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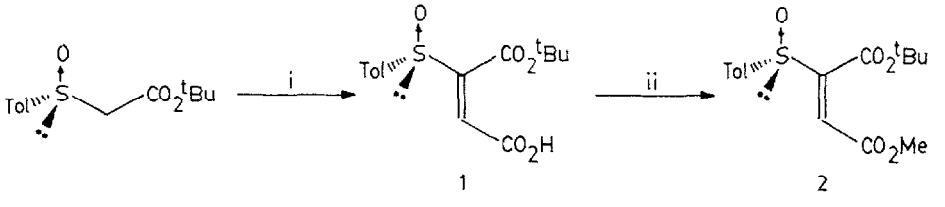
SYNTHESIS AND DIELS-ALDER REACTIONS OF *t*-BUTYL AND *t*-BUTYL, METHYL (*S*)s-2-*p*-TOLYLSULFINYLMALEATES, CHIRAL SYNTHETIC EQUIVALENTS OF MONOALKYL AND MIXED DIALKYL ACETYLENEDICARBOXYLATES

Inés Alonso, J. Carlos Carretero* and José L. García Ruano*

Departamento de Química (C-I). Universidad Autónoma de Madrid.
Cantoblanco, 28049-Madrid. SPAIN

SUMMARY: The reaction of *t*-butyl *p*-tolylsulfinylacetate with glyoxylic acid yielded maleate monoester **1**, whose methylation afforded asymmetric diester **2**. Conditions in which **1** and **2** react with cyclopentadiene exhibiting high *facial* and *endo* selectivities are reported.

The sulfinyl group has been used to control the *facial* selectivity of Diels-Alder reactions on vinylketosulfoxides.[1] The main problem of these substrates derived from their moderate or low reactivity as dienophiles. However very little attention has been paid to the synthesis of 2-sulfinylmaleates, although these dienophiles would be more reactive than vinylketosulfoxides, retaining their ability to control the stereochemistry of the cycloaddition. The synthesis of dimethyl (*R*)s-2-(10-isobornylsulfinyl)maleate and its behaviour as dienophile have been reported,[2] resulting an interesting chiral synthetic equivalent of dimethyl acetylenedicarboxylate, which is a versatile compound widely used for the preparation of several kinds of natural product.[3] Nevertheless, this synthetic equivalent has several limitations, arising from: i) the non-trivial chiral auxiliary (10-mercaptoisoborneol) required to synthesize this dienophile, ii) the low stereoselectivity observed in the synthesis of the thioether, precursor of the sulfinyl reagent and iii) the non-differentiation of the two ester groups present in the molecule (selective demethylation, as a previous step of the desulfinylation, was necessary to avoid symmetrization). In the present paper the synthesis of two new sulfinyl maleates avoiding the above disadvantages, and the reaction of these compounds with cyclopentadiene are reported.



1 2

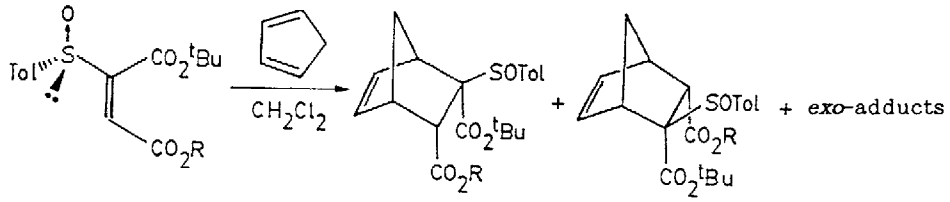
i) OCH-CO_2H/Et_3N/Pyrrolidine (DMF, rt); ii) $NaHCO_3$/MeI (DMF, rt).

Scheme 1

The most effective way to prepare both dienophiles is depicted in Scheme 1. The reaction of *t*-butyl acetate with (-)-(S)-menthyl *p*-toluenesulfinate in conditions previously reported[4]

affords (R)-*t*-butyl *p*-tolylsulfinylacetate, whose reaction in DMF with glyoxylic acid (2 equiv.) in the presence of triethylamine (3 equiv.) and pyrrolidine (0.35 equiv.), yielded monoester **1** (63% yield, $[\alpha]_D$=+181º, c=0.76, $CHCl_3$) stereoselectively. The treatment of **1** with $NaHCO_3$/MeI in DMF gave the mixed diester **2** (85% yield, $[\alpha]_D$=+179º, c=1.0, $CHCl_3$, e.e.>98%, determined by using Yb(hfc)$_3$ as chiral shift reagent). When reactions i) and ii) (Scheme 1) were carried out without isolation of compound 1, the overall yield in the synthesis of 2 rose to 72%.[5]

The results obtained in the reaction of **1** and **2** with cyclopentadiene in CH_2Cl_2 under different conditions [including the use of ultrasound (entry 9), H_2O as solvent[6] (entry 6), BH_3 as catalyst[7] (entry 5) and the addition of $LiClO_4$[8] (entry 12) and other Lewis acids] are collected in Scheme 2.



