Tetrahedron Letters,Vol.24,No.47,pp 5293-5296,1983 0040-4039/83 $3.00 + .00
Printed in Great Britain 

# TRANS ALKENES BY STEREOSELECTIVE REDUCTION OF α-$Ph_2PO$ KETONES: E-ISOSAFFROLE, E-ANETHOLE, AND FENICULIN

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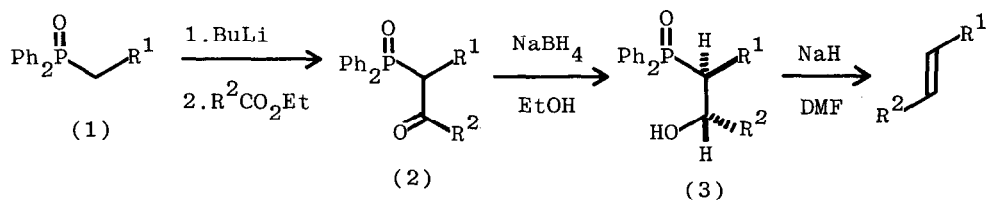
Summary. Conditions are described for the stereoselective reduction of α-$Ph_2PO$ ketones and stereospecific elimination from the resulting threo Horner-Wittig intermediates to give pure E-alkenes such as the title compounds.

The Wittig reaction is normally cis-selective[1] but it can be made reasonably trans-selective by choice of conditions or by Schlosser's modification[2] in which erythro intermediates are equilibrated to threo by an extra mole of base. The products are nevertheless formed as mixtures of E- and Z-isomers and separation can be difficult. Hence E-anethole[3] (5) can be made in 60% yield (80:20 E:Z) and E-isosaffrole[4] (6) in 57% yield (87:13 E:Z).[5]

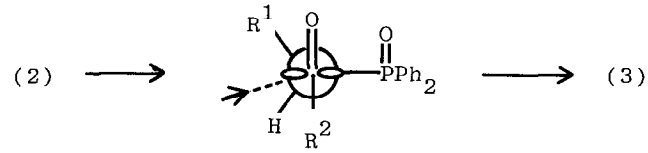
Our modification of the Horner-Wittig reaction,[6] using diphenylphosphinoyl ($Ph_2PO$) as the anion-stabilising group, avoids this difficulty by separation and purification of the crystalline erythro and threo intermediates which are synthesised by different stereoselective pathways. The route to E-alkenes involves acylation[7] of phosphine oxides (1), stereoselective reduction of ketones (2) to threo-alcohols (3), and stereospecific elimination. We now describe the effect of substituents on the stereoselectivity of the reduction, the choice of reducing agents, and a possible explanation.




(1) (2) (3)

With $R^2$=Ph, alkyl substituents ranging from Me to n-Bu and i-Bu (entries 1-5, table 1) have no effect on the stereoselectivity of reduction of ketone (2). Even $R^2$=i-Pr has little effect. With $R^1$=Me, changing the size of $R^2$ has a more marked effect, the larger substituents (entries 1,7-10) giving the higher selectivity. Cram's rule would explain the threo preference, but Felkin's

model[8] (4) with the largest group ($Ph_2PO$), and the bond with the lowest $\sigma^*$ (C-P) sitting at right angles to the plane of the carbonyl group, explains both the threo selectivity and the effect of substituents. Changing $R^1$ can reduce stereoselectivity only if $R^1$ competes with $Ph_2PO$ in size and low $\sigma^*$, but larger $R^2$ groups increase steroselectivity by making the contrast between $R^1$ and $R^2$ more emphatic.




(4)

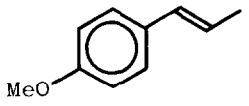
**Table 1**

Stereoselective Reduction of Ketones (2) with Sodium Borohydride in Ethanol

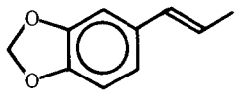
| Entry | $R^1$ | $R^2$ | Yield (2) | Yield (3) | threo: erythro | Yield E-Alkene | |
|---|---|---|---|---|---|---|---|
| 1 | Me | Ph | 83[a] | 89 | 89:11 | 81 | |
| 2 | Et | Ph | 65 | 88 | 89:11 | 80 | |
| 3 | n-Pr | Ph | 83 | 87 | 89:11 | 89 | |
| 4 | n-Bu | Ph | 81 | 81 | 89:11 | 94 | |
| 5 | $Me_2CHCH_2$ | Ph | 75 | 77 | 89:11 | 85 | |
| 6 | $Me_2CH$ | Ph | 69 | 75 | 83:17 | 85 | |
| 7 | Me | $C_6H_{11}$[b] | 84 | 87 | 91:9 | - | |
| 8 | Me | p-$MeOC_6H_4$ | 79 | 89 | 90:10 | 81 | E-anethole (5) |
| 9 | Me | c | 85 | 91 | 94:6 | 86 | E-isosaffrole (6) |
| 10 | Me | d | 61 | 74 | 90:10 | 71 | feniculin (11) |

a. Copper derivative and PhCOCl
b. Cyclohexyl
c. 3,4-Methylenedioxyphenyl
d. p-$Me_2C{=}CHCH_2OC_6H_4$

These reductions were all carried out with sodium borohydride in ethanol since these simple reaction conditions combine high yield with high stereoselectivity. Other reducing agents (table 2) gave lower yields or poor selectivity. The elimination step from threo-(3) to E-alkenes is totally stereospecific, unlike the corresponding erythro to Z-alkene conversion.[6] Hence pure E-anethole (5) and E-isosaffrole (6) (entries 8 and 9, table 1) can be made in good yield without a trace of the Z isomers.




