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Diels-Alder Reaction of (*S*)-2-*p*-Tolylsulfinyl-2-cyclopentenone with Dane's Diene: an Efficient Approach to the Enantioselective Preparation of Perhydro-cyclopenta[a]phenanthrenes

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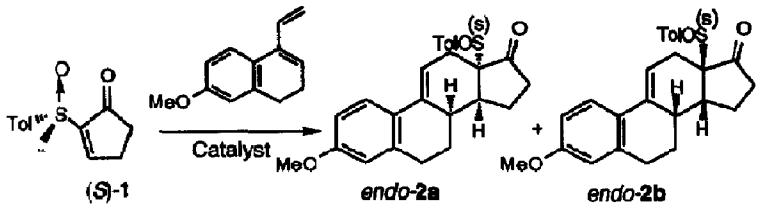
Abstract: The reactions of (*S*)-2-*p*-tolylsulfinyl-2-cyclopentenone with Dane's diene catalyzed by $EtAlCl_2$ yields adducts easily desulfinylated into optically pure perhydro-cyclopenta[a]phenanthrenes. The *endo*- (controlled by CO group) and regio- (controlled by the substituent at C-2 of diene) selectivities of the asymmetric Diels-Alder reaction are complete. The π-facial selectivity is also very high and dependent on both the sulfinyl configuration and the amount of $EtAlCl_2$ used.

The elegant work reported by Posner and *col.* on the conjugate addition of organometallic reagents to (*S*)-2-*p*-tolylsulfinyl-2-cyclopentenone (**1**) showed that this enantiomerically pure vinylsulfoxide can be used as a very interesting Michael acceptor in asymmetric synthesis[1]. As a part of our current interest in the use of optically pure vinylsulfoxides as efficient chiral dienophiles in asymmetric Diels-Alder reactions[2] we previously reported that the reaction of **1** with cyclopentadiene occurred with high stereoselectivity[3]. These results suggested that the Diels-Alder reaction of **1** with 6-methoxy-1-vinyl-3,4-dihydronaphthalene (Dane's diene)[4] could constitute an extremely direct approach to the enantioselective preparation of perhydro-cyclopenta[a]phenanthrenes. In fact, although in this straitghtforward approach to steroid skeletons (AB + D→ ABCD), Dane's diene has been used in the reaction with several achiral dienophiles to give racemic adducts[5] or optically active adducts if the reaction is conducted under chiral Lewis acid catalysis[6], to the best of our knowledge there are very few precedents concerning the enantioselective synthesis of steroids by using an optically pure 2-cyclopentenone[7].

As in the case of the Diels-Alder reaction with cyclopentadiene, the reaction of **1** with Dane's diene required also the presence of a Lewis acid as a catalyst. In scheme 1 and table 1 are summarized the most interesting results. Three catalysts were used, of these the best yields were obtained by using $EtAlCl_2$ (entries 3 to 9). With $AlCl_3$ and $TiCl_4$ (entries 1 and 2) we could not obtain conversions higher than 50%.[8] However, the most remarkable results concern the regio and stereoselectivity of the reaction. Among the eight possible adducts, only the two *endo*-adducts, *endo*-**2a** and *endo*-**2b**, were obtained. Cycloadditions took place with complete regioselectivity and *endo*-selectivity. Substituent at C-2 is responsible of the control of the regioselectivity, which is not surprising taking into account that its aromatic character extending conjugation of the dienic system has a greater influence on the coefficients of the involved orbitals (mainly HOMO) than that of the alkyl substituent at C-1. The strong *endo*-director effect of the carbonyl group can explain the observed *endo* selectivity, which is not too much affected by steric effects due to the nature of the favoured regioisomer.

According to the π-facial selectivity, the results are also remarkable. Thus, by using 1 equiv. of catalyst, we observe the exclusive formation of the adduct *endo*-**2a**, regardless of the mode of the addition and the temperature of chelation (entries 3,5,6). The addition of 2 equiv. of catalyst slightly decreases the π–facial selectivity (entry 4) when the reaction is carried out by addition of the solution of **1**, previously chelated with the catalyst, to the diene (inverse addition). This fact is much more important when the reaction is conducted under direct addition (entries 7 and 8). In these conditions, the selectivity is inverted and *endo*-**2b** became the major component of the mixture. The use of 4 equiv. of catalyst does not increase the selectivity and decreases the yield due to the formation of additional unidentified products (entry 9).



