

NEW SYNTHETIC METHODS: A GENERAL AND EFFICIENT  
 APPROACH TO RING-FUSED CYCLOHEPTADIENES<sup>1</sup>

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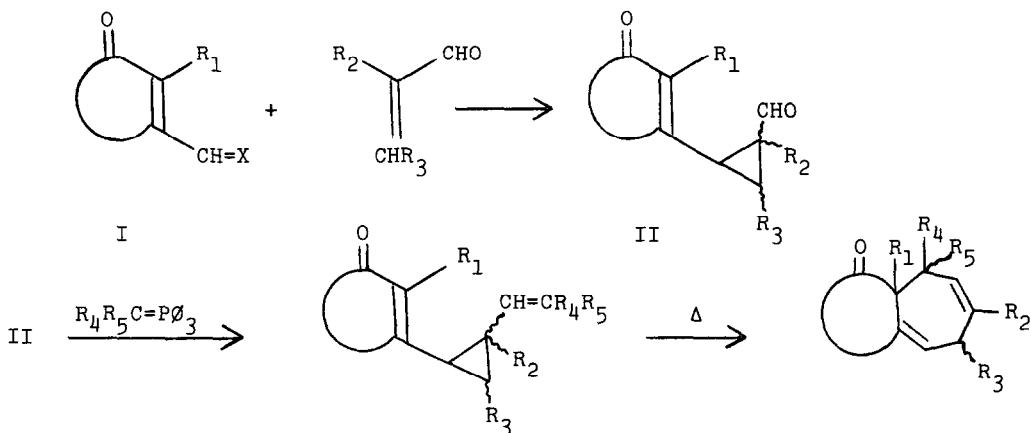
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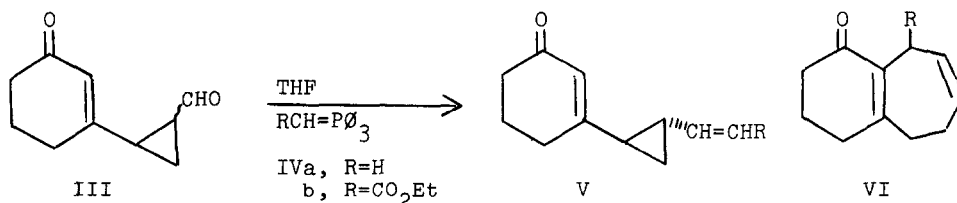
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The widespread occurrence of functionalized cycloheptane and ring-fused cycloheptane ring systems in numerous classes of natural products has made them the synthetic targets of many investigators.<sup>2</sup> Despite recent advances in hydroazulene syntheses,<sup>3</sup> there are almost no general and direct approaches to ring-fused cycloheptadienes which would also allow for incorporation of numerous labile functionalities. The compelling need for new and efficient methodology in this area of synthesis is reinforced by the isolation of many highly oxygenated sesquiterpene lactones which show significant antitumor activity.<sup>4</sup>

In this paper we wish to present a general and unique approach for constructing ring-fused cycloheptadienes. Our approach combines the three carbon backbone of an eneone sulfoxonium methylide (I), an  $\alpha, \beta$ -unsaturated aldehyde and a Wittig reagent to ultimately form the skeleton of the cycloheptadiene ring



In the accompanying communication, we described a new and efficient reaction of a cyclohexenone sulfoxonium methylide to produce highly functionalized vinyl cyclopropanes.<sup>5</sup> To illustrate the practicality and efficiency of the above scheme, we have utilized the cyclopropane adduct from acrolein (III), previously described.<sup>5</sup> When a 4:1 trans:cis mixture of this cyclopropane aldehyde was treated with one equivalent of either triphenylphosphonium methylide (IVa) or carbethoxy-triphenylphosphonium methylide (IVb) at room temperature, a selective Wittig reaction occurred at the aldehyde carbonyl. The major products from both reactions were the corresponding trans-divinyl cyclopropanes (Va and b).<sup>6</sup> The minor product in each case was the isomeric rearranged [5.4.0]-bicycloundecadiene ring system (VIa and b).

