Total Synthesis of Ecteinascidin 743

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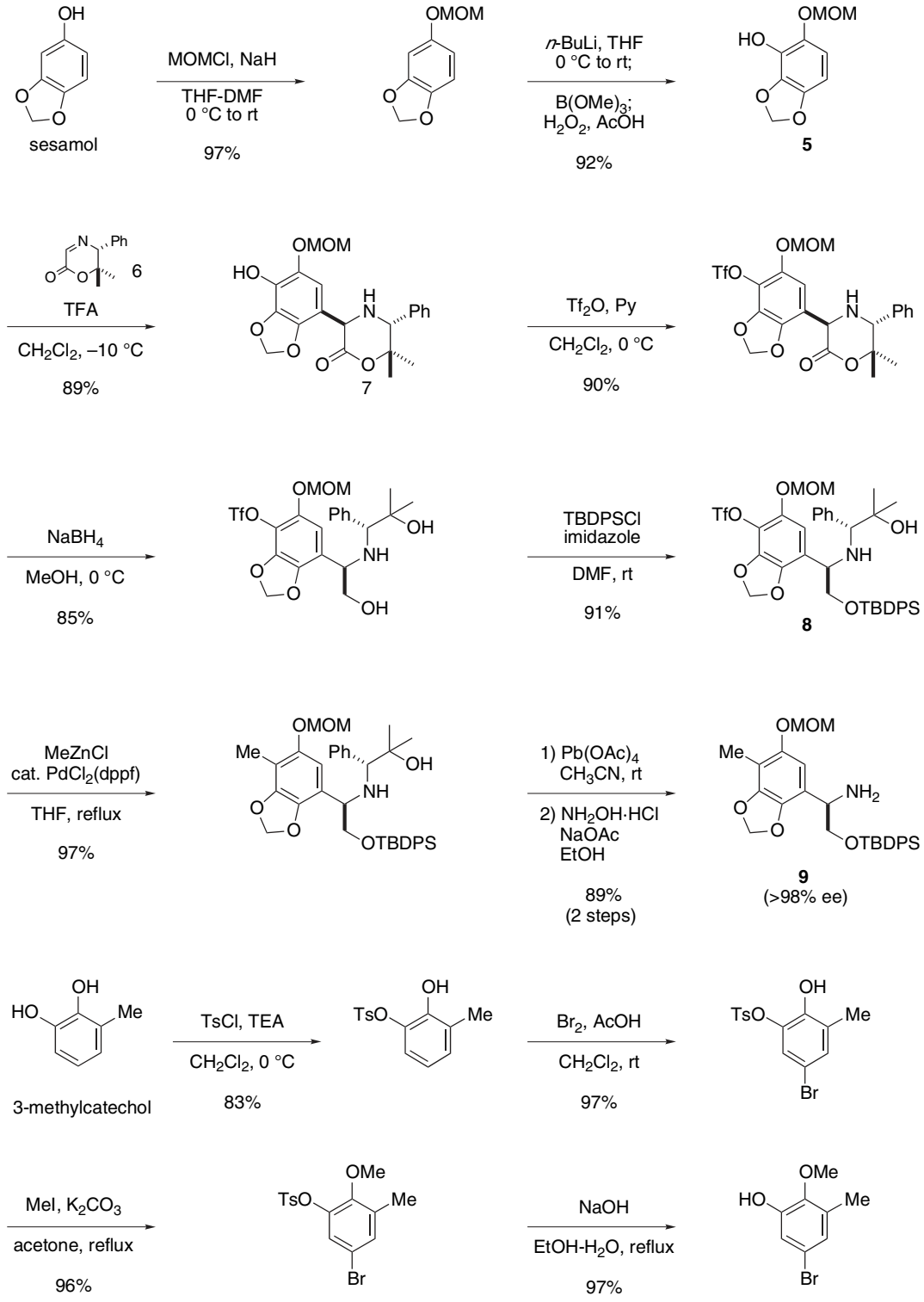
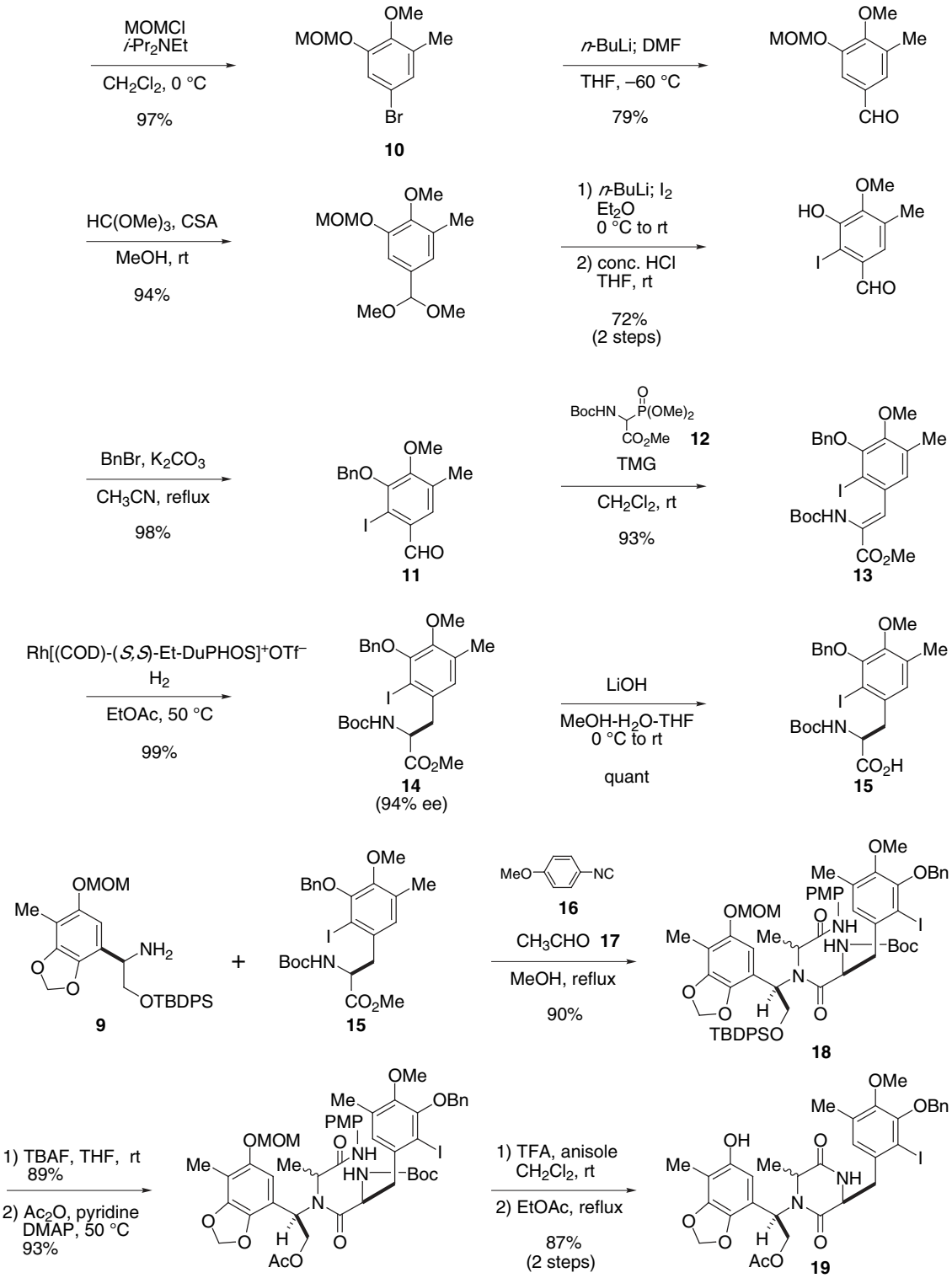
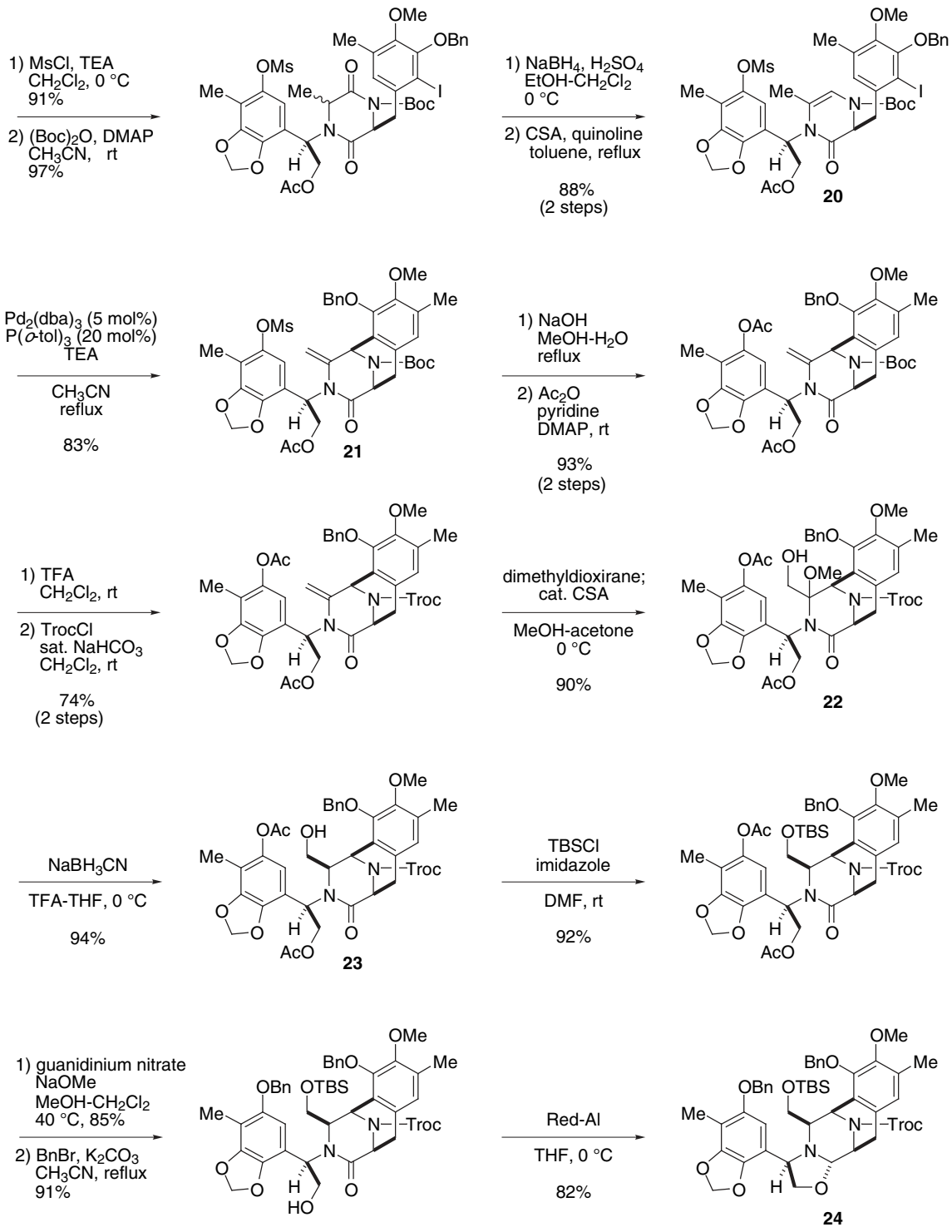
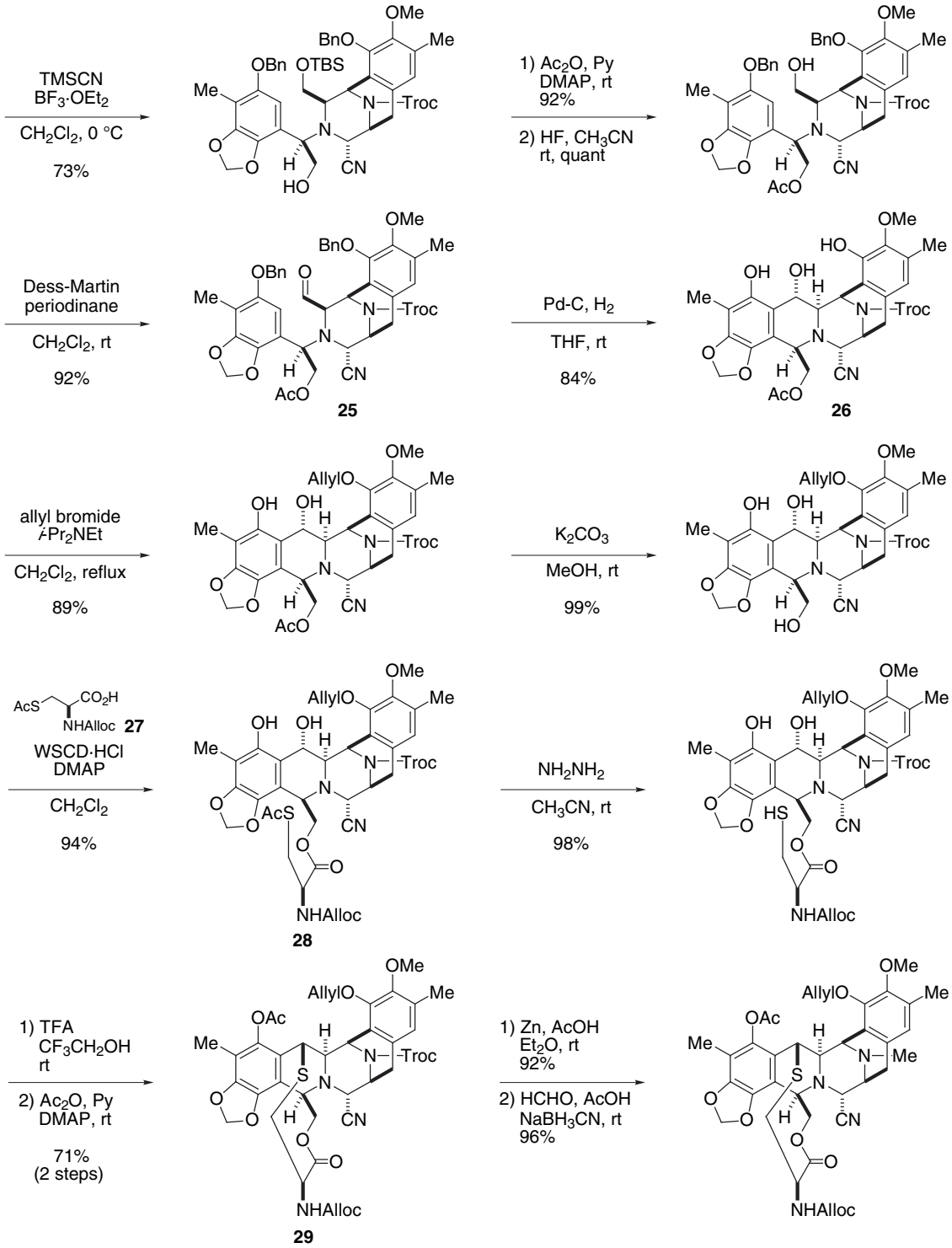
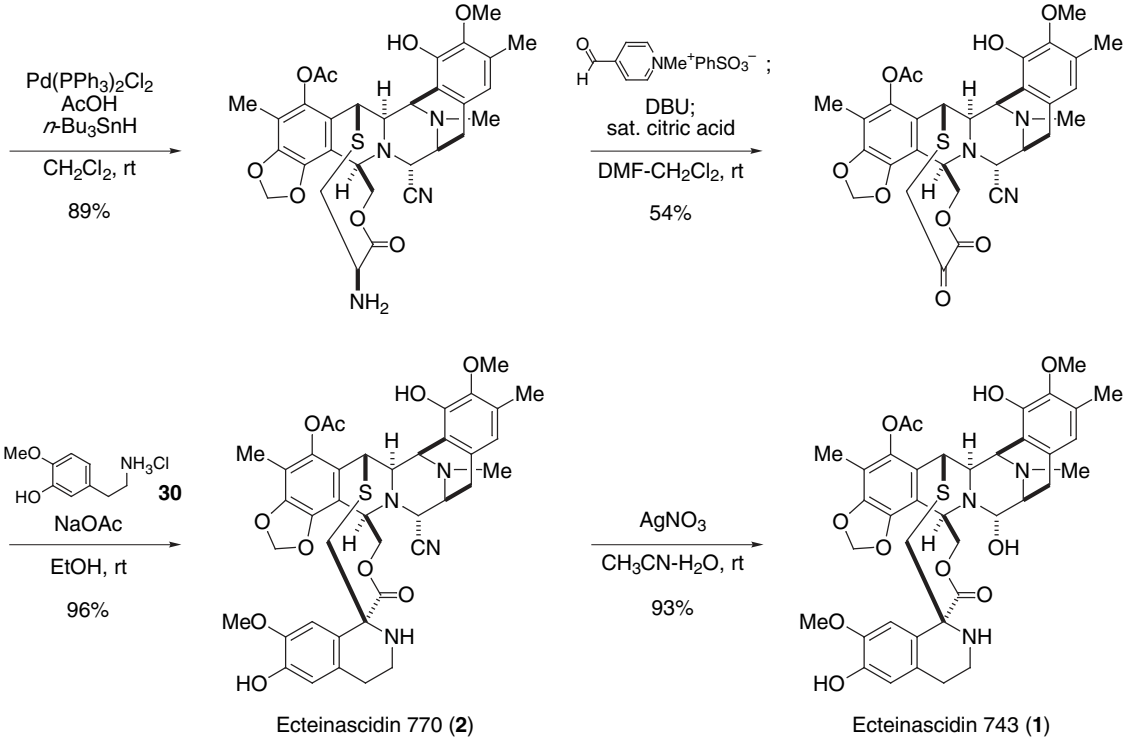
Supporting Information




MOMCl
i-Pr2NEt
CH2Cl2, 0 °C
97%
10
n-BuLi; DMF
THF, –60 °C
79%
HC(OMe)3, CSA
MeOH, rt
94%
1) n-BuLi; I2
Et2O
0 °C to rt
2) conc. HCl
THF, rt
72%
(2 steps)
BnBr, K2CO3
CH3CN, reflux
98%
11
12
TMG
CH2Cl2, rt
93%
13
Rh[(COD)-(S,S)-Et-DuPHOS]+OTf–
H2
EtOAc, 50 °C
99%
14
(94% ee)
LiOH
MeOH-H2O-THF
0 °C to rt
quant
15
9
16
CH3CHO 17
MeOH, reflux
90%
18
1) TBAF, THF, rt
89%
2) Ac2O, pyridine
DMAP, 50 °C
93%
1) TFA, anisole
CH2Cl2, rt
2) EtOAc, reflux
87%
(2 steps)
19


1) MsCl, TEA
CH2Cl2, 0 °C
91%
2) (Boc)2O, DMAP
CH3CN, rt
97%
1) NaBH4, H2SO4
EtOH-CH2Cl2
0 °C
2) CSA, quinoline
toluene, reflux
88%
(2 steps)
20
Pd2(dba)3 (5 mol%)
P(o-tol)3 (20 mol%)
TEA
CH3CN
reflux
83%
21
1) NaOH
MeOH-H2O
reflux
2) Ac2O
pyridine
DMAP, rt
93%
(2 steps)
1) TFA
CH2Cl2, rt
2) TrocCl
sat. NaHCO3
CH2Cl2, rt
74%
(2 steps)
dimethyldioxirane;
cat. CSA
MeOH-acetone
0 °C
90%
22
NaBH3CN
TFA-THF, 0 °C
94%
23
TBSCl
imidazole
DMF, rt
92%
1) guanidinium nitrate
NaOMe
MeOH-CH2Cl2
40 °C, 85%
2) BnBr, K2CO3
CH3CN, reflux
91%
Red-Al
THF, 0 °C
82%
24


TMSCN
BF3·OEt2
CH2Cl2, 0 °C
73%
1) Ac2O, Py
DMAP, rt
92%
2) HF, CH3CN
rt, quant
Dess-Martin
periodinane
CH2Cl2, rt
92%
Pd-C, H2
THF, rt
84%
25
26
allyl bromide
iPr2NEt
CH2Cl2, reflux
89%
K2CO3
MeOH, rt
99%
AcS
CO2H
NHAlloc 27
WSCD·HCl
DMAP
CH2Cl2
94%
NH2NH2
CH3CN, rt
98%
28
1) TFA
CF3CH2OH
rt
2) Ac2O, Py
DMAP, rt
71%
(2 steps)
1) Zn, AcOH
Et2O, rt
92%
2) HCHO, AcOH
NaBH3CN, rt
96%
29



Ecteinascidin 770 (**2**)

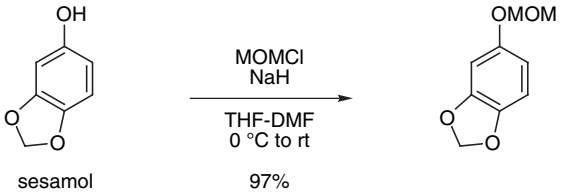
Ecteinascidin 743 (**1**)

Experimental Section

General

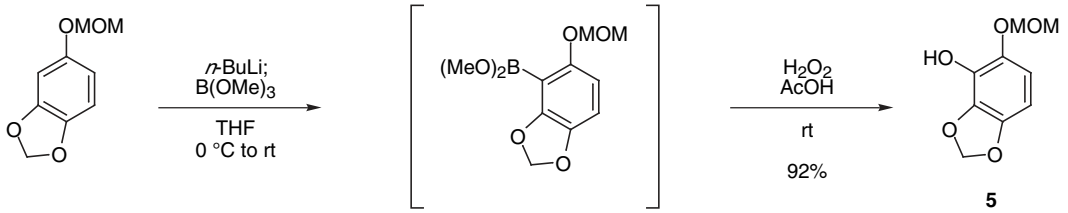
All non-aqueous reactions were carried out in oven-dried glass tubes under a slight positive pressure of argon unless otherwise noted. CH_2Cl_2 and toluene were distilled from calcium hydride. Dehydrated THF, Et_2O, CH_3CN, DMF, MeOH, and EtOH were purchased from Kanto Chemical Co., Inc. and stored over molecular sieves 3A or 4A. Pyridine, Et_3N and *i*-Pr_2NEt were dried over KOH. All other reagents were commercially available and used without further purification. Preparative flash chromatography was performed using Silica Gel 60 (spherical, 40-100 μm) purchased from Kanto Chemical Co., Inc. ^1H and ^{13}C NMR spectra were obtained on JEOL LA-400 MHz. IR spectra were recorded on a JASCO FT/IR-410 Fourier Transform Infrared Spectrophotometer. Mass spectra (MS) were obtained on a JEOL JMS-GCmate. Optical rotations were measured on a JASCO DIP-1000.

