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The Cyclopropylalkylidenecyclopropane Thermal Double Ring Expansion. A Novel Route to the Bicyclo[5.3.1]undecane Skeleton of the AB Ring System of Taxanes[1]

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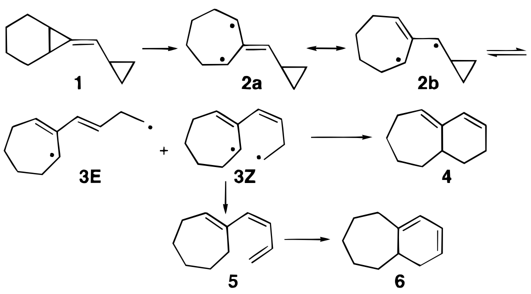
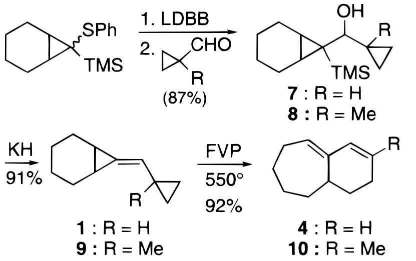
We present herein the first examples of a novel double ring expansion of cyclopropylalkylidenecyclopropanes resulting in six-membered rings. This reaction is based on the diene-like properties of vinylcyclopropanes[4] and is an analogue of the double ring expansion of fused allylidenecyclopropanes, a process providing efficient stereocontrolled access to fused five-membered ring systems.[5] The design of this new transformation was predicated on the mechanistic hypothesis outlined in Scheme 1. Homolysis of the strained doubly allylic bond in cyclopropylmethylidenecyclopropane (**1**) would produce a trimethylenemethane (TMM) diradical (**2**), which can be viewed as a cyclopropylcarbinyl radical that would be expected to open to a homoallylic radical (**3**).[6,7] Since no rapid (intramolecular) reactions, except reversion to **2**, are apparently available to the *E* isomer **3*E***, it is likely that **3*E*** can readily isomerize to **3*Z*** via **2**. Isomer **3*Z*** would hopefully close to a six- membered ring (e.g., **4**). A far less useful possibility is that diradical **3*Z*** could undergo a 1,5-hydrogen atom transfer leading to triene **5**, from which a different bicyclic diene (**6**) would be derived by electrocyclization.

In a test of the hypothesis, **1** and **9** were prepared by reductive lithiation technology as shown in Scheme 2,[5,8] and were subjected to flash vacuum pyrolysis (FVP) at 0.01 Torr to provide the double ring expanded dienes **4** and **10**, respectively, in excellent yields.[10] The identities of the compounds were established by a combination of NMR and UV/vis spectral data. The ^{1}H NMR spectrum favored structure **4** over **6**, and ^{1}H,^{1}H COSY and COLOC spectra convincingly favored **10** over the methylated analogue of **6**. In addition, two important features of the UV/vis spectrum of **4** secured its characterization. The calculated[11] wavelength of absorbance of a heteroannular diene such as **4** is 234 nm while that of a homoannular diene such as **6** is 273 nm. The s-*cis* dienes give maxima of lower intensity ($\epsilon = 10\ 000$) than the maxima of the *s-trans* dienes ($\epsilon = 20\ 000$). The observed $\lambda_{\max} = 238$ nm with a molar absorptivity (ϵ) of 17 900 strongly supports diene **4** as the rearrangement product.

