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INVESTIGATION OF VINYL-CYCLOPROPANE MONORADICAL CYCLIZATION-FRAGMENTATION AS A POSSIBLE ROUTE TOWARDS EIGHT-MEMBERED RINGS

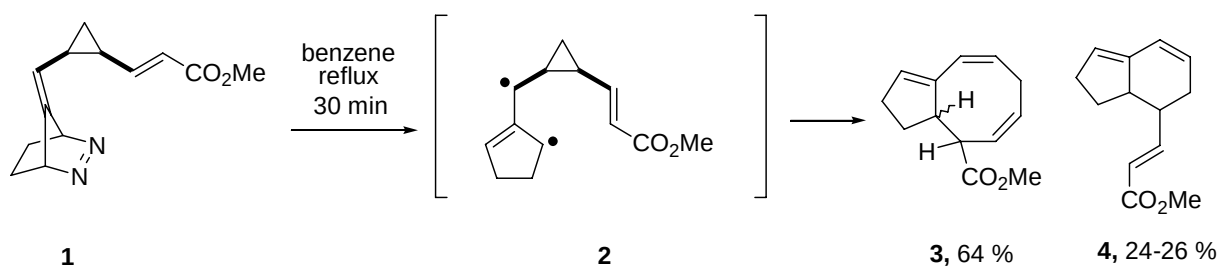
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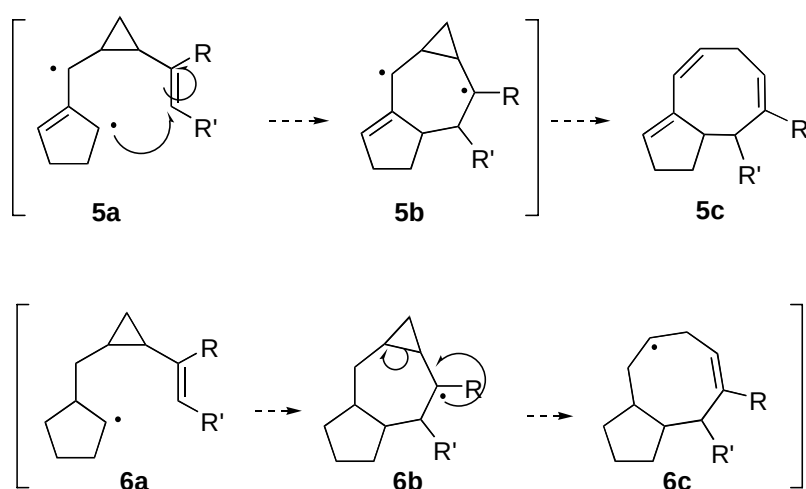
Abstract – A monoradical vinylcyclopropane cyclization-fragmentation route to eight-membered rings was investigated. 6-Exo-trig cyclization was preferred over the alternative 7-endo-trig cyclization, due to entropic factors and the position of a radical stabilizing electron withdrawing group. Changing position of the electron withdrawing group was not enough to entice 7-endo-trig cyclization.

Eight-membered heterocyclic and carbocyclic rings are found in many natural products. A number of strategies have been employed to tackle their synthesis.¹ One route that we have developed uses a vinylcyclopropane with an appended trimethylenemethane (TMM) diradical such as **2** to initiate a fragmentation-cyclization sequence that leads to both 6 and 8-membered rings.² For example, when the cyclopropyl diazene (**1**) was heated in refluxing benzene, both the [6.3.0] and [4.3.0] carbocyclic systems were produced (Scheme 1). We have applied this chemistry to the synthesis of a simplified taxotere model system.³