1 : R=H
2 : R=Me

3_{endo} 4_{endo} $3'_{endo}$ $4'_{endo}$

Entry	dienophile[a]	Catalyst (1.2 eq)	T(ºC)	react. time(h)	Products (%)[b] 3_{endo}	$3'_{endo}$	exo	Yield(%)[c]
1	1(3)	-	r.t.	1	89	6	5	[d]
2	1(3)	-	0	3	88	7	5	[d]
3	1(10)	-	-20	12	91	5	3	[d]
4	1(3)	$ZnBr_2$	-20	2	complex mixture[e]			
5	1(10)	BH_3.THF	-10	20	84	9	7	[d]
6	1(10)	[f]	r.t.	28	30	47[g]	-	[d]
					4_{endo}	$4'_{endo}$	exo	
7	2(10)	-	r.t.	41	58	17	25	93
8	2(6)	$ZnBr_2$	0	2	12	79	9	88
9	2(6)	$ZnBr_2$[h]	0	2	9	82	9	90
10	2(6)	$ZnBr_2$	-20	7	6	89	5	95
11	2(10)	SiO_2[i]	r.t.	2	33	45	22	90
12	2(5)	$LiClO_4$[j]	r.t.	4	31	48	21	91
13	2(6)	BF_3.OEt_2	-20	7	43	37	20	81[k]

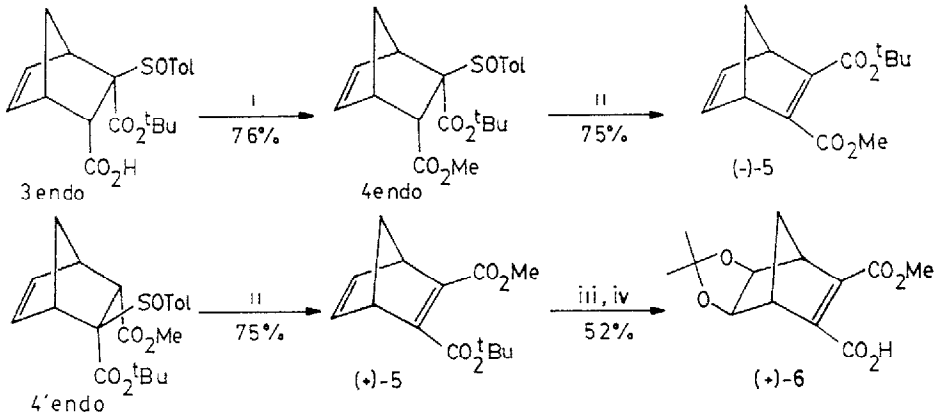
[a] equivalents of diene in brackets; [b] by ^{1}H-nmr; [c] in pure adducts after chromatography; [d] see ref. 9; [e] signals corresponding to at least six adducts (some of them without t-butyl group) were observed; [f] solvent : H_2O/$NaHCO_3$(1.2 eq.); [g] 23% of starting dienophile was recovered; [h] Reaction carried out under sonication; [i] Weight ratio SiO_2/2 = 10:1; [j] 5M solution in ether; [k] 19% of starting dienophile was recovered.

Scheme 2

For compound **1**, the highest *endo/exo* and *facial* selectivities were achieved at -20ºC in the absence of Lewis acids (entry 3: *endo/exo* = 32, $3_{endo}/3'_{endo}$=18), whereas the best results for compound **2** were obtained at -20ºC in the presence of 1.2 equiv. of $ZnBr_2$ (entry 10[10]: *endo/exo* = 19, $4'_{endo}/4_{endo}$ = 15). Interestingly, opposite facial selectivities were exhibited

by 1 and 2 under the above mentioned conditions. Adducts 3 and 4 could be easily correlated by methylation (MeI/$NaHCO_3$/DMF), and *exo*-adducts were separated from the mixture of *endo*-adducts by flash chromatography (CH_2Cl_2:Et_2O=30:1).

