Tetrahedron Letters,Vol.24,No.25,pp 2603-2606,1983 0040-4039/83 $3.00 + .00
Printed in Great Britain

STEREO-CONTROLLED SYNTHESIS OF γ,δ-UNSATURATED KETONES BY THE HORNER-WITTIG REACTION

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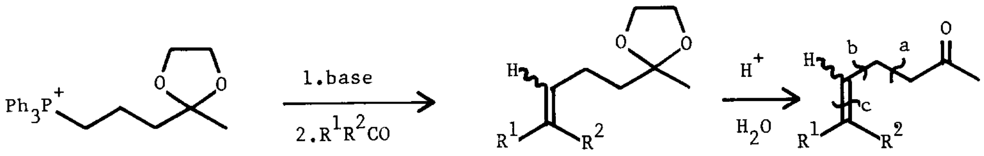
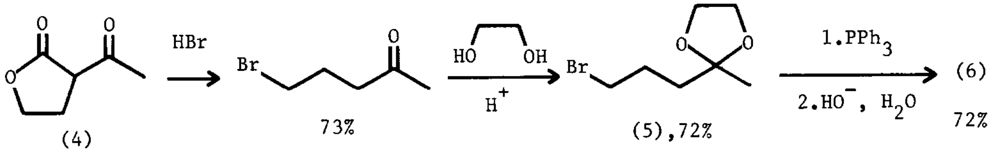
E and Z isomers of γ,δ-unsaturated ketals may separately be prepared by the Horner-Wittig reaction between 5-diphenylphosphinoylpentan-2-one ethylene acetal (6) and aldehydes, esters, or ketones.

Stereo-controlled synthesis of γ,δ-enones (3) is usually attempted by the Claisen rearrangement,[1] the Wittig reaction,[2,3] or via an acetylene.[3] Of these, the Claisen route is trans selective,[4] the Wittig cis selective, whilst the acetylene route could in principle be used for either isomer. The strategy of the Claisen route is stereocontrolled allylation of a ketone [disconnection a on (3)]. The acetylene (disconnection b) behaves as a stereoselective vinyl anion. The Wittig, being the only method which joins the starting materials by the new double bond (disconnection c), depends on the stereoselectivity of (1) to (2) and the usually difficult separation of geometrical isomers of (2) or (3) to obtain pure cis alkene.



(1) (2) (3)

The Horner variant of the Wittig reaction[5] allows the isolation and purification of adducts, e.g. (7), from which single geometrical isomers of olefins may be made by stereospecific elimination. Our stereoselective synthesis of either diastereoisomer of these adducts[6] can be used for di- and tri-substituted alkenes and we now report that it can also be used to make single geometrical isomers of γ,δ-unsaturated ketals from phosphine oxide (6).



Phosphine oxide (6) can be made from available lactone (4) *via* γ-bromoketal (5) and triphenylphosphine without isolating intermediate (1). Treatment of (6) with BuLi at 0°C (Scheme 1) and addition of aldehydes gives good yields of adducts which are easily separated into *erythro* (7) and *threo* (10) diastereoisomers by chromatography on silica. Stereoselectivity varies from 3:1 in favour of (7) for R=Me or Ph to 1:1 for branched substituents, R=i-Pr or cyclohexyl (Table 1). Acylation of the phosphine oxide (6) with esters[6,7] gives ketones (9) which can be reduced with sodium borohydride to the same adducts (7) and (10) but with the opposite stereoselectivity : about 1:3 in favour of (10) in those cases tried. Elimination of diphenylphosphinate from either diastereoisomer (7) or (10) (NaH, DMF, 50°C) is stereospecific and gives good yields of single diastereoisomers (8) or (11) respectively (Scheme 1 and Table 1).

