A Stereoselective Approach to the Core Structure of the Polyoxin and Nikkomycin Antibiotics

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Dedicated to the memory of Professor Ray Lemieux, in honor of his many contributions to organic chemistry.

Abstract: A stereoselective synthesis of the core structure of the polyoxin and nikkomycin antibiotics is described. Notable elements of the synthesis include the use of an IBX-based oxidation protocol in the high-yielding production of ribosyl aldehydes, and the use of a diastereoselective zinc-mediated acetylide addition for the generation of the C-5 stereocenter. The synthesis only requires three chromatographic purifications and should be amenable to the large-scale preparation of numerous polyoxin analogs.

Key words: antifungal agents, amino acids, carbohydrates, diastereoselectivity, stereoselective synthesis

As part of our ongoing program to develop novel inhibitors of fungal chitin synthase,[1] we desired efficient synthetic access to the microbial secondary metabolite uracil polyoxin C (**1**). Polyoxin C is the simplest member of a large class of peptide-nucleoside hybrid natural products that are distinguished by their competitive inhibition of chitin synthase (Figure 1).[2] As a result of this inhibitory activity, the polyoxins and the related nikkomycins have long been regarded as possible lead compounds for antifungal drug discovery. However, despite medicinal chemistry studies that involved extensive variation of the amino acid side-chain,[3] no member of this class has emerged as an effective antifungal agent. Nonetheless, we felt that the polyoxin scaffold would be a useful starting point for inhibitor design due to its modular structure and several points of possible diversity, and below describe a formal asymmetric synthesis of polyoxin C.

Several total and formal syntheses of the polyoxin C amino acid have been recorded, using both chiral pool and de novo construction approaches.[3a,4] We chose ribose as a starting material due to its commercial availability and low cost. Perhaps more importantly, beginning with ribose allows for eventual variation of the nucleoside base during analog synthesis. With this strategy in mind, we recognized the central challenges of such a synthesis as being one-carbon homologation of C5 of ribose and controlled generation of the C5 stereocenter.

The most direct approach would then involve generation of an aldehyde from a protected form of ribose followed by addition of a carbon nucleophile in a stereoselective

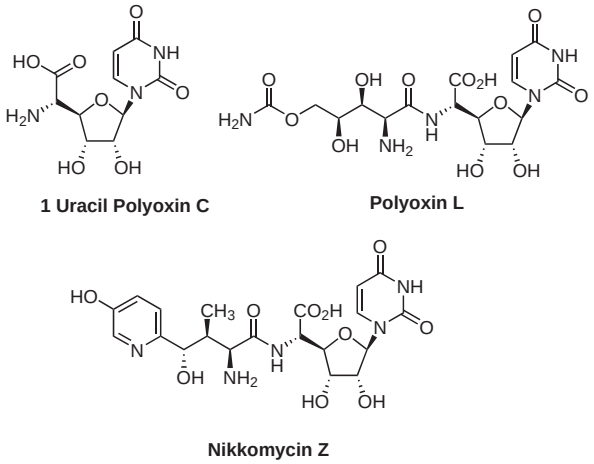
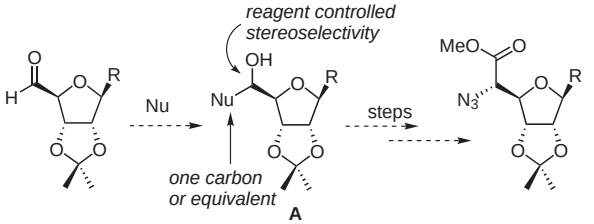


Figure 1

fashion to provide the homologated ribose derivative (**A**, Scheme 1).[5] Conversion of the nucleophilic component to a carboxylate, followed by simple functional group interconversion and protecting group manipulation would then lead to polyoxin C and analogs thereof. Previous polyoxin syntheses have featured highly stereocontrolled nucleophilic additions to ribose-based electrophiles, albeit to nitro-olefin and nitrone species.[4e,i] Recent work has shown that only modest stereocontrol can be achieved by addition of a vinyl Grignard reagent or a lithium acetylide to aldehyde **3**.[4l,6] Thus, we adopted a strategy based on reagent rather than substrate control.