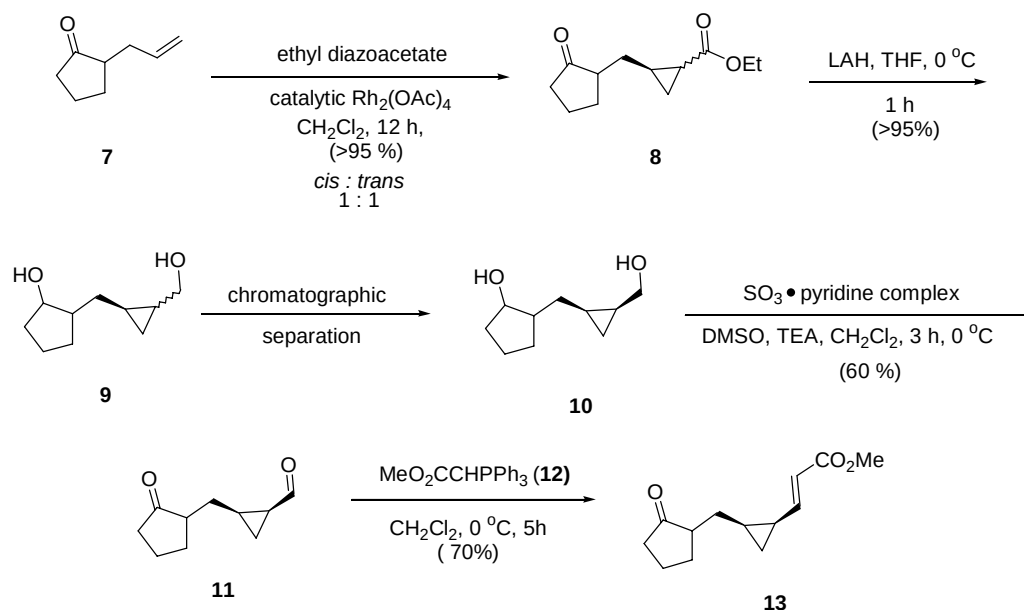
Scheme 1. TMM Vinylcyclopropane route to the [6.3.0] ring system

One path that accounts for the formation of the eight-membered ring begins with a 7-endo-trig cyclization of diyl (**5a**) to afford the distonic cyclopropyldicarbonyl diyl (**5b**) whose collapse leads to **5c** (Scheme 2). In an effort to examine these ideas in greater detail and to expand upon the scope of the chemistry, we elected to explore a related monoradical (**6a**). We wished to determine whether it would close onto the appended vinylcyclopropane moiety to afford **6b** and subsequently undergo fragmentation similar to that observed in the TMM diyl chemistry. Kilburn has used a similar cyclization-fragmentation strategy; there, too, a methylenecyclopropane served as a radical trap.⁴

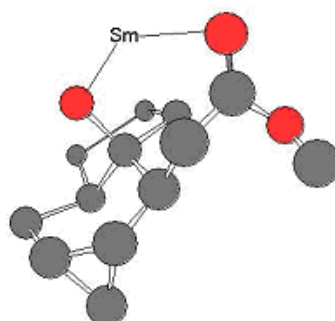
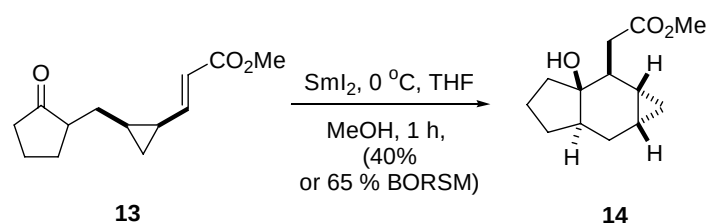


Scheme 2. Diyl (**5a**) and its monoradical counterpart (**6b**)

Our preliminary studies focused upon vinylcyclopropane (**13**). We assumed that a viable cyclization substrate would require a *cis* stereochemistry about the cyclopropane ring since a *trans* relationship would place the odd electron and the alkene too far apart to allow direct cyclization. The synthesis of vinylcyclopropane (**13**) is illustrated in Scheme 3. 2-Allylcyclopentanone (**7**) was cyclopropanated using ethyl diazoacetate and a catalytic amount of dirhodium tetraacetate. The reaction generated a 1:1 *cis/trans* mixture of cyclopropyl ester (**8**). The mixture of diastereomeric cyclopropyl esters (**8**) was then reduced using lithium aluminum hydride. Careful chromatography efficiently provided the necessary *cis*-cyclopropane (**10**). Cyclopropyl alcohol (**10**) was subjected to a Parikh-Doering oxidation to give **11**.⁵ The cyclopropyl aldehyde (**11**) was then treated with the stabilized Wittig reagent (**12**) to give the α , β -unsaturated ester (**13**). The atom connectivity of **13** was confirmed using a ^1H - ^1H COSY analysis and the stereochemistry was established using nOe analysis.