(5)



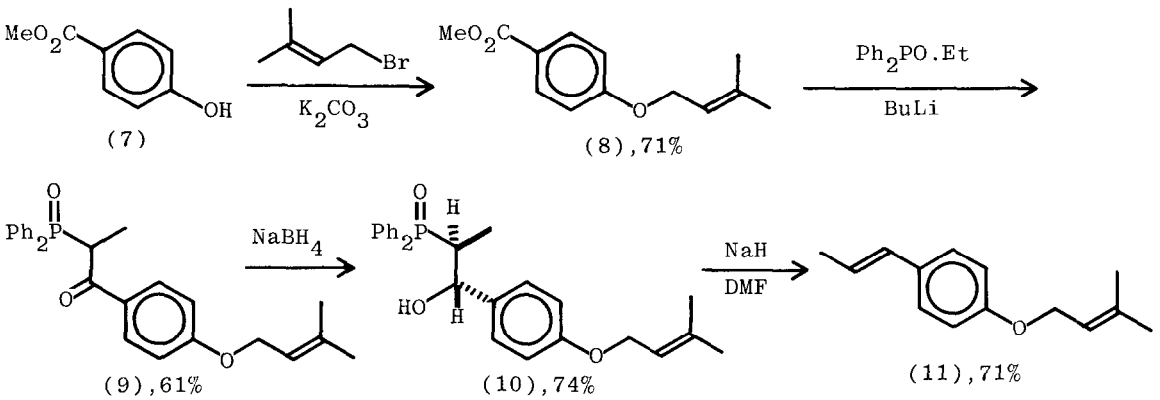

(6)

**Table 2**

Stereoselectivity in the Reduction of (2, $R^1$=Me, $R^2$=Ph)

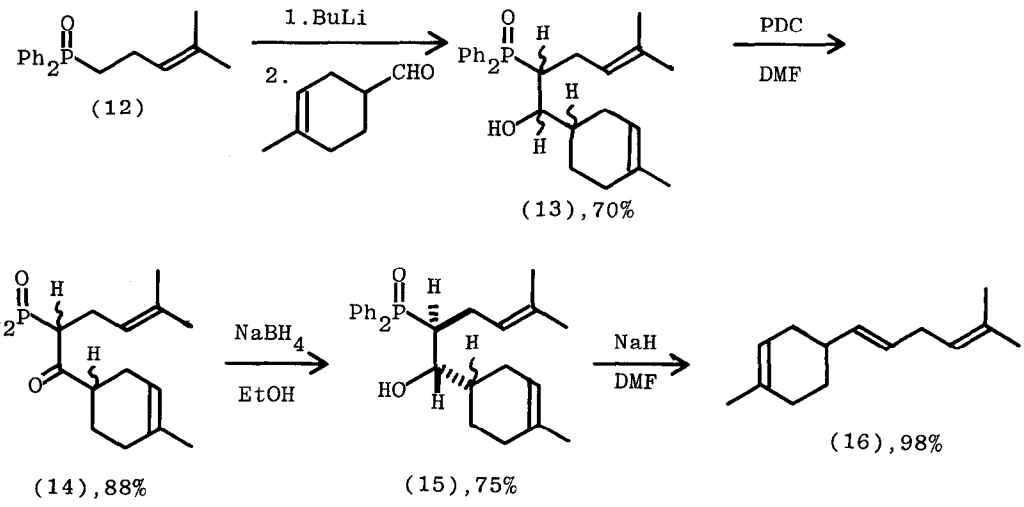
| Entry | Reagent | Conditions | Yield Threo-(3) | Threo: Erythro | Recovered Ketone (2) |
|---|---|---|---|---|---|
| 1 | $NaBH_4$ | EtOH, reflux | 89 | 89:11 | 0 |
| 2 | $B_2H_6$ | THF, 25 °C | 71 | 73:27 | 0 |
| 3 | $LiAlH_4$ | THF, 0 °C | 55[a] | 56:44 | 0 |
| 4 | $LiAlH(OBu\text{-}t)_3$ | PhMe, reflux | (50)[b] | high | 50 |
| 5 | $H_2/PtO_2$ | MeOH, 25 °C | (50)[b] | high | 50 |

a. $Ph_2PO$ is reduced to $Ph_2P$ but reoxidised by air during work-up.
b. Not separated from erythro (3).




We have already used this route in a synthesis of E-6-nonenol, a pheromone of the Mediterranean fruit fly,[6] and E-γ,δ-unsaturated ketals[9] and now report a short synthesis of feniculin (11), a constituent of fennel and star anise,[10] as a further illustration of the compatibility of the method with other functional groups. More surprisingly, pure E-triene (16) was made from phosphine oxide[11] (12). Aldehyde addition to (12) gave a mixture of diastereoisomers (13) which was oxidised to ketone (14) and stereoselectively reduced to (15). Whether the third chiral centre in (15) is defined or not, flash chromatography gave a crystalline alcohol in 75% yield which gave only E-(16) on elimination. The two vital chiral centres in (15) evidently have the threo relationship.

We thank Glaxo Group Research and SERC for a grant (to A.D.B.) and Dr Barry Price for many helpful discussions.




(12)

(13),70%

(14),88%

(15),75%

(16),98%

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(Received in UK 7 September 1983)