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Novel synthesis of CP-734432, an EP4 agonist, using Sharpless asymmetric dihydroxylation

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ABSTRACT

A novel and efficient asymmetric route to CP-734432, a lactam analog of PGE2, that shows selective agonism against the EP4 receptor subtype, is reported herein. The key steps include a Heck coupling to introduce the aryl ring at C-16 and a highly diastereoselective Sharpless asymmetric dihydroxylation to set the C-15 center.

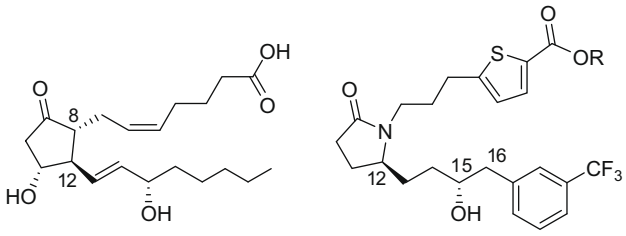
Prostaglandin E2 (PGE2, **1**, Fig. 1) is one of the primary products of cyclooxygenase-initiated arachidonic acid metabolism. Prostanoids such as PGE2 are lipid mediators that play key regulatory roles in various biological events such as vascular hypertension, inflammation, and tumorigenesis. PGE2 is the endogenous ligand for four EP receptor subtypes EP1, EP2, EP3, and EP4 which are cell surface, seven-transmembrane domain receptors that belong to the G-protein-coupled rhodopsin-type superfamily.[1–6] The critical role of EP4 receptor agonism in PGE2-mediated bone anabolic effects is well-precedented and provides a potential therapy for osteoporosis.[7–9]

PGE2 exhibits high affinity toward the four EP receptor subtypes, however, it is not selective toward the individual subtypes and has some cross-reactivity with at least one other prostanoid receptor.[10] In addition, natural prostaglandins are metabolically short-lived and exhibit chemical instability.[11,12] Thus numerous efforts have focused on discovering analogs of PGE2 with improved EP4 receptor selectivity, stability, and pharmacological properties. These efforts have unveiled a new class of lactam analogs of PGE2 wherein the 11α-hydroxy-containing cyclopentanone ring is replaced with a lactam.[13–18] Other heterocyclic rings such as the pyrazolidin-3-one have also been evaluated as a replacement.[19] Further modifications to the C-8 and C-12 side chains in these lactams have been shown to render both metabolic stability and EP4 selectivity.

Cameron et al. have previously reported one such lactam analog, CP-734432 (**2**, Fig. 1).[17] This compound has a receptor affinity at the human EP4 receptor (IC_{50} 2 nM) with 125-fold selectivity over the human EP2 receptor and >500-fold selectivity over human EP1 and EP3 receptors. The isopropyl ester prodrug of **2**, PF-4475270 (**3**) is a novel ocular hypotensive compound effectively lowering intraocular pressure in dogs.[20] Herein, we report a novel and efficient asymmetric route to this potent EP4 agonist **2** and its prodrug **3**.

Most efforts to synthesize these type of lactam analogs have relied on a common strategy of utilizing a Horner–Wadsworth–Emmons (HWE) reaction of an aldehyde **6** with the corresponding phosphonate **7** to afford the (*E*)-enone **8** and the reduction of this enone to the allylic alcohol **9** (Scheme 1).[13,14,17] Reduction of this allylic alcohol under catalytic hydrogenation conditions provided the saturated alcohol **10**.

The reduction of the enone **8** is typically carried out using either hydride-based methods and subsequent resolution of the diastereomers or by asymmetric reduction using CBS-oxazaborolidine reduction. On applying the CBS-oxazaborolidine reduction[21] in



1 (Prostaglandin E_2)

2 (CP-734432, R = H)
3 (PF-4475270, R = *i*-Pr)

Figure 1. PGE2 and lactam analogs CP-734432 (**2**) and PF-4475270 (**3**).

