

## A Tandem Oxy-Cope–Transannular Ring Closure Route to Polyquinanes

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A common goal in many synthetic endeavors is to develop efficient and reliable methods for the construction of highly functionalized intermediates in as few steps as possible. One solution to this problem involves the utilization of tandem reaction sequences that combine the power of two or more reactions and result in the formation of several chemical bonds in a single operation.<sup>1</sup> Reported here are the preliminary results of a study of a tandem reaction sequence leading to a general synthesis of polyquinanes from readily available starting materials. Specifically, bicyclo[3.2.0]heptenones such as **1a**,<sup>2</sup> upon addition of an appropriate vinylolithium reagent followed by warming and subsequent basic workup, were observed to form highly functionalized polycyclic products (e.g., **4**) via a tandem oxy-Cope–transannular ring closure reaction sequence (Scheme 1).<sup>3–6</sup>

The required bicycloheptenone precursors **1a–c** were prepared by the methods shown in Scheme 2.<sup>2,7</sup> Addition of methylolithium to dimethyl squarate (**5**) followed by addition of trifluoroacetic anhydride (TFAA) and quenching with anhydrous methanol gave ketal **6** (75%).<sup>7b,8</sup> Treatment of **6** with an appropriate vinylolithium followed by addition of TFAA and basic workup gave cyclobutenones **7a–c** (70–77%). 1,2-Addition of allylmagnesium bromide to **7a–c** followed by hydrolysis of the ketal group afforded the keto alcohols **8a–c** (75–85%), which were subsequently converted to the trimethylsilyl ether derivatives **9a–c** (70–83%) under standard conditions.<sup>9</sup> Thermolysis of cyclobutenones **9a–c** in refluxing toluene then provided bicycloheptenones **1a–c** in nearly

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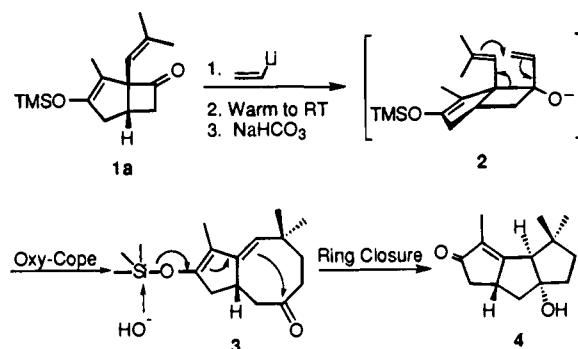
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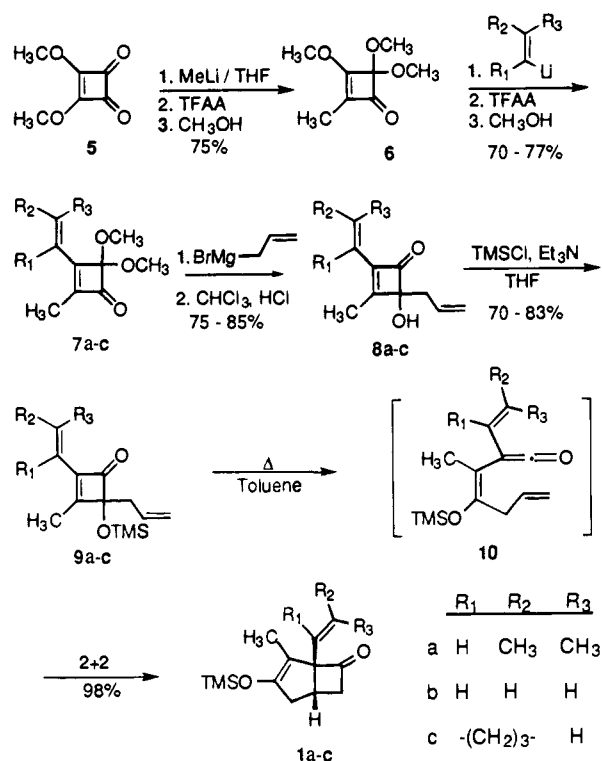
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### Scheme 1



