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A SHORT SYNTHESIS OF (-)-PROSTAGLANDIN E_1[1]

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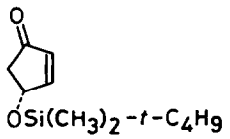
Summary: (-)-Prostaglandin E_1 has been prepared from (R)-4-t-butyldimethylsiloxy-2-cyclopentenone by using as a key operation the tandem organocopper conjugate addition/nitroolefin Michael trapping of the resulting enolate intermediate.

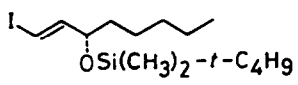
Regiospecific trapping with electrophiles of enolates generated from 2-cyclenones and lithium diorganocuprates provides a useful tool for the synthesis of 2,3-difunctionalized cyclic ketones.[2] In certain cases, replacement of the organocuprate complexes by organocopper reagents of type $RCu[P(n\text{-}C_4H_9)_3]_n$ (n = 2 or 3, empirical formula)[3] results in remarkable increase in the efficiency and selectivity of the three-component coupling processes.[4,5]

We found that an enolate which was generated by the reaction of 2-cyclopentenone or its derivatives and an organocopper compound, formed from an alkyl- or alkenyllithium, copper(I) iodide, and tributylphosphine (1:1:2–3 ratio), underwent Michael addition across nitroolefins at -78 to -30 °C to give 2,3-disubstituted cyclopentanones in fair to good yield.[6]

This procedure allows a single-step construction of the prostaglandin (PG) skeleton using the chiral building blocks, 1 and 2, and the Michael acceptor 3.[7] First, a vinylcopper reagent was prepared by treatment of the optically pure vinylic iodide 2,[4,9] $[\alpha]_D^{21}$ -30.6° (c 1.57, CCl_4) with 2 equiv of t-butyllithium in ether at -78 °C for 2 h followed by addition of an ethereal solution of copper(I) iodide (1 equiv) and tributylphosphine (2 equiv). Reaction of this reagent with 0.77 equiv of the optically active enone 1,[4,8] $[\alpha]_D^{22}$ +63.2° (c 1.04, CH_3OH, 94.3% ee[10]), at -78 °C for 15 min and then at -40 °C for 1 h, followed by treatment with 0.77 equiv of the nitroolefin 3 at -78 °C for 15 min and at -40 °C for 1 h gave the condensation product 4[11] in 42% yield based on the enone 1. Reduction of the nitro compound 4 with tributyltin hydride (10 equiv) in refluxing toluene containing azobisisobutyronitrile (0.5 equiv)[12] afforded 5 in 30% isolated yield, homogeneous as judged by ^{13}C NMR analysis. Desilylation of 5 with hydrogen fluoride—pyridine in acetonitrile (room temperature, 2.5 h) produced PGE_1 methyl ester (6) (86%), $[\alpha]_D^{21}$ -52° (c 0.30, CH_3OH) (lit.[9] $[\alpha]_D^{23}$ -53.8° (c 1.04, CH_3OH)). Hydrolysis of 6 with pig liver esterase[13] (room temperature, 4 h) completed the synthesis of (-)-PGE_1 (7) (86%), $[\alpha]_D^{21}$ -55° (c 0.73, THF), mp 115–116 °C (recrystallized from ethyl acetate) (lit.[14] $[\alpha]_D^{20}$ -54.3° (c 1.0, THF), mp 115–116 °C). Synthetic 6 and 7 were identical with the authentic materials in all respects (IR, NMR, MS, and TLC). Thus the present method, though is still to be optimized, provides the shortest entry (only four steps from 1) to natural PGE_1.



1



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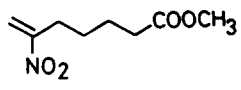

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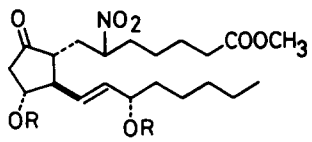
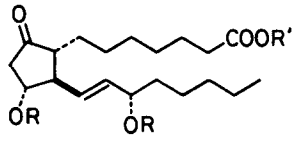


4, R = $Si(CH_3)_2$-t-C_4H_9



5, R = $Si(CH_3)_2$-t-C_4H_9; R' = CH_3

6, R = H; R' = CH_3

7, R = R' = H

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6. For example, combination of 2-cyclopentenone, n-$C_4H_9Cu[P(n\text{-}C_4H_9)_3]_2$,[3] and 2-nitropropene afforded 3-butyl-2-(2-nitroprop-1-yl)cyclopentanone in 66% yield. Reaction of 4-t-butyldimethylsiloxy-2-cyclopentenone, (E)-n-$C_5H_{11}CH[OSi(CH_3)_2\text{-}t\text{-}C_4H_9]CH{=}CHCu[P(n\text{-}C_4H_9)_3]_2$, and nitroethylene produced the coupling product in 27% yield.
7. For related PG synthesis via tandem cuprate conjugate addition/Michael reaction, see: ref 2d. For other entries starting from 4-hydroxy-2-cyclopentenone derivatives, see ref 2b, 4, and 8.
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