Prostaglandin Total Synthesis Enabled by the Organocatalytic Dimerization of Succinaldehyde

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In memory of Stuart Warren: a gentleman, a scholar, and a dedicated teacher of chemistry.
Abstract: Prostaglandins have been attractive targets in total synthesis for over 50 years, resulting in the development of new synthetic strategies and methodologies that have served the broader chemical community. However, these molecules are not just of academic interest, a number of prostaglandin analogues are used in the clinic, and some are even on the WHO list of essential medicines. In this personal account, we describe our own approach to the family of prostaglandins, which centers around the synthesis of a key enal intermediate, formed from the l-proline catalysed dimerization of succinaldehyde. We highlight the discovery and further optimization of this key reaction, its scale up, and subsequent application to a range of prostaglandins.

Keywords: Prostaglandins, Total Synthesis, Organocatalysis, Aldol Reaction, Asymmetric Synthesis

1. Introduction
Prostaglandins (PGs) are a unique family of diverse eicosanoid lipid mediators that act as local hormones within the body. When required, they are synthesised on demand and act either at (autocrine) or adjacent to (paracrine) their site of synthesis.[1] They are implicated in numerous biological processes but are key players in generating the inflammatory response associated with tissue damage.[2] Pioneering research into prostaglandins began in the 1930s with notable contributions from both von Euler and Goldblatt,[3] but it was not until the late 1950s that their chemical structures began to be elucidated, thanks to the seminal work of Bergström and Samuelsson.[4]

1.1. Biological Significance and Medicinal Use of the Prostaglandins
Since their discovery and subsequent structural elucidation, considerable efforts in both industry and academia have focused on understanding the diverse range of biological functions that prostaglandins regulate. These functions include pain signaling, inflammation, fever, smooth muscle contraction and relaxation, and modulation of platelet aggregation.[1,5] Due to their biological significance, prostaglandins and their analogues have emerged as important molecules in the treatment of a range of medical conditions. For example, the compounds latanoprost, travoprost, and bimatoprost are PGF$_{2\alpha}$ analogues used to treat glaucoma, a cause of irreversible blindness.[5] Development of prostaglandin analogues is still ongoing, as evidenced by the recent approval of tafluprost and latanoprostene bunod, both for the treatment of ocular hypertension,[7] as well as a number of PGF$_{2\alpha}$ analogues for the reduction of adipose tissue around the eyes.[8]

2. Previous syntheses of PGF$_{2\alpha}$
The complex structure of prostaglandins, together with their broad spectrum of biological activity fueled intense research activity from the synthetic community, comparable to that generated from β-lactam antibiotics and steroids. Woodward,[9] Corey,[10] Stork,[11] Noyori,[12] Danishefsky,[13] and many others contributed ingenious strategies and developed new methodologies of general utility in the construction of these complex molecules.[14] Corey completed the first total synthesis of PGF$_{2\alpha}$[10] by exploiting the stereocontrol from a Diels Alder reaction to ultimately create a bicyclic lactone (subsequently dubbed the "Corey lactone") housing the functionality and stereochemistry required to access not just PGF$_{2\alpha}$ but also a whole range of prostaglandins and their analogues (Scheme 1).

In the fifty years since the Corey lactone was first reported, a number of impressive strategies have emerged to prepare this crucial intermediate.[10,14,15] Most notably, a dramatic gram-scale synthesis of the lactone was recently reported by Hayashi in a one-pot sequence in only 152 minutes.[16] Hayashi has
also successfully synthesised several prostanoids through the use of similar organocatalytic methodology.\textsuperscript{[17]}

2.1. Stork’s Radical Trapping Approach

It is relevant to discuss Stork’s synthesis of PGF\textsubscript{2\alpha} since our own route was partly inspired by his elegant use of a radical cyclisation/trapping sequence (Scheme 2).\textsuperscript{[11]} In Stork’s case, $\alpha$-iodoacetal 1 (accessed in 7 steps from cyclopentadiene) was subjected to homolytic cleavage of the C–I bond using his catalytic tin hydride method.\textsuperscript{[18]} The radical generated then underwent Ueno-Stork cyclisation\textsuperscript{[19]} to give bicyclic acetal 2 and produce an intermediary radical that trapped the Stork-Ganem reagent\textsuperscript{[20]} exclusively on the exo face of the bicycle, creating two new C–C bonds and installing the $\omega$-sidechain of PGF\textsubscript{2\alpha} in one exquisitely orchestrated sequence.

