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TYPE II INTRAMOLECULAR ANNULATIONS BETWEEN VINYLCARBENOIDS AND FURANS

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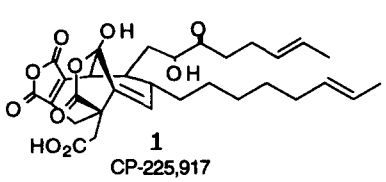
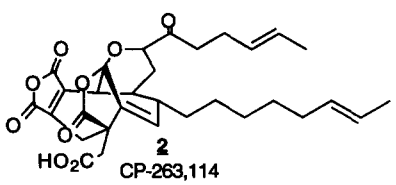
Abstract: Rhodium(II) octanoate catalyzed intramolecular reactions between vinyldiazomethanes and furans result in the formation of polycyclic systems by a tandem cyclopropanation/Cope rearrangement.

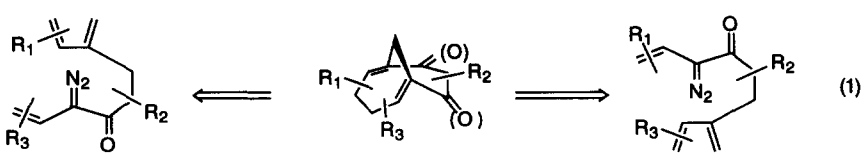
Two recently isolated terpenes, CP-225,917 (**1**) and CP-263,114 (**2**) are of considerable interest because they are novel inhibitors of squalene synthetase and protein farnesyl synthetase.[1] A particularly interesting feature of their structures is the existence of an anti-Bredt double bond within the [4.3.1]-bicyclic framework. Motivated by the unusual structure of these terpenes, we have begun to explore an approach for their synthesis by an intramolecular type II annulation[2] between vinylcarbenoids and dienes (eq 1).[3] Previously, we have demonstrated that the intramolecular reaction between dienes and vinylcarbenoids is a useful method for the stereoselective synthesis of fused cycloheptadiene systems,[4] and the extension of this chemistry to type II annulations, where the tether is attached to the internal carbon of the diene, could be a flexible approach for the synthesis of **1** and **2**. The results of studies to determine the feasibility of intramolecular type II annulations between vinylcarbenoids and dienes are presented here.



1
CP-225,917

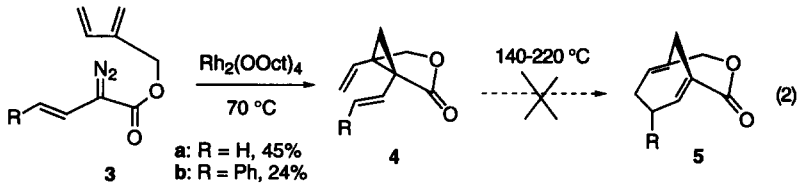


2
CP-263,114



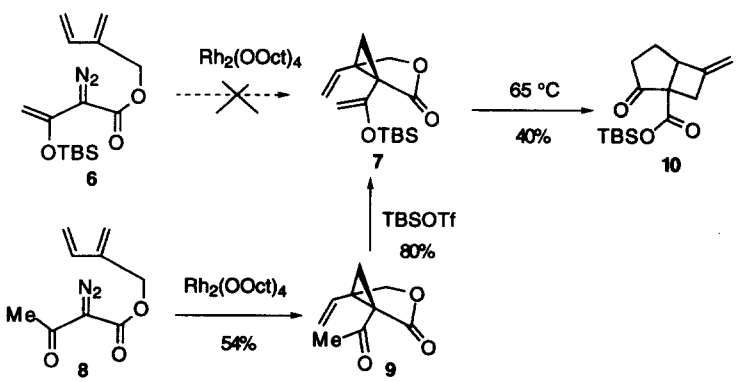
(1)

The initial studies centered around using isoprene as the diene component. Rhodium(II) octanoate catalyzed decomposition of the vinyldiazomethanes **3**[5] resulted in the formation of the *cis*-divinylcyclopropanes **4** in moderate yield; however, the subsequent Cope rearrangement of **4** to **5** could not be accomplished. Both divinylcyclopropanes **4** were stable to heating to 140 °C while under more extreme conditions they decomposed to uncharacterizable material. The inability of **4** to undergo the Cope rearrangement is in stark contrast to simple divinylcyclopropanes that typically rearrange at room temperature or below, and may be caused by the strain that would exist in the product **5**, due to the presence of the anti-Bredt double bonds.

