Nature Reviews Chemistry | Published online 2 Aug 2017; doi:10.1038/s41570-017-0067

TOTAL SYNTHESIS

Closing the box on (+)-dendrowardol C

> Structures comprising several fused rings are particularly challenging

With nine contiguous stereocentres and a unique tetracyclic core, the sesquiterpenoid (+)-dendrowardol C is a daunting target for total synthesis. A new short communication from Helene Wolleb and Erick Carreira describes this achievement in *Angewandte Chemie International Edition*.

(+)-Dendrowardol C was first described in 2013, following its isolation from the Asian orchid *Dendrobium wardianum* Warner. These orchids have been used in traditional Chinese medicines, with reported effects that include fever reduction and stimulation of saliva. "Structures comprising several fused rings are particularly challenging, and these in general have been of interest to us for quite some time," comments Carreira.

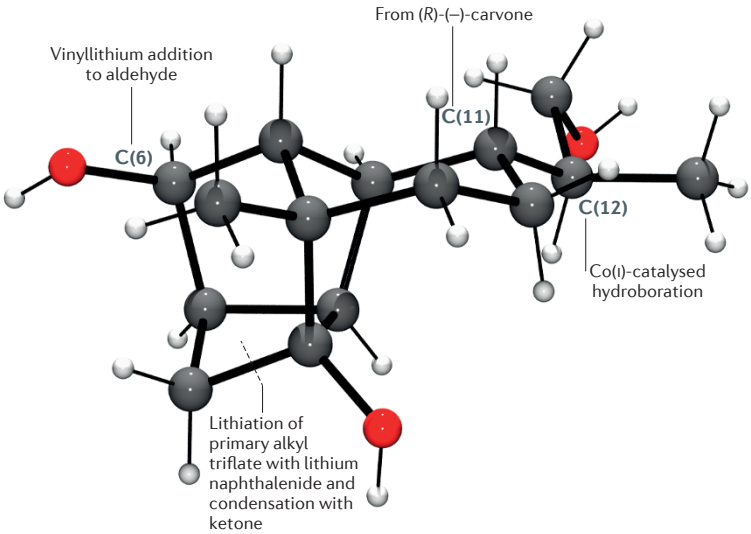
Their initial retrosynthetic analysis focused on a late-stage [2+2] cycloaddition as a means to install the cyclobutane moiety. It was envisaged that the necessary bicyclic intermediate could be accessed from (*R*)-(−)-carvone, a readily available precursor that features the correct stereochemistry at C(11). In the forward sense, the preparation of the intermediate was straightforward and relied on an intramolecular aldol condensation to form the five-membered ring. Installation of the C(6) stereocentre involved the Felkin–Anh addition of vinyllithium to an aldehyde, a reaction that provided a 4:1 diastereomeric ratio of products in favour of that with the desired (*R*)-stereochemistry at this site.

With the key bicyclic compound in hand, they began exploring the installation of the cyclobutane moiety. "Our first approach involved photochemical [2+2] cycloaddition chemistry, a typical disconnection for a cyclobutane," notes Carreira. However, regardless of the conditions explored, the desired regioselectivity could not be obtained. He submits that the failure of the photocycloaddition probably follows from the inherent biases of the caged structure, which consistently gave the undesired regioisomeric cyclobutane, even when they tried some standard and not-so-standard tricks of the trade.

Switching to a stepwise approach, directed epoxidation of the allylic alcohol, followed by regioselective 5-*enolexo*-*exo*-tet epoxide opening and trapping as the triflate, provided a reactive γ-triflyloxy ketone. This species was subjected to conditions — involving the generation of a lithium naphthalenide — originally developed by Miguel Yus and co-workers for the lithiation of simple alkyl triflates. Although the methodology had not previously been applied to such elaborate substrates, it did afford modest yields of the desired cyclobutane on condensation with the nearby ketone. Wolleb and Carreira further optimized their method after observing that the reaction proceeded best in solvents of low dielectric constant, media that are not typically ideal for the generation and use of lithium arenides. "We believe the origins of this stem from a variety of mechanistic pathways involving different options for the metalation by the lithium naphthalenide," Carreira postulates. The approach might find general use in cyclization reactions that are otherwise difficult to orchestrate.

Installing the final C(12) stereocentre was the last challenge, one which could not be met using traditional and chiral boron-mediated strategies. Instead, asymmetric hydroboration using a chiral Co(I) catalyst installed the requisite stereochemistry (d.r. 4:1).

Mina Razzak, Chief Editor, Nature Reviews Disease Primers



David Schilter/Macmillan Publishers Limited

ORIGINAL ARTICLE Wolleb, H. & Carreira, E. M. Total synthesis of (+)-dendrowardol C. *Angew. Chem. Int. Ed.* http://dx.doi.org/10.1002/anie.201705809 (2017)