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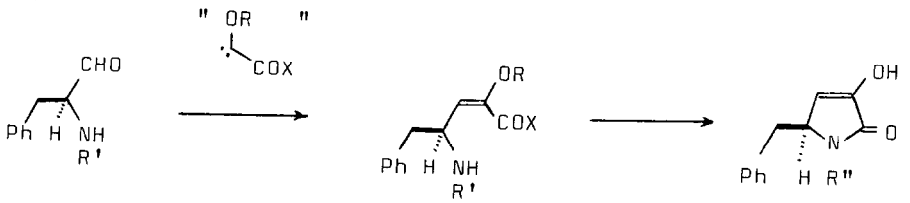
NEW ACYL ANION EQUIVALENT. A SHORT ROUTE TO THE ENOL LACTAM INTERMEDIATE IN CYTOCHALASIN SYNTHESIS

Eiichi Nakamura[1]
Department of Chemistry, Columbia University,
New York, NY 10027

Abstract: The preparation and Emmons-Horner reactions of various α-alkoxyphosphonoacetates were examined. The latter reactions proceeded with considerable stereoselectivity, which allowed the efficient preparation of an intermediate in cytochalasin synthesis.

The chiral enol lactam 3 is a key intermediate in the synthesis of cytochalasins reported from Columbia.[2] Our efforts to improve its preparation along the line shown below[3] required a new acyl anion equivalent which satisfies the following: 1) stereoselective formation of 2, i.e. the E-isomer; 2) (controlled) sequential removal of the protective groups on 2; 3) retention of the chirality of the starting 1-phenylalaninal derivative (1).



1 2 3

A group of phosphonate reagents, e.g. 4f,[4] have been known for a while to achieve the desired type of reaction. However, consideration of the above requirements necessitated some modifications, i.e., the preparation of the appropriately protected analogs, 4b~e.

The parent compound 4a was obtained in a straightfoward manner. Heating a mixture of dimethylphosphite and methyl glyoxalate hydrate[5] under acidic conditions with continuous removal of water gave 4a in over 90% yield: CH-O at δ 4.70 (d, J = 16 Hz) on ^{1}H NMR ($CDCl_3$). In agreement with some related results,[6] methoxyl groups on the ester and phosphonate moieties were expected to enhance the E-selectivity of the Emmons-Horner reaction with α-branched aldehydes, e.g., 1. The alcohol 4a was then protected by standard methods to the various protected derivatives: 4b (ethyl vinyl ether, p-toluenesulfonic acid (PTS), 80% yield); 4c (dihydropyran, PTS, 80%); 4d (2-methoxypropene, PTS, 60%); 4e (tert-butyldimethylsilyl chloride, 4-dimethylaminopyridine, triethylamine, 25%).

Generation of the anions of 4b~e could be performed either with LDA or NaH in THF. Addition of an aldehyde to a solution of the anion at -40 °C followed by warming up to 0 °C gave a good yield of the expected enol ether.

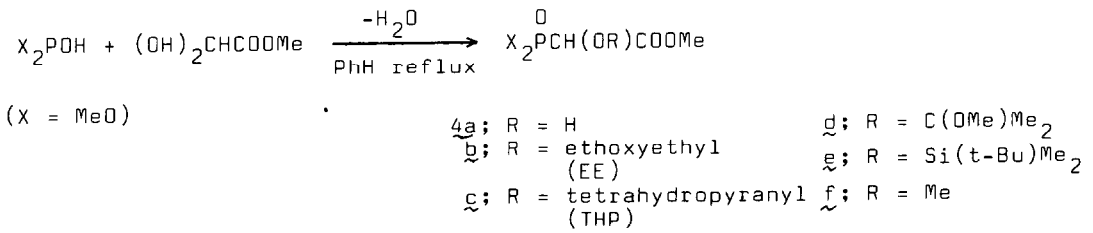
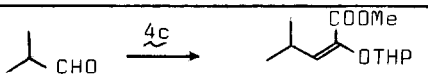
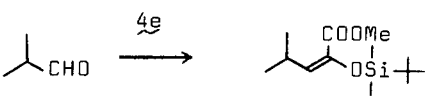
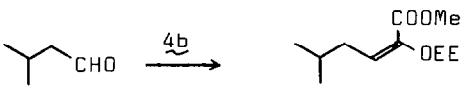
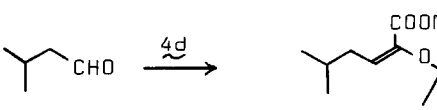


