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THE STEREOCHEMICALLY CONTROLLED HORNER-WITTIG ROUTE TO UNSATURATED ACIDS: THE BAEYER-VILLIGER REARRANGEMENT OF α-(1-Ph_2PO-ALKYL)-CYCLOHEXANONES

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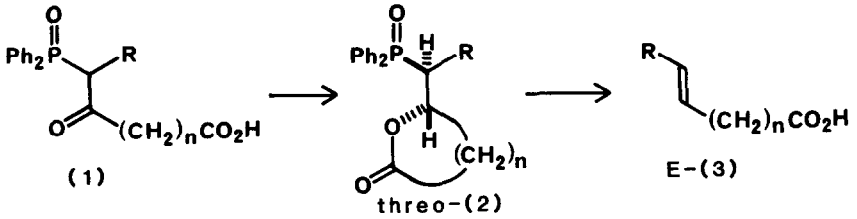
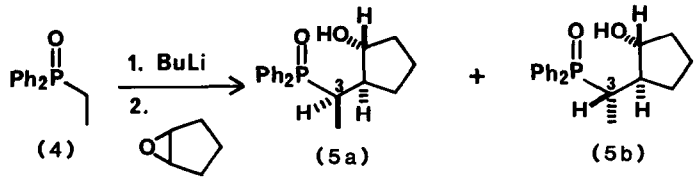
Lithiated alkyl diphenylphosphine oxides attack cyclic epoxides with high stereoselectivity: Baeyer-Villiger rearrangement of the derived ketones gives Horner-Wittig intermediates for the synthesis of Z unsaturated acids.

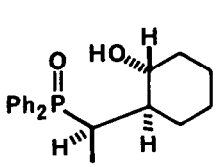
The stereoselective reduction of keto-acids (1) and purification of the lactones (2) provides[1] a route to pure E-isomers of unsaturated acids (3). The Z-isomers were also prepared by this route from the minor lactones erythro-(2) but material conversion was necessarily poor. We now report an alternative approach to lactones (2; n=3) which allows high material conversion into either the threo or the erythro series from the same starting materials.



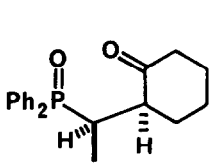
The lithium derivative of the phosphine oxide (4) attacks cyclopentene or cyclohexene oxide with high stereoselectivity[2] at chiral centre C-3, the ratio of isomers being 90:10 for (5a):(5b) and 84:16 for (6a):(6b).[3] The diastereoisomers are easily separated by flash chromatography and purified by crystallisation. Oxidation (NaOCl/HOAc)[4] gave the corresponding ketones (7a) and (7b) with no epimerisation. The ketone (7a) from the major alcohol (6a) epimerises (presumably by enolisation) on standing in HOAc and can be converted into the ketone (7b) in 87% yield from (6a) by slow (1 week) crystallisation from the minimum amount of EtOAc and a trace of HOAc. Thus either ketone may be obtained in reasonable yield from (4): (7a) in 63.5% via (6a), and (7b) in 62% yield via the unpurified alcohol mixture.



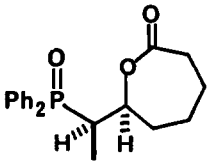
Baeyer-Villiger rearrangement on both ketones (7) was stereospecific and nearly completely regioselective [24:1 in favour of (8a)] for (7a) giving (8a) in 89% yield. However, (7b) gave a 5:3 ratio of the regioisomers (8b) and (9b). We suppose this to be a stereoelectronic effect of C-P and C-C sigma bond interactions affected by conformation.[5] Fortunately, lactone[6] (8b) is the major isomer from our reduction route[1] via (1), and lactone (8a) leads to the cis-acid Z-(10) by hydrolysis of the lactone and elimination of $Ph_2PO_2^-$.



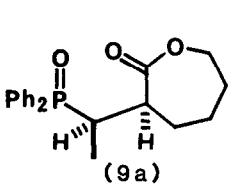
(6a)



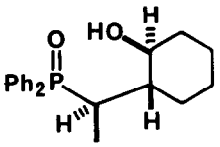
(7a)



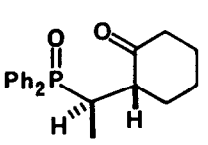
(8a)



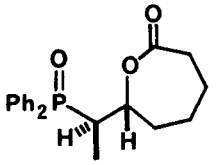
(9a)



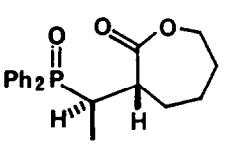
(6b)



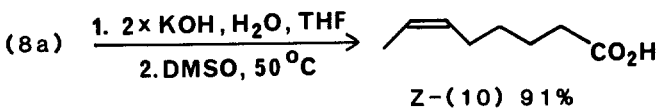
(7b)



(8b)



(9b)



Z-(10) 91%

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References

1. D. Levin and S. Warren, Tetrahedron Lett., 1985, **26**, 505.
2. The reaction is of course stereospecific for the two chiral centres on the ring, only the new chiral centre (C-3) is in question.
3. The structures of (5a) (M.P. Gomez-Sal and P. Raithby) and (6a) (W.B. Cruse and O. Kennard) come from X-ray crystal structure determinations.
4. R.V. Stevens, K.T. Chapman, C.A. Stubbs, W.W. Tam, and K.F. Albizati, Tetrahedron Lett., 1982, **23**, 4647, and references therein.
5. Effects of even more remote electronegative substituents on the regioselectivity of the Baeyer-Villiger rearrangement, also affected by conformation, have been reported; R. Noyori, T. Sato, and H. Kobayashi, Tetrahedron Lett., 1980, **21**, 2567, 2573.
6. The regioisomeric lactones (8b) and (9b) could not be separated by chromatography. This does not affect the Horner-Wittig elimination as hydrolysis of the mixed lactones gives a Horner-Wittig intermediate only from (8b) which we have already shown (ref. 1) gives E-oct-6-enoic acid on elimination.

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