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Diastereoselective Synthesis of 1-Deoxygalactonojirimycin, 1-Deoxyaltronojirimycin, and *N*-Boc-(2*S*,3*S*)-3-Hydroxypipecolic Acid via Proline Catalyzed α-Aminoxylation of Aldehydes

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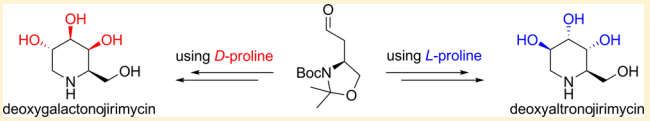
Supporting Information

ABSTRACT: An efficient synthesis of deoxygalactonojirimycin and deoxyaltronojirimycin through the use of proline catalyzed asymmetric α-aminoxylation of a higher homologue of Garner's aldehyde, derived from L-aspartic acid, is reported. The method is also used for a highly diastereoselective synthesis of the *N*-Boc derivative of (2*S*,3*S*)-3-hydroxypipecolic acid. The configuration of the proline catalyst used for the asymmetric aminoxylation step ultimately controls the absolute configuration of three adjacent stereogenic centers in the final products.



Polyhydroxylated piperidines are of remarkable interest ever since the discovery of nojirimycin in 1966 by Inuoye et al. from the strains of *Streptomyces*.[1] Naturally occurring and unnatural derivatives of these compounds (Figure 1), generally

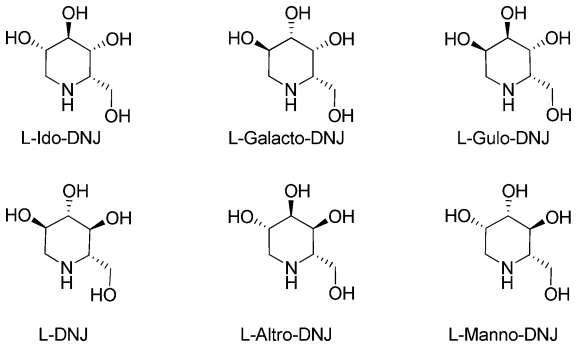


Figure 1. Examples of polyhydroxypiperidines.

known as imino- or azasugars, are potential therapeutics with anticancer, antidiabetic, antiobesity, antiviral, and fungicidal activity.[2] The biological properties of such compounds can be explained in terms of their structural resemblance to the oxygenated analogues found in nature. 1-Deoxygalactonojirimycin is one such example of unnatural polyhydroxy piperidine compounds with potent glycosidase inhibitory activity.[3] Here we report an efficient route to the synthesis of 1-deoxygalactonojirimicin (galacto-DNJ, **1**) and 1-deoxyaltronojirimycin (altro-DNJ, **2**) via organocatalytic asymmetric α-aminoxylation of the higher homologue **3** of Garner's aldehyde, derived from L-aspartic acid. We have extended the strategy to synthesize (2*S*,3*S*)-3-hydroxypipecolic acid (**4**) as an *N*-Boc derivative. Several medicinally important natural products such as febrifugine, swainsonine, and prosophylline have been synthesized from **4**.[4]

Most of the available syntheses of deoxynojirimycin and its various isomers are from sugars, amino acids, tartaric acid, and heterocyclic compounds.[5] Organocatalysis has been used widely for the synthesis of polyhydroxy piperidine and pyrrolidine derivatives in general. In addition to the mild reaction conditions and cost effectiveness, proline catalyzed reactions have gained wider acceptance from the possibility of generating stereocenters with either of the absolute configurations by using D-proline or L-proline as required.[6] α-Hydroxylation of aldehydes through proline catalyzed aminoxylation followed by reduction of the N−O bond is an attractive method to incorporate hydroxyl groups stereoselectively.[7] The aldehyde function is generally modified as an alcohol or as an alkene through Wittig reaction[8] prior to the reduction of the N−O bond. Here we report a successful application of this reaction to incorporate hydroxyl groups stereoselectively onto the aldehyde **3** to synthesize galacto-DNJ (**1**) and altro-DNJ (**2**). **1** and **2** differ in the stereochemistry of all the three hydroxyl groups present in them, and the current method achieves the highly selective synthesis of these two derivatives by changing L-proline to D-proline in the aminoxylation step.

Our strategy toward the synthesis of **1** and **2** from **3** is given in Scheme 1. Asymmetric aminoxylation of **3**, followed by stabilized Wittig reaction and reduction of the N−O bond, gives the secondary allyl alcohol **A**. Dihydroxylation of **A** followed by reduction of the ester to a primary alcohol and its activation as a mesylate gives **B**. Simultaneous deprotection of the *N*-Boc group and acidolysis of the oxazolidine ring in **B** gives primary amine **C** as a salt. Treatment of **C** with a suitable base leads to intramolecular displacement of the mesylate to give cyclic derivatives, which on deprotection can give **1** and **2**. The aldehyde **3** is a higher homologue of Garner's aldehyde,

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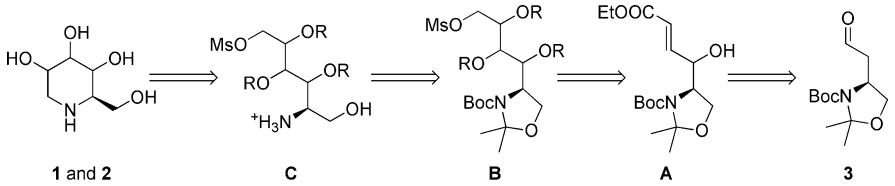
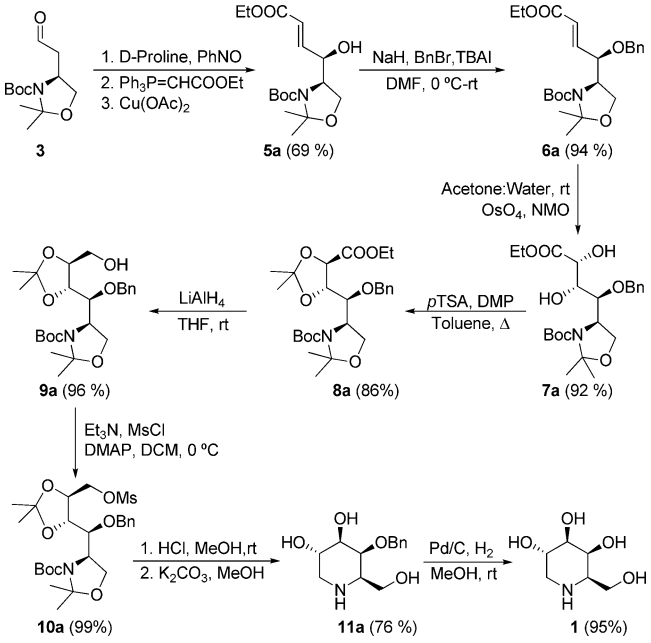
Scheme 1. Retrosynthetic Strategy for Compounds 1 and 2



