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Diels-Alder Reactions of 1-Sulfinyldienes with an Endocyclic Double Bond: The Unexpected Evolution of the N-Methylmaleimide Adducts.

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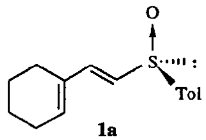
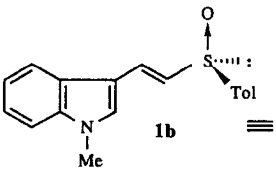
Abstract: (*R*)-(1*E*,3*E*)-2-Cyclohexenyl-1-vinyl-*p*-tolylsulfoxide **1a** and (*R*)-(1*E*,3*E*)-N-methyl-3-[2-(*p*-tolylsulfinyl) vinyl]-1H-indole **1b** reacted with N-methylmaleimide to give Diels-Alder adducts whose in situ evolution through a tandem sulfoxide-sulfenate rearrangement/dehydration/[4+2]-cycloaddition sequence afforded the all-*cis* substituted bicyclo [2,2,2] octene **7** in a highly stereoselective manner.

The use of 1-sulfinylsubstituted-1,3-butadienes in Diels-Alder reactions was first reported by Evans[1] in 1972. Since then, several groups studied the behaviour of 1-sulfinyl-2-(and 4-)heterosubstituted-1,3-butadienes,[2] and 2,5-dimethylthiophene-S-oxide[3] showing high *endo* and facial diastereoselectivities for their cycloadditions in some cases. Although both 1[4]- and 2-sulfinyldienes[5] are now available in enantiomerically pure form, only in the later case their [4+2] cycloadditions have been reported.[6]

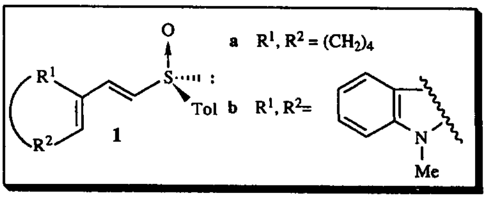
During the course of our studies related to the asymmetric Diels-Alder reactions with sulfinyl dienophiles,[7] we decided to extend our interest to non racemic acyclic 1-sulfinyl-1,3-butadienes.[8] The preliminary results of the cycloadditions with these susbtrates showed that high *endo* and facial diastereoselectivities could be achieved both in thermal and catalytic reactions with N-methylmaleimide, being possible to synthesize enantiomerically pure all-*cis* substituted cyclohexenols through the tandem Diels-Alder cycloaddition/[2,3]-sigmatropic rearrangement of the initially formed adducts. In continuation with our investigations we were interested in knowing the behaviour of 1-sulfinyldienes **1a-b** with an endocyclic double bond. The presence of a cycle in these dienes would give access to polycyclic systems not easily accessible by other way. Moreover, sulfinyl vinyl indole **1b** constitutes an optically active version of vinyl indoles that have been successfully used in the synthesis of alkaloids.[9] We describe in this letter the reactions of **1a-b** with N-methylmaleimide giving rise stereoselectively to highly substituted bicyclo [2,2,2] octenes **7a** and **7b** in a one-pot-four steps procedure.



