

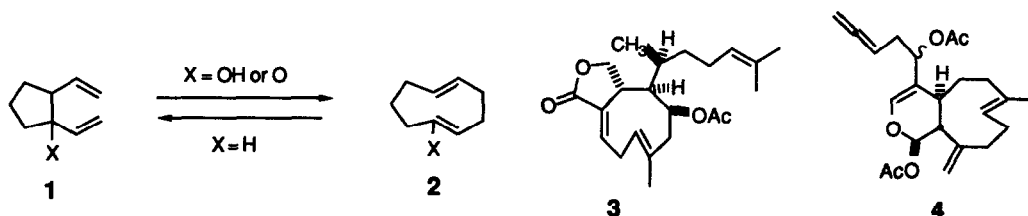
## Sequential Vinylcyclopropylcarbene<sup>1</sup> and Anionic Oxy-Cope Rearrangements: An Expedient Synthesis of Nine-Membered Rings<sup>†</sup>

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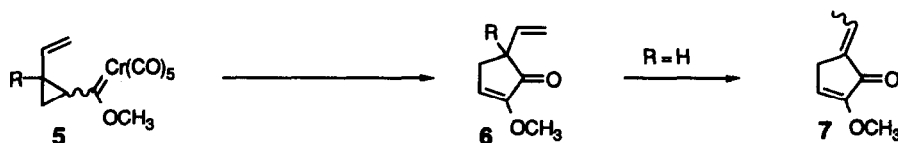
**Summary:** 5-Alkenyl-2-methoxy-2-cyclopentenones, readily available from thermolysis of 2-alkenylcyclopropylcarbene-chromium complexes, can be converted to nine-membered rings by treatment with vinylcerium reagents and subsequent anionic oxy-Cope rearrangement.

The nine-membered carbocyclic ring system is present in a variety of compounds of medicinal importance; examples include the recently-discovered anti-cancer agents 4-acetoxidyctyolactone (**3**)<sup>2</sup> and ginamallene (**4**)<sup>3</sup>. Methods for the construction of nine-membered rings are somewhat difficult due to the strain present in this ring system<sup>4</sup>. Unfortunately, simple Cope rearrangements of 1,2-divinylcyclopentane derivatives typically do not afford cyclononadiene derivatives upon thermolysis<sup>5</sup>, and 1,5-cyclononadiene derivatives typically revert via Cope rearrangement to 1,2-divinylcyclopentane derivatives. Oxy-Cope rearrangements<sup>6</sup> and anionic oxy-Cope rearrangements<sup>7</sup> of 1,2-divinylcyclopentane derivatives are effective methods for the construction of these ring systems, however 1,2-divinylcyclopentane derivatives are not readily accessible compounds. Typically, their synthesis involves addition of alkenylmetal derivatives to relatively inaccessible 2-alkenylcyclopentanones<sup>8</sup>. We recently reported that 2-alkenylcyclopropylcarbene-chromium complexes such as **5** produce 5-alkenylcyclopentanone derivatives such as **6** upon thermolysis at 65°C (Scheme 2)<sup>1</sup>. This reaction was found to be general for a wide variety of differently-substituted derivatives of these complexes. In cases where R = H, some of the product where the double bond had moved into conjugation (**7**) was also obtained. Complexes which do not contain the 2-alkenyl substituent did not undergo this rearrangement. Further mechanistic studies of this reaction are currently underway in our laboratory.

### Scheme 1



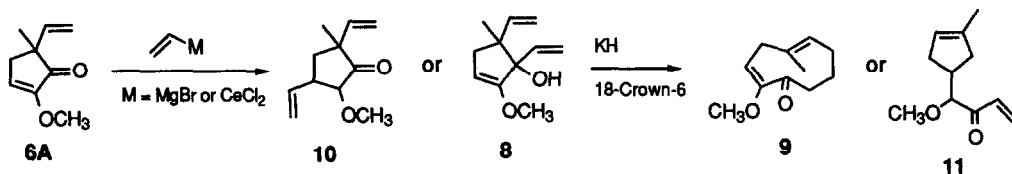
### Scheme 2



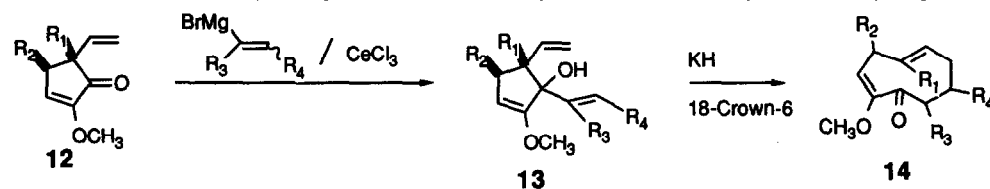
<sup>†</sup>Dedicated to the memory of Professor William J. Bailey