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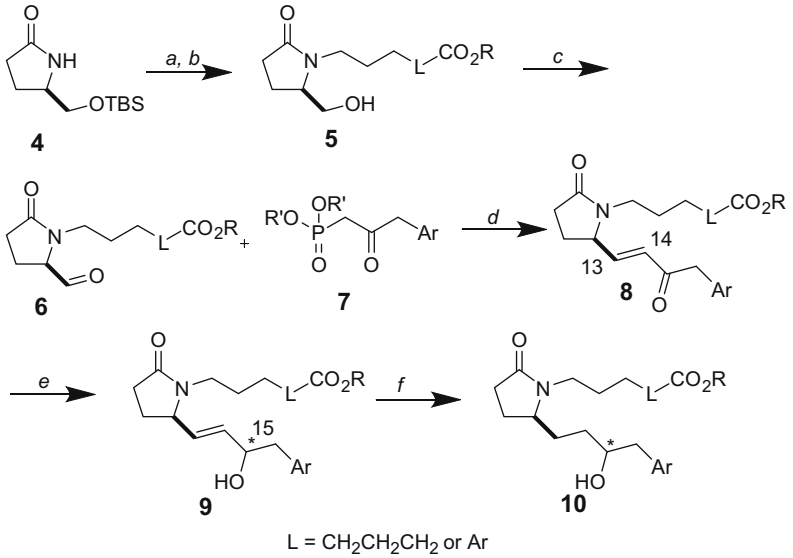


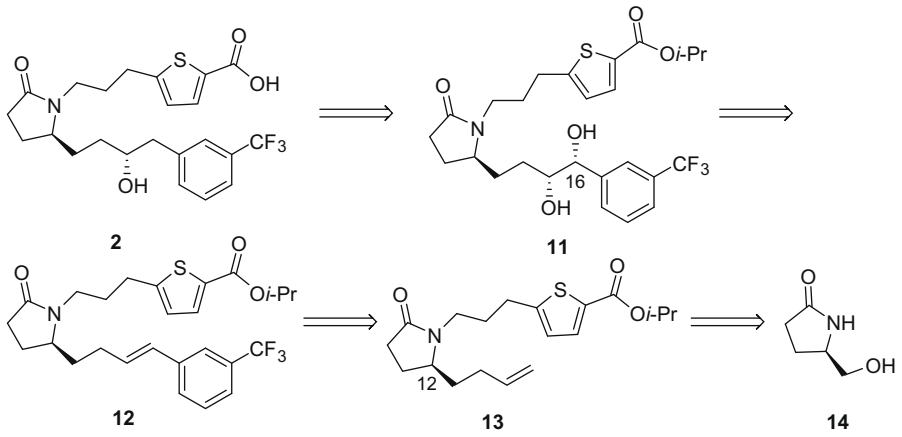
Scheme 1. Reagents: (a) NaHMDS, R′Br, DMF; (b) 1 N HCl, MeOH; (c) EDC, DMSO, pyridinium trifluoroacetate, benzene; (d) NaH; (e) $NaBH_4$ or catecholborane, (*R*)-2-Me-CBS-oxazaborolidine; (f) H_2, Pd/C.

the synthesis of **1**, we observed variable diasteroselectivity which necessitated the chiral separation of the diastereomers of the allylic alcohol equivalent to **9**. Literature reports of diastereoselective carbonyl reductions of closely related substrates with CBS-oxazaborolidine or BINAL-H have indicated temperature control, reagent quality, solvents, and substrate matching as critical variables that can easily erode diastereoselectivities.[22] Furthermore, substituent effects on the aryl ring at C-16 have shown to play a key role in potency against the EP4 receptor.[17] Thus, from the standpoint of analogue production, this route was also limited in its versatility to introduce various aryl groups at C-16 since this required the iterative and stepwise synthesis of the corresponding β-keto phosphonates. To overcome the aforementioned issues, we set out to explore a novel approach to this class of molecules.