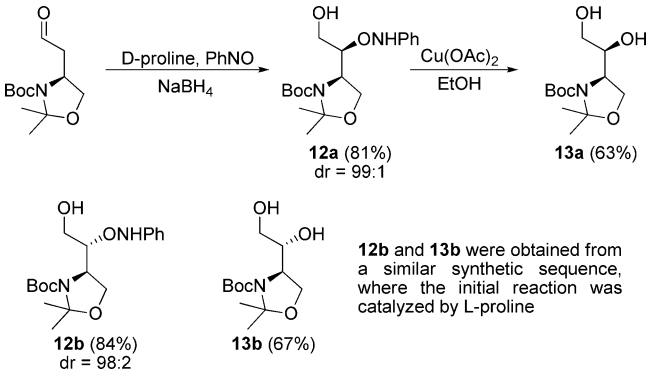
which has been used extensively for the synthesis of various iminosugars.[9] However, **3** has not been used for the synthesis of similar compounds. The asymmetric aminoxylation of **3** can be carried out with D- or L-proline to get different diastereomers of the intermediate **A** with high selectivity.

The aldehyde **3** was aminoxylated using D-proline (20 mol %) and PhNO (DMSO, 15 °C, 3 h) and was treated with the stabilized Wittig ylide, $Ph_3P{=}CHCOOEt$ (2.5 equiv in DCM at 0 °C) (Scheme 2). The crude product was filtered through a silica bed and was treated with $Cu(OAc)_2$ in EtOH to cleave the N−O bond, and the alcohol **5a** was obtained in 69% overall yield for the three steps. The diastereoselectivity for the aminoxylation reaction was estimated by reducing the aldehyde with $NaBH_4$ (instead of the Wittig reaction) and performing HPLC analysis of the crude alcohol (Scheme 3). It was observed that the aminoxylation reaction proceed with very high diastereoselectivity (≥99%). The secondary hydroxyl group in **5a** was protected as a benzyl derivative to get **6a** in 94% yield. Dihydroxylation of **6a** using the Upjohn conditions[9c,10] with OsO_4 (5 mol %) and NMO (2 equiv) in a mixture of acetone and water (8:1) yielded the diol **7a** in 92% as the only diastereomer. It was observed that dihydroxylation of **6a** with AD-mix-α and AD-mix-β were very cumbersome and the dihydroxylated products were not formed. The diol was protected as an acetonide using 2,2-dimethoxypropane (DMP) in the presence of TsOH in refluxing toluene to get **8a**, which was reduced with $LiAlH_4$ to get the primary alcohol **9a** in 91% yield from **7a**. The primary hydroxyl group was converted to the mesylate **10a** in excellent yield with MsCl in the presence of

Scheme 2. Synthesis of Galacto-DNJ (1) from 3



Scheme 3. Diastereoselective Synthesis of Diols 13a and 13b from 3



triethylamine and DMAP. Acidolysis of **10a** with methanolic HCl followed by treatment with K_2CO_3 yielded the 3-*O*-benzyl derivative **11a** of **1** in 76% yield. Use of organic bases such as diisopropylethylamine and triethylamine instead of K_2CO_3 for the cyclization reaction interfered with the purification of **11a**. Hydrogenolysis of the benzyl group using Pd/C and H_2 in methanol completed the synthesis of **1** in 35% overall yield from **3**.

The key step in the synthesis was the α-functionalization of **3** using PhNO, which proceeded with very high diastereoselectivity in the presence of both D-proline and L-proline. Dihydroxylation of the double bond in **6a** installed the diol exclusively *anti* to the *O*-benzyl group. In effect, the configuration of all the three hydroxyl functions in **1** were fixed by the selectivity achieved in the very first reaction of the synthetic sequence. In order to ascertain the stereoselectivity achieved in this reaction, aminoxylation of **3** catalyzed by D-proline and L-proline were followed with reduction of the aldehyde to an alcohol using $NaBH_4$ to get **12a** and **12b** respectively (Scheme 3). The diastereoselectivity of these reactions was analyzed using chiral HPLC by comparing the chromatograms with that of the product mixture formed in a reaction catalyzed by DL-proline. **12a** and **12b** were converted to the diols **13a** and **13b**, respectively by cleaving the N−O bond using $Cu(OAc)_2$.

Using a very similar strategy used for the synthesis of **1** and carrying out the initial α-aminoxylation of **3** in the presence of L-proline, we were able to synthesize 1-deoxyaltronojirimycin (**2**) in 37% overall yield (Scheme 4). The stereoselective formation of the hydroxyl group in **5b** controlled the dihydroxylation of the benzyl derivative **6b** using Upjohn conditions to get **7b** diastereoselectively. The diol **7b** was converted to **2** using the same sequence of reactions used for the synthesis of **1** from **7a**.