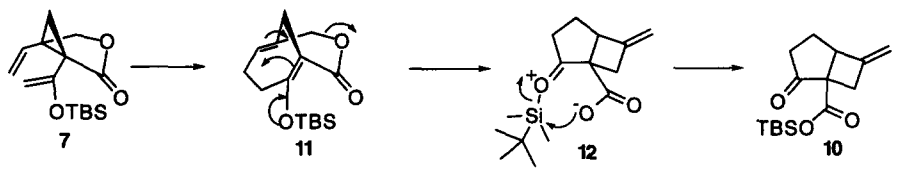


In order to try to develop a system that would undergo the desired reactions to the [4.3.1]-bicyclic framework, the rearrangement chemistry of more electron rich divinylcyclopropanes, such as **7**, was explored. Rhodium(II) octanoate catalyzed decomposition of the siloxy-substituted vinyldiazomethane **6**[5] did not result in an intramolecular cyclopropanation to form the divinylcyclopropane **7**. Consequently, an indirect approach to **7** was examined starting with the diazoacetoacetate **8**, which would be expected to generate a more electrophilic carbenoid than **6**. Rhodium(II) octanoate catalyzed decomposition of **8**, generated the vinylcyclopropane **9** in 54% yield, which was then silylated with TBDMSOTf to form the divinylcyclopropane **7** in 80% yield. The divinylcyclopropane **7** was stable at room temperature, but readily decomposed at heating to 65 °C. The product from this rearrangement, however, was not the desired [4.3.1]-bicyclic system, but the fused cyclobutane **10**.[6]

Scheme 1

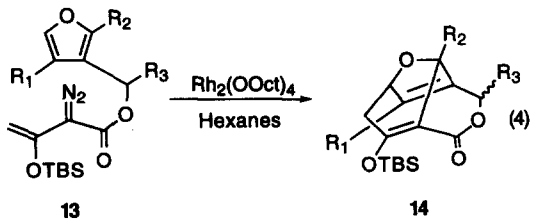


The formation of the unexpected fused cyclobutane **10** is a promising result because it is likely formed from the desired [4.3.1]-bicycle **11** (eq 3). Structure **11** would be expected to be rather unstable due to the presence of two formally anti-Bredt double bonds, and so, would be susceptible to a transannular rearrangement to form **12** and eventually **10**. If this mechanistic hypothesis is correct, it should be possible to isolate [4.3.1]-bicyclic products by introducing structural elements into them that would disfavor the transannular rearrangement. One way to achieve this would be to use a cyclic diene such that the resulting fused cyclobutane would be very strained and unlikely to be formed.



(3)

On the basis of the above discussion, the intramolecular reaction was explored using 3-substituted furans as substrates. Rhodium(II) octanoate catalyzed decomposition of **13a** resulted in the formation of the tricyclic product **14a**[6] in 83% yield. The structural assignment for **14a**, was readily made on the basis of the distinctive NMR signals[7] for the [3.2.1]-oxabicyclic fragment contained within the structure. As the intention of this exploratory study was to determine if this chemistry was sufficiently robust for its eventual use in the synthesis of **1** and **2**, further studies were carried out on more elaborate furan systems. Reaction of the 2-substituted furan **13b** or the 4-substituted furan **13c** resulted in the uneventful formation of the tricyclic system **14b**[6] (29% yield) and **14c**[6] (66% yield). The issue of relative stereocontrol was examined using the furan derivative **13d**. In this case, the tricyclic product **14d**[6] was formed as a 2 : 1 mixture of diastereomers.



(4)

	R_1	R_2	R_3	yield,%
a	H	H	H	83
b	H	Me	H	29
c	CH_2Bn	H	H	66
d	H	H	Et	48

In summary, type II cycloannulations between vinylcarbenoids and furans result in the rapid construction of fused [4.3.1]-bicyclic systems. Further studies are in progress to extend these novel transformations to the eventual synthesis of **1** and **2**.

