A Consice Enantioselective Synthesis of Iminosugar Derivatives

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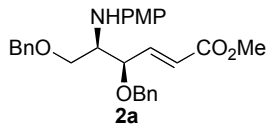
Supporting Information

General. ^{1}H NMR spectra were recorded on a Bruker AM-300 spectrometer and $CDCl_3$ 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 H_2O (15 mL), extracted with EtOAc (15 mL × 3), dried with $NaSO_4$, and evaporated in *vacuo*. Purification by silica gel chromatography (ethyl acetate/pentane = 1/7) gave α,β-unsaturated esters **2a** and **2b**.

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

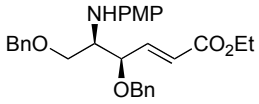


2a

Yield: 64%. Thick yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) 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). ^{13}C NMR (100 MHz, $CDCl_3$): 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, λ=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,4*R*,5*R*)-ethyl 5-(4-methoxyphenylamino)-4,6-bis(benzyloxy)hex-2-enoate 2b:



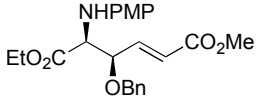
2b

Thick yellow oil. ^{1}H NMR(400 MHz, $CDCl_3$) δ 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, λ=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), α-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_2O (15 mL), extracted with EtOAc (15 mL × 3), dried with $NaSO_4$, and evaporated in *vacuo*. Purification by silica gel chromatography (from 9:1 to 6:1 Pentane–EtOAc) gave α,β-unsaturated ester **2c**, 45 %.

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



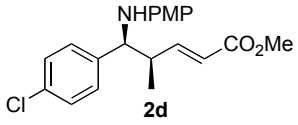
2c

Thick yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 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,

137.343, 128.702, 128.277, 128.239, 124.385, 115.591, 115.053, 78.302, 71.679, 61.846, 61.657, 55.929, 51.983, 14.330. $[\alpha]_D^{25}$ = -21.8 (*c* = 1.0, $CHCl_3$). The ee of **2c** was determined on the dihydroxylated compound **3c**.

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 –20ºC, and the propionaldehyde (1.5 mmol) was added to the reaction mixture in one portion. After 20 h vigorous stirring at -20ºC, 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 H_2O (15 mL), extracted with EtOAc (15 mL × 3), dried with $NaSO_4$, and evaporated *in vacuo*. Purification by silica gel chromatography (ethyl acetate/pentane = 1/7) gave α,β-unsaturated ester **2d**, 83%.



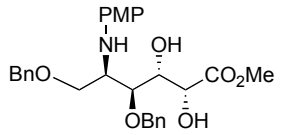
2d

Thick yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) 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). ^{13}C NMR (100 MHz, $CDCl_3$): 166.818, 152.532, 150.195, 140.916, 139.596, 133.147, 128.884, 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: t_R = 34.392 min; minor isomer: t_R = 31.602 min. $[\alpha]_D^{25}$ = -8.1 (*c* = 1.0, $CHCl_3$).

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

The NMO • H_2O (37 mg, 0.28mmol) and the solution of 4 wt. % OsO_4/water (0.28 uL, 0.0046 mmol, 5mol %) was added to a stirred solution of **2** (0.093 mmol) in acetone:H_2O-8:1 (0.9 mL). After stirring the reaction mixture overnight the a solution of 15% Na_2SO_3 was added and the acetone removed in *vacuo*. Next, the reaction mixture was extracted with EtOAc and the organic layer dried with $NaSO_4$, and evaporated in *vacuo*. Purification by silica gel chromatography (ethyl acetate/pentane mixtures) gave the desired galactonic acids **3**.

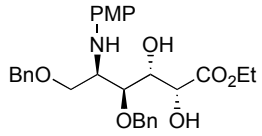
(2*R*,3*R*,4*S*,5*R*)-methyl-5-(4-methoxyphenylamino)-4,6-bis(benzyloxy)-2,3-dihydroxyhexanoate 3a:



3a

Dark wine-red syrup. ^{1}H NMR (400 MHz, $CDCl_3$) δ 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* =12.0 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* = 9.2Hz, *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, 138.071, 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).

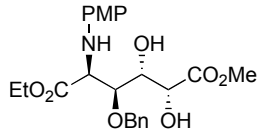
(2*R*,3*R*,4*S*,5*R*)-ethyl-5-(4-methoxyphenylamino)-4,6-bis(benzyloxy)-2,3-dihydroxyhexanoate 3b:



3b

Dark wine-red syrup. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.26 (m, 10H), 6.74 (d, *J* = 8.7 Hz, 2H), 6.63 (d, *J* = 8.7 Hz, 2H), 4.71 (d, *J* = 10.8 Hz, 1H), 4.54 (d, *J* = 11.2 Hz, 1H), 4.53 (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), 3.63 (dd, *J* = 9.3 Hz, *J* = 4.5 Hz, 1H), 3.55 (t, *J* = 9.0 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, 128.368, 128.201, 128.155, 128.064, 115.963, 115.174, 76.921, 74.410, 73.538, 72.172, 71.034, 68.583, 62.317, 55.997, 54.426, 14.353.; $[\alpha]_D^{25}$ = -34.8 (*c* = 0.97, $CHCl_3$).

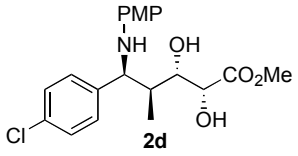
(2*S*,3*S*,4*R*,5*R*)-1-ethyl-6-methyl-2-(4-methoxyphenylamino)-3-(benzyloxy)-4,5-dihydroxyhexanedioate 3c:



3c

Dark wine-red syrup. ^{1}H NMR (400 MHz, $CDCl_3$) δ 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*-PrOH = 90:10, flow rate: 0.5 mL/min, λ = 240 nm): major isomer: t_R = 25.612 min; minor isomer: t_R = 29.031 min. $[\alpha]_D^{25}$ = -9.8 (*c* = 1.0, $CHCl_3$).

