

A Concise Synthesis of (+)-Polyoxamic Acid and (+)-5-*O*-Carbamoyl Polyoxamic Acid

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Abstract: We report the concise synthesis of (+)-polyoxamic acid and (+)-5-*O*-carbamoyl polyoxamic acid from L-xylose in seven or six steps, respectively. The key steps include a diastereoselective amination of *syn*-1,2-polybenzyl ethers using chlorosulfonyl isocyanate (CSI) and the one-pot introduction of carbamates into the allylic benzyl ether and primary hydroxyl moieties.

Key words: polyoxamic acid, polyoxin, chlorosulfonyl isocyanate, amination, sugar

α -Amino acids comprise a number of important building blocks of living systems, and are the principal components of naturally occurring biologically active compounds. These compounds and their derivatives have attracted considerable attention as potential medical agents on account of their interesting physiological and pharmacological activities.¹ As a consequence the development of methods for synthesizing α -amino acids has been an area of intense research over the last decade. Moreover, the increasing demand for these compounds has prompted the development of new synthetic methodologies.²

(+)-Polyoxamic acid (**1**; Figure 1) is an acyclic trihydroxylated α -amino acid that is used as an important synthetic building block for the formation of peptidyl nucleoside antifungal polyoxin J (**3**; Figure 1), which consists of thymine polyoxin C and 5-*O*-carbamoyl polyoxamic acid (**2**; Figure 1). In particular, polyoxin J, isolated from *Streptomyces cacaoi* var. *asoensis*,³ exhibits potent inhib-

itory activity against chitin synthase, which is an important component of the fungal cell wall structure. In addition, it has powerful therapeutic activity against the human pathogen, *Candida albicans*.⁴

Due to the potent biological activity and structural relationship with polyoxins, several synthetic approaches to produce polyoxamic acid (**1**) and its *O*-carbamoyl derivative **2** have been reported.⁵ However, these synthetic approaches involve a large number of steps. Therefore, the development of efficient and concise synthetic strategies for compounds **1** and **2** is still an active field.

As part of an ongoing research program directed towards the stereoselective amination of various allylic ethers us-

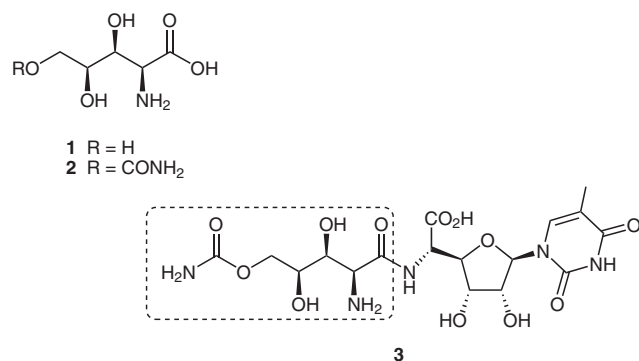


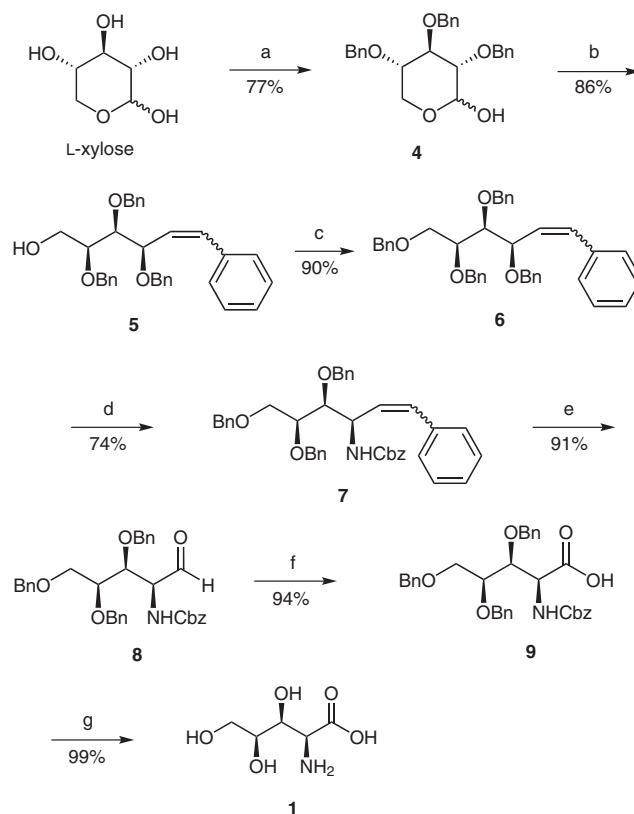
Figure 1 Structures of (+)-polyoxamic acid (**1**), (+)-5-*O*-carbamoyl polyoxamic acid (**2**), and polyoxin J (**3**)

