Concise, Scalable and Enantioselective Total Synthesis of Prostaglandins

Fuhao Zhang
Southern University of Science and Technology
Jingwen Zeng
Southern University of Science and Technology
Mohan Gao
Southern University of Science and Technology
Linzhou Wang
Southern University of Science and Technology
Gen-Qiang Chen
Southern University of Science and Technology
Yixin Lu
National University of Singapore https://orcid.org/0000-0002-5730-166X
Xumu Zhang (zhangxm@sustech.edu.cn)
Southern University of Science and Technology

Article

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Abstract

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

Main Text

Prostaglandins (PGs) are widely regarded as among the most significant natural isolates ever discovered owing to their broad range of bioactivities[1,2,3,4] and unique structures. To date, 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, the current synthesis of PGs still suffers from low yields and lengthy steps, and a concise and scalable synthetic route for a more efficient and green production of PGs and related drugs is still highly desirable. Herein, we report a practicability-oriented synthetic strategy for the enantioselective and divergent synthesis of PGs. In this work, multiply substituted five-membered rings in PGs were constructed efficiently *via* the key Zhang enyne cycloisomerization[7] with excellent selectivity (> 20:1 dr, 98% ee). In addition, the crucial chiral center on the scaffold of PGs was efficiently installed using the asymmetric hydrogenation method developed in our group (up to 98% yield and 98% *ee*)[8]. From our newly-proposed common intermediate, a series of PGs and related drugs could be produced in only two steps. Additionally, fluprostenol could be prepared on a 20-gram scale from readily available starting materials. Our new strategy for the synthesis of PGs will not only promote rapid access to the entire family of PGs but also serve as a versatile platform for synthesizing molecules containing highly functionalized five-membered rings.

Prostaglandins (PGs) were first discovered in the 1930s by von Euler[9], and their structures were identified in the 1960s by Bergström *et al.*[10,11,12]. PGs are a family of hormones that play a significant role in a wide range of essentially biological processes and pathogeneses[1,2,3,4,13]. The most complex prostaglandin, $PGF_{2\alpha}$ (Fig. 1; **1**), features a core cyclopentane bearing four contiguous stereocentres and two aliphatic side chains (Fig. 1a). Owing to their unique structures and broad spectra 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 with Corey's pioneering synthesis of $PGF_{2\alpha}$[14], Woodward[15], Stork[16], Noyori[17], Danishefsky[18], Aggarwal[19], Baran[20], Grubbs[21], Chen[22], and many other groups[22,23,24,25] also made important contributions to the development of new synthetic strategies for PGs[5,6,27]. From the perspective of applied science, PGs have displayed their importance and value in pharmaceutical chemistry. At

present, there are more than 20 drugs that are derived from PGs[5], including the billion-dollar drug bimatoprost (**4**) (Fig. 1a). The synthesis of some PGs and related drugs[28] mainly relies on the Corey[14] lactone (**10**), which was prepared from cyclopentadiene (**9**) in nine steps (Fig. 1b). However, additional multi-transformations were needed to access PGs from Corey lactone (**10**), with some even requiring more than ten steps[28]. In 2012, Aggarwal *et al.* described a novel short synthesis of $PGF_{2\alpha}$ *via* cascade aldol condensation, which could furnish the cyclopentane framework with two adjacent chiral centres in one step; however, low yields remain a great concern[19]. Although remarkable progress has been made in the total synthesis of PGs, the reported syntheses still suffer from low efficiency, lengthy sequences. Usually, these reported methods are also difficult to be scaled up. In particular, a readily approachable and transformable common intermediate is highly needed for achieving a divergent and flexible synthesis of the whole family of PGs. Herein, we report a concise and scalable total synthesis of $PGF_{2\alpha}$ in only 6 steps from readily available starting materials (Fig. 1c) as well as the synthesis of several PGs related drugs.

The major challenge in the asymmetric synthesis of PGs is to accurately control the stereochemistry of the four contiguous chiral centers on the core cyclopentane ring and arrange the appropriate functionalities for the installation of the two side chains. Some powerful ring formation reactions, such as Pauson-Khand reaction and Nazarov reaction[7], have been devised for furnishing five-membered rings. Enyne cycloisomerization can promptly increase the molecule complexity and establish stereocentres in a more predictable way, therefore, it represents another efficient and step-economical technique for the construction of five-membered rings[29]. Notably, the first rhodium-catalyzed cycloisomerization of 1,6-enyne was reported by our group in 2000[30] and was named as Zhang enyne cycloisomerization in 2014 (Fig. 2a)[7]. There are many advantages to this rhodium-catalyzed reaction. On one hand, excellent enantioselectivities could be achieved during the formation of various hetero or carbocyclic five-membered rings under mild conditions with inexpensive BINAP as the ligand. On the other hand, the regiochemistry and geometry of exocyclic olefins could be specifically controlled, allowing further manipulations easier.

As aforementioned, we believe that Zhang enyne cycloisomerization could serve as a suitable tool for building the core cyclopentane ring of PGs in a more efficient manner than that of previous synthetic techniques. Herein, we proposed an ideal standard 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[14]. Then, intermediate **12** could be traced back to **16** through successive reductions and deprotections. It was obvious that compound **16** was a typical product of Zhang enyne cycloisomerization originating from **17**. By nucleophilic addition, compound **17** could be converted to Weinreb amide **18**. The enantioenriched compound **18** was readily accessible through asymmetric hydrogenation, which is in our field of expertise. Furthermore, after conformational analysis, we conclude that the first stereogenic centre was able to induce the three other stereocentres in PGs.

