

Article

## Novel Routes to Angular and Linear Triquinanes *via* Radical Induced Epoxide Fragmentation-H-Abstraction-Cyclization Cascades

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Descritas abaixo estão as duas primeiras aplicações de nossa sequência, fragmentação de epóxido induzida por radicais-abstração de H-ciclização, na preparação de compostos triquinânicos. Estas reações sequenciadas forneceram a base para novas rotas levando a triquinanos lineares e angulares

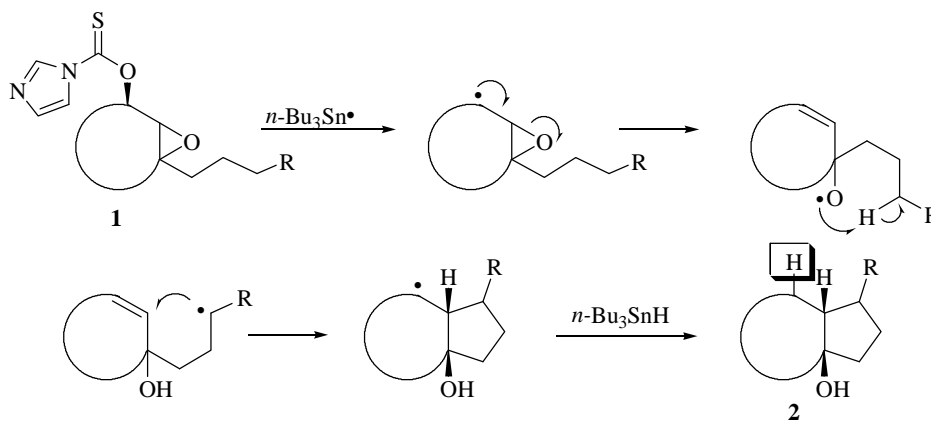
Reported below are the first two applications of our radical induced epoxide fragmentation-H-abstraction-cyclization sequence to triquinane compounds. This tandem sequence has provided the basis of novel routes to both linear and angular triquinanes.

**Keywords:** radical fragmentation, tandem reaction, triquinane synthesis, transannular cyclization

### Introduction

Free radical reactions form the basis of numerous tandem sequences, processes in which a cascade of two or more properly arranged reactions yield one or more bonds in a single stroke, often with predictable regio- and stereo-control<sup>1</sup>. Several interesting sequences have exploited radi-

cal induced fragmentation of strained ring compounds as the pivotal cascade triggering step<sup>2,3</sup>. The radical resulting from the fragmentation is often formed at a specific site in the molecule, and can then be utilized for other reactions. For some time we have been interested in using the radical induced fragmentation of epoxides as the key step in tandem sequences. We describe below two applications of one



Scheme 1.

such sequence, which provide novel routes to linear and angular triquinanes.

A few years ago we reported a radical induced epoxide fragmentation-H-abstraction-cyclization sequence that produces bicyclic compounds (Scheme 1)<sup>4,5</sup>. A limitation of this chemistry was that the final step in the sequence, the abstraction of a hydrogen from Bu<sub>3</sub>SnH, resulted in loss of functionality at the carbon where the radical was first generated. This situation stimulated us<sup>6</sup> (as well as others)<sup>7</sup> to develop variations that would extend the scope of this chemistry, so as to allow the synthesis of more highly functionalized products.

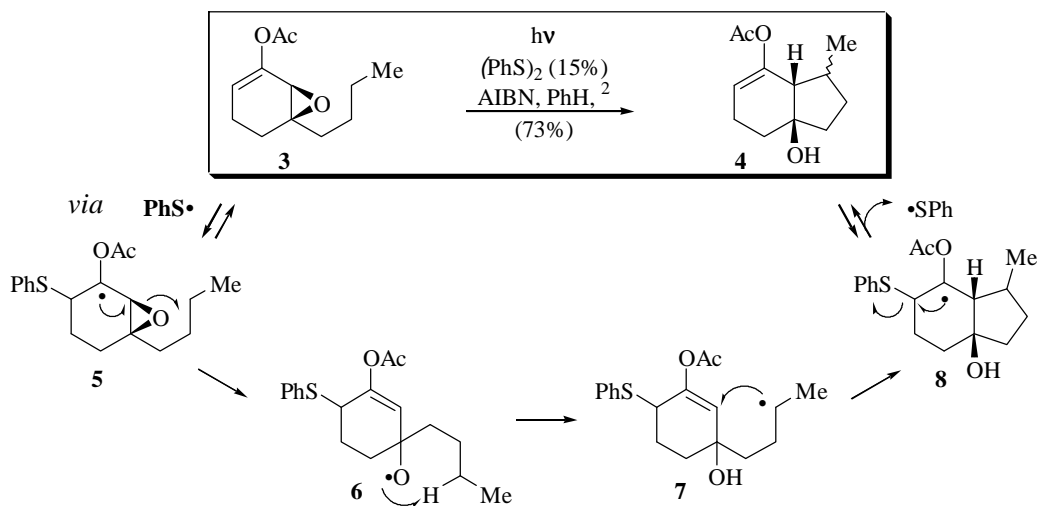
Specifically, we felt that the reaction sequence would be more useful in synthesis if the functionality at the original radical center could be retained in the product. Retention of an oxygen moiety in the product would be particularly useful, not only because of the presence of this substitution pattern in several natural products, but also because oxygenation in the product would allow for further elaboration in subsequent steps. The solution that we developed exploited the known reversible addition of thiyl radicals to olefins<sup>8-10</sup>. In the actual sequence (Scheme 2)<sup>6a</sup>, photolysis of enolacetate **3** in the presence of a catalytic amount of diphenyl disulfide afforded the desired bicyclic enolacetate **4**, presumably proceeding through the intermediates shown (**5-8**). The absence of a hydrogen source in the reaction mixture minimizes reduction as a competing

