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An Enantioselective Synthesis of (+)-Polyoxamic Acid via Phase-Transfer Catalytic Conjugate Addition and Asymmetric Dihydroxylation

Yeon-Ju Lee,[†] Yohan Park,[‡] Mi-hyun Kim,[‡] Sang-sup Jew,[‡] and Hyeung-geun Park*,[‡]

[†]*Marine Natural Products Chemistry Laboratory, Korea Ocean Research and Development Institute, Ansan 426-744, Korea, and* [‡]*Research Institute of Pharmaceutical Science and College of Pharmacy, Seoul National University, Seoul 151-742, Korea*

hgpk@snu.ac.kr

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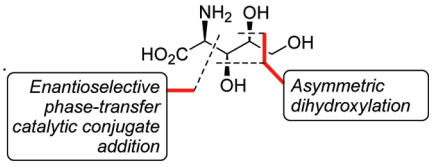
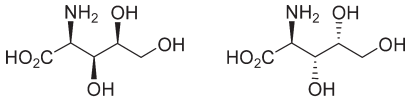


(+)-Polyoxamic acid

A new enantioselective synthetic method of (+)-polyoxamic acid is reported. (+)-Polyoxamic acid could be obtained in 7 steps with 46% overall yield from diphenylmethyl-glycineimine *tert*-butyl ester via an enantioselective phase-transfer conjugate addition (99% yield, 96% ee) and an asymmetric dihydroxylation (98% yield, 94% de) as the key reactions.

Polyoxamic acid (**1**) is an amino acid bearing three contiguous hydroxyl groups, two of which are attached to stereogenic centers.[1] It is a key component of peptidyl nucleoside antibiotics called polyoxins, which inhibit chitin synthetase of *Candida albicans*, a human fungi pathogen, and of various phytopathogenic fungi as well.[2]



1 **2**

On the other hand, 3,4-diepipolyoxamic acid (**2**) constitutes the structures of sphingofungins A−D, potent antifungal agents which inhibit serinepalmitoyl transferase to block the biosynthesis of sphingolipids.[3] In both cases of polyoxins and sphingofungins, it is well-known that 3,4-dihydroxy-amino acid moieties (**1** and **2**) are very important pharmacophores and their configurations are closely related to their biological activities.[4]

Due to their significance on the biological activities of polyoxins and sphingofungins along with their structural uniqueness, a variety of methods for the synthesis of polyoxamic acid and its stereoisomers have been developed over the past several years. Most commonly, they could be synthesized from chiral carbohydrates[5] or amino acids[6] depending on the stereogenic centers; however, only two methods were reported for the enantioselective synthesis of **1**.[7]

In continuation of our studies on the synthesis of non-proteinogenic amino acids of pharmaceutical interest through phase-transfer reactions, we tried to develop an enantioselective synthesis of **1**, which would later enable the synthesis of various stereoisomers of **1**, including **2**.

As shown in the retrosynthetic strategy (Scheme 1), the C2(*S*) chirality can, in principle, be induced by the enantioselective phase-transfer catalytic conjugate addition of diphenylmethylglycineimine *tert*-butyl ester (**4**).[8] Both C(3*S*) and C(4*S*) configurations of the dihydroxy group can be derived from asymmetric dihydroxylation of **2**, which can be obtained by olefination of **3**.

First, the phase-transfer catalytic conjugate addition was carried out with **4** and methyl acrylate to introduce an α-carbomethoxyethyl moiety of **3** under phase-transfer catalytic reaction conditions. But, much to our disappointment, only moderate enantioselectivity (68% ee) was observed.[9] In addition, significant racemization might be possible during the α-phenylselenylation of **3** in basic condition for olefination.

*Address correspondence to this author. Phone: 82-2-880-8264. Fax: 82-2-872-9129.

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(9) A Michael reaction between **5** and ethyl acrylate under the same condition (**12**, 50% KOH, CH_2Cl_2, 0 °C) as that depicted in Table 1 afforded the alkylated product with 68% ee in 87% yield.

