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Activation of the Ketone of 5-Cyclodecenones towards Thermal Transannular Cyclization to Give *trans*-Hydroazulenols

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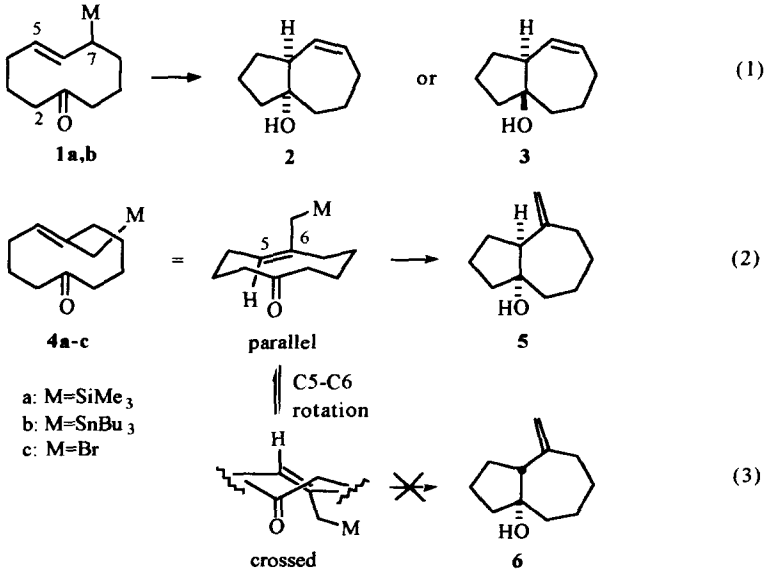
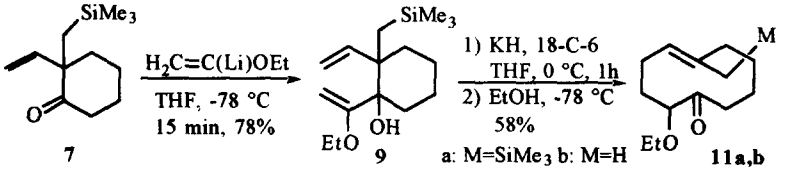
Abstract: The cyclization of 5-cyclodecenones substituted at C2 with an alkoxy group was examined. The alkoxy group sufficiently activates the ketone to allow for transannular cyclization upon heating, leading to trans fused hydroazulenols. In the cyclization of the 6-(trimethysilyl)methyl substituted 5-cyclodecenone, the TMS of the allylsilane is retained in the product, leading to a vinylsilane product. Both the thermal and acid-induced cyclizations lead to products with a trans relationship between the oxygen substituents. © 1997 Elsevier Science Ltd.

In the course of examining the transannular cyclizations of 5-cyclodecenones, we have found that the regio- and stereochemistry of the reaction can be controlled by substituents on the ring and by the choice of reaction conditions.[1-5] For example, fluoride-induced cyclization of 5-cyclodecenones **1a** and **4a** gave the cis fused hydroazulenols **2** and **5**, respectively.[1] The stereochemistry of these cyclizations is the result of cyclization from a "parallel" conformation, i.e. a conformer in which the C1-C10 and C5-C6 bonds are parallel to each other.[4,6] Our strategy for preparing the trans fused analogs depended on forcing a substrate to cyclize through a "crossed" conformation via an intramolecular Prins reaction(equation 3). Although we were unable to cyclize thermally the allylsilane **1a**, we found that the thermally more reactive allylstannane **1b** cyclized in refluxing benzene to give exclusively the trans fused hydroazulenol **3** with the endocyclic double bond.[2] However, our initial attempts at preparing the exocyclic analog **6** were unsuccessful. Heating allylsilane **4a** above 100 °C either in CCl_4 or neat led to a myriad of products, and our attempt to prepare the allylstannane



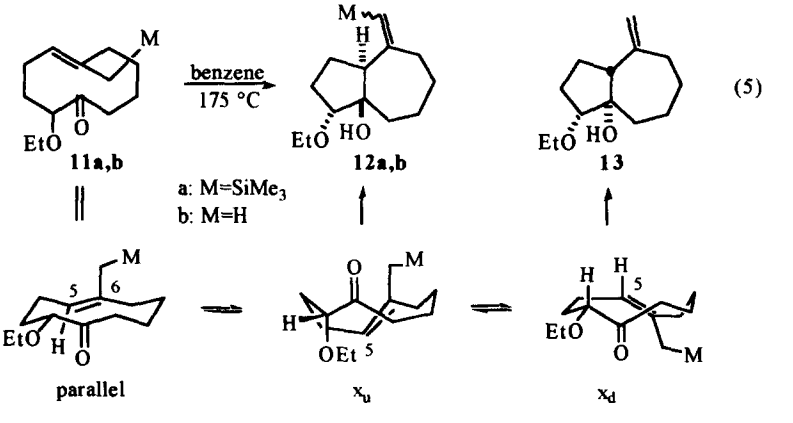
4b from allylsilane **4a**[7] led directly to the cis fused product **5**. For the purpose of generating the trans fused hydroazulene **6** with the exocyclic double, it appeared that the allylstannane was too reactive and the allylsilane not reactive enough for thermal cyclization.

