A Concise Enantioselective Synthesis of Iminosugar Derivatives

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Supporting Information

General. 1H NMR spectra were recorded on a Bruker AM-300 spectrometer and CDCl₃ as the solvent and with tetramethylsilane (TMS) as the internal standard; J-values are in Hz. The commercially obtained reagents were used without further purification. All the reactions were monitored by TLC with silica gel coated plates. Flash Column Chromatography was performed with Merck silica gel 60 (230-400 mesh) at increased pressure. The optical purities of the products were determined by HPLC analysis using a chiral stationary phase column. The HPLC was carried out using a Waters 2690 Millennium with photodiode array detector. Optical rotations were recorded on a Perkin Elemer 241 Polarimeter (λ = 589 nm, 1 dm cell). High-resolution mass spectra were recorded on an IonSpec FTMS mass spectrometer with a DHB-matrix.

Typical procedure for the one-pot tandem direct asymmetric Mannich/HWE reaction.

In a typical experiment, the aldehyde 1a (1.5 mmol) and p-anisidine (0.5 mmol) were added to a round-bottomed flask charged with proline (30 mol%) and 2 mL DMF. After being stirred for 48h at room temperature, LiBr (1.1 mmol) was added. To this stirred solution alkyl diethylphosphonoacetate (1.1 mmol) and DBU (1.1 mmol) were added. After being stirred for 1.5 h, the reaction mixture was poured into H₂O (15 mL), extracted with EtOAc (15 mL × 3), dried with Na₂SO₄, and evaporated in vacuo. Purification by silica gel chromatography (ethyl acetate/pentane = 1/7) gave α,β-unsaturated esters 2a and 2b.

(E,4R,5R)-methyl 5-(4-methoxyphenylamino)-4,6-bis(benzyloxy)hex-2-enoate 2a:

Yield: 64%. Thick yellow oil. 1H NMR (400 MHz, CDCl₃) δ 7.38-7.26 (m, 10H), 6.99 (dd, J = 16.0 Hz, J = 6.4 Hz, 1H), 6.72 (d, J = 8.8 Hz, 2H), 6.50 (d, J = 8.4 Hz, 2H), 6.06 (d, J = 16.0 Hz, 1H), 4.70-4.62 (m, 2H), 4.48-4.34 (m, 4H), 3.73 (s, 3H), 3.72 (s, 3H), 3.61-3.57 (m, 3H). 13C NMR (100 MHz, CDCl₃): 166.628, 152.342, 146.531, 141.265,
138.215, 137.942, 128.702, 128.633, 128.299, 128.193, 128.011, 127.981, 122.867, 115.205, 114.704, 74.944, 73.507, 72.119, 68.538, 57.218, 56.042, 51.832. **HPLC:** 95%ee (Daicel Chiralpak AS, \( i \)-hexane / \( i \)-PrOH = 98:2, flow rate: 0.5 mL/min, \( \lambda = 254 \) nm): major isomer: \( t_R = 22.727 \) min; minor isomer: \( t_R = 27.344 \) min.; [\( \alpha \)]\(_{D}^{25}\) = -11.5 (c = 0.92, CHCl\(_3\)); MALDI-TOF MS: 498.2258; C\(_{29}\)H\(_{33}\)NO\(_5\) (M+Na\(^+\): calcd 498.2256).

**(E,4R,5R)-ethyl 5-(4-methoxyphenylamino)-4,6-bis(benzyloxy)hex-2-enoate 2b:**

![Chemical structure of 2b]

