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Unified Strategy to Prostaglandins: Chemoenzymatic Total Synthesis of Cloprostenol, Bimatoprost, PGF_{2α}, Fluprostenol, and Travoprost Guided by Biocatalytic Retrosynthesis

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ABSTRACT: Development of efficient and stereoselective synthesis of prostaglandins (PGs) is of utmost importance, owing to their valuable medicinal applications and unique chemical structures. We report here a unified synthesis of PGs cloprostenol, bimatoprost, PGF_{2α}, fluprostenol, and travoprost from the readily available dichloro-containing bicyclic ketone **6a** guided by biocatalytic retrosynthesis, in 11-12 steps with 2.9-6.5% overall yields. A Baeyer-Villiger monooxygenase (BVMO)-catalyzed stereoselective oxidation of **6a** (99% ee), and a ketoreductase (KRED)-catalyzed diastereoselective reduction of enones **12** (87 : 13 to 99 : 1 dr) were utilized in combination for the first time to set the critical stereochemical configurations under mild conditions. Another key transformation was the copper (II)-catalyzed regioselective *p*-phenylbenzoylation of the secondary alcohol of diol **10** (3.8 : 1 rr). This study not only provides an alternative route to the highly stereoselective synthesis of PGs, but also showcases the usefulness and great potential of biocatalysis in construction of complex molecules.

Prostaglandins (PGs) are hormone-like lipid compounds often found in animals and human-beings¹, and they are shown to display a multitude of biological functions. To date, more than 20 PG analogs have been developed as the marketed medicines, such as the veterinary drugs cloprostenol (**1**) and fluprostenol (**4**), antiglaucoma drugs bimatoprost (**2**) and travoprost (**5**) (Fig. 1)¹. In particular, bimatoprost has recently become a block-buster drug. Because of their valuable medicinal applications and unique chemical structures, tremendous efforts have been devoted to the efficient synthesis of PGs¹⁻³. In fact, since Corey's landmark synthesis of prostaglandin F_{2α} (PGF_{2α}, **3**) in the late 1960s⁴, PGs have become one touchstone of state-of-the-art synthetic methodologies⁵⁻²³, as exemplified in the elegant synthesis recently reported by the groups of Aggarwal^{3,5-7}, Hayashi⁸⁻¹², Stoltz¹³, Fletcher¹⁴, and Baran²³. Very recently, our group has developed an efficient and modular synthesis of PGs (Scheme S1)²⁴. Crucial to our success was the stereocontrolled synthesis of the key lactone intermediate **7a** via a chiral spiro-phosphoric acid-catalyzed Baeyer-Villiger (B-V) oxidation of bicyclic ketone **6a** (Scheme S1).

Fig. 1 Structure of select prostaglandins: cloprostenol (1), bimatoprost (2), PGF_{2α} (3), fluprostenol (4), and travoprost (5).

The past two decades have witnessed the rapid development of biocatalysis into a sophisticated technology, mainly thanks to the ever-increasing bioinformatics and protein engineering tools²⁵⁻³¹. Compared to chemocatalysis, biocatalysis usually offers unparalleled chemo-, regio-, and stereoselectivity pivotal for efficient synthesis of complex molecules like pharmaceuticals and bioactive natural products^{29,30,32}. To harness the synthetic potential of these extraordinary selectivities and other advantageous properties inherent to biocatalysis (e.g. mild reaction conditions) more productively, Turner introduced the concept of biocatalytic retrosynthesis to the scientific community about seven years ago²⁵, which has since been widely and increasingly utilized when planning synthetic routes to target molecules³³⁻⁴². From retrosynthetic viewpoint, a biocatalytic reaction can be adopted in two distinct ways: either being used as an alternative approach to replace an equivalent chemical step, or being employed to fulfill a disconnection which is impossible to realize by traditional chemical means²⁵. As an example in the former scenario, ketoreductase (KRED)-catalyzed stereoselective reduction was demonstrated to be a milder and more sustainable process compared to (-)-DIP-Cl-mediated reduction, in the synthesis of a key chiral alcohol intermediate to the active pharmaceutical ingredient (API) montelukast⁴³. So far, the latter scenario has been less exploited²⁵. Recently, a regio- and stereoselective transformation from prochiral ketoenones to 2,6-disubstituted piperidines, a formidable task for classical chemical methods, was accomplished via an ω -transaminase triggered intramolecular aza-Michael reaction and subsequent epimerization³³. Continuing our interests in the development of efficient, stereoselective, and green synthesis of PGs, as well as application of biocatalysis to organic synthesis^{44,45}, herein we report a tractable, chemoenzymatic total synthesis of prostaglandins guided by biocatalytic retrosynthesis.

