

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

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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 dihydro 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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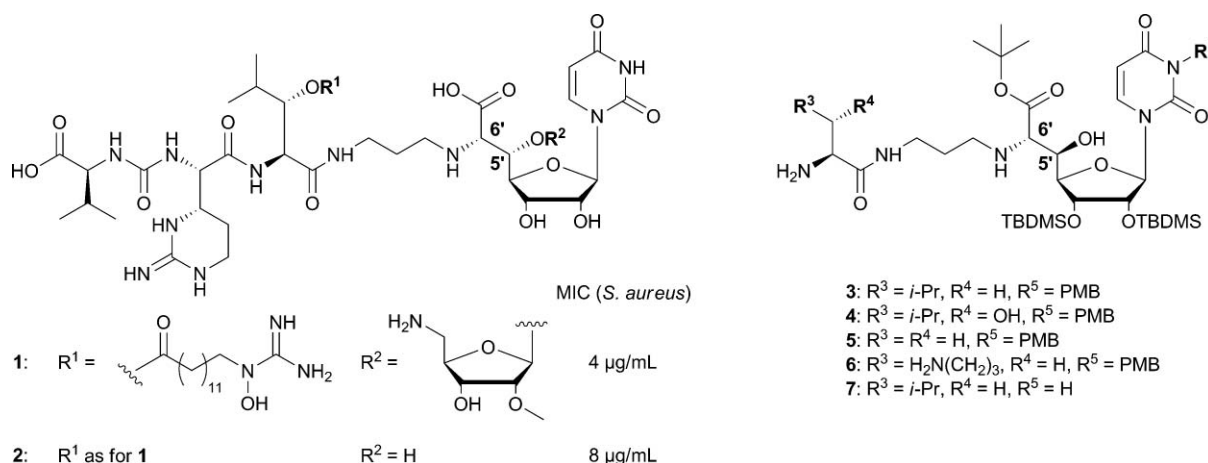
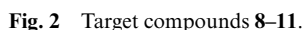


Fig. 1 Naturally occurring nucleoside antibiotics muraymycin A1 **1** and muraymycin A5 **2**⁹ and synthetic truncated 5'-*epi*-muraymycin analogues **3–7** displaying antibacterial activity^{10b} (MIC = minimal inhibitory concentration, PMB = *para*-methoxybenzyl, TBDMS = *tert*-butyldimethylsilyl).

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 dihydro 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 dihydro amino acid moiety was assigned based on established ¹H 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*)-dihydro 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 ¹H NMR). It is well established that (*S*,*S*)-Me-DUPHOS-Rh converts *N*-carbamate protected (*Z*)-dihydro 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 heterogeneous conditions using palladium on charcoal, a surprising substrate-controlled selectivity (*d.r.* >95:5 based on ¹H NMR) towards



12 $\xrightarrow[12, -78^{\circ}\text{C to } 0^{\circ}\text{C}, 16\text{ h}]{13, \text{KOt-Bu, or } 17, \text{KHMDS, THF}}$

(Z)-14: R = Boc 66 %
(Z)-18: R = Cbz 67 %

(E)-14: R = Boc 2 %
(E)-18: R = Cbz 6 %

13: R = Boc, R' = Et
17: R = Cbz, R' = Me

(Z)-14, H_2 , (S,S)-Me-DUPHOS-Rh, MeOH, r.t., 2 d, 92 %
(Z)-18, H_2 , (S,S)-Me-DUPHOS-Rh, MeOH, r.t., 3 d

(Z)-14, H_2 , 10 % Pd/C, MeOH, r.t., 2 d, 95 %
(Z)-18, H_2 , (R,R)-Me-DUPHOS-Rh, MeOH, r.t., 14 d

15 $\xrightarrow[34\%]{\text{HCl, EtOAc, r.t., 3 d}}$ **8**
16 $\xrightarrow[28\%]{\text{HCl, EtOAc, r.t., 3 d}}$ **9**
19 $\xrightarrow[86\% \text{ (one-pot from (Z)-18)}]{\text{H}_2, 10\% \text{ Pd/C, MeOH, r.t., 5 h}}$ **8**
20 $\xrightarrow[80\% \text{ (one-pot from (Z)-18)}]{\text{H}_2, 10\% \text{ Pd/C, MeOH, r.t., 5 h}}$ **9**

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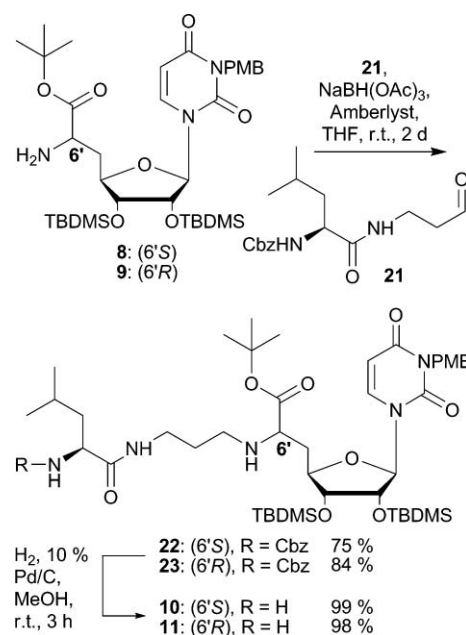
the other diastereomer with (6'*R*)-configuration was observed to give the according product **16** in 95% yield. For the synthesis of target building blocks **8** and **9**, the Boc group then had to be removed in the presence of both the *tert*-butyl ester and the silyl protecting groups. Though similar 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 ¹H NMR criteria for configurational assignment¹⁴ 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 ¹H-¹H 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 ¹H 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 ¹H 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 unambiguously 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 heterogeneous 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 (PPh₃)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.

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