MOM Ether



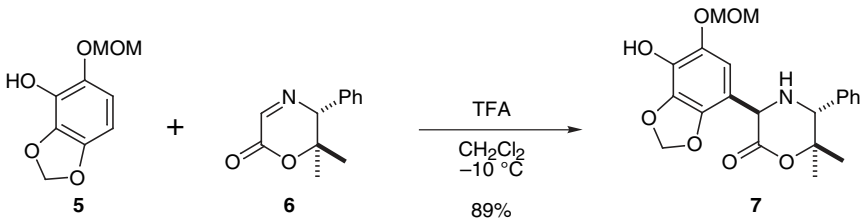
To a solution of NaH (60% w/w in mineral oil, 40 g, 1.0 mol, 1.0 equiv) in a mixture of THF (500 ml) and DMF (200 ml) at 0 °C was slowly added sesamol (138 g, 1.0 mol) in THF (300 ml), and the mixture was stirred at room temperature for 30 min. The reaction mixture was cooled to 0 °C, and to the solution was added chloromethyl methyl ether (84.5 g, 1.05 mol, 1.05 equiv) dropwise. The resulting slurry was allowed to warm to room temperature and stirred for additional 1h. To the reaction mixture were added *n*-hexane and H_2O, and the organic layer was separated. The aqueous phase was further extracted with hexane (200 ml x 2), and the combined organic phase was concentrated under reduced pressure. The residue was dissolved in *n*-hexane and washed with saturated aqueous NaCl. The organic phase was dried over Na_2SO_4, and concentrated under reduced pressure, and the crude product was purified by distillation (103 °C/0.35 mmHg) to afford the MOM ether (177 g, 0.97 mol, 97%) as a colorless oil. IR (neat film) 1244, 1215, 1176, 1153, 1099, 1069, 1040, 1004, 940, 922, 842, 813 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.71 (d, J = 8.4 Hz, 1H) 6.63 (s, 1H), 6.49 (d, J = 8.4 Hz, 1H), 5.90 (s, 2H), 5.08 (s, 2H), 3.46 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.5, 148.1, 142.5, 108.4, 108.0, 101.2, 99.7, 95.4, 55.8; HRMS (FAB^+) m/z: Calcd. for $C_9H_{10}O_4$ (M^+) 182.0579, found 182.0563.

Phenol 5



To a solution of the MOM ether (5.44 g, 29.9 mmol) in THF (100 ml) at 0 °C was added *n*-BuLi (3.02 M solution in *n*-hexane, 11.0 ml, 33.2 mmol, 1.1 equiv), and the mixture was allowed to warm to room temperature. After cooling to 0 °C, to the solution were sequentially added trimethylboronate (4.10 ml, 36.1 mmol, 1.2 equiv), AcOH (3.4 ml, 59 mmol, 2.0 equiv), and 7% aqueous H_2O_2 (26 ml, 60 mmol, 2.0 equiv). The resulting mixture was allowed to warm to room temperature and stirred for additional 4.5 h. To the reaction mixture were added saturated aqueous $(NH_4)_2SO_4$ (100 ml) and saturated aqueous Na_2SO_3 (50 ml), and the organic phase was separated. The aqueous phase was further extracted with $CHCl_3$, and the combined organic phase was concentrated under reduced pressure. The residue was diluted with $CHCl_3$ and washed with saturated aqueous $NaHCO_3$, and the organic phase was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash column chromatography (70% EtOAc in *n*-hexane) to afford **5** (5.42g, 27.3 mmol, 92%) as a yellow oil. IR (neat film) 3439, 1652, 1493, 1292, 1245, 1157, 1044, 932, 791cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.55 (d, *J* = 8.4 Hz, 1H), 6.45 (br, 1H), 6.32 (d, *J* = 8.4 Hz, 1H), 5.94 (s, 2H), 5.09 (s, 2H), 3.50 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.3, 141.3, 134.4, 132.0, 109.2, 101.6, 99.1, 97.3, 60.4, 56.3; HRMS (FAB$^+$) m/z: Calcd. for $C_9H_{10}O_5$ (M^+) 198.0528, found 198.0558.

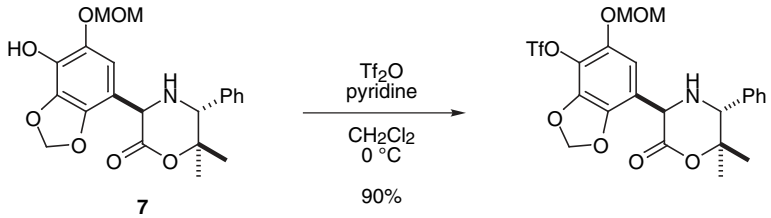
Aminolactone 7



5 **6** 89% **7**

To a mixture of **5** (19.8 g, 100 mmol) and **6** (20.3 g, 100 mmol) in CH_2Cl_2 (200 ml) at –10 °C was slowly added TFA (38 ml, 0.49 mol, 5 equiv) over 1.5 h. After addition was completed, the reaction mixture was stirred at this temperature for additional 40 min. To the reaction mixture was carefully added a mixture of Na_2CO_3 (40 g, 0.38 mol, 3.8 equiv) and H_2O (200 ml), and the resulting mixture was extracted with CH_2Cl_2. The organic layer was separated, and the aqueous phase was further extracted with CH_2Cl_2 (100 ml). The combined organic phase was washed with saturated aqueous NaCl, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (30% EtOAc in *n*-hexane) to afford **7** (35.6g, 89 mmol, 89%) as a yellow amorphous. $[\alpha]_D^{27}$ –75 ° (c = 1.7, $CHCl_3$); IR (neat film) 3327, 1724, 1506, 1457, 1299, 1151, 1118, 1082, 1049, 1101, 934 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.29-7.37 (m, 5H), 6.51 (s, 1H) 5,93 (s, 1H), 5,91 (s, 1H), 5.09 (d, *J* = 8,0 Hz, 1H), 5.05 (d, *J* = 8.0 Hz, 1H), 5.03 (s, 1H) 4.15 (s, 1H), 3.51 (s, 3H), 2.03 (br, 1H), 1.37 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.0, 141.8, 141.4, 138.2, 134.8, 132.4, 128.4, 128.3, 128.3, 111.6, 110.0, 101.9, 86.7, 61.0, 57.1, 56.4, 26.6, 22.0; HRMS (FAB^+) m/z: Calcd. for $C_{21}H_{23}NO_7$ (M^+) 401.1475, found 401.1467.

Triflate

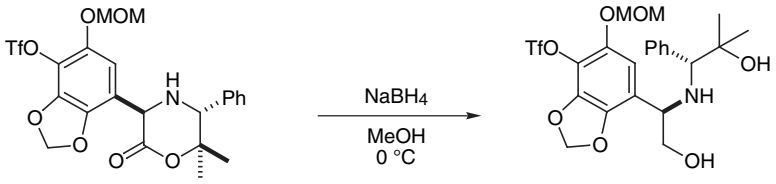


7 90%

To a mixture of **7** (242 mg, 0.603 mmol) and pyridine (0.15 ml, 1.9 mmol, 3.1 equiv) in CH_2Cl_2 (3.0 ml) at 0 °C was added Tf_2O (0.13 ml, 0.77 mmol, 1.3 equiv), and the resulting mixture was stirred for 5 minutes, poured into saturated aqueous $NaHCO_3$, and extracted with EtOAc. The organic phase was sequentially washed with 1M aqueous HCl, saturated aqueous $NaHCO_3$, and saturated aqueous NaCl. The solution was dried over anhydrous $MgSO_4$, and concentrated under reduced pressure, and the residue was purified by flash column chromatography (50% EtOAc in *n*-hexane) to afford the triflate (290 mg, 0.544 mmol, 90%) as a white foam. $[\alpha]_D^{26}$ –32 ° (c = 2.6, $CHCl_3$); IR (neat film) 3333, 1733, 1496, 1462, 1427, 1299, 1216, 1138, 1056, 999, 979, 936, 832 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32-7.40 (m, 5H), 6.71 (s, 1H) 6,06 (s, 1H), 6.03 (s, 1H), 5.19 (d, *J* = 5,8 Hz, 1H), 5.14 (d, *J* = 5.8 Hz, 1H), 5.09 (s, 1H) 4.23 (s, 1H), 3.49 (s, 3H), 2.01 (br, 1H), 1.40 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.8, 144.9, 141.2, 140.2, 137.8, 128.3, 128.2, 128.1, 123.1, 120.2, 116.7, 108.0,

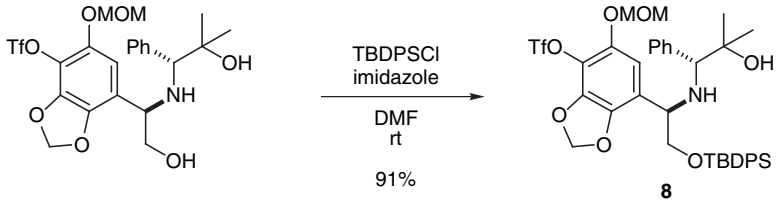
103.1, 95.9, 86.7, 61.3, 56.9, 56.3, 26.4, 21.8; HRMS (FAB$^+$) m/z: Calcd. for $C_{22}H_{22}F_3NO_9S$ (M^+) 533.0967, found 553.0993.

Amino Alcohol



To a solution of the triflate (4.70 g, 8.8 mmol) in MeOH (50 ml) at 0 °C was added $NaBH_4$ (1.33 g, 35 mmol, 4.0 equiv), and the mixture was stirred for 30 min. The reaction mixture was diluted with EtOAc (300 ml) and sequentially washed with 1M aqueous HCl (100 ml) and saturated aqueous $NaHCO_3$. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (60% EtOAc in *n*-hexane) to afford the amino alcohol (4.04 g, 7.5 mmol, 85%) as a colorless foam. $[\alpha]_D^{27}$ –102 ° (c = 1.7, $CHCl_3$). IR (neat film) 3398, 1497, 1456, 1426, 1218, 1136, 1054, 937, 833 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.25-7.33 (m, 5H), 6.63 (s, 1H) 5.94 (s, 1H), 5.93 (s, 1H), 5.11 (d, *J* = 6.8 Hz, 1H), 5.07 (d, *J* = 6.8 Hz, 1H), 3.65 (br, 1h), 3.52-3.64 (br, 2H), 3.50 (s, 3H), 3.39 (s, 1H), 2.71 (br, 1H), 1.11 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.8, 141.6, 139.9, 139.2, 128.7, 128.1, 127.5, 122.4, 120.9, 120.1, 116.9, 107.1, 102.9, 95.6, 72.7, 68.9, 64.9, 56.9, 56.3, 27.9, 23.8; HRMS (FAB$^+$) m/z: Calcd. for $C_{22}H_{26}F_3NO_9S$ (M^+) 537.1280, found 537.1222.

Silyl Ether 8

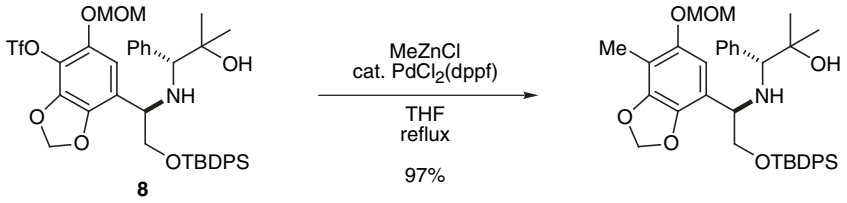


8

To a mixture of the amino alcohol (1.00 g, 1.86 mmol) and imidazole (0.63 g, 9.3 mmol, 5.0 equiv) in DMF was added TBDPSCl (1.22 ml, 4.7 mmol, 2.5 equiv), and the solution was stirred at room temperature and partitioned between Et_2O and H_2O. The ethereal layer was washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography (10% EtOAc in *n*-hexane) to afford **8** (1.31 g, 1.69 mmol, 91%) as a pale yellow oil. $[\alpha]_D^{27}$ –75 ° (c = 1.7, $CHCl_3$). IR (neat film) 3445, 1469, 1428, 1363, 1263, 1109, 1062, 991, 944, 826 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, *J* = 8.0 Hz, 2H), 7.56 (d, *J* = 8.0 Hz, 2H), 7.23-7.42 (m, 11H), 6.62 (s, 1H), 5.83 (s, 2H), 5.10 (d, *J* = 6.8 Hz, 1H), 5.08 (d, *J* = 6.8 Hz, 1H), 3.77 (dd, *J* = 6.0, 6.8 Hz, 1H), 3.67 (m, 2H), 3.47 (s, 3H), 3.37 (s, 1H), 3.34 (br, 1H), 1.09 (s, 6H), 1.08 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.7, 141.8, 139.8, 139.5, 135.6, 132.9, 129.7, 128.5,

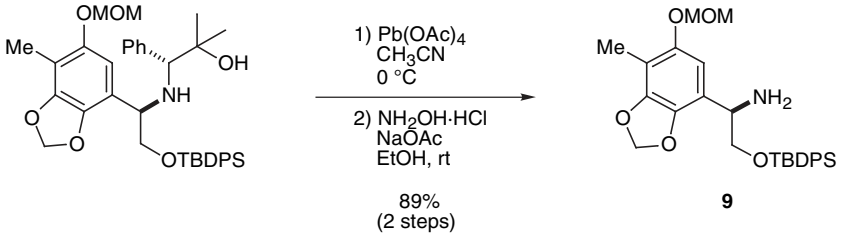
128.1, 127.7, 127.6, 127.4, 122.5, 121.0, 120.1, 116.9, 107.7, 102.7, 95.8, 72.2, 68.6, 66.4, 56.8, 56.3, 27.4, 26.8, 24.2, 19.2; HRMS (FAB$^+$) m/z: Calcd. for $C_{38}H_{45}F_3NO_9SSi$ $(M+H)^+$ 776.2536, found 776.2596.

Amino Alcohol



To a degassed solution of **8** (16.7 g, 21.5 mmol) in THF (105 ml) at 0 °C was added MeZnCl (2.0 M solution in THF, 37.5 ml, 75.1 mmol, 3.5 equiv), and the mixture was allowed to warm to room temperature. To the mixture was added $PdCl_2$(dppf) (314 mg, , 0.43 mmol, 2.0 mol%), and the resulting mixture was heated to reflux. After stirring for 1h, to the mixture was added $PdCl_2$(dppf) (472 mg, 0.65 mmol, 3.0 mol%), and the mixture was heated at reflux for additional 3.5 h. The reaction mixture was diluted with EtOAc and washed sequentially with 1N aqueous HCl, saturated aqueous $NaHCO_3$, and saturated aqueous NaCl. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (10% EtOAc in *n*-hexane) to afford the amino alcohol (13.4 g, 20.9 mmol, 97%) as a white amorphous. $[\alpha]_D^{26}$ –99 ° (c = 0.81, $CHCl_3$). IR (neat film) 3457, 2931, 1494, 1457, 1427, 1362, 1216, 1139, 1110, 1056, 1006, 936, 828 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, *J* = 6.8 Hz, 2H), 7.56 (d, *J* = 6.8 Hz, 2H), 7.22-7.47 (m, 11H), 6.30 (s, 1H), 5.77 (s, 2H), 5.03 (d, *J* = 5.6 Hz, 1H), 5.01 (d, *J* = 5.6 Hz, 1H), 3.83 (dd, *J* = 10.8, 10.8, 1H), 3.61-3.66 (m, 2H), 3.44 (s, 3H), 3.38 (s, 1H), 2.08 (s, 3H), 1.09 (s, 9H), 1.06 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.8, 146.6, 140.0, 139.7, 135.6, 135.6, 133.2, 133.1, 130.9, 130.4, 130.0, 129.7, 129.6, 128.5, 128.4, 128.0, 127.7, 127.6, 127.2, 117.7, 109.6, 107.0, 100.8, 95.6, 72.1, 68.5, 66.6, 57.7, 56.0, 27.3, 26.8, 24.0, 19.2. 8.8; HRMS (FAB$^+$) m/z: Calcd. for $C_{38}H_{47}NO_6Si$ (M^+) 641.3173, found 641.3156.

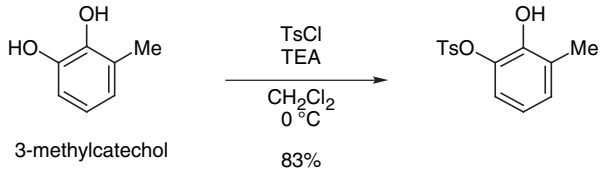
Amine 9



To a solution of the amino alcohol (640 mg, 1.0 mmol) in CH_3CN (12 ml) at 0 °C was added $Pb(OAc)_4$ (0.56 g, 1.26 mmol, 1.3 equiv). To the reaction mixture was added saturated aqueous $NaHCO_3$, and extracted with EtOAc. The organic layer was washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to afford the crude product, which was used in the next step without further purification. To a

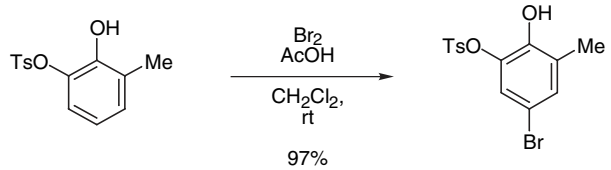
mixture of hydroxylamine hydrochloride (347 mg, 5.0 mmol, 5.0 equiv) and sodium acetate (410 mg, 5.0 mmol, 5.0 equiv) in EtOH (10 ml) at room temperature was added the crude product, and the resulting slurry was stirred for 1.5 h. The reaction mixture was diluted with EtOAc, filtered through a pad of Celite, and concentrated under reduced pressure. The residue was dissolved in EtOAc, and sequentially washed with 1N aqueous HCl, saturated aqueous $NaHCO_3$, and saturated aqueous NaCl. The organic layer was dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The resulting crude product was purified by flash column chromatography (EtOAc) to afford **9** (436mg, 0.88 mmol, 89% in 2 steps, >98% ee (ee was determined by ^{1}H NMR analysis of the corresponding (*R*)-MTPA amide)) as a yellow oil. $[\alpha]_D^{23}$ –2.0 ° (c = 1.3, $CHCl_3$). IR (neat film) 1440, 1115, 1062, 991, 938, 826 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61-7.65 (m, 4H), 7.35-7.45 (m, 6H), 6.57 (s, 1H), 5.81 (s, 2H), 5.09 (s, 2H), 4.16 (dd, *J* = 6.8, 4.8 Hz, 1H), 3.87 (dd, *J* = 10.0, 4.8 Hz, 1H), 3.76 (dd, *J* = 10.0, 6.8 Hz, 1H), 3.48 (s, 3H), 2.14 (s, 3H), 1.08 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.8, 146.1, 139.1, 135.5, 135.5, 133.4, 133.3, 129.5, 129.5, 127.5, 120.7, 109.1, 105.8, 100.7, 95.7, 68.1, 55.9, 53.4, 26.7, 19.1, 8.8; HRMS (FAB$^+$) m/z: Calcd. for $C_{28}H_{36}NO_5Si$ $(M+H)^+$ 494.2363, found 494.2387.

Tosylate



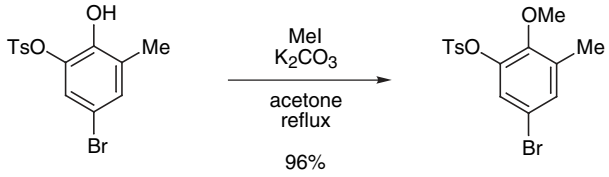
To a mixture of 3-methylcatechol (185 mg, 1.49 mmol) and TEA (0.315 ml, 2.26 mmol, 1.5 equiv) in CH_2Cl_2 (3.0 ml) at 0 °C was added *p*-toluenesulfonyl chloride (292 mg, 1.53 mmol, 1.03 equiv) portionwise. The reaction mixture was diluted with CH_2Cl_2, and sequentially washed with 10% aqueous citric acid and saturated aqueous NaCl. The organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash column chromatography (20% EtOAc in *n*-hexane) to afford the tosylate (345 mg, 1.24 mmol, 83%) as a white solid. IR (neat film) 3488, 1597, 1473, 1373, 1249, 1199, 1173, 1092, 1007, 941, 785 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.0 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 6.99 (d, *J* = 7.6 Hz, 1H), 6.64 (dd, *J* = 8.0, 7.6 Hz, 1H), 6.58 (d, *J* = 8.0 Hz, 1H), 6.01 (s, 1H), 2.46 (s, 3H), 2.24 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.6, 146.1, 137.0, 131.3, 129.9, 129.5, 128.6, 127.8, 120.3, 119.8, 21.7, 15.9; HRMS (FAB$^+$) m/z: Calcd. for $C_{14}H_{14}O_4S$ (M^+) 278.0613, found 278.0639.

Bromide



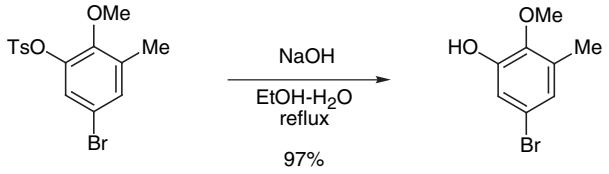
To a mixture of the tosylate (193 mg, 0.693 mmol) and acetic acid (0.20 ml, 3.5 mmol, 5.0 equiv) in CH_2Cl_2 (2.5 ml) at room temperature was added bromine (36.0 μl, 0.70 mmol, 1.0 equiv). After stirring for 30 min, the reaction mixture was poured into saturated aqueous Na_2SO_3 and extracted with CH_2Cl_2, and the organic layer was sequentially washed with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (20% EtOAc in *n*-hexane) to afford the bromide (240 mg, 0.672 mmol, 97%) as a white solid. IR (neat film) 3503, 1569, 1482, 1373, 1204, 1175, 1090, 1013, 961, 870, 815 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, J = 8.5 Hz, 2H), 7.38 (d, J = 8.5 Hz, 2H), 7.14 (d, J = 2 Hz, 1H), 6.75 (d, J = 2 Hz, 1H), 5.97 (s, 1H), 2.49 (s, 3H), 2.22 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.5, 146.0, 137.0, 132.3, 130.9, 130.1, 129.6, 128.6, 123.3, 110.8, 21.8, 15.8; HRMS (FAB$^+$) m/z: Calcd. for $C_{14}H_{14}BrO_4S$ $(M+H)^+$ 356.9796, found 356.9792.

