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An Efficient Synthesis of 3-Hetero-13,14-dihydro Prostaglandin $F_{1\alpha}$ Analogues

Jianxin Gu,[†] Michelle J. Dirr,[‡] Yili Wang,[‡] David L. Soper,[‡] Biswanath De,[‡] John A. Wos,[‡] and Carl R. Johnson*,[†]

Department of Chemistry, Wayne State University, Detroit, Michigan 48202-3489, and Procter & Gamble Pharmaceuticals, 8700 Mason-Montgomery Road, Mason, Ohio 45040-8006

crj@chem.wayne.edu

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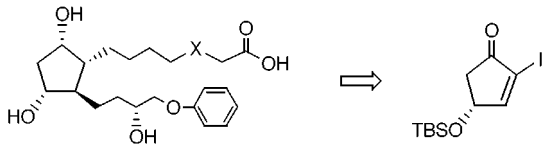
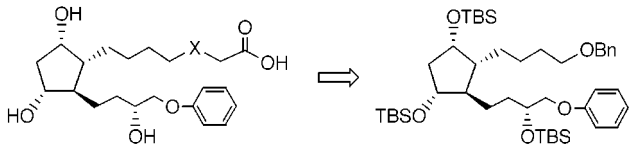
ABSTRACT



A new class of 3-hetero-13,14-dihydro prostaglandin $F_{1\alpha}$ analogues was synthesized from a common intermediate. The latter was constructed via a two-step, three-component process. The lower chain, containing the 15-(phenoxymethyl) group, was synthesized in enantiopure form using Jacobsen's (salen)Co-catalyzed kinetic resolution of a terminal epoxide with phenol.

The identification and cloning of multiple prostaglandin receptor subtypes[1] has resulted in renewed enthusiasm for the development of highly receptor-selective prostaglandin derivatives. Ideally, such compounds would exhibit desirable activity without the side effects associated with indiscriminate binding to multiple receptors. As a part of research program in designing highly receptor-selective $PGF_{2\alpha}$ analogues as potential bone anabolic agents for the treatment of osteoporosis,[2] we disclose an efficient synthesis of a novel class of saturated PGF analogues **1a**−**g** from a common intermediate, **2** (Scheme 1).

Scheme 1



1a-g **2**

Many interesting synthetic methods have been developed for the synthesis of prostaglandins, including Corey's 2-fold Wittig approach,[3] the two-component process,[4] the three-component coupling methodology,[5,6] and, recently, an approach based on ring closing alkyne metathesis or alkyne cross metathesis.[7] The overall strategy of our syntheses is based on the three-component, two-step process developed in our laboratories (Scheme 2)[6] which has a convergent

[†] Wayne State University.
[‡] Procter & Gamble Pharmaceuticals.

(1) Coleman, R. A.; Smith, W. L.; Narumiya, S. *Pharmacol. Rev.* **1994**, *46*, 205−229.
(2) Wang, Y.; Wos, J. A.; Dirr, M. J.; Soper, D. L.; DeLong, M. A.; Mieling, G. E.; De, B.; Amburgey, J. S.; Suchanek, E. G.; Taylor, C. J. *J. Med. Chem.* **2000**, *43*, 945−952.
(3) Corey, E. J.; Weinshenker, N. M.; Schaaf, T. K.; Huber, W. *J. Am. Chem. Soc.* **1969**, *91*, 5675.
(4) Sih, C. J.; Price, P.; Sood, R.; Salomon, R. G.; Peruzzotti, G.; Casey, M. *J. Am. Chem. Soc.* **1972**, *94*, 3643.
(5) Noyori, R.; Suzuki, M.; *Chemtracts: Org. Chem.* **1990**, 173.
(6) Johnson, C. R.; Braun, M. P. *J. Am. Chem. Soc.* **1993**, *115*, 11014−11015.
(7) (a) Furstner, A.; Grela, K.; Mathes, C.; Lehmann, C. W. *J. Am. Chem. Soc.* **2000**, *122*, 11799−11805. (b) Furstner, A.; Grela, K. *Angew. Chem., Int. Ed.* **2000**, *39*, 1234−1235.

