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Diphenylphosphinoyl Lactones in the Control of Remote Stereochemistry

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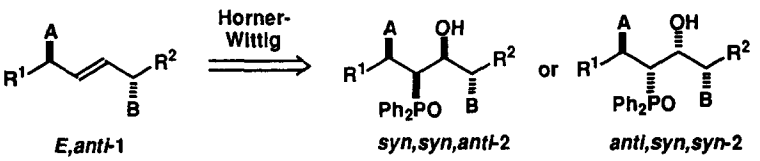
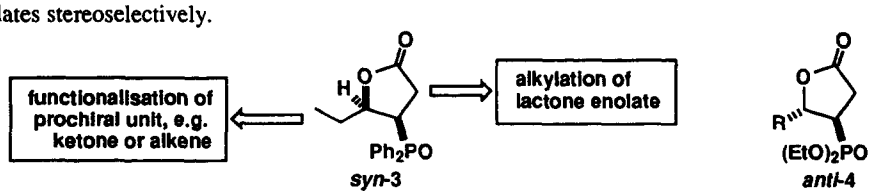
Abstract: *E*-alkenes with three stereogenic centres related 1,4- and 1,5- across the double bond can be prepared with good stereoselectivity from 3-diphenylphosphinoyl-4-alkenyl butyrolactones by alkylation, epoxidation, epoxide opening by a nucleophile, reduction and Horner-Wittig elimination.

Our programme of using phosphine oxides to control remote stereochemistry aims at the totally selective synthesis of all possible stereoisomers of compounds such as **1** with stereogenic centres flanking C=C double bonds of fixed configuration.[1] Our method is to use the Horner-Wittig reaction to deliver the double bond by the *syn* elimination of $Ph_2PO_2^-$ from two stereogenic centres in the middle of a row of at least four, as in **2**, thus leaving the outside centres at least 1,4-related. Chemistry to control the two middle centres is well established and we report on a new approach to the control of the outside centres by chemoselective alkylation of lactone enolates in the presence of a diphenylphosphinoyl group.



We chose to work with lactones such as **3** because we believed we could control new stereogenic centres in both directions as represented in scheme 1. Functionalisation of a prochiral alkene should develop centres on the left hand side - we have already used reactions such as the oxidation of an alkene[1,2] to control centres corresponding to CHB in **2**. We believed we could control centres to the right hand side by the alkylation of lactone enolates because Bodalski[3] had already prepared phosphonate-lactones **4** and alkylated their enolates stereoselectively.



Scheme 1: Development of Sterogenic Centres from a 3-Ph_2PO-butyrolactone

We found that the best method to prepare lactones **3** in high yield was the alkylation of ketones[1,4] **5** with ethyl bromacetate (NaH, THF, 0 °C), hydrolysis of the esters **6** with an excess of LiOH and reduction of the acids **6** with $NaBH_4$ in EtOH (table 1). Yields were better when the ester **6** was not isolated. This

sequence is highly stereoselective, the *syn* isomer of lactones **3** being formed in almost quantitative yield. This is a result of the Felkin approach **8** often found with α-Ph_2PO-ketones.[1,4] Treatment of the esters **6** with $NaBH_4$ resulted in over-reduction and the formation of diols **9** which were actually useful in assigning the *syn* stereochemistry.[4]

