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ENANTIOSPECIFIC SYNTHESIS OF (-) (*2S, 3S*)-2-AMINO-3,4-HYDROXYBUTYRIC ACID FROM β-LACTAM

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Abstract:
The azetidine nucleus is ubiquitous in β-lactam antibiotics and possesses inherent ring strain. Therefore, it could serve as a crucial building block in synthesizing bioactive natural and unnatural compounds of diverse medicinal interest. An extensive study has been made in this field to harnessing the potential of β-lactam ring strain in the design and synthesis of a wide array of heterocyclic scaffolds present in natural products. Herein we wish to report the synthesis of unnatural isomers of (-) (*2S, 3S*)-2-amino-3,4-hydroxybutyric acid featuring as prevalent structural motifs of polyoxins a plant-derived antibiotic based on reductive cleavage of N-(CO) bond of lactam ring as the key reaction followed by other desired chemical manipulations.

Keywords:β-lactam,Antibiotics, Polyoxines, Amino-acid, enantiospecific, Chiral auxiliary.

Introduction: β-Hydroxy-α-amino acids are a prevalent structural motif found in a wide array of naturally occurring bioactive peptides, antibiotics, and polyoxins[1–6]. These compounds play a pivotal role in many biochemical cycles in the living system and display several noteworthy biological activities from antibiotics to immunosuppressants. Therefore, the asymmetric synthesis of β-hydroxy -α-amino acid has been the most thriving research area in synthetic and medicinal chemistry. Owing to its great therapeutic potential, many scientific efforts have been made in this area to synthesize hydroxy amino acids' natural and unnatural analogs.

Banik *et al*. (1993) reported the enantiospecific synthesis of (-)-polyoxamic acid based on β-lactam synthon methods [7,8]. Subsequently, many other approaches, including, Saksena and Lovey et al. (1985) reported 5-*O*-carbamoyl polyoxamic acid using Overmann-Claisen rearrangement as the key reaction on the D/L-tartaric acid chiral template[9]. Park *et al.* (2010) enantioselective approach in the synthesis of (+)-polyoxamic acid *via* phase transfer catalytic conjugate addition followed by asymmetric hydroxylation[10]. The chemoenzymatic synthesis by Fadanvis *et al.* (2001)[1], Todd *et al* (2003) based on 2,3-Aziridino-γ-lactone strategy[11] and ether

directed aza-Claisen rearrangement by Suther *et al.* (2007)[12], are notable examples of asymmetric synthesis of polyoxamic acid.

However, apart from these efforts, several other noteworthy syntheses have also been reported, like aldol reaction of benzophenone glycinates[13], Sharpless asymmetric epoxidation of allyl alcohols[14], Strecker reaction of protected glyceraldehyde's[15], osmylation of viny threonine and threonine aldolase inspired reaction of glycine[16].

Polyoxamic acid **1** is a *syn*-3,4-dihydroxy α-amino acid having three contiguous stereocenters found in

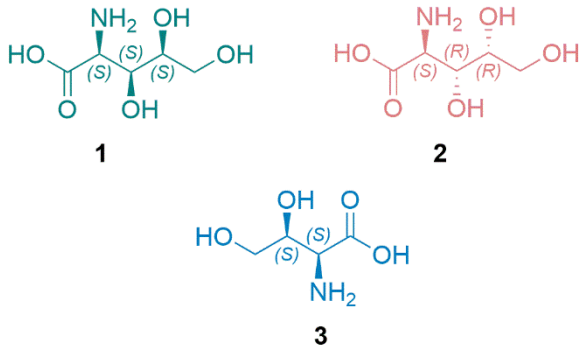


FIG. 1 (**1**) Polyoxamic acid (**2**) 3,4-diepipolyoxamic acid (**3**) 4-hydroxy-L-threonine

naturally occurring polyoxins a peptidyl nucleoside antibiotic having an inhibitory activity of chitin synthetase in *Candida albicans* cell wall of a pathogenic fungus[4]. However, 3,4-diepoxyoxamic acid **2** is the prevalent structural motif of the potential antifungal agent sphingofungin **A-D** display inherent inhibitory activity of serine palmitoyltransferase responsible for blocking the biosynthesis of sphingolipids[5] (**FIG. 1**).