Methyl Ether



To a mixture of the bromide (143 mg, 0.401 mmol) and K_2CO_3 (275 mg, 1.99 mmol, 5.0 equiv) in acetone (2.0 ml) was added iodomethane (75.0 μl, 1.20 mmol, 3.0 equiv), and the resulting slurry was heated at reflux for 1 h. After cooling, the mixture was diluted with Et_2O, filtered through a pad of Celite, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (20% Et_2O in *n*-hexane) to afford the methyl ether (142 mg, 0.385 mmol, 96%) as a colorless oil. IR (neat film) 1596, 1479, 1404, 1377, 1273, 1221, 1189, 1178, 1093, 1020, 969, 860, 814 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 8.3 Hz, 2H), 7.34 (d, J = 8 3 Hz, 2H), 7.20 (d, J = 2 Hz, 1H), 7.09 (d, J = 2 Hz, 1H), 3,69 (s, 3H), 2.47 (s, 3H), 2.20 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.1, 145.5, 142.7, 134.9, 132.7, 132.2, 129.7, 128.2, 124.3, 115.1, 60.6, 21.7, 15.8; HRMS (FAB$^+$) m/z: Calcd. for $C_{15}H_{15}BrO_4S$ (M^+) 369.9874, found 369.9835.

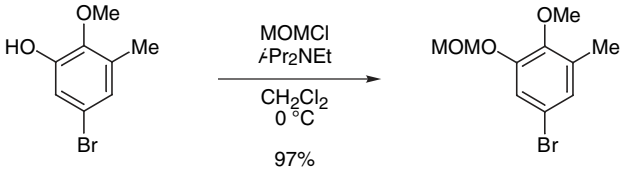
Phenol



To a solution of the methyl ether (98.9 mg, 0.267 mmol) in EtOH (1.5 ml) was added 2 M aqueous NaOH (0.20 ml, 0.40 mmol, 1.5 equiv), and the mixture was heated at reflux for 30 min. After cooling, the reaction mixture was poured into 10% aqueous citric acid and extracted with Et_2O. The ethereal layer was washed with saturated aqueous NaCl, dried over

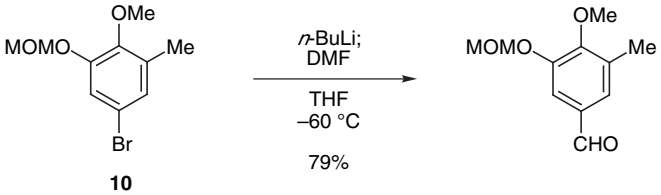
anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography (20% Et_2O in *n*-hexane) to afford the phenol (56.0 mg, 0.258 mmol, 97%) as a colorless oil: IR (neat film) 3336, 1717, 1457, 1367, 1249, 1160, 1065, 1003 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.96 (d, J = 2 Hz, 1H), 6.85 (d, J = 2 Hz, 1H), 5.67 (s, 1H), 3.77 (s, 3H), 2.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.6, 144.6, 132.5, 125.2, 116.8, 116.5, 60.7, 15.6; HRMS (FAB^+) m/z: Calcd. for $C_8H_9BrO_2$ (M^+) 215.9786, found 215.9809.

MOM Ether 10



To a mixture of the phenol (116 mg, 0.532 mmol) and *i*-Pr_2NEt (0.186 ml, 1.07 mmol, 2.0 equiv) in CH_2Cl_2 (1.5 ml) at 0 °C was added chloromethylmethyl ether (60 μl, 0.80 mmol, 1.5 equiv), and the reaction mixture was allowed to warm to room temperature, poured into 10% aqueous citric acid, and extracted with Et_2O. The ethereal layer was washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography (20% EtOAc in *n*-hexane) to afford **10** (136 mg, 0.521 mmol, 97%) as a colorless oil. IR (neat film) 1592, 1480, 1423, 1394, 1269, 1221, 1155, 1095, 1048, 1007 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.12 (s, 1H), 6.95 (s, 1H), 5.16 (s, 2H), 3.77 (s, 3H), 3.49 (s, 3H), 2.21 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.7, 147.2, 133.8, 126.8, 117.4, 115.8, 95.1, 60.1, 56.2, 15.7; HRMS (FAB$^+$) m/z: Calcd. for $C_{10}H_{13}BrO_3$ (M^+) 260.0048, found 260.0079.

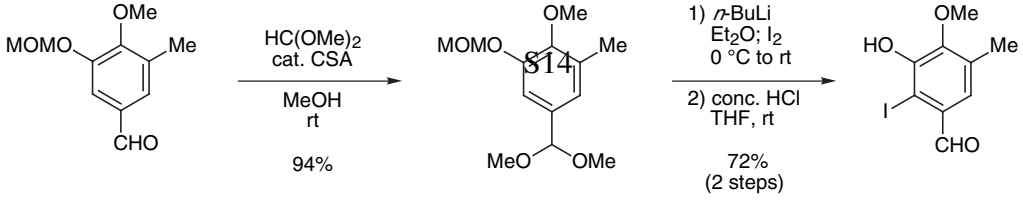
Benzaldehyde



10

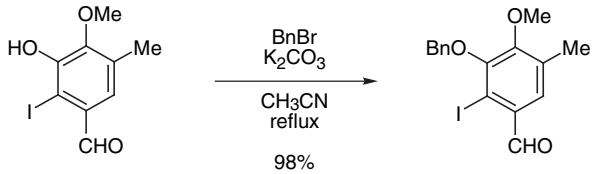
To a solution of **10** (114 g, 437 mmol) in THF (900 ml) at –78 °C was added *n*-BuLi (2.46 M solution in *n*-hexane, 270 ml, 664 mmol, 1.5 equiv), and to the resultant mixture was slowly added DMF (170 ml, 2.20 mol, 5.0 equiv), maintaining the internal temperature below –60 °C. The reaction mixture was allowed to warm to room temperature, quenched with H_2O, and concentrated under reduced pressure. The resulting residue was diluted with Et_2O, and sequentially washed with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl. The ethereal layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash column chromatography (30% Et_2O in *n*-hexane) to afford the benzaldehyde (73.0 g, 347 mmol, 79%) as a colorless oil. IR (neat film) 1699, 1585, 1488, 1451, 1382, 1299, 1235, 1155, 1133, 1099, 1051, 1003, 928, 863 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.83 (s, 1H), 7.49 (s, 1H), 7.36 (s, 1H), 5.25 (s, 2H), 3.90 (s, 3H), 3.51 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.2, 153.5, 150.5, 132.8, 132.1, 126.9, 114.2, 95.0, 60.3, 56.3, 16.0; HRMS (FAB$^+$) m/z: Calcd. for $C_{11}H_{14}O_4$ (M^+) 210.0892, found 210.0870.

Iodobenzaldehyde



To a mixture of the benzaldehyde (331 mg, 1.57 mmol) and trimethyl orthoformate (1.0 ml, 9.14 mmol, 5.8 equiv) in MeOH (5.0 ml) was added CSA (20.2 mg, 0.09 mmol, 5.5 mol%), and the resulting mixture was stirred at room temperature for 1 h. To the reaction mixture was added K_2CO_3 (103 mg, 0.75 mmol, 0.47 equiv) and concentrated to a small volume. The residue was dissolved in Et_2O and passed through a pad of basic alumina, and the ethereal solution was concentrated to afford the dimethylacetal (381mg, 1.49 mmol, 94%) as a colorless oil, which was used for the next reaction without further purification. To a solution of the dimethyl acetal (381 mg, 1.49 mmol) in Et_2O (4.0 ml) at 0 °C was added *n*-BuLi (2.46 M solution in *n*-hexane, 0.95 ml, 2.34 mmol, 1.57 equiv), and the resulting mixture was allowed to warm to room temperature. After cooling to 0 °C, to the reaction mixture was added a solution of I_2 (648 mg, 2.55 mmol, 1.7 equiv) in Et_2O (3.0 ml), and the reaction was quenched with H_2O, and partitioned between EtOAc and saturated aqueous Na_2SO_3. The organic layer was washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The resulting crude yellow syrup was dissolved in THF (5.0 ml), and to the solution at room temperature was added concentrated HCl solution (2.0 ml). After stirring for 15 min, the reaction mixture was neutralized with saturated aqueous $NaHCO_3$ and extracted with EtOAc. The organic phase was washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated. The resulting crude product was dissolved in CH_2Cl_2 and filtered through a pad of silica gel, and the filtrate was concentrated, and triturated with *n*-hexane to afford the iodobenzaldehyde (314 mg, 1.07 mmol, 72% in 2 steps) as a yellow solid. IR (neat film) 3389, 1670, 1583, 1464, 1412, 1299, 1247, 1127, 997 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.0 (s, 1H), 7.37 (s, 1H), 6.43 (bs, 1H), 3.89 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.9, 149.9, 149.2, 131.3, 130.9, 125.3, 125.3, 60.8, 15.8; HRMS (FAB$^+$) m/z: Calcd. for $C_9H_9IO_3$ (M^+) 291.9596, found 291.9583.

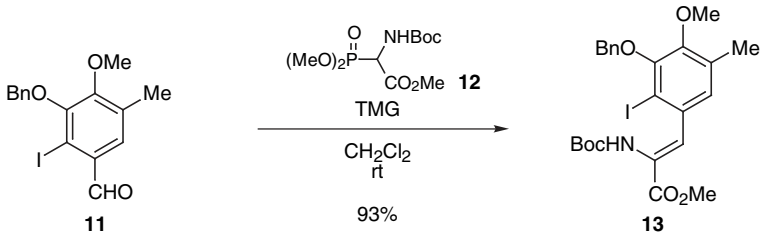
Benzyl Ether 11



11

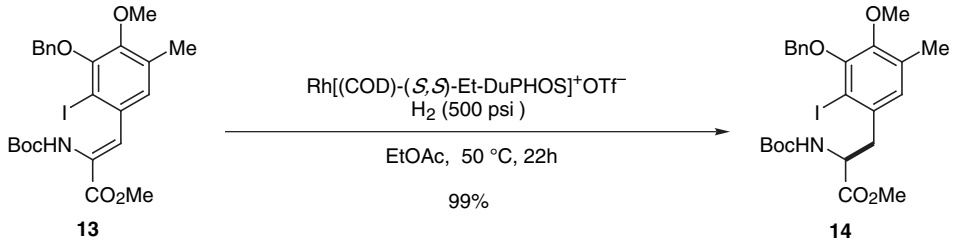
To a mixture of the iodobenzaldehyde (325 mg, 1.11 mmol) and K_2CO_3 (465 mg, 3.37 mmmol, 3.07 equiv) in CH_3CN (3.0 ml) was added benzyl bromide (140 μl, 1.18 mmol, 1.05 equiv), and the resulting mixture was heated at reflux for 40 min. The reaction mixture was diluted with CH_2Cl_2, filtered through a pad of Celite, and concentrated under reduced pressure. The residue was purified by flash column chromatography (50% CH_2Cl_2 in *n*-hexane) to afford **11** (415 mg, 1.09 mmol, 98%) as a yellow solid. IR (neat film) 1684, 1576, 1464, 1303, 1153, 1068, 1005 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.0 (s, 1H), 7.60 (d, 8.0 Hz, 2H), 7.59 (s, 1H), 7.30-7.45 (m, 3H), 5.01 (s, 2H), 3.93 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195 3, 157.1, 151.3, 136.3, 133.3, 131.3, 128.7, 128.5, 128.4, 128.2. 98.2, 74.9, 60.6, 15.7; HRMS (FAB$^+$) m/z: Calcd. for $C_{16}H_{15}IO_3$ (M^+) 382.0066, found 382.0083.

Dehydroamino Ester 13



To a mixture of **11** (8.30 g, 21.7 mmol) and phosphonate **12** (7.76 g, 26.1 mmol, 1.2 equiv) in CH_2Cl_2 (100 ml) at 10 °C was added *N,N,N',N'*-tetramethylguanidine (4.10 ml, 32.7 mmol, 1.5 equiv), and the mixture was allowed to warm to room temperature and stirred for 24 h. The reaction mixture was sequentially washed with 10% aqueous citric acid and saturated aqueous $NaHCO_3$, and the organic layer was dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (30% EtOAc in *n*-hexane) to afford **13** (11.2 g, 20.2 mmol, 93%) as a yellow solid. Recrystallization of the crude product from EtOAc/*n*-hexane also afforded a pure sample of **13**. IR (neat film) 3336, 1717, 1457, 1367, 1249, 1160, 1065, 1003 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.60 (d. *J* = 6.8 Hz, 2H), 7.36-7.60 (m, 3H), 7.24 (s, 1H), 7.20 (s, 1H), 5.00 (s, 2H), 3.88 (s, 3H), 3.86 (s, 3H), 2.23 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6, 152.4, 151.6, 151.5, 136.8, 134.2, 132.5, 131.7, 128.7, 128.4, 128.2, 126.8, 125.4, 96.9, 80.9, 74.6, 60.5, 52.7, 28.0, 15.8; HRMS (FAB$^+$) m/z: Calcd. for $C_{24}H_{28}INO_6$ (M^+) 553.0961, found 553.0982.

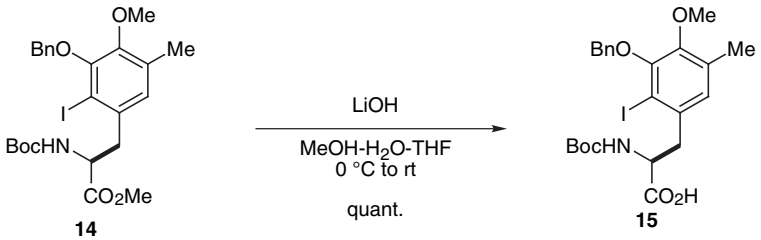
Amino Ester 14



A degassed mixture of **13** (5.04 g, 9.10 mmol) and Rh[(COD)-(*S*,*S*)-Et-DuPHOS]$^+$TfO$^-$ (99.0 mg, 0.14 mmol, 1.5 mol%) in EtOAc (30 ml) was placed in a high pressure Parr reactor and sealed under hydrogen (500 psi). After stirring at 50 °C for 22 h, the solution was concentrated under reduced pressure, and the residue was purified by flash column chromatography (50% EtOAc in *n*-hexane) to afford **14** (5.01 g, 9.02 mmol, 99%, 94% ee) as a pale yellow foam. Enantiomeric excess was determined by chiral HPLC (Chiralcel OD column, 97:3 *n*-hexane/2-propanol). $[\alpha]_D^{27}$ +7.4 ° (c = 1.1, $CHCl_3$); IR (neat film) 3374, 1746, 1711, 1510, 1457, 1363, 1162, 1068, 1003 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.8 Hz, 2H), 7.32-7.45 (m, 3H), 6.85 (s, 1H), 5.06 (d, *J* = 8.8 Hz, 1H), 4.99 (s, 1H), 4.62 (ddd, *J* = 9.2, 8.8, 5.6 Hz, 1H), 3.82 (s, 3H), 3.72 (s, 3H), 3.28 (dd, *J* = 14.4, 5.6 Hz, 1H), 3.09 (dd, *J* = 14.4, 9.2 Hz, 1H), 2.23 (s, 3H), 1.43 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 154.9, 151.7, 150.4, 136.9, 135.4, 132.3, 128.6, 128.4, 128.1, 127.8, 97.0, 79.8, 74.5, 60.4, 53.8, 52.3, 42.7, 28.2, 15.6; HRMS (FAB$^+$) m/z: Calcd. for $C_{24}H_{31}INO_6$ $(M+H)^+$ 556.1196, found

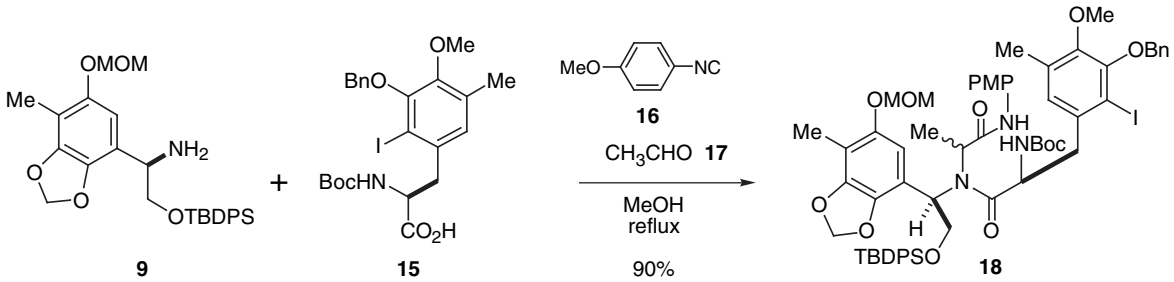
556.1222.

Carboxylic Acid 15



To a solution of **14** (5.01 g, 9.02 mmol) in a mixture of MeOH (40 ml), H_2O (10 ml), and THF (10 ml) at 0 °C was added lithium hydroxide (750 mg, 17.9 mmol, 2.0 equiv), and the mixture was allowed to warm to room temperature. The reaction mixture was diluted with benzene and concentrated under reduced pressure. To the residue was added 10% aqueous citric acid, and the resulting suspension was extracted with EtOAc. The organic layer was washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to afford **15** (4.90 g, 9.05 mmol, quant) as a white foam. $[\alpha]_D^{27}$ –14 ° (c = 5.0, $CHCl_3$). IR (neat film) 3309, 2560, 1716, 1497, 1471, 1404, 1368, 1307, 1243, 1163, 1063, 1008, 907, 845, 804 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.61 (br, 2H), 7.36-7.44 (br, 3H), 6.90 (s, 1H), 5.00 (br, 2H), 4.63 (br, 1H), 3.83 (s, 3H), 3.43 (br, 1H), 2.94-3.20 (br, 1H), 2.25 (s, 3H), 1.10-1.40 (br, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.2, 175.4, 156.7, 155.2, 151.4, 150.4, 150.3, 136.9, 135.8, 135.3, 132.3, 132.2, 128.7, 128.6, 128.4, 128.4, 128.1, 127.9, 97.1, 96.7, 81.1, 80.1, 77.2, 74.5, 60.4, 60.3, 54.1, 53.8, 53.7, 44.6, 42.3, 42.2, 42.2, 28.2, 27.9, 15.6; HRMS (FAB^+) m/z: Calcd. for $C_{23}H_{29}INO_6$ $(M+H)^+$ 542.1039, found 542.1083.

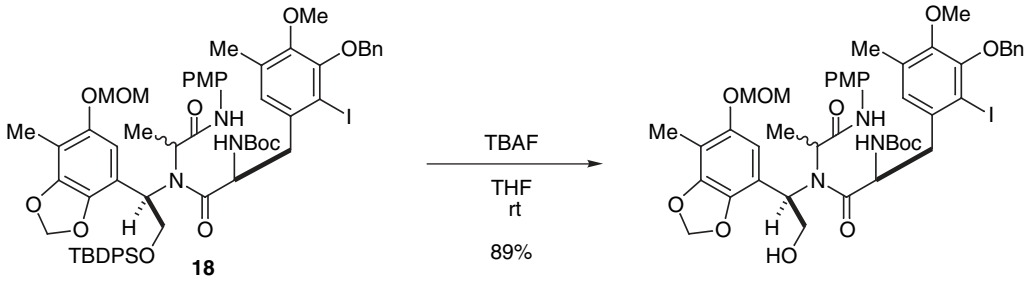
Amide 18 (epimeric mixture)



To a mixture of amine **9** (9.63 g, 19.5 mmol), carboxylic acid **15** (10.57 g, 19.5 mmol, 1.0 equiv), and *p*-methoxy isocyanide (PMP-NC) (**16**) (3.90 g, 29.3 mmol, 1.5 equiv) in MeOH (200 ml) at room temperature was added acetaldehyde (**17**) (22 ml, 0.39 mol, 20 equiv), and the resulting solution was heated at reflux for 1 h. The reaction mixture was concentrated under reduced pressure, and the resulting orange syrup was purified by flash column chromatography (40% EtOAc in *n*-hexane) to afford **18** (21.02 g, 17.6 mmol, 90%) as a yellow solid. IR (neat film) 3315, 1699, 1687, 1511, 1463, 1428, 1367, 1245, 1159, 1112, 1062, 826 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.60-9.20 (m, 1H), 7.25-7.75 (m, 17H), 6.50-7.20 (m, 4H), 4.80-5.85 (m, 9H), 3.90-4.80 (m, 3H), 3.60-3.85 (m, 6H), 3.40-3.50 (m, 3H),

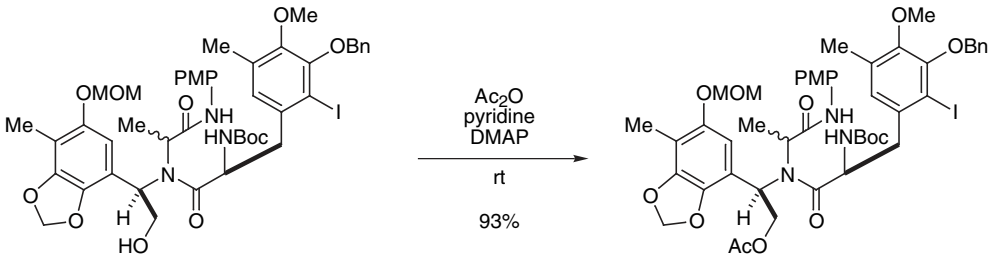
2.90-3.50 (m, 2H), 1.85-2.25 (m, 6H), 0.75-1.50 (m, 21H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4, 172.0, 171.3, 170.1, 168.7, 167.9, 156.2, 156.1, 155.9, 155.6, 155.3, 154.3, 151.5, 151.4, 151.3, 151.0, 150.9, 150.8, 150.5, 150.1, 150.0, 146.9, 146.5, 139.8, 139.7, 136.8, 136.7, 136.6, 136.5, 135.6, 135.5, 135.4, 135.3, 135.2, 132.6, 132.5, 132.4, 132.2, 132.1, 132.0, 131.6, 131.1, 131.0, 129.9, 129.7, 129.6, 129.3, 128.5, 128.4, 128.3, 128.2, 128.0, 127.9, 127.7, 127.5, 127.4, 127.3, 123.0, 121.7, 121.5, 120.5, 113.7, 113.5, 113.4, 113.3, 113.1, 110.9, 106.2, 106.0, 100.9, 100.8, 100.6, 97.5, 96.7, 96.6, 96.2, 95.8, 95.5, 95.3, 80.6, 80.5, 80.3, 79.3, 79.0, 74.4, 74.3, 71.5, 70.4, 62.6, 62.5, 60.2, 60.1, 59.7, 57.2, 56.2, 56.1, 55.9, 55.1, 54.5, 54.4, 51.5, 51.3, 42.9, 41.8, 41.1, 41.1, 28.1, 28.0, 27.9, 27.8, 27.1, 27.0, 26.9, 26.4, 19.1, 19.0, 18.9, 17.8, 17.1, 15.4, 15.3, 15.2, 15.1, 14.9, 14.8, 8.8, 8.7, 8.5; LRMS (FAB$^+$) m/z: 1193.4 (M^+).