(2*S*,3*S*)-3-Hydroxypipecolic acid (**4**) is an important intermediate in the synthesis of a number of natural products. We envisaged that **4** could easily be synthesized from **6b** in a few steps. Accordingly, reduction of **6b** with $LiBH_4$ led to

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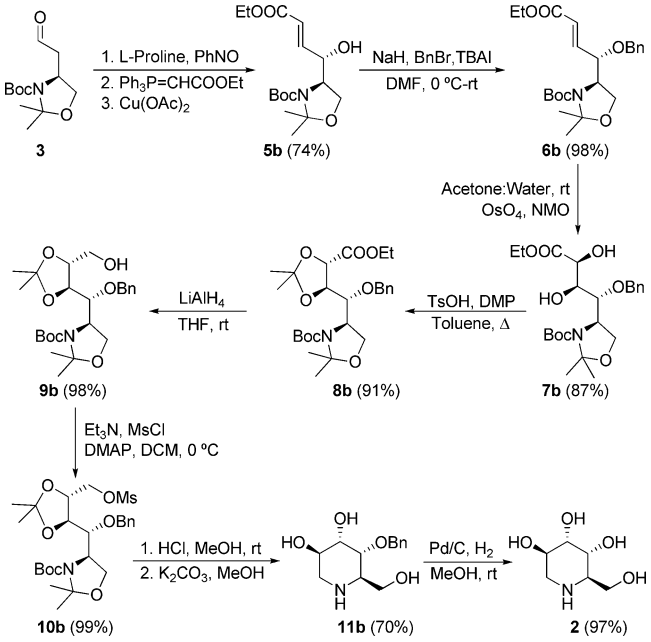
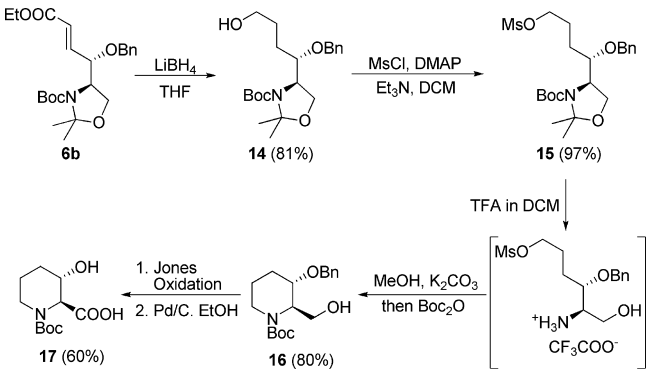
Scheme 4. Synthesis of Altro-DNJ (2) from 3



complete reduction of the α,β-unsaturated ester moiety to give the primary alcohol **14**. The mesylate **15** was prepared by treating **14** with MsCl and triethylamine in the presence of a catalytic amount of DMAP. Acidolysis of the oxazolidine ring and deprotection of the Boc group using TFA (10%) in DCM yielded a free amine, which was not separated. Cyclization of the free amine by displacing the mesylate was achieved in the presence of K_2CO_3 in methanol. The secondary amino group in the cyclized product was protected as a Boc derivative by the addition of Boc_2O into the reaction mixture to get **16** in 80% yield. The absolute configuration of **16** was confirmed by comparing its optical rotation and spectral data with the reported values.[11,4b] Jones oxidation of the primary alcohol group in **16** and hydrogenolysis of the crude product gave the *N*-Boc derivative **17** of **4** in 60% yield (Scheme 5).

Scheme 5. Synthesis of *N*-Boc Derivative 17 of (2*S*,3*S*)-3-Hydroxypipecolic Acid (4)



In conclusion, a diastereoselective synthesis of 1-deoxygalactonojirimycin (**1**), 1-deoxyaltronojirimycin (**2**), and an *N*-Boc derivative (**17**) of (2*S*,3*S*)-3-hydroxypipecolic acid is achieved from an inexpensive starting material **3**. Proline catalyzed α-aminoxylation and directed dihydroxylation of olefins are the key steps in the synthesis. The asymmetric organocatalytic aminoxylation and stereoselective dihydroxylation under Upjohn conditions proceeded with very high selectivity. The reported procedure provides one of the shortest routes to the synthesis of the title compounds.

EXPERIMENTAL SECTION

General Information. All the chemicals were purchased from commercial sources and were used without further purification. All newly reported compounds were characterized by using ^1H and ^{13}C NMR spectra. The ^1H NMR signals are referenced to tetramethylsilane (δ = 0.00 ppm), and the ^{13}C NMR peaks are referenced to residual $CHCl_3$ signal (δ = 77.0 ppm). The chemical shifts are reported in parts per million (ppm) and coupling constants in hertz (Hz). The multiplicities are assigned as s (singlet), d (doublet), t (triplet), bs (broad singlet), dd (double doublet), and m (multiplet). The presence of rotamers arising from the *N*-Boc group has led to poor resolution of the ^1H NMR spectra and duplication of signals in the ^{13}C NMR spectra. High resolution electrospray ionization mass spectroscopy was used to confirm the molecular formula of synthesized compounds. Column chromatography was done using 100−200 mesh silica gel and neutral alumina, and appropriate mixtures of petroleum ether and ethyl acetate were used as eluent. The diastereomeric ratios of the products were determined by normal phase chiral HPLC using *i*-PrOH/hexane (5/95) as eluent and 0.5 mL flow rate. Optical rotation was measured using a 5.0 mL cell with a 10 dm path length, and the values are reported as $[\alpha]_D^{25}$ (*c* in g per 100 mL of solvent).

Synthesis of 5a and 5b from 3. To a stirred solution of **3** (0.243 g, 1 mmol) and nitrosobenzene (0.140 g, 1.3 mmol) in anhydrous DMSO (5 mL) was added L-proline or D-proline (0.023 g, 20 mol %) at 15 °C. The mixture was stirred vigorously until the color changed from deep green to orange red (~3 h). After the color change, the reaction mixture was brought to 0 °C and the Wittig salt $Ph_3P{=}CHCOOEt$ (1.044 g, 3 mmol) in dichloromethane (DCM) (20 mL) was added slowly and the reaction was monitored through thin layer chromatography (TLC) (3 h). After completion of the reaction, the reaction mixture was extracted with DCM (50 mL) and was washed with water (25 mL) and brine (25 mL). The solution containing the crude product was dried over Na_2SO_4, and DCM was removed under reduced pressure. The residue was dissolved in DCM (10 mL) and was passed through a small silica bed, and the crude products were taken to the next step leading to the cleavage of N−O bond.

The crude residue (0.420 g, 1 mmol) from the previous reaction was dissolved in ethanol (10 mL), $Cu(OAc)_2$ (0.054 g, 30 mol %) was added, and the solution was stirred well for 10 h. After completion of the reaction as observed from TLC, the reaction mixture was quenched with ammonium chloride and extracted with DCM (20 mL) and was washed with brine (20 mL) and dried over Na_2SO_4. The crude reaction mixture was purified through column chromatography.