Following thermal rearrangement of $\alpha$-silyl ketone 3 to the trimethylsilyl enol ether and subsequent Saequsa-Ito oxidation to enone 4, Stork quickly finished the synthesis of PGF\textsubscript{2\alpha} in three further steps, furnishing the natural product in 13 total steps from cyclopentadiene.

The high stereocontrol observed in the trapping of radical 2 is due to the convex shape of the bicyclic intermediate, which favours attack from the more exposed exo face – a strategy we were keen to exploit in our own total synthesis of PGF\textsubscript{2\alpha}.

3. Retrosynthetic Analysis of PGF\textsubscript{2\alpha}

We considered developing an alternative approach to PGF\textsubscript{2\alpha} that focused on synthesising a strategically functionalized bicycle that incorporated both the cyclopentane core of the natural product and two functional group handles at an appropriate oxidation level to facilitate the introduction of the sidechains.\textsuperscript{[21]}

In line with other syntheses of PGF\textsubscript{2\alpha} our retrosynthesis...
began by disconnecting the C5/C6 Z-alkene with a Wittig reaction to give hemiacetal 5 (Scheme 3).[9,11,13,14] From this point our retrosynthesis departed all previous routes. We considered functional group interconversion (FGI) of the C11 alcohol to an electron withdrawing group such as an aldehyde. This would allow for disconnection of the ω-sidechain by a conjugate addition process, the stereochemistry of which should be controlled by the convex shape of bicyclic enal 6, as discussed above. Key enal 6 could then be disconnected back to hemiacetal 7/trialdehyde 8 through an aldol condensation and then further back to succinaldehyde through an additional aldol reaction. It was envisaged that the stereodetermining step of this process could be carried out by an l-proline catalysed aldol dimerization of succinaldehyde.[21]

In this account we chart the many difficulties we faced in the development of this synthesis, the most challenging of which was the l-proline catalysed dimerization of succinaldehyde. We therefore heated 2,5-dimethoxytetrahydrofuran in water and after extraction of the reaction mixture, we observed near complete consumption of the acetal and considerable amounts of succinaldehyde, together with some partially hydrolysed material.

We were able to scale-up the hydrolysis to provide multi-gram quantities of succinaldehyde (Scheme 4, A). Practically, this involved heating 2,5-dimethoxytetrahydrofuran (140 mL) in water (420 mL) at 75 °C for 4 h, followed by removal of methanol and water by distillation at 120 °C for 4 h (400 mL of distillate was collected). After numerous extractions with dichloromethane (CH2Cl2) (70 × 25 mL), MgSO4 drying, and concentration of the extracts in 250 ml batches we obtained succinaldehyde of high purity but in variable yields.

Succinaldehyde produced in this way was obtained as a pale-yellow liquid and could be distilled under reduced pressure, but it was prone to polymerisation in just a few hours. It was either used directly after distillation or was stored as a solution in CH2Cl2 at −20 °C and used within 48 h. This procedure provided sufficient quantities of succinaldehyde for our initial investigations but the tedious and numerous extractions, and concentration of the resultant extracts in batches pushed us to develop a more effective protocol for large scale synthesis. Instead of trying to extract the water soluble succinaldehyde into an organic solvent we decided to focus on azeotropic removal of the water (Scheme 4, B). We found that after distilling off most of the water and methanol under neutral conditions,[23] Smith used the resulting solution of succinaldehyde directly, without further purification; however, we needed to purify it in order to avoid the hydrolysis by-products from interfering in our subsequent aldol reaction.

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(MeOH), addition of 2-methyltetrahydrofuran (2-MeTHF) allowed for azeotropic removal of water (Dean-Stark, 95 °C, 8 h) and gave succinaldehyde as a solution in 2-MeTHF. Both THF, and more importantly 2-MeTHF, turned out to be suitable solvents for the subsequent aldol reaction.

