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Parallel Synthesis of Prostaglandin E_1 Analogues

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The first demonstration of the rapid parallel synthesis of diverse prostaglandin derivatives is reported. Upper (α-) side chain diversity was introduced to core **1** via the parallel Suzuki coupling of hydroborated alkenes. Conversion to the enones **3** and **9** was followed by the addition of the lower (ω-) side chains as higher-order cuprates **4**. Upper side chains incorporating an *N*-acylsulfonamide protecting group were further transformed into prostaglandin amide analogues. Cleavage from support with HF/pyridine followed by scavenging provided 26 prostaglandin E_1 analogues in high purity.

Prostaglandins mediate a host of responses in the body and have found use in a variety of clinical applications.[1] For example, the synthetic prostaglandin AH 13205 (Figure 1) is available for the relief of intraocular pressure as caused by glaucoma,[2] while sulprostone is used in conjunction with RU-486 as an abortifacient.[3] Notwithstanding these uses, prostaglandins remain a significant, largely untapped resource of potential drugs since the desired activities for many clinical applications have been difficult to attain without undesired side effects. The recent identification and cloning of multiple prostaglandin receptor subtypes[4] has resulted in considerable renewed enthusiasm toward the development of highly subtype selective prostaglandin derivatives that exhibit desirable activities without side effects.

Methodology for the parallel synthesis of prostaglandins would be of considerable utility in defining key structural determinants for attaining specificity toward individual prostaglandin subtypes. However, prostaglandins continue to be challenging synthetic targets because they contain multiple chiral centers and are often sensitive to both acidic and basic conditions. Early synthetic methods developed by Corey provide access to a broad range of prostaglandin derivatives[5] and have been employed in industrial production.[1] More recently, two-[6] and three-component[7] strategies have enabled the use of more modular approaches to prostaglandin synthesis. Unfortunately, these solution-phase methods are not amenable to the rapid parallel synthesis of multiple diverse prostaglandin analogues.[8]

Previously, we reported general solid-phase synthesis methodology that provides access to prostaglandin E_1 (PGE_1), PGE_2, PGF_1, and PGF_2 derivatives with diverse functionality displayed in the upper (α-) and lower (ω-) side chains (Figure 2).[9] Herein, we report the first demonstration of the rapid parallel synthesis of diverse prostaglandins by the preparation of a set of 26 PGE_1 analogues designed to target the unique binding pocket within the designed TA202 mutant of the prostaglandin EP_3 receptor (vide infra).[10]

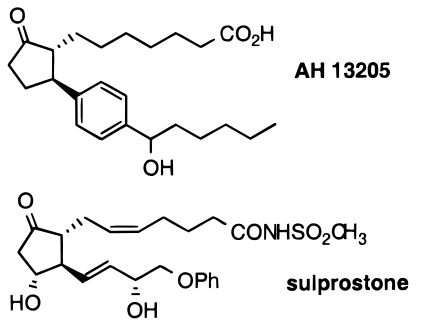

Figure 1. Synthetic prostaglandin pharmaceuticals.

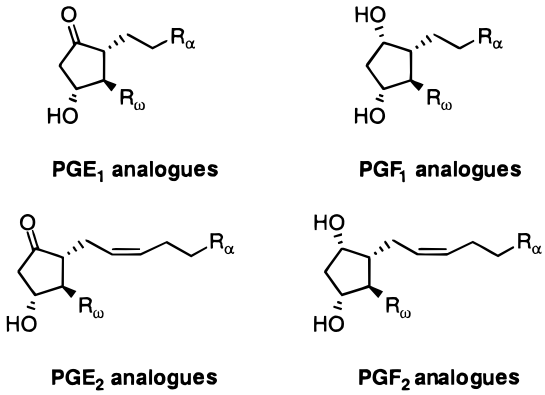

Figure 2. Prostaglandin analogues accessible by solid-phase methods.

Library Design

A number of elements of the prostaglandin structure dramatically impact prostaglandin receptor binding. In addition to the substitution pattern and stereochemical display about the cyclopentane core, the α- and ω-side chains are critical determinants for prostaglandin receptor affinity and specificity. Of particular interest is the C-1 carboxylic acid of the α-chain (Figure 3), conserved among all natural prostaglandins. Nearly all synthetic prostaglandins contain a C-1 acid often modified as an ester prodrug, which undergoes rapid hydrolysis in vivo. Breyer has performed a series of studies aimed at identifying the key residues for prostaglandin recognition of the prostaglandin EP_3 receptor, which modulates hepatic glucose metabolism, neurotrans-

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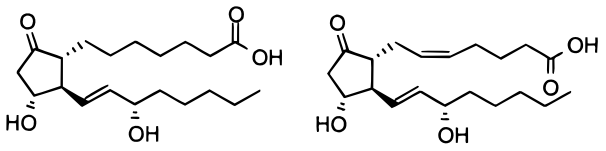


Figure 3. Natural prostaglandin E derivatives.

