Stereoselective synthesis of (+)-polyoxamic acid based on the synthesis of chiral oxazine†

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Received 20th November 2007, Accepted 28th January 2008
First published as an Advance Article on the web 6th March 2008
DOI: 10.1039/b717961h

A concise, stereocontrolled synthesis of (+)-polyoxamic acid was achieved. Starting from *trans*-oxazoline as a chiral building block, the key step involves diastereoselective oxazine formation catalyzed by palladium(0).

Introduction

Polyoxamic acid (**1**) is the key component amino acid of the polyoxins,[1] which have exhibited high inhibitory potencies against chitin synthetase of *Candida albicans*, a human fungal pathogen, and of various phytopathogenic fungi (Fig. 1).[2] Inhibition of the chitin synthetase enzyme leads to the disruption of the biosynthesis of chitin, an essential component of the fungal cell wall. A number of its synthetic approaches have been reported due to its three contiguous stereocenters and its interesting biological activities.[3,4] Many synthetic studies are based on carbohydrate chemistry, the use of chiral auxiliaries or asymmetric synthesis in the presence of a chiral ligand. Despite their potential practicality, there remains the need for a more general, efficient and a stereoselective approach to polyoxamic acid.

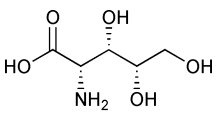

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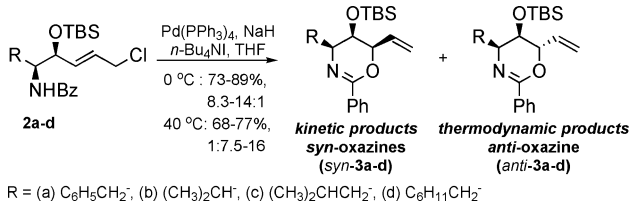
Fig. 1 (+)-Polyoxamic acid.

On the basis of our previous research, we anticipated that the palladium(0)-catalyzed oxazine formation of a γ-allyl benzamide having a benzoyl substituent as an *N*-protection group in the presence of $Pd(PPh_3)_4$, NaH and *n*-Bu_4NI might proceed with high stereoselectivity. Unlike other palladium catalyzed reactions, the diastereoselectivity of oxazine ring formation is predominantly controlled by the temperature.[5]

Our study into intramolecular oxazine formation from **2a–d** has shown that the stereoselectivity of these cyclizations can be critically dependent upon whether the reaction temperature results in kinetic or thermodynamic control of the products (Scheme 1). Starting from allyl chlorides **2a–d**, both *syn*-**3a–d** and *anti*-**3a–d** isomers can be stereoselectively prepared by changing only the reaction temperature; *syn*-**3a–d** under kinetic control (0 °C) and *anti*-**3a–d** under thermodynamic control (40 °C).



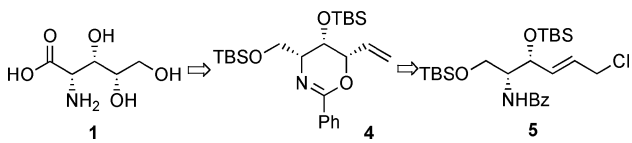
R = (a) $C_6H_5CH_2^-$, (b) $(CH_3)_2CH^-$, (c) $(CH_3)_2CHCH_2^-$, (d) $C_6H_{11}CH_2^-$

Scheme 1

As part of this program, we developed a novel strategy for the synthesis of (+)-polyoxamic acid that utilizes oxazine as a chiral building block.

Results and discussion

We envisioned that the intramolecular palladium(0)-catalyzed oxazine formation of benzamide **5** would generate the oxazine **4** bearing a pendant vinyl group that could be elaborated to the alcohol as shown in Scheme 2. It was also anticipated that the primary alcohol of **4** could be converted to carboxylic acid *via* oxidation.



Scheme 2 Retrosynthetic analysis.

