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https://doi.org/10.1038/s41557-021-00706-1
nature chemistry

Concise, scalable and enantioselective total synthesis of prostaglandins

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Prostaglandins are among the most important natural isolates owing to their broad range of bioactivities and unique structures. However, current methods for the synthesis of prostaglandins suffer from low yields and lengthy steps. Here, we report a practicability-oriented synthetic strategy for the enantioselective and divergent synthesis of prostaglandins. In this approach, the multiply substituted five-membered rings in prostaglandins were constructed via the key enyne cycloisomerization with excellent selectivity (>20:1 d.r., 98% e.e.). The crucial chiral centre on the scaffold of the prostaglandins was installed using the asymmetric hydrogenation method (up to 98% yield and 98% e.e.). From our versatile common intermediates, a series of prostaglandins and related drugs could be produced in two steps, and fluprostenol could be prepared on a 20-gram scale.

Prostaglandins (PGs) are widely regarded as among the most important natural isolates ever discovered because of their broad range of bioactivities[1–4] and unique structures. So far, more than 20 prostaglandin analogues have been marketed worldwide[5]. The development of efficient methods to synthesize PGs has been a goal of synthetic chemists for almost 50 years[5,6]. However, current methods for the synthesis of PGs still suffer from low yields and lengthy steps. A concise and scalable synthetic route for more efficient and green production of PGs and related drugs is highly desirable. In this work, multiply substituted five-membered rings in PGs were constructed efficiently via the key enyne cycloisomerization developed by our group[7,8], with excellent stereoselectivity (>20:1 d.r., 98% e.e.). In addition, the crucial chiral centre on the scaffold of the PGs was efficiently installed using the asymmetric hydrogenation method developed by our group (with up to 98% yield and 98% e.e.)[9]. From our common intermediate, a series of PGs and related drugs could be produced in only two steps. Additionally, fluprostenol could be prepared on a 20-g scale from readily available starting materials.

The PGs were discovered in the 1930s by von Euler[10], and their structures were identified in the 1960s by Bergström and colleagues[11–13]. PGs are a family of hormones that play important roles in a wide range of essential biological processes and pathogeneses[1–4,14]. The most complex prostaglandin, $PGF_{2\alpha}$ (**1**, Fig. 1), features a core cyclopentane bearing four contiguous stereocentres and two aliphatic side chains (Fig. 1a). Owing to their unique structures and broad range of biological activities, PGs have drawn extensive interest in basic research and have become popular targets for organic chemists since the 1970s[5,6]. Following Corey's pioneering synthesis of $PGF_{2\alpha}$[15], Woodward[16], Stork[17], Noyori[18], Danishefsky[19], Aggarwal[20], Baran[21], Grubbs[22], Chen[23] and many other groups[24–27] have made important contributions to the development of synthetic strategies for PGs[5,6,28]. From the perspective of applied science, PGs have demonstrated their importance and value in pharmaceutical chemistry. At present, there are more than 20 drugs (such as **2**, **3**, **4**, **5**, **6**, **7** and **8** in Fig. 1a) that are derived from PGs[5], including the billion-dollar drug bimatoprost (**4**; Fig. 1a). The syntheses of some PGs and related drugs[29] have mainly relied on the Corey lactone (**10**)[15], which is prepared from cyclopentadiene (**9**) in nine steps (Fig. 1b). However, additional multi-transformations were needed to access PGs from the Corey lactone (**10**), with some even requiring more than 10 steps[29]. In 2012, Aggarwal et al. described a novel short synthesis of $PGF_{2\alpha}$ via a cascade aldol condensation that could furnish the cyclopentane framework with two adjacent chiral centres in one step[20,30]. Although remarkable progress has been made in the total synthesis of PGs, the development of a concise and scalable route to PGs is still required. In particular, a readily approachable and transformable common intermediate is very much needed for the divergent and flexible synthesis of the whole family of PGs. In this Article, we report a concise and scalable total synthesis of $PGF_{2\alpha}$ (Fig. 1c; only six steps from **11**), as well as several PG-related drugs from readily available starting materials, with enyne cycloisomerization[7,8] and asymmetric hydrogenation as the key steps.