We were drawn to the method recently disclosed by Carreira and co-workers for in-situ generation of zinc acetylides in the presence of *N*-methyl ephedrine and an aldehyde substrate, leading to enantiomerically enriched propargyl alcohols.[7] The mild reaction conditions and stereoselectivity of this process were critical in our



Scheme 1 General strategy for polyoxin synthesis.

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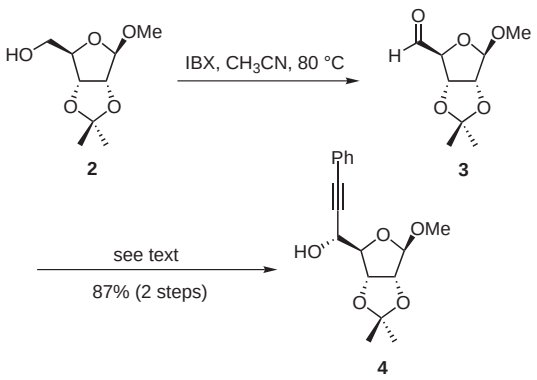
choice, since the ribosyl aldehyde chosen for study is noted for its general instability, as well as for low diastereofacial bias to incoming nucleophiles.[4l,8] It was envisioned that the alkyne would act as a one-carbon synthetic equivalent after oxidative cleavage (Scheme 1).

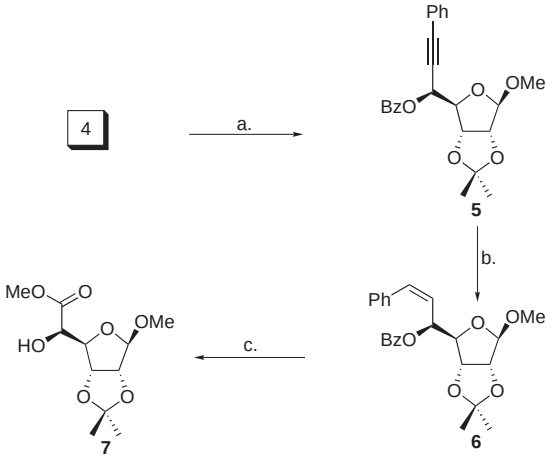
Aldehyde **3** was efficiently prepared from known alcohol **2** using our recently reported *o*-iodoxybenzoic acid (IBX)-based protocol and subjected to the appropriate conditions for acetylide addition (Scheme 2).[9–11] In an early experiment, addition of phenyl acetylene to aldehyde **3** using the reported conditions gave an approximately 60% yield of diastereomerically pure propargyl alcohol, along with inseparable side products. Under optimized conditions [2.0 equiv of phenyl acetylene, 2.1 equiv each of NEt_3 and $Zn(OTf)_2$, 2.2 equiv (–)-*N*-methyl ephedrine, toluene, 18 hours], the alcohol **4** could be isolated in 87% yield over two steps (IBX oxidation and acetylide addition).[12] Notably, the product was obtained without detectable impurities (^{1}H NMR, 400 MHz) after a simple aqueous workup, and the *N*-methyl ephedrine was recovered in high yield using acid-base extraction. Based on literature precedent,[7a] we expected that the newly formed stereocenter would be of the *R* configuration, and this was confirmed via chemical correlation (vide infra).



Scheme 2

The acetylide addition described above deserves further comment. The use of (–)-*N*-methyl ephedrine as ligand gives the *R* alcohol with high diastereoselectivity, but use of the antipode of the chiral auxiliary results in an extremely sluggish reaction. Inspection of the crude reaction mixture revealed an approximately 3:1 mixture of isomers favoring the *S* alcohol along with several decomposition products. Matched/mismatched stereoselectivity has been noted for this reaction by Carreira,[7d] but it is surprising in the case of aldehyde **3** to see such a strong effect, given the low inherent facial bias to metal acetylides previously noted.[4l]

