Stereoselective Synthesis of (+)-Polyoxamic Acid Starting with a Chiral Aziridine

Hojong Yoon,[a] Taebo Sim*[a,b]

[a] Chemical Kinomics Research Center, Korea Institute of Science and Technology, Hwarangro 14-gil 5, Seongbuk-gu, Seoul 136-791, Republic of Korea

[b] KU-KIST Graduate School of Converging Science and Technology, 145, Anam-ro, Seongbuk-gu, Seoul, 136-713, Republic of Korea
Fax +82(2)9585189; E-mail: tbsim@kist.re.kr

Received: 27.08.2013; Accepted after revision: 13.09.2013

Abstract: An efficient and stereoselective synthesis of (+)-polyoxamic acid was developed. The route starts with the commercially available 1-(*R*)-α-methylbenzylaziridine-2-methanol, a substance that has not been used previously as a starting material for the preparation of this target. The route also features the use of a stereocontrolled Sharpless asymmetric dihydroxylation reaction, promoted by AD-mix-α, which is followed by a regioselective aziridine ring-opening process, to generate the basic skeleton of target natural product. Subsequent oxidation and global deprotection produces (+)-polyoxamic acid.

Key words: polyhydroxylated amino acid, (+)-polyoxamic acid, natural product synthesis, chiral aziridine, asymmetric dihydroxylation

Polyoxins are a family of natural peptidyl nucleosidic antibiotics isolated from *Streptomyces cacoi* var. *aseonsis*[1] in 1965. Members of this family possess potent biological activities against the chitin synthetase of *Candida albicans*, a human fungal pathogen, and of various other phytopathogenic fungi. As a result, polyoxins have been utilized as agricultural fungicides.[2] (+)-Polyoxamic acid (**1**), a polyhydroxy amino acid derived by mild hydrolysis of the polyoxins, has received great attention owing to the fact that it has a unique structural motif that is commonly found in a variety of polyoxins (Figure 1).

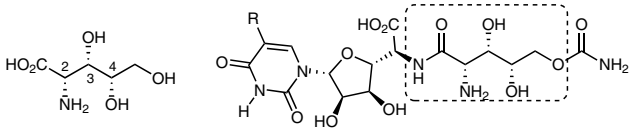


Figure 1 (+)-Polyoxamic acid (**1**) and polyoxins

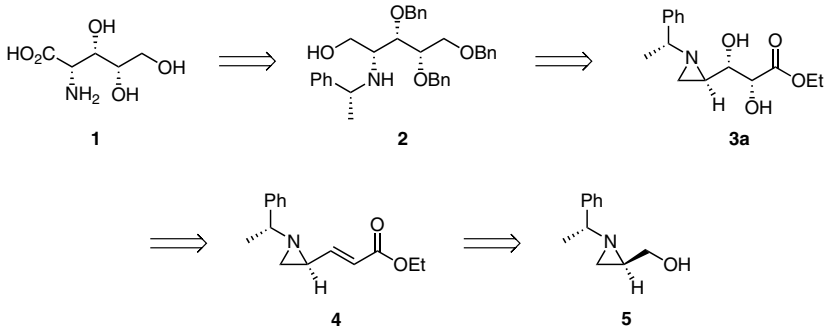
(+)-Polyoxamic acid (**1**), which is comprised of five carbons that are all functionalized, possesses the contiguous stereogenic centers. A number of routes for the synthesis of this substance have been described, nearly all of which use chiral substances (e.g., carbohydrates) as starting materials. One exception to this general trend is found in the route for the preparation of **1** that utilized an enantioselective phase-transfer conjugate addition reaction followed by an asymmetric dihydroxylation process.[3] In the others, the amino group of (+)-polyoxamic acid was introduced enantioselectively by employing either (1) a palladium-assisted allylation reaction using a chiral ligand comprised of 2-diphenylphosphinobenzoic acid and a chiral diamine,[4] (2) an asymmetric organocatalytic Mannich reaction,[5] (3) a stereoselective [3,3]-sigmatropic rearrangement of an allylic trifluoroacetimidate,[6] (4) a regioselective iodocyclization reaction of a trichloroacetimidate,[7] or (5) a stereospecific bromohydration reaction using a chiral auxiliary.[8] In addition, Sharpless asymmetric dihydroxylation reactions of *E*-allylic alcohol[9] and vinyl oxazolidine[10] intermediates have been unsuccessfully explored for stereoselective introduction of the C3/C4 and C4/C5 diol moieties in **1**.[9,10]

