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syn-Selective dihydroxylation of γ-amino-α,β-unsaturated (*Z*)-esters from D-serine: stereoselective synthesis of D-iminolyxitol

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Abstract—An efficient and stereoselective synthesis of D-iminolyxitol, a potent α-galactosidase inhibitor, is achieved in 11 steps over 45% overall yield from *N*-Boc-*O*-Bn-D-serine. The key step involves the OsO_4-catalyzed *syn*-selective dihydroxylation reaction of the acyclic γ-amino-α,β-unsaturated (*Z*)-ester controlled by an *N*-diphenylmethylene group.

1. Introduction

We have been interested in stereoselective dihydroxylation reactions of chiral allylic amines, because of their simplicity and efficiency for obtaining a vicinal amino diol moiety that is widespread in bioactive compounds (Fig. 1).[1] Although asymmetric induction in the OsO_4-catalyzed dihydroxylation reactions of acyclic allylic alcohols is well known,[2] poor and inconsistent stereochemical results are often observed for acyclic allylic amines with flexible conformations.[2b,3] Sometimes even the well-established Sharpless asymmetric dihydroxylation reactions show mixed results.[4]

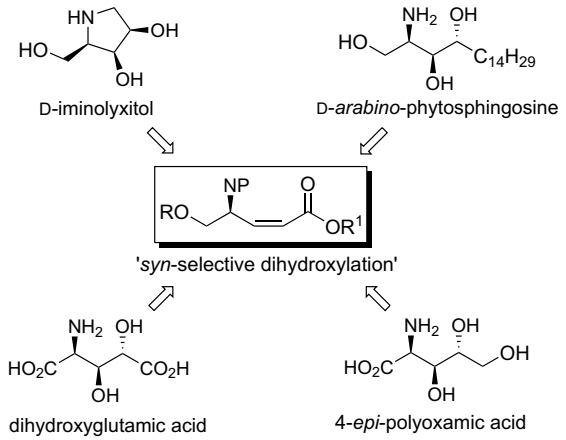

Figure 1. Bioactive compounds available from *syn*-selective dihydroxylation of (*Z*)-esters derived from D-serine.

Recently we have reported the OsO_4-catalyzed dihydroxylation reactions of chiral acyclic allylic amines with good to high diastereoselectivity, without using any chiral auxiliaries.[5] Among these, the dihydroxylations of the γ-amino-α,β-unsaturated (*Z*)-esters resulted in high *syn*-selectivity (>13:1), whereas the same osmylation reactions of the corresponding (*E*)-esters yielded the opposite *anti*-selectivity of approximately a 12:1 ratio. These opposite selectivities were made possible by simply introducing a diarylmethylene group into the amino group of γ-amino-α,β-unsaturated esters.[5b] As an application, we have successfully achieved an efficient and stereoselective synthesis of protected (2*R*,3*R*,4*S*)-4,7-diamino-2,3-dihydroxyheptanoic acid, which is a key constituent of biologically active marine peptides, callipeltins A and D and neamphamide A.[6]

We have envisioned that several bioactive amino alcohols shown in Figure 1 could be effectively obtained from the *syn*-stereoselective dihydroxylation reactions of γ-amino-α,β-unsaturated (*Z*)-esters derived from an amino acid, D-serine. Herein we report an efficient and stereoselective synthesis of D-iminolyxitol hydrochloride utilizing the *N*-diarylmethylene-controlled osmylation protocol. D-Iminolyxitol is a potent α-galactosidase inhibitor (IC_{50} 0.2 μM)[7] that has a potential use in the treatment of viral infections, diabetes, or even cancers.[8,9h] Most of the synthetic studies reported to date for D- or L-iminolyxitol are based on