We have recently developed an efficient preparation of *trans*-oxazoline **6** in enantiopure form from D-*N*-benzoylserinol by employing the palladium(0)-catalyzed intramolecular cyclization reaction.[6]

The synthesis of **1** began with ozonolysis of **6**[6c,6f] to give the desired allyl chloride **9** following the sequence of our previous papers (Scheme 3).[5,6c,6f]

However, the preparation of allyl chloride **9** *via* **6** from D-*N*-benzoylserinol was plagued by protecting group manipulations and functional group interconversions, leading to synthetic inefficiency. Consequently, a new method for synthesizing **9** was

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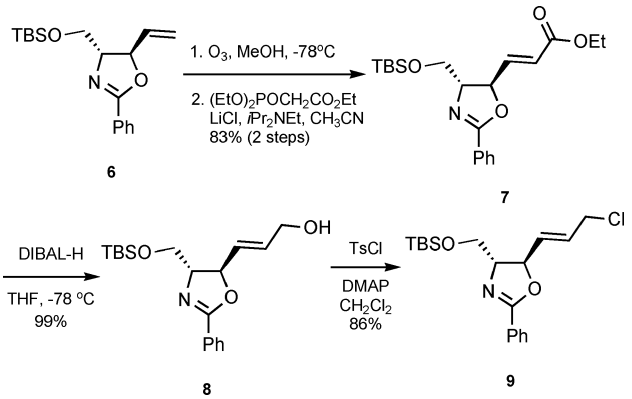
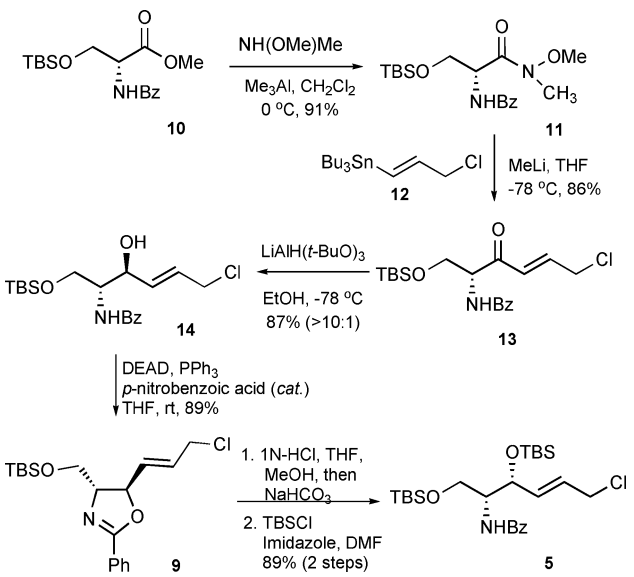
† Electronic supplementary information (ESI) available: Synthetic and characterization data for compounds **7–9**, **11**, **13–14** and **5**. See DOI: 10.1039/b717961h



Scheme 3

conceived (Scheme 4). The ester **10** was readily converted into Weinreb amide **11** by treatment with *N*,*O*-dimethylhydroxylamine in the presence of trimethylaluminium in 91% yield. Reaction of Weinreb amide **11** with vinyltin **12** and MeLi in THF at −78 °C gave α,β-unsaturated ketone **13** in 86% yield. To investigate the *anti*-selective reduction, amino ketone **13** was treated with various reducing agents and we found that reaction with lithium tri-*tert*-butoxyaluminohydride in ethanol at −78 °C gave the desired alcohol **14** as the major compound in good yield (87%) with excellent stereoselectivity (*anti*–*syn* = 10 : 1).[7] A *p*-nitrobenzoic acid-catalyzed Mitsunobu-type reaction of *anti*-amino alcohol **14** gave the *trans*-oxazoline **9** in good yield (89%). The spectroscopic data of the resulting cyclization precursor **9** were completely identical to those of the compound formed from oxazoline **6**.

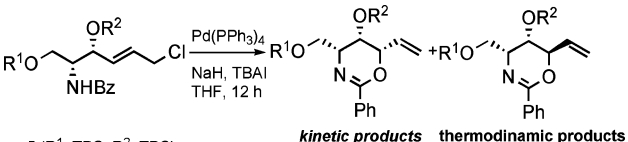


Scheme 4

The subsequent acid-catalyzed hydrolysis of the oxazoline, followed by the addition of sodium bicarbonate to increase the pH of the reaction mixture to 9.0 furnished the *syn*-amino alcohol. The protection of the resulting alcohols by TBSCl afforded the cyclization precursor **5** in 89% yield.