Thick yellow oil. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.37-7.26 (m, 10H), 6.97 (dd, \( J = 16.0 \) Hz, \( J = 6.4 \) Hz, 1H), 6.71 (d, \( J = 9.2 \) Hz, 2H), 6.50 (d, \( J = 8.8 \) Hz, 2H), 6.04 (dd, \( J = 15.6 \) Hz, \( J = 1.2 \) Hz, 1H), 4.70-4.63 (m, 2H), 4.48-4.34 (m, 4H), 4.16 (q, \( J = 7.2 \) Hz, 2H), 3.73 (s, 3H), 3.61-3.56 (m, 3H), 1.27 (t, \( J = 7.2 \) Hz, 3H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): 166.234, 152.365, 146.182, 141.369, 138.269, 138.011, 128.717, 128.656, 128.315, 128.193, 128.026, 127.988, 123.360, 115.212, 114.772, 77.081, 73.515, 72.104, 68.599, 60.716, 57.279, 56.035, 14.474. HPLC: 95%ee (Daicel Chiralpak AS, \( i \)-hexane / \( i \)-PrOH = 98:2, flow rate: 0.5 mL/min, \( \lambda = 254 \) nm): major isomer: \( t_R = 29.728 \) min; minor isomer: \( t_R = 37.719 \) min. [\( \alpha \)]\(_{D}^{25}\) = -10.7 (c = 1.7, CHCl\(_3\)).

**Typical procedure for the one-pot asymmetric assembly of 2c.**

The aldehyde 1a (1.5 mmol), \( \alpha \)-glyoxylate (0.55 mmol) and \( p \)-anisidine (0.5 mmol) were added to a round-bottomed flask charged with proline (30 mol %) and 2 mL DMF. After being stirred for 48h at room temperature, LiBr (1.1 mmol) was added. To this stirred solution methyl diethylphosphonoacetate (1.1 mmol) and DBU (1.1 mmol) were added. After being stirred for 1.5 h, the reaction mixture was poured into H\(_2\)O (15 mL), extracted with EtOAc (15 mL \( \times \) 3), dried with NaSO\(_4\), and evaporated in vacuo. Purification by silica gel chromatography (from 9:1 to 6:1 Pentane–EtOAc) gave \( \alpha,\beta \)-unsaturated ester 2c, 45 %.

**(E,4R,5S)-6-ethyl 1-methyl 5-(4-methoxyphenylamino)-4-(benzyloxy)hex-2-enedioate 2c:**

![Chemical structure of 2c]

Thick yellow oil. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.37-7.26 (m, 5H), 7.09 (dd, \( J = 15.6 \) Hz, \( J = 6.8 \) Hz, 1H), 6.73 (d, \( J = 9.2 \) Hz, 2H), 6.54 (d, \( J = 8.8 \) Hz, 2H), 6.11 (dd, \( J = 15.6 \) Hz, \( J = 0.8 \) Hz, 1H), 4.65 (d, \( J = 12.0 \) Hz, 1H), 4.38-4.45 (m, 1H), 4.37 (d, \( J = 12.0 \) Hz, 1H), 4.16-4.04 (m, 3H), 3.75 (s, 3H), 3.72 (s, 3H), 1.55 (t, \( J = 7.2 \) Hz, 3H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): 171.484, 166.264, 153.131, 144.642, 141.197,
Typical procedure for the one-pot asymmetric assembly of 2d:

A mixture of the acceptor 4-chlorobenzaldehyde (0.5 mmol) and p-anisidine (0.55 mmol) in DMF (1.0 mL) was stirred for 30 minutes in the presence of a catalytic amount of proline (10 mol%) at room temperature. Next, the temperature of the reaction mixture was decreased to −20 ºC, and the propionaldehyde (1.5 mmol) was added to the reaction mixture in one portion. After 20 h vigorous stirring at −20 ºC, LiBr (1.5 mmol) was added at room temperature. To this stirred solution triethylphosphonomethylate (1.5 mmol) and DBU (1.5 mmol) were added. After being stirred for 1.5 h, the reaction mixture was poured into H₂O (15 mL), extracted with EtOAc (15 mL × 3), dried with Na₂SO₄, and evaporated in vacuo. Purification by silica gel chromatography (ethyl acetate/pentane = 1/7) gave α,β-unsaturated ester 2d, 83%.

