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A unified strategy to prostaglandins: chemoenzymatic total synthesis of cloprostenol, bimatoprost, $PGF_{2\alpha}$, fluprostenol, and travoprost guided by biocatalytic retrosynthesis†

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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, $PGF_{2\alpha}$, fluprostenol, and travoprost from the readily available dichloro-containing bicyclic ketone **6a** guided by biocatalytic retrosynthesis, in 11–12 steps with 3.8–8.4% overall yields. An unprecedented 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** (9.3 : 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.

Introduction

Prostaglandins (PGs) are hormone-like lipid compounds often found in animals and human-beings,[1] and they are shown to display a multitude of biological functions. To date, more than 20 PG analogs have been developed as marketed medicines, such as the veterinary drugs cloprostenol (**1**) and fluprostenol (**4**), and antiglaucoma drugs bimatoprost (**2**) and travoprost (**5**) (Fig. 1).[1c] 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 PGs.[1,2] In fact, since Corey's landmark synthesis of prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$, **3**) in the late 1960s,[3] PGs have become one touchstone of state-of-the-art synthetic methodologies,[4] as exemplified in the elegant synthesis recently reported by the groups of Aggarwal,[2,4a–c] Hayashi,[4d–h] Grubbs,[4i] Fletcher,[4j] Nicolaou[4k,l] and Baran.[4m] Our group has developed an efficient and modular synthesis of PGs (Scheme S1†).[5] 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†).

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 tools.[6] Compared to chemocatalysis, biocatalysis usually offers

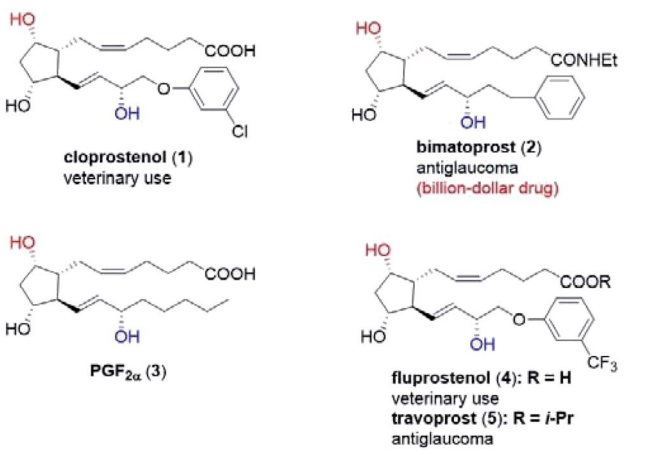

Fig. 1 Structure of selected prostaglandins: cloprostenol (**1**), bimatoprost (**2**), $PGF_{2\alpha}$ (**3**), fluprostenol (**4**), and travoprost (**5**).

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unparalleled chemo-, regio-, and stereoselectivity pivotal for efficient synthesis of complex molecules like pharmaceuticals and bioactive natural products.[6e,f,7] 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 ago,[6a] which has since been widely and increasingly utilized when planning synthetic routes to target molecules.[8] From a 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 means.[6a] 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) montelukast.[9] So far, the latter scenario has been less exploited.[6a] 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 epimerization.[8a] In continuation of our interest in the development of efficient, stereoselective, and green synthesis of PGs, as well as application of biocatalysis to organic synthesis,[10] herein we report a tractable, chemoenzymatic total synthesis of prostaglandins guided by biocatalytic retrosynthesis.

Results and discussion

In our biocatalytic retrosynthesis (Fig. 2), cloprostenol (**1**), bimatoprost (**2**), $PGF_{2\alpha}$ (**3**), and fluprostenol (**4**), prostaglandins

