Solid-Phase Synthesis of Diverse E- and F-Series Prostaglandins

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The naturally occurring prostaglandins have important and wide-ranging biological activities, and many synthetic analogues have been developed as drugs and as pharmacological tools. Prostaglandins (PGs) are complex structures that display functionality of defined stereochemistry about a cyclopentane core. They are also delicate structures that are often sensitive to both acidic and basic reaction conditions. Thus, the general synthesis of these molecules continues to provide a standard for demonstrating the versatility of new synthesis methods.[1] In this paper, we describe general solid-phase methods for the rapid preparation of members of several of the structurally distinct PG classes.[2]

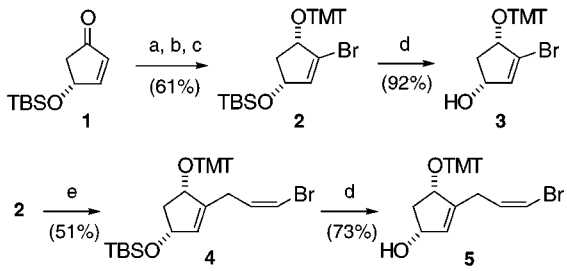
A common synthesis sequence has been devised that provides access to both 1- and 2-series PGs as either E or F derivatives. The common synthesis sequence is based upon the display of functionality about two central cyclopentane core structures. Core structure **3** provides access to 1-series PGs, while core structure **5** provides access to 2-series derivatives (Scheme 1).

The core structures are synthesized from TBS-protected (*R*)-4-hydroxycyclopenten-2-one (Scheme 1). The α-bromine atom is introduced using bromine and Et_3N in CH_2Cl_2. Reduction under Luche conditions with $NaBH_4$ and $CeCl_3$ then provides the monoprotected diol with 6:1−8:1 selectivity favoring the cis epimer.[3] The diastereomerically pure cis isomer can be obtained by crystallization from pentane at −20 °C.[4] Protection with the trimethoxytrityl (TMT) group (TMT-Cl, pyridine, DMAP, 50 °C) and desilylation (TBAF, THF) then provides **3**, the core alcohol for the 1-series PGs. Halogen−metal exchange on **2** with *t*-BuLi followed by the addition of CuCN and then (*Z*)-1,3-dibromo-1-propene provides **4**. The TBS group is then removed using TBAF in THF to provide **5**, the core alcohol for synthesis of the 2-series PGs.

To load alcohols **3** and **5** onto the solid support, we employ a dibutylsilyl chloride-substituted resin that is prepared according to the general procedure of Farrall and Frechet.[5] Reaction of the dibutylsilyl chloride resin with alcohol **3** or **5** in CH_2Cl_2 with imidazole provides the support-bound alcohol. The alcohol loading levels are rapidly and precisely determined by acid-mediated TMT cleavage (1 M formic acid in CH_2Cl_2, 5 min) followed by spectrophotometric quantitation of the released TMT cation. The loading levels range from 0.35 to 0.45 mmol/g over multiple runs.

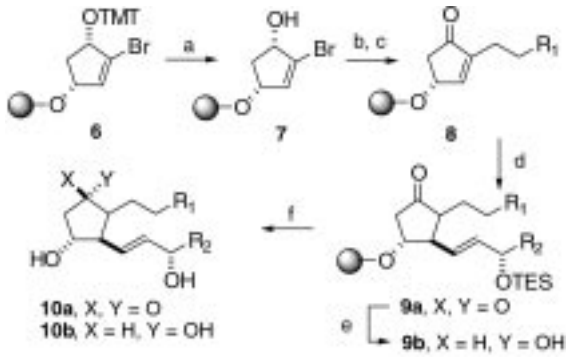
Both the acid-labile TMT protecting group and the nature of the alkyl groups on silicon required careful optimization.

Scheme 1[a]



[a] Reagents and conditions: (a) Br_2, CH_2Cl_2, 0 °C; then Et_3N, 0 °C to rt; (b) $CeCl_3$, $NaBH_4$, CH_3OH, −78 °C; (c) TMT-Cl, pyridine, DMAP, 50 °C; (d) TBAF, THF, rt; (e) *t*-BuLi, CuCN, (Z)-1,3-dibromo-1-propene, −78 °C.

