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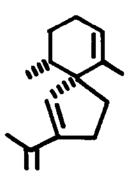
THE DIELS-ALDER REACTION OF α-ETHENYLIDENE CYCLANONES : A STEREOSELECTIVE APPROACH TO SPIROCYCLIC COMPOUNDS.

Jean-Louis GRAS* and Anne GUERIN

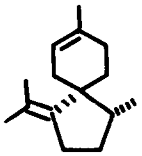
U.A. 109, Laboratoire de Synthèse Organique - Université d'AIX-MARSEILLE III
Rue Henri Poincaré - F-13397 MARSEILLE CEDEX 13

SUMMARY : The BF_3:Et_2O catalyzed Diels-Alder reaction of α-ethenylidene cyclanones constitutes a highly stereoselective route to spirocyclic dienones.

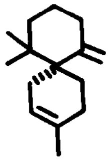
Spirocycles represent challenging targets in both natural product or theoretical chemistry, and the construction of quaternary carbon-center remains as a fundamental test of synthetic methodology (1). Specially the spiro |4.5.| decane and spiro |5.5| undecane systems have attracted the attention of many synthetic chemists, as they constitute basic carbon frameworks found in sesquiterpenes of the spirovetivane, acorane or chamigrane classes :



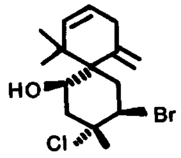
α-vetispirene



γ-acoradiene



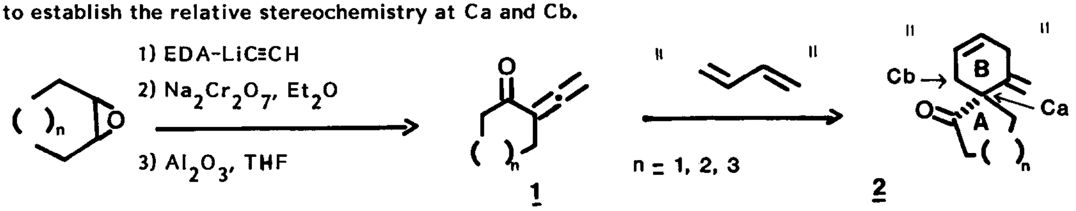
β-chamigrene



nidifidienol

We have initiated an investigation aimed at the stereoselective construction of functionalized spirodienones 2, which may be further converted to a large family of spirovetivanes or related compounds.

Allenic ketones are valuable intermediates in organic synthesis and behave as dienophiles in highly stereocontrolled Diels-Alder reactions (2). The approach herein is to use the Diels-Alder addition of α-ethenylidene cyclanones 1 as the key step both to generate the spirocyclic center and to establish the relative stereochemistry at Ca and Cb.



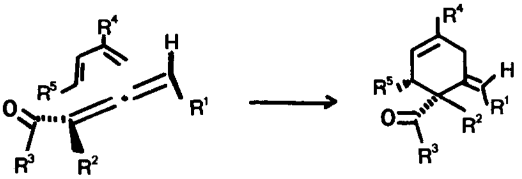
In fact, the Diels-Alder reaction of methylene cyclanones or lactones has been earlier investigated (1,3), and recently used to prepare some spiroacoranes (4). We found that the present cycloaddition of α-ethenylidene cyclanones 1 is performed under much milder experimental conditions, affords a better control on the stereochemical issues, and provides an important extra functionality on ring B when compared with the reaction of methylene cyclanones.

Ethenylidene cyclopenta-, cyclohexa-, cycloheptanones are readily prepared from oxiranes (5), and although they can be easily handled, they show some propansity to dimerize or polymerize when heated for a few hour period of time. Thus various Lewis acid catalysts were tested for efficacy during cycloaddition of compounds 1, and the choice of the catalyst appeared to be of decisive importance. Several aluminium chlorides, $SnCl_4$, $TiCl_4$ led mainly to chlorenones, after transfer of a chlorine atom to the sp hybridized central carbon atom of the allenic moiety (6). Finally, $ZnCl_2$, BF_3:Et_2O provided more satisfactory results, with the boro compound being the most effective to afford spirocycles 2 in fair to good yields (Table I).

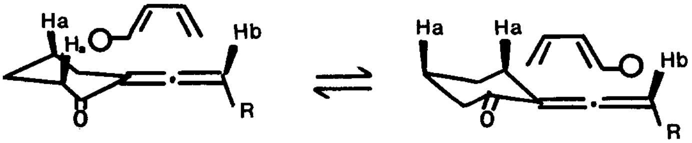
Noticeable are the very mild conditions of this Diels-Alder addition : the reagents are dissolved in benzene, stirred at low temperature under argon atmosphere, and the reaction reaches completion after relatively short periods of time. Various experiments indicate that the reactivity of cyclanones 1 increases with the strain of the cycle and with the substitution on the acyclic sp^2 carbon atom at the end of the allenic entity (ketone 6). Although there is the possibility of ethenylidene cyclanones acting as a diene, in the event little evidence of the formation of the resulting adducts is detected.

Critical to the full efficiency of the envisioned synthesis was the requirement that the Diels-Alder reaction of 1 be both regio- and stereoselective. Previous work from this laboratory indicated the strong orientating effects during the course of the Diels-Alder addition of acyclic allenic ketones to unsymmetrical dienes : exclusively a 1,2-disubstituted cyclohexene (with piperylene) or a largely predominant 1,4-disubstituted cyclohexene (with isoprene) is formed (Scheme 1) (2).