Table 1. EP_3 Receptor Binding Specificity: Esters vs Acids[a]

agonist	K_I (nM) wild type	K_I (nM) TA202
PGE_1	1.4	0.7
PGE_1 methyl ester	380	10
PGE_2	1.6	1.1
PGE_2 methyl ester	1600	13

[a] Reference 10.

mitter release, and gastric acid secretion.[11] Breyer has created a mutant of the prostaglandin EP_3 receptor (TA202) that dramatically increases the in vitro activity of prostaglandin methyl esters to a level that is comparable with that of the free acid form (Table 1).[10] These mutant receptors provide an exceptional opportunity to characterize the physiological response for completely selective activation of the EP_3 receptor in animals without any activation of the other prostaglandin receptors. The data suggest prostaglandin derivatives lacking the C-1 carboxylic acid that maintain high affinity to the mutant EP_3 receptor could be used to selectively activate this receptor in heterozygous transgenic mice.[12]

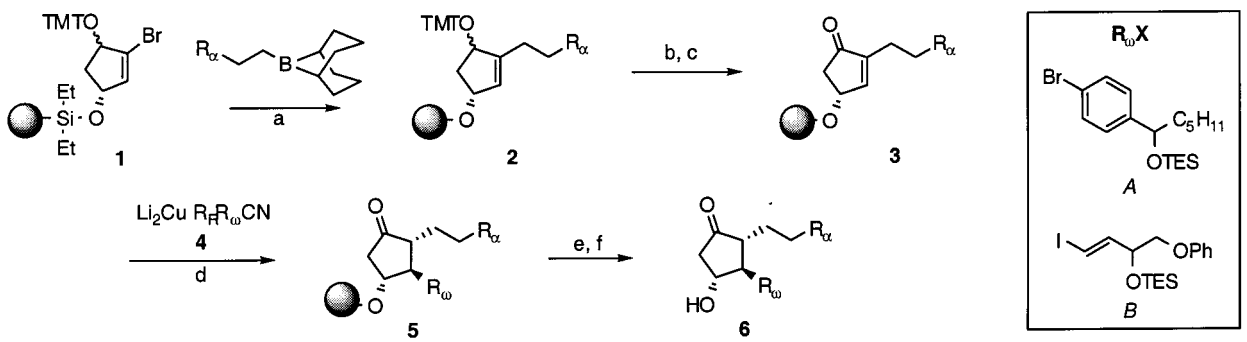
In developing compounds to specifically target the mutant EP_3 receptor, we maintained two design goals: (1) improved biostability over PGE_1 and PGE_2 methyl esters, and (2) enhanced affinity relative to the prostaglandin methyl esters. We therefore chose to prepare prostaglandin derivatives with two classes of α-side chains: aliphatic side chains that are devoid of the carboxylic acid functionality and carboxamide side chains that should be more biostable than the corresponding ester derivatives. The lower (ω-) side chain is also known to bias the selectivity of prostaglandin ligands toward specific prostaglandin receptors.[13] We therefore chose to incorporate the ω-side chain present in sulprostone (Figure 1), which provides some selectivity toward EP_3. Additionally, we selected the ω-side chain present in AH 13205 (Figure 1), which targets EP_2 for potential studies targeting mutants of the EP_2 receptor.

Parallel Synthesis Approach. The general synthetic plan for prostaglandin E_1 analogues is shown in Scheme 1. This methodology incorporates a sequence of transformations that is compatible with the diversity introduced in the side chains. In addition, the methodology is also tolerated by the sensitive core structure. The core scaffold, **1**,[9] is attached to the solid support using a trialkylsilane linkage, which enables orthogonal cleavage with fluoride reagents at the end of the sequence.[14] Diversity in the α-chain is then introduced through Suzuki coupling of alkenes that are hydroborated in situ. Subsequent removal of the trimethoxytrityl protecting group from **2** with dilute formic acid results in complete deprotection with minimal loss of the core molecule from support (≤5%). Mild oxidation with Dess−Martin periodinane provides the enones, **3**, for conjugate addition of the ω-chain components through higher-order cuprate additions (vide infra). Significantly, cleavage from support is accomplished using conditions that do not introduce byproducts that are difficult to remove from the final products. In particular, cleavage is accomplished using dilute HF/pyridine in THF over 2 h. The remaining fluoride anions are removed from the final product as volatile silyl fluoride derivatives upon reaction with methoxytrimethylsilane according to the procedure of Hu and Porco.[15]

To transfer both the aryl and alkenyl side chains, *A* and *B*, respectively, the choice of a retained "dummy" ligand, R_R, (Scheme 1) is critical. The use of thiophene as a "dummy" ligand has been demonstrated to be compatible with the transfer of aryl and alkyl groups,[16] providing a general strategy for the incorporation of the ω-chains. Lithiation of *A* and *B* with *tert*-butyllithium[17] in combination with lithium 2-thienylcyanocuprate produces the higher-order cuprates which are added to slurried resin at −78 °C (Scheme 2). It is then necessary to raise the temperature of the reaction slurries to −20 °C for about 1 h for the reactions to proceed.[18] Higher temperatures and longer reaction times result in significant loss of products from the resin. The reactions are then quenched at −78 °C with dilute acetic acid in THF to ensure that high selectivity for the trans-substituted products **5** is obtained.

