Novel 5′-deoxy nucleosyl amino acid scaffolds for the synthesis of muraymycin analogues†

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Received 18th February 2010, Accepted 1st April 2010
First published as an Advance Article on the web 12th April 2010
DOI: 10.1039/c003092a

Naturally occurring nucleoside antibiotics such as muraymycins represent promising lead structures for the development of novel antibacterial agents. A concise synthesis of 5′-deoxy muraymycin derivatives has been developed. The key step was the highly stereoselective asymmetric hydrogenation of suitable didehydro amino acid precursors, providing unique nucleosyl amino acid structures.

Due to emerging resistances of bacteria towards established antibiotics,[1] the development of novel antibacterial agents has become one of the main objectives of medicinal chemistry in recent years. Ideally, drug candidates with antimicrobial potency should display new or yet unexploited modes of action.[2] This is the case for the inhibition of the bacterial membrane protein translocase I (MraY), a key enzyme in the early stages of peptidoglycan biosynthesis,[3,4] which has recently drawn attention as a promising drug target.[5]

One valuable approach in drug development is to employ natural products as lead structures.[6] They can be of particular importance whenever structural information about the target protein is difficult to obtain, as it is often the case for membrane proteins. For MraY, naturally occurring nucleoside antibiotics have been reported to act as inhibitors.[7] These natural products are distinctly characterised by the unique structures of their nucleoside-derived moieties. Three subclasses of nucleoside antibiotics, the liposidomycins, caprazamycins and muraymycins, as well as the muraymycin-like FR-900493, have a common (5′*S*,6′*S*)-uridine-derived core structure, characterised by C–C-bond linkage of the 5′-carbon atom of the uridine unit to a glycine moiety (C-6′) as well as aminoribosylation of the 5′-hydroxy group.[7]

Structure–activity relationship (SAR) studies have been reported for synthetic analogues of the caprazamycins,[8] indicating a crucial role of the aminoribosyl unit for the retention of antibacterial activity towards *Mycobacterium tuberculosis*.[8c] In case of the muraymycins, a comparison of the 19 isolated naturally occurring derivatives provides different SAR insights: the activities of aminoribosylated muraymycin A1 **1** and non-aminoribosylated muraymycin A5 **2** against several bacteria including *Staphylococcus aureus* do not differ dramatically (Fig. 1).[9] In addition, (semi-)synthetic analogues of the muraymycins have been investigated.[10] Remarkable results were obtained for the SAR of synthetic truncated muraymycin derivatives (*e.g.* **3**–**7**, Fig. 1): firstly, the absolute configuration at the 5′-position was required to be (*R*) in order to obtain good activities, *i.e.* only 5′-*epi*-analogues with respect to the (5′*S*)-configured natural products were active. Secondly, the presence of some synthetic protecting groups (*tert*-butyl ester, *tert*-butyldimethylsilyl (TBDMS) groups) turned out to be a prerequisite for antibacterial potency.[10b]

In order to obtain novel structurally simplified nucleoside scaffolds for the synthesis of muraymycin analogues, it was envisaged to prepare 5′-deoxy derivatives lacking the site for aminoribosylation. In addition, 5′-deoxy nucleosyl amino acid

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† Electronic Supplementary Information (ESI) available: Experimental procedures for all syntheses, ^{1}H and ^{13}C NMR spectra of all compounds, details of the ^{1}H-^{1}H NOESY NMR experiment. See DOI: 10.1039/c003092a

