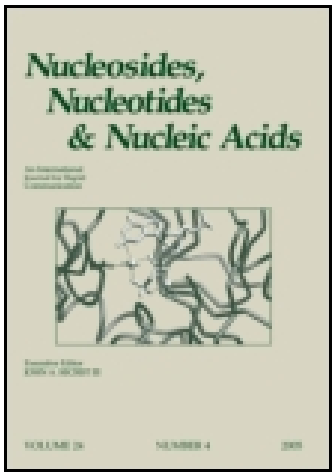

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Bi- and Tricyclic Nucleoside Derivatives Restricted in S-Type Conformations and Obtained by RCM-Reactions

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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 bi- or 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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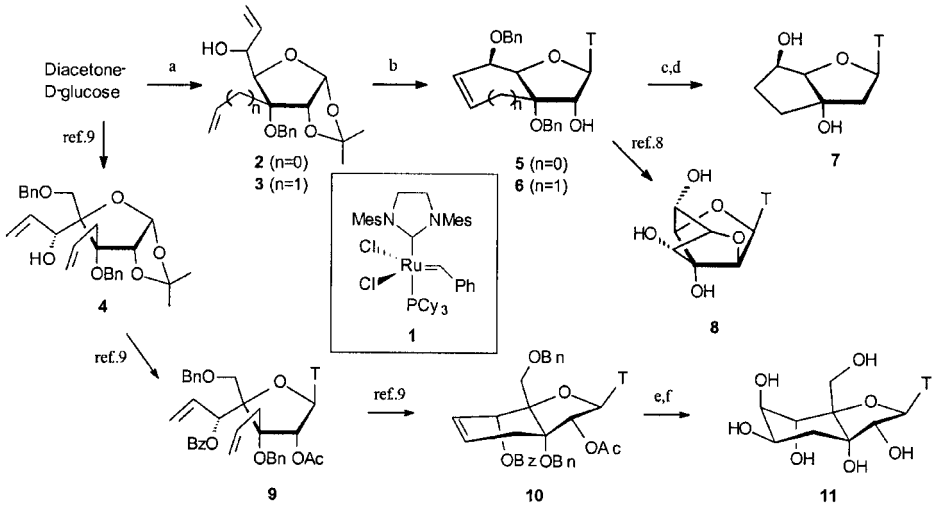

Scheme 1. a) n = 0: ref. 7.; n=1: five similar steps, 70%; b) n = 0: ref. 7; n = 1: six similar steps, 43%; c) i. $(Im)_2CS$, CH_3CN, toluene; ii. Bu_3SnH, AIBN, CH_3CN, 61%; d) H_2, $Pd(OH)_2$-C, EtOH, 75%; e) OsO_4, NMO, THF, H_2O, 52%; f) i. NaOMe, MeOH; ii. H_2, $Pd(OH)_2$-C, MeOH, 71%. T = thymin-1-yl.

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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