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Enantiospecific Total Synthesis of (−)-Polyoxamic Acid Using 2,3-Aziridino-γ-lactone Methodology

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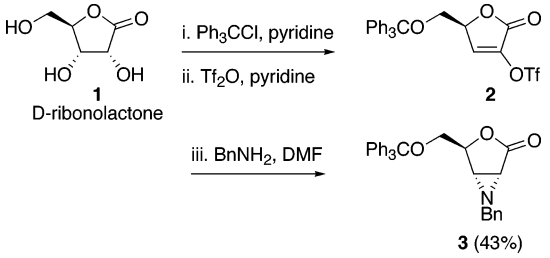
Abstract: The non-natural enantiomer of polyoxamic acid was synthesized in six steps from 2,3-aziridino-γ-lactone **7** with an overall yield of 10%. The key step of the strategy is a deprotection-protection sequence on the nitrogen atom of the aziridine ring required for aziridine activation toward nucleophilic ring opening.

Aziridines are highly useful intermediates for the preparation of nitrogen-containing compounds. Their value is reflected by the numerous studies that have been and are still conducted to optimize their preparation and behavior and to enhance the scope of their applications in the total synthesis of natural and/or biologically active products.[1−3] Among the large variety of substituted aziridines described, aziridine 2-carboxylates hold a prominent place as precursors of α- and β-amino acids.[4] Good regiocontrol of nucleophilic ring opening of these species can generally be achieved allowing isolation of the desired substituted amino acid.[1b,5]

By analogy with aziridine 2-carboxylates, 2,3-aziridino-γ-lactones have been shown by us to be versatile precursors for the preparation of optically pure polysubstituted amino acids.[5,6] A first application of our methodology was the total synthesis of 3,4-disubstituted glutamic acids in connection with the search for new ligands of the excitatory amino acid receptors of the central nervous system.[6f−h] However, the preparation of these bicyclic aziridines starting from pentoses required 13 steps. Such a strategy was not compatible with structure−activity studies or its application to the total synthesis of natural products. We therefore recently devised a much shorter synthesis of 2,3-aziridino-γ-lactones, thereby circumventing this problem.[7] In three steps starting from D-ribonolactone **1**, the key intermediate **3** could be obtained stereoselectively via 1,4-addition of benzylamine to triflate **2** with an overall yield of 43% (Scheme 1).

SCHEME 1



With this methodology in hand, its initial application to the total synthesis of polyoxamic acid **4** was envisaged. The latter is a structural constituent of polyoxins, a class of peptidyl-nucleoside antifungal antibiotics.[8] Numerous studies have been dedicated to the synthesis of polyoxamic acid, most of them based on use of the chiral pool.[9] The non-natural enantiomer of **4** has also been prepared in the same enantiospecific manner.[10] According to our strategy, synthesis of natural (+)-polyoxamic acid required use of L-sugars and notably L-ribonolactone for construction of the stereochemically appropriate 2,3-

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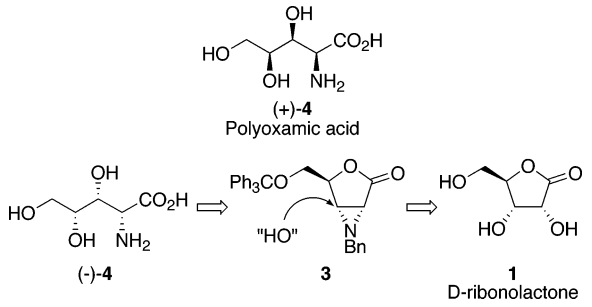
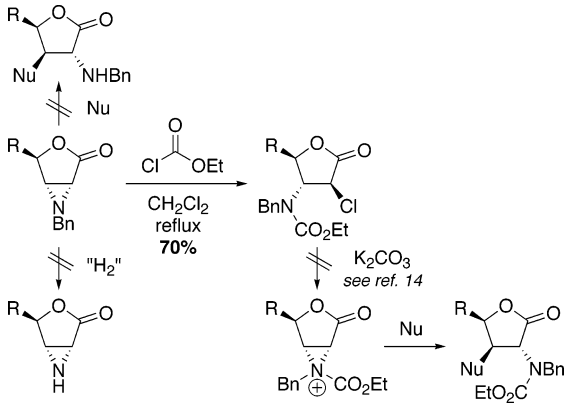


FIGURE 1. Retrosynthetic analysis of (−)-polyoxamic acid.