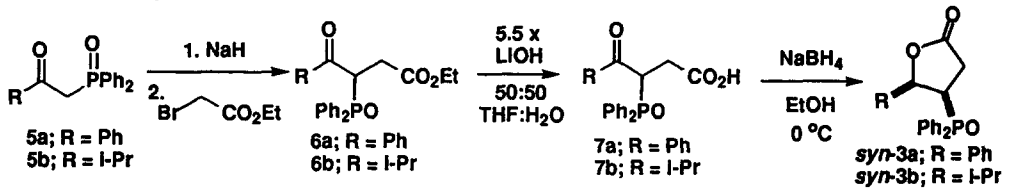
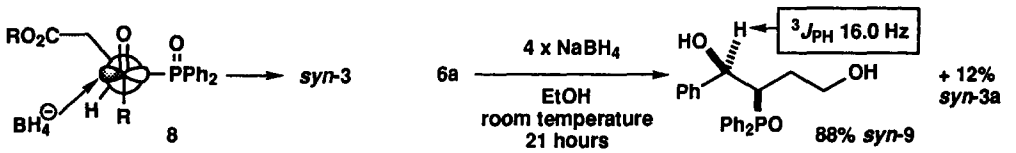
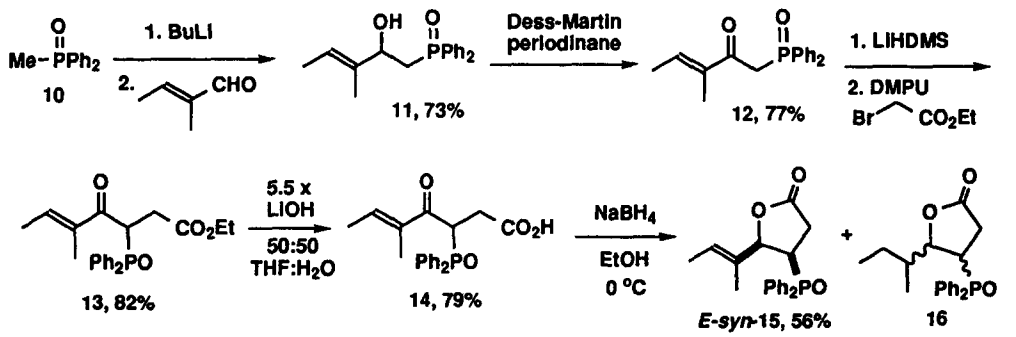


Table 1; Synthesis of *syn*-lactones **3**.

R	Yield (%) Keto-ester **6**	Yield (%) Keto-acid **7**	Yield (%) **7** by one-pot route from **5**	Yield (%) Lactone **3**	Stereochemistry (*syn:anti*-**3**)
Ph	91	78	88	91	98:2
i-Pr	96	-	79	96	94:6



Lactones **3** with a prochiral alkene unit in the side chain R were best made by the route shown in scheme 2. Alone among the oxidising agents tried, the Dess-Martin periodinane gave good yields of the enone **12**. Alkylation with ethyl bromoacetate gave better yields (82%) with lithium hexamethyldisilazide (LiHMDS) and five equivalents of DMPU than with NaH (62%). It was essential to isolate the ketoester **13** and remove DMPU before the hydrolysis and reduction, so the one-step procedure could not be used. Reduction was very stereoselective for *syn*-**15** (97:3) but not very regioselective (60:40 ratio of 1,2- to 1,4-reduction; 6% of a mixture of diastereoisomers of **16** could also be isolated). To our surprise[5] and disappointment, the Luche reduction gave even more 1,4-reduction (55:45).



Scheme 2: Synthesis of Alkenyl-lactone *E-syn*-**15**

The lithium enolates of the lactones **3** and **15** were formed with lithium hexamethyldisilazide without removal of the proton next to the Ph_2PO group. Indeed treatment of Ph_2PO.Me with LiHMDS gave a

crystalline dimeric complex[6] without deprotonation of the methyl group. Efficient alkylation required ten equivalents of the alkyl halide and ten equivalents of DMPU. Good yields were then obtained with high *anti*-selectivity (table 2). It is hardly surprising that planar lactone enolates react on the opposite side to the two large groups already present.

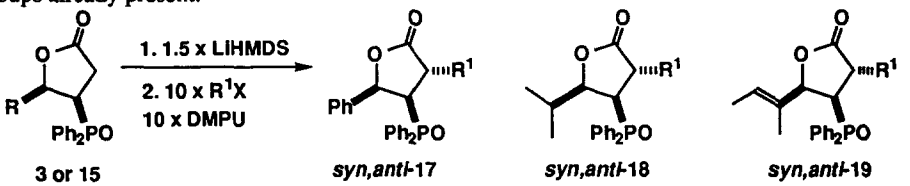
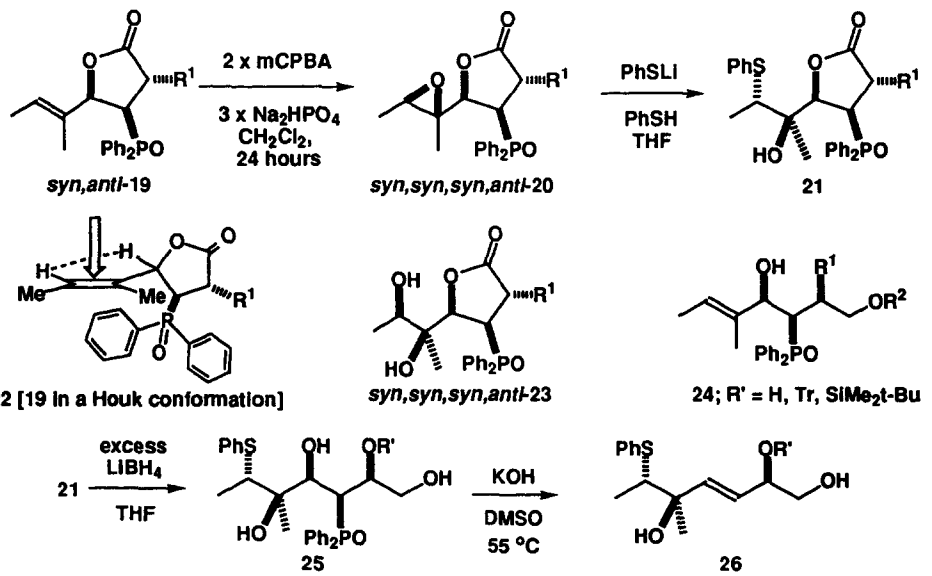