As depicted in Fig. 3, we initiated our synthesis of PGs with the asymmetric hydrogenation of the easily available Weinreb amide **11**. Nevertheless, potential obstacles went beyond our anticipation 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 (see supplementary table S1 for details), Ir(I)/f-amphox was found to be the best catalyst, and compound **11** can be hydrogenated and protected by TBS in one pot to produce compound **18** in 70% yield and 94% *ee* (S/C = 1000). In the next step, the nucleophilic addition of lithiated **19** to Weinreb amide **18** provided 1,6-enyne **17** in 96% yield. Other four 1,6-enyne substrates bearing different alkyne moieties (e.g., diethylacetal propiolaldehyde, triethylsilyl propargyl alcohol, trimethylsilylacetylene, and free acetylene) were obtained as well (see supplementary Figure S3 for details). Under the standard protocol, only the cycloisomerization of substrate **17** proceeded smoothly and afforded the desired product in high yield. (*S*)-BINAP matched better with the enyne substrate by delivering **16** in 85% yield and 98% *ee*. In contrast, (*R*)-BINAP could only give **16** with < 10% yield and 40% *ee*. 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 following a stepwise manner (see supplementary information for details). In the conjugate 1,4-reduction, Ph_2SiH_2 and $Sn(^nBu)_3H$ both have similar performance in gaining excellent diastereoselectivity (dr > 20:1). In the later stereo-controlled 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 TBAF to give **20**. The relative configuration of these two key intermediates was further determined by X-ray crystallographic analysis. The single crystal of compound (±)-**21** derived from racemic **20** showed that all stereocentres exactly matched those of $PGF_{2\alpha}$ (Fig. 3, for details see the supplementary information).

We customized different synthetic methods for various ω side chains (Fig. 4). Compounds **22** and **23** could be hydrogenated enantioselectively on the gram scale with the protocol developed by our group[8] with excellent yields and enantioselectivity. Resulting diols **24** and **25** were transformed into corresponding epoxides **26** and **27** through mono-tosylation and intramolecular nucleophilic substitution. Treatment of deprotonated trimethyl sulfonium iodide with epoxides led to allylic alcohols **28** and **29** (Fig. 4a). The chiral tertiary allylic alcohol **32** was conveniently obtained from **30** *via* Sharpless epoxidation and 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, 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% yield, respectively (Fig. 4c).

With the enantioenriched key intermediates **12** and **28**, the cross-metathesis reaction was tested with the assistance of the Hoveyda-Grubbs 2nd generation catalyst (Fig. 5a)[22]. 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 6 steps from **11** with 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 8 steps from **11** (additional hydrogenation and esterification steps were needed for Latanoprost). Carboprost (**5**), and cloprostenol (**40**) were synthesized in 23% and 19% overall yield, respectively, in 6 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 cross metatheses of **20** and **38** as a representative, 26 g of acetal **41** could be obtained in 81% yield (93% brsm.) 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 would render PGs containing carbonyl groups, such as PGA, PGB and PGE[6], easy 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 a moderate yield. PGE_2 (**2**) could be obtained after one-step *cis*-cross metathesis of **45** according to the reported procedure[25].

Conclusion

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In conclusion, we have successfully achieved the short, highly enantioselective, and scalable syntheses of PGs with Zhang enyne cycloisomerization as the key step from readily available starting materials. In this synthesis, the asymmetric hydrogenation protocol developed in our group played a critical role in introducing key stereogenic centers. 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 would help to expand the existing chemical space of PGs and provide access to more promising therapeutic analogues. We have also presented that the key Zhang enyne cycloisomerization could offer a novel strategic insight into designing new synthetic routes towards multi-functionalized five-membered rings. In particular, this work has a high possibility to be developed into industrial production. Therefore, a new renaissance of new medicinal chemistry programs on PGs is foreseeable.

Declarations

Data availability

The X-ray crystallographic coordinates for structures of **21** (derivative of **12** and **20**) have been deposited at the Cambridge Crystallographic Data Centre (CCDC) under deposition no. CCDC 2013314. The data can be obtained free of charge from the Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif. The experimental procedures and characterization of all new compounds are provided in Supplementary Information. The authors declare that all other data supporting the findings of this study are available within this Article and its Supplementary Information or from the authors upon reasonable request.

Additional information

Supplementary 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 G.-Q. C or to X. Z.

Competing interests

The authors declare no competing interests.