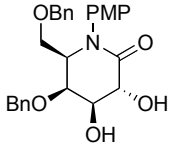
2d:



2d

Dark wine-red syrup. ^{1}H NMR (400 MHz, $CDCl_3$) (dr = 2:1) δ (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, 3H); (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, 60.4, 55.7, 53.2, 43.2, 9.0.

(3*R*,4*R*,5*S*,6*R*)-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).

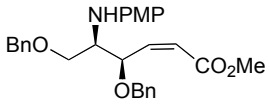


4a

Green-yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.26 (m, 8H), 7.19-7.16 (m, 2H), 7.00 (d, *J* = 8.8 Hz, 2H), 6.89 (d, *J* = 8.8 Hz, 2H), 5.01 (d, *J* = 10.8 Hz, 1H), 4.68 (d, *J* = 11.2 Hz, 1H), 4.57 (d, *J* =8.8 Hz, 1H), 4.35-4.22 (m, 3H), 4.13-4.10 (m, 1H), 4.02-3.81 (m, 1H), 3.81 (s, 3H), 3.33 (t, *J* = 8.8 Hz, 1H), 3.22 (dd, *J* = 8.8 Hz, *J* = 4.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 172.220, 159.170, 138.481, 137.555, 132.320, 128.800, 128.679, 128.504, 128.125, 128.064, 127.897, 114.969, 75.063, 74.539, 73.667, 73.310, 71.208, 67.711, 61.019, 55.686; $[\alpha]_D^{25}$ = -19.9 (*c* = 1.05, $CHCl_3$); MALDI-TOF MS: 486.5122; $C_{27}H_{29}NO_6$ (M+Na^+: calcd 486.5120).

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-a,β -unsaturated ester **2e**, 56% (122mg), *Z*/*E* = 4/1 (two steps).

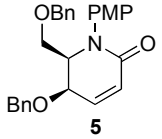
(Z,4*R*,5*R*)-methyl 5-(4-methoxyphenylamino)-4,6-bis(benzyloxy)hex-2-enoate 2e:



2e

Thick yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 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). ^{13}C NMR (100 MHz, $CDCl_3$): 166.476, 152.266, 149.247, 141.834, 138.640, 138.451, 128.565, 128.535, 128.246, 127.988, 127.943, 127.753, 121.942, 115.151, 114.734, 74.236, 73.325, 71.997, 69.289, 57.818, 56.042, 51.627. HPLC: 92%ee (Daicel Chiralpak AS, *i*-hexane / *i*-PrOH = 98:2, flow rate: 0.5 mL/min, λ=254 nm): major isomer: t_R = 25.634 min; minor isomer: t_R = 22.418 min; $[\alpha]_D^{25}$ = -74.0 (*c* = 1.01, $CHCl_3$).

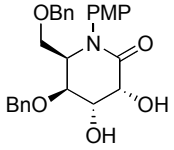
(5*R*,6*R*)-5-(benzyloxy)-6-((benzyloxy)methyl)-5,6-dihydro-1-(4-methoxyphenyl)pyridin-2(1H)-one 5: A solution of 2e (59 mg, 0.13 mmol) in AcOH/MeOH (3.2 mL, 1:7/, V/V) were refluxed for 3 days under the atmosphere of N_2. Then the reaction mixture was concentrated *in vacuo*. Purification by column chromatography (ethyl acetate/pentane = 1/4) over silica gel gave lactam 5 70% (41mg).



5

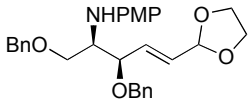
Thick brown-yellow oil ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.18 (m, 12H), 6.88 (d, *J* = 8.8 Hz, 2H), 6.56 (dq, *J* = 10.0 Hz, *J* = 2.4 Hz, *J* = 1.8 Hz, 1H), 6.00 (d, *J* = 10.0 Hz, 1H), 4.75 (dt, *J* = 6.0 Hz, *J* = 1.8 Hz, 1H), 4.65 (d, *J* =11.2 Hz, 1H), 4.60 (d, *J* =11.6 Hz, 1H), 4.43 (d, *J* =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, 134.339, 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, $CHCl_3$).

(3*R*,4*S*,5*S*,6*R*)-5-(benzyloxy)-6-((benzyloxy)methyl)-3,4-dihydroxy-1-(4-methoxyphenyl)piperidin-2-one 4b: The NMO • H_2O (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_2SO_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).



4b Yellow solid. $[\alpha]_D^{25}$ = -2.8 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 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 ºC 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%.

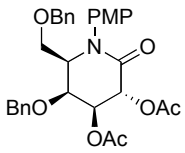


6 Yellow-brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.22 (m, 10H), 6.73 (d, *J* = 8.7 Hz, 2H), 6.73 (d, *J* = 8.7 Hz, 2H), 5.90 (dd, *J* = 11.3 Hz, *J* = 9.3 Hz, 2H), 5.56 (dd, *J* = 11.4 Hz, *J* = 7.2 Hz, 1H), 5.39 (d, *J* = 7.2 Hz, 1H), 4.64 (d, *J* = 11.4 Hz, 2H), 4.52 (d, *J* = 12.0 Hz, 1H), 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, λ=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-(benzyloxy)-6-((benzyloxy)methyl)-3,4-di-acetoxy-1-(4-methoxyphenyl)piperidin-2-one 7b:

The sugar **4a** (58mg, 0.126 mmol) was dissolved in CH_2Cl_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

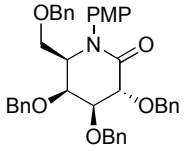
analyses. The reactions were quenched by extraction with EtOAc. Purification by silica gel chromatography (ethyl acetate/pentane = 1/2) gave compound **14** 96 % (66 mg).



7b 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), 4.15-4.11 (m, 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), 2.09 (s, 3H), 2.04 (s, 3H). ^{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, 127.913, 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, $CHCl_3$).