Thick yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 7.28 (d, J = 8.4 Hz, 2H), 7.21 (d, J = 8.4 Hz, 2H), 6.91 (dd, J = 15.6 Hz, J = 7.6 Hz, 1H), 6.68 (d, J = 8.8 Hz, 2H), 6.42 (d, J = 8.8 Hz, 2H), 5.87 (dd, J = 16.0 Hz, J = 1.2 Hz, 1H), 4.34 (d, J = 4.8 Hz, 1H), 3.73 (s, 3H), 3.68 (s, 3H), 2.82-2.77 (m, 1H), 1.06 (d, J = 6.4 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃): 166.818, 152.532, 150.195, 140.916, 139.596, 133.147, 128.846, 122.215, 115.091, 114.992, 61.915, 55.898, 51.832, 42.887, 14.975. HPLC: 96% ee (Daicel Chiralpak AS, i-hexane / i-PrOH = 96:4, flow rate: 0.5 mL/min, λ=254 nm): major isomer: tᵣ = 34.392 min; minor isomer: tᵣ = 31.602 min. [α]D²⁵ = -8.1 (c = 1.0, CHCl₃).

Typical procedure for the dihydroxylation of chiral amines 2 to galactonoc acids 3:

The NMO · H₂O (37 mg, 0.28mmol) and the solution of 4 wt. % OsO₄/water (0.28 uL, 0.0046 mmol, 5mol %) was added to a stirred solution of 2 (0.093 mmol) in acetone:H₂O-8:1 (0.9 mL). After stirring the reaction mixture overnight the solution of 15% Na₂SO₃ was added and the acetone removed in vacuo. Next, the reaction mixture was extracted with EtOAc and the organic layer dried with Na₂SO₄, and evaporated in vacuo. Purification by silica gel chromatography (ethyl acetate/pentane mixtures) gave the desired galactonic acids 3.

(2R,3R,4S,5R)-methyl-5-(4-methoxyphenylamino)-4,6-bis(benzyloxy)-2,3-dihydroxyhexanoate 3a:
Dark wine-red syrup. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.37-7.26 (m, 10H), 6.75 (d, $J = 8.8$ Hz, 2H), 6.62 (d, $J = 8.8$ Hz, 2H), 4.71 (d, $J = 11.2$ Hz, 1H), 4.54 (d, $J = 11.2$ Hz, 1H), 4.52 (d, $J = 10.0$ Hz, 1H), 4.43 (d, $J = 12.0$ Hz, 2H), 4.20 (dd, $J = 8.4$ Hz, $J = 1.6$ Hz, 1H), 4.00-3.95 (m, 2H), 3.78 (s, 3H), 3.74 (s, 3H), 3.62 (dd, $J = 9.2$ Hz, $J = 4.8$ Hz, 1H), 3.55 (t, $J = 9.3$ Hz, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$): 174.405, 153.055, 140.689, 138.155, 128.717, 128.679, 128.337, 128.201, 128.163, 128.079, 115.948, 115.182, 76.921, 74.380, 73.538, 72.202, 71.064, 68.568, 55.997, 54.396, 53.008. [\[\alpha\]$_D^{25}$] = -119 (c = 0.62, CHCl$_3$). MALDI-TOF MS: 532.2312; C$_{29}$H$_{35}$NO$_7$ (M+Na$^+$: calcd 532.2311).

$(2R,3R,4S,5R)$-ethyl-5-(4-methoxyphenylamino)-4,6-bis(benzyloxy)-2,3-dihydroxyhexanoate 3b:

Dark wine-red syrup. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.37-7.26 (m, 10H), 6.75 (d, $J = 8.8$ Hz, 2H), 6.62 (d, $J = 8.8$ Hz, 2H), 4.71 (d, $J = 10.8$ Hz, 1H), 4.54 (d, $J = 11.2$ Hz, 1H), 4.52 (d, $J = 11.7$ Hz, 1H), 4.70-4.63 (m, 2H), 4.45-4.39 (m, 2H), 4.26-4.17 (m, 3H), 4.00-3.95 (m, 2H), 3.74 (s, 3H), 3.55 (t, $J = 9.3$ Hz, 1H), 1.26 (t, $J = 7.2$ Hz, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$): 173.987, 153.033, 140.727, 138.185, 138.079, 128.717, 128.679, 128.155, 128.064, 115.022, 79.895, 74.114, 71.565, 70.730, 61.581, 58.698, 55.913, 53.205, 14.353.; [\[\alpha\]$_D^{25}$] = -34.8 (c = 0.97, CHCl$_3$).

