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Phosphonoxins II: Diastereoselective Synthesis of Phosphonic Acid Analogues of Polyoxins

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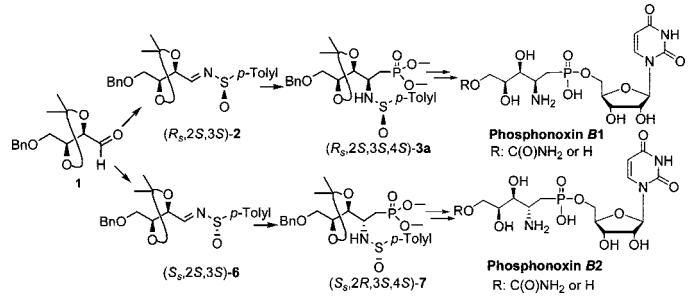
ABSTRACT



A diastereoselective synthesis of polyoxin analogues termed phosphonoxin *B*1 and *B*2 has been achieved. The key step was sulfinimine-mediated asymmetric formation of (R_S,2*S*,3*S*,4*S*)-β-aminophosphonate 3a or (S_S,2*R*,3*S*,4*S*)-β-aminophosphonate 7 as the major diastereoisomer. A double stereodifferentiation effect was not observed, and the diastereoselectivity is controlled by the absolute configuration of the sulfinyl group.

Chitin is an essential component of the cell walls of nearly all zoopathogenic and phytopathogenic fungi. In addition, chitin or a chitin-like polysaccharide is essential for arthropods, ascarids, and many protozoans,[1] and therefore, inhibition of chitin synthesis is an attractive target for antifungal and antiparasitic chemotherapeutics.[2] Biosynthesis of this polysaccharide is catalyzed by chitin synthase using uridine diphosphoryl-*N*-acetylglucosamine (UDP-GlcNAc) as the glycosyl donor.[3] While many chitin synthases have been described, little is known concerning the detailed structure of the chitin synthases, and therefore, modification of natural product inhibitors often provides a useful route to novel inhibitors.[4] Such natural products include the peptidylnucleoside derivatives polyoxins and nikkomycins.[5] These are competitive inhibitors of chitin synthases and exhibit antifungal, insecticidal, and acaricidal activities.[6] However, clinical utility of these natural products is compromised by their poor bioavailability and metabolic instability resulting in decrease of their efficacy and high inhibitory concentrations (millimolar range).[7,8] Thus, structural modifications of

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polyoxins have become the subject of much interest over the years.[9] We recently published synthesis and antigiardial activity of a new class of nucleoside phosphonate derivatives that, because of their passing resemblance to polyoxins, we named *phosphonoxins*.[10] This report describes the design and asymmetric synthesis of novel phosphonoxin derivatives based on polyoxins (Figure 1). Because these represent the

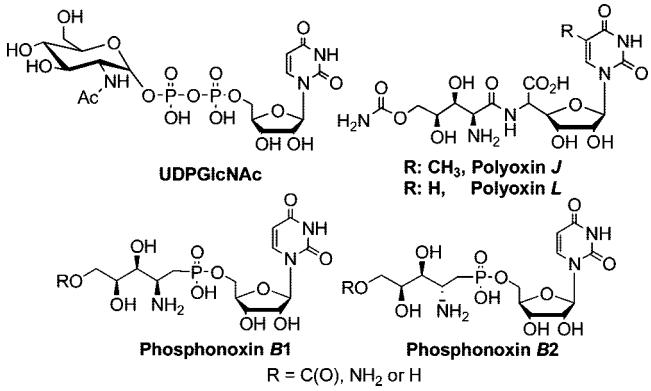


Figure 1. UDPGlcNAc, polyoxins J, L, and the phosphonoxins.

second generation of such derivatives we refer to them as *phosphonoxin B1* and *B2*. These analogues are assembled from a phosphonic acid analog (**9a**) or (**9b**) of polyoxamic acid and uridine (Figure 2). In contrast to the nikkomycins

