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A NOVEL AND EFFICIENT ROUTE TO PROSTANOID INTERMEDIATES

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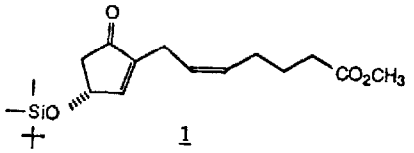
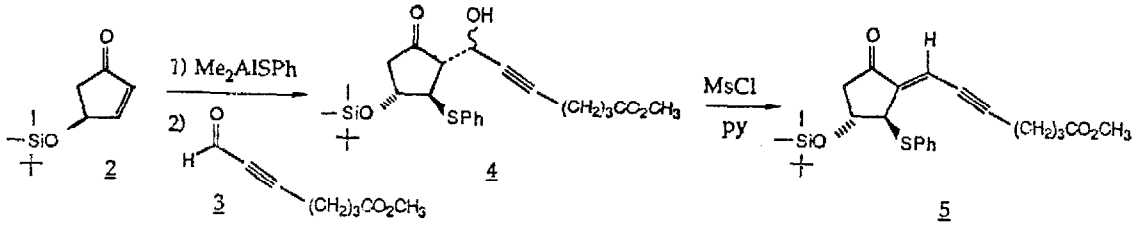
ABSTRACT: A novel and operationally simple route has been demonstrated for the conversion of cyclopentenone 2 into prostaglandin precursor 1 via an interesting zinc mediated reduction-elimination sequence.

A frequently used synthetic strategy for the construction of prostaglandins involves the conjugate addition of an organocuprate to an α-substituted 4-hydroxy-2-cyclopentenone[1] Accordingly, a number of routes exist for the preparation of valuable cyclopentenone intermediates such as 1, a precursor to several pharmacologically interesting prostanoids[2] Nevertheless, we sought a new and efficient pathway for the preparation of 1.



1

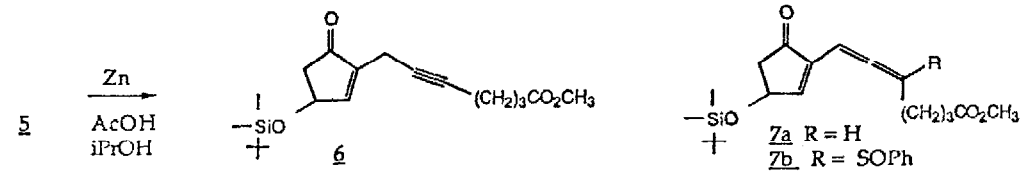
The starting material for this synthesis was the silyl-protected 4-hydroxy-2-cyclopentenone 2[3]. It is known that alkylaluminum thiolates can add in a 1,4 manner to a 2-cyclopentenone generating an aluminum enolate which can then undergo an aldol reaction[4]. Thus, reaction of 2 with dimethylaluminum benzenethiolate followed by addition of propargylic aldehyde 3[5] provided a 3:1 ratio of diastereomeric alcohols 4[6]. Reaction of the crude alcohols with methanesulfonyl chloride (4.1 equiv., 0° → R.T.) in pyridine resulted dehydration to form enone 5 as the Z-isomer (>20:1) in 80% overall yield from 2.



2 3 4 5

Several reagents were studied in an effort to perform a conjugate reduction of enone followed by β-elimination of thiophenol to produce the desired cyclopentenone 6. Reaction

(10 equiv) and acetic acid (2.5 equiv) in isopropanol (0.02M, 24 h, R.T.) reacted with 5 to



give, reproducibly, a 55% yield of 6[7]. To our knowledge this is the first reported example of this type of synthetic transformation[8]. It was thought that the efficiency of this zinc reduction - elimination would be improved if 5 were oxidized to the corresponding sulfoxide prior to conversion to 6. Interestingly, however, when 5 was oxidized with m-chloroperbenzoic acid (1 equiv, -78°→ R.T.) the major product was not the expected allylic sulfoxide but rather the rearranged allenic cyclopentenone 7b (42% yield)[9].

The synthesis of prostanoid intermediate 1 was completed by selectively reducing the acetylenic moiety of 6 to a cis-olefin through hydrogenation over Lindlar catalyst (89%, 15 h, 21°). Thus, we have developed a short and novel route for the conversion of cyclopentenone 2 into prostaglandin precursor 1 in 4 steps and 40% overall yield.[10]

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6. All new compounds had satisfactory IR, ^{1}H NMR and MS data.

7. Suzuki, M.; Kawagishi, T.; Suzuki, T.; Noyori, R. Tetrahedron Lett. 23, 4057 (1982).

8. ^{1}H NMR analysis of the crude reaction mixture, before chromatography, indicates that reduction and elimination occur in situ, not during product isolation and purification.

9. For a related rearrangement see Okamura, W. H.; Shen, G.-Y.; Tapia, R. J. Am. Chem. Soc. 108, 5018 (1986).

10. This synthetic sequence has been accomplished on a 250 mg. scale.

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