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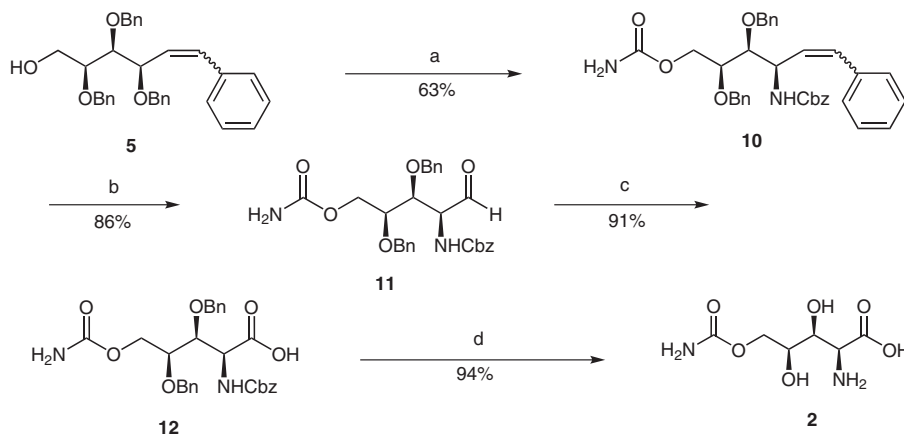
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Scheme 1 Reagents and conditions: (a) (i) MeOH, SOCl₂, reflux, 4 h; (ii) NaH, BnBr, DMF–THF (1:1), r.t., 24 h; (iii) 1 M H₂SO₄, AcOH, 1,4-dioxane, reflux, 12 h; (b) NaH, BnPPH₃Cl, DMSO, THF, 60 °C, 2 h; (c) NaH, BnBr, DMF–THF (1:1), r.t., 8 h; (d) (i) CSI, Na₂CO₃, toluene–hexane (10:1), –20 °C, 36 h; (ii) 25% Na₂SO₃, r.t., 24 h; (e) (i) O₃, CH₂Cl₂, –78 °C, 1 h; (ii) PPh₃, r.t., 1 h; (f) NaClO₂, NaH₂PO₄, 2-methyl-2-butene, *t*-BuOH, H₂O, r.t., 3 h; (g) (i) Pd/C, H₂, 6 N HCl, MeOH, r.t., 12 h; (ii) DOWEX-50Wx8.



Scheme 2 Reagents and conditions: (a) (i) CSI, toluene–hexane (10:1), -20°C , 36 h; (ii) 25% Na_2SO_3 , r.t., 24 h; (iii) 6 N HCl, EtOAc, r.t., 2 h; (b) (i) O_3 , CH_2Cl_2 , -78°C , 1 h; (ii) PPh_3 , r.t., 1 h; (c) NaClO_2 , NaH_2PO_4 , 2-methyl-2-butene, *t*-BuOH, H_2O , r.t., 3 h; (d) (i) Pd/C, H_2 , 6 N HCl, MeOH, r.t., 12 h; (ii) DOWEX-50Wx8.