Results

Biocatalytic retrosynthesis. In our biocatalytic retrosynthesis (Fig. 2), cloprostenol (**1**), bimatoprost (**2**), PGF_{2α} (**3**), and fluprostenol (**4**), prostaglandins containing an allylic alcohol moiety on the ω-side-chain, could be synthesized from lactones **13a-13d** through a three-step sequence of *p*-phenylbenzoyl (PPB) ester hydrolysis, DIBAL-H reduction, and Wittig olefination. We envisioned that the crucial stereogenic center of the ω-side-chain of **13a-13d** could be installed via a KRED-catalyzed diastereoselective reduction of enones **12a-12d**, which were prepared from C₁₁-OH-PPB-protected Corey alcohol **11** (prostaglandin numbering) through primary alcohol oxidation, followed by Horner-Wadsworth-Emmons (HWE) olefination. It was hoped that **11** might be furnished via a catalyst-controlled regioselective *p*-phenylbenzoylation of the C₁₁-OH of the known diol **10**⁴⁶⁻⁴⁹, which was synthesized from lactone **7a** via a three-step sequence of dechlorination, Prins reaction, and deformylation. At this stage, the key lactone **7a** was envisioned to be accessible through a Baeyer-Villiger monooxygenase (BVMO)-catalyzed stereoselective oxidation of bicyclic ketone **6a**. Notably, our previous study on chiral spiro-phosphoric acid-catalyzed B-V oxidation suggested it was beneficial to introduce the dichloro functionality into the cyclobutanone ring of **6a**. Firstly, formation of normal lactone (NL) **7a** becomes more favored because of the electron-withdrawing effect of the dichloro group (Scheme S1). Secondly, the formed abnormal lactone (AL) **8** could be readily converted to the easily removable cyclopentene dicarboxylic acid **9** during the reaction workup, thus facilitating the isolation of the desired **7a** (Scheme S1). Finally, travoprost (**5**) can be synthesized from fluprostenol (**4**) via a late-stage *i*-propyl ester formation reaction⁶.

Fig. 2 Biocatalytic retrosynthesis of prostaglandins 1-4.

CHMO_{Rhodo1}-catalyzed oxidation of bicyclic ketones 6. Our study commenced with the development of a feasible BVMO-catalyzed stereoselective oxidation of **6a**, which has not yet been reported, to the best of our knowledge. In contrast, bicyclo[3.2.0]hept-2-en-6-one (**14**), a bicyclic ketone lacking the dichloro functionality in comparison to **6a**, was routinely employed as the model substrate in BVMO-catalyzed oxidation reactions (Scheme S2)⁵⁰⁻⁵². A regiodivergent conversion of **14** has been observed for most BVMOs, resulting in the formation of the enantioenriched NL **15** and AL **16** in similar amounts (Scheme S2). Under such circumstance, the separation of **15** and **16** is troublesome. Occasionally, BVMO with regio- plus enantioselectivity towards **14** has been disclosed. For instance, the Grogan group has reported that BVMO-MO14, an enzyme originating from *Rhodococcus jostii*, was able to catalyze the resolution of **14** to furnish NL **15** and the residual enantiomer of **14** both with excellent enantiomeric purity (Scheme S2)⁵³. In the present study, three “regiodivergent” BVMOs, namely CHMO_{Rhodo1}⁵⁴, CHMO_{Arthro}⁵⁴, and

