An Efficient Approach to Optically Active Benzoprostacyclins by a Two-component Coupling Process

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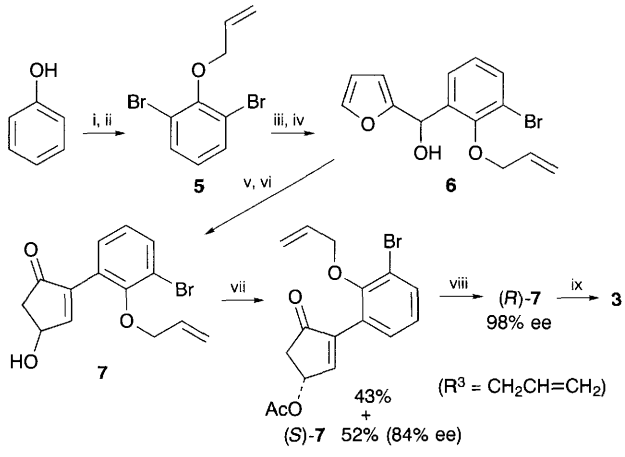
A highly efficient and practical synthesis of enantiomerically pure benzoprostacyclins, chemically stable and therapeutically useful prostaglandin I_2 analogues, is developed which includes an efficient preparation of 2-[3-bromo-2-(allyloxy)phenyl]-4-siloxycyclopent-2-en-1-one **3** in optically active form and the conjugate addition of ω side-chains onto **3** followed by cyclization to the key intermediate (1*R*, 2*R*, 3'*S*)-2-*endo*-siloxy-1-*exo*-(3'-siloxyalk-1-enyl)-3*a*,8*b*-*cis*-2,3,3*a*,8*b*-tetrahydro-1*H*-5-bromocyclopenta[*b*]benzofuran **4**.

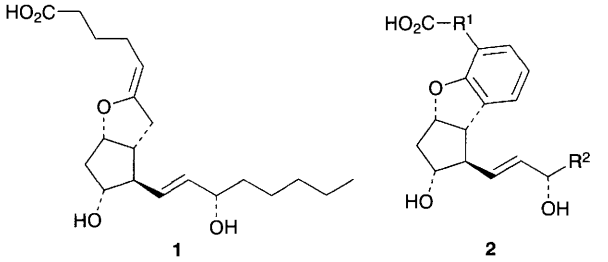
Since the discovery of prostacyclin (**1**, PGI_2), a number of chemically and metabolically stable PGI_2 analogues have been developed as clinically effective antithrombotic agents.[1] Among these, benzoprostacyclins **2** developed by Toray Industries Inc. are some of the most attractive compounds.[2] Available synthetic approaches to the benzoprostacyclins, however, are linear and rather inefficient.[3] Herein we report a highly efficient, convergent approach to benzoprostacyclins. Our approach is based on a two-component coupling process,[4] the key steps of which are summarized in Scheme 1.

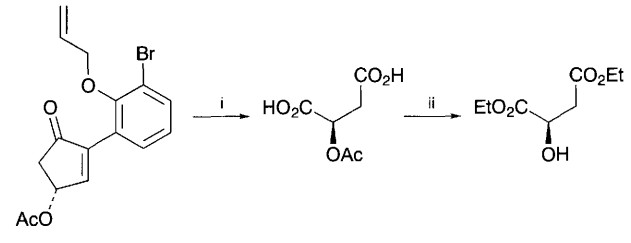
The five membered ring intermediate **3** was prepared in an optically active form according to the procedure shown in Scheme 2. The lithiation of the allyl ether of 2,6-dibromophenol **5** (prepared from phenol in two steps, 86% yield)[5] followed by treatment with 2-furaldehyde provided furyl alcohol **6** which in turn was converted into the hydroxy enone **7**[6] by successive treatment with toluene-*p*-sulfonic acid and chloral[7] (43% yield from **5**). The compound **7** was then subjected to enzymatic resolution using porcine pancreatic lipase (PPL) as catalyst and vinyl acetate as both solvent and irreversible transesterification reagent.[8] The resulting acetate was separated (43% yield) from the unreacted alcohol and was treated with guanidine[9] to afford (*R*)-**7** (62% yield), the enantiomeric excess of which was found to be 98% by Mosher ester analysis while its absolute configuration was confirmed to be *R* by derivatization to the known D-(+)-diethyl malate according to the procedure shown in Scheme 3. The remaining alcohol isolated in 52% yield was also confirmed to have 84% e.e. Finally, the reaction of (*R*)-**7** with Bu^tMe_2SiCl in the presence of Et_3N and DMAP provided **3**† (R^3 = $CH_2CH{=}CH_2$) in quantitative yield.