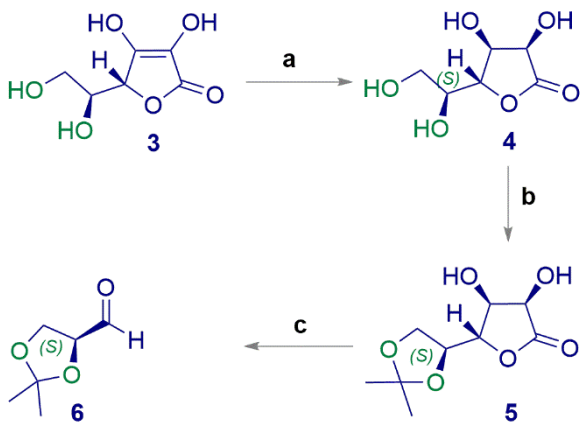
Results and Discussions: Our group has been demonstrated the synthesis of enantioenriched β-lactam and its chemical manipulation in the synthesis of heterocyclic scaffolds of diverse medicinal interest using carbohydrate as a potential chiral auxiliary[17–19]. For instance, we have a transformed the *cis*-3-hydroxy β-lactam in enantiospecific synthesis of (-)-polyoxamic acid using *tri*-isopropylidene-D-mannitol as a chiral adjuvant[7]. Apart from these, we also have accomplished the synthesis of β-lactams having (*3R*) configuration at C_3 position using D-(*R*) -(+)-glyceraldehyde acetonide derived imine *via* Staudinger ketene-imine [2+2] cycloaddition reaction[20].

The 4-hydroxy-L-threonine is an important secondary metabolite produced during a metabolic reaction in Escherichia coli and Saccharomyces cerevisiae (Baker's yeast). It has also been produced as the oxidative product of sphingosine, the amino alcohol backbone of sphingolipids. A few syntheses of D- (+)-hydroxy threonine compound has been reported in the literature. However, synthesis of the non-natural from 4-hydroxy-L-threonine has not been reported by any methods.

Based on our investigation on β-lactam, we envisioned that our work on optically active β-lactam is suitable for the preparation of 4-hydroxy-L-threonine. The synthesis of this chiral hydroxy amino acid is not reported in the literature by any other groups. We herein design the synthesis of 4-hydroxy-L-threonine based on β-lactam synthon methods.

It is anticipated that the desired *3S* absolute stereochemistry of (+)-polyoxamic acid and 4-hydroxy L-threonine **3** could be easily achieved by employing *L*-(S)-glyceraldehyde in asymmetric Staudinger ketene-imine [2+2] cycloaddition reaction in β-lactam synthesis.

SCHEME 1

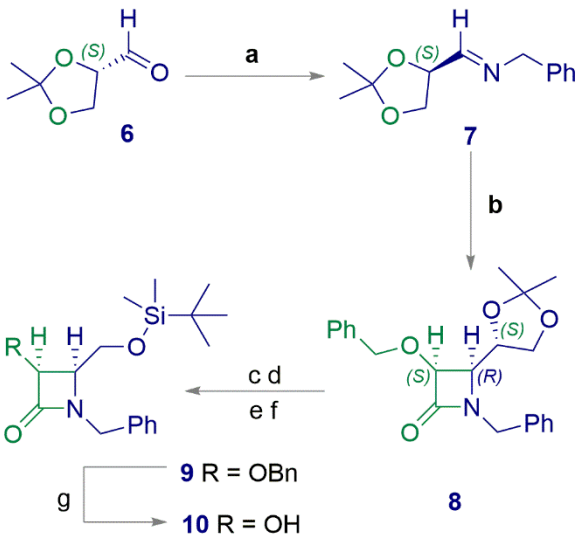


Reagents and Conditions: (**a**) H_2 / Pd-C (10 mol %, 50^0C, 50 psi, 24h, 99%; **(b**) DMF, PTSA, 10^0C then isopropenyl methyl ether; 24h, 70%; (**c**) NaIO4, THF: H_2O (3:1), 2.5h, 69%