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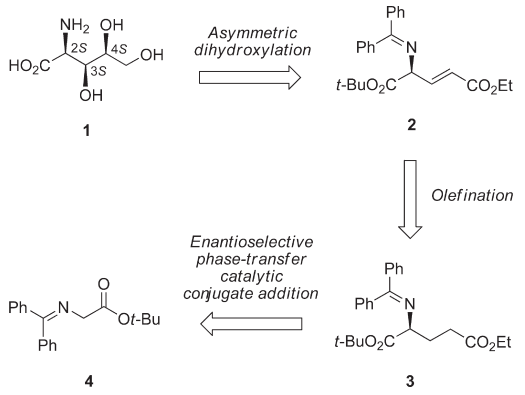
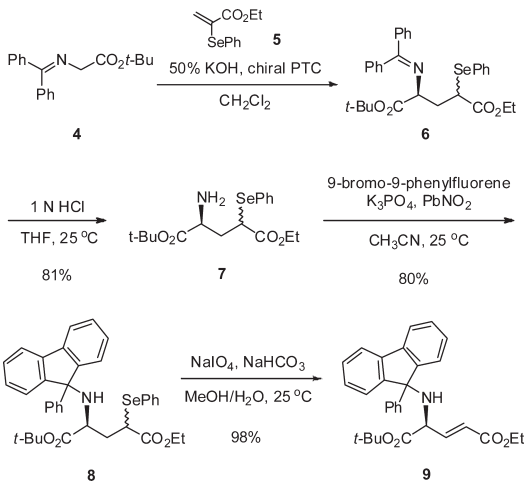
SCHEME 1. Retrosynthesis of (+)-Polyoxamic Acid (1)



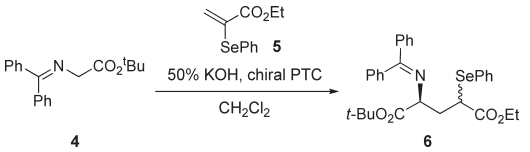
SCHEME 2. Synthesis of 3,4-Didehydroamino Acid 3a



So our strategy needed modification and we chose ethyl α-phenylselenylacrylate (**5**)[10] as an alternate Michael acceptor, which already contains a phenylselenyl group. The phase-transfer catalytic Michael addition was performed with **4** and ethyl α-phenylselenylacrylate (**5**) under PTC conditions with 50% aqueous KOH in CH_2Cl_2 (Scheme 2).

To find an optimal catalyst for the conjugate addition, five representative catalysts[11] (PTCs, **10**−**14**, Table 1), which exhibited excellent catalytic efficiencies in the enantioselective catalytic conjugate addition of **4**, were examined. As shown in Table 1, all of the catalysts provided **6** as 1:1 mixtures of diastereomers in almost quantitative chemical yields, but the enantioselectivities were dramatically dependent on the PTC catalysts. Among the catalysts used, catalyst **12** yielded the highest enantioselectivity at 0 °C (entry 3, 90% ee) and even higher enantioselectivity was observed at −20 °C (entry 4, 96% ee). The stereoselectivities were determined by the diastereomer ratios of **6** as well as enantiomer ratios of **9** using chiral column chromatography.[12] In all cases examined, the ratio of

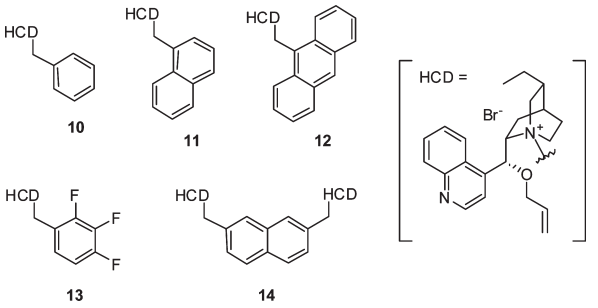
TABLE 1. Enantioselective Phase-Transfer Catalytic Conjugate Addition of 5[a]



entry	chiral PTC	temp (°C)	time (h)	yield of **6**[b] (%)	% ee of **9**[c,d]
1	**10**	0	1	99	48
2	**11**	0	2	99	59
3	**12**	0	1	99	90
4	**12**	−20	1	99	96
5	**13**	0	1	98	78
6	**14**	0	2	99	69