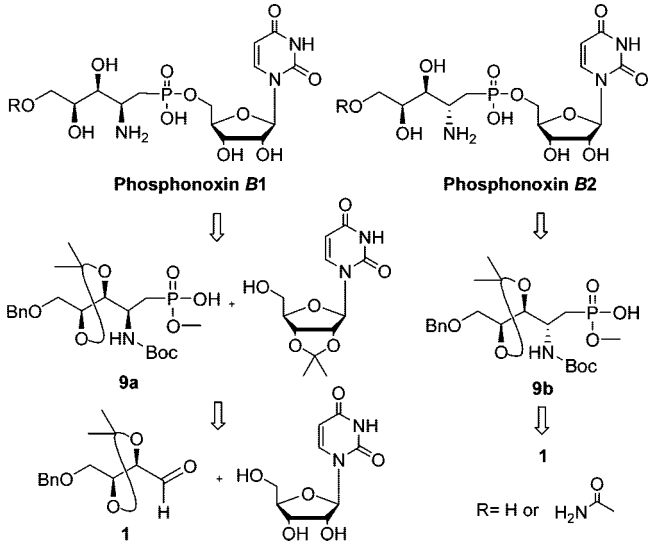
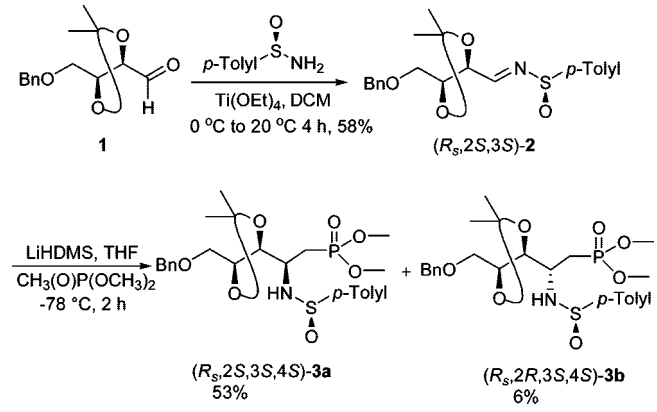


Figure 2. Retrosynthesis.

and polyoxins, the phosphonoxins described here are not peptides but are nucleoside phosphonates. Such phosphonates are able to penetrate cells and are chemically and enzymatically stable.[11]

Our synthesis began with the preparation of the key intermediate, **2**, obtained by the $Ti(OEt)_4$-assisted condensation of commercially available (*R*)-(−)-*p*-toluenesulfinamide (Aldrich) with the known 4-*O*-benzyl-2,3-*O*-isopropylidine-L-threose **1** (Scheme 1[12–14]). This aldehyde is readily prepared from

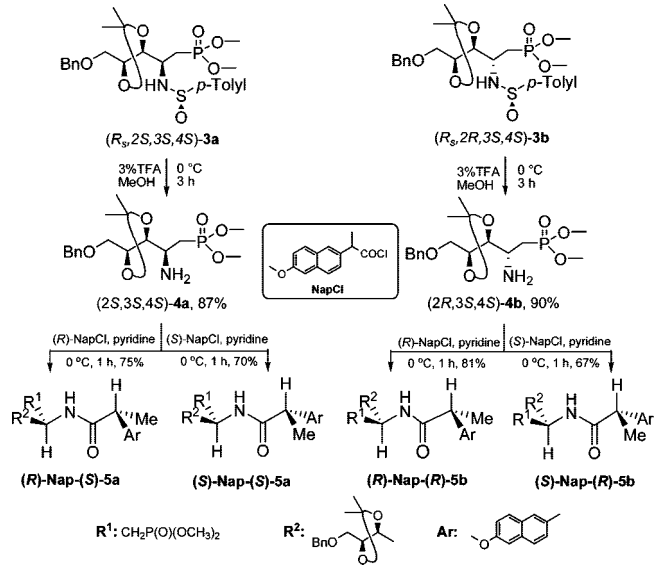
Scheme 1



commercially available (+)-diethyl-L-tartrate.[14,15] Diastereoselective addition of the α-phosphonate carbanion generated by treatment of dimethyl methylphosphonate with LiHMDS[12,13] to the enantiopure sulfinimine **2** (controlled by the configuration of the sulfinyl group)[12,14] afforded a 9:1 mixture of the diastereomers **3a** and **3b** (Scheme 1). The diastereoisomers were separated by flash chromatography, giving the major diastereoisomer **3a** in 53% yield.