Alcohol (epimeric mixture)



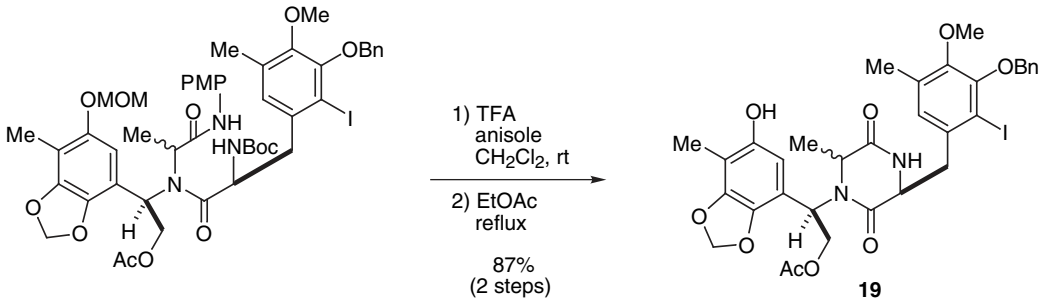
To a solution of **18** (21.02 g, 17.6 mmol) in THF (200 ml) at room temperature was added TBAF (1M solution in THF, 20 ml, 020 mmol, 1.1 equiv), and the mixture was stirred for 30 min. The reaction mixture was diluted with a mixture of EtOAc and *n*-hexane and concentrated under reduced pressure. The residue was purified by flash column chromatography (EtOAc) to afford the alcohol (14.90 g, 15.6 mmol, 89%) as a yellow solid. IR (neat film) 3309, 1699, 1694, 1652, 1511, 1435, 1367, 1304, 1245, 1170, 1112, 1060, 1008 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 & 7.91 (br, 1H), 7.31-7.63 (m, 5H), 6.81-7.10 (m, 3H), 6.46-6.74 (m, 2H), 5.81-5.97 (m, 2H), 5.59-5.73 (m, 1H), 5.30-5.46 (m, 1H), 4.78-5.30 (m, 6H), 4.33-4.52 (m, 1H), 3.90-4.13 (m, 2H), 3.70-3.88 (m, 3H), 3.79 (s, 3H), 2.78-3.67 (m, 3H), 3.47 & 3.41 (s, 3H), 2.05-2.37 (m, 6H), 1.09-1.47 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 170.5, 156.3, 156.2, 156.1, 154.6, 15.5, 151.4, 151.2, 151.1, 151.0, 150.6, 150.5, 151.2, 146.8, 140.2, 137.1, 137.0, 136.9, 135.9, 132.3, 131.8, 131.0, 130.6, 129.2, 128.7, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 122.2, 122.1, 122.0, 121.9, 121.8, 121.7, 121.6, 121.3, 116.7, 114.2, 114.1, 114.0, 113.9, 113.8, 113.7, 113.6, 113.4, 111.2, 105.9, 105.7, 101.2, 100.9, 97.2, 95.7, 95.5, 95.2, 79.9, 79.7, 79.4, 78.9, 77.6, 74.6, 74.5, 74.4, 68.5, 60.5, 60.4, 60.3, 58.1, 56.4, 56.3, 56.2, 56.0, 55.3, 54.0, 53.7, 50.4, 43.2, 42.3, 28.3, 28.1, 28.0, 21.0, 20.2, 15.6, 15.5, 15.4, 14.9, 14.0, 13.9, 9.0, 8.9, 8.7; LRMS (FAB^+) m/z: 955.4 (M^+).

Acetate (epimeric mixture)



The alcohol (14.90 g, 15.6 mmol) was dissolved in a mixture of acetic anhydride (30 ml) and pyridine (60 ml), and to the solution at room temperature was added DMAP (97 mg, 0.79 mmol, 0.05 equiv). The reaction mixture was stirred at 50 °C for 30 min, and concentrated under reduced pressure. The residue was diluted with toluene and concentrated under reduced pressure. The crude product was purified by flash column chromatography (60% EtOAc in *n*-hexane) to afford the acetate (14.54 g, 14.6 mmol, 93%) as a yellow solid. IR (neat film) 3318, 1743, 1700, 1511, 1436, 1368, 1304, 1245, 1170, 1112, 1060, 830 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.90-9.30 (m, 1H), 7.55 (d, J = 6.8 Hz, 2H), 7.20-7.50 (m, 5H), 6.30-7.20 (m, 2H), 6.80 (d, J = 6.8 Hz, 2H), 5.84-5.88 (br, 2H), 5.60-5.80 (m, 2H), 5.20-5.45 (m, 2H), 5.00-5.20 (m, 2H), 4.93-4.97 (m, 2H), 4.70-4.90 (m, 1H), 4.40-4.70 (m, 1H), 3.65-3.80 (m, 6H), 3.35-3.50 (m, 3H), 2.90-3.35 (m, 1H), 1.80-2.25 (m, 9H), 1.10-1.55 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.6, 173.2, 172.7, 172.0, 170.1, 170.0, 169.7, 169.5, 169.5, 169.4, 168.2, 168.2, 156.4, 156.1, 155.8, 155.2, 154.3, 151.5, 151.3, 151.2, 151.2, 151.1, 150.6, 150.3, 147.1, 146.8, 146.6, 140.0, 139.8, 139.3, 136.8, 136.7, 136.7, 136.7, 136.5, 135.0, 134.9, 134.6, 132.5, 132.0, 131.1, 131.0, 130.1, 128.8, 128.5, 128.4, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 121.8, 121.8, 121.8, 121.6, 121.4, 121.2, 120.6, 113.9, 113.9, 113.8, 113.5, 113.1, 112.6, 112.1, 111.7, 111.3, 105.9, 105.7, 105.3, 101.1, 101.0, 100.7, 96.8, 96.5, 95.9, 95.4, 95.4, 95.1, 79.6, 79.1, 74.4, 70.6, 62.0, 60.3, 60.2, 57.3, 56.5, 56.2, 56.0, 55.8, 55.2, 50.6, 50.1, 43.5, 28.1, 28.0, 27.9, 27.8, 20.9, 20.7, 17.6, 15.3, 14.8, 8.8; LRMS (FAB^+) m/z: 997.3 (M^+).

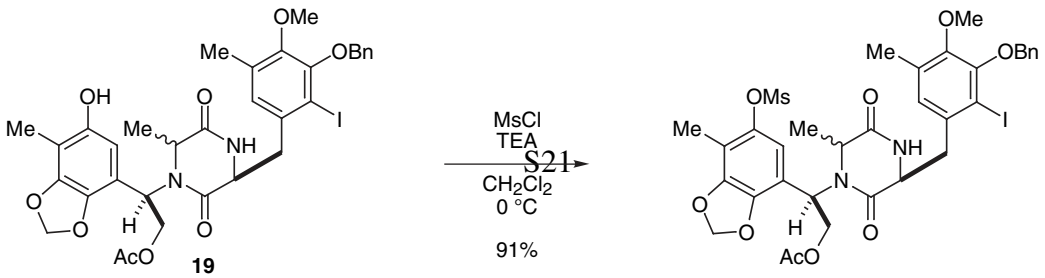
Diketopiperazine 19 (epimeric mixture)



19

To a mixture of the acetate (14.5 g, 14.5 mmol) and anisole (79 ml, 0.73 mol, 50 equiv) in CH_2Cl_2 (290 ml) at 0 °C was added TFA (58 ml, 0.75 mol, 52 equiv), and the mixture was allowed to warm to room temperature and stirred for 9 h. The resulting red solution was poured into water and extracted with EtOAc. The organic phase was separated, and sequentially washed with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl. The solution was dried over anhydrous $MgSO_4$, concentrated under reduced pressure to a volume of about 300 ml, and heated at reflux for 1h. The reaction mixture was concentrated under reduced pressure, and the resultant residue was purified by flash column chromatography (70% EtOAc in *n*-hexane) to afford **19** (19.7 g, 27.0 mmol, 87% in 2 steps) as a pale brown amorphous. **19a** (minor isomer) IR (neat film) 3345, 1752, 1683, 1652, 1456, 1306, 1232, 1093, 1037, 1007 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, *J* = 8.2, 2H), 7.38-7.41 (m, 3H), 6.85 (s, 1H), 6.23 (s, 1H), 6.20 (br, 1H), 5.89 (s, 1H), 5.86 (s, 1H), 5.70 (dd, *J* = 8.4, 7.2 Hz, 1H), 4.95 (s, 2H), 4.69 (dd, *J* = 11.0, 7.2 Hz, 1H), 4.57 (dd, *J* = 11.0, 8.4 Hz, 1H), 4.29 (dd, *J* = 9.3, 3.9 Hz, 1H), 3.88 (q, *J* = 7.1 Hz, 1H), 3.80 (s, 3H), 3.46 (dd, *J* = 13.7, 3.9 Hz, 1H), 3.21 (dd, *J* = 13.7, 9.3 Hz, 1H), 2.21 (s, 3H), 2.09 (s, 3H), 2.05 (s, 3H), 1.45 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 168.7, 166.5, 151.8, 15.0, 151.0, 147.0, 139.0, 136.7, 134.5, 133.2, 128.6, 128.4, 128.2, 128.1, 111.8, 109.1, 106.3, 100.9, 97.3, 74.6, 62.7, 60.4, 57.0, 55.0, 44.9, 21.2, 20.8, 15.5, 8.7; LRMS (FAB^+) m/z: 731.3 $(M+H)^+$. **19b** (major isomer) IR (neat film) 3374, 1751, 1683, 1651, 1430, 1314, 1265, 1233, 1094, 1040, 1006 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 8.3 Hz, 2H), 7.36-7.43 (m, 3H), 6.86 (s, 1H), 6.40 (s, 1H), 5.93 (s, 1H), 5.92 (s, 1H), 5.62 (dd, *J* = 8.9, 5.8 Hz, 1H), 5.50 (s, 1H), 5.15 (br, 1H), 5.03 (d, *J* = 6.8 Hz, 1H), 5.01 (d, *J* = 6.8 Hz, 1H), 4.76 (dd, *J* = 11.7, 8.9 Hz, 1H), 4.60 (dd, *J* = 11.7, 5.8 Hz, 1H), 4.34 (dd, *J* = 10.7, 3.9 Hz, 1H), 4.18 (q, *J* = 7.1 Hz, 1H), 3.84 (s, 3H), 3.81 (dd, *J* = 14.2, 3.9 Hz, 1H), 2.84 (dd, *J* = 14.2, 10.7 Hz, 1H), 2.25 (s, 3H), 2.13 (s, 3H), 2.07 (s, 3H), 1.15 (d, *J* = 7.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 170.3, 166.9, 152.2, 151.0, 150.8, 146.8, 138.9, 136.6, 134.1, 133.4, 128.6, 128.4, 128.3, 128.2, 112.5, 108.9, 106.5, 101.0, 96.2, 74.6, 62.0, 60.4, 54.9, 53.3, 52.5, 41.5, 20.8, 18.0, 15.6, 8.7; LRMS (FAB^+) m/z: 731.4 $(M+H)^+$.

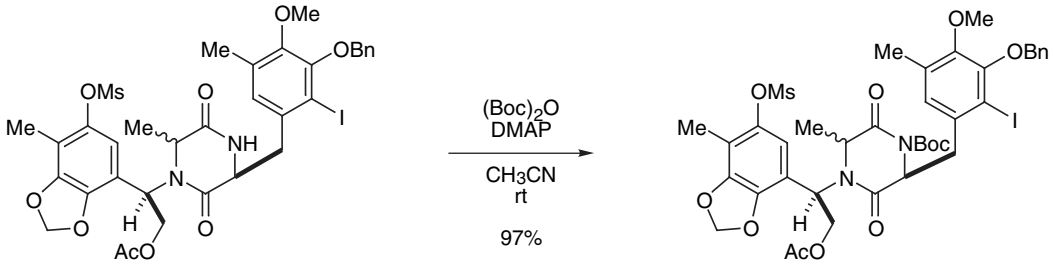
Mesylate (epimeric mixture)



19

To a mixture of **154** (19.3 g, 26.4 mmol) and TEA (11.8 ml, 84.6 mmol, 3.2 equiv) in CH_2Cl_2 (100 ml) at 0 °C was slowly added methanesulfonyl chloride (2.60 ml, 33.8 mmol, 1.3 equiv). After stirring at 0 °C for 1h, the reaction mixture was diluted with EtOAc (400 ml), and sequentially washed with 6% aqueous NaCl (230 ml), saturated aqueous $NaHCO_3$, and saturated aqueous NaCl. The organic phase was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography (70% EtOAc in *n*-hexane) to afford the mesylate (19.4 g, 24.0 mmol, 91%) as a pale yellow amorphous. minor isomer: IR (neat film) 1743, 1685, 1424, 1367, 1307, 1230, 1172, 1126, 1065, 1006, 970 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, *J* = 8.0 Hz, 2H), 7.32-7.41 (m, 3H), 6.87 (s, 1H), 6.83 (s, 1H), 6.02 (d, *J* = 2.0 Hz, 1H), 5.99 (s, 2H), 5.49 (dd, *J* = 8.0, 8.0 Hz, 1H), 4.99 (d, *J* = 10.8 Hz, 1H), 4.96 (d, *J* = 10.8 Hz, 1H), 4.67 (dd, *J* = 12.0, 8.0 Hz, 1H), 4.62 (dd, *J* = 12.0, 8.0 Hz, 1H), 4.34 (ddd, *J* = 8.8, 4.0, 2.0 Hz, 1H), 3.81 (s, 3H), 3.80 (q, *J* = 6.8 Hz, 1H), 3.49 (dd, *J* = 14.0, 4.0 Hz, 1H), 3.18 (s, 3H), 3.17 (dd, *J* = 14.0, 8.8 Hz, 1H), 2.21 (s, 3H), 2.20 (s, 3H), 2.05 (s, 3H), 1.38 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 168.1, 165.6, 151.9, 151.0, 147.1, 144.0, 142.4, 136.6, 134.4, 133.1, 128.6, 128.4, 128.3, 128.2, 115.1, 113.3, 102.1, 97.1, 74.6, 62.0, 60.4, 56.7, 55.2, 54.3, 45.0, 37.9, 21.1, 20.7, 15.5, 9.8; HRMS (FAB^+) m/z: Calcd. for $C_{32}H_{34}IN_2O_9S$ $(M–AcO)^+$ 749.1029, found 749.1046. major isomer: IR (neat film) 1743, 1688, 1424, 1367, 1312, 1229, 1173, 1132, 1065, 1006, 970 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 6.8 Hz, 2H), 7.29-7.39 (m, 3H), 6.91, (s, 1H), 6.84 (s, 1H), 6.00 (s, 2H), 5.64 (s, 1H), 5.42 (dd, *J* = 8.0, 6.0 Hz, 1H), 4.99 (d, *J* = 7.2 Hz, 1H), 4.96 (d, *J* = 7.2 Hz, 1H), 4.75 (dd, *J* = 11.6, 8.0 Hz, 1H), 4.66 (dd, *J* = 11.6, 6.0 Hz, 1H), 4.35 (dd, *J* = 10.8, 4.0 Hz, 1H), 4.11 (q, *J* = 8.0 Hz, 1H), 3.80 (s, 3H), 3.68 (dd, *J* = 13.8, 4.0 Hz, 1H), 3.19 (s, 3H), 2.83 (dd, *J* = 13.8, 10.8 Hz, 1H), 2.21 (s, 3H), 2.20 (s, 3H), 2.04 (s, 3H), 1.21 (d, *J* = 8.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 169.5, 166.2, 151.9, 150.8, 146.8, 144.0, 142.3, 136.5, 134.1, 133.1, 128.4, 128.2, 128.0, 115.1, 115.1, 113.9, 102.0, 96.1, 74.4, 61.5, 60.2, 56.2, 53.2, 52.3, 41.2, 37.7, 20.6, 17.8, 15.5, 14.0, 9.8; HRMS (FAB^+) m/z: Calcd. for $C_{32}H_{34}IN_2O_9S$ $(M–AcO)^+$ 749.1029, found 749.0997.

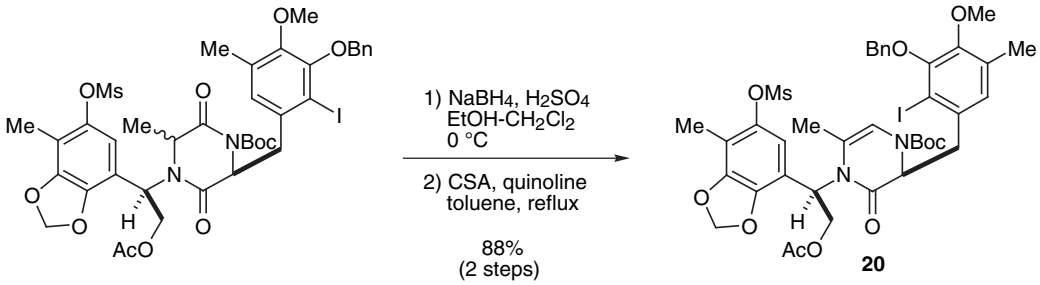
Imide (epimeric mixture)



To a mixture of the mesylate (3.00 g, 3.71 mmol) and $(Boc)_2O$ (1.36 g, 6.22 mmol, 1.7 equiv) in CH_3CN (15 ml) was added DMAP (45 mg, 0.37 mmol, 0.1 equiv), and the solution was stirred at room temperature for 6.5 h. The reaction mixture was diluted with EtOAc, and sequentially washed with 0.5 M aqueous HCl, saturated aqueous $NaHCO_3$, and saturated aqueous NaCl. The organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography (50% EtOAc in

n-hexane) to afford the imide (3.27 g, 3.60 mmol, 97%) as a pale yellow amorphous. minor isomer: IR (neat film) 1775, 1733, 1670, 1455, 1429, 1368, 1308, 1285, 1244, 1172, 1148, 1066, 1007, 970, 937 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 6.8 Hz, 2H), 7.33-7.41 (m, 3H), 6.87 (s, 1H), 6.82 (s, 1H), 5.97 (s, 1H), 5.96 (s, 1H), 5.56 (dd, *J* = 8.0, 8.0 Hz, 1H), 5.14 (dd, *J* = 8.0, 4.8 Hz, 1H), 4.95 (d, *J* = 10.0 Hz, 1H), 4.91 (d, *J* = 10.0 Hz, 1H), 4.63 (dd, *J* = 10.8, 8.0 Hz, 1H), 4.56 (dd, *J* = 10.8, 8.0 Hz, 1H), 3.98 (q, *J* = 8.0, 1H), 3.78 (s, 3H), 3.53 (dd, *J* = 14.8, 4.8 Hz, 1H), 3.23 (dd, *J* = 14.8, 8.0 Hz, 1H), 3.16 (s, 3H), 2.20 (s, 3H), 2.19 (s, 3H), 2.03 (s, 3H), 1.45 (d, *J* = 8.0 Hz, 3H), 1.34 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 167.8, 166.0, 151.8, 150.9, 149.5, 147.3, 144.1, 142.5, 136.8, 134.9, 132.9, 128.7, 128.4, 128.4, 128.2, 115.3, 115.1, 113.1, 102.1, 97.5, 84.4, 74.6, 62.0, 60.4, 59.5, 56.5, 56.5, 53.5, 44.6, 38.0, 27.8, 20.8, 20.8, 15.5, 9.9; LRMS (FAB^+) m/z: 909.1 $(M+H)^+$. major isomer: IR (film) 1777, 1737, 1672, 1468, 1455, 1424, 1368, 1308, 1285, 1245, 1172, 1150, 1064, 1008, 970, 934 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 6.8 Hz, 2H), 7.32-7.41 (m, 3H), 7.04 (s, 1H), 6.73 (s, 1H), 6.02 (s, 1H), 5.99 (s, 1H), 5.08 (dd, *J* = 10.0, 4.0 Hz, 1H), 4.91 (s, 2H), 4.80-4.90 (m, 3H), 4.30 (q, *J* = 6.8 Hz, 1H), 3.77 (s, 3H), 3.28 (dd, *J* = 13.6, 4.8 Hz, 1H), 3.19 (s, 3H), 3.01 (dd, *J* = 8.8, 4.8 Hz, 1H), 2.19 (s, 3H), 2.13 (s, 3H), 2.02 (s, 3H), 1.69 (d, *J* = 6.8 Hz, 3H), 1.29 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 167.7, 167.5, 151.5, 150.6, 149.4, 146.6, 143.5, 142.3, 136.7, 134.1, 132.5, 128.5, 128.3, 128.1, 128.1, 115.1, 115.1, 114.8, 101.8, 97.3, 83.8, 74.4, 62.4, 60.3, 58.7, 56.8, 52.7, 42.5, 37.7, 27.5, 20.7, 16.7, 15.3, 9.8; LRMS (FAB^+) m/z: 909.2 $(M+H)^+$.