CHMO_{Brevil}⁵⁵, as well as the “regioselective” enzyme BVMO-MO14, are examined in the oxidation of **6a**. On one hand, moderate to high conversion of **6a** and formation of trace-amounts of the desired **7a** ($\leq 5\%$) were observed in the CHMO_{Arthro}-, CHMO_{Brevil}-, and BVMO-MO14-catalyzed reactions (Table S2). On the other hand, **6a** was completely consumed in the CHMO_{Rhodol}-catalyzed reaction, but the yield of **7a** was only 25% (Table 1, entry 1, also see Table S2), much lower than 50% maximum theoretical yield for a resolution event. To account for this mass imbalance, we investigated the stability of **6a** and *racemic-7a*. In the absence of BVMO, it was found that **6a** and *racemic-7a* decomposed readily, with only 58% and 66% remaining, respectively, after incubation for 90 minutes (Figure S5). Presumably, the electron-withdrawing dichloro group makes the carbonyl more electron-deficient, hence rendering **6a** and **7a** more susceptible to hydrolysis. To improve the yield of **7a**, CHMO_{Rhodol}-catalyzed oxidation reactions were carried out under different pHs (Table 1, entry 2 and 3) or at different temperatures (Table 1, entry 4 and 5). No significant improvement was achieved. Next, five organic solvents were screened in an effort to mitigate decomposition and increase product yield (Table 1, entry 6-10). To our delight, the use of methyl tert-butyl ether (MTBE) and 2-methoxyethanol (MME) significantly increased the yield of **7a** to 38% and 36%, respectively. Not only the yield, but the enantiomeric purity of **7a** were revealed to be dependent on the co-solvents employed. While the use of MTBE resulted in an inferior enantiomeric purity (73% ee), no adverse effect was observed when using MME. Hence, the latter solvent was chosen for the remaining study. Gratifyingly, a preparative-scale oxidation of **6a** under the above optimized condition furnished the desired **7a** in 38% isolated yield with 99% ee (Table 1, Entry 11). Notably, thus generated **7a** possessed a superior enantiomeric purity to that prepared using our chiral spiro-phosphoric acid catalysis method (99% ee versus 95% ee), highlighting the stereoselectivity advantage of using enzyme

catalysis. The chemical structure and the stereochemical assignment of **7a** were unambiguously established by X-ray crystallography. Cyclopentene dicarboxylic acid **9**, resulting from the hydrolysis of abnormal lactone **8**, was isolated in 35% yield.

Table 1. CHMO_{Rhodo1}-catalyzed oxidation of **6a.^a**

Entry	Co-solvent	pH	6a remained (%) ^b	yield of 7a (%) ^b	Ee of 7a (%) ^c
1	N.A. ^d	7.5	0	25	99
2	N.A.	7.0	0	26	N.D. ^e
3	N.A.	6.5	6	26	N.D.
4 ^f	N.A.	7.5	0	22	N.D.
5 ^g	N.A.	7.5	0	22	N.D.
6	Cyclohexane	7.5	23	23	N.D.
7	DMSO	7.5	0	28	N.D.
8	MTBE	7.5	0	38	73
9	Dioxane	7.5	0	32	82
10	MME	7.5	0	36	99
11 ^h	MME	7.5	0	40 (38 ⁱ)	99

^aReaction conditions (1 mL): **6a** (10 mM), glucose (60 mM), NADP⁺ (0.2 mM), FAD (0.05 mM), 0.79 mL of 20% (w/v) cell-free extract (CFE) of CHMO_{Rhodo1} in NaPi buffer (50 mM), 0.016 mL of 15% (w/v) CFE of glucose dehydrogenase (GDH) in NaPi buffer (50 mM, pH 7.0), and 0.1 mL co-solvent (if applicable) in NaPi buffer (50 mM). Reaction mixtures were incubated at 25 °C with 200 rpm shaking for 90 min. ^bDetermined by GC analysis using undecane as the internal standard. ^cDetermined by SFC analysis. ^dNot Applicable (N.A.). ^eNot Determined (N.D.). ^fThe reaction temperature was 30 °C. ^gThe reaction temperature was 35 °C. ^hThe reaction volume was 50 mL. ⁱIsolated yield.