The conversion of **3** into **4** was carried out as illustrated in Scheme 4. The reaction of **3** (R^3 = $CH_2CH{=}CH_2$) with higher ordered mixed cuprate **8** prepared from optically pure (*S*, *E*)-3-(*tert*-butyldimethylsiloxy)-1-iodooct-1-ene[10] and (2-thienyl)-Cu(CN)Li[11] furnished the 1,4-addition product **9** in 91% yield. Reduction of the carbonyl group at C-9 (PG numbering) in **9** with DIBAL-H at −78 °C provided two inseparable diastereomers of **10** (9α-**10** and 9β-**10**) which in turn were converted into **11** by treatment with morpholine in the presence of Pd catalyst.[12] The cyclization of **11** under Mitsunobu conditions provided **4** (R^2 = n-C_5H_{11}) and some olefinic compound(s) presumably derived from 9α-**11** by dehydration between the benzylic hydrogen and the hydroxy group. Column chromatography on silica gel of the crude mixture afforded **4**‡ (R^2 = n-C_5H_{11}) in 35% overall yield from **9**.

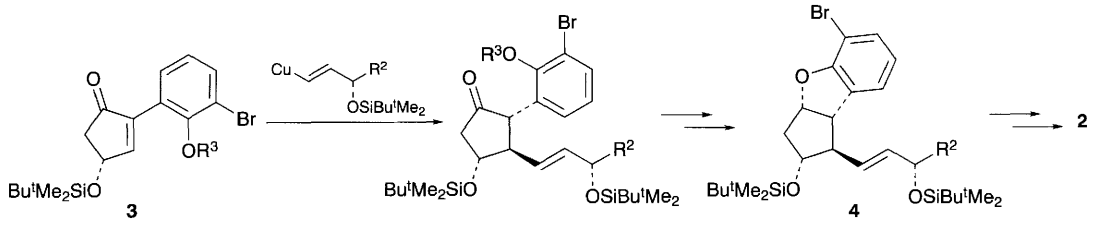


Scheme 2 *Reagents and conditions*: i, Br_2, Bu^tNH_2; ii, allyl bromide, K_2CO_3; iii, Bu^nLi; iv, 2-furaldehyde, −78 °C; v, *p*-TsOH, THF–H_2O 8 : 1; vi, Cl_3CCHO (cat.), Et_3N; vii PPL, vinyl acetate, room temp., 4d.; viii, guanidine; ix, Bu^tMe_2SiCl, Et_3N, DMAP



