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Alkenyl Diols by *E*-Selective Horner-Wittig Elimination: Formal Synthesis of Any Isomer (*RR*, *RS*, *SR* or *SS*) Bearing 1,5-Related Stereogenic Centres Across an *E* Double Bond

Adam Nelson and Stuart Warren*

University Chemical Laboratory, Lensfield Road, Cambridge, CB2 1EW England

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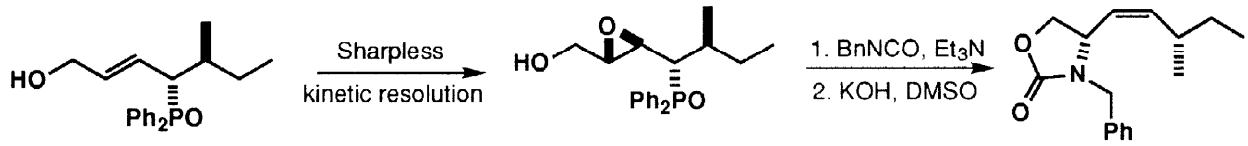
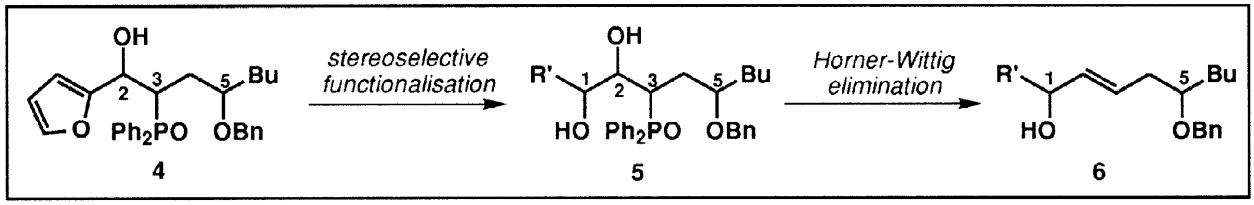
Abstract: Oxidation of diastereomerically pure diphenylphosphinoyl furans [e.g. 4-benzyloxy-2-diphenylphosphinoyl 1-(2'-furyl) octan-1-ol] with *m*-CPBA, followed by reduction with sodium borohydride, gives triols with four stereochemically controlled stereogenic centres. (*E*)-Selective Horner-Wittig elimination removes the middle two stereogenic centres to yield diols with 1,5-related stereogenic centres across a *trans* double bond. © 1998 Elsevier Science Ltd. All rights reserved.

We have used the diphenylphosphinoyl group as a powerful stereodirecting group[1] in the synthesis of racemic allylic alcohols[2] and allylic sulfides[3] with 1,4-related stereogenic centres across double bonds of fixed configuration. The aim of our synthetic programme is to synthesize all possible stereoisomers of alkenes such as **3** by removing two stereogenic centres from a row of at least four, as in **2**, by stereospecific Horner-Wittig elimination. For example, we used both Sharpless kinetic resolution[4] and diastereoselective epoxidation[5] with *m*-CPBA to complete the formal synthesis of eight isomers of epoxy alcohol **2** and hence all eight stereoisomers of alkenyl oxazolidinone **3**.[6]



1 **2** **3**

We now describe the formal synthesis of all eight stereoisomers of β-hydroxy phosphine oxide **4** and show how these compounds can be used to synthesize any isomer of allylic alcohols **6** with 1,5-related stereogenic centres across a *trans* double bond. As part of our general strategy, the furan ring of β-hydroxy phosphine oxides **4** can be transformed into a useful prochiral unit and reduced to give compounds **5** with four controlled stereogenic centres. Horner-Wittig elimination then extrudes diphenylphosphinic acid from **5** to give *E*-alkenes **6** with 1,5-related stereogenic centres.