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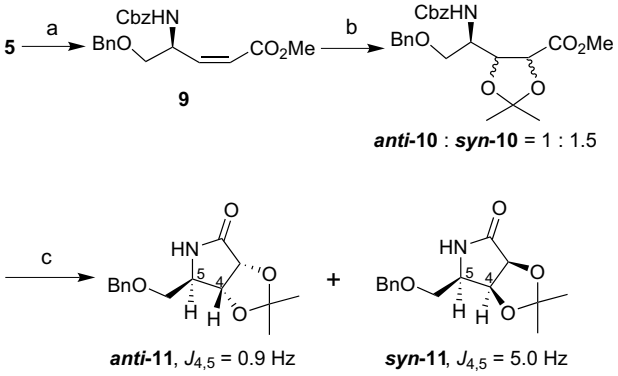
elaboration of the chiral pool, such as carbohydrates and amino acid derivatives.[9] There is one synthetic report employing the OsO_4-catalyzed dihydroxylation of the γ-amino-α,β-unsaturated (*Z*)-ester for L-iminolyxitol from an L-serine derivative.[9f] Without using a chiral reagent, the facial selectivity of the dihydroxylation reaction was low (3.2:1) for the desired *syn*-isomer.

2. Results and discussion

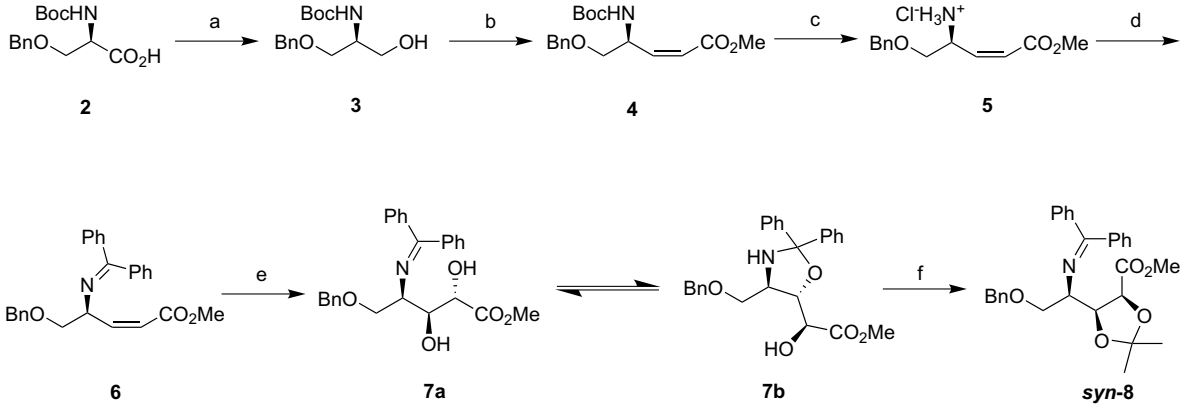
The synthesis was started from commercially available *N*-Boc-*O*-Bn-D-serine **2** (Scheme 1). Carboxylic acid **2** was converted to mixed anhydride using *i*-butyl chloroformate and TEA, while the following reduction of the crude mixed anhydride with $NaBH_4$ in MeOH gave alcohol **3** in 92% yield over two steps. Oxidation of **3** with Dess–Martin periodinane gave the corresponding aldehyde which was used without purification to minimize possible racemization. The (*Z*)-selective Horner–Emmons olefination of the aldehyde intermediate with Still's reagent[10] gave α,β-unsaturated (*Z*)-ester **4** with a ratio of more than 20:1. The minor (*E*)-isomer could be separated using silica gel column chromatography. The Boc group of **4** was selectively removed with dry HCl in MeOH to give the desired allylic amine as its crude hydrochloride salt **5** that was used for the next step without purification. An *O*-TBDMS derivative of **2** was also examined to produce the corresponding derivative of **5** through the same reaction pathway. However, the TBDMS group on the oxygen atom was so labile under the acidic conditions that the undesired product was obtained. Thus, the *O*-Bn group was chosen to be a suitable protecting group of the primary alcohol of **2**. The *N*-diphenylmethylene group was easily introduced by a simple transamination reaction between the crude salt **5** and commercially available benzophenone imine, to give the desired product **6** in 92% yield from **4**.[11]

The OsO_4-catalyzed dihydroxylation reaction of γ-amino-α,β-unsaturated (*Z*)-ester **6** gave **7** in 82% yield. The correct diastereomeric ratio of **7** could not be determined at this stage because of the facile equilibrium between acyclic diol **7a** and cyclic oxazolidine **7b**. Thus, the two hydroxyl groups of **7a** were protected into an isopropylidene unit under mild acidic conditions to give a diastereomeric mixture of **8**, *syn*-**8** and *anti*-**8**, which showed a more than 10:1 ratio for the desired *syn*-isomer as expected. Its ratio was measured by both ^1H NMR spectroscopy and GC analysis. The minor isomer *anti*-**8** could be separated by column chromatography.