To this end, we have synthesized the L-(S)-glyceraldehyde acetonide **6** from L-Ascorbic acid **3** following the procedure developed by Hubschwerlin[21]. The synthesis of L-(S)-glyceraldehyde has commenced by the Pd/C induced reduction of L-Ascorbic acid into corresponding L- gluno-1,4-lactone **4** followed by the selective protection of the *vic*-diol with isopropenyl methyl ether to isopropylidene-L-gluno-1,4-lactone **5.** The oxidative cleavage with sodium meta periodate of frunanose *vic*-diol leads to the formation of the L-(S)-glyceraldehyde **6** as an unstable liquid and is used for the next step without any further purification (SCHEME 1).

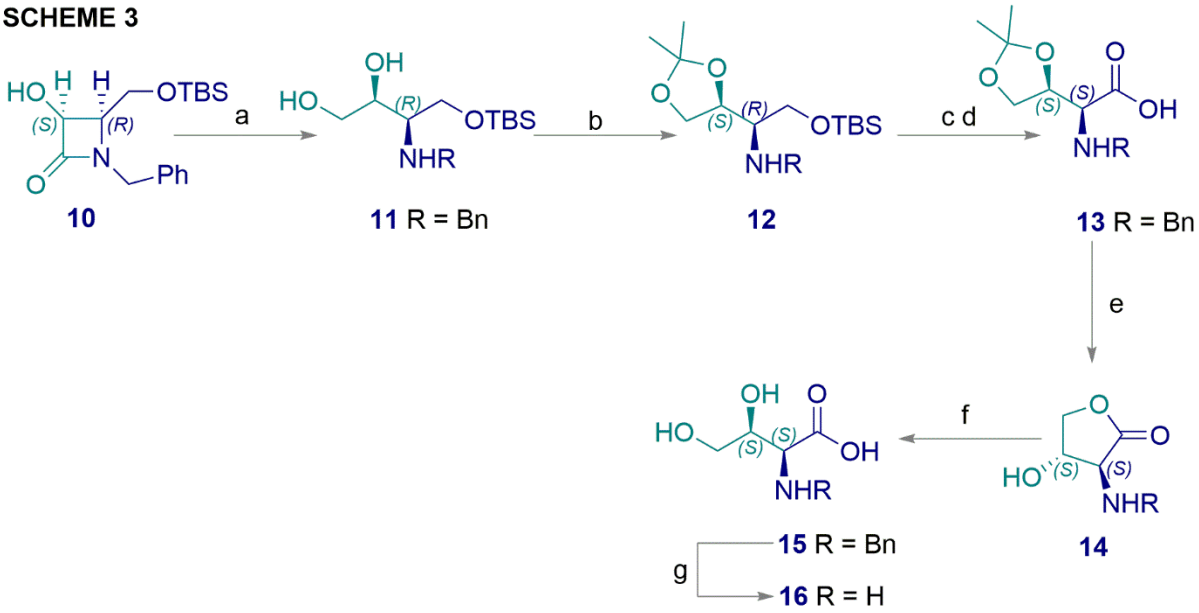
The desired β-lactam was prepared following the acid chloride-imine cycloaddition strategy. For instance, imine **7** derived from optically active L-glyceraldehyde acetonide **6** and benzylamine on reaction with benzyloxyacetyl chloride in the presence of triethylamine afforded a single optically active β-lactam **8** in excellent yield after column chromatography. The isopropylidene group in β-lactam **8** was then deprotected by using Ferric (III) chloride to obtained diol, which upon subsequent oxidation with sodium periodate followed by sodium borohydride reduction of resulting aldehyde to obtained 1^0 hydroxyl functionalities. The hydroxy function was then protected as silyl ether to afford the β-lactam **9** in 80% overall yield after four consecutive sets of reactions. The 3-*O*-benzyloxy-β-lactam **9** has been conveniently converted to *cis*-3-hydroxy β-lactam **10** in very good yield (90%) by ammonium formate mediated chemoselective hydrogenation of *O*-benzyloxy group under microwave irradiation (SCHEME 2).