4 **5** **6**

Lithiation of phosphine oxide[7] **7** in THF, and reaction with furfural, gave only the ^{2,3}*anti* β-hydroxy phosphine oxides **4a** and **4b** (82:18, 61%) which were separable by HPLC. In toluene, the sense of the 1,3 stereocontrol was reversed (**4a**:**4b** 43:57, 56%), though the addition reaction was less ^{2,3}*anti* selective than in THF.[9] The 1,3 stereoselectivity could also be reversed by reacting lithiated **7** with esters:[8] acylation with

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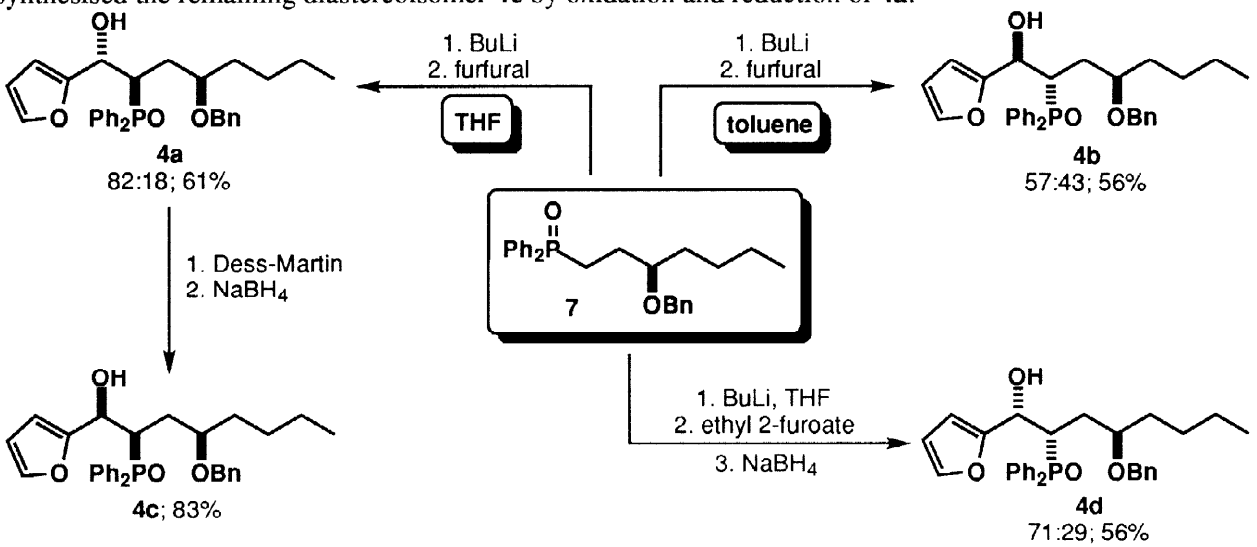
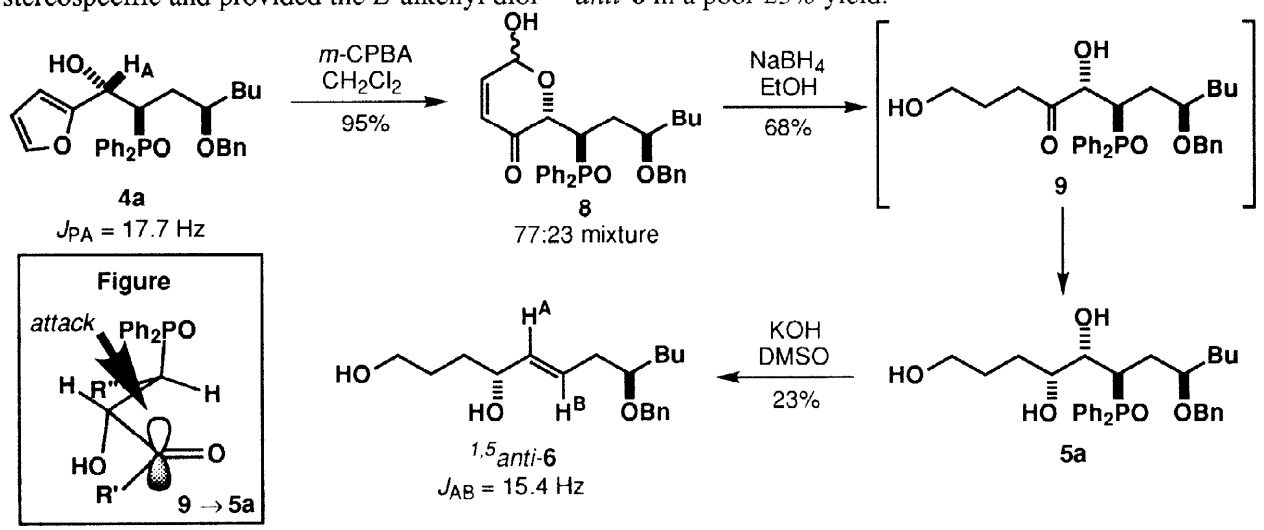
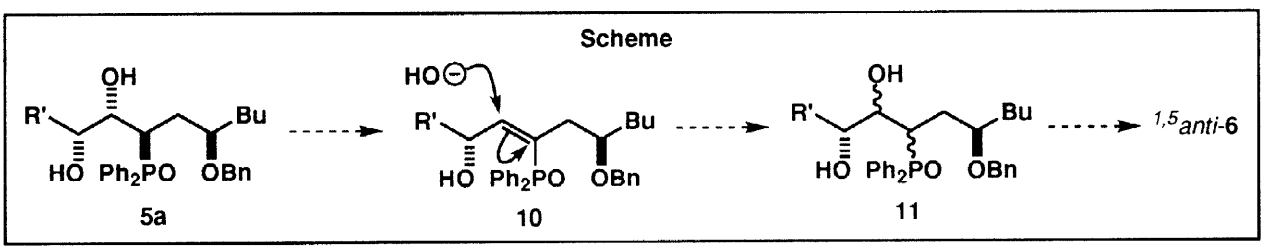
ethyl 2-furoate and reduction with sodium borohydride,[10] provided the ^{2,3}*syn* β-hydroxy phosphine oxides **4d** and **4c** (71:29) in 56% yield over the two steps. Beak has also shown that the sense of the stereoselectivity of S_E2 reactions of configurationally unstable organolithiums[11] can depend on the electrophile used.[12] We synthesised the remaining diastereoisomer **4c** by oxidation and reduction of **4a**.



