Scalable Synthesis of Cortistatin A and Related Structures

*Jun Shi, Georg Manolikakes,[†] Chien-Hung Yeh,[†] Carlos A. Guerrero, Ryan A. Shenvi, Hiroki Shigehisa, and Phil S. Baran**

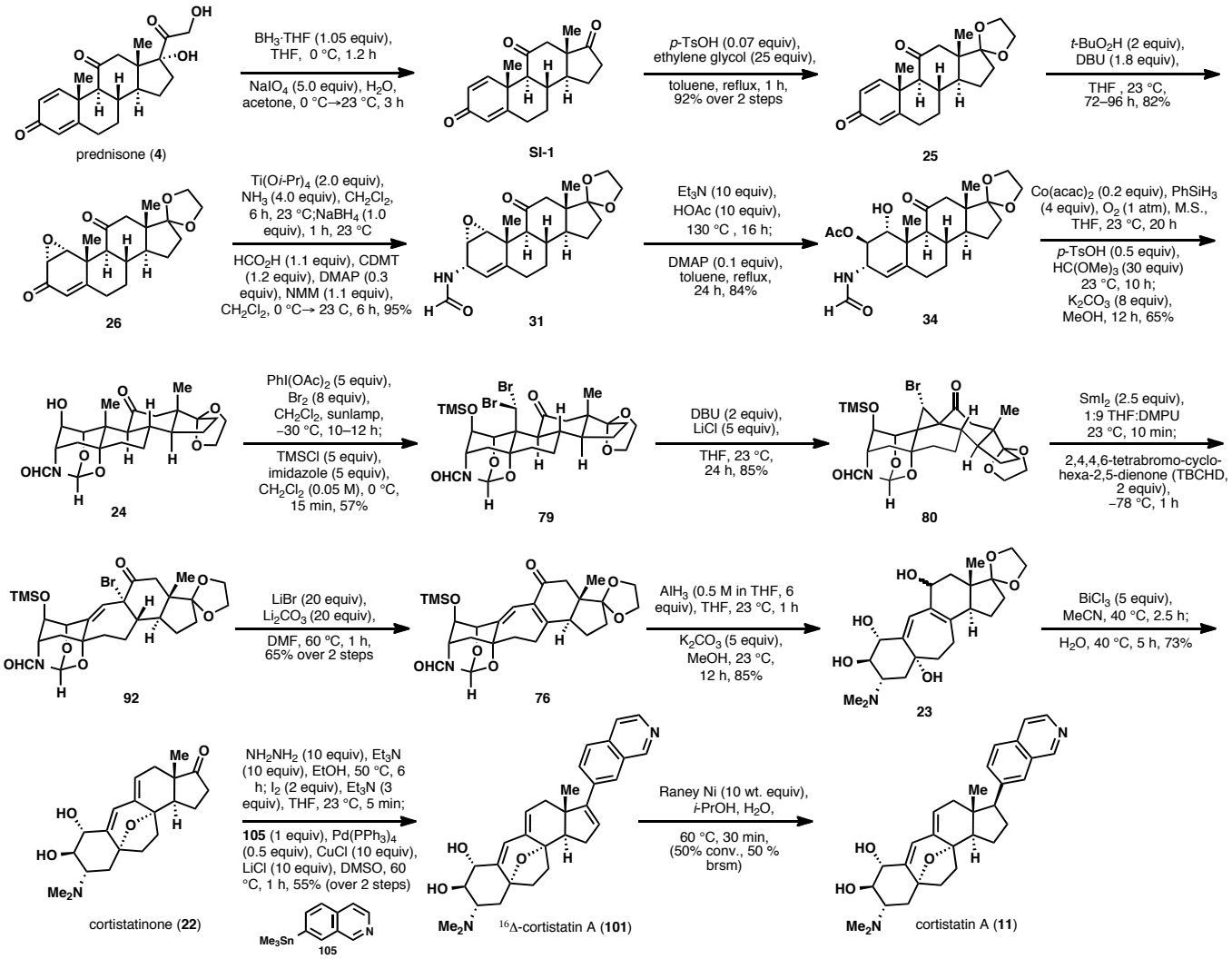
Contribution from the Department of Chemistry, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037

SUPPORTING INFORMATION

Table of Contents

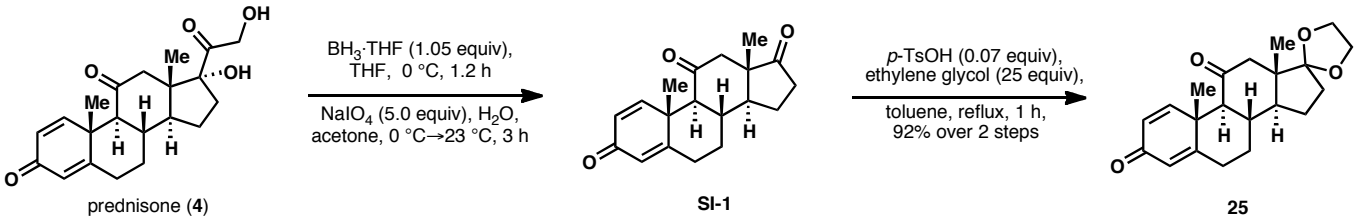
[†] These authors contributed equally to this paper.

General procedures. All reactions were carried out under a nitrogen atmosphere with dry solvents using anhydrous conditions unless otherwise stated. Dry tetrahydrofuran (THF), diethyl ether, dichloromethane (CH_2Cl_2), benzene, toluene, methanol (MeOH), acetonitrile, 1,2-dimethoxyethane (DME), *N,N*-dimethylformamide (DMF), and triethylamine (Et_3N) were obtained by passing these previously degassed solvents through activated alumina columns. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials, unless otherwise stated. Reactions were monitored by thin layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as the visualizing agent and an acidic mixture of anisaldehyde, phosphomolybdic acid, or ceric ammonium molybdate, or basic aqueous potassium permangante ($KMnO_4$), and heat as developing agents. E. Merck silica gel (60, particle size 0.043–0.063 mm) was used for flash column chromatography. Preparative thin layer chromatography (PTLC) separations were carried out on 0.25 or 0.5 mm E. Merck silica gel plates (60F-254). NMR spectra were recorded on Bruker DRX-600, DRX-500, and AMX-400 or Varian Inova-400 instruments and calibrated using residual undeuterated solvent as an internal reference ($CHCl_3$ @ 7.26 ppm ^{1}H NMR, 77.0 ppm ^{13}C NMR). The following abbreviations (or combinations thereof) were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad. High-resolution mass spectra (HRMS) were recorded on Agilent LC/MSD TOF time-of-flight mass spectrometer by electrospray ionization time of flight reflectron experiments. IR spectra were recorded on a Perkin Elmer Spectrum BX FTIR spectrometer. Melting points were recorded on a Fisher-Johns 12-144 melting point apparatus.



Scheme S-1: Synthesis of cortistatin A with improved conditions

Experimental



Compound 25: To a suspension of prednisone (53.3 g, 149 mmol) in anhydrous THF (496 mL, 0.3 M)

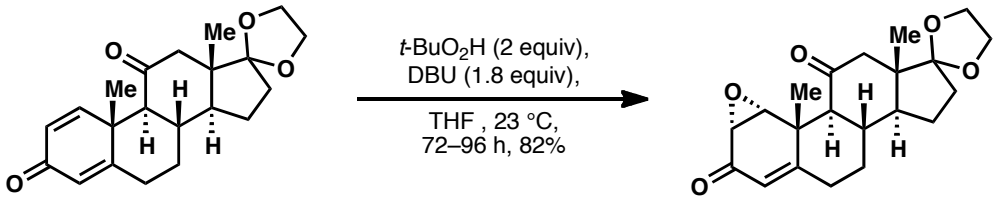
was added BH_3·THF (1 M in THF, 149 mL, 149 mmol, 1.0 equiv) *via* syringe over 30 min at 0 °C. After the reagent addition was complete, the cooling bath was removed. The suspension gradually turned into a clear solution. After 20 min, additional BH_3·THF (1 M in THF, 7.4 mL, 7.4 mmol, 0.05 equiv) was added. After another 20 minutes, all starting material had been consumed. The reaction was cooled to 0 °C and approximately 500 mL of 1:1 acetone:water was added slowly. Then $NaIO_4$ (159 g, 743 mmol, 5 equiv) was added over 5 min. The resulting suspension was stirred vigorously for 3 h at ambient temperature, during which the reaction thickened and became difficult to stir. After the reaction was complete, the suspension was filtered over Celite® and evaporated until the majority of acetone and THF had been removed. The resulting suspension was poured into a separatory funnel and the reaction vessel was rinsed repeatedly with EtOAc. The contents of the separatory funnel were diluted with 500 mL EtOAc. The separatory funnel was capped, shaken, and the layers were separated. The aqueous portion was extracted three more times with EtOAc (3 × 200 mL). The combined organic portions were washed with sat. aq. $Na_2S_2O_3$ (500 mL), water (500 mL) and sat. aq. NaCl (500 mL). The solution was dried over $MgSO_4$ and concentrated to give an off-white solid that was sufficiently pure for ketalization.

Note: the triol cleavage can be accomplished with as few as 2 equivalents of $NaIO_4$, but this requires stirring overnight for full consumption of the triol.

One fourth of the trione so produced was ketalized as follows: to this portion of crude trione as a suspension in toluene (620 mL, 0.06 M) was added ethylene glycol (52 mL, 929 mmol, 25 equiv) and *p*-TsOH·H_2O (513 mg, 2.69 mmol, 0.0725 equiv). The reaction vessel was incorporated into a standard Dean-Stark setup and immersed in an oil bath preheated to 135 °C and stirred vigorously. After 55 min, the reaction was lifted out of the oil bath and allowed to cool. The contents of the reaction vessel were poured into a separatory funnel and the reaction vessel was rinsed with EtOAc; this was also added to the separatory funnel. The layers were allowed to settle and the ethylene glycol was separated from the

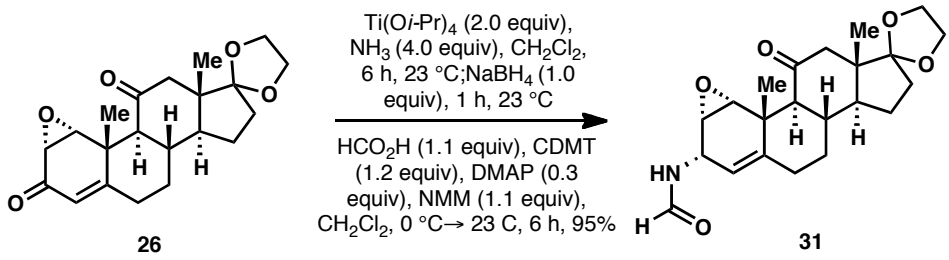
organic layer. The organic layer was neutralized with sat. aq. $NaHCO_3$ (100 mL) and the layers were again separated. The aqueous portion was extracted twice with EtOAc (2 × 100 mL). The organic portions were combined, washed with sat. aq. NaCl (200 mL), dried over $MgSO_4$, and concentrated. The remaining trione was ketalized in the same manner and the crude portions were combined and crystallized from boiling EtOAc followed by cooling at 4 °C. The first crop of crystals was 37.25 g, the second was 7.63 g, and the third was 1.81 g, for a total of 46.69 g (92%) of the known title compound.

Note: the heating time for the ketalization is specific for the scale specified. The reaction was conducted in a 1 L round bottom flask immersed in a 190 mm (diameter) × 100 mm (depth) oil bath. The heating time reflects a balance between full consumption of starting material and over-ketalization.



25 **26**

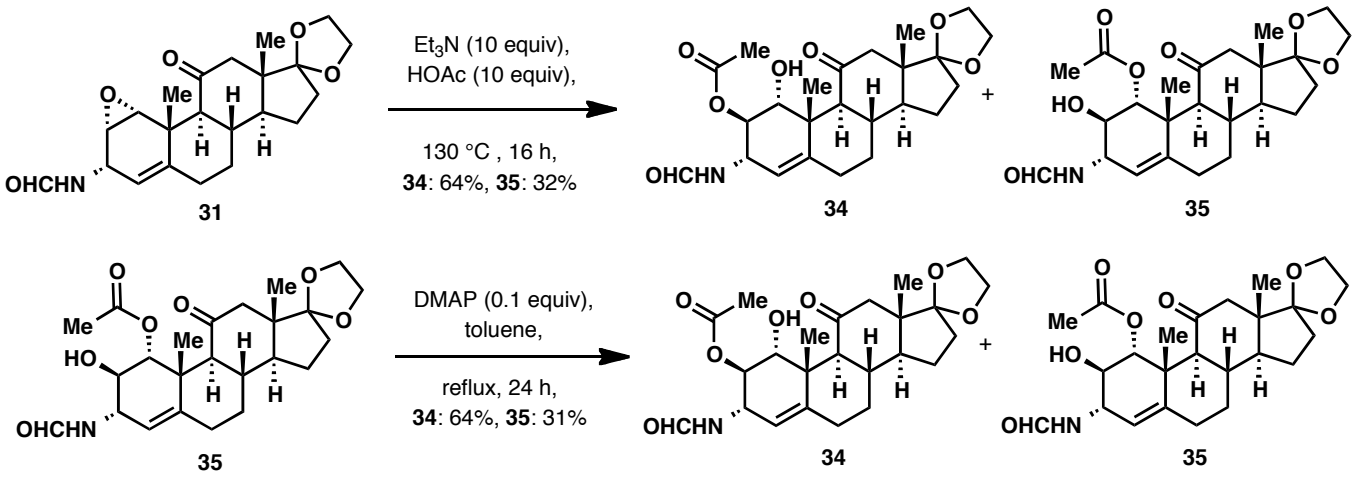
Compound 26: To a solution of dienone **25** (100 g, 292 mmol) in THF (292 mL, 1.0 M) was added 70% aq. TBHP (80 mL, 484 mmol, 2.0 equiv) and DBU (80 mL, 535 mmol, 1.83 equiv) and the reaction mixture was stirred at ambient temperature for 72 h. The reaction mixture was quenched by the addition of sat. aq. $Na_2S_2O_3$ (300 mL) and stirred vigorously for 2 h. The resulting biphasic mixture was extracted twice with EtOAc (2 × 600 mL). The combined organic phase was washed twice with sat. aq. $Na_2S_2O_3$ (2 × 200 mL) and once with water (200 mL) and sat. aq. NaCl (200 mL). It was then dried over $MgSO_4$ and concentrated *in vacuo*. The residue so obtained was purified by flash column chromatography (hexanes:EtOAc 2:1) furnishing epoxy enone **26** (85.8 g, 82%) as a white solid. Analytical data are identical to the original.[1]



Compound 31: *i*. To a solution of compound **26** (20.2 g, 56 mmol) in CH_2Cl_2 (110 mL 0.5 M) was added NH_3 (112 mL, 2 M in EtOH, 224 mmol, 4 equiv) and Ti(O*i*-Pr)$_4$ (34 ml, 112 mmol, 2 equiv) The flask was capped tight with a septum and the reaction mixture stirred for 6-7 h at ambient temperature. Then $NaBH_4$ (2.12 g, 56 mmol, 1 equiv) was added slowly and stirring continued for 1 h. The reaction mixture was diluted with CH_2Cl_2 (110 ml) and poured slowly into a sat. aq. potassium sodium tartrate (200 ml). The resulting biphasic mixture was stirred vigorously for 16 h. Water (200 mL) was added and the phases were separated. The aqueous layer was extracted twice with CH_2Cl_2 (2 x 150 mL). The organic portions were combined, washed with sat. aq. NaCl (150 mL) and dried over $MgSO_4$ and concentrated *in vacuo*. The resulting off-white foam/solid is sufficiently pure for the formylation step.

ii. The crude amine from the previous reaction was dissolved in CH_2Cl_2 (190 mL, 0.3 M). To this solution were added in the following order at ambient temperature: formic acid (2.35 mL, 62 mmol, 1.1 equiv), 2-chloro-4,6-dimethoxy-1,3,5-triazine (CDMT, 11.9 g, 68 mmol, 1.2 equiv) and DMAP (2.05 g, 16.8 mmol, 0.3 equiv). The resulting suspension was cooled to 0 °C and *N*-methyl-morpholine (6.8 mL, 62 mmol, 1.1 equiv) was added dropwise *via* syringe. The reaction was warmed to ambient temperature and stirred for 6 h. Then water (200 mL) was added to the reaction and the resulting biphasic mixture extracted twice with CH_2Cl_2 (2 x 150 mL). The combined organic portions were washed with sat. aq. NaCl (150 mL), dried over $MgSO_4$ and concentrated *in* vacuo. The residue so obtained was purified by flash column chromatography (silica gel, CH_2Cl_2:acetone 4:1) furnishing formamide **31** (20.5 g, 95 %) as

a white foam. Analytical data are identical to the original.[1]



Compounds 34 and 35: Et_3N (76 mL, 550 mmol, 10 equiv) and HOAc (31.4 mL, 550 mmol, 10 equiv) were mixed in a sealed tube cooled with a water bath. The resulting solution was stirred for 10 min. Then the epoxide **31** (21.3 g, 55 mmol) was added, the tube sealed with a Teflon screwcap and the reaction heated to 130 °C for 16 h. After cooling to ambient temperature, the mixture was diluted with CH_2Cl_2 (500 mL) and washed with water (200 mL), 1 M HCl (200 mL), sat. aq. $NaHCO_3$ (200 mL), water (200 mL) and sat. aq. NaCl (200 mL). The organic portion was dried over $MgSO_4$ and concentrated. Purification of the crude residue by flash column chromatography (CH_2Cl_2:acetone 6:1 to 2:1) yielded the desired product **34** (15.75 g,) together with the undesired regioisomer **35** (7.85 g). **35** can be recycled by the following procedure. A mixture of the undesired regioisomer **35** (7.85 g, 17.6 mmol) and DMAP (220 mg, 1.8 mmol, 0.1 equiv) in toluene (88 ml, 0.2 M) was heated to reflux for 24 h. The reaction was allowed to cool and concentrated *in vacuo*. Purification of the crude residue by flash column chromatography (CH_2Cl_2:acetone 6:1 to 2:1) yielded the desired regioisomer **34** (5.0 g, 84% from **31**) along with **35** (2.4 g, 10% from **31**).