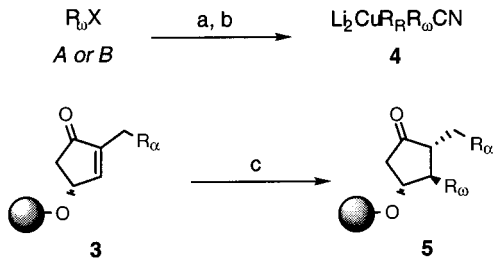
Whereas simple alkanes in the α-chain were accessed via hydroboration followed by Suzuki coupling to vinyl bromide **1**, carboxamide derivatives require an alternate procedure

Scheme 1[a]



[a] Reagents and conditions: (a) $Pd(PPh_3)_4$, 2 M Na_2CO_3, THF, 70 °C, 12 h; (b) 1 M HCO_2H, CH_2Cl_2, 5 min; (c) Dess−Martin periodinane, CH_2Cl_2, 54 °C, 2 h; (d) THF, −78 °C to −20 °C to −78 °C then 10% AcOH/THF; (e) HF/pyr, THF; (f) TMSOMe.

Scheme 2[a]



[a] Reagents and conditions: (a) *t*-BuLi, THF, −78 °C; (b) $LiCuCNR_R$, THF, −78 °C to 0 °C to −78 °C; (c) **4**, −78 °C to −20 °C to −78 °C then 10% AcOH/THF.

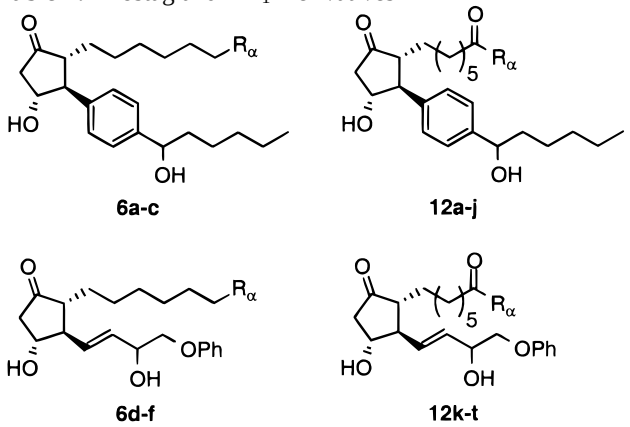
(Scheme 3). Introduction of the 9-BBN adduct of *N*-acylsulfonamide **7**[9] to the vinyl bromide core **1** under Suzuki coupling conditions provides **8**. Trimethoxytrityl deprotection and subsequent Dess−Martin oxidation to the enone **9** is followed by conjugate addition of higher-order cuprates to introduce the ω-chain (vide infra). Activation of the *N*-acylsulfonamide for displacement with diverse nucleophiles is then accomplished by *N*-cyanomethylation with bromoacetonitrile, providing **10**. Addition of diverse amines to **10** then provides the desired amide products, **12a**−**t**, after cleavage from support.

Using the described synthetic methodology, a model library of straight chain alkyl groups and amide derivatives in the α-chain were prepared targeting the mutant receptors of EP_2 and EP_3. The final prostaglandin amides, **12a**−**t**, and alkyl derivatives, **6a**−**f**, were obtained by cleavage from the resin using dilute HF/pyridine in THF over 2 h. The remaining fluoride anions were scavenged using methoxytrimethylsilane,[15] followed by filtration and concentration. Products were obtained in moderate to good yields and high purity (Table 2) as determined by ^{1}H NMR. (^{1}H NMR spectra for all final compounds are provided in the Supporting Information.)

Conclusion

Twenty-six PGE_1 analogues targeting designed mutants of the prostaglandin EP_2 and EP_3 receptors have been prepared by using parallel synthesis methods. Diversity in both the α- and ω-chains has been incorporated using general methods in a parallel format, providing access to a library of prostaglandin analogues in high purity. The biological activity of these derivatives toward the prostaglandin EP_3 mutant receptor is currently being explored, and the application of these methods to other receptor targets is being examined.