We have now developed an efficient and stereoselective route for the synthesis of (+)-polyoxamic acid, which begins with a commercially available chiral aziridine that until now has not been utilized as a starting material for the preparation of this target. A retrosynthetic analysis version of the new approach, illustrated in Scheme 1, suggests that the target can be synthesized by oxidation of the primary alcohol group in the protected polyhydroxyamino alcohol **2** followed by global deprotection. Employing this strategy, **2** would be generated through regioselective acid-catalyzed ring opening of the dihydroxy aziridine **3**, formed stereoselectively employing Sharpless asymmetric dihydroxylation of (*E*)-3-(aziridin-2-yl)acrylate **4**. Finally, aziridinyl acrylate **4** would be produced from commercially available 1-(*R*)-α-methylbenzylaziridine-2-methanol (**5**) by using an oxidation-olefination sequence.

The route for the synthesis of (+)-polyoxamic acid (**1**) commences with the preparation of the (*E*)-3-(aziridin-2-yl)acrylate **4**. This was accomplished through Swern oxidation of the alcohol moiety in **5** and subsequent Horner–Wadsworth–Emmons olefination of the resulting aldehyde using triethyl phosphonoacetate. This sequence produced **5** in 72% overall yield as chromatographically (silica gel) separable 98:2 mixture of *trans*- and *cis*-isomers. It should be noted that, because it contains five differentially functionalized carbons, **4** should serve as a

SYNTHESIS 2013, 45, 3276–3280
Advanced online publication: 26.09.2013
DOI: 10.1055/s-0033-1338545; Art ID: SS-2013-F0593-OP
© Georg Thieme Verlag Stuttgart · New York

Downloaded by: University of Pittsburgh. Copyrighted material.



Scheme 1 Retrosynthetic analysis toward (+)-polyoxamic acid (**1**)

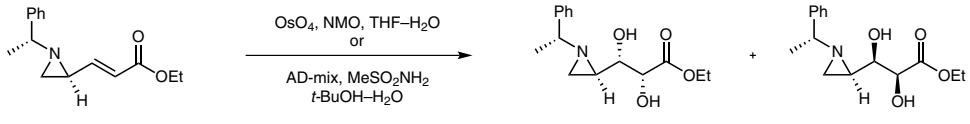
versatile intermediate for the synthesis of various natural products.

Several issues were considered before attempting the asymmetric dihydroxylation reaction of (*E*)-3-(aziridin-2-yl)acrylate **4**. Earlier, it was shown that the diastereoselectivities of dihydroxylation reactions of (*E*)-2-vinylaziridines, carried out using osmium tetroxide in the absence of chiral ligands, are low and variable depending on substituents present on the olefin moiety.[11] In addition, it has been reported that (*E*)-3-(aziridin-2-yl)acrylates, whose amine moieties are protected by electron-withdrawing groups, can be diastereoselectively dihydroxylated using osmium tetroxide in the absence of chiral ligands.[12] In recent efforts in our laboratory, we have shown that dihydroxylation reaction of *N*-(*R*)-1-phenylethyl-protected aziridin-*Z*-enoate using osmium tetroxide leads to nondiastereoselective (dr = ca. 1:1) production of a diol product but, in contrast, that the process proceeds with a high level of diastereoselectivity when the Sharpless AD-mix-β reagent combination is employed.[13]

Based on these early observations, we explored several methods for the dihydroxylation of (*E*)-3-(aziridin-2-yl)acrylate **4**, including the use of osmium tetroxide in the absence of a chiral ligand and Sharpless asymmetric dihydroxylation conditions with either the AD-mix-α or AD-mix-β reagent combinations (Table 1). In a manner that is similar to an observation we made earlier,[13] dihydroxylation of **4** promoted by osmium tetroxide in the absence of a chiral ligand took place to form diol **3** as a near equimolar mixture of diastereomers **3a** and **3b**. In contrast, the reaction carried out by using AD-mix-α took place at room temperature with a reasonable level of diastereoselectivity (dr of **3a**/**3b** = 4:1). Moreover, a higher level of diastereoselectivity (dr = 10:1) was achieved by running this reaction at 0 °C for a longer time period (36 h). Thus, this approach enables ready control of the absolute stereochemistry at the three contiguous chiral centers in the amino-*syn*-diol moiety and, as such, it could be the key component of synthetic approaches to several polyhydroxylated amine alkaloid natural products.[14]