Compound 34:

R_f = 0.44 (1:1 CH_2Cl_2:acetone)

$[\alpha]_D$ = +54.7 ° (*c* = 0.5, $CHCl_3$)

HRMS (*m*/*z*): calcd for $C_{24}H_{34}NO_7$ $[M+H]^+$, 448.2330; found, 448.2329;

IR (film) ν_{max} = 3391, 2973, 2946, 1734, 1654, 1501, 1376, 1238, 1167, 1101, 1032 cm^{-1};

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.09 (s, 1 H), 5.72 (d, *J* = 9.0 Hz, 1H), 5.64 (d, *J* = 3.6 Hz, 1H), 5.37 (d, *J* = 4.8 Hz, 1H), 4.50 (bs, 1 H), 4.00 (bs, 1 H), 3.94 – 3.88 (m, 2 H), 3.85 – 3.78 (m, 2 H), 3.45 (bs, 1 H), 2.49 (d, *J* = 12.0 Hz, 1 H), 2.38 – 2.33 (m, 1 H), 2.27 (d, *J* = 10.8 Hz, 1 H), 2.19 – 2.14 (m, 1 H), 2.04 – 2.01 (m, 4 H), 1.94 – 1.90 (m, 3 H), 1.93 (s, 3 H), 1.84 – 1.80 (m, 1 H), 1.46 (s, 3 H), 1.38 – 1.35 (m, 1 H), 1.14 – 1.08 (m, 1 H), 0.80 (s, 3 H);

^{13}C NMR (150 MHz, $CDCl_3$) δ 210.2, 169.0, 160.2, 144.6, 117.6, 116.2, 75.2, 68.7, 65.3, 64.5, 57.5, 49.3, 49.2 (2 C), 46.9, 39.4, 36.5, 34.3, 32.1, 32.0, 22.2, 21.0, 19.5, 14.9.

Compound 35:

R_f = 0.43 (1:1 CH_2Cl_2:acetone)

$[\alpha]_D$ = 118 ° (*c* = 0.5, $CHCl_3$)

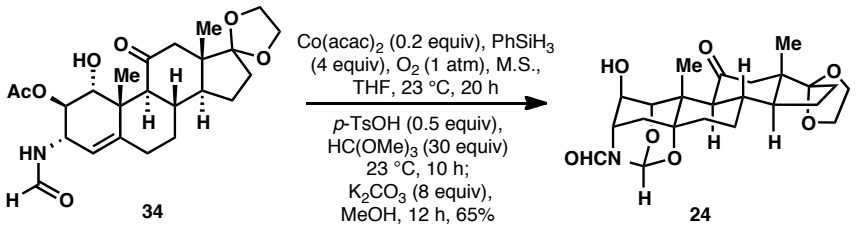
HRMS (*m*/*z*): calcd for $C_{24}H_{34}NO_7$ $[M+H]^+$, 448.233; found, 448.2320;

IR (film) ν_{max} = 3380, 2973, 2923, 2845, 1734, 1698, 1664, 1501, 1436, 1375, 1313, 1239, 1053, 1033 cm^{-1};

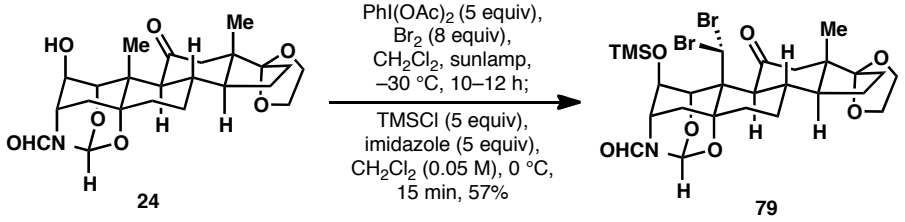
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.10 (s, 1 H), 5.66 (d, *J* = 3.9 Hz, 1H), 5.64 – 5.60 (m, 1 H), 5.37 (d, *J* = 4.8 Hz, 1 H), 4.54 – 4.49 (m, 1 H), 4.05 – 4.00 (m, 1 H), 3.96 – 3.88 (m, 2 H), 3.86 – 3.77 (m, 2 H), 3.03 (d, *J* = 4.7 Hz, 1 H), 2.51 (t, *J* = 11.4 Hz, 1 H), 2.41 – 2.33 (m, 1 H), 2.28 (t, *J* = 10.4 Hz, 1 H), 2.21 – 2.13 (m, 1 H), 2.08 – 1.97 (m, 3 H), 1.94 (s, 3 H), 1.94 – 1.86 (m, 2 H), 1.86 – 1.79 (m, 1 H), 1.78 (s, 1 H), 1.47 (s, 3 H), 1.41 – 1.34 (m, 1 H), 1.16 – 1.05 (m, 1 H), 0.81 (s, 3 H);

^{13}C NMR (150 MHz, $CDCl_3$) δ 210.1, 168.9, 160.0, 144.7, 117.6, 116.2, 75.2, 68.8, 65.3, 64.6, 57.5, 49.3,

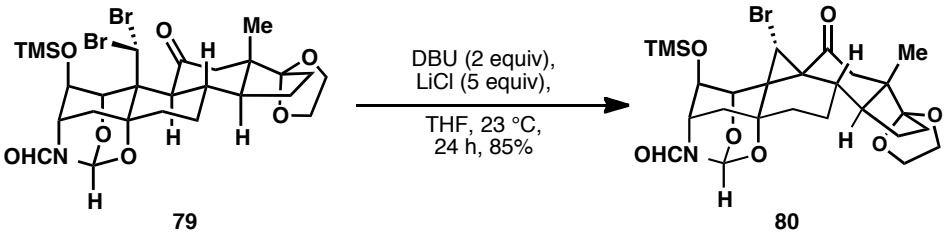
49.2 (2 C), 46.9, 39.4, 36.5, 34.2, 32.1, 32.0, 22.2, 21.0, 19.6, 14.9.



Compound 24: To a solution of compound **34** (3 g, 6.71 mmol, azeotroped with toluene twice) in THF (67 mL, 0.1 M) was added $Co(acac)_2$ (342 mg, 1.34 mmol, 0.20 equiv) and molecular sieves (4Å, 3.3 g, 1.1 wt equiv) . Fresh distilled $PhSiH_3$ (3.3 mL, 26.8 mmol, 4 equiv) was added slowly via sringepump over 8 h while bubbling O_2 through the stirred solution. Then the stirring was continued under an O_2 atmosphere (no bubbling) at ambient temperature for approximately 12 h. The suspension was then filtered over Celite®, to remove the molecular sieves and to the resulting solution was added $HC(OMe)_3$ (21 mL, 191 mmol, 30 equiv) and *p*-TsOH·H_2O (680 mg, 3.6 mmol, 0.5 equiv). The mixture was stirred until full consumption of the intermediate (8–10 h) as judged by TLC analysis, MeOH (60 mL) was added followed by K_2CO_3 (7.8 g, 56.5 mmol, 8 equiv). The reaction was stirred at ambient temperature for 12 h. The reaction was then diluted with EtOAc (300 mL), washed with 1 M aq. HCl (60 mL), sat. aq. $NaHCO_3$ (100 mL), H_2O (80 mL), and sat. aq. NaCl (80 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The residue so obtained was purified by flash column chromatorgraphy (CH_2Cl_2:acetone 5:1) furnishing **24** (1.9 g, 65%). Analytical data are identical to the original.[1]

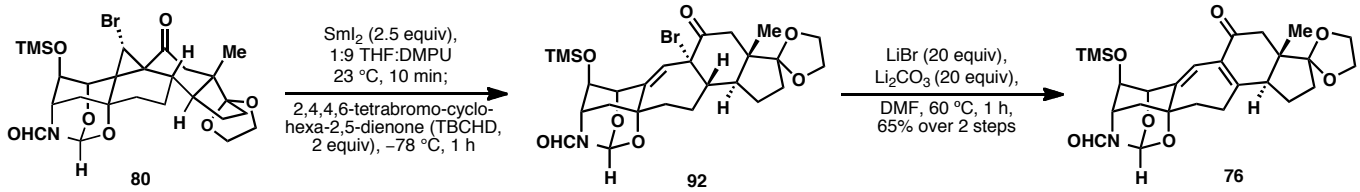


Compound 79: Alcohol **24** (1.01 g, 2.32 mmol) and $PhI(OAc)_2$ (3.74 g, 11.6 mmol, 5 equiv) were dissolved in CH_2Cl_2 (23 mL, 0.1 M) at room temperature under Ar. After cooling to –30°C, Br_2 (954 μL, 18.6 mmol, 8 equiv) was added. The temperature was maintained between –30 and –36 °C with sunlamp irradiation (75 W, 18 inches above surface of cooling bath) for 10 hours. Irradiation was then halted, the reaction was diluted with ice-cold CH_2Cl_2 (200 mL), and the crude mixture was shaken with 10% aq. $Na_2S_2O_3$ (100 mL) until colorless. The aqueous layer was back-extracted twice with CH_2Cl_2 (2 × 100 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo* at 5 °C to about 40 mL. At 0 °C, imidazole (0.79 g, 11.7 mmol, 5 equiv) and TMSCl (1.5 mL, 11.7 mmol, 5 equiv) were added. After 15 minutes, the reaction was diluted with EtOAc (200 mL), washed with water (20 mL), then sat. aq. $NaHCO_3$ (20 mL), then sat. aq. NaCl (10 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (1:2 EtOAc:hexanes) afforded dibromide **79** (877 mg, 57%) as a white foam. Analytical data are identical to the original.[1]

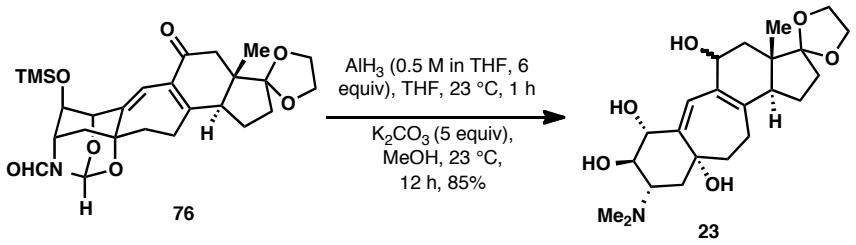


Compound 80: Dibromide **79** (2.3 g, 3.4 mmol) was dissolved in THF (70 mL, 0.05 M) and freshly flame-dried LiCl (719 mg, 17 mmol, 5 equiv) was added, followed by dry DBU (1.0 mL, 6.8 mmol, 2 equiv). The reaction mixture was stirred for 24 hours, at which point it was diluted with EtOAc (100 mL), washed with twice with water (100 mL), and once with brine (100 mL). The aqueous layer was extracted twice with CH_2Cl_2; these portions were added to the organic phase, which was dried with $MgSO_4$, filtered, and concentrated *in vacuo*. Flash colum Chromatography (1:3 EtOAc:hexanes) afforded

bromocylopropane **80** (1.7 g, 85%) as a colorless foam. Analytical data are identical to the original.[1]



Compound 76: Bromocyclopropane **80** (1.5 g, 2.6 mmol) was dissolved in dry THF (128 ml, 0.02 M) under Ar and freshly distilled DMPU (14.3 ml) was added. The solution was bubbled with Ar for 30 min, after which SmI_2 (65 ml, 6.5 mmol, 0.1 M in THF, 2.5 equiv) was quickly added. After 10 min, the reaction was cooled to –78°C and a 0.12 M solution of 2,4,4,6-tetrabromo-2,5-cyclohexadienone (TBCHD) in CH_2Cl_2 (43.3 ml, 5.2 mmol, 2 equiv) was added. The reaction mixture was kept at –78°C over 1 h, at which point it was quenched with sat. aq. $NaHCO_3$ solution (100 ml). The aqueous layer was extracted four times with EtOAc (4 × 150 mL) and the combined organic portions were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Chromatography on silica (1:3 EtOAc:hexanes) furnished **92** as a white foam. **92** was dissolved in dry DMF (26 ml, 0.1 M) and to this solution were added LiBr (4.5 g, 52 mmol, 20 equiv) and Li_2CO_3 (3.8 mg, 52 mmol, 20 equiv). The reaction mixture was stirred at 60 °C for 1 h, at which point it was diluted with Et_2O (400 mL), washed with sat. aq. $NaHCO_3$ (100 mL) and H_2O (4 × 100 mL), dried with $MgSO_4$, filtered, and concentrated *in vacuo*. Chromatography on silica (1:2 EtOAc:hexanes) afforded dienone **76** (845 mg, 65%) as a white solid. Analytical data are identical to the original.[1]



Compound 23: A freshly prepared solution of AlH_3 (34.2 mL, 17.1 mmol, 6 equiv, 0.5 M in THF) was added to dienone **76** (1.46 g, 2.85 mmol) in THF (28.5 mL, 0.1 M) at ambient temperature. After stirring vigorously for 1 h, methanol (28.5 mL) was added dropwise, followed by K_2CO_3 (1.97g, 14.3 mmol, 5 equiv). This suspension was then stirred for 12 h, at which point it was diluted with CH_2Cl_2 (100 mL) and sat. aq. sodium potassium tartrate (100 mL). The organic phase was removed and the aqueous layer extracted three more times with CH_2Cl_2 (3 × 100 mL). Drying over Na_2SO_4, filtration, concentration *in vacuo*, and yielded **23** (1.0 g, 85%, 1:1 inseparable mixture of diastereomers) as a white foam.