Compound ***5a:*** column chromatography (80:20 petroleum ether/EtOAc); clear oil (0.230 g, 69%). $[\alpha]_D^{27}$: +59.2 (*c* 0.80, $CHCl_3$). IR (thin film): 3447, 2925, 1698, 1457, 1366, 1259, 1172, 1093 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ = 6.91−6.87 (m, 1H), 6.13−6.10 (m, 1H), 4.53−4.39 (m, 1H), 4.19−4.13 (m, 2H), 4.03−4.00 (m, 1H), 3.91−3.83 (m, 2H), 1.44 (bs, 15H), 1.25 (m, 3H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 166.3, 154.8, 146.4, 122.2, 94.4, 81.7, 72.9, 64.1, 61.6, 60.5, 28.4, 27.0, 14.2 ppm. HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{16}H_{28}NO_6$ 330.1917, found 330.1917.

Compound ***5b:*** column chromatography (80:20 petroleum ether/EtOAc); clear oil (0.240 g, 74%). $[\alpha]_D^{27}$: +28.7 (*c* 0.20, $CHCl_3$). IR (thin film): 3447, 2925, 1698, 1457, 1366, 1259, 1172, 1093 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ = 6.95−6.91 (m, 1H), 6.17−6.12 (m, 1H), 4.40 (bs, 1H), 4.23−3.84 (m, 5H), 1.49, 1.44 (bs, 15H), 1.27−1.22 (m, 3H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 166.3, 154.6, 146.6, 122.0, 94.8, 81.7, 73.8, 65.1, 62.2, 60.3, 28.3, 26.1, 14.3 ppm. HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{16}H_{28}NO_6$ 330.1917, found 330.1917.

Synthesis of 6 from 5. The alcohol **5** (0.33 g, 1 mmol) was dissolved in dry DMF (5 mL) in an oven-dried two neck round-

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bottom flask, and the solution was cooled to 0 °C. Benzyl bromide (0.18 mL, 1.5 mmol) and tetrabutylammonium iodide, TBAI (0.073 g, 20 mol %), were added to the stirred solution followed with NaH (0.060 g, 1.5 mmol), and the reaction mixture was brought to rt and was stirred for 6 h. After completion of the reaction (TLC), excess NaH was quenched with water and and the mixture was extracted with diethyl ether (20 mL), washed with brine, and dried using Na_2SO_4. The solvents were removed under reduced pressure, and the crude mixture was purified through column chromatography.

Compound ***6a:*** column chromatography (92:8 petroleum ether/EtOAc); clear oil (0.394 g, 94%). $[\alpha]_D^{27}$: +35.8 (*c* 0.68, $CHCl_3$). IR (thin film): 2979, 2933, 1721, 1703, 1388, 1365, 1260, 1173, 1092 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ = 7.36−7.26 (m, 5H), 6.96−6.89 (m, 1H), 6.09−6.02 (m, 1H), 4.65−4.05 (m, 7H), 3.94−3.90 (m, 1H), 1.48 (bs, 9H), 1.41 (bs, 3H), 1.34 (bs, 3H), 1.30−1.27 (m, 3H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz) (mixture of rotamers): δ = 166.0, 165.8, 152.7, 151.8, 144.6, 144.1, 138.0, 137.8, 128.6, 127.9, 127.7, 127.6, 124.2, 123.8, 94.6, 94.1, 80.7, 80.2, 71.9, 71.3, 63.4, 63.1, 60.6, 60.5, 59.4, 59.2, 28.4, 26.4, 25.6, 24.2, 22.8, 14.3 ppm. HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ calcd for $C_{23}H_{33}NNaO_6$ 442.2206, found 442.2202.

Compound ***6b:*** column chromatography (92:8 petroleum ether/EtOAc); clear oil (0.410 g, 98%). $[\alpha]_D^{27}$: +20.20 (*c* 0.48, $CHCl_3$). IR (thin film): 2979, 2933, 1721, 1703, 1388, 1365, 1260, 1173, 1092 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ = 7.37−7.26 (m, 5H), 6.90−6.82 (m, 1H), 6.01−5.97 (m, 1H), 4.60−4.57 (m, 1H), 4.39−4.34 (m, 1H), 4.29−4.16 (m, 2H), 4.05−3.97 (m, 2H), 3.93−3.87 (m, 2H), 1.50, 1.39 (bs, 15H), 1.32−1.28 (m, 3H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz) (mixture of rotamers): δ = 165.9, 151.8, 145.8, 137.7, 137.4, 128.6, 128.4, 127.9, 124.2, 123.5, 94.5, 94.0, 80.4, 79.4, 71.9, 65.3, 64.3, 60.7, 60.6, 59.9, 29.7, 27.2, 27.1, 24.8, 23.0, 14.3 ppm. HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ calcd for $C_{23}H_{33}NNaO_6$ 442.2206, found 442.2202.

Synthesis of 7 from 6. A 0.1 M solution of OsO_4 in toluene (0.5 mL, 5 mol %) followed by a 50% solution of *N*-methylmorpholine *N*-oxide (0.46 mL, 2 mmol) were added slowly at 0 °C to a stirred solution of the alkene (0.419 g, 1 mmol) in acetone/water (8:1, 9 mL). After completion of the reaction as observed through TLC (24 h), the reaction mixture was stirred with sodium sulfite (0.013 g, 1 mmol) at 0 °C for 1 h. The crude product was extracted with ethyl acetate (2 × 10) and was dried over Na_2SO_4. Solvents were removed under reduced pressure, and the crude mixture was purified through column chromatography.

Compound ***7a:*** column chromatography (70:30 petroleum ether/EtOAc); oily (0.394 g, 92%). $[\alpha]_D^{27}$: +49.6 (*c* 0.60, $CHCl_3$). IR (thin film): 3416, 2978, 2933, 1743, 1694, 1664, 1397, 1376, 1366, 1066 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ = 7.40−7.25 (m, 5H), 5.11−5.10 (m, 1H), 4.86−4.84 (m, 1H), 4.63−4.61 (m, 1H), 4.44−4.39 (m, 2H), 4.32−4.27 (m, 1H), 4.19−4.01 (m, 2H), 3.80−3.71 (m, 2H), 1.60 (s, 3H), 1.52 (s, 3H), 1.46 (s, 9H), 1.24−1.22 (m, 3H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 173.9, 154.8, 138.2, 128.7, 128.4, 127.4, 95.2, 81.3, 75.3, 71.5, 70.8, 66.5, 61.6, 56.4, 28.4, 26.1, 24.7, 14.1 ppm. HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ calcd for $C_{23}H_{35}NNaO_8$ 476.2260, found 476.2266.

