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ORGANOPALLADIUM APPROACHES TO PROSTAGLANDINS. 10. AN EFFICIENT SYNTHESIS OF PROSTAGLANDIN E_2 VIA VINYLPALLADATION OF 4-CYCLOPENTENE-1,3-DIOL

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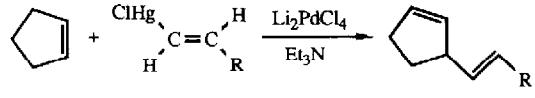
Summary. Prostaglandin E_2 is synthesized by an efficient two step sequence involving (1) preparation of ketol **4** via vinylpalladation of 4-cyclopentene-1,3-diol using either vinylmercurial **1** or vinylic iodide **5**, and (2) subsequent regio- and stereoselective alkylation via sequential dianion generation, tin enolate formation, and organic halide addition.

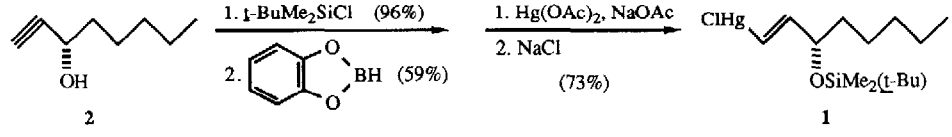
Prostaglandins are an extremely important, physiologically active class of compounds whose synthesis has received a great deal of attention in recent years.[1-3] Most efficient of the present methodology for the synthesis of prostaglandins are three-component coupling processes[4] involving organocopper conjugate addition to enones[5-10] and derivatives[11] and subsequent trapping of the resulting enolate. We wish to report an entirely new, very efficient, organopalladium-based, three component coupling process for the synthesis of prostaglandins, and more specifically prostaglandin E_2 (PGE_2).

Our approach involves the palladium-promoted vinylation of cycloalkenes.[12] We have recently reported the facile coupling of cycloalkenes and vinylpalladium intermediates derived from vinylmercurials (eq. 1).[13] We reasoned that analogous chemistry using enantiomerically



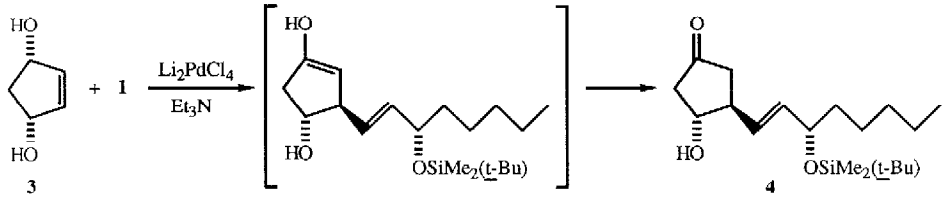
(1)

pure vinylmercurial **1**,[14] easily prepared[15] from (S)-1-octyn-3-ol (**2**)[16] (eq. 2), and readily available 4-cyclopentene-1,3-diol (**3**)[17] should afford an intermediate appropriately



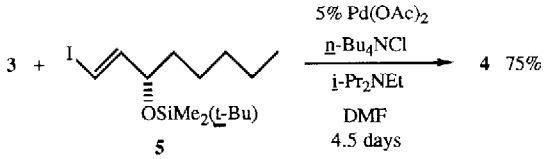
(2)

functionalized for further elaboration to PGE_2. Indeed, this reaction[18] affords a 70% isolated, unoptimized yield of hydroxyketone **4**[19] as a 1:1 mixture of diastereomers (from addition to opposite ends of the carbon-carbon double bond) (eq. 3). This reaction appears to be a very general route to ketols such as **4**. However, this approach suffers the obvious disadvantage that one must prepare an organomercurial and the reaction requires stoichiometric amounts of palladium.



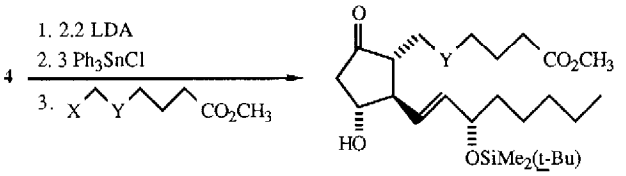
(3)

Recent work in our laboratories[20] and those of others[21] on the palladium-catalyzed inter- and intramolecular arylation and vinylation of cycloalkenes using the corresponding organic halides suggested that intermolecular vinylation of diol **3** might provide a more convenient route to ketol **4**. In fact, the room temperature reaction[22] of enantiomerically pure vinylic iodide **5** [prepared most conveniently from (S)-1-octyn-3-ol via silylation and subsequent hydrozirconation-iodination[23,24]] and diol **3** afforded a diastereomeric mixture of ketol **4** in 75% isolated, unoptimized yield (eq. 4).



(4)

At first glance the regio- and stereospecific alkylation of ketol **4** appears an insurmountable problem. After examining a variety of possible solutions, we have found that treatment of ketol **4** with 2.2 equiv of lithium diisopropylamide (LDA) in THF at -78°C for 60 mins, takes advantage of prior alkoxide formation to regioselectively generate the desired enolate (eq. 5). Direct alkylation of this intermediate did not afford clean products.