Author contributions

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

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Figures

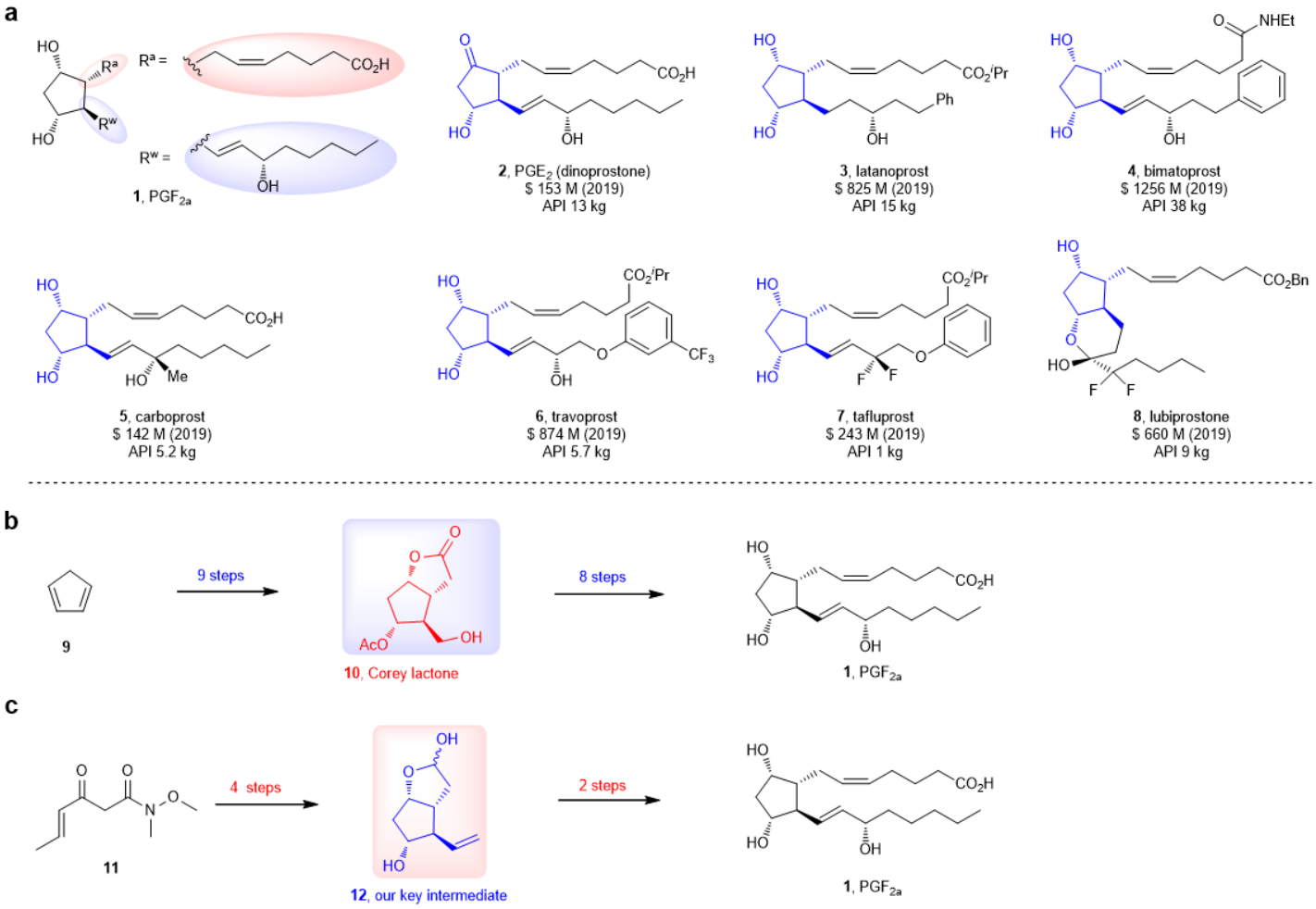
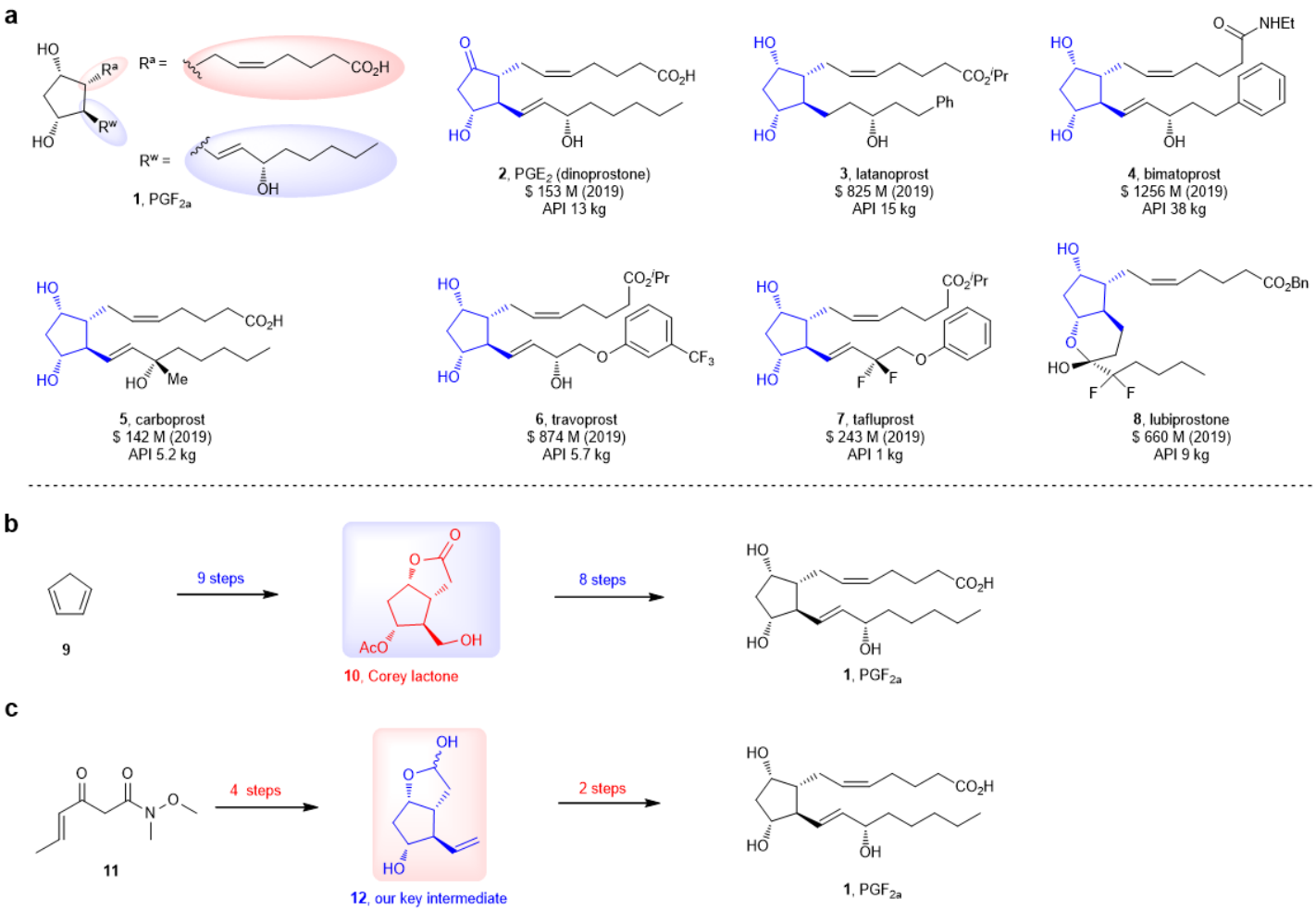


Figure 1

PGs and their synthetic methods. a, Representative examples of PGs and related drugs, the sales data were obtained from IMS database. b, Corey's synthesis of PGF2α via Corey lactone. c, Our concise synthesis of PGF2α via our proposed key intermediate. API, active pharmaceutical ingredient.



