LETTER

doi:10.1038/nature11411

Stereocontrolled organocatalytic synthesis of prostaglandin $PGF_{2\alpha}$ in seven steps

Graeme Coulthard[1], William Erb[1] & Varinder K. Aggarwal[1]

Prostaglandins are hormone-like chemical messengers that regulate a broad range of physiological activities, including blood circulation, digestion and reproduction[1,2]. Their biological activities and their complex molecular architectures have made prostaglandins popular targets for synthetic organic chemists for over 40 years[3,4]. Prostaglandin analogues are widely used as pharmaceuticals and some, such as latanoprost, which is used to treat glaucoma[5,6], have become billion-dollar drugs. Previously reported syntheses of these compounds are quite lengthy, and every chemical step costs time and energy, generates waste and is accompanied by material losses. Using a new bond disconnection, here we report a concise synthesis of the most complex prostaglandin, $PGF_{2\alpha}$, with high levels of control of relative and absolute stereochemistry, and fewer steps. The key step is an aldol cascade reaction of succinaldehyde using proline organocatalysis to create a bicyclic enal in one step and an enantiomeric excess of 98%. This intermediate bicyclic enal is fully primed with the appropriate functionality for attachment of the remaining groups[7]. Access to this bicyclic enal will not only render existing prostaglandin-based drugs more affordable, but will also facilitate the rapid exploration of related chemical structures around the ubiquitous five-membered ring motif, such as potentially therapeutic prostaglandin analogues.

Prostaglandins, such as $PGF_{2\alpha}$ (Fig. 1; **1**), are hormones that are responsible for the control of a myriad of essential biological processes from sleep to pain, fever to inflammation, menstruation to birth, and constriction of blood vessels to blood clotting[1,2,8]. They are derived from arachidonic acid and are transformed by prostaglandin synthetase into a number of structurally related carbocyclic molecules. These sensitive and labile molecules are not stored in the body but are synthesized in response to stimuli. They were discovered in the early 1930s by von Euler[9] and by the mid-1960s the structures of the first family of prostaglandins was uncovered by Bergström *et al.* (see refs 2 and 10 for reviews). The complex structures of prostaglandins, together with their broad spectrum of biological activity, fuelled intense research activity into their synthesis, comparable to that generated from β-lactam antibiotics and steroids. Woodward[11], Corey[12], Stork[13], Noyori[14], Danishefsky[15] and many others contributed ingenious strategies and developed new methodologies of general use in the construction of these complex molecules[3–5]. But prostaglandins and their analogues are not only of academic interest, they have also found their way into a considerable number of pharmaceuticals. For example, an analogue of $PGF_{2\alpha}$ (**1**), latanoprost (**2**), is used in the treatment of glaucoma[16], and achieved sales of $1.75 billion in 2010 (ref. 17).

The manufacture of latanoprost[6] requires 20 steps and uses the original strategy developed by Corey *et al.*[18] in the synthesis of the related prostaglandin, $PGF_{2\alpha}$. Corey's synthesis involved the formation of a key intermediate, the Corey lactone (**3**), in nine steps from cyclopentadiene (**4**). From this lactone, they were able to assemble the entire family of prostaglandins[12], and specifically $PGF_{2\alpha}$, in eight further steps[18].

In our analysis for the synthesis of prostaglandins and in common with other syntheses of $PGF_{2\alpha}$,[13,15,19] we recognized that lactol **5** was an ideal late-stage intermediate because it enabled the incorporation of the upper side-chain with control of double-bond geometry through a Wittig reaction. At this point our retrosynthetic analysis departed from all previous syntheses. We were interested in disconnecting the C12–C13 bond[20], because we recognized that the bicyclic lactol could control the stereochemistry of the 1,4-addition of the lower side-chain onto a suitable Michael acceptor **6**. By selecting an aldehyde as the electron withdrawing group of the Michael acceptor, the enal **7** could be disconnected back to a simple aldol dimerization of succinaldehyde (**8**), a process that could be rendered asymmetric through proline (**9**) catalysis[21,22].

