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Syn or *Anti* Selective Michael Addition of Allyl Phenyl Sulphone and Phenyl Prenyl Sulphone to Enoates Derived From D-Mannitol.

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Abstract: Prenyl and allyl sulphones (**3a,b**) were deprotonated with BuLi in THF and the resulting carbanions were allowed to react with enoates prepared from D-(+)-mannitol. A major diastereomer (control at the two newly created stereogenic centers) was obtained from enoates ***E*-1b-c** (Ethyl and t-Butyl ester, respectively) in d.e. up to 90 %. S*yn*-stereoselectivities were observed when the reactions were stopped at r.t. while at -78^0 C *anti*-stereoselectivities predominated. Enoate ***E*-1a** (methyl ester) led to anti-addition regardless the temperature at which the reaction was quenched. However, a *syn*-stereoselectivity was found when the reaction was run in the presence of HMPA. The stereochemical assignments for both newly generated stereogenic centers were based on the transformation of the adducts into the corresponding β,γ-disubstituted γ-lactones, followed by measurements of ^{1}H,^{1}H coupling constants and nOe experiments.

Prenyl and allyl moieties are commonly found in the structure of many interesting natural products.[1] Both cationic[2] and anionic[3] synthons have been used as intermediates for introduction of such unities in synthetically useful chemical yields and high regio and stereoselectivities.

In this letter we describe the stereoselective Michael addition of prenylsulphone (**3a**) and allylsulphone (**3b**) to a chiral enoate ***E*-1a** (Me ester) prepared from D-mannitol.[4] The ethyl and t-butyl ester derivatives of ***E*-1a** , enoates ***E*-1b** and ***E*-1c** respectively, were also used as acceptors, in this study.

Our first results involved the addition of **3a** to the enoate ***E*-1a** (scheme 1). Deprotonation of **3a** (BuLi, THF, 0 °C, 0.5h) resulted in a red anion. The reaction vessel was cooled to -78 °C and ***E*-1a** was added. In one protocol, the reaction was kept at -78 °C for 1 hour and then it was quenched with aqueous NH_4Cl (entry 1). Alternatively the pot temperature was increased to r.t., kept then for 2h, and then quenched (entry 2). The products obtained according to both protocols displayed identical ^{1}H NMR and ^{13}C NMR spectra. The C-C bond formed resulted from a Michael addition involving exclusively the carbon at the α-position of the sulphone group (high regioselectivities for both reagents), with high degree of control at the two newly generated stereogenic centers (stereoselectivity ≥ 90 %). The structure of the addition product was shown to be ***anti*-2a$_1$** through its transformation into the corresponding lactone acetate ***trans*-5**.[5-6] In sharp contrast, the selectivity could be reversed when the Michael addition step was performed in the presence of HMPA, followed by quenching of the reaction at r.t. (entry 3, scheme 1). This adduct had its structure assignned as ***syn*-2a$_1$** through its transformation into the lactone acetate ***cis*-5**.[5]