Stereochemical configuration of the amino moiety of *β*-aminophosphonates **3a** and **3b** was established by removal of the chiral auxiliary followed by derivatization of the resulting free amines **4a** and **4b** with the commercially available (*R*) and (*S*)-naproxen acid chlorides (Scheme 2) using a standard method.[16] As established by Gajda and coworkers, the R^2 substituent should be shielded by the

Scheme 2



naphthyl ring in (*R*)-Nap-(*S*)-**5a** ($\Delta\delta^{RS}(R^2) < 0$),[17] while the dimethoxyphosphorylmethyl group should be deshielded by the amide group ($\Delta\delta^{RS}[P(O)(OMe)_2] > 0$). However, the opposite should be observed for the amides (*R*)-**5b**, where the dimethoxyphosphorylmethyl group should be shielded in (*R*)-Nap-(*R*)-**5b** ($\Delta\delta^{RS}$ $[P(O)(OMe)_2] < 0$), whereas the R^2 substituent should be shielded by the aryl group in (*S*)-Nap-(*R*)-**5b** ($\Delta\delta^{RS}(R^2) < 0$). Consistent with the above, the presence of the naphthyl ring in the amide (*S*)-**5a** resulted in $\Delta\delta^{RS} > 0$ (red) of the dimethoxyphosphorylmethyl group and $\Delta\delta^{RS} < 0$ (blue) of the R^2 substituent (Figure 3). The

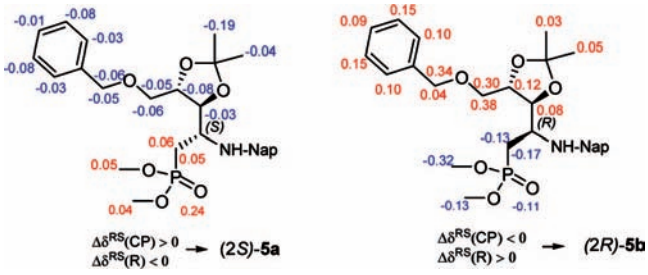
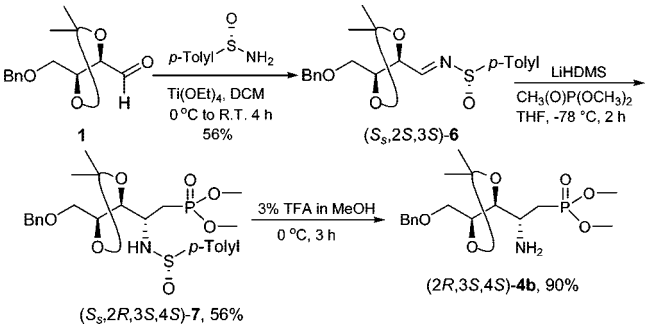


Figure 3. NMR determination of configuration of **5a** and **5b**.

opposite $\Delta\delta^{RS}$ was observed with **5b** ($\Delta\delta^{RS}[P(O)(OMe)_2] < 0$, $\Delta\delta^{RS}(R^2) > 0$) confirming the (*R*) configuration of the amino moiety of **5b**. Thus, by the conversion into the naproxen amides, the major diastereoisomer **3a** was determined to be R_S,2*S*,3*S*,4*S* (oil, $[\alpha]^{23}_D = -58.5$, *c* 0.9, $CHCl_3$, 53% yield) and minor isomer (R_S,2*R*,3*S*,4*S*)-**3b** (oil, $[\alpha]^{23}_D = -71.3$, *c* 0.4, $CHCl_3$, 6% yield).