ing chlorosulfonyl isocyanate (CSI),⁶ and the application of this method to the total synthesis of polyhydroxylated alkaloids,⁷ we became interested in developing an efficient synthetic route to (+)-polyoxamic acid (**1**) and (+)-5-*O*-carbamoyl polyoxamic acid (**2**). This paper reports the concise synthesis of compounds **1** and **2** via the diastereoselective amination of *syn*-1,2-dibenzyl ethers **5** and **6** using CSI and the one-pot introduction of the carbamate moieties into allylic benzyl ether and primary hydroxyl group.

The synthesis of compound **1** began with 2,3,4-tri-*O*-benzyl-L-xylopyranose (**4**), which could be easily prepared from commercially available L-xylose according to the methodology reported in the literature (Scheme 1).^{7g}

A Wittig olefination of compound **4** with DMSO anion in THF at 60°C afforded the olefin **5** as a ca. 2.2:1 mixture of *cis/trans* isomers in 86% yield.⁸ The hydroxyl moiety of compound **5** was then converted into the tetrabenzyl ether **6** in 90% yield.⁹ The regioselective and diastereoselective CSI reaction of compound **6** was carried out in a mixture of toluene and hexane (10:1) at -20°C for 36 hours, followed by desulfonylation with aqueous 25% sodium sulfite solution to give the desired *syn*-1,2-amino alcohol **7** with diastereoselectivity (*syn/anti* = 8.8:1 by NMR analysis) in 74% yield.¹⁰ The diastereoselectivity of compound **7** can be explained by the neighboring group effect, whereby the NHCbz group orientation retains its original configuration through double inversion of the configuration.^{7g} Ozonolysis of compound **7** afforded a separable mixture of desirable aldehyde **8**¹¹ and its diastereomer. Finally, Pinnick oxidation¹² provided the acid **9**,¹³ which was then hydrogenated using Pd/C to afford (+)-polyoxamic acid (**1**)¹⁴ with a specific rotation, $[\alpha]_{\text{D}}^{25} +2.2$ (*c* 1.0, H_2O) {lit.^{5y} $[\alpha]_{\text{D}}^{25} +2.1$ (*c* 1.0, H_2O)}, and identical spectral data (^1H and ^{13}C NMR) to that reported in the literature.^{5a}

For the synthesis of 5-*O*-carbamoyl polyoxamic acid (**2**) as a side chain of polyoxin J, we initially focused on a one-pot preparation of bis-carbamate **10** from compound **5** via

the CSI-mediated stereoselective amination of the cinamyl benzyl ether moiety and the urethane elaboration of the alcohol moiety (Scheme 2). A reaction of compound **5** with CSI in the presence of Na_2CO_3 at -20°C , followed by reduction of the *N*-chlorosulfonyl group, furnished the desired bis-carbamate **10** in low yield (12%). However, in the absence of Na_2CO_3 , treatment of compound **5** with eight equivalents of CSI followed by work-up using 6 N HCl provided the desired compound **10**, in 63% yield, with a diastereoselectivity of 7.2:1.¹⁵ These results suggest that a reaction of CSI with the alcohol moiety under basic conditions might accelerate the polymerization of urethane in the product. Ozonolysis of compound **10** and the subsequent Pinnick oxidation furnished the acid **12** in 78% overall yield. Fortunately, the minor *anti* diastereomer of the desired aldehyde **11** could be removed completely (cat. 11%) by column chromatography.¹⁶ Hydrogenation of compound **12**¹⁷ followed by resin purification gave the (+)-5-*O*-carbamoyl polyoxamic acid (**2**) in 94% yield.¹⁸ The spectral data (^1H NMR and ^{13}C NMR) and specific rotation of compound **2** were in full agreement with the reported literature values.^{5y,z}

In conclusion, we have reported the concise synthesis of (+)-polyoxamic acid and 5-*O*-carbamoyl polyoxamic acid as pivotal components of polyoxin J. The key steps in the route involve the diastereoselective amination of *syn*-1,2-polybenzyl ethers using chlorosulfonyl isocyanate and the one-pot introduction of the carbamate moiety into the allylic benzyl ether and primary hydroxyl group.