SCHEME 2



aziridino-γ-lactone. Thus, given the poor availability of such derivatives, we turned our attention for reasons of convenience to (−)-polyoxamic acid, whose retrosynthetic analysis is described in Figure 1.

Before attempting this synthesis, selection of the appropriate protecting groups ensuring efficient ring opening of the 2,3-aziridino-γ-lactone moiety was required. The 5-*O*-trityl group of compound **3** was presumed not to be stable enough to survive the acidic and thermal conditions generally necessary for aziridine ring opening by an alcohol. We therefore chose to protect the 5-O position with a bulky *tert*-butyldiphenylsilyl group, which like the trityl group can be selectively introduced at the primary alcohol position. Initial experiments also revealed that the *N*-benzyl protecting group of **3** was not suitable for clean nucleophilic aziridine ring opening (Scheme 2). Several conditions have been described for the opening of *N*-alkyl aziridines,[11] but all failed when applied to *N*-benzyl-2,3-aziridino-γ-lactones. This lack of reactivity was attributed to the poor electron-withdrawing character of the benzyl group and the competitive reactivity of the lactone function. N-Deprotection thus became necessary in order to install a more activating function but all attempts to do so (reductive debenzylation with hydrogen, ammonium formate, or sodium naphthalenide) were unsuccessful. Similarly, application of a chloroformate-mediated dealkylation reaction of the tertiary amine[12] unfortunately led to aziridine ring opening by chloride ion,[13] which could not be further exploited.[14]

In view of these results, other primary amines were considered for the preparation of suitably N-protected 2,3-aziridino-γ-lactones. We thus turned our attention to methoxy-substituted benzylamines. Such electron-rich nitrogen sources should display a higher reactivity in the tandem Michael-type addition/cyclization leading to the aziridine. Moreover, we presumed that their cleavage under oxidative conditions by use of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) or ceric ammonium nitrate (CAN) would be compatible with the aziridine ring.

Preliminary experiments with *p*-methoxybenzylamine confirmed our assumptions to some extent, though more satisfactory results were obtained by use of the more reactive 3,4-dimethoxybenzyl (DMB) moiety. Thus, regioselective silylation of compound **1** followed by treatment of the resulting diol **5** with triflic anhydride under basic conditions led to the moderately stable monotriflate **6** (Scheme 3). The latter reacted with 3,4-dimethoxybenzylamine to afford compound **7** as a white solid in 35% overall yield from **1**. As previously observed and indicated by ^{1}H and ^{13}C NMR spectra,[7] the formation of aziridine **7** is diastereoselective as a result of a Michael-type addition of 3,4-dimethoxybenzylamine to the face opposite to that of the bulky silyl group at C-5. Careful control of the reaction conditions, i.e., dropwise addition of the amine followed by 30 min of stirring at −60 °C in DMF, appeared crucial to prevent concomitant lactone ring opening. Subsequent removal of the DMB moiety was then efficiently carried out with DDQ in a 10:1 mixture of dichloromethane and water. The resulting N-deprotected aziridine was not isolated but was immediately reacted with benzyl chloroformate to afford the *N*-Cbz derivative **8** in an overall yield of 78%.[15]

