inference, examination of how peer influence varies across behaviours[5], and evaluation of the social and structural conditions under which influence is more or less likely to propagate will all be essential to our understanding of the spread of behaviour change through human populations.

Advancing our understanding of peer influence in networks is the first step towards designing 'network interventions' that can promote positive behaviours in human populations, or contain negative ones[15]. It is perhaps obvious that this is relevant to, for example, targeted advertising and viral marketing. But such interventions also have the potential to promote positive social changes, such as increasing the rate of HIV testing, reducing violence, improving adherence to exercise, or increasing political mobilization and awareness. In this way, the science of social influence may have dramatic implications for products, politics and public health. ■

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ORGANIC SYNTHESIS

A biochemical messenger made easily

Biochemicals known as prostaglandins are challenging targets for synthetic organic chemistry. Yet by channelling the reactivity of a simple reactant, a powerful synthesis of one such compound has been achieved. SEE LETTER P.278

ERIK J. SORENSEN

Chemical messengers called prostaglandins are present in nearly all mammalian tissues. These elusive molecules mediate an extraordinary number of biological processes — including the regulation of body temperature, the contraction and relaxation of the human uterus, the aggregation of platelets in blood and cellular responses to inflammation. They have therefore been the targets of wide-ranging research[1] since the 1930s. In particular, their unique molecular architectures and great therapeutic potential have fired the creative imagination of synthetic organic chemists[2,3]. Writing on page 278 of this issue, Coulthard *et al.*[4] report one of the cleverest syntheses of one such molecule, prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$), to date. The conciseness of their approach may open up new opportunities for drug discovery.

Prostaglandins contain two fat-soluble hydrocarbon chains on opposite sides of a ring of five carbon atoms (Fig. 1). Nature synthesizes $PGF_{2\alpha}$ and its analogues from arachidonic acid (a polyunsaturated fatty acid) and two molecules of oxygen, with a little help from some key enzymes. Although nearly every nucleated cell is capable of biosynthesizing prostaglandins, these compounds are short-lived and exceedingly difficult to isolate from biological samples. Since the late 1960s, chemists have therefore devised creative strategies for producing prostaglandins from simple chemicals in the laboratory. The development of dependable laboratory syntheses has contributed substantially to our knowledge of the compounds' remarkable range of pharmacological properties, as well as their relevance to human health.

Ideas about the preparation of $PGF_{2\alpha}$ have resulted in a diversity of pathways[5–9] — a diversity that demonstrates how well the principles of organic chemistry can be used to plan and execute synthetic routes to structurally complex molecules (Fig. 1). The approach now reported by Coulthard *et al.* will be praised for its remarkable brevity and for the bold strategy that guided it. The structural relationship between the simple starting material, succindialdehyde, and the coveted target is distant, and yet the authors perceived that a union of two molecules of succindialdehyde in a single laboratory operation might produce an intermediate hemiacetal compound that is tantalizingly close to the structure of $PGF_{2\alpha}$ (Fig. 2).

The risky aspect of the authors' strategy concerns the intrinsic reactivity of succindialdehyde and its potential to take part in undesired, polymer-forming reactions. Few chemists, even those of adventurous spirit, would have believed that a useful synthesis of the hemiacetal could be achieved as Coulthard *et al.* anticipated, through the direct pairing of two molecules of succindialdehyde in sequential carbon–carbon-bond-forming reactions known as aldol reactions. The great thing is that, not only did this direct approach work well, but it also achieved high stereoselectivity — it produced mostly one mirror-image isomer (enantiomer) of the product. This is crucial, because the biological activity of prostaglandins depends on their enantiomeric form.

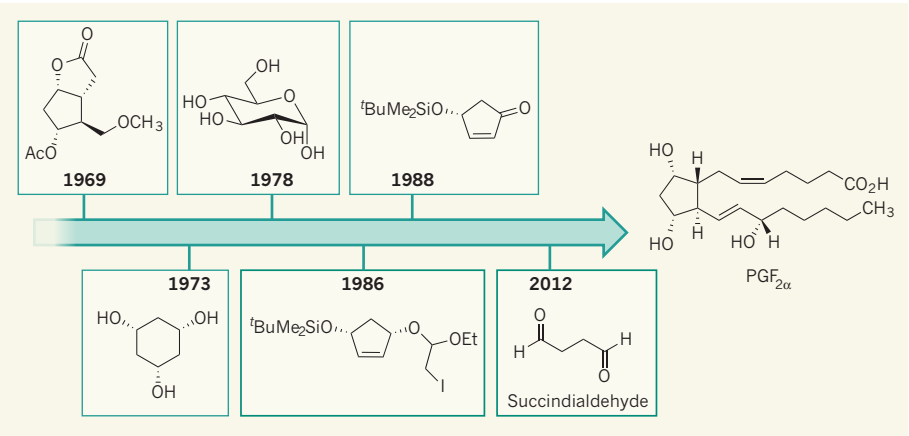

Figure 1 | Landmark syntheses of prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$). The $PGF_{2\alpha}$ biochemical has long acted as a testing ground for organic synthesis. The dates of selected syntheses[5–9] are indicated, along with the molecule that acted as the starting point or key intermediate for each synthesis. Coulthard *et al.*[4] now report a concise synthesis of $PGF_{2\alpha}$ that starts from succindialdehyde. Ac is acetyl, $COCH_3$; Me is methyl, CH_3; Et is ethyl, C_2H_5; ^{t}Bu is tertiary butyl, $(CH_3)_3C$.

