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FACIAL SELECTIVITY IN DIELS-ALDER REACTION OF 4,4-DISUBSTITUTED 2,5-CYCLOHEXADIENONES

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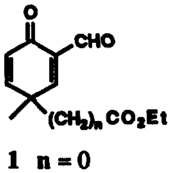
Abstract: A mechanistically interesting and synthetically useful reversal of facial selectivity was observed for the Diels-Alder reaction of several structurally closely related 4,4-disubstituted 2,5-cyclohexadienones. While the addition of **2** and **3** to dienes occurred preferentially from the C-4 methyl side in each case as expected based on steric grounds, the reaction of **1** and **16** with dienes proceeded in all cases virtually exclusively from the C-4 ester face.

In approaches to the total synthesis of diterpenoids of the *cis*-clerodane family,[1,2] the Diels-Alder addition of 4,4-disubstituted 2,5-cyclohexadienone **1**, or its homologues **2** and **3** to a suitably substituted 1,3-butadiene presents itself as an attractive general route. Whereas 2-cyclohexenones activated with an additional electron-withdrawing group at C-2 have been shown to be good dienophiles,[3] little is known about the facial selectivity of compounds possessing nonequivalent substituents at C-4.[4] Since in virtually all of the natural *cis*-clerodanes the stereochemistry of the three contiguous chiral centers (C-5, C-9 and C-10) to be induced by the cycloaddition is arranged in a special manner as shown in solidago lactone IV (**4**),[5] the facial selectivity is crucial to the success of the Diels-Alder approach. On the basis of steric grounds,[6] it was expected that the addition of diene to compounds **1**, **2** and **3** should occur preferentially, in each case, from the less hindered methyl face. In order to confirm this desired facial preference, we have examined the reactions of dienone aldehydes **1**, **2** and **3** with several dienes. Herein we wish to describe an interesting reversal of facial selectivity.

Dienone aldehyde **3** was readily prepared from enone **5**[7] by formylation[8] and phenylselenenylation-oxidative elimination.[9] Its addition to 1,3-butadiene in dichloromethane at room temperature under zinc chloride catalysis gave, as expected, isomer **6a** as the predominant product (76%), resulting from the addition from the sterically less hindered methyl face, along with a small amount (15%) of epimer **6b**. The stereochemistry of these products was readily confirmed by NOE experiments, results of which are diagrammatically summarized in Fig. 1 and 2. Similar facial selectivity was observed for the cycloaddition of compound **3** with *trans*-piperylene carried out in refluxing benzene. The reaction gave rise to a *ca.* 80% yield of two diastereomeric mixtures **7a** and **7b** (2.2 : 1), each consisting of a pair of epimers in *ca.* 10 : 1 ratio. Again the major isomers **7a** were produced as a result of the addition from the methyl side of the dienophile. Similarly, dienone aldehyde **2** derived from the known enone **8**[10] was found to undergo Diels-Alder reaction in a facial selective manner with 1,3-butadiene and *trans*-piperylene at room temperature in dichloromethane in the presence of zinc chloride, albeit to a somewhat lesser degree. With 1,3-butadiene, adducts **9a** and **9b** (for NOE results, see Fig. 3 and 4) were formed in a ratio of 1.7 : 1 and a combined yield of 90%. In the case of *trans*-piperylene, a 90% yield of two diastereomeric adducts **10a** and **10b**[11] was obtained in 1.2 : 1 ratio. These results were again consistent with the expectation.

The zinc chloride catalyzed cycloaddition of dienone aldehyde 1 (prepared from enone ester 11[12]) and 1,3-butadiene in dichloromethane at room temperature gave virtually a single adduct in 90% yield. To our surprise, this compound was shown by the NOE experiments (Fig. 5) to possess structure 12 resulting from the addition from the ester side. This selectivity, which was totally unexpected in light of the relative van der Waals sizes estimated for the carbomethoxy group (n = 12.1) and methyl group (n = 8.5),[13] was found to be consistent in several other reactions examined using a variety of substituted 1,3-butadienes under both thermal and Lewis acid catalyzed conditions. An examination of the results summarized in Table 1 reveals a strong preference for addition from the ester side in all the cases. Several additional observations are noteworthy. (a) The reaction with *trans*-piperylene gave mainly stereoisomer 13 as a result of the *endo*-addition with respect to the dienone moiety. This selectivity was enhanced from thermal conditions (Entry 2) to Lewis acid catalysis (Entries 3 and 4). Interestingly, the addition of (*E*)-2-methyl-1,3-pentadiene (Entry 5) gave mainly stereoisomer 14 as a



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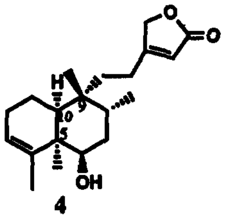
2 n = 1
3 n = 2



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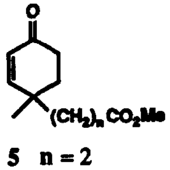
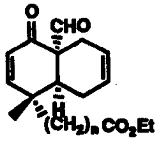
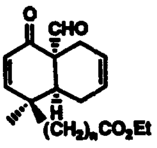


