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Asymmetric Diels-Alder Reactions of γ-Alkoxy-α-sulfinylbutenolides

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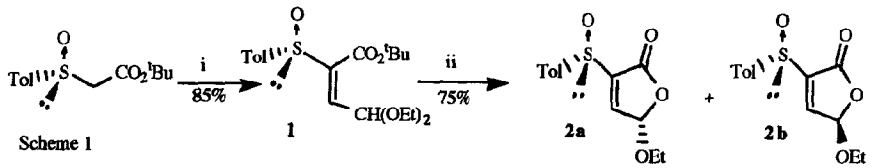
Abstract: The synthesis of the enantiomerically pure 5-ethoxy-3-*p*-tolylsulfinyl-2(5H)-furanones (**2a** and **2b**) and the study of their behaviour as dienophiles in asymmetric Diels-Alder reactions with cyclopentadiene are reported. Depending on the reaction conditions, the π-facial selectivity is mainly controlled by the sulfur or C-5 configurations.

Although chiral butenolides have played an important role as building blocks in the asymmetric synthesis of various natural products, very few reports have been published concerning their use as chiral dienophiles in asymmetric Diels-Alder reactions.[2,3] Despite the fact previously reported that 5-alkoxy-2(5H)-furanones control efficiently the π-facial selectivity, these dienophiles show two important limitations. Firstly, the reactivity is rather low, which determines the need of using high temperatures or pressures. Secondly, the regioselectivity of these cycloadditions is usually low or moderate.[4] Taking into account the dienophilic activating character of the sulfinyl group and the fact that α,β-unsaturated sulfoxides have shown to be able to control efficiently the π-facial selectivity and the regioselectivity of their cycloadditions,[5] we decided to incorporte the SOTol group into 5-alkoxy-2(5H)-furanone structures.[6] In this paper we report the synthesis of the enantiomerically pure 5-ethoxy-3-sulfinylbutenolides **2a** and **2b**, and the results concerning their reaction with cyclopentadiene. The symmetrical character of the diene limit the goal of this paper to check the effect of the sulfinyl group on the reactivity and to explore the competence of the two chiral centers (sulfur and C-5) in the control of the π-facial selectivity.



Scheme 1

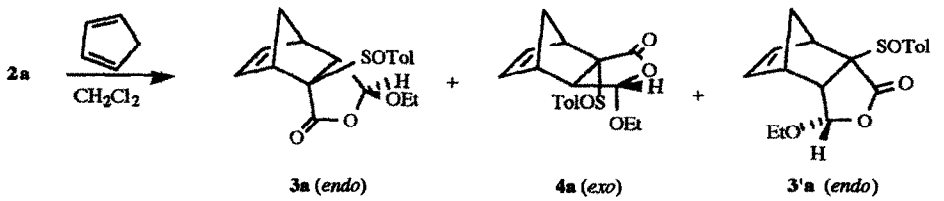
[i] $CHO\text{-}CH(OEt)_2$ (2 eq.), piperidine (2 eq.), CH_3CN, 60ºC, 60h. [ii] CF_3CO_2H, CH_2Cl_2, -20ºC, 30 min.

The synthetic sequence used to prepare the dienophiles **2a** and **2b** is depicted in Scheme 1. The reaction of (R)-*t*-butyl *p*-tolylsulfinyl acetate[5c] with glioxal diethylmonoketal in the presence of piperidine, yielded compound **1** (85% yield after chromatographic purification) as a 20:1 mixture of E:Z regioisomers. The treatment of (E)-**1**, which was easily purified by crystallization, with CF_3CO_2H (CH_2Cl_2, -20ºC, 30 min.) afforded a 1:1 equilibrium mixture of the ethoxy sulfinyl butenolides **2a** and **2b** which were purified and separated by flash chromatography.[7]

The results obtained in thermal and catalyzed reactions of **2a** and **2b** with cyclopentadiene in CH_2Cl_2 are collected in Tables 1 and 2. In the absence of catalyst, both dienophiles reacted completely at room temperature in 18 h giving a mixture of adducts. This fact gives evidence for a substantial increase of the reactivity with respect to

that observed for 5-alkoxybutenolides.The major components of these mixtures (**3a** and **3b** respectively) were separated by flash chromatography.[8]

Table 1: Reaction of **2a** with cyclopentadiene.

