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The Vinylcyclopropane Moiety as an Efficient Intramolecular Trap for Carbocations. A High Yield Process for the Formation of Eleven-Membered Carbocyclic Structures

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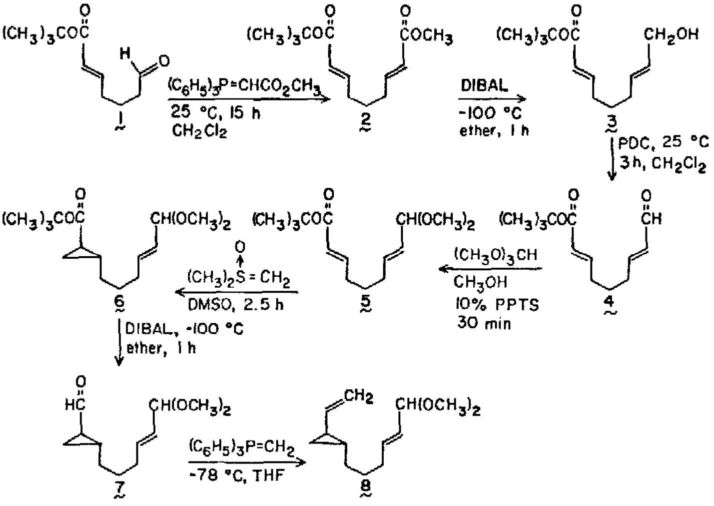
Abstract: Eleven-membered carbocyclic structures can be generated in high yield by the intramolecular trapping of an allyl cation by a vinylcyclopropane moiety.

While nature is credited with the development of cationic biosynthetic pathways to 10-, 11-, 12-, and 14-membered carbocyclic skeletons,[2] attempts to duplicate this feat in the laboratory has led to mixed results. Although intramolecular cyclizations of carbocations to form "medium and large" carbocyclic rings have been observed, yields are generally low and complex mixtures are often formed.[3] Our initial work in this area,[4] coupled with a consideration of the earlier work in the literature,[3] has led us to two premises. First, increasing the stability of the initially generated carbocation should lead to improved yields and specificity in these cyclizations.[5] Second, the use of the vinylcyclopropane moiety as the intramolecular carbocation "trap" should lead to improved yields and specificity.[4,6] If these two premises are correct, the deduction might be made that the incorporation of these two features into the same molecule would lead to high yields of products with readily controlled specificity. We now wish to present results which demonstrate that this deduction is warranted.

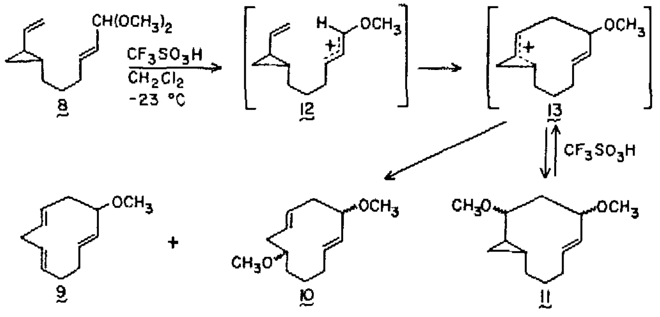
In order to accomplish the desired functionality described above, we carried out the synthesis outlined in Scheme 1. We chose the vinyl-substituted acetal moiety as the stabilized carbocation precursor based on our previous successful use of this cation in intermolecular ionic Diels-Alder reactions.[7] Starting with **1**,[4,8] a standard Wittig reaction was used to obtain **2** in 91% yield.[9] DIBAL reduction of **2** resulted in selective reduction of the methyl ester to give **3** in 69% yield. Pyridinium dichromate oxidation of 3 gave an 86% yield of **4**, which was converted to the acetal **5** in 97% yield with trimethyl orthoformate and pyridinium *p*-toluenesulfonate as the catalyst. Treatment of **5** with dimethylsulfoxonium methylide gave a 61% yield of the cyclopropyl ester **6**. Reduction of **6** with DIBAL at -100 °C for 1 h gave 51% of recovered **6** and 42% of

SCHEME 1



7 (87% yield based on unrecovered **6**). Conversion of **7** into **8** was accomplished in 90% yield through the use of triphenylphosphonium methylide. With the synthesis of **8**, we felt we had in hand an ideal substrate for testing our theory. The vinylcyclopropane moiety of **8** should constitute an ideal trap for a carbocation, while a variety of reagents should convert the acetal moiety of **8** into a relatively stable methoxyl-substituted allyl cation.