1a

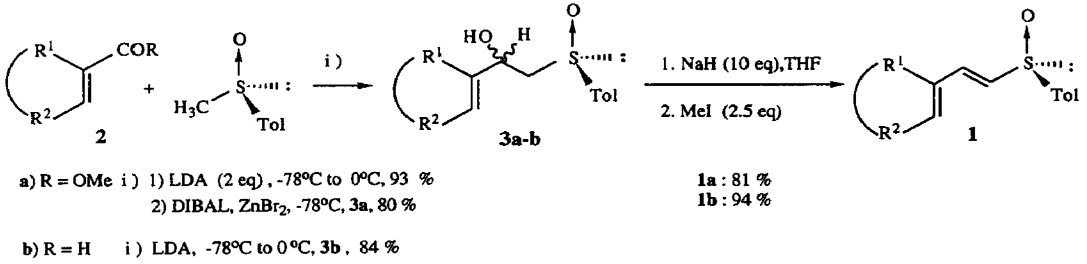


1b



The synthesis of dienes **1a-b** in enantiomerically pure formhas been carried out as shown in Scheme 2 starting from commercially available methyl 1-cyclohexene carboxylate **2a** or N-methyl indole-3-carboxaldehyde **2b** following the procedure previously described by us[4c] but slightly modified. Thus, addition of (*R*)-methyl-*p*-

tolylsulfoxide lithium carbanion (2 eq) to **2a** gave the corresponding ß-ketosulfoxide[10] whose reduction with DIBAL/$ZnBr_2$[11] yielded diastereomerically pure (R_2,R_S) carbinol[12] **3a** that was further transformed in the diene **1a** by treatment with NaH/MeI[13] in a 81% yield. In a similar way, diene **1b** was synthesized from the mixture of (R_2,R_S) and (S_2,R_S) carbinols **3b** obtained in the addition of aldehyde **2b** to methyl *p*-tolylsulfinyl lithium carbanion.



a) R = OMe i) 1) LDA (2 eq), -78°C to 0°C, 93 %
2) DIBAL, $ZnBr_2$, -78°C, **3a**, 80 %

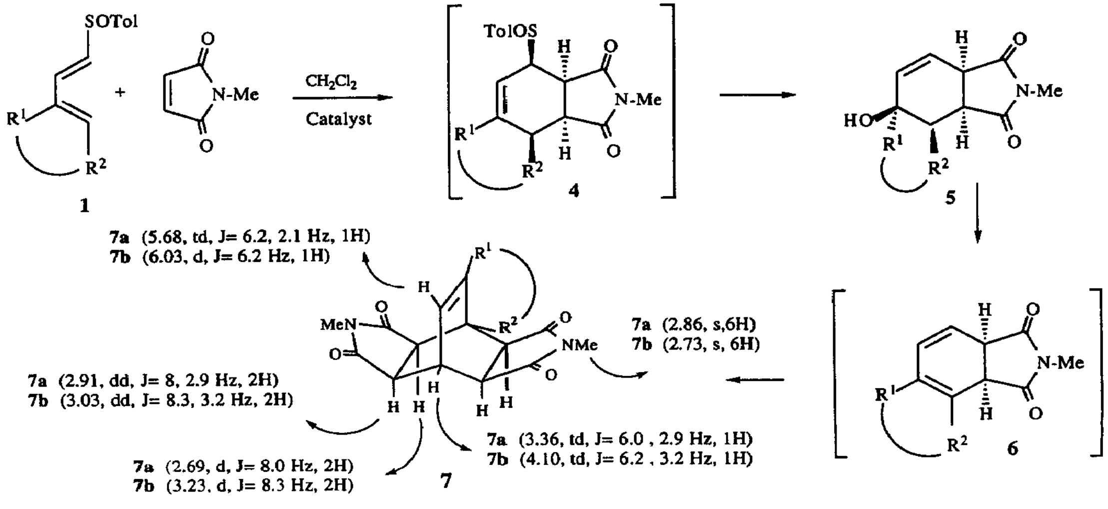
b) R = H i) LDA, -78°C to 0°C, **3b**, 84 %

1a : 81 %
1b : 94 %

Scheme 1

Dienes **1a-b** were submitted to reaction with N-methylmaleimide (3 eq.) both in thermal and catalytic conditionsat room temperature The results are shown in Scheme 2 and Table 1. As it can be seen, thermal reaction of **1a** took place very slowly (60 days) to give a clean mixture of cyclohexenol **5a**[10] and compound **7a**[10] in a 34:66 ratio (entry 1) that could be separated by flash chromatography (eluent hexane:ethyl acetate/7:3 to 3:7) and fully characterized. In the presence of an equimolecular amount of dienophile a similar relative ratio of **5a** and **7a** was observed after 60 days but the reaction was not complete. In the presence of $SnCl_4$ as catalyst we observed a significantly faster evolution of the reaction mixture (5 days) to afford exclusively compound **7a** in a 71% yield. The use of other catalysts such as $ZnBr_2$ or $Eu(fod)_3$ did not allow to accelerate the process and gave complex reaction mixtures.