Table 2; Alkylation of Lactones **3** and **15**

Lactone	Alkyl Halide R^1X	Product[a]	Yield (%)	Stereochemistry
syn-**3a**	EtI	*syn,anti*-**17b**; R^1=Et	91	>95:5
syn-**3a**	$PhCH_2Br$	*syn,anti*-**17c**; $R^1=CH_2Ph$	88	>95:5
syn-**3b**	MeI	*syn,anti*-**18a**; R^1=Me	82	>98:2
syn-**3b**	EtI	*syn,anti*-**18b**; R^1=Et	92	>95:5
E,syn-**15**	MeI	*syn,anti*-**19a**; R^1=Me	98	>97:3
E,syn-**15**	EtI	*syn,anti*-**19b**; R^1=Et	98	>97:3
E,syn-**15**	$PhCH_2Br$	*syn,anti*-**19c**; $R^1=CH_2Ph$	100	>97:3

[a]Products are labelled **a** if R=Me, **b** if R=Et, or **c** if $R=CH_2Ph$.

The success of the stereoselective alkylation leads on to the extension of the family of stereogenic centres to the left (diagram on page 1) by development of the prochiral alkene unit. Epoxidation proved to be highly *syn* selective giving *syn,syn,syn,anti*-**20** in good yield (table 3) presumably via the Houk conformation **22**. Attack then occurs from the diastereotopic face opposite the Ph_2PO group.[7]



Other methods were not so stereoselective. Our Sharpless-style racemic dihydroxylation procedure gave moderate stereoselectivity in favour of hydroxylation *syn* to the Ph_2PO group and we were able to isolate[2] reasonable yields of both diastereoisomers of diols **23**. Reduction of lactones **19** ($NaBH_4$ in EtOH) gave near quantitative yields of the promising diols **24**; R'=H but neither they, nor protected versions of them, gave useful stereoselective dihydroxylations or epoxidations.

The epoxides **20** were opened stereospecifically and in good yield by PhSLi buffered with PhSH to give adducts **21** which were reduced with excess $LiBH_4$ in THF to give the open chain triols **25**. Horner-Wittig elimination with KOH in DMSO gave the alkenes **26** in reasonable yield. The elimination was totally *syn*-specific and only the *E*-alkenes were produced ($^3J_{CH=CH}$ 15.6 Hz). All other stereochemical assignments were made by ^1H and ^{13}C NMR correlations with an X-ray crystal structure of the epoxide *syn,syn,syn,anti*-**20** determined by Inés Alonso and Isabel López-Solera of this department.

Table 3; Epoxidation and Preparation of Alkenes with Remote Stereochemical Control

Lactone	Stereoselectivity of epoxidation	Isolated yield of *syn*-Epoxide **20**	PhS adduct **21** yield	Triol **25** yield	Alkene **26** yield
19a	92:8	90%	85%	86%	53%
19b	84:16	63%	89%	79%	77%

The role of the lactone in this sequence is worthy of comment. Originally envisaged simply as a means of introducing a stereogenic centre by alkylation, it also directed the epoxidation better than any open chain groups and protected the products from Payne rearrangements by blocking the neighbouring hydroxyl group. Finally, it was remarkably easily reduced with sodium or lithium borohydride to reveal that hydroxyl group which is necessary for the Horner-Wittig elimination. The nearest analogy to this work is Hoppe's synthesis[8] of protected triols by Peterson elimination from 3-$PhMe_2Si$-butyrolactones.

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References and Notes

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7. In this diagram the dashed line simply shows that the two hydrogen atoms are in the plane of the alkene and does *not* imply a hydrogen bond.
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