Compound 23 (mixture of diastereomers):

R_f = 0.47 (2:8 NEt_3: EtOAc)

$[\alpha]_D$ = + 74.7 ° (*c* = 1.6, CH_2Cl_2)

HRMS (*m*/*z*): calcd for $C_{23}H_{36}NO_6$ $[M+H]^+$, 422.2537; found, 422.2551;

IR (film) ν_{max} = 3368, 2942, 2878, 1699, 1458, 1303, 1096, 965, 734 cm^{-1};

Diastereomer **23-1**

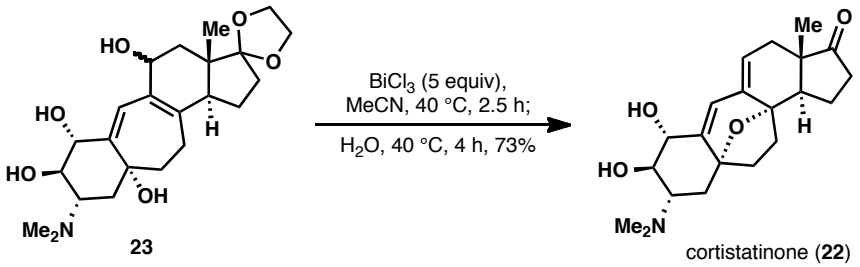
^1H NMR (600 MHz, CD_3OD) δ 6.19 (s, 1 H), 4.29 – 4.26 (m, 2 H), 4.12 – 4.10 (m, 1 H), 3.95 – 3.90 (m, 4 H), 2.86 – 2.80 (m, 1 H), 2.49 (s, 6 H), 2.37 – 2.10 (m, 4 H), 2.05 – 1.61 (m, 6 H), 1.57 – 1.36 (m, 3 H), 0.96 (s, 3 H);

^{13}C NMR (150 MHz, CD_3OD) δ 147.4, 140.8, 132.4, 129.9, 119.8, 83.4, 74.7, 71.7, 71.4, 66.8, 66.3, 65.6, 49.7, 48.9, 43.2, 42.9, 41.3, 39.0, 35.9, 35.2, 25.5, 23.7, 15.0;

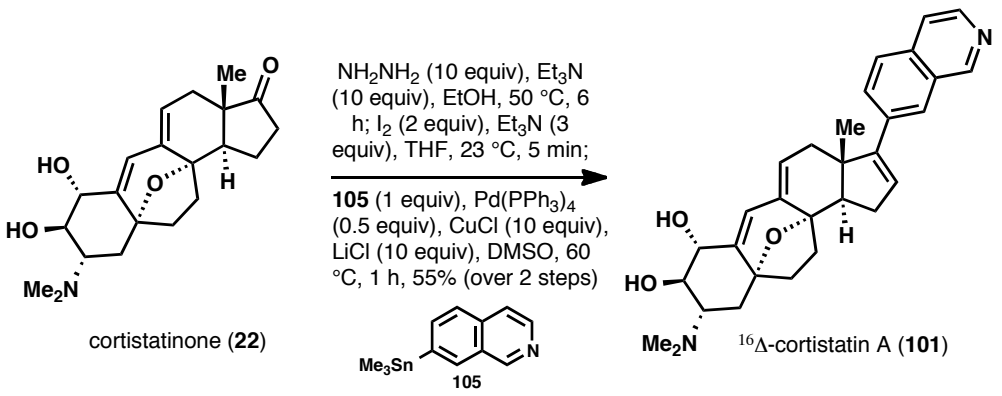
Diastereomer **23-2**

^{1}H NMR (600 MHz, CD_3OD) δ 6.03 (s, 1 H), 4.25 – 4.19 (m, 2 H), 4.09 – 4.07 (m, 1 H), 3.99 – 3.80 (m, 4 H), 2.63 – 2.57 (m, 1 H), 2.47 (s, 6 H), 2.31 – 2.09 (m, 4 H), 2.07 – 1.61 (m, 6 H), 1.57 – 1.36 (m, 4 H), 0.81 (s, 3 H);

^{13}C NMR (150 MHz, CD_3OD) δ 145.7, 141.1, 130.6, 129.8, 119.7, 83.1, 74.6, 71.5, 71.3, 66.7, 66.4, 65.6, 48.8, 45.2, 43.3, 42.9, 41.4, 40.6, 36.2, 35.5, 25.5, 23.7, 16.1.

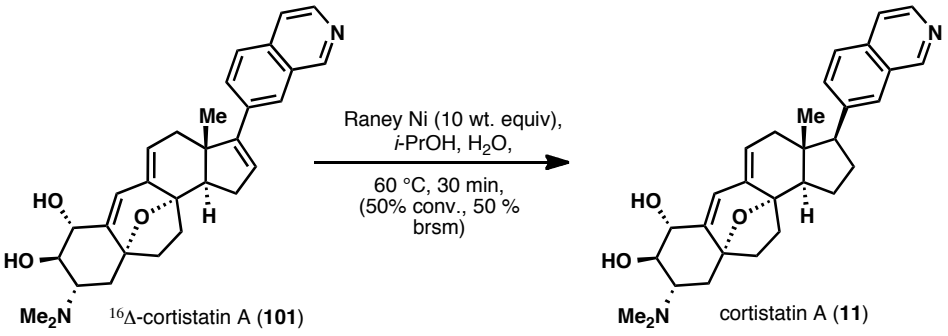


Cortistatinone (22): To a solution of **23** (1.02g, 2.42 mmol) in MeCN (484 mL, 0.005 M) was added $BiCl_3$ (1.52 g, 4.84 mmol, 2 equiv) and the reaction was warmed to 40 °C for 2 h. Then, additional $BiCl_3$ (762 mg, 2.42 mmol, 1 equiv) was added to the reaction mixture at 40 °C for 30 min. Then, H_2O (150 mL) and $BiCl_3$ (1.52 g, 4.84 mmol, 2 equiv) was added to the reaction mixture at 40 °C. After 4 h, sat. aq. $NaHCO_3$ (300 mL) was added to the reaction and the mixture extracted three times with EtOAc (3 × 500 mL). The combined organic portions were washed sat. aq. NaCl (500 mL), dried over Na_2SO_4 and the volatiles removed *in vacuo*. The residue so obtained was purified by flash column chromatography (silica gel, MeOH:CH_2Cl_2:Et_3N 90:10:1) furnishing compound **22** (642 mg, 73%)as a white foam. Analytical data are identical to the original.[1]

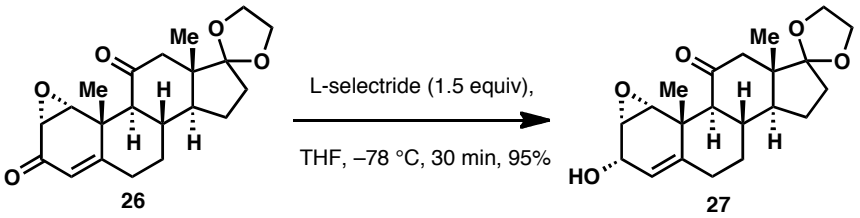


Compound 101: To a solution of cortistatinone (**22**) (200 mg, 0.56 mmol) in absolute EtOH (9.3 mL, 0.06 M) were added hydrazine monohydrate (0.28 mL, 5.6 mmol, 10 equiv) and Et_3N (0.78 mL, 5.6 mmol, 10 equiv). The reaction was immersed in a preheated oil bath at 50 °C for 6 h, after which the reaction was allowed to cool and the solvent removed *in vacuo*. The residue so obtained was dissolved in THF (9.3 mL, 0.06 M), and Et_3N (0.23 mL, 1.68 mmol, 3 equiv) was added. A stock solution of I_2 (283 mg, 1.12 mmol, 2 equiv) in THF (2.83 mL) was prepared and added dropwise to the reaction mixture; addition was halted when the iodine was not decolorized after 30 sec. The reaction was then diluted with EtOAc (50 mL) and washed with sat. aq. $Na_2S_2O_3$ (50 mL). The aqueous layer was extracted four times with EtOAc (4 × 50 mL). The combined organic portions were washed with sat. aq. NaCl (10 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo* to furnish vinyl iodide which was carried forward directly without purification. The residue from the previous reaction (yield assumed to be quantitative) was dissolved in DMSO (9.3 mL, 0.06 M). To this solution was added 7-trimethylstannylisoquinoline (164 mg, 0.56 mmol, 1 equiv), CuCl (554 mg, 5.6 mmol, 10 equiv), LiCl (235 mg, 5.6 mmol, 10 equiv) and $Pd(PPh_3)_4$ (323 mg, 0.28 mmol, 0.5 equiv). The reaction was degassed by bubbling argon through the solution for 10 min. It was then immersed in a preheated oil bath at 60°C for 1 h. The reaction was then diluted with EtOAc (25 mL) and washed with 5% aq. NH_4OH. The aqueous layer was extracted four times (4 × 25 ml) with EtOAc. The combined organic portions were washed wth sat. aq. NaCl (25 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue so obtained was purified by (silica, NH_3 deactivation; 10% MeOH :

CH_2Cl_2) furnishing vinylisoquinoline **101** (145 mg, 55% from cortistatinone **22**) as a yellow foam. Analytical data are identical to the original.[1]



(+)-Cortistatin A (1): For this procedure, Raney nickel (1.0 g) was washed with H_2O (3 × 5 mL), sat. aq. Rochelle's salt (3 × 5 mL), H_2O (5 × 5 mL), MeOH (3 × 5 mL), and H_2O again (3 × 5 mL, all supernatants were removed with pipette) after which it was stored under H_2O (10 mL). To **101** (10 mg, 63 μmol) in *i*-PrOH (3 mL) and H_2O (0.3 mL), was added the washed Raney nickel (100 mg, 10 wt. equiv, which includes water). The heterogeneous reaction was warmed to 60 °C while stirring vigorously for 30 min, at which point the reaction had progressed to approximately 50% conversion, as judged by LCMS. Removal of the supernatant, followed by washing of the Raney nickel catalyst with 1:1 MeOH:EtOAc (20 mL), and concentration of the combined filtrates yielded a colorless residue, which was purified by HPLC (Eclipse XDB-C8 column, 9.4 mm × 25 cm; gradient = 1%→30% MeCN:H_2O over 30 min), yielding recovered **26** (15 mg) and (+)-cortistatin A (2.3 mg, 50% conversion, 50% brsm) as a white solid. Analytical data are identical to the original.[1]



Compound 27: To a solution of compound **26** (1.00 g, 2.8 mmol) in THF (28 mL, 0.1 M) at –78 °C was added dropwise a solution of L-Selectride (4.2 mL, 1.0 M THF solution, 4.2 mmol, 1.5 equiv). After 30 minutes, 40 mL of sat. aq. NH_4Cl were added at –78 °C. The reaction mixture was allowed to warm to ambient temperature, after which it was diluted H_2O (100 mL) and EtOAc (100 mL) and extracted. The aqueous portion was extracted a second time with EtOAc (50 mL). The combined organic portions were washed with sat. aq. NaCl (100 mL), dried over anhydrous $MgSO_4$, and concentrated. The residue was purified by column chromatography (1:1 hexanes:EtOAc) furnishing compound **27** (959 mg, 20:1 diastereomeric mixture, 95 %) as a white solid (data reported for major diastereomer only).

R_f = 0.24 (1:1 hexanes:EtOAc)

$[\alpha]_D$ = + 102 ° (*c* = 0.1, $CHCl_3$)

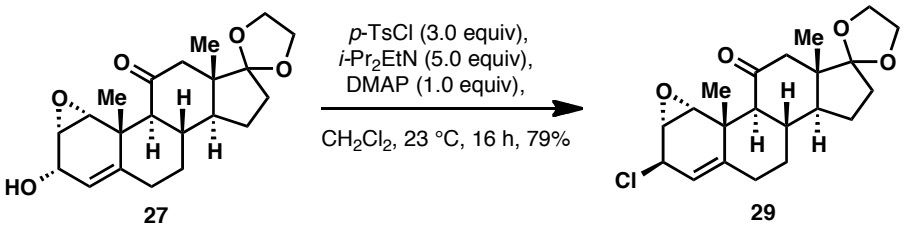
m.p. = 78–80 ºC

HRMS (*m*/*z*): calcd for $C_{21}H_{28}O_5Na$ $[M+Na]^+$, 383.1829; found, 383.1829;

IR (film) ν_{max} = 3452, 2970, 2929, 2886, 1703, 1458, 1434, 1384, 1313, 1276, 1228, 1172, 1104, 1038 cm^{-1};

^1H NMR (600 MHz, $CDCl_3$) δ 5.17 – 5.11 (m, 1 H), 4.33 – 4.29 (m, 1 H), 4.02 (d, *J* = 4.3 Hz, 1 H), 3.96 – 3.88 (m, 2 H), 3.85 – 3.78 (m, 2 H), 3.49 (td, *J* = 5.9, 2.5 Hz, 1H), 2.69 (d, *J* = 12.4 Hz, 1 H), 2.32 – 2.18 (m, 2 H), 2.12 – 1.98 (m, 4 H), 1.96 – 1.88 (m, 1 H), 1.86 – 1.74 (m, 4 H), 1.42 – 1.32 (m, 1 H), 1.29 (s, 3 H), 1.15 – 1.06 (m, 1 H), 0.84 (s, 3H);

^{13}C NMR (150 MHz, $CDCl_3$) δ 210.7, 141.4, 118.8, 117.6, 65.4, 64.6 (2 C), 59.9, 57.6, 56.3, 49.8, 49.2, 48.8, 37.3, 37.0, 34.2, 31.8, 31.6, 22.2, 17.9, 14.9.



Compound 29: To a solution of compound **27** (400 mg, 1.1 mmol) in anhydrous CH_2Cl_2 (11 mL, 0.1 M) at ambient temperature were added *p*-toluenesulfonyl chloride (630 mg, 3.3 mmol, 3 equiv), *i*-Pr_2EtN (0.96 mL, 5.5 mmol, 5 equiv), and DMAP (134 mg, 1.1 mmol, 1 equiv). The reaction was allowed to stir at ambient temperature for 16 h, after which it was diluted with 30 mL of H_2O and extracted with EtOAc (3 x 25 mL). The combined organic portions were washed with sat. aq. $NaHCO_3$ (30 mL) and sat. aq. NaCl (30 mL), dried over $MgSO_4$. The solvent was removed *in vacuo* and the crude material purified by silica gel flash chromatography (4:1 hexanes:EtOAc) to afford compound **29** (330 mg, 79 %, 9:1 mixture of diastereomers) as a white solid (data reported for major diastereomer only).

R_f = 0.35 (3:1 hexanes:EtOAc)

$[\alpha]_D$ = -21.0 ° (*c* = 0.1, $CHCl_3$)

m.p. = 138–141 ºC

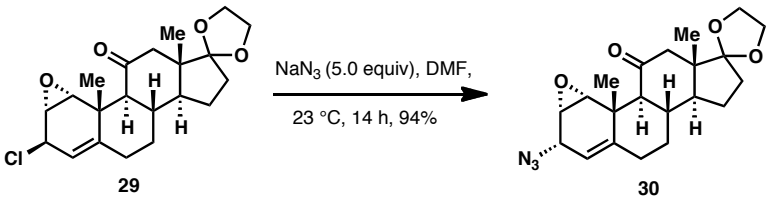
HRMS (*m*/*z*): calcd for $C_{21}H_{28}ClO_4$ $[M+H]^+$, 379.1671; found, 379.1671;

IR (film) ν_{max} = 2971, 2938, 2883, 1742, 1703, 1662, 1457, 1437, 1384, 1207, 1174, 1104, 1053, 1042 cm^{-1};

^1H NMR (600 MHz, $CDCl_3$) δ 5.35 – 5.31 (m, 1 H), 4.76 – 4.72 (m, 1 H), 3.96 (d, *J* = 3.9 Hz, 1 H), 3.95 – 3.88 (m, 2 H), 3.85 – 3.78 (m, 2 H), 3.47 – 3.45 (m, 1 H), 2.68 (d, *J* = 12.5 Hz, 1 H), 2.39 – 2.21 (m, 2 H), 2.16 – 1.98 (m, 4 H), 1.96 – 1.76 (m, 4 H), 1.44 (s, 3 H), 1.39 – 1.32 (m, 1 H), 1.15 – 1.05 (m, 1 H), 0.84 (s, 3 H);

^{13}C NMR (150 MHz, $CDCl_3$) δ 210.4, 142.6, 117.6, 115.9, 65.4, 64.6, 57.5, 57.4, 55.0, 51.6, 49.8, 49.2,

48.7, 38.00, 36.9, 34.2, 31.7, 31.6, 22.1, 17.8, 14.9.



Compound 30: To a solution of compound **29** (95 mg, 0.25 mmol) in DMF (2.5 mL, 0.1 M) at ambient temperature was added sodium azide (82 mg, 1.25 mmol, 5 equiv). The reaction was allowed to stir at ambient temperature for 14 h, after which it was diluted with 35 mL of EtOAc The resulting mixture was washed twice with H_2O and sat. aq. NaCl and dried over $MgSO_4$. The solvent was removed *in vacuo* and the crude material purified by silica gel flash chromatography (3:1 hexanes:EtOAc) to afford compound **30** (91 mg, 94 %, 9:1 mixture of diastereomers) as a white solid.