We have previously demonstrated that, in the presence of boron trifluoride etherate, ring opening of 2,3-aziridino-γ-lactones by alcohols occurs regioselectively at C-3.[5] In the context of the present synthesis, we first attempted to open the aziridine ring of **8** with benzyl alcohol. Unexpectedly, however, no reaction was observed.[16] In contrast, use of allyl alcohol resulted in formation of allyl ether **9** in an acceptable yield of 53%. Subsequent removal of the allyl group then proved troublesome. After several experiments, it was found that use of selenium dioxide in the presence of acetic acid in dioxane[17] cleanly afforded the hydroxy derivative **10** in 60% yield. Finally, sequential removal of the silyl and the Cbz groups provided, after purification on a basic anion exchange column (AG1-X4), (−)-polyoxamic acid **4**. The optical

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(15) The Cbz group was chosen for its ease of deprotection. The *N*-(acetyl), *N*-(*tert*-butyloxycarbonyl) and *N*-(tosyl) analogues of compound **8** could also be obtained under the same conditions with a yield of 80%, 85%, and 83%, respectively.

(16) In the case of compound **8**, the steric bulk of the silyl group could explain the lack of reactivity of the aziridine towards benzyl alcohol.

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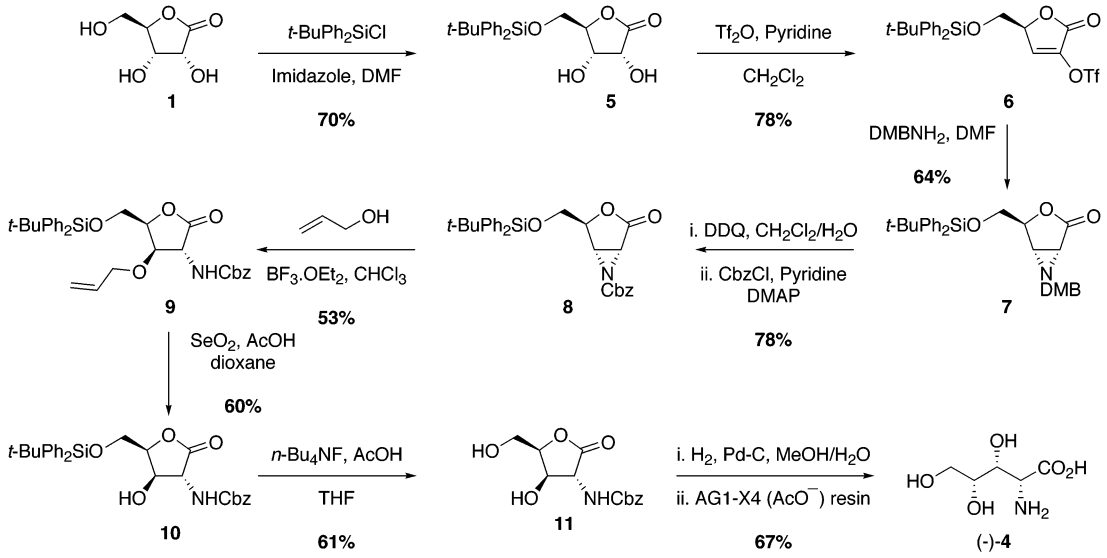
SCHEME 3. Synthesis of (−)-Polyoxamic Acid 4



rotation of the latter, i.e. $[\alpha]^{21}_D$ −2.4 (*c* 0.52, H_2O), showed good agreement with those reported in the literature for (−)-**4** ($[\alpha]^{24}_D$ −2.5 (*c* 1.0, H_2O))[10b] and (+)-**4** ($[\alpha]^{23}_D$ +2.8 (*c* 1.0, H_2O)).[8]

In conclusion, an enantiospecific synthesis of (−)-polyoxamic acid was accomplished from 2,3-aziridino-γ-lactone **7** in six steps with an overall yield of 10%. A notable feature of the strategy is a sequence of deprotection-protection reactions applied to compound **7** that occurred in 78% yield without aziridine ring opening. It allowed the replacement of an *N*-dimethoxybenzyl group by a more activating electron-withdrawing moiety, in this case a carbobenzyloxy group. This methodology is now being applied to the preparation of unusual natural amino acids and particularly of α-substituted β-amino acids accessible from 2,3-aziridino-γ-lactones by reaction with soft nucleophiles.[5]