(3*R*,4*S*,5*S*,6*R*)-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_2SO_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%.

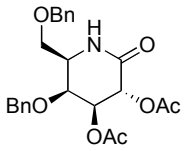


7a Light yellow-oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43-7.41 (m, 2H), 7.37-7.25 (m, 16H), 7.13-7.11 (m, 2H), 7.02 (d, *J* = 8.8 Hz, 2H), 6.89 (d, *J* = 8.8 Hz, 2H), 5.23 (d, *J* = 10.8 Hz, 1H), 5.01 (d, *J* = 10.8 Hz, 1H), 4.84 (d, *J* = 11.2 Hz, 1H), 4.80 (d, *J* = 10.8 Hz, 1H), 4.74 (d, *J* = 12.0 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, 138.686, 138.564, 138.489, 137.821, 132.381, 129.005, 128.891, 128.618, 128.595, 128.535, 128.489, 128.019, 127.935, 127.905, 127.852, 127.746, 114.795, 80.373, 78.378, 75.821, 74.812, 73.591, 73.515, 73.113, 68.773, 60.003, 55.678.

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

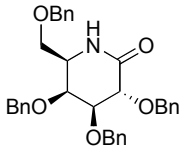
A solution of $(NH_4)_2Ce(NO_3)_6$ (210 mg, 3.0eq) in water (0.6 mL) was added dropwise to a solution of **7b** (69 mg, 0.127 mmol) in CH_3CN (0.6 mL) at 0 °C. The mixture was

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_2SO_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).



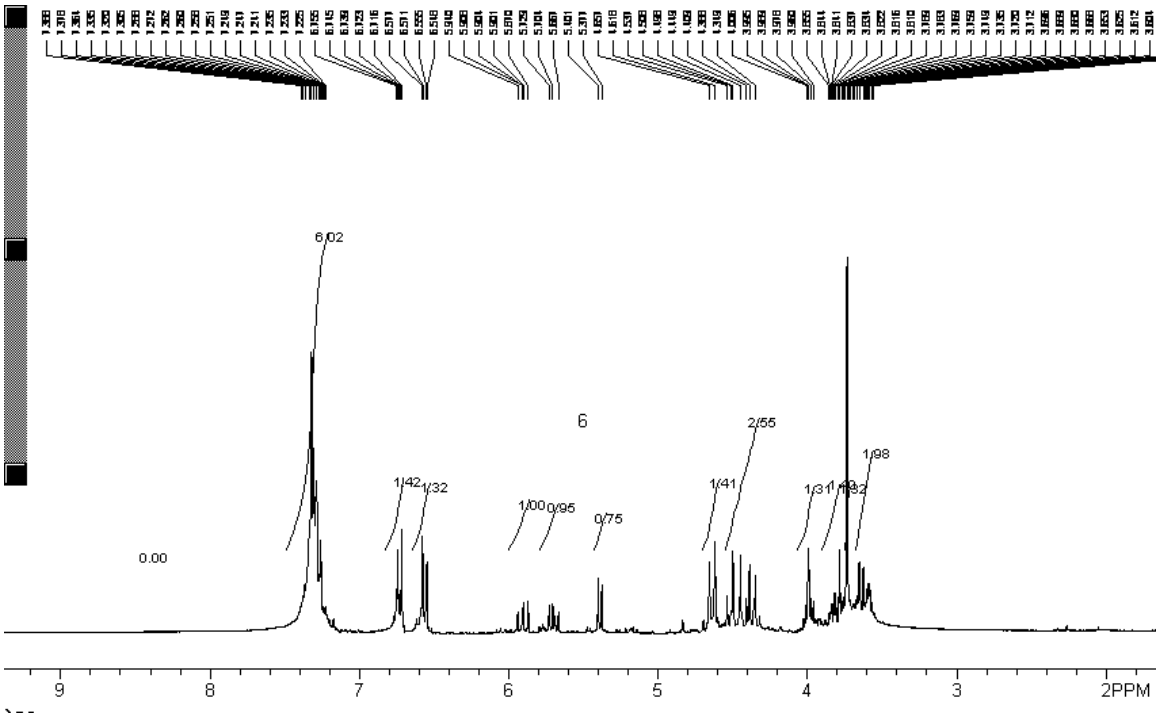
8b Clear-oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.24 (m, 10H), 5.99 (bs, 1H), 5.56 (d, *J* = 10.8 Hz, 1H), 5.32 (dd, *J* = 10.8 Hz, *J* = 2.0 Hz, 1H), 4.76 (d, *J* = 11.6 Hz, 1H), 4.52 (d, *J* =11.6 Hz, 1H), 4.55 (d, *J* = 11.6 Hz, 1H), 4.45 (d, *J* = 12.0 Hz, 1H), 4.09 (bs, 1H), 3.80-3.77 (m, 1H), 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). ^{13}C NMR (100 MHz, $CDCl_3$): 170.399, 170.361, 166.643, 137.282, 137.244, 128.800, 128. 777, 128.459, 128.360, 128.330, 128.072, 75.214, 73.788, 73.613, 73.037, 69.805, 69.630, 53.622, 21.097, 20.968. $[\alpha]_D^{25}$ = +51.8 (*c* = 1.0, $CHCl_3$).

