monomer, however, the team led by Thomas used two different enantiopure β-lactone derivatives with opposite configurations at their sole stereocentres (Fig. 1c). As a consequence, this stereocontrolled process was elegantly transformed into a sequence-controlled process.

For example, it was demonstrated that the copolymerization of (*R*)-β-butyrolactone and (*S*)-4-ethoxymethyl-2-propiolactone led to the formation of polymers with almost perfect alternating sequences — both co-monomer units are co-polymerized in a precise –ABABAB– order. In addition to these building blocks, this technique was also extended to other cyclic-ester monomers containing methyl-, butyl- or perfluorobutyl-methyl- substituents). Furthermore, some preliminary results described in this work clearly indicate that the control over co-monomer sequences has a marked influence on the macroscopic properties of the resulting polyesters. For instance, the mechanical properties and the rates of biodegradation of these polymers could be adjusted using this sequence-controlled polymerization strategy.

These new results are undeniably promising and may stimulate more research on this topic. Yet it should be noted that such alternating sequences — although rare — are not unprecedented in synthetic polymer chemistry[4]. In fact, the originality of the work reported by Thomas and co-workers lies more in the method than in the products. Indeed, this new approach points out that co-monomer sequences can be regulated using a careful catalyst design. Such a conclusion was, of course, already drawn by nature millions of years ago. Catalyst-assisted monomer insertion is one of the strategies used by nature for controlling co-monomer sequences[4]. However, these biological processes rely on highly complex biocatalysts such as polymerases or ribosomes, which are at present beyond the reach of synthetic chemists. In this context, the work of Thomas and co-workers clearly shows that much simpler catalytic systems can also lead to the synthesis of macromolecules with controlled primary structures.

It will certainly still take many years of development before synthetic sequence-ordered polymers as complex as myoglobin can be made. Nevertheless, the strategy developed by Thomas and colleagues, together with some other recent interesting concepts[7,8], suggests that the control of co-monomer sequences in synthetic polymerizations is not an unreasonable goal. The technological implications of such sequence-defined macromolecules are potentially vast because the materials' properties could be controlled down at the atomic level — way below that possible with present polymer nanotechnology. For example, one could foresee tailor-made macromolecular reactors for energy conversion, or fully synthetic enzymes that could be prepared on a large scale for industrial organocatalysis. That day has obviously not arrived yet, but these appealing hypotheses undoubtedly emphasize that the control of polymer sequences is one of the central challenges of contemporary macromolecular science. ❐

Jean-François Lutz is in the Department of Nanotechnology for Life Science, Fraunhofer Institute for Applied Polymer Research, Geiselbergstrasse 69, Potsdam 14476, Germany.
e-mail: lutz@iap.fhg.de

References

1. Kendrew, J. C. *et al. Nature* **181,** 662–666 (1960).
2. Matyjaszewski, K. & Tsarevsky, N. V. *Nature Chem.* **1,** 276–288 (2009).
3. Grayson, S. M. *Nature Chem.* **1,** 178–179 (2009).
4. Badi, N. & Lutz, J.-F. *Chem. Soc. Rev.* **38,** 3383–3390 (2009).
5. Kramer, J. W. *et al. J. Am. Chem. Soc.* **131,** 16042–16044 (2009).
6. Thomas, C. M. *Chem. Soc. Rev.* **39,** 165–173 (2010).
7. Kleiner, R. E., Brudno, Y., Birnbaum, M. E. & Liu, D. R. *J. Am. Chem. Soc.* **130,** 4646–4659 (2008).
8. Ida, S., Terashima, T., Ouchi, M. & Sawamoto, M. *J. Am. Chem. Soc.* **131,** 10808–10809 (2009).

ENZYME CATALYSIS

Sweet flexibility

An enzyme that is unusually tolerant of a truly broad range of substrates can catalyse aldol-type chemistry on sugars in which the various hydroxyl groups are protected. The new methodology combines some of the most important advantages of enzyme and small-molecule catalysis.

Benjamin G. Davis

Chemistry is a beautiful collection of mechanistic pathways and molecular strategies that can in some cases provide many ways to approach the same problem. One intriguing example of this is provided by ever more convergent approaches to understanding, designing and using catalysis in synthesis. Two largely separate fields of research — those of biocatalysis and organocatalysis — illustrate this well. Using the same fundamental principles of general acid/base, Lewis acid/base and nucleophilic catalysis along with umpolung/repolarization, both fields tune their mechanisms to purpose, partly through design and partly through appreciation of the simple beauty of evolved chemistry.