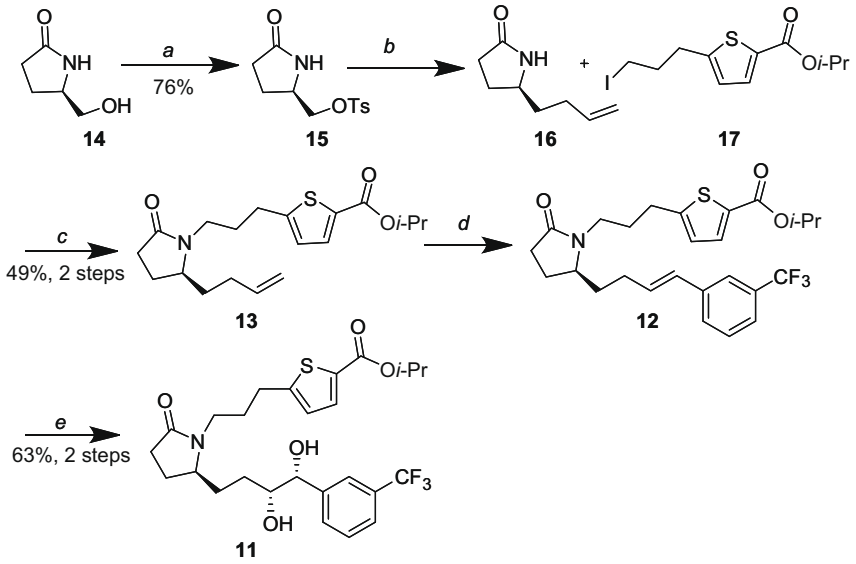
To this end, we envisioned a retrosynthetic plan (Scheme 2) that proceeds through the diol **11**, which could be obtained through the asymmetric dihydroxylation of olefin **12**. The subsequent deoxygenation of the interim benzylic alcohol at C16 in diol **11** would provide access to **2**. This disconnection offered the advantage of setting the key C-15 center chiral center in a highly diastereoselective fashion via the reliable Sharpless asymmetric dihydroxylation of an (*E*)-styrene **12**. More importantly, this design could also address the versatility issue in the introduction of the aryl ring at C-16 by employing a Heck coupling which would permit variations on the aryl ring using readily available aryl iodides. Thus in the case of **2**, the aryl group in the styrene **12** could be introduced via the Heck coupling of terminal olefin **13** with readily available *m*-trifluoromethyl phenyl iodide. The olefin could be obtained from the D-pyroglutaminol **14**.

The synthesis of **2** begins with the tosylation of the commercially available D-pyroglutaminol **14** to provide compound **15** in 76% yield (Scheme 3). Allylation of this tosylate with allyl magnesium chloride (2 equiv) gave the terminal olefin **16**.[23] The thiophene containing side chain was then introduced via alkylation of the pyrrolidinone amide **16** using NaHMDS and alkyl iodide **17** providing compound **12** in 49% yield over two steps. A Heck coupling of *m*-trifluoromethyl phenyl iodide with the terminal olefin **13** using Jeffrey's conditions gave the *E*-olefin **12** in 63% yield.[24,25] The key step of setting the *R*-alcohol C-15 stereocenter using Sharpless asymmetric dihydroxylation[26] was achieved with dihydroquinidine-based ADmix-β to provide the desired (*R,R*) diol **11** in > 96:4 dr (63% yield over two steps).

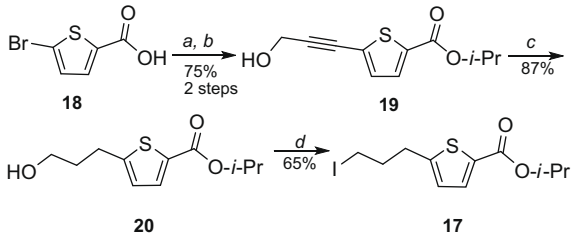
The thiophene containing alkyl iodide **17** was synthesized starting from commercially available 5-bromothiophene-2-carboxylic



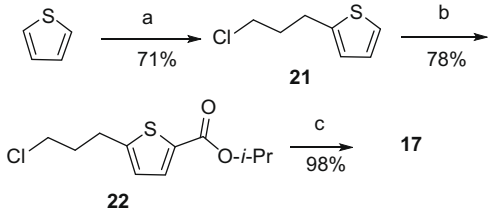
Scheme 2. Retrosynthesis of CP-734432 (**2**).



Scheme 3. Reagents and conditions: (a) TsCl, Et_3N, DMAP, CH_2Cl_2; (b) allylmagnesium chloride, THF/Et_2O (5:3) 0 °C to rt; (c) i. NaHMDS, DMF 0 °C to rt; (d) *m*-trifluoromethyl phenyl iodide, $Pd(OAc)_2$, $NaHCO_3$, *n*-Bu_4NCl, DMF, 40 °C; (e) ADmix-β, $CH_3SO_2NH_2$, *t*-BuOH, H_2O, 0 °C.

