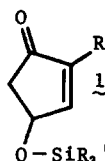


FORMALDEHYDE TRAPPING OF ZIRCONIUM ENOLATES:
A CONVENIENT ROUTE TO PROSTAGLANDIN DERIVATIVES

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We recently reported¹ the Ni-catalyzed conjugate addition of zirconium alkenyls² to α,β -unsaturated carbonyl compounds. This route gives high yields of the desired product on hydrolysis of the resulting zirconium enolate. While studying possible applications of this reaction to prostaglandin synthesis, we demonstrated that it was possible to perform conjugate addition to 1, thereby obtaining a protected PGE₁ analog as product.³ Still, a more versatile route which would allow variation of the α -side chain as well as the β - was clearly needed.

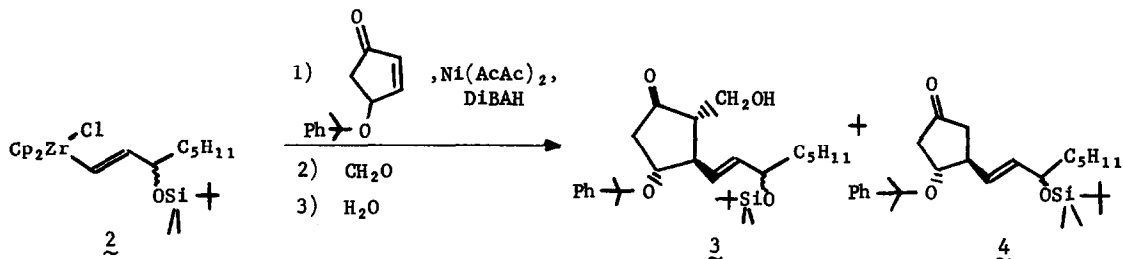


(R = alkyl)

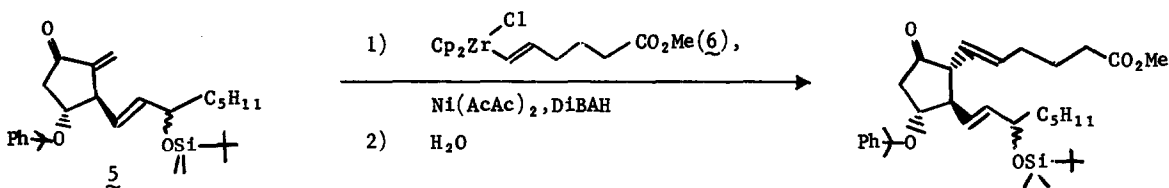
The study of the chemistry of enolates formed by conjugate addition of Zr alkenyls to simple α,β -enones has been initiated. Efforts to add an α -side chain by alkylation of these enolates with alkyl and allyl halides have been unsuccessful so far. These enolates do, however, react with monomeric formaldehyde to give, after hydrolysis, high yields of α -(hydroxymethyl)cycloalkanones such as those previously prepared by Stork and Isobe in connection with their elegant studies of prostaglandin synthesis.^{4,5} This is illustrated as follows: the t-butyldimethylsilyl ether of 1-octyn-3-ol⁶ is converted stereospecifically to the desired zirconium alkenyl by reaction² with Cp₂Zr(H)Cl in toluene at room temperature under N₂. Filtration followed by evaporation of the solvent affords the orange oil Cp₂Zr(Cl)(E-3-t-butyldimethylsiloxy-1-octenyl),⁷ 2. A solution of 2 (532 mg, 0.771 mmole) and 4-cumyloxy-cyclopent-2-enone⁵ (93.2 mg, 0.401 mmole) in 10 ml THF is added dropwise over 20 to 30 min to a premixed solution of Ni(AcAc)₂ (24 mg, 0.093 mmole) and i-Bu₂AlH (0.07 ml of a 1.27 M solution in toluene) in 3 ml THF at 0° under N₂. The reaction mixture is stirred an additional 4 hrs at 0°, then added via cannula to a solution of dry formaldehyde in ether (14.2 mmole in

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70 ml ether). This mixture is stirred 15 min and is then hydrolyzed with aq NH_4Cl , extracted with ether, washed with brine and saturated NaHCO_3 solutions, and dried over Na_2SO_4 . Products are collected using medium pressure liquid chromatography on Merck silica gel using 20% ethyl acetate in hexane as eluent. Compound **3** is isolated in 68% yield (based on **5**). Conjugate adduct **4** is also obtained (11%) (the yield of the formaldehyde trapping step based on total enolate, therefore, is 87%). Other protecting groups (trimethylsilyl-, ethoxyethyl-, benzyloxy-methyl-) may also be used in this procedure.



Conjugate addition of appropriate α -side chains to **5** (prepared⁴ from **3**) makes possible an array of convergent syntheses of prostaglandin derivatives in variation of Stork's synthesis of PGE_2 . For example, in preliminary studies we have prepared the protected 5-*trans*- PGE_2 methyl ester by conjugate addition to **5** of zirconium alkenyl **6**.¹⁰ We are now continuing our studies of carbon-carbon bond formation using enolates prepared by the Ni-Al-Zr system.



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- ¹³C NMR of this product showed that the amounts of the natural and 15-*epi* diastereomers were present in approximately equal amounts.
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- Prepared by the method of E. J. Corey [*J. Am. Chem. Soc.*, **94**, 6190 (1972)].
- (In C_6D_6 , δ , multiplicity, H): 6.8 (d, 1, $J = 19$ Hz), 5.9 (s, 10), ≈ 5.9 (m, 1, hidden by Cp protons), 3.95 (m, 1), 1.1-1.8 (m, 8), 1.1 (s, 9), 1.1 (m, 3), 0.20 (s, 3), 0.17 (s, 3).
- It was found⁹ that addition of $i\text{-Bu}_2\text{AlH}$ to $\text{Ni}(\text{AcAc})_2$ (1:1) gives a catalyst which enables shortened reaction times for conjugate addition solely compared with those required employing solely $\text{Ni}(\text{AcAc})_2$.¹
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- (In C_6D_6 , δ , multiplicity, H): 6.8 (d, 1, $J = 19$ Hz), 5.8 (s, 10), ≈ 5.8 (m, 1, hidden by Cp protons), 3.4 (s, 3), 2.4-1.4 (m, 6).

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