Supporting Information I

Total Synthesis of 1,4a-di-*epi*-*ent*-Pancratistatin, Exemplifying a Stereodivergent Approach to Pancratistatin Isomers

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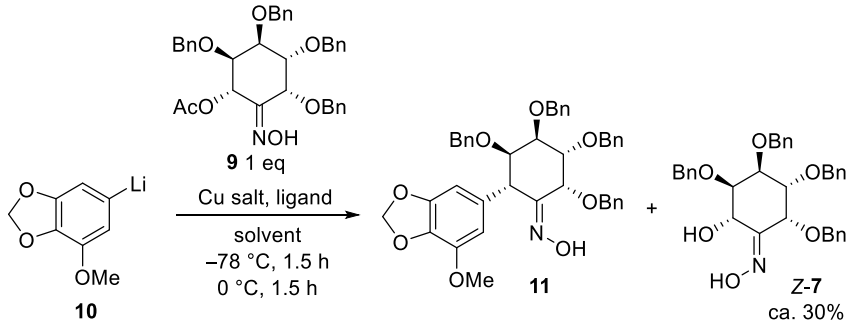
Contents

1. General Remarks

All anhydrous reactions were carried out under a positive atmosphere of argon in dried glassware. Dehydrated solvents were purchased for the reactions and used without further desiccation. Analytical thin-layer chromatography was performed on Merck TLC silica gel $60F_{254}$ silica gel plates. Visualization was accomplished with molibudenium phosphate, *p*-anisaldehyde, Hannessian's cocktail or ninhydrin. Column chromatography was performed using Silica Gel 60N (particle size 0.040–0.050 mm) purchased from Kanto Chemical Co., Inc. NMR spectra were recorded using a Bruker AV400N or Bruker AV500N in the stated solvents using tetramethylsilane as an internal standard. Chemical shifts were reported in parts per million (ppm) on the δ scale from an internal standard (NMR descriptions: s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sext = sextet, sept = septet, oct = octet, m = multiplet, br = broad). Coupling constants, *J*, are reported in Hertz. Mass spectra were recorded on a Waters/Micromass SQD2, MICROMASS® LCT PREMIERTM (ESI-TOF). Optical rotations were measured using a JASCO P-2200 polarimeter (concentration in $g \cdot dL^{-1}$). IR was measured using a JEOL FT-IR 6200. Melting point was determined on J-SCIENCE RFS-10. Unless otherwise noted, reagents were used without further purification.

2. Optimization of arylation of 8

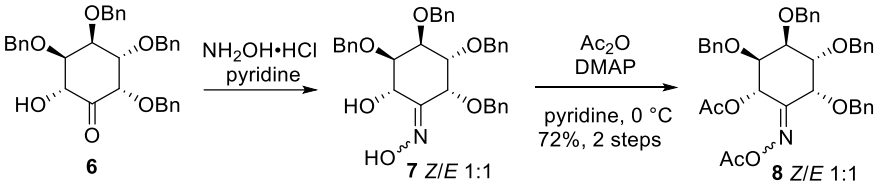
Table S1. Optimization of arylation of 9



entry	solvent	oxime (mmol)	Cu salt	Ar_2CuLi (mmol)	ligand (mmol)	yield of 11
1	THF	0.20	CuCN	0.40	none	22%
2	THF	0.20	CuCN	0.60	none	25%
3	THF	0.40	CuCN	1.20	none	29%
4	THF	0.40	CuCN	1.20	DME (2.40)	45%
5	THF	0.40	CuCN	1.20	TMEDA (2.40)	37%
6	Et_2O	0.40	CuCN	1.20	DME (2.40)	22%
7	toluene	0.40	CuCN	1.20	DME (2.40)	24%
8	THF	0.40	CuTc	1.20	DME (2.40)	28%
9	THF	0.40	CuOAc	1.20	DME (2.40)	13%
10	THF	1.60	CuCN	4.80	DME (9.60)	43%

3. Experimental procedure for the synthesis of compounds

(1*S*,3*R*,4*R*,5*S*,6*R*)-2-Acetoxyimino-3,4,5,6-tetrabenzyloxy-cyclohexyl acetate (9)



To a solution of **6**[1] (884 mg, 1.64 mmol) in pyridine (15 mL) was added $NH_2OH{\cdot}HCl$ (568 mg, 8.20 mmol), and the solution was stirred at rt for 1.5 h. The solution was diluted with EtOAc (20 mL), washed with H_2O (20 mL x 3) and brine, dried over Na_2SO_4, and concentrated under vacuum to give crude oxime as a pale brown oil (710 mg). To a solution of above-obtained product in CH_2Cl_2 (6.00 mL) were added pyridine (1.00 mL, 12.8 mmol), DMAP (10 mg, 0.26 mmol), and Ac_2O (1.30 mL, 12.8 mmol) at 0 °C. The mixture was stirred at the same temperature for 2 h, and then quenched by the addition of H_2O (10 mL). The whole was extracted with $CHCl_3$ (3 x 20 mL), and the combined organic layers were washed with brine (60 mL), dried over Na_2SO_4, concentrated in vacuo, and the residue was purified by silica gel column chromatography (EtOAc/hexane 1:4) to give **8** (754 mg, 1.18mmol, 72% over 2 steps) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40–7.25 (m, 40H), 6.04 (dd, *J* = 1.5, 4.0 Hz, 1H), 5.58 (dd, *J* = 1.5, 4.0 Hz, 1H), 5.08 (dd, *J* = 1.5, 3.5 Hz, 1H), 4.87 (d, *J* = 12.0 Hz, 1H), 4.78 (d, *J* = 12.0 Hz, 2H), 4.74 (dd, *J* = 4.5, 12.0 Hz, 2H), 4.66 (dd, *J* = 5.0, 12.5 Hz, 2H), 4.64 (d, *J* = 12.0 Hz, 2H), 4.63 (d, *J* = 12.0 Hz, 2H), 4.60 (d, *J* = 12.0 Hz, 2H), 4.57 (dd, *J* = 4.0, 12.0 Hz, 2H), 4.22 (d, *J* = 12.0 Hz, 1H), 4.31(d, *J* = 12.0 Hz, 1H), 4.28 (dd, *J* = 3.0, 10.0 Hz, 1H), 4.26 (dd, *J* = 3.0, 10.0 Hz, 1H), 4.06 (dd, *J* = 4.0, 10.0 Hz, 1 H), 3.97 (m, 2H), 3.95 (dd, *J* = 3.5, 10.0 Hz, 1H), 2.15 (s, 3H), 2.01 (s, 3H), 1.96 (s, 3H), 1.84 (s, 3H).

