



Nucleosides, Nucleotides and Nucleic Acids

Publication details, including instructions for authors and subscription information:

<http://www.tandfonline.com/loi/Incn20>

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

Nanna Albæk ^a, Jacob Ravn ^a, Morten Freitag ^a, Helena Thomasen ^a, Nanna K. Christensen ^a, Michael Petersen ^a & Poul Nielsen ^{a b}

^a Nucleic Acid Center, Department of Chemistry, University of Southern Denmark, Odense M, Denmark

^b The Panum Institute, University of Copenhagen, Blegdamsvej 3, Copenhagen, DK-2200, Denmark

Published online: 31 Aug 2006.

To cite this article: Nanna Albæk, Jacob Ravn, Morten Freitag, Helena Thomasen, Nanna K. Christensen, Michael Petersen & Poul Nielsen (2003) Bi- and Tricyclic Nucleoside Derivatives Restricted in S-Type Conformations and Obtained by RCM-Reactions, *Nucleosides, Nucleotides and Nucleic Acids*, 22:5-8, 723-725, DOI: [10.1081/NCN-120022619](https://doi.org/10.1081/NCN-120022619)

To link to this article: <http://dx.doi.org/10.1081/NCN-120022619>

PLEASE SCROLL DOWN FOR ARTICLE

Taylor & Francis makes every effort to ensure the accuracy of all the information (the "Content") contained in the publications on our platform. However, Taylor & Francis, our agents, and our licensors make no representations or warranties whatsoever as to the accuracy, completeness, or suitability for any purpose of the Content. Any opinions and views expressed in this publication are the opinions and views of the authors, and are not the views of or endorsed by Taylor & Francis. The accuracy of the Content should not be relied upon and should be independently verified with primary sources of information. Taylor and Francis shall not be liable for any losses, actions, claims, proceedings, demands, costs, expenses, damages, and other liabilities whatsoever or howsoever caused arising directly or indirectly in connection with, in relation to or arising out of the use of the Content.

This article may be used for research, teaching, and private study purposes. Any substantial or systematic reproduction, redistribution, reselling, loan, sub-licensing, systematic supply, or distribution in any form to anyone is expressly forbidden. Terms & Conditions of access and use can be found at <http://www.tandfonline.com/page/terms-and-conditions>

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

Nanna Albæk, Jacob Ravn, Morten Freitag, Helena Thomasen,
Nanna K. Christensen, Michael Petersen, and Poul Nielsen*

Nucleic Acid Center, Department of Chemistry, University of
Southern Denmark, Odense M, Denmark

ABSTRACT

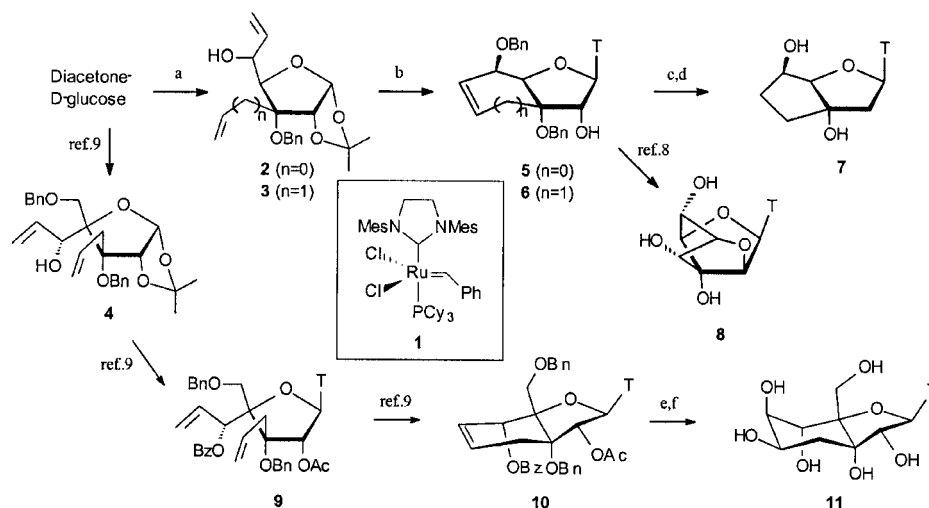
Ring-closing metathesis (RCM) is applied as a new and powerful technology in the construction of nucleoside analogues that are conformationally restricted in S-type conformations due to additional 3',4'- and/or 3',5'-linkages.

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]

*Correspondence: Poul Nielsen, The Panum Institute, University of Copenhagen, Blegdamsvej 3, DK-2200 Copenhagen, Denmark; Fax: +45 35 39 60 42; E-mail: pen@imbg.ku.dk.





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. $(\text{Im})_2\text{CS}$, CH_3CN , toluene; ii. Bu_3SnH , AIBN, CH_3CN , 61%; d) H_2 , $\text{Pd}(\text{OH})_2\text{-C}$, EtOH , 75%; e) OsO_4 , NMO, THF, H_2O , 52%; f) i. NaOMe, MeOH; ii. H_2 , $\text{Pd}(\text{OH})_2\text{-C}$, MeOH, 71%. T = thymine-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.

ACKNOWLEDGMENT

The Nucleic Acid Center is funded by the Danish National Research Foundation for the studies on nucleic acid chemical biology.

REFERENCES

1. Meldgaard, M.; Wengel, J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3539–3554.
2. Leumann, C.J. *Bioorg. Med. Chem.* **2002**, *10*, 841–854.
3. Koshkin, A.A.; Singh, S.K.; Nielsen, P.; Rajwanshi, V.K.; Kumar, R.; Meldgaard, M.; Olsen, C.E.; Wengel, J. *Tetrahedron* **1998**, *54*, 3607–3630.
4. Obika, S.; Nanbu, D.; Hari, Y.; Andoh, J.; Morio, K.; Doi, T.; Imanishi, T. *Tetrahedron Lett.* **1998**, *39*, 5401–5404.
5. Tarköy, M.; Bolli, M.; Schweizer, B.; Leumann, C. *Helv. Chim. Acta* **1993**, *76*, 481–510.
6. Trnka, T.M.; Grubbs, R.H. *Acc. Chem. Res.* **2001**, *34*, 18–29.
7. Ravn, J.; Nielsen, P. *J. Chem. Soc., Perkin Trans. 1* **2001**, 985–993.
8. Ravn, J.; Thorup, T.; Nielsen, P. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1855–1861.
9. Thomasen, H.; Meldgaard, M.; Freitag, M.; Petersen, M.; Wengel, J.; Nielsen, P. *Chem. Comm.* **2002**, 1888–1889.