Under the conditions of $Pd(PPh_3)_4$, NaH, and *n*-Bu_4NI in THF at 0 °C, the stereoselective intramolecular cyclization of the allyl chloride **5** afforded the oxazine *syn*-**4** and *anti*-**4′** as a

Table 1 Oxazine formation catalyzed by Pd(0)



5 (R^1=TBS, R^2=TBS) — **4** — **4′**
15 (R^1=TBS, R^2=PMB) — **17** — **17′**
16 (R^1=MOM, R^2=TBS) — **18** — **18′**

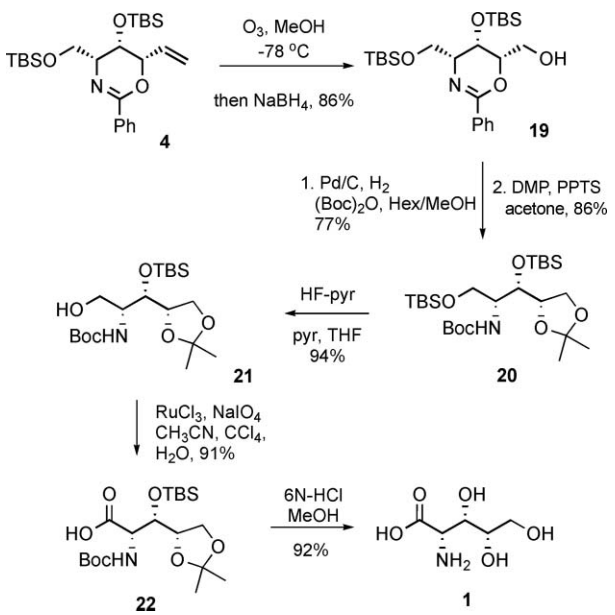
Entry	Substrate	Temp./°C	Yield[a] (%)	Ratio[b] (*syn*–*anti*)
1	**5**	0	84	9.5 : 1
2	**5**	*rt*	75	3 : 1
3	**5**	50	68	1 : 9
4	**15**	0	65	1 : 1
5	**16**	0	69	10 : 1

[a] Yields refer to the isolated and mixture products. [b] Ratio was determined by ^{1}H NMR.

9.5 : 1 mixture of the *syn*–*anti* isomer (^{1}H NMR) in a good yield (Table 1, entry 1). The reaction at rt showed lower selectivity, where the *syn*–*anti* ratio was 3 : 1 (entry 2). But when the reaction temperature was increased to 50 °C, the reaction showed a different diastereoselectivity. The *anti*-**4′** was obtained as the major isomer (1 : 9, entry 3). In the case of the less bulky PMB group, the selectivity was not good (entry 4). The change of the protection group of the primary alcohol did not affect the selectivity (entry 5).

It is interesting that the palladium-catalyzed reaction was so dependent on temperature. The stereochemistry of the major diastereomer **4** was assumed to be *syn* in the light of our previous results[5,8] and was finally confirmed by its conversion into (+)-polyoxamic acid.

Completion of the synthesis of (+)-polyoxamic acid is shown in Scheme 5. The terminal olefin of the *syn,syn* oxazine **4** was converted into the primary alcohol **19** *via* ozonolysis and



Scheme 5

subsequent sodium borohydride reduction in 86% yield. The oxazine ring was cleaved by treatment with Pd/C under a hydrogen atmosphere in the presence of $(Boc)_2O$ and the diol was protected as an acetonide to afford **20**. Regioselective desilylation of the primary alcohol to give alcohol **21** occurred by addition of a HF–pyridine complex to a mixture of pyridine and the acetonide **20**. The hydroxyl group was then oxidized to **22** with ruthenium trichloride–sodium periodate in 91% yield. Finally, the acetonide, TBS and Boc protecting groups were removed by treatment with 6 N HCl in methanol, which was purified by ion-exchange chromatography through a Dowex 50 W X8(H^+) to give the (+)-polyoxamic acid **1** as a white solid. The spectroscopic data for synthetic **1** showed good agreement with those reported. The optical rotation of **1**, $[a]_D^{25}$ +2.3° (*c* 1.0, H_2O), compared to the reported value,[4] $[a]_D^{25}$ +2.1° (*c* 1.0, H_2O), confirms the identity of the absolute configuration.

Conclusions

In summary, we report a new asymmetric synthetic method for (+)-polyoxamic acid utilizing oxazine **4**. The key feature in this strategy is the stereoselective intramolecular oxazine formation by palladium(0).