Compound ***7b:*** column chromatography (70:30 petroleum ether/EtOAc); clear oil (0.394 g, 87%). $[\alpha]_D^{27}$: +30.6 (*c* 0.60, $CHCl_3$). IR (thin film): 3416, 2978, 2933, 1743, 1694, 1664, 1397, 1376, 1366, 1066 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ = 7.37−7.24 (m, 5H), 4.76−4.74 (m, 1H), 4.64−4.61 (m, 1H), 4.40 (bs, 1H), 4.32−4.13 (m, 5H), 4.04−4.00 (m, 1H), 3.72−3.70 (m, 1H), 1.57, 1.49 (bs, 15H), 1.25−1.23 (m, 3H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 173.8, 153.1, 138.1, 128.4, 128.0, 127.8, 94.2, 80.9, 77.6, 75.0, 73.4, 70.6, 63.0, 62.1, 58.6, 29.7, 28.5, 14.2 ppm. HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ calcd for $C_{23}H_{35}NNaO_8$ 476.2260, found 476.2266.

Synthesis of 8a and 8b. Dimethoxypropane (0.37 mL, 3 mmol) and a catalytic amount of TsOH (0.034 g, 0.2 mmol) were added to a stirred solution of the diol **7** (0.453 g, 1 mmol) in dry toluene (10 mL) and refluxed for 1 h. Reaction was quenched with saturated $NaHCO_3$ solution (5 mL), extracted with diethyl ether, dried over Na_2SO_4, and concentrated under reduced pressure. Crude products were purified by column chromatography.

Compound ***8a:*** column chromatography (90:10 petroleum ether/EtOAc); clear oil (0.424 g, 86%). $[\alpha]_D^{27}$: +59.6 (*c* 0.30, $CHCl_3$). IR (thin film): 2934, 2981, 1748, 1698, 1455, 1390, 1259, 1092 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ = 7.29−7.25 (m, 5H), 4.72−4.46 (m, 4H), 4.29−3.88 (m, 6H), 1.63−1.34 (bs, 21H), 1.23−1.11 (m, 3H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz) (mixture of rotamers): δ = 171.4, 171.2, 152.7, 152.2, 138.2, 138.0, 128.3, 127.7, 127.5, 111.6, 111.5, 94.7, 94.2, 80.2, 79.8, 79.0, 78.7, 74.4, 73.8, 64.4, 63.5, 61.4, 57.2, 56.8, 28.4, 27.1, 27.0, 26.4, 26.1, 25.9, 24.2, 22.9, 14.0 ppm. HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ calcd for $C_{26}H_{39}NNaO_8$ 516.2573, found 516.2570.

Compound ***8b:*** column chromatography (90:10 petroleum ether/EtOAc); clear oil (0.438 g, 89%). $[\alpha]_D^{27}$: +0.69 (*c* 0.80, $CHCl_3$). IR (thin film): 2934, 2981, 1748, 1698, 1455, 1390, 1259, 1092 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ = 7.35−7.23 (m, 5H), 4.75−4.65 (m, 2H), 4.46−4.30 (m, 3H), 4.24−3.99 (m, 5H), 1.47−1.45 (bs, 15H), 1.36 (s, 3H), 1.26−1.19 (m, 6H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz) (mixture of rotamers): δ = 171.2, 152.7, 138.1, 128.3, 127.7, 111.8, 94.5, 93.7, 80.3, 79.8, 76.6, 74.1, 63.8, 63.4, 61.5, 57.9, 57.2, 29.7, 28.5, 27.0, 26.5, 25.4, 14.1 ppm. HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ calcd for $C_{26}H_{39}NNaO_8$ 516.2573, found 516.2570.

Synthesis of 9a and 9b. Solution of the ester **8** (0.493 g, 1 mmol) in 5 mL of THF was added dropwise to a suspension of $LiAlH_4$ (0.042 g, 1.1 mmol) in THF (5 mL) under nitrogen atmosphere. After completion of the reaction as observed from TLC, reaction was quenched with ethanol (1 mL) and NH_4Cl solution (4 mL). The reaction mixture was filtered through a Celite pad, and the filtrate was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash chromatography.

Compound ***9a:*** column chromatography (70:30 petroleum ether/EtOAc); clear oil (0.437 g, 97%). $[\alpha]_D^{27}$: +22.7 (*c* 0.80, $CHCl_3$). IR (thin film): 3484, 2981, 2932, 1694, 1392, 1366, 1255, 1076 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ = 7.34−7.25 (m, 5H), 4.72−4.53 (m, 2H), 4.31−3.87 (m, 6H), 3.79−3.65 (m, 2H), 2.25−2.23 (bs, 1H), 1.47−1.43 (bs, 15H), 1.35 (bs, 6H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz) (mixture of rotamers): δ = 152.6, 151.9, 137.6, 137.4, 128.6, 128.5, 128.2, 127.9, 109.5, 109.4, 94.9, 94.3, 80.7, 80.6, 80.1, 79.9, 76.1, 73.8, 73.6, 64.0, 63.6, 63.4, 57.3, 56.9, 29.7, 28.5, 27.1, 27.0, 26.8, 26.0, 25.3, 24.2, 22.8 ppm. HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ calcd for $C_{24}H_{37}NaNO_7$ 474.2468, found 474.2460.

Compound ***9b:*** column chromatography (70:30 petroleum ether/EtOAc); clear oil (0.442 g, 98%). $[\alpha]_D^{27}$: −1.0 (*c* 0.48, $CHCl_3$). IR (thin film): 3484, 2981, 2932, 1694, 1392, 1366, 1255, 1076 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ = 7.35−7.24 (m, 5H), 4.89−4.54 (m, 2H), 4.24−4.10 (m, 3H), 3.97−3.78 (m, 3H), 3.66−3.53 (m, 2H), 1.55−1.49 (bs, 15H), 1.38−1.34 (bs, 6H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 153.0, 137.4, 128.5, 128.2, 128.0, 108.9, 94.2, 80.8, 80.5, 79.1, 77.9, 74.7, 63.7, 62.9, 58.3, 29.7, 28.5, 27.1, 26.8, 25.2 ppm. HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ calcd for $C_{24}H_{37}NNaO_7$ 474.2468, found 474.2460.

