Tetrahedron Letters, Vol.27, No.2, pp 259-262, 1986 0040-4039/86 $3.00 + .00
Printed in Great Britain

STEREOCHEMICALLY CONTROLLED SYNTHESIS OF UNSATURATED HYDROXY-ACIDS BY THE HORNER-WITTIG REACTION

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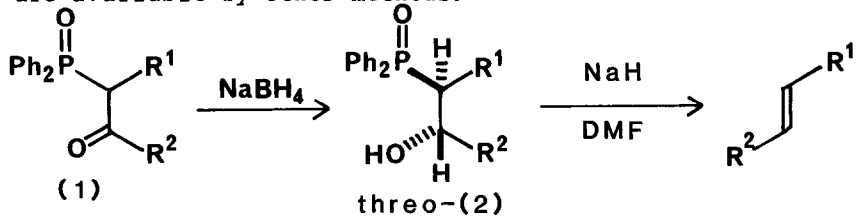
α-Ph_2PO-Ketones containing OH and CO_2R groups are stereoselectively reduced by $NaBH_4$ under $CeCl_3$ catalysis to give Horner-Wittig intermediates for the synthesis of E-isomers of unsaturated hydroxy-acids.

We have described the synthesis of single isomers (E or Z) of unsaturated alcohols[1,2,3] and unsaturated acids[4] by the threo-selective reduction of α-diphenylphosphinoyl(Ph_2PO-)ketones (1) and the stereospecific elimination of $Ph_2PO_2^-$ from the pure crystalline intermediates (2). We now describe the synthesis of α-Ph_2PO-ketones containing both functional groups [R^1 in (1) having a hydroxyl group and R^2 having a carboxyl group], their stereoselective reduction, and the synthesis of unsaturated hydroxyacids. Related Wittig reactions have been used to synthesise leukotriene B analogues,[5,6] and related compounds are available by other methods.[7]



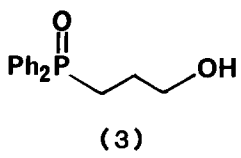
(1) threo-(2)

C-Acylation of the ω-Ph_2PO-alcohols (3-5) can be achieved (table 1) either by protection (t-$BuPh_2SiCl$) and reaction of the copper derivative[4] with the half ester-half acid chloride (6), or by O-acylation of the alcohols (3-5) with (6) or (7) catalysed by 4-dimethylaminopyridine (DMAP) followed by O➤C acyl transfer[3] initiated by three equivalents of LDA. Remarkably, the second ester group in (11) does not interfere with this reaction.

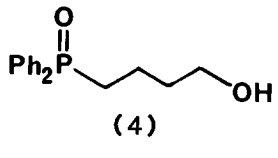
Table 1: Synthesis of Keto-Esters (12)

Starting Material	Acylating Agent	n	m	Method	Yield (%) (8)/(11)	Product	Yield (%) (12)
(3)	(6)	2	2	B	100	(12a)	78
(3)	(7)	2	3	B	98	(12b)	71
(4)	(6)	3	2	B	91	(12c)	69
(4)	(7)	3	3	B	84	(12d)	61
(5)	(6)	a	2	A	96	(9)	66
(5)	(6)	a	2	B	98	(17)	79

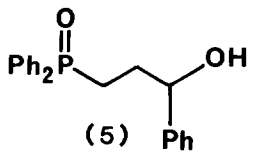
a. see diagrams (5), (9), and (17).