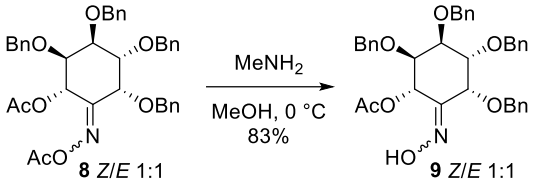
^{13}C NMR (101 MHz, $CDCl_3$): δ 169.5 (C), 169.4 (C), 167.8 (C x 2), 157.9 (C), 157.4 (C), 138.6 (C), 138.5 (C), 138.4 (C), 138.2 (C), 137.7 (C), 137.5 (C x 2), 137.3 (C), 128.3 (CH), 128.2 (CH), 127.8 (CH),127.7 (CH x 2), 127.6 (CH), 78.0 (CH), 77.9 (CH), 75.9 (CH), 75.7 (CH), 75.6 (CH), 73.8 (CH_2), 73.6 (CH_2), 73.4 (CH_2), 73.0 (CH_2), 72.6 (CH_2), 72.5 (CH_2), 71.1 (CH), 71.0 (CH_2), 69.2 (CH), 20.8 (CH_3), 20.7 (CH_3), 20.5 (CH_3), 19.4 (CH_3).

LRMS (ESI) *m/z* 660 (M + Na).

HRMS (ESI) (*m/z*): $[M + Na]^+$ calcd for $C_{38}H_{39}NO_8Na$, 660.2573; found, 660.2562.

IR (neat): 3542, 3087, 3063, 3030, 2870, 1779, 1752, 1637.

(1*S*,2*R*,3*S*,4*R*,5*R*)-2,3,4,5-Tetrabenzyloxy-6-hydroxyiminocyclohexyl acetate (9)



To an ice-cold solution of **8** (511 mg, 0.800 mmol) in MeOH (40 mL) was added a 0.2 M solution of $MeNH_2$ in MeOH (4 mL, 0.8 mmol) dropwise over 5 min. After that, the mixture was concentrated in vacuo, and the residue was purified by silica gel column chromatography (EtOAc/hexane 1:3) to give **9** (396 mg, 0.664 mmol, 81% yield) as a pale yellow oil.

$[\alpha]_D^{28}$ 71.73 (*c* 1.00, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40–7.27 (m, 40H), 6.27 (dd, *J* = 1.5, 4.0 Hz, 1H), 5.44 (dd, *J* = 1.5, 4.0 Hz, 1H), 5.28 (dd, *J* = 1.5, 4.0 Hz, 1H), 4.83 (t, *J* = 11.5 Hz, 2 H), 4.76 (d, *J* = 4.0 Hz, 1H), 4.73 (d, *J* = 4.0 Hz, 1H), 4.70 (d, *J* = 4.0 Hz, 2H), 4.66 (d, *J* = 4.0 Hz, 2H), 4.63 (d, *J* = 12.0 Hz, 2H), 4.62 (d, *J* = 12.0 Hz, 2H), 4.58 (d, *J* = 12.0 Hz, 2H), 4.55 (d, *J* = 12.0 Hz, 2H), 4.36 (dd, *J* = 6.5, 12.5 Hz, 2H), 4.30 (dd, *J* = 1.5, 4.0 Hz, 1H), 4.27 (t, *J* = 3.0 Hz, 1H), 4.01 (dd, *J* = 4.0, 10.0 Hz, 1H), 3,95 (t, *J* = 4.0 Hz, 1H), 3.90 (t, *J* = 3.5 Hz, 1H) 1.91 (s, 3H x 2).

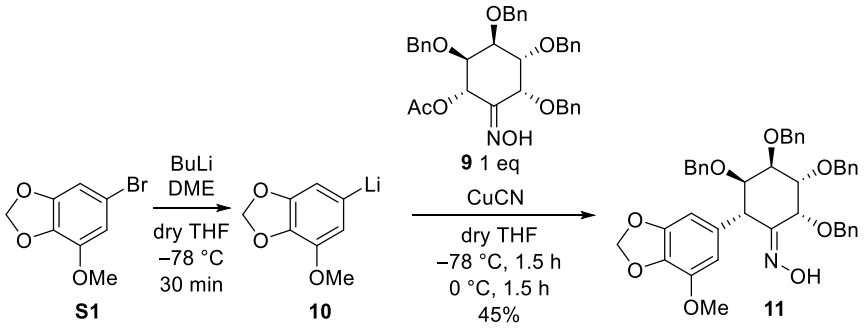
^{13}C NMR (125 MHz, $CDCl_3$): δ 170.0 (C x 2), 151.0 (C x 2), 150.4 (C x 2), 138.7 (C x 2), 138.6 (C x 2), 138.1 (C), 137.8 (C), 137.6 (C x 2), 128.3 (C x 4), 128.2 (C x 2), 128.1 (C), 128.0 (C), 127.9 (C), 127.8 (C), 127.6 (C), 127.5 (C x 3), 127.4 (C), 77.9 (CH), 76.0 (CH), 75.5 (CH), 75.3 (CH), 75.0 (CH), 73.6 (CH_2), 72.5 (CH_2), 72.4 (CH_2), 71.5 (CH), 71.0 (CH_2), 69.8 (CH_2), 67.4 (CH), 21.0 (CH_3), 20.8 (CH_3).

LRMS (ESI) *m/z* 618 (M + Na).

HRMS (ESI) (*m/z*): $[M + Na]^+$ calcd for $C_{36}H_{37}NO_7Na$, 618.2468; found, 618.2480.

IR (neat): 3324, 3063, 3030, 2872, 1740, 1496, 1454, 1371, 1227, 1113.

(2*R*,3*R*,4*R*,5*R*,6*S*)-2,3,4,5-Tetrabenzyloxy-6-(7-methoxybenzo[d][1,3]dioxol-5-yl)cyclohexan-1-one oxime (11)



A 20 mL flask was charged with 6-bromo-4-methoxybenzo[d][1,3]dioxole (**S1**)[2] (835 mg, 3.60 mmol) and THF (9.0 mL). The resulting solution was cooled to –78 °C and a 1.34 M hexane solution of BuLi (2.70 mL, 3.60 mmol) was added dropwise over 1 min, and then the mixture was stirred for 30 min to

give a solution of the organolithium reagent **10**. To a suspension of CuCN powder (162 mg, 1.80 mmol) in THF (4.5 mL) was added the solution of **10** via a cannula at 0 °C. The mixture was stirred at 0 °C for 20 min, and then cooled to –78 °C. After that, a solution of **9** (375 mg, 0.600 mmol) in THF (2 mL + 0.5 mL x2 for wash) was added to the mixture via a cannula. The resulting mixture was stirred at –78 °C for 1 h, and at 0 °C for 1 h, and then brought to rt. The reaction was quenched with saturated aqueous NH_4Cl (20 mL), and the whole was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, concentrated under reduced pressure, and purified by silica gel column chromatography (hexane/EtOAc 9:1) to give **11** (186 mg, 0.271 mmol, 45% yield) as a yellow oil.