Scheme 2[a]



[a] Reagents and conditions: (a) 1 M $HCOOH/CH_2Cl_2$, rt; (b) alkyl-9-BBN derivative, $Pd(PPh_3)_4$, 2 M Na_2CO_3, THF 65 °C; (c) Dess−Martin peridinane, CH_2Cl_2, 45 °C; (d) alkyne, Cp_2ZrHCl, CuCN, 3 equiv of CH_3Li, THF, −78 to −20 °C; (e) L-Selectride, THF, −78 °C; (f) 17.5% HF/pyridine, THF, rt.

Our initial work was carried out using the dimethoxytrityl (DMT) protecting group on the core structures and using diisopropylsilyl chloride substituted resin.[6] However, we found that alcohols linked through the diisopropylsilyl linker do not cleave readily in dilute HF/pyridine, one of the few cleavage reagents compatible with the β-hydroxy ketone E series PGs.[1a] In contrast, with the dibutylsilyl linker, complete release from support is observed in less than 2 h using dilute HF/pyridine. Replacement of the DMT group with the more labile TMT protecting group is necessary to minimize cleavage from support (<5%) during alcohol deprotection.

The first element of diversity is introduced by a Suzuki cross-coupling reaction as is shown in Scheme 2 for 1-series PG derivatives. The Suzuki reaction is particularly appealing because functionality may be directly incorporated from the large number of available terminal alkenes by in situ hydroboration.[7] The use of a Suzuki coupling approach was inspired by the elegant chemistry that Johnson and Braun have developed for 1-series PG synthesis in solution, where Suzuki cross-coupling reactions were carried out upon 2-iodo-4-(silyloxy)cyclopent-2-enone at room temperature using $PdCl_2$(dppf) with Ph_3As as the catalyst.[1b] We chose to employ cyclopentenol cores **3** and **5** because we found that the conditions required to ensure complete Suzuki cross-coupling for diverse alkylboranes on support resulted in decomposition of the corresponding base-labile β-alkoxy ketones for some derivatives.

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Table 1. Prostaglandins Synthesized on Support

entry	cmpd	class	series	R_1 or Z-R_3	yield[a] (%)
1	**14a**	E	2	$CH_2CH_2OCH_3$	52
2	**14a**	E	2	$(CH_2)_3CH_3$	54
3	**14a**	E	2	$CH_2CH_2OCH_3$[b]	50
4	**14b**	F	2	$CH_2CH_2OCH_3$	54
5	**10a**	E	1	$(CH_2)_3CH_3$	60
6	**10b**	F	1	$(CH_2)_3CH_3$	54
7	**18a**	E	1	$NHSO_2Ph$	55
8	**18a**	E	1	$NHCH_2Ph$	58
9	**18a**	E	1	OCH_2CH_3	55
10	**18b**	F	1	OCH_3	49
11	**18b**	F	1	$OCH(CH_3)_2$	57

[a] Yields of analytically pure material based upon the TMT quantitation of support-bound core 3 or 5. [b] This derivative was synthesized using TES-protected (±)-4,4′dimethyl-1-octyn-3-ol. For all other derivatives, $R_2 = (CH_2)_4CH_3$.

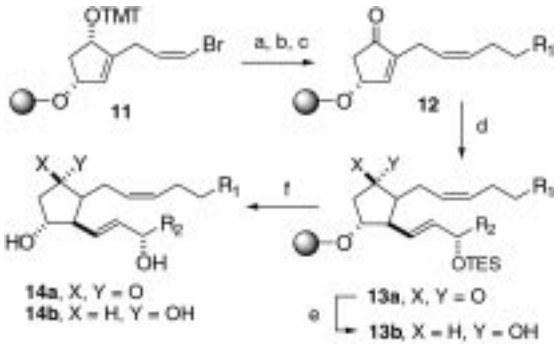
Suzuki coupling reactions are accomplished using standard conditions [$Pd(PPh_3)_4$ as catalyst with 2 M Na_2CO_3 as the base in refluxing THF] and with 5 equiv of an alkyl 9-BBN derivative prepared by in situ hydroboration of an alkene (Scheme 2). The secondary alcohol is then oxidized using 3 equiv of Dess−Martin periodinane in refluxing CH_2Cl_2 for 2 h to provide enones **8**. A number of other oxidants were explored but either did not result in complete oxidation or resulted in some cleavage of the intermediate from the support.