The major challenge in the asymmetric synthesis of PGs is to accurately control the stereochemistry of the four contiguous chiral centres on the core cyclopentane ring and arrange the appropriate functionalities for the installation of the two side chains. In contrast to some powerful ring-formation reactions, such as the Pauson–Khand and Nazarov reactions, that have been devised for furnishing five-membered rings, enyne cycloisomerization can promptly increase the molecule complexity and establish stereocentres in a more predictable way, so it represents another efficient and step-economical technique for the construction of five-membered rings[31]. In 2000, the rhodium-catalysed cycloisomerization of 1,6-enyne was reported by our group[8], and the reaction was termed a name reaction in 2014 (Fig. 2a)[7]. This rhodium-catalysed cycloisomerization reaction has many advantages. On the one hand, excellent enantioselectivities could be achieved during the formation of various hetero or carbocyclic five-membered rings under mild conditions with inexpensive 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP) as the ligand. On the other hand, the regiochemistry and geometry of exocyclic olefins could be specifically controlled, making further manipulations easier.

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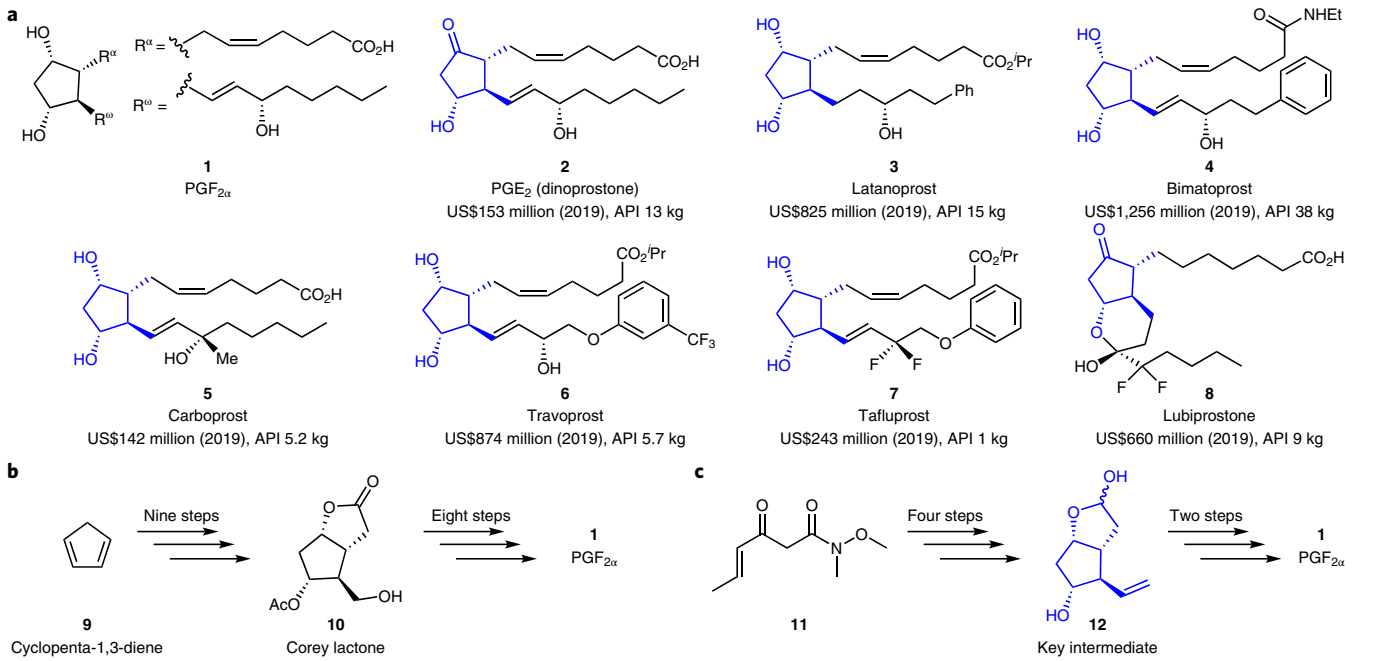

Fig. 1 | PGs and their synthetic methods. a, Representative examples of PGs and related drugs. The sales data were obtained from Clarivate Cortellis Generics Intelligence on 9 July 2020, and the statistical interval is from 1 April 2018 to 31 March 2019 (https://www.cortellis.com/generics). **b**, Corey's synthesis of $PGF_{2\alpha}$ via Corey lactone **10** (ref. [15]). **c**, Our concise synthesis of $PGF_{2\alpha}$ via key intermediate **12**. API, active pharmaceutical ingredient.

As mentioned, we rationalized that our enyne cycloisomerization could serve as a suitable tool for building the core cyclopentane ring of PGs in a more efficient manner than previous synthetic techniques. Here, we propose an ideal intermediate **12** (Fig. 2b), primed with proper functionalities for connection of the two side chains. From this intermediate and with different α- and ω-chains, $PGF_{2\alpha}$-series compounds can be rapidly obtained through Grubbs cross-metathesis and Wittig olefination. Then, intermediate **12** can be traced back to **16** through successive reductions and deprotections. It was obvious that compound **16** is a typical product of our enyne cycloisomerization originating from **17**. By nucleophilic addition, Weinreb amide **18** can be converted to compound **17**. Enantioenriched compound **18** is readily accessible through asymmetric hydrogenation. Furthermore, after conformational analysis, we conclude that the first stereogenic centre was able to induce the other three stereocentres in the PGs.