$[\alpha]_D^{21}$ –18.31 (*c* 1.00, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.53 (s, 1H), 7.37–7.25 (m, 15H), 7.23–7.20 (m, 3H), 7.13–7.11 (m, 2H), 6.37 (s, 1H), 6.31 (s, 1H), 5.84 (dd, *J* = 1.5, 5.5 Hz, 2H), 5.31 (d, *J* = 3.5 Hz, 1H), 4.83 (d, *J* = 12.0 Hz, 1H), 4.70 (d, *J* = 12.0 Hz, 1H), 4.64 (d, *J* = 12.0 Hz, 1H), 4.63 (s, 2H), 4.57 (d, *J* = 12.0 Hz, 1H), 4.30 (dd, *J* = 2.5, 9.0 Hz, 1H), 4.27 (s, 2H) , 4.25 (t, *J* = 3.5 Hz, 1H), 4.00 (dd, *J* = 3.5, 8.5 Hz, 1H), 3.90 (d, *J* = 4 Hz, 1H), 3.53 (s, 3H).

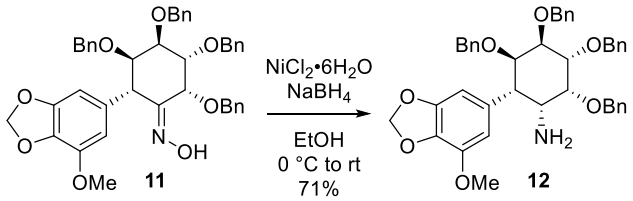
^{13}C NMR (125 MHz, $CDCl_3$): δ 156.0 (C), 148.8 (C), 143.2 (C), 138.8 (C), 138.6 (C), 138.2 (C), 137.8 (C), 133.8 (C), 132.8 (C),128.4 (CH), 128.3 (CH), 128.2 (CH x 2), 128.0 (CH), 127.9 (CH x 2), 127.8 (CH), 127.7 (CH x 2), 127.6 (CH x 3), 127.5 (CH), 127.4 (CH), 107.1 (CH), 101.5 (CH), 101.3 (CH_2), 77.9 (CH), 77.4 (CH), 76.7 (CH), 73.3 (CH_2), 72.4 (CH_2 x 2), 71.6 (CH_2), 68.6 (CH), 58.2 (CH), 56.5 (CH_3).

LRMS (ESI) *m/z* 710 (M + Na).

HRMS (ESI) (*m/z*): $[M+Na]^+$ calcd for $C_{42}H_{41}NO_8Na$, 710.2730; found, 710.2700.

IR (neat): 3333, 3063, 3030, 2927, 1718,1633, 1496, 1453, 1206, 1090, 1040.

(1*R*,2*R*,3*R*,4*R*,5*R*,6*S*)-2,3,4,5-Tetrabenzyloxy-6-(7-methoxybenzo[d][1,3]dioxol-5-yl)cyclohexan-1-amine (26)



To a mixture of **11** (135 mg, 0.196 mmol), EtOH (3.0 mL), and $NiCl_2 \cdot 6H_2O$ (132 mg, 0.392 mmol) was added $NaBH_4$ (106 mg, 2.85 mmol) portion-wise at 0 °C, and stirred at rt for 1.5 h. Then, the mixture was cooled to 0 °C and $NaBH_4$ (106 mg, 2.85 mmol) was added. The mixture was stirred at rt for 2 h. After that, the reaction mixture were added EtOAc (20 mL) and H_2O (20 mL). Then, the whole was filtered through celite pad, and successively washed with EtOAc (20 mL x 3). The

combined organic layers were washed with H_2O and brine, dried over Na_2SO_4, concentrated under reduced pressure, and purified by silica gel column chromatography (hexane/EtOAc 1:1 to 1:40) to give **12** (94 mg, 0.14 mmol, 71%) as a pale yellow oil.

$[\alpha]_D^{20}$ 5.02 (*c* 0.10, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37–7.25 (m, 16H), 7.20–7.16 (m, 2H), 7.13–7.10 (m, 2H), 6.47 (s, 1H), 6.45 (s, 1H), 5..94 (dd, *J* = 1.5, 6.0 Hz, 2H), 4.76 (d, *J* = 12.0 Hz, 1H), 4.64 (d, *J* = 12.0 Hz, 1H), 4.57 (d, *J* = 12.0 Hz, 1H), 4.56 (d, *J* = 12..0 Hz, 1H), 4.46 (d, *J* = 12.0 Hz, 1H), 4.39 (d, *J* = 12.0 Hz, 1H), 4.37 (d, *J* = 4.0 Hz, 2H), 4.22 (dd, *J* = 6.0 Hz, 12.0 Hz, 1H), 3.95–3.92 (m, 1H), 3.92–3.89 (m, 1H), 3.95–3.83 (m, 1H), 3.85 (s, 3H), 3.36 (t, *J* = 4.0 Hz, 1H), 3.31 (dd, *J* = 4.0 Hz, 12.0 Hz, 1H).

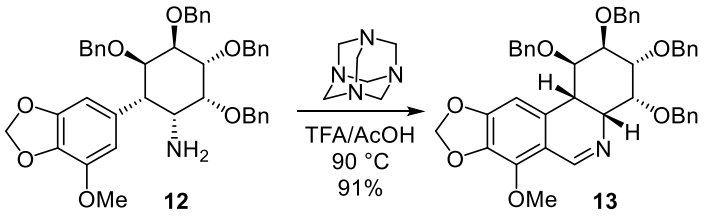
^{13}C NMR (100 MHz, $CDCl_3$): δ 148.4 (C), 143.2 (C), 138.6 (C), 138.5 (C), 138.4 (C), 138.1 (C), 128.4 (CH x 2), 128.3 (CH x3), 128.1 (CH x 2), 128.3 (CH), 128.0 (CH), 127.9 (CH), 127.8 (CH x 3), 127.7 (CH x 2), 127.6 (CH x 2), 127.5 (CH x 2), 108.9 (CH), 103.2 (CH), 101.2 (CH_2), 78.1 (CH), 76.2 (CH), 74.6 (CH), 73.8 (CH_2), 73.7 (CH), 73.0 (CH2), 71.7 (CH_2), 70.8 (CH_2), 56.5 (CH_3), 55.1 (CH), 47.3 (CH).