Owing to severe difficulties encountered in the separation of the diastereomers, a mixture of diols **3a** and **3b** was employed in the next step along the route (Scheme 2). Accordingly, reduction using $LiAlH_4$ and subsequent benzyl protection of the alcohol moieties in the intermediate triol led to generation of tribenzyloxy aziridine **6** in 74% yield (2 steps). Separation of the stereoisomer mixture to produce the desired diastereomer **6** was accomplished at this

Table 1 Dihydroxylation Reactions of (*E*)-3-(Aziridin-2-yl)acrylate **4**

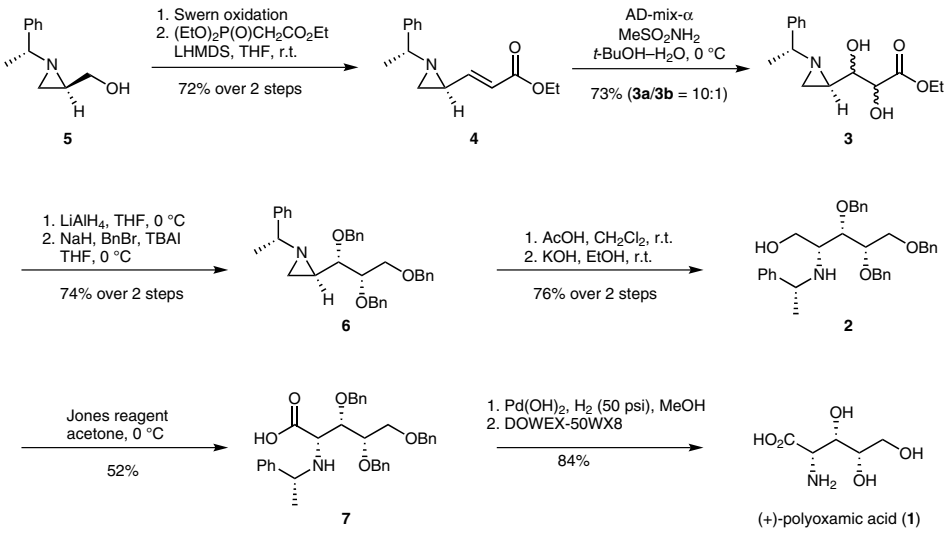


Reagent	**3a**[a]	**3b**[a]	Temp	Yield (%)[b]	Time (h)
OsO_4, NMO[c]	1	1	r.t. or 0 °C	87	6
AD-mix-α[d]	4	1	r.t.	78	24
AD-mix-α[d]	10	1	0 °C	73	36
AD-mix-β[d]	1	4	r.t.	76	24
AD-mix-β[d]	1	10	0 °C	69	36

[a] Ratio of **3a**/**3b** was determined by ^1H NMR spectroscopy.
[b] Mixture of **3a** and **3b**.
[c] OsO_4 (0.05 equiv), NMO (1.2 equiv), THF–H_2O = 3: 1 (0.1 M).
[d] AD-mix (1000% w/w), $MeSO_2NH_2$ (1.5 equiv), *t*-BuOH–H_2O = 1: 1 (0.1 M).

© Georg Thieme Verlag Stuttgart · New York

Downloaded by: University of Pittsburgh. Copyrighted material.



Scheme 2 Synthesis of (+)-polyoxamic acid (**1**) starting with the chiral aziridine **5**

stage by using flash column chromatography (silica gel), thus enabling the production of this key intermediate in greater than 1 g quantities. Next, regioselective aziridine ring-opening reaction[15] of **6** was successfully carried out using excess acetic acid in CH_2Cl_2. This process afforded the monoacetate ester, which without purification was subjected to treatment with potassium hydroxide in ethanol to form the corresponding alcohol **2** in a 76% yield (2 steps).