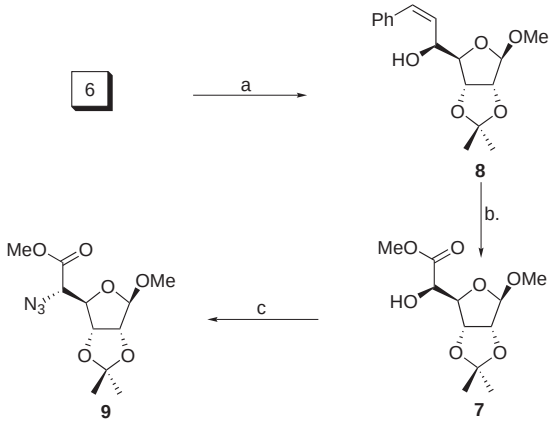
With a convenient route to intermediate **4** in hand, we completed a formal synthesis of polyoxin C by converting **4** to intermediate **7**,[4l] and then to compound **9** (Scheme 4), which had been reported in the literature on three separate occasions.[4i,l,o] This required oxidative cleavage of the alkyne as well as installation of the azide moiety with overall retention of stereochemistry. Toward this end (Scheme 3), **4** was subjected to a Mitsunobu inversion with benzoic acid to give the corresponding benzoate **5** in 86% yield after chromatography.[13]



Scheme 3 Reagents and Conditions: (a) $PhCO_2H$, PPh_3, DEAD, THF, 0 °C, 86%; (b) H_2, $Pd/BaSO_4$, quinoline, THF, 48 h, 96%; (c) i. $KMNO_4$, acetone, r.t.; ii. LiOH, THF/H_2O, r.t.; iii. $TMSCHN_2$, MeOH/PhH, r.t., 29% from **6**.

Numerous attempts to directly cleave the alkyne of intermediate **5** and related compounds were unsuccessful, so it was necessary to reduce the triple bond prior to cleavage. In the event, compound **5** was hydrogenated over $Pd/BaSO_4$ in the presence of quinoline to give olefin **6** in 96% yield. The sequence of oxidative scission with $KMnO_4$, benzoate cleavage, and esterification with TMS–diazomethane gave the key intermediate **7** in 28% overall yield from **6** after chromatography.[14] Spectroscopic data for this compound matched those reported in the literature,[4l] and thus served to confirm the relative stereochemistry of **4**.

An alternate route from **6** to **7** was devised to improve yield and efficiency (Scheme 4). The allylic benzoate **6** was subjected to methanolysis to give alcohol **8** in 90%



Scheme 4 Reagents and Conditions: (a) NaOMe, MeOH, 65 °C, 90%; (b) O_3, NaOH, CH_2Cl_2/MeOH, –78 °C, 55%; (c) HN_3, PPh_3, DEAD, $THF/PhCH_3$, 0 °C, h, 80%.

yield. The olefin was then converted to hydroxy ester **7** via ozonolysis under basic conditions in moderate yield.[15] By utilizing the route depicted in Scheme 4, the overall yield of **4** to **7** was increased by a factor of two. Hydroxy-ester **7** could be then be directly converted to azide **9** in 80% yield via a Mitsunobu reaction with hydrazoic acid.

In conclusion, we have developed an efficient synthesis of the polyoxin scaffold **9** from ribose, which proceeds with minimal purification in 22% overall yield (8 steps, average yield/step of 83.5%) and is amenable to multi-gram scale. Notable features include the use of our newly developed IBX oxidation protocol and a highly diastereoselective zinc-mediated asymmetric acetylide addition.[7,10] Current efforts are focused on the synthesis and biological evaluation of polyoxin analogs and results will be reported in due course.

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(5) (a) Early studies involved the use of uridine as a starting material, with the intention of utilizing an asymmetric Ugi condensation or an asymmetric Strecker reaction as the key operation. Unfortunately, the required imine derivatives were either unstable or resulted in poor selectivity upon nucleophilic addition. In the ribose series, the key stereocenter could be formed using a chiral auxiliary-mediated Strecker reaction, but the resulting amino-nitrile could not be hydrolyzed. (b) For the asymmetric Ugi reaction, see: Kunz, H.; Pfrengle, W.; Sager, W. *Tetrahedron Lett.* **1989**, *30*, 4109. (c) For a catalytic asymmetric Strecker reaction, see: Sigman, M. S.; Vachal, P.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2000**, *39*, 1279. (d) For an auxiliary-based Strecker reaction, see: Davis, F. A.; Portonovo, P. S.; Reddy, R. E.; Chiu, Y.-H. *J. Org. Chem.* **1996**, *61*, 440.