LRMS (ESI) *m/z* 696 (M + Na).

HRMS (ESI) (*m/z*): $[M+Na]^+$ calcd for $C_{42}H_{43}NO_7Na$, 696.2937; found, 696.2914.

IR (neat): 3395, 3085, 3061, 3029, 2877, 1633, 1508, 1452, 1433,1361, 1318, 1202, 1096, 1045, 928, 912, 735, 699.

(1*R*,2*R*,3*R*,4*R*,4a*R*,11b*S*)-1,2,3,4-Tetrabenzyloxy-7-methoxy-1,2,3,4,4a,11b-hexahydro-[1,3]dioxolo[4,5-j]phenanthridine (13)



To a solution of amine **12** (94 mg, 0.14 mmol) in AcOH/TFA (2.4 mL, 3:1) was added hexamethylenetetramine (112 mg, 0.75 mmol) at room temperature, and the resulting mixture was stirred at 90 °C for 5 h. Then, the reaction mixture was concentrated under reduced pressure. Then, MeOH (10 mL) and $NaHCO_3$ (4.8 g) were carefully added. After that, the mixture was loaded onto Celite pad which was successively washed with EtOAc (20 mL x3). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (20 mL) and brine (20 mL), dried over Na_2SO_4, concentrated under reduced pressure, and purified by silica gel column chromatography (hexane/EtOAc 1:2) to give **13** (87 mg, 0.13 mmol, 91%) as a yellow oil.

$[\alpha]_D^{28}$ 36.08 (*c* 1.01, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.64 (s, 1H), 7.37–7.10 (m, 18H), 7.00 (s, 2H), 6.51 (s, 1H), 5.93 (d, *J* = 8.0 Hz, 2H), 4.96 (d, *J* = 12.0 Hz, 1H), 4.70 (t, *J* = 12.0 Hz, 1H), 4.61 (d, *J* = 12.0 Hz, 2H), 4.54 (t, *J* = 12..0 Hz, 1H), 4.40 (d, *J* = 12.0 Hz, 1H), 4.04 (s, 3H), 4.04 (d, *J* = 12.0 Hz, 2H), 3.94 (d, *J* = 12.0 Hz, 2H), 3.89 (d, *J* = 8.0 Hz, 1H), 3.70 (s, 1H), 3.62 (d, *J* = 10.5 Hz, 1H) , 2.96 (dd, *J* = 4.5, 10.5 Hz, 1H).

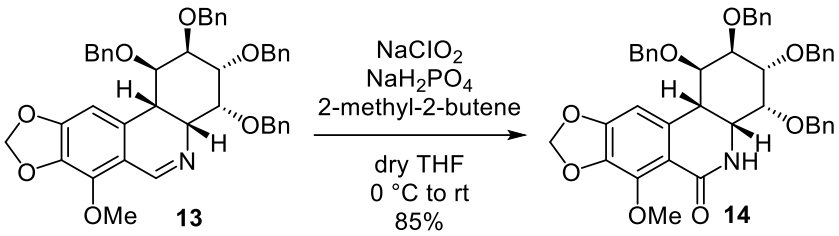
^{13}C NMR (125 MHz, $CDCl_3$): δ 153.1 (CH), 150.5 (C), 141.2 (C), 139.5 (C), 138.7 (C), 138.6 (C), 138.2 (C), 134.9 (C), 133.5 (C),128.6 (CH), 128.4 (CH), 128.3 (CH), 128.2 (CH), 128.1 (CH x 2), 128.1 (CH), 128.0 (CH), 127.9 (CH), 127.8 (CH x 2), 127.7 (CH), 127.6 (CH), 127.3 (CH), 127.2 (CH), 114.3 (C), 105.5 (CH), 101.1 (CH_2), 76.3 (CH), 75.4 (CH), 75.3 (CH), 74.3 (CH), 73.1 (CH_2), 73.0 (CH_2), 72.2 (CH_2), 71.0 (CH_2), 60.0 (CH_3),57,4 (CH), 36.7 (CH).

LRMS (ESI) *m/z* 706 (M + Na).

HRMS (ESI) (*m*/*z*): $[M+H]^+$ calcd for $C_{43}H_{41}NNaO_7$, 684.2961; found, 684.2949.

IR (neat): 3086, 3062, 3029, 2869, 1730, 1689, 1631, 1597, 1496, 1479, 1454, 1376, 1304, 1235, 1096, 1045, 1028, 910, 874, 734, 698.

(1*R*,2*R*,3*R*,4*R*,4a*R*,11b*S*)-1,2,3,4-Tetrabenzyloxy-7-methoxy-1,3,4,4a,5,11b-hexahydro-[1,3]dioxolo[4,5-j]phenanthridin-6(2*H*)-one (14)



To a solution of imine **13** (79 mg, 0.11 mmol) in THF (1.1 mL) were added 2-methyl-2-butene (0.64 mL, 5.5 mmol), water (1.1 mL), $NaH_2PO_4 \cdot 2H_2O$ (246 mg, 2.20 mmol), and $NaClO_2$ (330 mg, 2.20 mmol) at 0 °C. The mixture was warmed to rt slowly in an ice–water bath. Then, saturated aqueous Na_2SO_3 (5 mL) was added, and the whole was extracted with EtOAc (10 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4, concentrated in vacuo, and purified by column chromatography (EtOAc/hexane 1:1) to afford the title compound **14** (91 mg, 0.13 mmol, 85%) as pale yellow oil.

$[\alpha]_D^{28}$ 117.67 (*c* 1.02, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40–7.20 (m, 16H), 7.18 (dt, *J* = 8.0 Hz, 2 Hz, 4H), 7.07 (dd, *J* = 7.0 Hz, 6 Hz, 2H), 6.58 (s, 1H), 6.34 (s, 1H),6.00 (s, 2H), 4.67 (d, *J* = 12.0 Hz, 1H), 4.58 (d, *J* = 12.0 Hz, 1H), 4.54 (d, *J* = 12.0 Hz, 1H), 4.40 (d, *J* = 12..0 Hz, 2H), 4.38 (d, *J* = 12.0 Hz, 1H), 4.17 (m, 1H), 4.07 (d, *J* = 12.0 Hz, 2H), 4.06 (s, 3H), 3.93 (dd, *J* = 10.5 Hz, 2 Hz, 1H), 3.85 (m, 2H), 3.68 (t, *J* = 3.0 Hz, 1 H), 3.05 (dd, *J* = 10.5 Hz, 3 H, 1H).