Several oxidizing agents were explored to carry out the transformation of the primary alcohol group in **2** to the corresponding carboxylic acid in **7**. While PDC/DMF[16] and CrO_3/2·pyridine[17] promoted reaction resulted in the formation of substantial amounts of by-products, and while significant levels of substrate decomposition and sluggish reactivity were accompanied with respective Dess–Martin periodinane[18] and $RuCl_3/NaIO_4$[19] oxidations, the conversion of **2** to **7** took place with modest efficiency (52%) using the Jones reagent (Scheme 2).

In studies targeted at accomplishing simultaneous deprotection of the *O*-benzyl and *N*-phenylethyl protecting groups in **7**, we observed that, contrary to expectations, the removal of the *N*-phenylethyl group was sluggish, even with prolonged reaction times (4 d), when catalytic amounts of Pd/C or $Pd(OH)_2$ were used under 1 atmosphere of H_2. Furthermore, inclusion of catalytic amounts of several acids (e.g., AcOH, HCl, TFA, HCO_2H) as well as the use of catalytic hydrogen transfer employing ammonium formate in refluxing MeOH[20] failed to bring about nitrogen deprotection.

However, we observed that simultaneous *O*-benzyl and *N*-phenylethyl group deprotection can be accomplished by using excess $Pd(OH)_2$ under a high pressure hydrogen atmosphere (50 psi, 12 h).[21] The product generated in this process was subjected to ion-exchange chromatography on Dowex-50WX8 (H^+ form) using 0.6 M aqueous NH_4OH as the eluent. This procedure afforded the free base form of (+)-polyoxamic acid (**1**) in 84% yield (Scheme 2). The identity of the synthetic material was confirmed by comparing its spectroscopic properties and optical rotation ($[\alpha]_D^{23.5}$ +2.2 (*c* 0.17, H_2O) {Lit. $[\alpha]_D^{23}$ +2.1 (*c* 1.0, H_2O)}) to those reported earlier for the natural product.[22]

In conclusion, in the work described above, a route for the stereoselective and facile synthesis of (+)-polyoxamic acid (**1**) has been developed. The sequence involves 9 steps, three of which do not require product purification, and provides the target in a 12.9% overall yield. The strategy employed in this stereoselective synthesis of (+)-polyoxamic acid uniquely utilizes an enantiomerically pure chiral aziridine as the starting material. Moreover, other interesting features of the approach include the use of Sharpless asymmetric dihydroxylation and a regioselective aziridine ring-opening process. This general strategy has the potential of being applicable to enantioselective syntheses of several other polyhydroxylated amine natural products.

Reactions were monitored by TLC with 0.25 mm E. Merck precoated silica gel plates (60 F_{254}). Reaction progress was monitored by TLC analysis using a UV lamp, ninhydrin, or *p*-anisaldehyde stain for detection purpose. Purification of reaction products was carried out by flash chromatography using Kieselgel 60 Art. 9385 (230–400 mesh). The purity of all compounds was over 95% and was analyzed using Waters LCMS system (Waters 2998 Photodiode Array Detector, Waters 3100 Mass Detector, Waters SFO System Fluidics Organizer, Water 2545 Binary Gradient Module, Waters Reagent Manager, Waters 2767 Sample Manager) using SunFire™ C18 column (4.6 × 50 mm, 5 μm particle size): solvent gradient = 60% (or 95%) A at 0 min, 1% A at 5 min. Solvent A = 0.035% TFA in H_2O; Solvent B = 0.035% TFA in MeOH; flow rate : 3.0 (or 2.5) mL/min. ^1H and ^{13}C NMR spectra were obtained using a Bruker 400 MHz FT-NMR (400 MHz for ^1H, and 100 MHz for ^{13}C) spectrometer. Chemical shifts are reported relative to $CHCl_3$ (δ = 7.26) for ^1H NMR and $CHCl_3$ (δ = 77.2) for ^{13}C NMR or D_2O for ^1H (δ = 4.80) and D_2O for ^{13}C NMR. Standard abbreviations are used for denoting the signal multiplicities. High-resolution mass spectra (HRMS) were recorded on a QTOF mass spectrometer.

Downloaded by: University of Pittsburgh. Copyrighted material.

