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# STEREOCHEMICALLY CONTROLLED SYNTHESIS OF UNSATURATED ACIDS VIA DIPHENYLPHOSPHINOYL($Ph_2PO$)-KETOACIDS

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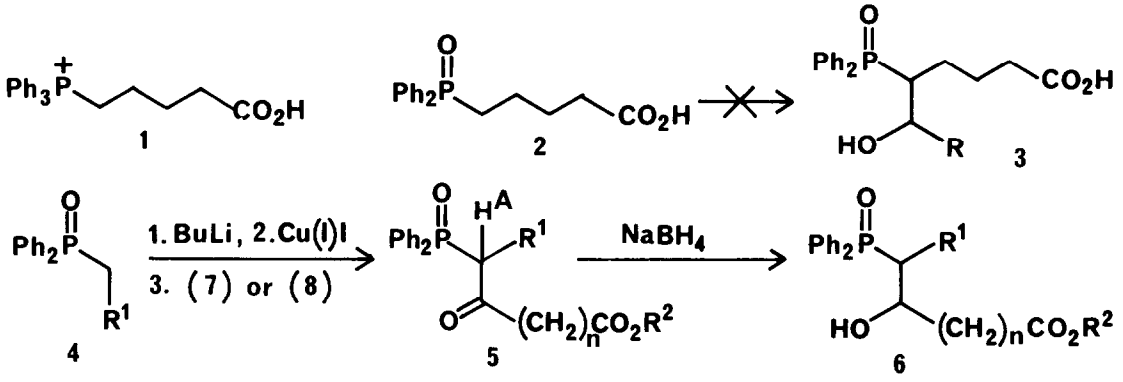
Acylation of phosphine oxide anions with derivatives of cyclic anhydrides or oxidative cleavage of cyclic allyl phosphine oxides gives $Ph_2PO$-ketoacids: reduction, separation of diastereoisomers, and completion of the Horner-Wittig reaction gives single isomers (E or Z) of unsaturated acids.

Phosphonium salts such as (1) have been widely used to make unsaturated carboxylic acids, particularly in prostaglandin synthesis.[1] The phosphine oxide (2) does not however give a satisfactory Horner-Wittig reaction so that our stereocontrolled olefin synthesis[2-4] cannot be applied directly to unsaturated acids, but we now report that reduction of $Ph_2PO$-ketoacids (5) gives the transposed intermediates (6 cf. 3) and hence single isomers (E or Z) of unsaturated acids.





We have used the acylation of lithium derivatives of phosphine oxides (4) with esters[3] and lactones[4] to make α-$Ph_2PO$-ketones. Acylation with succinic anhydride or the half acid chlorides (7) or (8) under a variety of conditions gave poor yields of adducts and much recovered starting material (4), probably by transfer of the acidic proton ($H^A$ in 5) to the lithium derivative of (4) during the reaction. Replacement of the lithium by the less basic copper derivative of (4) gave good yields of (5) in reactions with the half acid chlorides (table 1).

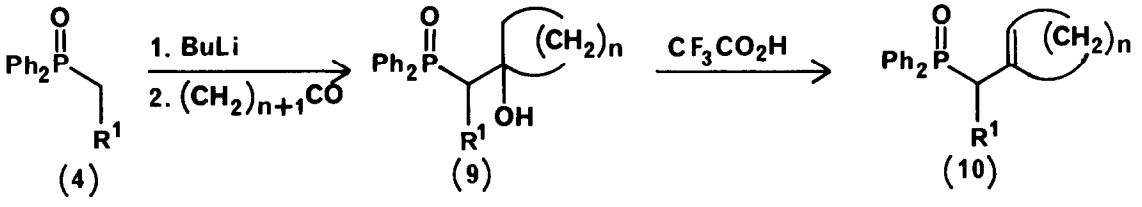
Alternatively, the two carbonyl groups in ketoacid (5) suggested a reconnection strategy[6] particularly as we had already made the cyclic allyl phosphine oxides (10) from cyclic ketones.[7,8] Oxidative cleavage of the double bond in (10) by ozone with oxidative workup, or better by $RuO_2$ and $NaIO_4$,[9] gave the ketoacids (5, $R^2$=H) or esters (5, $R^2$=Me) after esterification. This method is not suitable for (5, n=2) as cyclobutanone would be needed,[8] but that series can be made by acylation with (7). Medium and large rings are suitable for the oxidative cleavage route as both cyclic alcohols (9, n=8 and 12) dehydrate cleanly to the allyl phosphine oxides (10). We have prepared compounds with n = 2,3,4 by these routes (Table 1).