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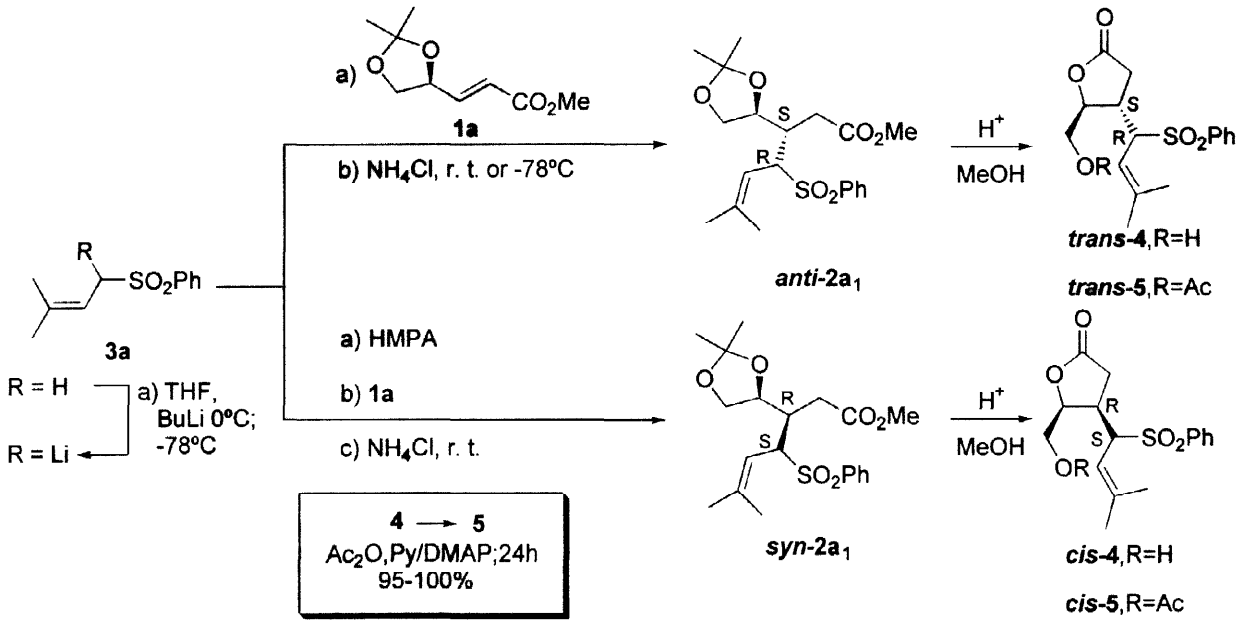
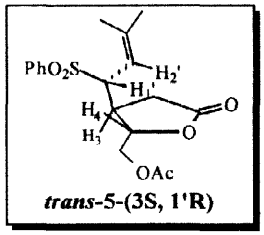


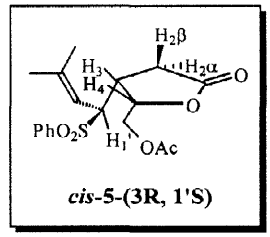
Entry	1	3	Solvent	Temp.	Yield (%)	*Anti* : *Syn*
1	**a**	**a**	THF	-78°C	60	≥ 95 : 5
2	**a**	**a**	THF	r.t.	57	≥ 95 : 5
3	**a**	**a**	THF/HMPA	r.t.	66	≤ 5 : 95

Scheme 1



J H3, H4 = 4,4Hz;
J H3, H1' = 5,5Hz.
angle H3, H1' = 140°

Irradiation of :
H4, 3,53% nOe at H1'
H2α, 1,35% nOe at HAr
H2β, 5,04% nOe at H2'



J H3, H4 = 7,9Hz;
J H3, H1' = 10,5Hz.
angle H3, H1'= 159°

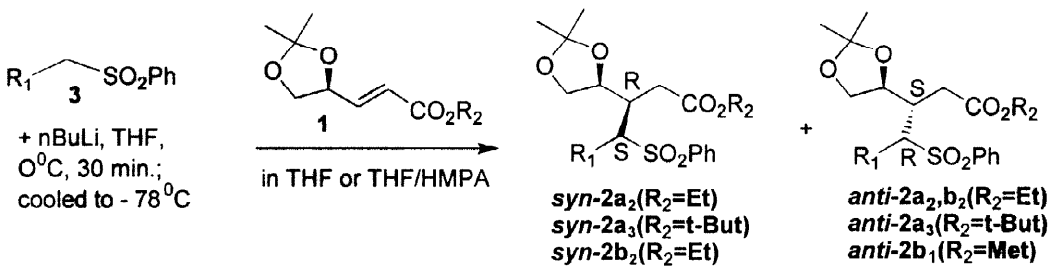
Irradiation of :
H4, 2,40% nOe at H3
H2α, 1,29% nOe at H2'
H5a, 2,54% nOe at H1'
and 0,61% nOe at HAr

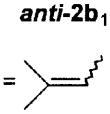
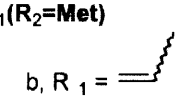
Figure 1