$(2S,3S,4R,5R)$-1-ethyl-6-methyl-2-(4-methoxyphenylamino)-3-(benzyloxy)-4,5-dihydroxyhexanedioate 3c:

Dark wine-red syrup. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.38-7.26 (m, 5H), 6.76 (d, $J = 8.8$ Hz, 2H), 6.70 (d, $J = 8.8$ Hz, 2H), 4.63 (d, $J = 10.8$ Hz, 1H), 4.55 (d, $J = 11.2$ Hz, 1H), 4.50 (bs, 1H), 4.46 (bs, 1H), 4.27 (q, $J = 6.8$ Hz, 2H), 4.16-4.08 (m, 2H), 3.80 (s, 3H), 3.73 (s, 3H), 1.21 (t, $J = 6.8$ Hz, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$): 174.261, 173.305, 153.465, 141.220, 137.533, 128.732, 128.451, 128.360, 116.472, 115.022, 79.895, 74.114, 71.565, 70.730, 61.581, 58.698, 55.913, 53.205, 14.421. HPLC: 96%ee (Daicel Chiralpak ODH, i-hexane / i-ProOH = 90:10, flow rate: 0.5 mL/min, $\lambda$ = 240 nm): major isomer: $t_R = 25.612$ min; minor isomer: $t_R = 29.031$ min. [\[\alpha\]$_D^{25}$] = -9.8 (c = 1.0, CHCl$_3$).
2d:

Dark wine-red syrup. \(^1\)H NMR (400 MHz, CDCl\(_3\)) (dr = 2:1) \(\delta\) (major) 7.30-7.21 (m, 4H), 6.70 (d, \(J = 8.7\) Hz, 2H), 6.56 (d, \(J = 8.9\) Hz, 2H), 4.86 (d, \(J = 2.8\) Hz, 1H), 4.26 (d, \(J = 1.6\) Hz, 1H), 4.02 (m, 1H), 3.92 (dd, \(J = 8.8, 1.6\) Hz, 1H), 3.82 (s, 3H), 3.69 (s, 3H), 0.89 (d, \(J = 7.3\) Hz, 1H), 6.46 (d, \(J = 8.9\) Hz, 1H), 4.57 (m, 0.5H), 4.33 (d, \(J = 2.7\) Hz, 0.5H), 4.29 (m, 0.5H), 3.80 (s, 1.5H), 3.75 (m, 0.5H), 3.69 (s, 1.5H), 0.96 (d, \(J = 7.1\) Hz, 1.5H); (minor) 7.22-7.13 (m, 2H), 6.67 (d, \(J = 8.7\) Hz, 1H), 6.46 (d, \(J = 8.9\) Hz, 1H), 4.57 (m, 0.5H), 4.33 (d, \(J = 2.7\) Hz, 0.5H), 4.29 (m, 0.5H), 3.80 (s, 1.5H), 3.75 (m, 0.5H), 3.69 (s, 1.5H), 0.96 (d, \(J = 7.1\) Hz, 1.5H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): (major) 174.2, 153.0, 140.6, 140.0, 133.0, 129.0, 128.7, 116.1, 115.0, 74.6, 72.2, 59.0, 56.0, 53.1, 41.4, 11.4.; (minor) 173.9, 152.7, 141.0, 140.7, 132.7, 128.5, 128.4, 115.4, 115.0, 75.2, 72.4, 60.5, 55.7, 53.2, 43.2, 9.0.