Cyclopentenone **6A** is a potential precursor to nine-membered ring-containing compounds. Treatment of **6A** with vinyl anion equivalents would lead to alcohols such as **8**. Oxy-Cope or anionic oxy-Cope rearrangements of **8** could then provide either cyclononadienone derivative **9** or cyclopentene derivative **11**. Treatment of compound **6A** with vinylmagnesium bromide leads to a quantitative yield of adducts which are unstable to chromatographic purification. Examination of the crude reaction mixture by infrared spectroscopy showed carbonyl bands in the region of  $1740\text{ cm}^{-1}$ , which is suggestive of a cyclopentanone derivative, as well as an O-H stretch at  $3500\text{ cm}^{-1}$ , suggestive of the desired alcohol derivative. The crude reaction mixture was treated with potassium hydride / 18-crown-6 in THF to give the desired nine-membered ring derivative **9** in 11% yield. Presumably, the low yield is due to inefficiency in the vinyl anion addition step; the cyclopentanone absorption in the infrared could arise from compound **10**, which is the result of a Michael addition reaction. Side reactions of this type can be suppressed using organocerium reagents, formed by addition of anhydrous cerium trichloride to the reaction mixture<sup>9</sup>. Addition of cerium trichloride to the reaction mixture does in fact suppress the Michael addition reaction (no absorption at  $1740\text{ cm}^{-1}$  in the crude trienol), and the yield for the conversion of cyclopentenone **6A** to cyclononadienone **9** is now 48%.

**Scheme 3**



**Table** Reaction of 2-Alkenylcyclopentanones with Alkenyllithiums Followed by Anionic Oxy-Cope Rearrangement.



Entry <sup>a</sup>	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	R <sub>4</sub>	Yield 13 <sup>b</sup>	Yield 14 <sup>c,d</sup>	E/Z 15
A	CH <sub>3</sub>	H	H	H	85%	50%	100:0
B	CH <sub>3</sub>	H	CH <sub>3</sub>	H	95%	53%	100:0
C	CH <sub>3</sub>	H	H	CH <sub>3</sub>	93%	57%	100:0
D	CH <sub>3</sub>	H	H	Ph	91%	51%	100:0
E <sup>e</sup>	R <sub>1</sub> , R <sub>2</sub> = -(CH <sub>2</sub> ) <sub>4</sub> -		CH <sub>3</sub>	H	89%	47%	100:0
F <sup>e</sup>	R <sub>1</sub> , R <sub>2</sub> = -(CH <sub>2</sub> ) <sub>4</sub> -		H	H	87%	56%	100:0
G <sup>e</sup>	R <sub>1</sub> , R <sub>2</sub> = -(CH <sub>2</sub> ) <sub>5</sub> -		H	H	89%	47%	100:0

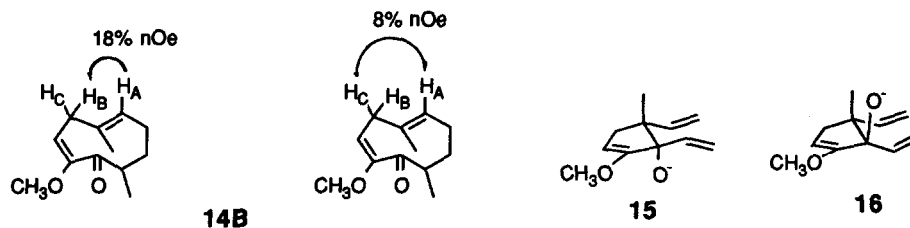
a. Table entry letters define substituents for **12**, **13**, **14**. b. For a procedure see reference 10. c. For a procedure see reference 11. d. The yield refers to compounds which are pure by combustion analysis or chromatographic (HPLC) analysis. e. See reference 1 for preparation of **12E-G**.

The generality of this four-carbon ring expansion has been tested with a variety of differently-substituted vinylcerium reagents. The results are presented above in the Table. The vinyl anion addition reaction appears to be insensitive to steric effects; good yields of adducts were obtained in all cases, even when  $R_3 \neq H$ . The

stereoselectivity of the addition reaction could not be determined since the alcohols were unstable to chromatographic purification. In all cases the Cope rearrangement reaction proceeded in about 50% yield, regardless of the substitution pattern on the vinyl group. In no case were products analogous to compound **11** obtained, presumably because the geometry required for this process is difficult to attain.

In all cases, a single alkene stereoisomer was formed. We have performed nOe studies on compound **14B**, and have assigned the E configuration to the newly-formed double bond. The  $^1\text{H}$  NMR spectrum of compound **14B** contains a triplet in the vinylic region at  $\delta$  5.15 and a doublet of doublets at  $\delta$  4.95. The resonance at  $\delta$  5.15 was significantly broadened, presumably due to long-range coupling interactions. This proton was assigned as the vinylic proton at the non-enol ether double bond ( $\text{H}_A$  in Figure 1). Irradiation of the doubly allylic proton at  $\delta$  3.05 ( $\text{H}_B$ ) produces an 18% enhancement in the vinylic resonance at  $\delta$  5.15. Irradiation of the other doubly allylic proton at  $\delta$  2.45 ( $\text{H}_C$ ) produces an 8% enhancement of the vinylic proton at  $\delta$  5.15. This is highly suggestive of the E-configuration about the newly-formed double bond. This would be the expected isomer if the Cope rearrangement proceeds through a chair transition state (e.g. **15**), or an extended boat transition state (e.g. **16**). We have inferred that the remaining entries also provide exclusively the E-alkene stereoisomer.