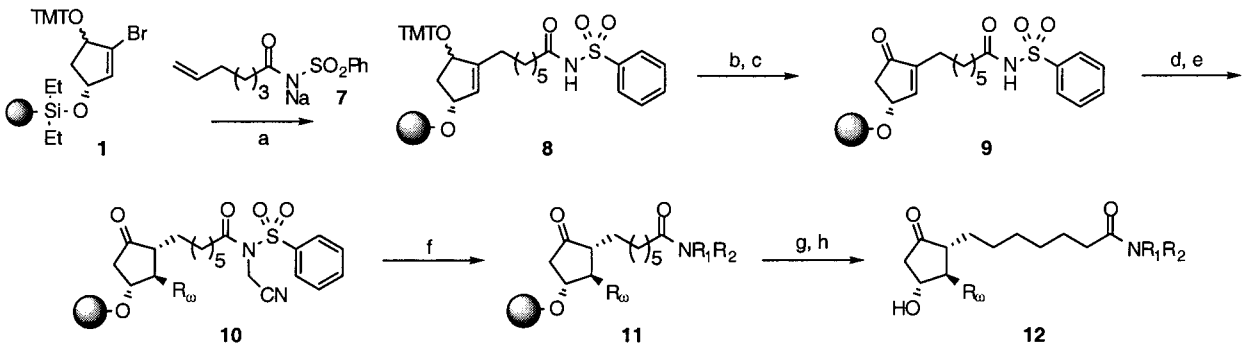
Table 2. Prostaglandin E_1 Derivatives[a]



compound	R_α	% yield
6a	CH_3	33
6b	CH_2CH_3	32
6c	$(CH_2)_2CH_3$	34
12a	$NHCH_3$	39
12b	$NH(CH_2)_2CH_3$	44
12c	$NH(CH_2)_3CH_3$	43
12d	$NHCH(CH_3)_2$	49
12e	$NH(CH_2)_2OCH_3$	32
12f	$NH(CH_2)_2N(CH_3)_2$	46
12g	$NHCH_2C_6H_5$	53
12h	$NH(CH_2)_2C_6H_5$	56
12i	$N(CH_3)_2$	46
12j	piperidyl	47
6d	CH_3	40
6e	CH_2CH_3	41
6f	$(CH_2)_2CH_3$	38
12k	$NHCH_3$	37
12l	$NH(CH_2)_2CH_3$	39
12m	$NH(CH_2)_3CH_3$	22
12n	$NHCH(CH_3)_2$	35
12o	$NH(CH_2)_2OCH_3$	47
12p	$NH(CH_2)_2N(CH_3)_2$	46
12q	$NHCH_2C_6H_5$	45
12r	$NH(CH_2)_2C_6H_5$	18
12s	$N(CH_3)_2$	44
12t	piperidyl	18

[a] Yields based upon the TMT quantitation of support-bound **1**, determined by ^{1}H NMR quantitation against 2,6-dimethoxytoluene as an internal standard.

Scheme 3[a]



[a] Reagents and conditions: (a) 9-BBN then $Pd(PPh_3)_4$, 2 M Na_2CO_3, THF, 70 °C, 12 h; (b) 1 M HCO_2H, CH_2Cl_2, 5 min; (c) Dess−Martin periodinane, CH_2Cl_2, 54 °C, 2 h; (d) **4**, THF, −78 °C to −20 °C to −78 °C then 10% AcOH/THF; (e) $BrCH_2CN$, *i*-Pr_2EtN, NMP; (f) HNR_1R_2, NMP; (g) HF/pyr, THF; (h) TMSOMe.

Experimental Section

General Methods. Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. Tetrakis(triphenylphosphine)palladium[19] and (1(*S*)-*O*-trimethoxytrityl)-2-bromo-cyclopent-2-ene-1,4-diol[9] were prepared according to literature procedures. Tetrahydrofuran and diethyl ether were distilled under N_2 from sodium/benzophenone ketyl immediately prior to use. Pyridine and dichloromethane were distilled under N_2 from calcium hydride. All reactions were run under dry nitrogen using standard techniques unless otherwise stated. Flash chromatography was performed using Merck 60 230−400 mesh silica gel. Thin-layer chromatography (TLC) analysis was performed with Merck Kieselgel 60 F_{254} plates and visualized using UV light and *p*-anisaldehyde staining. ^{1}H NMR and proton-decoupled ^{13}C NMR spectra were obtained with a Bruker DRX-500 spectrometer in $CDCl_3$ unless otherwise noted. Proton and carbon spectra chemical shifts are reported in ppm using residual $CHCl_3$ as an internal standard at 7.26 and 77.0 ppm, respectively. Broad amine and alcohol proton chemical shifts are not reported. Elemental analyses were performed by M-H-W Laboratories, Phoenix, AZ. PS-DES (polystyrene-diethylsilane) resin was graciously provided by Argonaut Technologies, San Carlos, CA. Parallel synthesis steps were performed on a Quest 210 organic synthesizer, Argonaut Technologies, San Carlos, CA.

