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STEREOCONTROLLED SYNTHESIS OF δ-HYDROXY ALLYLIC PHOSPHINE OXIDES BY ALLYLIC ESTER TRANSPOSITION

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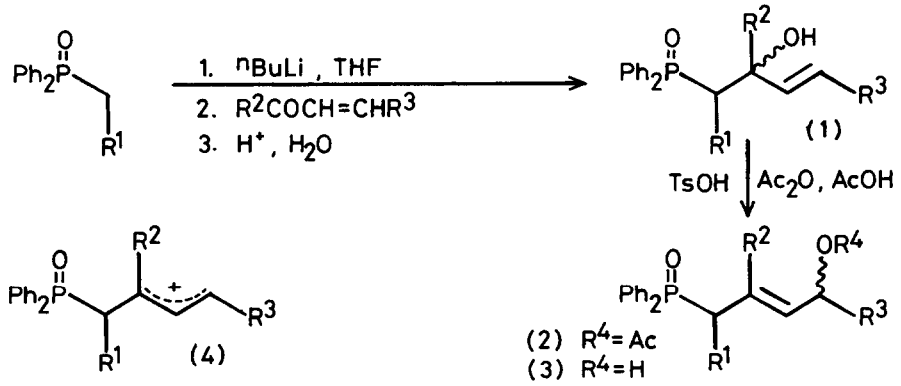
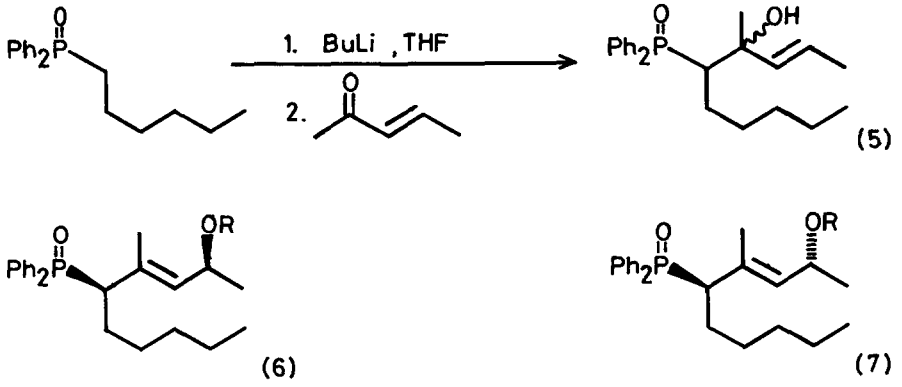
The title compounds (3) were synthesised by stereospecific [1,3] rearrangement, controlled by the Ph_2PO group, from single isomers of the Horner-Wittig adducts (1)