R_f = 0.38 (3:1 hexanes:EtOAc)

$[\alpha]_D$ = 167 º (*c* = 0.1, $CHCl_3$)

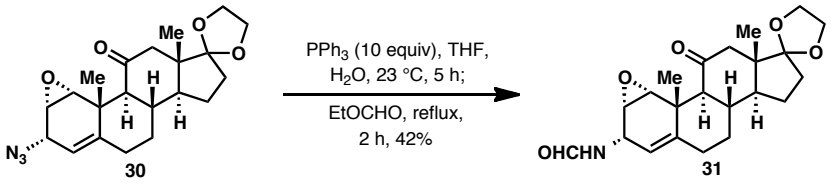
m.p. = 185–189 ºC

HRMS (*m*/*z*): calcd for $C_{21}H_{28}N_3O_4$ $[M+H]^+$, 386.2074; found, 386.2076;

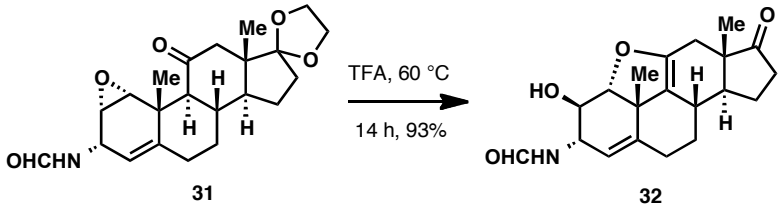
IR (film) ν_{max} = 2971, 2941, 2884, 2097, 1703, 1669, 1458, 1438, 1383, 1313, 1208, 1174, 1104, 1053, 1040 cm^{-1};

^1H NMR (600 MHz, $CDCl_3$) δ 5.17 – 5.13 (m, 1 H), 3.95 – 3.87 (m, 4 H), 3.85 – 3.78 (m, 2 H), 3.56 – 3.52 (m, 1 H), 2.70 (d, *J* = 12.4, 1 H), 2.31 – 2.24 (m, 2 H), 2.21 – 2.15 (m, 1 H), 2.11 – 1.99 (m, 3 H), 1.95 – 1.78 (m, 4 H), 1.39 – 1.34 (m, 1 H), 1.32 (s, 3 H), 1.19 – 1.11 (m, 1 H), 0.84 (s, 3 H);

^{13}C NMR (150 MHz, $CDCl_3$) δ 210.7, 144.5, 117.5, 113.5, 65.4, 64.6, 57.9, 57.7, 55.3, 55.1, 49.7, 49.2, 48.6, 37.4, 37.0, 34.1, 32.1, 31.7, 22.2, 17.8, 14.9.



Compound 31: Compound **30** (250 mg, 0.65 mmol) was dissolved THF (13 mL) and H_2O (1.3 mL). PPh_3 (1.7 g, 6.5 mmol, 10 equiv) was added and the reaction stirred at ambient temperature for 5 h. The reaction mixture was filtered through Celite® and concentrated *in vacuo*. The residue so obtained was dissolved in EtOCHO (13 mL, 0.5 M) and heated to reflux. After 2 h, the volatiles were removed *in vacuo* and the resulting residue was purified by flash column chromatography (CH_2Cl_2:acetone 4:1) furnishing formamide **31** (105 mg, 42 %) as a white foam. Analytical data are identical to the original.[1]



Compound 32: Epoxide **31** (50 mg, 0.13 mmol) was dissolved in 1.3 mL TFA. The resulting solution was heated to 60 ºC for 14 h. After cooling to ambient temperature, the solution was slowly poured onto 1 M NaOH (25 mL) and the resulting mixture stirred for 1 h. The mixture was extracted three times with CH_2Cl_2 (3 x 15 mL). The combined organic portions were washed with sat. aq. NaCl (25 mL), dried over $MgSO_4$ and concentrated *in* vacuo. The residue so obtained was purified by flash column chromatography (1:1 CH_2Cl_2:acetone) furnishing compound **32** (37 mg, 93 %) as a white foam.

R_f = 0.41 (1:1 CH_2Cl_2:acetone)

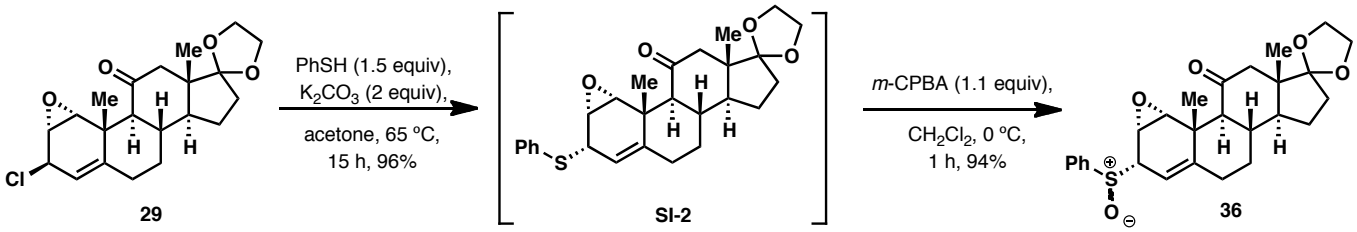
$[\alpha]_D$ = 79.1 ° (*c* = 0.5, $CHCl_3$)

HRMS (*m*/*z*): calcd for $C_{20}H_{26}NO_4$ $[M+H]^+$, 344.1856; found, 344.1842;

IR (film) ν_{max} = 3342, 2961, 2925, 2850, 1737, 1664, 1533, 1450, 1371, 1252, 1212, 1179, 1103, 1008 cm^{-1};

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.29 (s, 1 H), 5.81 (d, *J* = 6.3, 1 H), 5.19 (s, 1 H), 4.45 – 4.37 (m, 1 H), 4.32 (t, *J* = 8.1 Hz, 1 H), 3.47 (dd, *J* = 10.2, 8.4 Hz, 1 H), 2.54 (dd, *J* = 19.5, 8.9 Hz, 1 H), 2.35 – 2.15 (m, 5 H), 2.12 – 2.03 (m, 3 H), 1.71 – 1.56 (m, 3 H), 1.49 – 1.41 (m, 1 H), 1.26 (s, 3 H), 0.99 (s, 3 H);

^{13}C NMR (150 MHz, $CDCl_3$) δ 219.7, 162.0, 146.8, 144.4, 118.3, 115.6, 92.8, 75.1, 50.1, 49.5, 48.1, 48.0, 37.0, 34.6, 31.3, 31.0, 29.6, 24.8, 21.8, 14.6.



Compound 36: *i*. To a solution of compound **29** (95 mg, 0.25 mmol) in acetone (2.5 mL, 0.1 M) were added K_2CO_3 (69 mg, 0.5 mmol, 2 equiv) and thiophenol (39 μL, 0.38 mmol, 1.5 equiv). The resulting mixture was heated to 65 ºC for 15 h. After cooling to ambient temperature, the solvent was removed *in vacuo*. The obtained residue was taken up in H_2O and extracted three times with EtOAc (3 x 15 mL). The combined organic portions were washed with sat. aq. NaCl and dried over $MgSO_4$. The solvent was removed *in vacuo* and the crude material purified by silica gel flash chromatography (3:1 hexanes:EtOAc) to afford compound **SI-2** (102 mg, 96 %, 9:1 mixture of diastereomers) as a white solid. *ii*. A solution of compound **SI-2** (100 mg, 0.22 mmol) in CH_2Cl_2 (2.2 mL, 0.1 M) was cooled to 0 ºC. *m*-CPBA (60 mg, purity 70 %, 0.24 mmol, 1.1 equiv) was added and the reaction was stirred for at 0 ºC. After 1 h the mixture was poured onto 10 % aqueous $Na_2S_2O_3$ and the resulting biphasic mixture was extracted three times with EtOAc (3 x 15 mL). The combined organic portions were washed with sat. aq. $NaHCO_3$ (30 mL), sat. aq. NaCl (30 mL) and dried over $MgSO_4$. The solvent was removed *in vacuo* and

the crude material purified by silica gel flash chromatography (3:1 hexanes:EtOAc) to afford a mixture of diastereomers **36** (98 mg, 94 %) as a white foam (data reported for major diastereomer only).

R_f = 0.21 (1:1 EtOAc:hexanes)

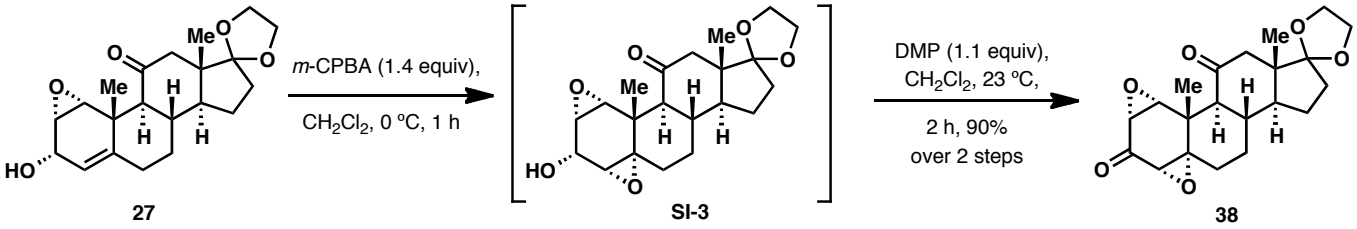
$[\alpha]_D$ = + 118.5 º (*c* = 0.2, CH_2Cl_2)

HRMS (*m*/*z*): calcd for $C_{27}H_{33}O_5S$ $[M+H]^+$, 469.2043; found, 469.2034;

IR (film) ν_{max} = 2973, 2938, 2880, 1703, 1443, 1313, 1171, 1103, 1044, 1019, 753, 690 cm^{-1};

^1H NMR (600 MHz, $CDCl_3$) δ 7.83 – 7.80 (m, 2 H), 7.56 – 7.53 (m, 3 H), 5.67 – 5.64 (m, 1 H), 3.96 – 3.87 (m, 3 H), 3.86 – 3.77 (m, 3 H), 3.52 (dd, *J* = 5.9, 2.9 Hz, 1 H), 2.77 – 2.72 (m, 1 H), 2.70 (d, *J* = 12.4, 1 H), 2.32 – 2.22 (m, 2 H), 2.12 – 1.98 (m, 3 H), 1.94 – 1.74 (m, 4 H), 1.39 – 1.33 (m, 1 H), 1.32 (s, 3 H), 1.23 – 1.12 (m, 1 H), 0.84 (s, 3 H);

^{13}C NMR (150 MHz, $CDCl_3$) δ 210.7, 144.7, 142.0, 131.7, 129.2 (2 C), 125.0 (2 C), 117.5, 110.0, 65.4, 64.6, 64.5, 58.8, 57.8, 49.9, 49.5, 49.2, 48.6, 37.4, 37.0, 34.1, 32.0, 31.9, 22.1, 17.8, 15.0.



Compound 38: *i*. A solution of compound **27** (200 mg, 0.55 mmol) in CH_2Cl_2 (5.5 mL, 0.1 M) was cooled to 0 ºC. *m*-CPBA (190 mg, purity 70 %, 0.24 mmol, 1.4 equiv) was added and the reaction was stirred for at 0 ºC. After 1 h the mixture was poured onto 10 % aqueous $Na_2S_2O_3$ (30 mL) and the resulting biphasic mixture was extracted three times with EtOAc (3 x 25 mL). The combined organic portions were washed with sat. aq. $NaHCO_3$ (30 mL), sat. aq. NaCl (30 mL), dried over $MgSO_4$ and the volatiles removed *in vacuo* to yield the crude *bis*-epoxide **SI-3**.

ii. The aforementioned crude *bis*-epoxide **SI-3** was dissolved in CH_2Cl_2 (11 mL, 0.05 M). DMP (257 mg,

0.61 mmol, 1.1 equiv) was added and the mixture stirred for 2 h at ambient temperature. Then the mixture was poured onto 10 % aq. $Na_2S_2O_3$ (30 mL) and the resulting biphasic mixture was extracted three times with EtOAc (3 x 25 mL). The combined organic portions were washed with sat. aq. $NaHCO_3$ (30 mL), sat. aq. NaCl (30 mL), dried over $MgSO_4$ and the volatiles removed *in vacuo*. The residue so obtained was purified by flash column chromatography (hexanes:EtOAc 2:1) furnishing compound **38** (185 mg, 90 % over two steps) as a white foam.

R_f = 0.41 (1:1 EtOAc:hexanes)

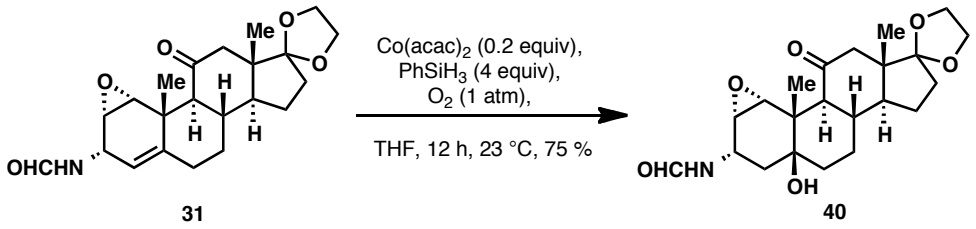
$[\alpha]_D$ = + 59 ° (c = 0.1, CH_2Cl_2)

HRMS (m/z): calcd for $C_{21}H_{27}O_6$ $[M+H]^+$, 375.1802; found, 375.1800;

IR (film) ν_{max} = 2944, 2878, 1702, 1173, 1105, 1033, 922, 771 cm^{-1};

^1H NMR (600 MHz, $CDCl_3$) δ 4.26 (d, J = 4.3 Hz, 1 H), 3.98 – 3.90 (m, 2 H), 3.87 – 3.79 (m, 2 H), 3.36 (dd, J = 4.3, 2.5 Hz, 1 H), 3.25 (d, J = 2.5 Hz, 1 H), 2.86 (d, J = 11.4 Hz, 1 H), 2.79 (d, J = 12.1 Hz, 1 H), 2.26 – 2.18 (m, 2 H), 2.13 (d, J = 12.1 Hz, 1 H), 2.05 (ddd, J = 15.0, 11.8, 3.5 Hz, 1 H), 1.99 – 1.92 (m, 2 H), 1.89 – 1.81 (m, 2 H), 1.57 (ddd, J = 15.0, 11.8, 3.5 Hz, 1 H), 1.41 – 1.32 (m, 4 H), 1.04 – 0.99 (m, 1 H), 0.863 (s, 3 H);

^{13}C NMR (150 MHz, $CDCl_3$) δ 210.5, 200.4, 117.3, 73.8, 65.4, 64.6, 64.3, 63.1, 56.6, 55.8, 49.6, 49.5, 48.6, 36.7, 36.7, 34.2, 30.6, 28.6, 22.1, 17.0, 15.0.



Compund 40: To a solution of compound **31** (100 mg, 0.26 mmol) in THF (5.5 mL, 0.05 M) was added $Co(acac)_2$ (13.4 mg, 52 μmol, 0.2 equiv). The reaction mixture was saturated with O_2 by bubbling O_2

through the stirred solution for 30 min. Then freshly distilled $PhSiH_3$ (0.15 mL, 1.1 mmol, 4 equiv) was added over 5 min. Stirring was continued under an static O_2-atmosphere (no bubbling) for 12 h. The reaction was then diluted with EtOAc (25 mL), washed with 1 M aq. HCl (10 mL), sat. aq. $NaHCO_3$ (10 mL), H_2O (10 mL), and sat. aq. NaCl (10 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The residue so obtained was purified by flash column chromatography (CH_2Cl_2:acetone 5:1) furnishing **40** (79 mg, 75%) as a white foam.

R_f = 0.31 (2:1 CH_2Cl_2:acetone)

$[\alpha]_D$ = + 22.5 º (*c* = 0.2, CH_2Cl_2)

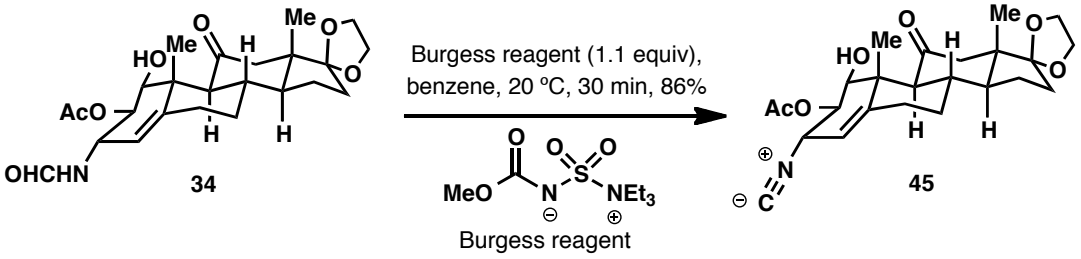
m.p. = 134–138 ºC

HRMS (*m*/*z*): calcd for $C_{22}H_{32}NO_6$ $[M+H]^+$, 406.2224; found, 406.2233;

IR (film) ν_{max} = 3324, 2947, 2875, 1702, 1671, 1526, 1385, 1167, 1056, 1028, 753 cm^{-1};

^1H NMR (600 MHz, $CDCl_3$) δ 8.15 (s, 1 H), 5.89 (d, *J* = 8.9 Hz, 1 H), 4.84 (dd, *J* = 17.1, 9.0 Hz, 1 H), 3.95 – 3.89 (m, 2 H), 3.84 – 3.79 (m, 2 H), 3.51 (d, *J* = 3.8 Hz, 1 H), 3.34 (s, 1 H), 2.65 (d, *J* = 13.1 Hz, 1 H), 2.27(d, *J* = 11.4 Hz, 1 H), 2.12(d, *J* = 13.0 Hz, 1 H), 2.06 – 1.95 (m, 2 H), 1.94 – 1.87 (m, 1 H), 1.82 – 1.76 (m, 1 H), 1.74 (s, 1 H), 1.72 – 1.63 (m, 3 H), 1.61 – 1.42 (m, 3 H), 1.39 – 1.30 (m, 1 H), 1.27 (s, 3 H), 1.12 – 1.02 (m, 1 H), 0.81 (s, 3 H);

^{13}C NMR (150 MHz, $CDCl_3$) δ 209.9, 160.8, 117.7, 72.7, 65.4, 64.6, 61.6, 57.1, 56.9, 49.0, 49.0, 48.5, 43.0, 38.0, 37.0, 35.7, 34.1, 34.0, 27.9, 22.2, 15.0, 14.5.