Loading of 1-Bromo-3-hydroxy-5-[(trimethoxytrityl)-oxy]-cyclopent-1-ene. A 150 mL peptide flask was charged with 4.00 g (0.960 mmol/g, 3.84 mmol) of PS-DES resin and CH_2Cl_2 (40 mL), and gentle agitation with N_2 was begun. Then 1,3-dichloro-5,5-dimethylhydantoin (3.03 g, 15.4 mmol) was solvated in CH_2Cl_2 (8 mL) and added to the resin slurry. A reflux condenser was fit to the flask and the mixture agitated for 1 h. (Additional CH_2Cl_2 was added occasionally to maintain a constant volume.) The reaction mixture was drained, and the beads were washed with distilled CH_2Cl_2 (5×) and then blown down with a steady N_2 stream.

Imidazole (0.915 g, 13.4 mmol) and core alcohol (5.90 g, 11.5 mmol) were solvated in CH_2Cl_2 (46 mL). This mixture was then added to the silyl chloride resin above in one portion. The slurry was agitated with N_2 for 4 h while shielded from light. The reaction mixture was drained, and the beads were washed with DMF (3×), 1:1 DMF/H_2O (3×), 1:1 THF/H_2O (3×), THF (3×), and Et_2O (3×) and dried in vacuo to provide resin **1**. TMT quantitation (ϵ_{484} = 87 100) gave a loading level of 0.48 mmol/g (75% loading efficiency).

Preparation of 2 by Parallel Suzuki−Miyuara couplings. A 2 dram vial was charged with 0.105 g (0.936 mmol) of 9-BBN dimer followed by 0.864 mmol of a terminal alkene (Scheme 1, $R_\alpha = C_5H_{11}$, C_6H_{13}, C_7H_{15}). The reaction mixture was stirred at room temperature for 6 h. The Quest 210 was fit with septum luer plugs and three 10 mL reaction vessels (RVs) which were then charged with approximately 0.300 g of vinyl bromide resin **1** (0.48 mmol/g, 0.14 mmol) as a slurry in THF. The solvent was drained, and the RVs were purged with nitrogen for 1 h. To each of the borane solutions was added approximately 23 mg (0.020 mmol) of $Pd(PPh_3)_4$, and then the mixture was transferred to the Quest RVs via syringe. Degassed 2.0 M Na_2CO_3 (870 μL) was then added to each RV, and agitation was begun (2.0 s stroke, 75% upward). The resin slurry was agitated at 67 °C for 12 h while shielded from light and then was allowed to cool to room temperature before being drained. The beads were then washed successively with DMF (3×), DMF/H_2O (3×), DMF (3×), and CH_2Cl_2 (3×) and were then flushed with nitrogen for 1 h, providing **2** which was used directly in the next step.

Preparation of 3 by Parallel Deprotection and Oxidation. Resin **2** (0.48 mmol/g, 0.14 mmol) was slurried in CH_2Cl_2 and drained. A 1 M HCO_2H solution in CH_2Cl_2 (approximately 2 mL) was then added, and the resin slurry was agitated (2.0 s stroke, 75% upward). The solution was removed after 1.0 min, and the beads were quickly rinsed with CH_2Cl_2 (3×). The procedure was repeated four times. The resin was washed with DMF (3×) and CH_2Cl_2 (3×) and then blown down with N_2.

The deprotected resin was then resolvated in CH_2Cl_2 and drained. Then 3.6 mL of a 0.14 M stock solution of Dess−Martin periodinane (0.50 mmol, 3.5 equiv) in CH_2Cl_2 was added, and the resin slurry was heated at reflux with agitation (2.0 s stroke, 75% upward) for 2 h. The reaction slurry was cooled to room temperature, and the solution was removed. The beads were washed with DMF (3×), CH_2Cl_2 (3×), and Et_2O (3×) and dried in vacuo, providing **3**.

1-(4-Bromophenyl)hexan-1-ol. A solution of 0.555 g (3.00 mmol) of 4-bromobenzaldehyde in 6.0 mL of THF was added dropwise to a solution of pentylmagnesium bromide (3.00 mL, 6.00 mmol in diethyl ether) in 4 mL of THF. The reaction was stirred overnight and then quenched by the slow addition of cold saturated NH_4Cl. The layers were separated, and the organic phase was washed with 1 M HCl (3×). The aqueous layer was then back-extracted with CH_2Cl_2 (3×). The combined organic layers were dried over Na_2SO_4 and concentrated to provide a pale yellow oil (0.766 g, 99%). The spectra were in agreement with the literature compound.[20]