\((3R,4R,5S,6R)-5-(benzyloxy)-6-((benzyloxy)methyl)-3,4-dihydroxy-1-(4-
 methoxyphenyl)piperidin-2-one 4a: A solution of 3a (97 mg, 0.21 mmol) in
 AcOH/MeOH (4.0 mL, 1/7, V/V) was refluxed for 3 days under N\(_2\) atmosphere. Next, then the reaction mixture was concentrated in vacuo. Purification by column chromatography (ethyl acetate/pentane = 4/1) over silica gel gave lactam 4a 74% (71mg).

\((Z,4R,5R)-methyl\ 5-(4-methoxyphenylamino)-4,6-bis(benzyloxy)hex-2-enoate 2e:

Asymmetric synthesis of 2e: The aldehyde (1.5 mmol) and \(p\)-anisidine (0.5 mmol) were added to a round-bottomed flask charged with proline (30 mol %) in DMF (2 mL). After being stirred for 48h at room temperature, the desired product aldehyde 3 was isolated by silica gel chromatography. Then, olefination of the aldehyde 3 with triphenylphosphane in methanol produced the Z-\(\alpha,\beta\) -unsaturated ester 2e, 56% (122mg), \(Z/E = 4/1\) (two steps).
Thick yellow oil. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.20-7.30 (m, 10H), 6.72 (d, $J = 9.0$ Hz, 2H), 6.53 (d, $J = 9.0$ Hz, 2H), 6.40 (dd, $J = 12.0$ Hz, $J = 8.7$ Hz, 1H), 5.91 (d, $J = 11.7$ Hz, 1H), 5.40 (d, $J = 12.0$ Hz, 1H), 4.57 (d, $J = 11.7$ Hz, 2H), 4.44 (d, $J = 12.0$ Hz, 1H), 4.41 (d, $J = 11.7$ Hz, 1H), 3.78-3.52 (m, 1H), 3.72 (s, 3H), 3.66 (s, 3H), 3.61-3.57 (m, 2H).


HPLC: 92%ee (Daicel Chiralpak AS, $i$-hexane / $i$-PrOH = 98:2, flow rate: 0.5 mL/min, $\lambda$=254 nm): major isomer: $t_R = 25.634$ min; minor isomer: $t_R = 22.418$ min; $[\alpha]_D^{25} = -74.0$ (c = 1.01, CHCl$_3$).

(5R,6R)-5-(benzyloxy)-6-((benzyloxy)methyl)-5,6-dihydro-1-(4-methoxyphenyl)pyridin-2(1H)-one 5: A solution of 2e (59 mg, 0.13 mmol) in AcOH/MeOH (3.2 mL, 1:7, V/V) were refluxed for 3 days under the atmosphere of N$_2$. Then the reaction mixture was concentrated in vacuo. Purification by column chromatography (ethyl acetate/pentane = 1/4) over silica gel gave lactam 5 70% (41mg).

Thick brown-yellow oil $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.37-7.18 (m, 12H), 6.88 (d, $J = 8.8$ Hz, 2H), 6.56 (dq, $J = 10.0$ Hz, $J = 2.4$ Hz, 1H), 6.00 (d, $J = 10.0$ Hz, 1H), 4.75 (dt, $J = 6.0$ Hz, $J = 1.8$ Hz, 1H), 4.65 (d, $J = 11.2$ Hz, 1H), 4.60 (d, $J = 11.6$ Hz, 1H), 4.43 (d, $J = 2.4$ Hz, 2H), 4.14-4.12 (m, 1H), 3.86 (dd, $J = 10.0$ Hz, $J = 4.8$ Hz , 1H), 3.81 (s, 3H), 3.79 (dd, $J = 10.0$ Hz, $J = 4.8$ Hz , 1H). $^{13}$C NMR (100 MHz, CDCl$_3$): 163.732, 158.503, 140.689, 138.124, 137.578, 128.914, 128.808, 128.550, 128.307, 127.958, 127.821, 127.753, 125.667, 114.499, 73.545, 72.673, 71.861, 68.105, 62.119, 55.678. $[\alpha]_D^{25} = -57.9$ (c = 1.0, CHCl$_3$).