The configurations at C3 and C1' in lactones ***trans*-5** and ***cis*-5** are proposed on the basis of ^{1}H NMR data and nOe experiments (Figure 1).[4,7] In ***trans*-5**, the coupling constant measured between H3 and H4 (JH3,H4 = 4.4 Hz) suggests a *trans* relationship between these hydrogens and, as a consequence, a ***S*** configuration at C3 in adduct ***anti*-2a$_1$**. The absence of nOe in H3 upon irradiation of H4 confirmed this assumption. On the other hand, nOe and J measurements indicated that conformational constraints lock the substituents around C3-C1' bond. The mesasured coupling constant between H3 and H1' (J = 5.5 Hz; $\theta \cong$ 140°) suggests an *anti* relationship between them, thereby requiring H1' to be located over the lactone ring. This arrangement was confirmed by an enhancement of 3.53% at H1', after irradiation of H4. The 1.35% nOe observed for the aromatic hydrogens after irradiation of H2α, and 5.02% nOe observed at H2', after irradiation of H2β suggests a ***R*** configuration for C1' stereogenic center.

Additionally, the *cis* relationship between H3 and H4 in ***cis*-5** was confirmed by their coupling constant (7.9 Hz) and 2.4 % nOe at H3 following irradiation of H4. The position of H1' was also suggested by the coupling constant between H3 and H1' (J = 10.5 Hz; $\theta \cong 159°$) and confirmed by an enhancement of 2.54% at H1', after irradiation of H5a. The ***S*** configuration for C1' was proposed on the basis 1.29% nOe at H2' after irradiation of H2α. Furthermore, an enhancement of 0.6% in the absorption of the phenyl group protons upon irradiation of H5a, although small, also suggests this configuration.

The next step was to study the additon of **3a** to enoates ***E*-1b** and ***E*-1c**, in order to investigate a possible role of the ester moiety in the enoate on the stereoselection. The results obtained are described in scheme 2.[8] In contrast with the results observed for ***E*-1a**, the stereoselection of the addition of **3a** to ***E*-1b** depended on the temperature at which the reaction was stopped (entries 1 and 2). At -78 °C, the major adduct obtained was ***anti*-2a$_2$** (entry 1, de ≥ 95 :5), while ***syn*-2a$_2$** (entry 2, de ≥ 95 :5) predominates when the reaction was allowed to warm to r.t. and, after 2h, quenched with aqueous NH_4Cl. Similar results were obtained when enoate ***E*-1c** was used as an acceptor (entries 4 and 5). The *anti*-selectivity (adduct ***anti*-2b$_1$**, R_2=Me) was also obtained when the carbanion of **3b** was added to ***E*-1a** and the reaction was quenched at r.t. (entry 6). The same selectivity (adduct ***anti*-2b$_2$**, R_2=Et) was obtained when ***E*-2b** was used as acceptor and the reaction was quenched at -78 °C (entry 7).



For **1**: **a**, $R_2 = CH_3$; **b**, $R_2 = CH_3CH_2$; **c**, $R_2 = (CH_3)_3C$ For **2 and 3**: a, R_1 =  b, R_1 = 

Entry	1	3	Solvent	Temp.	Yield (%)	*Anti* : *Syn*
1	**b**	**a**	THF	-78°C	65	≥ 95 : 5
2	**b**	**a**	THF	r.t.	55	≤ 5 : 95
3	**b**	**a**	THF/HMPA	r.t.	60	≤ 5 : 95
4	**c**	**a**	THF	r.t.	56	≤ 5 : 95
5	**c**	**a**	THF	-78°C	60	≥ 95 : 5
6	**a**	**b**	THF	r.t.	67	≥ 95 : 5
7	**b**	**b**	THF	-78°C	64	≥ 95 : 5
8	**a**	**b**	THF	-78°C	63	≥ 95 : 5

Scheme 2

For the experiments showed in scheme 2 a kinetically controlled product distribution seems to operate when the additions to ***E*-2b** (Ethyl ester) and ***E*-2c** (t-Butyl ester) are developed and quenched at -78 °C. Under these conditions ***anti*-2b-c** adducts were formed in high stereoselectivities. The same reactions when quenched after 2h at r.t. (thermodynamic control) led to ***syn*-2b-c** in high *syn*-stereoselectivities. On the other hand, only *anti* adducts (***anti*-2a$_1$** (3S, 1'R) and ***anti*-2b$_1$** (3S)) were formed for the addition of **3a** and **3b** to ***E*-1a,** regardless of the temperature at which the reaction was quenched.