Diversity in the lower side chain is readily introduced by the addition of vinyl cuprates, which are prepared in situ from readily accessible terminal alkynes by hydrozirconation followed by transmetalation using the chemistry developed by Lipshutz and co-workers. After investigating a number of hydrozirconation/transmetalation procedures,[8] we found that the use of 5 equiv of a vinyl cuprate prepared by the procedure of Babiak and co-workers[8b] gives the best results. The PGE derivative **10a** may be cleaved from the support using 17.5% HF/pyridine at 0.2 M in THF for 2 h. Alternatively, the PGF derivative **10b** can be prepared by reduction of the support-bound PGE derivative **9a** with 10 equiv of L-Selectride at −78 °C for 1 h and subsequent cleavage from support. As shown in entries 5−11 in Table 1, the final 1-series PGs are isolated in analytically pure form in 49−60% overall yields after purification by filtration through silica gel. All of the prostaglandin products were obtained in greater than 95% diastereomeric purity as would be expected on the basis of analogous cuprate addition chemistry in solution.

The synthesis of the 2-series PGs is shown in Scheme 3. The steps are almost identical to the 1-series derivatives; however, the TMT group may be removed either before or after the Suzuki coupling step. As shown in entries 1−4 of Table 1, the pure 2-series derivatives are isolated in comparable 50−54% overall yields after filtration through silica gel.

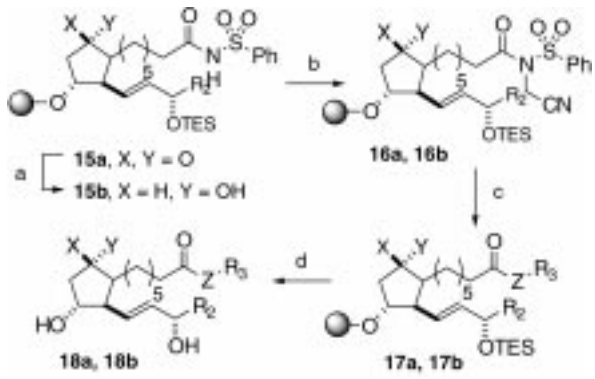
All naturally occurring PGs and many synthetic derivatives incorporate carboxylic acids or acid derivatives in the upper side chain. To introduce diverse functionality at this

Scheme 3[a]



[a] Reagents and conditions: (a) alkyl-9-BBN derivative, $Pd(PPh_3)_4$, 2 M Na_2CO_3, THF 65 °C; (b) 1 M $HCOOH/CH_2Cl_2$, rt; (c) Dess−Martin periodinane, CH_2Cl_2, 45 °C; (d) alkyne, Cp_2ZrHCl, CuCN, 3 equiv of CH_3Li, THF, −78 to −20 °C; (e) L-Selectride, THF, −78 °C; (f) 17.5% HF/pyridine, THF, rt.

Scheme 4[a]



[a] Reagents and conditions: (a) L-Selectride, THF, −78 °C; (b) 1 M $BrCH_2CN$, 0.5 M *i*-Pr_2EtN, NMP, rt; (c) 1 M amine, NMP, rt; or 2 M alcohol, DMAP, NMP, 50 °C; (d) 17.5% HF/pyridine, THF, rt.

site, we chose to incorporate carboxylic acid functionality protected as an *N*-acylbenzenesulfonamide. *N*-Acylsulfonamides are stable to all of the reaction conditions in the synthetic sequence, including the reduction with L-Selectride that provides the F-series PGs. Sulfonamides **15a** or **15b** (Scheme 4) are prepared according to the general procedures to obtain 1-series PGs (Scheme 2). Activation is then accomplished by treatment with 1 M bromoacetonitrile and 0.5 M *i*-Pr_2EtN.[9] The activated sulfonamides **16a** or **16b** are displaced with an amine nucleophile or an alcohol using DMAP as catalyst. Representative PG esters and amides synthesized by this method are isolated in 49−58% overall yields after release from support as shown in entries 8−11, Table 1.

In conclusion, we have developed general and efficient methods for the synthesis of a variety of PG derivatives on solid support. We are currently using this chemistry for the parallel synthesis of PG derivatives to identify novel PGs for use as pharmacological tools.

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Supporting Information Available: Experimental details for the synthesis and characterization of all compounds (32 pages).

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