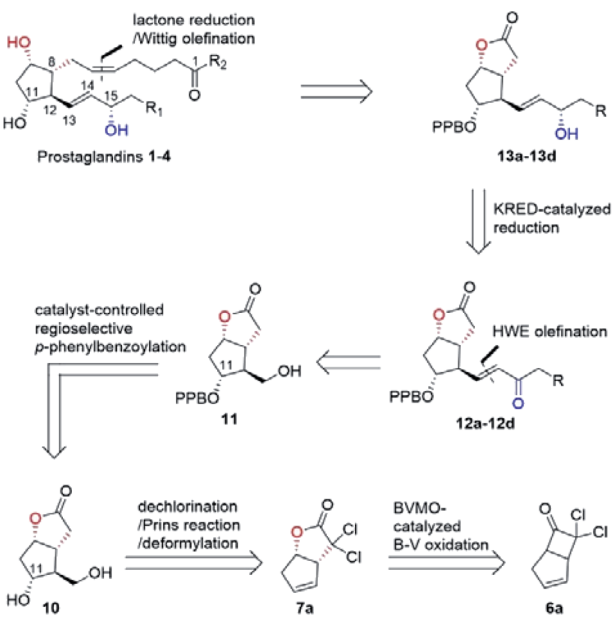
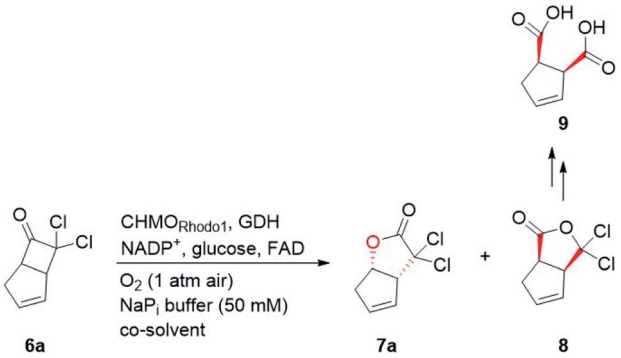


Fig. 2 Biocatalytic retrosynthesis of prostaglandins **1**–**4**.

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 C_{11}-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 C_{11}-OH of the known diol **10**,[11] which was synthesized from lactone **7a** *via* a three-step sequence of dechlorination, the 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**. Finally, travoprost (**5**) can be synthesized from fluprostenol (**4**) *via* a late-stage i-propyl ester formation reaction.[4b]

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†).[12] A regiodivergent conversion of **14** has been observed for most BVMOs, resulting in the formation of the enantioenriched normal lactone (NL) **15** and abnormal lactone (AL) **16** in similar amounts (Scheme S2†). Under such circumstances, the separation of **15** and **16** is troublesome. On the other hand, our previous study on chiral spiro-phosphoric acid-catalyzed B–V oxidation suggested that it was beneficial to introduce the dichloro functionality into the cyclobutanone ring of **6a**. Firstly, formation of NL **7a** becomes more favored because of the electron-withdrawing effect of the dichloro group (Scheme S1†). Secondly, the formed 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†). Therefore, we were interested in the development of BVMO-catalyzed oxidation of dichloro-containing bicyclic ketone **6a** to lactone **7a**, which has not been reported, to the best of our knowledge. In the present study, three "regiodivergent" BVMOs, namely $CHMO_{Rhodo1}$,[13] $CHMO_{Arthro}$,[13] and $CHMO_{Brevi1}$,[14] as well as the unique "regioselective" enzyme BVMO-MO14 originating from *Rhodococcus jostii*,[15] 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** (≤5%) were observed in the $CHMO_{Arthro}$-, $CHMO_{Brevi1}$-, and BVMO-MO14-catalyzed reactions (Table S2†). On the other hand, **6a** was completely consumed in the $CHMO_{Rhodo1}$-catalyzed reaction, but the yield of **7a** was only 25% (Table 1, entry 1, also see Table S2†), much lower than the 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 (Fig. S5†). Presumably, the electron-withdrawing dichloro group makes the carbonyl more electron-deficient, hence rendering **6a** and **7a** more susceptible to hydrolysis as

Table 1 $CHMO_{Rhodo1}$-catalyzed oxidation of **6a**[a]



Entry	Co-solvent	pH	**6a** remaining[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

[a] Reaction 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 NaP_i buffer (50 mM), 0.016 mL of 15% (w/v) CFE of glucose dehydrogenase (GDH) in NaP_i buffer (50 mM, pH 7.0), and 0.1 mL co-solvent (if applicable) in NaP_i buffer (50 mM). Reaction mixtures were incubated at 25 °C with 200 rpm shaking for 90 min. [b] Determined by GC analysis using undecane as the internal standard. [c] Determined by SFC analysis. [d] Not applicable (N.A.). [e] Not determined (N.D.). [f] The reaction temperature was 30 °C. [g] The reaction temperature was 35 °C. [h] The reaction volume was 50 mL (0.5 mmol scale). [i] Isolated yield.