[1-(4-Bromophenyl)-hexyloxy]triethylsilane (*A*). To a solution of 1-(4-bromophenyl)hexan-1-ol (6.8 g, 26 mmol) in CH_2Cl_2 (130 mL) was added imidazole (2.7 g, 40 mmol) followed by triethylsilyl chloride (4.9 mL, 29 mmol) via syringe, giving a precipitate immediately. After 30 min, the reaction mixture was filtered through a medium frit, concentrated, and chromatographed on silica gel (9:1 hexanes/EtOAc, 1% Et_3N) to give 8.6 g (88%) of cuprate precursor *A*. ^{1}H NMR δ 0.52 (m, 6 H), 0.85−0.90 (m, 12 H), 1.26 (m, 6 H), 1.57 (m, 1 H), 1.67 (m, 1 H), 4.59 (dd, J = 5.8, 6.3, 1 H), 7.18 (d, J = 8.2, 2 H), 7.42 (d, J = 8.3, 2 H). ^{13}C NMR δ 4.8, 6.7, 14.0, 22.5, 25.1, 31.7, 40. 8, 74.3, 120.4, 127.6, 131.0, 145.0. IR (neat) 1484, 1458, 1085, 1070, 1010 cm^{-1}. Anal. Calcd for $C_{18}H_{31}BrOSi$: C, 58.21; H, 8.41. Found: C, 58.01; H, 8.25.

Phenoxyacetaldehyde. To a 2 L three-neck flask fit with both a 250 mL and a 500 mL addition funnel and a mechanical stirrer was added CH_2Cl_2 (500 mL). The reaction flask was cooled to −54 °C in a CH_3CN−dry ice bath before the addition of oxalyl chloride (20.0 mL, 220 mmol). After 10 min, DMSO (34.0 mL, 440 mmol) in CH_2Cl_2 (100 mL)

was added dropwise over 15 min, and then the reaction solution was stirred an additional 10 min. 2-Phenoxyethanol (25.1 mL, 200 mmol) dissolved in CH_2Cl_2 (200 mL) was then added dropwise over 15 min, giving a colorless slurry. The reaction slurry was stirred about 30 min before the addition of Et_3N (112 mL, 800 mmol) via syringe, giving a pink solution. After 10 min, the bath was lowered and water (800 mL) was added with stirring. The solution was allowed to warm to room temperature over 1 h, the layers separated, and then the aqueous layer was extracted with CH_2Cl_2 (4×). The combined organic layers were then washed with 1 N HCl (5×), brine (2×), and saturated aqueous $NaHCO_3$ (3×), dried over $MgSO_4$, and concentrated at 30 °C to a pale brown oil (26.5 g, 97%) that matched the literature compound.[21] Stored at −15 °C as crude mixture.

4-Phenoxy-1-butyn-3-ol. A solution of phenoxyacetaldehyde (26.5 g, 195 mmol) in THF (200 mL) was added dropwise to a 0.5 M solution of ethynylmagnesium chloride in THF. The addition was allowed to go overnight and was then quenched with cold saturated NH_4Cl. The layers were separated, and the aqueous phase was extracted with Et_2O (3×). The combined organic layers were dried over Na_2SO_4 and concentrated to provide a yellow−orange solid (29.7 g, 94%). The spectra were in agreement with the literature compound.[22]

3-[(Triethylsilyl)oxy]-4-phenoxy-1-butyne. To a solution of 4-phenoxy-1-butyn-3-ol (0.705 g, 4.35 mmol) in CH_2Cl_2 (22 mL) was added imidazole (0.444 g, 6.53 mmol) followed by triethylsilyl chloride (0.800 mL, 4.78 mmol) via syringe, giving a precipitate immediately. After 30 min, the reaction mixture was filtered through a medium frit, concentrated, and chromatographed on silica gel (9:1 hexanes/EtOAc, 1% Et_3N) to give 1.04 g (87%) of the silyl ether. ^{1}H NMR δ 0.70 (q, J = 7.9, 6 H), 1.01 (t, J = 7.9, 9 H), 2.47 (s, 1 H), 4.09 (m, 2 H), 4.75 (dd, J = 4.9, 6.2, 1 H), 6.93 (d, J = 7.9, 2 H), 6.97 (dd, J = 7.3, 7.4, 1 H), 7.29 (dd, J = 7.6, 8.2, 2 H). ^{13}C NMR δ 4.6, 6.6, 61.8, 72.0, 73.3, 82.4, 114.6, 121.0, 129.4, 158.5. IR (neat) 3307, 2119, 1600, 1496, 1246, 1117 cm^{-1}. Anal. Calcd for $C_{16}H_{24}O_2Si$: C, 69.52; H, 8.75. Found: C, 69.11; H, 8.75.