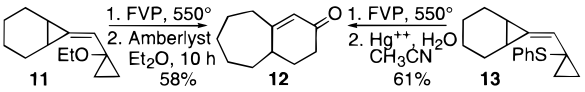
Scheme 1



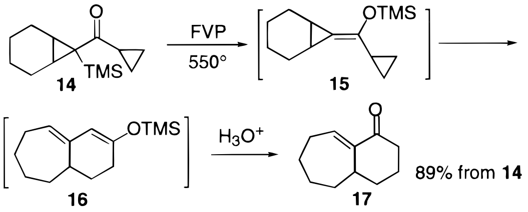
Scheme 2



Scheme 3



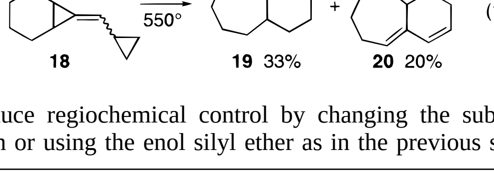
Scheme 4



Having demonstrated the general viability of the proposed rearrangement and ruled out complications via hydrogen transfer (see Scheme 1), we set out to expand the scope and define the limitations of this double ring expansion reaction. To introduce functionality into the six-membered ring, compounds **11** and **13** were subjected to FVP to provide mixtures of ethers which were hydrolyzed to enone **12** (Scheme 3).

Another substitution pattern was available from acylcyclopropylsilane **14**. Thermolysis led, via sequential Brook[12] and ring-expansion rearrangements, to enone **17** in high yield after treatment of the intermediate enol silyl ether **16** with 10% aqueous HCl in THF for 2 min (Scheme 4).

The incorporation of functionality into the seven-membered ring was possible via thermal ring expansion of **18**. However, unlike the analogous allylidencyclopropyl ketone rearrangement,[5] the regioselectivity was unsatisfactory (eq 1). It may be possible to induce regiochemical control by changing the substitution pattern or using the enol silyl ether as in the previous study.[5]



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[1] Taken in part from the M.S. Theses of C. A. Shook, 1993, and J. A. Jamison, 1994, and the Ph.D. Thesis of H. Liu, 1997, University of Pittsburgh.

[2] Andrew Mellon Predoctoral Fellow (1996−1997).

[3] Deceased February 13, 1993.

[4] Wender, P. A.; Takahashi, H.; Witulski, B. *J. Am. Chem. Soc.* **1995**, *117*, 4720−4721 and citations therein.

[5] Shook, C. A.; Romberger, M. L.; Jung, S.-H.; Xiao, M.; Sherbine, J.; Zhang, B.; Lin, F.-T.; Cohen, T. *J. Am. Chem. Soc.* **1993**, *115*, 10754−10773. Davidson, E. R.; Gajewski, J. J.; Shook, C. A.; Cohen, T. *J. Am. Chem. Soc.* **1995**, *117*, 8495−8501.

[6] Griller, D.; Ingold, K. U. *Acc. Chem. Res.* **1980**, *13*, 317−323.

[7] During the course of this investigation, two studies on the cyclopropylcarbinyl ring opening of TMM diradicals were published. Adam, W.; Finzel, R. *J. Am. Chem. Soc.* **1992**, *114*, 4563−4568. Paul, G. C.; Gajewski, J. *J. Org. Chem.* **1996**, *61*, 1399−1404.

[8] Cohen, T.; Bhupathy, M. *Acc. Chem. Res.* **1989**, *22*, 152−161. LDBB is 4,4′-di-*tert*-butylbiphenylide.[9]

[9] Freeman, P. K.; Hutchinson, L. L. *J. Org. Chem.* **1980**, *45*, 1924−1930; **1983**, *48*, 4705−4713.

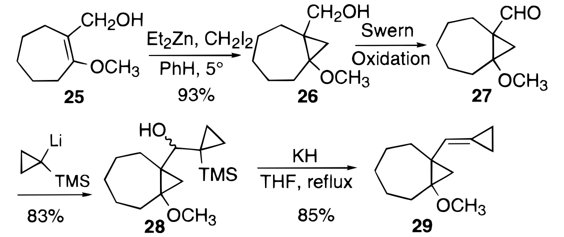
[10] New compounds were characterized by IR and NMR spectroscopy and provided satisfactory exact mass analyses.

[11] Fieser, L. F.; Fieser, M. *Steroids*; Reinhold: New York, 1959; pp 15−24.