To determine the relative stereochemistry of the newly generated two hydroxyl groups of **7a**, a significant amount of the dihydroxylation product with an *anti* configuration was needed. As shown in Scheme 2, the other diastereomeric mixture of the dihydroxylation product **10** containing each isomer in a similar ratio was prepared from an *N*-Cbz derivative of α,β-unsaturated (*Z*)-ester **9** that was in turn derived from **5**. When (*Z*)-ester **9** was subjected to the same dihydroxylation protocol, about a 1.5:1 mixture of the diastereomeric diols was obtained. Its two hydroxyl groups were also transformed into an isopropylidene group of **10**. The relative stereochemistry of each diastereomer of **10** was determined by converting **10** into a mixture of γ-lactams **11**, *anti*-**11** and *syn*-**11**, and comparing their $J_{4,5}$ values (Scheme 2). The selective reduction of **10** with Pd/C and HCO_2NH_4 under refluxing MeOH conditions gave the desired γ-lactams **11** without reducing the *O*-benzyl



Scheme 2. (a) CbzCl, $NaHCO_3$, 75%; (b) (i) OsO_4, NMO; (ii) 2,2-DMP, PPTS, 75% over 2 steps; (c) 10% Pd/C, HCO_2NH_4, 23% for *anti*-**11**, 30% for *syn*-**11**.



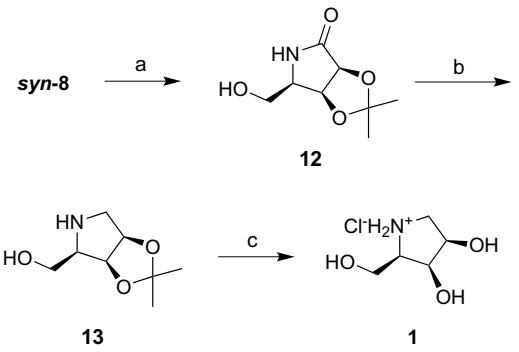
Scheme 1. (a) (i) *i*-Butyl chloroformate, TEA; (ii) $NaBH_4$, 92% over 2 steps; (b) (i) Dess–Martin periodinane; (ii) $(CF_3CH_2O)_2P(O)CH_2CO_2Me$, KHMDS, 18-crown-6, 88% over 2 steps; (c) AcCl in MeOH; (d) benzophenone imine, 92% over 2 steps; (e) OsO_4, NMO, 82%; (f) 2,2-DMP, PPTS, 89%.

group, which were then separated by silica gel column chromatography. It has been reported that the value of $J_{4,5}$ of *cis*-γ-lactams is larger than that of *trans*-γ-lactams with the similar structures.[5b,6,12] The $J_{4,5}$ value of *anti*-**11** was 0.9 Hz, whereas that of *syn*-**11** was 5.0 Hz. Treatment of acetonide *syn*-**8** under the same reduction conditions yielded an identical γ-lactam product with *syn*-**11**. Therefore, the relative configuration of the major diol isomer of **7** should be *syn* to that of the amino group. Further evidence of the assignment of the relative stereochemistry was established by converting the major isomer *syn*-**8** into the target compound, D-iminolyxitol hydrochloride (see below).

We also applied the same dihydroxylation reaction conditions to the *N*-Boc derivative **4**, which showed similar facial selectivity (<1.5:1) to that of the Cbz derivative **9**. These results strongly support our previous results that the achiral *N*-diphenylmethylene group can enhance the *syn*-selectivity to a great extent in the case of γ-amino-α,β-unsaturated (*Z*)-esters, compared with the widely used *N*-carbamate derivatives. In addition, the *N*-diphenylmethylene group can be used as a protecting group in some reactions and could serve dual purposes.[11] The *syn*-selectivity observed from **6** has been explained by the *N*-outside conformation of the *N*-diphenylmethylene group in the acyclic γ-amino-α,β-unsaturated (*Z*)-esters.[5b,6] The selectivity difference between the carbamate groups and the *N*-diphenylmethylene group has also been described.