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References and Notes

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5. The synthesis of the vinylcarbenoid precursors was achieved from the corresponding alcohols using the general procedures described in: Davies, H. M. L.; Matasi, J. J.; Ahmed, G. *J. Org. Chem.* **1996**, *61*, 2305.

6. ^{1}H NMR ($CDCl_3$) δ **10:** 0.28 (s, 6 H), 0.91 (s, 9 H), 2.07 (dddd, 1 H, *J* = 0.9, 1.5, 9.2, 13.1 Hz), 2.19 (dddd, 1 H, *J* = 3.0, 4.3, 8.2, 13.1 Hz), 2.47 (ddd, 1 H, *J* = 3.0, 9.2, 18.5 Hz), 2.68 (ddd, 1 H, *J* = 1.5, 8.2, 18.5 Hz), 2.71 (ddd, 1 H, *J* = 2.0, 2.0, 16.8 Hz), 3.40 (ddd, 1 H, *J* = 2.0, 2.0, 16.8 Hz), 3.77 (dddd, 1 H, *J* = 0.9, 2.0, 2.0, 4.3 Hz), 5.01 (dq, 1 H, *J* = 2.0, 2.4 Hz), 5.04 (dq, 1 H, *J* = 2.0, 2.4 Hz); **14a:** 0.20 (s, 3 H), 0.23 (s, 3 H), 0.90 (s, 9 H), 1.75 (d, 1 H, *J* = 17.6 Hz), 2.81 (dd, 1 H, *J* = 5.4, 17.6 Hz), 4.95 (d, 1 H, *J* = 12.6 Hz), 4.97 (s, 1 H), 5.04 (d, 1 H, *J* = 12.6 Hz), 5.28 (d, 1 H, *J* = 5.4 Hz), 5.36 (s, 1 H); **14b:** 0.21 (s, 3 H), 0.24 (s, 3 H), 0.91 (s, 9 H), 1.55 (s, 3 H), 1.76 (d, 1 H, *J* = 17.4 Hz), 2.81 (dd, 1 H, *J* = 6.4, 17.4 Hz), 4.95 (s, 2 H), 5.23 (d, 1 H, *J* = 6.4 Hz), 5.35 (s, 1 H); **14c:** 0.20 (s, 3 H), 0.25 (s, 3 H), 0.92 (s, 9 H), 1.97 (d, 1 H, *J* = 17.6 Hz), 2.76 (dd, 1 H, *J* = 6.8, 17.6 Hz), 4.08 (d, 1 H, *J* = 12.7 Hz), 4.13 (d, 1 H, *J* = 12.7 Hz), 4.44 (d, 1 H, *J* = 11.7 Hz), 4.50 (d, 1 H, *J* = 11.7 Hz), 4.89 (s, 1 H), 4.96 (s, 2 H), 5.31 (d, 1 H, *J* = 6.8 Hz), 7.28-7.38 (m, 5 H); **14d**: major isomer 0.21 (s, 3 H), 0.24 (s, 3 H), 0.91 (s, 9 H), 1.00 (t, 3 H, *J* = 7.5 Hz), 1.73 (d, 1 H, *J* = 17.7 Hz), 1.78-1.83 (m, 1 H), 1.94-2.01 (m, 1 H), 2.79 (dd, 1 H, *J* = 4.6, 17.7 Hz), 4.93 (s, 1 H), 4.96 (t, 1 H, *J* = 6.7 Hz), 5.27 (d, 1 H, *J* = 4.6 Hz), 5.30 (s, 1 H); minor isomer 0.19 (s, 3 H), 0.23 (s, 3 H), 0.90 (s, 9 H), 0.98 (t, 3 H, *J* = 7.5 Hz), 1.68 (d, 1 H, *J* = 17.5 Hz), 1.72-1.81 (m, 1 H), 1.93-2.00 (m, 1 H), 2.79 (dd, 1 H, *J* = 6.1, 17.5 Hz), 4.91 (s, 1 H), 5.12 (t, 1 H, *J* = 5.6 Hz), 5.26-5.29 (m, 2 H).

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