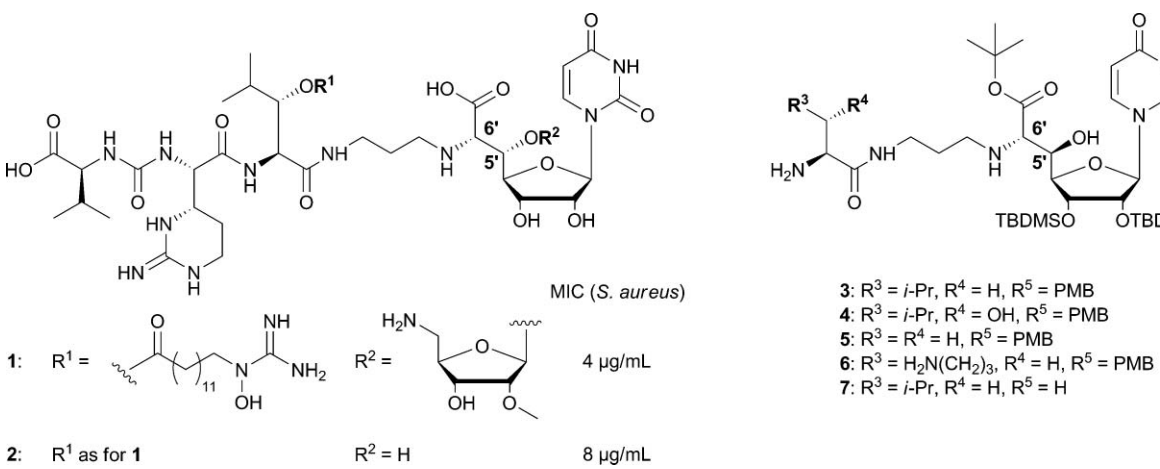


Fig. 1 Naturally occurring nucleoside antibiotics muraymycin A1 **1** and muraymycin A5 **2**[9] and synthetic truncated 5′-*epi*-muraymycin analogues **3**–**7** displaying antibacterial activity[10b] (MIC = minimal inhibitory concentration, PMB = *para*-methoxybenzyl, TBDMS = *tert*-butyldimethylsilyl).

structures should provide insights into the role of the 5′-hydroxy group in case of truncated muraymycin analogues such as **3–7** (Fig. 1). Our objective therefore was to synthesise target compounds **8** and **9** with (6′*S*)- and (6′*R*)-configuration, respectively, from a common precursor in a stereocontrolled way. Thus, the influence of the configuration in 6′-position can also be elucidated. Both **8** and **9**, which might also serve as suitably protected building blocks for the synthesis of more complex muraymycin analogues, were converted into their corresponding derivatives **10** and **11**, respectively, which represent 5′-deoxy analogues of **3** for SAR studies on truncated muraymycin derivatives (Fig. 2).

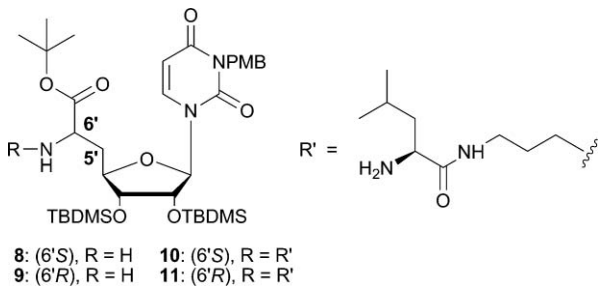
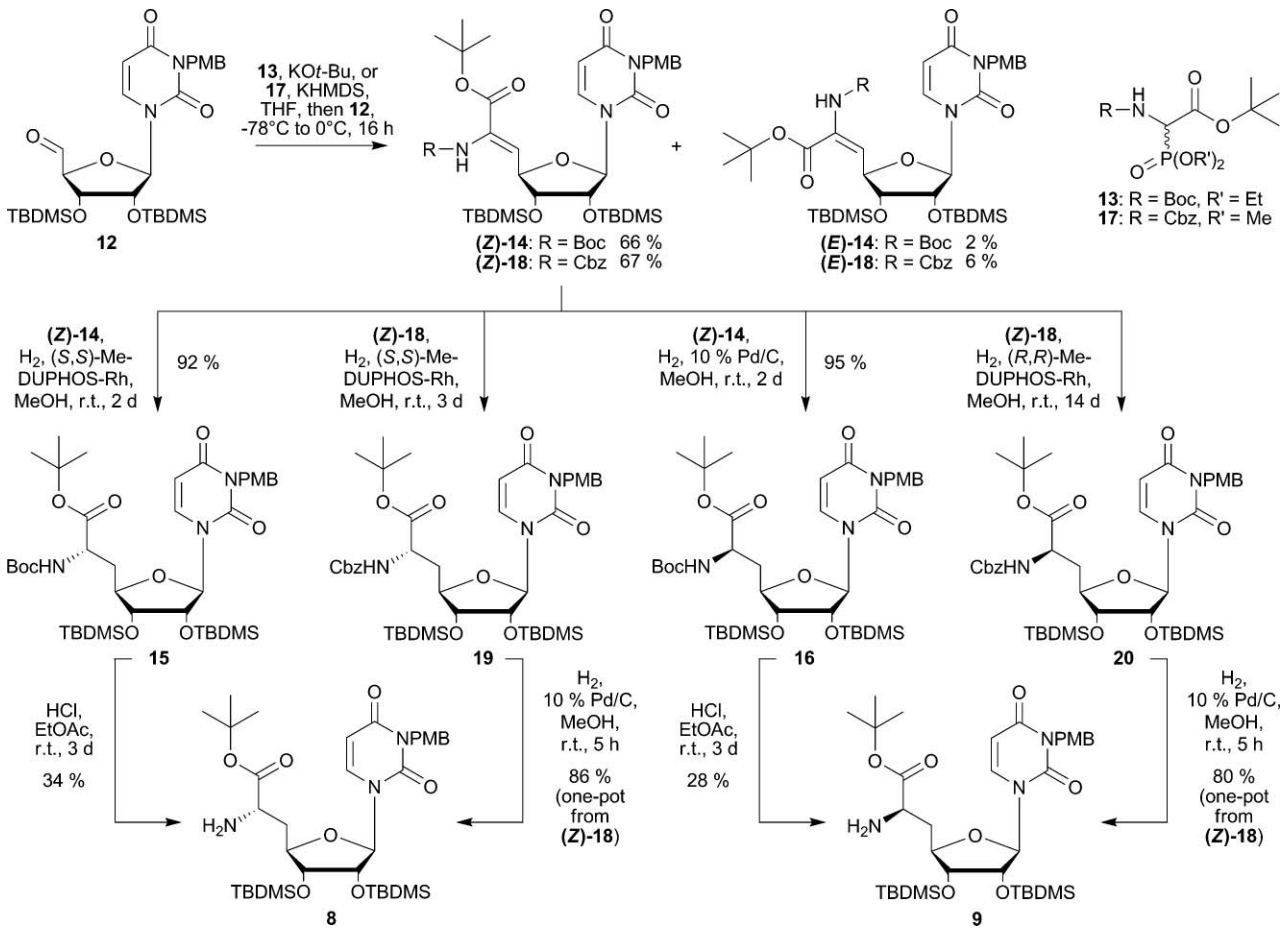