It should be noted that the stereochemical results observed in the present study are complementary to those obtained from the similar *N*-Boc-*N,O*-isopropylidene-protected γ-amino-α,β-unsaturated (*Z*)-ester derivative, as reported by Koskinen and Chen, which showed exclusive *anti*-selectivity with a similar dihydroxylation protocol without a chiral reagent.[13] It is also interesting to compare the different sense of selectivity in the similar dihydroxylation reactions of the two α,β-unsaturated (*Z*)-esters with a similar structure. One with a chiral 2-aryloxazoline ring showed an inherent *syn*-selectivity (*syn*:*anti* = 3.2:1),[9f] whereas the other with a chiral *N*-Boc oxazolidine ring resulted in the exclusive *anti*-selectivity (*syn*:*anti* = 0:1).[13]

Scheme 3 shows the final stage of the synthetic procedure for D-iminolyxitol hydrochloride from *syn*-**8**. Upon treatment of acetonide *syn*-**8** with $Pd(OH)_2/C$ and a H_2 gas in MeOH, both the *N*-diphenylmethylene and *O*-benzyl groups of the *syn*-**8** isomer were removed and the concomitant cyclization resulted in γ-lactam **12** in 83% yield as a single isomer. Reduction of lactam **12** with BH_3·THF under the refluxing THF conditions provided pyrrolidine **13** in excellent yield. Finally, acidic hydrolysis of **13** gave D-iminolyxitol hydrochloride **1** in a quantitative yield. Its spectroscopic data of ^1H and ^{13}C NMR were well in accordance with the literature values.[9i]



Scheme 3. (a) 20% $Pd(OH)_2/C$, H_2, 83%; (b) BH_3·THF, THF, reflux, quantitative; (c) MeOH, aq HCl, rt, quantitative.

3. Conclusions

A *syn*-selective OsO_4-catalyzed dihydroxylation of the acyclic γ-amino-α,β-unsaturated (*Z*)-ester derived from D-serine was achieved with a more than 10:1 ratio. The achiral *N*-diphenylmethylene group that was easily introduced was very effective in controlling the flexible acyclic conformation of γ-amino-α,β-unsaturated (*Z*)-ester **6**. The stereoselectivity observed was quite high compared to that of the *N*-carbamate derivatives and complementary to that of the *N*-Boc-*N,O*-isopropylidene derivative. As a result, an efficient and stereoselective synthesis of D-iminolyxitol was achieved. The target compound, D-iminolyxitol hydrochloride **1**, was synthesized in 11 steps and 45% overall yield from commercially available *N*-Boc-*O*-Bn-D-serine **2**. The present *syn*-selective dihydroxylation method should be useful in stereoselective syntheses of other bioactive compounds with an amino diol moiety as well as the compounds shown in Figure 1.

4. Experimental

General methods. Materials were obtained from commercial suppliers and used without further purification. Methylene chloride was distilled from calcium hydride immediately prior to use. Likewise THF was distilled from sodium benzophenone ketyl. MeOH was dried with molecular sieves (4 Å). Air or moisture sensitive reactions were conducted under nitrogen atmosphere using oven-dried glassware and the standard syringe/septa technique. The reactions were monitored with a SiO_2 TLC plate under UV light (254 nm) followed by visualization with a ninhydrin solution. Column chromatography was performed on silica gel 60 (70–230 mesh). Optical rotations were determined at ambient temperature with a digital polarimeter and were the average of more than five measurements. ^1H NMR spectra were measured at 300 MHz in $CDCl_3$ unless stated otherwise and data were reported as follows in ppm (δ) from an internal standard (TMS, 0.0 ppm): chemical shift (multiplicity, integration, coupling constant in Hz).