Results and discussion

As depicted in Fig. 3, we initiated our synthesis of PGs with the asymmetric hydrogenation of the easily available Weinreb amide **11**. Nevertheless, the potential obstacles exceeded those anticipated due to the low reactivity of compound **11** and the instability of the reduced product under certain basic conditions. One apparent side reaction was the retro aldol-type reaction, which released crotonaldehyde. After an extensive screening of the reaction conditions

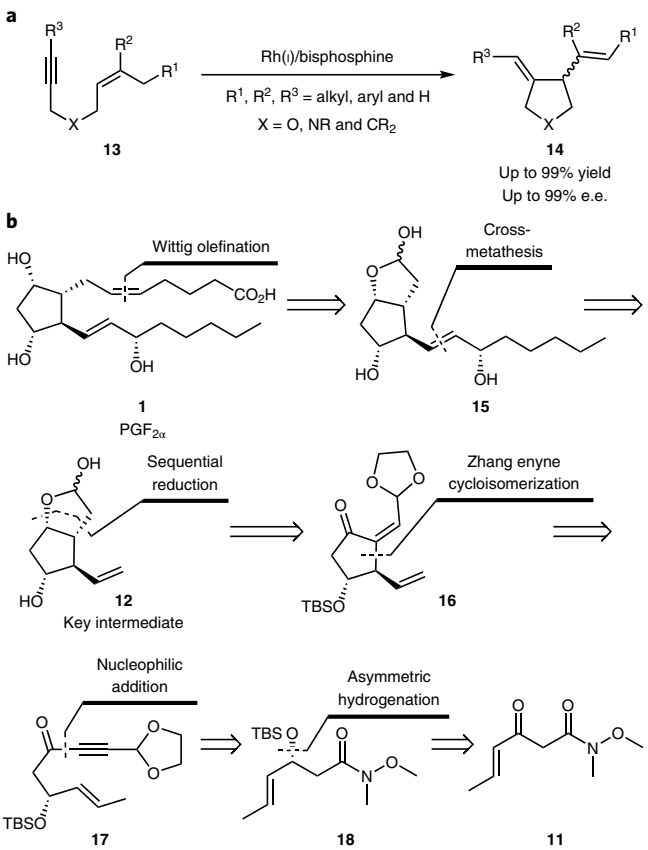

Fig. 2 | Our retrosynthetic analysis based on enyne cycloisomerization. **a**, The enyne cycloisomerization developed by our group can afford various five-membered rings with high yield and enantioselectivity[7,8]. R refers to an electron-withdrawing substituent such as a sulfonyl or ester group. **b**, Retrosynthetic analysis of $PGF_{2\alpha}$ (**1**). The key strategies include (i) Wittig olefination and cross-metathesis for the installation of α- and ω-chains, respectively, (ii) sequential reduction for the construction of two continuous stereocentres, (iii) the key enyne cycloisomerization to assemble the core five-membered ring in $PGF_{2\alpha}$ (**1**), (iv) nucleophilic addition to introduce the alkyne moiety for enyne cycloisomerization, (v) construction of the chiral alcohol via the asymmetric hydrogenation protocol developed by our group. TBS, *tert*-butyldimethylsilyl.