Fig. 2 Target compounds **8–11**.

The synthetic route reported in this work started from protected uridine-5′-aldehyde **12** (Scheme 1), which can easily be obtained from uridine in an overall yield of 66% over 4 steps.[11] Wittig–Horner reaction of aldehyde **12** with the *N*-Boc-protected phosphonate **13**[12] provided didehydro amino acid **(*Z*)-14** in a yield of 66% and, as expected,[13] with high diastereoselectivity. Thus, only 2% of the diastereomer **(*E*)-14** was found and isolated by column chromatography. The configuration of the didehydro amino acid moiety was assigned based on established ^{1}H NMR criteria for this class of compounds.[14] Only the (*Z*)-isomer was required for the subsequent asymmetric hydrogenation as it is reported that asymmetric hydrogenation using rhodium catalysts occurs more rapidly and with significantly better stereoselectivities for (*Z*)-didehydro amino acids than for the (*E*)-isomers.[15] Consequently, hydrogenation of **(*Z*)-14** in the presence of the chiral rhodium catalyst (+)-1,2-bis-((2*S*,5*S*)-2,5-dimethylphospholano)-benzene-(cyclooctadiene)-rhodium(I) tetrafluoroborate ((*S*,*S*)-Me-DUPHOS-Rh)[16a] provided product **15** in an excellent yield of 92% and with high diastereoselectivity (*d.r.* >97 : 3 based on ^{1}H NMR). It is well established that (*S*,*S*)-Me-DUPHOS-Rh converts *N*-carbamate protected (*Z*)-didehydro amino acid esters selectively into L-amino acids.[12,16b] As there was clear evidence of the asymmetric homogenous hydrogenation of **(*Z*)-14** being a catalyst-controlled reaction (*vide infra*), the stereochemistry at the C-6′ position of **15** could therefore be assigned as (*S*). In contrast, when precursor **(*Z*)-14** was hydrogenated under heterogenous conditions using palladium on charcoal, a surprising substrate-controlled selectivity (*d.r.* >95 : 5 based on ^{1}H NMR) towards