Experimental Section

5-*O*-(*tert*-Butyldiphenylsilyl)-D-ribono-γ-lactone, 5. To a solution of D-ribonolactone **1** (4 g, 0.027 mol) in DMF (27 mL) held at 0 °C under argon, were successively added imidazole (4.04 g, 2.2 equiv) and *tert*-butyldiphenylsilyl chloride (7.6 mL, 1.1 equiv). After 30 min of stirring at 0 °C, the mixture was warmed to room temperature and stirred for an additional 30 min. The reaction solution was diluted with ethyl acetate (35 mL) and water (35 mL). The layers were separated, and the aqueous phase was extracted with ethyl acetate (2 × 30 mL). The organic extracts were combined, washed with water (2 × 30 mL), dried over magnesium sulfate, and evaporated to dryness. The resulting residue was purified by flash chromatography on silica gel (heptane/ethyl acetate 2:1) to afford compound **5** (7.3 g, 0.0189 mol, 70%) as a white solid. Selected data: mp 69.5−71 °C (lit.[18] 65−70 °C); $[\alpha]^{21}_D$ +43 (*c* 1.35, $CHCl_3$) (lit.[18] $[\alpha]^{21}_D$ +46.3 (*c* 0.84, $CHCl_3$));^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.99 (s, 9H), 3.81 (m, 2H), 4.05 (broad s, 1H), 4.52 (m, 2H), 4.88 (broad d, 1H), 7.2−7.6 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.2, 26.5, 63.4, 69.4, 70.3, 85.6, 128.1, 130.2, 131.8, 132.2, 135.5, 135.6, 176.8; IR (film) ν 3362, 1782, 1427, 1178, 1113, 701 cm^{-1}.

(5*R*)-[5-(*tert*-Butyldiphenylsilyloxymethyl)-2-(5*H*)-furanon-3-yl]trifluoromethanesulfonate, 6. To a solution of compound **5** (3.5 g, 9.1 mmol) in dichloromethane (85 mL) held at −78 °C under argon were successively added pyridine (3.5 mL, 5.0 equiv) and a solution of trifluoromethanesulfonic anhydride (4.2 mL, 2.7 equiv) in dichloromethane (30 mL). After 15 min of stirring at −78 °C, the reaction mixture was slowly warmed to −25 °C over a period of 3 h. The reaction solution was then poured into cold diethyl ether (110 mL). The precipitate was filtered, and the filtrate was evaporated under reduced pressure at 0 °C. The resulting residue was purified by flash chromatography on silica gel (heptane/ethyl acetate 2:1) to afford compound **6** (3.55 g, 7.1 mmol, 78%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.98 (s, 9H), 3.84 (ddd, 2H, *J* = 11.5, 4.5, 3.8 Hz), 4.98 (td, 1H, *J* = 4.1, 1.8 Hz), 7.03 (d, 1H, *J* = 1.9 Hz), 7.2−7.6 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 22.7, 26.6, 62.7, 88.1, 121.0, 128.0, 128.3, 130.2, 132.0, 132.2, 135.5, 135.7, 138.0, 163.6; IR (film) ν 3073, 2934, 2861, 1792, 1656, 1433, 1221, 1137, 1104, 703 cm^{-1}; ESMS *m*/*z* 539 [M + K^+], 523 [M + Na^+], 501 [M + H^+]. HRESMS *m*/*z* calcd for $C_{22}H_{23}F_3O_6SSi$ 523.0834 [M + Na^+], found 523.0823.