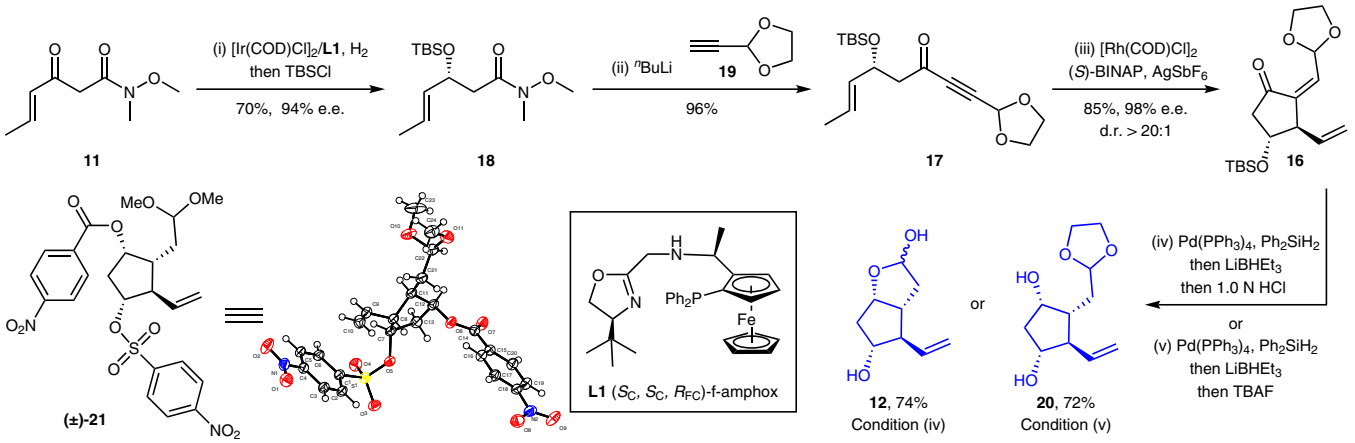

Fig. 3 | Efficient synthesis of key intermediates 12 and 20. Starting material **11** was enantioselectively hydrogenated and protected by TBS in one pot to afford **18**, which was further converted to substrate **17** for enyne cycloisomerization. The expected enyne cycloisomerization reaction of compound **17** proceeded smoothly to give compound **16**. The conjugate double bond and carbonyl group were reduced by Ph_2SiH_2 and $LiBHEt_3$, respectively. The TBS and acetal protecting groups were then removed in aqueous HCl solution to afford **12**, or TBS was detached in tetrabutylammonium fluoride (TBAF) to give **20**. The relative configuration of the key intermediate was determined via single crystal analysis of compound (±)-**21**. Reagents and reaction conditions: (i) $[Ir(COD)Cl]_2$/**L1** (0.1 mol%, S/C = 1,000), KOMe (5 mol%), toluene, 60 atm H_2, room temperature (RT), 24 h; then TBSCl (1.5 equiv.), imidazole (2.0 equiv.), dimethylformamide (DMF), 70%. (ii) ^{n}BuLi (3.5 equiv.), **19** (3.5 equiv.), tetrahydrofuran (THF), −78 °C to −20 °C, 96%. (iii) $[Rh(COD)Cl]_2$ (0.05 equiv.), (*S*)-BINAP (0.1 equiv.), $AgSbF_6$ (0.12 equiv.), 1,2-dichloroethane (DCE), RT, 5 min, 85%. (iv) $Pd(PPh_3)_4$ (0.02 equiv.), $ZnCl_2$ (1.1 equiv.), Ph_2SiH_2 (1.1 equiv.), THF, 50 °C; then $LiBHEt_3$ (3.0 equiv.), −78 °C; then 1.0 N HCl, RT, 74%. (v) $Pd(PPh_3)_4$ (0.02 equiv.), $ZnCl_2$ (1.1 equiv.), Ph_2SiH_2 (1.1 equiv.), THF, 50 °C; then $LiBHEt_3$ (3.0 equiv.), −78 °C; then KF (5.0 equiv.), TBAF (5.0 equiv.), Na_2SO_4, 72%. S/C, substrate/catalyst; TBSCl, *tert*-butyldimethylsilyl chloride; COD, 1,5-cyclooctadiene.