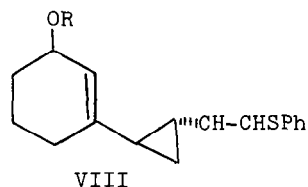
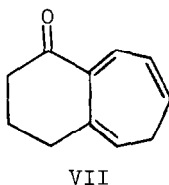
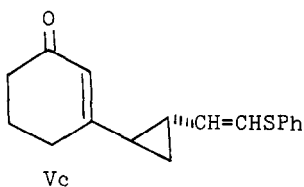


The structure of VIa was confirmed by partial hydrogenation to the known [5.4.0]-bicycloundeceneone.<sup>7</sup> The well-documented thermal instability of cis-divinyl cyclopropanes<sup>8</sup> once again revealed itself in the cis-divinyl Wittig products derived from this cis-aldehyde of III. In addition to the initial Cope rearrangement at room temperature, a subsequent 1,3 hydrogen shift occurred to form the conjugated enenone (VI).

To complete the final phase of our synthetic scheme all that remained was to convert the trans-divinyl cyclopropanes (V) to the same rearranged cycloheptadienes VI. This was expected to be quite straight forward in view of the recent work of Baldwin<sup>9</sup> and Pettus<sup>10</sup> who observed facile thermal rearrangements of various trans-divinyl cyclopropanes at temperatures well below 200°C. In fact, when cyclopropanes IIIa and IIIb were subjected to vpc analysis, at 180°C (11), they were quantitatively converted to isomers VIa and b respectively. An NMR time study of the rearrangement of the trans-divinyl cyclopropanes showed a t<sub>1/2</sub> of eight hours at 140°C. Thus, both cis and trans-cyclopropane isomers can be quantitatively converted to the same rearranged products. The overall

isolated yields for the synthesis of compounds VIa and VIb from the starting (3-oxo-1-cyclohexenyl) dimethyl-sulfoxonium methylide were in excess of 60% for VIa and 70% for VIb, making the overall scheme quite efficient.

In order to introduce a potential oxygen functionality in the cycloheptadiene ring, phenylthio triphenylphosphonium methylide IVc (R=SPh) was reacted with the cyclopropane aldehyde III. The expected trans-divinylcyclopropane Vc was isolated in 65% yield, along with a small amount (15%) of the ketotriene VII.



Thus, it appears that the excellent leaving group of benzenethiol was eliminated after the Cope rearrangement, even at room temperature. When the divinylcyclopropane Vc was heated at 120° for six hours, benzenethiol was again eliminated and a mixture of isomeric ketotrienes was produced.

Since the presence of the ketone functionality undoubtedly assists the facile elimination of the benzenethiol, it was selectively reduced with lithium aluminum hydride in ether at -78°. The allylic alcohol VIIIa (R=H) was produced in quantitative yield and was easily converted to its t-butyldimethylsilyl ether VIIIb (R=t-BuSiMe<sub>2</sub>). All attempts so far to thermally rearrange compounds VIIIa and VIIIb have resulted in partial or total elimination of the phenylthio moiety. While it was not possible to retain the phenylthio moiety in the final step of our synthetic scheme, the reduction of the enone carbonyl prior to thermal rearrangement should prove to be a valuable step towards preventing the migration of the double bond in the original cycloheptadiene.

In summary, our synthetic approach to ring-fused cycloheptadienes offers a wide spectrum of substitution patterns in the cycloheptadiene ring and in the cyclic enone containing the initial sulfoxonium methylide. In addition, the utilization of both cis and trans cyclopropane isomers for the same end makes the methodology outlined above quite efficient and convenient. We are currently applying the above approach to the synthesis of functionalized hydroazulenes and tricyclic cycloheptadienes.

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