Other bicyclic cyclobutanones were employed as substrates to evaluate the feasibility of CHMO_{Rhodo1}-catalyzed oxidation reaction (Fig. 3). Firstly, ketone **6b** without an olefin moiety was well recognized by CHMO_{Rhodo1}, furnishing the desired normal lactone **7b** in 30% isolated yield with 99% ee. Secondly, the size of the fused ring seemed to play an important role in this enzyme-catalyzed B-V oxidation process. For instance, the oxidation of substrates containing a 5-membered or 6-membered fused ring (**6b**, **6c**, **6d**, **6e**) occurred smoothly, affording the corresponding lactones **7b**, **7c**, **7d**, and **7e** in 22-34% isolated yield with 91-99% ee. However, ketone **6f** with an 8-membered fused ring could not be converted by CHMO_{Rhodo1} and no desired lactone **7f** was detected. It is possible that the overlarge size of this fused ring prevents a proper binding of **6f** to CHMO_{Rhodo1}.

Fig. 3 Substrate scope of CHMO_{Rhodo1}-catalyzed B-V oxidation of bicyclic cyclobutanones.

Synthesis of diol **10 in continuous flow.** The transformation of **7a** into the known diol **10** was realized via a three-step sequence in flow chemistry, which was significantly more time-

economical compared to batch reactions (Fig. 4)²⁴. Firstly, a continuous flow dechlorination of **7a** was accomplished in a packed bed reactor (Shenzhen E-zheng tech Co., Ltd) filled with zinc powder at 70 °C under 7 bar back-pressure with 10 min residence time, giving NL **15** in 90% yield. Then NL **15** was dissolved in a 10 : 1 HCOOH/H₂SO₄ solution containing pre-dissolved paraformaldehyde, and the mixture was pumped into a 0.5 mL PTFE reactor coil (i.d. = 0.8 mm) at 70 °C under 17 bar back-pressure with 15 min residence time to afford crude **17** as the major product with full conversion by Prins reaction. After neutralization and removing the inorganic salt, the crude **17** in MeOH combined with NaOMe was pumped into a 0.5 mL PTFE reactor coil via a *T*-junction to complete deformylation followed by quenching with AcOH to give diol **10** smoothly in 81% yield over two steps (Fig. 4).

Fig. 4 Conversion of lactone **7a** into diol **10** in continuous flow.

Regioselective *p*-phenylbenzoylation of diol **10.** With access to diol **10**, the site-selective protection of C₁₁-OH could now commence. In the traditional total synthesis of PGs, the three-step choreography of protecting group manipulations of diol **10** would establish a C₁₁-OH-protected Corey alcohol motif present within PGs, aiding purification and imparting chemoselectivity in subsequent transformations⁵⁶⁻⁵⁸. However, this strategy is not step-economic for PG synthesis. To circumvent this limitation, we recently developed a directly regioselective oxidation of the primary alcohol of **10** by using a modified TEMPO/PhI(OAc)₂ protocol into C₁₁-OH non-masked Corey aldehyde for joining the ω-side-chain via Horner-Wadsworth-Emmons (HWE) olefination^{24,59}. While seemingly straightforward, successful implementation of our strategy would not be attractive and practical in the large-scale synthesis of prostaglandins, because the most of oil prostaglandin intermediates obtained in this protecting-group-free chemistry are unstable. Therefore, designing a one-step method for catalyst-controlled site-selective *p*-phenylbenzoylation of C₁₁-OH in **10** would represent a valuable goal that promises to the streamlined access to the stable and nicely crystalline C₁₁-OH-PPB-protected Corey alcohol **11** (Fig. 2)^{60,61}.

With this assumption in mind, the *p*-phenylbenzoylation of diol **10** was first conducted under a typical acylation condition as reported by the Dong group⁶². As summarized in Table 2, monoesters **11** and **18** were both formed in 8% and 16% yields, respectively (entry 1). When the reaction temperature was lowered to -20 °C, only trace amount of **18** (<5%) was obtained (Table 2, entry 2). The use of copper salt and appropriate ligands/additives were previously demonstrated to promote regioselective acylation of substrates containing multiple hydroxyl groups⁴⁶⁻⁴⁹. In the present study, we found CuCl₂ alone could accelerate the reaction, and importantly, the desired **11** was afforded in 48% yield as the major product (Table 2, entry 3). To further improve the