In similar thermal conditions (R)-methyl-3-[2-(-*p*-tolylsulfinyl)-vinyl]-1H-indole **1b** underwent polymerization. According to the known Diels-Alder reactivity other vinyl indoles,[9,14] the more appropriate catalysts for these reactions are molecular sieves. Thus we checked the use of highly activated 4Å molecular sieves as mild catalysts for the cycloaddition of **1b**. Under these conditions (Table 1, entry 3) the reaction was complete after 10 days affording a 76 % yield of the compound **7b**.



Scheme 2

Table 1. Diels-Alder reactions of dienes **1a-b** with N-methyl maleimide

Entry	Diene	Catalyst	Reaction Time (days)	5:7	% Yield
1	**1a**	---	60	**5a**:**7a** 34:66	79
2	**1a**	$SnCl_4$ [a]	5	**5a**:**7a** 0:100	71
3	**1b**	4Å Mol sieves[b]	10	**5b**:**7b** 0:100	76

a) 6 eq. b) ratio diene / molecular sieves = 1 : 9 (weight).

The structural characterization of compounds **7** was established on the basis of their spectrocopic parameters[10], mainly NMR including H,H-COSY and HMQC experiences. The presence of the substituted bicyclo[2,2,2]octene[15] in compounds **7** as well as their molecular symmetry is mainly supported by the presence of 4 signals in their ^1H NMR spectra for all 4 sets of heterotopic methine hydrogen atoms shown in Scheme 2 which exhibit a characteristic multiplicity. Moreover the all-*cis* relative configuration of these protons in the bicyclo[2,2,2]octene is consistent with the values of the coupling constants measured in the spectrum which are shown in Scheme 2. This structural assignment is also consistent with the stereochemical course of the reactions giving rise to **7** as it can be seen by the sequel.

The unexpected formation of compound **7** could be easily explained in term of the reactions sequence recorded in Scheme 2. Thus cycloaddition between dienes **1** and N-methyl maleimide gave the corresponding Diels-Alder *endo* adducts **4** with an allylic sulfoxide which yielded cyclohexenols **5** trough a highly stereoselective sulfoxide-sulfenate rearrangement.[16] The formation of **5** is favoured by the excess of N-methyl maleimide which acts as thiophilic agent.[8] The isolation of compound **5a**, resulting from the reaction of **1a**, allowed to demonstrate its participation in the process. The dehydration of these cyclohexenols, took place spontaneously probably favoured by the high stability of the resulting 5,6-*cis*-disubstituted-1,3-cyclohexadiene **6**, which in the case of the indole derivative, shows a very extended conjugation justifying the fast transformation of **5b** and preventing its isolation. Further evolution of dienes **6** through a new Diels-Alder cycloaddition with N-methyl maleimide explains the formation of the bicyclo [2,2,2] octene derivatives **7**. The reaction between **6** and the dienophile takes place through the more favourable *endo* approach on the less hindered face of the diene, opposite to the succinimide ring to give the adduct with the stereochemistry indicated in Scheme 2. This possible evolution must be taken into account when Diels-Alder reactions of 1-sulfinylsubstituted dienes were studied.

In conclusion, the results described in this paper indicate that the 1-sulfinyl substituted dienes with an endocyclic double bond **1a-b** are able to react with N-methylmaleimide, but, the resulting Diels-Alder adducts are not isolable, undergoing in situ a tandem sulfoxide-sulfenate rearrangement/dehydration/[4+2]-cycloaddition sequence. This sequence provides a stereoselective route to the highly substituted bicyclo[2,2,2]octene framework, not easily accessible by other way.