Synthesis of 10a and 10b. The alcohol **9** (0.451 g, 1 mmol) was dissolved in dry DCM (10 mL) under nitrogen atmosphere at 0 °C. To this cooled solution were added triethylamine (0.28 mL, 2 mmol), methanesulfonyl chloride (0.12 mL, 1.5 mmol), and 4-(*N*,*N*-dimethylamino)pyridine, DMAP (0.018 g, 0.15 mmol), slowly one after the other. After complete disappearance of **9** from TLC, reaction was quenched with saturated citric acid solution (5 mL), extracted with dichloromethane (25 mL), and dried over Na_2SO_4 and the solvents were removed under reduced pressure. The crude product was purified by column chromatography.

Compound ***10a:*** column chromatography (70:30 petroleum ether/EtOAc); clear oil (0.523 g, 99%). $[\alpha]_D^{27}$: +13.2 (*c* 1.00, $CHCl_3$). IR (thin film): 2981, 2934, 1698, 1392, 1364, 1257, 1176, 1083 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ = 7.35−7.25 (m, 5H), 4.80−4.73 (m, 1H), 4.71−4.43 (m, 2H), 4.30−4.04 (m, 4H), 3.97−3.87 (m, 2H), 3.69−3.56 (m, 1H), 2.92 (s, 3H), 1.65−1.43 (bs, 15H), 1.36−1.31 (bs, 6H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz) (mixture of rotamers): δ = 152.6, 151.8, 137.5, 137.4, 128.7, 128.6, 128.3, 128.0, 110.5, 110.4,

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95.0, 94.4, 80.2, 79.9, 79.6, 78.3, 78.2, 75.0, 73.7, 73.5, 70.5, 70.4, 63.7, 63.2, 57.1, 56.6, 37.5, 37.4, 28.6, 28.5, 27.1, 26.9, 25.9, 25.2, 24.1, 22.8 ppm. HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{25}H_{39}NNaO_9S$ 552.2243, found 552.2247.

Compound ***10b:*** column chromatography (70:30 petroleum ether/EtOAc); clear oil (0.523 g, 99%). $[\alpha]_D^{27}$: +23.0 (c 0.56, $CHCl_3$). IR (thin film): 3484, 2981, 2932, 1694, 1392, 1366, 1255, 1076 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ = 7.36−7.26 (m, 5H), 4.87−4.73 (m, 1H), 4.53−4.50 (m, 1H), 4.30−4.26 (m, 2H), 4.19−4.00 (m, 4H), 3.90−3.85 (m, 1H), 3.69−3.56 (m, 1H), 2.92 (s, 3H), 1.55−1.50 (bs, 15H), 1.36−1.34 (bs, 6H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 152.8, 137.4, 128.7, 128.4, 128.2, 110.4, 94.1, 80.5, 76.4, 74.5, 69.8, 63.1, 58.5, 37.5, 29.7, 28.5, 27.1, 26.8, 26.3, 25.3 ppm. HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{25}H_{39}NNaO_9S$ 552.2243, found 552.2247.

Synthesis of 11a and 11b. To a stirred solution of the mesylate **10** (0.529 g, 1 mmol) in dry methanol (10 mL) at 0 °C was added freshly prepared 3 N HCl in ethyl acetate (4 mL) slowly, and the mixture was stirred well for 2 h. The solvents were removed under reduced pressure, the residue was dissolved in dry methanol (5 mL), and anhydrous K_2CO_3 (0.276 g, 2 mmol) was added to this solution at 0 °C and stirred well overnight. The reaction mixture was filtered through a Celite pad, and the solvents were removed under reduced pressure. The crude product was purified through column chromatography.

Compound ***11a:*** column chromatography (80:20:1 $CHCl_3$/MeOH/NH_3 (25% in H_2O); clear oil (0.192 g, 76%). $[\alpha]_D^{27}$: +8.8 (c 0.50, MeOH). IR (thin film): 3484, 2924, 2854, 1170, 1072 cm^{-1}. ^1H NMR (CD_3OD, 400 MHz): δ = 7.40−7.23 (m, 5H), 4.96−4.93 (m, 1H), 4.63−4.59 (m, 1H), 4.04−3.89 (m, 2H), 3.85−3.71 (m, 1H), 3.63−3.53 (m, 2H), 3.29−3.27 (m, 1H), 3.22−3.17 (m, 1H), 3.05−3.01 (m, 1H) ppm. ^{13}C NMR (CD_3OD, 100 MHz): δ = 138.4, 128.8, 127.7, 127.3, 73.6, 70.6, 69.1, 67.2, 60.4, 55.0, 45.1 ppm. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{13}H_{19}NO_4$ 254.1392, found 254.1397.

Compound ***11b:*** column chromatography (80:20:1 $CHCl_3$/MeOH/NH_3 (25% in H_2O); clear oil (0.177 g, 70%). $[\alpha]_D^{27}$: +38.6 (c 0.52, MeOH). IR (thin film): 3484, 2924, 2854, 1170, 1072 cm^{-1}. ^1H NMR (CD_3OD, 400 MHz): δ = 7.38−7.22 (m, 5H), 4.68−4.65 (m, 1H), 4.50−4.47 (m, 1H), 4.11−4.09 (m, 1H), 3.78−3.72 (m, 3H), 3.69−3.66 (m, 1H), 3.07−3.03 (m, 1H), 2.99−2.88 (m, 1H), 2.74−2.71 (m, 1H) ppm. ^{13}C NMR (CD_3OD, 100 MHz): δ = 138.4, 128.1, 128.0, 127.5, 75.8, 75.4, 75.0, 67.0, 60.1, 59.9 ppm. HRMS (ESI-TOF) m/z: $[M + H]^+$ m/z calcd for $C_{13}H_{19}NO_4$ 254.1392, found 254.1397.

Synthesis of 1 and 2. To a stirred solution of the benzyl derivative **11** (0.253 g, 1 mmol) in dry methanol was added 10% Pd/C (catalytic). The reaction mixture was stirred overnight under H_2 atmosphere. The reaction mixture was filtered through a Celite pad, and the solvents were removed under reduced pressure.