 © Georg Thieme Verlag Stuttgart · New York

Ethyl 3-{(*R*)-1-[(*R*)-1-Phenylethyl]aziridin-2-yl}prop-2-enoate (4)

To a solution of $(COCl)_2$ (4.1 mL, 47.73 mmol) in CH_2Cl_2 (100 mL) was slowly added DMSO (7 mL, 99.43 mmol) at –78 °C. After 30 min, a solution of **5** (7.05 g, 39.77 mmol) in CH_2Cl_2 (80 mL) was added. After 30 min, Et_3N (22 mL, 119.3 mmol) was added at –78 °C and the reaction mixture was stirred for 30 min at 0 °C. The mixture was quenched with H_2O (50 mL) and then extracted with CH_2Cl_2 (2 × 200 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. The resulting aldehyde was used in the next step without further purification. To a solution of the aldehyde in THF (80 mL) was added triethyl phosphonoacetate at r.t. After 10 min at r.t., LHMDS (47.7 mL, 47.7 mmol, 1 M in THF) was added. The mixture was stirred for 1 h at r.t., then quenched with H_2O (20 mL), and extracted with EtOAc (2 × 100 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. The resulting crude product was purified by silica gel flash column chromatography with EtOAc–hexane (1:6) to afford the title product **4**; yield: 7.02 g (28.63 mmol, 72% over 2 steps); yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39–7.23 (m, 5 H), 6.76 (dd, *J* = 7.6, 15.6 Hz, 1 H), 6.13 (d, *J* = 15.6 Hz, 1 H), 4.20 (q, *J* = 7.2 Hz, 2 H), 2.54 (q, *J* = 6.4 Hz, 1 H), 2.16–2.11 (m, 1 H), 1.80 (d, *J* = 3.2 Hz, 1 H), 1.66 (d, *J* = 6.4 Hz, 1 H), 1.43 (d, *J* = 6.6 Hz, 3 H), 1.29 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.38, 148.63, 144.28, 128.59, 127.39, 126.95, 122.05, 70.14, 60.51, 39.83, 36.49, 23.42, 14.46.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{20}NO_2$: 246.1489; found: 246.1494.

Ethyl 2,3-Dihydroxy-3-{(*R*)-1-[(*R*)-1-phenylethyl]aziridin-2-yl}propanoate (3)

To a solution of **4** (2.7g, 13.3 mmol) in *t*-BuOH–H_2O (55 mL/55 mL) were added AD-mix-α (27 g) and $MeSO_2NH_2$ (1.57 g, 16.6 mmol) at 0 °C. The reaction mixture was stirred for 36 h, washed with sat. aq Na_2SO_3 (3 × 20 mL), and then partitioned between CH_2Cl_2 (300 mL) and H_2O (200 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL) and the combined organic layers were washed with brine (200 mL), dried ($MgSO_4$), filtered through a pad of Celite, and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography with EtOAc–hexane (2:3 to 1:1) to afford the diol **3** (diastereomeric mixture, **3a**/**3b** = 10:1); yield: 2.25 g (9.71 mmol, 73%); yellow oil.

The diastereomeric mixture **3** from column chromatography was further purified by preparative TLC (eluent: EtOAc–hexane, 1:2 to 2:3) to collect small amount of the desired diastereomer **3a**.

Diastereomer 3a

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.23 (m, 5 H), 4.29–4.23 (m, 3 H), 3.72 (dd, *J* = 2.4, 6.4 Hz, 1 H), 3.55 (br s, 2 H), 2.61 (q, *J* = 6.4 Hz, 1 H), 2.05–2.01 (m, 1 H), 1.71 (d, *J* = 3.2 Hz, 1 H), 1.48 (d, *J* = 6.4 Hz, 3 H), 1.40 (d, *J* = 6.4 Hz, 1 H), 1.29 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.92, 144.37, 128.62, 127.38, 127.00, 73.42, 72.12, 69.43, 62.16, 41.62, 30.87, 23.44, 14.42.

HRMS-ESI: *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{21}NO_4$ + Na: 302.1363; found: 302.1368.