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(11) Other methods of oxidation investigated (e.g. PCC, Swern, CrO_3/pyridine, TPAP, IBX/DMSO, Dess–Martin) proved to be much less reliable for this transformation, being difficult to reproduce and providing aldehyde of lower purity than with IBX.

(12) **Experimental Details for the Synthesis of Compound 4**: The alcohol **2** (6.2 g, 30.18 mmol, 1.0 equiv) was dissolved in 250 mL CH_3CN and IBX (16.9 g, 60.35 mmol, 2.0 equiv) was added. The flask was fitted with a reflux condenser and the suspension was immersed in an oil bath heated to 80 °C with vigorous stirring. After 75 min, an aliquot was removed and analyzed by ^{1}H NMR, which indicated consumption of starting material and clean conversion to product. The reaction was stopped, cooled to room temperature and filtered, washing the flask and filter thoroughly with EtOAc. The combined filtrate and washings were combined and concentrated to yield a white, glassy semi-solid, which was used without further purification in the next step. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.56 (s, 1 H), 5.08 (s, 1 H), 5.04 (d, 1 H, J = 8 Hz), 4.48 (d, 1 H, J = 8 Hz), 4.46 (s, 1 H), 3.44 (s, 3 H), 1.48 (s, 3 H), 1.32 (s, 3 H). An oven-dried 1 L round bottom flask was cooled under N_2, then charged with (–)-*N*-methyl ephedrine (11.9 g, 66.39 mmol, 2.2 equiv) and $Zn(OTf)_2$ (23.0 g, 63.37 mmol, 2.1 equiv), and purged with N_2. Freshly distilled NEt_3 (8.9 mL, 63.37 mmol, 2.1 equiv) was added via syringe, followed by 250 mL anhydrous

toluene via cannula. The heterogeneous mixture was stirred vigorously for 2 h, and phenyl acetylene (6.6 mL, 60.35 mmol, 2.0 equiv) was added via syringe. After stirring for an additional 30 min, the aldehyde **3** (azeotropically dried twice with benzene) was added in 80 mL toluene via cannula. The reaction was stirred overnight (approx. 18 h), at which time TLC analysis showed formation of a new, UV-active spot (R_f 0.24, 30% ethyl acetate in hexanes). The reaction was stopped, diluted with 300 mL EtOAc, and poured into a separatory funnel containing 700 mL 0.1 M sodium EDTA. The aqueous layer was removed and extracted twice with EtOAc (approx 300 mL each). The combined organics were washed twice with 0.1 M sodium EDTA (500 mL total), 3 times with 1.0 M HCl (to remove and recycle *N*-methyl ephedrine), and brine, then dried over Na_2SO_4, filtered and concentrated to afford pure **4** as a brown semi-solid (8.05 g, 26.5 mmol, 87.6% over 2 steps). R_f = 0.24 (20% in EtOAc / hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46–7.48 (m, 2 H), 7.30–7.32 (m, 3 H), 5.08 (d, 1 H, *J* = 6 Hz), 5.03 (s, 1 H), 4.71 (br s, 1 H), 4.63 (d, 1 H, 6 Hz), 4.55 (d, 1 H, *J* = 2 Hz), 3.99 (br s, 1 H), 3.48 (s, 3 H), 1.50 (s, 3 H), 1.35 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 131.7, 128.5, 128.1, 122.1, 112.2, 110.7, 91.0, 86.5, 85.6, 85.5, 80.8, 64.4, 55.9, 26.4, 24.8; FTIR (thin film; NaCl) 3415, 2986, 2943, 1492, 1375, 1212, 1095, 1037, 868, 763 cm^{-1}; HRMS (DCI) *m/z*: (M + NH_4^+) calc. for $C_{17}H_{24}O_5N$ 322.1654, found 322.1657.

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