5 n = 2
8 n = 1
11 n = 0



6a n = 2
9a n = 1



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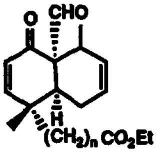
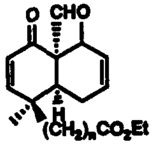


7a n = 2
10a n = 1



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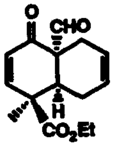
10b n = 1



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Figures. NOE Data for Compounds 6a, 6b, 9a, 9b and 12

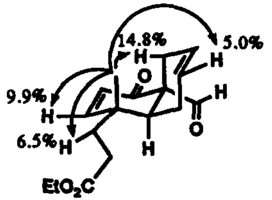


Fig. 1

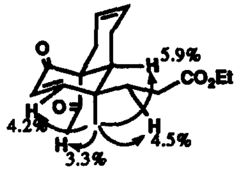


Fig. 2

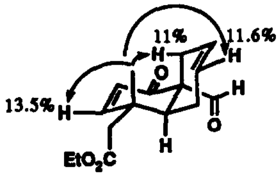


Fig. 3

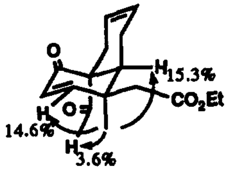


Fig. 4

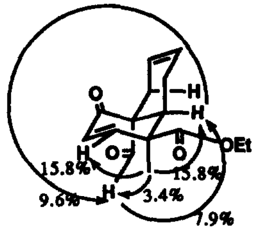
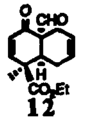
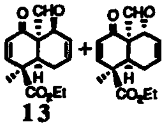
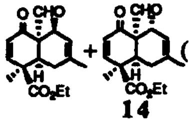
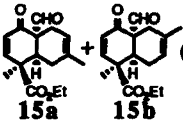
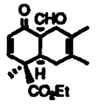
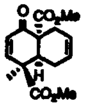
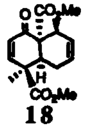


Fig. 5

Table 1. Diels-Alder Reactions of Dienophiles **1** and **16**

Entry	Dieno-phile	Diene[a]	Catalyst (equiv)[b]	Temp. (°C)	Time (h)	Isolated Yield (%)[c]	Products (ratio)
1	1		$ZnCl_2$ (3)	23	18	90	 **12**
2	1		-	78	24	95	 **13** (4.5 : 1)
3	1		$ZnCl_2$ (3)	0	5	95	**13**
4	1		$FeCl_3$ (2)	-78	2	60	**13**
5	1		-	78	8	95	 **14** (1 : 3)
6	1		-	78	42	30[d]	 **15a** **15b** (2.2 : 1)
7	1		$ZnCl_2$ (3)	-20	24	90	**15a** + **15b** (4.7 : 1)
8	1		-	78	45	60[e]	
9	16		$ZnCl_2$ (2)	23	16	95	 **17**
10	16		$ZnCl_2$ (2)	0	4.5	~100	 **18**

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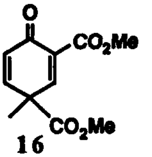
[a] Ten equivalents of diene were used in each case with the exception of 1,3-butadiene in which case a saturated solution in dichloromethane was used. [b] All Lewis acid catalysed reactions were carried out in dichloromethane. Benzene was used as the solvent for thermal reactions. [c] Yields are based on the amount of starting material applied. [d] The starting material was recovered in 65%. [e] The starting material was recovered in 30%.

consequence of the preferential addition *endo* to the α,β-unsaturated aldehyde moiety. The changeover of the *endo*-selectivity could be rationalized by invoking the steric interaction between the C-2 methyl group of the diene and the C-4 substituent of the dienophile as previously observed for 2-carbomethoxy-4,4-dimethyl-2,5-cyclohexadienone.[14] (b) Also in agreement with the previous findings[14] was the addition of isoprene to compound **1** (Entries 6 and 7); both *para* (**15a**) and *anti-para* (**15b**) adducts were produced. In refluxing benzene the reaction was slow and the two isomers were obtained in 2.2 : 1 ratio in favor of *para* adduct **15a** (Entry 6). Both the reaction rate and the regioselectivity were markedly improved when zinc chloride was employed as a catalyst (entry 7).[14]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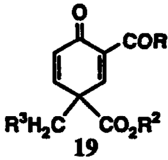
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We have also examined the Diels-Alder reaction of the ester analogue **16** which was readily obtained by carbomethoxylation[15] of **11** followed by a phenylselenenylation-oxidation process. The facial selectivity of this dienophile was found to be essentially the same as that observed for dienone aldehyde **1**. Its addition to 1,3-butadiene (Entry 9) and *trans*-piperylene (Entry 10) using zinc chloride as a catalyst gave adducts **17** and **18**, each in near quantitative yield.

The high degree of facial selectivity observed for compounds **1** and **16** is most unusual and has strong synthetic implications. An extrapolation of the above results suggests that the ester group in compounds of general type **19** could serve as a directing group for facial selectivity in Diels-Alder reactions. Mechanistically, several factors may contribute to the remarkable facial control exerted by the ester group. This constitutes the subject matter of our current investigation.[16]

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