However, isolation of succinaldehyde as a solution in 2-MeTHF made subsequent aldol reaction optimization more challenging as we were constrained to this solvent. Therefore, we sought to develop an effective azeotropic procedure that would facilitate isolation of neat succinaldehyde (Scheme 4, C). In this respect, our latest procedure – which can be performed on a 50–200 g scale using standard lab glassware or a jacketed reactor vessel system – allowed us to isolate succinaldehyde in 60–70 % yield as a neat liquid. Following initial hydrolysis of 2,5-dimethoxytetrahydrofuran (90 °C, 2 h) and subsequent distillation to remove most of the water and MeOH, azeotropic removal of the remaining water was performed with toluene under reduced pressure. Finally, distillation of the crude material under reduced pressure delivered the desired succinaldehyde for use in the subsequent l-proline catalysed dimerization.

4.2. Initial Investigations of the l-Proline Catalysed Aldol Reaction of Succinaldehyde

With a reliable route to succinaldehyde in hand, we investigated the subsequent l-proline catalysed aldol reaction in both DMSO and THF at room temperature. However, no desired enal product 6 was formed in either case. A broad range of l-proline-like catalysts were tested in a range of solvents but in no case was any product even detected.

The challenge of the reaction was perhaps not surprising as the product from the first aldol is the highly reactive trialdehyde 8, which can undergo a myriad of unproductive reaction pathways (Scheme 5). We wanted trialdehyde 8 to form hemiacetal 7 before ultimately undergoing an aldol condensation to give enal 6. However, it could equally form less hindered hemiacetal 12, undergo elimination to give enal 11 or even perform further aldol reactions with succinaldehyde to give oligomeric mixtures. Indeed, all we saw were gummy reaction mixtures indicative of oligomer formation. At this point we could have given up on our quest, but instead we decided to break down the problem. We asked ourselves, which of the two steps was problematic: the first intermolecular aldol reaction or the second intramolecular aldol reaction followed by dehydration? Typically, intermolecular reactions are more difficult than intramolecular reactions but here the opposite was true.

To model the first step of our process, we studied the l-proline catalysed aldol reaction of aldehyde 15 bearing a methyl ester in the 4-position instead of another aldehyde (Scheme 6). We thought that the aldol product 16 from such a reaction would be more stable and less likely to undergo further side reactions.

The l-proline catalysed dimerization of aldehyde 15 led to a 61 % yield of aldol product 16 with a diastereomeric ratio of 3.6:1. This successfully showed that the first aldol step of our process should work well and tolerate a carbonyl group in the 4-position.

In order to model the second step, we chose to investigate dialdehyde 18 as it contains a 1,6-dialdehyde with the correct relative stereochemistry but on a more stable lactone, rather than a hemiacetal (Scheme 7). Dialdehyde 18 was prepared by...
ozonolysis of known cyclohexene 17 and used without purification in the subsequent aldol condensation. Addition of l-proline to dialdehyde 18 in THF only gave a 5% yield of lactone product 19 (over 2 steps), quickly demonstrating that it was a poor catalyst for the second step of our process. This result surprised us initially, as we had expected the intramolecular aldol to be much easier than the intermolecular aldol. However, a review of the literature highlighted the sensitivity of this intramolecular step to subtle structural changes. For example, Afonso showed that the nature of the 1,6-dialdehyde bridge can make all the difference between success and failure of this step: the imide bridge of intermolecular aldol. However, we had expected the intramolecular aldol to be much easier than the intermolecular aldol. For example, Afonso showed that the nature of the 1,6-dialdehyde bridge can make all the difference between success and failure of this step: the imide bridge of intermolecular aldol. However, we had expected the intramolecular aldol to be much easier than the intermolecular aldol.

In Corey’s synthesis of gibberellic acid, he used dibenzylammonium trifluoroacetate ([Bn2NH2][OCOCF3]) to effect the aldol condensation of a 1,6-dialdehyde to an enal. We therefore explored the use of this catalyst and were delighted to find that in our model system, lactone 19 was obtained in 51% yield over 2 steps (Scheme 7).

This result indicated that we needed a combination of catalysts to be successful: l-proline for the first step and then dibenzylammonium trifluoroacetate for the second step. However, could each catalyst work independently, performing their desired role without interference from each other? For example, dibenzylammonium trifluoroacetate should not catalyse the first aldol, otherwise we would get material with low e.r., and it must not prevent the first catalyst from performing its role, otherwise we would get low yields of product. These issues were explored next.

