Synthetic chemists have been interested in making complanadine A, as well as its many alkaloid cousins, for two main reasons. The first is to generate sufficient supplies of the compound to explore its biological activity. Complanadine A has potential as a medicine for regenerating neurons, and other structurally related compounds already constitute the basis for drug-discovery programmes in the fight against Alzheimer's disease. The second reason is that the connectivity of atoms and bonds in complanadine A makes it an ideal target with which to explore the power of tools and strategies for organic synthesis. The synthetic challenge is, in fact, readily underestimated.

On paper it is easy to see that the structure of complanadine A contains two identical pieces, the structures of which correspond to that of the natural product lycodine (Fig. 1). But in practice, uniting two lycodine molecules to form the desired dimeric product is almost impossible to achieve selectively, because different carbon atoms in each lycodine unit must be connected.

There are few attractive options available for solving such a synthetic problem. One choice would be to fashion two different precursors, each based on the monomeric unit, but with extra chemical groups attached to the carbon atoms that need to be connected. These chemical groups would then allow a bond to form controllably between the key carbons. Although this approach is almost guaranteed to work, it requires two separate synthetic endeavours to prepare each fragment, thereby doubling the total effort and financial outlay involved. Another possibility would be to simply target the monomer, in the hope that some process can be developed to dimerize it into the final structure without forming large amounts of unwanted side products. This idea is conceptually attractive, but history reveals that such dimerizations are rarely achieved in the absence of the enzymes used for such purposes in nature.

Fischer and Sarpong[1] and Siegel and colleagues[2] have developed a third, potentially powerful approach that is effectively a hybrid of the two methods discussed above. In their strategy, a single intermediate is prepared and then differentiated into two different analogues of the monomer at a late stage of the synthesis. These analogues are then connected using a controlled carbon–carbon bond-forming reaction.

In Fischer and Sarpong's work[1], the late-stage intermediate was a lycodine derivative (a triflate; Fig. 1a). The authors converted this compound into another intermediate (known as a boronic ester) in a two-step process that involved an inventive use of a recently discovered iridium-catalysed reaction[5]. This process 'desymmetrized' the reactivity of the lycodine — that is, it allowed the authors to form a bond between different carbon atoms in the triflate and the boronate ester, yielding the non-symmetrical core of complanadine A.

Siegel and colleagues' late-stage intermediate[2], an alkyne–nitrile, was less obviously related to lycodine (Fig. 1b). In particular, it lacked a pyridine ring system (a nitrogen-containing ring of atoms, similar to benzene). The authors used a [2+2+2] reaction[6] to build a pyridine ring into their intermediate, modified the product in two steps and then reacted the resulting compound with another alkyne–nitrile in a second [2+2+2] reaction to form the core structure of complanadine A. Usually, [2+2+2] reactions yield multiple products, but Siegel and colleagues developed and optimized their system to give them the control needed for success, thereby enabling them to 'desymmetrize' their single building block in a different way from that used by Fischer and Sarpong[1], and thus to ultimately access the non-symmetrical target.

Because the two research groups evaluated the structure of complanadine A from distinct perspectives, both of these syntheses[1,2] involve very different steps. Yet both teams found creative ways to use the idea of symmetry inherent in a common intermediate, coupled with powerful synthetic methods, to ultimately fashion the target molecule. These papers, when taken together, may well reveal how to access other non-symmetrical dimeric structures and offer advances towards what is potentially the biggest challenge for twenty-first-century synthetic chemistry: not just preparing a given target molecule, but doing so with a level of efficiency and cost-effectiveness that rivals that of nature itself. ■

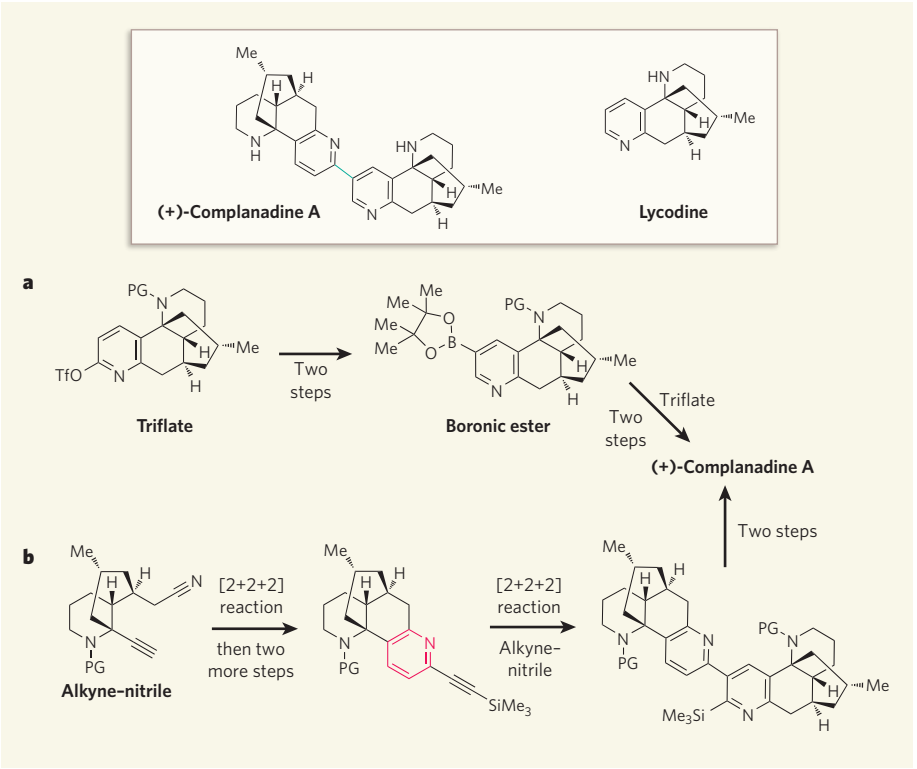

Figure 1 | Synthetic routes to complanadine A. The natural product complanadine A consists of two identical structural units, which correspond to another natural product, lycodine. The bond between the two lycodines in complanadine A (green) connects different carbon atoms in each unit. Me represents a methyl group. **a**, Fischer and Sarpong[1] prepared complanadine A by making a lycodine analogue (a triflate) as an intermediate. They converted this in two steps to a boronic ester, which they then reacted with another equivalent of the triflate, forming the target molecule in two steps from the boronic ester. Tf represents SO_2CF_3. PG is a protecting group — a chemical group that prevents the nitrogen atom to which it is attached from taking part in unwanted reactions. **b**, Siegel and colleagues[2] used a different key precursor, an alkyne–nitrile, in their synthesis of complanadine A. They subjected this precursor to a [2+2+2] reaction to form the pyridine ring (red) of lycodine, and modified the product in a further two steps. The authors reacted the resulting compound with another alkyne–nitrile in a second [2+2+2] reaction, generating an intermediate that contained the core structure of complanadine A. They then converted this intermediate into complanadine A in two steps.

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Correction
The News & Views article "Nuclear physics: Doubly magic tin" by Paul Cottle (*Nature* **465,** 430–431; 2010) gave the isotope of lead as lead-28 (^{28}Pb), when the correct notation is of course lead-208 (^{208}Pb).