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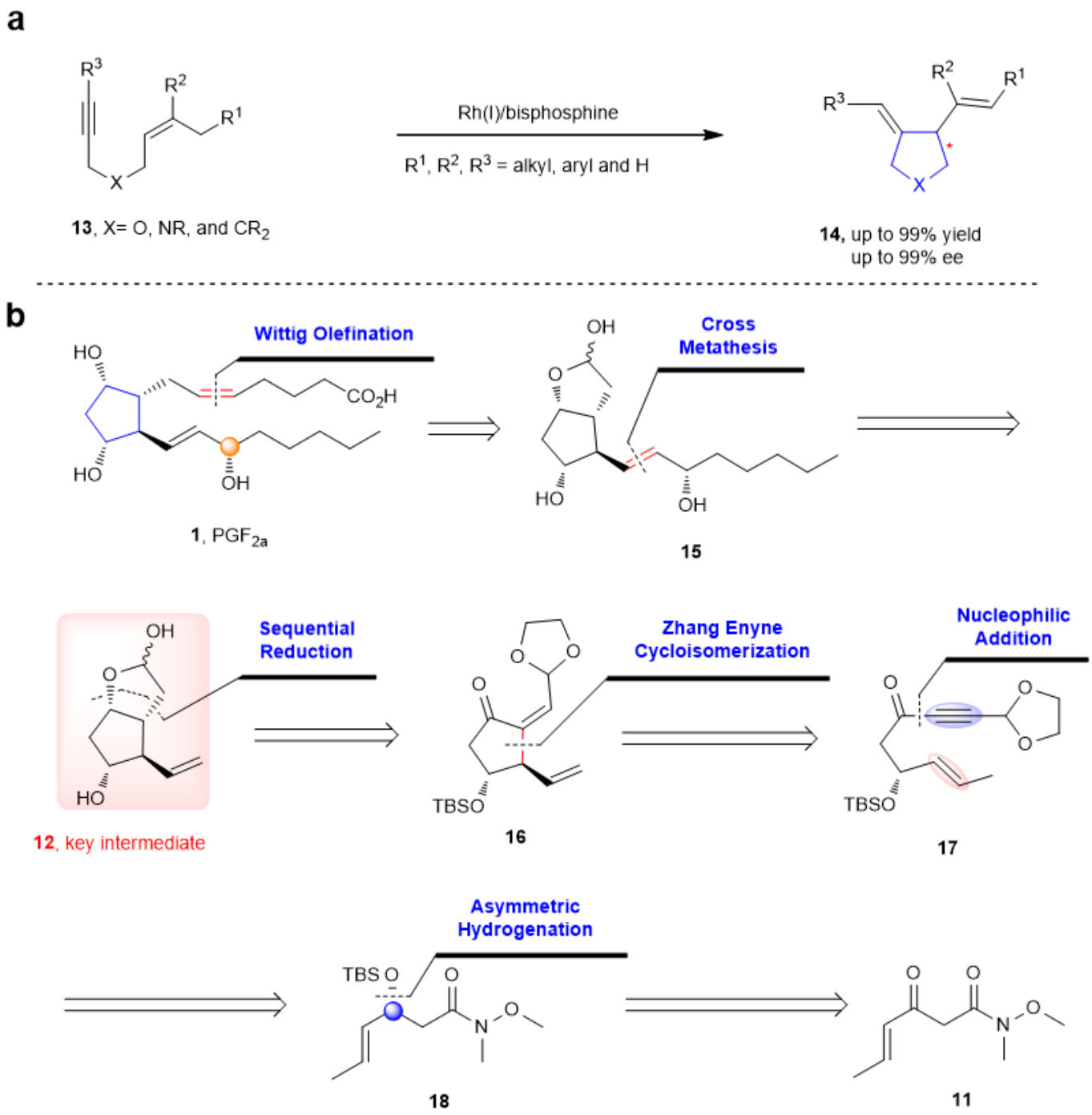
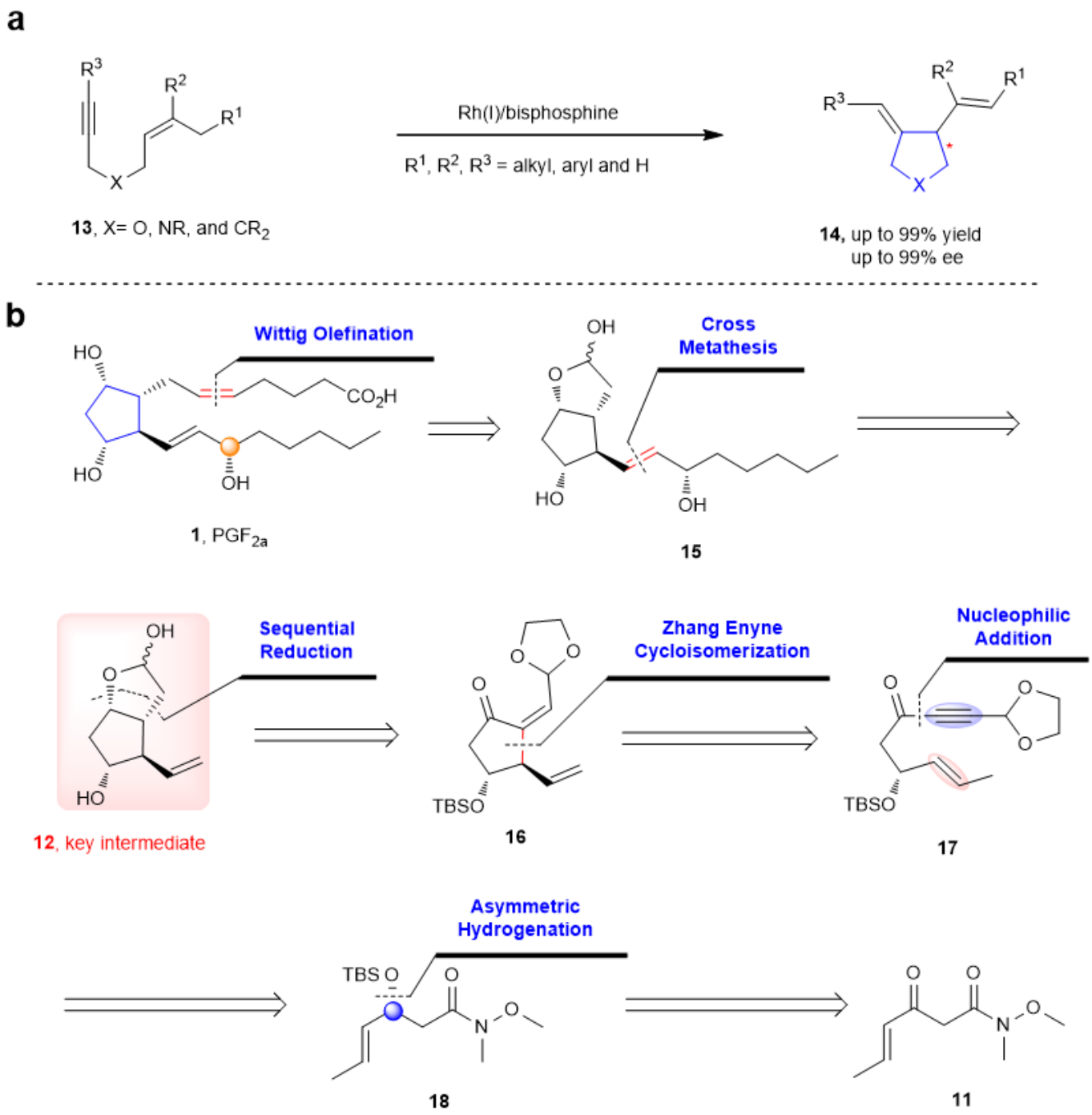