(1*R*,4*S*,5*S*)-4-(*tert*-Butyldiphenylsilyloxymethyl)-*N*-(3′,4′-dimethoxybenzyl)-3-oxa-6-azabicyclo[3.1.0]hexan-2-one, 7. To a solution of compound **6** (3.55 g, 7.1 mmol) in DMF (35 mL) held at −60 °C under argon was added dropwise 3,4-dimethoxybenzylamine (1.6 mL, 1.5 equiv). The reaction mixture was stirred for 30 min at −60 °C before being diluted with ethyl acetate (40 mL) and water (40 mL). The layers were separated, and the aqueous phase was extracted with ethyl acetate (2 × 30 mL). The combined organic extracts were dried over magnesium sulfate and evaporated to dryness. The resulting oily residue was purified by flash chromatography on silica gel (heptane/ethyl acetate 2:1). The aziridine-γ-lactone **7** (2.35 g, 4.5 mmol, 64%) was isolated as a viscous oil that crystallized on standing. Mp 46−47 °C; $[\alpha]^{21}_D$ +15 (*c* 1.075, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.97 (s, 9H), 2.71 (AB syst, 2H, *J* = 4.3 Hz), 3.43 (AB syst, 2H, *J* = 13.4 Hz), 3.78 (dd, 2H, *J* = 11.4, 2.9 Hz), 3.93 (s, 6H), 3.93 (dd, 1H, *J* = 11.4, 3.9 Hz), 4.37 (m, 1H), 6.76−7.64 (m, 13H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.1, 26.7, 39.9, 44.2, 55.9, 60.9, 63.5, 80.2, 111.1, 120.1, 127.9, 129.7, 130.8, 132.8, 135.5, 149.1, 172.0; IR (film) ν 3071, 2933, 1781, 1516, 1113, 704 cm^{-1}; EIMS *m*/*z* 517 [M + H − TBDPS$^+$]. Anal. Calcd for $C_{30}H_{35}NO_5Si$: C, 69.60; H, 6.81; N, 2.71. Found: C, 69.12; H, 6.87; N, 2.51.

(1*R*,4*S*,5*S*)-*N*-(Benzyloxycarbonyl)-4-(*tert*-butyldiphenylsilyloxymethyl)-3-oxa-6-azabicyclo[3.1.0]hexan-2-one, 8. A solution of compound **7** (1.7 g, 3.3 mmol) and DDQ (0.75 g, 1.0 equiv) in a 10:1 mixture of dichloromethane and water (36.3 mL) was stirred for 24 h at room temperature. Pyridine (4 mL, 15 equiv), benzyl chloroformate (0.95 mL, 2.0 equiv), and DMAP (81 mg, 0.1 equiv) were then successively added, and the mixture was stirred for 2 h at room temperature. At the end of the

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reaction period, dichloromethane (10 mL) was added followed by 10% aqueous HCl (20 mL). The aqueous layer was separated, and the organic phase was successively washed with 10% aqueous HCl (30 mL), saturated aqueous $NaHCO_3$ solution (30 mL), and water (30 mL) before being dried over magnesium sulfate and evaporated to dryness. The resulting residue was purified by flash chromatography on silica gel (heptane/ethyl acetate 4:1) to give aziridine-γ-lactone **8** (1.29 g, 2.57 mmol, 78%) as a colorless oil. $[\alpha]^{21}_D$ −2 (*c* 1.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.97 (s, 9H), 3.45 (AB syst, 2H, J = 3.0 Hz), 3.71 (dd, 1H, J = 11.8, 1.8 Hz), 3.93 (dd, 1H, J = 11.8, 2.7 Hz), 4.62 (m, 1H), 5.10 (AB syst, 2H, J = 11.9 Hz), 7.2−7.7 (m, 15H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.2, 26.7, 37.9, 42.3, 63.5, 69.3, 128.1, 128.5, 128.7, 130.2, 131.9, 132.5, 134.8, 135.5, 135.7, 158.5, 168.9; IR (film) ν 3070, 2930, 1792, 1734, 1112, 701 cm^{-1}; EIMS *m*/*z* 540 [M + K$^+$], 524 [M + Na$^+$], 502 [M + H $^+$]. Anal. Calcd for $C_{29}H_{31}NO_5Si$: C, 69.43; H, 6.23; N, 2.79. Found: C, 69.12; H, 6.14; N, 2.59.

