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Unidirectional Thermal Electrocyclic Ring Forming Reactions of Methylenecyclobutenes from Vinylallenes in the Retinoid Series

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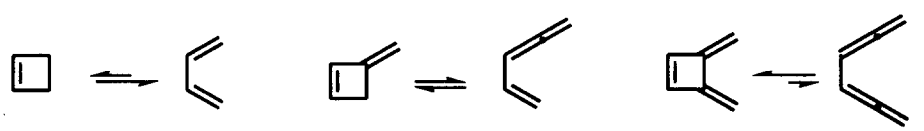
Abstract: A unidirectional, regiospecific formation of methylenecyclobutenes from substituted divinylallenes related to the 11,7-retroretinoids has been found at temperatures considerably lower than the parent system. Kinetic data are reported for the examples studied and an ab initio study is presented which favors a non-planar twist structure for the diene subunit undergoing cyclization.

Electrocyclic ring opening reactions of substituted cyclobutenes and ring closure reactions of butadienes (prototype processes **1--2**, **3--4**, **5--6**) are under intense scrutiny both from the theoretical and from the synthetic point of view.[1-5] In general, for the transformation **1--2**, the substituted 1,3-butadienes are highly thermodynamically favored to such an extent that the conrotatory ring opening of 3-substituted cyclobutenes[2], which shows a preference for outward rotation as the substituent becomes a more powerful electron donor, provided the experimental background to coin the term "torquoselectivity" by Houk and coworkers.[3]



1 **2** **3** **4** **5** **6**

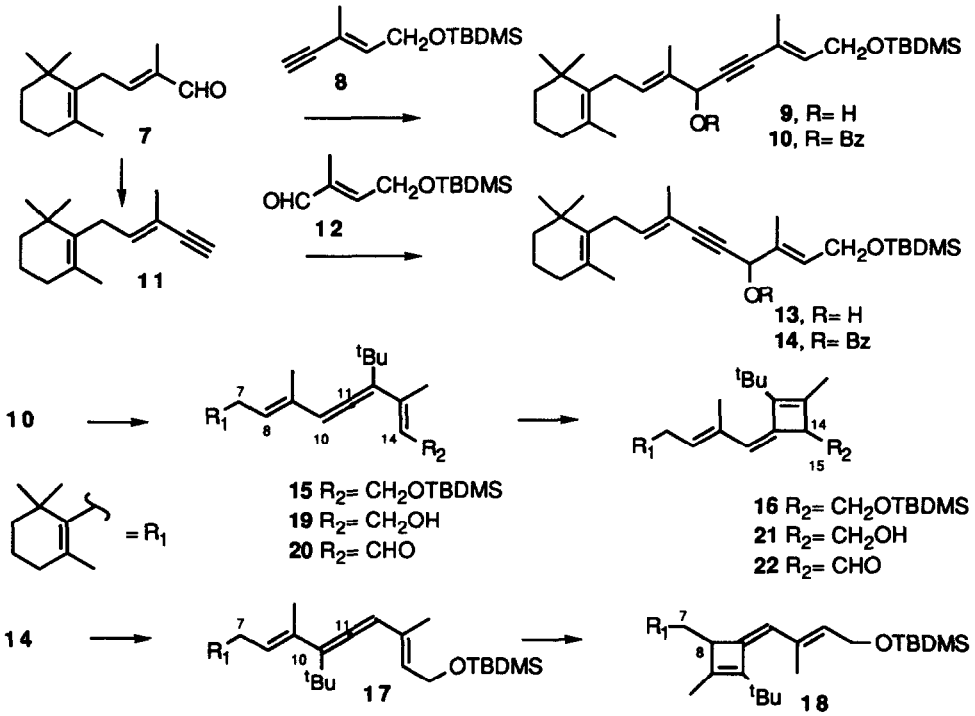
On the other hand, the electrocyclic ring closure of substituted bisallenes (transformation **6--5**) occurs in the gas phase at 300-350 °C to afford 3,4-alkylidenecyclobutenes, the latter being enthalpically favored despite their highly strained structure. Exhaustive theoretical and experimental contributions defined its conrotatory nature, with a modest selectivity of rotation governed by steric effects of substituents at the allene termini.[4]

For the interconversion **3-4**, in the parent system and in substituted cases, an equilibrium mixture (*ca.* 1:1) of both components was found.[5] The energy balance between the enthalpically favored methylenecyclobutene **3** and the entropically favored vinylallene **4** determined the dominant role played by the entropy on the position of the equilibrium at the temperatures at which these were measured (360-435 °C).