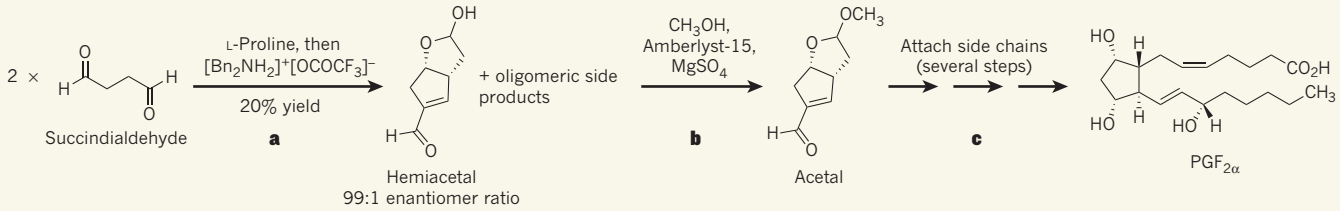

Figure 2 | A concise synthesis of $PGF_{2\alpha}$. **a**, In Coulthard and colleagues' synthesis[4], two equivalents of succindialdehyde react with each other to produce a hemiacetal when treated with catalytic L-proline, and then with another catalyst (an amine salt, $[Bn_2NH_2]^+[OCOCF_3]^-$), in the same reaction vessel. The product is obtained in 20% yield as a 99:1 ratio of enantiomers (mirror-image isomers); the major isomer is depicted. Oligomeric side products are also formed, but are easily removed by filtration. Bn is benzyl, $CH_2C_6H_5$. **b**, The hemiacetal is treated with methanol (CH_3OH), an acid (Amberlyst-15) and magnesium sulphate ($MgSO_4$) to yield an acetal, which contains most of the features needed for the ring component of $PGF_{2\alpha}$. **c**, The authors completed the synthesis by attaching two side chains to the acetal.

The authors discovered that the sequential addition of two organic catalysts to a solution of succindialdehyde is key to the formation of the desired hemiacetal. The first catalyst was the amino acid proline, and the second was an amine salt. The development of this process was supported by earlier studies of proline-catalysed aldol reactions[10–12] and ring-forming aldol reactions induced by amine salts[13] at room temperature.

Although the yield of hemiacetal isolated from the reaction was moderate (20%), Coulthard *et al.* removed most of the undesired oligomeric side products by filtration. A simple chromatographic purification step then afforded the product as the major component of a 99:1 mixture of enantiomers. Any possible concerns about the yield for this impressive transformation are assuaged by the authors' demonstration that 15 grams of a key prostaglandin building block (an acetal; Fig. 2) can be produced in only two steps from succindialdehyde — a large quantity to take forward for the rest of the synthesis.

With its ring of five carbon atoms and newly formed stereogenic centres (carbon atoms around which different geometric arrangements of bonds generate different enantiomers), the acetal building block is a close approximation of the core structure of the prostaglandins. By exploiting the reactive alkene group and the rigid molecular shape of the building block, Coulthard *et al.* attached one of the two hydrocarbon side chains of $PGF_{2\alpha}$ to the desired site on the five-membered ring. Then, in the final phase of the synthesis, the authors efficiently connected the second side chain using a reaction developed by E. J. Corey in his influential syntheses of prostaglandins[5]. In all, only seven operations were needed to transmute the simple compound succindialdehyde into $PGF_{2\alpha}$. For comparison, Corey's synthesis required 17 steps, starting from the simple molecule cyclopentadiene.

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For more on prostaglandin synthesis, see:
go.nature.com/tbqz85

Finding a way to prepare prostaglandins and their analogues in a few steps from commonplace chemicals is still highly alluring for many researchers, especially those in the pharmaceutical industry. The brevity of Coulthard and colleagues' synthesis of $PGF_{2\alpha}$ sets a new standard, and their approach should be applicable to other members of the prostaglandin class, as well as to new structures that have some of the molecular features of prostaglandins. The authors' achievement also calls to mind a much earlier groundbreaking use of succindialdehyde in chemical synthesis — Robert Robinson's synthesis of tropinone[14], a precursor to the drug atropine, in 1917. Some of the power and simplicity of that classic work is seen in Coulthard and colleagues' remarkable solution to the problem of building prostaglandins. ■

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CELL BIOLOGY

Dormant and restless skin stem cells

It has been unclear whether a uniform group of stem cells gives rise to most cells in the epidermis. A study reveals the presence of at least two stem-cell populations that have different proliferative abilities. SEE ARTICLE P.257

LAURA DE ROSA & MICHELE DE LUCA

All renewing tissues, such as blood and skin, are sustained and repaired by a small population of resident stem cells. These cells have the ability to self-renew and to generate committed progenitor cells that differentiate into the cell lineages of the tissue of origin. However, the nature and the specific activities of stem and progenitor cells at different body sites are a matter of debate. For example, several theories have been proposed regarding the epidermis, the outer covering of the skin (Fig. 1). On page 257 of this issue, Mascré *et al.*[1] provide compelling evidence for the existence of two cell populations that differ in their proliferative dynamics, their gene-expression profile and their ability to repair the epidermis after injury.

To investigate the origin, location, proliferation and fate of stem cells in mouse-tail epidermis, the authors used genetic lineage tracing — a technique that allows *in vivo* fluorescent marking of specific cell types and