Acknowledgment

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- (8) Characterization data for **5**: $[\alpha]_D^{25}$ -25.8 (c 1.0, CHCl₃). IR (CH₂Cl₂): 3450, 3011, 2866, 1513, 1494, 1055 cm⁻¹. *cis*-Isomer: ¹H NMR (500 MHz, CDCl₃): δ = 2.22–2.24 (br, 1 H), 3.45 (dd, J = 12.5, 3.5 Hz, 1 H), 3.68 (dd, J = 11.5, 3.5 Hz, 1 H), 3.78–3.83 (m, 2 H), 4.19 (d, J = 12.0 Hz, 1 H), 4.57–4.82 (m, 6 H), 5.88 (dd, J = 12.0, 10.0 Hz, 1 H), 6.78 (d, J = 12.0 Hz, 1 H), 7.07–7.40 (m, 20 H). ¹³C NMR (125 MHz, CDCl₃): δ = 61.63, 70.40, 73.15, 73.21, 75.38, 80.27, 82.47, 126.85, 127.54, 127.88, 127.98, 128.13, 128.31, 128.55, 128.56, 128.61, 128.77, 129.12, 133.99, 136.66, 137.82, 138.48. *trans*-Isomer: ¹H NMR (500 MHz, CDCl₃): δ = 2.22–2.24 (br, 1 H), 3.61 (dd, J = 11.5, 3.5 Hz, 1 H), 3.72–3.77 (m, 3 H), 4.30 (dd, J = 7.5, 4.0 Hz, 1 H), 4.45 (d, J = 11.5 Hz, 1 H), 4.60–4.82 (m, 5 H), 6.22 (d, J = 16.0, 7.5 Hz, 1 H), 6.59 (d, J = 16.0 Hz, 1 H), 7.07–7.40 (m, 20 H). ¹³C NMR (125 MHz, CDCl₃): δ = 61.78, 71.03, 72.96, 75.15, 79.70, 80.49, 82.22, 126.84, 127.53, 127.87, 127.94, 127.97, 128.04, 128.17, 128.42, 128.56, 128.60, 128.65, 128.77, 128.83, 129.94, 133.82, 133.99, 138.68. HRMS (FAB): m/z [M + H⁺] calcd for C₃₃H₃₅O₄: 495.2535; found: 495.2525.
- (9) Characterization data for **6**: $[\alpha]_D^{25}$ -33.8 (c 0.5, CHCl₃). IR (CH₂Cl₂): 2864, 2360, 1541, 1496, 1454, 1395, 1352, 1027, 1089, 1028, 914, 806, 736 cm⁻¹. *cis*-Isomer: ¹H NMR (500 MHz, CDCl₃): δ = 3.23 (d, J = 9.0 Hz, 1 H), 3.57–3.59 (m, 1 H), 3.92 (br s, 2 H), 4.12 (d, J = 12.0 Hz, 1 H), 4.25 (d, J = 12.0 Hz, 1 H), 4.41–4.88 (m, 7 H), 5.89 (t, J = 10.0 Hz, 1 H), 6.77 (d, J = 10.0 Hz, 1 H), 7.01–7.39 (m, 25 H). ¹³C NMR (125 MHz, CDCl₃): δ = 69.59, 70.16, 73.17, 73.47, 75.74, 78.90, 82.51, 126.85, 127.43, 127.72, 127.75, 127.89, 128.03, 128.31, 128.43, 