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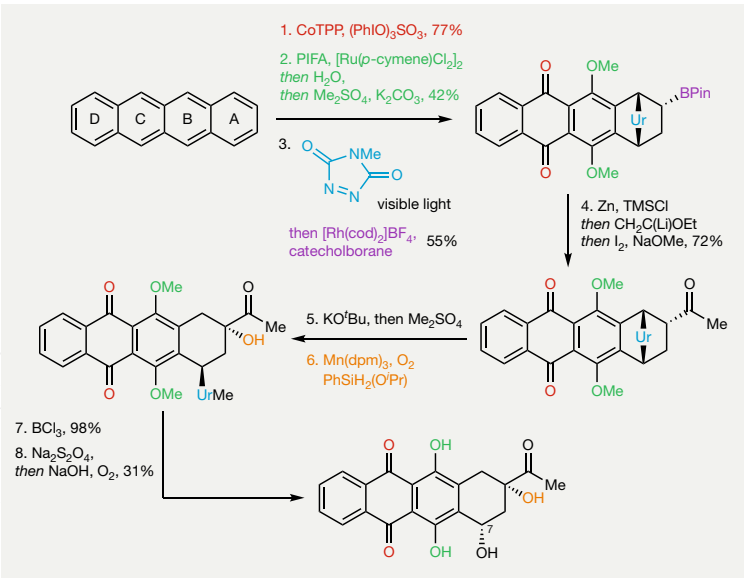
SYNTHETIC STRATEGY

Changing the rings

Idarubicin is an anticancer agent with superior pharmacological properties to the bacterial polyketides to which it is related. Its discovery was the result of medicinal chemistry efforts exploring different oxygenation of the tetracyclic aglycone portion of the structure. To date, all synthetic approaches to analogues of these structures have involved strategies that build the tetracyclic core through cyclization reactions. Writing in the *Journal of the American Chemical Society*, David Sarlah and co-workers, from the University of Illinois, USA, have now described an approach that relies instead on decorating the core structure, starting from the simple tetracyclic aromatic compound tetracene.

The synthesis begins by setting up the correct oxidation levels in the two central rings. The first step is a cobalt-catalysed oxidation of the C ring to its quinone form, using a hypervalent iodine reagent as the terminal oxidant. Oxidation of the B ring proved more difficult, with several direct arene oxidation methods unable to provide the desired product; therefore, Sarlah and co-workers turned to C–H activation methods. Coordination of the C ring quinone to a ruthenium catalyst is presumed to place the active metal centre in close proximity to the reacting C–H bond. The initial reaction product is a trifluoroacetate ester (derived from phenyliodine bis(trifluoroacetate), PIFA) that is subsequently hydrolysed and the phenol methylated.

Sarlah and co-workers were then able to apply their previously reported method for dearomative dihydroxylation of arenes to functionalize the terminal ring.



Credit: Stephen G. Davey/Springer Nature Limited

A visible-light-promoted cycloaddition reaction with *N*-methyl-1,2,4-triazoline-3,5-dione (MTAD) dearomatizes the A ring and the resulting alkene undergoes a rhodium-catalysed hydroboration. The selectivity of the cycloaddition is driven by the electron rich nature of the A ring.

A plan to use Suzuki-type coupling to add the final two carbon fragments proved unsuccessful. A Zweifel olefination proved to be a better alternative, but only after the development of a clever in situ masking of the C-ring quinone.

The bridging urazole moiety that resulted from the earlier cycloaddition reaction was opened in an elimination reaction that delivered an olefin ready for a manganese-catalysed Mukaiyama hydration.

Removal of the methyl ether protecting groups on the B-ring hydroquinone proceeded smoothly but the conversion of the urazole into a hydroxyl proved far more difficult. Sarlah and co-workers eventually found inspiration from some known bioreactivity of the anthracyclines. Reduction with sodium dithionate in the presence of base gave the 7-deoxygenated product. A rapid saturation of the reaction mixture with oxygen delivered the product directly in reasonable yield and the remaining 7-deoxy product could be oxidized to provide additional idarubicinone using known chemistry.

Overall, Sarlah and co-workers' route delivers (±)-idarubicinone — the aglycone of idarubicin — in eight steps and 2% yield from tetracene.

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ORIGINAL ARTICLE Dennis, D. G. et al. Synthesis of (±)-idarubicinone via global functionalization of tetracene. *J. Am. Chem. Soc.* https://doi.org/10.1021/jacs.9b05370 (2019)