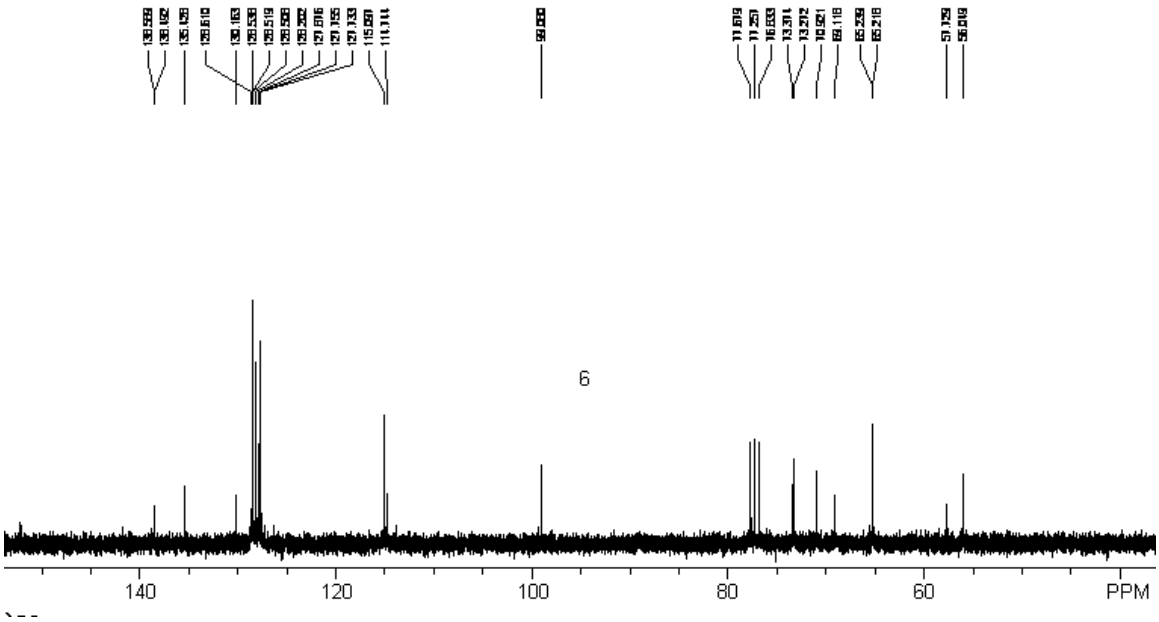
(3*R*,4*S*,5*S*,6*R*)-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl)piperidin-2-one 8a:
A solution of $(NH_4)_2Ce(NO_3)_6$ (210 mg, 3.0eq) in water (0.6 mL) was added dropwise to a solution of **7a** (0.127 mmol) in CH_3CN (0.6 mL) at 0ºC. The mixture was stirred at this temperature for 4h. Then, water (0.8 mL) was added, and this mixture was extracted with EtOAc and dried over Na_2SO_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 **9a** 36%.

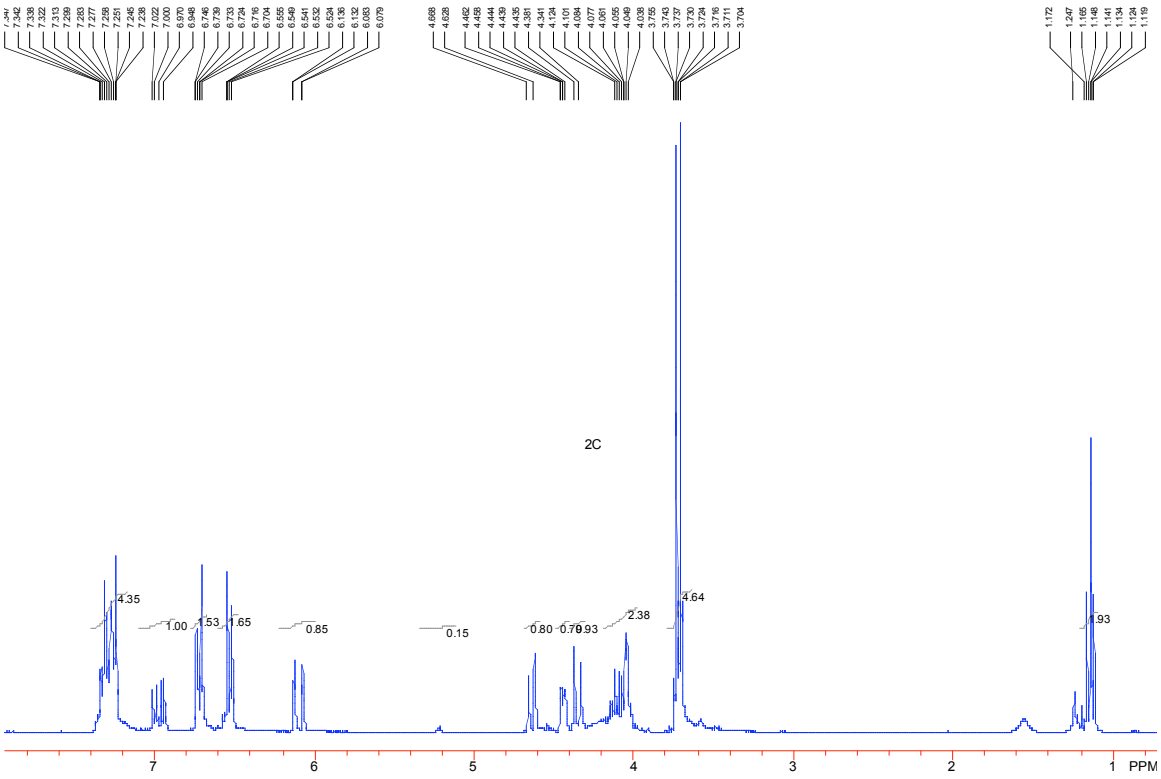


8a Clear-oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44-7.11 (m, 20H), 5.86 (bs, 1H), 5.23 (d, *J* = 11.2 Hz, 1H), 4.91 (d, *J* = 11.6 Hz, 1H), 4.82 (d, *J* = 11.2 Hz, 1H), 4.79 (d, *J* = 12.0 Hz, 1H), 4.68 (d, *J* = 11.6 Hz, 1H), 4.56 (d, *J* = 11.6 Hz, 1H), 4.49 (d, *J* = 11.6 Hz, 1H), 4.42 (d, *J* = 11.6 Hz, 1H), 4.34 (d, *J* = 9.2 Hz, 1H), 3.97 (bs, 1H), 3.83 (dd, *J* = 9.2 Hz, *J* = 1.6 Hz, 1H), 3.58-3.52 (m, 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], $[a]_D^{25}$ = +68.0 (*c* = 0.38, $CHCl_3$)); MALDI-TOF MS: 560.2414; $C_{34}H_{35}NO_5$ (M+Na^+: calcd 560.2413).