4.1. (2*S*)-3-Benzyloxy-2-(*tert*-butoxycarbonylamino)propan-1-ol 3

To a solution of carboxylic acid **2** (0.500 g, 1.69 mmol) in DME (10 mL) at 0 °C were added *i*-butyl chloroformate (0.242 mL, 1.86 mmol) and triethylamine (0.470 mL, 3.39 mmol). After 10 min, the precipitated ammonium salt

was removed by filtration and the residue was washed with DME (10 mL × 2). A solution of sodium borohydride (0.320 g, 8.47 mmol) in MeOH (3 mL) was added to the filtered DME solution at 0 °C. The reaction mixture was stirred for another 20 min. The reaction was then quenched with a saturated aq NH_4Cl solution (20 mL). The resulting mixture was extracted with EtOAc (15 mL × 2). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude colorless oil. The crude product was purified by silica gel column chromatography (hexane/EtOAc = 2:1) to give alcohol **3** (437 mg, 1.55 mmol, 92%) as a colorless oil. $R_f = 0.52$ (hexane/EtOAc = 1:1); $[\alpha]_D^{23} = -7.6$ (*c* 0.92, $CHCl_3$); ^1H NMR δ 1.45 (s, 9H), 2.57 (br s, 1H), 3.63–3.84 (m, 5H), 4.53 (s, 2H), 5.18 (br s, 1H), 7.26–7.36 (m, 5H); ^{13}C NMR δ 28.4, 51.5, 64.2, 70.8, 73.5, 79.7, 127.7, 127.9, 128.5, 137.6, 156.1; HRMS (CI) calcd for $C_{15}H_{24}NO_4$ $[M+H]^+$: 282.1705; found, 282.1703.

4.2. Methyl (2*Z*,4*S*)-5-benzyloxy-4-(*tert*-butoxycarbonylamino)pent-2-enoate 4

To a solution of amino alcohol **3** (4.54 g, 16.1 mmol) in dry CH_2Cl_2 (15 mL), Dess–Martin periodinane (15 wt % solution in DCM, 50 mL, 24.2 mmol) was added at room temperature. The mixture was stirred for 1.5 h at room temperature. After the reaction was completed, a saturated aq $NaHCO_3$ solution (50 mL) was added to quench the reaction. The aqueous layer was washed with DCM (50 mL × 2). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to give the crude aldehyde as a colorless oil. To a solution of bis(2,2,2-trifluoroethyl) (methoxycarbonylmethyl)phosphonate (6.41 g, 20.2 mmol) and 18-crown-6 (21.3 g, 80.2 mmol) in dry THF (30 mL) at −78 °C was added KHMDS (0.5 M in toluene, 40.3 mL, 20.2 mmol). After 15 min, the above crude aldehyde in dry THF (20 mL) was added dropwise. The resulting mixture was stirred for 2 h at −78 °C. After the starting material disappeared on TLC, the reaction was quenched with a saturated aq NH_4Cl solution (100 mL). The aqueous layer was extracted with EtOAc (40 mL × 2). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude product. The crude residue was purified by silica gel column chromatography (hexane/EtOAc = 8:1) to give (*Z*)-ester **4** as a colorless oil (4.75 g, 14.2 mmol, 88% over 2 steps). $R_f = 0.52$ (hexane/EtOAc = 2:1); $[\alpha]_D^{23} = -4.2$ (*c* 1.43, $CHCl_3$); ^1H NMR (400 MHz) δ 1.43 (s, 9H), 3.64 (m, 1H), 3.68–3.72 (m, 1H), 3.71 (s, 3H), 4.52 (d, 1H, $J = 11.9$), 4.55 (d, 1H, $J = 11.9$), 5.25 (br s, 1H), 5.34–5.38 (m, 1H), 5.85 (dd, 1H, $J = 1.1$, 11.7), 6.23 (dd, 1H, $J = 8.0$, 11.7), 7.27–7.37 (m, 5H); ^{13}C NMR δ 28.5, 49.4, 51.5, 72.2, 73.3, 79.7, 120.2, 127.8, 127.9, 128.5, 137.9, 149.4, 155.6, 166.2; HRMS (CI) calcd for $C_{18}H_{26}NO_5$ $[M+H]^+$: 336.1811; found, 336.1814.