In our studies of the synthesis and biological properties of retroretinoids with vinylallene structure, we had the opportunity to study the thermal behaviour of vinylallenes **15** and **17**. Compared to other members of this series of vinylallenes,[6a] compounds **15** and **17** (lacking an allylic hydrogen at a terminal Z-ene) cannot experience alternative more favored sigmatropic shifts ([1,5]-H[6b], [1,7]-H[6c]) or 6π electrocyclizations[6c,d] (as in

the conjugated dienylallene case). Additionally, the presence of the *tert*-butyl group in the allene avoided [1,3]-sigmatropic hydrogen shifts to dienes, observed in other cases.[7] We wish to report the thermal unidirectional conversion of substituted vinylallenes to the corresponding methylenecyclobutenes. Noteworthy are the milder conditions compared to the prototype **3-4** and the regioselectivity of the process. Preliminary ab initio calculations suggest steric effects are mainly responsible for the observed selectivity.

Substituted vinylallenes **15** and **17** (formally 11,7-retroretinoids) were synthesized in 71% yield following stablished protocols by SN2' displacement of propargylic benzoates (**10** and **14**, respectively) by higher order cyano cuprates in diethyl ether at -78 °C.[8] Precursor alcohol **9** was prepared in 93% yield by attack of alkyne **8** (as lithium salt) on known C15-aldehyde **7**[9]. Alcohol **9** in turn provided benzoate **10** in 87% yield upon treatment with n-BuLi at -78 °C followed by benzoyl chloride. The same aldehyde **7** was used as starting material for the one-carbon homologation (Ph_3PCBr_2, CH_2Cl_2, 0 °C; then n-BuLi, THF, -78 °C; 65% combined yield) to alkyne **11**. Finally, coupling of the lithium salt of **11** with aldehyde **12**[10] provided in 86% yield isomeric propargylic alcohol **13**, which gave propargylic benzoate **14** (93% yield) under similar conditions used for **9**.



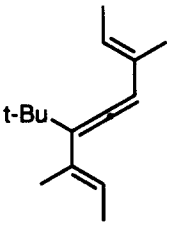
Comprehensive thermal studies were first done with TBDMS-ether protected vinylallenol **15**. For thermal reactions, diluted solutions of vinylallene **15** in benzene-d_6 were heated in sealed NMR tubes at appropriate temperatures (range 90-110 °C). The NMR spectra of the solution were recorded periodically and the ratios of vinylallenes to methylenecyclobutenes were determined by integration of the NMR spectra (H_{10} signal) without line broadening. Good first-order irreversible kinetic plots of the data were obtained. The plot of ln k versus 1/T gave values for the activation parameters for this reaction of $\Delta H^{\#}$= 26.6 ± 1.3 Kcal/mol and $\Delta S^{\#}$= 7.4 ± 0.4

cal/mol·K. The linearity of this plot suggests that this reaction is a truly unimolecular process, with an activation energy of 27.3 Kcal/mol.

Specially suggestive of the methylenecyclobutene structure **16** are the signals for the H_{14}-H_{15} substructure [(δ 3.40 ppm, dd, J= 8.2 Hz and 3.7 Hz, 1H, H_{14}); (δ 3.71 ppm, dd, J= 10.0 Hz and 8.2 Hz, 1H, H_{15b}); (δ 4.19 ppm, J= 10.0 Hz and 3.7 Hz, 1H, H_{15a})]. From the NMR data it was also observed that the diene subunit C_8-C_{12} (retinoid numbering) remained unaltered, clearly indicating a regioselective process. The regioselectivity is not dependent upon the electronic nature of the vinylallene terminus, because aldehyde **20** (obtained in 78% combined yield by fluoride-induced deprotection of silylether **15** to give **19** followed by manganese dioxide oxidation to **20**) afforded an analogous cyclobutene **22** (vinylallenol **19** behaved as **15** and provided compound **21**). However, the electrocyclization is retarded by the introduction of this electron-withdrawing group, as shown by comparison of the half-life times at 100 °C (7.2 h for **15** vs. 24.1 h for aldehyde **20**).

Similar results were obtained on thermolysis of the protected isomeric vinylallenol **17**. Again the process is regioselective affording the more substituted methylenecyclobutene **18**, although the threshold for the cyclization was higher (110 °C) and on increasing the concentration other processes compete.

