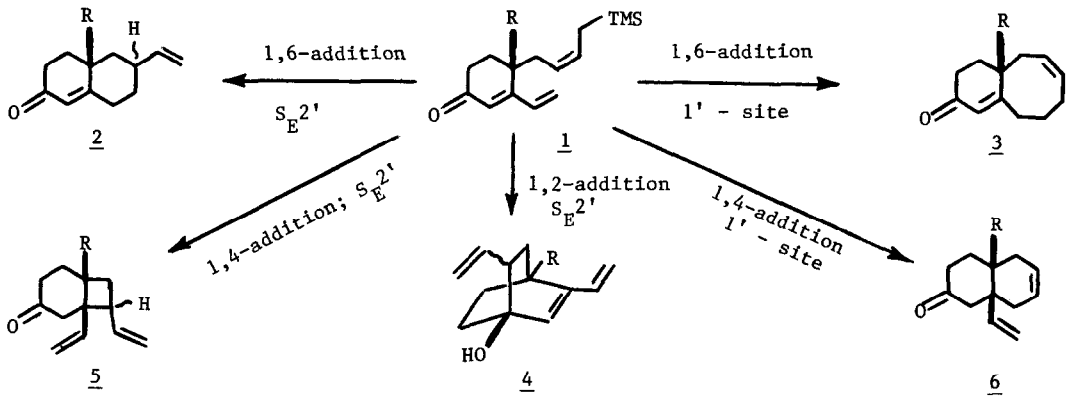
Tetrahedron Letters,Vol.26,No.23,pp 2751-2754,1985 0040-4039/85 $3.00 + .00
Printed in Great Britain

A NEW APPROACH FOR THE FORMATION OF FUSED CYCLOOCTANE OR CYCLOHEXANE RINGS

George Majetich*, Ken Hull, and Richard Desmond
University of Georgia, Athens, Georgia 30602

SUMMARY: The intramolecular regioselective addition of unsymmetrical allylsilanes to conjugated dienones is shown to permit facile entry into 5-6, 6-6, 5-8, and 6-8 bicyclic ring systems.[1]

In the preceding Letter we reported that the reaction catalyst directly influence regioselectivity in the intramolecular addition of allylsilanes to conjugated dienones.[2] In this communication we disclose a similiar effect of reaction catalyst upon systems which contain several potential nucleophilic sites, in addition to multiple electrophilic centers. We found that this approach to ring formation is useful for the construction of bicyclic systems possessing either a six- or an eight-membered ring.[3]



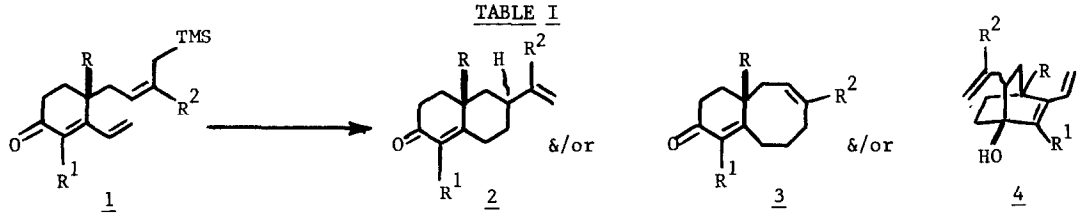
Of the five possible modes of cyclization shown above, we expected that under Lewis acid-catalysis only the 6,6-bicyclic enone **2** would be formed due to the propensity of the intramolecular Sakurai reaction to undergo 1,6-addition with conjugated dienones.[2] This was verified when only enone **2a** was produced in 77% yield after trienone **1a** was treated with ethylaluminum dichloride.[4,5]

The outcome of the fluoride-induced cyclization , however, was more difficult to predict. A basic axiom of ring closure reactions holds that formation of three-, five-, six-, and seven-membered rings is favored over the formation of four-, eight-, nine-, and ten-membered rings;[6] thus, normal kinetic preferences dictated that octalones **2** or **6** should predominate. Alternatively, related studies from our laboratories[7] suggest that the fluoride-induced additions proceed via an S_E2' mechanism.[8] These factors imply that enone **2** (the Lewis acid-catalyzed product) should also be generated by the fluoride-initiated

procedure. 1,4-Conjugate addition of the ambident allylic nucleophile could generate ketones **5** and **6**; however, their formation was not expected because of the hindered steric environment at the β-position of the dienone unit. The formation of 6,8-bicyclic enone **3** was not anticipated due to kinetic arguments.[6] Remarkably, treatment of trienone **1a** with a stoichiometric amount of fluoride ion produced the fused cyclooctane **3a** in 35% yield, together with a 32% yield of the intramolecular 1,2-adduct **4a**.[9]