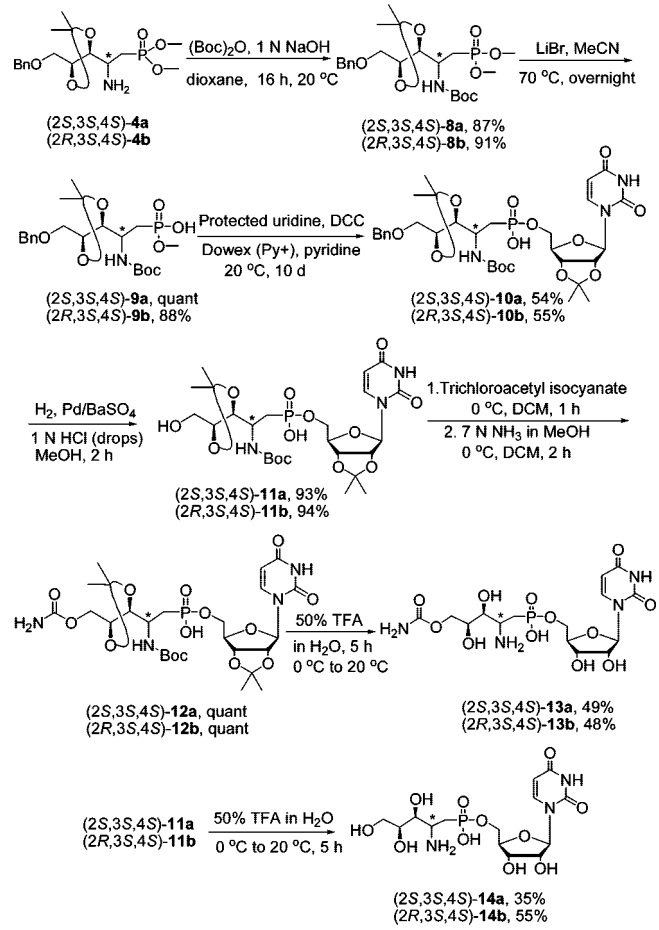
The synthesis of (S_S,2*R*,3*S*,4*S*)-**7** (oil, $[\alpha]^{23}_D = +39.5$, *c*2.5, $CHCl_3$) was accomplished from enantiomerically pure sulfinimine (*S*)-**6** (Scheme 3) starting from (*S*)-(−)-*p*- toluenesulfinamide and **1**. The absolute configuration of *β*-aminophosphonate **7** was confirmed by same method used for **3**, showing that the tartrate moiety of sulfinimine **2** or **6** did not significantly affect the diastereoselectivity in generation of phosphonates **3a** or **7**.

Scheme 3



With the *β*-aminophosphonate in hand, the amino moieties of **4** were protected ($(Boc)_2O$) giving intermediates **8** (Scheme 4). Attempts to generate the corresponding free phosphonates of **8** with TMSBr resulted in removal of the isopropylidine group therefore selective monodemethylation of phosphonic diesters **8** with LiBr was carried out.[9] Treatment of the resulting phosphonates, **9**, with 2′,3′-isopropylidine uridine, DCC and Dowex 50 WX8-200 (pyridinium form) resulted in coupling with the uridine and removal of the remaining methyl group from the phosphonate moiety in a one pot procedure.[9] The benzyl ether of resulting phosphonates, **10**, was cleaved with hydrogen in the presence of palladium on barium sulfate in dilute methanolic HCl to afford the primary alcohols **11**. Treatment of **11** with trichloroacetyl isocyanate followed by NH_3 in methanol (7 N) gave carbamates **12**.[18] Finally, deprotection of **11** and **12** with 50% TFA in H_2O at 0 °C (1 h) and then warming to room

Scheme 4



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temperature (3 h) gave the target phosphonoxins **13** and **14**.[19] The crude products were precipitated from the reaction mixture with ethanol, and the resulting solids were dissolved in water and purified by RP-HPLC to afford the targets **13a**($[\alpha]^{26}_D = +3.3$, *c* 0.09, H_2O), **13b** ($[\alpha]^{23}_D = +1.4$, *c* 0.07, H_2O), **14a** ($[\alpha]^{27}_D = +28.6$, *c* 0.03, H_2O), and **14b** ($[\alpha]^{23}_D = +10.8$, *c* 0.06, H_2O).

In summary, we designed and synthesized novel phosphonate analogues of polyoxins, called phosphonoxins. The key step in synthesis of the phosphonoxins is addition of lithium dimethyl methylphosphonate to enantiopure sulfinimines derived from the tartrate derivative 4-*O*-benzyl-2,3-*O*-isopropylidine-L-threose. Study of the antifungal and antiprotozoal properties of these agents is in progress and will be described in due course.

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Supporting Information Available: Experimental procedures and ^1H, ^{13}C, and ^{31}P NMR spectra of the reaction products. This material is available free of charge via the Internet at http://pubs.acs.org.

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