Scheme 1



In the case of ethenylidene cyclanones, the selectivity between all the possible transition states leading to 2 depends also on new steric factors, brought in by the axial protons of the carbocycle. These protons (Ha) compete sterically with the out-of-plane allenic proton of the non-reacting double bond (Hb), as illustrated in scheme 2 concerning the six member ring.



4

R=H

Scheme 2

Scheme 3

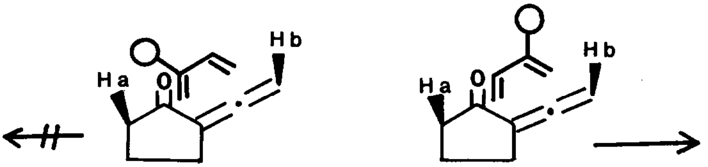


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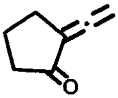
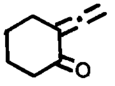
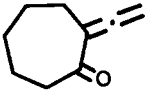
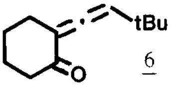
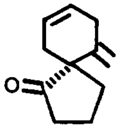
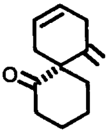
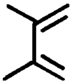
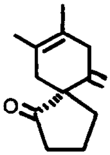
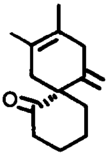
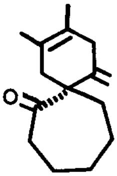
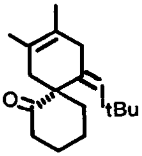
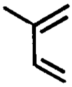
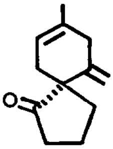
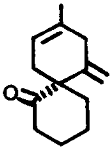
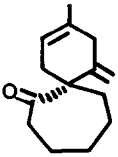
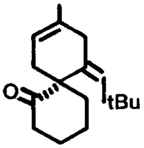
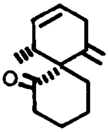
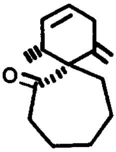
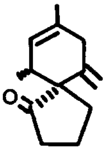
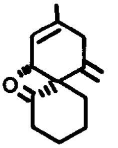
TABLE I	 3	 4	 5	 6
	 0 to 18° C 2h30 13%	 -30 to 18° C 5h 52%	-	-
	 -30° 36 min 82%	 -30° 20 min 86%	 -30° 100 min 88%	 -30° 10 min 77%
	 7 -25° 70 min 58%	 8 -30° 25 min 69%	 9 -30 to 18° 7h 63%	 10 -30° 25 min 74%
	 11 0° 90 min 46% + one isomer <10%	 12 -30° 4h 48% + isomers ~15%	 13 -20 to 18° 6h 57%	-
 *	 14 -30° 1h 28%	 15 -30° 20 min 34% + one isomer 5%	 16 -30 to -8° 2h45 48% + one isomer 2.5%	-

*Experiments of this series were performed just once, thus not optimized. All reactions were carried out in benzene solutions, using BF_3:Et_2O as catalyst (16 %) and 5 equivalents of diene (3 of 1,3-dimethylbutadiene). Yields refer to isolated products after column chromatography (silica gel, elution with pentane-ether mixtures). Each adduct was fully characterized on the basis of its high field (200 MHz) ^1H and ^{13}C NMR spectra, and gave satisfactory elementar analysis. Full description of the adducts will be reported elsewhere.

Thus, during the addition to isoprene, the steric hindrance by Ha adds to the electronic directing effects, and exclusively the 1,4-disubstituted cyclohexenes 7, 8, 9, 10 are detected (Scheme 3).

Addition to piperylene affords 1,2-disubstituted cis-cyclohexenes with the following selectivities : cycloheptanone 13 as sole product, cyclopentanone 11 along with one minor isomer, cyclohexanone 12 largely dominating among other isomers. These minor isomers could not be obtained in pure form nor identified, but a coupled gc/ms analysis confirms the expected mass. The isolated spirodienones are the ones expected from normal electronic directing effects. A closer examination of molecular models clearly reveals that the regiochemical outcome of the addition to piperylene (ortho methylated product) is enhanced by the steric hindrance by Hb, while its stereochemical outcome (endo) is partially linked to the steric hindrance by Ha. The respective conformations of the cyclanones 3, 4, 5, account very well for the observed purity of the corresponding adducts 11, 12, 13. The steric hindrance by Ha in the ketone 4 may force the exo approach and two opposite orientations of piperylene to partially operate (Scheme 2). This effect is observed in a lesser extent during the addition of cyclopentanone 3, while the reaction of cycloheptanone 5 is much comparable to the earlier studied acyclic case.

The addition of 1,3-dimethylbutadiene which combines the substitution pattern in both isoprene and piperylene, is governed by Ha and leads to the corresponding spiroketones with a very high selectivity.

On a synthetic point of view, the Diels-Alder reaction of α-ethenylidene cyclanones affords a viable method for the stereoselective construction of functionalized spiroketones. The most interesting features provided by this methodology are : the accessibility of the required precursors, the very mild reaction conditions, the high selectivity observed during the course of the crutial formation of the quaternary center, and the fact that the two cycles in the resulting adducts are differentially functionalized.

Further manipulations of these functional groups should allow the synthese of many spiro compounds alike or isomeric with natural products of economic importance. Thus, the versatility of this stereoselective approach to functionalized spirocycles opens a new dimension to the use of allenic ketones in synthesis.

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