previously suggested.[16] To improve the yield of **7a**, $CHMO_{Rhodo1}$-catalyzed oxidation reactions were carried out at different pHs (Table 1, entries 2 and 3) or at different temperatures (Table 1, entries 4 and 5). No significant improvement was achieved. Next, five organic solvents were screened in an effort to increase the product yield (Table 1, entries 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 also the enantiomeric purity of **7a** was 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 semi-preparative-scale (0.5 mmol) oxidation of **6a** under the above optimized conditions furnished the desired **7a** in 38% isolated yield with 99% ee (Table 1, entry 11). Hence, we have realized the BVMO-catalyzed oxidation of **6a**, which is prone to hydrolysis, to normal lactone **7a** under buffer conditions in good yield and excellent stereoselectivity for the first time. The chemical structure and the stereochemical assignment of **7a** were unambiguously established by X-ray crystallography (Fig. 3). Cyclopentene dicarboxylic acid **9**, resulting from the hydrolysis of abnormal lactone **8**, was isolated in 35% yield with 82% ee (determined upon derivatization, see Scheme S6† for details).

Other bicyclic cyclobutanones were employed as substrates to evaluate the feasibility of the $CHMO_{Rhodo1}$-catalyzed oxidation reaction (Fig. 3). Firstly, ketone **6b** without an olefin moiety

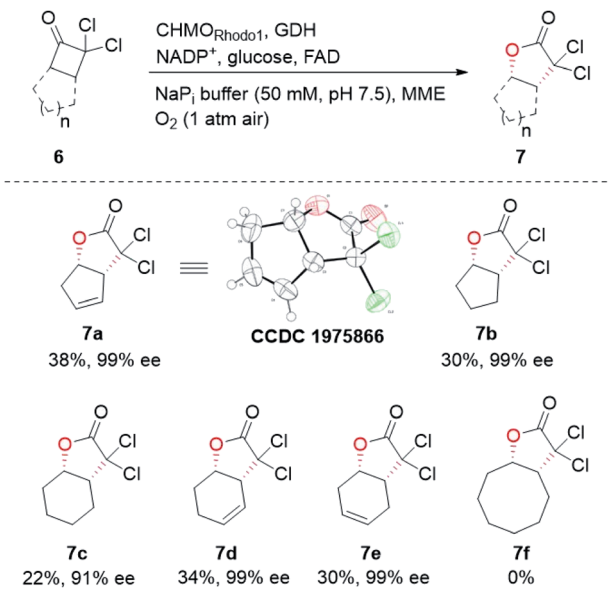


Fig. 3 Substrate scope of $CHMO_{Rhodo1}$-catalyzed B–V oxidation of bicyclic cyclobutanones.

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–6e**) occurred smoothly, affording the corresponding lactones **7b–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 $CHMO_{Rhodo1}$.

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).[5] 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 $HCOOH/H_2SO_4$ 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 the 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).

With access to diol **10**, the site-selective protection of C_{11}-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 C_{11}-OH-protected Corey alcohol motif present within PGs, aiding purification and imparting chemoselectivity in subsequent transformations.[17] 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 to C_{11}-OH non-masked Corey aldehyde for joining the ω-side-chain *via* Horner–Wadsworth–Emmons (HWE) olefination.[5,18] While seemingly straightforward, successful implementation of our strategy would not be attractive and practical in the large-scale synthesis of prostaglandins, because most of the 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 C_{11}-OH in **10** would represent a valuable goal that promises streamlined access to the stable and nicely crystalline C_{11}-OH-PPB-protected Corey alcohol **11** (Fig. 2).[19]