4.3. The L-Proline Catalysed Aldol Reaction of Succinaldehyde Revisited

The aldol reaction cascade of succinaldehyde was therefore tested with a combination of l-proline and [Bn2NH2][OCOCF3] (Table 1). Unfortunately, when the two catalysts were added together no product was obtained (entry 1). This was perplexing, as we knew from our model studies that l-proline could catalyse the first aldol reaction and [Bn2NH2][OCOCF3] could catalyse the second. We therefore tried adding the catalysts sequentially: l-proline was added first and then after an arbitrary time of 4 h, [Bn2NH2][OCOCF3] was added. Finally, we were successful, and the product was obtained in 7% yield (entry 2). Crucially, the e.r. was found to be 99 : 1 by chiral GC analysis, showing that [Bn2NH2][OCOCF3] was not promoting the first aldol reaction; this being done exclusively by l-proline. Clearly the timing of the addition of the second catalyst was critical, if it was added too early it interfered with the l-proline catalysed aldol and if it was added too late the succinaldehyde simply oligomerised, and so we spent some time investigating this facet of the reaction. The optimum time to add the second catalyst was found to peak at around 10 h after addition of l-proline (entry 4), which gave enal 6 in 13% yield.

The reaction was subsequently scaled up (entry 6) and, after formation of methyl acetal 24 (MeOH, Amberlyst 15, MgSO4) from crude enal 6, we were able to successfully isolate 15 g (13% yield) of desired product in 99 : 1 e.r. for use in our total synthesis. However, it was still particularly challenging to isolate and purify the desired product from the oligomeric side-products.

Table 1. Initial optimization of the synthesis of enal 6.  

| Entry | t [h] | Yield [%] |
|-------|------|-----------|
| 1     | 0    | <1        |
| 2     | 4    | 7         |
| 3     | 6    | 11        |
| 4     | 10   | 13        |
| 5     | 24   | 13        |
| 6    | 20   | 13        |

[a] Reaction conditions (unless otherwise stated): Succinaldehyde (2.32 mmol), l-proline (2 mol%), THF (2 m), RT, t [h]; then: [Bn2NH2][OCOCF3] (2 mol%), THF (1 m), RT, 14 h. [b] Yields determined by 1H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard; results are an average of five experiments. [c] The NMR yields given here are lower than originally reported as relaxation delay was not applied during initial optimization studies; [d] 109.5 g succinaldehyde (1.272 mol) was used; isolated yield determined after formation of methyl acetal 24.

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5. The Total Synthesis of prostaglandin PGF$_{2\alpha}$

5.1. Development of a 1,4-conjugate Addition

Having achieved a scalable synthesis of enal 6 we embarked on the total synthesis of PGF$_{2\alpha}$ as described in our proposed route (Scheme 9).

Following protection of enal 6 as its methyl acetal 24, the next step required 1,4-conjugate addition of an alkanyl nucleophile to the α,β-unsaturated aldehyde of 24. Initially, we focused our efforts on using an organocuprate, a process which had precedent in previous prostanoïd syntheses.\[26\] We chose to use a mixed cuprate with a non-transferable ligand to avoid wasting the valuable alkanyl sidechain. In this respect, we were attracted to Lipshutz’s higher order cyanocuprates, which can transfer a vinyl group in the presence of a thienyl group.\[27\] Thus, we prepared mixed cuprate 28 then reacted it with 24 to give aldehyde 25 as a mixture of two diastereoisomers at the C$_{11}$ aldehyde centre (Scheme 10), showing that conjugate addition had occurred with complete facial selectivity, as expected based on Stork’s PGF$_{2\alpha}$ synthesis (Section 2.1.)

5.2. Investigations into an Oxidative Cleavage Reaction

With the ω-sidechain installed, the next challenge was to perform oxidative cleavage of the aldehyde, which proved to be more difficult than expected. We initially attempted a copper-catalysed oxidative cleavage process using copper acetate (CuOAc)$_2$ and 1,4-Diazabicyclo[2.2.2]octane (DABCO) under O$_2$,\[28\] but in our case the aldehyde of 25 was consumed very slowly, with no identifiable products characterised.

The failure of the copper-catalysed oxidative cleavage reaction led us to investigate an alternative approach involving Rubottom oxidation (Scheme 11). Following 1,4-conjugate addition of mixed cuprate 28 and trapping of the enolate with trimethylsilyl chloride (TMSCl), silyl enol ether 29 was epoxidised with m-CPBA. However, instead of giving α-hydroxyaldehyde 31 as expected, we obtained mixed acetal 30. A related reaction had previously been reported by Pinnick.\[29\] Cleavage of this mixed acetal with TBAF then gave desired α-hydroxyaldehyde 31 in 39% over 2 steps. Subsequent reduction with NaBH$_4$ followed by oxidative cleavage with NaIO$_4$ gave ketone 26, which was stereoselectively reduced with NaBH$_4$ from the less hindered exo face, giving alcohol 27. While this was a lengthy and rather inefficient sequence, one positive outcome was the observation that NaBH$_4$ could
provide us with the required C\textsubscript{11} alcohol as a single diastereoisomer from ketone 26.