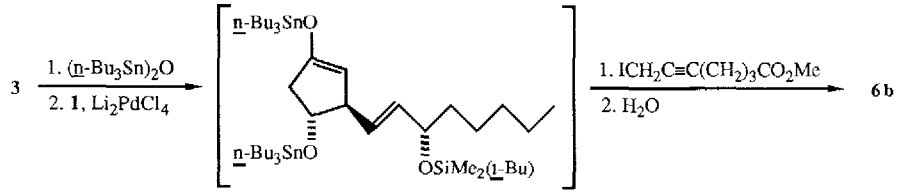
6a Y = Z- CH=CH
6b Y = C≡C

(5)

However, prior treatment with 3 equiv of Ph_3SnCl[25] (-78°C, 15 min) and low temperature alkylation (5 equiv alkyl halide; HMPA; -78°C for 20 mins, then -30 to -20°C for 7 h) using methyl cis-7-bromo-5-heptenoate gave a 17% yield of 11,15-bis(O-tert-butyldimethylsilyl) PGE_2 methyl ester after further silylation (necessary to separate **6a** from **4**). Using the corresponding, relatively unstable allylic iodide, the yield was raised to 24% (36% yield based on recovered silylated starting material). Spectral data for both compounds were consistent with that reported earlier for 11,15-bis(O-tert-butyldimethylsilyl) PGE_2 methyl ester.[26] However, best results were obtained using the corresponding propargylic iodide which afforded the corresponding readily separable acetylenic PGE_2 derivative **6b** in 51% isolated yield. All yields from this alkylation sequence are unoptimized. The two acetylenic diastereomers could be separated at this stage by column chromatography [2:1 hexane/EtOAc, R_f = 0.16 and 0.18 (PGE_2 stereochemistry)]. Conversion to the corresponding bis(O-tert-

butyldimethylsilyl) derivative and comparison of ^{13}C NMR spectral data with that reported earlier[5] confirm the structural assignment.

Preliminary experiments indicate that this highly efficient approach to prostaglandins can be accomplished *in a single step* by sequentially converting the starting diol **3** to a distannyl ether and effecting the organopalladium coupling and alkylation all *in situ* (eq. 6), but the yields at present are less than 25% and further work on this reaction is required.



(6)

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(14) Vinylmercurial **1**: mp 46.5-47.5°C; $[\alpha]_D^{20}$ = -19.99° (c 1.896, $HCCl_3$); Anal. C, H, Hg; IR (nujol) 1255, 1085, 835, 775 cm^{-1}; ^1H NMR ($DCCl_3$) δ 0.02 (s, 3 H, $SiCH_3$) 0.04 (s, 3 H, $SiCH_3$), 0.89 (br s, 12 H, t-Bu and CH_3), 1.27 (m, 6 H, CH_2's), 1.49 (m, 2 H, $SiOCHCH_2$), 4.14 (dt, 1 H, J = 4.7 and 5.2 Hz, CHOSi), 5.90 (dd, 1 H, J = 17.5 and 4.7 Hz, CH=CHg), 5.98 (d, 1 H, J = 17.5 Hz, =CHHg).

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(16) (S)-1-Octyn-3-ol (**2**): $[\alpha]_D^{20}$ = -5.91 (c 2.066, $HCCl_3$).

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(18) This reaction was carried out by adding vinylmercurial **1** (1.05 mmol) to diol **3** (10.5 mmol), Et_3N (3.15 mmol), $PdCl_2$ (1.05 mmol), and LiCl (2.10 mmol) dissolved in 15 ml of THF at -78°C, allowing the reaction mixture to slowly warm to room temperature for 2 h and stirring at that temperature for 21 h.

(19) Hydroxyketone **4**: R_f 0.31 (2:1 hexane/EtOAc); IR (neat) 3430 (OH), 1748 (C=O), 1245, 1055, 950 cm^{-1}; ^1H NMR ($DCCl_3$) δ 0.01 (s, 3 H, $SiCH_3$), 0.02 (s, 3 H, $SiCH_3$), 0.89 (br s, 12 H, t-Bu and CH_3), 1.26 (m, 6 H, CH_2's), 1.42 (m, 2 H, $SiOCHCH_2$), 2.08 (dd, 1 H, J = 18.3 and 4 Hz, one diastereomer of O=CCHCHR), 2.11 (dd, 1 H, J = 18.3 and 4 Hz, other diastereomer of O=CCHCHR), 2.23 (dd, 1 H, J = 18.3 and 6.9 Hz, O=CCHCHOH), 2.28 (d, 1 H, J = 3 Hz, OH), 2.59 (overlapping dd, 2 H, J = 18.3 and 7.5 Hz, CHCOCH), 2.76 (looks like q, 1 H, J = 6-7 Hz, CHOH), 4.07 (looks like q, 1 H, J = 6 Hz, CHOSi); ^{13}C NMR ($DCCl_3$) δ -4.75, -4.29, 13.92, 18.14, 22.50, 24.84, 25.82, 31.67, 38.17, 42.53, 46.11, 47.21, 73.03, 73.81, 128.50, 135.91, 215.32; mass spectrum, m/e 322.2322 [calcd for $C_{19}H_{34}O_2Si$ (M-H_2O), 322.2328].

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(22) The reaction was carried out by stirring for 4.5 days at room temperature compounds **3** (5 mmol) and **5** (0.5 mmol) with n-Bu_4NCl (0.5 mmol), i-Pr_2NEt (1.25 mmol) and $Pd(OAc)_2$ (6 mg) in DMF (1 ml).

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