Compound 45: Compound **34** (250 mg, 0.56 mmol) was dissolved in 5.6 mL anhydrous benzene (0.1 M) and the temperature adjusted to 20 ºC (waterbath). Burgess reagent (148 mg, 0.62 mmol, 1.1 equiv) was added and the reaction stirred at 20 ºC for 30 min. The reaction was diluted with EtOAc (20 mL) and washed with sat. aq. $NaHCO_3$. The aqueous phase was extracted two times with EtOAc (2 x 25 mL). The combined organic portions were washed sat. aq. NaCl (20 mL), dried over $MgSO_4$ and the volatiles removed *in vacuo*. The residue so obtained was purified by flash column chromatography (1:1 hexanes:EtOAc) furnishing compound **45** (206 mg, 86 %) as a white foam.

R_f = 0.35 (1:1 EtOAc:hexanes)

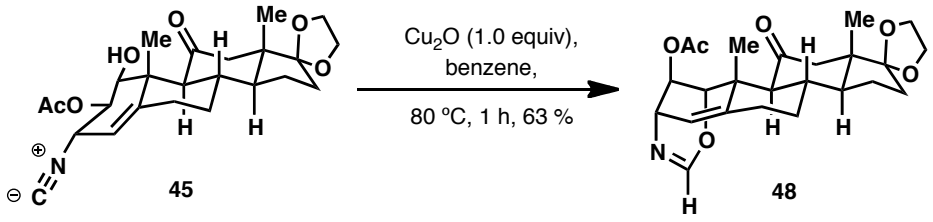
$[\alpha]_D$ = + 159 º (*c* = 0.1, CH_2Cl_2)

HRMS (*m*/*z*): calcd for $C_{24}H_{32}NO_6$ $[M+H]^+$, 430.2224; found, 430.2224;

IR (film) ν_{max} = 2948, 2140, 1748, 1702, 1372, 1220, 1052, 1033, 772 cm^{-1};

^1H NMR (600 MHz, $CDCl_3$) δ 5.38 (d, *J* = 3.5 Hz, 1 H), 5.24 (dd, *J* = 5.4, 3.6 Hz, 1 H), 4.35 (t, *J* = 5.6 Hz, 1 H), 4.07 (dd, *J* = 6.4, 3.4 Hz, 1 H), 3.96 – 3.88 (m, 2 H), 3.89 – 3.77 (m, 2 H), 2.72 – 2.68 (m, 2 H), 2.64 (d, *J* = 11.3 Hz, 1 H), 2.35 – 2.26 (m, 1 H), 2.19 – 2.15 (m, 1 H), 2.13 – 2.00 (m, 6 H), 1.96 – 1.87 (m, 3 H), 1.85 – 1.79 (m, 1 H), 1.40 – 1.32 (m, 4 H), 1.26 – 1.18 (m, 1 H), 0.82 (s, 3 H);

^{13}C NMR (150 MHz, $CDCl_3$) δ 213.1, 169.5, 156.6, 146.4, 117.5, 112.9, 71.7, 71.5, 65.4, 64.6, 57.4, 50.3, 49.5, 49.4, 48.8, 41.4, 36.9, 34.2, 31.9, 31.8, 22.2, 20.9, 19.3, 15.0.



Compound 48: To a degassed solution of compound **45** (115 mg, 0.27 mmol) in anhydrous benzene (5 mL, 0.05 M) was added Cu_2O (39 mg, 0.27 mmol, 1 equiv). The resulting mixture was heated to 80 ºC for 1 h. After cooling to ambient temperature the mixture was diluted with CH_2Cl_2 (15 mL) and filtered through a layer of Celite®. Purification of the crude residue obtained after concentration *in vacuo* was performed by flash column chromatography (CH_2Cl_2:acetone 7:1) yielded compound **48** (72 mg, 63 %).

R_f = 0.48 (4:1 CH_2Cl_2:acetone)

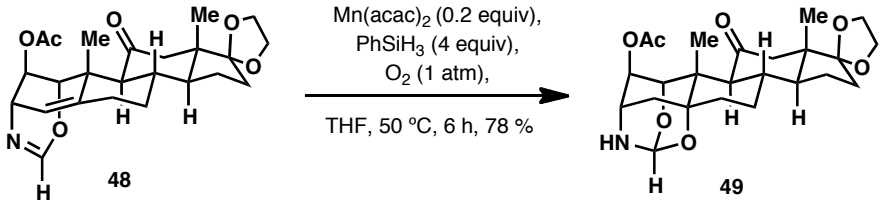
$[\alpha]_D$ = + 120 ° (*c* = 0.2, CH_2Cl_2)

HRMS (*m*/*z*): calcd for $C_{24}H_{32}NO_6$ $[M+H]^+$, 430.2224; found, 430.2223;

IR (film) ν_{max} = 3386, 2946, 1738, 1703, 1644, 1371, 1235, 1175, 1104, 754 cm^{-1};

^1H NMR (600 MHz, $CDCl_3$) δ 6.82 (s, 1 H), 5.71 (d, *J* = 6.1 Hz, 1 H), 5.22 (dd, *J* = 4.2, 2.8 Hz, 1 H), 5.15 – 5.11 (m, 1 H), 3.96 – 3.87 (m, 2 H), 3.85 – 3.79 (m, 3 H), 2.65 (d, *J* = 12.5 Hz, 1 H), 2.31 – 2.23 (m, 1 H), 2.17 – 2.10 (m, 2 H), 2.08 (s, 1 H), 2.06 (s, 3 H), 2.04 – 1.98 (m, 2 H), 1.97 – 1.85 (m, 3 H), 1.84 – 1.77 (m, 1 H), 1.41 – 1.32 (m, 4 H), 1.11 – 1.02 (m, 1 H), 0.86 – 0.81(s, 3 H);

^{13}C NMR (150 MHz, $CDCl_3$) δ 210.4, 169.7, 148.9, 142.9, 120.4, 117.6, 74.6, 66.1, 65.4, 64.6, 58.1, 49.3, 49.2, 48.9, 47.5, 43.3, 36.3, 34.2, 32.1, 31.2, 22.2, 21.1, 18.6, 15.0.



Compound 49: To a solution of compound **48** (65 mg, 0.15 mmol) in THF (3.0 mL, 0.05 M) was added $Mn(acac)_2$ (7.6 mg, 30 μmol, 0.2 equiv). The reaction mixture was saturated with O_2 by bubbling O_2 through the stirred solution for 30 min. Then, freshly distilled $PhSiH_3$ (74 μL, 0.6 mmol, 4 equiv) was added at once. The mixture was heated to 50 ºC. Stirring was continued at this temperature under an

static O_2-atmosphere (no bubbling) for 6 h. The reaction was then diluted with EtOAc (15 mL), washed with 1 M aq. HCl (10 mL), sat. aq. $NaHCO_3$ (10 mL), H_2O (10 mL), and sat. aq. NaCl (10 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The residue so obtained was purified by flash column chromatography (CH_2Cl_2:acetone 4:1) furnishing **49 (**52 mg, 78%) as a white foam.

R_f = 0.28 (4:1 CH_2Cl_2:acetone)

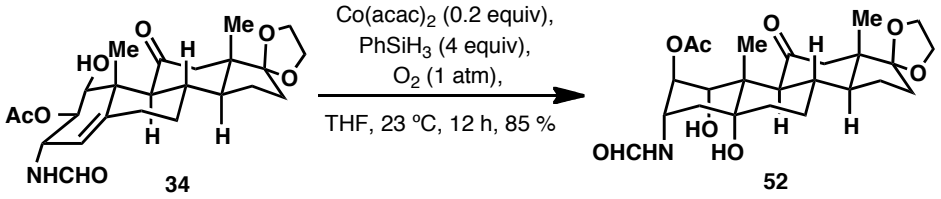
$[\alpha]_D$ = + 13 ° (*c* = 0.2, CH_2Cl_2)

HRMS (*m*/*z*): calcd for $C_{24}H_{34}NO_7$ $[M+H]^+$, 448.2335; found, 448.2333;

IR (film) ν_{max} = 1744, 1701, 1236, 1175, 1109, 755 cm^{-1};

^1H NMR (600 MHz, $CDCl_3$) δ 5.41 (s, 1 H), 5.32 (s, 1 H), 4.72 – 4.68 (m, 1 H), 3.97 – 3.88 (m, 2 H), 3.84 – 3.78 (m, 2 H), 3.31 (d, *J* = 11.4 Hz, 2 H), 2.70 (d, *J* = 12.5 Hz, 1 H), 2.22 – 2.15 (m, 2 H), 2.09 (s, 3 H), 2.07 – 1.99 (m, 3 H), 1.96 – 1.89 (m, 1 H), 1.88 – 1.79 (m, 3 H), 1.72 – 1.63 (m, 1 H), 1.55 – 1.47 (m, 2 H), 1.42 – 1.29 (m, 2 H), 1.25 (s, 3 H), 0.80 (s, 3 H);

^{13}C NMR (150 MHz, $CDCl_3$) δ 212.7, 170.4, 118.6, 98.2, 75.7, 72.8, 72.3, 66.3, 65.5, 54.0, 50.7, 50.3, 49.7, 47.9, 40.0, 36.3, 35.1, 33.1, 32.0, 25.6, 23.0, 22.1, 16.0, 15.8.



Compound 52: To a solution of compound **34** (112 mg, 0.25 mmol) in THF (5.0 mL, 0.05 M) was added $Co(acac)_2$ (12.8 mg, 50 μmol, 0.2 equiv). The reaction mixture was saturated with O_2 by bubbling O_2 through the stirred solution for 30 min. Then freshly distilled $PhSiH_3$ (0.14 mL, 1.0 mmol, 4 equiv) was added over 5 min. Stirring was continued under an static O_2-atmosphere (no bubbling) for 12 h. The reaction was then diluted with EtOAc (25 mL), washed with 1 M aq. HCl (10 mL), sat. aq. $NaHCO_3$ (10

mL), H_2O (10 mL), and sat. aq. NaCl (10 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The residue so obtained was purified by flash column chromatography (CH_2Cl_2:acetone 3:1) furnishing **52** (99 mg, 85%) as a white foam.

R_f = 0.21 (90:10:2 CH_2Cl_2:MeOH:Et_3N)

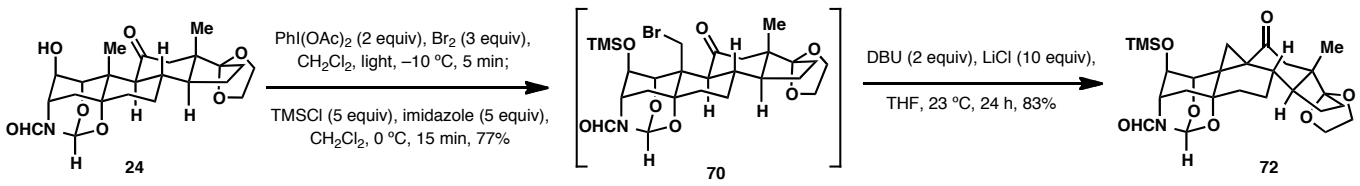
$[\alpha]_D$ = – 19 º (*c* = 0.1, CH_2Cl_2)

HRMS (*m*/*z*): calcd for $C_{24}H_{36}NO_8$ $[M+H]^+$, 466.2435; found, 466.2432;

IR (film) ν_{max} = 3388, 2942, 2879, 1735, 1702, 1665, 1503, 1432, 1382, 1239, 1175, 1112, 1050, 771 cm^{-1};

^1H NMR (600 MHz, $CDCl_3$) δ 8.06 (s, 1 H), 5.13 – 5.07 (m, 1 H), 4.55 – 4.51 (m, 1 H), 4.30 – 4.20 (m, 2 H), 3.96 – 3.88 (m, 2 H), 3.86 – 3.78 (m, 2 H), 2.91 (d, *J* = 11.3 Hz, 1 H), 2.71 (d, *J* = 12.5 Hz, 1 H), 2.22 – 2.11 (m, 2 H), 2.07 (s, 3 H), 2.05 – 1.98 (m, 2 H), 1.96 – 1.85 (m, 2 H), 1.87 – 1.78 (m, 3 H), 1.69 – 1.50 (m, 4 H), 1.46 – 1.38 (m, 1 H), 1.37 – 1.30 (m, 1 H), 1.19 (s, 3 H), 0.78 (s, 3 H);

^{13}C NMR (150 MHz, $CDCl_3$) δ 212.2, 170.3, 160.7, 117.7, 75.6, 75.4, 73.4, 65.4, 64.6, 52.0, 49.7, 49.5, 49.0, 44.9, 41.4, 35.9, 35.6, 34.2, 33.8, 25.3, 22.1, 21.3, 16.2, 15.0.



Compound 72: *i.* Alcohol **24** (103 mg, 0.24 mmol) and $PhI(OAc)_2$ (153 mg, 0.47 mmol, 2 equiv) were dissolved in CH_2Cl_2 (2.4 mL, 0.1 M) at room temperature under Ar. After cooling to –10 °C, Br_2 (19 μL, 0.72 mmol, 3 equiv) was added and the reaction mixture was irradiated with a sunlamp (100 W) for 5 min. Irradiation was then halted, the reaction was diluted with ice-cold CH_2Cl_2 (30 mL), and the crude mixture was washed with 10% $Na_2S_2O_3$ (50 mL) until colorless. The aqueous layer was back-extracted twice with CH_2Cl_2 (20 mL), dried with $MgSO_4$, filtered, and concentrated *in vacuo* at 5 °C to about 10

mL. At 0 °C, imidazole (82 mg, 1.2 mmol, 5 equiv) and TMSCl (152 μL, 1.2 mmol, 5 equiv) were added. After 15 minutes, the reaction was diluted with EtOAc (50 mL), washed with water (20 mL), then $NaHCO_3$ (sat. aq.) (20 mL), then brine, dried with $MgSO_4$, filtered, and concentrated *in vacuo*. Chromatography on silica (2:5 EtOAc:hexanes) afforded bromide **70** (107 mg, 77%) as a white foam.

ii. bromide **70** (207 mg, 0.19 mmol) was dissolved in THF (3.8 mL, 0.05 M) and freshly flame-dried LiCl (40 mg, 0.95 mmol, 5 equiv) was added, followed by dry DBU (57 μL, 0.38 mmol, 2 equiv). The reaction mixture was stirred for 24 hours, at which point it was diluted with EtOAc (30 mL), washed with twice with water (10 mL), and once with brine (10 mL). The aqueous layer was extracted twice with CH_2Cl_2 (2 × 20 mL); these portions were added to the organic phase, which was dried with $MgSO_4$, filtered, and concentrated *in vacuo*. Chromatography on silica (1:2 EtOAc:hexanes) afforded cylopropane **72** (79 mg, 83%) as a colorless foam.