To address the regioselectivity outcome, we have calculated the geometries of the divinylallene using ab initio molecular orbital studies at the 6-31G* level with the Gaussian 92 program.[11] At a first approximation, we performed a complete geometry optimization for the two components (**24** and **25**) of a truncated model **23** of the reactant, assuming that each terminal butene unit has no effect on the cyclization of the perpendicular vinylallene.



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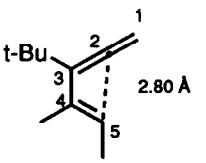

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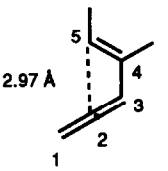

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Two observations pertaining to the experimental results stem from the calculated structures: first, through a conformational search obtained by C_3-C_4 bond rotation, it was determined that the most stable conformation for vinylallene **25** is *s-trans* (dihedral angle 180.0°, in agreement with calculations in similar systems[12]) whereas for the 3-*tert*-butyl derivative **24** is a non-planar twist structure (dihedral angle 68.3°) closer to the reactive *s-cis* conformation; second, on forcing an s-*cis* conformation (the one involved in the electrocyclization) the optimized geometries for the individual vinylallenes suggest that the 0.17 Å difference in C_2-C_5 distance might favor the cyclization of the 3-*tert*-butyl-4-methyl 1,2,4-hexatriene **24** compared to the unsubstituted **25**.

In summary, a new reaction of vitamin A-related vinylallenes that affords methylenecyclobutenes has been described. Additional work exploring its structural properties and chemical reactivity is in progress.[13]

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13. All key intermediates showed the expected spectral properties and gave satisfactory HRMS. ^{1}H-NMR data for cyclobutene **16**: ($CDCl_3$) δ 0.12 (6H, s, Si-2CH_3), 0.99 (9H, s, Si-t-Bu), 1.07 and 1.08 (2 x 3H, 2 s, C_1-2CH_3), 1.21 (9H, s, C_{12}-tBu), 1.44-1.65 (4H, m, $2H_2$ and $2H_3$), 1.62 (3H, s, C_5-CH_3), 1.91 (2H, t, J= 6.0 Hz, $2H_4$), 1.95 (3H, d, J~ 0.8 Hz, C_9-CH_3), 2.05 (3H, s, C_{13}-CH_3), 2.92 (2H, d, J= 6.5 Hz, $2H_7$), 3.40 (1H, dd, J= 8.2 Hz and 3.7 Hz, H_{14}), 3.71 (1H, dd, J= 10.0 Hz and 8.2 Hz, H_{15b}), 4.19 (1H, dd, J= 10.0 Hz and 3.7 Hz, H_{15a}), 5.52 (1H, t, J= 6.5 Hz, H_8), 5.95 (1H, s, H_{10}). Significant ^{1}H-NMR data for cyclobutene **18**: (C_6D_6) δ 1.08 and 1.09 (2 x 3H, 2 s, C_1-2CH_3), 1.27 (9H, s, C_{10}-tBu), 1.71 (3H, s, C_5-CH_3), 1.92 (6H, s, C_9-CH_3 and C_{13}-CH_3), 2.52 (1H, dd, J= 14.1 Hz and 10.7 Hz, H_{7b}), 2.80 (1H, dd, J= 14.1 Hz and 6.1 Hz, H_{7a}), 3.55 (1H, dd, J= 10.7 Hz and 6.1 Hz, H_8), 4.44 (2H, d, J= 6.1 Hz, $2H_{15}$), 5.88 (1H, s, H_{12}). Significant ^{1}H-NMR data for cyclobutene **22**: ($CDCl_3$) δ 1.05 and 1.06 (2 x 3H, 2 s, C_1-2CH_3), 1.12 (9H, s, C_{12}-tBu), 1.59 and 1.61 (6H, 2 s, C_5-CH_3 and C_{13}-CH_3), 1.86 (3H, d, J= 1.0 Hz, C_9-CH_3), 2.87 (2H, d, J= 6.5 Hz, $2H_7$), 3.81 (1H, d, J= 5.9 Hz, H_{14}), 5.60 (1H, tq, J= 6.5 Hz and 1.0 Hz, H_8), 6.21 (1H, s, H_{10}), 9.27 (1H, d, J= 5.9 Hz, H_{15}).

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