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NOVEL APPROACH TO SEVEN-MEMBERED RINGS BY THE INTRAMOLECULAR TANDEM CYCLOPROPANATION/COPE REARRANGEMENT SEQUENCE

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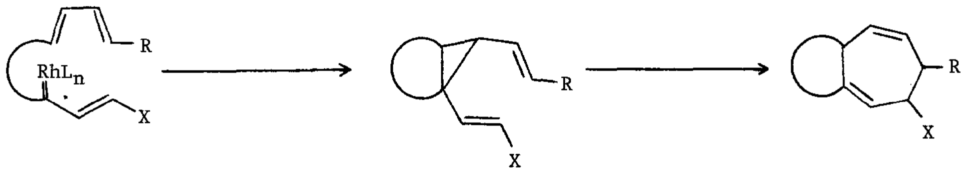
Abstract: The intramolecular tandem cyclopropanation/Cope rearrangement sequence between rhodium(II) acetate stabilized vinylcarbenoids and dienes is a feasible method for the stereospecific synthesis of fused seven-membered rings.

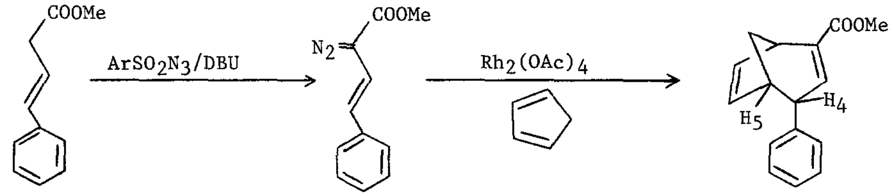
The Cope rearrangement of divinylcyclopropanes offers an attractive entry into seven-membered rings[1] and has been used in the synthesis of certain natural products[2]. These include the dictyopterenes[2a-c] and karahanaenone,[2d,e] and also polycyclic systems such as (±)-β-himachalene[2f], (±)-damsinic acid,[2g], (±)-confertin[2g] and (±)-quadrone[2h]. Recently, we have reported that rhodium(II) acetate stabilized vinylcarbenoids undergo a formal [3 + 4] cycloaddition with cyclopentadiene[3a] and furans[3b,c]. The mechanism of this reaction proceeds through cyclopropanation followed by a Cope rearrangement of the divinylcyclopropane intermediate, and due to this, the reactions with the cyclic dienes have been stereospecific. A direct entry to a variety of compounds containing fused seven-membered rings, such as the pseudoguaianes and other sesquiterpenes, could be provided by the intramolecular version of this reaction (Scheme 1). In this paper, we demonstrate that such reactions are indeed feasible, even with simple dienes, and proceed with excellent stereocontrol.

Scheme 1



Electron withdrawing functionality stabilize vinyldiazomethanes, and in our earlier work[3], the vinylcarbenoid precursors possessed two ester groups. The synthesis of substrates for the intramolecular studies would be greatly simplified if vinyldiazomethanes containing only one ester group could be used. In order to examine this possibility, methyl 4-phenylbutenoate (1) was treated with p-acetamidobenzenesulfonyl azide[4] and DBU as base, and this resulted in the formation of the vinyldiazomethane **2** in 78% yield, with exclusive diazotization alpha to the carbonyl. Even though **2** slowly decomposed over the course of a few hours, reaction of freshly prepared **2** with rhodium(II) acetate in the presence of cyclopentadiene gave the endo [3 + 4] cycloadduct **3**[5] in 74% yield ($J_{H-4,\ H-5} = 4.4$ Hz).