3-*O*-Allyl-2-*N*-(benzyloxycarbonyl)amino-5-*O*-(*tert*-butyldiphenylsilyl)-2-deoxy-D-xylono-1,4-lactone, 9. Boron trifluoride etherate (66 μL, 2.0 equiv) was added to a solution of compound **8** (130 mg, 0.26 mmol) in a mixture of allyl alcohol (0.6 mL) and chloroform (1.5 mL) held at 0 °C under argon. The reaction mixture was stirred for 20 h at 50 °C. At the end of the reaction period, ethyl acetate (10 mL) was added followed by saturated aqueous $NaHCO_3$ solution (10 mL). The aqueous layer was separated and extracted with ethyl acetate (2 × 5 mL). The combined organic extracts were dried over magnesium sulfate and evaporated to dryness. The resulting oily residue was purified by flash chromatography on silica gel (heptane/ethyl acetate 5:1) to give compound **9** (77 mg, 0.14 mmol, 53%) as a colorless oil. $[\alpha]^{21}_D$ +40 (*c* 1.03, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.99 (s, 9H), 3.88 (AB syst, 2H, J = 11.5 Hz), 4.12 (m, 1H), 4.59 (m, 1H), 4.75 (m, 1H), 5.06 (s, 2H), 5.02−5.20 (m, 3H), 5.86 (m, 1H), 7.28−7.75 (m, 15H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.4, 26.8, 57.1, 61.7, 67.8, 71.9, 72.5, 78.7, 118.4, 128.1, 128.5, 128.6, 128.9, 129.0, 130.3, 134.2, 136.1, 136.3, 156.7, 172.6; IR (film) ν 3339, 2929, 1791, 1724, 1527, 1427, 1111, 702 cm^{-1}; EIMS *m*/*z* 598 [M + K$^+$], 582 [M + Na$^+$]. Anal. Calcd for $C_{32}H_{37}NO_6Si$: C, 68.67; H, 6.66; N, 2.50. Found: C, 68.35; H, 6.79; N, 1.91.

2-*N*-(Benzyloxycarbonyl)amino-5-*O*-(*tert*-butyldiphenylsilyl)-2-deoxy-D-xylono-1,4-lactone, 10. To a solution of allyl ether **9** (630 mg, 1.13 mmol) in 1,4-dioxane (8 mL) were added selenium dioxide (138 mg, 1.1 equiv) and acetic acid (97 μL, 1.5 equiv). The reaction mixture was heated under reflux for 3 h. At the end of the reaction period, the residual salts were filtered off and washed with ethyl acetate. The filtrate and washings were evaporated to dryness, and the resulting oily residue was purified by flash chromatography on silica gel (heptane/ethyl acetate 4:1) to give compound **10** (350 mg, 0.67 mmol, 60%) as a slightly colored solid. Mp 47−49 °C; $[\alpha]^{21}_D$ +36 (*c* 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.95 (s, 9H), 3.82 (dd, 1H, J = 11.7, 2.4 Hz), 4.03 (d, 1H, J = 11.7 Hz), 4.58 (m, 1H), 4.71 (dd, 1H, J = 8.2, 2.5 Hz), 5.10 (s, 2H), 5.54 (s, 1H), 7.32−7.85 (m, 15H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.0, 26.8, 58.0, 60.9, 67.8, 74.9, 79.6, 127.9, 128.2, 128.5, 128.7, 129.9, 135.6, 157.8, 172.3; IR (film) ν 3409, 3342, 2929, 2857, 1778, 1705, 1525, 1428, 1112, 1045, 702 cm^{-1}; EIMS *m*/*z* 558 [M + K$^+$], 542 [M + Na$^+$]. HRESMS *m*/*z* calcd for $C_{29}H_{33}NO_6Si$ 542.1975 [M + Na$^+$], found 542.1978.