R_f = 0.41 (1:1 EtOAc:hexanes)

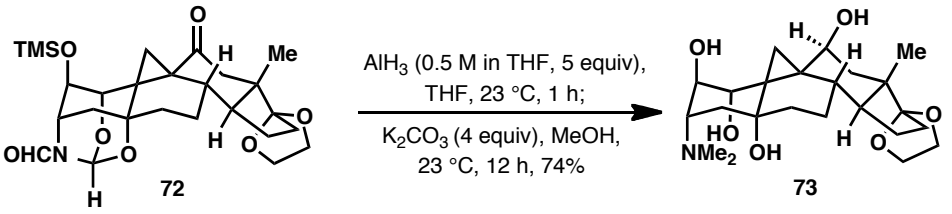
$[\alpha]_D$ = + 47 ° (*c* = 0.1, CH_2Cl_2)

HRMS (*m*/*z*): calcd for $C_{26}H_{38}NO_7Si$ $[M+H]^+$, 504.2412; found, 504.2406;

IR (film) ν_{max} = 2950, 2880, 1682, 1425, 1253, 1123, 1008, 844, 757 cm^{-1};

^1H NMR (600 MHz, $CDCl_3$) δ 8.20 (s, 1 H), 5.81 (s, 1H), 4.57 (brs, 1 H), 4.12 (d, *J* = 2.3 Hz, 1 H), 3.98 – 3.80 (m, 4 H), 2.72 (dd, *J* = 15.2, 0.9 Hz, 1H), 2.34 (d, *J* = 15.2 Hz, 1H), 2.22 (dd, *J* = 13.1, 2.4 Hz, 1H), 2.21 – 2.15 (m, 1 H), 2.11 – 2.07 (m, 1 H), 2.00 – 1.90 (m, 2 H), 1.89 – 1.81 (m, 3 H), 1.79 (dd, *J* = 13.0, 3.3 Hz, 1H), 1.64 – 1.50 (m, 2 H), 1.43 – 1.29 (m, 3 H), 0.91 (s, 3 H), 0.87 (d, *J* = 4.9 Hz, 1H), 0.71 (s, 9H);

^{13}C NMR (150 MHz, $CDCl_3$) δ 209.4, 157.7, 118.3, 96.9, 72.8, 70.1, 67.6, 65.4, 64.6, 50.6, 49.7, 47.3, 46.1, 37.9, 36.5, 33.8, 33.6, 32.4, 30.7, 27.0, 24.2, 22.1, 15.2, -0.1 (3 C).



Compound 73: A freshly prepared solution of AlH_3 (2.2 mL, 1.1 mmol, 5 equiv, 0.5 M in THF) was added to **72** (51 mg, 0.11 mmol) in THF (1.1 mL, 0.1 M) at ambient temperature. After stirring vigorously for 1 h, methanol (0.6 mL) was added dropwise, followed by K_2CO_3 (60 mg, 0.44 mmol, 4 equiv). This suspension was then stirred for 12 h. Then, the reaction mixture was diluted with CH_2Cl_2 (30 mL) and sat. aq. sodium potassium tartrate (10 mL). The organic phase was removed and the aqueous layer extracted two more times with CH_2Cl_2 (30 mL). Drying over $MgSO_4$, filtration, concentration *in vacuo*, and chromatography on silica (100:10:1 MeOH:CH_2Cl_2:NH_3H_2O) yielded **73** (34 mg, 74%) as white foam.

R_f = 0.41 (90:10:2 CH_2Cl_2:MeOH: NH_3H_2O)

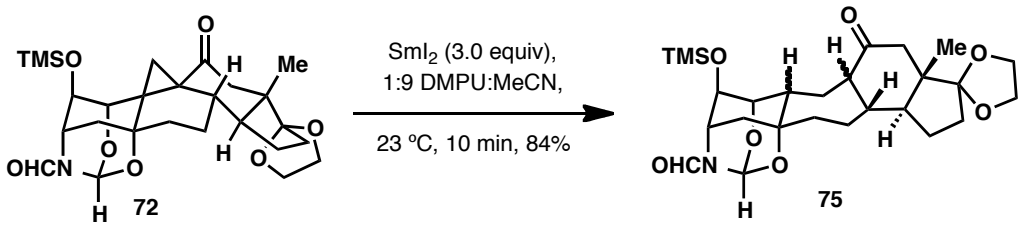
$[\alpha]_D$ = + 34 ° (*c* = 0.5, CH_2Cl_2)

HRMS (*m*/*z*): calcd for $C_{23}H_{38}NO_6$ $[M+H]^+$, 424.2694; found 424.2696;

IR (film) ν_{max} = 3398, 2936, 2875, 2783, 1456, 1165, 1100, 1054, 1038, 967, 897 cm^{-1};

^1H NMR (600 MHz, CD_3OD) δ 4.27 – 4.25 (m, 1 H), 3.87 – 3.75 (m, 5 H), 3.47 – 3.43 (m, 1 H), 2.90 – 2.85 (m, 1 H), 2.50 (s, 6 H), 2.18 – 2.03 (m, 3 H), 1.98 – 1.89 (m, 2 H), 1.82 – 1.65 (m, 3 H), 1.56 – 1.40 (m, 5 H), 1.32 – 1.24 (m, 1 H), 1.07 (s, 3 H), 0.88 (d, *J* = 5.6 Hz, 1 H), 0.74 (d, *J* = 5.6 Hz, 1 H);

^{13}C NMR (150 MHz, CD_3OD) δ 120.8, 81.0, 73.6, 73.2, 72.9, 66.1, 65.6, 65.3, 64.4, 49.3, 46.9, 42.2, 38.1, 35.6, 34.9, 34.7, 34.6, 32.9, 31.9, 24.1, 21.3, 20.2, 17.2.



Compound 75: Cyclopropane **72** (50 mg, 0.1 mmol) was dissolved in CH_3CN (2 mL, 0.05 M) under Ar and freshly distilled DMPU (0.22 mL) was added. The solution was bubbled with Ar for 10 min, after which SmI_2 (3.0 mL, 0.3 mmol, 3.0 equiv, 0.1 M in THF) was quickly added. After stirring for 10 min at ambient temperature sat. aq. NH_4Cl (10 mL) was added and the biphasic mixture extracted three times with EtOAc (3 x 15 mL). The combined organic portions were washed sat. aq. NaCl (30 mL), dried over $MgSO_4$ and the volatiles removed *in vacuo*. The residue so obtained was purified by flash column chromatography (1:1 hexanes:EtOAc) furnishing compound **75** (42 mg, 84 %) as a white foam (data report for major diastereomer only).

R_f = 0.41 (1:1 EtOAc:hexanes)

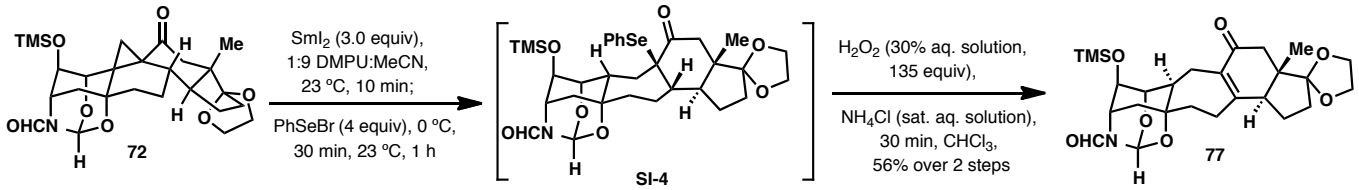
$[\alpha]_D$ = + 27 ° (*c* = 0.2, CH_2Cl_2)

HRMS (*m*/*z*): calcd for $C_{26}H_{40}NO_7Si$ $[M+H]^+$, 506.2568; found, 506.2580;

IR (film) ν_{max} = 3360, 2952, 2884, 1711, 1679, 1431, 1319, 1254, 1124, 1030, 1004, 876, 844, 757 cm^{-1};

^1H NMR (600 MHz, $CDCl_3$) δ 8.18 (s, 1 H), 5.78 (s, 1 H), 4.50 (s, 1 H), 4.05 – 3.75 (m, 4 H), 2.74 – 2.60 (m, 2 H), 2.26 (d, *J* = 13.6, 1 H), 2.17 – 1.95 (m, 6 H), 1.94 – 1.80 (m, 4 H), 1.76 – 1.65 (m, 2 H), 1.54 – 1.21 (m, 5 H), 0.79 (s, 3 H), 0.19 (s, 9 H);

^{13}C NMR (150 MHz, $CDCl_3$) δ 211.5, 176.6, 157.5, 117.6, 96.9, 77.5, 66.7, 65.9, 65.4, 64.5, 59.5, 49.4, 48.5, 47.5, 47.0, 43.9, 41.0, 33.7, 29.7, 27.5, 25.0, 22.5, 15.2, - 0.1 (3 C).



Compound 77: *i*. Cyclopropane **72** (50 mg, 0.1 mmol) was dissolved in CH_3CN (1.8 mL, 0.05 M) under Ar and freshly distilled DMPU (0.2 mL) was added. The solution was bubbled with Ar for 10 min, after which SmI_2 (3.0 mL, 0.3 mmol, 3.0 equiv, 0.1 M in THF) was quickly added. After stirring for 10 min at ambient temperature the mixture was cooled to 0 ºC. PhSeBr (2 mL, 0.4 mmol, 4 equiv, 0.2 M in CH_3CN) was added and stirring was continued for 30 min at 0 ºC and then for 1 h at ambient temperature. Sat. aq. $NaHCO_3$ (15 mL) was added to the reaction and the mixture extracted three times with EtOAc (3 x 15 mL). The combined organic portions were washed sat. aq. NaCl, dried over $MgSO_4$ and the volatiles removed *in vacuo*. The residue so obtained was purified by flash column chromatography (silica gel, hexane/EtOAc 1:1) furnishing compound **SI-4** (43 mg) as a white foam.

ii. A solution of compound **SI-4** (43 mg) in CH_3Cl (3 mL) and sat. aq. NH_4Cl (1 mL) was cooled to 0 ºC. H_2O_2 (30% aqueous solution, 1 mL) was added dropwise. Stirring was continued at this temperature for 30 min. The reaction was diluted with H_2O and extracted three times with CH_2Cl_2 (3 x 15 mL). The combined organic portions were washed sat. aq. NaCl, dried over $MgSO_4$ and the volatiles removed *in vacuo*. The residue so obtained was purified by flash column chromatography (1:1 hexanes:EtOAc) furnishing compound **77** (28 mg, 56 % over two steps) as a white solid.

R_f = 0.31 (1:1 EtOAc:hexanes)

$[\alpha]_D$ = + 37.3 º (*c* = 0.3, CH_2Cl_2)

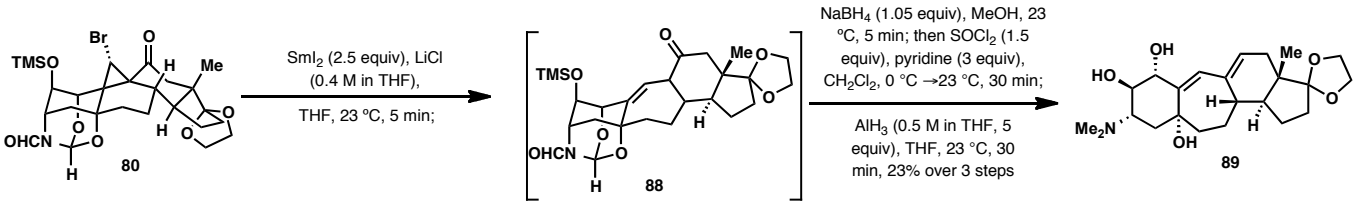
m.p. = 93–96 ºC

HRMS (*m*/*z*): calcd for $C_{26}H_{38}NO_7Si$ $[M+H]^+$, 504.2412; found, 504.2414;

IR (film) ν_{max} = 2950, 2890, 1660, 1616, 1427, 1253, 1124, 1081, 1031, 1001, 874, 844, 753 cm^{-1};

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.18 (s, 1 H), 5.76 (s, 1 H), 4.56 (s, 1 H), 4.10 – 3.81 (m, 4 H), 3.08 (s, 1 H), 2.88 (d, *J* = 15.1 Hz, 1 H), 2.71 (d, *J* = 13.0 Hz, 1 H), 2.62 (d, *J* = 16.1 Hz, 1 H), 2.41 – 2.21 (m, 3 H), 2.20 – 2.01 (m, 3 H), 2.20 – 2.01 (m, 3 H), 2.00 – 1.90 (m, 2 H), 1.70 – 1.60 (m, 2 H), 1.44 (t, *J* = 13.4 Hz, 1 H), 0.86 (s, 3 H), 0.18 (s, 9 H);

^{13}C NMR (150 MHz, $CDCl_3$) δ 197.8, 176.6, 160.0, 157.5, 136.3, 117.7, 96.4, 77.6, 75.3, 66.5, 65.5, 64.6, 48.5, 47.3, 46.5, 43.9, 37.1, 33.3, 27.2, 24.2, 23.7, 22.5, 14.7, - 0.1 (3 C).



Compound 89: *i*. compound **80** (25 mg, 42 μmol) was dissolved in THF (0.4 M LiCl in THF solution, 2.1 ml) under Ar. The solution was bubbled with Ar for 10 min, after which SmI_2 (1.3 mL, 0.13 mmol, 2.5 equiv, 0.1 M in THF) was quickly added. After stirring for 5 min at ambient temperature, sat. aq. $NaHCO_3$ (15 mL) was added to the reaction and the mixture extracted three times with EtOAc (3 x 15 mL). The combined organic portions were washed sat. aq. NaCl (30 mL), dried over $MgSO_4$ and the volatiles removed *in vacuo*. The compound **88** was used in crude form for the next reaction directly.

ii. **88** was was dissolved in MeOH (2.1 ml) and $NaBH_4$ (1.6 mg, 44 μmol, 1.05 equiv) was added. After stirring for 5 min at ambient temperature, sat. aq. $NaHCO_3$ (15 mL) was added to the reaction and the mixture extracted three times with EtOAc (3 x 15 mL). The combined organic portions were washed sat. aq. NaCl, dried over $MgSO_4$ and the volatiles removed *in vacuo*. The residue was then dissolved in CH_2Cl_2 (2.1 ml) and pyridine (10 μL, 0.126 mmol, 3 equiv) was added. At 0 ºC, $SOCl_2$ (5 μL, 63 μmol, 1.5 equiv) was added into reaction mixture and then warmed up to ambient temperature for 30 min. Sat. aq. $NaHCO_3$ (15 mL) was added to the reaction and the mixture extracted three times with EtOAc (3 x 15

mL). The combined organic portions were washed sat. aq. NaCl (30 mL), dried over $MgSO_4$ and the volatiles removed *in vacuo*.

iii. A freshly prepared solution of AlH_3 (0.42 mL, 0.2 mmol, 5 equiv, 0.5 M in THF) was added to abovementioned residue in THF (2.1 mL) at ambient temperature. After stirring vigorously for 30 min, the reaction mixture was diluted with CH_2Cl_2 (25 mL) and sat. aq. sodium potassium tartrate (10 mL). The organic phase was removed and the aqueous layer extracted two more times with CH_2Cl_2 (10 mL). Drying over $MgSO_4$, filtration, concentration *in vacuo*, and chromatography on silica (100:10:1 MeOH:CH_2Cl_2:NH_3H_2O) yielded **89** (4 mg, 23% overall yield) as a white foam.

R_f = 0.35 (MeOH: CH_2Cl_2:NH_4OH = 100:10:1)

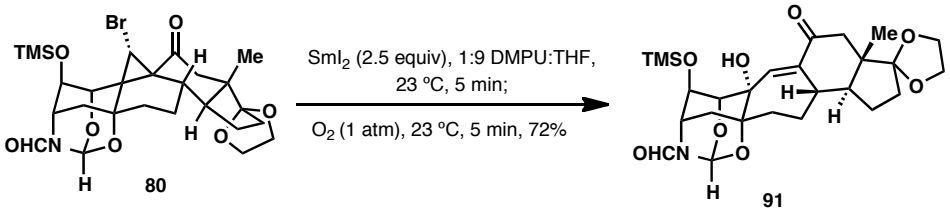
$[\alpha]_D$ = + 1.6 º (*c* = 0.12, CH_2Cl_2)

HRMS (*m*/*z*): calcd for $C_{23}H_{36}NO_5$ $[M+H]^+$, 406.2588; found, 406.2599;

IR (film) ν_{max} = 3367, 2890, 1458, 1174, 1101, 1038, 1027, 951 cm^{-1};

^1H NMR (600 MHz, $CDCl_3$) δ 6.18 (s, 1 H), 5.85 (t, *J* = 2.5 Hz, 1 H), 4.32 (brs, 1 H), 4.16 (d, *J* = 3.7 Hz, 1 H), 3.97 – 3.80 (m, 5 H), 2.63 (bs, 1H), 2.57 (s, 6 H), 2.52 – 2.42 (m, 2 H), 2.14 – 2.03 (m, 2 H), 2.02 – 1.90 (m, 3 H), 1.88 – 1.76 (m, 3 H), 1.75 – 1.62 (m, 4 H), 1.38 – 1.25 (m, 2 H), 0.84 (s, 3 H);

^{13}C NMR (150 MHz, $CDCl_3$) δ 137.8, 136.4, 135.9, 132.9, 118.7, 81.6, 73.2, 68.8, 66.4, 65.2, 64.5, 46.1, 44.4, 44.0, 43.4, 35.2, 33.6, 33.0, 29.7, 24.3, 23.3, 14.9.