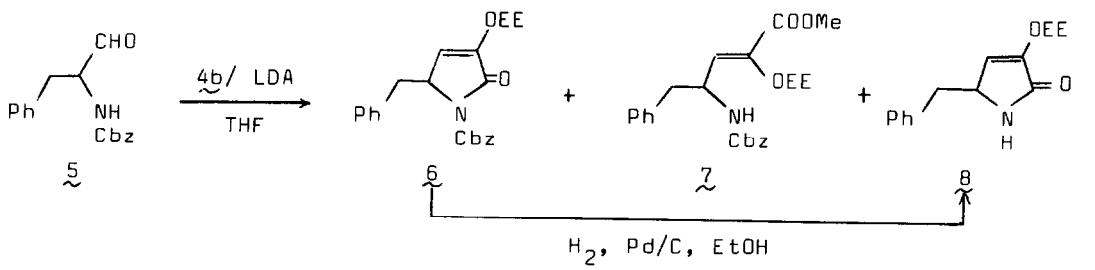
Table Emmons-Horner Reactions of Phosphonoacetates 4.[a]

		E:Z[b]	Olefinic protons E and Z (δ)		%yield
	4c	82:18	5.58	6.05	63
	4e	94:6	5.27	5.80	78
	4b	74:26	5.73	5.33	75
	4d	55:45	5.72	6.25	68

[a] With LDA at -40 °C to 0 °C in THF. [b] Determined by ^{1}H NMR in $CDCl_3$.

The reaction showed considerable stereoselectivity. An α-branched aldehyde gave the expected E-isomer as major product, whereas a β-branched one exhibited rather poor selectivity. The protective groups on the phosphonate also influence the stereochemical outcome, as well as the reaction rate (e.g., 4d reacted much slower than 4b at -40 °C).

To our great satisfaction, the desired E-selectivity was also oberved with a phenylalaninal derivative, and a short route to the lactam 3 was thus secured. dl-Cbz-Phenylalaninal 5[7] was added to a THF solution of the lithiated 4b at -40 °C, and the mixture was gradually warmed to 0 °C. The product mixture obtained after aqueous workup consisted of a mixture of 6, 7, and occasionally 8. The amount of 8 formed under the reaction conditions was variable, but selective and complete conversion of 6 to 8 (with the formation of benzyl methyl carbonate) was observed after prolonged stirring at room temperature (ca. 2 h). Alternatively, the Cbz-lactam 6 was selectively hydrogenolyzed by treating a mixture of 6~8 with hydrogen (10% Pd/C) in ethanol at atmospheric pressure. The overall yield from 5 to 8 was about 70%.[8] The E-Z selectivity of the reaction (6+8/7 based on ^{1}H NMR and isolation) was about 85/15, an E-Z ratio as high as the one observed for isoburyraldehyde. Acetylation (Ac_2O/DMAP/Et_3N) and liberation of the hydroxyl group (AcOH/H_2O/THF) gave (±)-3 (R" = Ac) which was identical with the authentic sample.[2]



Preparation of 4a

Dimethyl tartrate (30.1 g, 0.17 mol) was oxidized with H_5IO_6 (38.5 g, 0.17 mol) at 0 °C in 180 ml of ether.[5] The resulting methyl glyoxalate hydrate was decanted and concentrated to a syrup to which dimethylphosphite (31.0 g, 0.28 mol) was added. The mixture was dissolved in benzene (150 ml) and heated with a Dean-Stark trap under nitrogen. When the formation of water had stopped, the bulk of the solvent was removed and the residue was passed through 40 g of silica gel (dry ethyl acetate and hexane). The title compound was obtained as a white solid (44.2 g, 95% yield) and used directly for the next reaction.

Preparation of 4c

The hydroxyester 4a (10.2 g, 60.7 mmol) and PTS (0.2 g) was dissolved in methylene chloride (30 ml), and dihydropyran (6.1 ml) was added slowly at 0 °C. Addition of triethylamine until neutrality followed by concentration and column chromatography gave the title ester in 67% yield (10.2 g).

General Procedure for the Olefin Forming Reaction

The ester 4 (1.0 mmol) in 1 ml THF was added to LDA (1.0 mmol) in 1 ml THF/hexane at -40 °C. The mixture was stirred at -40 °C for 5 minutes and gradually warmed to 0 °C during 20 minutes. Aqueous workup followed by chromatography gave the expected enoate. The E-Z ratio was determined by integrating the vinyl proton signals on ^{1}H NMR.

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References and Notes

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(8) The synthesis of the optically active 3 from l-phenylalnine has also been achieved by the present route: Stork, G. and Nakamura, E.; unpublished result.

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