With this assumption in mind, the *p*-phenylbenzoylation of diol **10** was first conducted under typical acylation conditions as reported by the Dong group.[20] 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 a trace amount of **18** (<5%) was obtained (entry 2). The use of copper salt and appropriate ligands/additives was previously demonstrated to promote regioselective acylation of substrates containing multiple hydroxyl groups.[11] In the present study, we found that $CuCl_2$ alone could accelerate the reaction, and importantly, the desired **11** was afforded in 48% yield as the major product (entry 3). To further improve the regioselectivity, several additives were tested. When chiral bisoxazoline compounds **Ad1** and **Ad2**, the two commonly used ligands/additives previously in regioselective acylation reactions,[11] were examined first, the undesired monoester **18** was predominantly generated (entries 4 and 5). To our delight, the use of additives **Ad3–Ad6** containing a pyridine moiety favoured the formation of **11** (entries 6–9). In particular, the ratio of **11** to **18** was improved to 4.3 : 1 when **Ad4** was attempted (entry 7, also see Fig. S6 and S7†). Encouraged by these results, we further designed and synthesized compounds **Ad7–Ad12** based on the structure of **Ad4**. Upon screening (entries 10–15), a regioisomeric ratio of 6.4 : 1 was accomplished by using compound **Ad9** containing a fluorene moiety as the additive (entry 12). Optimization of reaction conditions, including temperature, time, and the amount of DIPEA, further increased the regioisomeric ratio to 9.3 : 1, furnishing the desired monoester **11** in 73% isolated yield (entry 17). Taken together, by using a cheap copper(II) salt and an achiral additive **Ad9**, the regioselective *p*-phenylbenzoylation of diol **10** to the desired monoester **11** was realized in good yield and regioisomeric ratio. We believe that this regioselective *p*-phenylbenzoylation reaction will find wide application in the synthesis of prostaglandins. The detailed mechanism of this copper(II)-catalyzed regioselective acylation reaction warrants investigation in the future.

With the key C_{11}-OH-PPB-protected Corey alcohol **11** in hand, we then turned our attention 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 C_{11}-OH-PPB-protected Corey aldehyde[20,21] and set the stage for the C_{13}–C_{14} HWE olefination. Addition of the crude aldehyde **20** to the

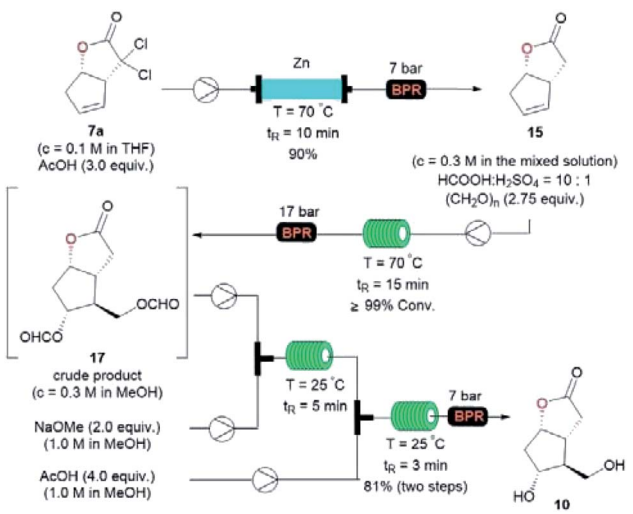
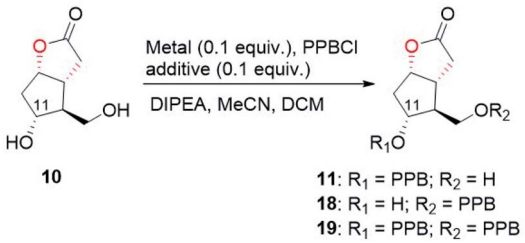
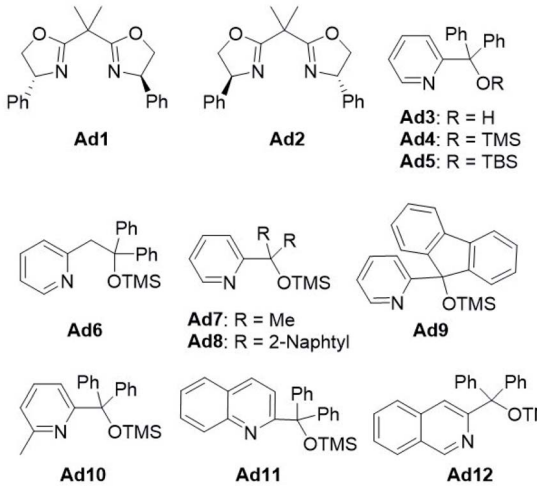


Fig. 4 Conversion of lactone **7a** into diol **10** in continuous flow.

