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SYNTHESIS OF CHIRAL β-ALKOXY-α,β-UNSATURATED KETONES

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Summary : The title compounds are synthesized in one-pot from the easily available sodium salts of unsymmetrical 1,3-dicarbonyl derivatives and chiral alkoxides.

Diels-Alder additions still play a major role in preparative organic chemistry and asymmetric induction in such reactions represents a challenge in synthetic methodology. Diastereofacial selectivity has been achieved with more or less success using chiral dienes[1] and/or chiral dienophiles[2] and/or chiral catalysts.[3] Previously[4], Danishefsky described an interesting and powerful improvement by using lanthanide derivatives as catalysts for hetero Diels-Alder reactions. More recently, the simultaneous use of chiral dienes and a chiral catalyst allowed high asymmetric induction.[5] However such reactions require chiral "Danishefsky-like" dienes prepared from the corresponding ketones 1. The usefulness of the method prompts us to report our synthesis of these ketones where the chiral part is introduced in good yields from the alcohols ROH as starting material.

Simple aliphatic analogues of ketones 1 or the corresponding aldehydes have been previously prepared from 1,3-dicarbonyl compounds either through acetal derivatives[6] or by alkylation of the sodium salt with strong electrophiles.[7] In the case of aldehydes, two methods used alkoxides as starting material : one by addition to methyl propiolate followed by reduction to the alcohol and oxidation to the aldehyde[8], the other by addition-elimination to a tosylate derived from the symmetrical sodium salt of malonaldehyde.[9] We now report that this last reaction can be extended to several unsymmetrical sodium salts 2 of 1,3-dicarbonyl derivatives[10] and a variety of complex chiral alcohols to give regio- and stereoselectively chiral β-alkoxy-α,β-unsaturated ketones which are the direct precursors of chiral "Danishefsky-like" dienes.[11]

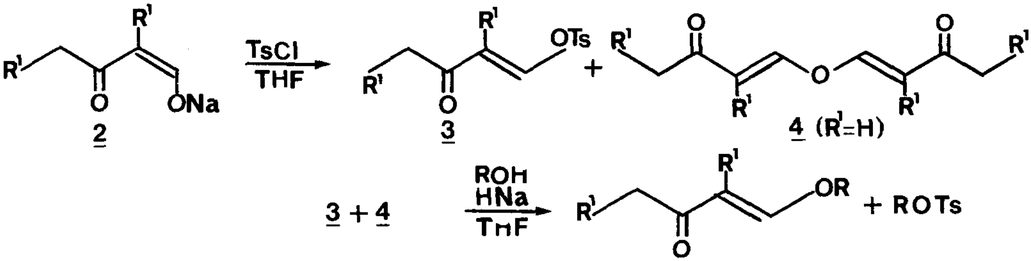
The reaction is performed in two steps in the same pot. Excess of compound 2 (1.5 eq) treated in THF with tosyl chloride give the intermediate β-tosyloxy-α,β-unsaturated ketones 3 along with the crystalline dimer 4 (5-10%). Addition of the chiral alcohol (0.7 eq) followed by HNa (excess) gave compound 1. In the case of R^1=H, the structure of the intermediates 3 and 4 have been established after rapid silica-gel chromatography (ether-hexane,2:1). The highly unstable compound 3 has been shown by ^{1}H NMR to be a mixture of 90:10 in favour of the trans isomer. Compound 4 can be separated in the crystalline form (m.p. 115°).[12] It must be noted that as well 3 as 4 give rise to compound 1 in the conditions of the reaction. Finally 4 can be obtained as the only product if a large excess of sodium salt 2 is used after 4-5 days at room temperature.
The results are summarized in table I.

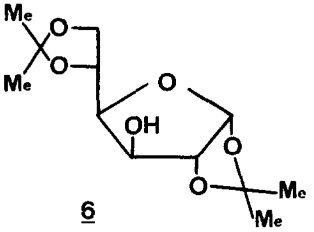
In the case of R^1=H, good yields are obtained (the lowest yield 67% (entry 2) can be explained by the well known low reactivity of the 4-hydroxyl group in D-glucopyranoside). In the case of R^1=Me, lower yields are obtained due to the formation of tosylate 5. This competing reaction can be repressed by using the more bulky 2,4,6-triisopropyl benzenesulfonyl chloride (TIPBSCl) (entry 5).In all cases, compounds 1 are obtained with complete regio- and stereoselectivities. Spectroscopic data (^{1}H and ^{13}C NMR) are consistent with the presence of only one stereoisomer. For compounds 1 (R^1=H) ^{1}H NMR indicates the presence of exclusively the trans isomer, $J_{3,4}$=13-14 Hz.

Table I

entry	2	$ArSO_2Cl$	ROH	Yields*(%)		$[\alpha]_D^{20}$ (CH_2Cl_2)
				5	1	1
1	R^1=H	TsCl	6	0	82	-32.8°
2	R^1=H	TsCl	7	0	67	+99.6°
3	R^1=H	TsCl	8	0	78	-99.5°
4	R^1=Me	TsCl	6	72	20	-25.5°
5	R^1=Me	TIPBSCl	6	62	31	
6	R^1=Me	TsCl	7	66	27	+85.4°
7	R^1=Me	TsCl	8	49	42	-66.6°

*After silicagel chromatography. All compounds have been fully characterized by ^1H and/or ^{13}C NMR spectroscopy and by elemental analysis.





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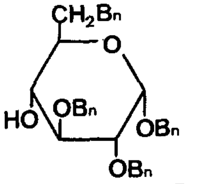

7 (Bn=CH$_2$Ph)

(-)-PhCH(OCH$_3$)CH$_2$OH

8

Syntheses of dienes and cycloaddition are now under way in our laboratory.

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11. In ref.^{5} Danishefsky used menthyloxy diene prepared from ketones 1 with R = menthyl. This ketone is prepared by exchange reaction with ketone 1 (R^1=Me).
12. Compound 4 has been obtained as a by-product in synthesis of vinylogous acyl phosphates (m.p.115-116°),G.W.Fisher,P.Schneider,Chem.Ber.,106, 435,1973

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