[a]The reaction was carried out with 3.0 equiv of **5** and 10.0 equiv of 50% KOH in the presence of chiral catalysts (10 mol %) in methylene chloride. [b]Isolated yields after purification by column chromatography. [c]Enantiopurity was determined by HPLC analysis, using a chiral column (DAICEL Chiralcel AD-H) with hexanes/2-propanol (volume ratio = 99:1) as a solvent. In this case, it was established by analysis of the racemate, of which enantiomers were fully resolved. [d]Diastereomer ratios of **6** correspond to enantiomer ratios of **9**. See the Supporting Infomation for details.

the two major diasteromers to the two minor diastereomers of **6** was in accordance with the enantiomer ratio of **9**. The absolute stereochemistry of C(2) in the conjugate addition adduct (**6**) was confirmed by comparison of the optical rotation of the final product **1** with the reported value.[6f]



Next, the direct oxidation of selenyl ester **6** was avoided due to the tendency of isomerization of the olefinated product **2** to the more conjugated benzophenone imine 2,3-didehydroglutamate.[13] To prevent the isomerization, a benzophenone imine group was hydrolyzed to **7** in acidic conditions. The resulting amino ester was protected with a 9-phenylfluorenyl (Pf) group by treatment with 9-bromo-9-phenylfluorene in the presence of K_3PO_4 and $PbNO_2$, which proved to prevent the isomerization by stereoelectronic hindrance.[14] *N*-9-Phenylfluorenyl-glutamate **8** was then converted to 3,4-didehydroglutamate **9** by using $NaIO_4$ and $NaHCO_3$ at an ambient temperature with 98% yield without isomerization.

With 3,4-dihydroglutamate **9** in hand, efforts have been made to find the optimal conditions for asymmetric dihydroxylation (Table 2). Without any ligand, less than 2% conversion of **9** to **15** was observed with quantitative recovery of the starting material after 24 h (entry 1). In the presence of

(10) For the preparation, see: Berlin, S.; Engman, L. *Tetrahedron Lett.* **2000**, *41*, 3701.

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(12) The diastereomer ratio of **6** corresponds to the enantiomer ratio of **9**. See the Supporting Infomation for details.

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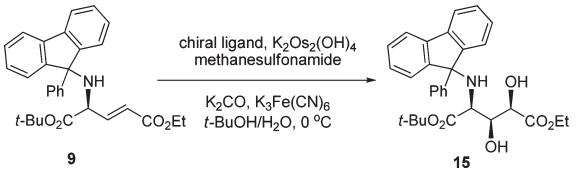
TABLE 2. Asymmetric Dihydroxylation of 9[a]

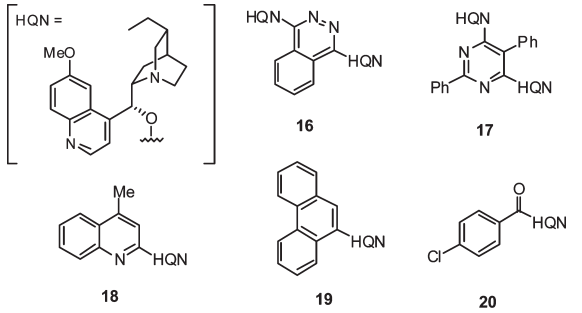


9 15

entry	ligand	time (h)	yield[b] (%)	% de[c]
1	none	24	< 2	
2	DABCO	24	84	< 2
3	**16**	3.5	91	75
4	**17**	4.0	88	83
5	**18**	2.5	91	87
6	**19**	5.0	93	88
7	**20**	3.5	99	94

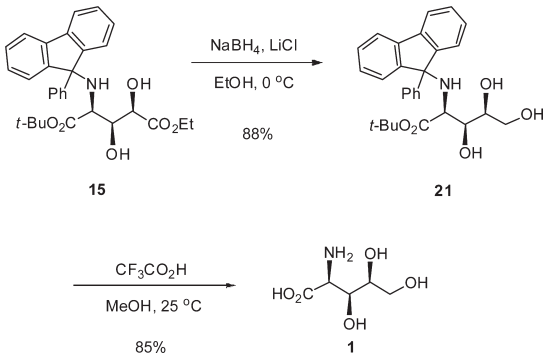
[a]See the Supporting Infomation for detailed reaction conditions. [b]Isolated yields after purification by column chromatography. [c]Diastereopurity was determined by HPLC analysis, using a chiral column (DAICEL Chiralcel AD-H) with hexanes/2-propanol (volume ratio = 92:8) as a solvent.