Figure 2

Our retrosynthetic analysis based on Zhang enyne cycloisomerization. a. Zhang enyne cycloisomerization. b. Retrosynthetic analysis. TBS, tert-butyldimethylsilyl.



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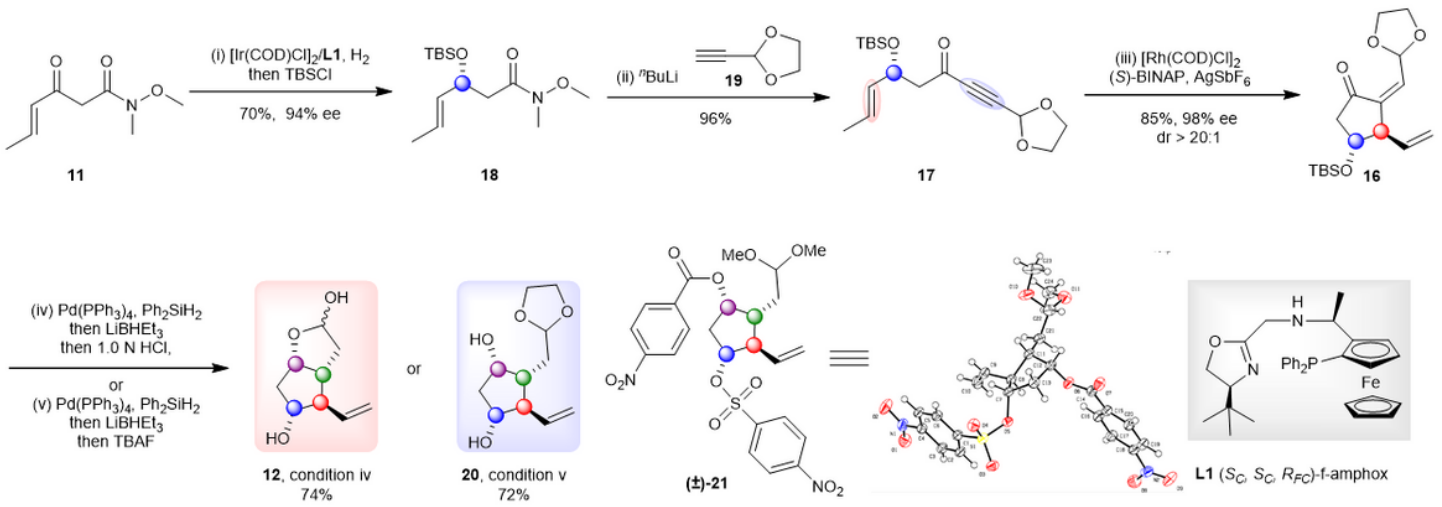
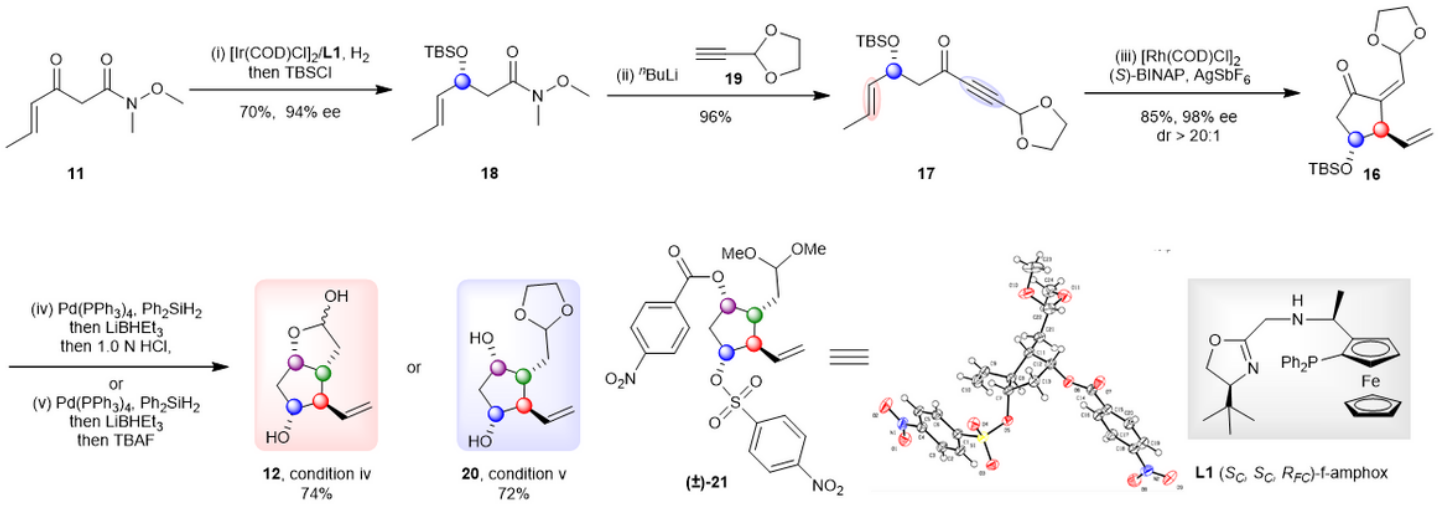