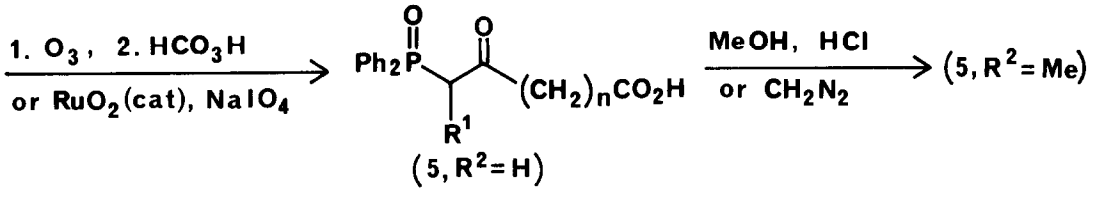
Table 1

**Synthesis of $Ph_2PO$-ketoacids and Esters (5)**

| Product | $R^1$ | $R^2$ | n | Method* | Yields (9) | (10) | (5) |
|---|---|---|---|---|---|---|---|
| (5a) | Me | Me | 2 | A | - | - | 60% |
| (5b) | $n\text{-}C_5H_{11}$ | Me | 2 | A | - | - | 73% |
| (5c) | $n\text{-}C_{14}H_{29}$ | H | 3 | B1 | 77% | 75% | 92% |
| (5d) | H | H | 4 | B2 | 77% | 95% | 55% |
| (5e) | Me | Me | 4 | B2 | 80% | 84% | 62% |
| | | | | B1 | " | " | 57% |
| (5f) | $n\text{-}C_{13}H_{27}$ | H | 4 | - | 81% | 81% | - |

*Method A: acylation of copper derivative with (7) or (8), method B: oxidative cleavage of (10): B1 is 1.$O_3$, 2.$HCO_3H$, B2 is $RuO_2$, $NaIO_4$, and esterification




Reduction of ketoacids (5, $R^2$=H) or esters (5, $R^2$=Me) with sodium borohydride in methanol or ethanol at room temperature gave the Horner-Wittig intermediates (11) in good yield but with only moderate stereoselectivity (Table 2). The threo isomer is favoured, as in the unfunctionalised series[2,3] and comparison between $CO_2H$, $CO_2Me$, and $CH_2OH$ as chain endings in structure (15) (Table 2) shows that stereoselectivity increases slightly as n increases (more so for $CH_2OH$ than for $CO_2R$), and that $CO_2H$ gives slightly better stereoselectivity than $CO_2Me$.

Diastereoisomers of the hydroxy acids or esters (11) were usually difficult to separate, but lactones (12) (made with $CF_3CO_2H$ if n=2 or TsOH if n=3,4) could be separated by flash chromatography[5] and crystallisation. Treatment of the lactones (12) with 2.1 equivalents of KOH in aqueous THF gave the potassium salts (13) which were freeze-dried to avoid foaming. Dissolution in DMSO at 50 °C completed the Horner-Wittig reaction,[2] the extra equivalent of KOH acting as base, and gave single isomers of the unsaturated acids, E-(14) from threo-(12) and Z-(14) from erythro-(12) (Table 2). Thus we obtained both isomers of 6-octenoic acid (14e) and 4-decenoic acid (14b) and E-5-eicosenoic acid (14c) in >97% purity.[10] Erythro lactone (12c) contained 10% threo lactone and hence our Z-5-eicosenoic acid contained 10% E isomer.[10]

