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Conformationally Restricted Dinucleotides: Tandem Ring-Closing Metathesis and Hydrogenation Approach

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ABSTRACT

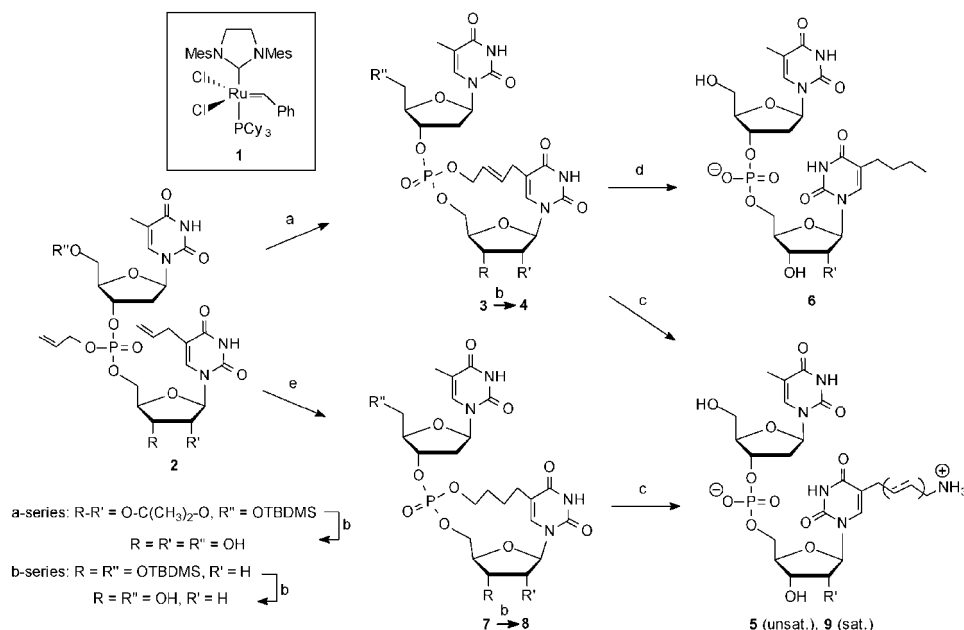
Cyclic dinucleotides with saturated connections between a nucleobase and the phosphate are synthesised using a tandem ring-closing metathesis (RCM) and hydrogenation protocol and found to be significantly stabilised towards ammonia.

Key Words: Conformational restriction; Dinucleotides; Ring-closing metathesis.

Conformationally restricted nucleic acid fragments such as dinucleotides have been introduced as mimics of tertiary nucleic acid structures.^[1] The introduction of the functional group tolerant ruthenium catalysts for metathesis reactions^[2] has opened new ways for introducing large rings into biomolecules such as peptide structures.^[3] We have applied RCM-reactions in the synthesis of conformationally restricted di- and trinucleotide structures containing unsaturated rings involving phosphotriester internucleoside linkages.^[4–6] Hereby, we present the application

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Scheme 1. a) **1**, CH₂Cl₂; b) 90% TFA; c) conc. NH₃; d) H₂, Pd/C, MeOH; e) **1**, CH₂Cl₂ then 1000 psi H₂.

of **1** as an efficient metathesis and hydrogenation catalyst^[7] towards cyclic dinucleotides.^[5,6]

Two different dinucleotides **2a/b** each containing two allyl-groups were prepared from standard phosphoramidite chemistry (Sch. 1). RCM-reactions using **1** afforded the two cyclic dinucleotides **3a/b** in medium yields.^[5,6] These were conveniently treated with TFA to give deprotected compounds **4a/b**. However, instability towards basic conditions was exemplified by the fast and quantitative reactions with ammonia affording **5a/b**. This base lability could at least in part be deduced to the allylic nature of the phosphotriester moiety. Therefore, **4a** was treated with standard palladium catalysed hydrogenation conditions giving, surprisingly, the doubly reduced compound **6a**. This problem was solved by using **1** as both RCM and hydrogenation catalyst.^[7] Thus, the dinucleotides **2a/b** were treated with **1**, and after completion of the RCM reaction as monitored by TLC, the reaction mixture was subjected to 1000 psi H₂ and the saturated cyclic dinucleotides **7a/b** were obtained in good yields.^[6] Deprotection afforded **8a/b**. Subsequently, these compounds were subjected to ammonia and found to be significantly more stable than the unsaturated counterparts **4a/b** affording only very slowly the ring-opened dinucleotides **9a/b**.

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