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THE USE OF 3-PHENYLSELENOBUTANAL AS A CROTONALDEHYDE EQUIVALENT IN SYNTHESIS

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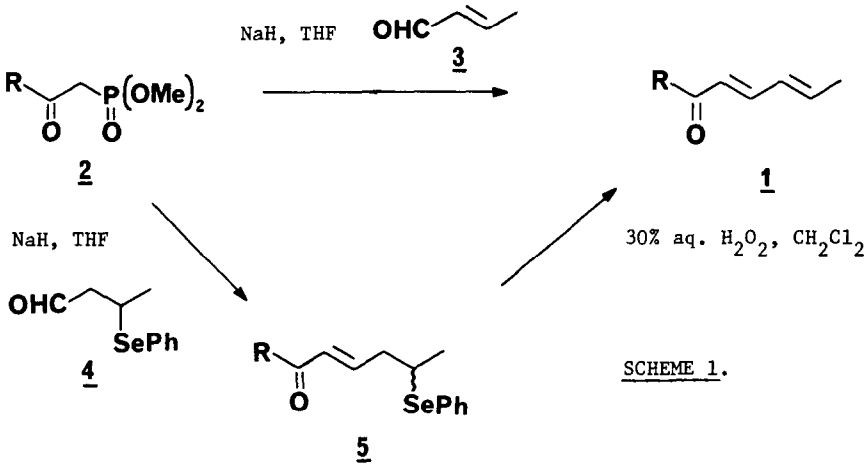
Summary - Condensation of β-ketophosphonates with 3-phenylselenobutanal affords α,β-unsaturated-γ-phenylseleno ketones which upon oxidation-elimination give (E,E)-ketodienes in high overall yield.

During a project concerned with the total synthesis of various complex polycyclic natural products we required access to ketodienes such as 1. A plausible route to such a system could involve the condensation of a β-ketophosphonate 2 with crotonaldehyde 3, (Scheme 1).[1] Unfortunately, in our hands these condensations proved to be low yielding, and isolation of the product by chromatography failed to give consistently pure samples for further manipulation.

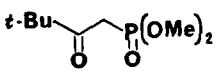
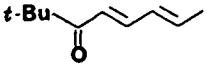
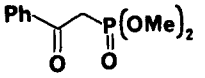
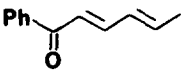
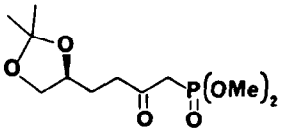
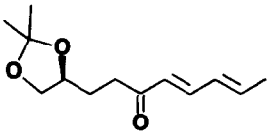
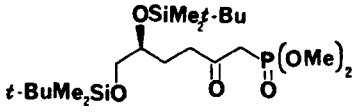
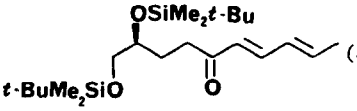
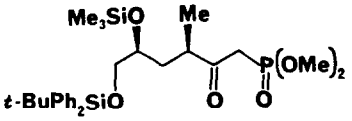
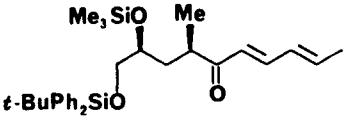


SCHEME 1.

Masamune, Roush and coworkers[2] have described a mild olefination procedure for the reaction of phosphonate anions with base-sensitive aldehydes. As our problem appeared to be associated with the stability and reactivity of crotonaldehyde, we sought an alternative "masked" form of this aldehyde that would overcome our difficulties. In this Letter, we demonstrate that 3-phenylselenobutanal 4,[3] readily prepared in 74% yield from the reaction of crotonaldehyde with sodium phenylselenide,[4] is a convenient and practical synthetic equivalent to crotonaldehyde. Condensation of the anion of various β-ketophosphonates[5] with

4 proceeded smoothly to afford (E)-α,β-unsaturated-γ-phenylseleno ketones 5 under mild conditions (NaH, THF, 0°, 10 min; add 4 in THF, 0°,-20 min.) Treatment of the pure products 5 with excess 30% hydrogen peroxide at 0° in CH_2Cl_2 gave the (E,E)-ketodienes 1 in high overall yield. Pertinent examples are shown by the examples in Table 1.[6]

Table 1

β-Ketophosphonate	Keto-diene (Yield, %)#
 **6**	 (87) **11**
 **7**	 (85) **12**
 **8** $[\alpha]_D$ -2.0°, C= 1.45	 (80) **13** $[\alpha]_D$ -43.1°, C= 1.21
 **9** $[\alpha]_D$ -41.0°, C= 1.77	 (80) **14** $[\alpha]_D$ -9.4°, C= 1.45
 **10** $[\alpha]_D$ -43.9°, C= 2.20	 (72) **15** $[\alpha]_D$ -24.7°, C= 2.07

Overall yields (2 steps) refer to chromatographically isolated product.