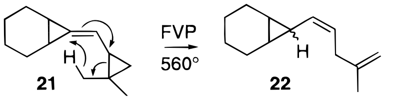
[12] Brook, A. G. *Acc. Chem. Res.* **1974**, *7*, 77−84.

S0002-7863(97)03232-0 CCC: $15.00

Scheme 5

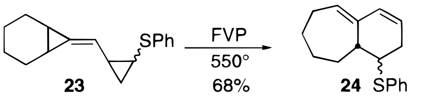


One limitation of this rearrangement was discovered when **21** was pyrolyzed. Although the major product could not be separated from minor impurities, it is clear from prominent peaks in its ^{1}H NMR spectrum that it is diene **22**, derived from a [1,5]-sigmatropic hydrogen shift from a methyl group oriented cis to the vinyl group, rather that a fused bicyclic system (eq 2). Such intramolecular retroene reactions are known to be of particularly low activation energy.[13] A similar result was observed starting with the trans monomethyl cyclopropane; presumably a facile trans–cis isomerization[14] occurred resulting in the cis isomer which can undergo the [1,5]-hydrogen shift.



(2)

This limitation on the otherwise synthetically useful rearrangement should apply only to substituents at the 2-position of the saturated cyclopropane ring which possesses a transferable hydrogen. Thus, **23** (1:1 mixture of cis/trans isomers) was subjected to standard FVP conditions at 550 °C to provide a 1:1 mixture of endo/exo dienes **24** in 68% yield (eq 3).

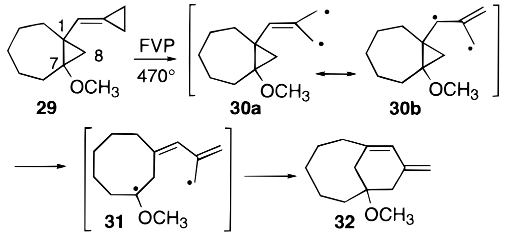


(3)

Even substituents at the 2-position which do possess a hydrogen atom may not interfere with the rearrangement provided the substituent is a part of a ring that is fused to the saturated cyclopropane and the alkylidenecyclopropane is attached at the bridgehead of this bicyclic system. In this case, the vinyl and alkyl substituents must be trans disposed on the saturated cyclopropane and trans–cis isomerization is precluded by the fused ring junction. As an example of such a system, we chose **29**, and its preparation from **25**[15] is shown in Scheme 5.

If ring expansion of **29** proceeded as hoped, this concept would lead to a completely novel entry to bicyclo[*n*.3.1] bridged systems of the type found as the key structural feature of interesting natural products. As seen in Scheme 6, the TMM diradical **30**, generated via homolysis of the allylic cyclopropane bond in **29**, could lead to the diradical **31**, resulting in the bridged bicyclic compound **32**.[16] In the event, subjecting **29** to flash vacuum pyrolysis at 470 °C led to a mixture from which **32** was isolated in 38% yield. The structure was confirmed by two-dimensional NMR spectroscopy. Compound **32** bears some of the structural features of the taxol AB ring system,[20] such as the bridgehead alkene, the central B ring which is difficult to form because of entropic and enthalpic factors associated with medium-sized rings, an appropriately placed oxygen function, and a methylene group that could be used as a handle for further manipulation.

Scheme 6



In summary, the cyclopropylalkylidenecyclopropane thermal double ring expansion allows for the flexible and efficient synthesis of a variety of fused and bridged bicyclic six-membered rings. For the most part, the yields range from fair to excellent. The less satisfactory yield in the conversion **29** → **32** must be weighed against the exceedingly concise approach to a complex ring system bearing some key structural features of important natural products, including the taxanes. The results warrant exploitation of this method in greater depth. Literature knowledge of the interaction of transition metal complexes with alkylidenecyclopropanes[21] and metal–mediated cleavage of cyclopropanes[4] makes it appear likely that the same ring expansion can be executed with transition metal catalysts under milder conditions.

