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THE ALDOL ADDITION REACTION BETWEEN γ-OXYGENATED CARBOXYLIC ESTERS DERIVED FROM 2,6-DIMETHYLPHENOL AND PIPERONAL.

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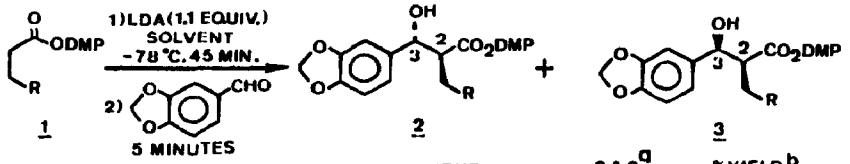
Abstract: The stereoselectivity of the aldol addition reaction between γ-oxygenated DMP-esters 1a-b and piperonal depends on the nature of the γ-oxygenated substituent. A syn-diastereoselectivity was observed from 1a. This reverse selectivity is due to the chelation properties of the ketal moiety leading preferentially to the Z-enolate 7a by altering the transition state of the deprotonation step.

The aldol addition reaction between the lithium enolates derived from esters of 2,6-dimethylphenol (DMP) and aldehydes, under kinetic conditions, occurs with good simple diastereoselection, leading to anti-adducts.[1] Excellent diastereofacial selections can also be obtained when the lithium enolates are transformed into chiral titanium enolates before the addition of the electrophiles.[2] These results have been interpreted assuming the preferential formation of E-enolates in the deprotonation step and the stereoselective reaction of these species with the aldehydes via the Zimmerman-Traxler chair-like transition states.

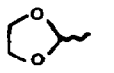
We studied the reaction of the lithium enolates derived from the DMP-esters 1a-b[3] with piperonal (scheme 1). The noteworthy effect of the oxygenated functions in the γ-position of these esters on the stereoselectivity prompted us to report these results. As shown in scheme 1, a reverse stereoselectivity was obtained when 1a was used as substrate (entry 1), leading preferentially to the syn-adduct 3a. In contrast, 1b led to the anti-adduct 2b with good stereoselectivity (entry 3). The preference for the anti-adduct was also observed for 1c (entry 4). The syn-stereoselection observed in entry 1 can be enhanced by using HMPA as the co-solvent (entry 2).[4]

In order to understand the results shown in scheme 1, we decided to investigate the stereoselectivity of the deprotonation step. Thus, the lithium enolates formed in entries 1-3 were trapped with TBDMS-Cl[5] instead piperonal. As shown in scheme 2, ester 1b (entry 3) led stereoselectively

to the expected E-ketene-sylyl-ketal 4b. On the other hand, 1a led preferentially to the Z-isomer 5a (entry 1). When HMPA was the co-solvent in the deprotonation step, the expected Z-enolates were the main products obtained from 1a and 1b (entries 2, 4).[6]



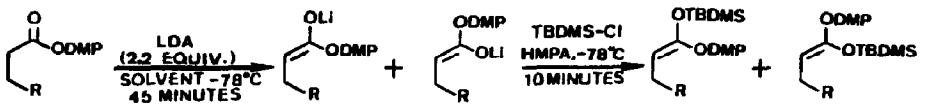
1 2 3

ENTRY	1	R	SOLVENT	2 : 3[a]	%YIELD[b]
1	a		THF	34 : 66	75
2	a		THF-20%HMPA	5 : 95	77
3	b	$CH_2OTBDMS$	THF	90 : 10	70
4	c	$CH=CH_2$	THF	90 : 10	76

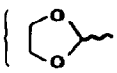
a) Ratios determined by ^1H NMR (300MHz) from the signals of H_2 and H_3. For 2a: J_{23}=7.99Hz; for 3a: J_{23}=5.86Hz; for 2b: J_{23}=7.98Hz; for 2c: J_{23}=7.99Hz. See reference 4.

b) After flash-chromatography on silica gel by using 10% AcOEt in n-hexane as the eluant. The isomers were not separated.

Scheme 1



1 6 7 4 5

ENTRY	1	R	SOLVENT	4 : 5[a]	%YIELD[b]
1	a		THF	34 : 66	73
2	a		THF-30%HMPA	2 : 98	90
3	b	$CH_2OTBDMS$	THF	90 : 10	82
4	b	$CH_2OTBDMS$	THF-30%HMPA	10 : 90	90

a) Stereochemistries and ratios determined by ^1H NMR (200MHz). See reference 6.