Researchers from both fields eye the other, appreciative of their respective advantages and aware of shortcomings. Both too are familiar with some notional midpoint occupied by a hypothetical catalyst that is blessed with sufficient conformational stability to allow predictable manipulation of functional groups within a tertiary structure; a hybrid catalyst, perhaps, that would also possess some modicum of the breadth of traditional, small-molecule synthetic organic chemistry. And the resulting catalyst would have the perfect blend of selectivity, reactivity and yet tolerance — and therein lies the rub. Which of these is the most highly valued?

Often the enzymology community — those interested in the function of enzymes in a biological context — may be puzzled by the value placed on synthetic utility by those interested in biocatalysis, where substrate tolerance and product yield might outweigh rate considerations or even other measures of efficiency such as catalyst loading, concentration and the ease with which products are extracted. The position becomes perhaps more polarized when we set synthetic small-molecule catalysis against the use of enzymes. This is particularly so if we want to use enzymes to catalyse transformations of unnatural substrates or even those bearing protecting groups. Discussions on these topics often result in the development of sophistic arguments; comments pitted against each other in exchanges might include: "Can

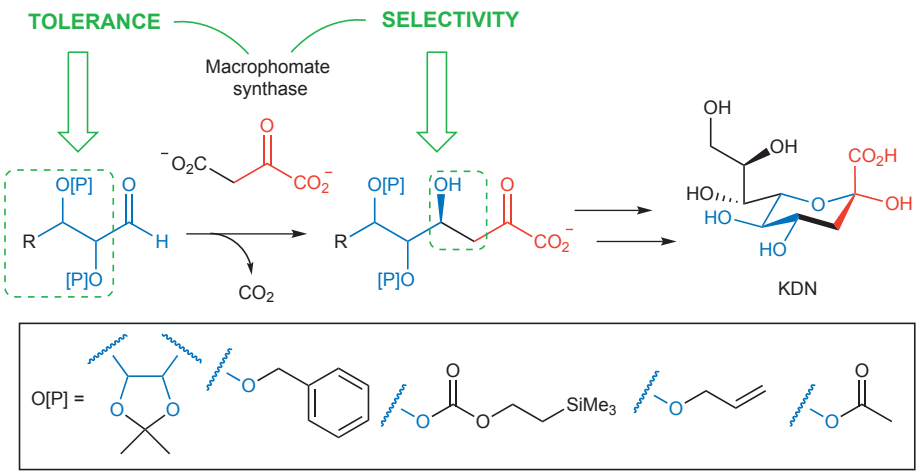

Figure 1 | The broad synthetic utility of macrophomate synthase that comes from a combination based on tolerance and selectivity. The enzyme accepts a wide variety of differentially protected sugars as substrates (R represents the remainder of an up to six-carbon chain bearing many protected alcohols). It then catalyses the decarboxylation of oxaloacetate and reaction of the resulting enolate with the aldehyde group of the substrate in a stereoselective aldol-type reaction. As an example of the utility the synthesis of KDN — a nine-carbon sugar found in bacterial cell-wall carbohydrates — can be achieved in just six steps.

enzymes perform a Wittig reaction?" or "The mol% (catalyst loading) of enzymes is far lower (and therefore better) than that of any small-molecule system". Both are arguments that I would suggest miss the point.

The point, instead, might be to explore the generality of mechanism and to understand its broader applicability in useful catalysis — no matter what its origin and paying no heed to dogma. Writing in *Nature Chemistry*, Don Hilvert, Peter Seeberger and co-workers show the value of this approach by producing an intriguing enzyme system[1]. They have succeeded in using an enzyme that tolerates protecting groups (delivering products that therefore may be inserted into standard synthetic routes) and that while showing great substrate breadth also maintains its useful synthetic charm — that of high stereoselectivity (as well as overall chemoselectivity) in the key C–C bond forming event.

Macrophomate synthase (MPS) has been previously studied by the Hilvert group as a Diels–Alderase candidate[2] — it achieves a formal Diels–Alder-like transformation in certain systems through a mechanism that relies on a two-step (Michael–aldol) pathway. Decarboxylation of oxaloacetate *in situ* generates an enolate nucleophile that then reacts with a suitable electrophile. The small-molecule version of this reaction can be applied to the synthesis of higher sugars (those with carbon chains longer than six), and is sometimes referred to as the Cornforth reaction[3], but despite the utility of the overall transformation it requires harsh reaction conditions and thus there are many cases in which it cannot be applied.