***E*-3-[(Triethylsilyl)oxy]-1-iodo-4-phenoxy-1-butene (*B*).** To a solution of 9.68 g (35.0 mmol) of 3-[(triethylsilyl)-oxy]-4-phenoxy-1-butyne in THF (117 mL) was added 3.40 mL (42.0 mmol) of pyridine. The flask was purged with argon before the additon of 10.8 g (42.0 mmol) of zirconocene hydridochloride. With shielding from light, the reaction slurry was stirred at room temperature for 30 min, giving a brown solution. Then 8.88 g (35.0 mmol) of I_2 in approximately 5 mL of THF was added via syringe, first giving a yellow solution which then turned brown. After 10 min, the reaction mixture was diluted with about 500 mL of pentanes and then quickly filtered through a plug of silica gel saturated with 9:1 hexanes/EtOAc, 1% Et_3N. Chromatography with 9:1 hexanes/EtOAc, 1% Et_3N afforded 9.50 g (67%) of cuprate precursor *B*. ^{1}H NMR δ 0.66 (q, J = 7.9, 6 H), 0.99 (t, J = 7.9, 9 H), 3.88 (m, 2 H), 4.49 (q, J = 5.4, 1 H), 6.49 (d, J = 14.4, 1 H), 6.70 (dd, J = 5.2, 14.4, 1 H), 6.89 (d, J = 7.9, 2 H), 6.97 (t, J = 7.3, 1 H), 7.30 (t, J = 7.9, 2 H). ^{13}C NMR δ 4.8, 6.7, 71.2, 73.4, 78.1, 114.4, 120.9, 129.4, 145.4, 158.5. IR (neat) 3062, 3039, 1600, 1496, 1245 cm^{-1}. Anal. Calcd for $C_{16}H_{25}IO_2Si$: C, 47.53; H, 6.23. Found: C, 47.32; H, 6.25.

General Procedure for Cuprate Addition To Prepare Intermediates 5 and 10. To a −78 °C solution of the aryl bromide, *A*, or vinyl iodide, *B*, (5 equiv to loading) was added freshly titrated *tert*-butyllithium (10 equiv to loading). This mixture was then stirred for 3 h at −78 °C. In a separate flask, a solution of thiophene (5.25 equiv to loading) in THF was cooled to −78 °C for 10 min before the flask is charged with 5 equiv (to loading) of butyllithium (0.37 M total concentration of solution). The reaction mixture was then stirred at 0 °C in an ice bath for 1 h before being cooled to −78 °C. The lithiothiophene solution was then transferred via Teflon cannula to a −78 °C slurry of 5 equiv (to loading) of CuCN (briefly flame-dried under nitrogen purge) in THF (0.43 M final concentration). After 5 min at −78 °C, the slurry was warmed to room temperature for approximately 10 min at which point the solution becomes homogeneous and turns a tan color. This solution was then cooled back to −78 °C for 10 min before the vinyl- or aryllithium solution was added via Teflon cannula. The cuprate solution is then warmed to 0 °C for 5 min and then cooled to −78 °C. The cuprate solution was then added via cannula to a slurry of enone resin (**3** or **9**) in THF (0.1 M final concentration of cuprate reagent) at −78 °C. The reaction slurry was stirred at −78 °C for 20 min, warmed to −20 °C for 20 min to 1 h, and cooled back to −78 °C for about 10 min before quenching with cold 10% AcOH in THF. The slurry was then warmed to room temperature for about 10 min, and the resin was transferred to a fritted syringe. The beads were washed with 1:1 DMF/H_2O (3×), MeOH (3×), DMF (3×), CH_2Cl_2 (3×), and Et_2O (3×).

Suzuki−Miyuara Coupling To Prepare Intermediate 8. To a solution of alkene **7** (1.81 g, 6.25 mmol) in THF (23 mL) was added 0.703 g (5.76 mmol) of 9-BBN dimer. The reaction mixture was stirred 6 h at room temperature. A 50 mL flask was charged with 2.0 g (0.48 mmol/g, 0.96 mmol) of vinyl bromide resin **1** and 0.155 g (0.134 mmol) of Pd-$(PPh_3)_4$ and purged with N_2 for 15 min. The borane solution was then transferred to the resin via Teflon cannula followed by the addition of 5.8 mL of degassed 2.0 M Na_2CO_3 via syringe. The flask was then fit with a degassed condenser, shielded from light, and heated to 70 °C with slow stirring of the slurry for 12 h. The reaction mixture was then allowed to cool to room temperature before being drained, and the resin was then washed with 1:1 DMF/H_2O (3×), DMF (3×), and CH_2Cl_2 (3×). The resulting resin **8** was used directly in the next step.