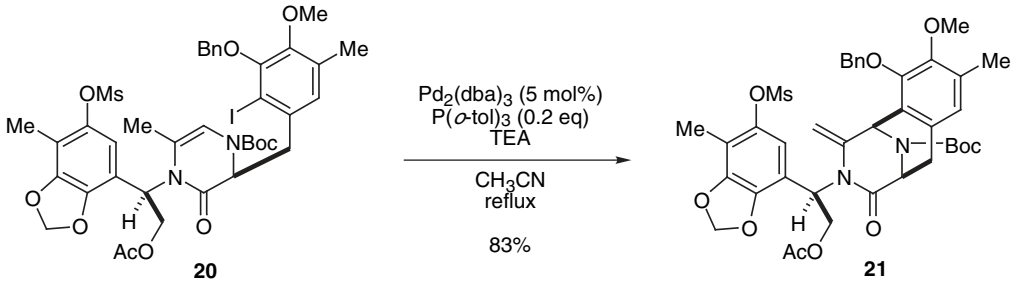
Enamide 20



To a solution of the imide (4.11 g, 4.52 mmol) in a mixture of EtOH (100 ml) and CH_2Cl_2 (10 ml) at 0 °C was added H_2SO_4 (3.0 M solution in EtOH, 3.0 ml, 9.0 mmol, 2.0 equiv), and to the mixture was added $NaBH_4$ (867 mg, 22,9 mmol, 5.1 equiv) portionwise. Excess reagent was quenched with acetone (10 ml), and the mixture was neutralized with saturated aqueous $NaHCO_3$ (50 ml), diluted with EtOAc, and filtered through a pad of Celite. The filtrate was concentrated under reduced pressure, and the residue was partitioned between EtOAc and saturated aqueous $NaHCO_3$. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure to give the crude aminal (4.19 g), which was used in the next step without further purification. To a solution of the aminal in toluene (40 ml) were added CSA (1.07 g, 4.61 mmol, 1.0 equiv) and quinoline (0.82 ml, 7.0 mmol, 1.5 equiv), and the resulting mixture was heated at reflux for 3 h. The reaction mixture was diluted with EtOAc, and sequentially washed with 1M aqueous HCl, saturated aqueous $NaHCO_3$, and saturated aqueous NaCl. The

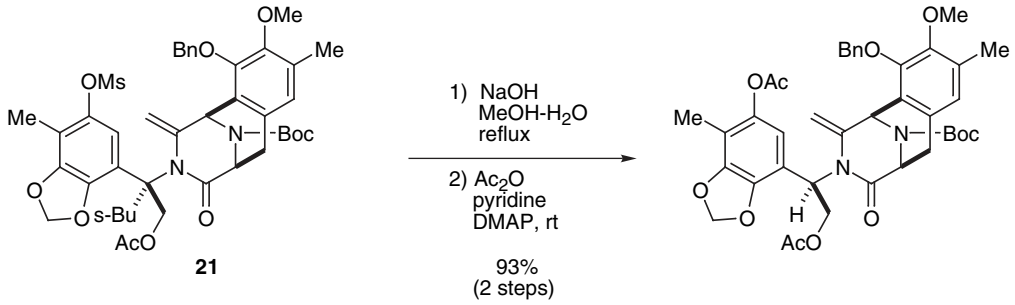
organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography (50% EtOAc in *n*-hexane) to afford **20** (3.54 g, 3.97 mmol, 88% in 2 steps) as a yellow foam. $[\alpha]_D^{27}$ +2.9 ° (c = 3.0, $CHCl_3$). IR (neat film) 1742, 1692, 1463, 1418, 1362, 1336, 1240, 1172, 1065, 1005, 962, 890, 805 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 6.8 Hz, 2H), 7.36-7.44 (m, 3H), 6.87 (br, 1H), 6.69 (s, 1H), 6.21 (s, 1H), 6.01 (s, 1H), 5.96 (s, 1H), 4.97 (s, 2H), 4.93 (br, 1H), 4.85 (br, 2H), 3.80 (s, 3H), 3,19 (s, 3H), 2.91 (br, 2H), 2.22 (s, 3H), 2.20 (s, 3H), 2.05 (s, 3H), 1.32 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 151.5, 151.3, 151.1, 150.9, 150.1, 150.1, 150.1, 146.7, 143.1, 143.0, 142.2, 142.1, 136.7, 136.6, 135.8, 134.7, 134.7, 132.0, 131.5, 129.2, 129.1, 128.4, 128.4, 128.2, 127.9, 127.9, 127.9, 127.7, 127.5, 126.2, 121.3, 120.8, 115.4, 115.2, 114.0, 113.9, 101.7, 97.0, 96.5, 80.8, 80.7, 77.3, 77.2, 77.0, 76.7, 74.2, 62.4, 62.3, 60.1, 60.0, 57.2, 55.7, 39.1, 38.8, 37.4, 37.4, 27.8, 27.5, 20.4, 16.3, 15.2, 9.6; HRMS (FAB^+) m/z: Calcd. for $C_{39}H_{45}IN_2O_{12}S$ (M^+) 892.1738, found 892.1750.

Tricycle 21



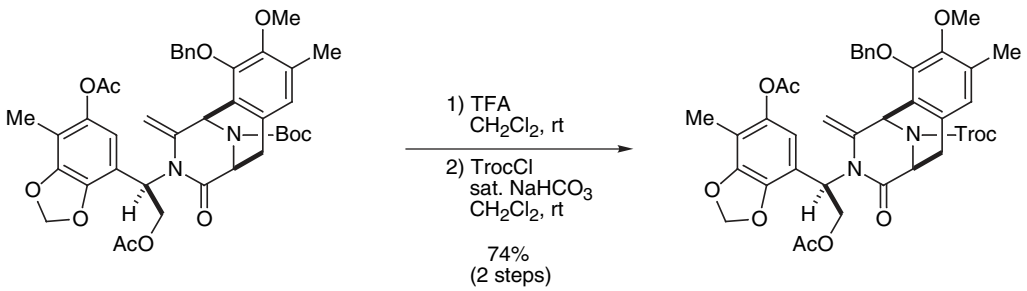
To a degassed mixture of **20** (6.27 g, 7.02 mmol), tris(*o*-tolyl)phosphine (428 mg, 1.41 mmol, 0.2 equiv), and TEA (4.0 ml, 29 mmol, 4.1 equiv) in CH_3CN (50 ml) under argon was added tris(dibenzylideneacetone)dipalladium(0) ($Pd_2(dba)_3$) (325 mg, 0.36 mmol, 5 mol%), and the solution was heated at reflux for 2 h. The reaction mixture was diluted with EtOAc and concentrated under reduced pressure. The residue was dissolved in EtOAc and sequentially washed with 10% aqueous citric acid, saturated aqueous $NaHCO_3$, and saturated aqueous NaCl. The organic phase was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash column chromatography (50% EtOAc in *n*-hexane) to afford **21** (4.44 g, 5.81 mmol, 83%) as a yellow solid. $[\alpha]_D^{27}$ +38 ° (c = 1.9, $CHCl_3$); IR (neat film) 1743, 1699, 1636, 1424, 1367, 1309, 1233, 1173, 1113, 1065, 861, 808 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.26-7.70 (m, 5H), 6.60-6.75 (br, 1H), 6.30-6.50 (br, 1H), 5.65-6.20 (br, 3H), 4.20-5.30 (br, 8H), 3.80 (s, 3H), 3.09 (s, 3H), 2.90-3.30 (br, 2H), 2.24 (s, 3H), 2.15 (s, 3H), 1.68 (s, 3H), 1.46 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 149.7, 148.8, 147.0, 142.9, 142.6, 137.6, 132.3, 128.5, 127.8, 125.7, 115.2, 115.2, 114.0, 113.2, 113.1, 113.0, 113.0, 112.9, 101.8, 96.3, 95.4, 81.1, 74.1, 73.7, 60.3, 60.2, 59.9, 54.0, 54.0, 52.6, 50.5, 50.5, 37.5, 31.9, 28.3, 20.1, 15.7, 9.9; HRMS (FAB^+) m/z: Calcd. for $C_{39}H_{45}N_2O_{12}S$ $(M+H)^+$ 765.2693, found 765.2653.

Acetate



To a solution of **21** (120 mg, 0.157 mmol) in MeOH (1.5 ml) was added 2 M aqueous NaOH (0.5 ml, 1 mmol, 6 equiv), and the resulting mixture was heated at reflux for 2.5 h. The reaction mixture was diluted with a mixture of Et_2O and H_2O, acidified with 1 M aqueous HCl, and extracted with EtOAc. The organic phase was sequentially washed with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. To a solution of the crude product in CH_2Cl_2 (1 ml) at room temperature were added pyridine (0.26ml, 3.2 mmol, 20 equiv), acetic anhydride (0.15 ml, 1.6 mmol, 10 equiv), and DMAP (1 mg, 0.008 mmol). The reaction mixture was concentrated under reduced pressure, and the residue was purified by flash column chromatography (30% EtOAc in *n*-hexane) to afford the acetate (106 mg, 0.145 mmol, 93% in 2 steps) as a white solid. $[\alpha]_D^{26}$ +47 ° (c = 1.3, $CHCl_3$); IR (neat film) 1766, 1746, 1699, 1634, 1484, 1427, 1368, 1307, 1208, 1183, 1109, 1081, 937, 913, 862; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26-7.42 (m, 5H), 6.64 (br, 1H), 6.13 (br, 1H), 5.70-5.95 (br, 3H), 4.15-5.30 (br, 8H), 3.73 (s, 3H), 2.90-3.20 (br, 2H), 2.19 (s, 3H), 2.17 (s, 3H), 1.89 (s, 3H), 1.51 (s, 3H), 1.39 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 169.2, 169.1, 149.8, 149.7, 149.7, 148.8, 146.8, 146.8, 146.7, 144.3, 141.8, 140.4, 137.6, 137.6, 137.6, 132.1, 132.1, 128.6, 128.5, 128.0, 128.0, 128.0, 127.9, 127.9, 127.8, 127.8, 127.7, 127.7, 127.7, 127.6, 127.6, 127.5, 127.5, 127.5, 127.5, 125.7, 125.7, 125.7, 125.7, 115.3, 115.2, 115.2, 115.2, 115.2, 112.6, 112.2, 112.2, 112.2, 112.2, 101.6, 101.5, 81.0, 81.0, 81.0, 74.1, 74.1, 74.1, 73.6, 60.2, 59.6, 54.0, 52.8, 52.7, 52.7, 52.5, 52.5, 50.8, 50.8, 50.7, 50.7, 50.7, 32.0, 28.3, 20.6, 20.6, 20.0, 15.7, 9.3; HRMS (FAB$^+$) m/z: Calcd. for $C_{40}H_{45}N_2O_{11}$ $(M+H)^+$ 729.3024, found 729.3038.

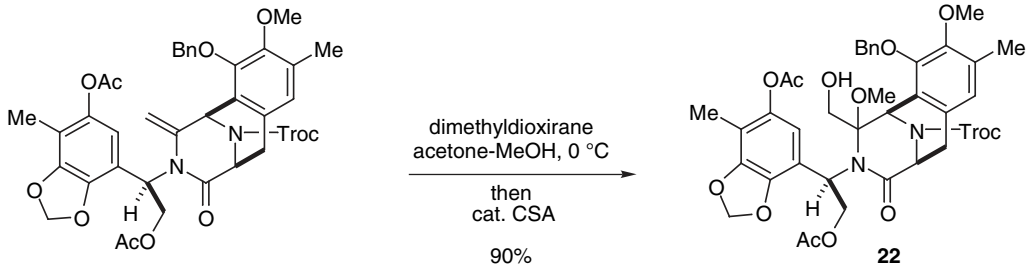
Enamide



To a solution of the acetate (2.56 g, 3.51 mmol) in CH_2Cl_2 (12 ml) was added TFA (3.0 ml, 39

mmol, 11 equiv), and the resulting mixture was stirred at room temperature for 4 h. The reaction mixture was carefully poured into cold saturated aqueous $NaHCO_3$, and extracted with CH_2Cl_2. The organic layer was concentrated under reduced pressure, and the resulting brown oil was dissolved in a mixture of CH_2Cl_2 (12 ml) and saturated aqueous $NaHCO_3$ (20 ml). To the two-phase mixture at 0 °C was added 2,2,2-trichloroethyl chloroformate (0.47 ml, 3.5 mmol, 1.0 equiv), and the reaction mixture was vigorously stirred for 10 min. The organic phase was separated, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (40% EtOAc in *n*-hexane) to afford the enamide (2.08 g, 2.59 mmol, 74% in 2 steps) as a white foam. $[\alpha]_D^{26}$ +40 ° (c = 1.1, $CHCl_3$); IR (neat film) 1763, 1724, 1684, 1636, 1486, 1429, 1368, 1353, 1298, 1222, 1209, 1184, 1124, 1078, 1031, 913, 863; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.50 (m, 5H), 6.72 & 6.74 (s, 1H), 6.22 & 6.20 (s, 1H), 6.00 & 5.96 (s, 1H), 5.87 & 5.77 (s, 2H), 4.50-5.25 (m, 9H), 4.37 & 4.29 (s, 1H), 3.79 (s, 3H), 3.10-3.30 (m, 2H), 2.25 (s, 3H), 2.24 (s, 3H), 1.95 (s, 3H), 1.55 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 169.2, 149.8, 144.3, 141.8, 137.4, 132.5, 128.5, 128.5, 127.9, 127.8, 127.6, 125.7, 124.8, 115.0, 112.5, 112.2, 101.5, 95.1, 75.0, 74.0, 73.8, 60.2, 53.9, 53.3, 52.5, 32.2, 31.8, 20.6, 19.9, 15.7, 9.2; HRMS (FAB$^+$) m/z: Calcd. for $C_{38}H_{37}Cl_3N_2O_{11}$ (M^+) 802.1463, found 802.1413.

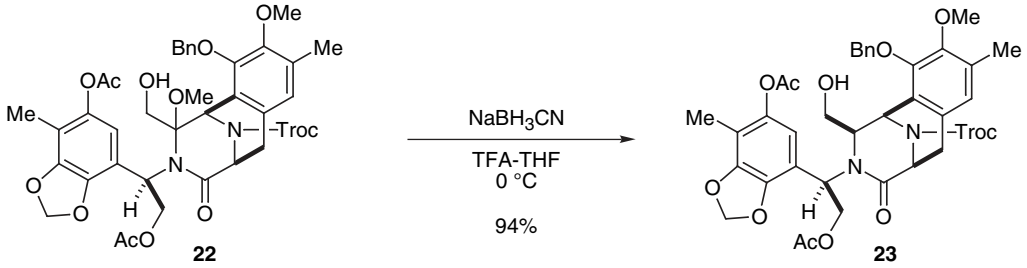
Methoxyalcohol 22



To a solution of the enamide (681 mg, 0.847 mmol) in MeOH (15.0 ml) at 0 °C was added freshly prepared dimethyldioxirane (0.1 M solution in acetone, 15 ml, 1.5 mmol, 2 equiv), and the resulting mixture was stirred at this temperature for 2 h. To the reaction mixture was added anhydrous Na_2SO_4 (10 g), and the resulting slurry was stirred for 10 minutes. To the reaction mixture was added CSA (7.2 mg, 0.03 mmol, 4 mol%) and allowed to warm to room temperature, and the mixture was neutralized with pyridine (25 μl, 0.31 mmol, 0.4 equiv), filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (50% EtOAc in *n*-hexane) to afford **22** (652 mg, 0.765 mmol, 90%) as a yellow foam. $[\alpha]_D^{23}$ +66 ° (c = 1.3, $CHCl_3$); IR (neat film) 3445, 1722, 1668, 1418, 1369, 1339, 1300, 1228, 1183, 1124, 1097 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.60 (m, 5H), 6.60-6.80 (br, 2H), 5.78-5.95 (br, 3H), 5.28 (br, 1H), 5.16 (br, 1H), 5.06 (br, 1H), 4.75-4.95 (m, 4H), 4.60-4.75 (m, 2H), 3.82 & 3.76 (s, 3H), 3.65-3.90 (m, 1H), 3.61 & 3.50 (s, 3H), 3.45 (dd, *J* = 12.0, 6.0 Hz, 1H), 3.27 & 3.25 (dd, *J* = 16.0, 8.0 Hz, 1H), 3.13 & 3.12 (d, *J* = 16.0 Hz, 1H), 2.25 (s, 3H), 2.21 (s, 3H), 2.01 (s, 3H), 1.91 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 170.8, 170.3, 170.2, 168.7, 151.7, 151.6, 149.5, 149.4, 148.6, 148.1, 145.9, 145.9,

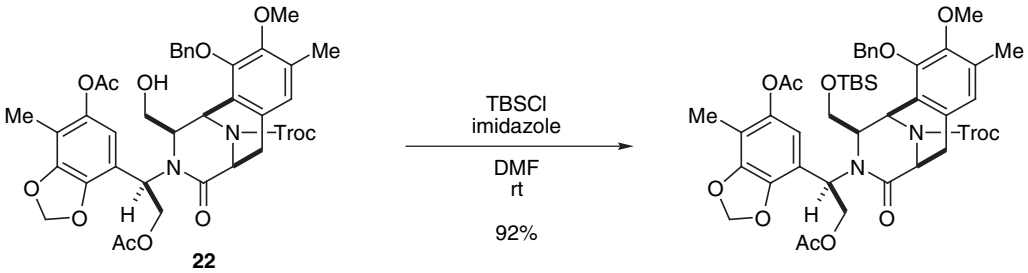
144.2, 141.8, 141.7, 136.4, 136.2, 133.1, 132.9, 129.3, 129.1, 129.0, 128.6, 128.5, 128.4, 128.2, 128.0, 127.6, 126.6, 126.5, 123.6, 123.3, 116.7, 114.3, 114.2, 112.8, 112.7, 101.3, 101.3, 95.0, 94.8, 93.3, 92.9, 77.2, 76.2, 75.3, 75.2, 74.9, 63.5, 62.8, 62.1, 60.3, 53.2, 52.7, 51.6, 51.2, 51.2, 51.0, 50.8, 50.3, 30.5, 29.9, 20.8, 20.4, 15.7, 9.2; HRMS (FAB$^+$) m/z: Calcd. for $C_{38}H_{38}Cl_3N_2O_{12}$ (M–MeO)$^+$ 819.1490, found 819.1467.

Alcohol 23



To a solution of sodium cyanoborohydride (330 mg, 5.25 mmol, 10 equiv) in TFA (9.0 ml) at 0 °C was added **22** (440 mg, 0.516 mmol) in THF (1.5 ml), and the resulting mixture was stirred at this temperature for 30 min. The reaction mixture was diluted with $CHCl_3$ and carefully poured into vigorously stirred saturated aqueous $NaHCO_3$. The organic layer was separated, washed with saturated aqueous NaCl, and concentrated under reduced pressure. The residue was purified by flash column chromatography (50% EtOAc in *n*-hexane) to afford **23** (400 mg, 0.535 mmol, 94%) as a white foam. $[\alpha]_D^{22}$ +33 ° (c = 1.2, $CHCl_3$); IR (neat film) 3510, 1764, 1722, 1664, 1484, 1428, 1369, 1342, 1304, 1227, 1185, 1126, 1062, 938, 911 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J*= 6.8 Hz, 2H), 7.38-7.48 (m, 3H), 6.83 & 6.80 (s, 1H), 6.36 & 6.33 (s, 1H), 5.78-5.87 (m, 3H), 5.40 (br, 1H), 5.26-5.30 (m, 1H), 5.11-5.16 (m, 1H), 4.70-4.93 (m, 3H), 4.52 (br, 1H), 4.44 (m, 1H), 3.91 & 3.87 (s, 3H), 3.55-3.65 (br, 2H), 3.00-3.30 (m, 3H), 2.29 & 2.28 (s, 3H), 2.22 (s, 3H), 1.95 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 170.3, 170.2, 169.8, 169.1, 152.0, 151.6, 149.4, 149.0, 148.5, 146.5, 146.4, 144.3, 144.2, 142.0, 142.0, 135.2, 135.2, 133.4, 133.2, 129.4, 129.2, 129.2, 129.1, 129.0, 129.0, 128.9, 127.3, 127.2, 122.3, 121.8, 113.7, 113.5, 113.1, 113.0, 101.7, 101.6, 95.2, 95.1, 77.2, 76.4, 75.2, 75.1, 62.7, 62.6, 60.5, 60.5, 59.5, 53.9, 53.2, 47.5, 46.9, 31.9, 31.6, 20.7, 20.6, 20.6, 15.7, 9.3; HRMS (FAB$^+$) m/z: Calcd. for $C_{38}H_{40}Cl_3N_2O_{12}$ (M+H)$^+$ 821.1647, found 821.1671.

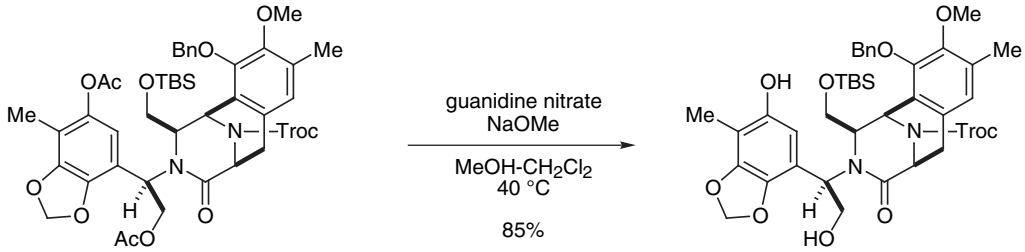
Silyl Ether



To a mixture of **23** (101 mg, 0.123 mmol) and imidazole (21.3 mg 0.313 mmol, 2.5 equiv) in

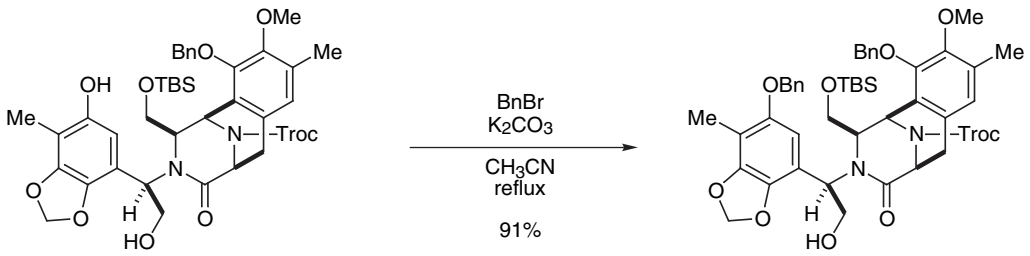
DMF (0.10 ml) was added TBSCl (28.0 mg, 0.186 mmol, 1.5 equiv), and the mixture was stirred at room temperature for 2h. The reaction mixture was directly purified by flash column chromatography (40% EtOAc in *n*-hexane) to afford the silyl ether (106 mg, 0.127 mmol, 92%) as a colorless oil. $[\alpha]_D^{23}$ –8.0 ° (c = 1.3, $CHCl_3$); IR (neat film) 1766, 1723, 1669, 1424, 1368, 1340, 1299, 1255, 1208, 1184, 1126, 1097, 1036, 1006, 935, 908, 838 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32-7.60 (m, 5H), 6.78 & 6.78 (s, 1H), 5.99 & 5.98 (s, 1H), 5.68-5.78 (m, 2H), 5.60-5.68 (m, 2H), 5.13-5.28 (br, 1H), 4.96-5.07 (br, 1H), 4.64-4.90 (m, 5H), 4.49 (dd, *J* = 15.6, 12.0 Hz, 1H), 4.17 (ddd, *J* = 15.6, 8.8, 4.0 Hz, 1H), 3.87 & 3.84 (s, 3H), 3.21 (dd, *J* = 12.0, 8.8 Hz, 1H), 3.17 (br, 2H), 2.29 & 2.28 (s, 3H), 2.18 (s, 3H), 2.02 & 2.00 (s, 3H), 1.91 (s, 3H), 0.69 & 0.68 (s, 9H), –0.26 & –0.29 (s, 3H), –0.33 & –0.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 168.9, 168.8, 168.5, 153.4, 152.2, 151.5, 150.0, 148.6, 148.1, 146.1, 145.0, 143.7, 143.2, 141.1, 141.1, 139.4, 136.7, 134.4, 132.7, 132.5, 129.3, 129.1, 128.9, 128.7, 128.7, 128.6, 128.5, 128.4, 126.1, 123.2, 122.7, 116.8, 113.0, 113.0, 111.4, 101.0, 101.0, 95.3, 95.1, 75.5, 75.2, 75.1, 67.3, 66.5, 62.7, 62.7, 62.6, 60.3, 60.3, 55.0, 54.9, 53.5, 52.8, 48.1, 47.5, 31.9, 31.7, 25.5, 20.9, 20.9, 20.6, 17.8, 17.8, 15.9, 9.1, –5.9, –6.0, –6.1, –6.3; HRMS (FAB$^+$) m/z: Calcd. for $C_{14}H_{54}Cl_3N_2O_{12}Si$ $(M+H)^+$ 935.2511, found 935.2400.