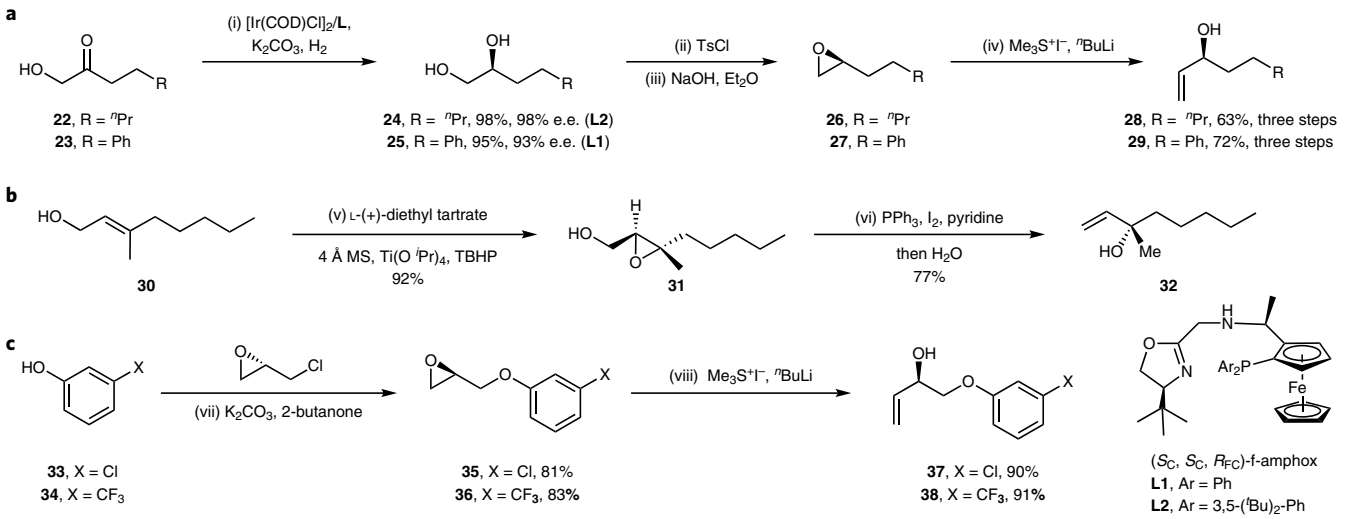

Fig. 4 | Highly efficient synthesis of the ω-chains of PGs. a, Synthesis of side chains **28** and **29**. The α-hydroxyl ketones **22** and **23** were reduced via our asymmetric hydrogenation protocol and converted to epoxides **26** and **27** via selective protection and intramolecular substitution. The epoxides were then transformed into terminal alkenes **28** and **29**. **b**, Synthesis of side chain **32**. The enantioenriched tertiary alcohol **32** was synthesized from **30** in two steps, which includes an asymmetric Sharpless epoxidation. **c**, Synthesis of side chains **37** and **38**. **37** and **38** were prepared from readily available epichlorohydrin and substituted phenols in two steps. The phenols first attack the terminal carbon of the epoxides, which results in the reversion of the configurations of the epoxides. Reagents and reaction conditions: (i) $[Ir(COD)Cl]_2$/**L2** (0.1 mol%) for **22**, $[Ir(COD)Cl]_2$/**L1** (0.1 mol%) for **23**, K_2CO_3 (1 mol%), ^{i}PrOH, 50 atm H_2, RT, 24 h, S/C = 1,000. (ii) TsCl (1.1 equiv.), pyridine (1.5 equiv.), DCM, RT. (iii) NaOH (5.0 equiv.), Et_2O. (iv) $Me_3S^+I^-$ (5.0 equiv.), ^{n}BuLi (5.0 equiv.), THF. (v) L-(+)-diethyl tartrate (0.6 equiv.), 4-Å MS, $Ti(O^iPr)_4$ (0.5 equiv.), TBHP (2.0 equiv.), DCM, −20 °C, 92%. (vi) PPh_3 (3.0 equiv.), I_2 (2.0 equiv.), pyridine (3.8 equiv.), 0 °C; then H_2O (1.0 equiv.), 40 °C, 77%. (vii) K_2CO_3 (2.0 equiv.), 2-butanone, 120 °C. (viii) $Me_3S^+I^-$ (5.0 equiv.), ^{n}BuLi (5.0 equiv.), THF. TBHP, *tert*-butyl hydroperoxide; TsCl, *p*-toluenesulfonyl chloride.

(Supplementary Table 1 provides details), Ir(I)/f-amphox was found to be the best catalyst, and compound **11** could be hydrogenated and protected by TBS in one pot to produce compound **18** in 70% yield and 94% e.e. (substrate/catalyst = 1,000). In the next step, the nucleophilic addition of lithiated **19** to Weinreb amide **18** provided 1,6-enyne **17** in 96% yield. Four other 1,6-enyne substrates bearing different alkyne moieties (for example, diethylacetal propiolaldehyde, triethylsilyl propargyl alcohol, trimethylsilylacetylene and