Deprotection and Oxidation To Provide 9. Approximately 2.0 g (0.48 mmol/g, 0.96 mmol) of resin **8** was slurried in CH_2Cl_2, and then the solvent was drained. A 1 M HCO_2H solution in CH_2Cl_2 (30 mL) was then added, and the slurry was agitated. The solution was removed after 1.0 min, and the beads were quickly rinsed with CH_2Cl_2 (3×). The procedure was repeated four times. The resin was washed with DMF (3×) and CH_2Cl_2 (3×) and then blown down with N_2. The resin was then slurried in CH_2Cl_2 (24 mL) followed by the addition of 1.43 g (3.36 mmol) of

Dess−Martin periodinane. The flask was fit with a reflux condenser, and the slurry was heated at reflux with gentle stirring for 2 h. The reaction slurry was cooled to room temperature, and the solution was removed. The beads were washed with DMF (3×), CH_2Cl_2 (3×), and Et_2O (3×) and dried in vacuo, providing resin **9**.

***N*-Cyanomethylation To Provide 10.** After cuprate addition to **9**, 0.813 g (0.450 mmol/g, 0.366 mmol) of resin was transferred to a 35 mL fritted syringe and was slurried in 11 mL of 1-methyl-2-pyrrolidinone (NMP). To the slurry was then added 0.96 mL (5.5 mmol, 15 equiv) of diisopropylethylamine and 0.77 mL (11 mmol, 30 equiv) of bromoacetonitrile. The reaction slurry was slowly stirred overnight. The solution was drained, and the beads were then washed with NMP (3×, with one wash extended for 1 h), CH_2Cl_2 (3×), and Et_2O (4×) and dried in vacuo, providing the activated resin **10**.

Amine Displacement of Activated *N*-Acylsulfonamide 10*A* and 10*B*. Resin **10** was divided into 10 1 dram vials (approx 30 mg each) and transferred to Quest 210 RVs as a slurry in THF. The RVs were then drained and blown down briefly with nitrogen. The resin was then slurried in 0.90 mL of NMP, and approximately 0.10 mL of each amine was added to an RV, giving an approx 1 M solution of each amine. (Methylamine and dimethylamine were used as 2.0 M solutions in THF and were consequently diluted with NMP to provide 1 M solutions.) Agitation (3.0 s stroke, 75% upward) for 1 h was followed by draining and then washing the beads with DMF (3×), CH_2Cl_2 (3×), and Et_2O (3×). The resulting amide resin **11** was then flushed with a stream of nitrogen for about 30 min and cleaved directly afterward.

Parallel Cleavage and Scavenging To Provide 12a−t. Resin **11** was slurried in 0.80 mL of a 0.4 M solution of 17.5% HF/pyridine in THF in a 5 mL Quest RV and agitated (2.5 s stroke, 67% upward) for 2.5 h. Then 0.14 mL of methoxytrimethylsilane (3 equiv to HF) was added, and the agitation continued for 2 h. The solution was then drained and collected. After the beads were washed with THF (3×), the filtrates were combined and concentrated to a yellow−orange oily solid. The cleaved compounds were dissolved in $CDCl_3$ and then split into two equal portions, and a standard solution of 2,6-dimethoxytoluene in $CDCl_3$ was added to one of the portions and a ^{1}H NMR taken of each. The yields of the final, crude compounds were then determined by the integration ratio of the standard versus a characteristic peak of the final products.

Representative Spectral Data. 6e: ^{1}H NMR δ 7.31 (dd, J = 6.9, 9.2, 2 H), 6.99 (t, J = 7.3, 1 H), 6.92 (d, J = 7.8, 2 H), 5.83 (m, 2 H), 4.60 (m, 1 H), 4.12 (m, 1 H), 4.04 (m, 1 H), 3.93 (m, 1 H), 2.76 (dd, J = 7.3, 19.5, 1 H), 2.45 (m, 1 H), 2.25 (dd, J = 10.5, 17.7, 1 H), 2.06 (m, 1 H), 1.65−1.50 (m, 4 H), 1.45−1.20 (m, 10 H), 0.87 (t, J = 6.9, 3 H); HRMS (FABMS) calcd for $[M + Li]^+$ ($C_{23}H_{34}LiO_4$) 381.26171, found 381.26065.

12f: ^{1}H NMR δ 7.36 (d, J = 8.1, 2 H), 7.27 (m, 2 H), 4.66 (m, 1 H), 4.40 (m, 1 H), 3.30 (m, 3 H), 2.87 (m, 1 H), 2.40 (m, 4 H), 2.23 (m, 8 H), 1.96 (m, 2 H), 1.84−1.57 (m, 2 H), 1.50−1.25 (m, 6 H), 1.20−0.95 (m, 8 H), 0.88 (t, J = 6.7, 3 H); HRMS (FABMS) calcd for $[M + H]^+$ ($C_{28}H_{47}N_2O_4$) 475.35358, found 475.35448.

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Supporting Information Available. ^{1}H NMR spectra for final prostaglandins **6a−f** and **12a−t** are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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