Acknowledgment. This paper is dedicated to the memory of Paul Dowd, a pioneer in TMM and much other chemistry. We are grateful to the National Institutes of Health for financial support, Dr. F.-T. Lin for recording the 2-D NMR spectra, and Professor Raymond L. Funk of Pennsylvania State University for insightful suggestions that played an important role in stimulating this work.

Supporting Information Available: Experimental procedures and details of compound characterization, including 1D and 2D NMR spectra of **32** (27 pages). See any current masthead page for ordering and Internet access instructions.

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[13] Hudlicky, T.; Reed, J. W. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 5, pp 899–970.

[14] Roth, W. R.; König, J. *Justus Liebigs Ann. Chem.* **1965**, *688*, 28–39. Ellis, R. J.; Frey, H. M. *J. Chem. Soc.* **1964**, 5578–5583.

[15] Compound **25** was prepared in 66% yield (see the Supporting Information) from the methyl acetal of cycloheptanone by a modification of a literature method involving the Vilsmeier reaction followed by Red-Al reduction of the resulting aldehyde. Pellet, M.; Huet, F. *Tetrahedron* **1988**, *44*, 4463–4468.

[16] The alternative exo mode of cleavage of the cyclopropane ring in **30** could lead to a primary radical which would cyclize to a nonbridged bicyclic system. While there is no evidence for this mode of cleavage for **29**, preliminary experiments (unpublished work of H. Liu and M. Thiruvazhi) on the pyrolysis of the analogue of **29** lacking the methoxy group gave a mixture of products, the ^{1}H NMR spectrum of which suggested that both modes of cleavage had occurred. The regioselectivity of the ring opening of cyclopropylcarbinyl radicals is not reflective solely of radical stabilities and apparent C–C bond strengths,[17] and the literature contains numerous examples that cyclopropylcarbinyl radical ring-opening reactions are subject to stereoelectronic control which requires a maximum overlap between the SOMO and the bond to be ruptured.[18] Examination of a molecular model of the TMM diradical expected from pyrolysis of the desmethoxy substrate indicates that breaking the C1–C8 bond is somewhat favored as the stereoelectronic effect comes into play, even though a less-stable primary radical results. These preliminary experiments led us to attempt the pyrolysis of **29**, in which the transition state for endo opening should be favored by the additional stabilization of radical **31** due to its tertiary nature and the overlap of its SOMO with the nonbonding oxygen orbital. It is known that the kinetic acceleration caused by a methoxy group on a cyclopropylcarbinyl radical ring opening is somewhat greater than an order of magnitude.[19]

[17] (a) Martinez, F. N.; Schlegel, H. B.; Newcomb, M. *J. Org. Chem.* **1996**, *61*, 8547–8550. (b) Mariano, P. S.; Bay, E. *J. Org. Chem.* **1980**, *45*, 1763–1769. Bowry, V. W.; Lusztyk, J.; Ingold, K. U. *J. Am. Chem. Soc.* **1991**, *113*, 5687–5698.

[18] For examples, see: Destabel, C.; Kilburn, J. D.; Knight, J. *Tetrahedron Lett.* **1993**, *34*, 3151–3154. Beckwith, A. L. J.; Phillipou, G. *Aust. J. Chem.* **1976**, *29*, 123–131. Dauben, W. G.; Wolf, R. E. *J. Org. Chem.* **1970**, *35*, 374–379.

[19] Newcomb, M.; Chestney, D. L. *J. Am. Chem. Soc.* **1994**, *116*, 9753–9754 and citations therein. However, in this case the methoxy group was trans to the group bearing the odd electron.

[20] Nicolaou, K. C.; Dai, W.-M.; Guy, R. K. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 15–44.

[21] For an excellent review, see: Binger, P.; Büch, H. M. *Topics Curr. Chem.* **1987**, *135*, 77–149. For recent work, see: Corlay, H.; Motherwell, W. B.; Pennell, A. M. K.; Shipman, M.; Slawin, A. M. Z.; Williams, D. J. *Tetrahedron* **1996**, *52*, 4883–4902.