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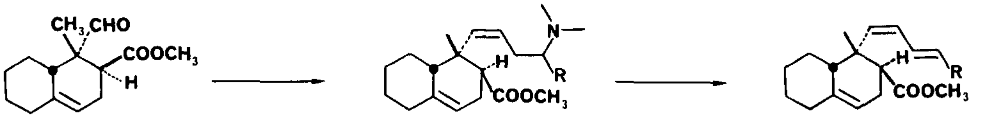
# HIGHLY REACTIVE EQUIVALENTS OF ALLYLIDENETRIPHENYLPHOSPHORANES FOR THE STEREOSPECIFIC SYNTHESIS OF 1,3-DIENES BY CIS-OLEFINATION OF HINDERED ALDEHYDES

E. J. Corey and Manoj C. Desai
Department of Chemistry, Harvard University, Cambridge, Massachusetts 02138

Summary: Ylides derived from 3-dimethylaminopropyltriphenylphosphonium salts react smoothly and stereospecifically with even hindered aldehydes to form Z-olefins which are easily converted to 1,3-dienes.

In connection with research which recently led to the total synthesis of (±)-retigeranic acid,[1] we had occasion to study the reaction of the model aldehyde 1[2] with allylidenetriphenylphosphorane as a route to the Z-diene ester 2. We were surprised to discover that even under forcing conditions (>5 equiv of phosphorane in tetrahydrofuran (THF)-hexamethylphosphorictriamide at 23° for 8 hr) none of the desired diene could be detected by careful isolation and thin layer chromatographic (tlc) analysis. The aldehyde ester 1 was converted only to very polar products evidently resulting from reaction of the γ-carbon of allylidenetriphenylphosphorane, a problem which has previously been observed.[3] Attempts to overcome the difficulty using as reagents (1-diphenylphosphino)allyltitanium[4] or E-1-trimethylsilyl-1-propene-3-pinacolboronate[5] were unsuccessful. We therefore turned to development of a new reagent. Excellent results in terms of yield, stereospecificity, and convenience were obtained with the ylide 4 from 3-dimethylaminopropyltriphenylphosphonium bromide (3). This paper describes our experiments in this area.

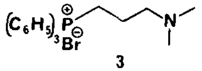
The phosphonium bromide 3 was synthesized readily by the sequence: (1) reaction of triphenylphosphine with excess 1,3-dibromopropane in benzene at 80° for 15 hr to give 3-bromopropyltriphenylphosphonium bromide as a colorless crystalline solid (85%), and (2) subsequent reaction with excess dimethylamine in absolute ethanol at 23° for 15 hr to give 3 as a colorless solid in 83% yield. Conversion of the phosphonium salt 3 to a salt-free solution of the ylide 4 was effected by reaction with potassium hexamethyldisilazide in toluene at 23° for 1 hr. Wittig coupling of a toluene solution of 4 with 1 occurred smoothly at 23° for 2 hr to form 5 in 81% yield. Oxidation of 5 with 1.2 equiv of m-chloroperbenzoic acid in chloroform at 0° gave the corresponding N-oxide which underwent Cope elimination at 50° for 4 hr to afford 2 in 80% yield. None of the E isomer of 2 could be detected by $^1$H NMR analysis.



1

5, R = H
7, R = CH3

2, R = H
8, R = CH3



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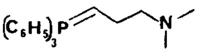

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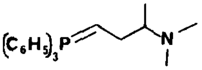

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The ylide 6 was similarly found to be a far superior reagent to E-crotonylidenetriphenylphosphorane for the synthesis of Z,E-dienes. Thus, reaction of 6 (prepared from 1,3-dibromobutane by a sequence paralleling that outlined above for the synthesis of 4) with 1 (in toluene, 2 hr at 23°) provided the Z-Wittig product 7 (82%) which was transformed stereospecifically into Z,E diene 8 in 65% overall yield by peracid oxidation and Cope elimination as described for 5 ⟶ 2.