This result inspired us to investigate an alternative protocol where we considered using ozonolysis to cleave the more electron-rich silyl enol ether of 29 in the presence of the disubstituted alkene. It was clearly going to be tricky to stop the addition of ozone once all the silyl enol ether had been consumed, but fortunately there are a wide variety of dyes available to assist. A dye can be selected which is less electron-rich than the alkene you want to cleave but more electron-rich than the one you want to keep. We tested several dyes and found that Sudan III was the most successful dye as its colour began to fade just as consumption of silyl enol ether 29 was nearly complete. This dye was used as a guide, with careful thin-layer chromatographic (TLC) monitoring, to decide when to terminate ozonolysis. At the end of the reaction, nitrogen was bubbled through and the mixture treated with NaBH\textsubscript{4}, which first cleaved the ozonides and then stereoselectively reduced the ketone that was formed.

In the optimized procedure (Scheme 12): 1,4-conjugate addition of mixed cuprate 28 with methyl acetal 24, followed by trapping of the resultant enolate with TMSCl gave silyl enol ether 29, which after work-up, underwent chemoselective ozonolysis of the more electron-rich silyl enol ether to give, after NaBH\textsubscript{4} reduction, alcohol 27 on gram-scale.

5.3. Completion of the Synthesis of PGF\textsubscript{2\alpha}

Removal of the TBS group and concomitant hydrolysis of the methyl acetal in 27 was achieved using conditions described by Stork (Scheme 13). Triol 5 was found to be somewhat unstable and so we carried out the Wittig reaction immediately. Phosphonium salt 32 was deprotonated using potassium tert-butoxide (KO\textsubscript{t}-Bu) in THF and reacted with hemiacetal 5. The reaction proceeded cleanly and PGF\textsubscript{2\alpha} was isolated in 57% yield over 2 steps on 157 mg scale, or 47% yield over on 2 steps on 1.9 g scale.

In summary, we have developed a short (7 step) synthesis of prostaglandin PGF\textsubscript{2\alpha} from inexpensive and commercially available 2,5-dimethoxytetrahydrofuran. The key step, an organocatalytic dimerization of succinaldehyde, proved to be exceptionally challenging but by breaking it down into its constituent parts we were able to discover that two different catalysts were required: \textit{l}-proline to perform the first aldol reaction and [Bn\textsubscript{2}NH\textsubscript{2}][OCOCF\textsubscript{3}] to induce the intramolecular aldol condensation. This gave the desired enal 6 in high e.r. and fully primed with suitable functionality to directly introduce the remaining sidechains. We quickly recognised that bicyclic enal 6, like the Corey lactone, was an ideal building block not just for PGF\textsubscript{2\alpha} but for the whole prostaglandin family. However, in order to realize this vision, there was still an issue we needed to address. The Achilles heel of the synthesis was the low yield and difficult purification required in the aldol dimerization of succinaldehyde. As such, considerable effort was devoted to developing a more efficient aldol reaction.

6. Re-Optimization of the Organocatalysed Aldol to the Key Enal

In order to improve our process, we started a further re-optimization campaign, re-evaluating both aldol reaction steps in the enal synthesis. Initial re-optimization studies (Table 2) demonstrated a slight increase in yield from standard conditions (14%, entry 1) by switching the solvent from THF to acetonitrile (MeCN) (16%, entry 2), and a further increase by diluting the concentration of the first aldol step (19%, entry 3). However, at this stage we observed complications during purification of enal 6, where a drop in isolated yield was observed (19% NMR yield -9% isolated yield) due to the formation of

\[\text{Scheme 12. Oxidative cleavage of silyl enol ether 29 by selective ozonolysis.}^{[21]}\]