Simplistically, therefore, this could be considered an example of aldol activity to be placed within a class of catalytic transformations alongside organocatalytic approaches[4], those performed by aldolases[5] or even autocatalytic methods[6]. Aldol-like processes, by virtue of the types of molecules they produce, are of course well-suited to sugar syntheses[7–11]. Indeed, some nice examples include the use of aldolases with some tolerance to create, for example, iminosugars or neuraminic acids. This is also the way that nature creates most of the higher sugars, although typically in a restricted one-sugar-one-enzyme manner.

Others have demonstrated elegant examples of targeting quite specific changes in stereoselectivity in aldolases that make sugars[10], or found enzymes with good breadth for certain substrates in a given aldolase[11]. Here, however, the MPS enzyme becomes a truly effective aldolase, accepting a striking range of aldehydes as substrates. These include sugar aldehydes with three to six carbons (adding three carbons in each case, Fig. 1), those containing protecting groups (ether, acetals, allyl, benzyl, silylether and esters) in combination, and even enantiomeric aldehydes (albeit that some mismatching causes reduced stereoselectivity). Such tolerant enzymes are rare and their power is shown here by an expeditious six-step synthesis of KDN (a nine-carbon sugar found in bacterial cell walls). Not all is smoothness-and-light; the substrates, trivially, need to be soluble and some peracetates (sugars with acetate protecting groups on all hydroxyl groups) were, interestingly, not tolerated.

The excitement and power of the system reported by Hilvert, Seeberger and co-workers is that the products of the enzyme-catalysed reaction can be carried directly into standard chemical synthesis for subsequent transformations. This seamlessness is really a consequence of the ability of the enzyme to tolerate appropriate protecting groups. So often, so-called chemo-enzymatic routes are forced to compromise on solvent, for example, or the functional groups that can be included — such that one intermediate may be shunted effectively into the next strategic process. Here the enzymatic transformation dovetails itself with the carbohydrate chemistry allowing neat access to higher deoxy sugars and even subsequent regiocontrol in ring-closing reactions.

The value of this research and other shining examples (such as the collaborative use of epimerizations pioneered by Fleet and Izumori[12]) is that they point the way to effective use of biocatalysis. The key is the proper union of tolerance and selectivity. This is true for both sugar synthesis — where a higher functional group density rewards selective approaches — or for more simple compounds. The result, as shown in these examples, is much needed: ready but selective access to diverse but systematically related — and therefore information-rich — collections of compounds. ❐

Benjamin G. Davis is in the Department of Chemistry at the University of Oxford, Mansfield Road, Oxford, OX1 3TA, UK.
e-mail: Ben.Davis@chem.ox.ac.uk

References

1. Gillingham, D. G., Stallforth, P., Adibekian, A., Seeberger, P. H. & Hilvert, D. *Nature Chem.* **2,** 102–105 (2010).
2. Serafimov, J. M., Gillingham, D., Kuster, S. & Hilvert, D. *J. Am. Chem. Soc.* **130,** 7798–7799 (2008).
3. Cornforth, J. W., Firth, M. E. & Gottschalk, A. *Biochem. J.* **68,** 57–61 (1958).
4. Bertelsen, S. & Jørgensen, K. A. *Chem. Soc. Rev.* **38,** 2178–2189 (2009).
5. Dean, S. M., Greenberg, W. A. & Wong, C.-H. *Adv. Synth. Catal.* **349,** 1308–1320 (2007).
6. Butlerov, A. M. *Z. Chem.* **4,** 549–560 (1861).
7. Lin, C. H., Sugai, T., Halcomb, R. L., Ichikawa, Y. & Wong, C.-H. *J. Am. Chem. Soc.* **114,** 10138–10145 (1992).
8. Northrup, A. B. & MacMillan, D. W. C. *Science* **305,** 1752–1755 (2004).
9. Gardner, P. M., Winzer, K. & Davis, B. G. *Nature Chem.* **1,** 377–383 (2009).
10. Williams, G. J., Domann, S., Nelson, A. & Berry, A. *Proc. Natl Acad. Sci. USA* **100,** 3143–3148 (2003).
11. Lamble, H. J., Danson M. J., Hough D. W. & Bull S. D. *Chem. Commun.* 124–126 (2005).
12. Rao, D. *et al. Tetrahedron Lett.* **50,** 3559–3563 (2009).