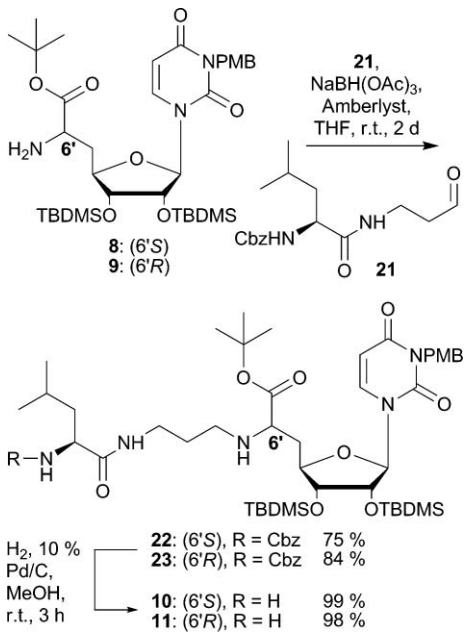
Scheme 1 Synthesis of 5′-deoxy nucleosyl amino acid building blocks **8** and **9**.

the other diastereomer with (6′*R*)-configuration was observed to give the according product **16** in 95% yield. For the synthesis of target bulding blocks **8** and **9**, the Boc group then had to be removed in the presence of both the *tert*-butyl ester and the silyl protecting groups. Though similar transformations employing hydrogen chloride in ethyl acetate have been previously reported,[17] the obtained yields of **8** and **9** (34% and 28%, respectively) were not satisfactory (Scheme 1). Most notably, prolonged reaction times in order to obtain sufficient conversion of the starting material led to unwanted side reactions such as cleavage of the silyl ether moieties.

Due to this limitation of the synthetic route utilising *N*-Boc protection, it was then decided to change the amino protecting group. Using phosphonate **17**[18] for the Wittig–Horner step, *N*-Cbz protected didehydro amino acids **(*Z*)-18** and **(*E*)-18** were isolated in 67% and 6% yield, respectively, after column chromatography (Scheme 1). Surprisingly, application of the established ^{1}H NMR criteria for configurational assignment[14] was inconclusive in this case. Based on the results previously obtained with the *N*-Boc strategy, it was the most likely conclusion to propose the (*Z*)-configuration for the major product in this case as well. This was experimentally supported by the results of the subsequent hydrogenation reactions (*vide infra*) as well as a ^{1}H-^{1}H NOESY NMR experiment.[19] When diastereomerically pure **(*Z*)-18** was used for the asymmetric hydrogenation in the presence of (*S*,*S*)-Me-DUPHOS-Rh, *N*-Cbz protected nucleosyl amino acid **19** was obtained. The *N*-protecting group could then be cleaved in a simple one-pot manner by further hydrogenation after the addition of palladium on charcoal to provide **8** directly in a good yield of 86% and with excellent diastereoselectivity (*d.r.* >97 : 3 based on ^{1}H NMR). In order to avoid hydrogenolysis of the Cbz group prior to reduction of the double bond, (*R*,*R*)-Me-DUPHOS-Rh was used instead of palladium on charcoal (*vide supra*) for the synthesis of **20**, finally providing the (6′*R*)-configured congener **9** after subsequent hydrogenolysis of the Cbz group. This one-pot sequence provided **9** in good yield (80%) and excellent diastereoselectivity (*d.r.* >97 : 3 based on ^{1}H NMR, Scheme 1). The products **8** and **9** obtained *via* the *N*-Cbz route were identical to those furnished by the *N*-Boc approach, which was unambigously proven by NMR spectroscopy. Thus, nucleosyl amino acid building blocks **8** and **9** were synthesised from uridine in overall yields of 38% and 35%, respectively, over 6 steps *via* the *N*-Cbz protecting group strategy.

The reaction periods of the asymmetric hydrogenation transformations of **(*Z*)-18** needed for sufficient conversions differed significantly for the two Me-DUPHOS-Rh catalysts. This might indicate the combination of **(*Z*)-18** with (*S*,*S*)-Me-DUPHOS-Rh to represent the matched case, while the reaction using (*R*,*R*)-Me-DUPHOS-Rh might have suffered from a mismatched situation. As diastereoselectivities were very high in both cases, catalyst (*i.e.* ligand) control clearly dominated over any potential substrate control resulting from the chiral nucleoside moiety. This was at least the case for homogenous hydrogenation, while substrate control could be observed for heterogenous hydrogenation of the Boc-protected derivative **(*Z*)-14** (*vide supra*). Attempts to perform the hydrogenation of **(*Z*)-18** in the presence of the achiral Wilkinson catalyst $(PPh_3)_3RhCl$ surprisingly gave no conversion. However, due to the clear evidence of the asymmetric homogenous hydrogenation reaction being a catalyst-controlled transformation and the well-established stereoselectivity of Me-DUPHOS-Rh catalysts,[12,16b] assignment of the stereochemistry at C-6′ was feasible.

