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TOTAL SYNTHESIS

Polyketides as easy as ABC (and D)

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The structural and functional complexity of polyketides makes it hard to fathom how such elaborate molecules can be derived from simple chains of alternating methylene and carbonyl groups, which in turn come from acetyl coenzyme A. The pool of polyketides available to us includes the tetracenomycins — secondary metabolites of *Streptomyces glaucescens* — some of which are active against Gram-positive bacteria and L1210 leukaemia cells. The biological activity of these tetracene-related natural products has motivated chemists to prepare them in the laboratory. This is a challenging endeavour in view of their stereochemical complexity, which perhaps explains why these molecules had not yielded to chemical synthesis despite being known for 30–40 years. A team led by Keisuke Suzuki and Hiroshi Takikawa recently addressed this, and they report in *Angewandte Chemie International Edition* the clever use of benzyne chemistry and benzoin cyclizations to assemble tetracenomycins C and X with remarkable stereocontrol.

The tetracenomycins contain four oxidized rings fused in a motif that can be expediently accessed using cycloadditions. The C-ring of the tetracenomycins is derived from the benzyl ether of 2,6-diiodo-3,5-ditosyloxyphenol. This molecule is set up for two cycloadditions: a [2+2] reaction with an α-alkoxy ketene silyl acetal and a [4+2] cycloaddition with a suitably functionalized tri-substituted furan — a novel substrate for this reaction.

The [4+2] cycloaddition gave the D-ring with the requisite regioselectivity, after which deoxygenation and desilylation of the product afforded the CD-ring system with a cyclobutanone fused to the C-ring. Takikawa and co-workers used their recently-developed oxidative ring-opening technology to convert the cyclobutanone oxime to a nitrile oxide with an *ortho*-dimethylacetal substituent. A further cycloaddition — the intermolecular reaction of the nitrile oxide group with an α,β-unsaturated ketone — afforded an isoxazoline with a pendant ketone poised near an aldehyde on the C-ring.

Earlier work had seen Suzuki develop a ketone–aldehyde benzoin cyclization, which was put to good use here. Oxidation of the isoxazoline and treatment of the resulting product with a chiral carbene catalyst triggered C–C bond formation with the native stereochemistry at the C4a alcohol. The alcohol was protected with $C_6D_5CD_2$, the methylene of which, on account of kinetic isotope effects, is less susceptible to oxidative degradation than is the methylene in natural abundance benzyl $C_6H_5CH_2$. Indeed, after opening the isoxazole ring to give two ketones — one each on the A- and B-rings — it proved necessary to use oxidizing conditions to remove the C4 protecting group and unmask the C4 ketone in the latter stages of the synthetic route. Stereoselective reduction of this ketone and removal of the $C_6D_5CD_2$ group gave tetracenomycin C, one face of which is decorated with three alcohols at the contiguous C4, C4a and C12a sites (the C12a alcohol is methylated in tetracenomycin X).

The total synthesis of the tetracenomycins is impressive in that many intermediates en route to the densely functionalized natural products feature partially oxidized rings and thus may be susceptible to further oxidation in much the same way that, for example, 1,4-cyclohexadiene is easily dehydrogenated to benzene. Overall, tetracenomycin C was prepared from commercially available compounds in 1.3% yield over 18 steps. In considering the elegant series of cycloadditions, "the convergent methodology would allow *de novo* construction of complex natural products, as well as congeners inaccessible from natural sources," explain Takikawa and Suzuki. By contrast, *S. glaucescens* bacteria synthesize the tetracenomycins in a rather different way, one in which the three *cis* hydroxy groups are installed in a single enzymatic reaction. For Suzuki and Takikawa, reproducing such a remarkable transformation seems to be a tantalizing aspirational goal.

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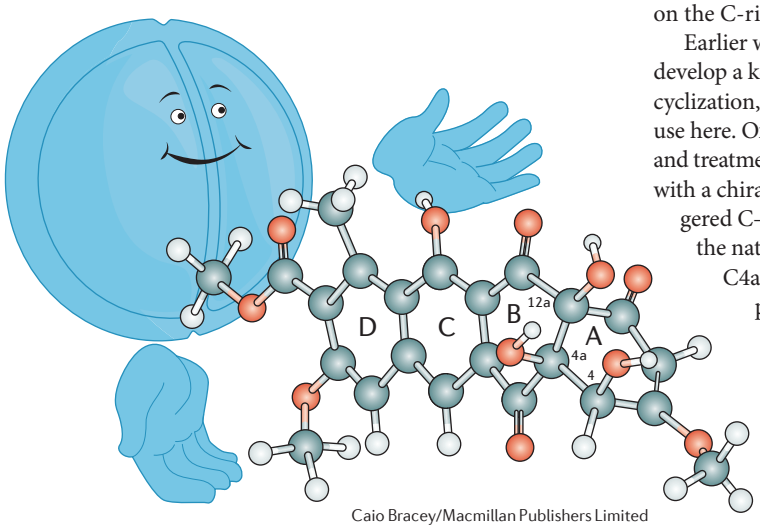

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