Experimental

General methods

Optical rotations were measured on a JASCO DIP 1020 digital polarimeter. ^{1}H NMR spectra were recorded at Varian inova FT-NMR 500 MHz in $CDCl_3$. ^{13}C NMR spectra were recorded at 125 MHz in $CDCl_3$. Chemical shifts are reported as δ values in ppm relative to $CHCl_3$ (7.26) in $CDCl_3$. IR spectra were measured on a Bruker FT-IR spectrometer. The high resolution mass spectra (FAB-MS) were taken on a JMS-700 Mstation. Flash chromatography was executed with Merck Kiesegel 60 (230–400 mesh) using mixtures of ethyl acetate and hexane as eluants. Ethyl acetate and hexane were dried and purified by distillation prior to use. Tetrahydrofuran (THF) and diethylether (Et_2O) were distilled over sodium and benzophenone (indicator). Methylene chloride (CH_2Cl_2) was shaken with concentrated sulfuric acid, dried over potassium carbonate, and distilled. Commercially available compounds were used without further purification.

(4*R*,5*S*,6*S*)-5-(*tert*-Butyldimethylsilyloxy)-4-((*tert*-butyldimethylsilyloxy)-methyl)-2-phenyl-6-vinyl-5,6-dihydro-4*H*-1,3-oxazine (4). NaH (60% in mineral oil, 64 mg, 1.61 mmol) and *n*-Bu_4NI (263 mg, 0.80 mmol) were added to a stirred solution of allyl chloride **5** (400 mg, 0.80 mmol) in dry THF (30 mL) at 0 °C. After being stirred for 5 min, $Pd(PPh_3)_4$ (186 mg, 0.16 mmol) was added to the mixture and stirring was allowed to continue for 12 h at the same temperature. The reaction mixture was filtered through a pad of silica and then evaporated under reduced pressure to give the crude product. Purification of this material by silica gel chromatography (ethyl acetate–hexane = 1 : 30) gave **4** (320 mg, 84%) as a colorless oil; $[a]_D^{25}$ +14.0 (*c* 1.0, $CHCl_3$); IR (neat) 2954, 2929, 2885, 2857, 1660, 1472, 1282, 1255, 1115, 836, 776, 696 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.07–0.14 (m, 12H), 0.83–0.97 (m, 18H), 3.59 (m, 1H), 3.71–3.75 (t, J = 10 Hz, 1H), 3.87–3.90 (dd, J = 10, 5 Hz, 1H), 4.20 (dd, J = 2, 1.5 Hz, 1H), 4.71 (dd, J = 6, 1.5 Hz, 1H), 5.35 (d, J = 10 Hz, 1H), 5.48–5.52 (d, J = 18 Hz, 1H), 6.00–6.07 (ddd, J = 18, 10, 6 Hz, 1H), 7.28–7.42 (m, 3H), 7.93–7.95 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.90, −4.88, −4.01, −3.57, 18.28, 18.44, 18.52, 18.56, 25.95, 26.16, 26.26, 26.27, 60.22, 63.47, 64.84, 79.93, 118.05, 127.46, 128.17, 130.41, 133.90, 135.53, 155.56; HRMS(M^+) *m*/*z* calcd for $C_{25}H_{43}NO_3Si_2$ 461.2781 found 461.2779.

((4*R*,5*S*,6*R*)-5-(*tert*-Butyldimethylsilyloxy)-4-((*tert*-butyldimethylsilyloxy)-methyl)-2-phenyl-5,6-dihydro-4*H*-1,3-oxazin-6-yl)-methanol (19). A solution of the oxazine **4** (520 mg, 1.13 mmol) in methanol (40 mL) was cooled to −78 °C. Ozone was passed through the solution until the starting material had been consumed (TLC analysis). The resulting blue solution was purged with oxygen for 10 min, and sodium borohydride (51 mg, 1.35 mmol) was then added. After the mixture had been stirred at rt for 30 min, saturated aqueous NH_4Cl was added. The reaction mixture was extracted with EtOAc, and washed with brine, dried over anhydrous $MgSO_4$, and then concentrated under reduced pressure, followed by purification by silica gel chromatography affording alcohol **19** (451 mg, 86%) as a white solid; M.p. 157 °C; $[a]_D^{25}$ +3.57 (*c* 1.0, $CHCl_3$); IR (neat) ν_{max}: 2939, 2858, 1651, 1464, 1155, 839 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.10–0.18 (m, 12H), 0.84 (s, 9H), 0.96 (s, 9H), 3.52–3.55 (m, 1H), 3.70–3.74 (t, J = 10.0 Hz, 1H), 3.79–3.82 (br, 1H), 3.87–3.91 (dd, J = 10.0, 5.0 Hz, 1H), 3.95–3.99 (dd, J = 11.0, 7.5 Hz, 1H), 4.29 (dd, J = 2.0, 1.0 Hz, 1H), 4.31–4.33 (ddd, J = 7.0, 6.0, 1.0 Hz, 1H), 7.35–7.43 (m, 3H), 7.88–7.90 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.88, −4.28, −4.02, 18.53, 18.57, 25.97, 26.05, 26.21, 26.23, 26.26, 26.27, 60.11, 61.87, 63.09, 63.16, 79.69, 127.44, 128.21, 130.53, 133.84, 155.46; HRMS (FAB$^+$) (M^+ + H) *m*/*z* calcd for $C_{24}H_{44}NO_4Si_2$ 466.2809 found 466.2805.