**3-Dimethylaminopropyltriphenylphosphonium Bromide(3).** A stirred solution of 1,3-dibromopropane (9.6 ml, 95 mmole), triphenylphosphine (5.0 g, 19 mmole) in benzene (10 ml) under an atmosphere of nitrogen was heated at 70° for 15 hr, then cooled to 0°, diluted with 50 ml of ether and filtered. The colorless crystals of 3-bromopropyltriphenylphosphonium bromide were washed with cold ether and dried under vacuum (7.5 g, 85%). A cold (0°) stirred suspension of this salt (10.0 g, 22 mmole) in absolute ethanol (200 ml) containing 20 ml of dimethylamine was stirred at 23° for 15 hr. At the end of this period ethanol and excess dimethylamine were removed under reduced pressure and the residue was taken up in methylene chloride (300 ml) and shaken with saturated aqueous sodium sulfate (5 ml). The organic phase was passed through a short bed of anhydrous sodium sulfate, dried over $MgSO_4$ and evaporated to give 3 as colorless oil which solidified when freed of solvent from toluene (2x30 ml) under reduced pressure. The solid was dried over $P_2O_5$-KOH *in vacuo* (7.7 g, 83%). $^1H$ NMR ($CDCl_3$, 270 MHz): δ 2.0 - 2.2 (m, 2H), 2.5 (s, 6H), 3.15 - 3.33 (m, 2H), 3.8 - 3.98 (m, 2H), 7.6 - 7.9 (m, 15H).

**Synthesis of 5.** To a stirred suspension of 3 (382 mg, 0.89 mmole) in toluene (5 ml) under nitrogen at 23°, a freshly prepared solution of potassium hexamethyldisilazide (0.89 mmole, 1M) in toluene was added. After stirring at 23° for 1 hr the reaction mixture was centrifuged and the supernatant layer (red in color) was transferred under nitrogen to a dried round bottom flask and concentrated. To this, aldehyde ester 1 (50 mg, 0.21 mmole) in toluene was added and the mixture was stirred at 23° for 2 hr. The reaction was then quenched with saturated sodium bicarbonate and the product was isolated by extractive workup (ethyl ether) and flash chromatography (ethyl acetate) affording 5 (52 mg, 81%). IR ($CCl_4$): 2915, 1735, 1165 $cm.^{-1}$ $^1H$ NMR ($CDCl_3$, 270 MHz): δ 1 - 1.28 (m, 2H), 1.3 (s, 3H), 1.7 - 2.2 (m, 7H), 2.2 (s, 6H), 2.2 - 2.4 (m, 6H), 2.62 (dd, 1H, J=5.7, 9.7 Hz), 3.62 (s, 3H), 5.2 - 5.4 (m, 3H).

**Conversion of 5 to 2.** A solution of *m*-chloroperbenzoic acid (28 mg, 0.17 mmole) in chloroform (250 µl) was added gradually at 0 - 5° to an ice-cooled, stirred solution of 5 (46 mg, 0.15 mmole) in chloroform (1 ml). Stirring was continued for 0.5 hr and the excess of MCPBA was decomposed by addition of dimethyl sulfide (200 µl). The reaction mixture was diluted with methylene chloride (20 ml), and washed with sodium bicarbonate, water, and dried ($MgSO_4$). Methylene chloride was removed under reduced pressure to furnish N-oxide which was heated at 50° (30 mm) for 4 hr. Filtration of the product in $CH_2Cl_2$ through short silica gel column afforded 2 (31 mg, 80%). IR ($CCl_4$): 2915, 1735, 1165 $cm.^{-1}$ $^1H$ NMR ($CDCl_3$, 270 MHz): δ 1 - 1.32 (m, 4H), 1.38 (s, 3H), 1.7 - 2.4 (m, 7H), 2.68 (dd, 1H, J=5.9, 9.2 Hz), 3.65 (s, 3H), 5.05 - 5.22 (two d's, 2H, J=5.61, 16.4 Hz), 5.3 (bs, 1H), 5.42 (d, 1H, J=11.5 Hz), 5.8 (t, 1H, J=11.5 Hz), 6.77 (dt, 1H, J=11.5, 16.4 Hz).[6]

## References and Notes

1. E. J. Corey, M. C. Desai, and T. A. Engler, J. Am. Chem. Soc., 107, 4339 (1985).
2. The aldehyde ester 1 was synthesized by Diels-Alder reaction of neat 1-vinylcyclohexene with methyl 3-formyl-*cis*-crotonate [W. W. Epstein and A. C. Sonntag, J. Org. Chem., 32, 3390 (1967)] at 160° for 3 hr (78% yield of product containing *ca*. 14% of the position isomeric adduct).
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