Several derivatives of **1** were examined to determine the generality of these cyclizations (Tables I and II). Three comments summarize our results. First, the Lewis acid-catalyzed procedure produced the expected fused cyclohexane ring compounds in good yields. More significantly, in all cases, only a single isomer of the olefinic side-chain was obtained; such diastereoselection has considerable synthetic potential.[10] Second, the fluoride-induced additions predominately favored the formation of the eight-membered ring products, albeit in modest yields.[4b] Preliminary results indicate that a Z geometry of the allylsilane moiety is an important feature. When substrates consisting of mixtures of Z and E isomers were cyclized, lower yields of the eight-membered ring product, together with small amounts (5→10% yield) of protodesilylation products were obtained; no protodesilylation products were observed when pure Z allylsilanes were studied.[11] Finally, the cyclohexadienone series produced 1,2-adducts (i.e., **4a** and **4b**) as by-products, unlike the cyclopentadienone series which afforded side-products resulting from 1,4-addition via the primary center of the allylic nucleophile (i.e., **9a** and **9b**).[13]

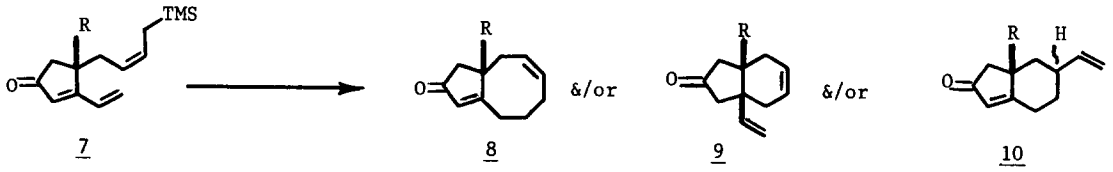
TABLE I



	R	R^1	R^2	CATALYST			
a)	CH_3	H	H	$F^{\ominus}$	0%	35%	32%
				$EtAlCl_2$	77%	0%	0%
b)	H	H	H	$F^{\ominus}$	0%	12%	22%
				$EtAlCl_2$	68%	0%	0%
c)	CH_3	H	H*	$F^{\ominus}$	0%	22%**	32%**
				$EtAlCl_2$	75%	0%	0%
d)	CH_3	CH_3	H	$F^{\ominus}$	0%	65%	34%
				$EtAlCl_2$	80%	0%	0%
e)	CH_3	H	CH_3	$F^{\ominus}$	0%	42%**	12%**
				$EtAlCl_2$	70%	0%	0%

* mixture of Z and E isomers; @ 4:1
** 5→10% protodesilylation observed

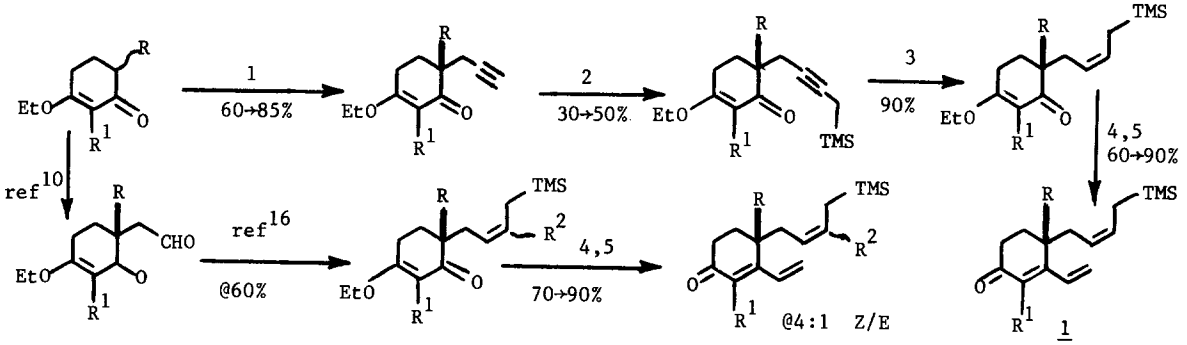
TABLE II



7 8 9 10

	R	CATALYST			
a)	CH_3	$F^{\ominus}$	33%	23%	0%
		$EtAlCl_2$	0%	0%	60%
b)	H	$F^{\ominus}$	28%	16%	0%
		$EtAlCl_2$	0%	0%	41%

Synthetic routes to the substrates having a Z allylsilane moiety use the following sequence: 1) alkylation of the kinetic enolate of the appropriately methylated 3-ethoxy-2-cyclohexenone (or cyclopentenone) derivative[14] with propargyl bromide; 2) selective generation of the lithium salt of the alkyne, followed by alkylation with trimethylsilylmethyl triflate;[15] 3) reduction using H_2 and Pd on barium sulfate; 4) addition of vinyllithium; and 5) acid-catalyzed hydrolysis. The preparation of substrates **1c** and **1d** utilized Seyferth's methodolgy to make allylsilanes using trimethylsilyl-substituted phosphoranes.[16] In both cases, the Z isomer predominated in approximately a 4:1 ratio.