Phenol



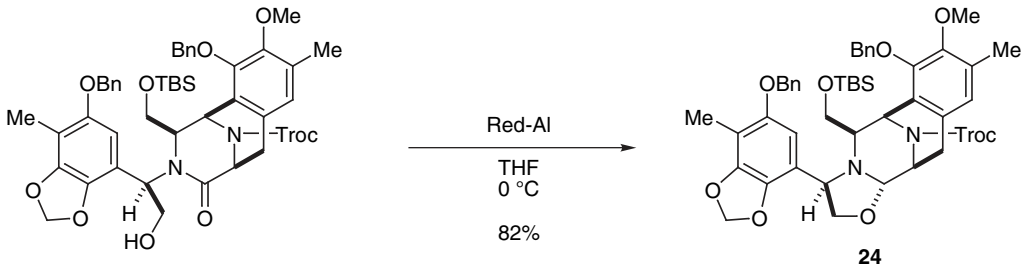
The alcohol (524 mg, 0.560 mmol) was dissolved in guanidine/guanidinium nitrate solution (8.0 ml)[29]. The mixture was stirred at 40 °C for 2.5 h. The reaction mixture was diluted with EtOAc, and sequentially washed with 1M HCl, saturate aqueous $NaHCO_3$, and saturated aqueous NaCl. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography (50% EtoAc in *n*-hexane) to afford the phenol (405 mg, 0.475 mmol, 85%) as a yellow foam. $[\alpha]_D^{23}$ –34 ° (c = 1.5, $CHCl_3$); IR (neat film) 3309, 1723, 1640, 1423, 1345, 1304, 1257, 1133, 1127, 1095, 838 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35-7.54 (m, 5H), 6.87 & 6.83 (s, 1H), 6.30 (br, 1H), 5.35-5.73 (m, 5H), 5.17-5.28 (m, 1H), 5.06-5.16 (m, 1H), 4.98 & 4.90 (d, *J* = 12.0 Hz, 1H), 4.60-4.86 (m, 3H), 4.27-4.40 (m, 3H), 4.08 (br, 1H), 3.80 &3.74 (s, 3H), 3.15-3.35 (m, 3H), 2.28 (s, 3H), 1.94 & 1.91 (s, 3H), 0,69 & 0.68 (s, 9H), –0.27 & –0.30 (s, 3H), –0.32 & –0.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.9, 151.3, 150.1, 149.4, 148.7, 146.0, 136.6, 136.4, 133.2, 132.8, 129.2, 129.1, 128.7, 128.7, 128.6, 128.5, 128.4, 128.4, 126.5, 126.3, 123.2, 116.1, 106.3, 106.2, 105.0, 100.2, 95.0, 75.5, 75.3, 75.1, 68.3, 67.3, 63.1, 62.9, 62.0, 60.2, 58.7, 58.7, 53.6, 53.0, 48.8, 47.9, 32.2, 25.5, 17.8, 17.8, 15.6, 15.6, 8.4, 8.4, –5.9, –6.0, –6.1, –6.2; HRMS (FAB$^+$) m/z: Calcd. for $C_{40}H_{50}Cl_3N_2O_{10}Si$ $(M+H)^+$ 851.2300, found 851.2337.

Benzyl Ether



To a mixture of the phenol (404 mg, 0.474 mmol) and K_2CO_3 (196 mg, 1.42 mmol, 3.0 equiv) in CH_3CN (6.0 ml) was added benzyl bromide (73.0 μl, 0.615 mmol, 1.3 equiv), and the resulting mixture was heated at reflux for 1 h. After cooling, the reaction mixture was diluted with $CHCl_3$ and filtered through a pad of Celite. The filtrate was concentrated under reduced pressure, and the residue was purified by flash column chromatography (50% EtOAc in *n*-hexane) to afford the benzyl ether (409 mg, 0.434 mmol, 91%) as a yellow foam. $[\alpha]_D^{23}$ –37 ° (c = 2.1, $CHCl_3$); IR (neat film) 3749, 1717, 1419, 1340, 1253, 1111, 838 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.30-7.60 (m, 10H), 6.77 & 6.73 (s, 1H), 5.83 (s, 1H), 5.77 (br, 2H), 5.69 (s, 1H), 5.51 (br, 1H), 5.22 & 5.21 (d, *J* = 10.0 Hz, 1H), 5.14 (br, 1H), 5.00 & 4.88 (d, *J* = 11.6 Hz, 1H), 4.74 (d, *J* = 11.6 Hz, 1H), 4.68 (d, *J* = 10.0 Hz, 1H), 4.59 (d, *J* = 10 8 Hz, 1H), 4.50 & 4.46 (d, *J* = 11,6 Hz, 1H), 4.37 & 4.25 (br, 1H), 4.30 & 4.29 (d, *J* = 10.8 Hz, 1H), 4.05 & 3.95 (br, 2H), 3.80 & 3.75 (s, 3H), 3.13-3.37 (m, 3H), 1.99 & 1.96 (s, 9H), –0.27 & –0.32 (s, 3H), –0.33 & –0.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 152.1, 152.1, 150.0, 148.8, 146.2, 137.2, 137.1, 136.5, 133.1, 129.2, 128.7, 128.7, 128.6, 128.6, 128.5, 128.5, 128.0, 127.9, 127.8, 126.4, 126.3, 123.3, 115.8, 108.1, 102.6, 100.6, 75.5, 75.3, 75.2, 70.8, 67.5, 66.7, 63.5, 62.3, 60.3, 60.3, 59.8, 53.4, 52.7, 47.9, 47.2, 32.0, 31.5, 25.5, 22.6, 17.8, 15.5, 14.1, 8.7, –5.9, –6.0, –6.3; LRMS (FAB^+) m/z: 940.5 (M^+).

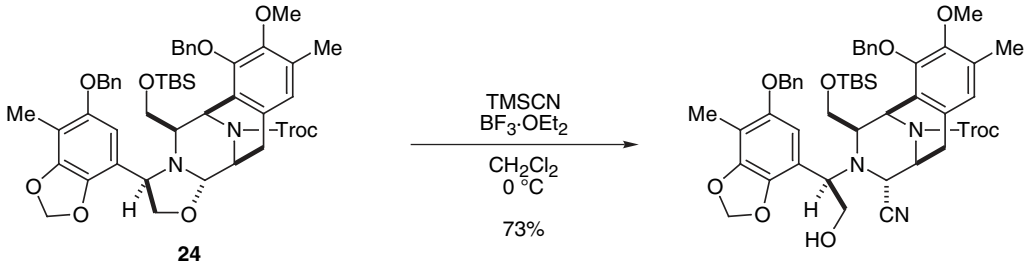
Oxazolidine 24



24

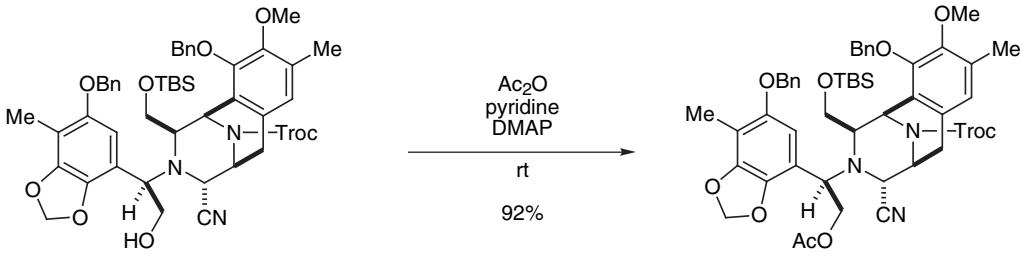
To a solution of the benzyl ether (224 mg, 0.238 mmol) in THF (2.0 ml) at 0 °C was slowly added Red-Al (1.3 M solution in toluene, 0.25 ml, 0.325 mmol, 1.4 equiv). The reaction mixture was quenched with 1M aqueous HCl, and extracted with EtOAc. The organic layer was sequentially washed with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (30% EtOAc in *n*-hexane) to afford **24** (181 mg, 0.195 mmol, 82%) as a white foam. $[\alpha]_D^{22}$ –37 ° (c = 1.2, $CHCl_3$); IR (neat film) 1717, 1435, 1263, 1118, 1024, 840 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 8.0 Hz, 1H), 7.50 (d, *J* = 6.8 Hz, 1H), 7.26-7.49 (m, 8H), 6.77 & 6.73 (s, 1H), 6.41 & 6.40 (s, 1H) 5.86 (s, 1H), 5.77 (s, 1H), 5.57 & 5.51 (s, 1H), 5.41 (br, 1H), 5.21 (dd, *J* = 10.4, 10.4 Hz, 1H), 4.93 (dd, *J* = 7.2, 6.0 Hz, 1H), 4.69-5.02 (m, 5H), 4.20-4.35 (m, 3H), 3.87 & 3.83 (s, 3H), 3.74 (m, 1H), 3.14-3.35 (m, 3H), 2.73 (dd, *J* = 17.6, 6.0 Hz, 1H), 2.21 (s, 3H), 2.09 (s, 3H), 0.71 & 0.69 (s, 9H), –0.21 & –0.26 (s, 3H), –0.27 & –0.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.1, 153.5, 151.8, 149.5, 149.4, 148.1, 147.6, 146.5, 138.2, 137.4, 137.3, 131.4, 131.2, 130.2, 129.9, 128.6, 128.5, 128.4, 128.3, 128.0, 127.9, 127.7, 127.7, 127.2, 127.2, 125.5, 125.0, 124.4, 120.7, 120.6, 107.9, 101.9, 101.7, 100.7, 100.6, 95.4, 92.1, 92.1, 75.5, 75.2, 75.0, 74.8, 70.3, 68.9, 68.3, 68.1, 66.7, 66.6, 60.5, 60.3, 60.2, 60.1, 60.0, 59.9, 48.5, 48.1, 47.5, 46.7, 30.7, 30.5, 25.6, 17.8, 15.7, 15.7, 8.7, –5.9, –5.9, –6.0, –6.0; LRMS (FAB^+) m/z: 925.3 $(M+H)^+$.

Aminonitrile



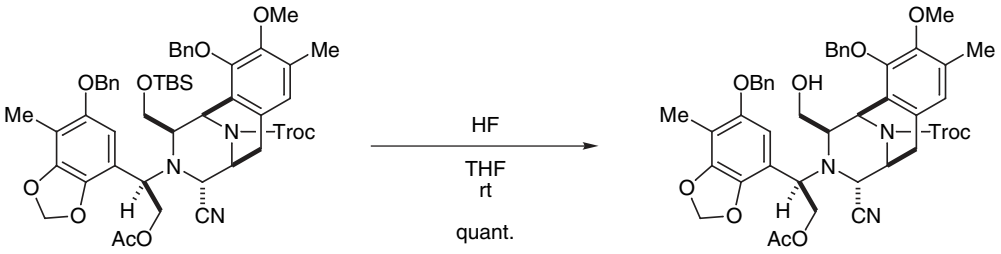
To a mixture of **24** (295 mg, 0.318 mmol) and trimethylsilyl cyanide (127 μl, 0.952 mmol, 3.0 equiv) in CH_2Cl_2 (5.0 ml) at 0 °C was added $BF_3{\cdot}OEt_2$ (1.0 M solution in CH_2Cl_2, 480 μl, 0.48 mmol, 1.5 equiv). The reaction mixture was poured into cold saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure, and the resulting crude product was purified by flash column chromatography (50% EtOAc in *n*-hexane) to afford the aminonitrile (221 mg, 0.23 mmol, 73%) as a white solid. $[\alpha]_D^{23}$ +47 ° (c = 1.6, $CHCl_3$); IR (neat film) 3457, 1718, 1498, 1429, 1309, 1259, 1120, 1065, 902 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.26-7.60 (m, 10H), 6.46 & 6.50 (s, 1H), 5.92 & 5.91 (s, 1H), 5.63 (s, 1H), 5.30-5.47 (m, 2H), 4.85-5.30 (m, 3H), 4.65-4.80 (m, 2H), 4.35-4.53 (m, 2H), 4.20-4.35 (m, 2H), 3.88 & 3.82 (s, 3H), 3.80-4.00 (m, 2H), 3.35-3.50 (m, 2H), 3.15 & 3.20 (d, *J* = 8.0 Hz, 1H), 2.75 & 2.80 (dd, *J* = 17.0, 6.0 Hz, 1H), 2.20 & 2.19 (s, 3H), 2.17 (s, 3H), 1.60 & 1.50 (d, *J* = 17.0 Hz, 1H), 0.77 & 0.75 (s, 9H), –0.04 & –0.10 (s, 3H), –0.09 & –0.15 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.7, 152.3, 151.2, 151.0, 149.0, 148.9, 147.6, 147.0, 146.6, 139.5, 139.5, 137.5, 137.3, 137.1, 131.5, 131.1, 130.9, 130.6, 128.9, 128.7, 128.6, 128.5, 128.2, 128.1, 128.1, 127.9, 127.8, 127.1, 125.4, 125.1, 125.0, 124.8, 117.8, 117.7, 115.8, 109.6, 109.5, 103.5, 100.5, 95.2, 75.8, 75.3, 75.1, 75.0, 70.5, 70.3, 63.7, 63.6, 62.5, 61.9, 60.3, 60.2, 56.3, 56.1, 51.1, 50.9, 50.4, 49.6, 49.3, 49.1, 29.9, 29.7, 25.7, 18.2, 18.2, 15.6, 8.9, –5.6, –5.7, –6.0, –6.2; HRMS (FAB^+) m/z: Calcd. for $C_{47}H_{56}Cl_3N_2O_9Si$ $(M–CN)^+$ 925.2820, found 925.2774.

Acetate



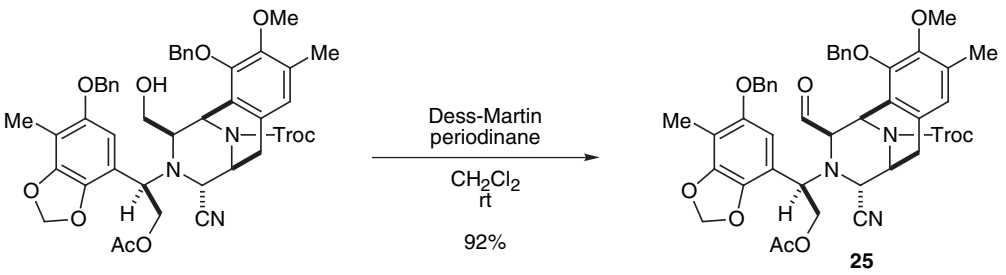
To a solution of the aminonitrile (221 mg, 0.232 mmol) in a mixture of acetic anhydride (1.0 ml) and pyridine (2.0 ml) was added DMAP (5.6 mg, 0.05 mmol, 0.2 equiv), and the mixture was stirred at room temperature. The reaction mixture was concentrated under reduced pressure, and the resulting residue was purified by flash column chromatography (30% EtOAc in *n*-hexane) to afford the acetate (213 mg, 0.214 mmol, 92%) as a white solid. $[\alpha]_D^{23}$ +50 ° (c = 1.8, $CHCl_3$); IR (neat film) 1720, 1430, 1251, 1122, 840cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26-7.65 (m, 10H), 6.52, 6.49 (s, 1H), 6.10 (br, 1H), 5.67 (s, 1H), 5.50 & 5.35 (s, 1H), 5.37 (s, 1H), 4.55-5.30 (m, 8H), 5.50-5.55 (m, 3H), 3.89 & 3.83 (s, 3H), 3.65-3.80 (br, 1H), 3.40-3.55 (br, 2H), 2.85 & 2.80 (dd, *J* = 17.6, 8.0 Hz, 1H), 2.20-2.30 (br, 6H), 1.90-2.00 (br, 3H), 1.53 & 1.65 (d, *J* = 17.0 Hz, 1H), 0.77 (br, 9H), –0.04 & –0.11 (s, 3H), –0.08 & –0.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 170.1, 152.6, 152.2, 151.0, 150.8, 149.0, 148.9, 147.6, 147.0, 146.7, 139.7, 139.7, 137.6, 137.4, 137.2, 131.2, 130.9, 130.6, 128.6, 128.6, 128.5, 128.4, 128.4, 128.1, 128.0, 127.8, 127.7, 127.1, 125.4, 124.9, 124.9, 124.8, 117.9, 1117.9, 117.8, 115.6, 115.6, 109.4, 109.3, 103.6, 103.5, 100.5, 95.2, 95.1, 75.6, 75.2, 75.1, 74.8, 70.4, 70.2, 63.3, 63.1, 61.9, 61.2, 60.2, 59.3, 54.2, 54.0, 51.8, 51.6, 50.2, 49.3, 49.1, 48.7, 29.8, 29.7, 25.7, 20.8, 20.8, 18.1, 18.1, 15.5, 8.9, –5.7, –5.8, -6.0, –6.1; LRMS (FAB$^+$) m/z: 993.5 (M$^+$).

Alcohol



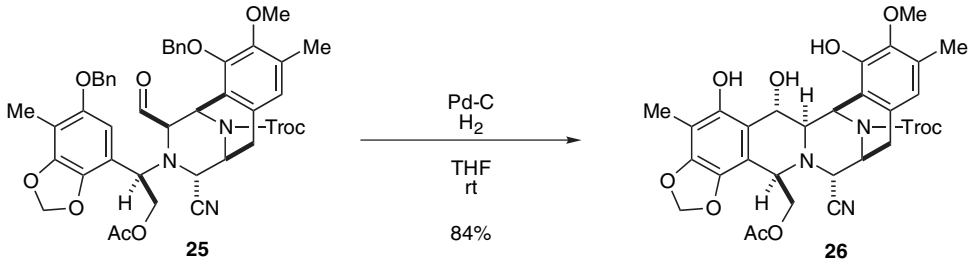
To a solution of the acetate (200 mg, 0.20 mmol) in CH_3CN (2.0 ml) was added HF (48 wt. % solution in H_2O, 1.0 ml, 28 mmol), and the mixture was stirred at room temperature for 3 h. The reaction mixture was poured into saturated aqueous $NaHCO_3$ and extracted with EtOAc. The organic layer was washed with saturated aqueous NaCl, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography (40% EtOAc in *n*-hexane) to afford the alcohol (180 mg, 0.20 mmol, quant) as a white foam. $[\alpha]_D^{24}$ +67 ° (c = 2.3, $CHCl_3$); IR (neat film) 3504, 1717, 1453, 1436, 1373, 1312, 1258, 1236, 1122, 1058 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.26-7.70 (m, 10H), 6.60 & 6.56 (s, 1H), 5.85 (s, 1H), 5.70 (s, 1H), 5.69 & 5.59 (s, 1H), 5.48 & 5.46 (s, 1H), 5.23 & 5.25 (d, *J* = 10 Hz, 1H), 4.80-5.02 (m, 4H), 4.50-4.75 (m, 3H), 4.35 (m, 1H), 4.10 (m, 1H), 3.98 (m, 1H), 3.93 & 3.85 (s, 3H), 3.75 (m, 1H), 3.58 & 3.52 (d, *J* = 2.0 Hz, 1H), 3.48 (m, 1H), 3.30 (m, 1H), 2.95 & 2.88 (dd, *J* = 17.2, 8.0 Hz, 1H), 2.19 (s, 3H), 2.16 (s, 3H), 2.07 (s, 3H), 1.80 & 1.69 (d, *J* = 17.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 170.3, 152.8, 152.3, 151.5, 151.3, 148.5, 148.4, 148.1, 147.4, 146.6, 139.2, 139.2, 137.2, 137.1, 135.8, 135.6, 131.5, 131.4, 131.2, 131.1, 128.9, 128.8, 127.9, 127.8, 127.0, 125.6, 124.6, 124.1, 117.4, 117.4, 114.5, 110.0, 109.9, 103.4, 100.7, 95.2, 95.1, 75.3, 75.1, 70.4, 70.3, 61.3, 61.3, 61.2, 60.6, 60.6, 60.5, 59.9, 53.4, 53.1, 51.8, 51.6, 50.1, 49.0, 48.8, 48.3, 30.1, 29.9, 20.8, 15.6, 8.9; HRMS (FAB^+) m/z: Calcd. for $C_{43}H_{44}Cl_3N_2O_{10}$ $(M–CN)^+$ 853.2061, found 853.2082.

