A Two-Step, Three-Component Synthesis of PGE_1: Utilization of α-Iodoenones in Pd(0)-Catalyzed Cross-Couplings of Organoboranes†

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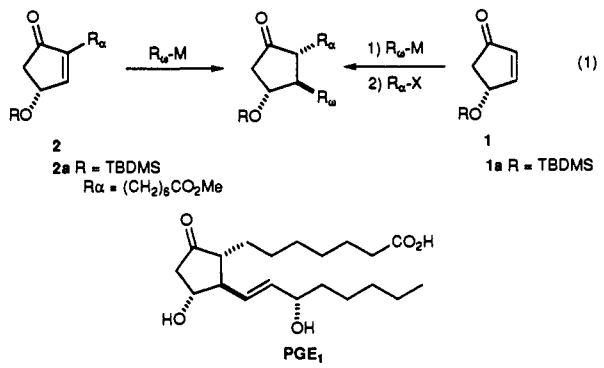
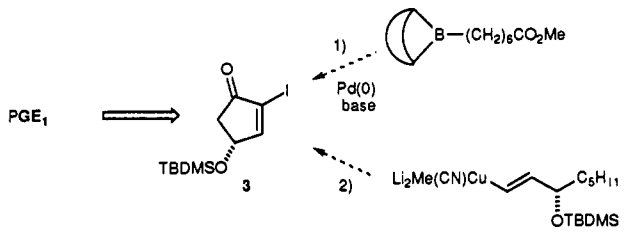
General and efficient syntheses of prostaglandins (PGs) have been the subject of much effort over the past 3 decades.[1] Aside from the widely applied but lengthy Corey synthesis,[2] two other popular approaches have emerged from these efforts: the three-component coupling process[3] and the two-component (conjugate addition) process[4] (eq 1). The one-pot, three-component coupling



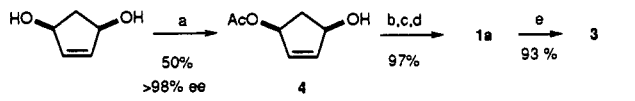
synthesis is one of the most elegant and efficient means of assembling PGs. The use of (*R*)-4-(*tert*-butyldimethylsiloxy)-2-cyclopentenone (**1a**) as an enantiopure component in this process is a particular advantage due to its ease of preparation.[3b] Despite the attractiveness of this approach and the improvements which have been made upon it,[5] several limitations still exist. Most important are the problems of enolate equilibrium and β-alkoxide elimination associated with alkylation of the intermediate enolate, problems which are especially evident when trapping with unactivated electrophiles such as a halide corresponding to the α-chain of PGE_1. As a result, the two component synthesis [conjugate addition of R_ω to a 4(*R*)-alkoxy-2-alkyl-2-cyclopentenone (**2**)] has remained a highly studied and valuable route to PGs. The limiting factor of this approach has been the availability of the enantiopure α-alkylcyclopentenones **2**.[6]

We now report on an exceptionally simple and efficient synthesis of the PGE_1 precursor **2a** from the readily available cyclopentenone **1a**.[7] Our concept was to employ our recently described synthesis of α-iodoenones in the synthesis of cyclopentenone intermediates capable of transition-metal-catalyzed cross-coupling with the α-side chain.[8] A similar coupling process has been realized with use of aryl- and alkenyltin and -zinc reagents;[9] however, it was our feeling that chemistry developed by Suzuki for Pd(0)-catalyzed cross-coupling of alkylboranes with aryl or alkenyl halides would be much more promising for this application.[10] The Suzuki reaction is particularly attractive in that the organoboron reagents are easily prepared (*in situ*, if desired) and, in most cases, display little reactivity with other functionalities. In addition, Pd(0)-catalyzed coupling occurs under mildly basic conditions and is tolerant of a wide range of functionality (ketone, aldehyde, ester, nitrile, alcohol, etc.), making the overall process highly adept in the synthesis of delicate compounds such as PGs. Through an extensive survey of reaction conditions employed by Suzuki in the coupling of 9-alkyl-9-BBN reagents with vinyl or aryl halides, we have formulated a general synthesis of α-alkenones from α-iodoenones.[11]

Scheme I



Scheme II[a]



[a] (a) SP-435, isopropenyl acetate, 50 °C. (b) TBDMSCl, imidazole, DMF. (c) NaCN, MeOH. (d) PDC, CH_2Cl_2. (e) I_2 (1.8 equiv), pyridine/CCl_4 (3:2).

Our overall approach (Scheme I) is a two-step, three-component coupling synthesis in which the side chains are installed in reverse fashion (R_α followed by R_ω) to the traditional process. In this way we have allowed for a wide variety of α- and ω-side chains and avoided the problems of electrophilic capture chemistry. We have demonstrated the utility of this technique in the synthesis of the natural PGE_1 methyl ester; this approach should prove highly adaptable toward the syntheses of many PG analogs.

Although many syntheses of the enantiopure ring and lower side-chain components[3b] have been reported, we chose to employ some newly developed chemistry from our laboratory with the use of the biocatalyst SP-435.[12] The enone **1a** was prepared by SP-435-catalyzed asymmetrization of *cis*-1,4-cyclopentenediol to give **4**[12] followed by protecting group manipulation and oxidation (Scheme II). α-Iodination of **1a** was efficiently accomplished with iodine and pyridine[8] to give **3** {$[\alpha]^{22}_D$ +24.3 (*c* 0.60, $CHCl_3$); mp 38.5 °C} in 93% yield. The enantiopure

† Dedicated to Prof. C. J. Sih, University of Wisconsin, on the occasion of his 60th birthday.