1. Overkleeft, Herman S.; Wiltenburg, Jim van; Pandit, Upendra K. *Tetrahedron*. **1994**, 4215-4224.



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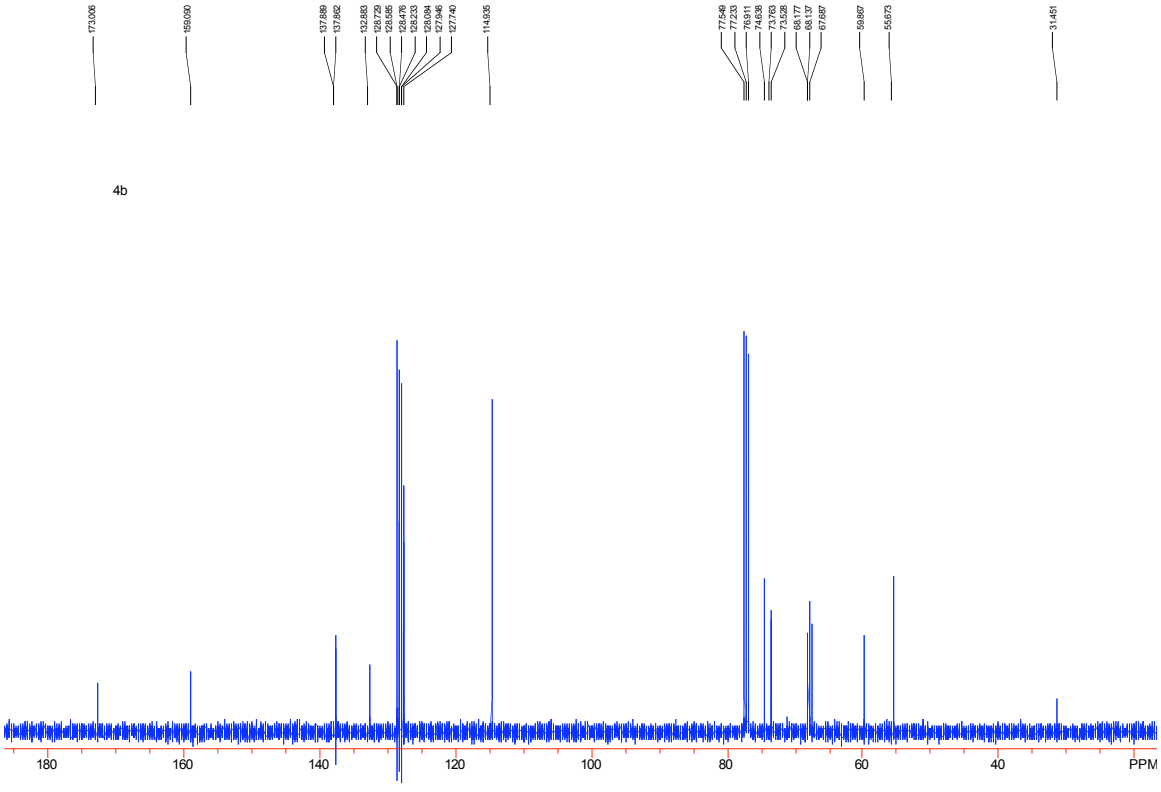
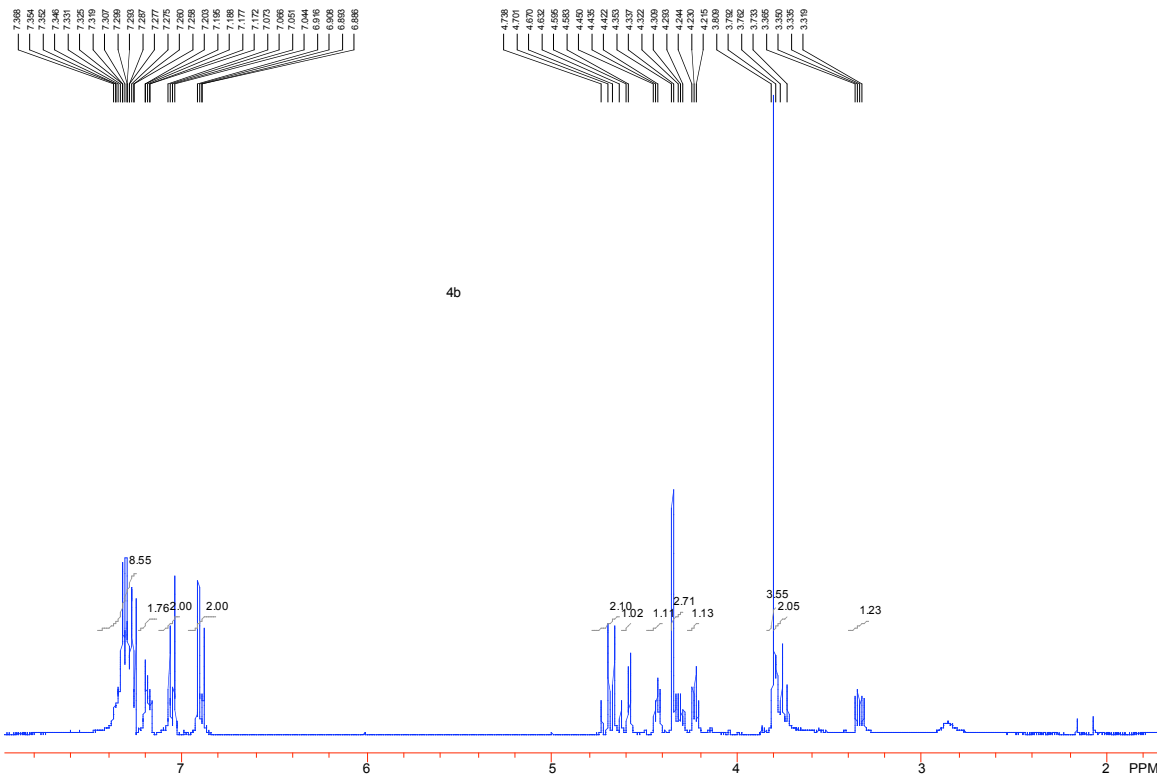
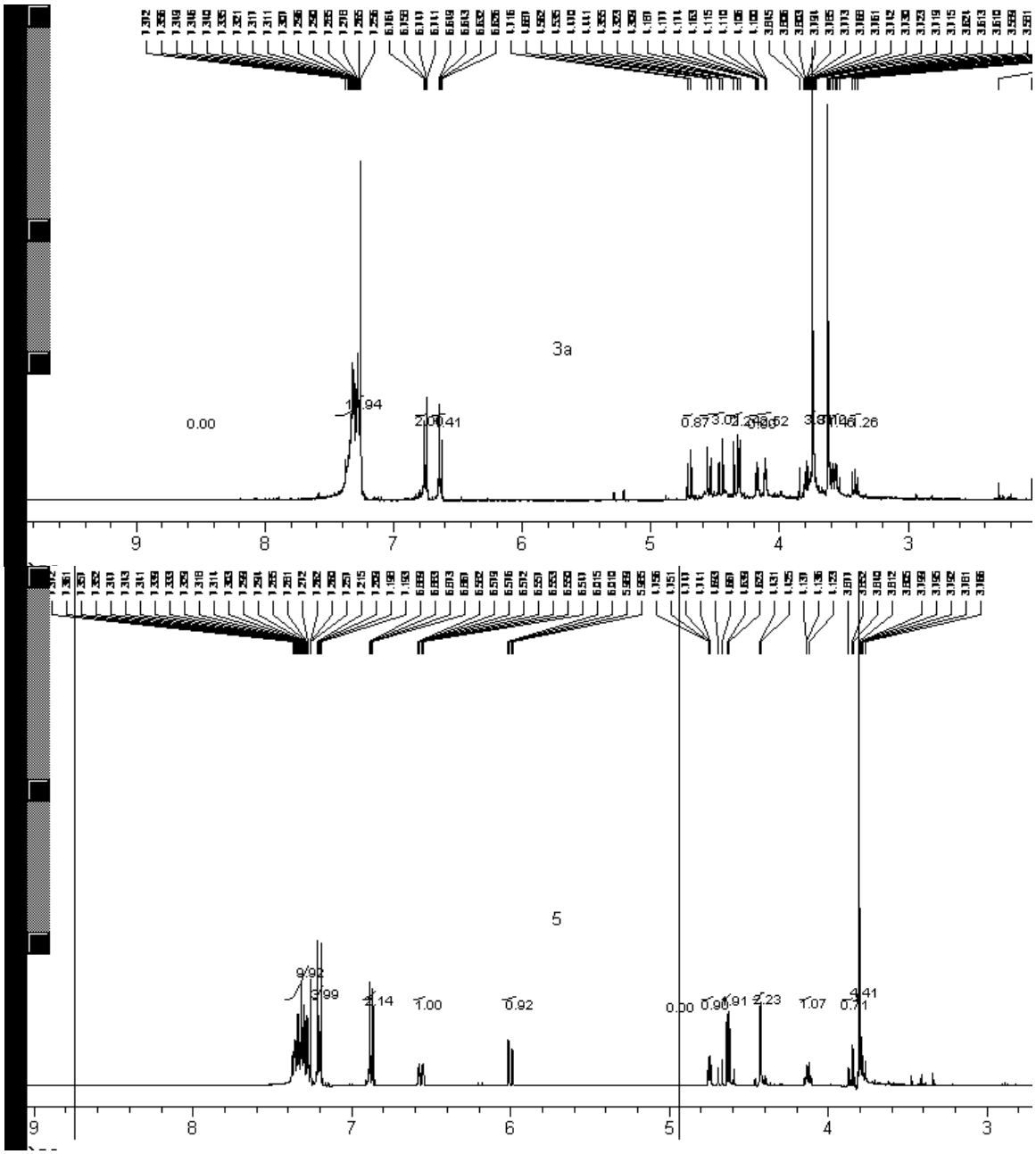
PPM