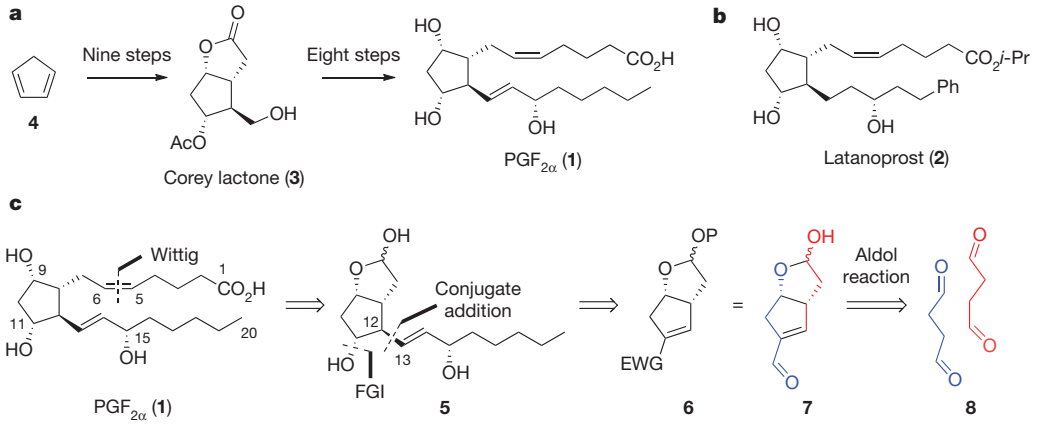


Figure 1 | Prostaglandins in nature and medicine. **a**, General schematic of Corey's synthesis of $PGF_{2\alpha}$. **b**, The molecular structure of latanoprost (**2**), a $PGF_{2\alpha}$ analogue used for the treatment of glaucoma. **c**, Our retrosynthetic analysis of $PGF_{2\alpha}$. The numbered carbon atoms are referred to in the main text. FGI, functional group interconversion. Ph, phenyl. EWG, electron withdrawing group. i-Pr, isopropyl, $CH(CH_3)_2$.

[1]School of Chemistry, University of Bristol, Cantock's Close, Bristol BS8 1TS, UK.

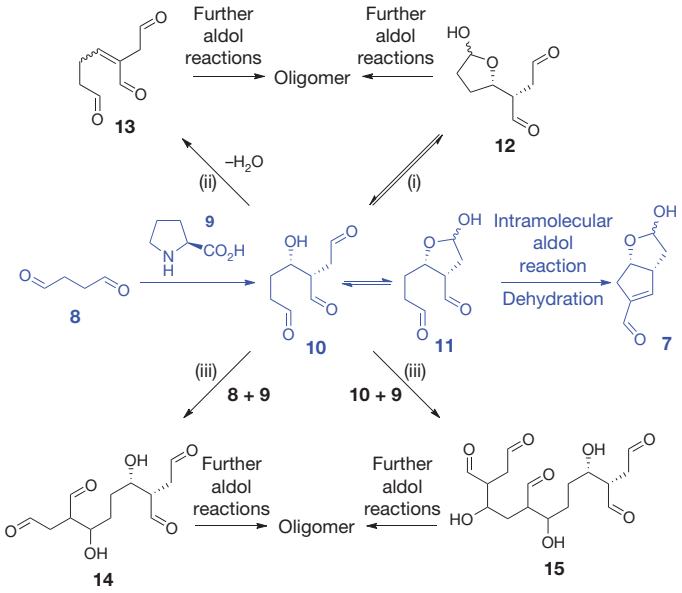


Figure 2 | Potential reaction pathways of the proline-catalysed aldol reaction of succinaldehyde. The desired pathway is shown in blue; others are labelled (i) to (iii) and described in the main text.

However, the 'simple' concept shown in the retrosynthesis belies a highly complex reaction cascade (blue, Fig. 2) with many potential pitfalls (black, Fig. 2): (i) the aldol product **10** is required to form the less favoured hemiacetal **11**, bearing *cis* substituents in the 5-membered ring, but not the *trans* hemiacetal **12**; (ii) the hemiacetal **11** is required to undergo an intramolecular second aldol and eliminate to give **7** but aldol **10** itself should not eliminate to give **13**; (iii) aldol **10** is a reactive trialdehyde which will be prone to undergo further aldol reactions with succinaldehyde (**8**) or with itself, leading to **14** and **15** and ultimately oligomers.