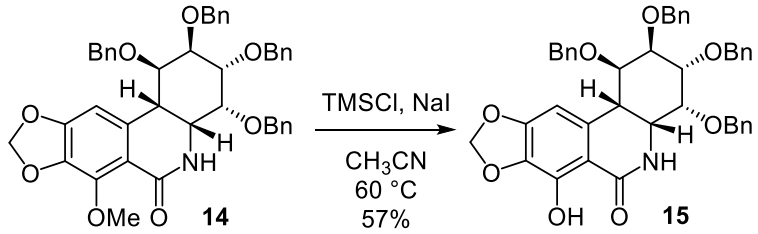
^{13}C NMR (125 MHz, $CDCl_3$): δ . 163.0 (C), 150.7 (C), 144.5 (C), 138.3 (C), 138.2 (C), 138.0 (C), 137.7 (C), 137.6 (C), 136.8 (C),128.4 (CH x 2), 128.2 (CH), 128.0 (CH), 127.8 (CH x 2), 127.7 (CH x2), 127.5 (CH), 115.8 (C), 105.3 (CH), 101.5 (CH_2), 77.2 (CH), 76.9 (CH), 75.4 (CH), 75.0 (CH), 73.4 (CH_2 x2), 72.9 (CH_2), 72.9 (CH), 70.6 (CH_2), 60.9 (CH_3), 50.4 (CH), 40.5 (CH).

LRMS (ESI) *m/z* 722 (M + Na).

HRMS (ESI) (*m/z*): $[M + Na]^+$ calcd for $C_{43}H_{41}NNaO_8$, 722.2730; found, 722.2701.

IR (neat): 3411, 3086, 3062, 3029, 2926, 2850, 1659, 1608, 1475, 1454, 1496, 1475, 1454, 1396, 1350, 1267, 1216, 1094, 1053, 1026, 888, 738, 698.

(1*R*,2*R*,3*R*,4*R*,4a*R*,11b*S*)-1,2,3,4-Tetrabenzyloxy-7-hydroxy-1,3,4,4a,5,11b-hexahydro-[1,3]dioxolo[4,5-j]phenanthridin-6(2*H*)-one (15)



To a solution of **14** (50 mg, 0.070 mmol) in CH_3CN (5 mL) were added NaI (10 mg 0.070 mmol) and TMSCl (4 v/v% in CH_3CN, 0.25 mL, 0.090 mmol) at rt, and the reaction mixture was stirred at 60 °C for 1 h. Then, the reaction mixture was quenched with H_2O at 0 °C, diluted with EtOAc, washed with brine, dried over Na_2SO_4, concentrated in vacuo, and purified by silica gel column chromatography (hexane/EtOAc 3:1) to give **15** (28 mg, 0.040 mmol, 57%) as a yellow oil.

$[\alpha]_D^{22}$ –3.95 (*c* 0.94, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 12.43 (s, 1H), 7.40–7.20 (m, 14H), 7.20–7.15 (m, 4H), 7.10–7.00 (m, 2H), 6.43 (s, 1H), 6.33 (s, 1H), 6.04 (s, 1H), 6.00 (s, 1H), 4.69 (d, *J* = 12.0 Hz, 1H), 4.51 (t, *J* = 12.0 Hz, 2H), 4.41 (t, *J* = 12.0 Hz, 2H), 4.44 (s, 1H), 4.40 (d, *J* = 10.0 Hz, 2H), 4.20 (t, *J* = 3.0 Hz, 1H), 4.63 (s, 2H), 3.88 (t, *J* = 3.0 Hz, 1H), 3.86 (t, *J* = 3.0 Hz, 1H), 3.82 (t, *J* = 3.0 Hz, 1H), 3.70 (t, *J* = 3.0 Hz, 1H), 3.10 (dd, *J* = 3.0 Hz, 10.0 Hz, 1H).

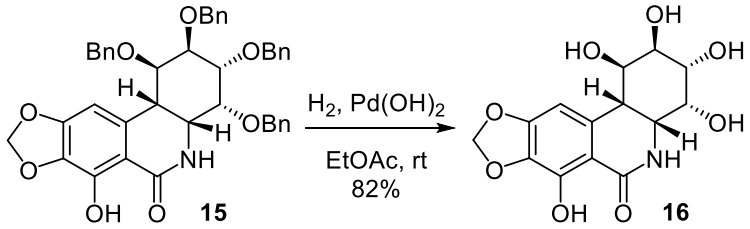
^{13}C NMR (100 MHz, $CDCl_3$): δ 168.4 (C), 151.7 (C),.145.8 (C), 138.3 (C), 138.1 (C), 137.7 (C), 137.4 (C), 135.2 (C), 133.2 (C), 128 (CH x 10), 127 (CH x 10), 107.0 (C), 102.7 (CH), 102.0 (CH_2), 76.3 (CH), 75.2 (CH), 75.0 (CH), 73.5 (CH_2), 73.2 (CH_2), 73.0 (CH), 72.9 (CH_2), 71.0 (CH_2), 51.4 (CH), 39.1 (CH).

LRMS (ESI) *m/z* 708 (M + Na).

HRMS (ESI) (*m/z*): $[M + Na]^+$ calcd for $C_{42}H_{39}NNaO_8$, 708.2573; found, 708.2555.

IR (neat): 3650, 3420, 3216, 1064, 3032, 2896, 1732, 1678, 1601, 1491, 1460, 1229, 1125, 1015, 838, 743, 696.

(1*R*,2*R*,3*R*,4*R*,4a*R*,11b*S*)-1,2,3,4,7-Pentahydroxy-1,3,4,4a,5,11b-hexahydro-[1,3]dioxolo[4,5-j]phenanthridin-6(2*H*)-one (16)



To a solution of **15** (25 mg, 0.035 mmol) in EtOAc (5 mL) at room temperature was added 20% $Pd(OH)_2/C$ (100 mg, 0.140 mmol) at rt, and stirred under 1 atom of H_2 atomosphere for 9 h. Then, the reaction mixture was filtered through filter paper, washed with MeOH, and the filtrate was concentrated in vacuo to afford **16** (9.3 mg, 0.029 mmol, 82%) as a white solid. Decomposes above 250 °C.