As an efficient stereoselective synthesis of the unprecedented 5′-deoxy nucleosyl amino acid scaffolds **8** and **9** could be achieved, it was desired to convert them into muraymycin derivatives **10** and **11**, respectively, representing analogues of the reportedly bioactive compound **3**.[10b] Both amines **8** and **9** were therefore reacted with aldehyde **21**[10b,20] in reductive amination transformations, affording **22** and **23** in 75% and 84% yield, respectively. Final Cbz deprotection under hydrogenolytic conditions then gave target compounds **10** and **11** in nearly quantitative yields (Scheme 2).



Scheme 2 Synthesis of muraymycin analogues **10** and **11**.

In conclusion, we report the synthesis of novel 5′-deoxy nucleosyl amino acid scaffolds derived from the nucleosidic core structure of several natural products, including muraymycin and caprazamycin antibiotics. A highly efficient and stereoselective approach using asymmetric hydrogenation of a common didehydro amino acid precursor provided both the (6′*S*)- and (6′*R*)-configured building blocks **8** and **9**, which can be used for the preparation of novel non-aminoribosylated muraymycin analogues for SAR studies. The results obtained for this synthetic key step are of major general importance for the synthesis of α-amino acid derivatives with highly functionalised side chains. The obtained excellent diastereoselectivities highlight the enormous versatility and broad substrate scope of the Me-DUPHOS-Rh catalysts in the hydrogenation of complex substrates. Compounds **8** and **9** were used for the concise synthesis of two analogues **10** and **11** of an established bioactive truncated muraymycin derivative. The biological evaluation of these 5′-deoxy muraymycins as part of a detailed SAR study on muraymycin analogues is currently being carried out.

Acknowledgements

We thank the Deutsche Forschungsgemeinschaft (DFG, SFB 803 "Functionality controlled by organization in and between membranes") and the Fonds der Chemischen Industrie (FCI) for financial support. Donation of laboratory equipment by the BASF SE is gratefully acknowledged.