**Figure 1.** Determination of Double-Bond Stereochemistry in **14**.



In summary, we have presented a method for the net formation of nine-membered rings. The use of the vinylcyclopropylcarbene rearrangement followed by anionic oxy-Cope rearrangement allows for the synthesis of a variety of substitution patterns on the nine-membered ring. We are actively further investigating the scope and limitations of this highly useful transformation.

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8. 1,2-Divinylcyclopentanols are usually obtained from cyclopentene oxide derivatives via the sequence of vinyl anion addition, oxidation of the homoallylic alcohol to the corresponding  $\beta,\gamma$ -unsaturated ketone, and addition of vinyl anion to the ketone<sup>6</sup>. This method does not work if C-2 is tetrasubstituted.
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10. A 25mL round bottom flask fitted with a rubber septum containing cerium trichloride heptahydrate (0.611 g, 1.60 mmol) was heated to 150°C under vacuum (0.005 mmHg) for a period of 24 h. Heating for shorter periods of time led to irreproducible yield of **13**. The flask was then cooled to 0°C and THF (6 mL) was added. The solution was allowed to stir at 25°C for 2 h, the solution was then cooled to -78°C, and a solution of 2-propenylmagnesium bromide (2.1 mL of an 0.7M THF solution, 1.5 mmol) was added via syringe. The mixture was stirred for 1.5 h at -78°C and a solution of compound **6A** (0.050 g, 0.33 mmol) in THF (8 mL) was added dropwise via syringe over a 15 min period. The solution was stirred at -78°C for 1 h and then poured into a 4% solution of acetic acid in water in a separatory funnel. The mixture was extracted with ether and the combined ether layers were washed with saturated aqueous sodium bicarbonate and saturated aqueous sodium chloride solutions. The ether layer was dried over magnesium sulfate and the solvent was removed on a rotary evaporator. The residue after evaporation (0.061 g, 95%) was used immediately in the Cope rearrangement reaction without further purification.
11. To a 25mL flask fitted with a septum under nitrogen containing potassium hydride (0.180 g of a 35% mineral oil dispersion, 1.60 mmol) was added pentane (10 mL). The mixture was stirred vigorously for 5 min and then the solid was allowed to settle. The pentane was decanted, and the above process was repeated two times. THF (10 mL) was added, and to the resulting suspension was added via syringe a solution of compound **13B** (0.061 g, 0.31 mmol) and 18-crown-6 (0.42 g, 1.6 mmol) in THF (5 mL). The solution was stirred for 30 min at 25°C and then cooled to -78°C and ethanol (1.0 mL) was added very slowly. The mixture was poured into a mixture of saturated ammonium chloride and petroleum ether in a separatory funnel. The organic layer was washed with water and saturated aqueous sodium chloride, dried over magnesium sulfate, and the solvent was removed on a rotary evaporator. The residue after evaporation was purified by flash chromatography on silica gel using 9:1 hexane:ethyl acetate as the eluent. After removal of the solvent, a colorless oil (0.033 g, 53%) identified as compound **14B** was obtained. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  5.15 (t, 1H, J = 8.3 Hz); 4.95 (dd, 1H, J = 9.3, 5.1 Hz); 3.55 (s, 3H); 3.05 (dd, 1H, J = 15.0, 5.1 Hz); 2.85 (quintet of doublets, 1H, J = 7.0, 3.2 Hz); 2.45 (dd, 1H, J = 15.0, 9.3 Hz); 2.20 - 1.50 (m, 4H); 1.60 (br s, 3H); 1.00 (d, 3H, J = 7.0 Hz). <sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  208.7, 157.5, 138.2, 124.2, 97.1, 55.2, 46.1, 33.8, 26.8, 26.4, 22.9, 18.7. IR (CDCl<sub>3</sub>): 3038 (w), 2985 (s), 2945 (vs), 2895 (m), 2880 (m), 1710 (vs), 1655 (m), 1470 (s), 1390 (m), 1245 (m), 1210 (s), 1170 (w), 1128 (m), 1105 (m), 1090 (m), 1075 (m), 1045 (m) cm<sup>-1</sup>. MS (EI): 194 (M, 20), 179 (6), 166 (7), 151 (45), 137 (31), 124 (100), 109 (99). High res MS: calcd. for C<sub>12</sub>H<sub>18</sub>O<sub>2</sub>: 194.1307. Found: 194.1312.

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