process, allowing the reaction to be performed at a lower temperature with minimal  $\beta$ -scission as a competing side-reaction.

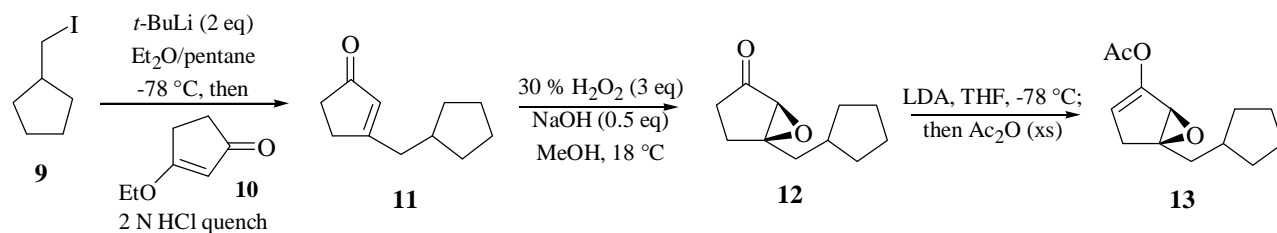
### Linear Triquinane Synthesis

The good to excellent results obtained with various enolacetate substrates suggested that this sequence would also allow the synthesis of complex, polycyclic products. Our long-standing interest in triquinanes<sup>11</sup> stimulated us to devise novel routes to polyquinanes<sup>12</sup> based on this methodology. The precursor to a linear triquinane was prepared readily, as shown in Scheme 3. Cyclopentylmethyl iodide was prepared in three steps from cyclopentyl bromide, in good yield. Lithium-iodide exchange using *t*-BuLi followed by addition of 3-ethoxy-2-cyclopenten-1-one and treatment with 2N HCl afforded the  $\beta$ -substituted cyclopentenone **11** in good yield (76%). Exposure to basic hydrogen peroxide converted enone **11** to ketoepoxide **12** (44%). Kinetic deprotonation and low temperature quenching with acetic anhydride gave the desired precursor (36%, unoptimized) for testing the cascade leading to a linear triquinane.

It was gratifying to find that photolysis of a benzene solution of **13** in the presence of 25 mol% Ph<sub>2</sub>S<sub>2</sub> and 10 mol% AIBN afforded the desired linear triquinane **14** in 60% yield, as a mixture of diastereomers (Eq. 1). Extensive NMR analysis revealed that the major isomer **14a** had the



Scheme 2.



Scheme 3.