Notes and references

1 G. Taubes, *Science*, 2008, **321**, 356.
2 C. Walsh, *Nat. Rev. Microbiol.*, 2003, **1**, 65.
3 (*a*) W. G. Struve and F. C. Neuhaus, *Biochem. Biophys. Res. Commun.*, 1965, **18**, 6; (*b*) W. G. Struve, R. K. Sinha, F. C. Neuhaus and M. S. Prime, *Biochemistry*, 1966, **5**, 82; (*c*) M. G. Heydanek, W. G. Struve and F. C. Neuhaus, *Biochemistry*, 1969, **8**, 1214; (*d*) M. Ikeda, M. Wachi, H. K. Jung, F. Ishino and M. Matsuhashi, *J. Bacteriol.*, 1991, **173**, 1021; (*e*) D. S. Boyle and W. D. Donachie, *J. Bacteriol.*, 1998, **180**, 6429.
4 (*a*) A. Bouhss, D. Mengin-Lecreulx, D. Le Beller and J. van Heijenoort, *Mol. Microbiol.*, 1999, **34**, 576; (*b*) A. J. Lloyd, P. E. Brandish, A. M. Gilbey and T. D. H. Bugg, *J. Bacteriol.*, 2004, **186**, 1747; (*c*) A. Bouhss, M. Crouvoisier, D. Blanot and D. Mengin-Lecreulx, *J. Biol. Chem.*, 2004, **279**, 29974; (*d*) T. Stachyra, C. Dini, P. Ferrari, A. Bouhss, J. van Heijernoort, D. Mengin-Lecreulx, D. Blanot, J. Biton and D. Le Beller, *Antimicrob. Agents Chemother.*, 2004, **48**, 897.
5 (*a*) C. Dini, *Curr. Top. Med. Chem.*, 2005, **5**, 1221; (*b*) T. D. H. Bugg, A. J. Lloyd and D. I. Roper, *Infect. Disord.: Drug Targets*, 2006, **6**, 85.
6 F. J. Dekker, M. A. Koch and H. Waldmann, *Curr. Opin. Chem. Biol.*, 2005, **9**, 232.
7 K.-I. Kimura and T. D. H. Bugg, *Nat. Prod. Rep.*, 2003, **20**, 252.
8 (*a*) S. Hirano, S. Ichikawa and A. Matsuda, *J. Org. Chem.*, 2008, **73**, 569; (*b*) S. Hirano, S. Ichikawa and A. Matsuda, *Bioorg. Med. Chem.*, 2008, **16**, 428; (*c*) S. Hirano, S. Ichikawa and A. Matsuda, *Bioorg. Med. Chem.*, 2008, **16**, 5123.
9 L. A. McDonald, L. R. Barbieri, G. T. Carter, E. Lenoy, J. Lotvin, P. J. Petersen, M. M. Siegel, G. Singh and R. T. Williamson, *J. Am. Chem. Soc.*, 2002, **124**, 10260.
10 (*a*) Y.-I. Lin, Z. Li, G. D. Francisco, L. A. McDonald, R. A. Davis, G. Singh, Y. Yang and T. S. Mansour, *Bioorg. Med. Chem. Lett.*, 2002, **12**, 2341; (*b*) A. Yamashita, E. Norton, P. J. Petersen, B. A. Rasmussen, G. Singh, Y. Yang, T. S. Mansour and D. M. Ho, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 3345.
11 A. P. Spork, S. Koppermann and C. Ducho, *Synlett*, 2009, 2503.
12 C. Ducho, R. B. Hamed, E. T. Batchelar, J. L. Sorensen, B. Odell and C. J. Schofield, *Org. Biomol. Chem.*, 2009, **7**, 2770.
13 U. Schmidt, H. Griesser, V. Leitenberger, A. Lieberknecht, R. Mangold, R. Meyer and B. Riedl, *Synthesis*, 1992, 487.
14 R. Mazurkiewicz, A. Kuźnik, M. Grymel and N. Kuźnik, *Magn. Reson. Chem.*, 2005, **43**, 36.
15 B. D. Vineyard, W. S. Knowles, M. J. Sabacky, G. L. Bachman and D. J. Wienkauff, *J. Am. Chem. Soc.*, 1977, **99**, 5946.
16 (*a*) M. J. Burk, *J. Am. Chem. Soc.*, 1991, **113**, 8518; (*b*) T. Masquelin, E. Broger, K. Müller, R. Schmid and D. Obrecht, *Helv. Chim. Acta*, 1994, **77**, 1395.
17 (*a*) F. S. Gibson, S. C. Bergmeier and H. Rapoport, *J. Org. Chem.*, 1994, **59**, 3216; (*b*) F. Cavelier and C. Enjalbal, *Tetrahedron Lett.*, 1996, **37**, 5131.
18 (*a*) U. Schmidt, A. Lieberknecht, U. Schanbacher, T. Beuttler and J. Wild, *Angew. Chem.*, 1982, **94**, 797; U. Schmidt, A. Lieberknecht, U. Schanbacher, T. Beuttler and J. Wild, *Angew. Chem., Int. Ed. Engl.*, 1982, **21**, 776; (*b*) U. Schmidt, A. Lieberknecht and J. Wild, *Synthesis*, 1984, 53; (*c*) U. Schmidt and J. Wild, *Liebigs Ann. Chem.*, 1985, 1882; (*d*) R. Hamzavi, F. Dolle, B. Tavitian, O. Dahl and P. E. Nielsen, *Bioconjugate Chem.*, 2003, **14**, 941.
19 *N*-methylation of **(*Z*)-18** at the carbamate moiety with methyl iodide provided a derivative suitable for ^{1}H-^{1}H NOESY NMR investigations. The observed cross peak of the *N*-methyl group to H–4′ of the ribose moiety represented a nuclear Overhauser effect (nOe) indicating (*Z*)-configuration of the olefin motif. Details are described in the ESI.†.
20 M. Y. H. Lai, M. A. Brimble, D. J. Callis, P. W. R. Harris, M. S. Levi and F. Sieg, *Bioorg. Med. Chem.*, 2005, **13**, 533.