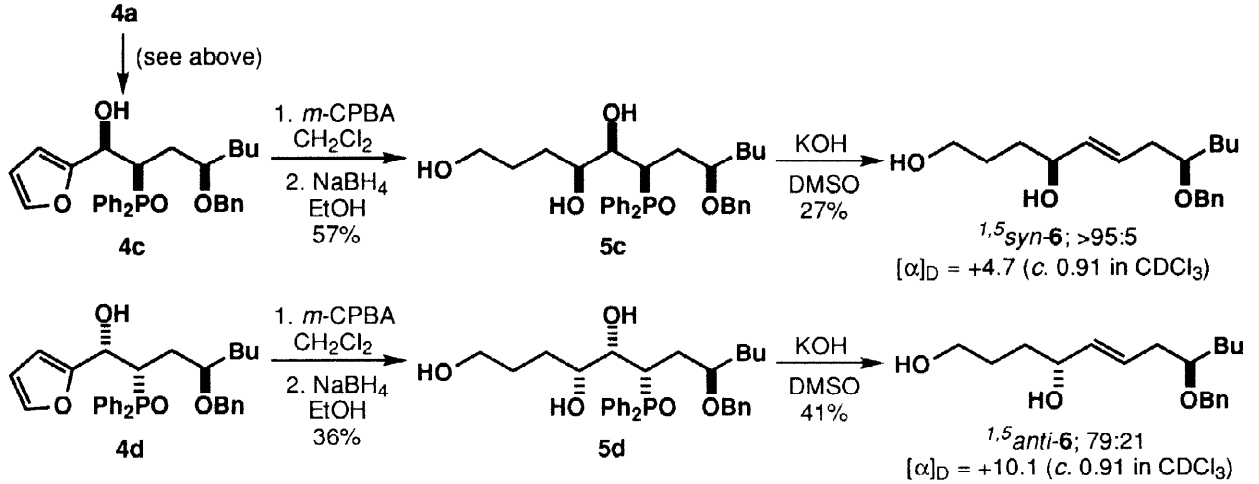
Oxidative rearrangement[13-15] of β-hydroxy phosphine oxide **4a** gave the enone **8** (as a 77:23 mixture of anomers) which was reduced[16] with sodium borohydride to give the triol **5a** as a single diastereoisomer. We suggest that this reaction is 1,2 *syn* selective,[17] proceeding under Felkin-Anh control[19] *via* the transition state shown in the Figure. Horner-Wittig elimination of **5a** (an *anti* β-hydroxy phosphine oxide[20]) was not stereospecific and provided the *E*-alkenyl diol ^{1,5}*anti*-**6** in a poor 23% yield.