Aldehyde 25



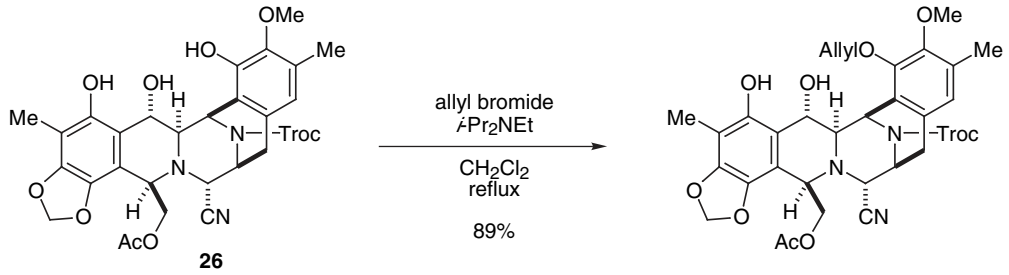
To a solution of the alcohol (180 mg, 0.204 mmol) in CH_2Cl_2 (2.5 ml) at room temperature was added Dess-Martin periodinane (103 mg, 0.243 mmol, 1.2 equiv), and the resulting slurry was stirred at room temperature for 40 min. Excess reagent was quenched with 2-propanol (2 drops), and the mixture was diluted with Et_2O, filtered through a pad of Celite, and concentrated under reduced pressure. The residue was dissolved in EtOAc, and sequentially washed with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl. The organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure, and the resultant residue was purified by flash column chromatography (40% EtOAc in *n*-hexane) to afford **25** (165 mg, 0.188 mmol, 92%) as a white foam. $[\alpha]_D^{24}$ +23 ° (c = 0.90, $CHCl_3$); IR (neat film) 1732, 1607, 1584, 1488, 1428, 1382, 1315, 1238, 1122, 1035, 939, 906, 826 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.17 & 9.12 (d, *J* = 2.8 Hz), 7.23-7.45 (m, 10H), 6.61 & 6.59 (s, 1H), 5.93 (br, 1H), 5.80 (br, 1H), 5.75 & 5.72 (br, 1H), 5.62 (br, 1H), 5.21 & 5.18 (d, *J* = 10.8 Hz, 1H), 4.65-5.00 (m, 8H), 4.27-4.52 (m, 3H), 3.78 & 3.71 (s, 3H), 3.68 (br, 1H), 3.13 & 3.08 (dd, *J* = 17.6, 8.0 Hz, 1H), 2.12 (br, 1H), 2.04-2.11 (br, 6H), 2.01 & 2.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.9, 196.4, 170.2, 152.4, 152.1, 146.7, 139.8, 137.1, 137.1, 132.0, 130.5, 128.6, 128.5, 128.4, 128.0, 128.0, 127.9, 127.9, 127.8, 127.2, 127.2, 127.0, 125.0, 124.9, 123.9, 113.5, 113.4, 110.4, 103.9, 100.9, 95.0, 75.3, 75.3, 74.4, 70.5, 70.4, 68.9, 68.4, 62.3, 60.5, 60.4, 56.8, 51.8, 51.7, 50.1, 49.1, 47.2, 30.0, 20.9, 15.8, 9.0; HRMS (FAB^+) m/z: Calcd. for $C_{44}H_{42}Cl_3N_3O_{10}$ (M^+) 877.1936, found 877.1921.

Pentacycle 26



A mixture of **25** (51.2 mg, 0.058 mmol) and 10% palladium on carbon (AD-type (wet, 50 % water), purchased from Kawaken Fine Chemicals Co., 51.1 mg, 0.024 mmol, 0.41 equiv) in THF (1.2 ml) was stirred under 1 atm of hydrogen at room temperature for 18 h. The reaction mixture was filtered through a pad of Cellite, and concentrated under reduced pressure. The resulting crude product was purified by flash column chromatography (50% EtOAc in *n*-hexane) to afford **26** (34.2 mg, 0.049 mmol, 84%) as a yellow film. $[\alpha]_D^{24}$ +23 ° (c = 1.4, $CHCl_3$); IR (neat film) 3749, 1722, 1623, 1587, 1501, 1435, 1380, 1317, 1265, 1232, 1127, 1105, 1056, 1032, 1012, 965 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.55 (s, 1H), 5.92 (s, 1H), 5.85 &5.80 (s, 1H), 5.83 (s, 1H), 4.91 & 4.87 (d, *J* = 8.0 Hz, 1H), 4.87 & 4.85 (d, *J* = 11.6 Hz, 1H), 4.69 & 4.67 (d, *J* = 11.6 Hz, 1H), 4.48 (d, *J* = 10.4 Hz, 1H), 4.46 (m, 1H), 4.19 (br, 1H), 4.07 (br, 1H), 3.77 & 3.76 (s, 3H), 3.66 (dd, *J* = 10.8, 8.0 Hz, 1H), 3.34 & 3.31 (dd, *J* = 10.4, 2.8 Hz, 1H), 3.25 (dd, *J* = 17.6, 8.0 Hz, 1H), 2.85 & 2.80 (d, *J* = 17.6 Hz, 1H), 2.25 & 2.24 (s, 3H), 2.09 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 153.1, 152.5, 149.3, 149.2, 145.9, 145.9, 144.0, 143.7, 142.5, 142.3, 135.4, 135.3, 131,6, 131.3, 130.1, 130.1, 123.2, 122.9, 117.0, 116.9, 115.9, 115.8, 110.0, 109.9, 108.0, 101.0, 95.3, 95.0, 75.3, 75.1, 68.9, 68.8, 64.1, 61.6, 61.5, 61.1, 61.0, 58.9, 58.8, 56.3, 49.6, 48.9, 47.1, 46.4, 30.5, 29.6, 20.2, 15.7, 15.7, 8.6; HRMS (FAB^+) m/z: Calcd. for $C_{30}H_{30}Cl_3N_3O_{10}$ (M^+) 697.0997, found 697.0983.

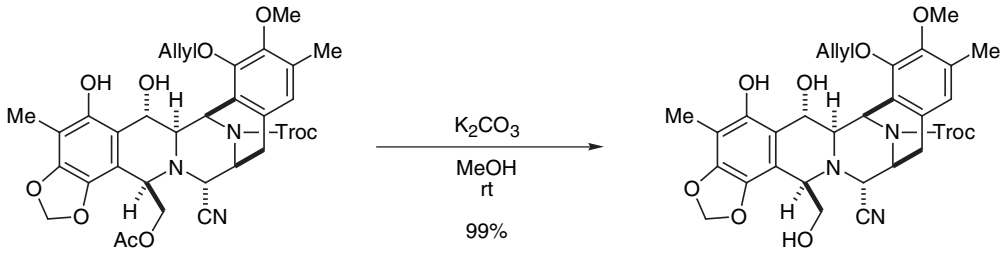
Allyl Ether



26

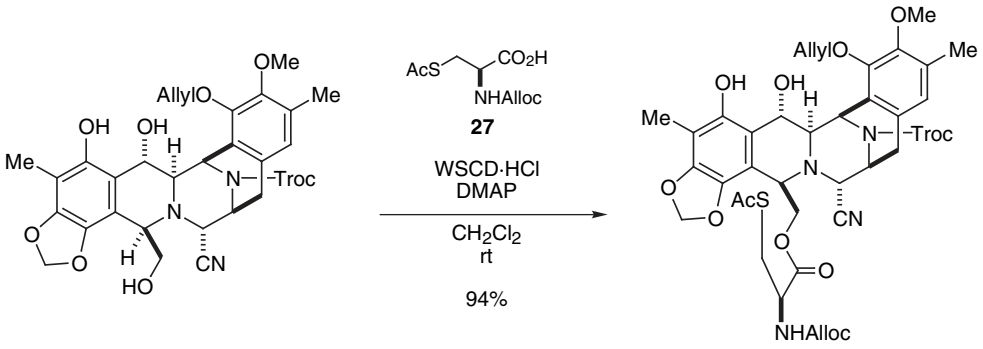
To a mixture of **26** (34.2 mg, 0.049 mmol) and *i*-Pr_2NEt (0.20 ml, 1.2 mmol, 24 equiv) in CH_2Cl_2 (1.2 ml) was added allyl bromide (40 μl, 0.47 mmol, 10 equiv), and the resulting mixture was heated at reflux for 3 h. The reaction mixture was diluted with CH_2Cl_2, and sequentially washed with 1M aqueous HCl, saturated aqueous $NaHCO_3$, and saturated aqueous NaCl. The organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (50% EtoAc in *n*-hexane) to afford the allyl ether (32.3 mg, 0.044 mmol, 89%) as a colorless film. $[\alpha]_D^{23}$ +33 ° (c = 1.2, $CHCl_3$); IR (neat film) 3290, 1724, 1435, 1378, 1338, 1313, 1297, 1264, 1227, 1125, 1102, 1057, 1032, 1013, 967, 940, 914, 827 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.65 & 9.62 (s, 1H), 6.78 & 6.76 (s, 1H), 6.22 (m, 1H), 6.12 & 6.10 (d, *J* = 17,6 Hz, 1H), 5.92 (s, 1H), 5.84 & 5.83 (s, 1H), 5.78 & 5.68 (s, 1H), 5.37-5.60 (m, 2H), 4.75-5.00 (m, 3H), 4.69 & 4.69 (d, *J* = 11.6 Hz, 1H), 4.40-4.56 (m, 2H), 4.30-4.40 (m, 1H), 4.10-4.19 (m, 1H), 4.02-4.10 (m, 1H), 3.83 & 3.82 (s, 3H), 3.65 (m, 1H), 3.17-3.32 (m, 2H), 2.85 (d, *J* = 17 6 Hz, 1H), 2.24 & 2.23 (s, 3H), 2.09 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 170.2, 152.9, 152.2, 149.4, 149.4, 148.5, 147.4, 146.9, 146.0, 145.9, 135.4, 135.4, 132.6, 132.5, 132.0, 131.4, 131.0, 127.0, 123.9, 123.1, 121.8, 121.3, 115.8, 110.0, 109.9, 109.9, 108.1, 101.1, 95.1, 76.3, 75.8, 75.6, 75.3, 69.0, 68.9, 64.2, 61.9, 61.5, 60.7, 60.6, 58.9, 56.5, 56.4, 49.8, 48.5, 47.3, 47.0, 30.4, 30.3, 20.3, 15.7, 14.3, 8.6; HRMS (FAB^+) m/z: Calcd. for $C_{33}H_{34}Cl_3N_3O_{10}$ (M^+) 737.1310, found 737.1328.

Alcohol



To a solution of the allyl ether (32.3 mg, 0.044 mmol) in MeOH (0.6 ml) was added K_2CO_3 (70.8 mg, 0.51 mmol, 12 equiv), and the resulting slurry was stirred at room temperature for 30 min. The reaction mixture was diluted with EtOAc, and sequentially washed with 10% aqueous citric acid, saturated aqueous $NaHCO_3$, and saturated aqueous NaCl. The organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The resulting crude product was purified by flash column chromatography (50% EtOAc in *n*-hexane) to afford the alcohol (30.3 mg, 0.044 mmol, 99%) as a colorless film. $[\alpha]_D^{26}$ +44 ° (c = 1.1, $CHCl_3$); IR (neat film) 3298, 1720, 1486, 1434, 1378, 1336, 1315, 1267, 1229, 1125, 1058, 1032, 965, 827 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.59 & 9.57 (s, 1H), 6.81 & 6.78 (s, 1H), 6.20 (m, 1H), 5.65-5.95 (m, 4H), 5.40-5.60 (m, 2H), 4.60-5.00 (m, 4H), 4.50 (m, 2H), 4,20-4.40 (m, 2H), 4.00 (m, 1H), 3.84 & 3.82 (s, 3H), 3.60 (m, 1H), 3.20-3.35 (m, 3H), 2.86 (d, *J* = 17.6 Hz, 1H), 2.24 & 2.23 (s, 3H), 2.06 & 2.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.8, 152.2, 149.4, 149.3, 148.7, 148.7, 147.4, 147.0, 145.8, 135.4, 135.3, 133.0, 132.7, 132.0, 130.5, 130.1, 126.5, 126.5, 123.8, 123.0, 121.7, 121.3, 115.7, 115.7, 110.2, 109.5, 109.4, 107.9, 100.9, 100.9, 95.1, 15.0, 77.2, 76.1, 75.6, 75.5, 75.2, 68.9, 68.7, 68.5, 65.5, 65.5, 62.0, 61.4, 60.6, 60.6, 59.3, 59.3, 58.3, 58.2, 49.8, 48.6, 47.4, 47.0, 30.7, 30.7, 30.6, 15.8; HRMS (FAB^+) m/z: Calcd. for $C_{30}H_{32}Cl_3N_2O_9$ $(M–CN)^+$ 669.1173, found 669.1201.

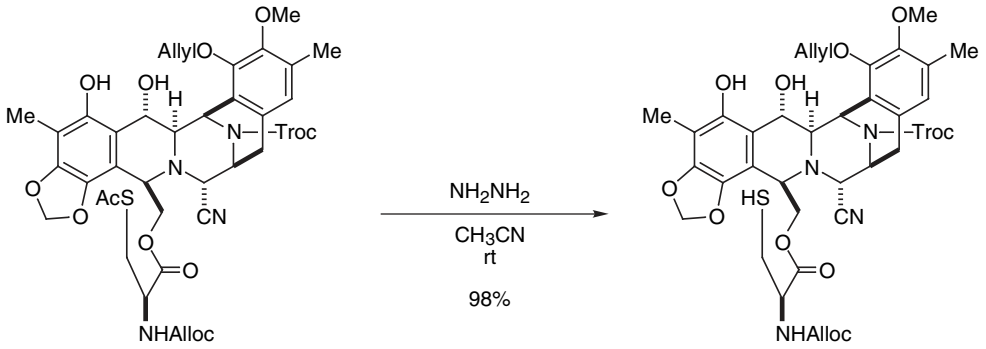
Ester 28



28

To a mixture of the alcohol (51.0 mg, 0.073 mmol) and acid **27** (42.7 mg, 0.173 mmol, 2.4 equiv) in CH_2Cl_2 (1.6 ml) at room temperature was added WSCD·HCl (37.2 mg, 0.194 mmol, 2.7 equiv) followed by DMAP (1.0 mg, 0.008 mmol, 0.1 equiv). After 10 min., the reaction mixture was diluted with CH_2Cl_2, and sequentially washed with 1M aqueous HCl, saturated aqueous $NaHCO_3$, and saturated aqueous NaCl. The organic phase was concentrated under reduced pressure, and the residue was purified by flash column chromatography (50% EtOAc in *n*-hexane) to afford **28** (64.0 mg, 0.070 mmol, 94%) as a pale yellow film. $[\alpha]_D^{21}$ +24 ° (c = 0.5, $CHCl_3$); IR (neat film) 3351, 1725, 1520, 1436, 1262, 1214, 1129, 1102, 1057 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.62 & 9.63 (s, 1H), 6.78 & 6.75 (s, 1H), 5.75-6.30 (m, 5 H), 5.00-5.75 (m, 6 H), 4.63-5.03 (m, 3H), 4.45-4.63 (m, 5H), 4.05-4.45 (m, 3H), 3.80-3.90 (br, 2H), 3.75 (s, 3H), 2.80-3.50 (m, 4H), 2.05-2.45 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.0, 169.8, 154.7, 152.0, 151.3, 148.7, 141.3, 131.7, 131.6, 131.5, 131.2, 131.2, 130.0, 125.8, 120.7, 117.2, 117.1, 108.1, 100.1, 74.4, 68.0, 65.1, 60.8, 59.9, 58.4, 55.3, 52.7, 52.0, 49.0, 46.1, 30.3, 29.7, 15.0, 15.0, 13.2, 7.7; HRMS (FAB^+) m/z: Calcd. for $C_{40}H_{43}Cl_3N_4O_{13}S$ (M^+) 924.1613, found 924.1609.

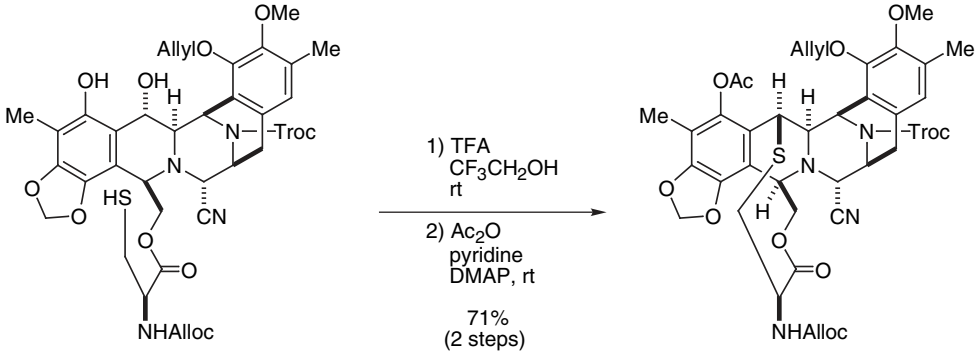
Thiol



28

To a solution of **28** (29.5 mg, 0.032 mmol) in CH_3CN (0.80 ml) was added hydrazine solution (the upper phase of a 1:3 (v/v) mixture of hydrazine hydrate and CH_3CN_3, 35 μl), and the resulting mixture was stirred at room temperature for 80 min. The reaction mixture was diluted with $CHCl_3$ and sequentially washed with 1M aqueous HCl, saturated aqueous $NaHCO_3$, and saturated aqueous NaCl. The organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford the thiol (27.8 mg, 0.031 mmol, 98%) as a colorless film. $[\alpha]_D^{24}$ +23 ° (c = 1.1, $CHCl_3$); IR (neat film) 3297, 1718, 1507, 1436, 1375, 1338, 1298, 1263, 1125, 1102, 1059, 1032, 1013, 968, 939, 827 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.50-9.65 (m, 1H), 7.26-7.40 (m, 5H), 6.72-6.83 (m, 1H), 6.23 (m, 1H), 6.12 & 6.09 (d, *J* = 4.0 Hz, 1H), 5.95 (s, 1H), 5.88 (m, 1H), 5.81 (s, 1H), 5.79 & 5.69 (s, 1H) 5.20-5.60 (m, 4H), 4.77-5.02 (m, 3H), 4.63-4.72 (m, 1H), 4.27-4.64 (m, 4H), 4.08-4.27 (m, 3H), 3.95-4.68 (m, 1H), 3.87 (s, 3H), 3.89 (s, 3H), 3.15-3.35 (m, 2H), 2.70-3.05 (m, 1H), 2.88 (d, *J* = 17.6 Hz, 1H), 2.50-2.70 (m, 2H), 2.24 & 2.25 (s, 3H), 2.08 (s, 3H), 0.85-1.45 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 169.5, 155.3, 152.8, 152.2, 149.6, 149.5, 148.6, 148.5, 147.5, 147.0, 145.9, 135.4, 135.3, 132.7, 132.5, 132.4, 132.4, 132.3, 132.0, 132.0, 131.0, 130.6, 126.7, 126.6, 123.9, 123.2, 121.7, 121.6, 121.1, 118.4, 118.2, 118.1, 115.6, 115.6, 110.0, 109.9, 109.2, 108.4, 108.2, 101.0, 95.2, 95.1, 76.2, 75.6, 75.6, 75.3, 68.9, 68.7, 68.6, 66.2, 66.1, 66.0, 65.1, 61.9, 61.4, 60.8, 60.7, 59.1, 58.8, 56.7, 55.2, 55.1, 54.8, 52.8, 49.7, 48.4, 47.1, 46.9, 46.8, 31.6, 30.5, 30.3, 30.1, 27.2, 26.8, 26.5, 22.6, 15.9, 15.8, 15.8, 14.2, 14.1, 8.6; HRMS (FAB^+) m/z: Calcd. for $C_{38}H_{41}Cl_3N_4O_{12}S$ (M^+) 882.1507, found 882.1577.

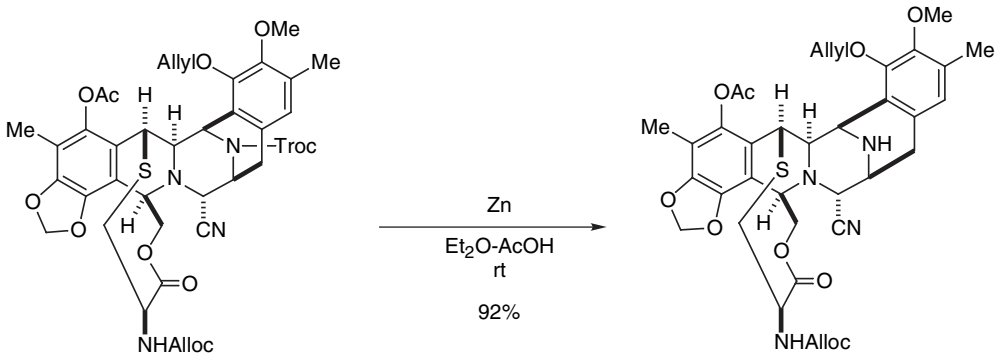
Sulfide 29



29

To a solution of the thiol (24.6 mg, 0.028 mmol) in 2,2,2-trifluoroethanol (3.0 ml) at room temperature was added TFA (10% solution in 2,2,2-trifluoroethanol, 0.15ml, 0.19 mmol, 7 equiv), and the mixture was stirred at room temperature for 3 h. The reaction mixture was diluted with a large excess of benzene (50 ml), and concentrated under reduced pressure. The resulting yellow syrup was dissolved in a mixture of acetic anhydride (0.1 ml) and pyridine (0.2ml). To the mixture at room temperature was added DMAP (1.5 mg, 0.012 mmol, 0.4 equiv), and the reaction was stirred for 30 min and concentrated under reduced pressure. The residue was purified by PTLC (30% EtOAc in *n*-hexane) to afford the sulfide **29** (18.0 mg, 0.020 mmol, 71% in 2 steps) as a colorless film. $[\alpha]_D^{23}$ –22 ° (c = 1.1, $CHCl_3$); IR (neat film) 3402, 1759, 1721, 1510, 1431, 1372, 1332, 1309, 1265, 1236, 1193, 1125, 1101, 1087, 1060, 1029, 1007, 983, 916, 826 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.79 & 6.78 (s, 1H), 6.18 (m, 1H), 6.10 (s, 1H), 6.01 & 5.99 (s, 1H), 5.94 (m, 1H), 5.45-5.68 (m, 2H), 5.22-5.35 (m, 3H), 4.97-5.15 (m, 3H), 4.65-4.90 (m, 3H), 4.42-4.63 (m, 5H), 4.33 (br, 1H), 4.15-4.27 (m, 4H), 3.81 & 3.78 (s, 3H), 3.43 (s, 1H), 3.12-3.29 (m, 2H), 2.30-2.38 (m, 2H), 2.29 & 2.28 (s, 3H), 2.26 & 2.25 (s, 3H), 2.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 168.6, 168.5, 155.3, 152.6, 152.2, 149.5, 148.9, 148.8, 148.7, 146.0, 146.0, 141.0, 140.3, 140.3, 134.6, 134.5, 132.9, 132.7, 132.7, 132.6, 130.1, 129.6, 127.1, 126.5, 125.1, 125.0, 119.5, 119.4, 118.1, 116.2, 116.2, 116.2, 116.0, 115.9, 113.9, 112.7, 112.6, 102.1, 102.1, 95.2, 95.0, 75.3, 75.3, 73.4, 72.7, 65.9, 61.3, 61.3, 60.4, 60.4, 60.4, 59.4, 59.4, 58.4, 58.2, 58.0, 57.7, 53.8, 49.0, 48.1, 47.9, 47.7, 41.2, 41.1, 32.9, 32.9, 28.1, 27.7, 20.5, 20.4, 15.8, 15.8, 9.6; HRMS (FAB^+) m/z: Calcd. for $C_{40}H_{41}Cl_3N_4O_{12}S$ (M^+) 906.1507, found 906.1494.