4b
PPM

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5
4
3
5
9.92
2.99
2.14
1.00
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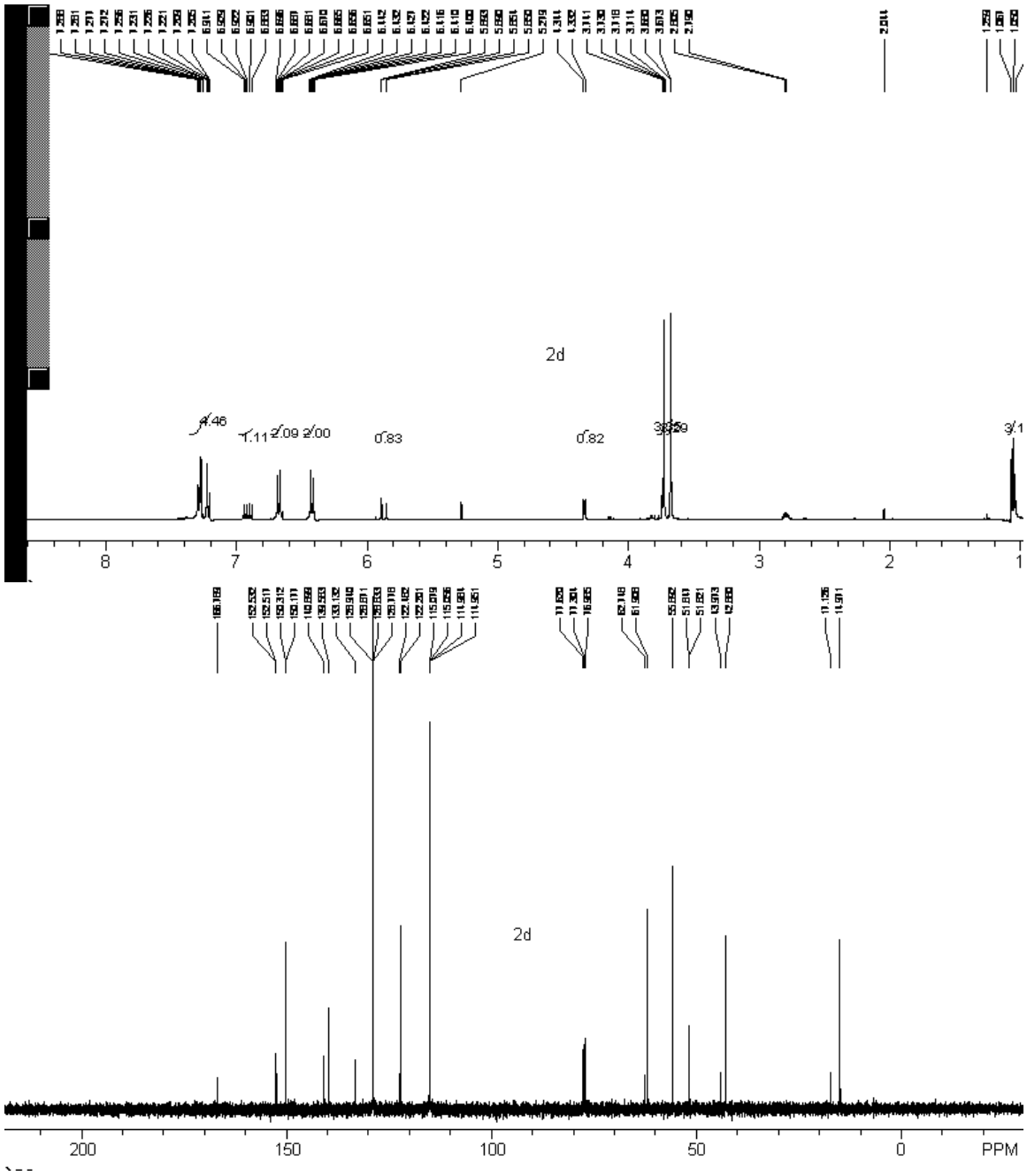
4
3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2d
