Synthesis of Prostaglandin E_2 Methyl Ester on a Soluble-Polymer Support for the Construction of Prostanoid Libraries

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The prostaglandin family of natural products constitute perhaps the most physiologically potent nonprotein molecules found in mammals. They play a vital role in the processes of inflammation, tissue repair, and immune response.[1] Given their enormous potential therapeutic benefits, extensive efforts have been directed at the design and synthesis of pharmacologically useful analogues.[2] The screening of large numbers of compounds would greatly improve the probability of finding appropriate biological activity.

Combinatorial chemistry has developed into an important tool for drug discovery.[3] However, to fully empower this technology, it remains necessary to adapt the construction of more complicated reactions and molecules to the solid-phase,[4] liquid-phase,[5] or fluorous system[6] methods. Prostaglandins represent a challenging target and have served as a proving ground for new synthetic strategies for over 3 decades. The preeminent approaches that have been applied to the assembly of the prostaglandin framework are the linear/multistep Corey-type plan,[7] the two-component process,[8] and the three-component coupling methodology.[9] The convergent nature and synthetic flexibility of the three-component synthesis pioneered by Noyori, and then modified by others,[10] is often the most desirable. Herein, we report the application of a three-component coupling strategy[10a] in the efficient liquid-phase synthesis of PGE_2.

Two principal formats for a polymer-supported prostaglandin synthesis can be conceptualized. The three components **A**, **B**, and **C** represent, respectively, the cyclopentanoid ring, the α-chain, and the ω-chain of a prostaglandin derivative. We have chosen to exploit strategy I in our current research. To

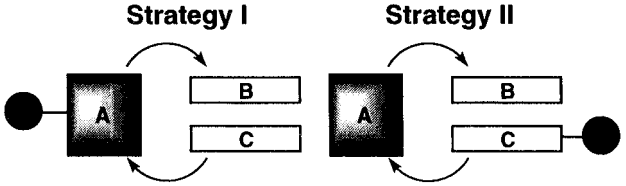

Figure 1.

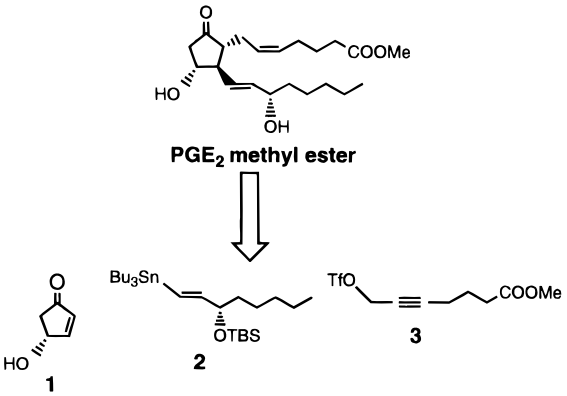

Figure 2. Chemical building blocks used in the construction of PGE_2 methyl ester.

this end, a set of chemical building blocks were selected for the construction of PGE_2 methyl ester.[11] The choice of a suitable support was the key step in the design in that it required compatibility with some extreme reaction and workup conditions.[12] Poly(ethylene glycol) (PEG) has been shown to be an excellent polymer for liquid-phase synthesis.[5] However, PEG was not applicable here due to its low solubility in tetrahydrofuran (THF) at the low temperatures (−78 °C) necessary in the synthesis. PEG also poses a problem during the removal of excess organometallic reagents and inorganic materials due to its water solubility. Hence, a soluble non-cross-linked chloromethylated polystyrene (NCPS) previously used for peptide synthesis[13] was investigated as a support in the prostaglandin synthesis. This copolymer is readily prepared and the functional group content easily controlled, and then quantified via NMR, by using varying ratios of starting monomers. Non-cross-linked polystyrene has remarkable solubility properties that are amenable to organic chemistry. It is soluble in THF, dichloromethane, chloroform, and ethyl acetate even at low temperatures (−78 °C) and is insoluble in water and methanol. These features allow implementation of solvent extraction techniques used in traditional organic synthesis in conjunction with the polymer crystallization techniques currently used in the PEG liquid-phase approach.[5] Consequently, after the homogeneous reaction of supported intermediates, the polymer-bound products can be diluted with dichloromethane or ethyl acetate and the organic layer subjected to the usual aqueous extractions. Methanol is then used to precipitate the polymer and its uniquely bound product as a solid to remove excess reactants and