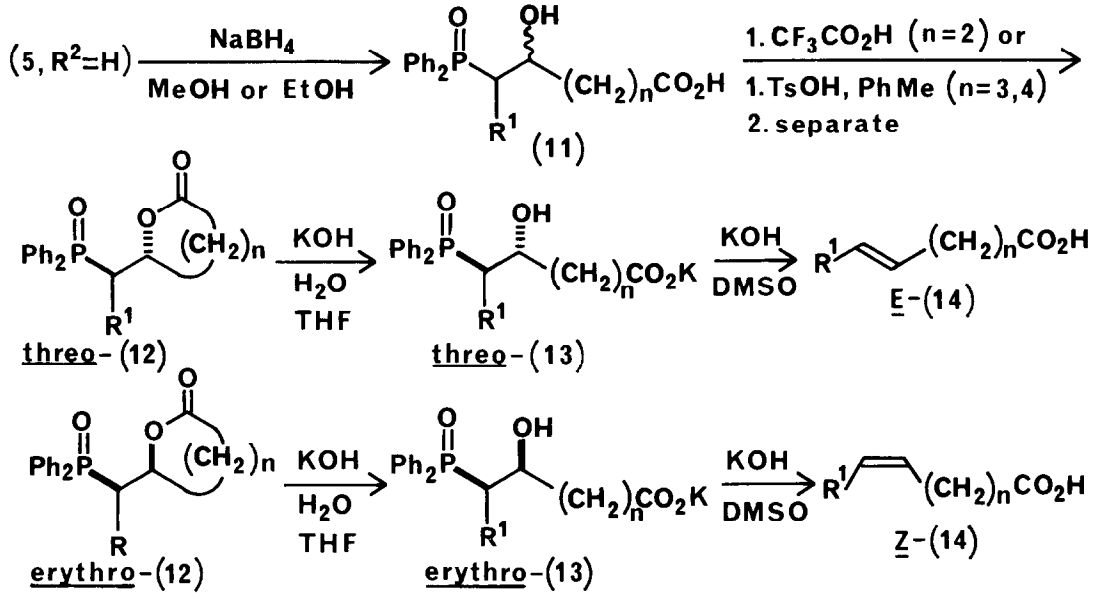
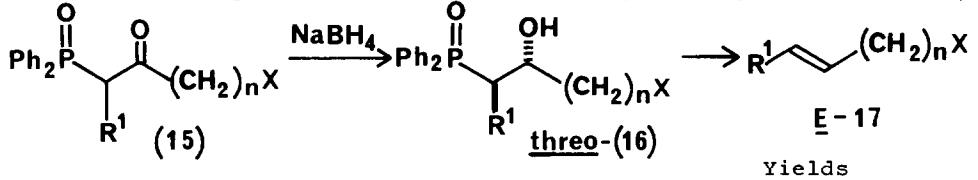