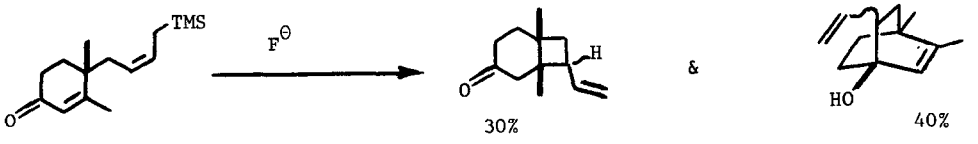


In conclusion, we have developed two and useful pathways for ring formation. Fused cyclooctane rings may be prepared via fluoride-induced addition of unsymmetrical allylsilanes to conjugated dienones. Alternatively, fused cyclohexane rings may be generated from the same intermediate by an intramolecular Sakurai reaction. In addition, this latter process proceeds with remarkable diastereoselection.

Acknowledgements: Special thanks are extended to Mr. Thomas Shawe for technical assistance in the early stages of this work. This research was supported by a grant from the University of Georgia Research Foundation, Inc.

REFERENCES:

1. This work was presented in part at the 188th National Meeting of the American Chemical Society in Philadelphia, Pa., August 1984; Abstract No. ORGN 140 and the 36th Southeastern Regional Meeting of the American Chemical Society at Raleigh, N.C., October 1984; Abstract No. ORGN 420.
2. Majetich, G.; Defauw, J.; Desmond, R. preceding Letter.
3. Growing interest in cyclooctane-containing natural products has generated numerous new ways to prepare this medium-size ring: Anionic oxy-Cope Rearrangements: a) Gadwood, R. C.; Lett, R. M.; Wissinger, J. E. J. Am. Chem. Soc., **1984**, 106, 3869; b) Gadwood, R. C.; Lett, R. M. J. Org. Chem., **1982**, 47, 2268; c) Paquette, L. A.; Andres, D. R.; Springer, J. P. J. Org. Chem., **1983**, 48, 1147; d) Uma, R.; Swaminathan, S.; Rajagopalan, K. Tetrahedron Lett., **1984**, 25, 5825; Claisen Rearrangement: e) Kinney, W. A.; Coghlan, M. J.; Paquette, L. A. J. Am. Chem. Soc., **1984**, 106, 6868; Intramolecular Diels Alder Reaction: f) Shea, K. J.; Davis, P. D. Angew. Chem. Int. Ed. Engl., **1983**, 22, 419; g) Brown, P. A.; Jenkins, P. R.; Fawcett, J; Russell, D. R. J. Chem. Soc., Chem. Commun., **1984**, 253; h) Sakan, K.; Craven, B. M. J. Am. Chem. Soc., **1984**, 105, 3732; i) Sakan, K.; Smith, D. A. Tetrahedron Lett., **1984**, 25, 2081; Other Approaches: j) Trost, B. M.; Fray, M. J. Tetrahedron Lett., **1984**, 25, 4605; k) Swindell, C. S.; deSolms, S. J. Tetrahedron Lett., **1984**, 25, 3797.
4. a) The spectroscopic data obtained for all new compounds were fully consistent with the assigned structures; b) Reaction conditions have not been optimized; c) All yields are isolated yields.
5. The experimental procedure employed for the Lewis acid-catalyzed cyclizations is described in reference 2.
6. For example, it is known that the formation of a six-membered ring is kinetically preferred over that of an eight-membered ring by a factor of about 10^4: Galli, C.; Illuminati, G.; Mandolini, L.; Tamborra, P. J. Am. Chem. Soc., **1977**, 99, 2591; b) Illuminati, G.; Mandolini, L.; Masci, B. J. Am. Chem. Soc., **1975**, 97, 4960.
7. A relevant example of cyclization products which can only be accounted for via an S_E2' mechanism is shown below. (Unpublished results of Mr. Richard Desmond) For additional examples see the subsequent manuscript.



8. Sleezer, B.; Winstein, R.; Young, J. J. Am. Chem. Soc., **1963**, 85, 1980.
9. The experimental procedure employed for the fluoride-induced cyclizations is described in Majetich, G.; Desmond, R.; Casares, A. M. Tetrahedron Lett., **1983**, 24, 1913
10. We have exploited this selectivity in stereoselective synthesis of (±) nootkatone and (±) valencene; a manuscript is in press.
11. On several occassion we have observed that allylsilanes possessing an E geometry readily undergo desilylation upon attempted purification.
12. Several mechanistic explanations can account for the formation of the eight-membered ring: a) direct 1,6-conjugate addition via the primary center of the allylic nucleophile; b) 1,4-conjugate addition via an S_E2' process giving rise to a 1,2-divinylcyclobutane product, such as 5, which readily undergoes a 3,3-sigmatropic rearrangement,[13] followed by olefin isomerization to produce the observed enone; or c) a concerted[3,5] sigmatropic rearrangement involving only one of the epimers of the 1,2-adduct 4. As yet we lack sufficient evidence to determine which mechanistic pathway is involved.
13. Rhoads, S. J.; Raulins, N. R. Organic Reactions, **1975**, 22, 1.
14. Stork, G.; Danheiser, R. L. J. Org. Chem., **1973**, 38, 1775.
15. Chiu, S. K.; Peterson, P. E. Tetrahedron Lett., **1980**, 4047.
16. Seyferth, D.; Wursthorn, K. R.; Mammarella, R. E. J. Org. Chem., **1977**, 42, 3104.

(Received in USA 15 January 1985)