Figure 3

Efficient synthesis of key intermediates 12 and 20. (i) [Ir(COD)Cl]2/L1 (0.1 mol%), KOMe (5 mol%), toluene, 60 atm H2, RT, 24 h; then TBSCl (1.5 equiv.), imidazole (2.0 equiv.), DMF, 70%. (ii) nBuLi (3.5 equiv.), 19 (3.5 equiv.), THF, -78 °C to -20 °C, 96%. (iii) [Rh(COD)Cl]2 (0.05 equiv.), (S)-BINAP (0.1 equiv.), AgSbF6 (0.12 equiv.), DCE, RT, 5 min, 85%. (iv) Pd(PPh3)4 (0.02 equiv.), ZnCl2 (1.1 equiv.), Ph2SiH2 (1.1 equiv.), THF, 50 °C; then LiBHEt3 (3.0 equiv.), -78 °C; then 1.0 N HCl, RT, 74%. (v) Pd(PPh3)4 (0.02 equiv.), ZnCl2 (1.1 equiv.), Ph2SiH2 (1.1 equiv.), THF, 50 °C; then LiBHEt3 (3.0 equiv.), -78 °C; then KF (5.0 equiv.), TBAF (5.0 equiv.), Na2SO4, 72%. THF, tetrahydrofuran. TBSCl, tert-butyldimethylsilyl chloride.



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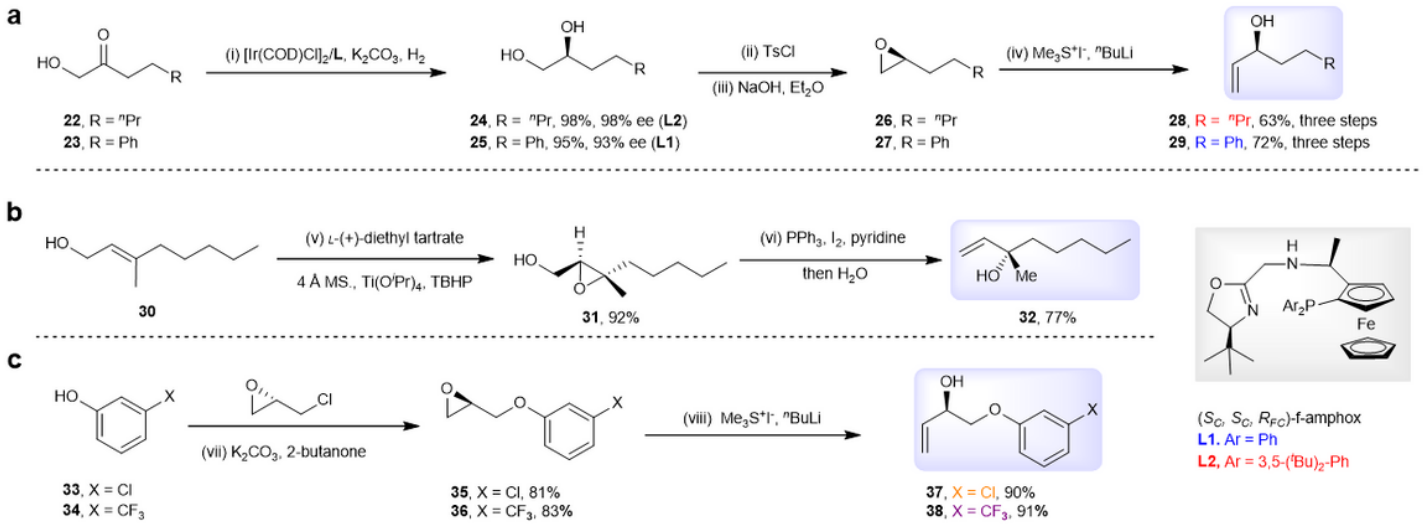
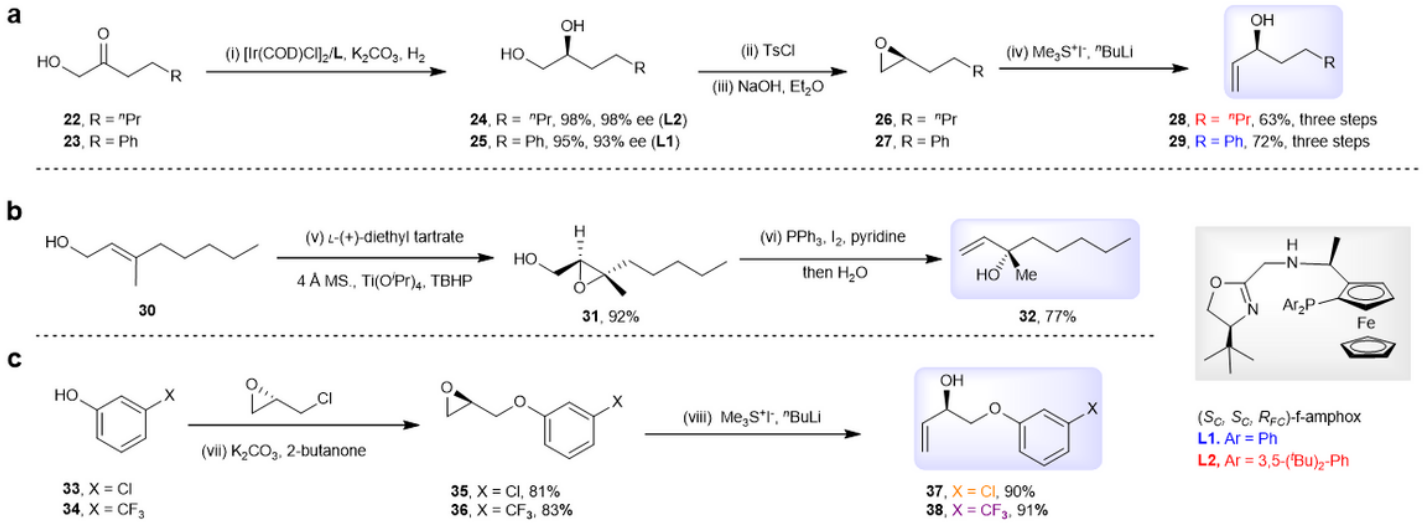