$[\alpha]_D^{22}$ 56.76 (*c* 0.55, MeOH).

^{1}H NMR (400 MHz, DMSO-d_6): δ 12.94 (s, 1H), 7.32 (s, 1H), 6.41 (s, 1H), 6.03 (s, 1H), 6.01 (s, 1H), 5.10 (s, 1H), 5.00 (s, 1H), 4.94 (s, 1H), 3.90–3.84 (m, 3H), 3.72–3.69 (m, 2H), 2.89 (d, *J* = 8.0 Hz, 1H).

^{1}H NMR (500 MHz, CD_3OD): δ 6.44 (s, 1H), 5.99 (s, 1H), 5.98 (s, 1H), 4.09 (t, *J* = 3.0 Hz, 1H), 4.03 (t, *J* = 3.0 Hz, 1H), 3.99 (t, *J* = 3.0 Hz, 1H), 3.94 (t, *J* = 3.0 Hz, 1H), 3.93–3.90 (m, 1H), 3.00 (dd, *J* = 3.0, 8.0 Hz, 1H).

^{13}C NMR (125 MHz, DMSO-d_6): δ 168.8 (C), 151.4 (C), 145.4 (C), 137.6 (C), 132.4 (C), 107.0 (C), 102.0 (CH_2), 102.0 (CH), 73.4 (CH), 73.3 (CH), 66.9 (CH), 66.8 (CH), 54.2 (CH), 40.0 (CH).

LRMS (ESI) *m/z* 324 $(M - H)^-$.

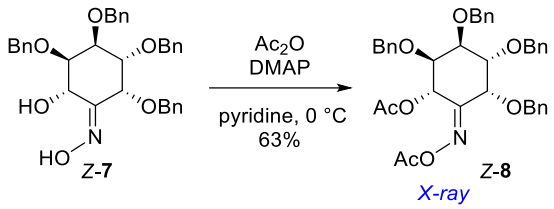
HRMS (ESI) (*m*/ *z*): $[M - H]^-$ calcd for $C_{14}H_{14}NO_8$, 324.0719; found, 324.0718.

IR (KBr): 2907, 1719, 1677, 1470, 1355, 1278, 1218, 1084, 1030, 880, 843, 815, 778.

4. Experimental procedure for X-ray.

Data collection and Structure solution details: Single crystal X-ray data for compound *Z*-**8** and **S3** were collected on a Rigaku XtaLaB P200 diffractometer Cu-Kα radiation. Data collection, cell refinement, data reduction and analysis were carried out with the CrysAlisPro (Rigaku Oxford Diffraction). These structures were solved by intrinsic phasing methods with the SHELXT program and refines using SHELXL[3] with anisotropic displacement parameters for non-H atoms. CCDC 2343575 and CCDC 2343576 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif.

(1*S*,3*R*,4*R*,5*S*,6*R*,*Z*)-2-Acetoxyimino-3,4,5,6-tetrabenzyloxy-cyclohexyl acetate (*Z*-8)



To a solution of *Z*-**7** (100 mg, 0.180 mml) in CH_2Cl_2 (2.00 mL) were added pyridine (0.11 mL, 0.98 mmol), DMAP (2 mg, 0.05 mmol), and Ac_2O (0.11 mL, 0.98 mmol) at 0 °C. The mixture was stirred at the same temperature for 1.5 h, and then quenched by the addition of H_2O (5 mL). The whole was extracted with $CHCl_3$ (3 x 3 mL), and the combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, concentrated in vacuo, and the residue was purified by silica gel column chromatography (EtOAc/hexane 1:4) to give *Z*-**8** (72 mg, 0.11 mmol, 63% over 2 steps) as a white solid of **mp** 108–109 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.40–7.25 (m, 20H), 6.04 (dd, *J* = 1.5, 4.0 Hz, 1H), 4.87 (d, *J* = 12.0 Hz, 1H), 4.74 (dd, *J* = 4.5, 12.0 Hz, 1H), 4.66 (d, *J* = 12.0 Hz, 1H), 4.64 (d, 12.0 Hz, 1H), 4.63 (d, 12.0 Hz, 1H), 4.61 (d, *J* = 12.0 Hz, 1H), 4.58 (d, *J* = 4.0 Hz, 1H), 4.55 (dd, *J* = 4.0, 12.0 Hz, 1H), 4.43 (d, *J* = 12.0 Hz, 1H), 4.28 (dd, *J* = 3.0, 10.0 Hz, 1H), 4.06 (dd, *J* = 4.0, 10.0 Hz, 1 H), 3.97 (t, *J* = 4.0 Hz, 2H), 2.16 (s, 3H), 1.85 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 169.5 (C), 167.7 (C), 157.4 (C), 138.6 (C), 138.3 (C), 137.7 (C), 137.3 (C), 128.5 (CH), 128.4 (CH), 128.3 (CH), 128.2 (CH), 127.9 (CH), 127.8 (CH x 2), 127.7 (CH x 2), 78.0 (CH), 75.7 (CH), 75.6 (CH), 73.8 (CH_2), 73.4 (CH_2), 73.0 (CH_2), 72.6 (CH_2), 72.5 (CH_2), 71.2 (CH), 71.1 (CH_2), 70.8 (CH), 20.5 (CH_3), 19.4 (CH_3).

LRMS (ESI) *m/z* 660 (M + Na).

HRMS (ESI) (*m/z*): $[M + Na]^+$ calcd for $C_{38}H_{39}NO_8Na$, 660.2573; found, 660.2562.

IR (neat): 3542, 3087, 3063, 3030, 2870, 1779, 1752, 1637.

X-ray crystallographic data for compound *Z*-**8** (CCDC 2343575).

Single crystals of *Z*-**8** were obtained by slow evaporation of a solution containing *Z*-**8** in chloroform at room temperature. A suitable crystal was selected and the crystal data and structure refinement results for compound *Z*-**8** are listed in the Table S2.

