Take aim

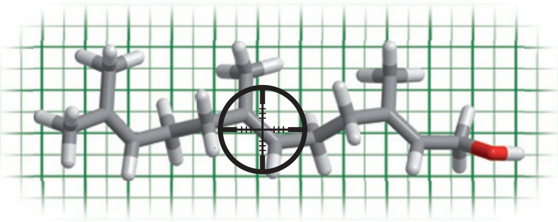
A collection of articles in this issue focuses on the ability to selectively perform a reaction at just one specific site in a complex molecule that contains many other similarly reactive sites.

Natural product structures often inspire the development of synthetic methodology and, as a consequence, they also provide the ultimate testing ground for new reactions to prove their worth. Some of these compounds are pursued by the synthetic community because they have intriguing or even beautiful structures — although beauty is certainly in the eye of the beholder. But perhaps the most often cited reason is that these compounds frequently display interesting biological activities or therapeutic potential.

That is not to say, however, that in seeking new therapies we cannot also try to improve on nature. The particularly (and somewhat disturbingly) common view among the general public — that 'there is a herb for that' — is more to do with nature's ability to produce such an enormous and diverse range of structures than any grand plan to provide a cure for each and every disease. Although any given natural product may have evolved with a particular biological purpose in the context of its source, its usefulness as a treatment outside of this arena is often nothing more than a coincidence.

If natural products are to be used as a starting point for identifying new bioactive molecules — rather than being the ultimate goal themselves — then there are, in the broadest terms, two different strategies. The first is a bottom-up approach that gradually builds up to the structure, making fragments and analogues of the complete structure that retain the desirable activity but are synthetically easier to make. This tactic has recently been successful in identifying clinical leads for HIV treatment[1]. The second approach — which might be defined as top-down — is to start with the natural product itself (or sometimes a known drug) and attempt to modify it by adding or removing functionality and then identifying new structures with improved properties. In this latter approach, however, the starting compound typically contains more than one copy of the same functional group in addition to functional groups that have very similar reactivities. Finding reactants (and conditions) that enable the synthetic chemist to reliably target just one position out of many similar ones in a particular molecule can be a technically demanding challenge.

Two Articles in this issue take aim at this problem of site-selective functionalization: Scott Miller and Phillip Lichtor describe[2] the identification of peptide-based catalysts for the selective monoepoxidation of farnesol and related polyenes. Taking a different approach, Martin Burke and co-workers investigate[3] selective acylation reactions of amphotericin B — a potent antifungal agent that bears several reactive hydroxyl groups.



In an accompanying News and Views article, Pamela Tadross and Eric Jacobsen comment[4] on how these approaches are themselves, complementary. Burke's approach, they explain, "relies on maximizing the very subtle reactivity differences intrinsic to the molecule by drawing on fundamental mechanistic principles. [Miller's] relies on the power of structural diversity and screening to identify catalysts for selective functionalization." Although they conclude that it is not yet possible to say whether these methods will offer a general approach to late-stage modification of other natural products, they suggest that the foundation has been laid for future studies. One intriguing possibility is that the presence of a polyene subunit within amphotericin B hints at the potential use of Miller's method to modify the antifungal target of Burke's work.

An orthogonal approach to selective functionalization of complex molecules was recently described[5] by Andreas Herrmann and co-workers, taking advantage of the ability of nucleic acid aptamers to selectively bind to small molecules. The aptamers serve as non-covalent protecting groups by shielding many of the functional groups in the small molecules they bind, while leaving others exposed for a reaction to occur. An aptameric protecting group will necessarily be highly specific for a given molecule and will not offer much (if any) generality in substrate scope; however, techniques developed in molecular biology may enable new aptamers to be evolved for other targets or alternative reactions.

Philip Kocienski once described the use of protecting groups in synthesis as something that "Like death and taxes… cannot [be] elude[d]"[6]. It is interesting to note then, that at a time when researchers often take pains to avoid protecting groups[7] in target-oriented synthesis (the bottom-up approach), a protecting group strategy — albeit one that is non-covalent and aims to protect several functional groups at once — can potentially provide selectivity in the complementary top-down approach. Although the use of protecting-group strategies might decrease overall efficiency[8] in target-oriented synthesis, the approach developed by Herrmann and co-workers could improve the efficiency with which new targets can be identified.

The process of drug discovery involves both the identification of an active molecule and its synthesis. Developing reaction conditions that enable similar groups to be distinguished not only has the potential to make target identification easier, but could also improve the efficiency with which those targets are ultimately synthesized. For example, in an ongoing project, Phil Baran and co-workers are working towards[9] a synthesis of Taxol (and related taxanes) in which the construction of the carbon framework and its decoration with many and various functional groups are separated. In so doing they are aiming to improve the redox economy in the synthesis and mimic the way that nature makes these products. Completion of such an ambitious goal will rely on further developments in both reagent-controlled selective reactions and a deeper understanding of the intrinsic reactivity of complex substrates. ❒

References

1. DeChristopher, B. A. *et al. Nature Chem.* **4,** 705–710 (2012).
2. Lichtor, P. A. & Miller, S. J. *Nature Chem.* **4,** 990–995 (2012).
3. Wilcock, B. C. *et al. Nature Chem.* **4,** 996–1003 (2012).
4. Tadross, P. M. & Jacobsen, E. N. *Nature Chem.* **4,** 963–965 (2012).
5. Bastian, A. A., Marcozzi, A. & Herrmann, A. *Nature Chem.* **4,** 789–793 (2012).
6. Kocienski, P. A. *Protecting Groups* (Georg Thieme, 1994).
7. Young, I. S. & Baran, P. S. *Nature Chem.* **1,** 193–205 (2009).
8. Newhouse, T., Baran, P. S. & Hoffmann, R. W. *Chem. Soc. Rev.* **38,** 3010–3021 (2009).
9. Mendoza A., Ishihara, Y. & Baran, P. S. *Nature Chem.* **4,** 21–25 (2012).