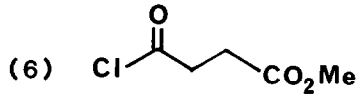
(3)

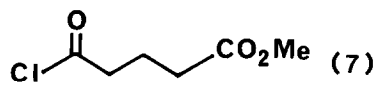


(4)



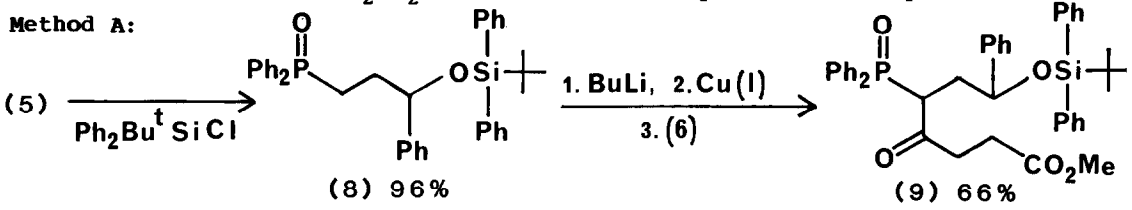
(5)



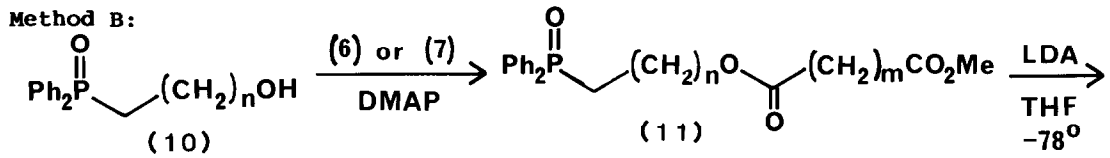


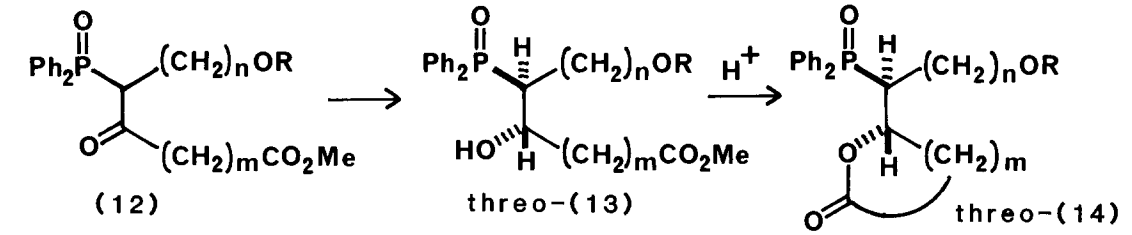
The acyl transfer products (12; R=H) exist partly as hemiacetals (n.m.r.) and form enol ethers readily. Even dissolving (12; R=H) in $CDCl_3$ gives the enol ether unless the $CDCl_3$ is first passed down a column of alumina. These hydroxy-ketones (12) are best characterised as their 3,5-dinitrobenzoates (acid chloride, DMAP, CH_2Cl_2) which have the expected n.m.r. spectra.

Method A:

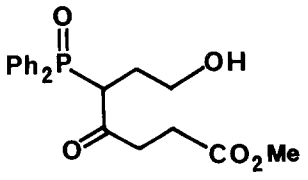


Method B:

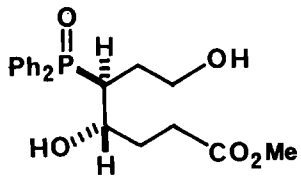




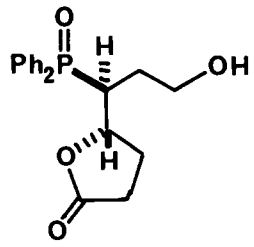
Stereoselective reduction of the ketones (12) and purification of the products before Horner-Wittig elimination presented some problems.[8] Reduction of the hydroxy-keto-ester (12a) with $NaBH_4$ in MeOH gave (13a) which cyclised easily (TsOH, CH_2Cl_2, room temperature) to the lactone (14a) in 64% overall yield and moderate (2.2:1 in favour of threo) stereoselectivity. However, neither (14a) nor its silyl (t-$BuMe_2Si$ or t-$BuPh_2Si$) ethers nor its p-nitrobenzoate could be separated into diastereoisomers by chromatography. Fortunately $NaBH_4/CeCl_3$, introduced by Luche[9] for the regioselective reduction of enones, gave high threo selectivity at -78 °C so that crystalline threo-(14a) could be isolated in 77% yield. From a more detailed analysis of analogous compounds, it appears that the free alcohol is essential for this effect, which may arise from the combination of a bulky reducing agent[10] and chelation of Ce^{3+} by OH, CO, and PO. As far as we are aware, this is the first example of $NaBH_4/CeCl_3$ giving high stereoselectivity in acyclic systems.[11]



