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Regio- and Stereochemical Variations in Diels-Alder Reactions

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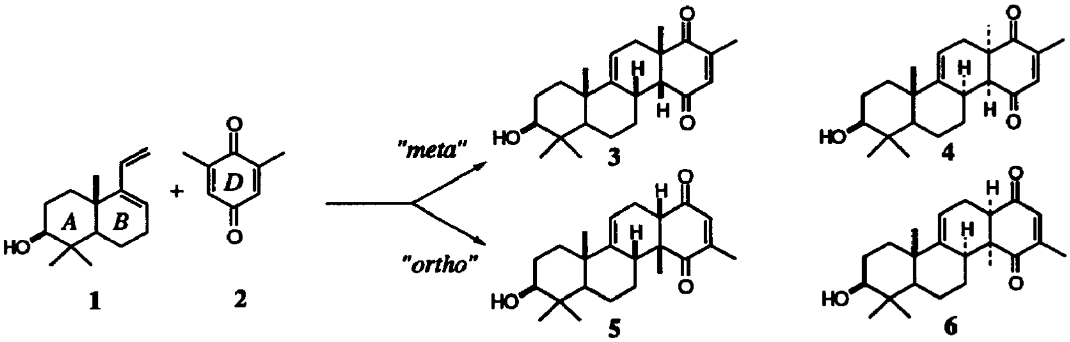
Abstract: *The AB+D —> ABCD approach for the synthesis of the tetracyclic intermediates 3-6 is reinvestigated. Water, high-pressure, LiCl and scandium triflate-mediated Diels-Alder reactions of 1 and 2 are reported.*

In an approach to the synthesis of isoarborinol[1] and of its CDE-"antipode" fernenol, through tetracyclic ABCD intermediates, we have demonstrated that the stereochemistry of the Diels-Alder reaction of the diene **1** and the quinone **2** can be varied, using various Lewis acid catalysts.[2] An appropriate manipulation of the functionalities in the D-ring moiety followed by the annulation of the E ring has then led successfully to pentacyclic derivatives related to arborane and fernane.[3] No conditions could however be found, which would give selectively only one of the intermediates **3** or **4** required, and this has led us to study other conditions. Even though we have made no progress towards our synthetic goal of a selective Diels-Alder reaction, leading to a single product, we describe now some rather striking observations, and the results observed in the presence of water, and of the scandium triflate introduced as a Diels-Alder catalyst by Kobayashi.[4]



The Table summarizes our new results, and compares them with a few of our earlier ones. Scandium triflate was used in various solvents, and gave in every case mixtures of three of the endo[5] adducts, **3**, **4** (predominant, resulting from the "*meta* " orientation), and **5**, (minor, resulting from the "*ortho* " orientation) (runs *1* - *4*). However, in wet tetrahydrofuran (run *4*) or in water, with a little methylene chloride as a thinner (run *5*), the selectivity became highly favorable towards the *ortho* orientation, **5** and **6** being now the exclusive or nearly exclusive products.

Entry Nr	Conditions	Molar Ratio*	Solvent	Temp. °C	Time h	Yield %	3	4	5	6
1	Sc(OTf)$_3$	1	MeCN	- 40	6	96	56	30	14	
2	"	"	CH$_2$Cl$_2$	- 78	8	92	77	15	8	
3	"	0.1	"	4	17	72	67	22	11	
4	"	"	THF-H$_2$O 9:1	25	21	18			75	25
5	"	1	CH$_2$Cl$_2$-H$_2$O 1:10	25	20	96	2		77	21
6	LiCl-5 M		H$_2$O	25	7	79			76	24
7	10 kbar		CH$_2$Cl$_2$	50	24	96			75	25
8			PhMe-H$_2$O 1:15	25	24	67			75	25
9	AlCl$_3$**	1.2	CH$_2$Cl$_2$	-70	2	80	58	42		
10	TiCl$_4$**	1.3	"	-78	3	70	89	11		
11	Eu(fod)$_3$**	2	"	25	24				42	58
12			C$_6$H$_6$	Reflux	20	96			100	