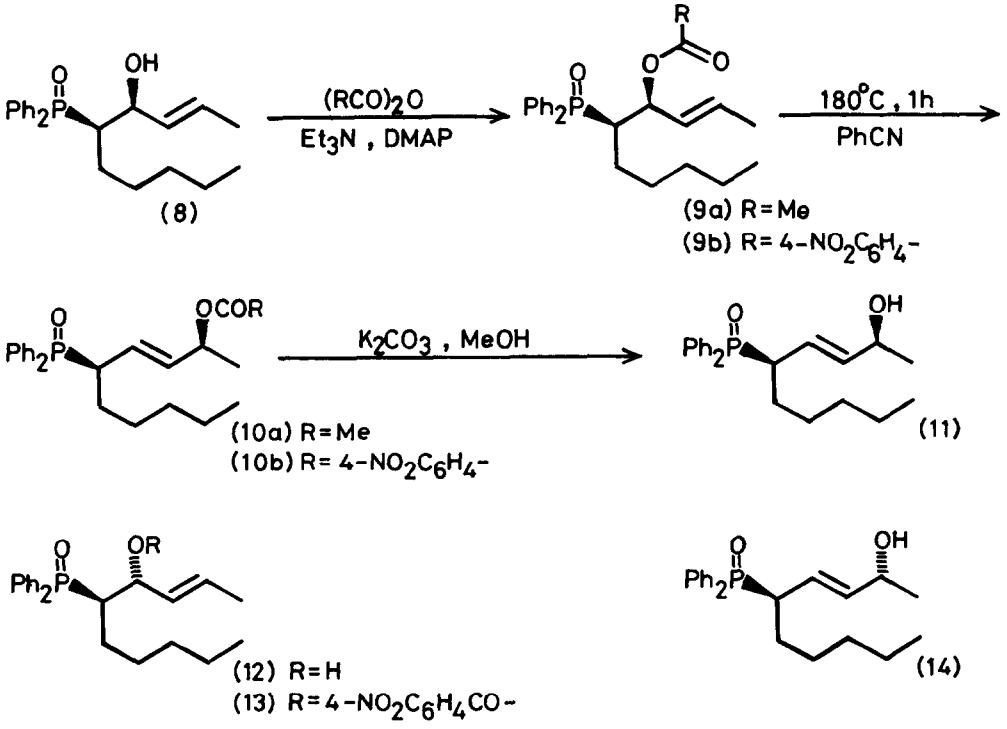
We have recently reported[1] the synthesis of δ-hydroxy-allylic phosphine oxides (3) as intermediates in the synthesis of diene alcohols. The allylic transposition involved (1 - 2) is driven by the diphenylphosphinoyl (Ph_2PO) group (R^2 can be H), which also controls the E-geometry of the double bond in the product (2). In connection with other work,[2] control over the chiral centres at either end of this double bond - they have a 1,4 relationship - was also needed.



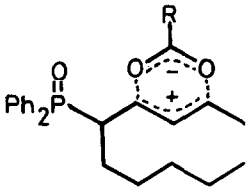
The two diastereoisomers of Horner-Wittig adducts (1) are in general readily separable by chromatography or crystallisation. For example, addition of the preformed anion of hexyldiphenylphosphine oxide to MeCO.CH=CHMe gave a 2:1 mixture of diastereoisomers of adduct (5). The mixture or either separated diastereoisomer rearranged under acidic conditions (Ac_2O, AcOH, TsOH) to about the same mixture of diastereoisomers of the transposed acetates (6 and 7, R=Ac) with about 1.5:1 stereoselectivity in favour of isomer (6) (1.7:1 for the mixture, 1.3:1 and 2.0:1 for the diastereoisomers). Evidently the stable trisubstituted allylic cation (4, R^1=n-C_5H_{11}, R^2=R^3=Me) is an essentially free intermediate. Direct rearrangement of the mixed alcohols (5) (aqueous HCl, dioxan) gave a 2:1 mixture of alcohols (6 and 7, R=H), favouring the same diastereoisomer (6) in low yield.



Addition of the same phosphine oxide to crotonaldehyde gave the separate diastereoisomers (8) (57% on a 20 g scale) and (12) (29%) after fractional crystallisation. The erythro isomer (8) is favoured as usual in these additions.[3] Rearrangement of the separated diastereoisomers under the same conditions gave a modest stereospecificity: (8) gave 65% (10a) and 35% of its diastereoisomer, (12) gave 35% of (10a) and 65% of its diastereoisomer. The less stable disubstituted allyl cation (4, $R^1=C_5H_{11}$, $R^2=H$, $R^3=Me$) is not an entirely free intermediate. These diastereoisomers of (2) and (3), unlike those of (1), could be separated only with great difficulty, and a stereospecific rearrangement would clearly be better.