### Scheme 2



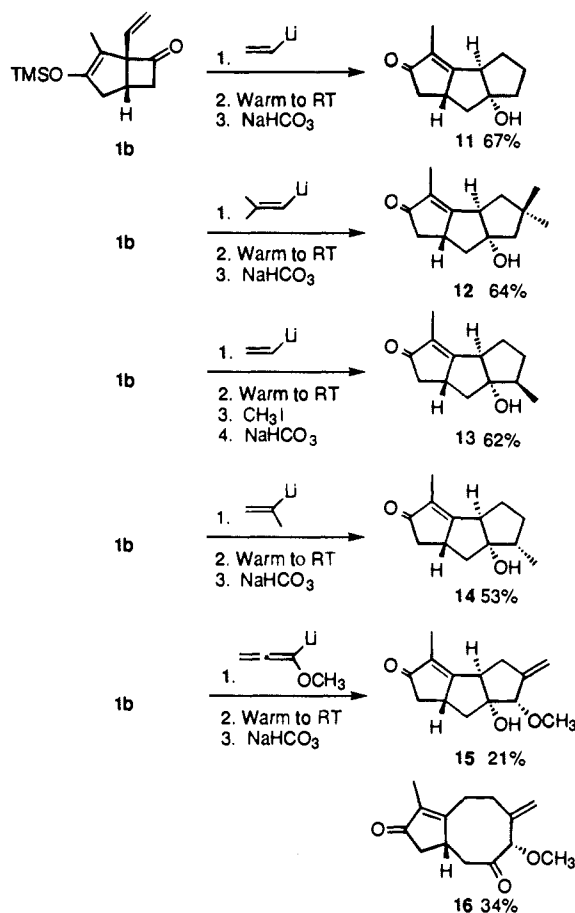
quantitative yield via intramolecular [2+2] cycloaddition of dienylketene intermediates **10a–c**.<sup>2</sup>

The new tandem reaction provides a regioselective route to highly substituted triquinanes (Scheme 3). For example, treatment of bicycloheptenone **1b** with either vinylolithium or 1-lithio-2-methylpropene followed by the usual workup gave tricycle **11** (67%) or **12** (64%), respectively. Additional substitution patterns are realized by stereoselective alkylation of the enolate intermediate prior to transannular ring closure. Specifically, addition of vinylolithium to bicycloheptenone **1b** followed by warming and quenching of the resulting enolate with methyl iodide prior to standard workup yielded triquinane **13** (62%) as a single diastereomer. In contrast, addition of 2-lithiopropene to **1b** afforded the diastereomer **14** (53%).

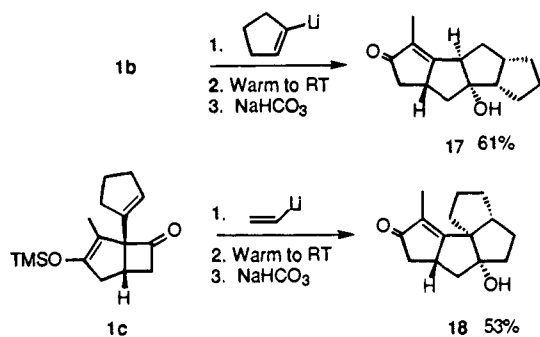
Additional functionality may be introduced into the tricyclic products by the use of substituted vinyl anions. Thus, addition of 1-lithio-1-methoxyallene<sup>10</sup> to bicycloheptenone **1b** followed by standard workup provided triquinane **15** (21%) and bicyclo[6.3.0]undecene **16** (34%). While **15** results from the expected tandem reaction including convex face protonation of the enolate, compound **16** forms via protonation, hydrolysis, and tautomerization of the enolate intermediate. The introduction

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## Scheme 3



## Scheme 4



of an additional  $\text{sp}^2$ -hybridized carbon into the eight-membered ring apparently provides a conformation that is less susceptible to transannular ring closure.

As shown in Scheme 4, the new reaction sequence is not limited to the formation of tricyclic products. Treatment of 1b with cyclopentenyllithium followed by the usual workup provided the linearly fused tetracycle 17 (61%). Similarly, treatment of 1c with vinyl lithium gave the angularly fused analog 18 (53%).

The structure assignments of the new compounds reported here are in agreement with their observed spectral data. In addition, they are either directly or indirectly assigned on the basis of single-crystal X-ray structure determination. Specifically, the structures of compounds 4, 14, and 18 were determined by X-ray crystallography. Having the structure of 14 allows the unambiguous assignment of its epimer, 13. Knowing the three-dimensional structures of 4, 13, and 14 provides the foundation for the reasonable assignments of the related polyquinanes, 11, 12, 15, and 17. Thus, these compounds, like 14 and 18, apparently all stem from convex face protonation of the enolate generated in the oxy-Cope rearrangement prior to transannular ring closure.

In conclusion, the following significant points are noted: (1) the tandem oxy-Cope/transannular ring closure sequence represents an important advance in the preparation of highly functionalized polyquinanes and contributes to the already considerable synthetic utility of cyclobutenone derivatives;<sup>4ab,7,11</sup> (2) synthesis of the bicyclo[3.2.0]heptenones as outlined in Scheme 2 is noteworthy not only because it provides an efficient route to these versatile synthetic intermediates but also because it presents a general and selective route to vinylketenes of the appropriate geometry to allow facile intramolecular [2+2] cycloadditions;<sup>12</sup> (3) we anticipate that the tandem reaction will be applicable to the synthesis of several members of the polyquinane family of natural products<sup>4,13</sup> and are currently investigating these possibilities in our laboratory.

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**Supporting Information Available:** Experimental details for the synthesis of 1a–c, 4, 6, 7a–c, 8a–c, 9a–c, and 11–18 (10 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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