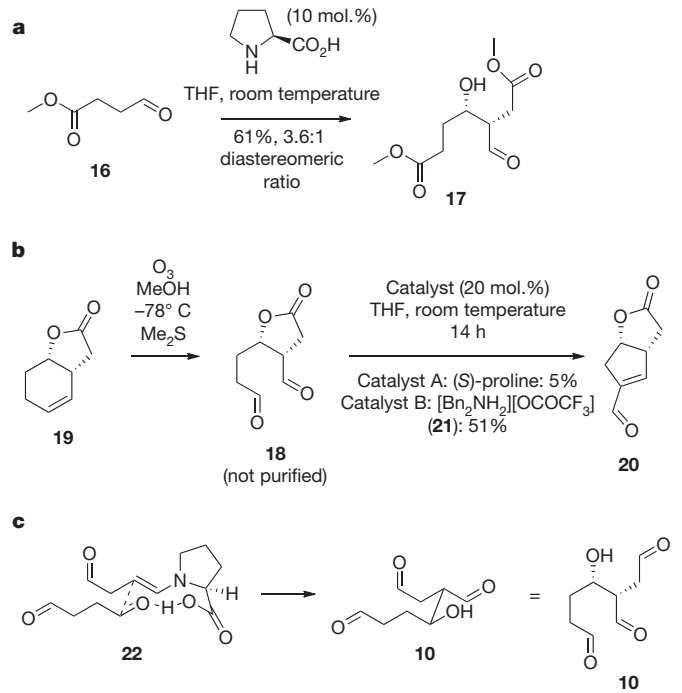


Figure 3 | Model studies. **a**, Model studies to investigate the intermolecular proline-catalysed aldol reaction of aldehydes bearing an ester at the 4-position. **b**, Model studies to investigate an intramolecular aldol reaction and dehydration. **c**, A transition state structure accounting for the observed enantioselectivity.

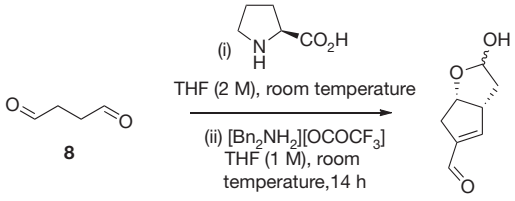
Perhaps unsurprisingly, the desired aldol proved highly challenging to realize in practice: treatment of succinaldehyde with proline in a range of solvents and under a variety of conditions did not deliver any of the desired bicyclic product but instead gave oligomeric material. We therefore deconstructed the reaction cascade to determine which of the two steps, the initial aldol step or the second aldol and dehydration step, was causing the problem.

Model aldehyde **16** was treated with proline (**9**) and aldol product **17** was obtained as a 3.6:1 mixture of diastereoisomers in moderate yield (Fig. 3a)[23]. This showed that aldol reactions of aldehydes bearing a carbonyl group in the 4-position were suitable substrates for the proline-catalysed aldol reaction.

To test the second aldol and dehydration step, model dialdehyde **18** was prepared by ozonolysis of the known lactone **19** (Fig. 3b)[24]. However, treatment of this dialdehyde with proline (catalyst A) provided only low conversion to the expected enal **20**, clearly indicating that the second step was the hurdle in the reaction cascade. We therefore explored alternative catalysts and found that $[Bn_2NH_2][OCOCF_3]$ (**21,** catalyst B)[25] was much more effective, giving enal **20** in 51% isolated yield (from **19**).

We therefore tested the aldol reaction cascade of succinaldehyde with a combination of proline and $[Bn_2NH_2][OCOCF_3]$ in a range of solvents and under a variety of conditions (see the Supplementary Information for full details). This time the reaction was successful; selected data, illustrative of the process, is summarized in Table 1. The reaction could be conducted at (unusually) low loadings of both catalysts and at relatively high concentration (2 M) (entries 1–3 in Table 1). The sequenced addition of the two catalysts and the timing was critical to the success of the reaction: if $[Bn_2NH_2][OCOCF_3]$ was present at the outset (entry 4 in Table 1), or not added at all (see earlier discussion), the reaction failed. We spent some time investigating this facet of the reaction because the low yield is a consequence of oligomerization of the intermediate trialdehyde. As the concentration of the trialdehyde builds up it is prone to undergo further aldol reactions with succinaldehyde, leading to oligomers. The second catalyst seemed to inhibit the initial proline-catalysed aldol reaction, so consecutive addition of the two catalysts was required. The optimum time to add the second catalyst was found to be dependent on the amount of proline catalyst used: using just 2% proline, the yield of the lactol **7** increased with increasing time before the addition of the second catalyst (entries 5–8 in Table 1), peaking at around 10 h. The reaction could also be conducted with just 1% proline but considerably longer reaction times were required (entry 9 in Table 1).