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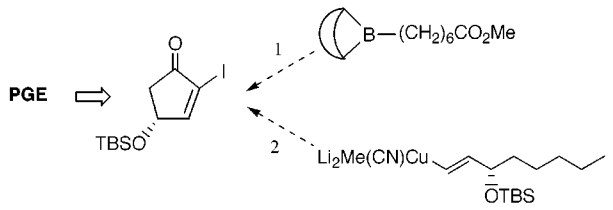
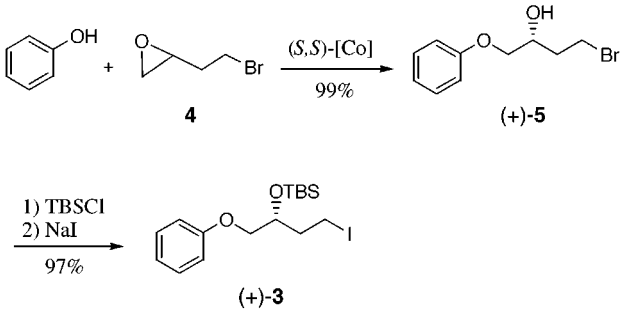
Scheme 2



nature and synthetic flexibility, especially in the introduction of diverse α-chains.

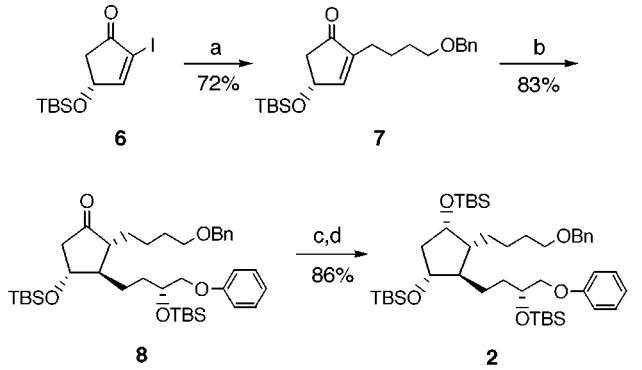
The preparation of enantiopure lower chain precursor **3** was essential for the construction of common intermediate **2**. This was accomplished using Jacobsen methodology[8] by mixing 1 equiv of phenol and 2.2 equiv of epoxide **4** in the presence of (*S*,*S*)-(salen)Co[OC(CF_3)$_3$]. The resulting kinetic resolution provided **5** in nearly quantitative yield on the basis of phenol with an ee greater than 98%.[9] The required lower chain precursor (+)-**3** was then synthesized from (+)-**5** in two steps (Scheme 3).[10]

Scheme 3



Synthesis of common intermediate **2** is outlined in Scheme 4. The upper chain bearing a benzyl-protected hydroxyl functionality was installed via a Suzuki cross-coupling reaction between a 9-BBN derivative generated in situ from benzyl 3-butenyl ether and iodoenone **6**[6] catalyzed by $PdCl_2$-(dppf); the coupling product **7** was isolated in 72% yield. Conjugate addition of the lower chain component was successfully achieved by treatment of enone **7** with a high-order cuprate generated by lithiation of iodide **3** with *tert*-butyllithium[11] in combination with lithium 2-thienylcyanocuprate[12] to give **8** in 83% yield. Reduction of **8** with L-Selectride at −78 °C proceeded smoothly to provide the

Scheme 4[a]