Scheme 3. Synthesis of Vinylcyclopropane (**13**)

We elected to use samarium diiodide as the single electron reductant to generate ketyl radical (**16**) (see Figure 1). Thus, when **13** was added via cannula to a solution of samarium diiodide in THF at 0 °C, compound (**14**), the product of a 6-exo-trig cyclization, was generated in a 40 % isolated yield (65 % BORSM, Scheme 4).⁶ The atom connectivity for **14** was determined using ^1H - ^1H COSY and ^1H - ^{13}C HMQC analysis and the stereochemistry was established by using nOe analysis. Samarium chelation can be invoked to explain the stereochemical outcome of the cyclization reaction. Of course, there are many examples of the stereocontrolled synthesis of medium sized rings involving samarium chelates.⁷

Scheme 4. Cyclization of vinylcyclopropane (**13**) to give tricyclic 5-6-3 system

The observed 6-exo-trig cyclization of **16** is not unanticipated, given that the relative rates of cyclization for hydrocarbon radicals has shown that a 7-endo-trig cyclization is 45 times slower than a 6-exo-trig cyclization.⁸ In addition, the 6-exo-trig cyclization of **16** leads to ester stabilized radical (**17**), while the 7-endo-trig cyclization pathway leads to **15**, a non-stabilized radical (Figure 1).

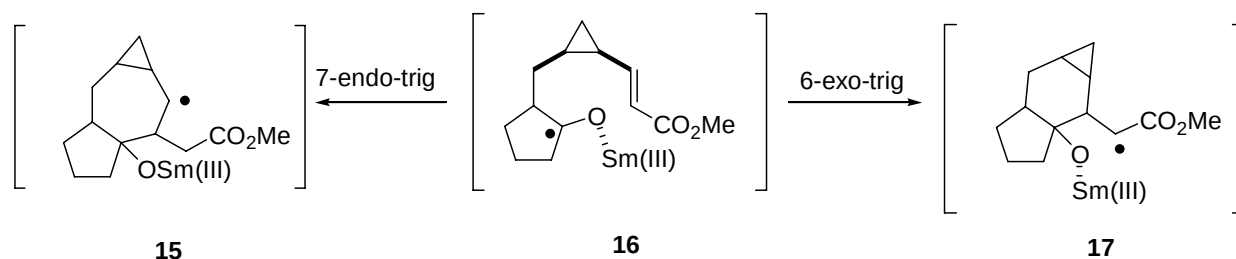
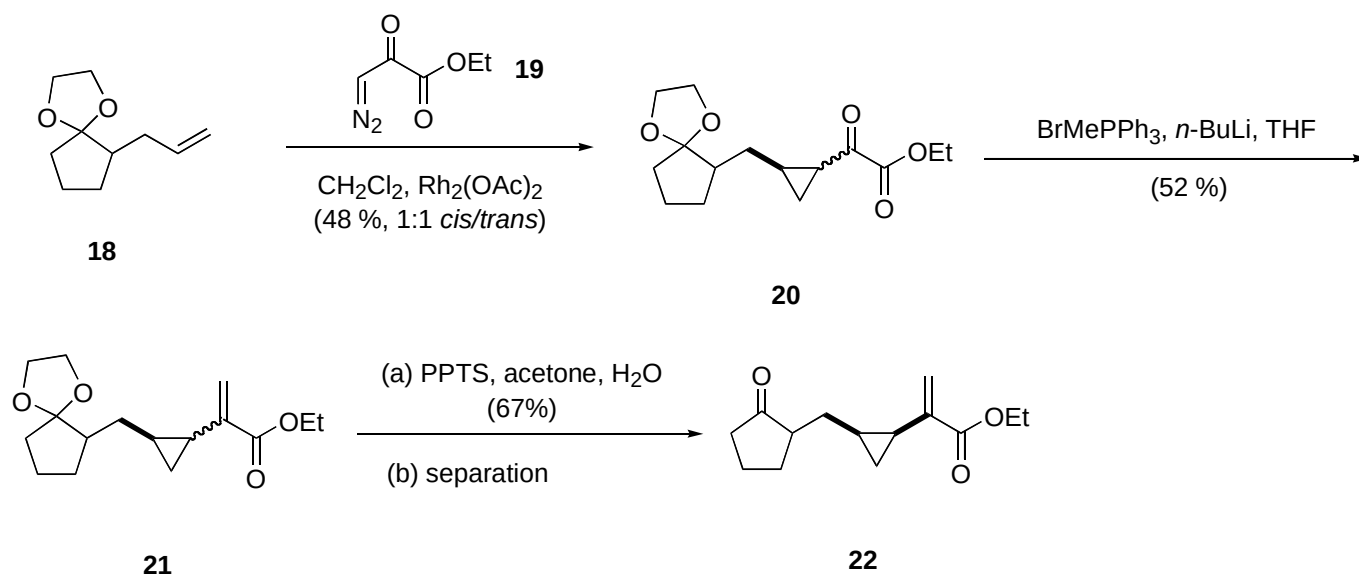