Table 1 | Effect of catalyst loading and time delay on yield



Entry	(*S*)-proline (mol.%)	Time (h)	Yield (%)
1	10	2	14
2	5	2	16
3	5	4	19
4	2	0	~2
5	2	4	10
6	2	6	16
7	2	10	20
8	2	24	20
9	1	24	18

Reactions were carried out on 200 mg of succinaldehyde **8**. 'Time' refers to the time before $[Bn_2NH_2][OCOCF_3]$ (2 mol.%) was added and the reaction was diluted to 1 M. The yield is the NMR (nuclear magnetic resonance) yield based on an internal standard (1,3,5-trimethoxybenzene); results are an average of five reactions.

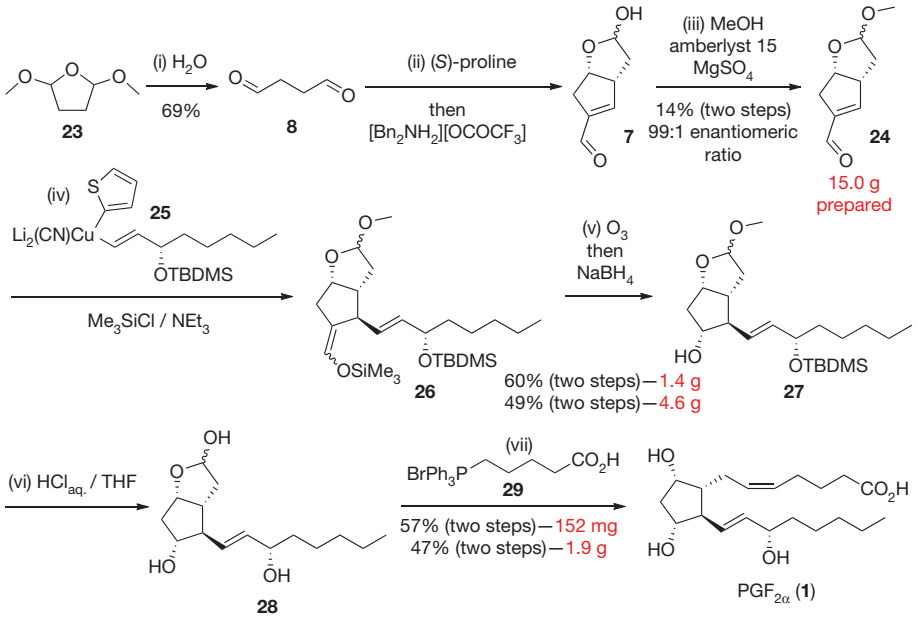


Figure 4 | A concise asymmetric synthesis of $PGF_{2\alpha}$ (1). Reaction conditions are as follows (see the Supplementary Information for full details). (i), H_2O, at 75 °C for 4 h, then at 115 °C to distil MeOH and H_2O. (ii), (*S*)-proline (2 mol.%), THF (2 M), at room temperature for 20 h, then $[Bn_2NH_2][OCOCF_3]$ (2 mol.%), THF (1 M), at room temperature for 14 h. (iii), MeOH (2.0 equivalents), amberlyst 15, $MgSO_4$, CH_2Cl_2, at room temperature for 14 h. (iv), **25** (1.1 equivalents), THF, then Me_3SiCl, Et_3N. (v), O_3, CH_2Cl_2/MeOH (3:1), −78 °C, then $NaBH_4$ (3 equivalents), at −78 °C to room temperature. (vi), 1.5% aqueous HCl/THF (3:2), at room temperature for 16 h. (vii), (4-carboxybutyl)(triphenyl)phosphonium bromide (6 equivalents), potassium *tert*-butoxide (12 equivalents), THF, at 0 °C to room temperature. TBDMS, *tert*-butyldimethylsilyl.