(3R,4S,5S,6R)-5-(benzyloxy)-6-((benzyloxy)methyl)-3,4-dihydroxy-1-(4-methoxyphenyl)piperidin-2-one 4b: The NMO · H$_2$O (19 mg, 0.14 mmol) and the solution of 2.5 wt. % OsO$_4$ in t-ButOH ( 44 uL, 0.0035mmol, 5mol %) were added to a stirred solution of 5 (30 mg, 0.07 mmol) in Acetone/t-ButOH (2 mL, 1/1, V/V). After 5h of stirring a solution of 15% Na$_2$SO$_3$ was added to the reaction mixture. Next, the acetone was removed under reduced pressure and the reaction mixture was extracted with EtOAc. The organic layer was dried with NaSO$_4$, and evaporated in vacuo. Purification by silica gel chromatography (ethyl acetate/pentane = 3/1) gave 4b 80% (26mg ).
Yellow solid. $[\alpha]_D^{25} = -2.8$ (c = 1.0, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.37-7.26 (m, 8H), 7.20-7.17 (m, 2H), 7.06 (d, $J$ = 8.7 Hz, 2H), 6.90 (d, $J$ = 9.3 Hz, 2H), 4.72 (d, $J$ = 11.4 Hz, 1H), 4.65 (d, $J$ = 11.4 Hz, 1H), 4.59 (d, $J$ = 3.6 Hz, 1H), 4.35 (bs, 2H), 4.31 (dd, $J$ = 8.4 Hz, $J$ = 4.2 Hz, 1H), 4.23 (t, $J$ = 4.2 Hz, 1H), 3.74 (t, $J$ = 9.0 Hz, 1H), 3.34 (dd, $J$ = 8.7 Hz, $J$ = 4.5 Hz, 1H).

$^{13}$C NMR (100 MHz, CDCl$_3$): 173.024, 159.102, 137.897, 137.874, 132.897, 128.740, 128.595, 128.489, 128.246, 128.095, 127.958, 127.753, 114.947, 74.645, 73.773, 73.538, 68.189, 68.143, 67.696, 59.874, 55.678. MALDI-TOF MS: 486.5121; C$_{27}$H$_{29}$NO$_6$ (M+Na$^+$: calcd 486.5120).

**One-pot asymmetric synthesis of 6:** The aldehyde 1a (1.5 mmol) and p-anisidine (0.5 mmol) were added to a round-bottomed flask charged with proline (30 mol %) in DMF (2 mL). After being stirred for 48h at room temperature, (1,3-dioxolan-2-ylmethyl)triphenylphosphonium bromide (1.5 mmol) and 2 mL dry DMF were added and the temperature increased to 80 $^\circ$C under nitrogen. Next, a solution of lithium ethoxide in ethanol (1.5mL, 1.5mmol, $M$ = 1.0 $M$) was slowly added while stirring for 3h. The solution was stirred overnight at this temperature. After being cooled to room temperature, water (20 mL) was added, and the mixture was carefully extracted with ether several times. The solvent was removed, and the residue chromatographed on silica gel (ethyl acetate/pentane from 1/9 to 1/7 ) to give product 6, 31%.

Yellow-brown solid. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.39-7.22 (m, 10H), 6.73 (d, $J$ = 8.7 Hz, 2H), 6.73 (d, $J$ = 8.7 Hz, 2H), 5.90 (dd, $J$ = 11.3 Hz, $J$ = 9.3 Hz, 2H), 5.56 (dd, $J$ = 11.4 Hz, $J$ = 7.2 Hz, 1H), 5.39 (d, $J$ = 7.2 Hz, 1H), 4.64 (d, $J$ = 11.4 Hz, 2H), 4.52 (d, $J$ = 12.0 Hz, 1H), 4.43 (d, $J$ = 12.0 Hz, 1H), 4.37 (d, $J$ = 12.0 Hz, 1H), 4.01-3.96 (m, 2H), 3.84-3.79 (m, 2H), 3.74 (s, 3H), 3.67-3.58 (m, 3H).