128.52, 128.59, 128.62, 128.78, 129.22, 130.48, 133.55, 136.78, 138.10, 138.95. *trans*-Isomer: ¹H NMR (500 MHz, CDCl₃): δ = 3.60–3.66 (m, 2 H), 3.64 (dd, J = 10.0, 4.5 Hz, 1 H), 3.76 (dd, J = 6.0, 4.5 Hz, 1 H), 4.29–4.39 (m, 1 H), 4.41–4.88 (m, 8 H), 6.16 (dd, J = 12.5, 7.5 Hz, 1 H), 6.52 (d, J = 12.5 Hz, 1 H), 7.01–7.39 (m, 25 H). ¹³C NMR (125 MHz, CDCl₃): δ = 70.36, 70.95, 73.34, 73.56, 75.43, 80.14, 81.21, 81.97, 116.53, 127.30, 127.56, 127.76, 127.84, 127.99, 128.20, 128.42, 128.50, 128.55, 128.61, 128.72, 128.96, 130.47, 133.71, 136.84, 138.51, 139.12. HRMS (FAB): m/z [M + H⁺] calcd for C₄₀H₄₁O₄: 585.3005; found: 585.3010.
- (10) Characterization data for **7**: $[\alpha]_D^{25}$ +25.8 (c 1.0, CHCl₃). IR (CH₂Cl₂): 3030, 2867, 1719, 1491, 1454, 1214, 1090, 1027, 967, 737, 697 cm⁻¹. *cis*-Isomer: ¹H NMR (500 MHz, CDCl₃): δ = 3.53–3.73 (m, 3 H), 3.85 (dd, J = 7.0, 2.0 Hz, 1 H), 4.35 (d, J = 12.0 Hz, 1 H), 4.48–6.63 (m, 4 H), 4.82 (d, J = 11.0 Hz, 1 H), 5.06 (br m, 3 H), 5.37 (d, J = 8.0 Hz, 1 H), 5.72 (dd, J = 12.0, 9.5 Hz, 1 H), 6.52 (d, J = 12.0 Hz, 1 H), 7.18–7.44 (m, 25 H). ¹³C NMR (125 MHz, CDCl₃): δ = 49.83, 66.97, 69.39, 73.27, 73.59, 75.64, 80.25, 82.21, 127.38, 127.74, 127.83, 128.01, 128.08, 128.29, 128.51, 128.54, 128.59, 128.72, 128.97, 130.85, 131.02, 136.61, 138.48, 138.71, 155.86. *trans*-Isomer: ¹H NMR (500 MHz, CDCl₃): δ = 3.68 (br, 1 H), 3.78 (br m, 2 H), 3.86 (br, 1 H), 4.54–4.66 (m, 5 H), 4.72 (d, J = 12.0 Hz, 1 H), 4.79 (d, J = 12.0 Hz, 1 H), 5.11 (s, 2 H), 5.44 (br, 1 H), 6.15 (dd, J = 16.0, 5.5 Hz, 1 H), 6.50 (d, J = 16.0 Hz, 1 H), 7.25–7.36 (m, 25 H). ¹³C NMR (125 MHz, CDCl₃): δ = 53.79, 67.07, 69.79, 73.40, 73.75, 75.22, 80.24, 81.30, 126.73, 127.78, 127.83, 127.90, 128.00, 128.04, 128.11, 128.36, 128.43, 128.58, 128.61, 128.63, 128.71, 128.75, 131.00, 136.75, 136.95,