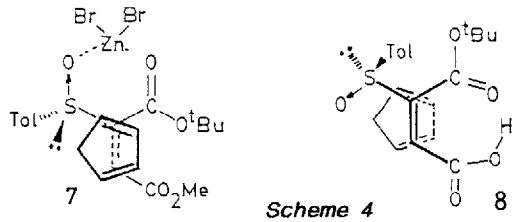
The *endo* structure of the major adducts (**3**$_{endo}$ and **4'**$_{endo}$)[11] has been unequivocally established by intramolecular halolactonization reactions,[12] and their absolute configuration by chemical correlation of compound (+)-**5**[13] (obtained by basic elimination of the sulfinyl group from **4'**$_{endo}$) with the previously reported compound (+)-**6**[14] (Scheme 3). The reaction of **4**$_{endo}$ with DBU/toluene, at 50°C, gave the enantiomer (-)-5 (Scheme 3).



i) $NaHCO_3$/MeI (DMF,rt); ii) DBU (toluene, 50°C); iii) OsO_4/$ONMe_3$ (*t*-BuOH, rt); iv) $(MeO)_2CMe_2$/*p*-TsOH (acetone, reflux).

Scheme 3

The observed facial selectivity for diester 2 in the presence of $ZnBr_2$ can be explained assuming the attack of diene on the chelate 7 (S-*trans* conformation), where the upper face is less hindered to the cyclopentadiene approach. In the case of monoester 1, the intramolecular hydrogen bond presumably determines the preference for the S-*cis* conformation 8, in which the favoured face is the opposite to that of the chelate 7 (see Scheme 4). The opposite *facial* selectivity exhibited for compound 1 in CH_2Cl_2 and H_2O (entries 3 and 6 in Scheme 2) are in agreement with this hypothesis.