\[\text{Scheme 13. Completion of the synthesis of PGF}_{2\alpha}^{[21]}\]
undesired hemiaminal 33, which resulted from condensation of \([\text{Bn}_2\text{NH}_2][\text{OCOCF}_3]\) with enal 6 during silica gel chromatography. We therefore screened alternative second catalysts and found that thiomorpholinium trifluoroacetate (\([\text{S(CH}_2)_4\text{NH}_2][\text{OCOCF}_3]\)) was effective, providing enal 6 in both a 20% NMR and isolated yield (entry 4). We were also able to cut the reaction time for the second step from 24 hours to 2 hours by heating the reaction mixture at 65 °C for 2 h, an alteration which also improved the yield to 23% (entry 5). At this point, we conducted an extended solvent screen where we observed that ethyl acetate (EtOAc) gave a visually cleaner reaction profile (less oligomerisation) with a yield of 21% (cf. 23% for MeCN) and 12% residual succinaldehyde (cf. 6% for MeCN) (entry 6). Finally, further assessment of concentration and time revealed that by using an initial concentration of 0.75 M for the first aldol and extending the reaction time from 24 to 40 h, followed by dilution of the reaction to 0.20 M for the second aldol and heating to 65 °C for 2 h, gave an NMR yield of 33% with an isolated yield of 31% on a 0.5 g scale (entry 8). Graphically, the reaction has been presented in Figure 1.

Work-up and purification of the reaction had always been challenging due to the water-soluble nature of enal 6 and the large amount of oligomers present. This often-meant multiple extractions of the aqueous layer were needed to isolate enal 6. However, a recent report highlighting the beneficial effects of using Na2SO4 to “salt-out” water-soluble compounds

| Entry | Solvent | Cat. X | T [°C] | t [h] | Conc. 1 [m] | Conc. 2 [m] | Yield [%] | Residual Succinaldehyde [%] |
|-------|---------|--------|--------|-------|-------------|-------------|-----------|-----------------------------|
| 1     | THF     | A      | RT     | 14    | 2.0         | 1.0         | 14        | –                           |
| 2     | MeCN    | A      | RT     | 20    | 2.0         | 1.0         | 16        | –                           |
| 3     | MeCN    | A [c]  | RT     | 24    | 1.0         | 1.0         | 19 (9)    | –                           |
| 4     | MeCN    | B [c]  | RT     | 24    | 1.0         | 1.0         | 20 (20)   | –                           |
| 5     | MeCN    | B      | 65     | 2     | 2.0         | 2.0         | 23        | 6                           |
| 6     | EtOAc   | B      | 65     | 2     | 0.5         | 0.5         | 28        | 19                          |
| 7     | EtOAc   | B      | 65     | 2     | 0.75        | 0.2         | 33 (31)   | 17                          |
| 8     | EtOAc   | B      | 65     | 2     | 0.75        | 0.35        | 32 (29)   | 19                          |

[a] Reaction conditions (unless otherwise stated): Succinaldehyde (5.81 mmol), L-proline (2 mol%), solvent (X m), RT; then: 2nd catalyst (2 mol%), [b] Yields determined by 1H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard (isolated yields in parentheses). [c] 5 mol% of the 2nd catalyst was used. [d] 40 h reaction time for 1st step. [e] 50 g succinaldehyde (581 mmol) was used.

Figure 1. Image A represents the reaction immediately after the addition of L-proline. Image B shows the reaction after 40 h at RT with L-proline, and C shows the reaction at 65 °C, immediately after the addition of second catalyst ([S(CH2)4NH2][OCOCF3]). The reaction ultimately turns a deep purple colour (image D) that is likely due to the formation of oligomeric material. The KMnO4 stained TLC of the reaction mixture before work-up is shown in image E, where: the upper spot is residual succinaldehyde 9, the middle spot is product enal 6, and the baseline spot is oligomeric material (O.M.).
prompted us to reinvestigate aqueous work-ups.\textsuperscript{[33]} Using this strategy, full recovery of enal \textit{6} could be effected with just 3 × ethyl acetate extractions of the reaction mixture from an aqueous solution of Na\textsubscript{2}SO\textsubscript{4} (17 % \textit{w/w}). The crude material was then purified by column chromatography using pre-treated wet silica, which was found to retain any residual succinaldehyde and oligomeric material. Ultimately, the process could be scaled up \textit{100 ×} from 0.5 g (5.81 mmol) to 50 g (581 mmol) of succinaldehyde with minimal drop in yield: 31 % (0.14 g enal \textit{6}) on 0.5 g scale and 29 % (12.8 g enal \textit{6}) on 50 g scale (entry 9).\textsuperscript{[32]}