- 138.38, 138.75, 156.04. HRMS (FAB): m/z [M + H⁺] calcd for C₄₁H₄₂NO₅: 628.3063; found: 628.3062.
- (11) Characterization data for **8**: [α]_D²⁵ –7.5 (*c* 1.0, CHCl₃). IR (CH₂Cl₂): 3060, 1717, 1541, 1508, 1456, 1091, 697 cm^{–1}. ¹H NMR (300 MHz, CDCl₃): δ = 3.58–3.66 (m, 3 H), 3.72–3.78 (m, 1 H), 4.34 (br, 1 H), 4.44 (d, *J* = 11.7 Hz, 1 H), 4.46 (s, 2 H), 4.59 (d, *J* = 11.7 Hz, 1 H), 4.73 (s, 2 H), 5.12 (d, *J* = 15.6 Hz, 1 H), 5.16 (d, *J* = 15.6 Hz, 1 H), 5.62 (br d, *J* = 5.7 Hz, 1 H), 7.27–7.41 (m, 20 H), 9.73 (s, 1 H). ¹³C NMR (125 MHz, CDCl₃): δ = 60.19, 67.41, 69.67, 73.05, 73.71, 74.23, 76.69, 78.59, 128.01, 128.14, 128.36, 128.52, 128.59, 128.67, 128.72, 128.75, 128.81, 136.29, 137.62, 137.70, 138.10, 156.38, 197.629. HRMS (FAB): m/z [M + H⁺] calcd for C₃₄H₃₆NO₆: 554.2543; found: 554.2543.
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- (13) Characterization data for **9**: [α]_D²⁵ –12.5 (*c* 0.5, CHCl₃). IR (CH₂Cl₂): 3421, 3031, 2870, 2360, 1716, 1507, 1455, 1397, 1214, 1092, 737, 698 cm^{–1}. ¹H NMR (300 MHz, CDCl₃): δ = 3.60–3.86 (m, 4 H), 4.40–4.78 (m, 7 H), 5.14 (s, 2 H), 5.61 (br, 1 H), 7.30–7.36 (m, 20 H). ¹³C NMR (125 MHz, CDCl₃): δ = 54.21, 67.49, 69.18, 73.32, 73.70, 75.13, 76.68, 78.31, 78.69, 127.95, 128.30, 128.43, 128.59, 128.63, 128.70, 128.76, 132.36, 136.29, 137.34, 138.14, 156.65, 174.37. HRMS (FAB): m/z [M + H⁺] calcd for C₃₄H₃₆NO₇: 570.2498; found: 570.2492.
- (14) Characterization data for **1**: [α]_D²⁵ +2.2 (*c* 1.0, H₂O); mp 170–174 °C (dec.). ¹H NMR (300 MHz, D₂O): δ = 4.21 (dd, *J* = 3.3, 2.7 Hz, 1 H), 3.93–3.87 (m, 2 H), 3.72–3.60 (m, 2 H). ¹³C NMR (125 MHz, D₂O): δ = 172.83, 73.33, 68.26, 62.63, 58.16. HRMS (CI): m/z [M + H⁺] calcd for C₅H₁₂NO₅: 166.0715; found: 166.0716.
- (15) Characterization data for **10**: [α]_D²⁵ +35.6 (*c* 0.5, CHCl₃). IR (CH₂Cl₂): 3425, 2939, 2865, 2360, 1716, 1507, 1456, 1339, 1067, 697 cm^{–1}. *cis*-Isomer: ¹H NMR (300 MHz, CDCl₃): δ = 3.64–3.72 (m, 2 H), 4.17 (br s, 2 H), 4.55 (d, *J* = 11.1 Hz, 1 H), 4.61 (d, *J* = 11.1 Hz, 1 H), 4.65 (d, *J* = 11.1 Hz, 1 H), 4.85 (d, *J* = 11.1 Hz, 1 H), 5.10 (s, 2 H), 5.18 (t, *J* = 8.4 Hz, 1 H), 5.47 (d, *J* = 7.2 Hz, 1 H), 5.75 (dd, *J* = 11.4, 9.3 Hz, 1 H), 6.54 (d, *J* = 11.4 Hz, 1 H), 7.23–7.42 (m, 20 