Scheme 1

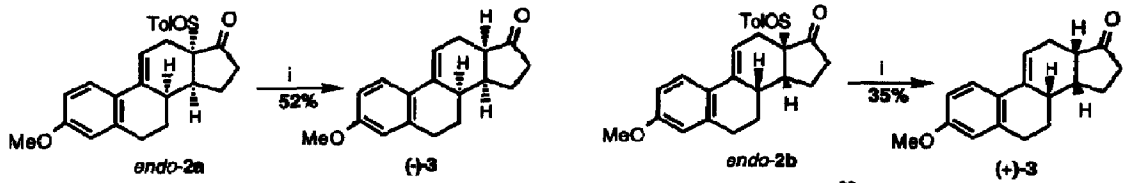
Table 1. Results obtained in the reaction of 1 with the Dane' s diene under catalysis.

Entry	Catalyst (equiv.)	Solvent	Equiv Diene	T(°C)	t(h)	Conversion (%)[a]	*Endo*-**2a** /*endo* **2b**[a]	Yield[b]
1	$TiCl_4$	CH_2Cl_2	6	-78	7	50	67/33	40
2	$AlCl_3$	Toluene	4	-20	26	50	95/5	47
3	$EtAlCl_2$ (1)[c]	CH_2Cl_2	3	-25	3	100	>98/2	86
4	$EtAlCl_2$ (2)[c]	CH_2Cl_2	3	-25	3	100	87/13	80
5	$EtAlCl_2$ (1)[d,e]	CH_2Cl_2	3	-25	4	100	>98/2	93
6	$EtAlCl_2$ (1)[d]	CH_2Cl_2	3	-25	2	100	>98/2	91
7	$EtAlCl_2$ (2)[d]	CH_2Cl_2	3	-25	1	100	29/71	90
8	$EtAlCl_2$ (2.2)[d]	CH_2Cl_2	1	-20	2	75	22/78	47
9	$EtAlCl_2$ (4)[d]	CH_2Cl_2	3	-25	1	100	34/66	60

[a] Determined by ^1H-NMR analysis on the crude mixtures.[b] Overall yield *endo*-**2a** + *endo*-**2b** after chromatography.
[c] Inverse addition (see text). [d] Direct addition. [e] Chelation temperature.

It is important to note that adducts *endo*-**2a** and *endo*-**2b** are not stable at rt, evolving slowly into a mixture of unsaturated products by pyrolytic elimination of the sulfinyl group.[9] This determines that the crude mixture obtained after cycloaddition must be readily purified by flash chromatography (preferentially performed at 0-5°C) and once the adducts **2** are separated and isolated they must be immediately transformed. In fact, the *endo*-configuration of the adduct *endo*-**2a** has been unequivocally established by X-Ray analysis (figure 1) of the product (-)-**3**, obtained after the reductive elimination of the sulfinyl group on *endo*-**2a** (Al-Hg, THF-H_2O, 0°C) (scheme 2). Additionally, the *endo*-structure of compound *endo*-**2b** was deduced from the fact that it was converted into the enantiomer (+)-**3** after reductive elimination of the sulfinyl group. Thus, the Diels-Alder reaction of **1** with the Dane's diene in the presence of 1 equiv. of $EtAlCl_2$, followed by reductive elimination of the sulfinyl group afforded, in 48% overall yield, the optically pure perhydro-cyclopenta[a]phenanthrene (-)-**3**.

Unfortunately, the stereochemistry of the adduct **3** (*cis,cis* stereochemistry at C_8-C_{14}-C_{13}) is not the usual *trans,trans* in steroid skeletons.



$[\alpha]_D^{20}$= -222.2 (c= 0.52, $CHCl_3$) $[\alpha]_D^{20}$= +217.7 (c= 0.7, $CHCl_3$)

i: Al(Hg), THF-H_2O (9:1), 0°C, 3h

Scheme 2

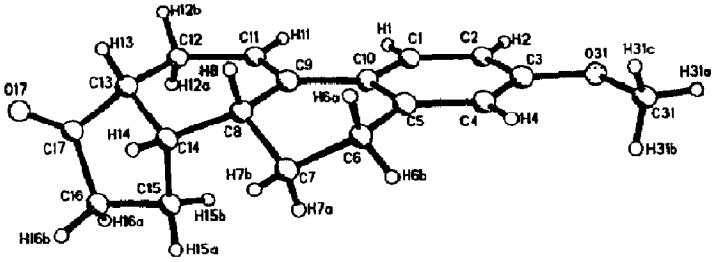
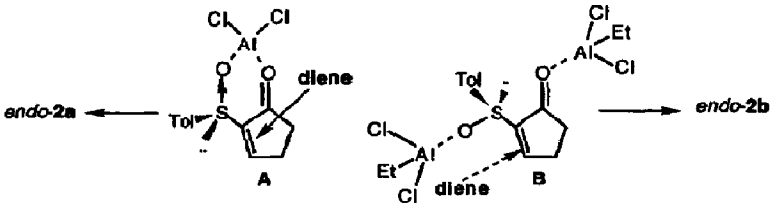


Fig.1: X-Ray crystal structure of compound (-)-3.