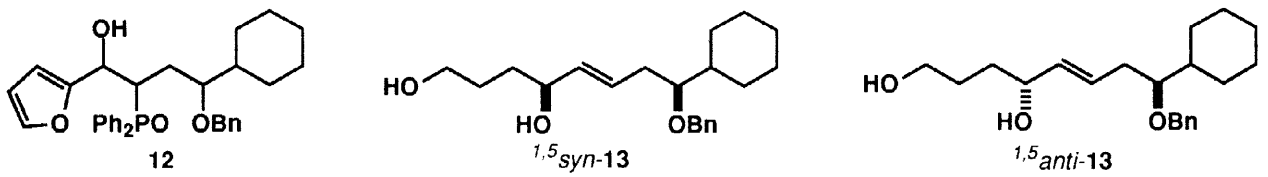


There are many examples of Horner-Wittig eliminations in which the usual *syn* stereospecificity[10] has been lost,[21] and most of these can be explained by particularly favourable reverse Horner-Wittig addition

followed by recombination. In our case, however, we suggest that the loss of stereospecificity stems from the precedented[22] elimination of β,γ-dihydroxyphosphine oxides (such as **5a**) to vinyl phosphine oxides (e.g. **10**). Readdition of hydroxide to **10**, and Horner-Wittig elimination, would then give the *E*-alkenyl diol ^{1,5}***anti*-6** (see Scheme). Despite the loss of stereospecificity in the elimination step, the use of single diastereoisomers throughout the sequence is of fundamental importance: the β-hydroxy phosphine oxide unit contains two "relay" stereogenic centres which control the flow of stereochemical information along the molecule.



Diols ^{1,5}*syn*- and ^{1,5}*anti*-**6** were synthesized from the *syn* β-hydroxy phosphine oxides[20] **4c** and **4d**. Oxidation of the furan rings of **4c-d**, and reduction with sodium borohydride, gave triols **5c-d** as single diastereoisomers.[23] Horner-Wittig elimination of these triols gave (*E*)-alkenyl diols **6** in poor to moderate yield.[24] The relative stereochemistry and diastereomeric purity[25] of the diols **6** were established by careful comparison of their 500 MHz ^{1}H NMR spectra and by using Mosher's method for determining the absolute stereochemistry of secondary alcohols.[26,27] We also synthesized the diols ^{1,5}*anti*- and ^{1,5}*syn*-**13** (as 74:26 and 70:30 mixtures) from mixtures of the cyclohexyl-substituted phosphine oxides **12**.



Our work neatly complements the Lewis acid mediated reactions between chiral allylic stannanes and aldehydes which inevitably lead to products with remote stereogenic centres separated by a *cis* double bond.[28] The remote stereochemical relationships in our molecules are built up more slowly, but the syntheses of our starting materials are easier than those of optically active allylic stannanes.[28] Furthermore, our route allows the synthesis of both ^{1,5}*syn and* ^{1,5}*anti* isomers **6** and **13** and both enantiomeric series can be prepared by careful choice of the ligand used to introduce asymmetry into the reaction sequence.

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