

C–C ACTIVATION

Remodelling (*R*)-carvone

Where C–H activation can achieve highly useful peripheral functionalization, C–C activation will afford even more deep-seated structural changes and expand the diversity of the structures we can access.



Methods for forming C–C bonds are at the heart of organic synthesis. Once formed, these bonds are among the strongest single bonds, and methods that break them using transition metals — also known as C–C activation — are relatively rare. Now, Richmond Sarpong and co-workers have reported a total synthesis of the diterpene natural product (–)-xishacorene B starting from (*R*)-carvone that relies on a C–C activation process, specifically a β -carbon elimination.

As is often the case with natural product total synthesis, the interest in xishacorene B stems from its potential biological activity. First isolated in 2017, preliminary screening has shown that xishacorene B may act to promote the production of white blood cells and therefore have useful immunological properties. To find out, a synthetic route will be essential, however, as the natural product is isolated in just 0.0008% yield from dried coral harvested off the coast of China.

“We’ve been particularly interested in developing C–C activation reactions because this would allow us to use readily available and inexpensive starting

materials or to remodel existing molecules to produce novel frameworks,” says Sarpong. “We have shown in earlier work towards this goal that we can remodel the six-membered ring of carvone and introduce a quaternary stereocentre in the process. Our approach to the xishacorenes is the first time we’ve applied this concept in total synthesis.”

Xishacorene B (pictured) is a hydrocarbon. This gives the perception of simplicity, but in reality it means that there are no functional groups to guide bond formation. Starting with epoxy carvone, Sarpong and co-workers followed a previous protocol to access a bis-hydroxylated cyclobutane. Structures containing such strained rings are susceptible to C–C activation and reaction with a vinyl iodide in the presence of a Pd(0) complex results in ring opening and cross-coupling to afford a new cyclohexanone intermediate.

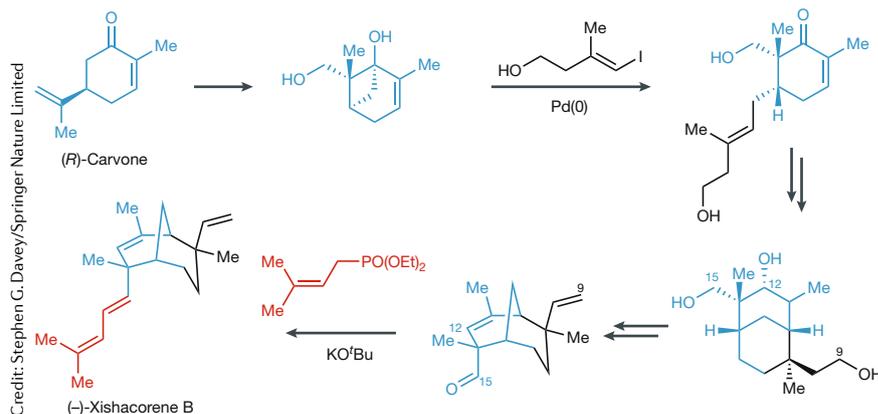
A planned hydrogen atom transfer (HAT) reaction to construct the key [3.3.1]bicycle of the natural product proved challenging, providing only inseparable mixtures of products. “We believe these HAT reactions are powerful for organic

synthesis, but for the purposes of this total synthesis, bromination followed by radical cyclization proved very successful,” says Sarpong. Reduction of the cyclized product affords a triol intermediate in which the core structure of xishacorene B including the two quaternary stereocentres is set.

The completion of the total synthesis requires that the oxygen functionalities that have provided reactive handles thus far must be removed. Iodination and treatment with base provided the desired diene structure but not quite as the researchers had first anticipated. “We initially assumed that iodination followed by elimination had occurred at C9 and C12, but we came to appreciate — with the help of an astute reviewer — that iodination of both primary alcohols followed by migration of the oxygen at C12 by formation and then ring opening of an oxetane gives the same result,” explains Sarpong.

Oxidation of the resulting primary alcohol to the aldehyde followed by Horner–Wadsworth–Emmons olefination afforded the natural product. “We believe that C–C activation can ultimately attain the same level of utility that is now being seen for C–H activation,” says Sarpong. “Where C–H activation can achieve highly useful peripheral functionalization, C–C activation will afford even more deep-seated structural changes and expand the diversity of the structures we can access.”

Stephen G. Davey



Credit: Stephen G. Davey/Springer Nature Limited

ORIGINAL ARTICLE Kerschgens, I. et al. Total synthesis of (–)-xishacorene B from (*R*)-carvone using a C–C activation strategy. *J. Am. Chem. Soc.* **140**, 9810–9813 (2018)
FURTHER READING Nairoukh, Z. et al. Merging C–H and C–C bond cleavage in organic synthesis. *Nat. Rev. Chem.* **1**, 0035 (2017)