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**	54	14	2	4.0 : 1
7	$CuCl_2$	**Ad4**	57	13	2	4.3 : 1
8	$CuCl_2$	**Ad5**	40	18	2	2.2 : 1
9	$CuCl_2$	**Ad6**	57	20	2	2.9 : 1
10	$CuCl_2$	**Ad7**	59	19	2	3.0 : 1
11	$CuCl_2$	**Ad8**	55	15	3	3.6 : 1
12	$CuCl_2$	**Ad9**	58	9	2	6.4 : 1
13	$CuCl_2$	**Ad10**	49	18	3	2.8 : 1
14	$CuCl_2$	**Ad11**	52	22	2	2.4 : 1
15	$CuCl_2$	**Ad12**	50	17	2	3.0 : 1
16[e]	$CuCl_2$	**Ad9**	66	8	2	8.1 : 1
17[f]	$CuCl_2$	**Ad9**	83 (73[g])	9	2	9.3 : 1

[a] Reaction conditions (1.5 mL): **10** (0.1 mmol), PPBCl (0.1 mmol), DIPEA (0.1 mmol), $CuCl_2$ (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. [b] Determined by ^{1}H NMR analysis of the reaction crude using 1,3,5-trimethoxybenzene as the internal standard. [c] Reaction run at room temperature. [d] Not applicable (N.A.). [e] Stirred at −10 °C for 24 h. [f] Reaction scale (1 mmol), DIPEA (1.2 equiv.), stirred at −10 °C for 60 h. [g] Isolated yield.

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 C_{13}–C_{14} double bond judged by the ^{1}H NMR spectral analysis.[22]

Stereoselective reduction of the keto functionality of the 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 reduction.[23] 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

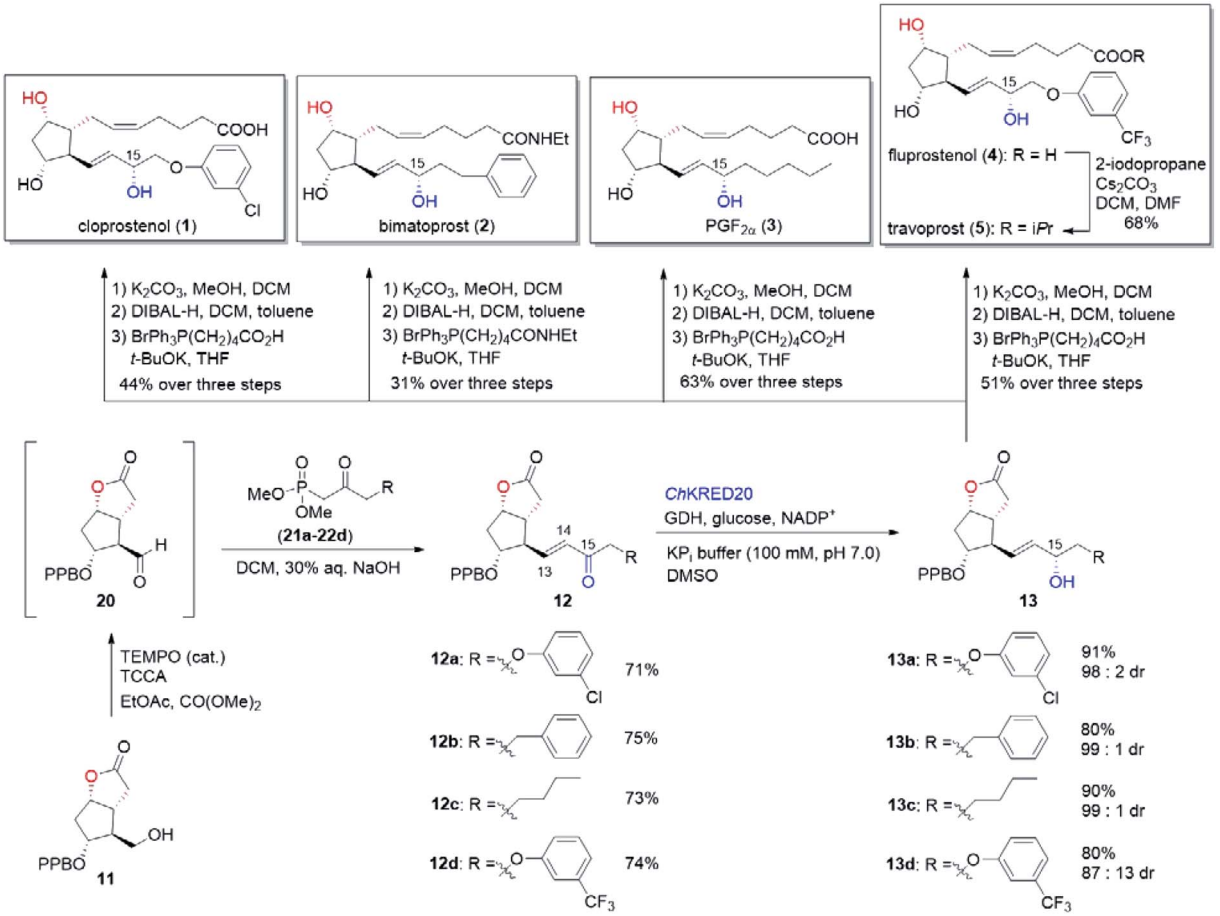
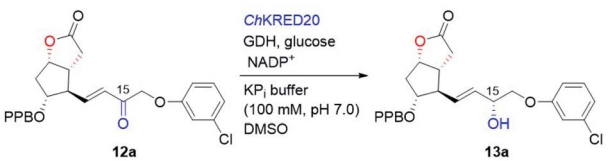