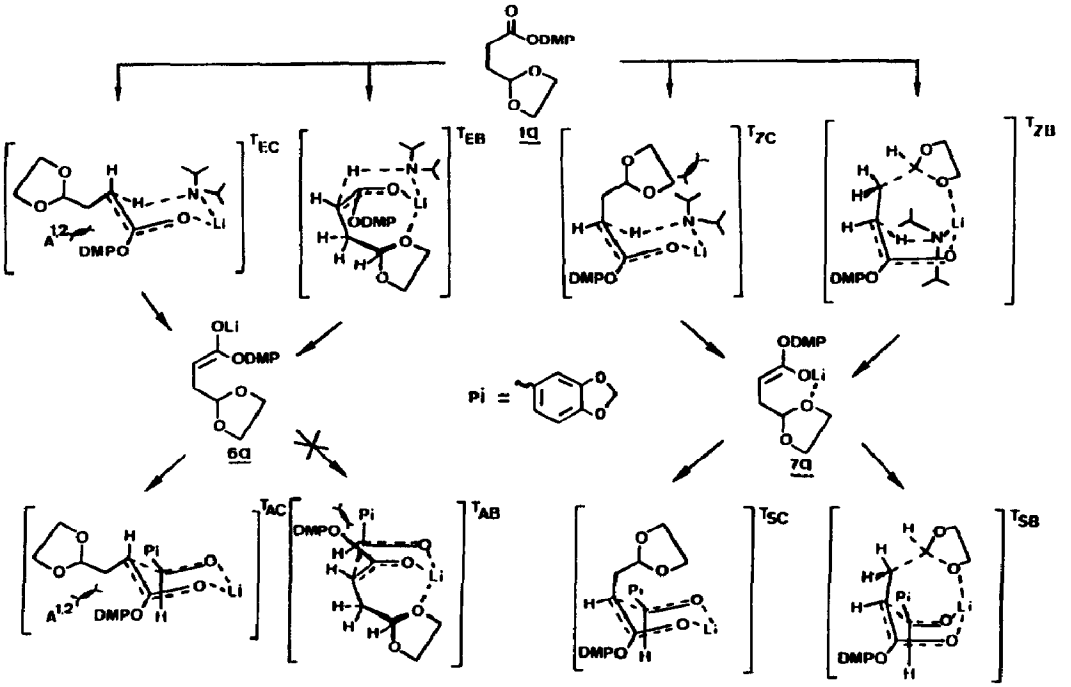
b) From the crude mixtures, since these products are unstable in silica gel or by heating.

Scheme 2

Comparing the data of schemes 1 and 2 (entries 1) one can observe that the ratios 2a/3a and 4a/5a are identical. It shows that the reverse stereoselectivity observed on the aldol reaction between 1a and piperonal is due mainly to the chelation properties of the ketal moiety, changing the mechanism of the deprotonation step. If chelated transition states are operating in the aldolization step between the lithium enolates 6a and 7a with piperonal (scheme 1), they don't alter the stereoselectivity expected from the non-chelated Zimmerman-Traxler chair-like transition states. A mechanistic rationale that explains the stereoselectivity of the deproton-

ation step is shown in scheme 3. The E-enolate 6a could be formed from 1a via the expected chair-like transition state T_{EC} although the participation of the boat-like transition state T_{EB} could not be excluded. On the other hand, T_{ZC} can be excluded as the pathway leading to 7a, due to a strong 1,3-diaxial interaction between the ketal group and the isopropyl group.[1] The steric interaction present in T_{ZC} could be released in the chelated boat-like transition state T_{ZB}. In fact, to explain the predominance of the Z-enolate 7a in the deprotonation of 1a, one can assume that T_{ZB} is the more stable among the transition states shown in scheme 3. When 1b was employed as substrate, chelated transition states as T_{EB} and T_{ZB} would be prevented due to the presence of the bulky TBDMS group.[7] The stereoselectivities observed when HMPA was used as the co-solvent were expected and can be explained by assuming open transition states for both deprotonation and aldolization steps.[5]

The effect of α and β-heteroatoms reverting the usual E-stereoselectivities in the kinetic deprotonation of carbonylated compounds is well known.[1,8] On the other hand, to our knowledge only few examples of the effect of the γ-heteroatoms are known.[9] In these cases the step where the chelation effect is operating was not determined. Our results clearly show that the presence of the ethyleneglicol ketal moiety in the γ-position of DMP-esters alter the stereochemical outcome of the enolate formation.