Deoxygalactonojirimycin ***1:*** clear oil (0.158 g, 97%). $[\alpha]_D^{27}$: +9.5 (c 1.20, MeOH). IR (thin film): 3480, 2924, 2853, 1464, 1082 cm^{-1}. ^1H NMR (CD_3OD, 400 MHz): δ = 4.05−3.66 (m, 5H), 3.32−2.97 (m, 3H) ppm. ^{13}C NMR (CD_3OD, 100 MHz): δ = 74.1, 67.7, 65.7, 60.5, 59.8 ppm. HRMS (ESI-TOF) m/z: $[M + H]^+$ m/z calcd for $C_6H_{14}NO_4$ 164.0923, found 164.0928.

Deoxyaltronojirimycin ***2:*** clear oil (0.154 g, 95%). $[\alpha]_D^{27}$: +8.2 (c 1.00, MeOH). IR (thin film): 3480, 2924, 2853, 1464, 1082 cm^{-1}. ^1H NMR (CD_3OD, 400 MHz): δ = 4.07−3.85 (m, 3H), 3.83−3.71 (m, 2H), 3.45−3.42 (m, 1H), 3.31−3.27 (m, 1H), 3.19−3.16 (m, 1H) ppm. ^{13}C NMR (CD_3OD, 100 MHz): δ = 69.6, 67.5, 64.4, 59.2, 56.4, 44.5 ppm. HRMS (ESI-TOF) m/z: $[M + H]^+$ m/z calcd for $C_6H_{14}NO_4$ 164.0923, found 164.0928.

Synthesis of 14. $LiBH_4$ (0.048 g, 2.2 mmol) was added to a stirred solution of the ester **6b** (0.419 g, 1 mmol) in dry THF (5 mL) at 0 °C, and the stirring was continued overnight at rt. The reaction was quenched with ethanol and saturated $NaHCO_3$ solution. The reaction mixture was filtered through a Celite pad, and the filtrate was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash chromatography. Column chromatography (70:30 petroleum ether/EtOAc); clear oil (0.306 g, 81%). $[\alpha]_D^{27}$: +52.5 (c 0.56, $CHCl_3$). IR (thin film): 3453, 2977, 2935, 2872, 1695, 1391, 1365 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.32−7.24 (m, 5H), 4.55 (bs, 2H), 4.14−4.11 (m, 1H), 3.98−3.88 (m, 2H), 3.68−3.50 (m, 3H), 1.58−1.55 (m, 4H), 1.49, 1.47 (bs, 15H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 153.5, 138.4, 128.4, 128.0, 127.7, 94.1, 80.6, 73.4, 72.7, 64.0, 62.6, 59.8, 28.5, 27.8, 27.2, 26.9, 25.1 ppm. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{21}H_{34}NO_5$ 380.2431, found 380.2437.

Compound 15. The alcohol **14** (0.379 g, 1 mmol) was dissolved in dry dichloromethane (10 mL) under nitrogen atmosphere at 0 °C. To this cooled solution were added triethylamine (0.28 mL, 2 mmol), methanesulfonyl chloride (0.12 mL, 1.5 mmol), and DMAP (0.018 g, 0.15 mmol) one after the other. Reaction was monitored using TLC, and after the complete disappearance of **14**, reaction was quenched with saturated citric acid solution (5 mL), extracted with dichloromethane, and dried over Na_2SO_4 and the solvents were removed under reduced pressure. The crude mesylate **15** was purified by column chromatography. Column chromatography (70:30 petroleum ether/EtOAc); clear oil (0.452 g, 97%). $[\alpha]_D^{27}$: +9.2 (c 0.28, $CHCl_3$). IR (thin film): 2976, 2934, 1693, 1354, 1173, 1063 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.33−7.24 (m, 5H), 4.61−4.50 (m, 2H), 4.21−4.10 (m, 3H), 3.95−3.90 (m, 3H), 2.95 (s, 3H), 1.95−1.85 (m, 1H), 1.75−1.68 (m, 1H), 1.64−1.56 (m, 2H), 1.52, 1.48 (bs, 15H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz) (mixture of rotamers): δ = 156.0, 137.7, 128.7, 128.5, 128.2, 128.1, 127.8, 94.1, 80.4, 79.8, 73.0, 72.7, 70.3, 69.8, 63.8, 62.2, 60.0, 53.2, 37.4, 31.0, 28.5, 28.4, 27.4, 26.8, 25.1 ppm. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{22}H_{36}NO_7S$ 458.2212, found 458.2210.

Synthesis of 16. The mesylate **15** (0.457 g, 1 mmol) was treated with trifluoroacetic acid (0.5 mL) in dichloromethane (5 mL) at 0 °C until its complete disappearance from TLC. Solvents were removed under reduced pressure and treated with triethylamine (0.4 mL, 3 mmol) in methanol for 15 h. Boc anhydride (0.344 mL, 1.5 mmol) was added to the reaction mixture, and the stirring was continued for 3 h. Solvents were removed under reduced pressure, and the crude product was purified through column chromatography. Column chromatography (70:30 petroleum ether/EtOAc); clear oil (0.240 g, 70%). $[\alpha]_D^{27}$: −40.1 (c 0.34, $CHCl_3$). Lit.[11] $[\alpha]_D^{25}$: −37.5 (c 0.50, $CHCl_3$). Lit.[4b] $[\alpha]_D^{23}$ for enantiomer of **16**: +39.5 (c 1.73, $CHCl_3$). Lit.[4b] $[\alpha]_D^{20}$: −40.1 (c 0.9, $CHCl_3$). IR (thin film): 3430, 2930, 1687, 1664, 1365, 1273, 1173, 1053 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.33−7.22 (m, 5H), 4.62−4.59 (m, 1H), 4.52−4.46 (m, 2H), 4.00−3.93 (m, 1H), 3.77−3.72 (m, 1H), 3.63−3.55 (m, 2H), 2.89−2.83 (m, 1H), 1.94−1.84 (m, 2H), 1.61−1.53 (m, 1H), 1.44 (s, 9H), 1.40−1.36 (m, 1H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 156.5, 138.6, 128.3, 127.6, 127.5, 80.0, 71.5, 70.2, 60.8, 55.7, 39.8, 28.5, 25.3, 19.6 ppm. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{18}H_{28}NO_4$ 322.2018, found 322.2013.