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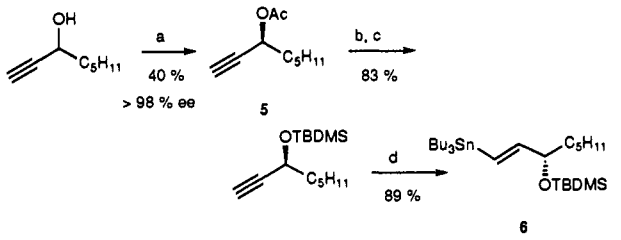
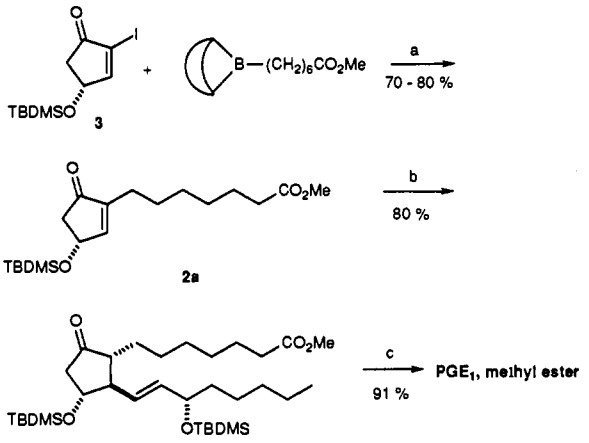
Scheme III[a]



[a] (a) SP-435, isopropenyl acetate, 25 °C. (b) NaCN, MeOH. (c) TBDMSCl, imidazole, DMF. (d) Bu_3SnH, AIBN, 110 °C.

Scheme IV[a]



[a] (a) 1.5 equiv of borane, $PdCl_2$(dppf) 5 mol %, Ph_3As 10 mol %, Cs_2CO_3 (1.8 equiv), DMF/THF/H_2O, 25 °C. (b) (i) vinyl cuprate derived from stannane **6**, THF, −78 °C; (ii) saturated aqueous NH_4Cl. (c) HF, pyridine, CH_3CN.

lower chain precursor was produced through an enzymatic resolution of commercially available 1-octyn-3-ol to give the (*S*)-acetate **5** in high ee (Scheme III).[13] This material was easily transformed to the (*E*)-vinylstannane **6** according to the literature route.[14] Finally, methyl 6-heptenoate, required for hydroboration with 9-BBN-H to afford the α-side chain, was prepared by treatment of the commercially available carboxylic acid with diazomethane.

With the three components of the molecule in hand, we were able to perform the α-alkylation and traditional conjugate addition chemistry to obtain the PGE_1 methyl ester as shown in Scheme IV. We have found that cesium carbonate in a DMF/THF/water system gives the best results in the cross-coupling. It is curious to note that the presence of water was absolutely necessary under all conditions tested for cross-coupling to occur; this limitation is not normally observed with the Suzuki reaction. Other protic solvents such methanol proved unsatisfactory. To reduce the amount of β-hydride elimination from the transmetalated complex, we favored the use of the bis(diphenylphosphino)-ferrocene palladium(II) chloride [$PdCl_2$(dppf)] catalyst.[15] The coligand triphenylarsine was also used, as its presence gave a higher turnover rate and cleaner reaction.[16] Under these conditions, cyclopentenone **2a** was obtained in 70–80% yield.[17] Conjugate addition of the ω-side chain and deprotection were easily accomplished according to literature procedures to give the PGE_1 methyl ester in good yield (54% overall from enone **1a**).[3b,18,19]

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Supplementary Material Available: General experimental, preparation of **3**, spectroscopic data on **2a** (1 page). Ordering information is given on any current masthead page.

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(17) General coupling procedure. Methyl 7-(3(*R*)-(*tert*-butyldimethylsiloxy)-5-oxo-1-cyclopenten-1-yl)heptanoate (2a). To a flame-dried round-bottomed flask were added methyl 6-heptenoate (0.631 g, 4.44 mmol) and THF (4 mL). The solution was cooled to −10 °C, and a THF solution of 9-BBN-H (0.5 M, 8.9 mL, 4.44 mmol) was added dropwise over 15 min. The solution was allowed to warm to room temperature and stirred an additional 4 h, at which point approximately 50% of the THF was removed under reduced pressure. When the above operation was complete, in a separate flask α-iodoenone **3** (1.00 g, 2.96 mmol) was added to a mixture of Cs_2CO_3 (1.74 g, 5.34 mmol), $PdCl_2$(ddpf) (0.065 g, 3 mol %), Ph_3As (0.054 g, 10 mol %), and DMF (10 mL). Water (0.64 mL, 12 equiv) was then added with vigorous stirring, followed by addition of the above THF solution of the borane. After being stirred for 0.5–1.5 h, the contents of the flask were poured into water (100 mL) and extracted into diethyl ether (150 mL). The organics were washed with 1 N HCl (1 × 50 mL), 10% NH_4OH (1 × 50 mL), water (1 × 50 mL), and brine (1 × 50 mL) and dried over $MgSO_4$. Filtration followed by removal of solvent and chromatography (15:1 petroleum ether–ethyl acetate) yielded the title compound (0.803 g, 77%) as a clear oil: $[\alpha]^{22}_D$ +21.8 (*c* 0.660, MeOH), {lit.[4b] $[\alpha]^{21}_D$ +22.8 (*c* 0.404, MeOH)}.

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