Figure 4

Highly efficient synthesis of the ω chains of PGs. a, Synthesis of side chains 28 and 29. b, Synthesis of side chain 32. c, Synthesis of side chains 37 and 38. (i) [Ir(COD)Cl]2/L2 (0.1 mol%) for 22, [Ir(COD)Cl]2/L1 (0.1 mol%) for 23, K2CO3 (1 mol%), iPrOH, 50 atm H2, RT, 24 h, S/C = 1000. (ii) TsCl (1.1 equiv.), pyridine (1.5 equiv.), DCM, RT. (iii) NaOH (5.0 equiv.), Et2O. (iv) Me3S+I- (5.0 equiv.), nBuLi (5.0 equiv.), THF. (v) L-(+)-diethyl tartrate (0.6 equiv.), 4 Å MS., Ti(OiPr)4 (0.5 equiv.), TBHP (2.0 equiv.), DCM, -20 °C, 92%. (vi) PPh3 (3.0 equiv.), I2 (2.0 equiv.), pyridine (3.8 equiv.), 0 °C; then H2O (1.0 equiv.), 40 °C, 77%. (vii). K2CO3 (2.0 equiv.), 2-butanone, 120 °C. (viii) Me3S+I- (5.0 equiv.), nBuLi (5.0 equiv.), THF. TBHP, tert-butyl hydroperoxide.