The reaction was conducted at relatively high concentration, which greatly assisted the scale-up of the reaction. Despite the low yield, work-up and purification of the enal was straightforward as the oligomeric side products could be largely removed by filtration, leaving a relatively pure crude material. Partial purification through a plug of silica gave the desired enal **7** in about 16% yield and with an enantiomeric ratio of 99:1, on the multigram scale. The absolute stereochemistry of the product was ultimately established through the synthesis of $PGF_{2\alpha}$ (**1**) and follows from the List–Houk model for this type of reaction (transition-state structure **22**, Fig. 3c)[26]. A mixture of diastereoisomers of trialdehyde **10** was expected to be formed (a diastereoisomeric ratio of about 3.6:1 was expected from results with the model compound **16**) but as the minor diastereoisomer cannot give the alternative diastereomeric enal it must be consumed by the formation of oligomers.

The complete synthesis of $PGF_{2\alpha}$ from commercially available materials is shown in Fig. 4. Heating 2,5-dimethoxytetrahydrofuran **23** (41 g) in water followed by evaporation and extraction gave crude dialdehyde[27] which was directly subjected to the aldol reaction as described above. The hemi-acetal **7** was converted into a 2:1 inconsequential diastereoisomeric mixture of methoxy acetals **24** which were carried through the subsequent reaction sequence. On a large scale (285 g of **23**), further modifications were required owing to the partial decomposition of the dialdehyde during the extended time needed to remove the larger volume of solvent used for extraction. Instead, we found that after distillation of the methanol (MeOH) and most of the water, azeotropic removal of the remaining water using 2-MeTHF (2-methyltetrahydrofuran) provided a solution of the dialdehyde in a solvent (2-MeTHF) that could be used directly in the aldol reaction. Using this improved and simplified protocol, from 109.5 g of inexpensive succinaldehyde we were able to obtain 15.0 g of pure methoxy acetal **24** in 14% yield over two steps. Conjugate addition of the mixed vinyl cuprate[28] **25** to 4.0 g of methoxy acetal **24** followed by trapping with TMSCl (trimethylsilyl chloride) furnished the silyl enol ether **26**. Subsequent controlled ozonolysis followed by treatment with $NaBH_4$ gave the alcohol **27** (4.6 g, 49% over two steps). As planned, these two steps occurred with complete stereocontrol at the newly created stereogenic centres. Finally, simultaneous deprotection of the acetal and silyl ether with aqueous HCl followed by Wittig reaction with the phosphonium salt **29** (ref. 29) gave 1.9 g of the target molecule $PGF_{2\alpha}$ (**1**), which was identical in all respects to the natural product[30].

Thus, we have developed a short (seven steps) synthesis of prostaglandin $PGF_{2\alpha}$ from inexpensive 2,5-dimethoxytetrahydrofuran **23**. The key step is an organocatalytic aldol dimerization reaction of succinaldehyde, which generates the bicyclic enal **7** in high enantiomeric ratio and fully primed with functionality suitable to introduce the required side chains directly. The aldol cascade required proline to perform the first aldol reaction and a second catalyst ($[Bn_2NH_2][OCOCF_3]$) to induce an intramolecular aldol reaction and elimination. Although the aldol reaction was low-yielding, the enantioselectivity was very high, isolation and purification was straightforward and the reaction could be conducted on the multigram scale. Its application in a short synthesis of the most complex of prostaglandins, $PGF_{2\alpha}$, has been demonstrated. Indeed, the bicyclic enal **7** is an ideal building block not just for the cost-effective synthesis of the whole family of prostaglandins, but for also exploring the chemical space around the ubiquitous five-membered carbocyclic ring motif, where other biologically active molecules undoubtedly lie.

METHODS SUMMARY

Procedure for formation of methoxyacetal 24. A solution of succinaldehyde **8** (109.5 g, 1.27 mol) in 2-MeTHF (650 ml) was stirred at room temperature (20 °C) (*S*)-proline (2.93 g, 25.4 mmol, 0.02 equivalents) was added and the reaction stirred at room temperature for 20 h. THF (650 ml) was added, followed by $[Bn_2NH_2][OCOCF_3]$ (8.43 g, 25.4 mmol, 0.02 equivalents). The reaction was stirred for a further 14 h. Celite (60 g) was added to the reaction and the volume of the reaction mixture was reduced by three quarters under reduced pressure. *tert*-Butyl methyl ether (TBME) (975 ml) was added slowly and with vigorous stirring of the mixture. The mixture was stirred for 20 min before filtration of the resulting solids. The solids were washed with TBME (3 × 150 ml) and the filtrate was concentrated under reduced pressure. The material was purified by column chromatography (about 600 g silica), eluting with petrol/EtOAc (6:4 to 5:5), to give the lactol **7** (as an approximately 2:1 mixture of diastereoisomers), as a brown oil.