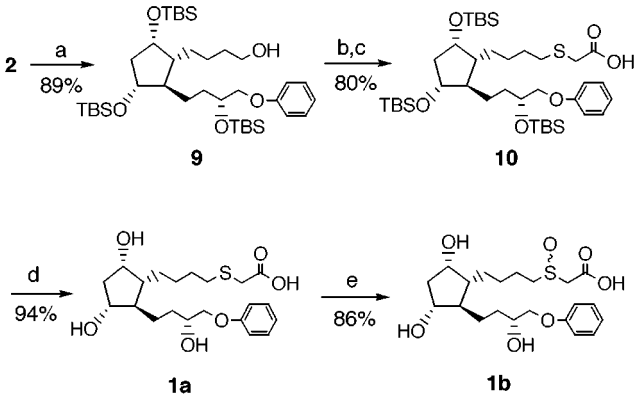


[a] (a) Benzyl 3-butenyl ether (1.5 equiv), 9-BBN (0.5 M in THF, 1.5 equiv), $PdCl_2$(dppf) (5 mol %), K_3PO_4 (2 equiv), DMF-THF−H_2O, rt; (b) **3** (1.3 equiv), *tert*-BuLi (2.7 equiv), ThCu(CN)Li (1.1 equiv), pentane−Et_2O, −78 to −20 °C; (c) L-Selectride (1.2 equiv), THF, −78 °C; (d) TBSCl, imidazole, DMF, rt.

α-alcohol with good enantioselectivity (92:8 α/β). Protection of the three hydroxyl groups as TBS ethers under standard conditions and subsequent purification by silica gel chromatography provided the enantiopure intermediate **2**.[13]

The late stage of the synthesis involved the transformation of **2** in a series of steps into a variety of prostaglandin analogues incorporating glycine or mercaptoacetic acid into the upper chain. For the introduction of the mercaptoacetic acid moiety, the benzyl protecting group in compound **2** was first removed by hydrogenation on 5% Pd/C in 89% yield (Scheme 5). The resulting hydroxyl was converted to the

Scheme 5[a]



[a] (a) H_2, 5% Pd/C, EtOAc, rt; (b) MsCl, Et_3N, CH_2Cl_2,0 °C; (c) mercaptoacetic acid, NaH, DMSO, rt; (d) H_2SiF_6, CH_3CN, rt; (e) Bu_4NIO_4, CH_2Cl_2−MeOH, rt.

corresponding mesylate; subsequent nucleophilic displacement with the disodium salt of mercaptoacetic acid in DMSO afforded **10** in 80% yield (two steps). The DeShong protocol (H_2SiF_6/CH_3CN)[14] was the most effective and convenient way to remove all TBS protecting groups in the present case

(8) Ready, J. M.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1999**, *121*, 6086−6087.

(9) The enantiopurity was determined via NMR analysis of its corresponding Mosher ester. **5** exhibited the following physical data: colorless needles, mp 40−41 °C, $[\alpha]^{23}_D$ = 8.5 (*c* 1.0, $CHCl_3$).

(10) (+)-**3**: colorless needles, mp: 28 °C, $[\alpha]^{23}_D$ = 19.3 (*c* 1.16, $CHCl_3$).

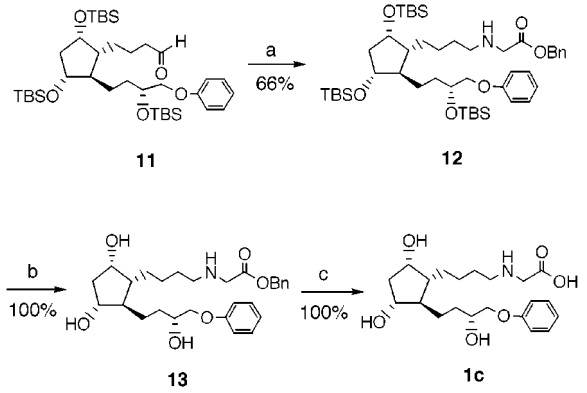
(11) (a) Bailey, W. F.; Punzalan, E. R. *J. Org. Chem.* **1990**, *55*, 5404. (b) Negishi, E.; Swanson, D. R.; Rousset, C. R. *J. Org. Chem.* **1990**, *55*, 5406.