Scheme 3

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2. Duthaler, R.O., Herold, P., Lottenbach, W., Oertle, K., Riediker, M., Angew. Chem., Int. Ed. Engl., 1989, 28, 495.
3. Compounds 1a,b were prepared by opening succinic anhydride with 2,6-dimethylphenol (CH2Cl2, cat. DMAP, rt., overnight, 94%). For 1a it was followed by reduction (BH3.Et2O, THF, -20°C to rt., overnight, 98%), oxidation (oxalyl chloride, DMSO, CH2Cl2, -60°C then Et3N, 99%) and ketal formation (ethylene-glicol, cat. TsOH, toluene, reflux, 1h, 93%). For 1b the alcoholic intermediate was reacted with TBDMS-Cl (Et3N, DMAP, CHCl2, rt., overnight, 87%). Compound 1c was prepared from 4-hexenoic acid (2,6-dimethylphenol, DCC, cat. DMAP, CH2Cl2, rt., 4 days, 63%).
4. For 2a: ^{1}H NMR (300MHz, CDCl3): δ=6.94(s, 3H); 6.87-6.68(m, 3H); 5.95 (s, 2H); 4.88(t, 1H, J=5.16Hz); 4.79(d, 1H,J=7.99Hz); 3.90-3.70 (m, 4H); 3.17(m, 1H); 3.35-2.90(sl, OH); 2.31-2.20(m, 1H); 2.13-1.84(m, 1H); 1.91(s, 3H). For 3a: ^{1}H NMR (300MHz, CDCl3): δ=6.93(s, 3H); 6.87 -6.67(m, 3H); 5.94(s, 2H); 5.05(d, 1H, J=5.86Hz); 4.97(t, 1H, J=4.57 Hz); 3.90-3.70(m, 4H); 3.17(m, 1H); 3.35-2.90 (sl, OH); 2.31-2.20(m, 1H); 2.13-1.84(m, 1H); 2.13-1.84(m, 1H); 2.02(s, 3H). For 2b: ^{1}H NMR (300MHz, CDCl3): δ=6.88(s, 3H); 6.84-6.75(m, 3H); 5.97(s, 2H); 5.07(d, 1H, J=7.98Hz); 3.66(t, 1H, J=7.12Hz); 2.83-2.74(m, 1H); 2.20(s, 3H); 1.89-1.53(m, 1H+OH); 0.90(s, 9H); 0.07(s, 6H).
5. Ireland, R.E.; Müller, R.H.; Williard, A.K., J. Am. Chem. Soc., 1976, 98, 2868.
6. For the mixture of 4a and 5a: ^{1}H NMR (200MHz, CDCl3): δ=7.06-6.92 (m, 3H of 4a and 5a); 4.96(t, J=4.8Hz, 1H of 4a); 4.75(t, J=4.8Hz, 1H of 5a); 4.05-3.74(m, A2B2 of 4a and 5a); 3.67(t, J=7.2Hz, 1H of 4a); 3.11 (t, J=7.2Hz, 1H of 5a) 2.55(dd, J=7.20 and 4.85Hz, 2H of 4a; 2.30(dd, J=7.20 and 4.85Hz, 2H of 5a); 2.20(S, 6H of 4a and 5a); 2.20(s, 6H of 4a and 5a). For 4b: ^{1}H NMR (200MHz, CDCl3): δ=7.08-6.88(m, 3H); 3.67 (t, 2H, J=7.1Hz); 3.64(t, 1H, J=7.2Hz); 2.30(q, 2H, J=7.15Hz); 2.21(s, 6H); 0.90(s, 18H); 0.07(s, 6H); 0.05(s, 6H). For 5b: ^{1}H NMR (200MHz, CDCl3); δ=7.08-6.96(m, 3H); 3.44(t, 2H, J=7.2Hz); 3.04(t, 1H, J=7.2 Hz); 2.20(s, 6H); 2.20-2.09 (m, 2H); 0.83(s, 18H); 0.20(s, 12H).
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8. a) Heathcock, C.H.; Hagen, J.P.; Jarvi, E.T.; Pirrung, M.C.; Young, S.D., J. Am. Chem. Soc., 1981, 103, 4972; b) Evans, D.A., in "Asymmetric Synthesis", Morrison, J.D., ed., Academic Press: New York, vol. 3, Part B, pp. 80 and references cited therein; c) Heathcock, C.H.; Pirrung, M.C.; Young, S.D.; Hagen, J.P.; Jarvi, E.T.; Badertscher, U., Marki, H.-P.; Montgomery, S., J. Am. Chem. Soc., 1984, 106, 8161; d) Heathcock, C.H.; Arseniyadis, S., Tetrahedron Lett., 1985, 26, 600; e) Asao, N.; Uyehara, T.; Yamamoto, Y., Tetrahedron, 1990, 46, 456.
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