Fig. 5 Completion of the chemoenzymatic total synthesis of cloprostenol (**1**), bimatoprost (**2**), $PGF_{2\alpha}$ (**3**), fluprostenol (**4**), and travoprost (**5**).

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.[9,10b,24] The Pietruszka group has reported an elegant chemoenzymatic total synthesis of travoprost.[25] Ketoreductase was employed to stereoselectively prepare the chiral alcohol containing the ω-side-chain, which was then attached to the cyclopentenone ring *via* a three-component coupling strategy. Recombinantly over-expressed KRED-catalyzed stereoselective reduction of pre-assembled enone intermediates to prostaglandins, such as enones **12**, has not been reported, to the best of our knowledge.

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 *Ch*KRED20 giving the best performance (Table 3, entry 1, also see Table S3†).[26] 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**

Table 3 *Ch*KRED20-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

[a] Reaction conditions (0.5 mL): **12a** (5 mM or 10 mM), glucose (2 equiv. relative to **12a**), $NADP^+$ (0.2 mM), *Ch*KRED20 (1 mg mL^{-1}), 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. [b] Determined by SFC analysis. [c] The reaction volume was 40 mL and the reaction time was 33 h. [d] Isolated yield.

and improve the conversion, reactions with a larger amount of the co-solvent DMSO were attempted. Indeed, the conversions of **12a** were increased to 58% and 71% (Table 3, entries 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 that efficient reduction of the higher concentration of **12a** would become possible by optimization of the reaction and protein engineering in the future.[6d,27] Pleasingly, *Ch*KRED20-catalyzed reduction of **12a** under the optimized conditions at a semi-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 as α by comparing to that of **13a** prepared using (−)-DIP-Cl-mediated reduction.[28] 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, $PGF_{2\alpha}$, fluprostenol, and travoprost (Fig. 5). When enones **12b–12d** with different ω-side-chains were subjected to *Ch*KRED20-catalyzed reduction, the desired allylic alcohols **13b–13d** were isolated in 80–90% yields with 87 : 13 to 99 : 1 dr. Analogous to the above synthesis of cloprostenol (**1**), bimatoprost (**2**), $PGF_{2\alpha}$ (**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 (**4**) to travoprost (**5**) was accomplished in 68% yield by using 2-iodopropane and Cs_2CO_3 in the mixed solvent of DCM and DMF.[4b] Our chemoenzymatic synthesis of cloprostenol (**1**), bimatoprost (**2**), $PGF_{2\alpha}$ (**3**), fluprostenol (**4**), and travoprost (**5**) was completed in 11–12 steps from bicyclic ketone **6a** with 3.8–8.4% overall yields.

Conclusions

In summary, a unified, biocatalytic retrosynthesis-guided route has been developed for the synthesis of cloprostenol (**1**), bimatoprost (**2**), $PGF_{2\alpha}$ (**3**), fluprostenol (**4**), and travoprost (**5**) from the readily available dichloro-containing bicyclic ketone **6a** in 11–12 steps with 3.8–8.4% overall yields, featuring a BVMO-catalyzed stereoselective oxidation of **6a** (99% ee), a time-economical three-step transformation of **7a** into diol **10** using flow chemistry, a copper(II)-catalyzed regioselective *p*-phenylbenzoylation of the secondary alcohol of diol **10** (9.3 : 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.

Data availability

The experimental data is included in the ESI.

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., and P. T. performed the experiments and analyzed the data. All authors discussed the results and commented on the paper.

Conflicts of interest

There are no conflicts to declare.

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