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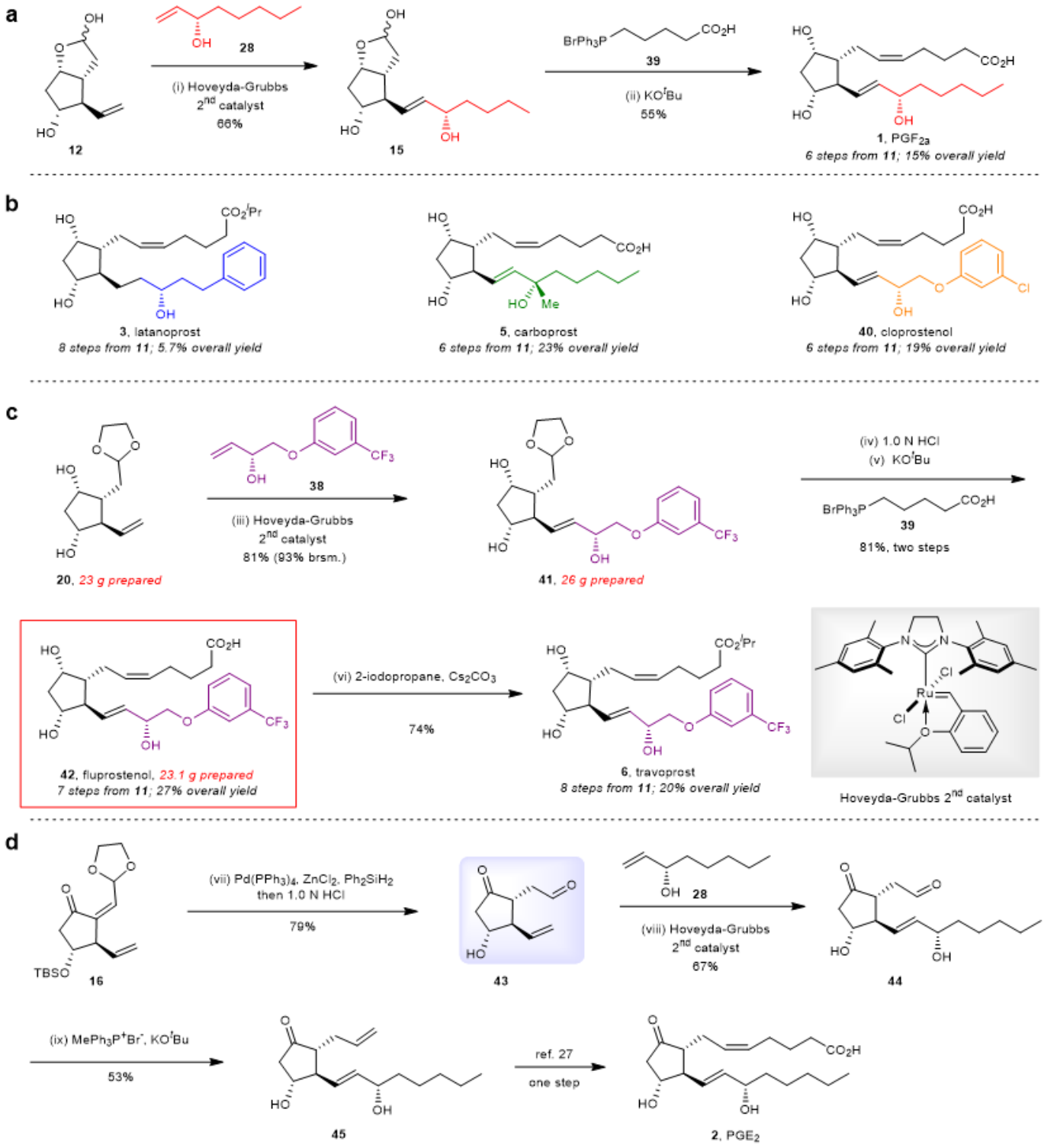
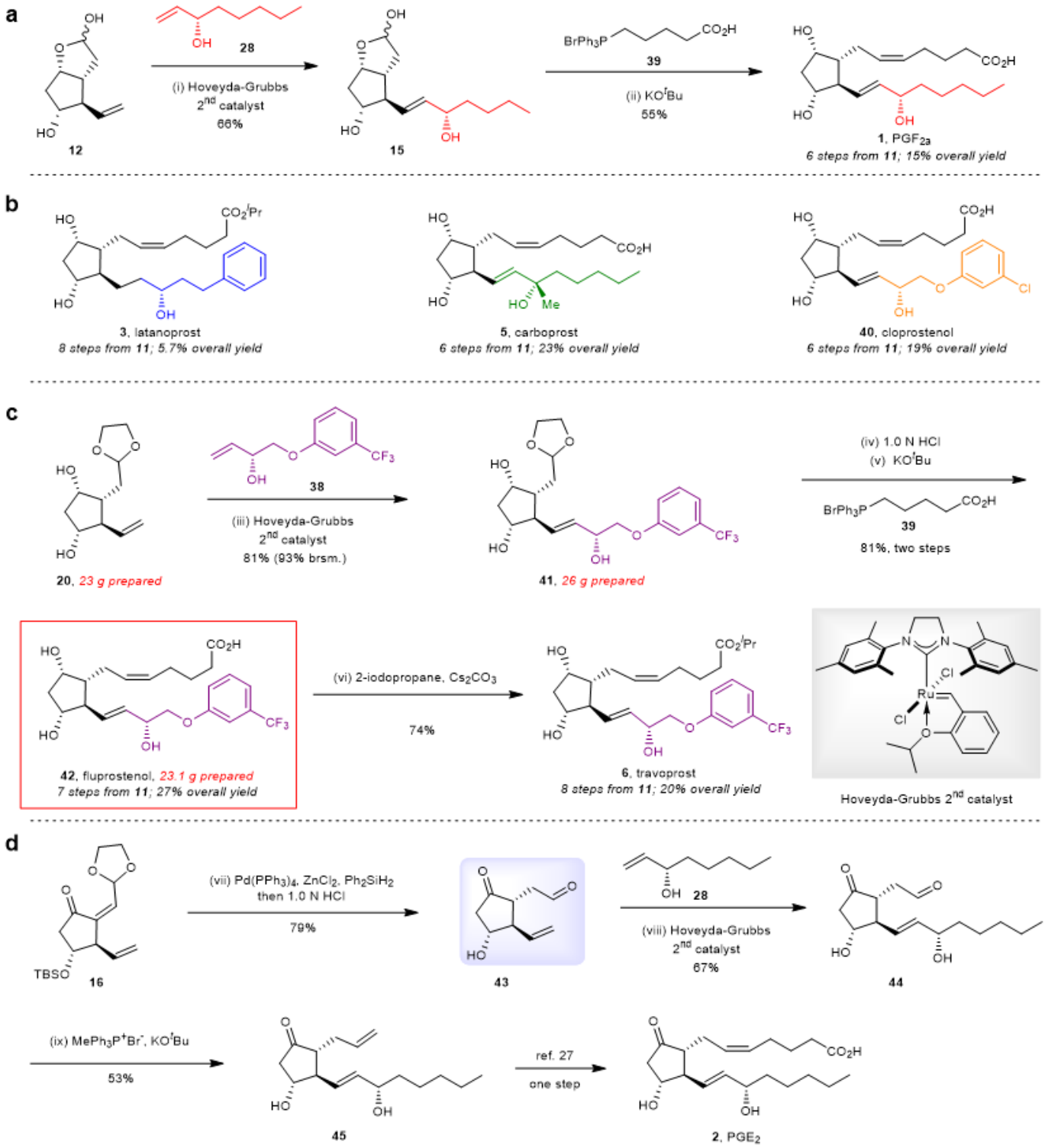


Figure 5

Completion of the total synthesis of PGs. a, Completion of the total synthesis of PGF2α. b, Synthesis of latanoprost, cloprostenol and carboprost. c, Twenty-gram scale synthesis of fluprostenol and travoprost. d, Formal synthesis of PGE2. (i) Hoveyda-Grubbs 2nd catalyst (0.2 equiv.), 28 (10.0 equiv.), DCM, 66%. (ii) KOtBu (16.0 equiv.), 39 (8.0 equiv.), THF, RT, 55%. (iii) Hoveyda-Grubbs 2nd catalyst (0.07 equiv.), 38 (3.0 equiv.), 81% (93% brsm.). (iv) 1.0 N HCl, THF, RT. (v) KOtBu (16.0 equiv.), 39 (8.0 equiv.), THF, RT, 81%, two

steps. (vi) 2-iodopropane (2.0 equiv.), Cs2CO3 (1.5 equiv.), DMF, RT, 74%. (vii) Pd(PPh3)4 (0.02 equiv.), ZnCl2 (1.1 equiv.), Ph2SiH2 (1.1 equiv.), THF, 50 °C; then 1.0 N HCl, RT, 79%. (viii) Hoveyda-Grubbs 2nd catalyst (0.2 equiv.), 28 (10.0 equiv.), DCM, 67%. (ix) MePh3P+Br- (3.0 equiv.), KOtBu (3.0 equiv.), THF, RT, 55%. brsm., based on recovered starting material.



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