Synthesis of 17. To a stirred solution of **16** (0. 32 g, 1 mmol) in acetone (17 mL) at 0 °C was added freshly prepared 1 M Jones reagent (4 mL), and the mixture was stirred well for 3 h at rt. The reaction was quenched with isopropyl alcohol and then was diluted with diethyl ether. The organic layer was washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was dissolved in dry methanol (10 mL), 10% Pd/C (catalytic) was added, and the mixture was stirred well under H_2 atmosphere at rt. for 6 h. After the successful completion, the reaction mixture was filtered through Celite and the filtrate was concentrated under reduced pressure. The crude product was purified by column chromatography. Column chromatography (60:40 petroleum ether/EtOAc); clear oil (0.159 g, 60%). $[\alpha]_D^{27}$: −10.2 (c 0.40, $CHCl_3$). IR (thin film): 3433, 2928, 1672, 1393, 1368, 1254, 1171, 1147, 987 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 4.65−4.58 (m, 1H), 4.40−4.35 (m, 1H), 3.94−3.89 (m, 1H), 3.12−2.98 (m, 1H), 1.92−1.81 (m, 1H), 1.75−1.68 (m, 1H), 1.55−1.49 (m, 2H), 1.42 (s, 9H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 173.5, 156.9, 79.7, 65.5, 62.4, 40.4, 29.4, 27.3, 17.9 ppm. HRMS (ESI-TOF) m/z: $[M - H]^+$ calcd for $C_{11}H_{18}NO_5$ 244.1185, found 244.1189.

Synthesis of 12a and 12b. To a stirred solution of **3** (0.243 g, 1 mmol) and nitrosobenzene (0.140 g, 1.3 mmol) in anhydrous DMSO

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(5 mL) was added L- or D-proline (0.023 g, 20 mol %) at 15 °C. The mixture was stirred vigorously until the color changed from deep green to orange red (~3 h). The reaction mixture was brought to 0 °C, and $NaBH_4$ (0.076 g, 2 mmol) was added in ethanol to the cooled solution and was stirred vigorously. After completion of the reaction as observed in TLC, the reaction was quenched with saturated NH_4Cl solution and was extracted with ethyl acetate. The aqueous layer was washed with ethyl acetate (20 mL), the organic layers were combined, washed with brine (25 mL), and dried over Na_2SO_4, and the solvents were removed under reduced pressure. The crude products were purified through column chromatography.

Compound ***12a:*** column chromatography (75:25 petroleum ether/EtOAc); clear oil (0.285 g, 81%). The dr was determined by chiral HPLC using a ChiraSelect OM column (τ minor = nil; τ major = 12.28 min). $[\alpha]_D^{27}$: −10.3 (*c* 0.27, $CHCl_3$). IR (thin film): 3432, 3274, 2978, 2932, 1669, 1398, 1378, 1367, 1170, 1108 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ = 7.24−7.20 (m, 2H), 6.96−6.90 (m, 3H), 4.49−3.85 (m, 6H), 1.46−1.38 (bs, 15H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 153.8, 148.4, 129.0, 122.4, 115.1, 94.4, 83.2, 81.1, 65.0, 61.9, 56.1, 28.4, 26.9, 24.4 ppm. HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ calcd for $C_{18}H_{28}N_2NaO_5$ 375.1896, found 375.1894.

Compound ***12b:*** column chromatography (75:25 petroleum ether/EtOAc); clear oil (0.295 g, 84%). The dr was determined by chiral HPLC using a ChiraSelect OM column (τ minor = 13.55; τ major = 26.50 min). $[\alpha]_D^{27}$: +45.3 (*c* 0.42, $CHCl_3$). IR (thin film): 3432, 3274, 2978, 2932, 1669, 1398, 1378, 1367, 1170, 1108 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ = 7.26−7.22 (m, 2H), 7.01−6.99 (m, 2H), 6.99−6.92 (m, 1H), 4.27−4.25 (m, 1H), 4.21−4.17 (m, 1H), 4.10−4.04 (m, 1H), 3.97−3.94 (m, 1H), 3.76−3.74 (m, 1H), 3.56−3.52 (m, 1H), 1.52, 1.49 (bs, 15H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 154.2, 148.6, 128.0, 122.4, 115.0, 94.0, 83.4, 81.8, 65.5, 59.2, 55.3, 28.4, 27.6, 24.3 ppm. HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ calcd for $C_{18}H_{28}N_2NaO_5$ 375.1896, found 375.1894.

Synthesis of 13a and 13b. $Cu(OAc)_2$ (0.054 g, 0.3 mmol) was added to a stirred solution of **12** (0.352 g, 1 mmol) in ethanol, and the reaction was monitored using TLC. After completion of the reaction, it was quenched with saturated NH_4Cl solution, extracted with DCM, washed with brine (25 mL), and dried over Na_2SO_4 and the solvents were removed under reduced pressure. The crude product was purified by column chromatography.

Compound ***13a:*** column chromatography (65:35 petroleum ether/EtOAc); clear oil (0.174 g, 67%). $[\alpha]_D^{27}$: +6.2 (*c* 0.24, $CHCl_3$). IR (thin film): 3432, 3274, 2978, 2932, 1669, 1398, 1378, 1367, 1170, 1108 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ = 4.11−3.85 (m, 4H), 3.62−3.40 (m, 2H), 1.51, 1.48 (bs, 15H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 154.5, 94.0, 81.7, 72.3, 65.8, 62.3, 58.4, 28.3, 27.5, 24.0 ppm. HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ calcd for $C_{12}H_{23}NNaO_5$ 284.1474, found 284.1473.

Compound ***13b:*** column chromatography (65:35 petroleum ether/EtOAc); clear oil (0.164 g, 63%). $[\alpha]_D^{27}$: +19.5 (*c* 0.40, $CHCl_3$). IR (thin film): 3432, 3274, 2978, 2932, 1669, 1398, 1378, 1367, 1170, 1108 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ = 4.19 (bs, 1H), 4.06−3.79 (m, 3H), 3.58−3.52 (m, 2H), 1.49, 1.48 (s, 15H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 155.2, 94.3, 81.8, 74.5, 65.2, 63.6, 58.7, 28.4, 26.9, 24.2 ppm. HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ calcd for $C_{12}H_{23}NNaO_5$ 284.1474, found 284.1473.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^1H and ^{13}C spectra for all the new compounds and HPLC data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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