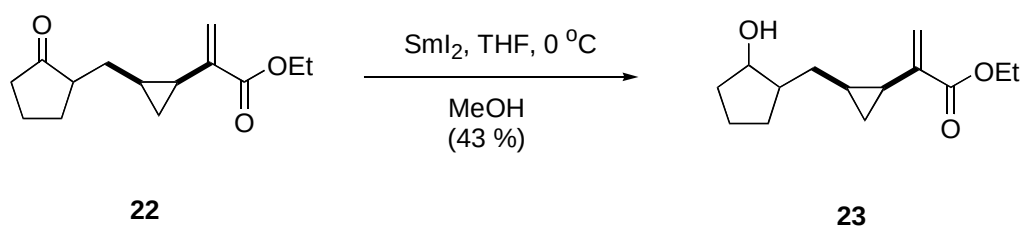
Figure 1. 7-endo-trig pathway vs. 6-exo-trig pathway

We elected to change the position of the electron withdrawing group in an effort to promote the 7-endo-trig pathway and chose vinylcyclopropane (**22**) as the substrate of interest. Its synthesis, outlined in Scheme 5, began when ethylene ketal (**18**) was treated with ethyl diazopyruvate (**19**) and a catalytic amount of dirhodium tetraacetate to give cyclopropane (**20**) as a mixture of diastereomers. Olefination of cyclopropyl ketone (**20**) proceeded smoothly to give the α , β -unsaturated ester (**21**). Deprotection of cyclopropane (**21**) using PPTS to give the anticipated ketone also proceeded smoothly. Careful chromatography allowed for the separation of the *cis/trans* cyclopropane isomers. The atom connectivity of **22** was once again established using ^1H - ^1H COSY analysis and the stereochemistry was confirmed by using nOe.



Scheme 5. Synthesis of Vinylcyclopropane (**22**)

Treatment of **22** with samarium diiodide afforded secondary alcohol (**23**) (Scheme 6), the product of reduction without cyclization, with the rest of the mass consisting of starting material.⁹ The most likely source of "H" atom in the reduction is the solvent, THF. It has been observed that THF complexes with Sm(II) and is present when samarium coordinates to the carbonyl prior to reduction (assuming an inner sphere process). The THF is then readily available as a hydrogen atom donor. Molander has described this phenomenon when studying additives such as HMPA in intramolecular SmI₂ cyclizations.¹⁰ The HMPA preferentially complexes with the Sm(II) and THF is excluded from the coordination sphere, thereby reducing the likelihood of hydrogen atom abstraction leading to uncyclized product.



Scheme 6. Reduction of (**22**) to give secondary alcohol (**23**)

Although we have been unsuccessful in gaining access to eight-membered rings thus far, our efforts continue. One intriguing option is to replace one of the cyclopropyl carbons with an oxygen or a nitrogen atom, in an effort to use the chemistry as a route to oxygen and nitrogen containing heterocycles. Our continuing studies in this area are underway and the results will be reported in due course.