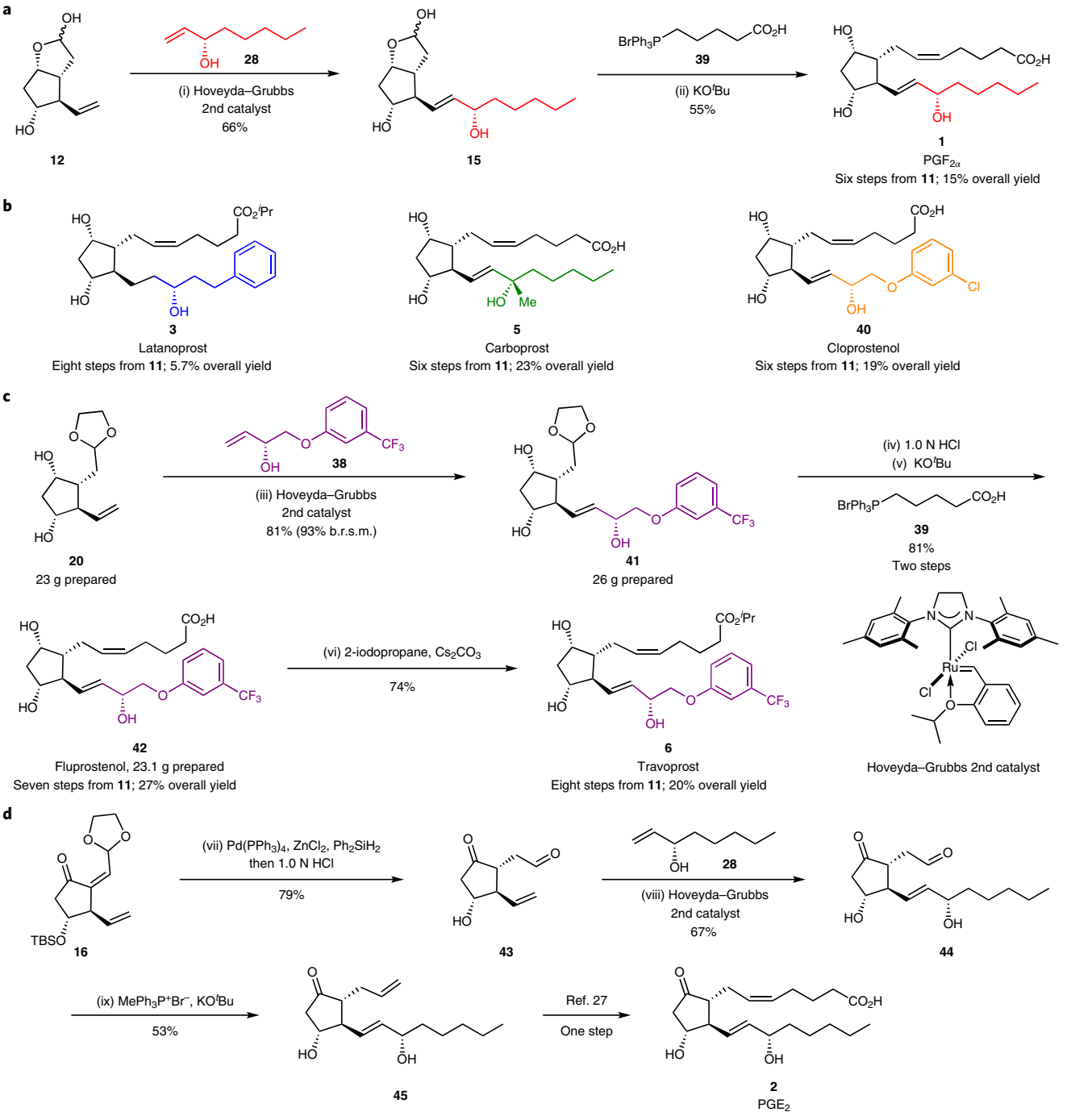

Fig. 5 | Completion of the total synthesis of PGs. a, Completion of the total synthesis of $PGF_{2\alpha}$. The synthesis of $PGF_{2\alpha}$ was accomplished after orthogonal cross-metathesis and the Wittig reaction. **b**, Following similar operations, intermediate **12** was successfully converted to latanoprost (**3**), carboprost (**5**) and cloprostenol (**40**). **c**, The 20-g scale synthesis of fluprostenol and travoprost. Because intermediate **20** is more stable than intermediate **12**, we scaled up the synthesis utilizing intermediate **20**. **d**, Formal synthesis of PGE_2 (**2**). Reduction of the conjugate double bond and deprotection gave **43**. Compound **43** underwent a cross-metathesis and the Wittig reaction to afford **45**, which has been used in the synthesis of PGE_2[27]. Reagents and reaction conditions: (i) Hoveyda–Grubbs second catalyst (0.2 equiv.), **28** (10.0 equiv.), DCM, 66%. (ii) KO^{t}Bu (16.0 equiv.), **39** (8.0 equiv.), THF, RT, 55%. (iii) Hoveyda–Grubbs second catalyst (0.07 equiv.), **38** (3.0 equiv.), 81% (93% based on recovered starting material, b.r.s.m.). (iv) 1.0 N HCl, THF, RT. (v) KO^{t}Bu (16.0 equiv.), **39** (8.0 equiv.), THF, RT, 81%, two steps. (vi) 2-iodopropane (2.0 equiv.), Cs_2CO_3 (1.5 equiv.), DMF, RT, 74%. (vii) $Pd(PPh_3)_4$ (0.02 equiv.), $ZnCl_2$ (1.1 equiv.), Ph_2SiH_2 (1.1 equiv.), THF, 50 °C; then 1.0 N HCl, RT, 79%. (viii) Hoveyda–Grubbs second catalyst (0.2 equiv.), **28** (10.0 equiv.), DCM, 67%. (ix) $MePh_3P^+Br^-$ (3.0 equiv.), KO^{t}Bu (3.0 equiv.), THF, RT, 55%.

