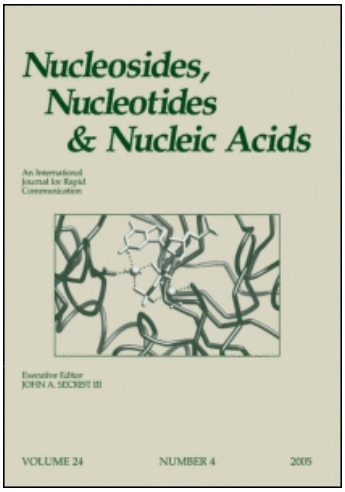


Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

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[ab]
[a] Nucleic Acid Center, Department of Chemistry, University of Southern Denmark, Odense M, Denmark [b] The Panum Institute, University of Copenhagen, Copenhagen, Denmark

Online publication date: 09 August 2003

To cite this Article Albæk, Nanna , Ravn, Jacob , Freitag, Morten , Thomasen, Helena , Christensen, Nanna K. , Petersen, Michael and Nielsen, Poul(2003) 'Bi- and Tricyclic Nucleoside Derivatives Restricted in S-Type Conformations and Obtained by RCM-Reactions', Nucleosides, Nucleotides and Nucleic Acids, 22: 5, 723 — 725
To link to this Article: DOI: 10.1081/NCN-120022619
URL: http://dx.doi.org/10.1081/NCN-120022619

NUCLEOSIDES, NUCLEOTIDES & NUCLEIC ACIDS
Vol. 22, Nos. 5–8, pp. 723–725, 2003

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

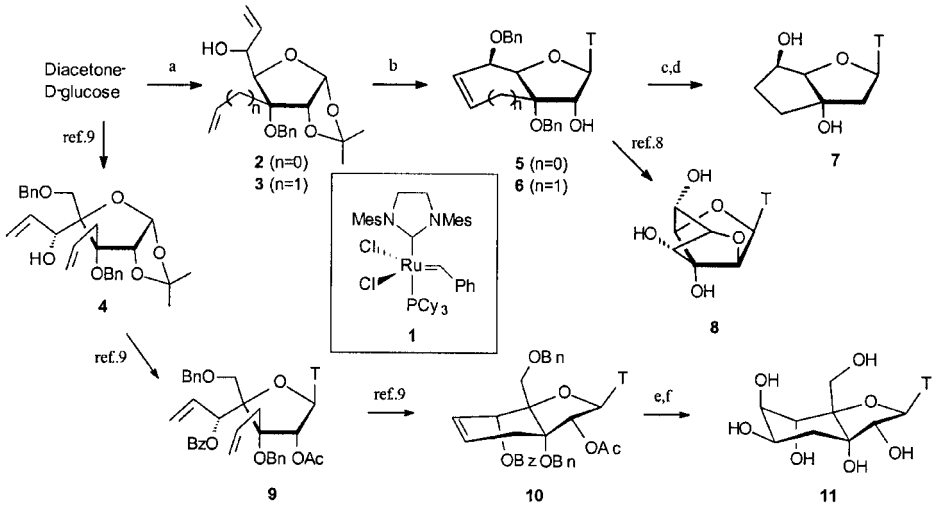
Ring-closing metathesis (RCM) is applied as a new and powerful technology in the construction of nucleoside analogues that are conformationally restricted in S-type conformations due to additional 3′,4′- and/or 3′,5′-linkages.

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.

DOI: 10.1081/NCN-120022619
1525-7770 (Print); 1532-2335 (Online)



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.

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.

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016