$^{13}$C NMR (100 MHz, CDCl$_3$): 152.189, 141.724, 138.604, 138.509, 135.446, 130.177, 128.552, 128.534, 128.218, 127.896, 127.771, 127.750, 115.115, 114.759, 99.093, 73.380, 73.282, 70.928, 69.125, 65.231, 57.734, 56.056. HPLC: 85%ee (Daicel Chiralpak ODH, i-hexane / i-PrOH = 96:4, flow rate: 0.5 mL/min, $\lambda$=254 nm): major isomer: $t_R$ = 30.876 min; minor isomer: $t_R$ = 41.519 min. $[\alpha]_D^{25} = -33.5$ (c = 1.0, CHCl$_3$).

(3$R$4$R$5$S$6$R$)-5-(benzylxoy)-6-((benzylxoy)methyl)-3,4-di-acetoxy-1-(4-methoxyphenyl)piperidin-2-one 7b:

The sugar 4a (58mg, 0.126 mmol) was dissolved in CH$_2$Cl$_2$ (4 mL) followed by addition of excess acetic anhydride and a catalytic amount of DMAP. The reaction was stirred at room temperature until all the start-material had been acetylated as determined by TLC.
analyses. The reactions were quenched by extraction with EtOAc. Purification by silica gel chromatography (ethyl acetate/pentane = 1/2) gave compound 14 96 % (66 mg).

Light yellow oil. $^1$H NMR (400 MHz, CDCl$_3$) δ 7.37-7.25 (m, 8H), 7.19-7.17 (m, 2H), 7.04 (d, $J = 8.0$ Hz, 2H), 6.88 (d, $J = 8.0$ Hz, 2H), 5.70 (d, $J = 10.4$ Hz, 1H), 5.55-5.53 (m, 1H), 4.81 (d, $J = 11.2$ Hz, 1H), 4.63 (d, $J = 11.2$ Hz, 1H), 4.44-4.31 (m, 1H), 4.32 (d, $J = 11.2$ Hz, 1H), 4.28 (d, $J = 11.6$ Hz, 1H), 3.80 (s, 3H), 3.63 (t, $J = 9.2$ Hz, 1H), 3.20 (dd, $J = 8.4$ Hz, $J = 4.4$ Hz, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$): 170.657, 170.384, 166.871, 159.193, 138.041, 137.609, 131.744, 128.846, 128.793, 128.644, 128.133, 128.087, 127.996, 114.856, 75.556, 73.682, 72.316, 70.738, 67.832, 59.593, 55.686, 21.120, 20.968.

$[\alpha]_D^{25} = +18.9$ (c = 1.0, CHCl$_3$).

(3R,4S,5S,6R)-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl)-1-(4-methoxyphenyl) piperidin-2-one 7a:

To a stirred solution of sugar 4a (15 mg, 0.032 mmol) in dry THF (1 ml) was added sodium hydride (6 mg, 60% dispersion in mineral oil, 4.0eq) at 0°C, the resulting mixture was stirred for 30 min and benzyl bromide (16 µL, 4.0eq) was added. The suspension was allowed to warm to 4°C and stirred for overnight. Saturated aqueous ammonium chloride was added. The layers were separated and the aqueous layer was extracted with ethyl acetate and dried over Na$_2$SO$_4$. After filtration and evaporation of solvents in vacuo, the crude product was purified by flash chromatography (from 5:1 to 2:1 Pentane–EtOAc) to afford the product 7a, 34%.