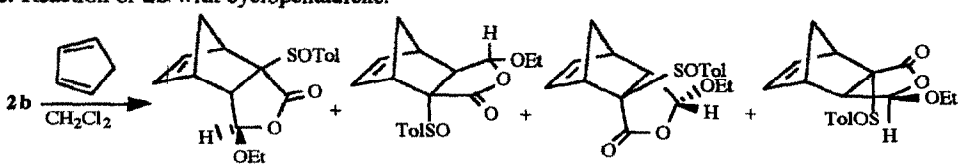


3a (*endo*) **4a** (*exo*) **3'a** (*endo*)

Catal.[a]	T (ºC)	t (h)	Adducts ratio[b] 3a	4a	3'a	Yield (%)[c]
----	rt	18	79	10	11	87
$ZnBr_2$	0	1	83	17	0	84
$Eu(fod)_3$	0	12	75	19	6	88
$TiCl_4$	-78	5	(Decomposition)			

[a] 1.2 eq. of catalyst. [b] Determined by ^{1}H-nmr from the crude mixtures. [c] In pure products after chromatography.

Table 2: Reaction of **2b** with cyclopentadiene.



3b (*endo*) **4b** (*exo*) **3'b** (*endo*) **4'b** (*exo*)

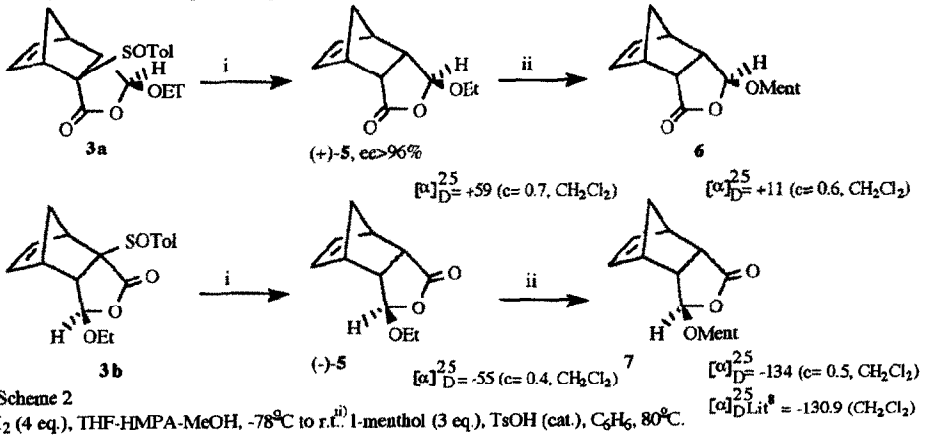
Catal.[a]	T (ºC)	t (h)	Adducts ratio[b] 3b	4b	3'b	4'b	Yield (%)[c]
----	rt	18	88	12	0	0	85
$ZnBr_2$	0	1	10	0	22	20	[d]
$Eu(fod)_3$	0	12	62	12	14	12	84

a, b, c See table 1. [d] 48% of a 5:1 mixture of adducts **3a** and **4a** was also obtained, showing the partial isomerization of **2b** to **2a** prior to the cycloaddition.[9]

The stereochemistry of the major products **3a** and **3b** has been established by chemical correlation with products of known structure. Thus, the hydrogenolysis of both adducts with SmI_2[10] gave the enantiomers (+)-**5** (46% yield) and (-)-**5** (55% yield) respectively (Scheme 2) with the same value but the opposite sign of their specific rotation. Compound (+)-**5** appeared to be enantiomerically pure within detection limits, according to the analysis of its ^{1}H-nmr spectrum with Pr(hfc)3. This result shows that the starting dienophiles **2a** and **2b** are also optically pure and that no epimerization occurs during the cycloaddition reaction. Compound *endo*-(±)-**5** was directly obtained by reaction of 5-ethoxy-2(5H)-furanone with cyclopentadiene.[11] Furthermore, the *endo*- or *exo*-character of the minor adducts has been established by ^{1}H-nmr.[12]

In order to demostrate the absolute configuration of the dienophiles and adducts, we have transformed both enantiomers of **5** into their 5-menthyloxy derivatives (compounds **6** and **7**) by reaction with *l*-menthol, catalyzed by TsOH (Scheme 2). Compound **7**, obtained from (-)-**5**, is identical to the adduct resulting in the reaction of cyclopentadiene with (5R)-5-(*l*-menthyloxy)-2(5H)-furanone, whose absolute configuration had been reported by