H). ¹³C NMR (125 MHz, CDCl₃): δ = 49.43, 62.86, 67.22, 73.43, 75.95, 78.70, 83.19, 126.78, 127.48, 127.91, 128.09, 128.21, 128.36, 128.53, 128.77, 130.84, 131.64, 136.74, 136.86, 138.07, 138.13, 138.25, 156.15, 156.52. *trans*-Isomer: ¹H NMR (300 MHz, CDCl₃): δ = 3.80–3.90 (m, 2 H), 4.32–4.37 (m, 2 H), 4.61–4.85 (m, 5 H), 5.13 (s, 2 H), 5.48–5.50 (m, 1 H), 6.15 (dd, *J* = 15.6, 6.0 Hz, 1 H), 6.58 (d, *J* = 15.6 Hz, 1 H), 7.23–7.42 (m, 20 H). ¹³C NMR (125 MHz, CDCl₃): δ = 53.43, 63.13, 66.84, 73.07, 75.47, 77.71, 78.59, 82.01, 126.08, 126.85, 127.90, 128.03, 128.17, 128.29, 128.30, 128.67, 128.81, 131.24, 136.76, 136.85, 137.61, 138.07, 156.26, 156.68. HRMS (FAB): m/z [M + H⁺] calcd for C₃₅H₃₇N₂O₆: 581.2652; found: 581.2655.
- (16) Characterization data for **11**: [α]_D²⁵ –7.5 (*c* 1.0, CHCl₃). IR (CH₂Cl₂): 3444, 2972, 2360, 1716, 1508, 1456, 1418, 1339, 1067, 739, 698 cm^{–1}. ¹H NMR (300 MHz, CDCl₃): δ = 3.72–3.73 (m 1 H), 4.17–4.74 (m, 9 H), 5.10–5.15 (m, 2 H), 5.64 (d, *J* = 6.5 Hz, 1 H), 7.27–7.42 (m, 15 H), 9.67 (s, 1 H). ¹³C NMR (125 MHz, CDCl₃): δ = 60.03, 62.83, 67.53, 73.10, 74.33, 75.79, 77.91, 128.30, 128.34, 128.47, 128.55, 128.65, 128.69, 128.77, 128.84, 136.24, 137.32, 137.39, 156.39, 156.61, 198.01. HRMS (FAB): m/z [M + H⁺] calcd for C₂₈H₃₁N₂O₇: 507.2131; found: 507.2142.
- (17) Characterization data for **12**: [α]_D²⁵ –10.4 (*c* 1.0, CHCl₃). IR (CH₂Cl₂): 3365, 3032, 2965, 2360, 1716, 1508, 1456, 1339, 1220, 1066, 740, 698 cm^{–1}. ¹H NMR (500 MHz, CD₃OD): δ = 3.79 (br, 1 H), 4.08 (dd, *J* = 12.0, 5.0 Hz, 1 H), 4.30 (d, *J* = 7.0 Hz, 1 H), 4.41 (br d, *J* = 12.0 Hz, 1 H), 4.51 (s, 1 H), 4.57–4.73 (m, 4 H), 5.08–5.14 (m, 2 H), 7.24–7.37 (m, 15 H). ¹³C NMR (125 MHz, CD₃OD): δ = 63.26, 66.68, 72.88, 74.66, 78.79, 79.33, 127.50, 127.64, 127.80, 127.96, 128.06, 128.13, 128.29, 136.98, 138.29, 138.47, 157.75, 158.39, 176.12. HRMS (FAB): m/z [M + Na⁺] calcd for C₂₈H₃₀N₂O₈Na: 545.1900; found: 545.1903.
- (18) Characterization data for **2**: [α]_D²⁵ +1.2 (*c* 1.0, H₂O); mp 215–220 °C (dec.). ¹H NMR (500 MHz, D₂O): δ = 4.17 (br m, 1 H), 4.09–4.04 (m, 3 H), 3.82 (br m, 1 H). ¹³C NMR (125 MHz, D₂O): δ = 172.95, 159.35, 71.07, 68.28, 65.76, 58.13. HRMS (FAB): m/z [M + H⁺] calcd for C₆H₁₃N₂O₆: 209.0774; found: 209.0776.