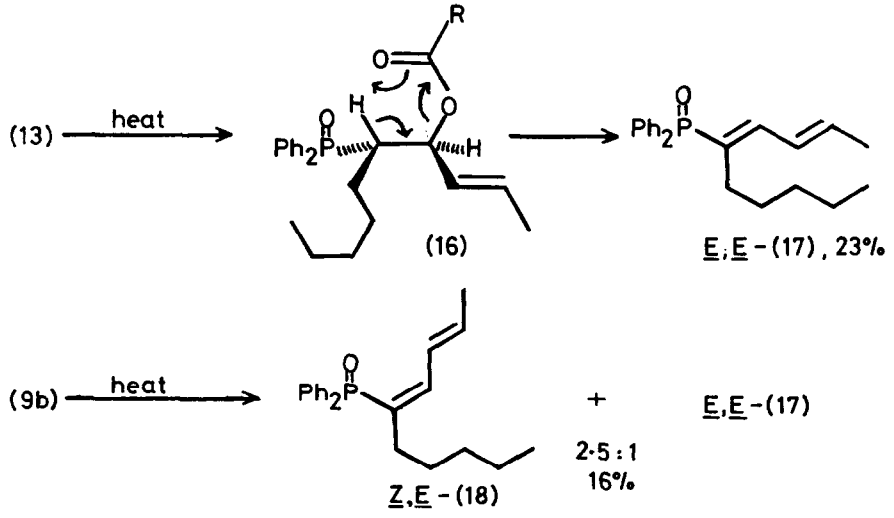


Without acid catalysis, the free allylic cation (4) is not produced and the transition state for allylic ester rearrangements in neutral solution is a Cope-like ion pair (e.g. 15).[5] These rearrangements require a higher temperature, a polar solvent, and an electron-withdrawing esterifying group, but can be stereospecific. Under basic conditions [4-dimethylaminopyridine (DMAP) and the carboxylic anhydride] adduct (8) gave the p-nitrobenzoate (9b) without epimerisation or rearrangement. Heating this ester (9b) in benzonitrile (180 °C, 1 h) gave complete rearrangement, driven by steric repulsion between the ester and Ph_2PO groups, to give the E-allylic ester (10b) with greater than 95% stereospecificity.[6] Hydrolysis gave the single diastereoisomer (11) in 71% yield from (8). The threo diastereoisomer (12) similarly gave the alcohol (14) with greater than 95% stereospecificity and in 68% yield. The transition state (15) is evidently tightly bound enough to transform the 1,2 stereochemical relationship in (8) and (12) into the 1,4 relationship in (11) and (14) without loss. The allylic acetate (9a) did not rearrange under the same conditions and more forcing conditions gave dienes by loss of acetic acid.[7]

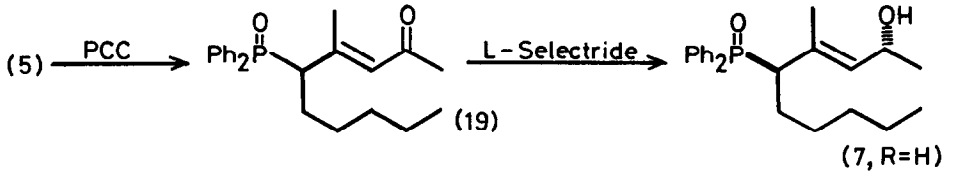


(15)

Elimination of p-nitrobenzoic acid was also a side-reaction in the thermal rearrangements. E,E-Diene (17) was formed stereospecifically in 23% yield by syn elimination (16) in the rearrangement of threo-(13) but the erythro-ester (9b) gave a 2.5:1 mixture of Z,E and E,E dienes (18) and (17) in 16% yield. The slower formation of the Z,E-diene (18) evidently allows a competing non-stereospecific elimination to occur.



An alternative method for the allylic rearrangement (1-3) can be used if R^2 is alkyl. For example, the adduct (5) was oxidised by pyridinium chlorochromate (PCC)[8] with allylic rearrangement,[9] to give the E-enone (19) in 60% overall yield. The enone was reduced by lithium tri-s-butyl borohydride (L-selectride)[10] with a remarkable 83% stereoselectivity [remarkable because the carbonyl group has a 1,4 relationship to the existing chiral centre in (19) and the trans double bond prevents chelation by Ph_2PO] to give the (2RS, 5RS) δ-hydroxy allylic phosphine oxide (7, R=H) in 81% yield. This diastereoisomer is the minor product of the rearrangement of alcohol (5).



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