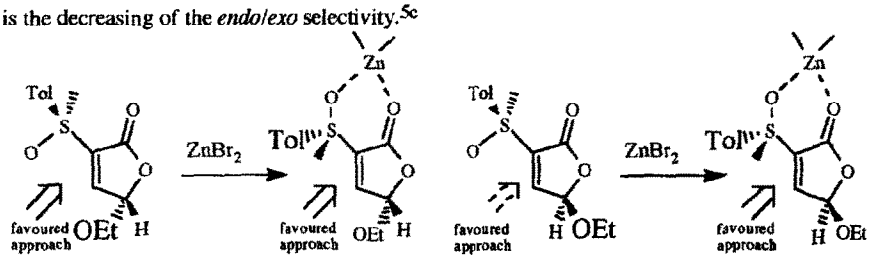
Feringa et al.[2] This result shows that the configuration of **2b** (starting dienophile of (-)-**5**) must be (*R*) at C-5 and therefore, the (*S*) configuration at C-5 must be assigned to **2a**. The results obtained by X-ray diffraction studies of compound **3a** (see ref. 8) unequivocally confirmed this conclusion.



Scheme 2

[i] SmI_2 (4 eq.), THF-HMPA-MeOH, -78°C to r.t. [ii] l-menthol (3 eq.), TsOH (cat.), C_6H_6, 80°C.

In the absence of Lewis acids as catalysts, the π-facial selectivity of the reactions with **2a** and **2b** is mainly controlled by the configuration at C-5 yielding as major compounds **3a** and **3b** respectively (the favoured diene approach takes place from the opposite face to that supporting the OEt group). In these conditions, the most reactive conformation around the C-S bond is that exhibiting the sulfinyl oxygen in *s-cis* arrangement which determines that the tendency imposed by the OEt group at C-5 was reinforced in the case of **2b** (complete π-facial selectivity is observed) and counteracted in **2a** (a 79:11 mixture of **3a** and **3'a** is obtained). By the contrary, the formation of the chelated species in the presence of $ZnBr_2$ determines a substantial increase of the steric hindrance for the approach of the diene to the face supporting the *p*-tolyl group. This determines that the steric effect exerced by the SOTol group is now higher than that of the OEt one (scheme 3). Therefore, the π-facial selectivity would be mainly governed by the sulfur configuration yielding **3a** and **3'b** as major adducts. The most significant effect of the $Eu(fod)_3$ is the decreasing of the *endo/exo* selectivity.[5c]



Scheme 3

We are currently working in the reactions of these and other similar dienophiles with asymmetric dienes in order to study the regioselectivity.