Acknowledgements. We thank DGICYT (PB-92-0162) and Acción Integrada Hispano Francesa (HF93-099) for financial support. M.B.C. thanks Ministerio de Educación y Ciencia for a fellowship.

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10. All new compounds were fully characterized by IR, ^1H and ^{13}C-NMR and MS or elemental analysis. **(+)-(*R*)-(*E*)-2-cyclohexenyl-1-vinyl-*p*-tolylsulfoxide (1a)**: m.p.: 72°C; $[\alpha]_D^{20}$ = +84 (c=1, $CHCl_3$); ^1H-NMR : 7.52 and 7.32 (AA'BB' system, 4H, *p*-Tol), 6.96 (d,1H, J =15 Hz, H_2), 6.18 (d, 1H, J = 15Hz, H_1), 6.12 (m, 1H, $H_{2'}$), 2.40 (s, 3H, CH_3-Ar), 2.19 (m, 2H, CH_2), 2.05 (m, 2H, CH_2, 1.75-1.52 (m, 4H, $2CH_2$). **(+)-(R)-(*E*)-N-methyl-3-[2-(*p*-tolylsulfinyl)-vinyl]-1H-indole (1b):** m.p: 100°C; $[\alpha]_D^{20}$ = +30 (c=1, $CHCl_3$); ^1H-NMR $[\alpha]_D^{20}$ = +30 (c=1, $CHCl_3$); ^1H-NMR : 7.75 (dd, 1H, J = 7.5 and 1Hz), 7.59 and 7.30 (AA'BB' system, 4H, *p*-Tol), 7.54 (d,1H, J =15 Hz, CH=CHSO), 7.37-7.14 (m, 3H, aromatics), 7.29 (s, 1H, CH-NMe), 6.77 (d,1H, J =15 Hz, CH=CHSO), 3.79 (s, 3H, NMe), 2.40 (s, 3H, CH_3-Ar); **5a-hydroxy-2-methyl-3a,5a,6,7,8,9,9a,9b-octahydrobenzo[e]isoindole-1,3-dione (5a)**: m.p: 138°C; $[\alpha]_D^{20}$ = -7.6 (c=1.39, $CHCl_3$); ^1H-NMR : 5.90 (m, 2H, H_4 and H_5), 3.55 (dd, 1H, $J_{H3a\text{-}H9b}$ = 8.4 Hz, $J_{H3a\text{-}H4a}$ = 2.6 Hz, H_{3a}), 2.94 (s, 3H, NMe), 2.88 (dd, 1H, $J_{H3a\text{-}H9b}$ = 8.4 Hz, $J_{H9a\text{-}H9b}$ = 5.9 Hz, H_{9b}). **Compound (7a)**: m.p: 260°C (dec.) ^1H-NMR data not recorded in Scheme 2: 2.74 (t, 2H, J=6.8 Hz), 2.69 (d, 2H, J=8Hz); 2.10 (dt, 2H, J=5.8, 2Hz); 1.77-1.65 (m, 2H); 1.44-1.32 (m, 2H) **Compound (7b)**: m.p: 94°C (dec.). ^1H-NMR (data not shown in Scheme 2): 7.26-7.03 (m, 2H, aromatics); 6.65-6.43 (m, 2H, aromatics); 3.32 (s, 3H, NMe indole).
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12. Configurational assignment of carbinol **3a** was based on the ^1H-NMR spectrum which agrees with other similar configurationally analog diastereomers already described: see ref. 11.
13. The use of an excess of NaH was critical to achieve the complete elimination of the intermediate methyl ether that was not isolated.
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15. In order to facilitate the comprehension of the structural assignement we use the name of bicyclo [2,2,2] octene for compounds **7** instead of the complex IUPAC name of these systems.
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