4.3. Methyl (2Z,4*S*)-5-benzyloxy-4-(diphenylmethyleneamino)pent-2-enoate 6

To a solution of (*Z*)-ester **4** (3.29 g, 9.8 mmol) in MeOH (30 mL) was added AcCl (6.9 mL, 98 mmol) dropwise at 0 °C. The solution was stirred for 3 h at room temperature. After the reaction was completed, the solvent was removed under reduced pressure to give amine·HCl salt **5** as a crude product, which was used without purification for the next transamination reaction. The crude amine·HCl salt was dissolved in dry DCM (30 mL) and benzophenonone imine (1.78 g, 9.8 mmol) was added at room temperature. The mixture was stirred for 18 h and the reaction was then quenched with a 10 wt % aq $NaHCO_3$ solution (30 mL). The aqueous layer was extracted with DCM (30 mL × 2). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude oil. The crude product was purified by silica gel column chromatography (hexane/EtOAc = 8:1) to give **6** as a yellowish oil (3.59 g, 8.99 mmol, 92%). $R_f = 0.64$ (hexane/EtOAc = 2:1); $[\alpha]_D^{23} = -72.8$ (*c* 1.1, $CHCl_3$); ^1H NMR δ 3.51 (s, 3H), 3.61 (dd, 1H, $J = 4.6$, 9.9), 3.72–3.78 (m, 1H), 4.47 (s, 2H), 5.40–5.47 (m, 1H), 5.80 (d, 1H, $J = 11.7$), 6.38 (dd, 1H, $J = 8.8$, 11.7), 7.12–7.16 (m, 2H), 7.27–7.41 (m, 11H), 7.62–7.65 (m, 2H); ^{13}C NMR δ 51.0, 60.8, 72.6, 73.1, 119.9, 127.3, 127.4, 128.0, 128.16, 128.21, 128.3, 128.6, 130.1, 136.9, 138.6, 139.9, 146.7, 165.9, 170.1; HRMS (CI) calcd for $C_{26}H_{26}NO_3$ $[M+H]^+$: 400.1913; found, 400.1913.

4.4. Methyl (2*S*,3*S*,4*R*)-5-benzyloxy-4-(diphenylmethylene)amino-2,3-isopropylidenedioxypentanoate *syn*-8

To a solution of olefin **6** (2.22 g, 5.55 mmol) in THF (20 mL) and H_2O (20 mL) were added NMO (1.63 g, 13.9 mmol) and OsO_4 (42 mg, 0.166 mmol) at room temperature. The resulting mixture was stirred for 24 h at room temperature. After the reaction was complete, a saturated aq Na_2SO_3 solution (10 mL) was added. The aqueous layer was extracted with EtOAc (30 mL × 2). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude product. The crude mixture was purified by silica gel column chromatography (hexane/EtOAc = 4:1) to give an equilibrium mixture **7** (1.98 g, 4.57 mmol, 82%). The purified product **7** was dissolved in benzene (150 mL) and 2,2-dimethoxypropane (10 mL). Pyridinium *p*-toluenesulfonate (PPTS, 345 mg, 1.37 mmol) was added to the above solution mixture. The mixture was then heated at reflux with a Dean-Stark trap for 4.5 h. After cooling the resulting mixture, the reaction solvent was evaporated under reduced pressure. The crude residue was dissolved in EtOAc (50 mL) and the resulting solution was washed with a saturated aq $NaHCO_3$ solution (50 mL × 2). The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude oil. The crude product was purified by silica gel column chromatography (hexane/EtOAc = 8:1) to give acetonide *syn*-**8** as a pale yellow oil (1.92 g, 4.05 mmol, 89%). $R_f = 0.48$ (hexane/EtOAc = 2:1); $[\alpha]_D^{24} = -28.0$ (*c* 0.72, $CHCl_3$); ^1H NMR (400 MHz) δ 1.38 (s, 3H), 1.64 (s, 3H), 3.32 (s, 3H), 3.58–3.68 (m, 2H), 3.82–3.86 (m, 1H), 4.37 (d, 1H, $J = 12.2$), 4.41 (d, 1H, $J = 12.2$), 4.56 (d, 1H, $J = 6.4$), 4.63 (dd, 1H, $J = 6.4$, 7.8), 7.23–7.42 (m, 13H), 7.62–7.65 (m, 2H); ^{13}C NMR δ 25.7, 26.5, 51.5, 61.5, 70.6, 72.9, 76.2, 77.7, 110.5, 127.37, 127.43, 127.86, 127.91, 128.1, 128.6, 128.8, 130.0, 136.6, 138.3, 140.0, 169.9, 170.6;

HRMS (CI) calcd for $C_{29}H_{32}NO_5$ $[M+H]^+$: 474.2280; found, 474.2280.