SCHEME 1

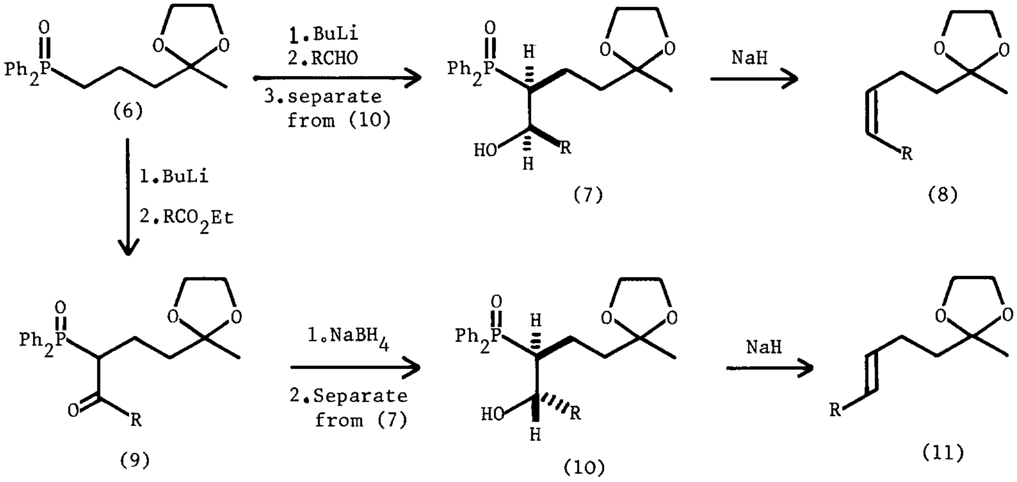
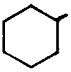
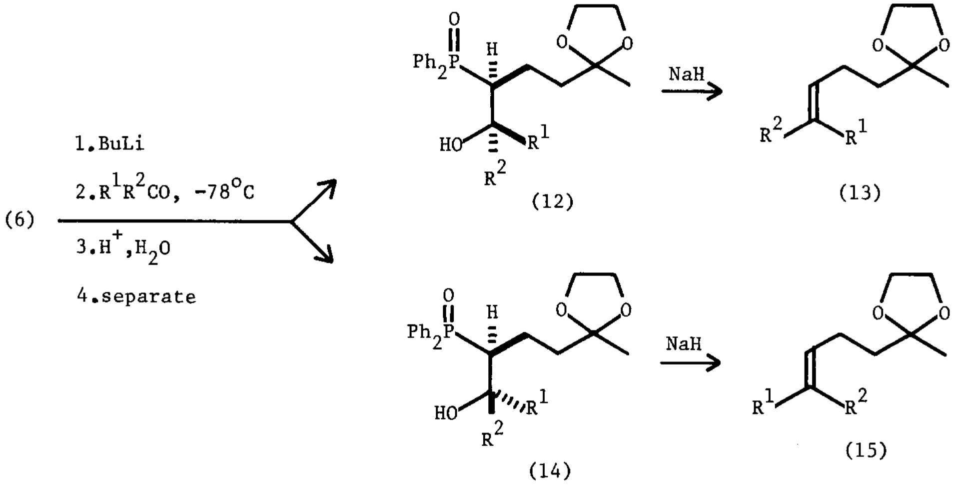


TABLE 1

		ROUTE A		ROUTE B			PRODUCTS	
Entry	R	Yield (7) + (10)	Ratio (7):(10)	Yield (9)	Yield (7) + (10)	Ratio (7):(10)	Yield (8)	Yield (11)
1.	H	68	-	-	-	-	63	-
2.	Me	75	3.2:1	71	91	1.3:6	76	80
3.	Et	62	2.5:1	-	-	-	-	-
4.	n-Pr	67	2.2:1	-	-	-	76	85
5.	n-Bu	78	1.7:1	61	81	1.2:4	83	72
6.	i-Pr	79	1:1	-	-	-	77	79
7.	Ph	72	3.8:1	64	84	1:3	90	83
8.		71	1:1	-	-	-	58	-

SCHEME 2



The anion of (6) also adds to ketones (Scheme 2) to give adducts (12) and (14), even with notoriously enolisable ketones (entries 4 and 7, Table 2). Stereoselectivity disappears in this series as expected,[6] but the chromatographic separation of (12) and (14) is straightforward and elimination again gives single geometrical isomers of alkenes (13) or (15).

Removal of the dioxolan protecting group (2 → 3) from compounds such as (8), (11), (13), and (15) is well known[2,3] and does not affect the geometry of a γ,δ-double bond so that this method provides pure E or Z-γ,δ-enones. The corresponding β,γ enones may be made by a similar method.[8]

TABLE 2

Addition of (6) to ketones (Scheme 2)

Entry	R^1	R^2	Adducts Yield (12) + (14)	 Ratio (12):(14)	Products Yield (13)	 Yield (15)
1.	Me	Et	77	1:1	73	81
2.	Me	n-Pr	56	1:1	-	-
3.	Me	i-Pr	62	0.9:1	82	67
4.	Me	Ph	71	1.1:1	-	-
5.	Me	Me	70	-	84	
6.	Et	Et	48	-	-	
7.	$(CH_2)_4$		51	-	-	
8.	$(CH_2)_5$		70	-	89	

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(Received in UK 8 April 1983)