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REGIOSELECTIVITY IN INTRAMOLECULAR ADDITION OF ALLYLSILANES TO CONJUGATED DIENONES

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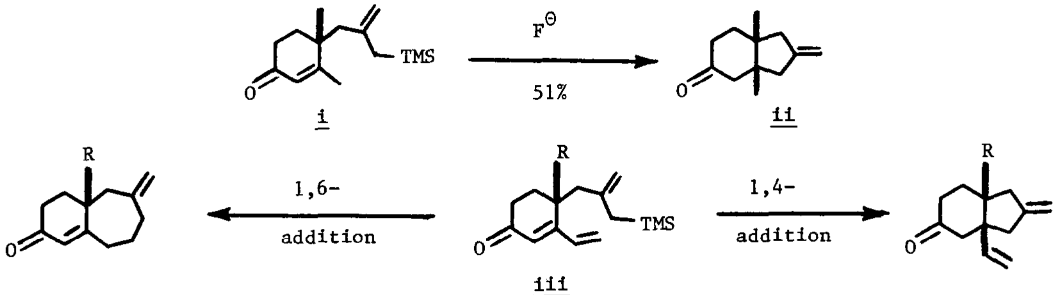
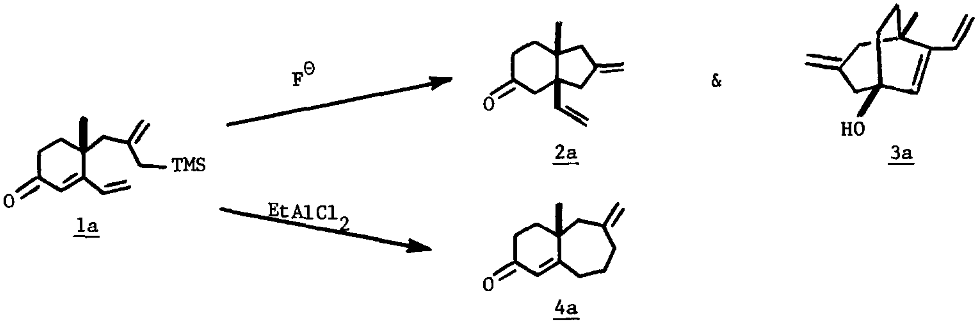
SUMMARY: The intramolecular addition of allylsilanes to conjugated dienones shows a divergence of regioselectivity as a function of reagent and substrate structure. The creation of 5-5, 6-5, 5-7, and 6-7 bicyclic ring systems is reported.[1]

The construction of carbocyclic rings is a fundamental process in organic chemistry. There has been considerable interest in ring-forming processes via the intramolecular Michael addition of stabilized[2] and unstabilized nucleophiles.[3] Previously we reported that the allylic nucleophile generated by treating an allylsilane with fluoride ion undergoes facile intramolecular conjugate addition to various Michael acceptors, generating cyclic systems i→ii).[4,5] In this communication we disclose the results of a study of the regiospecificity in intramolecular additions to enones containing a second conjugated double bond, e.g. iii. These early results show that this unprecedented method can be used for the efficient construction of seven-membered rings as well as the common ring sizes.



i ii iii

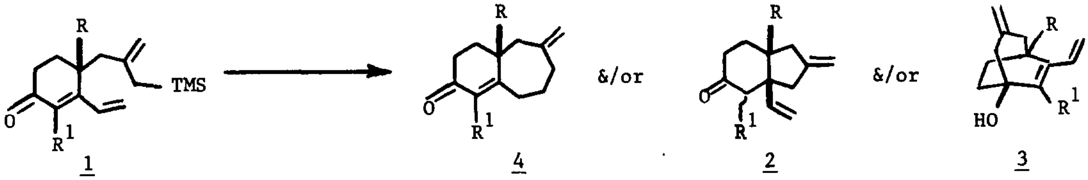
In the intramolecular additions to enone i, the allylic nucleophilic species can add either to the carbonyl (1,2) or to the conjugated olefin (1,4). Dienones such as iii have an additional option, 1,6-conjugate addition. In intermolecular reactions which also offer this alternative, Munch-Petersen and co-workers have shown that copper-catalyzed addition of Grignard reagents occurs at the terminal carbon atom of the conjugated system;[6] Marshall et al have reported that 1,4-conjugate addition of organocuprate reagents is favored when the competing electrophilic centers are in roughly equivalent steric environments.[7] Allylsilanes, as we showed earlier,[8] exclusively afford the 1,4-adduct in such intermolecular condensations with polyethylenic esters and nitriles. We now report that treatment of dienone 1a with fluoride ion produced hydrindanone 2a in 45% yield, accompanied by a 5% yield of alcohol 3a.[9,10]