SCHEME 2



Reagent and conditions: (**a**) $BnNH_2$ (1.equiv.), CH_2Cl_2 (anhy.), $4A^0$, MS, RT, 12 h, quant.;(**b**) $BnOCH_2COCl$ (1.5 equiv.), Et_3N (2.5 equiv.), CH_2Cl_2 (anhy.), 0^0C-RT, 12h, 70% (dr=100% *cis*); (**c**) $FeCl_3.6H_2O$ (1.5 equiv.), CH2Cl2 (anhy.), reflux, 1h; (**d**) $NaIO_4$ (2.0 equiv.), THF: H_2O (3:1), $NaHCO_3$ (2.0 equiv.), 0^0C, 1.5h; (**e**) $NaBH_4$ (1.5 equiv.), EtOH, 1h; (**f**) TBDMSCl (1.5 equiv.), Imidazole (1.0 equiv.); Et_3N (2.0 equiv.), CH_2Cl_2 (anhy.), 2.0 h, 80% (4 four steps); (g) NH_4COOH (2.equiv.), Pd/C (10 mol%), EtOH, MWI, 6h, 90% (*O* selective dehydrogenation)

SCHEME 3



Reagents and conditions: (**a**) $LiAlH_4$ (1.5 equiv.), Et_2O, 0°C-RT, 1h, 90%; (**b**) 2,2-dimethoxy propane (2.5 equiv.), Benzene, PTSA (cat.), reflux, 6 h, 80%; (**c**) TBAF (1.5 equiv.), THF, 0 °C-RT, 1.0 h, 90%; (**d**) KMnO4(aq), NaOH, 80%; (**e**) Fe. $Cl_3.6H_2O$, CH_2Cl_2, reflux, 6h then 1.0 M aq. KOH (PH 10-12), 80%; (**f**) 1.0 M KOH, THF: H_2O (3:1), then 2.0 N HCl, 2h,0°C-RT, 85%; (**g**) H_2/Pd-C (10 mol%), EtOH, 1.0 h, RT, 90%;

Reductive cleavage of the N (1)-CO (2) bond in β-lactam **10** could be achieved using lithium aluminum hydride to get N-benzyl β-hydroxy amino alcohol **11** in excellent yield.

The *vic*-diol **11** was protected as acetonide by refluxing with 2,3-dimethoxy propane in the presence of a catalytic amount of p-TsOH as a catalyst to get the acetonide **12** in 80% yield.

Furthermore, the silyl protecting group has deprotected with tetrabutylammonium fluoride in THF leads 1^0 hydroxyl functionalities which upon oxidation with aq. $KNMnO_4$ solution under alkaline conditions afforded the title compound **13** in an excellent yield. The isopropylidene moiety in compound **13** has been deprotected by refluxing with Ferric (III) chloride in anhydrous dichloromethane to obtain the free diol. However, it is gratifying to note that we got the mixture of anticipated *vic*-diol and butyrolactone **14** during the reaction's initial monitoring after two hours. The reaction mixture has been allowed to stir further for 6h. Upon complete consumption of starting material followed by basifying the reaction mixture using 1.0 M, aq KOH solution affords the lactone **14** with desired stereochemistry in 80% yield after silica gel column chromatography (60% EtOAc in hexane)**.**

The butyrolactone **14** was then hydrolyzed using 1.0 M aq. KOH solution THF: H_2O (3:1) at 0°C-RT for 2 h followed careful acidification to PH 5 (2N HCl) affords the N-benzyl 4-hydroxy-L-threonine **15** in very good yield. Furthermore, the N-benzyl protected 4-hydroxy-L-threonine was subjected to debenzylation by catalytic transfer hydrogenation using H_2/Pd-C in ethanol. It was afforded free amino alcohol **16** in 90% yield after removing the catalyst over sintered glass funnel followed by crystallization with H_2O/MeOH (SCHEME 3). The observed compound data will be compared to the literature-reported methods.

In conclusion, we have achieved the synthesis of 4-hydroxy-L-threonine, an

intriguing structural motif of polyoxins and may β-lactam antibiotics be starting from enantiomerically pure isopropylidene-S-glyceraldehyde in excellent yield.

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