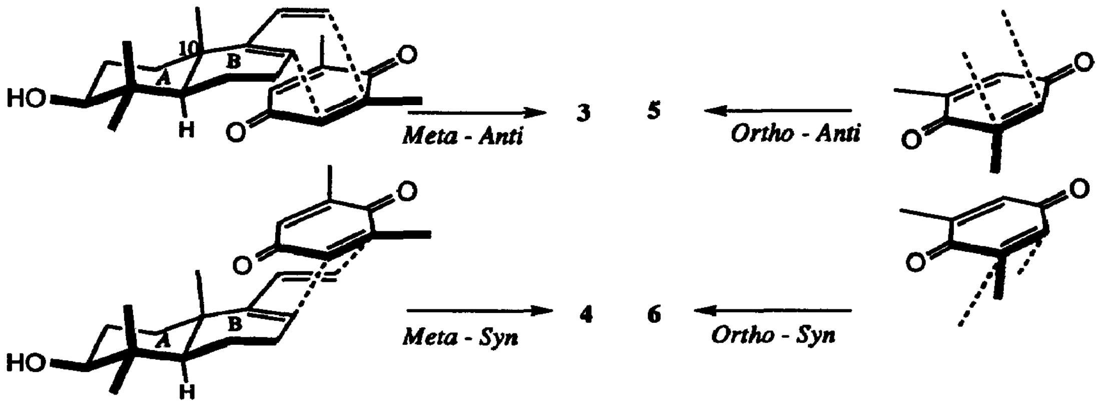
* : molar ratio of catalyst/diene 1; ** : from ref. 2 ; exp., see [8]

Table

The same selectivity in favour of **5** and **6** was observed without scandium triflate, in water (run *8*, with about 7 % toluene as a thinner, and with or without phosphate buffer at pH 7 - initially used to prevent acid-catalyzed isomerization of the diene[2], but later found unnecessary), or with a highly concentrated (5 M) solution of lithium chloride in water (run *6*, conditions increasing hydrophobic effects)[6,7] or under a hydrostatic pressure of 10 kbar (run *7*). As can be seen from the Table, under several sets of conditions, the conversion was practically quantitative, but mixtures were in every case obtained, except in boiling benzene (run *12*).

Comparing these new results with those obtained previously, we see that the various types of Lewis acids used give quite different products : aluminium and titanium chlorides give exclusively the products of *meta* orientation, Eu(fod)$_3$ exclusively those of *ortho* orientation, and scandium triflate, as mentioned above, mixed results.

The formation of the two diastereomers 3 and 5 results from bottom face attacks of the dienophile to the diastereotopic faces of the diene *via* an endo transition state as shown in Scheme 2. This approach of the dienophile *anti* to the C-10 angular methyl group was of course expected to be the preferred one. This is *nearly* the case, with one hardly significant exception (run *11*); in all the other cases, the other diastereomers, 4 and 6, resulting from the attack from the β-side, *syn* to the angular methyl group, are less abundant than their *anti* counterparts. However, with aluminium chloride (run *9*), this side-selectivity is minimal. One could have expected that the steric factors would always be in favour of those modes of attack where the methyl groups of the quinone are disposed away from the more congested portion of the transition state, *i.e.* that the *meta* isomers 3 and 4 would be favored over the *ortho* ones, 5 and 6. Such is not the case, and this must reflect the operation of electronic factors. It is particularly striking that the only one of the four isomers which can be obtained quantitatively is one of the *ortho-anti* ones, 5 (in boiling benzene, run *12*). Semi-empirical calculations using MOPAC 6.0, MINDO/3 are underway in an attempt to discover the dominant factors influencing the *ortho/meta* orientation.



While we do not have a convincing explanation for the change-over of regioselectivity revealed by our investigations, it is relevant to note that the Diels-Alder reaction between 1 and 2 can now be run under conditions leading to at least 40 % of each of the four diastereomers, and in every case except 4 to about 60 % or more. The only case of complete selectivity remains the thermal Diels-Alder reaction in refluxing benzene,[2] which quantitatively gives the single *anti*- adduct, 5, unfortunately not one that could be used in our synthetic project. In no case was any violation of the *endo*-rule observed.

The results shown above illustrate once again that hydrophobic effects play an important role in enhancing the reaction rate and that they can control product distribution. The relative importance of steric and electronic factors has yet to be elucidated. Furthermore, the eventuality of a role of the C-3β hydroxyl group as a factor controlling the π-facial selectivity may be worth investigating.

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8 - Structural assignments (orientation, and *syn/anti* and endo/exo selectivities) were done on the basis of high field NMR analysis. Diastereomeric ratios were determined by 400 MHz ^{1}H-NMR on the crude products and confirmed after diastereomer separation (silica gel flash chromatography, EtOAc:heptane 1:3).

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