Compound 91: Compound **80** (25 mg, 42 μmol) was dissolved in THF (2.1 mL, 0.02 M) under Ar and freshly distilled DMPU (0.23 mL) was added. The solution was bubbled with Ar for 10 min, after which

SmI_2 (1.3 mL, 0.13 mmol, 2.5 equiv, 0.1 M in THF) was quickly added. After stirring for 5 min at ambient temperature, the reaction mixture was bubbled with O_2 for 5 min. Then, sat. aq. $NaHCO_3$ (15 mL) was added to the reaction and the mixture extracted three times with EtOAc (3 x 15 mL). The combined organic portions were washed sat. aq. NaCl (30 mL), dried over $MgSO_4$ and the volatiles removed *in vacuo*. The residue so obtained was purified by flash column chromatography (hexanes:EtOAc 1:1) furnishing compound **91** (16 mg, 72%) as a white foam.

R_f = 0.25 (1:1 EtOAc:hexanes)

$[\alpha]_D$ = + 6.2 º (*c* = 1.07, CH_2Cl_2)

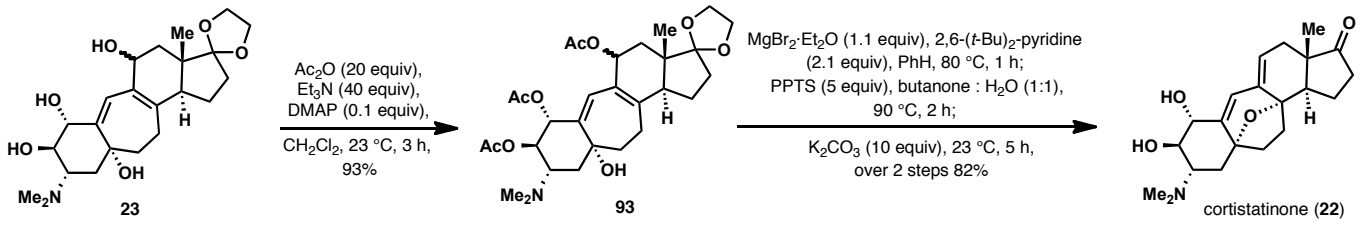
HRMS (*m*/*z*): calcd for $C_{26}H_{38}NO_8Si$ $[M+H]^+$, 542.2181; found, 542.2187;

IR (film) ν_{max} = 3462, 1685, 1316, 1087, 999, 686 cm^{-1};

m.p. = 165–168 ºC

^1H NMR (600 MHz, $CDCl_3$) δ 8.19 (s, 1 H), 6.64 (d, *J* = 2.7 Hz, 1 H), 5.77 (s, 1 H), 4.37 (s, 1 H), 4.18 – 4.15 (m, 1 H), 4.01 – 3.80 (m, 4 H), 3.57 (s, 1 H), 3.10 – 3.05 (m, 1 H), 2.64 – 2.59 (m, 1 H), 2.41 – 2.26 (m, 2 H), 2.21 – 2.09 (m, 3 H), 2.06 – 1.86 (m, 4 H), 1.79 – 1.52 (m, 3 H), 1.45 – 1.35 (m, 1 H), 0.89 (s, 3 H), 0.13 (s, 9 H);

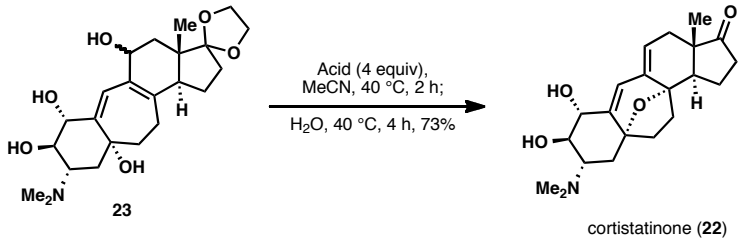
^{13}C NMR (150 MHz, $CDCl_3$) δ 199.5, 157.5, 138.4, 118.0, 95.6, 79.7, 70.1, 67.7, 66.5, 64.6, 64.5, 48.4, 46.7, 46.5, 46.1, 39.5, 39.3, 33.7, 33.3, 28.1, 24.0, 21.0, 15.5, - 0.4 (3 C).



Compound 22: i. Compound **23** (50 mg, 0.12 mmol) was dissolved in CH_2Cl_2 (2.3 mL, 0.05 M), followed by the addition of Et_3N (664 µL, 4.8 mmol, 40 equiv), Ac_2O (226 µL, 2.4 mmol, 20 equiv), and

DMAP (1.5 mg, 0.012 mmol, 0.1 equiv). After 3 h, the reaction mixture was diluted with CH_2Cl_2 (5 mL) and sat. aq. $NaHCO_3$ (1 mL). The organic phase was removed and the aqueous layer extracted two more times with CH_2Cl_2 (2 × 5 mL). Drying over Na_2SO_4, filtration, concentration *in vacuo*, and flash solumnchromatography (silica gel, 10% MeOH:EtOAc) yielded **93** (61 mg, 93%, mixture of diastereomers) as a white foam.

ii. To a solution of triacetate **93** (13 mg, 0.024 mmol) in PhH (4.7 mL, 0.005 M) was added 2,6-di-*t*-butylpyridine (10.7 μL, 0.047 mmol, 2 equiv) and MgBr2•Et2O (6.7 mg, 0.026 mmol, 1.1 equiv; dissolved in 0.26 mL MeCN) and the reaction was warmed to 78 °C. After 1 h, the reaction mixture was cooled to ambient temperature and filtered through Celite®, which was rinsed with two portions of EtOAc (2 × 2 mL). Concentration *in vacuo* delivered a yellow residue, which was immediately dissolved in butanone and water (1:1, 2.4 mL, 0.01 M) and heated at 90 °C with pyridinium *p*-toluenesulfonate (PPTS, 30 mg, 0.12 mmol, 5 equiv). After 2 h, the reaction was cooled to ambient temperature and K_2CO_3 was added. After 5 h, the reaction was concentrated *in vacuo*, and the residue was dissolved in CH_2Cl_2 (2 mL) and sat. aq. NaCl (1 mL) was added. The aqueous layer was extracted 5 times with CH_2Cl_2 (5 × 3 mL), and the combined organics were passed through a plug of Na_2SO_4, and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel, MeOH:CH_2Cl_2:Et_3N 90:10:1) furnishing compound **22** as a white foam (7.1 mg, 82%). Analytical data are identical to the original.[1]



Entry	Conditions	Isolated Yield
1	$Sc(OTf)_3$	12%
2	$InCl_3$	56%
3	$MgBr_2 \cdot Et_2O$	0%
4	$BiCl_3$	73%
5	HCl	40%
6	$Zn(OTf)_2$	0%

General procedure: To a solution of **23** (1 equiv) in MeCN (0.005 M) was added acid (4 equiv) and the reaction was warmed to 40 °C. After 2 h, H_2O was added to the reaction mixture at 40 °C. After 4 h, sat. aq. $NaHCO_3$ was added to the reaction and the mixture extracted three times with EtOAc. The combined organic portions were washed sat. aq. NaCl, dried over Na_2SO_4 and the volatiles removed *in vacuo*. The residue so obtained was purified by flash column chromatography (silica gel, MeOH:CH_2Cl_2:Et_3N 90:10:1) furnishing compound **22** as a white foam. Analytical data are identical to the original.[1]

$Sc(OTf)_3$: **23**(19 mg, 0.045 mmol), $Sc(OTf)_3$ (88 mg, 0.18 mmol), MeCN (4.5 mL), H_2O (1.5 mL), **22** (2 mg, 12%);

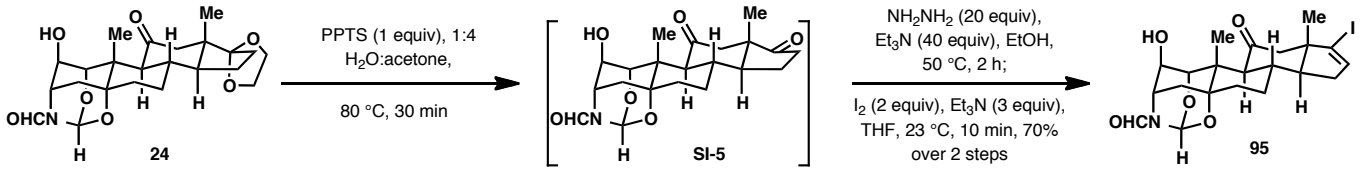
$InCl_3$: **23**(19 mg, 0.045 mmol), $InCl_3$ (40 mg, 0.18 mmol), MeCN (9 mL), H_2O (2.7 mL), **22** (9 mg, 56%);

$MgBr_2 \cdot Et_2O$: **23**(19 mg, 0.045 mmol), $MgBr_2 \cdot Et_2O$ (46 mg, 0.18 mmol), MeCN (9 mL), H_2O (2.7 mL), **22** (0 mg, 0%);

$BiCl_3$: **23**(19 mg, 0.045 mmol), $BiCl_3$ (56 mg, 0.18 mmol), MeCN (9 mL), H_2O (2.7 mL), **22** (12 mg, 73%);

HCl (1 M): **23**(19 mg, 0.045 mmol), HCl (0.18 mL, 1 M), MeCN (9 mL), H_2O (2.7 mL), **22** (6.5 mg, 40%);

$Zn(OTf)_2$: **23**(19 mg, 0.045 mmol), $Zn(OTf)_2$ (66 mg, 0.18 mmol), MeCN (4.5 mL), H_2O (2.7 mL), **22** (0 mg, 0%).



Compound 95: *i*. **24** (250 mg, 0.6 mmol) was dissolved in actone and water (4:1, 5.8 mL, 0.1 M) and heated at 80 °C with pyridinium *p*-toluenesulfonate (PPTS, 145 mg, 0.6 mmol, 1 equiv). After 30 min, the reaction was cooled to ambient temperature and sat. aq. $NaHCO_3$ (20 mL) was added three times with EtOAc (3 × 20mL). The combined organic portions were washed sat. aq. NaCl (30 mL), dried over Na_2SO_4 and the volatiles removed *in vacuo*. The resulting foam **SI-5** is sufficiently pure for the next step. *ii*. To a solution of the residue **SI-5** from previous reaction (234 mg, 0.6 mol) in absolute EtOH (10 mL, 0.06 M) were added hydrazine monohydrate (583 μL, 12 mmol, 20 equiv) and Et_3N (3.2 mL, 24 mmol, 40 equiv). The reaction was immersed in a preheated oil bath at 50 °C for 2 h, after which the reaction was allowed to cool and the solvent removed *in vacuo*. The residue so obtained was dissolved in THF (10 mL, 0.06 M), and Et_3N (251 μL, 1.8 mmol, 3 equiv) was added. A stock solution of I_2 (305 mg, 1.2 mmol, 2 equiv) in THF (2 mL) was prepared and added dropwise to the reaction mixture; addition was halted when the iodine was not decolorized after 30 sec. The reaction was then diluted with EtOAc (15 mL) and washed with sat. aq. $Na_2S_2O_3$(15 mL). The aqueous layer was extracted four times with EtOAc (4 × 10 mL). The combined organic portions were washed with sat. aq. NaCl (10 mL), dried over MgSO4, filtered, andconcentrated *in vacuo*. The residue so obtained was purified by flash column chromatography (3:7 EtOAc:hexanes) furnishing compound **95** (228 mg, 70%) as a white foam.

R_f = 0.53 (1:4 hexanes: EtOAc)

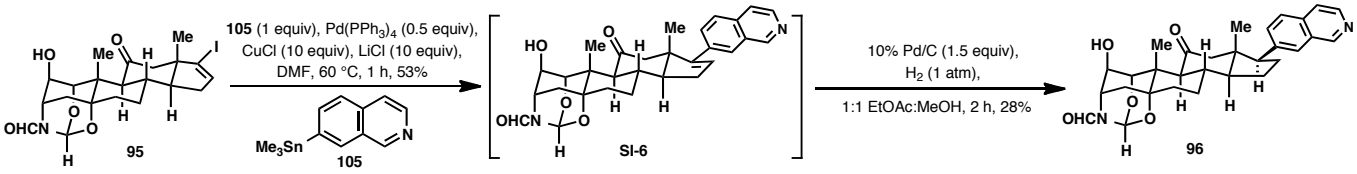
$[\alpha]_D$ = + 34.1 ° (*c* = 0.8, CH_2Cl_2)

HRMS (*m*/*z*): calcd for $C_{21}H_{27}INO_5$ $[M+H]^+$, 500.0928; found, 500.0941;

IR (film) ν_{max} = 3391, 2927, 1667, 1577, 1328, 1264, 1107, 987, 889, 670 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16 (s, 1 H), 6.22 – 6.19 (m, 1 H), 5.77 (s, 1 H), 4.89 – 4.86 (m, 1 H), 4.59 (s, 1 H), 4.25 – 4.21 (m, 1 H), 3.16 (d, *J* = 11.0, 1 H), 2.42 – 2.25 (m, 4 H), 2.14 – 2.00 (m, 2 H), 1.77 – 1.49 (m, 4 H), 1.39 (s, 3 H), 1.25 – 1.14 (m, 1 H), 0.95 – 0.86 (m, 2 H), 0.69 (s, 3 H);

^{13}C NMR (150 MHz, $CDCl_3$) δ 210.2, 157.4, 138.3, 107.9, 96.2, 74.7, 68.7, 55.0, 54.9, 53.3, 53.2, 46.8, 42.8, 39.5, 36.6, 34.3, 31.8, 29.6, 25.0, 16.9, 14.9.



Compound 96: *i*. **95** (110 mg, 0.22 mmol) was dissolved in DMF (3.7 mL, 0.06 M). To this solution was added 7-trimethylstannylisoquinoline **105** (65 mg, 0.22 mmol, 1 equiv), CuCl (218 mg, 2.2 mmol, 10 equiv), LiCl (93 mg, 2.2 mmol, 10 equiv) and $Pd(PPh_3)_4$ (127 mg, 0.11 mol, 0.5 equiv). The reaction was degassed by bubbling argon through the solution for 10 min. It was then immersed in a preheated oil bath at 60°C for 1 h. The reaction was then diluted with CH_2Cl_2 (15 mL) and washed with 5% aq. NH_4OH. The aqueous layer was extracted four times (4 × 50 ml) with CH_2Cl_2. The combined organic portions were washed with sat. aq. NaCl (15 mL), dried over MgSO4, filtered, and concentrated *in vacuo*. The residue so obtained was purified by flash column chromatography (3:7 EtOAc:hexanes) furnishing compound **SI-6** (55 mg, 53%).

ii. **SI-6** (5 mg, 10 μmol) was dissolved in EtOAc and MeOH (0.5 mL, 1:1 EtOAc :MeOH, 0.02 M). To this solution was added 10% Pd/C (16.5 mg, 15 μmol, 1.5 equiv), and bubbling H_2 through the stirred solution for 10 min. Then Stirring was continued under an static H_2-atmosphere for 2 h. The reaction mixture was filter through the silica pad, then purified by PTLC (EtOAc:hexanes 4:1) which afforded **96** (1.4 mg, 28%) as a clear oil.