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(11) PGE_2 itself contains a free carboxylic acid on the α-chain. A variety of acid and ester analogues will be desirable for preparation of libraries. Here we chose to construct the methyl ester derivative since the α-chain precursor was known in the literature. Synthesis of natural PGE_2 would entail utilization of an α-chain building block protected as an ester (i.e., trimethylsilyl ethyl) that could be cleanly removed under our subsequent deprotection conditions. Alternatively, methyl ester derivatives could be hydrolyzed by lipases (See ref 8a and Tanaka, T.; Toru, T.; Okamura, N.; Hazato, A.; Sugiura, S.; Manabe, K.; Kurozumi, S.; Suzuki, M.; Kawagishi, T.; Noyori, R. *Tetrahedron Lett.* **1983**, *24*, 4103).

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byproducts. This is especially important for modern syntheses that utilize a host of organic and organometallic reagents. Finally, because NCPS is a soluble polymer, NMR analysis of all intermediates may be accomplished in a nondestructive manner without the need for any specialized NMR techniques or equipment currently used in solid-phase synthesis.[14]

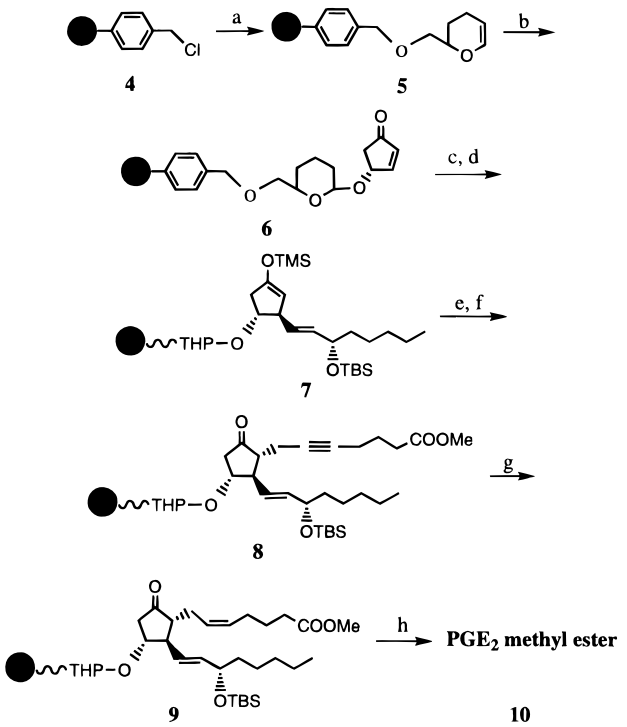
The NCPS was prepared by the copolymerization of styrene with 4-(chloromethyl)styrene (3 mol %) in the presence of 2,2′-azobis(isobutyronitrile) (AIBN) in benzene at 70 °C for 40 h. The loading value obtained and used for yield calculations in the prostaglandin synthesis was 0.3 mmol/g. The synthesis of PGE_2 methyl ester on this support is outlined in Scheme 1. The polymer **4** was dissolved in dimethylacetamide and treated with the sodium salt of 6-(hydroxymethyl)-3,4-dihydro-2*H*-pyran at room temperature.[15] The DHP-modified polymer was extracted with dichloromethane and washed with brine. After concentration of the organic layer, the polymer **5** was precipitated with methanol and approximately 100% of the polymer was recovered. Significantly, the polymer mass balance for each subsequent step in the synthesis was ≥97%. Furthermore, only a single polymer-bound species was detected by NMR in all cases.