regioselectivity, several additives were tested. While the use of additives **Ad1** and **Ad2** shifted the selectivity to favor the formation of **18** (Table 2, entry 4 and 5), to our delight, the ratio of **11** to **18** was improved to 3.8 : 1 when the *N*-methylated diphenylprolinol silyl ether **Ad3** was attempted (Table 2, entry 6, also see Figure S6 and S7). The desired monoester **11** was isolated in 57% yield. Intriguingly, the application of additives **Ad4** and **Ad5**, the enantiomer and the desilylated analog of **Ad3**, respectively, also gave comparable results (Table 2, entry 7 and 8). The detailed mechanism of this copper (II)-catalyzed regioselective acylation reaction warrants investigation in the future.

Table 2. Regioselective *p*-phenylbenzoylation of diol **10**.^a

Entry	Metal	Additive	Yield of 11 (%) ^b	Yield of 18 (%) ^b	Yield of 19 (%) ^b	Regioisomeric ratio (rr), 11 : 18
1 ^c	N.A. ^d	N.A.	8	16	1	1 : 2
2	N.A.	N.A.	0	<5	0	N.A.
3	CuCl ₂	N.A.	48	18	4	2.7 : 1
4	CuCl ₂	Ad1	13	63	0	1 : 4.8
5	CuCl ₂	Ad2	32	45	3	1 : 1.4

6	CuCl ₂	Ad3	58 (57 ^e)	15	3	3.8 : 1
7	CuCl ₂	Ad4	57	16	4	3.6 : 1
8	CuCl ₂	Ad5	48	14	6	3.4 : 1

^aReaction conditions (1.5 mL): **10** (0.1 mmol), PPBCl (0.1 mmol), DIPEA (0.1 mmol), CuCl₂ (0.1 equiv., if applicable), additive (0.1 equiv., if applicable) in MeCN (1 mL) and DCM (0.5 mL). Reaction mixtures were stirred at -20 °C for 14 h. ^bDetermined by ¹H NMR analysis of the reaction crude using 1,3,5-trimethoxybenzene as the internal standard. ^cReaction run at room temperature. ^dNot Applicable (N.A.). ^eIsolated yield.

Chemoenzymatic total synthesis of cloprostenol (1), bimatoprost (2), PGF_{2α} (3), fluprostenol (4), and travoprost (5). With the key C₁₁-OH-PPB-protected Corey alcohol **11** in hand, we then turned our attentions to efficiently install the ω-side-chain of PGs (Fig. 5). Oxidation of **11** with TEMPO and trichloroisocyanuric acid (TCCA) in ethyl acetate and dimethyl carbonate at 0 °C provided the desired crude C₁₁-OH-PPB-protected Corey aldehyde **20**⁶³⁻⁶⁵, and set the stage for the C₁₃-C₁₄ HWE olefination. Addition of the crude aldehyde **20** to the solutions of phosphonates **21a-21d** in dichloromethane in the presence of 30% aq. NaOH at 0 °C afforded the corresponding enones **12a-12d** in good isolated yields (71-75% over two steps) as a single geometric isomer with an (*E*)-configuration at the newly formed C₁₃-C₁₄ double bond judged by the ¹H NMR spectra analysis⁶⁶⁻⁶⁸.

Stereoselective reduction of the keto functionality of prostaglandin's ω-side-chain is dominated by chemical approaches, with biocatalytic reduction being rarely exploited. Recently, the Romano group reported an efficient and highly diastereoselective synthesis of a key allylic alcohol-containing intermediate to bimatoprost via the yeast *Pichia anomala*-mediated reduction⁶⁹. However, careful optimization of the biotransformation conditions was necessary in order to suppress the competing reduction of the carbon-carbon double bond by the enoate reductase

present in the same yeast. To alleviate this inconvenience, use of KREDs recombinantly over-expressed in *E. coli* should be a viable option. Due to their excellent stereoselectivity, broad substrate spectrum, good stability, and high volumetric productivity, such over-expressed KREDs either in isolated form (purified enzyme or crude-cell lysate) or in whole-cell form, have been widely adopted in the synthesis of pharmaceuticals and bioactive molecules^{43,45,70-72}. To the best of our knowledge, recombinantly over-expressed KRED-catalyzed stereoselective reduction has not yet been reported for PG synthesis.