(*R*)-1-[(*R*)-1-Phenylethyl]-2-[(1*S*,2*S*)-1,2,3-tri(benzyloxy)propyl]aziridine (6)

To a solution of **3** (1 g, 3.57 mmol) in THF (35 mL) was added $LiAlH_4$ (1.96 mL, 3.93 mmol, 2 M in THF) at 0 °C. The reaction mixture was stirred for 20 min at 0 °C, diluted with THF (35 mL), quenched with sat. Rochelle's solution (70 mL), and stirred for an additional 12 h at 0 °C. The mixture was filtered through a pad of Celite and partitioned between EtOAc (300 mL) and H_2O (100 mL). The aqueous layer was extracted with *i*-PrOH–$CHCl_3$ (1:4; 3 × 100 mL) and the combined organic layers were dried ($MgSO_4$), filtered through a pad of Celite, and concentrated in vacuo. The resulting alcohol was used in the next step without further purification. To a slurry of NaH (471 mg, 11.78 mmol, 60% dispersion in mineral oil) in THF (12 mL) was added a solution of the resulting alcohol in THF (12 mL) at 0 °C. After 1 h, BnBr (1.4 mL, 11.78 mmol) and TBAI (442 mg, 1.2 mmol) were added. The reaction mixture was stirred for 12 h at r.t., diluted with EtOAc (30 mL), quenched with H_2O (10 mL) at 0 °C and extracted with EtOAc (2 × 30 mL). The combined organic layers were washed with brine (30 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The resulting crude product was purified by silica gel flash chromatography with EtOAc–hexane (1:9) to afford the title product **6**; yield: 1.29 g (2.64 mmol, 74% over 2 steps); yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.25 (m, 20 H), 4.99 (d, *J* = 12.0 Hz, 1 H), 4.73 (d, *J* = 12.4 Hz, 2 H), 4.60 (d, *J* = 11.6 Hz, 1 H), 4.41 (s, 2 H), 3.65 (m, 3 H), 3.17 (dd, *J* = 2.8, 8.4 Hz, 1 H), 2.42 (q, *J* = 6.4 Hz, 1 H), 1.87–1.82 (m, 1 H), 1.50 (d, *J* = 6.4 Hz, 3 H), 1.42 (d, *J* = 6.8 Hz, 1 H), 1.06 (d, *J* = 6.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.90, 139.13, 138.79, 138.50, 128.57, 128.47, 128.42, 127.87, 127.84, 127.79, 127.71, 127.22, 127.09, 81.71, 79.37, 73.63, 73.41, 73.39, 70.43, 70.40, 41.69, 30.01, 23.61.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{34}H_{38}NO_3$: 508.2846; found: 508.2852.

(2*R*,3*S*,4*S*)-3,4,5-Tri(benzyloxy)-2-{[(*R*)-1-phenylethyl]amino}pentan-1-ol (2)

To a solution of **6** (340 mg, 0.67 mmol) in CH_2Cl_2 (2 mL) was added AcOH (0.38 mL, 6.7 mmol). The reaction mixture was stirred for 18 h at r.t., diluted with CH_2Cl_2 (20 mL), and quenched with sat. aq $NaHCO_3$ (100 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 200 mL) and the combined organic layers were washed with brine (100 mL), dried ($MgSO_4$), filtered through a pad of Celite, and concentrated in vacuo. The resulting acetate was used in the next step without further purification. To a solution of the acetate in EtOH (2 mL) was added KOH (113 mg, 2.1 mmol). The reaction mixture was stirred for 2 h at r.t., diluted with CH_2Cl_2 (20 mL), and quenched with H_2O (2 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL) and the combined organic layers were washed with brine (50 mL), dried ($MgSO_4$), filtered through a pad of Celite, and concentrated in vacuo. The resulting crude product was purified by silica gel flash chromatography with EtOAc–hexane (1:3) to afford the title product **2**; yield: 267 mg (0.51 mmol, 76% yield over 2 steps); yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.24 (m, 20 H), 4.81 (d, *J* = 11.6 Hz, 1 H), 4.73 (d, *J* = 11.6 Hz, 1 H), 4.69 (d, *J* = 12.0 Hz, 1 H), 4.58–4.53 (m, 3 H), 3.97 (q, *J* = 4.8 Hz, 1 H), 3.83 (q, *J* = 6.4 Hz, 1 H), 3.77–3.73 (m, 3 H), 3.37–3.29 (m, 2 H), 2.85 (q, *J* = 4.4 Hz, 1 H), 2.22 (br s, 1 H), 1.24 (d, *J* = 6.4 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.11, 138.02, 128.53, 128.50, 128.41, 128.38, 128.31, 128.16, 127.94, 127.77, 127.74, 127.72, 127.27, 126.80, 79.35, 78.14, 74.23. 73.44. 72.86, 69.85, 61.47, 56.95, 56.82, 23.78.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{34}H_{40}NO_4$: 526.2952; found: 526.2962