This residue, containing **7**, was dissolved in CH_2Cl_2 (190 ml) and stirred at room temperature. MeOH (5.47 g, 6.90 ml, 170.6 mmol, 2.0 equivalents based on about 13.4% of **7** detected by internal standard in the previous reaction) was

added via syringe. Amberlyst 15 (1.22 g) and $MgSO_4$ (25.2 g) were added in one portion and the reaction mixture was stirred at room temperature for 14 h. The reaction mixture was filtered through a sinter funnel and the solids washed with CH_2Cl_2 (3×60 ml). The filtrate was concentrated under reduced pressure and purified by column chromatography (about 300 g silica), eluting with petrol/EtOAc (9:1 to 4:1), to give the methyl acetal **24** (as an approximately 2:1 mixture of diastereoisomers, 15.0 g, 14.0% (over two steps from succinaldehyde)) as a yellow oil. See the Supplementary Information for characterization data.

Received 9 February; accepted 11 July 2012.
Published online 15 August 2012.

1. Funk, C. D. Prostaglandins and leukotrienes: advances in eicosanoid biology. *Science* **294,** 1871–1875 (2001).
2. Bindra, J. S. & Bindra, R. *Prostaglandin Synthesis* (Academic Press, 1977).
3. Bindra, J. S. in *The Total Synthesis of Natural Products* (ed. ApSimon, J.) Vol. 4 353–449 (Wiley, 1981).
4. Das, S., Chandrasekhar, S., Yadav, J. S. & Gree, R. Recent developments in the synthesis of prostaglandins and analogues. *Chem. Rev.* **107,** 3286–3337 (2007).
5. Collins, P. W. & Djuric, S. W. Synthesis of therapeutically useful prostaglandin and prostacyclin analogs. *Chem. Rev.* **93,** 1533–1564 (1993).
6. Nair, S. K. & Henegar, K. E. in *Modern Drug Synthesis* (eds Li, J. J. & Johnson, D. S.) Ch. 21 329–338 (Wiley, 2010).
7. Ungrin, M. D. *et al.* Key structural features of prostaglandin E_2 and prostanoid analogs involved in binding and activation of the human EP1 prostanoid receptor. *Mol. Pharmacol.* **59,** 1446–1456 (2001).
8. Stix, G. Better ways to target pain. *Sci. Am.* 68–71, http://www.scientificamerican.com/article.cfm?id=better-ways-to-target-pain (16 December 2006).
9. Von Euler, U. S. Information on the pharmacological effect of natural secretions and extracts from male accessory sexual glands. *Arch. Exp. Pathol. Pharm.* **175,** 78–84 (1934).
10. Flower, R. J. Prostaglandins, bioassay and inflammation. *Br. J. Pharmacol.* **147,** S182–S192 (2006).
11. Woodward, R. B. *et al.* Novel synthesis of prostaglandin $F_{2\alpha}$. *J. Am. Chem. Soc.* **95,** 6853–6855 (1973).
12. Corey, E. J. & Cheng, X.-M. *The Logic of Chemical Synthesis* (Wiley, 1995).
13. Stork, G., Sher, P. M. & Chen, H. L. Radical cyclization-trapping in the synthesis of natural products. A simple, stereocontrolled route to prostaglandin $F_{2\alpha}$. *J. Am. Chem. Soc.* **108,** 6384–6385 (1986).
14. Suzuki, M., Yanagisawa, A. & Noyori, R. Prostaglandin synthesis. 16. The three-component coupling synthesis of prostaglandins. *J. Am. Chem. Soc.* **110,** 4718–4726 (1988).
15. Danishefsky, S. J., Paz Cabal, M. & Chow, K. Novel stereospecific silyl group transfer reactions: practical routes to the prostaglandins. *J. Am. Chem. Soc.* **111,** 3456–3457 (1989).
16. Resul, B. *et al.* Phenyl-substituted prostaglandins: potent and selective antiglaucoma agents. *J. Med. Chem.* **36,** 243–248 (1993).
17. Pfizer reports fourth-quarter and full-year 2010 results; provides 2011 financial guidance and updates 2012 financial targets. http://www.pfizer.com/files/investors/presentations/q4performance_020111.pdf (2011).
