product **3** from the acyclic precursors **1** and **2**. The coupling of **1** and **2** could also lead to an oligomerative process, as shown in **4**. The efficient control of such an oligomerization could lead to a novel approach to the synthesis of homogeneous high-molecular weight materials that could serve as molecular scaffolds<sup>4</sup> and components for the synthesis of macromolecular devices.<sup>5</sup> However, the oligomerative cycloaddition of **1** and **2** in solution cannot readily be controlled. We report herein that oligomerization in this system can be precisely controlled in an iterative manner using solid-support technology.<sup>6–8</sup>

Acylation of (hydroxymethyl)polystyrene resin **5** (BACHEM, 0.37 mmol/g) with acryloyl chloride (10 equiv) led to the



formation of polymer-bound dienophile **6** in greater than >95% loading yield.<sup>9,10</sup> The immobilization of the dienophile facilitates the monoreaction of **7** with **6** to give **8** via exposure of **6** to an excess of bisdiene **7** (6 equiv, toluene reflux, 4 h).<sup>11</sup> The success of this first cycloaddition was confirmed by cleavage of the Diels–Alder adduct from the resin with Triton B and methyl iodide, affording methyl ester **9** in 91% overall yield as a mixture of cis and trans isomers.<sup>12</sup> The advantage of the cycloaddition using solid supports is underscored by the preparation of the same product **9** in only 51% yield in toluene solution from methyl acrylate and the same excess of bis-diene employed above.

The second cycloaddition was performed on the immobilized diene **8** with 6.5 equiv of the bisdienophile divinyl ketone **10** in the presence of 15 equiv of ZnCl<sub>2</sub> to give **11**, establishing the viability of the iterative cycloaddition reactions of both bis-diene **7** and bis-dienophile **10** on the solid

† Dedicated to Professor William von Eggers Doering, a brilliant teacher whose penetrating intellect and chemical insights have inspired us and so many others.

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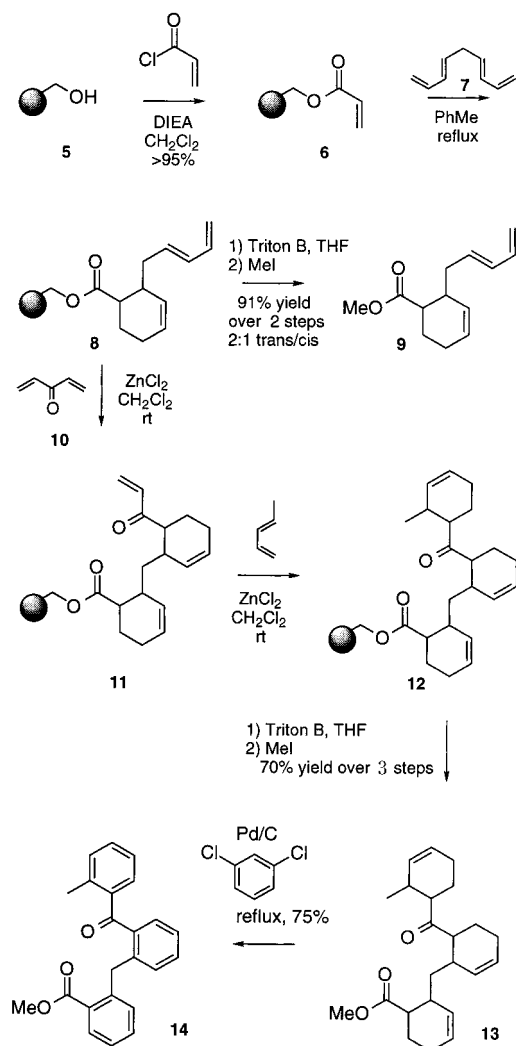
(9) The manufacturer describes a 0.9 mmol/g loading capacity for the hydroxymethyl resin. However, with a variety of acid chlorides, we have found that 0.37 mmol/g is a more realistic measure of the loading capacity. Our reported loading yield is therefore based on 0.37 mmol/g.

(10) In contrast to our recently reported studies on the Diels–Alder cycloaddition of immobilized Evans oxazolidinones (Winkler, J.; McCoull, W. *Tetrahedron Lett.* **1998**, 4935–4936), the very broad IR stretches for the carbonyl groups of **6**, **8**, **11**, and **12**, centered at 1722–1725 cm<sup>-1</sup>, precluded the use of FT-IR for the monitoring of these reactions.

(11) Prepared by the extrusion of sulfur dioxide (toluene reflux) from the product obtained from the alkylation of butadiene sulfone with 2,4-pentadienyl bromide (LHMDS, HMPA, –78 °C, 40% yield).

(12) All new compounds were purified (>95%) and characterized by <sup>1</sup>H and <sup>13</sup>C NMR, IR, and HRMS. See the Supporting Information for details.

Scheme 2



support. The remaining dienophilic moiety in **11** was "capped" with piperylene (16 equiv, 16 equiv of  $\text{ZnCl}_2$ ) to give

a new product **12**. Reaction of **12** with Triton B and iodomethane resulted in cleavage of the tricyclic Diels–Alder adduct from the polymer to give methyl ester **13** (70% yield over the three steps from **8**) as a mixture of six diastereomers as determined by 500 MHz  $^1\text{H}$  NMR.

Comparison of the efficiency of the overall transformation of **6** to **12** with the corresponding reactions in solution (using the same stoichiometries of bis-diene and bis-dienophile) reveals the importance of the solid support to the success of this sequence. The reaction of **9** with divinyl ketone **10** (6 equiv, 6 equiv of  $\text{ZnCl}_2$ ) led to the formation of the methyl ester corresponding to **8** in 60% yield, and the reaction of **8** with an excess of piperylene gave **13** in 79% yield. The overall yield of this triple Diels–Alder sequence on the polymer support is >65%, an almost 3-fold increase in efficiency over the same reactions in solution (24% overall yield).

To establish that the mixture of isomers represented by **13** did not include regioisomeric products, we examined the aromatization of **13**, which would lead to the convergence of stereoisomers, but not regioisomers, to a single product. Exposure of **13** to Pd/C in *m*-dichlorobenzene led to the formation of a single aromatic product **14** in 75% yield, establishing the viability of this approach for the controlled synthesis of oligomeric materials. Studies in our laboratory directed toward the control of the stereoselectivity of the oligomerization are currently underway, and our results will be reported in due course.

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**Supporting Information Available:** Experimental procedures and spectroscopic data for compounds **6–14** (16 pages).

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