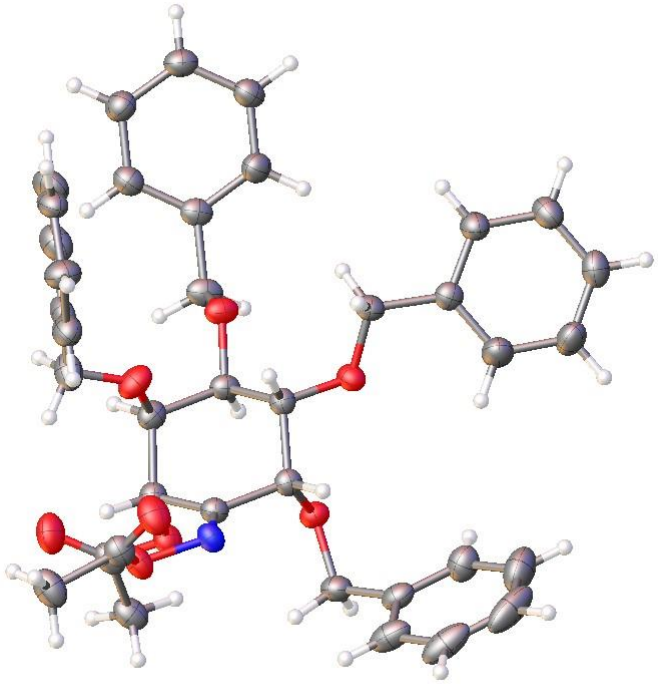


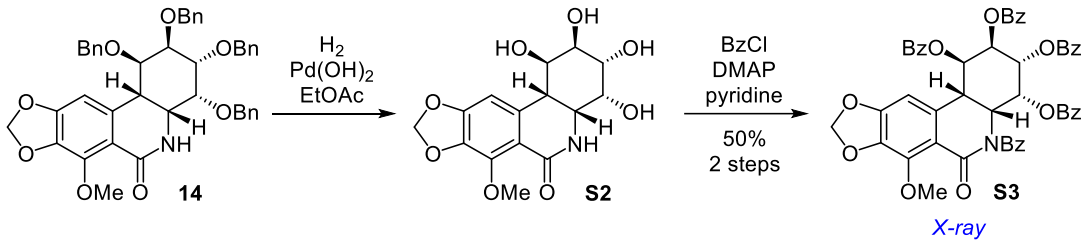
Figure S1. ORTEP view of the compound *Z*-**8** with thermal ellipsoids drawn at the 50% probability level

Table S2 Crystal data and structure refinement for *Z*-8.

Identification code	211228YYO_auto
Empirical formula	$C_{38}H_{39}NO_8$
Formula weight	637.70
Temperature/K	93.0
Crystal system	orthorhombic
Space group	$P2_12_12_1$
a/Å	7.7775(2)
b/Å	19.6476(4)
c/Å	22.0751(5)
α/°	90
β/°	90

γ/°	90
Volume/Å^3	3373.28(13)
Z	4
ρ_{calc}g/cm^3	1.256
μ/mm^{-1}	0.717
F(000)	1352.0
Crystal size/mm^3	0.1 × 0.1 × 0.1
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	6.022 to 144.534
Index ranges	-9 ≤ h ≤ 8, -23 ≤ k ≤ 23, -26 ≤ l ≤ 27
Reflections collected	24441
Independent reflections	6500 [R_{int} = 0.0373, R_{sigma} = 0.0251]
Data/restraints/parameters	6500/174/491
Goodness-of-fit on F^2	1.110
Final R indexes [I>=2σ (I)]	R_1 = 0.0374, wR_2 = 0.0987
Final R indexes [all data]	R_1 = 0.0411, wR_2 = 0.1048
Largest diff. peak/hole / e Å^{-3}	0.18/-0.18
Flack parameter	-0.05(9)

(1*R*,2*R*,3*R*,4*R*,4a*R*,11b*S*)-5-Benzoyl-7-methoxy-6-oxo-1,2,3,4,4a,5,6,11b-octahydro-[1,3]dioxolo[4,5-j]phenanthridine-1,2,3,4-tetrayl tetrabenzoate (S3)



To a solution of **14** (147 mg, 0.210 mmol) in EtOAc (10 mL) was added 20 % $Pd(OH)_2$/C (630 mg, 0.840 mmol) at room temperature, and stirred under 1 atom of H_2 atomosphere for 9 h. Then, the reaction mixture was filtered through filter paper, washed with MeOH, and the filtrate was concentrated in vacuo to afford **S2** (73 mg) as a white solid.

To a solution of the above-obtained solid in pyridine (1.5 mL) were added DMAP (6.0 mg, 0.15 mmol), and BzCl (0.40 mL, 3.4 mmol) at 0 °C, and the reaction mixture was stirred at room temperature for

2 h. After that, the reaction was quenched with H_2O (10 mL). The whole was extracted with EtOAc (3 x 20 mL), washed with brine (60 mL), dried over Na_2SO_4, concentrated in vacuo, and purified by silica gel column chromatography (EtOAc/hexane 1:2) to give **S3** (92 mg, 0.11 mmol, 50%) as a white solid of **mp** 115–117°C.

$[\alpha]_D^{22}$ –35.25 (*c* 1.00, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.14 (d, *J* = 7.0 Hz, 2H), 7.89 (d, *J* = 7.0 Hz, 2H), 7.70 (d, *J* = 7.0 Hz, 2H), 7.66 (t, *J* = 7.0 Hz, 2H), 7.62–7.44 (m, 7H), 7.44–7.28 (m, 9H), 7.19 (t, *J* = 8.0 Hz, 2 H), 6.78 (t, *J* = 3.0 Hz, 1H), 6.40 (t, *J* = 3.0 Hz, 1H), 6.32 (t, *J* = 3.0 Hz, 1H), 6.15 (s, 1H), 6.08 (s, 1H), 5.97 (dd, *J* = 3.0 Hz, 1H), 5.56 (dd, *J* = 3.0 Hz, 1H), 4.02 (dd, *J* = 3.0 Hz, 1H), 3.43 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 173.3 (C), 166.4 (C), 165.5 (C),.165.2 (C), 164.9 (C), 162.3 (C), 153.4 (C), 145.5 (C), 137.3 (C), 135.8 (C), 133.9 (CH), 133.6 (CH), 133.5 (C), 133.3 (CH), 131.4 (CH), 130.2 (CH), 130.0 (CH), 129.8 (CH), 129.7 (CH), 129.6 (CH), 128.7 (CH), 128.5 (CH), 128.3 (CH), 128.1 (CH), 128.0 (CH), 102.0 (CH_2), 99.0 (CH), 70.9 (CH), 69.0 (CH), 68.6 (CH), 68.1 (CH), 60.0 (CH_3), 51.4 (CH), 40.2 (CH).

LRMS (ESI) *m/z* 882 (M + Na).

HRMS (ESI) (*m/z*): $[M + Na]^+$ calcd for $C_{50}H_{37}NNaO_{13}$, 882.2163; found, 882.2177.