Light yellow oil. $^1$H NMR (400 MHz, CDCl$_3$) δ 7.43-7.41 (m, 2H), 7.37-7.25 (m, 16H), 7.13-7.11 (m, 2H), 7.02 (d, $J = 8.8$ Hz, 2H), 6.89 (d, $J = 8.8$ Hz, 2H), 5.23 (d, $J = 10.8$ Hz, 1H), 5.01 (d, $J = 10.8$ Hz, 1H), 4.84 (d, $J = 11.2$ Hz, 1H), 4.80 (d, $J = 10.8$ Hz, 1H), 4.74 (d, $J = 12.0$ Hz, 1H), 4.62 (d, $J = 11.2$ Hz, 1H), 4.53 (d, $J = 8.8$ Hz, 1H), 4.36-4.35 (m, 1H), 4.24 (bs, 2H), 3.97-3.92 (m, 2H), 3.80 (s, 3H), 3.67 (t, $J = 8.8$ Hz, 1H), 3.20 (dd, $J = 8.8$ Hz, $J = 4.8$ Hz, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$): 171.120, 158.988, 138.866, 138.564, 138.489, 137.821, 132.811, 132.381, 129.005, 128.891, 128.618, 114.856, 75.556, 73.682, 72.316, 70.738, 67.832, 59.593, 55.686, 20.968. $[\alpha]_D^{25} = +18.9$ (c = 1.0, CHCl$_3$).

(3R,4R,5S,6R)-5-(benzyloxy)-6-((benzyloxy)methyl)-3,4-di-acetoxy-piperidin-2-one 8b:

A solution of (NH$_4$)$_2$Ce(NO$_3$)$_6$ (210 mg, 3.0eq) in water (0.6 mL) was added dropwise to a solution of 7b (69 mg, 0.127 mmol) in CH$_3$CN (0.6 mL) at 0 °C. The mixture was
stirred at this temperature for 4 h. Then, water (0.8 mL) was added, and this mixture was extracted with EtOAc and dried over Na$_2$SO$_4$. After filtration and evaporation of solvents in vacuo, the crude product was purified by flash chromatography (from 3:1 to 1:2 Pentane–EtOAc) to afford the sugar 9b 40% (21mg).

**8b**

Clear-oil. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.38-7.24 (m, 10H), 5.99 (bs, 1H), 5.56 (d, $J = 10.8$ Hz, 1H), 5.32 (dd, $J = 10.8$ Hz, $J = 2.0$ Hz, 1H), 4.76 (d, $J = 11.6$ Hz, 1H), 4.52 (d, $J = 11.6$ Hz, 1H), 4.55 (d, $J = 11.6$ Hz, 1H), 4.45 (d, $J = 12.0$ Hz, 1H), 4.09 (bs, 1H), 3.80-3.77 (m, 1H), 3.80 (s, 3H), 3.51 (t, $J = 8.8$ Hz, 1H), 3.42 (dd, $J = 8.8$ Hz, $J = 4.4$ Hz, 1H), 2.13 (s, 3H), 2.05 (s, 3H).

**8a**

Clear-oil. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.44-7.11 (m, 20H), 5.86 (bs, 1H), 5.23 (d, $J = 11.2$ Hz, 1H), 4.91 (d, $J = 11.6$ Hz, 1H), 4.82 (d, $J = 11.2$ Hz, 1H), 4.79 (d, $J = 12.0$ Hz, 1H), 4.68 (d, $J = 11.6$ Hz, 1H), 4.56 (d, $J = 11.6$ Hz, 1H), 4.49 (d, $J = 11.6$ Hz, 1H), 4.42 (d, $J = 11.6$ Hz, 1H), 4.34 (d, $J = 9.2$ Hz, 1H), 3.97 (bs, 1H), 3.83 (dd, $J = 9.2$ Hz, $J = 2.0$ Hz, 2H), 3.43 (dd, $J = 8.0$ Hz, $J = 3.2$ Hz, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$): 170.751, 138.233, 138.104, 137.846, 137.315, 128.537, 128.431, 128.371, 128.361, 128.264, 128.006, 127.870, 127.733, 127.635, 127.574, 80.619, 77.319, 75.361, 74.056, 73.563, 73.161, 73.108, 70.468, 53.549; [$\alpha$]$_D^{25}$ = +62.0 (c = 0.1, CHCl$_3$) (lit$^1$, [$\alpha$]$_D^{25}$ = +68.0 (c = 0.38, CHCl$_3$)); MALDI-TOF MS: 560.2414; C$_{34}$H$_{35}$NO$_5$ (M+Na$^+$): calcd 560.2413.

# Supplementary Material (ESI) for Chemical Communications
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