(12a,R=H)

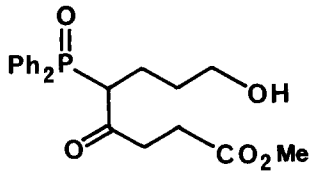


threo-(13a,R=H)

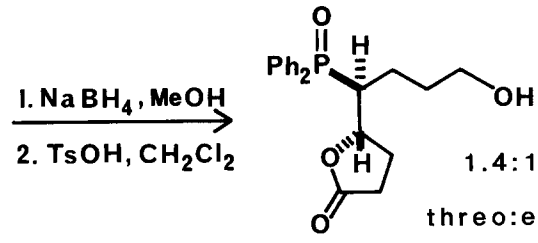


threo-(14a,R=H)

With the longer hydroxyalkyl chain (n=3), reduction of the keto-esters was again not very stereoselective, e.g. (12c; R=H) gives (14c; R=H) with 1.4:1 threo selectivity. Addition of $CeCl_3$ gave a lower yield and worse stereoselectivity and other reagents (table 2) gave an improved stereoselectivity but low yields. The lactones could not be separated, even by h.p.l.c .



(12c,R=H)



(14c,R=H) 69%

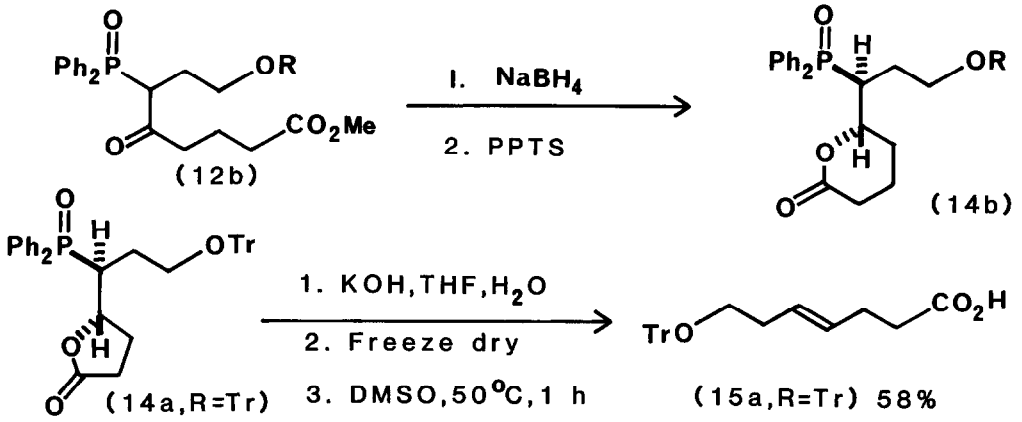
With the longer acid chain (m=3), the lactones do not form so easily, but treatment of the intermediates (13b, d) with pyridinium toluene-p-sulphonate (PPTS) gave good yields of lactone (14b, d) without epimerisation. In this series a protected version of the alcohol (12b; R=t-$BuPh_2Si$) was reduced in the presence of $CeCl_3$ with a 4:1 threo selectivity and 52% of crystalline (14b, R=t-$BuPh_2Si$) could be isolated. Cerium has no effect in two series: (12b, R=trityl) gave a 2:1 selectivity and with both side-chains longer (n=m=3), (12d, R=H) gave with or without $CeCl_3$ a 2.5:1 selectivity.