The regiospecific γ-substitution of allylsilanes with carbon electrophiles has been rigorously established.[11] It was anticipated that reaction of **1a** under Lewis acid catalysis would generate a cycloheptane ring owing to the differences in the steric environments of the competing electrophic centers. Indeed the intramolecular Sakurai reaction[12] produces the 6,7 fused bicyclic enone **4a** in 55% yield, uncontaminate by other products.[13]

The efficacy of these catalyst-dependent ring closures prompted us to examine a series of substituted 3-vinylcyclohexenones and the analogous cyclopentenones; representative results are shown in Tables I and II.[14]

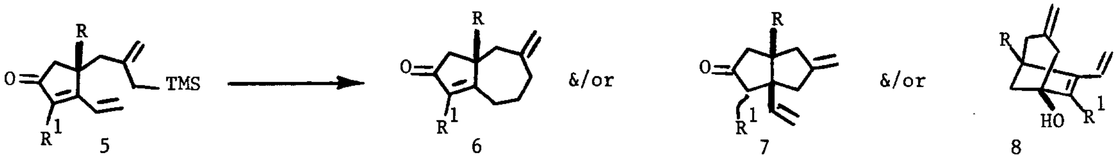
TABLE I



	R	R¹	CATALYST	4	2	3
a)	CH_3	H	F⊖	0%	45%	5%
			$EtAlCl_2$	55%	0%	0%
b)	H	H	F⊖	20%	11%	0%
			$EtAlCl_2$	49%	0%	0%
c)	CH_3	CH_3	F⊖	0%	54%	24%
			$EtAlCl_2$	90%	0%	0%
d)	H	CH_3	F⊖	72%	0%	0%
			$EtAlCl_2$	70%	0%	0%

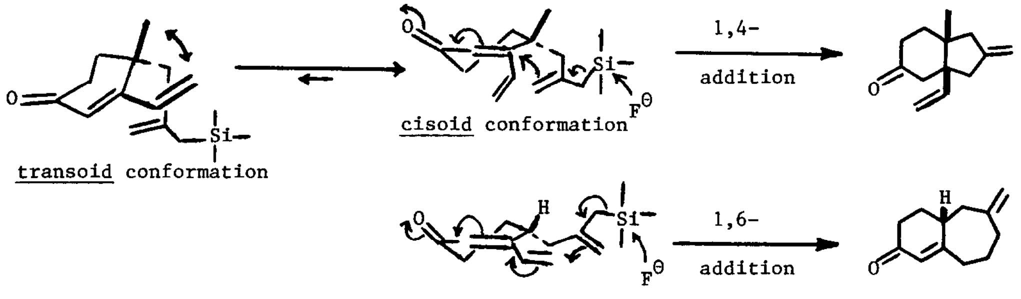
Some useful observations were made on the basis of these results. First, the intramolecular Sakurai condensation gave exclusively 1,6-conjugate addition to produce seven-membered rings in good yield. Second, the fluoride-induced cyclizations reveal a pronounced substrate-dependency; γ-substitution governed whether 1,4-or 1,6-conjugate addition predominated, e.g. **1c** and **1d**. Third, the fluoride-catalyzed additions of 3-vinylcyclopentenones produce significant quantities of 1,2 adducts, via kinetic control,[15] unlike the 3-vinylcyclohexenone systems. Fourth, the cyclizations of the simpliest cases, 1b and 5b, proved troublesome. Finally, no uncyclized side-products resulting from desilylation were observed.

TABLE II



R	R^1	CATALYST	6	7	8
a) CH_3	H	$F^{\ominus}$	0%	28%	33%
		$EtAlCl_2$	70%	0%	0%
b) H	H	$F^{\ominus}$	2%	2%	0%
		$EtAlCl_2$	46%	0%	0%
c) CH_3	CH_3	$F^{\ominus}$	0%	0%	96%
		$EtAlCl_2$	57%	0%	0%
d) H	CH_3	$F^{\ominus}$	25%	0%	23%
		$EtAlCl_2$	65%	0%	0%

We believe that substrate-dependency observed in the fluoride ion-catalyzed cyclizations is the consequence of an interplay of conformational and/or steric hindrance effects. Examination of Dreiding stereomodels suggest that non-bonded steric interactions between a C(4) substituent and the C(3) vinyl group forces the dienone moiety to assume a *cisoid* conformation, which preclude 1,6-nucleophilic attack (shown below). In contrast, the absence of a C(4) substituent allows the more stable *transoid* conformer to predominate, facilitating the intrinsically preferred 1,6 addition.