ACKNOWLEDGEMENTS

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6. (2a-Hydroxydecahydrocyclopropa[f]inden-2-yl)acetic acid methyl ester (**14**): In a flame dried 25 mL round bottomed flask was added 7.5 mL (0.75 mmol) of 0.1 M SmI₂ in THF via syringe. The solution was cooled to 0 °C. The SmI₂ solution was dark blue. Vinylcyclopropane (**13**) (0.062 g, 0.28 mmol) was dissolved in 2 mL of THF and then added dropwise via syringe to the SmI₂ solution. The reaction mixture was dark blue when the addition was complete. After 1 h, the solution turned yellow. TLC analysis indicated that the starting material was still present and a new spot appeared below the starting material. Methanol (0.1 mL, 0.08 g, 2.4 mmol) was added and the resulting solution stirred for 10 min. The reaction mixture was then quenched with 2 mL of saturated aqueous tartaric acid. The organic layer was separated and washed with another 2 mL of saturated aqueous tartaric acid, followed by washing with 2 mL of brine. The solvent was then removed *in vacuo* to afford the crude product. Purification using flash chromatography on silica gel eluting with 60 % diethyl ether in petroleum ether afforded the title compound (**14**) (0.062 g, 0.11 mmol, 40 % yield), along with 22 mg of the starting material. The yield based upon recovered starting material was 62 % (mass balance 82%). For (**14**), R_f = 0.45 (60 % Et₂O in petroleum ether, visualized with vanillin); ¹H NMR (400 MHz, CDCl₃) δ 2.79 (dd, *J* = 6.23 Hz, 14.65 Hz, 1H), 2.39 (dd, *J* = 8.43 Hz, 14.65 Hz, 1H), 1.95 (overlapping m, 3H), 1.55 – 1.70 (overlapping m, 7H), 1.4 (m, 1H), 1.2 (m, 3H), 0.80 – 0.90 (overlapping m, 3H), 0.41 (qd, *J* = 4.03 Hz, 1H), 0.2 (q, *J* = 4.40 Hz, 1H); ¹³C NMR (100 MHz) 174 (+), 83 (+), 52 (-), 49 (-), 44 (-) 36 (+), 33 (+), 27 (+), 24 (+), 16 (+), 14 (-), 7 (-); FTIR (neat) 3425, 2948, 2861, 1721, 1436, 1280, 1165, 1120, 1005, 986, 914, 876, 841, 811, 731, 690, 665, 654 cm⁻¹; LR-MS *m/z* (relative intensity) 192 (10), 164 (25), 149 (10), 132 (30), 120 (25), 108 (25), 95 (20), 84 (100), 67 (30), 59 (45), 41 (85); exact mass calcd for C₁₃H₂₀O₃; (M-OH)⁺ 207.138505., observed [HRMS (EI)] (M-OH)⁺ 207.137960.
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9. 2-[2-(2-Hydroxycyclopentylmethyl)cyclopropyl]acrylic acid ethyl ester (**23**): In a flame dried 25 mL round bottomed flask was added 12 mL (1.92 mmol) of 0.16 M SmI₂ in THF via syringe. The solution was cooled to 0 °C. Vinylcyclopropane (**22**) (0.226 g, 0.96 mmol), dissolved in THF (2 mL), was then added dropwise via syringe to the SmI₂ solution. The reaction mixture was dark blue when the addition was complete. After 2 h, the solution had turned yellow. TLC analysis indicated that starting material was still present and a new spot appeared below the starting material. Methanol (0.23 mL, 0.291 g, 7.7 mmol) was added to the reaction mixture and stirred for 10 min. A saturated aqueous solution of sodium-potassium tartrate containing 10 % potassium carbonate was

added (10 mL). The aqueous layer was extracted with methylene chloride (3 x 20 mL) and the combined organic layers were washed with brine (2 x 10 mL) and dried over magnesium sulfate. The solvent was then removed *in vacuo* to afford the crude product. Purification using flash chromatography on silica gel eluting with 60 % diethyl ether in petroleum ether to give the title compound (**23**) (0.064 g, 0.27 mmol, 28 % yield). The starting material (0.155 g) was also isolated during purification. Therefore, the yield of the reaction based upon recovered starting material was 90 %. The mass balance of the reaction was >95 %. For (**23**), ^1H NMR (400 MHz, CDCl_3) δ 5.99 (d, $J = 4.30$ Hz, 1H), 5.20 (d, $J = 4.30$ Hz, 1H), 4.20 (q, $J = 6.68$ Hz, 2H), 3.88 (m, 4H), 1.5 – 1.8 (m, 4H), 1.3 – 1.5 (m, 4H), 1.2 (m, 2H), 0.95 (t, $J = 7.32$, 3H), 0.8 (q, $J = 6.2$ Hz, 1H), 0.72 (q, $J = 6.2$ Hz, 1H), 0.59 (m, 2H); FTIR (neat) 3509, 2959, 1714, 1626, 1445, 1371, 1265, 1140, 1028, 912, 868, 857, 815, 731 cm^{-1} .

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