R_f = 0.29 (EtOAc)

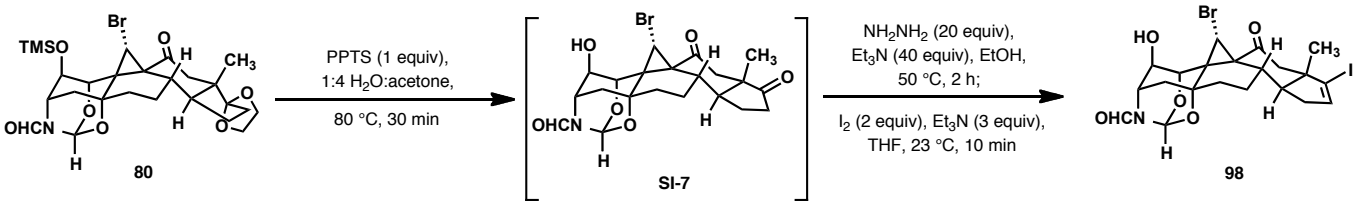
$[\alpha]_D$ = - 3 ° (*c* = 0.1, CH_2Cl_2)

HRMS (*m*/*z*): calcd for $C_{30}H_{35}N_2O_5$ $[M+H]^+$, 503.2546; found, 503.2535;

IR (film) ν_{max} = 2922, 2852, 1739, 1684, 1456, 1376, 1259, 1049, 797, 718 cm^{-1};

^1H NMR (600 MHz, $CDCl_3$) δ 9.24 (bs, 1 H), 8.52 (bs, 1 H), 8.18 (s, 1 H), 7.79 – 7.72 (m, 2 H), 7.71 – 7.59 (m, 1 H), 7.49 (d, *J* = 8.6 Hz, 1 H), 5.80 (s, 1 H), 4.78 (d, *J* = 2.6 Hz, 1 H), 4.60 (s, 1 H), 4.24 (s, 1 H), 3.28 (d, *J* = 11.2 Hz, 1 H), 3.17 (t, *J* = 9.7 Hz, 1 H), 2.56 – 2.42 (m, 2 H), 2.41 – 2.30 (m, 3 H), 2.25 – 2.16 (m, 3 H), 2.16 – 2.08 (m, 2 H), 2.08 – 1.94 (m, 2 H), 1.74 –1.59 (m, 3 H), 1.37 (s, 3 H), 0.46 (s, 3 H);

^{13}C NMR (150 MHz, $CDCl_3$) 210.8, 157.3, 152.2, 142.5, 138.9, 134.8, 131.8, 126.2, 126.1, 125.9, 120.2, 96.3, 77.4, 74.7, 68.7, 55.9, 55.4, 54.5, 53.4, 48.2, 46.8, 39.2, 35.6, 31.9, 29.7, 29.6, 26.4, 25.6, 24.0, 13.9.



Compound 98: **80** (50 mg, 86 μmol) was dissolved in actone and water (4:1, 0.86 mL, 0.1 M) and heated at 80 °C with pyridinium *p*-toluenesulfonate (PPTS, 16 mg, 86 μmol, 1 equiv). After 30 min, the reaction was cooled to ambient temperature and sat. aq. $NaHCO_3$ (20 mL) was added three times with EtOAc (3 × 20 mL). The combined organic portions were washed sat. aq. NaCl (30 mL), dried over Na_2SO_4 and the volatiles removed *in vacuo*. To a solution of the residue in absolute EtOH (1.4 mL, 0.06 M) were added hydrazine monohydrate (83 μL, 1.7 mmol, 20 equiv) and Et_3N (480 μL, 3.4 mmol, 40 equiv). The reaction was immersed in a preheated oil bath at 50 °C for 2 h, after which the reaction was allowed to cool and the solvent removed *in vacuo*. The residue **SI-7** so obtained was dissolved in THF (1.4 mL, 0.06

M), and Et_3N (36 μL, 258 mmol, 3 equiv) was added. A stock solution of I_2 (44 mg, 172 μmol, 2 equiv) in THF (0.14 mL) was prepared and added dropwise to the reaction mixture; addition was halted when the iodine was not decolorized after 30 sec. The reaction was then diluted with EtOAc (5 mL) and washed with sat. aq. $Na_2S_2O_3$ (5 mL). The aqueous layer was extracted four times with EtOAc (4 × 10 mL). The combined organic portions were washed with sat. aq. NaCl (10 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue so obtained was purified by flash column chromatography furnishing compound **98** (EtOAc:hexanes 3:7).

R_f = 0.69 (1:4 hexanes: EtOAc)

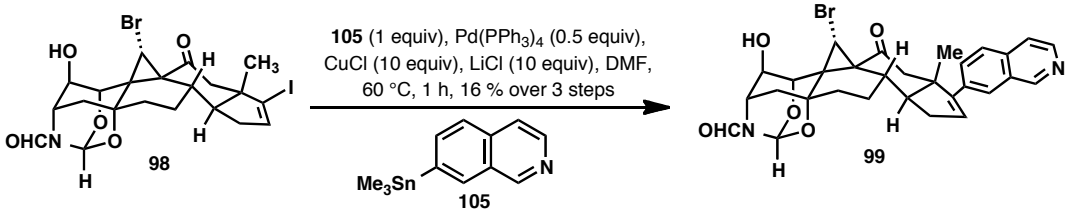
$[\alpha]_D$ = + 39.5 ° (*c* = 1.2, CH_2Cl_2)

HRMS (*m*/*z*): calcd for $C_{21}H_{24}BrINO_5$ $[M+H]^+$, 575.9877; found, 575.9893;

IR (film) ν_{max} = 3407, 3051, 1672, 1583, 1328, 1304, 1108, 1066, 873, 827, 766, 678 cm^{-1};

^1H NMR (600 MHz, $CDCl_3$) δ 8.21 (s, 1 H), 6.17 (bs, 1 H), 5.85 (s, 1 H), 5.44 (d, *J* = 3.7 Hz, 1 H), 4.71 (bs, 1 H), 4.29 (t, *J* = 3.4 Hz, 1H), 3.47 (s, 1 H), 2.56 – 2.32 (m, 3 H), 2.22 – 2.13 (m, 2 H), 2.10 – 2.03 (m, 1 H), 1.92 – 1.82 (m, 1 H), 1.73 – 1.51 (m, 3 H), 1.50 – 1.43 (s, 3 H), 1.39 – 1.20 (m, 2 H), 0.94 (s, 3H);

^{13}C NMR (150 MHz, $CDCl_3$) δ 204.7, 157.6, 137.7, 137.6, 107.4, 96.5, 91.0, 72.3, 69.1, 67.2, 54.6, 52.6, 49.2, 45.7, 40.0, 39.7 37.2, 35.0, 32.9, 31.9, 21.2, 18.0.



Compound 99: The abovementioned **98** was dissolved in DMF (1.43 mL, 0.06 M). To this solution was added 7-trimethylstannylisoquinoline **105** (25 mg, 86 μmol, 1 equiv), CuCl (85 mg, 860 μmol, 10 equiv),

LiCl (36 mg, 860 μmol, 10 equiv) and $Pd(PPh_3)_4$ (50 mg, 43 μmol, 0.5 equiv). The reaction was degassed by bubbling argon through the solution for 10 min. It was then immersed in a preheated oil bath at 60°C for 1 h. The reaction was then diluted with EtOAc (5 mL) and washed with 5% aq. NH_4OH. The aqueous layer was extracted four times (4 × 5 ml) with EtOAc. The combined organic portions were washed wth sat. aq. NaCl (5 mL), dried over MgSO4, filtered, and concentrated *in vacuo*. The residue so obtained was purified by PTLC (MeOH : CH_2Cl_2 9:1) furnishing **99** (8 mg, 16% from **80**) as a yellow foam.

R_f = 0.32 (EtOAc)

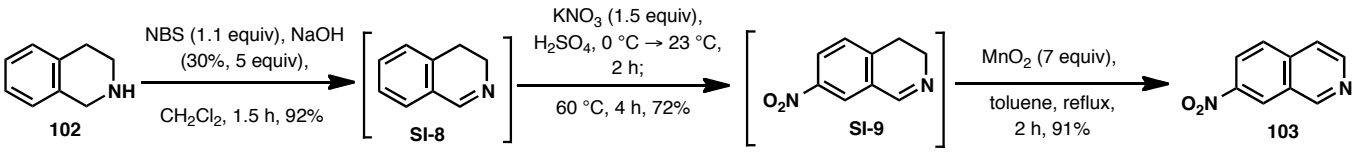
$[\alpha]_D$ = + 10.2 ° (*c* = 0.4, CH_2Cl_2)

HRMS (*m*/*z*): calcd for $C_{30}H_{30}BrN_2O_5$ $[M+H]^+$, 577.1332; found, 577.1314;

IR (film) ν_{max} = 3335, 2927, 2853, 1679, 1443, 1110, 1038, 936 cm^{-1};

^1H NMR (600 MHz, $CDCl_3$) δ 9.25 (s, 1 H), 8.51-8.50 (m, 1H), 8.22 (s, 1 H), 7.88 (s, 1 H), 7.77 (s, 2 H), 7.63 (d, *J* = 5.6 Hz, 1H), 6.96 (s, 1 H), 6.30 – 6.21 (m, 1 H), 5.78 (s, 1 H), 5.48 (d, *J* = 3.9 Hz, 1H), 4.74 (s, 1 H), 4.30 (s, 1 H), 3.55 (s, 1 H), 3.13 (d, *J* = 17.5 Hz, 1H), 2.81 – 2.74 (m, 2 H), 2.64 – 2.57 (m, 1 H), 2.58 – 2.46 (m, 1 H), 2.43 – 2.27 (m, 2 H), 2.09 – 2.01 (m, 2 H), 1.90 – 1.71 (m, 2 H), 1.65 – 1.52 (m, 2 H), 1.38 (s, 3H);

^{13}C NMR (150 MHz, $CDCl_3$) δ 205.5, 157.6, 152.6, 150.3, 142.9, 135.0, 134.3, 129.7, 128.8, 128.6, 126.7, 123.8, 120.2, 96.5, 72.5, 69.4, 67.3, 55.2, 54.1, 46.3, 40.1, 39.2, 36.9, 33.0, 29.9, 29.7, 29.6, 22.7, 21.3, 19.2.



Compound 103: **102** (10 g, 75 mmol) was dissolved in CH_2Cl_2 (150 mL, 0.5 M). NBS (15 g, 82.5 mmol, 1.1 equiv) was slowly added and the reaction mixture was stirred for 30 min at ambient temperature. To

this mixture 30 % NaOH (50 ml, 5 equiv) was added and the resulting biphasic mixture was stirred vigorously for 1 h. The organic layer was washed H_2O (200 ml) and 1 M HCl (200 mL). The acid extracts were basified to pH = 10 with 1 M NaOH (220 mL) and extracted with CH_2Cl_2 (2 × 400 mL). The organic portions was washed with sat. aq. NaCl (500 mL), dried over $MgSO_4$ and the volatiles removed *in vacuo*. The residue so obtained was purified by flash column chromatography (CH_2Cl_2:MeOH 15:1) furnishing compound **SI-8** (9 g, 92 %) as a colorless oil.[2]

ii. KNO_3 (10.5 g, 103 mmol, 1.5 equiv) was dissolved in H_2SO_4 (95-98%, 69 mL, 1 M). To this mixture **SI-8** (9 g, 69 mmol) was added at 0 °C and slowly warmed up to ambient temperature over 2 h. It was then immersed in a preheated oil bath at 60 °C for 4 h, after which the mixture was basified to pH = 10 with 3 M NaOH (500 mL) and extracted three times with CH_2Cl_2 (3 × 500 mL). The organic portions was washed with sat. aq. NaCl (500 mL), dried over $MgSO_4$ and the volatiles removed *in vacuo*. The residue so obtained was purified by flash column chromatography (1:1 EtOAc:Hexanes) furnishing compound **SI-9** (8.8 g, 72 %) as a colorless oil.

iii. A mixture of **SI-9** (8.8 g, 50 mmol) and MnO_2 (30 g, 350 mmol, 7 equiv) in toluene (250 ml, 0.2 M) was heated to reflux for 2 h. The reaction was allowed to cool, filteredc through Celite® and concentrated *in vacuo*. Purification of the crude residue by flash column chromatography (2:1 EtOAc:hexanes) yielded **103** (7.9 g, 91 %) as a yellow solid.

R_f = 0.64 (EtOAc)

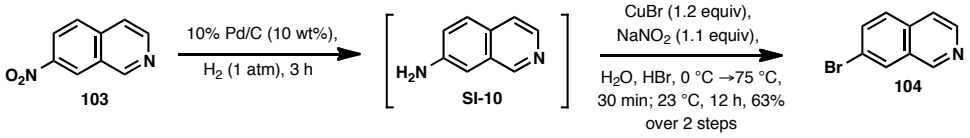
HRMS (*m*/*z*): calcd for $C_9H_7N_2O_2$ $[M+H]^+$, 175.0502; found, 175.0499;

IR (film) ν_{max} = 3074, 1666, 1629, 1582, 1135, 850, 803, 733 cm^{-1};

m.p. = 67–68 ºC

^1H NMR (500 MHz, $CDCl_3$) δ 9.48 (s, 1 H), 8.94 (d, *J* = 2.0 Hz, 1 H), 8.75 (s, 1 H), 8.46 (dd, *J* = 9.0, 2.2 Hz, 1 H), 7.99 (d, *J* = 9.0 Hz, 1 H), 7.78 (d, *J* = 5.5 Hz, 1 H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 154.2, 146.5, 138.1, 128.5 (2 C), 124.4 (2 C), 123.7 (2 C).



Compound 104: 103 (7.9 g, 46 mmol) was dissolved in MeOH (460 mL, 0.1 M). To this solution was added 10% Pd/C (790 mg, 10 wt%), and H_2 was bubbled through the stirred solution for 1 h. Stirring was continued under a static H_2-atmosphere for 2 h. The reaction mixture was filtered through the silica pad and concentrated *in vacuo*. This residue **SI-10** is sufficiently pure for the next step.

ii. **SI-10** was dissolved in H_2O (11.5 mL, 0.25 M) and HBr (48%, 11.5 mL, 0.25 M). To this mixture aq. 2.5 M $NaNO_3$ solution (20 mL, 50.6 mmol, 1.1 equiv) was added at 0 °C. After addition, this mixture was cannulated to a solution of CuBr (7.9 g, 55.2 mmol, 1.2 equiv) in HBr (48%, 11.5 mL) which was preheated at 75 °C. After cannulation, the mixture was cooled to ambient temperature and stirred for 12 h. The mixture was basified with 3 M NaOH (500 mL) to pH = 10 and extracted with CH_2Cl_2 three times (3 × 500 mL). The organic portion was washed with sat. aq. NaCl (700 mL), dried over $MgSO_4$ and the volatiles removed *in vacuo*. The residue so obtained was purified by flash column chromatography (EtOAc:hexanes 1:1) furnishing compound **104** (6.0 g, 63 % over 2 steps) as a white solid.[3]

R_f = 0.69 (1:1 hexanes: EtOAc)

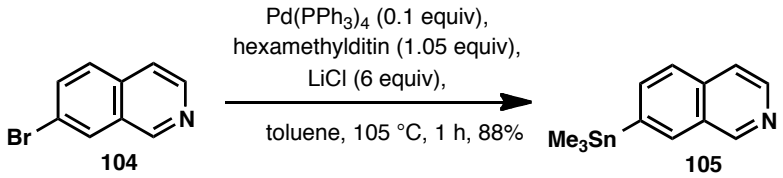
HRMS (*m*/*z*): calcd for C_9H_7BrN $[M+H]^+$, 207.9756; found, 207.9763;

IR (film) ν_{max} = 3407, 1661, 1572, 878, 835, 741, 674 cm^{-1};

m.p. = 174–178 ºC

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.15 (s, 1 H), 8.54 (d, *J* = 5.2 Hz, 1 H), 8.08 (s, 1 H), 7.75 – 7.70 (m, 1 H), 7.66 (d, *J* = 8.7 Hz, 1 H), 7.59 (d, *J* = 5.4 Hz, 1 H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 151.3, 143.4, 134.1, 133.7, 129.6, 128.1 (2 C), 120.8, 120.1.



Compound 105: To a solution of **104** (1.8 g, 8.6 mmol) in PhH (17 ml, 0.5 M) was added LiCl (2.2 g, 51.6 mmol, 6 equiv), $Pd(PPh_3)_4$ (993 mg, 0.86 mmol, 0.1 equiv) and hexamethylditin (3.0 g, 9.0 mmol, 1.05 equiv). The solution was bubbled with Ar in a sonicator for 10 min. The reaction was then warmed to 105 °C. After 1 h, the reaction was diluted by EtOAc (100 ml), filterd through Celite® and rinsed with two portions of EtOAc (2 x 50 mL). The organic portion was washed with sat. aq. $NaHCO_3$ (100 ml) and brine (100 ml), dried with $MgSO_4$, filtered, and concentrated *in vacuo*. Chromatography on silica (1:2 Et_2O:hexanes) afforded **104** (2.2 g, 88%) as a white solid. Analytical data are identical to the original.[1]

Reference:

(1) Shenvi, R. A.; Guerrero, C. A.; Shi, J.; Li, C.-C.; Baran, P. S. *J. Am. Chem. Soc.* **2008**, *130*, 7241–7243.

(2) Askin, D.; Angst, C.; Danishefsky, S. *J. Org. Chem.* **1987**, *52*, 622–635.

(3) McCoubrey, A.; Mathieson, D. W. *J. Chem. Soc.* **1951**, 2851–2853.