(12) Lipshutz, B. H.; Koerner, M.; Parker, D. A. *Tetrahedron Lett.* **1987**, *28*, 945−948.

and did not introduce byproducts that are difficult to remove. After simple workup, analogue **1a** was obtained in 94% yield; the second analogue, the corresponding sulfoxide **1b**, was synthesized by oxidation of **1a** with Bu_4NIO_4 in 86% yield.

Incorporation of the glycine moiety into the upper chain in intermediate **2** is depicted in Scheme 6. Reductive

Scheme 6[a]

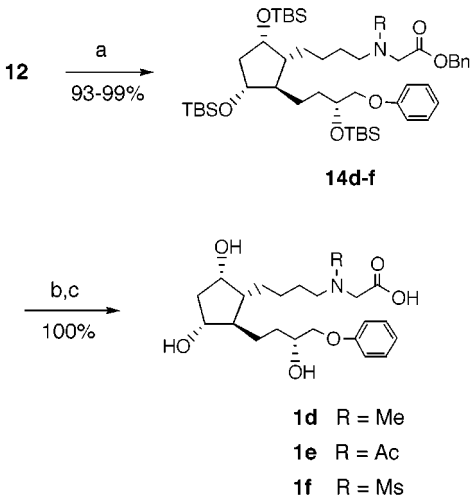


[a] (a) $NH_2CH_2CO_2Bn$·HCl, Et_3N, $NaCNBH_3$, MeOH, rt; (b) H_2SiF_6, CH_3CN, rt; (c) 1,4-cyclohexadiene, 10% Pd/C, EtOH, rt.

amination of aldehyde **11** with glycine benzyl ester using $NaCNBH_3$ in the presence of Et_3N provided **12** in 66% yield. Aldehyde **11** was available from the standard Swern oxidation of alcohol **9**. A key requirement for the success of this reductive amination reaction was that an equimolar amount of Et_3N and glycine ester hydrochloride salt be premixed with the aldehyde in MeOH prior to the addition of $NaCNBH_3$. Without the presence of Et_3N, the corresponding dimethyl ketal of aldehyde **11** was the sole product recovered. With H_2SiF_6, three TBS groups were removed in quantitative yield and subsequent catalytic transfer hydrogenation[15] quantitatively afforded analogue **1c**.

The syntheses of analogues incorporating various substituents at the secondary amine in compound **1c** started with intermediate **12** (Scheme 7). For the synthesis of the *N*-methyl derivative, reductive amination was used to introduce the *N*-methyl substitution. The Ac_2O/Et_3N/DMAP combination was used to install the *N*-acetyl group. The mesyl group was introduced with Ms_2O/Et_3N under standard

Scheme 7[a]

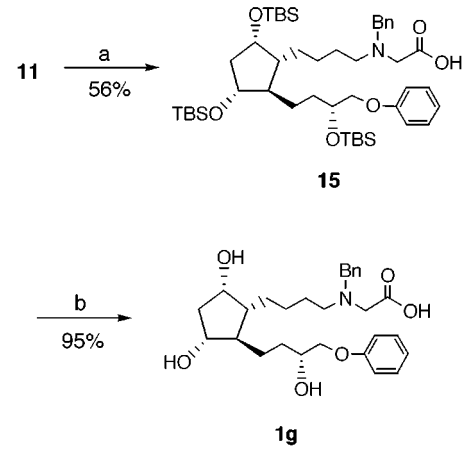


[a] (a) 1. R = Me: formaldehyde (37% in H_2O), $NaCNBH_3$, MeOH, 98%; 2. R = Ac: Ac_2O, Et_3N, DMAP, CH_2Cl_2, 99%; 3. R = Ms: Ms_2O, Et_3N, CH_2Cl_2, 93%; (b) H_2SiF_6, CH_3CN; (c) 1,4-cyclohexadiene, 10% Pd/C, EtOH.

conditions. In a manner identical to that described in Scheme 6, two deprotection steps led to analogues **1d**−**f** in excellent yields.