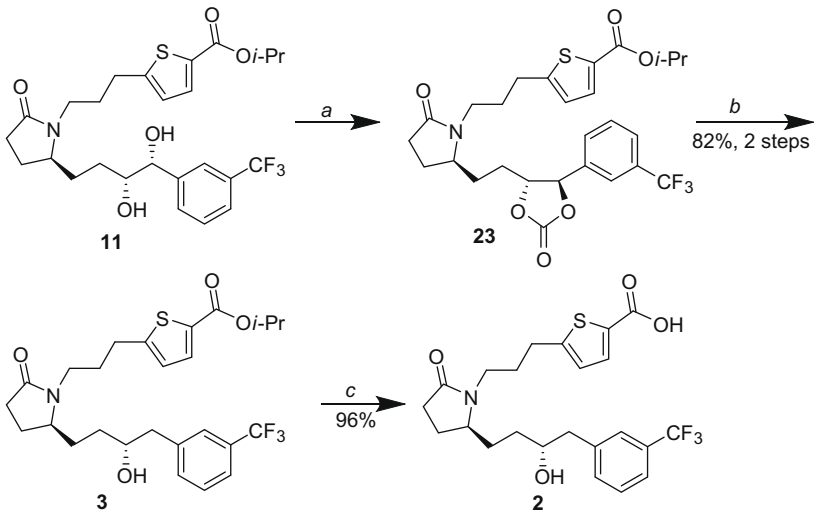


Scheme 4. Reagents and conditions: (a) isopropanol, HCl; (b) propargyl alcohol, $Pd(PPh_3)_4$, CuI, Et_2NH; (c) H_2, Pd/C; (d) PPh_3, I_2, imidazole.



Scheme 5. Reagents and conditions: (a) *n*-BuLi, −50 °C, 1-bromo-3-chloropropane, −78 °C to rt; (b) *n*-BuLi, −50 °C, isopropylchoroformate; −60 °C; (c) NaI, methyl ethylketone, 60 °C, 48 h.

acid (Scheme 4). Esterification under acidic conditions with isopropanol and subsequent Sonogashira coupling[27] with propargyl alcohol provided the alkyne **19**. Hydrogenation with Pd/C and treating the resultant saturated alcohol **20** with iodine, PPh_3, and imidazole[28] afforded **17**. An alternative three-step approach to **17**, that was more amenable to scaleup, was also developed starting from thiophene (Scheme 5). The modified route commences with the *ortho*-lithiation of thiophene and subsequent quenching of the anion with 1-bromo-3-chloropropane to provide the chloride **21**. A second lithiation at C-5 on the thiophene ring followed by acylation with isopropyl chloroformate gave the ester **22**. The conversion of the chloride to the iodide **17** was then achieved using Finkelstein conditions.



Scheme 6. Reagents and conditions: (a) CDI, THF, 50 °C; (b) H_2, 10% Pd/C, Et_3N, EtOH; (c) LiOH, MeOH, THF, H_2O.

In the end game of the synthesis, we evaluated concise ways to reduce the provisional benzylic alcohol functionality in diol **11** to the C-15 mono-alcohol **3** (Scheme 6). Attempts to effect a direct reduction of diol under catalytic hydrogenation[29,30] conditions with various catalysts, solvents, and additives as well as ionic hydrogenation conditions such as Et_3SiH/TFA[31] failed to give the reduced mono-alcohol.

The activation of the diol **11** by converting it to a carbonate was anticipated to facilitate a more facile hydrogenolysis.[32] Accordingly, the carbonate **23** was obtained by the reaction of diol with 1,1′-carbonyldiimidazole (CDI). The hydrogenolysis of this carbonate could be carried out under standard hydrogenation conditions (10% Pd/C) using triethylamine as an additive in ethanol to provide the mono-alcohol **3** (PF-4475270, 82%, two steps).[33] The diastereoselective purity and assignment of stereochemistry of the C-15 alcohol in **3** were determined by ^{1}H NMR analysis of the corresponding Mosher's ester.[34] The ester functionality in the penultimate **3** was hydrolyzed to the acid **2** (CP-734432) using lithium hydroxide.

In summary, we have demonstrated a novel, highly diastereoselective, and protection-free route to CP-733432 (**2**), a lactam analog of PGE2 and its prodrug **3** (PF-4475270). The key features of this synthesis are (a) the introduction of the C-16 aryl group via a Heck reaction that allows the use of readily available aryl halides as a source of diversity at this position (b) a highly enantioselective Sharpless dihydroxylation to set the crucial C-15 stereocenter, and (c) an efficient approach that precludes protection–deprotection steps that are characteristic of earlier approaches.

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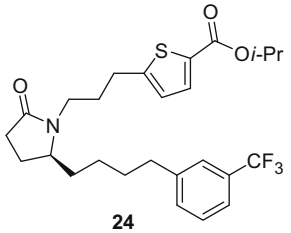
33. <10% of the separable overreduction product **24** was observed.



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