(*R*)-(+)-4-Hydroxy-2-cyclopenten-1-one (**1**)[16] was then attached to **5** through the hydroxyl group in the presence of PPTS in dichloromethane at 40 °C. The product was obtained using extraction and precipitation techniques (*vide supra*). The NMR spectrum indicated that the reaction was complete after 16 h.

The vinylstannane ω-chain building block **2** was synthesized from the corresponding alkyne,[17] and the triflate α-chain fragment **3**[10a] was prepared from the alcohol.[18] With the three components of the prostaglandin in hand, **2**, was added to the polymer-bound cyclopentenone **6** and $Li_2CuCNMe_2$ in THF at −78 °C. The resulting enolate was converted to a stable and isolable enol silyl ether intermediate upon treatment with chlorotrimethylsilane and triethylamine. Following our described combination workup (*vide supra*), the stable, pure polymer-bound product **7** was obtained. After addition of MeLi to **7** in THF at −23 °C, the enolate intermediate was trapped with the highly reactive triflate **3**. The standard workup afforded the complete 20-carbon prostaglandin framework **8** linked to NCPS. This acetylenic intermediate has been a valuable compound for the general synthesis of a wide spectrum of prostanoids.[19]

Partial hydrogenation of the acetylenic bond at the C5−C6 position (prostaglandin numbering) was accomplished over 5% $Pd/BaSO_4$ and gave the *Z* alkene **9**. Since NCPS is soluble in the benzene/cyclohexane reaction solvent, NMR could be used to follow the progress of the reduction. Both the appearance of the olefinic C5−C6 protons and the chemical shift change of the C4 and C7 protons were clearly observed.

Scheme 1[a]



[a] Reagents and conditions: (a) 3 equiv of 6-(hydroxymethyl)-3,4-dihydro-2*H*-pyran, 3.3 equiv of NaH, dimethylacetamide, rt, 24 h; (b) 3 equiv of **1**, 0.5 equiv of PPTS, CH_2Cl_2, 40 °C, 16 h; (c) 4.2 equiv of **2**, 3.9 equiv of $Li_2CuCNMe_2$, THF, −78 °C, 15 min; (d) 15 equiv of chlorotrimethylsilane, −78 °C, 30 min; 30 equiv of triethylamine, 0 °C, 15 min; (e) 3 equiv of MeLi, THF, −23 °C, 20 min; (f) 6 equiv of **3**, −78 °C, 10 min; −23 °C, 30 min; (g) H_2, 5% $Pd\text{-}BaSO_4$, quinoline, benzene/cyclohexane (1:1), 48 h; (h) 48% aqueous HF/THF (3:20, v/v), 45 °C, 6 h.

The cleavage of PGE_2 methyl ester from the support must be compatible with the sensitive β-ketol configuration. While several methods have been employed for THF-modified resins,[3b,15] here they resulted in partial or complete elimination of the C11 hydroxyl group. Several other THP deprotection conditions such as $AcOH/THF/H_2O$ or Amberite[20] gave incomplete and unclean reactions. Finally, it was discovered that 48% aqueous HF−THF (3:20 v/v) at 45 °C for 6 h, used for removal of the TBS protecting group,[21] also afforded efficient liberation of the product. A saturated $NaHCO_3$ wash removed HF. After removal of polymeric material by precipitation, the crude product showed only one major spot on TLC and contained <2% of the dehydration byproduct as measured by NMR. Flash chromatography afforded pure PGE_2 methyl ester **10**, identical to an authentic sample.[22,23] The overall yield was 37% for the eight chemical steps starting from **4**.[24]

We have shown that it is possible to prepare a complex natural product through liquid-phase synthesis. In addition, the NCPS method will complement the previous PEG-based approach for the construction of combinatorial libraries. The "convergent generation of diversity" from a "toolbox" of prostanoid components (enones, α-chains, and ω-chains), augmented with additional polymer-bound transformations, will enable the assembly of large arrays of potentially valuable compounds.

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Supporting Information Available: Synthetic details and spectral data for compounds **4**−**10** (13 pages). See any current masthead page for ordering and Internet access instructions.

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