Table 2: Stereoselective Reductions of Keto-Acid Derivatives (12)

Starting Compound	Material R	Reducing Agent	Product	Yield (%)	threo:erythro[a]
(12a)	H	$NaBH_4$	(14a)	64	2.2:1
		$NaBH_4$, $CeCl_3$	(14a)	77	>20:1
(12b)	Tr	$NaBH_4$	(13b)	94	2:1
		$NaBH_4$, $CeCl_3$	(13b)	80	2:1
	t-$BuPh_2Si$	$NaBH_4$	(13b)	99	1.8:1[b]
		$NaBH_4$, $CeCl_3$	(14b)	65	4.1:1[b]
(12c)	H	$NaBH_4$	(14c)	69	1.4:1
		$NaBH_4$, $CeCl_3$	(14c)	51	1.2:1
		$Zn(BH_4)_2$	(14c)	17	1.8:1
		$LiAl(t\text{-}BuO)_3H$	(14c)	33	3.5:1
(12d)	H	$NaBH_4$	(13d)	97	2.5:1
		$NaBH_4$, $CeCl_3$	(13d)	100	2.5:1

a. Ratios by n.m.r. integration. b. Ratio by h.p.l.c.

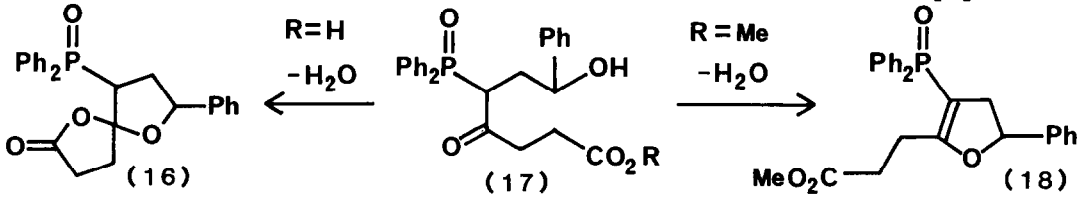
The final eliminations of $Ph_2PO_2^-$ can be carried out directly on the lactones using the methods developed for the acids,[4] but isolation of the products is difficult. It is better to protect the OH group as a trityl or silyl ether (or to use previously protected materials in the reductions). Thus (14a; R=trityl) gave the protected hydroxy-acid (15a, R=trityl).



We thank S.E.R.C. and Glaxo Group Research (Ware) for a CASE award, and Dr Eric Collington for many helpful discussions.

References

1. A.D. Buss, N. Greeves, D. Levin, P. Wallace, and S. Warren, Tetrahedron Lett., 1984, **25**, 357.
2. P.S.Brown, A.B.McElroy, and S.Warren, Tetrahedron Lett., 1985, **26**, 249.
3. P. Wallace and S. Warren, Tetrahedron Lett., 1985, **26**, 5713.
4. D. Levin and S. Warren, Tetrahedron Lett., 1985, **26**, 505.
5. R. Zamboni and J. Rokach, Tetrahedron Lett., 1983, **24**, 999; B.J. Fitzsimmons and J. Rokach, Ibid., 1984, **25**, 3043.
6. E.J. Corey and W. Su, Tetrahedron Lett., 1984, **25**, 5119.
7. E.J. Corey, K. Kyler, and N. Raju, Tetrahedron Lett., 1984, **25**, 5115.
8. Compounds (17) derived from (5) with an extra chiral centre have a marked tendency to form cyclised products such as the enol ether (18) and the spiro ketal-lactone (16), and will be described in the full paper.



9. A.L. Gemal and J.-L. Luche, J. Am. Chem. Soc., 1981, **103**, 5454.
10. A.B. Smith, B.H. Toder, R.E. Richmond, and S.J. Branca, J. Am. Chem. Soc., 1984, **106**, 4001, and references therein.
11. For related effects on ketones having an α-dibenzophosphole-5-oxide group, see J. Elliott and S. Warren, submitted to Tetrahedron Lett.

(Received in UK 5 November 1985)