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3. R. Casas, T. Parella, V. Branchadell, A. Oliva, R.M. Ortuño, A. Guingant., *Tetrahedron*, **1992**, *48*, 2659 (and references cited therein).
4. The substituent at C-5 is not able to control the regioselectivity in other similar dienophiles as 5-alkoxy-3-pyrrolin-2-one (see W. Koot, H. Hiemstra, W.N. Speckamp, *J. Org. Chem.*, **1992**, *57*, 1059).
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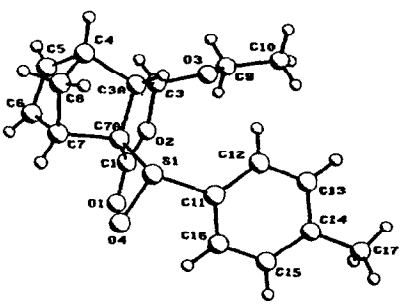
6. The sulfonyl group has been used to increase the dienophilic reactivity of the 5-alkoxy-2(5H)-furanones (J.C. de Jong, K.J. van den Berg, A.M. Leusen, B.L. Feringa, *Tetrahedron Lett.* **1991**, *32*, 7751).
7. **2a**: mp: 125-6ºC. $[\alpha]_D$= +356 (c=1, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ 1.28 (t, J=7.0 Hz, 3H), 2.40 (s, 3H), 3.7-4.0 (m, 2H), 5.91 (d, J=0.9 Hz, 1H), 7.32 and 7.68 (AA'BB' system, 4H) and 7.66 (d, J=0.9 Hz, 1H). ^{13}C-NMR ($CDCl_3$) δ 14.8, 21.4, 66.3, 102.1, 125.1, 130.1, 137.4, 143.0, 145.6, 148.1 and 164.4. **2b**: oil. $[\alpha]_D$= +205 (c=1, $CHCl_3$).^{1}H-NMR ($CDCl_3$) δ 1.24 (t, J=7.1 Hz, 3H), 2.40 (s, 3H), 3.65-3.95 (m, 2H), 6.00 (d, J=1.2 Hz, 1H), 7.33 and 7.69 (AA'BB' system, 4H) and 7.65 (d, J=1.2 Hz, 1H).^{13}C-NMR ($CDCl_3$) δ 14.8, 21.4, 66.7, 101.9, 125.3, 130.2, 137.5, 143.0, 145.6, 147.7, and 164.4
8. **3a**: mp: 143-4 ºC. $[\alpha]_D$= +90 (c=1, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ 0.98 (t, J=7.0 Hz, 3H), 1.71 (bd, J=9.3 Hz, 1H), 2.10 (bd, J=9.3 Hz, 1H), 2.41 (s, 3H), 2.95 (dd, J=4.2 and 1.5 Hz, 1H), 3.20-3.50 (m, 3H), 3.60 (m, 1H), 4.74 (d, J=1.5 Hz, 1H), 6.27 (dd, J=5.6 and 3.1 Hz, 1H), 6.36 (dd, J=5.6 and 2.9 Hz, 1H), 7.32 and 7.66 (AA'BB' system, 4H). ^{13}C-NMR ($CDCl_3$) δ 14.5, 21.5, 45.5, 48.0, 49.3, 51.2, 65.0, 76.8, 103.8, 126.3, 129.5, 135.9, 136.8, 137.5, 142.6 and 170.8. **3b**: mp: 102-3 ºC. $[\alpha]_D$= +38 (c=1, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ 0.81 (t, J=7.1 Hz, 3H), 1.61 (bd, J=9.0 Hz, 1H), 2.33 (bd, J=9.0 Hz, 1H), 2.40 (s, 3H), 3.00 (dd, J=4.3 and 1.5 Hz, 1H), 3.12-3.17 (m, 1H), 3.18 (q, J=7.1 Hz, 2H), 3.64 (bs, 1H), 4.68 (d, J=1.5 Hz, 1H), 6.39 (m, 2H), 7.28 and 7.52 (AA'BB' system, 4H). ^{13}C-NMR ($CDCl_3$) δ 14.4, 21.4, 44.0, 47.6, 48.8, 51.5, 64.9, 79.9, 105.3, 125.8, 129.5, 136.7, 137.5, 138.2, 142.1 and 172.4.



Three dimensional structure of one molecule of **3a** in the solid state

9. The treatment of the diastereomerically pure **2a** or **2b**, with $ZnBr_2$ (1 eq,) in CH_2Cl_2 at 0ºC, yielded a 1:1 mixture of both dienophiles. The equilibration takes place in less than 1h starting from **2b**, whereas **2a** requires 3h to reach the equilibrium composition.
10. The use of other desulfinylation reactions were unsuccessful. The reduction with Al(Hg) does not work and decomposition of the substrates was observed during the pyrolysis of **3a** and **3b** in boiling toluene or xylene. Furthermore, the treatment of the dienophiles with Raney Ni yields the products resulting in the reduction of the double bond, without hydrogenolysis of the C-S bond.
11. a) K. Alder, F. Fariña *An. Quim.* **1958**, *54-B*, 689. b) F. Fariña, M.V. Martin, M.C. Paredes, M.C. Ortega, A. Tito, *Heterocycles* **1984**, 22, 1733.
12. As assignment criteria for *endo*/*exo* stereochemistry, the *exo*-adducts show significant lower chemical shifts at the protons of the methylene bridge and at Cβ-H (proton at axial position in *exo*-adducts whereas at equatorial position in *endo*-adducts). Concerning an assignment criteria for the π-facial selectivity, $J_{\beta,\gamma}$= 1.5 Hz in adducts **3a**, **4a**, **3b** and **4b** while $J_{\beta,\gamma}$= 6-7 Hz in adducts **3'a**, **3'b** and **4'b**.