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Bi- and Tricyclic Nucleoside Derivatives Restricted in S-Type Conformations and Obtained by RCM-Reactions

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ABSTRACT

Ring-closing metathesis (RCM) is applied as a new and powerful technology in the construction of nucleoside analogues that are conformationally restricted in S-type conformations due to additional 3',4'- and/or 3',5'-linkages.

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

Nucleic acid analogues that are strongly conformationally restricted due to bior tricyclic nucleoside monomers have been introduced as potentially therapeutic and diagnostic agents. [1,2] LNA (Locked Nucleic Acid) is a nucleic acid analogue that displays unprecedented recognition of both DNA and RNA due to the bicyclic nucleoside monomers being perfect N-type conformational mimics. [3,4] Among several examples of S-type mimics, [1,2,5] however, the perfect one has not been obtained. We have recently applied the RCM-reaction (and the catalyst 1, Sch. 1)^[6]

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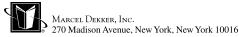
Scheme 1. a) n = 0: ref. 7.; n = 1: five similar steps, 70%; b) n = 0: ref. 7; n = 1: six similar steps, 43%; c) i. $(Im)_2CS$, CH_3CN , toluene; ii. Bu_3SnH , AIBN, CH_3CN , 61%; d) H_2 , $Pd(OH)_2$ -C, EtOH, 75%; e) OsO_4 , OsO_4 ,

as an efficient tool in the construction of new bi- and tricyclic nucleosides.^[7–9] Here, we present the recent synthetic results towards nucleosides that are restricted in S-type conformations.

As a very convenient general starting material, diacetone-α-D-glucose has been used as a skeleton for the incorporation of terminal double bonds as demonstrated in the construction of 2,^[7] 3 and 4^[9] via stereoselective Grignard reactions. After RCM-reactions and subsequent Vorbrüggen nucleobase couplings, 5^[7] and 6 have been obtained in high yields. The former has been used in an improved preparation of the well known bicycloDNA monomer 7^[5] as well as in the construction of a tricyclic nucleoside derivative 8.^[8] Also 4 has been transformed through standard steps to a nucleoside 9 and subsequently used in a very efficient RCM-reaction to afford the bicyclic nucleoside 10.^[9] This nucleoside has been used as a substrate for a dihydroxylation reaction giving, after deprotection, only one major product 11 as an example of a strongly conformationally restricted poly-hydroxylated bicyclic nucleoside. The configuration of 11 has been determined using Karplus equations and ¹H NMR in connection to ab initio calculations.

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