2-*N*-(Benzyloxycarbonyl)amino-2-deoxy-D-xylono-1,4-lactone, 11. To a solution of compound **10** (289 mg, 0.56 mmol) and acetic acid (32 μL, 1.0 equiv) in THF (1.6 mL) held at −60 °C under argon was added a 1 M solution of tetrabutylammonium fluoride in THF (0.56 mL, 1.0 equiv). After 30 min of stirring at −60 °C, the reaction mixture was gradually allowed to come to room temperature over 2 h. It was then diluted with ethyl acetate (10 mL) and washed with water (2 × 10 mL). The organic phase was dried over magnesium sulfate and evaporated to dryness. The resulting oily residue was purified by flash chromatography on silica gel (heptane/ethyl acetate 1:2 then 1:4) to afford compound **11** (96 mg, 0.34 mmol, 61%) as a white solid. Mp 101−103 °C; $[\alpha]^{21}_D$ +73 (*c* 1.00, EtOH); ^{1}H NMR (MeOD, 300 MHz) δ 3.89 (ABX syst, 2H, J = 12.6, 2.5, 2.3 Hz), 4.44 (d, 1H, J = 8.9 Hz), 4.52 (dd, 1H, J = 7.8, 2.1 Hz), 4.66 (t, 1H, J = 8.3 Hz), 5.10 (d, 2H), 7.26−7.48 (m, 5H); ^{13}C NMR (MeOD, 75 MHz) δ 58.7, 60.6, 67.8, 72.6, 81.5, 128.9, 129.1, 129.5, 138.0, 158.1, 175.4; IR (film) ν 3500−3300, 2953, 1779, 1700, 1532, 1428, 1278, 1034 cm^{-1}; EIMS *m*/*z* 320 [M + K$^+$], 304 [M + Na$^+$]. Anal. Calcd for $C_{13}H_{15}NO_6$: C, 55.51; H, 5.38; N, 4.98; O, 34.13. Found: C, 55.81; H, 5.46; N, 4.86; O, 33.91.

(−)-Polyoxamic Acid, (−)-4. A solution of compound **11** (66 mg, 0.24 mmol) in a 5:1 mixture of methanol and water (2.6 mL) was stirred at room temperature for 1 h under an atmosphere of hydrogen in the presence of a catalytic quantity of 10% palladium on charcoal (28 mg). The catalyst was then removed by filtration through Celite, and the solvents were evaporated under reduced pressure. The residue was purified by ion-exchange chromatography as follows: AG1-X4 resin (700 mg, OH^- form) was placed in a cotton-plugged pasteur pipet and washed successively with a 1 N solution of acetic acid (10 mL) and water until neutral pH (∼20 mL). A solution of the crude reaction mixture in water (10 mL) was brought to pH 9 by addition of 1 M NaOH and then applied to the resin. The column was first eluted with water until neutrality and then successively with 0.2 M (10 mL), 0.3 M (10 mL), 0.4 M (10 mL), and 0.5 M (10 mL) aqueous acetic acid. The combined ninhydrin-positive fractions were evaporated under reduced pressure, and the colorless solid residue was lyophilized for 24 h, affording compound (−)-**4** (26 mg, 0.26 mmol, 67%) as a white solid. Mp 151−153 °C (lit.[10a] 165−172 °C); $[\alpha]^{21}_D$ −2.4 (*c* 0.52, H_2O) (lit.[10b] $[\alpha]^{24}_D$ −2.5 (*c* 1.0, H_2O)); ^{13}C NMR (D_2O, 75 MHz) δ 58.3, 62.8, 68.4, 73.5, 173.0 (lit.[9j] ^{13}C NMR (D_2O, 75 MHz) δ 60.3, 64.7, 70.4, 75.4, 175.0); EIMS *m*/*z* 204 [M + K$^+$], 188 [M + Na$^+$], 166 [M + H$^+$].

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Supporting Information Available: General experimental procedures, ^{1}H NMR spectra of compounds **6**−**11**, and ^{13}C NMR spectrum of compound (−)-**4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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