free acetylene) were also obtained (see Supplementary Fig. 3 for details). Under the standard protocol, only the cycloisomerization of substrate **17** proceeded smoothly to afford the desired product in high yield. (*S*)-BINAP matched better with the enyne substrate by delivering **16** in 85% yield and 98% e.e. By contrast, (*R*)-BINAP could only give **16** with <10% yield and 40% e.e. Key intermediates

12 and **20** could be obtained from **16** in one pot by a sequential reduction in the presence of Ph_2SiH_2 and $LiBEt_3H$, followed by full or partial deprotection. This one-pot reaction could also proceed in a stepwise manner (see Supplementary Fig. 2 for details). In the conjugate 1,4-reduction, Ph_2SiH_2 and $Sn(^nBu)_3H$ both have similar performance in gaining excellent diastereoselectivity (d.r. > 20:1). In the later stereocontrolled 1,2-reduction, inexpensive super hydride was found to be the best reductant upon screening. Finally, the TBS and the acetal groups could be removed simultaneously with aqueous HCl solution to afford **12**, or TBS was selectively detached in the presence of tetrabutylammonium fluoride (TBAF) to give **20**. The relative configuration of these two key intermediates was further determined by X-ray crystallographic analysis. The single crystal analysis of compound (±)-**21** derived from racemic **20** showed that all stereocentres exactly matched those of $PGF_{2\alpha}$ (Fig. 3; for details see Supplementary Fig. 4).

We customized different synthetic methods for various ω side chains (Fig. 4). Compounds **22** and **23** could be hydrogenated enantioselectively on a gram scale with the protocol developed by our group[9], with excellent yields and enantioselectivity. The resulting diols **24** and **25** were then transformed into corresponding epoxides **26** and **27** through mono-tosylation and intramolecular nucleophilic substitution. Treatment of the epoxides with deprotonated trimethyl sulfonium iodide led to allylic alcohols **28** and **29**, respectively (Fig. 4a). The chiral tertiary allylic alcohol **32** was conveniently obtained from **30** via Sharpless epoxidation and a subsequent reductive ring-opening reaction (Fig. 4b). Another synthetic route for the ω side chains bearing different aromatic rings was also devised. Substituted phenols **33** and **34** were subjected to epichlorohydrin in the presence of K_2CO_3, affording epoxides **35** and **36** in high yields. Afterwards, following the same operations as employed for **26** and **27**, epoxides **35** and **36** were converted to the relevant allylic alcohols **37** and **38** in 90% and 91% yields, respectively (Fig. 4c).

With the enantioenriched key intermediates **12** and **28**, the cross-metathesis reaction was tested with the assistance of the Hoveyda–Grubbs second-generation catalyst (Fig. 5a)[24]. The desired product **15** was furnished in 66% yield. Finally, hemiacetal **15** underwent a Wittig reaction with phosphonium salt **39** to afford $PGF_{2\alpha}$ in 55% yield. Starting from readily available material **11**, the total synthesis of $PGF_{2\alpha}$ was thus accomplished in six steps from **11** in 15% overall yield. From versatile building block **12**, the synthesis of latanoprost (**3**), carboprost (**5**) and cloprostenol (**40**) were also achieved (Fig. 5b). Latanoprost (**3**) was synthesized in 5.7% overall yield after eight steps from **11** (additional hydrogenation and esterification steps were needed for latanoprost; Supplementary Fig. 6). Carboprost (**5**) and cloprostenol (**40**) were synthesized in 23% and 19% overall yields, respectively, in six steps from **11**. According to our investigation, intermediate **20** was more stable under cross-metathesis conditions and usually resulted in higher yields than **12**. A one-more-step longer yet more scalable route was thus invented based on intermediate **20**. Taking the cross-metatheses of **20** and **38** as representative, 26 g of acetal **41** could be obtained in 81% yield (93% based on recovered starting material) from 23 g of intermediate **20**. Hydrolysis of the acetal **41** in aqueous HCl followed by Wittig olefination gave 23.1 g of fluprostenol (**42**) in 81% yield. Travoprost (**6**) was then gathered in 74% yield after a simple esterification.