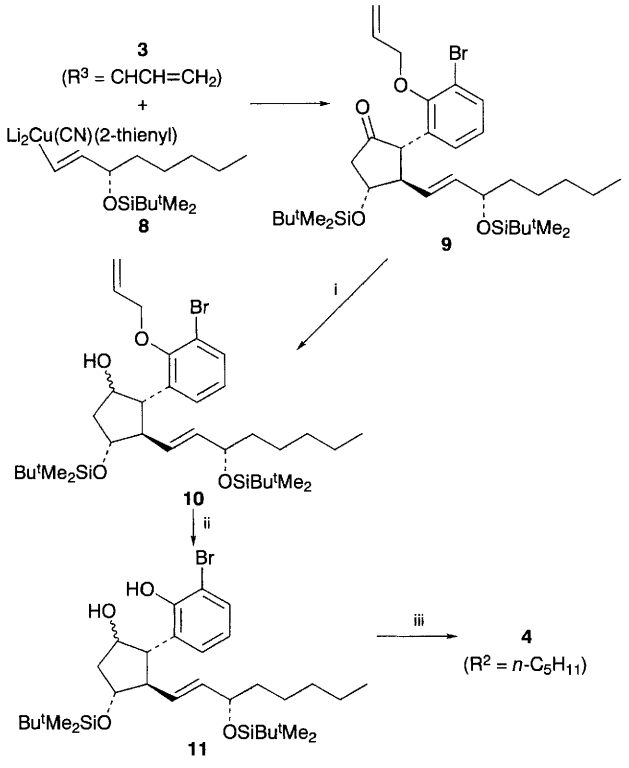


Scheme 3 *Reagents*: i, $NaIO_4$, $RuCl_3{\cdot}3H_2O$; ii, EtOH, H^+

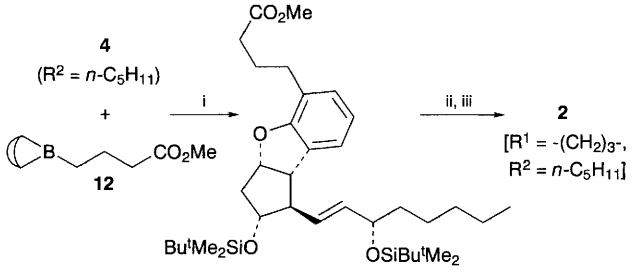


Scheme 1

It is possible to use compound **4** (R^2 = n-C_5H_{11}) to synthesize benzoprostacyclins having various α side-chain units by using the reactivity of the aryl bromide. For example, the synthesis of **2** [R^1 = $-(CH_2)_3-$, R^2 = n-C_5H_{11}] was carried out as shown in Scheme 5. Thus the Suzuki reaction[13] of **4** (R^2 = n-C_5H_{11}) with the organoborane **12** (prepared *in situ* by the hydroboration of methyl but-3-enoate with 9-BBN) in the presence of a Pd catalyst and K_3PO_4 afforded the coupling product in 83% yield which in turn was converted into **2**§ [R^1 = $-(CH_2)_3-$, R^2 = n-C_5H_{11}] by hydrolysis and protodesilylation in 88% overall yield.



Scheme 4 *Reagents and conditions*: i, DIBAL-H, −78 °C; ii, morpholine, $Pd_2(dba)_3{\cdot}CHCl_3$, Bu^n_3P; iii, $EtO_2CN{=}NCO_2Et$, PPh_3



Scheme 5 *Reagents*: i, $PdCl_2$ (dppf) (cat.), K_3PO_4, THF; ii, LiOH, MeOH, THF, H_2O; iii, 50% HF (aq), THF

This synthetic sequence is flexible allowing for a variety of α and ω side-chains and thus should prove highly adaptable toward the synthesis of a variety of benzoprostacyclins.

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Footnotes

† *Selected data* for **3**: (R^3 = $CH_2CH{=}CH_2$): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 (d, *J* 2.5 Hz, 1H), 7.54 (d, *J* 7.9 Hz, 2H), 7.03 (t, *J* 7.9 Hz, 1H), 6.02 (ddt, *J* 10.3, 17.1, 5.8 Hz, 1H), 5.19–5.40 (m, 2H), 4.99–5.04 (m, 1H), 4.21–4.40 (m, 2H), 2.90 (dd, *J* 6.1, 18.2 Hz, 1H), 2.44 (dd, *J* 2.3, 18.3 Hz, 1H), 0.92 (s, 9H), 0.15 (s, 6H).

‡ *Selected data* for **4**: (R^2 = n-C_5H_{11}): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23 (d, *J* 7.9 Hz, 1H), 7.04 (dt, *J* 7.3, 1.0 Hz, 1H), 6.68 (dd, *J* 7.3, 7.9 Hz, 1H), 5.57 (dd, *J* 4.8, 15.4 Hz, 1H), 5.50 (dd, *J* 6.4, 15.4 Hz, 2H), 5.26 (ddd, *J* 4.0, 7.3, 8.8 Hz, 1H), 4.06–4.13 (m, 1H), 3.91–3.99 (m, 1H), 3.59 (dd, *J* 6.3, 8.8 Hz, 1H), 2.56–2.64 (m, 1H), 2.41 (ddd, *J* 5.4, 7.3, 14.0 Hz, 1H), 2.09 (ddd, *J* 4.0, 6.6, 14.0 Hz, 1H), 1.21–1.56 (m, 8H), 0.89 (t, *J* 7.1 Hz, 1H), 0.90 and 0.73 (2s, 18H), 0.07, 0.05, 0.00 and −0.01 (4s, 12H); $[\alpha]_D^{21}$ + 53.9 (*c* 1.028, $CHCl_3$).

§ The optical rotation [($[\alpha]_D^{22}$ + 101 (*c* 0.445, MeOH), lit.[3b] $[\alpha]_D^{22}$ + 105 (*c* 0.48, MeOH)], mp 95–96 °C, lit.[3b] 96–97.5 °C), ^{1}H NMR, MS and IR data of **2** obtained were in good agreement with those reported.[3a,b]

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