Table 3. *ChKRED20*-catalyzed reduction of **12a**.^a

Entry	DMSO (v/v, %)	12a (mM)	Conv. (%) ^b	dr (C-15, α : β) ^b
1	3	10	43	97.8 : 2.2
2	5	10	58	97.4 : 2.6
3	10	10	71	96.7 : 3.3
4	20	10	83	93.9 : 6.1
5	10	5	90	97.9 : 2.1
6 ^c	10	5	96 (91 ^d)	97.9 : 2.1

^aReaction conditions (0.5 mL): **12a** (5 mM or 10 mM), glucose (2 equiv. relative to **12a**), NADP⁺ (0.2 mM), *ChKRED20* (1 mg/mL), 0.1 mL of 15% (w/v) cell-free extract (CFE) of GDH, and DMSO (v/v, 3-20%) in KP_i buffer (100 mM, pH 7.0). Reaction mixtures were incubated at 30 °C with 200 rpm shaking for 17 h. ^bDetermined by SFC analysis. ^cThe reaction volume was 40 mL and the reaction time was 33 h. ^dIsolated yield.

To this end, we examined the bioreduction of **12a** using a small library of in-house preserved KREDs (Table S3). Out of 15 enzymes tested, ten could not transform **12a** at all. The conversion of the rest five enzymatic reactions was in the range of 4-43%, with *ChKRED20* giving the best

performance (Table 3, entry 1, also see Table S3)^{73,74}. It was noticed that the low conversion of **12a** was to some extent due to its apparently poor solubility under current reaction conditions, which probably arises from its hydrophobic structure. To help solubilize **12a** and improve the conversion, reactions with larger amount of the co-solvent DMSO were attempted. Indeed, the conversions of **12a** were increased to 58% and 71% (Table 3, entry 2 and 3), respectively, when 5% and 10% of DMSO were used. Although using 20% of DMSO further improved the conversion to 83%, an inferior diastereoselectivity (93.9 : 6.1 dr) was obtained (Table 3, entry 4). On the other hand, decrease of the substrate concentration from 10 mM to 5 mM boosted the reaction conversion to 90%, and importantly the excellent diastereoselectivity (97.9 : 2.1 dr) was retained (Table 3, entry 5). We believe efficient reduction of higher concentration of **12a** would become possible by optimization of the reaction and protein engineering in the future^{28,75}. Pleasingly, *Ch*KRED20-catalyzed reduction of **12a** under the optimized condition at a preparative-scale occurred smoothly, delivering the desired allylic alcohol **13a** in 91% isolated yield with 97.9 : 2.1 dr (Table 3, entry 6). The configuration of the newly generated stereogenic center (C-15, prostaglandin numbering) was assigned to α by comparing to that of **13a** prepared using (-)-DIP-Cl-mediated reduction⁷⁶. From **13a**, hydrolysis of the PPB ester to alcohol, followed by the DIBAL-H mediated reduction of the lactone to the hemiacetal, and a final Wittig olefination furnished cloprostenol (**1**) in 44% over three steps (Fig. 5). The applicability of our developed route was further demonstrated by the synthesis of another four PGs: bimatoprost, PGF_{2 α} , fluprostenol, and travoprost (Fig. 5). When enones **12b**, **12c**, and **12d** with different ω -side-chains were subjected to *Ch*KRED20-catalyzed reduction, the desired allylic alcohols **13b**, **13c**, and **13d** were isolated in 80-90% yields with 87 : 13 to 99 : 1 dr. Analogous to the above synthesis of cloprostenol (**1**), bimatoprost (**2**), PGF_{2 α} (**3**), and fluprostenol (**4**) were prepared from **13b**, **13c**, and **13d** in a three-step sequence with 31%,

63%, and 51% yields, respectively. Finally, the transformation from fluprostenol to travoprost was accomplished in 68% yield by using 2-iodopropane and Cs_2CO_3 in the mixed solvent of DCM and DMF⁶. Our chemoenzymatic synthesis of cloprostenol, bimatoprost, $\text{PGF}_{2\alpha}$, fluprostenol, and travoprost were completed in 11-12 steps from bicyclic ketone **6a** with 2.9-6.5% overall yields.