the achiral ligand DABCO, the reaction proceeded efficiently (94% yield) to yield **15** with no stereoselectivity (< 2% de), indicating that the stereogenecity of C(2) does not affect the facial selectivities of 3,4-dihydroxylations (entry 2). As chiral ligands, five quinine derivatives (**16**−**20**) were examined. The absolute configuration of the products was determined by the application of the mnemonic devices for predicting facial selectivity in asymmetric dihydroxylations[15] and confirmed later by comparison of the optical rotation of final product **1** with the reported value.[6f] In the case of dimeric quinine derivative **16** and **17**, which usually provide highly enantioselective dihydroxylations,[15] moderate facial selectivities were observed (entries 3 and 4, 75% de and 83% de). Monomer ligands **18** and **19** were also examined and surprisingly, products were obtained with higher diastereoselectivities (entries 5 and 6, 87% de and 88% de). When **20** (HQN-CLB) was used as a chiral ligand based upon the expectation that reducing the steric hindrance of the chiral ligand might be beneficial, the highest diastereoselectivity (94% de) was obtained providing **15** in a quantitative yield. The successful results prompted us to apply HQD-CLB under the optimal conditions for the preparation of 3,4-diepipolyoxamic acid (**2**). However, much to our disappointment, only moderate enantioselectivity of 3,4-diepi-**15** with comparable chemical yield was obtained (42% de, 93% yield).



Treatment of **15** with $NaBH_4$/LiCl in methanol at 0 °C afforded aminotriol **21** with 88% yield, which upon treatment with trifluoroacetic acid provided (+)-polyoxamic acid (**1**) after purification by Dowex ion-exchange resin (Scheme 3). The physical characteristics of **1** were in full agreement with the reported values in the literature {($[\alpha]^{23}_D$ 2.5 (*c* 0.2, H_2O) (lit.[6f] $[\alpha]^{23}_D$ 2.8 (*c* 1.0, H_2O)}.

SCHEME 3. Completion of the Synthesis of 1



In conclusion, we have developed an efficient and enantioselective synthesis of (+)-polyoxamic acid from a commercially available diphenylmethyl glycineimine *tert*-butyl ester (**4**) in 7 steps (46% overall yield, 96% ee) by an enantioselective phase-transfer catalytic conjugate addition and asymmetric dihydroxylation. It is worthwhile to point out that all three stereogenic centers were constructed by the use of cinchona derived catalysts (**12**, **20**) which are easily prepared from inexpensive materials. Further applications to the synthesis of similar polyoxamic acid-type compounds with an aminotriol core structure including **2** are now under investigation.

Experimental Section

Representative Procedure for the Enantioselective Phase-Transfer Catalytic Alkylation of 4 (6). A solution of ethyl 2-(phenylselanyl)acrylate **5** (383 mg, 1.5 mmol) in dichloromethane (0.3 mL) was added to a solution of *N*-(diphenylmethylene)-glycine *tert*-butyl ester **4** (148 mg, 0.50 mmol) and chiral catalyst **12** (30.3 mg, 0.05 mmol) in dichloromethane (1.2 mL). The reaction mixture was then cooled to −20 °C, 50% aqueous KOH (0.56 mL) was added, and the resulting mixture was allowed to stir at −20 °C for 1.0 h. The resulting mixture was diluted with dichloromethane (20 mL), washed with water (2 × 5 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The resulting brown oil was purified by silica gel column chromatography to afford **6** (273 mg, 0.50 mmol, 99% yield) as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 (d, J = 7.0 Hz, 1H), 7.55 (d, J = 7.5 Hz, 1H), 7.53 (d, J = 7.0 Hz, 1H), 7.42−7.33 (m, 5H), 7.29−7.22 (m, 4H), 7.19−7.15 (m, 2H), 7.11 (dd, J = 2.5, 6.0 Hz, 1H), 4.10 (dd, J = 4.2, 9.5 Hz, 0.5H), 3.97−3.86 (m, 2H), 3.82−3.75 (m, 1H), 3.60 (dd, J = 6.5, 8.8 Hz, 0.5H), 2.54−2.48 (m, 1H), 2.44−2.40 (m, 0.5H), 2.30−2.24 (m, 0.5H), 1.36 (s, 4.5H), 1.35 (s, 4.5H), 1.04 (t, J = 7.0 Hz, 1.5H), 1.01 (t, J = 7.5 Hz, 1.5H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8, 172.5, 171.9, 171.4, 170.9, 170.5, 139.6, 139.5, 136.6, 136.4, 136.0, 135.8, 130.6, 130.5, 129.2, 129.1, 128.5, 128.5, 128.2, 128.1, 128.1, 128.0, 81.6, 81.5, 64.5, 64.1, 61.1, 61.0, 40.5, 40.3, 36.3, 35.1, 28.2, 28.2, 14.1, 14.0 ppm; IR (KBr) 3348, 2970, 1467, 1379, 1305, 1160, 1129, 952, 817, 760 cm^{-1}; LRMS (FAB$^+$) m/z 552.0 [M + H]$^+$; HRMS (ESI) [M + H]$^+$ calcd for $C_{30}H_{33}NO_4Se$ 552.1648, found 552.1641. $[\alpha]^{23}_D$ −10.7 (*c* 1.0, $CHCl_3$). The diasteromeric ratio was determined by HPLC analysis in comparison with authentic racemic materials. {DAICEL chiralpak AD-H, hexane:2-propanol = 99:1,