An important feature of this transformation is the exclusive formation of trans, trans dienes as evidenced by 400 MHz ^1H n.m.r. spectroscopy. Presumably, syn-elimination of the intermediate selenoxides occurs in such a fashion that the terminal methyl group adopts a trans orientation with respect to the β-vinyl proton, thus minimizing steric interactions during the selenoxide elimination.[7]

A representative procedure: To a solution of sodium hydride (145 mg, 6.05 mmoles; 242 mg of a 60% dispersion in mineral oil "pre-washed" with hexanes under argon) in THF (8 ml) at 0°, was added dropwise a solution of the β-ketophosphonate 8[6] (1.54 g, 5.5 mmoles) in THF (8 ml). The mixture was stirred at 0° under an argon atmosphere for 10 min.,and 3-phenylselenobutanal (1.5 g, 6.6 mmoles) in THF (8 ml) was added dropwise. After stirring at 0° for 20 min., saturated aqueous ammonium chloride (20 ml) was added and the mixture was extracted with ether (4 x 20 ml). The combined organic extracts were washed with water, brine, dried ($MgSO_4$), and evaporated under reduced pressure. Flash column chromatography (elution with hexanes, then with 1:8 ethyl acetate-hexanes) gave the intermediate α,β-unsaturated-γ-phenylseleno ketone as a pale yellow syrup. This compound was dissolved in dichloromethane (20 ml) and 30% hydrogen peroxide (5 ml) was added at 0°C. The mixture was stirred at 0° for 15 min, saturated sodium hydrogen carbonate solution (20 ml) was added, the mixture was extracted with ether (4 x 50 ml), and the combined organic extracts were processed as usual. Flash column chromatography (elution with 1:6 ethyl acetate-hexanes) gave the (E, E)-ketodiene 13 (0.987g, 80% overall) as a colorless syrup.

This operationally simple access to configurationally pure ketodienes should find a number of useful synthetic applications, notably in Diels-Alder type[8] reactions, where the diene component is necessarily derived from crotonaldehyde or its synthetic equivalent.

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References:

1. For aspects of the Horner-Wadsworth-Emmons reaction, see I. Gosley, A.G. Rowley, in "Organophosphorus Reagents in Organic Synthesis." J.I.G. Cadogan., Ed.; Academic Press; New York, 1979; Chap. 2. W.S. Wadsworth, Jr., Org. React., (1978) and references cited therein.

2. M.A. Blanchette, W. Choy, J.T. Davis, A.P. Essenfeld, S. Masamune, W.R. Roush, T. Sakai., Tetrahedron Lett., (1984), 25, 2183.

3. M.R. Detty., Tetrahedron Lett., (1978), 5087.

4. 3-Phenylselenobutanal was prepared as follows; To a solution of diphenyldiselenide (3.12 g, 10.0 mmoles) in ethanol (50 ml) at 0° was added sodium borohydride (0.68 g, 18.0 mmoles) in portions. A solution of crotonaldehyde (1.49 ml, 18.0 mmoles) in ethanol (10 ml) was added and the mixture stirred under an argon atmosphere for 1h. The mixture was acidified, extracted with ether and processed as usual. Flash column chromatography (elution with hexanes to remove residual diphenyl diselenide; then with 7:93 ethyl acetate-hexanes) gave 4, as a pale yellow syrup (3.0 g, 74%) 4; 400 MHz ^{1}H-n.m.r. ($CDCl_3$) δ 9.69 (1H, t, $J_{1,2A} = J_{1,2B} = 1.8$ Hz, 1-H), 7.60 - 7.53 (2H, m, ArH), 7.34 - 7.24 (3H, m, ArH), 3.69 (1H, app. sextet, $J_{2A,3} = J_{2B,3} = J_{3,4} = 6.8$ Hz, 3-H), 2.74 (1H, ddd, $J_{1,2B} = 1.8$ Hz, $J_{2B,\ 2A} = 17.2$ Hz, $J_{2B,\ 3} = 6.8$ Hz, 2-H_B), 2.68 (1H, ddd, $J_{1,2A} = 1.8$ Hz, $J_{2B,\ 2A} = 17.2$ Hz, $J_{2A,\ 3} = 6.8$ Hz, 2-H_A), 1.46 (3H, d, $J_{3,4} = 6.8$ Hz, 4-H). For an alternative synthesis, see ref. 3.

5. The β-ketophosphonates were prepared in 85-95% yields from the corresponding carboxylic acid chlorides (entry 6,7), methyl esters (entry 8) or lactones (entry 9, 10). For a recent method, see, K. Dietrich and R.W. Hoffmann, Tetrahedron Lett., (1985), 26, 6325, and references cited therein.

6. All compounds illustrated in Table 1 gave satisfactory 400 MHZ ^{1}H-n.m.r., high resolution mass spectra and i.r. data. Optical rotations were recorded in chloroform at 25°.

7. For example see, H.J. Reich, S.K. Shah., J. Amer. Chem. Soc.,, (1975), 97, 3250 and references cited therein.

8. For some excellent recent reviews on the intramolecular Diels-Alder reaction, see, R.G. Carlson, Ann. Rep. Med. Chem., (1974), 9, 270. G. Mehta., J. Chem. Educ., (1976), 53, 551; W. Oppolzer., Angew. Chem. Int. Ed. Engl., (1977), 16, 10; G. Brieger, J.N. Bennett., Chem. Rev., (1980), 80, 63; A.G. Fallis., Can. J. Chem., (1984), 62, 183; and references cited therein; L.A. Paquette in "Asymmetric Syntheses". J.D.Morrison, Ed.; Academic Press; New York, 1984; Vol. 3, 455.

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