***tert*-Butyl (5*S*,6*R*)-5-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2,3,3,9,9,10,10-octamethyl-4,8-dioxa-3,9-disilaundecan-6-ylcarbamate (20).** A solution of compound **19** (300 mg, 0.64 mmol) in a 3 : 2 mixture of hexane and methanol (10 mL) was stirred at room temperature for 12 h under an atmosphere of hydrogen in the presence of a catalytic quantity of 20% palladium hydroxide on charcoal (60 mg) and Boc_2O (562 mg, 2.58 mmol). The catalyst was then removed by filtration through Celite, and the solvents were evaporated under reduced pressure. The resulting residue was purified by silica gel chromatography (ethyl acetate–hexane = 1 : 8) to afford a diol (235 mg, 77%) as a white solid.

2,2-Dimethoxypropane (0.48 mL, 3.91 mmol) and pyridinium *p*-toluenesulfonate (12 mg, 0.049 mmol) were added to a stirred solution of the diol (235 mg, 0.49 mmol) in dry acetone (5 mL) at rt. After being stirred for 1 h, the reaction mixture was evaporated *in vacuo*, diluted with H_2O (10 ml), extracted with ethyl acetate, dried with $MgSO_4$, and evaporated *in vacuo.* Purification of this material by silica gel chromatography (ethyl acetate–hexane = 1 : 15) gave acetonide **20** (218 mg, 86%) as a colorless oil; $[a]_D^{25}$ +1.55 (*c* 1.0, $CHCl_3$); IR (neat) ν_{max}: 3452, 2930, 2858, 1719, 1493, 1254, 836 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.06 (s, 3H), 0.07 (s, 3H), 0.11 (s, 3H), 0.15 (s, 3H), 0.88–0.92 (m, 18H), 1.35 (s, 3H), 1.40 (s, 3H), 1.45 (s, 9H), 3.42–3.48 (m, 2H), 3.51–3.55 (m, 2H), 3.94–3.96 (m, 1H), 4.04–4.08 (m, 2H), 4.78 (d, J = 8.5 Hz, 1H-NH); ^{13}C NMR (125 MHz, $CDCl_3$) δ −5.16, −5.09, −4.85, −3.71, 18.26, 18.68, 25.88, 26.01, 26.34, 26.76, 28.59, 53.42, 61.64, 66.59, 72.27,

78.21, 79.61, 109.37, 155.64; HRMS (FAB$^+$) (M$^+$ + H) m/z calcd for $C_{25}H_{54}NO_6Si_2$ 520.3490 found 520.3491.