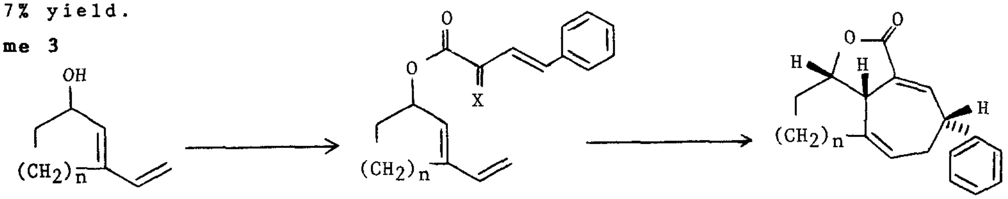
Scheme 2



1 2 3

Based on these observations, the vinyldiazomethanes **6** seemed to be ideal substrates to examine the feasibilty of the intramolecular reaction, and were prepared according to Scheme 3. 3-Vinylcyclohex-2-en-1-ol (4a)[6] was esterified with 4-phenylbutenoyl chloride in the presence of pyridine and DMAP to give **5a** in 91% yield, which on diazotization with p-acetamidobenzenesulfonyl azide[4] gave the carbenoid precursor **6a** in 81% yield. Rhodium(II) acetate catalyzed decomposition of **6a** in dichlromethane resulted in the clean formation of the [3 + 4] cycloadduct **7a**[5] in 61% yield as only one isomer. 3-Vinylcyclopent-2-en-1-ol (**4b**)[7] was similarly converted to the vinyldiazomethane **6b** and also underwent a stereospecific reaction on treatment with rhodium(II) acetate to give the cycloadduct **7b**[5] in 67% yield.

Scheme 3



4

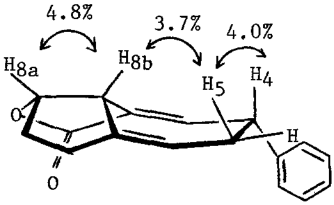
5 X = H,H

6 X = N_2

7

a n = 2; b n = 1

An important feature of these formal [3 + 4] cycloadditions is the controlled generation of two stereocenters. The stereochemistry of the products was determined by homonuclear NOE difference spectra[8], as illustrated for **7b**. Irradiation of H-5 (δ2.81) causes considerable enhancement of H-8b (δ4.27) and H-4 (δ3.90), which clearly shows that these protons are on the same face of the ring. The expected cis fusion of the five membered rings is readily confirmed by the large coupling constant (*J* = 9.2 Hz) and NOE enhancement between H-8b (δ4.27) and H-8a (δ4.80).



NOE data for 7b

In conclusion, the intramolecular [3 + 4] cycloaddition between vinylcarbenoids and dienes results in the rapid and stereospecific construction of fused seven-membered rings. Studies to determine the full scope of this reaction and its application to natural product synthesis are currently under investigation.

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5. ^{1}H NMR (200 mHz, $CDCl_3$) data for the cycloadducts:
   3:δ 7.45-7.05 (m, 5 H), 6.65 (ddd, 1 H, J = 2.6, 1.5, 1.3 Hz), 6.37 (dd,1 H, J = 5.6, 2.9 Hz), 5.28 (dd, 1 H, J = 5.6, 2.7 Hz), 3.80 (dd, 1 H, J = 4.4, 2.6 Hz), 3.77 (s, 3 H), 3.33 (ddd, 1 H, J = 4.9, 2.7, 1.3 Hz), 3.05 (dddd, 1 H, J = 4.9, 4.4, 2.9, 1.6 Hz), 2.24 (ddd, 1 H, J = 10.0, 4.9, 4.9 Hz), 2.00 (d, 1 H, J = 10.0 Hz).
   7a:δ 7.40-7.14 (m, 5 H), 6.99 (dd, 1 H, J = 4.5, 3.5 Hz), 5.35 (m, 1 H), 4.80 (ddd, 1 H, J = 8.6, 8.6, 4.6 Hz), 4.27 (m, 1 H), 3.90 (m, 1 H), 2.81 (br d, 1 H, J = 14.5 Hz), 2.36 (dd, 1 H, J = 14.5, 7.1 Hz), 2.25 (m, 2 H), 1.98 (m, 1 H), 1.73-1.48 (m, 3 H).
   7b:δ 7.40-7.14 (m, 5 H), 6.86 (dd, 1 H, J =7.8, 3.9 Hz), 5.41 (m, 1 H), 5.08 (ddd, 1 H, J =9.2, 7.1, 7.1 Hz), 4.20 (m, 1 H), 3.96 (m 1 H), 2.85 (br d, 1 H, J = 15.5 Hz), 2.49-2.26 (m, 4 H), 1.70 (m, 1 H).
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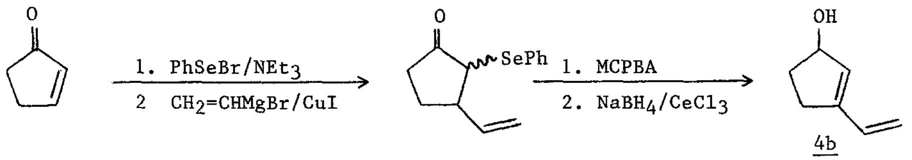
7. **4b** was prepared according to the following scheme:



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