It was not possible to establish the absolute configuration of compound (-)-**3** by X-Ray diffraction[10] because there were no heavy atoms present in the molecule to permit the observation of differences in intensity between Friedel opposite reflections. According to the geometrical parameters a *cis* arrangement for B,C and C,D-rings junctions can be deduced as it is shown in fig.1. Bond lengths and angles are normal comparing with those of other related structures.[11] Slight deformation of B-ring and of certain angles (C5-C10-C1, C5-C10-C9 and C5-C6-C7) could be explained based on repulsion between C1-C11 (d(H1-H11)= 2.069Å)[11a]. The most remarkable feature of this structure is its unusual planarity. According to previously reported cases,[12] if there are not steric interactions[12a] or conformational restrictions at D-ring,[12b] the conformations of B and C-rings should be half-chair, even in the presence of a C9-C11 double bond.[12c] However, as can be seen from fig. 1, the conformation of C-ring is half-boat, with H12b and H13 in an almost eclipsed position (torsion angle H12b-C12-C13-H13 = -22.6°).

The absolute configuration shown in scheme 2 for enantiomers (-) and (+)-**3** has been assigned based on the chelated model[2a,3] proposed in scheme 3 (**A**). The formation of *endo*-**2a** as major adduct, in reactions conducted with 1 equiv. of catalyst is explained by the approach of the diene from the less hindered face of the chelate **A**, resulting from the association of the catalyst with both oxygens of the β-ketosulfoxide (Scheme 3). The addition of a second equivalent of the catalyst could determine the formation of species associated with two molecules of catalyst (species **B**), which would exhibit the opossite π-facial selectivity.



Scheme 3

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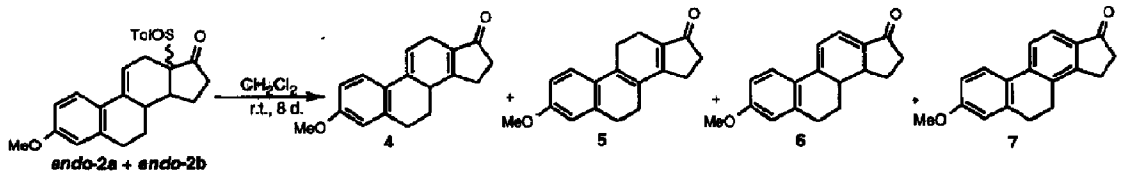
8.- The use of a higher amount of catalyst or longer reaction times did not improve the conversion rate.
9.- After standing the adducts *endo*-**2a** + *endo*-**2b** at rt for 8 days in CH_2Cl_2 a complex mixture of products **4** to **7** was obtained. If this elimination of the sulfinyl group was carried out in the presence of $P(OMe)_3$, in toluene at 50°C, the aryl ketone **7** was obtained in 59% after chromatography. On the other hand, if the reaction was performed at rt in the presence of $CaCO_3$ and in atmosphere of hydrogen the cyclohexadienes **4** and **5** were obtained in 58% and 19% yield respectively after chromatography. Compounds **5** and **7** have been recently prepared by other Diels-Alder strategy (Woski, S.A.; Koreeda, M. *J. Org. Chem.* **1992**, *57*, 5736).



10.- *Crystal Data* for (-)-**3**: $C_{18}H_{20}O_2$, M = 268.34, 268.34, monoclinic, space group $P2_1$,*a* = 7.046 (1), *b* = 5.845 (1), *c* = 16.886 (3) Å, β= 99.78 (3)°, Z = 2, *F* (000) = 288, *Dc* = 1.300 gcm^{-3}, λ (CuKα) =1.54178 Å, μ (CuKα) = 0.654 mm^{-1}. 2857 reflections (1435 unique) were collected on a Rigaku AFC7 four-circle diffractometer coupled to a copper target rotating anode X-ray source, using $\omega/2\theta$ method (5°< 2θ <155°). Three standard reflections were measured every 100 reflections as orientation and intensity control, and no significant intensity decay was observed. The structure was solved by direct methods [SHELXTL PLUS ,Program version 4.0, Siemens Analytical X-Ray Instruments, Madison, WI, **1990**] and refined by full-matrix least-squares based on F^2 to R = 0.028 with all non-H atoms anisotropic [SHELX 93, Program for Crystal Structure Refinement, G. M. Sheldrick, University of Göttingen, **1993**]; H-atoms were placed in idealised positions and allowed ride on the relevant C atom. Largest peak and hole in the final difference map 0.109 - 0.117 eÅ^{-3}. The atomic coordinates, bond distances and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre.
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