This study demonstrates that the choice of reaction catalyst directly influences the regioselectivity in the intramolecular addition of allylsilanes to conjugated dienones. We are exploiting the efficient construction of functionalized 6,7 skeletal systems in syntheses of perforenone-A (iv)[16a] and widdrol (v)[16b]. The utility of the fluoride ion-catalyzed process will be demonstrated with other synthetic objectives.

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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 at the 36th Southeastern Regional Meeting of the American Chemical Society at Raleigh, N.C., October, 1984; Abstract No. ORGN 420.
2. Stork, G.; Winkle, J. D.; Saccomano, N. A. Tetrahedron Lett., **1983**, 4934 and references cited therein.
3. For leading references see: a) Cooke, M. P., Jr. Tetrahedron Lett., **1979**, 2199; b) Cooke, M. P., Jr. J. Org. Chem., **1984**, 49, 1146.
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5. A comprehensive study of the fluoride-induced cyclization of a series of substituted cyclohexenones and cyclopentenones has been carried out: MS thesis, Richard Desmond, University of Georgia, **1984**.
6. a) Munch-Petersen, J. Bull. Soc. Chim. France, **1966**, 471; b) Bretting, C.; Munch-Petersen, J.; Jorgensen, P. M.; Refin, S. Acta Chem. Scand., **1960**, 14, 151; c) Munch-Petersen, J. Acta Chem. Scand., **1963**, 17, 2423; e) Daviaud, G.; Miginiac, P. Tetrahedron Lett., **1973**, 3348.
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8. Majetich, G.; Casares, A. M.; Chapman, D.; Behnke, M. Tetrahedron Lett., **1983**, 24, 1909.
9. a) The spectroscopic data obtained for all new compounds were fully consistent with the assigned structures; b) Reaction conditions have not been optimized. All yields are isolated yields.
10. The experimental procedure employed for the fluoride-induced cyclizations is described in references 4 & 8.
11. For a comprehensive review of allylsilanes in organic synthesis see Sakurai, H. Pure Appl. Chem., **1982**, 54, 1.
12. The intramolecular extension of the Sakurai reaction (Hosomi, A.; Sakurai, H. J. Am. Chem. Soc., **1977**, 99, 1673) has only recently received attention. For examples see a) Schinzer, D. Angew Chem. Int. Ed. Eng., **1984**, 23, 308; b) Wilson, S. R.; Price, M. F. J. Am. Chem. Soc., **1982**, 104, 1124.
13. The following experimental procedure is typical: To 41 mg (0.155 nmol) of dienone 1d in 1.5 mL of dry toluene at 0°C was added dropwise 0.107 mL (0.155 nmol) of a solution of 25% ethylaluminum dichloride in toluene (Alfa). The reaction mixture was stirred at 0°C for 30 min. The reaction mixture was diluted with reagent grade ether, washed with brine, dried over $MgSO_4$, filtered and concentrated. The crude residue was chromatographed to provide 21 mg (70%) of enone 2d.
14. The requisite enones 1a→d and 5a→d were conveniently prepared by the following sequence: a) alkylation of the kinetic enolate of the appropriate methylated 3-ethoxy-2-cyclohexenone (or cyclopentenone) derivative with 2-(trimethylsilyl)methallyl iodide [prepared from 2-(hydroxymethyl)-allyltrimethylsilane; Trost, B.; Chan, D. M. T. Org. Synth. **1984**, 62, 58]; b) addition of vinyllithium; and c) acid-catalyzed hydroylsis.
15. We have demonstrated that products **6**,**7**, and **8** are formed under kinetic control as all attempts to interconverta these products by either oxy-cope (**8**→**7**) or enolate cope (**7**→**8**) pathways failed.
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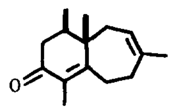
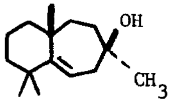
Perforenone-A (iv)





Widdrol (v)

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