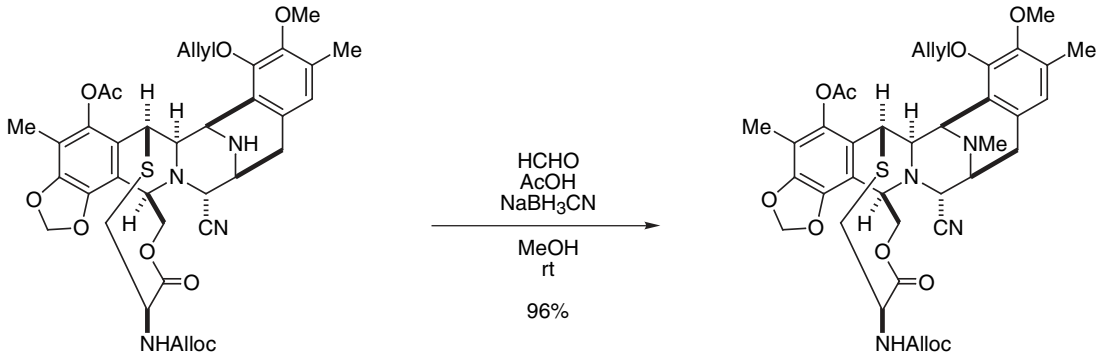
Amine



29

To a mixture of **29** (17.3 mg, 0.0190 mmol) and zinc powder (96.1 mg, 1.47 mmol, 78 equiv) in Et_2O (0.40 ml) at room temperature was added AcOH (0.20 ml), and the resulting slurry was stirred at room temperature for 2.5 hours. The reaction mixture was filtered through a pad of Celite, and the filtrate was concentrated under reduced pressure. The residue was dissolved in EtOAc, and sequentially washed with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl. The organic phase was concentrated under reduced pressure, and the crude product was purified by PTLC (50% EtOAc in *n*-hexane) to afford the amine (12.8 mg, 0.0175 mmol, 92%) as a colorless film. $[\alpha]_D^{22}$ –12 ° (c = 1.3, $CHCl_3$); IR (neat film) 3393, 1758, 1724, 1509, 1448, 1432, 1372, 1332, 1241, 1229, 1195, 1101, 1086, 1065, 915 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.80 (s, 1H), 6.09 (s, 1H), 6.08 (m, 1H), 6.00 (s, 1H), 5.95 (m, 1H), 5.44 (d, *J* = 17.6 Hz, 1H), 5.32 (d, *J* = 17.6 Hz, 1H), 5.26 (d, *J* = 12.4 Hz, 2H), 5.03 (d, *J* = 12.0 Hz, 1H), 4.70-4.80 (m, 2H), 4.26-4.55 (m, 5H), 4.25 (s, 1H), 4.10-4.19 (m, 2H), 3.83 (d, *J* = 8.8 Hz, 1H), 3.79 (s, 3H), 3.44 (d, *J* = 4.0 Hz, 1H), 3.10 (d, *J* = 17.6 Hz, 1H), 2.98 (dd, *J* = 17.6, 8.8 Hz, 1H), 2.28 (s, 3H), 2.27 (s, 3H), 2.05-2.40 (m, 2H), 2.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 168.6, 155.4, 148.6, 148.5, 145.8, 140.9, 140.3, 134.3, 132.8, 131.9, 130.4, 130.4, 125.2, 120.1, 118.0, 117.9, 116.7, 113.5, 113.2, 102.0, 73.0, 65.8, 61.4, 60.4, 60.4, 59.3, 58.8, 58.4, 53.8, 48.6, 47.9, 41.7, 32.6, 27.9, 20.4, 15.7, 9.6; HRMS (FAB^+) m/z: Calcd. for $C_{36}H_{40}N_3O_{10}S$ $(M–CN)^+$ 706.2434, found 706.2411.

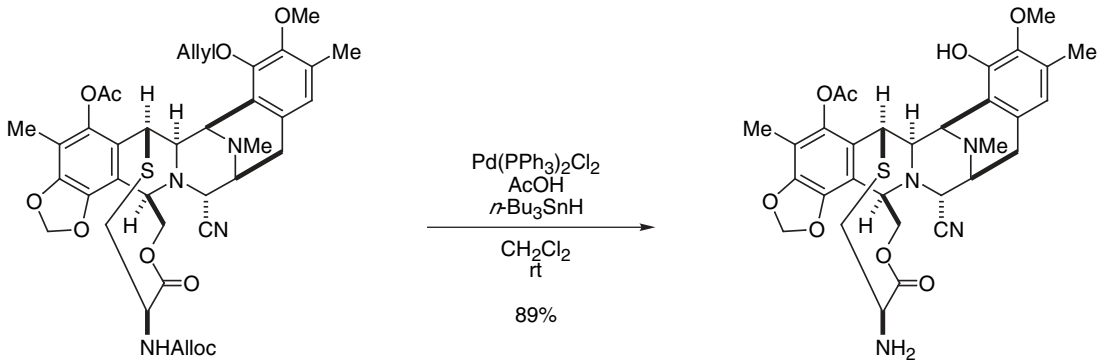
Methylamine



To a mixture of the amine (5.6 mg, 0.0076 mmol), formalin solution (30 μl), and sodium cyanoborohydride (12 mg, 0.19 mmol, 24 equiv) in MeOH (0.4 ml) was slowly added AcOH (0.10 ml), and the resulting mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure, and the residue was diluted with EtOAc and sequentially washed with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl. The organic layer was concentrated under reduced pressure, and the the residue was purified by PTLC (50% EtOAc in hexane) to afford the methylamine (5.5 mg, 0.0074 mmol, 96%) as a colorless film. $[\alpha]_D^{23}$ –26 ° (c = 0.9, $CHCl_3$); IR (neat film) 3401, 1759, 1724, 1507, 1446, 1372, 1331, 1235, 1194, 1145, 1106, 1088, 1067, 998, 915 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.78 (s, 1H), 6.08 (s, 1H), 6.08 (m, 1H), 5.99 (s, 1H), 5.96 (m, 1H), 5.45 (d, *J* = 17.6 Hz, 1H), 5.31 (d, *J* = 17.6 Hz, 1H), 5.25 (d, *J* = 10.8 Hz, 2H), 5.02 (d, *J* = 12.0 Hz, 1H), 4.80 (m, 2H), 4.40-4.55 (m, 3H), 4.27-4.40 (m, 2H), 4.24 (s, 1H), 4.19 (m, 1H), 4.16 (m, 2H), 3.79 (s, 3H), 3.35-3.45 (m, 2H), 2.85-2.97 (m, 2H), 2.29 (s, 3H), 2.27 (s, 3H), 2.20-2.40 (m, 1H), 2.20

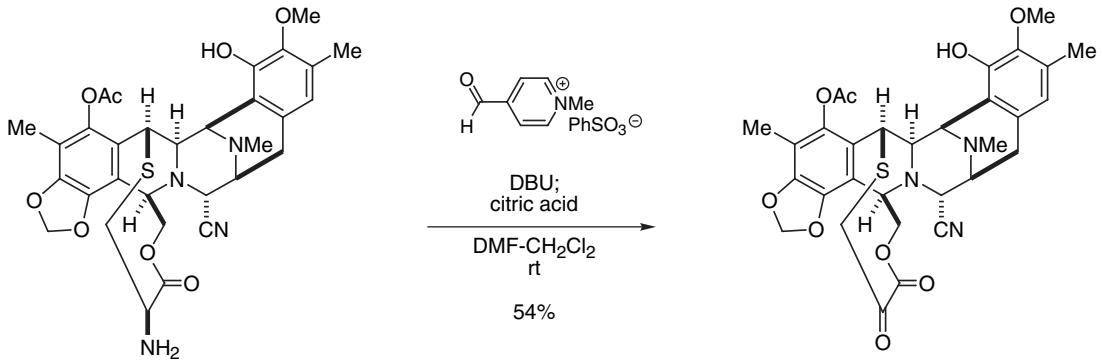
(s, 3H), 2.13 (d, J = 16.4 Hz, 1H), 2.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 168.6, 155.4, 150.8, 148.8, 145.7, 140.9, 140.3, 134.5, 132.8, 131.7, 129.9, 124.7, 124.6, 120.2, 118.0, 116.6, 113.5, 113.3, 102.0, 72.9, 65.8, 61.3, 60.4, 59.4, 59.2, 59.1, 55.0, 54.5, 53.8, 41.6, 41.5, 32.8, 23.7, 20.4, 15.7, 9.6; HRMS (FAB$^+$) m/z: Calcd. for $C_{38}H_{43}N_4O_{10}S$ $(M+H)^+$ 747.2700, found 747.2769

Aminophenol



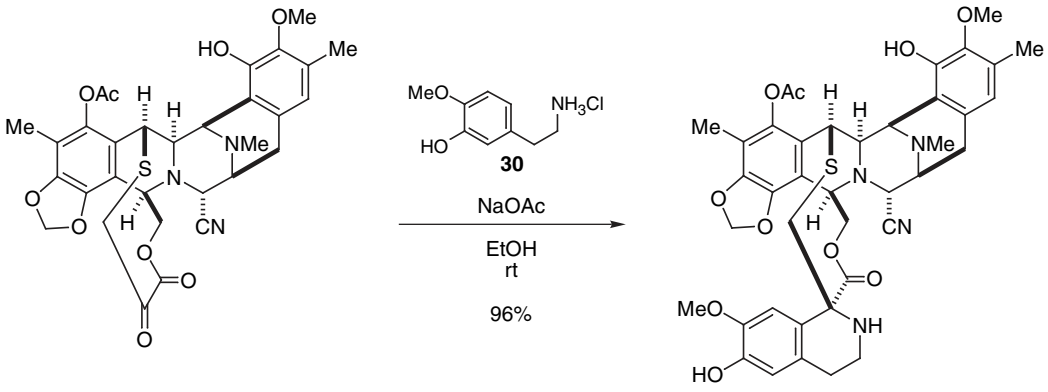
To a mixture of the methylamine (8.6 mg, 0.012 mmol), $Pd(PPh_3)_2Cl_2$ (3.2 mg, 0.0045 mmol, 0.4 equiv), and AcOH (15 μl, 0.26 mmol, 23 equiv) in CH_2Cl_2 (0.7 ml) was added tri-*n*-butyltin hydride (30 ml, 0.11 mmol, 10 equiv), and the resulting slurry was stirred at room temperature for 20 min. The reaction mixture was diluted with Et_2O, filtered through a pad of celite, and concentrated under reduced pressure. The residue was purified by flash column chromatography (10% (v/v) MeOH in CH_2Cl_2) to afford the aminophenol (6.4 mg, 0.010 mmol, 89%) as a white film. $[\alpha]_D^{22}$ –15 ° (c = 0.6, $CHCl_3$); IR (neat film) 1750, 1457, 1419, 1374, 1307, 1237, 1194, 1108, 1088, 1065, 1029, 915, 861 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.52 (s, 1H), 6.08 (s, 1H), 5.99 (s, 1H), 5.75 (s, 1H), 5.01 (d, J = 11.6 Hz, 1H), 4.53 (br, 1H), 4.25 (m, 2H), 4.18 (d, J = 2.0 Hz, 1H), 4.13 (dd, J = 11.6, 2.0 Hz, 1H), 3.78 (s, 3H), 3.41 (m, 2H), 3.27 (br, 1H), 2.91 (m, 2H), 2.20-2.30 (m, 2H), 2.30 (s, 3H), 2.28 (s, 3H), 2.18 (s, 3H), 2.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.5, 168.8, 148.0, 145.8, 143.0, 141.1, 140.5, 130.7, 129.4, 121.0, 120.6, 118.4, 113.9, 102.1, 61.5, 60.4, 60.2, 59.5, 59.3, 54.8, 54.2, 41.8, 41.7, 34.6, 28.1, 27.2, 24.0, 20.8, 15.8, 13.9, 9.8; HRMS (FAB$^+$) m/z: Calcd. for $C_{31}H_{35}N_4O_8S$ $(M+H)^+$ 623.2175, found 623.2201.

Ketolactone



To a solution of the aminophenol (3.7 mg, 0.0059 mmol) in a mixture of DMF (0.15 ml) and CH_2Cl_2 (0.15 ml) was added 4-formyl-1-methylpyridinium benzenesulfonate (16.5 mg, 0.057 mmol, 10 equiv), and the solution was stirred at room temperature for 15 min. To the mixture was added DBU (8.0 μl, 0.053 mmol, 9 equiv), and the resulting dark purple suspension was stirred at room temperature. After 25 min, to the mixture were added CH_2Cl_2 (0.30 ml) and saturated aqueous citric acid (10 drops). The resulting orange solution was stirred at room temperature for 40 min before it was partitioned between saturated aqueous $NaHCO_3$ and Et_2O. The ethereal layer was concentrated under reduced pressure, and the crude product was purified by PTLC (70% EtOAc in *n*-hexane) to afford the ketolactone (2.0 mg, 0.0032 mmol, 54%) as a white film. $[\alpha]_D^{22}$ +153 ° (c = 0.2, $CHCl_3$); IR (neat film) 3447, 1763, 1728, 1622, 1589, 1500, 1456, 1373, 1270, 1236, 1194, 1160, 1145, 1108, 1087, 1063 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.49 (s, 1H), 6.11 (s, 1H), 6.03 (s, 1H), 5.69 (s, 1H), 5.09 (d, *J* = 11.6 Hz, 1H), 4.66 (br, 1H), 4.39 (s, 1H), 4.24 (d, *J* = 4.8 Hz, 1H), 4.22 (d, *J* = 11.6 Hz, 1H), 4.16 (d, *J* = 2.8 Hz, 1H), 3.76 (s, 3H), 3.54 (d, *J* = 4.8 Hz, 1H), 3.43 (dd, *J* = 9.6, 2.8 Hz, 1H), 2.90 (dd, *J* = 18.4, 9.6 Hz, 1H), 2.84 (d, *J* = 13.6 Hz, 1H), 2.70 (d, *J* = 18.4 Hz, 1H), 2.57 (d, *J* = 13.6 Hz, 1H), 2.33 (s, 3H), 2.24 (s, 3H), 2.14 (s, 3H), 2.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.7, 168.5, 160.5, 147.1, 146.4, 142.9, 141.6, 140.7, 130.4, 129.8, 121.7, 121.7, 120.0, 117.9, 117.1, 113.5, 113.3, 102.2, 61.7, 61.4, 60.3, 59.8, 58.9, 54.6, 43.2, 41.6, 36.8, 24.1, 20.4, 15.8, 9.7; HRMS (FAB$^+$) m/z: Calcd. for $C_{31}H_{32}N_3O_9S$ $(M+H)^+$ 622.1859, found 622.1812.

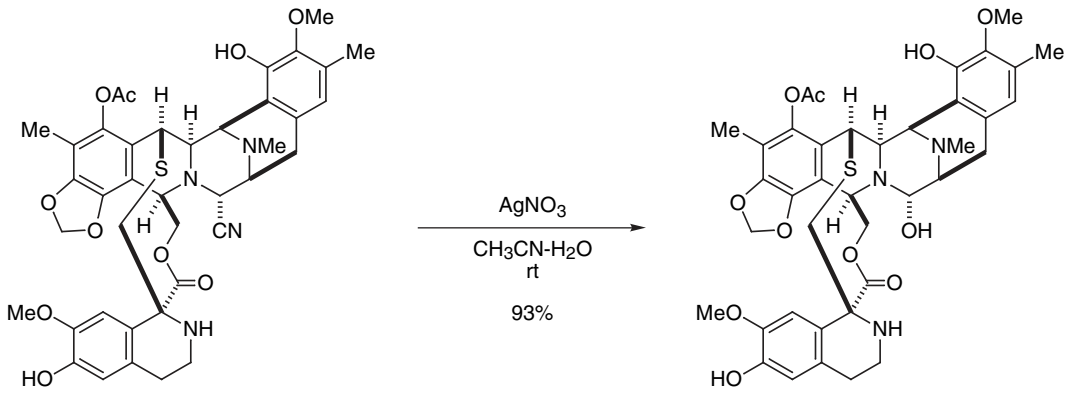
Ecteinascidin 770 (2)



Ecteinascidin 770 (**2**)

To a mixture of the ketolactone (2.0 mg, 0.0026 mmol) and amine **30** (12.4 mg, 0.062 mmol, 19 equiv) in EtOH (0.25 ml) at room temperature was added sodium acetate (7.4 mg, 0.090 mmol, 28 equiv), and the slurry was stirred at room temperature for 5.5 h. The reaction mixture was purified by PTLC (5% MeOH in CH_2Cl_2) to afford Et 770 (**2**) (2.4 mg, 0.0031 mmol, 96%) as a white film. $[\alpha]_D^{23}$ –57 ° (c = 0.2, $CHCl_3$); IR (neat film) 3437, 2931, 1743, 1591, 1507, 1456, 1369, 1236, 1193, 1107, 1087, 1053, 1028 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.60 (s, 1H), 6.48 (s, 1H), 6.45 (s, 1H), 6.05 (s, 1H), 5.98 (s, 1H), 5.73 (s, 1H), 5.38 (br, 1H), 5.02 (d, *J* = 11.6 Hz, 1H), 4.57 (br, 1H), 4.33 (s, 1H), 4.28 (d, *J* = 5.2 Hz, 1H), 4.19 (d, *J* = 2.8 Hz, 1H), 4.12 (dd, *J* = 11.6, 2.8 Hz, 1H), 3.79 (s, 3H), 3.63 (s, 3H), 3.51 (d, *J* = 4.8 Hz, 1H), 3.42 (m, 1H), 3.10 (ddd, *J* = 11.6, 10.8, 4.0 Hz, 1H), 2.94 (m, 2H), 2.78 (m, 1H), 2.62 (m, 1H), 2.47 (m, 1H), 2.35 (m, 1H), 2.32 (s, 3H), 2.27 (s, 3H), 2.20 (s, 3H), 2.09 (m, 1H), 2.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 168.1, 147.8, 145.3, 144.5, 144.3, 143.0, 141.3, 140.1, 130.8, 129.3, 129.1, 125.8, 121.2, 120.7, 118.2, 118.1, 114.1, 114.1, 113.4, 109.8, 101.9, 64.6, 61.1, 60.4, 60.0, 59.7, 59.5, 55.2, 54.7, 54.6, 42.2, 41.8, 41.6, 39.6, 28.8, 24.2, 20.5, 15.8, 9.7; HRMS (FAB+) m/z: Calcd. for $C_{40}H_{43}N_4O_{10}S$ $(MH)^+$ 744.2704, found 744.2698.

Ecteinascidin 743 (1)



Ecteinascidin 770 (**2**) Ecteinascidin 743 (**1**)

To a solution of Et 770 (**2**) (2.4 mg, 0.0031 mmol, 1.0 equiv) in a mixture of CH_3CN (0.3 ml) and water (0.2 ml) was added silver nitrate (10.2 mg, 0.060 mmol, 19 equiv), and the suspension was stirred at room temperature for 17 h. The reaction mixture was partitioned between EtOAc (2 ml x 3) and saturated aqueous $NaHCO_3$ (2 ml), and the combined organic layer (6 ml) was washed again with saturated aqueous $NaHCO_3$. The aqueous layer was further extracted with EtOAc (1.5 ml) and the combined organic layer (7.5 ml) was washed with saturated aqueous Na_2SO_4. The organic layer was concentrated under reduced pressure to afford Et 743 (**1**) (2.2 mg, 0.0029 mmol, 93%) as a pale yellow film. $[\alpha]_D^{22}$ –58 ° (c = 0.2, CH_2Cl_2); IR (neat film) 3347, 2930, 1763, 1741, 1590, 1509, 1458, 1431, 1369, 1237, 1195, 1122, 1109, 1088, 1053, 1029, 1003, 958, 916 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.61 (s, 1H), 6.47 (s, 1H), 6.45 (s, 1H), 6.02 (s, 1H), 5.94 (s, 1H), 5.69 (br, 1H), 5.39 (br, 1H), 5.13 (d, *J* = 11.2 Hz, 1H), 4.81 (s, 1H), 4.48 (d, *J* = 3.3 Hz, 1H), 4.48 (br, 1H), 4.16 (d, *J* = 5.1 Hz, 1H), 4.05 (dd, *J* = 11.2, 2.2 Hz, 1H), 3.79 (s, 3H), 3.62 (s, 3H), 3.57 (d, *J* = 4.9 Hz, 1H), 3.22 (br, 1H), 3.12 (ddd, *J* = 10.0, 10.0, 4.0 Hz, 1H), 2.82-2.97 (m, 2H), 2.81 (m, 1H), 2.60 (ddd, *J* = 15.9, 10.0, 4.0 Hz, 1H), 2.48 (ddd, *J* = 15.9, 4.0, 3.4 Hz, 1H), 2.37 (br, 1H), 2.32 (s, 3H), 2.27 (s, 3H), 2.20 (s, 3H) 2.19 (br, 1H), 2.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 168.3, 147.7, 145.1, 144.4, 144.2, 142.9, 141.3, 140.5, 131.5, 129.2, 129.1, 126.1, 121.8, 120.9, 117.9, 115.9, 114.0, 112.5, 109.8, 101.7, 82.1, 64.7, 61, 3, 60.4, 57.8, 57.7, 56.0, 55.1, 54.9, 42.2, 42.1, 41.4, 39.7, 28.9, 24.1, 20.5, 15.8, 9.7; HRMS (FAB^+) m/z: Calcd. for $C_{39}H_{42}N_3O_{10}S$ $(M–OH)^+$ 744.2591, found 744.2629.