(2*S*,3*S*,4*S*)-3,4,5-Tri(benzyloxy)-2-{[(*R*)-1-phenylethyl]amino}pentanoic Acid (7)

To a solution of **2** (110 mg, 0.209 mmol) in acetone (2 mL) was added Jones reagent (0.21 mL, 0.522 mmol, 2.5 M solution in H_2O) at 0 °C. The reaction mixture was stirred for 4 h at 0 °C, quenched with *i*-PrOH (0.1 mL), and filtered through a pad of Celite, and washed with CH_2Cl_2 (20 mL). The reaction mixture was partitioned between CH_2Cl_2 (50 mL) and H_2O (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL) and combined organic layers were washed with brine, dried ($MgSO_4$), filtered through a pad of Celite, and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography with EtOAc–hexane

Downloaded by: University of Pittsburgh. Copyrighted material.

(1:2) to CH_2Cl_2–MeOH (20:1) to afford the title product **7**; yield: 59 mg (0.11 mmol, 52%); white solid; mp 121–124 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42–7.19 (m, 18 H), 7.02–7.00 (m, 2 H) 4.70 (dd, *J* = 10.8, 14.4 Hz, 2 H), 4.56 (dd, *J* = 1.2, 5.2 Hz, 1 H), 4.50 (dd, *J* = 1.6, 11.2 Hz, 2 H), 4.46 (s, 2 H), 4.07 (q, *J* = 6.8 Hz, 1 H), 3.87 (dd, *J* = 4.0, 9.2 Hz, 1 H), 3.69 (dd, *J* = 4.4, 10.4 Hz, 1 H), 3.59 (dd, *J* = 4.4, 10.4 Hz, 1 H), 3.52 (d, *J* = 1.2 Hz, 1 H), 1.20 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.00, 137.37, 136.99, 129.15, 128.95, 128.70, 128.66, 128.43, 128.26, 128.23, 128.09, 128.00, 127.20, 79.36, 77.70, 75.01, 73.73, 72.75, 68.83, 60.29, 57.76, 19.82.

HRMS-ESI: *m*/*z* $[M + H]^+$ calcd for $C_{34}H_{38}NO_5$: 540.2744; found: 540.2749.

(+)-Polyoxamic Acid (1)

To a solution of **7** (59 mg, 0.109 mmol) in MeOH (10 mL) was added $Pd(OH)_2$ (59 mg). The reaction mixture was flushed with H_2 and stirred for 12 h under a H_2 atmosphere (50 psi) at r.t. The mixture was then filtered through a pad of Celite and concentrated in vacuo. The resulting crude solid was recrystallized from EtOH to give a white solid, which was subjected to ion-exchange chromatography on Dowex-50WX8 (H^+ form) using 0.6 M aq NH_4OH as eluent to afford (+)-polyoxamic acid (**1**); yield: 15 mg (0.091 mmol, 84%); white solid; mp 168–171 °C; $[\alpha]_D^{23.5}$ +2.2 (*c* 0.17, H_2O) {Lit.[22] $[\alpha]_D^{23}$ +2.1 (*c* 1.0, H_2O)}.

^{1}H NMR (400 MHz, D_2O): δ = 4.08 (t, *J* = 2.4 Hz, 1 H), 3.78–3.74 (m, 2 H), 3.57–3.48 (m, 2 H).

^{13}C NMR (100 MHz, D_2O): δ = 172.65, 73.12, 68.07, 62.43, 57.95.

HRMS: *m*/*z* $[M + Na]^+$ calcd for $C_5H_{11}NO_5$ + Na: 188.0529; found: 188.0535.

