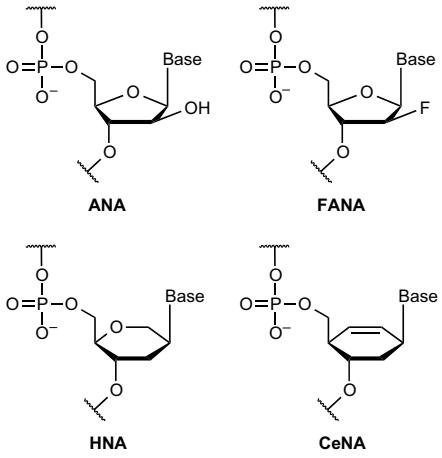
XENO-NUCLEIC ACIDS

Unnatural biocatalysts

Nature http://doi.org/xwd (2014)



Xeno-nucleic acids (XNAs) are synthetic genetic polymers containing non-natural components such as alternative nucleobases, sugars, or a connecting backbone with a different chemical structure. This introduction of a wider selection of functional building blocks could enable XNA sequences to participate in a wider selection of chemical reactions than their DNA or RNA equivalents. However, although XNAs have previously been shown to bind ligands and fold into defined structures, little was known about their ability to catalyse chemical reactions.

A team led by Philipp Holliger at the MRC Laboratory of Molecular Biology, Cambridge, UK, has now created a series of XNA sequences — which they call XNAzymes — that can act as catalysts. The XNAzymes were created using nucleic acid sequences in which the normal ribofuranose ring found in DNA and RNA was replaced with a synthetic analogue. Using four different sugars enabled the fabrication of XNAzymes based on four different types of XNA: arabino nucleic acids (ANA); 2′-fluoroarabino nucleic acids (FANA); hexitol nucleic acids (HNA); and cyclohexene nucleic acids (CeNA). To identify XNA sequences that could catalyse reactions, the team employed previously developed techniques for replicating and selecting XNA sequences. This led to the development of XNAzymes that could cleave a phosphodiester bond in RNA. XNAzymes from each of the four different types of XNA were shown to possess this RNA endonuclease-like activity.

A similar series of experiments using a different selection strategy identified XNAzymes that could act as RNA ligases by joining two RNA strands. Next, the team investigated whether XNAzymes with ligase activity could join two XNA strands. By carefully selecting both the XNAzyme and the XNA substrates, the team demonstrated that XNAzymes could repeatedly catalyse the iterative addition of short XNA substrates to form longer XNA oligomers of up to 100 nucleotides in length. In a final demonstration, an XNAzyme with ligase activity was shown to be capable of catalysing the formation of an XNAzyme with RNA endonuclease activity. These examples showed that XNA sequences can form a fully synthetic catalytic system. *RJ*

SELF-ASSEMBLY

Crystal milk

Angew. Chem. Int. Ed. http://doi.org/f2wn6k (2014)

Infants do not feed on what you would call 'a varied diet': day in, day out they get breast milk. One of its most nourishing components is fat, consisting of emulsified triglycerides, which the infant's digestive system has to break down into smaller

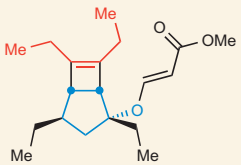
NATURAL PRODUCT SYNTHESIS

Tricycles and tribulations

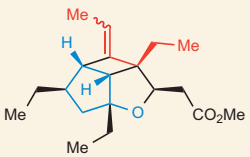
Angew. Chem. Int. Ed. http://dx.doi.org/10.1002/acie.201410419 (2014)

Hippolachnin A was first isolated from the South China Sea sponge *Hippospongia lachne* in 2013. Its crowded structure features a highly substituted cyclobutane ring and six contiguous stereocentres. Combined with its biological properties — potent antifungal activity and potential for the treatment of a number of diseases — these features make it an attractive synthetic target. Now, Eric Carreira and co-workers from ETH Zürich have reported the first total synthesis of (±)-hippolachnin A.

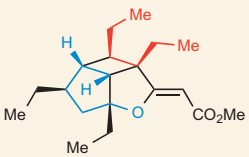
The synthesis begins with the construction of the fused cyclobutene intermediate **I**. A photocycloaddition between hex-3-yne and a readily available cyclopentenone (fragments in red and blue, respectively) produces the fused ring system. Two Grignard additions — one copper-catalysed 1,4-addition and one 1,2-addition — allow installation of the two ethyl side chains (shown in black). Subsequent alkenylation of the resultant tertiary alcohol produces **I**, which is primed for the tricycle-forming reaction. While iron-catalysed additions (proposed to proceed through activation of the alkene) resulted in tricycle formation, the stereochemistry of the product was found to be incorrect. An alternative rhodium-catalysed process gave the correct stereochemistry, but the product formed suggested that reaction was occurring by a Lewis-acid catalysed ene-type process rather than through β-C-H metalation as initially intended. The tricycle was still only formed in low yield however, and eventually Carreira and co-workers hit upon combined Lewis/Brønsted acid-catalysed conditions to form intermediate **II** in 65% yield as a 6:1 mixture of olefin diastereomers.



I



II



(±)-Hippolachnin A

Completion of the synthesis required a stereoselective reduction of the alkene in **II** followed by oxidation to produce the exocyclic double bond of the natural product. Computational modelling suggested that the desired product of hydrogenation would be thermodynamically less-favoured, but hydrogenation in the presence of Pearlman's catalyst provided the desired kinetic product. α-Phenylselenylation, followed by oxidation and elimination gave (±)-hippolachnin A. The synthesis proceeds in nine linear steps with an overall yield of 9%. *SD*