4.5. (3*S*,4*S*,5*R*)-5-Hydroxymethyl-3,4-isopropylidenedioxypyrrolidin-2-one 12

To a solution of acetonide *syn*-**8** (305 mg, 0.644 mmol) in MeOH (20 mL) was added $Pd(OH)_2/C$ (29 mg, 0.193 mmol, 20 wt % Pd). The reaction mixture was stirred under a H_2 balloon for 40 h. The reaction mixture was then filtered through a Celite pad to remove $Pd(OH)_2/C$. The filtrate was concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (DCM/MeOH = 10:1) to give γ-lactam **12** as a white solid (100 mg, 0.535 mmol, 83%). $R_f = 0.11$ (DCM/MeOH = 10:1); mp 122 °C; $[\alpha]_D^{23} = +22.9$ (*c* 0.71, MeOH); ^{1}H NMR (CD_3OD) δ 1.35 (s, 3H), 1.39 (s, 3H), 3.59–3.67 (m, 1H), 3.77–3.84 (m, 2H), 4.68 (d, 1H, $J = 5.7$), 4.80 (dd, 1H, $J = 4.2$, 5.7); ^{13}C NMR (CD_3OD) δ 26.1, 27.3, 57.8, 61.7, 76.7, 79.4, 113.8, 176.7; HRMS (CI) calcd for $C_8H_{14}NO_4$ $[M+H]^+$: 188.0923; found, 188.0923.

4.6. (3*S*,4*S*,5*R*)-5-Benzyloxymethyl-3,4-isopropylidenedioxypyrrolidin-2-one 11

To a mixture of *syn*-**10** and *anti*-**10** (135 mg, 0.304 mmol) in MeOH (15 mL) were added Pd/C (120 mg, 0.010 mmol, 10 wt % Pd) and ammonium formate (110 mg, 1.74 mmol). The reaction mixture was heated at reflux for 1 h. Then, the resulting mixture was filtered through a Celite pad to remove Pd/C. The filtrate was concentrated under reduced pressure. The crude diastereomeric mixture was purified and separated by silica gel column chromatography (hexane/EtOAc = 1:1) to give both *anti*-**11** (18 mg, 0.0649 mmol, 23%) and *syn*-**11** (24 mg, 0.0865 mmol, 30%), respectively, as a white solid.

anti-**11** $R_f = 0.20$ (hexane/EtOAc = 1:2); Mp 109–111 °C; $[\alpha]_D^{28} = +14.4$ (*c* 0.22, $CHCl_3$); ^{1}H NMR (400 MHz) δ 1.37 (s, 3H), 1.48 (s, 3H), 3.50 (d, 2H, $J = 3.7$), 3.80 (dt, 1H, $J = 0.9$, 3.7 Hz), 4.52 (s, 2H), 4.55 (dd, 1H, $J = 0.9$, 5.7), 4.62 (d, 1H, $J = 5.7$), 6.02 (br s, 1H), 7.27–7.38 (m, 5H); ^{13}C NMR (100 MHz) δ 25.7, 27.0, 57.8, 70.4, 73.6, 76.9, 77.8, 112.3, 127.6, 128.0, 128.5, 137.3, 174.6; HRMS (CI) calcd for $C_{15}H_{20}NO_4$ $[M+H]^+$: 278.1392; found, 278.1393.