(15) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483 and references cited therein.

flow rate = 1.0 mL/min, 23 °C, λ = 254 nm, retention times: 14.71 (minor), 18.79 (minor), 19.86 (major), 28.17 (major), 1.3:1.7:40:53 dr}.

Representative Procedure for the Asymmetric Dihydroxylation of 9 (15). To a solution of **9** (117 mg, 0.25 mmol) and methanesulfonamide (35 mg, 0.37 mmol) in *tert*-butanol (2.0 mL) and water (2.0 mL) was added K_2CO_3 (104 mg, 0.75 mmol) and chiral ligand **20** (23 mg, 0.05 mmol). The mixture was then cooled to 0 °C, then $K_3Fe(CN)_6$ (247 mg, 0.75 mmol) was added followed by $K_2OsO_2(OH)_4$ (9.2 mg, 0.025 mmol). The mixture was allowed to stir at 0 °C for 3.5 h, after which time the reaction was quenched by dropwise addition of saturated $NaHSO_3$ aqueous solution. The mixture was then diluted with ethyl acetate (20 mL), washed with water (2 × 5 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The resulting yellow oil was purified by silica gel column chromatography to afford **15** (125 mg, 0.25 mmol, 99% yield) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (d, J = 7.5 Hz, 2H), 7.38−7.29 (m, 5H), 7.21−7.14 (m, 6H), 4.17 (dd. J = 7.1 Hz, 2H), 4.02 (s, 1H), 3.72 (d, J = 5.5 Hz, 1H), 2.76 (d, J = 6.0 Hz, 1H), 1.23 (t, J = 7.1 Hz, 3H), 1.17 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.3, 171.8, 148.0, 147.8, 143.5, 141.1, 128.8, 128.5, 128.5, 128.2, 127.8, 127.4, 126.4, 125.8, 125.2, 120.3, 119.9, 82.4, 72.8, 72.3, 71.2, 61.6, 57.5, 27.8, 14.1 ppm; IR (KBr) 3492, 2979, 1734, 1451, 1394, 1369, 1213, 1155, 1073, 844, 754, 699 cm^{-1}; LRMS (FAB$^+$) m/z 504 $[M + H]^+$; HRMS (ESI) $[M + H]^+$ calcd for $C_{30}H_{34}O_6N$ 504.2386, found 504.2389. $[\alpha]^{23}_D$ 5.3 (c 1.0, $CHCl_3$). The diasteromeric ratio was determined by HPLC analysis in comparison with authentic racemic materials. {DAICEL chiralpak AD-H, hexane:2-propanol = 92:8, flow rate = 1.0 mL/min, 23 °C, λ = 254 nm, retention times: 13.92 (minor), 14.85 (minor), 18.48 (major), 32.66 (minor), 2.4:0.6:95.5:1.5 dr, 94% de from **9** (96% ee)}.

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Supporting Information Available: Characterizations of all compounds, additional experimental procedures, and analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.