***tert*-Butyl (1*S*,2*R*)-1-(*tert*-butyldimethylsilyloxy)-1-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-hydroxypropan-2-ylcarbamate (21).** To a solution of compound **20** (218 mg, 0.42 mmol) in THF (5 mL) held at 0 °C under argon was added pyridine (0.31 mL) and HF–pyridine complex (0.31 mL). After 30 min of stirring at 0 °C, the reaction mixture was gradually allowed to come to room temperature over 3 h. It was then diluted with ethyl acetate (10 mL) and washed with water (10 mL × 2). The organic phase was dried over $MgSO_4$ and evaporated to dryness. The resulting oily residue was purified by flash chromatography on silica gel (ethyl acetate–hexane = 8 : 1) to afford alcohol **21** (159 mg, 94%) as an oil. $[\alpha]_D^{25}$ +6.5 (*c* 1.0, $CHCl_3$); IR (neat) 3447, 2981, 2954, 2931, 2887, 2858, 1716, 1697, 1497, 1368, 1253, 1170, 1059, 835, 778 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.17 (s, 6H), 0.95 (s, 9H), 1.40 (s, 3H), 1.46 (s, 3H), 1.49 (s, 9H), 3.53 (dd, J = 11.0, 6.0 Hz, 1H), 3.65 (m, 1H), 3.79 (t, J = 7.8 Hz, 1H), 3.95–3.85 (m, 2H), 4.08 (t, J = 7.0 Hz, 1H), 4.21 (dd, J = 11.0, 7.0 Hz, 1H), 5.22 (d, J = 8.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.36, −4.19, 18.44, 26.03, 26.07, 26.15, 26.49, 28.62, 53.84, 60.76, 66.45, 71.21, 75.72, 79.91, 109.94, 156.06; HRMS (M$^+$ + H) m/z calcd for $C_{19}H_{40}NO_6Si$ 406.2625 found 406.2624.

(2*S*,3*S*)-2-(*tert*-Butoxycarbonylamino)-3-(*tert*-butyldimethylsilyloxy)-3-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)propanoic acid (22). To a solution of alcohol **21** (879 mg, 2.17 mmol) in carbon tetrachloride (15 mL), acetonitrile (15 mL) and water (23 mL) was added sodium periodate (2.78 mg, 13 mmol) and the mixture was stirred. After 5 min, $RuCl_3$ (67 mg, 0.32 mmol) was added and the stirring was continued at room temperature for 6 h. The mixture was filtered and the residue was washed with ethyl acetate (50 mL), washed with brine, dried and evaporated. The resulting residue was purified by flash chromatography on silica gel (ethyl acetate–hexane = 1 : 1) to afford the pure acid **22** (823 mg, 91%); $[\alpha]_D^{25}$ +8.6 (*c* 1.0, $CHCl_3$); IR (neat) 3450, 2931, 2857, 1718, 1503, 1369, 1254, 1161, 1115, 1069, 834 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.15–0.21 (m, 6H), 0.93 (s, 9H), 1.39 (s, 3H), 1.47 (s, 3H), 1.51 (s, 9H), 3.75 (m, 1H), 4.18–4.07 (m, 2H), 4.28 (m, 2H), 5.30 (d, J = 8.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −5.03, −3.96, 18.42, 25.69, 26.04, 26.71, 28.52, 31.21, 55.94, 66.18, 74.71, 80.76, 109.93, 156.04, 175.41; HRMS(FAB) (M$^+$ + H) m/z calcd for $C_{19}H_{38}NO_7Si$ 420.2418 found 420.2417.

(2*S*,3*S*,4*S*)-2-Amino-3,4,5-trihydroxypentanoic acid ((+)-polyoxamic acid, 1). To the acid **22** (134 mg, 0.32 mmol) in MeOH (3 mL) was added 6 N HCl and the mixture was kept at room temperature for 5 h. After concentration under reduced pressure, the residue was dissolved in aqueous ammonium hydroxide (0.6 M; 2 mL) and chromatographed through a column of Dowex 50 W X8 (H$^+$) to give polyoxamic acid **1** (49 mg, 92%): $[\alpha]_D^{25}$ +2.3° (*c* 1.0, H_2O), mp 161–165 °C (dec); (lit.[4] $[\alpha]_D^{25}$ +2.1° (*c* 1.0, H_2O), mp 162–168 °C (dec); ^{1}H NMR (300 MHz, D_2O) δ 3.76–3.72 (m, 2H), 3.98–3.95 (m, 2H), 4.29 (m, 1H); ^{13}C NMR (125 MHz, D_2O) δ 58.09, 62.52, 68.21, 73.25, 172.97; MS m/z calcd for $C_5H_{12}NO_5$ (M$^+$ + H) 165.07 found 165.1.

Acknowledgements

This work was financially supported by Yonsung Fine Chemicals Co., Ltd., and Seoul R & BD Program (10541).

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8 Compound **4** has almost similar TLC and ^{1}H NMR patterns to a previously reported benzyl oxazine compound. Protons of the terminal olefin and H^5 have peaks at 6.0 and 4.2 ppm. In addition, the coupling constant of the newly generated chiral center (H^5–H^6) of compound **4** has the same value, 1.5 Hz, as all *syn*-oxazine compounds previously reported.