Given our interest in derivatives of **6** as models for mimicking the tumor-promoting activity of the phorbol esters, it occurred to us that the reactivity of the other functional group participating in a thermal cyclization, the ketone, might be increased by introducing an electron-withdrawing substituent alpha to it. To this end we prepared cyclodecenone **11a**. Addition of freshly prepared ethoxyvinyllithium **8**[8] (3 equiv.) to the known cyclohexanone **7**[1] (THF, -78 °C) led to the divinylcyclohexanol **9**. The work-up in this reaction is crucial in order to avoid formation of significant amounts of the ketone (**10**) from hydration of the enol ether.[9] Anionic oxy-Cope rearrangement of divinylcyclohexanol **9** (excess KH, 1 equiv. 18-C-6, THF, 0 °C, 1 h) cleanly gave 5-cyclodecenone **11a**.



(4)

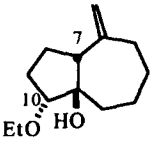
Upon heating as a dilute solution in benzene in a sealed vial at 175 °C (oil bath temperature), 5-cyclodecenone **11a** cyclized to give the trans fused hydroazulenol **12a** (52%, 65% based on recovered starting material). Heating at higher temperatures, e.g. 200 °C, led to dehydration of this product. The product **12a** is remarkable in two respects: only the trans,trans diastereomer was isolated, and the TMS group was retained in the product.[10] Cyclodecenone **11b** from desilylation in the oxy-Cope rearrangement of divinylcyclohexanol **9**[11] also cyclized under similar conditions to give hydroazulenol **12b** and a trace amount of what we believe is the other trans fused diastereomer **13** (68 % total yield, 85% based on recovered starting material). In comparing the cylizations of cyclodecenones **11a** and **11b**, the TMS substituent appears to retard slightly the thermal cyclization, but it also made the reaction more stereoselective. From the stereochemistry of the products, it can be inferred that the thermal cyclization of hydroazulenols **11a,b** took place from the crossed conformation (x_u) that orients the alkoxy substituent anti to the keto oxygen.



(5)

Although we were primarily interested in the thermal cyclization of **11a**, we also examined its cyclization under a variety of other conditions, which are listed in Table 1. The product ratios are kinetic results, i.e. resubjecting each product to the reaction conditions led to its recovery. Fluoride ion led to a mixture of both cis fused hydroazulenols (entry 1), while acids gave mixtures of both cis and trans ring fusion products (entries 2-5). Only the reaction with CF_3CO_2H showed significant selectivity, albeit not as selective as the thermal cyclization. Like the thermal cyclizations of **11a,b**, the acid-induced cyclizations gave only products with a trans relationship between the oxygen substituents, implying that there was no significant chelation effect in the Lewis-acid induced cyclizations.

Table 1. Cyclizations of Cyclodecenone 11a



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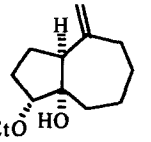

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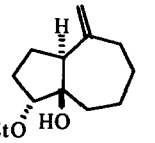

12b

entry	Reaction conditions	T (°C)	time	Yield (%)[a]	ratio of **14:15:12b**
1	n-Bu_4NF/THF	25	1 h	89	2 : 1 : 0
2	CF_3CO_2H/THF	25	5 h	91	1 : 0 : 5
3	$BF_3{\cdot}Et_2O/CH_2Cl_2$	-78	5 min	56	2.5 : 0 : 1
4	$MgBr_2/CH_2Cl_2/Et_2O$	-78	10 min	59	1 : 0 : 3
5	$SnCl_4$/THF	-78	2 h	86	1 : 0 : 2.5

[a]Yields refer to isolated and chromatographically pure products.

The relative stereochemistry of the hydroazulenols was assigned based on the expected differences in chemical shifts for the ^1H NMR spectra taken in $CDCl_3$ versus pyridine-d_5[12] (see Table 2). Hydroazulenols assigned the cis ring fusion had chemical shifts for the bridgehead hydrogen at C7 downfield 0.22-0.33 ppm in pyridine-d_5 compared to the chemical shift for the same hydrogen in $CDCl_3$. A similar effect in the chemical shift for the hydrogen on C10 was used to assign the relative stereochemistry between the ethoxy and hydroxyl groups.