In addition, the formal synthesis of PGE_2 (**2**) from **16** was also established (Fig. 5d). Another useful intermediate (**43**) possessing a carbonyl group was obtained by conjugated 1,4-reduction and simultaneous deprotection in one pot. Following cross-metathesis of **43** and allylic alcohol **28**, compound **44** was produced in 67% yield. This precursor renders PGs containing carbonyl groups, such as PGA, PGB and PGE[6], relatively easier to access. In an effort to obtain PGE_2 directly, **44** was subjected to phosphonium salt **39**, adhering to many classic Wittig olefination protocols. However, all attempts failed and only resulted in the decomposition of **44**. Fortunately, the aldehyde could be converted to terminal alkene (**45**) with moderate yield. PGE_2 (**2**) could be obtained after one-step *cis*-cross-metathesis of **45** according to the reported procedure[27].

Conclusion

In summary, we have successfully achieved the short, highly enantioselective and scalable syntheses of PGs with our enyne cycloisomerization as the key step from readily available starting materials. In this synthesis, the asymmetric hydrogenation protocol developed by our group played a critical role in introducing key stereogenic centres. All reactions could be carried out on a multi-gram scale and most on a decagram scale. Additionally, our common intermediates in this work, alongside various α and ω side chains, facilitated the divergent synthesis of PGs. These versatile common precursors will help to expand the existing chemical space of PGs and provide access to more promising therapeutic analogues. We have also shown that the key enyne cycloisomerization could offer a strategic insight into designing synthetic routes towards multi-functionalized five-membered rings. In particular, this work has a high possibility to be developed into industrial production.

Online content

Any methods, additional references, Nature Research reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at https://doi.org/10.1038/s41557-021-00706-1.

Received: 26 October 2020; Accepted: 14 April 2021;
Published online: 27 May 2021

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Methods

Procedure for the rhodium-catalysed decagram-scale enyne cycloisomerization. In an argon-filled glovebox, to a solution of **17** (17.3 g, 53.4 mmol) in degassed 1,2-dichloroethane (900 ml) at room temperature we successively added $[Rh(COD)Cl]_2$ (1.3 g, 2.67 mmol), (*S*)-BINAP (3.3 g, 5.34 mmol) and $AgSbF_6$ (2.2 g, 6.41 mmol). The mixture was stirred for 5 min at room temperature. The resulting mixture was filtered over a pad of silica gel then concentrated in vacuo. The crude residue was purified by silica gel column chromatography (8:1 petroleum ether:ethyl acetate) to give **16** (14.8 g, 45.4 mmol, 85%, 98% e.e.) as a light-yellow oil. The e.e. of the product was determined by HPLC on a Chiralpak OD-H column with hexane:isopropanol = 99:1; flow rate = 1.0 ml min^{-1}; UV detection at 254 nm; t_R = 8.39 min (major), t_R = 10.25 min (minor).

Data availability

Crystallographic data for the structures reported in this Article have been deposited at the Cambridge Crystallographic Data Centre, under deposition no. CCDC 2013314 (compound **21**). Copies of the data can be obtained free of charge via https://www.ccdc.cam.ac.uk/structures/. The experimental procedures and characterization of all new compounds are provided in the Supplementary Information. All other data supporting the findings of this study are available within this Article and its Supplementary Information.

Acknowledgements

X.Z. is indebted to the Southern University of Science and Technology (start-up fund), Shenzhen Science and Technology Innovation Committee (grant no. KQTD20150717103157174), Shenzhen Nobel Prize Scientists Laboratory Project (C17783101), Key-Area Research and Development Program of Guangdong Province (grant no. 2020B010188001), Innovative Team of Universities in Guangdong Province (grant no. 2020KCXTD016) and National Natural Science Foundation of China (grant no. 21991113). G.-Q.C. gratefully acknowledges the Youth Fund from the National Natural Science Foundation of China (grant no. 21901107).

Author contributions

F.Z. contributed to the conception and design of the experiments. F.Z. performed the experiments and analysed the data. F.Z. and J.Z. conducted the gram-scale preparation of fluprostenol. M.G. and L.W. synthesized several intermediates. Y.L. provided useful advice in the synthesis of PGE. F.Z. and G.-Q.C. co-wrote the manuscript. X.Z. and G.-Q.C. conceived and directed the investigations and composed the manuscript, with revisions provided by F.Z.

Competing interests

The authors declare no competing interests.

Additional information

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41557-021-00706-1.

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Peer review information *Nature Chemistry* thanks Fener Chen and the other, anonymous, reviewer(s) for their contribution to the peer review of this work.

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