Thus, the present methodology enables the preparation of the newly generated stereogenic centers at C3 and C1' in both configurations employing the same source of chirality.

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Experimental Section

Preparation of *anti*-2 and *syn*-2: To a stirred solution of **3a** (0.105g, 0.5mmol) in THF (1.0 mL) at 0 °C was added n-BuLi (0.55mmol). The resulting red solution was stirred for an additional 0.5 h and cooled to -78 °C. The enoate **1a-c** (0.55mmol) was added. The reaction was quenched with aqueous NH_4Cl, at -78 °C or r.t. to ***anti*-2**, while to ***syn*-2** the reaction was quenched with aqueous NH_4Cl, at r.t. after 2h, followed by extraction with AcOEt. The residue was purified by column chromatogrphy on silica gel (Hex/AcOEt).

Data for ***cis*-5**: ^{1}H-NMR (200 MHz, $CDCl_3$) δ 1.01 (**d**, *J* = 1.3 Hz, 3H, H4'), 1.66 (**d**, *J* = 1.4 Hz, 3H, H5'), 2.07 (**s**, 3H, H7), 2.40 (**dd**, *J* = 17.5 Hz, *J* = 11.6 Hz, 1H, H2β), 2.53 (**dd**, *J* = 17.5 Hz, *J* = 9.4 Hz, 1H, H2α), 3.45 - 3.69 (**m**, 1H, H3), 3.99 (**dd**, *J* = 10.5 Hz, *J* = 10.5 Hz, 1H, H1'), 4.55 (**dd**, *J* = 12.9 Hz, *J* = 2.7 Hz, 1H, H5b), 4.81 (**dd**, *J* = 12.9 Hz, *J* = 2.7 Hz, 1H, H5a), 5.04 (**dm**, *J* = 10.5 Hz, 1H, H2'), 5.16 (**ddd**, *J* = 7.9 Hz, *J* = 2.7 Hz, *J* = 2.7 Hz 1H, H4), 7.53 - 7.74 (**m**, 3H, H3'', H4'' e H5''), 7.79 - 7.85 (**m**, 2H, H2'' e H6'').

Data for ***trans*-5**: ^{1}H-NMR (200 MHz, $CDCl_3$) δ 1.09 (**d**, *J* = 1.4 Hz, 3H, H4'), 1.71 (**d**, *J* = 1.4 Hz 3H, H5'), 2.06 (**ss**, 3H, H7), 2.74 (**dd**, *J* = 18.4 Hz, *J* = 7.5 Hz, 1H, H2β) 2.90 (**dd**, *J* = 18.4 Hz, *J* = 9.3 Hz, 1H, H2α), 3.21 - 3.36, (**m**, 1H, H3), 3.92 (**dd**, *J* = 5.5 Hz, *J* = 11.0 Hz, 1H, H1'), 4.29 (**dd**, *J* = 12.5 Hz, *J* = 5.6 Hz, 1H, H5a), 4.41 (**dd**, *J* = 12.5 Hz, *J* = 3.0 Hz, 1H, H5b), 4.61 (**ddd**, *J* = 5.6 Hz, *J* = 4.4 Hz, *J* = 3.0 Hz, 1H, H4), 5.13 (**dm**, *J* = 11.0 Hz, 1H, H2'), 7.50 - 7.71 (**m**, 3H, H3'', H4'' e H5''), 7.79 - 7.85 (**m**, 2H, H2'' e H6'').

References and Notes

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5. The stereoselectivities were measured by ^{1}H NMR. For ***syn*-2a,b**: CH_2CO_2R, 2.1-2.3 ppm e 3.0-3.2ppm; R_2C=CRH, 5.17-5.18ppm. For ***anti*-2a,b**: CH_2CO_2R, 2.3-2.5ppm e 2.8-3.0ppm; R_2C=CRH, 5.12-5.13ppm.
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7. Hauser, F., Rhee, R., Ellenberger, S. *J. Org. Chem.*, **1984**, *49*, 2236.
8. The adducts ***anti*-2a$_{1-2}$** and ***cis*-2a$_{1-2}$** were transformed into the same lactones ***trans*-4** and ***cis*-4** respectively.