Table 2

**Stereoselectivity of Reduction of Ketoacids, Esters, and Alcohols (15)**

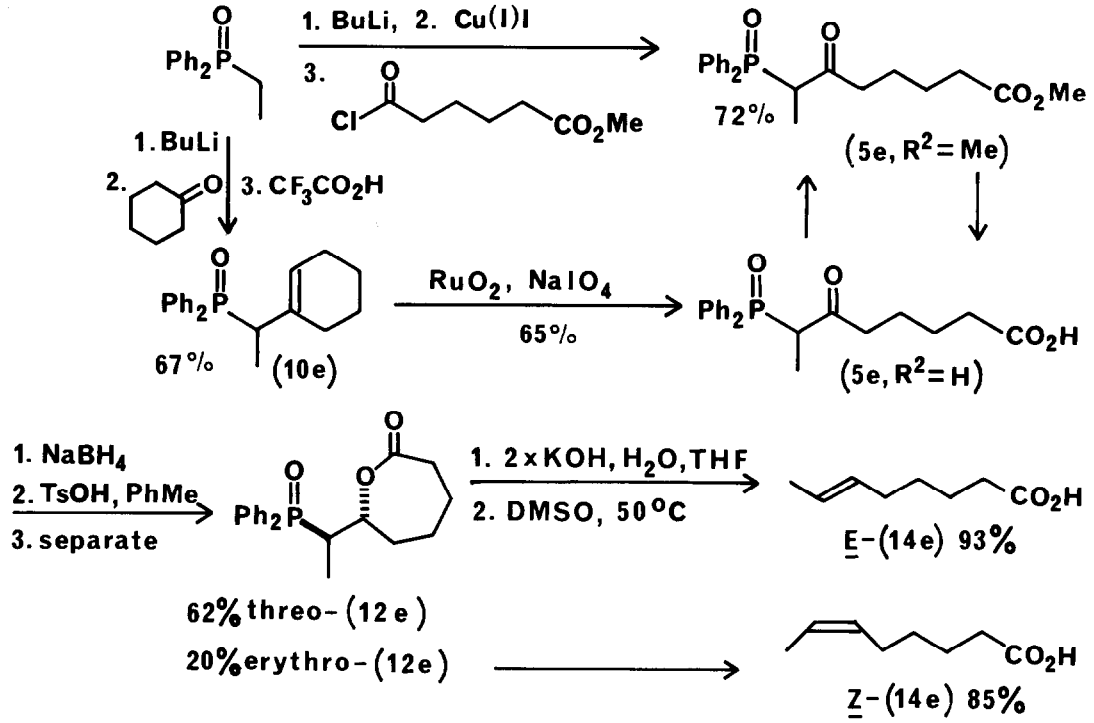



| Starting Material | n | $R^1$ | X | threo: erythro | Yields threo (12/16) | E-(14) E-(17) | erythro (12/16) | Z-(14) Z-(17) |
|---|---|---|---|---|---|---|---|---|
| (15a) | 2 | n-$C_5H_{11}$ | $CH_2OH$ | 1:1 | 43% | - | - | - |
| (5b) | 2 | n-$C_5H_{11}$ | $CO_2Me$ | 1.5:1 | 50%* | 73% | 34% | 55%* |
| (15b) | 3 | n-$C_4H_9$ | $CH_2OH$ | 3:1 | 68% | 96% | 14% | 98% |
| (5c) | 3 | n-$C_{14}H_{29}$ | $CO_2H$ | 1.9:1 | 51% | 88% | 8% | 55%[a] |
| (5e) | 4 | Me | $CO_2Me$ | 1.4:1 | - | - | - | - |
| | 4 | Me | $CO_2H$ | 1.9:1 | 62% | 93% | 20% | 85% |
| (15c) | 4 | Et | $CH_2OH$ | 6:1 | 85% | 98% | - | - |

*On a small scale by h.p.l.c.

[a]90% erythro and 10% threo-(5c) gave 95% Z and 5% E-(14c).

We summarise the synthesis of pure samples of each isomer of 5-octenoic acid.

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**References**

1. E. J. Corey, N. M. Weinshenker, T. K. Schaaf, and W. Huber, J. Am. Chem. Soc., 1969, **91**, 5675; J. S. Bindra and R. Bindra, "Prostaglandin Synthesis", Academic Press, New York, 1977, p 210ff.
2. A. D. Buss and S. Warren, J. Chem. Soc., Chem. Commun., 1981, 100; Tetrahedron Lett., 1983, **24**, 111, 3931.
3. A. D. Buss, R. Mason, and S. Warren, Tetrahedron Lett., 1983, **24**, 5293.
4. A. D. Buss, N. Greeves, P. Wallace, and S. Warren, Tetrahedron Lett., 1984, **25**, 357.
5. A. D. Buss, W. B. Cruse, O. Kennard, and S. Warren, J. Chem. Soc., Perkin Trans. 1, 1984, 243.
6. S. Warren, "Organic Synthesis: The Disconnection Approach", Wiley, Chichester, 1983, p 217ff.
7. A. H. Davidson, I. Fleming, J. I. Grayson, R. L. Snowden, and S. Warren, J. Chem. Soc., Perkin Trans. 1, 1977, 550; A. Bell, A. H. Davidson, C. Earnshaw, H. K. Norrish, R. S. Torr, D. B. Trowbridge, and S. Warren, Ibid., 1983, 2879.
8. A. H. Davidson, C. Earnshaw, J. I. Grayson, and S. Warren, J. Chem. Soc., Perkin Trans. 1, 1977, 1452.
9. P. H. J. Carlsen, T. Katsuki, V. S. Martin, and K. B. Sharpless, J. Org. Chem., 1981, **46**, 3936.
10. The methyl esters (14, $R^2$=Me) of the unsaturated acids were clearly separated by g.l.c. All E isomers were >99.9% pure, Z-(14f) was >99% and Z-(14b) >97% pure. Isomers were identified by the vicinal coupling constants between the olefinic protons: $J_{cis}$ 10.8 Hz, $J_{trans}$ 15.2-15.4 Hz.

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