Table 2. Chemical Shifts of the Hydrogens on C7 and C10 in $CDCl_3$ and Pyridine-d_5

	12a		**14**		**15**		**12b**	
	H(C7)	H(C10)	H(C7)	H(C10)	H(C7)	H(C10)	H(C7)	H(C10)
∂ (ppm) in pyridine-d_5	2.96	3.74	2.88	3.82	2.84	3.28	2.85	3.73
∂ (ppm) in $CDCl_3$	2.88	3.57	2.56	3.55	2.62	3.29	2.78	3.57
$\Delta\partial$	0.08	0.17	0.32	0.27	0.22	-0.01	0.07	0.16

In conclusion, introduction of an ethoxy group at C2 of a 5-cyclodecenone has led to the first observed thermal cyclization of this ring system functionalized with an allylsilane, which takes place with retention of the silyl substituent in the product. It is clear that the ethoxy group, but not the silyl group, is important to this cyclization, as the reaction also works in the absence of the silyl group, but not without the alkoxy group. As we had hope, the thermal cyclization led exclusively to the trans ring fusion in the hydroazulene product. Because of an asymmetric center within the 5-cyclodecenone that is retained in the transannular cyclization,

there are two possible diastereomers that can be formed with the trans ring fusion, but the thermal reaction is selective for the diastereomer with the trans relationship between the two oxygen substituents. Acid-induced cyclizations of the allylsilane-containing 5-cyclodecenone also led to a trans relationship between the two oxygen substituents, but to mixtures of both possible ring fusions. In contrast, fluoride-induced cyclization of the allylsilane was selective for the cis ring fusion, albeit as a mixture of both possible diastereomers. In both the acid- and fluoride-induced cyclizations, the TMS group reacted as expected, i.e. with loss of the TMS group.

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7. Reaction of allylsilane **4a** with Br_2 (THF, 0 °C, 48%) led to a 2:1 mixture of **4c**, which was relatively unstable, and its even less stable isomer 5-bromo-6-methylenecyclodecanone. Reaction of **4c** with Bu_3SnLi (THF, 0 °C, 50-90%) gave the cis fused hydroazulenol **5**.
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9. After 1 h at -78 °C, the reaction was diluted with a volume of Et_2O (-78 °C) equal to 1.5 times the volume of THF used in the reaction. Water (1/10 volume of Et_2O) was added, the reaction was warmed to about -5 °C, and, as quickly as possible, washed several times with water, dried with $MgSO_4$, filtered, evaporated and purified by flash chromatography (30:1 hexane/EtOAc). Using this procedure, divinylcyclohexanol **9** was prepared reproducibly in gram quantities without contamination by α-hydroxyketone **10**.
10. Only one alkene isomer was obtained in this experiment, but NOE experiments designed to determine the stereochemistry of the vinylsilane were ambiguous.
11. If the oxy-Cope rearrangement is carried out at room temperature with an excess of 18-crown-6, then [3,3]-sigmatropic rearrangement is accompanied by homo-Brook rearrangement, leading to desilylated cyclodecenones.
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13. ^{13}C NMR (50.3 MHz) data for: **9** (C_6D_6): ∂ 165.4, 146.6, 113.7, 83.1, 76.6, 62.7, 46.4, 31.4, 29.4, 23.5, 21.7, 21.6, 14.5, 1.1; **10** ($CDCl_3$): ∂ 213.5, 144.0, 116.1, 81.9, 46.0, 29.4, 29.2, 28.9, 23.0, 20.9, 20.6, 0.9; **11a** (C_6D_6): ∂ 213.0, 137.8, 124.7, 84.1, 64.9, 40.5, 36.5, 33.6, 25.5, 23.8, 21.9, 21.7, 15.7, -0.9; **11b** ($CDCl_3$): ∂ 215.2, 135.9, 127.4, 83.6, 64.9, 40.3, 36.5, 32.8, 25.0, 22.6, 21.5, 16.2, 15.5; **12a** ($CDCl_3$): ∂ 157.3, 125.4, 88.1, 80.2, 65.3, 52.1, 36.7, 36.1, 29.7, 26.3, 25.4, 20.9, 15.5, 0.3; **12b** ($CDCl_3$): ∂ 147.9, 112.5, 87.8, 80.5, 65.3, 49.5, 36.8 (two peaks), 29.6, 26.1, 25.5, 20.7, 15.5; **14** ($CDCl_3$): ∂ 150.1, 112.6, 88.1, 81.9, 65.2, 54.8, 33.6, 30.3, 28.8, 27.0, 24.8, 20.7, 15.6; **15** ($CDCl_3$): ∂ 152.4, 110.3, 85.8, 79.7, 65.4, 55.8, 38.2, 37.8, 31.9, 28.5, 24.8, 23.2, 15.6.

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