IR (KBr): 1730, 1616, 1451, 1263, 1176, 1097, 1068, 1030, 880, 799, 712.

X-ray crystallographic data for compound **S3** (CCDC 2343576).

Single crystals of **S3** were obtained by slow evaporation of a solution containing **S3** in the mixture of methylene chloride and methanol at room temperature. A suitable crystal was selected and the crystal data and structure refinement results for compound **S3** are listed in the Table S3.

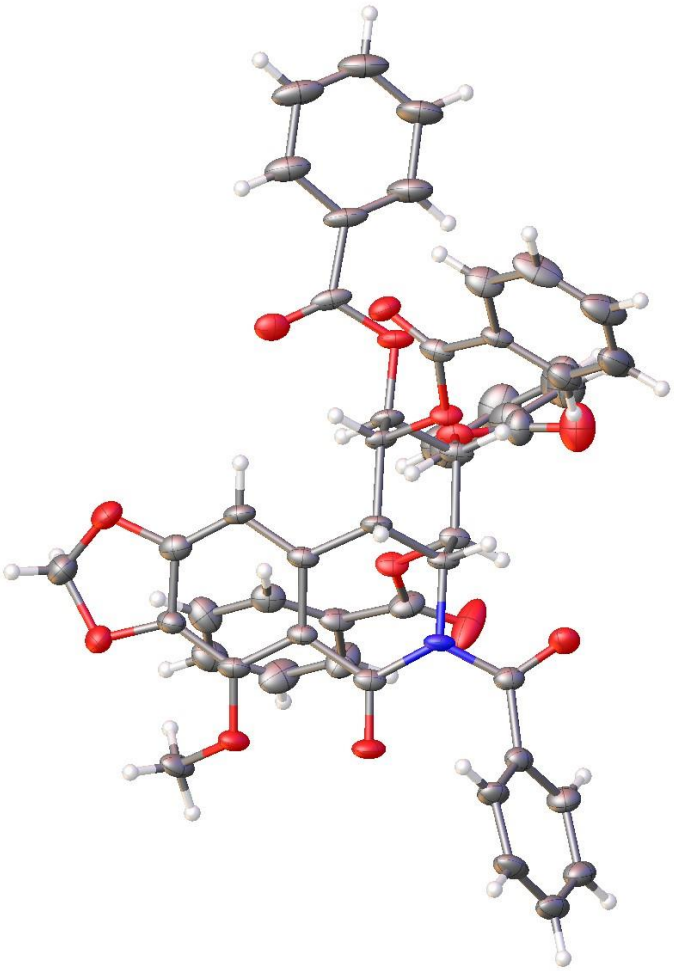


Figure S2. ORTEP view of the compound **S3** with thermal ellipsoids drawn at the 50% probability level (a solvent molecule is omitted)

Table S3 Crystal data and structure refinement for S3.

Identification code	220324yy2_auto
Empirical formula	$C_{51}H_{39}Cl_2NO_{13}$
Formula weight	944.73
Temperature/K	93.00
Crystal system	monoclinic
Space group	$P2_1$
a/Å	10.82580(10)
b/Å	13.1828(2)
c/Å	15.3126(2)

α/°	90
β/°	79.3630(10)
γ/°	90
Volume/Å^3	2147.78(5)
Z	2
ρ_{calc}g/cm^3	1.461
μ/mm^{-1}	1.976
F(000)	980.0
Crystal size/mm^3	0.2 × 0.2 × 0.1
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	5.872 to 145.766
Index ranges	-13 ≤ h ≤ 13, -14 ≤ k ≤ 16, -18 ≤ l ≤ 18
Reflections collected	55436
Independent reflections	7908 [R_{int} = 0.0881, R_{sigma} = 0.0340]
Data/restraints/parameters	7908/1/605
Goodness-of-fit on F^2	1.063
Final R indexes [I>=2σ (I)]	R_1 = 0.0816, wR_2 = 0.2214
Final R indexes [all data]	R_1 = 0.0849, wR_2 = 0.2299
Largest diff. peak/hole / e Å^{-3}	1.02/-1.12
Flack parameter	0.086(10)

5. Experimental procedure for biological assays

Cell viability assay

Human hepatoma Hep3B l lines (1×10^4) were plated on 96 well plate and incubated with Dulbecco's modified Eagle's medium (DMEM) containing 10% fetal bovine serum (FBS) for a day. The medium was replaced with DMEM 10% FBS containing compounds at 37 ◦C with 5% CO_2 for 24 hours. After treatment of compounds, the cells were treated with the Cell Counting Kit-8 (WST-8; Dojindo) according to the manufacturer's instructions. Briefly, the WST-8 reagent solution (10 μL) was added to each well of a 96 well microplate containing 100 μL of cells in the culture medium, and the plate was incubated for 2 h at 37 °C. Absorbance was measured at 450 nm using a microplate reader (Nivo Multimode Microplate Reader, PerkinElmer). Cell viability was expressed as a percentage of untreated (compound untreated). Cell survival rate (%) = (a-c) / (b-c) × 100 (a = absorbance at each concentration of compounds, b = absorbance at untreated, and c = absorbance of the blank).

Ferroptosis inhibitory activity assay

Hep3B cells (1×10^4) were plated on 96 well plate and incubated with DMEM containing 10% Fetal bovine serum (FBS) for overnight. The medium was replaced with DMEM 10% FBS containing compounds (10 μM) and 10 μM of erastin as a ferroptosis inducer. After simultaneous treatment of erastin and compounds at 37 ◦C with 5% CO_2 for 24 hours, the cells were treated with the Cell Counting Kit-8 according to the manufacturer's instructions. Ferrostatin-1 (10 μM) was used as positive controls for ferroptosis inhibitor.

Statistics

Group comparisons were performed using Student's t-test. Data are expressed as the mean ± standard deviation, and values were considered statistically significant at $P < 0.05$.

6. Reference

(1) a) Kang, B.; Sutou, T.; Wang, Y.; Kuwano, S.; Yamaoka, Y.; Takasu, K.; Yamada, K. *Adv. Synth. Catal.* **2015**, *357*, 131. b) Kang, B.; Wang, Y.; Kuwano, S.; Yamaoka, Y.; Takasu, K.; Yamada, K. *Chem. Commun.* **2017**, *53*, 4469.

(2) Loriot, M.; Robin, J. P.; Brown, E. *Tetrahedron* **1984**, *40*, 2529.

(3) G. M. A. Sheldrick. *Acta Crystallogr. A: Found. Adv.* **2008**, *64*, 112.