6.1. Application of the Key Enal Towards the Total Synthesis of Prostaglandins

In order to further establish our key enal \textit{6} as a viable building block for the total synthesis of prostaglandins, we initially targeted the antiglaucoma drugs, bimatoprost and latanoprost.\textsuperscript{[34]} This extension of our methodology to prostaglandin-based pharmaceutically-relevant compounds allowed us to demonstrate expedient access to life-changing medicines in short step count – 7 or 8 for bimatoprost and latanoprost, respectively – \textit{vs.} 17 or 19 \textit{via} the Corey lactone.\textsuperscript{[35,36]}

The hemiacetal of enal \textit{6} could either be converted to its methyl acetal \textit{24} (as a mixture of diastereoisomers) or to lactone \textit{19} using a Stahl oxidation.\textsuperscript{[37]} The advantage of the latter approach was that lactone \textit{19} could be recrystallised to >99:1 e.r. and carried through a synthesis as a single diastereomer, simplifying the subsequent steps (Scheme 14).

From enantioenriched lactone \textit{19}, both bimatoprost and latanoprost could be synthesised in 5–6 steps with high overall yields of 30–42 % (Scheme 15).\textsuperscript{[34]}

We were also able to apply our strategy to the synthesis of the veterinary drug Alfaprostol,\textsuperscript{[38]} where we utilized an underexplored but powerful 1,4-conjugate addition of an alkyne to introduce the lower \textit{ω}-sidechain (Scheme 16). Although alkynes are often used as non-transferable groups in mixed organocuprates,\textsuperscript{[39]} the addition of copper acetyldes to enals can be effected by using trimethylsilyl iodide (TMSI) as an activator.\textsuperscript{[40]} This approach greatly simplified both the 1,4-addition and the subsequent ozonolysis: the former due to a more facile generation of the copper acetylide compared to the time-consuming mixed cyanocuprate, and the latter due to a lack of competing ozonolysis of the lower \textit{ω}-sidechain. The total synthesis of Alfaprostol was subsequently completed in only 8 steps from enal \textit{6}.\textsuperscript{[38]}

Recognizing that we could use this approach to our advantage, we also targeted an alternative synthesis of PGF\textsubscript{2α}, where we would not have competing ozonolysis of the lower sidechain or have to synthesis the mixed organocuprate.\textsuperscript{[38]} Alkyne \textit{36} was subsequently prepared using the methodology described above and following TBAF deprotection, the resultant propargylic alcohol \textit{37} was subsequently converted to the (\textit{E})-crotyl alcohol by Chan reduction\textsuperscript{[41]} (Scheme 17).

The total synthesis of PGF\textsubscript{2α} was completed in two further steps from alcohol \textit{37}, and in only 8 steps total from enal \textit{6}.\textsuperscript{[38]}

Scheme 14. Differential protecting group strategies for enal \textit{6}.\textsuperscript{[34]}

Scheme 15. Total syntheses of both latanoprost and bimatoprost from a common lactone intermediate \textit{19}.\textsuperscript{[30]}

Scheme 16. Alkyne 1,4-conjugate addition strategy for introducing the lower \textit{ω}-sidechain of Alfaprostol.\textsuperscript{[38]}
7. Summary and Outlook

In summary, we have developed a simple-yet-complex organocatalysed aldol dimerization of succinaldehyde that delivers enal 6 in 29% yield, 99:1 e.r., and on decagram scale. We have utilized this key intermediate in the total synthesis of a wide range of medicinally relevant prostaglandins, and in almost half the number of steps previously reported.

We have also been able to demonstrate the versatility of enal 6 by successfully applying it to the total synthesis of stable prostacyclin and thromboxane analogues, again in considerably fewer steps. Like the Corey lactone, our enal 6 possesses the functionality and stereochemistry required to access a broad range of prostanoid-based natural products. This has enabled us to realize our vision of a universal approach to the total synthesis of the whole prostanoid family. The brevity of the synthesis facilitates analogues to be easily made and tested for biological activity. Indeed, the bicyclic enal 6 is an ideal building block not just for the cost-effective synthesis of the whole family of prostanoids, but for also exploring chemical space around the ubiquitous five-membered carboxylic ring motif, where other biologically active molecules remain to be discovered.

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