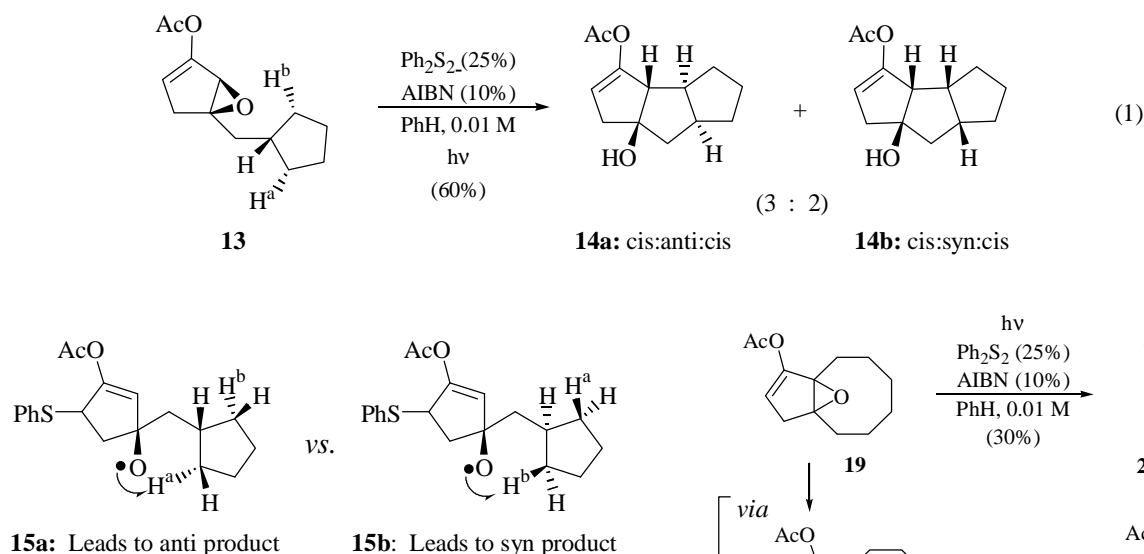


Figure 1.

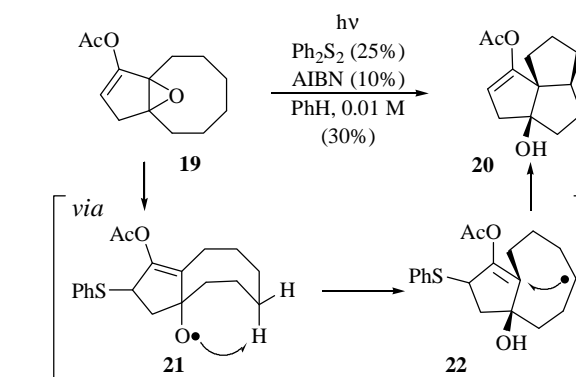
cis:anti:cis geometry and the minor isomer **14b** had the cis:syn:cis geometry.

The formation of both diastereomers can be understood by considering the factors affecting the 1,5-hydrogen translocation step, which represents the defining event in the tandem reaction (Fig. 1). Abstraction of  $\text{H}^a$  from the cyclopentyl ring would necessarily lead to the anti product, whereas abstraction of  $\text{H}^b$  would yield the syn product. In other words, the syn:anti selectivity is determined upon hydrogen abstraction. Although this reaction has not been optimized, the relatively good yield of the cyclized product indicates that this strategy could prove viable for the construction of more complex linear triquinanes.

### Angular Triquinane Synthesis

The precursor for the angular triquinane was prepared by a short sequence, as shown in Scheme 4. Treatment of cyclooctanone with dilithiated propargyl alcohol yielded the expected diol (44%), which underwent a tandem Rupe rearrangement–Nazarov cyclization upon treatment with concentrated  $\text{H}_2\text{SO}_4$  to yield the bicyclic enone **17** in good yield (75%)<sup>13</sup>. Epoxidation (72%), followed by treatment with LDA and acetic anhydride yielded the angular triquinane precursor **19** in 72% yield.

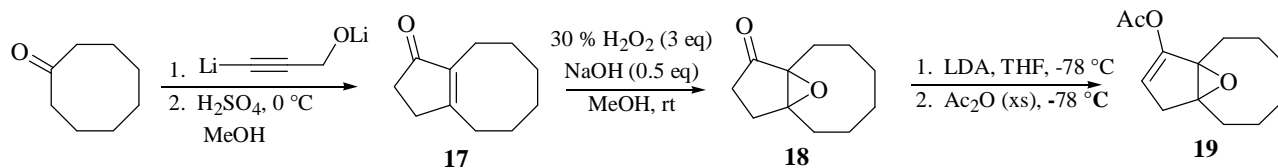
The key steps in the fragmentation-cyclization of the angular triquinane precursor **19** are the transannular 1,5-hy-



Scheme 5.

drogen abstraction (*cf.* **21**) and the transannular radical cyclization<sup>14</sup> leading to the formation of two new rings (Scheme 5). Photolysis of the bicyclic enolacetate with 25%  $\text{Ph}_2\text{S}_2$  and 10% AIBN resulted in the formation of the desired angular triquinane **20** in 30% isolated yield. Based on our experiences with other substrates, it seems likely that the yield of this reaction can be improved further, particularly by introducing radical stabilizing substituents into the cyclooctane portion of the molecule.

Described above are the first applications of our epoxide fragmentation tandem sequence to triquinane compounds. This methodology is versatile and has allowed the synthesis of both linear and angular triquinanes. Strategically, the present construction of triquinanes differs from many others in the literature in that the central ring is formed in the key step. With further development and refinement it should be possible to incorporate this radical sequence in routes to triquinane natural products. Overall, the present work highlights the power of the radical induced epoxide fragmentation-H-abstraction-cyclization sequence for the synthesis of complex compounds.



Scheme 4.

## Acknowledgment

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