18. Corey, E. J., Weinshenker, N. M., Schaaf, T. K. & Huber, W. Stereo-controlled synthesis of dl-prostaglandins $F_{2\alpha}$ and E_2. *J. Am. Chem. Soc.* **91,** 5675–5677 (1969).
19. Howard, C. C. *et al.* Total synthesis of prostaglandin-$F_{2\alpha}$ involving stereocontrolled and photo-induced reactions of bicyclo[3.2.0]heptanones. *J. Chem. Soc. Perkin Trans. I* 852–857 (1980).
20. Corey, E. J., Nicolaou, K. C. & Beames, D. J. A short synthetic route to prostaglandins utilizing position-selective epoxide opening by the vinyl Gilman reagent. *Tetrahedr. Lett.* **15,** 2439–2440 (1974).
21. Mukherjee, S., Yang, J. W., Hoffmann, S. & List, B. Asymmetric enamine catalysis. *Chem. Rev.* **107,** 5471–5569 (2007).
22. List, B., Lerner, R. A. & Barbas, C. F. Proline-catalyzed direct asymmetric aldol reactions. *J. Am. Chem. Soc.* **122,** 2395–2396 (2000).
23. Northrup, A. B. & MacMillan, D. W. C. The first direct and enantioselective cross-aldol reaction of aldehydes. *J. Am. Chem. Soc.* **124,** 6798–6799 (2002).
24. Corey, E. J. & Ravindranathan, T. A simple route to a key intermediate for the synthesis of 11-desoxyprostaglandins. *Tetrahedr. Lett.* **12,** 4753–4755 (1971).
25. Corey, E. J. *et al.* Stereospecific total synthesis of gibberellic acid. A key tricyclic intermediate. *J. Am. Chem. Soc.* **100,** 8031–8034 (1978).
26. Bahmanyar, S., Houk, K. N., Martin, H. J. & List, B. Quantum mechanical predictions of the stereoselectivities of proline-catalyzed asymmetric intermolecular aldol reactions. *J. Am. Chem. Soc.* **125,** 2475–2479 (2003).
27. Gourlay, B. S., Molesworth, P. P., Ryan, J. H. & Smith, J. A. A new and high yielding synthesis of unstable pyrroles via a modified Clauson-Kaas reaction. *Tetrahedr. Lett.* **47,** 799–801 (2006).
28. Lipshutz, B. H., Kozlowski, J. A., Parker, D. A., Nguyen, S. L. & McCarthy, K. E. More highly mixed, higher order cyanocuprates "R_T(2-thieny)Cu(CN)Li_2". Efficient reagents which promote selective ligand transfer. *J. Organomet. Chem.* **285,** 437–447 (1985).
29. de los Angeles Rey, M. *et al.* New synthetic strategies to vitamin D analogues modified at the side chain and D ring. Synthesis of 1α,25-dihydroxy-16-ene-vitamin D_3 and C-20 analogues. *J. Org. Chem.* **64,** 3196–3206 (1999).
30. Sheddan, N. A. & Mulzer, J. Cross metathesis as a general strategy for the synthesis of prostacyclin and prostaglandin analogues. *Org. Lett.* **8,** 3101–3104 (2006).

Supplementary Information is available in the online version of the paper.

Acknowledgements We thank EPSRC and the European Research Council (FP7/2007-2013, ERC grant no. 246785) for financial support. V.K.A. thanks the Royal Society for a Wolfson Research Merit Award and EPSRC for a Senior Research Fellowship.

Author Contributions G.C. and W.E. were involved in the discovery and subsequent development of the aldol reaction and G.C. applied it to $PGF_{2\alpha}$. V.K.A. conceived and directed the investigations and composed the manuscript with revisions provided by G.C. and W.E.

Author Information Reprints and permissions information is available at www.nature.com/reprints. The authors declare no competing financial interests. Readers are welcome to comment on the online version of the paper. Correspondence and requests for materials should be addressed to V.K.A. (v.aggarwal@bristol.ac.uk).