Fig. 5 Completion of the chemoenzymatic total synthesis of cloprostenol (1), bimatoprost (2), $\text{PGF}_{2\alpha}$ (3), fluprostenol (4), and travoprost (5).

Discussion

In summary, a unified, biocatalytic retrosynthesis-guided route has been developed for the synthesis of cloprostenol (**1**), bimatoprost (**2**), $\text{PGF}_{2\alpha}$ (**3**), fluprostenol (**4**), and travoprost (**5**) from

the readily available dichloro-containing bicyclic ketone **6a** in 11-12 steps with 2.9-6.5% overall yields, featuring a BVMO-catalyzed stereoselective oxidation of **6a** (99% ee), a copper (II)-catalyzed regioselective *p*-phenylbenzoylation of the secondary alcohol of diol **10** (3.8 : 1 rr), and a KRED-catalyzed diastereoselective reduction of enones **12** (87 : 13 to 99 : 1 dr). Compared to chemocatalytic reactions, these two key enzymatic transformations were performed under milder conditions and meanwhile exhibited superior stereoselectivity. Our study not only provides an alternative route to the highly stereoselective synthesis of prostaglandins, but also showcases the usefulness and great potential of biocatalysis in construction of complex molecules.

Methods

General. MeCN was freshly distilled from CaH₂ under N₂. THF was freshly distilled from Na under N₂ using benzophenone as the indicator. Unless otherwise specified, all reagents and solvents were purchased from commercial sources and used as received. ¹H NMR (400 MHz) and ¹³C NMR (100 MHz) spectra were recorded on a Bruker Avance 400 spectrometer in CDCl₃ using tetramethyl silane (TMS) as internal standards. Coupling constant (*J*) values are given in Hz. Multiplicities are designated by the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; br, broad; m, multiplet. Melting points were measured on MP450 full-automatic melting-point apparatus. Products were purified by flash column chromatography on silica gel purchased from Qingdao Haiyang Chemical Co., Ltd. Optical rotations were measured by a Rudolph AUTOPOL I Automatic Polarimeter. EI-MS were recorded on an Agilent 6890N/5975 spectrometer and ESI-MS were recorded on a Waters Micromass Quattro Micro spectrometer. HRMS (ESI) were recorded on a Bruker micrOTOF spectrometer. HPLC analysis were performed with SFC (Agilent 1260 Infinity II) using Daicel Chiralpak IA column (25 cm × 4.6 mm × 5 μm),

Chiralpak IF-3 column (25 cm × 4.6 mm × 5 μm), Chiralpak AD-H column (25 cm × 4.6 mm × 5 μm) and Chiralpak OD-H column (25 cm × 4.6 mm × 5 μm).

Data availability

Experimental procedures and characterization data of new compounds are available in Supplementary Information. The X-ray crystallographic data for compound **7a** reported in this study has been deposited at the Cambridge Crystallographic Data Centre (CCDC) under deposition numbers CCDC 1975866. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. Any further relevant data are available from the authors upon reasonable request.

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Author contributions

Z.H. and F.C. conceived and directed the project and wrote the paper with assistance from K.Z. K.Z., M.J., B.Y., G.Z., W.L., P.T. performed the experiments and analyzed the data. All authors discussed the results and commented on the paper.

Additional information

Supplementary information, enzyme information, and chemical compound information are available in the online version of the paper. Reprints and permissions information is available online at www.nature.com/reprints. Correspondence and requests for materials should be addressed to Z.H or to F.C.

Competing interests

The authors declare no competing interests.

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veterinary use

bimatoprost (2)
antiglaucoma
(billion-dollar drug)

PGF_{2α} (3)

fluprostenol (4): R = H
veterinary use
travoprost (5): R = *i*-Pr
antiglaucoma

Figure 1

Structure of select prostaglandins: cloprostenol (1), bimatoprost (2), PGF_{2α} (3) fluprostenol (4), and travoprost (5).

Figure 2

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