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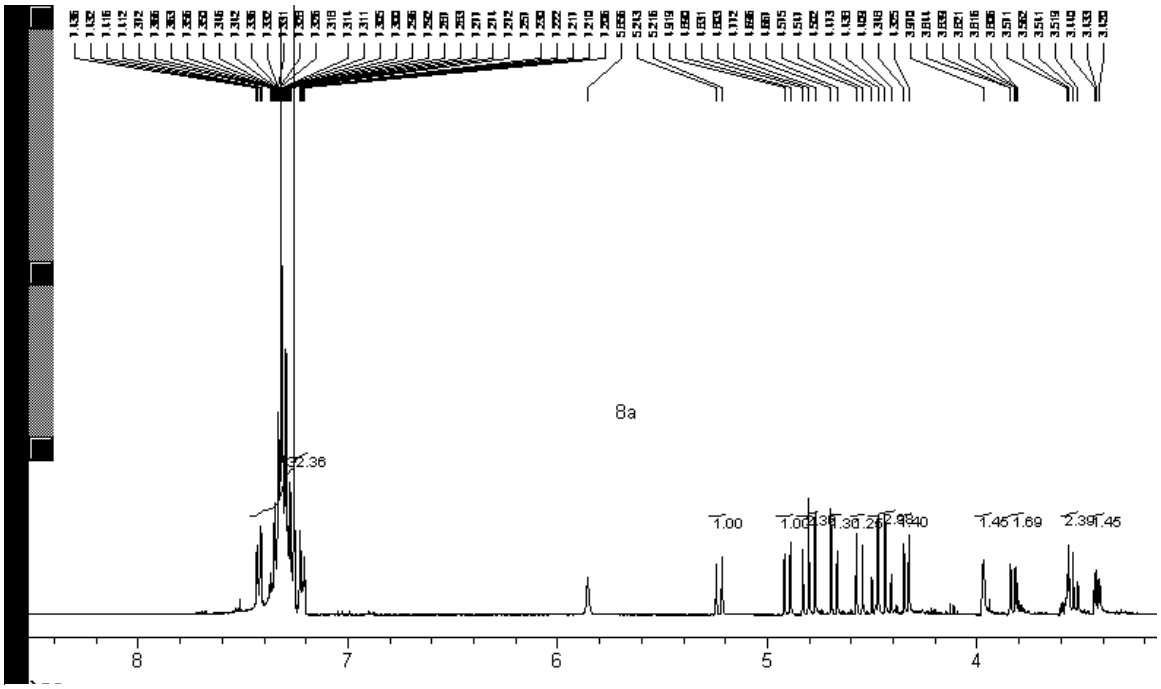
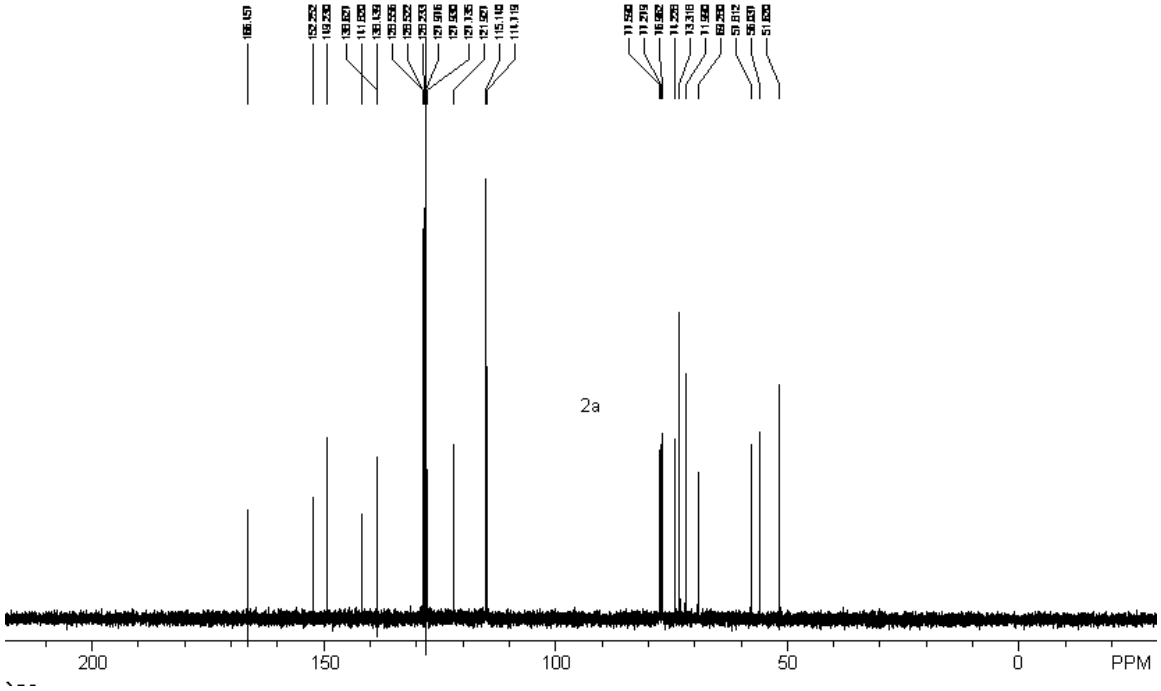
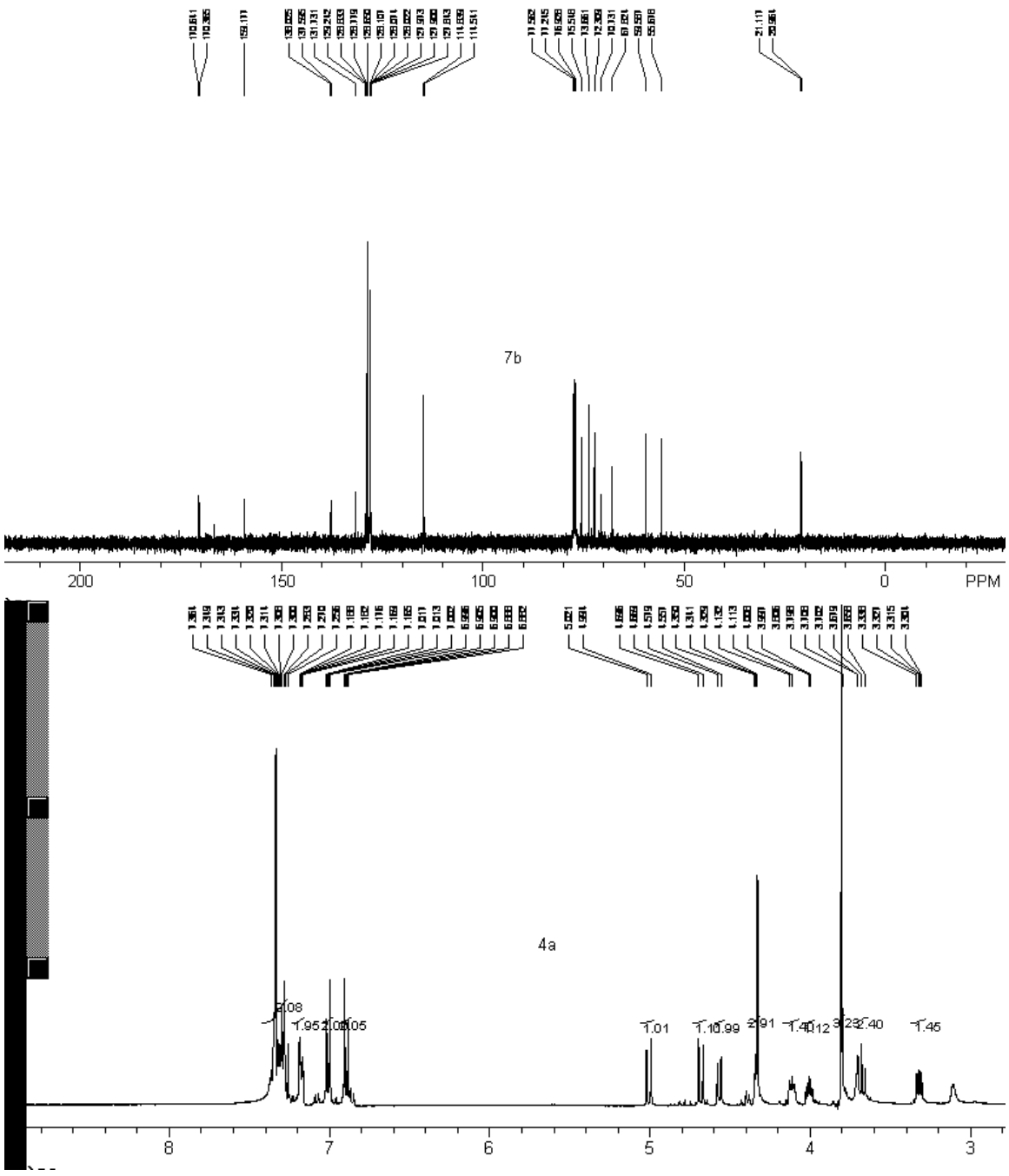
PPM






7b
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PPM
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2.40
1.45
8
7
6
5
4
3