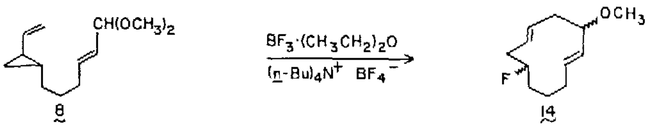
Treatment of a 5 mM solution of **8** in methylene chloride with 5 mol % of triflic acid at -23 °C for 3.5 h gave 32% of **9** and 54% of **10** (as a 5.4:1 diasteriomeric mixture).[10] When the reaction time was shortened



to 1.8 h and all other reaction conditions were the same, 16% of **8** was recovered and **11** appeared in 21%

yield as a 4:1 diastereomeric mixture, in addition to 24% of **9** and 25% of **10**. It was demonstrated through resubmission studies that, under the reaction conditions, **11** was converted to a mixture of **9** and **10**, which established **11** as an intermediate in the reaction. It would appear that **8** is initially converted to **12** which cyclizes in close to quantitative yield to produce **13**. Deprotonation of **13** gives **9**, while attack of methanol yields **10** and **11**. Through conversion back to **13**, **11** is consumed with **9** and **10** being formed.[11] When 200 mol % of methanol was added to the reaction mixture and the reaction was run for 6 h, **8** gave 7% of **9** and 84% of **10** (3.7:1 diastereomeric mixture).

The use of 25 mol % boron trifluoride etherate as the catalyst with 200 mol % of added methanol gave a 92% yield of **10** (4.4:1 diastereomeric mixture by ^{1}H NMR analysis) from **8**. In the absence of the added methanol, the boron trifluoride etherate catalyzed cyclization gave 20% of **10**, 17% of **11** and 45% of a new product. It was readily determined that this new material was **14** (6.5:1 mixture of diastereomers by ^{1}H NMR analysis).[12] The use of boron trifluoride etherate coupled with the presence of 150 mol % of tetra-*n*-butylammonium boron tetrafluoride converted **8** into **14** (5.7:1 mixture of diastereomers) in 81% yield. When a methylene chloride solution of **14** was treated with boron trifluoride etherate in the presence of 100 mol % of methanol, **10** was rapidly formed.



From the data presented above, it is apparent that cyclization reactions to form 11-membered rings can be carried out in high yield and with great specificity. These results support the contention that the presence of a vinylcyclopropane carbocation trap and a relatively long-lived alkoxyl-substituted allyl cation make an excellent reactive pair for cyclizations which might be expected to be entropically unfavorable.

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References and Footnotes

1. National Science Foundation Fellow, 1984-1987.
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8. The preparation of **1** involved the treatment of glutaraldehyde with 1,1-dimethylethyl triphenylphosphoranylideneacetate which gave 1,1-dimethylethyl (2E)-7-oxoheptenoate in 78% yield.[4]
9. Satisfactory elemental analyses and/or exact mass molecular weights were obtained on all new compounds. All compounds had IR, ^{1}H NMR, and ^{13}C NMR spectra which were consistent with the assigned structures.
10. The diastereomer ratio was determined to be 5.5:1 by capillary GLC and 5.3:1 by ^{1}H NMR analysis.
11. Control experiments demonstrated that **9** and **10** were not readily interconverted under the reaction conditions.
12. For selected examples of fluoride ion capture by a carbocation from boron tetrafluoride anion see the papers of Balenkova in reference 6.

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