Scheme 4

ACKNOWLEDGEMENTS

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5.- Compound **1**. ^{1}H-nmr: 1.27 [*s*, 9H, (CH_3)$_3$C], 2.41 (*s*, 3H, CH_3-C_6H_4), 6.95 (*s*, 1H, *H-2*), 7.31 and 7.56 (*two doublets*, 2H each, J=8.0 Hz, *aromatic protons*), 9.0 (*bs*, 1H, CO_2H). ^{13}C-nmr: 21.31, 27.28, 84.44, 126.16, 126.61(2C), 129.95(2C), 136.99, 143.29, 150.21, 160.34, 166.31.
Compound **2**. ^{1}H-nmr: 1.28 [*s*, 9H, (CH_3)$_3$C], 2.41 (*s*, 3H, CH_3-C_6H_4), 3.81 (*s*, 3H, CO_2CH_3), 6.89 (*s*, 1H, *H-3*), 7.31 and 7.57 (*two doublets*, 2H each, J=8.0 Hz, *aromatic protons*). ^{13}C-nmr: 21.36, 27.45, 52.24, 84.05, 124.56, 126.44(2C), 129.94(2C), 137.30, 143.10, 152.12, 160.45, 164.33.
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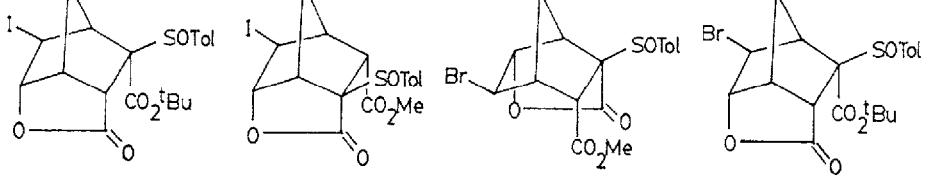
8.- P. A. Grieco, J. J. Nunes and M. D. Gaul; *J. Am. Chem. Soc.*, **1990**, *112*, 4595.
9.- Almost quantitative yields were obtained in crude adducts **3**. These adducts were transformed into their methyl esters **4**, and then purified by flash chromatography. The overall yields of this sequence ranges in 75-85%.
10.- In order to minimize the acidic hydrolysis of the *t*-butyl ester, the cycloadditions must be carried out on diluted solutions. Thus, yield in adducts **4** was 95% from a solution 0.15 M, decreasing till 58% when such solution was 0.4 M.
11.- Compound **3$_{endo}$**. ^{1}H-nmr: 1.17 [*s*, 9H, (CH_3)$_3$C], 1.31 (*bd*, 1H, J=9.0 Hz, *H-7*), 2.06 (*bd*, 1H, J= 9.0 Hz, *H-7'*), 2.40 (*s*, 3H, CH_3-C_6H_4), 3.15 (*bs*,1H, *H-4'*), 3.48 (*bs*, 1H, *H-1*), 3.68 (*d*, 1H, J=3.04 Hz, *H-3*), 6.09 (*dd*, 1H, J=3.0 and 5.4 Hz, *H-6*), 6.62 (*dd*, 1H, J=3.0 and 5.4 Hz, *H-5*), 7.27 and 7.63 (*two doublets*, 2H each, J=8.0 Hz, *aromatic protons*), 9.7 (*bs*, 1H, CO_2H). ^{13}C-nmr: 21.48, 27.44(3C), 44.81, 46.09, 46.32, 53.92, 81.51, 83.78, 126.84(2C), 129.14 (2C), 133.46, 137.14, 141.50, 142.54, 165.81 and 176.17.
Compound **4'$_{endo}$**. ^{1}H-nmr: 1.31 [*s*, 9H, (CH_3)$_3$C], 1.38 (*dt*, 1H, J=1.6 and 9.1 Hz, *H-7*), 1.98 (*bd*, 1H, J= 9.1 Hz, *H-7'*), 2.42 (*s*, 3H, CH_3-C_6H_4), 3.16 (*bs*,1H, *H-4*), 3.27 (*bs*, 1H, *H-1*), 3.55 (*d*, 1H, J=4.2 Hz, *H-3*), 3.56 (*s*, 3H, OCH_3), 6.13 (*dd*, 1H, J=3.0 and 5.5 Hz, *H-6*), 6.57 (*dd*, 1H, J=3.0 and 5.5 Hz, *H-5*) 7.31 and 7.64 (*two doublets*, 2H each, J=8.3 Hz, *aromatic protons*). ^{13}C-nmr: 21.10, 27.52(3C), 44.75, 46.44, 49.49, 49.77, 51.13, 80.97, 82.56, 125.84(2C), 128.86 (2C), 134.06, 136.77, 140.08, 141.72, 165.70 and 171.55.
12.- The treatment of **3$_{endo}$** with $NaHCO_3/I_2/KI$ gave the yodolactone **9** (76% yield). The reaction of **4'$_{endo}$** with HCO_2H followed by treatment with $I_2/NaHCO_3/KI$ afforded the yodolactone **10** (38% yield). The methylation of **3$_{endo}$** yielded **4$_{endo}$**,[^{1}H-nmr: 1.30 [*s*, 9H, (CH_3)$_3$C], 1.32 (*bd*, 1H, J=9.0 Hz, *H-7*), 2.16 (*bd*, 1H, J= 9.0 Hz, *H-7'*), 2.40 (*s*, 3H, CH_3-C_6H_4), 3.10 (*bs*,1H, *H-4*), 3.27 (*s*, 3H, OCH_3), 3.54 (*bs*, 1H, *H-1*), 3.57 (*d*, 1H, J=3.1 Hz, *H-3*), 6.10 (*dd*, 1H, J=3.0 and 5.5 Hz, *H-6*), 6.73 (*dd*, 1H, J=3.0 and 5.5 Hz, *H-5*) 7.26 and 7.62 (*two doublets*, 2H each, J=8.5 Hz, *aromatic protons*). ^{13}C-nmr: 21.37, 27.82(3C), 44.30, 44.41, 45.62, 50.86, 54.94, 80.96, 83.28, 126.67(2C), 128.76 (2C), 133.00, 138.24, 142.04, 142.43, 166.36 and 172.31] which reacted with Br_2 (1.2 eq) in $CHCl_3$ during 24 h. at room temperature (R. Nesi, D. Giomi, S. Papaleo and M. Corti, *J. Org. Chem.*, **1990**, *55*, 1227) yielding a mixture of bromolactones, where **11** and **12** could be identified. These results show the *endo* character of the adducts and the *cis* stereochemistry of the dienophiles **1** and **2**.



9 **10** **11** **12**

13.- Compound (+)-**5** was obtained from a 15:1 mixture of **4'$_{endo}$+4$_{endo}$** adducts (entry 10 in Scheme 2). Its optical purity (e.e.=87%, $[\alpha]_D$=+3.0°, c=1.16, $CHCl_3$) was estimated by ^{1}H-nmr [Yb(hfc)$_3$ as chiral shift reagent].
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