syn-**11** $R_f = 0.14$ (hexane/EtOAc = 1:2); Mp 109–111 °C; $[\alpha]_D^{28} = -4.8$ (*c* 0.18, $CHCl_3$); ^{1}H NMR (400 MHz with D_2O) δ 1.36 (s, 3H), 1.44 (s, 3H), 3.57 (t, 1H, $J = 9.5$), 3.78 (dd, 1H, $J = 4.1$, 9.5), 3.88–3.92 (m, 1H), 4.53 (d, 1H, $J = 11.7$), 4.58 (d, 1H, $J = 11.7$), 4.65 (d, 1H. $J = 6.0$), 4.74 (dd, 1H, $J = 5.0$, 6.0), 7.27–7.39 (m, 5H); ^{13}C NMR δ 25.9, 26.9, 54.4, 69.6, 73.6, 75.0, 77.5, 113.1, 127.8, 128.0, 128.5, 137.4, 173.1; HRMS (CI) calcd for $C_{15}H_{20}NO_4$ $[M+H]^+$: 278.1392; found, 278.1391.

4.7. (2*R*,3*S*,4*R*)-2-Hydroxymethyl-3,4-isopropylidenedioxypyrrolidine 13

To a solution of γ-lactam **12** (118 mg, 0.630 mmol) in THF (15 mL) was added BH_3·THF (5.0 mL, 1.0 M in THF, 5.0 mmol) at 0 °C. Then, the reaction mixture was heated at reflux. After the reaction was complete, the reaction mixture was cooled to 0 °C and methanol (10 mL) was slowly added to quench the reaction. The reaction solvent was evaporated under reduced pressure. The crude mixture was purified by silica gel column chromatography (hexane/EtOAc = 1:1) to give compound **13** (109 mg, 0.629 mmol, quantitative) as a white solid. $R_f = 0.3$ (hexane/EtOAc = 1:1); mp 92 °C; $[\alpha]_D^{25} = -48.2$ (*c* 0.12, $CHCl_3$); ^{1}H NMR δ 1.33 (s, 3H), 1.51 (s, 3H), 2.64 (dd, 1H, $J = 3.5$, 10.6), 2.74–2.81 (m, 1H), 2.82–2.92 (m, 1H), 3.50 (dd, 1H, $J = 4.7$, 13.9), 4.05–4.11 (m, 1H), 4.12–4.22 (m, 1H), 4.68 (br s, 1H), 4.75 (dd, 1H, $J = 4.2$, 5.5), 4.87 (t, 1H, $J = 5.5$); ^{13}C NMR δ 23.2, 25.6, 57.9, 59.4, 68.4, 77.9, 81.9, 111.5; HRMS (CI) calcd for $C_8H_{16}NO_3$ $[M+H]^+$: 174.1130; found, 174.1131.

4.8. D-Iminolyxitol [(2*R*,3*S*,4*R*)-3,4-dihydroxy-2-hydroxymethylpyrrolidine] hydrochloride 1

To a solution of pyrrolidine **13** (15 mg, 0.087 mmol) in MeOH (1 mL) was added an aq solution of 6 M HCl (1 mL). Then the reaction mixture was stirred for 30 min at room temperature. The solvent was evaporated under reduced pressure to give D-iminolyxitol hydrochloride **1** as a white solid (14.7 mg, 0.087 mmol, quantitative). Mp 161–163 °C [lit.[9a] mp 159–161 °C]; $[\alpha]_D^{27} = +15.4$ (*c* 0.56, H_2O) {lit.[9a] $[\alpha]_D^{20} = +19.8$ (*c* 0.45, H_2O); L-iminolyxitol: lit.[9f] $[\alpha]_D^{20} = -13.2$ (*c* 0.014, H_2O)}; ^{1}H NMR (D_2O) δ 3.18 (dd, 1H, $J = 7.3$, 12.1), 3.50 (dd, 1H, $J = 7.3$, 12.1), 3.68–3.74 (m, 1H), 3.86 (dd, 1H, $J = 8.4$, 12.1), 3.96 (dd, 1H, $J = 5.0$, 12.1 Hz), 4.32 (t, 1H, $J = 4.0$), 4.47 (m, 1H); ^{13}C NMR (D_2O) δ 47.8, 58.4, 63.3, 70.6, 70.8; HRMS (CI) calcd for $C_5H_{12}NO_3$ $[M-Cl]^+$: 134.0817; found, 134.0817.

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