A two-step sequence was used to synthesize the *N*-benzyl-protected analogue **1g** (Scheme 8). Treatment of aldehyde

Scheme 8[a]



[a] (a) $BnNHCH_2CO_2H$·HCl, $NaCNBH_3$, Et_3N, MeOH−Et_2O, rt; (b) H_2SiF_6, CH_3CN, rt.

11 with *N*-benzylglycine using $NaCNBH_3$ in the presence of Et_3N gave **15** in 56% yield. Deprotection of **15** using H_2SiF_6 in CH_3CN afforded the target compound **1g** in 95% yield.

The receptor binding affinities of these saturated PG analogues, **1a**−**g**, were then measured by their abilities to displace various radiolabeled PG ligands in COS-7 cells

(13) Optical and spectral data for **2**: colorless oil, $[\alpha]^{23}_D = 11.1$ (*c* 3.2, $CHCl_3$); ^1H NMR($CDCl_3$) δ 7.35−7.25 (m, 7H), 6.96−6.86 (m, 3H), 4.50 (s, 2H), 4.08−4.03 (m, 1H), 4.01−3.95 (m, 1H), 3.86−3.74 (m, 3H), 3.49−3.44 (m, 2H), 2.16−2.07 (m, 1H), 1.77−1.21 (m, 13H), 0.9 (s, 9H), 0.88 (s, 9H), 0.87 (s, 9H), 0.11 (s, 3H), 0.09 (s, 3H), 0.04 (s, 6H), 0.02 (s, 3H), 0.01 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 158.50, 138.66, 129.36, 128.29, 127.54, 127.39, 120.49, 114.28, 76.80, 72.80, 71.94, 71.62, 71.39, 70.58, 49.77, 47.91, 44.50, 31.63, 30.21, 27.21, 26.65, 25.93, 25.86, 25.83, 24.48, 18.18, 18.00, 17.85, −4.07, −4.19, −4.23, −4.68, −4.79, −5.10; HRMS calcd for $C_{44}H_{78}O_5Si_3$, (M^+) 770.5157, (M − C_4H_9) 713.4453, found 713.4455.

(14) Pilcher, A. S.; Hill, D. K.; Shimshock, S. J.; Waltermire, R. E.; DeShong, P. J. *J. Org. Chem.* **1992**, *57*, 2492..

(15) Felix, A. M.; Heimer, E. P.; Lambros, T. J.; Tzougraki, C.; Meienhofer, J. *J. Org. Chem.* **1978**, *43*, 4194.

transiently transfected with human prostaglandin membrane.[2] Data for compounds **1a** and **1c**[16] are shown in Table 1.

Table 1. Binding Affinity of **1a** and **1c** [IC_{50} (nM)]

entry	hFP	hEP1	hEP2	hEP3	hEP4	hTP	hDP	hIP
1a	137	1000	$>10^4$	760	$>10^4$	$>10^4$	$>10^4$	$>10^4$
1c	$>10^4$							

In conclusion, a very efficient process was developed for the synthesis of advanced intermediate **2**. From this common precursor, a total of seven novel prostaglandin analogues were synthesized. A method was developed to make the lower chain precursor containing a phenoxy group in enantiopure form and to install it efficiently. Preliminary biological results suggested that analogues of this type may be useful as agents in cases where metabolism concerns such as β-oxidation may prevent use of more traditional FP agonists due to shorter half-lives.[17]

Supporting Information Available: Experimental procedures and characterization data for all new compounds and ^1H and ^{13}C NMR spectra for intermediate **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) The binding affinity of compound **1c** for the other prostaglandin receptors was not further tested as it showed poor activity toward hFP receptor [$IC_{50} > 10^4$ (nM)]. Compounds **1b** and **1d**−**g** showed a biological profile similar to that exhibited by **1c**.

(17) For a review on the metabolism of $PGF_{2\alpha}$, see: Roberts, L. J., II; *CRC Handbook of Eicosanoids: Prostaglandins and Related Lipids*, Vol. 1, part A; 1987; pp 233−244.