Acknowledgment

This research was supported by Korea Institute of Science and Technology and a grant (NRF-2011-0028676) from the creative/challenging research program of National Research Foundation of Korea.

References

(1) (a) Isono, K.; Asahi, K.; Suzuki, S. *J. Am. Chem. Soc.* **1969**, *91*, 7490. (b) Isono, K.; Suzuki, S. *Heterocycles* **1979**, *13*, 333.
(2) (a) Naider, F.; Shenbagamurthi, P.; Steinfeld, A. S.; Smith, H. A.; Boney, C.; Becker, J. M. *Antimicrob. Agents Chemother.* **1983**, *24*, 787. (b) Shenbagamurthi, P.; Smith, H. A.; Becker, J. M.; Naider, F. *J. Med. Chem.* **1986**, *29*, 802.
(3) Lee, Y. J.; Park, Y.; Kim, M. H.; Jew, S. S.; Park, H. G. *J. Org. Chem.* **2011**, *76*, 740.
(4) Trost, B. M.; Krueger, A. C.; Bunt, R. C.; Zambrano, J. *J. Am. Chem. Soc.* **1996**, *118*, 6520.
(5) Enders, D.; Vrettou, M. *Synthesis* **2006**, 2155.
(6) (a) Savage, I.; Thomas, E. *J. Chem. Soc., Chem. Commun.* **1989**, 717. (b) Savage, I.; Thomas, E. J.; Wilson, P. D. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3291.
(7) Kim, K. S.; Lee, Y. J.; Kim, J. H.; Sung, D. K. *Chem. Commun.* **2002**, 1116.
(8) Raghavan, S.; Joseph, S. C. *Tetrahedron Lett.* **2003**, *44*, 6713.
(9) Matsuura, F.; Hamada, Y.; Shioiri, T. *Tetrahedron Lett.* **1994**, *35*, 733.
(10) Veeresa, G.; Datta, A. *Tetrahedron Lett.* **1998**, *39*, 119.
(11) Yoon, H. J.; Kim, Y. W.; Lee, B. K.; Lee, W. K.; Kim, Y.; Ha, H. J. *Chem. Commun.* **2007**, 79.
(12) Righi, G.; Mandic', E.; Naponiello, G. C. M.; Bovicelli, P.; Tirotta, I. *Tetrahedron* **2012**, *68*, 2984.
(13) Lee, B. K.; Choi, H. G.; Roh, E. J.; Lee, W. K.; Sim, T. *Tetrahedron Lett.* **2013**, *54*, 553.
(14) Watson, A. A.; Fleet, G. W. J.; Asano, N.; Molyneux, R. J.; Nash, R. J. *Phytochemistry* **2001**, *56*, 265.
(15) Choi, S. K.; Lee, J. S.; Kim, J. H.; Lee, W. K. *J. Org. Chem.* **1997**, *62*, 743.
(16) Andres, J. M.; de Elena, N.; Pedrosa, R. *Tetrahedron* **2000**, *56*, 1523.
(17) Ratcliff, R.; Rodehors, R. *J. Org. Chem.* **1970**, *35*, 4000.
(18) Barfoot, C. W.; Harvey, J. E.; Kenworthy, M. N.; Kilburn, J. P.; Ahmed, M.; Taylor, R. J. K. *Tetrahedron* **2005**, *61*, 3403.
(19) Joo, J. E.; Pham, V. T.; Tian, Y. S.; Chung, Y. S.; Oh, C. Y.; Lee, K. Y.; Ham, W. H. *Org. Biomol. Chem.* **2008**, *6*, 1498.
(20) Dhavale, D. D.; Saha, N. N.; Desai, V. N. *J. Org. Chem.* **1997**, *62*, 7482.
(21) Tsimilaza, A.; Tite, T.; Boutefnouchet, S.; Lallemand, M. C.; Tillequin, F.; Husson, H. P. *Tetrahedron: Asymmetry* **2007**, *18*, 1585.
(22) Saksena, A. K.; Lovey, R. G.; Girijavallabhan, V. M.; Ganguly, A. K.; Mcphail, A. T. *J. Org. Chem.* **1986**, *51*, 5024.

Downloaded by: University of Pittsburgh. Copyrighted material.

 © Georg Thieme Verlag Stuttgart · New York