Total Synthesis of (±)-Agelastatin A, A Potent Inhibitor of Osteopontin (OPN)–Mediated Neoplastic Transformations

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Supporting Information, Part 1

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Table of Contents

General Procedures

All non-aqueous reactions were carried out in oven-dried (120 °C) glassware under an atmosphere of dry argon or nitrogen, unless otherwise noted. Except as otherwise indicated, all reactions were magnetically stirred and monitored by analytical thin-layer chromatography using Merck pre-coated silica gel plates with F_{254} indicator. Visualization was accomplished by UV light and/or potassium permanganate solution. Flash column chromatography was performed according to the method of Still[1] using silica gel 60 (mesh 230-400) supplied by Silicycle. Yields refer to chromatographically and spectrographically pure compounds, unless otherwise noted.

Materials

Toluene, xylenes, pyridine, dimethylsulfoxide (DMSO),[2] and *N*,*N*-dimethylformamide (DMF) were distilled from calcium hydride, under an atmosphere of dry nitrogen and stored over activated 4Å molecular sieves. Anhydrous tetrahydofuran (THF), dichloromethane (CH_2Cl_2), and methanol (MeOH) were obtained from a PureSolv™ solvent purification system. (2*R**,4*S**)-Acetic acid 4-hydroxy-cyclopent-2-enyl ester (**9**) was prepared according to the method of Deardorff and Myles,[3] while IBX (2-iodoxybenzoic acid) was prepared according to the method of Boeckman, Shao, and Mullins.[4] All other reagents and starting materials, unless otherwise noted, were purchased from commercial vendors and used without further purification.

Instrumentation

All melting points were determined in open Pyrex capillaries using a Thomas Hoover Unimelt melting point apparatus and are uncorrected. Infrared spectra were recorded as thin films on sodium chloride plates, unless otherwise noted using an ATI Mattson Genesis Series FTIR spectrometer. ^{1}H and ^{13}C and

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1. Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

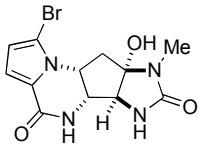
2. Fumiss, B. S. *Vogel's Textbook of Practical Organic Chemistry,* 5th ed.; Wiley: New York**,** 1989; p 412.

3. Deardorff, D., R.; Myles, D., C. *Org. Synth.* **1993**, *Coll. Vol. 8*, 13.

4. Boeckman, R., K.; Shao, P.; Mullins, J., J. *Org. Synth.* **2004**, *Coll. Vol. 10*, 696.

NMR spectra were recorded on a Bruker Advance 400 (400 MHz ^{1}H, 100 MHz ^{13}C) or a Bruker Avance 500 (500 MHz ^{1}H, 125 MHz ^{13}C). Chemical shift values (δ) are reported in ppm relative to residual chloroform (δ 7.27 ppm for ^{1}H; δ 77.23 ppm for ^{13}C), residual acetone (δ 2.05 ppm for ^{1}H; δ 29.92 ppm for ^{13}C), residual methanol (δ 3.31 ppm for ^{1}H; δ 49.15 ppm for ^{13}C) and residual DMSO (δ 2.50 ppm for ^{1}H; δ 39.51 ^{13}C). Multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), m (multiplet) and br (broad). DEPT 135 and two-dimensional (COSY, HMQC, HMBC, NOESY) NMR experiments were employed, where appropriate, to aid in the assignment of signals in the ^{1}H NMR spectra. High-resolution electron spray ionization mass spectra (HRMS-ESI) were obtained on a Micromass QTOF 2, at the University of Illinois Research Resources Center or on a Micromass Q-TOF Ultima at the Mass Spectroscopy Laboratory at the University of Illinois, Urbana-Champaign.

Table 1. Tabular Comparison of Spectral Data for Agelastatin A.

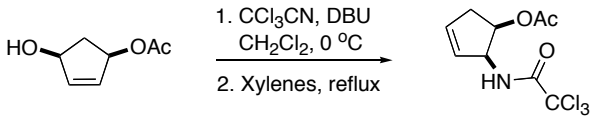
(±)-Agelastatin A				(-)-Agelastatin A[5]	
δ ^{1}H (ppm)[a]	δ ^{13}C (ppm)[b]	$\Delta\delta_H$	$\Delta\delta_C$	δ ^{1}H (ppm)[c]	δ ^{13}C (ppm)[d]
2.09 (t, *J* = 12.9 Hz, 1 H)	24.2	0.00	0.0	2.09 (dd, *J* = 12.6, 12.6 Hz, 1 H)	24.2
2.64 (dd, *J* = 6.0, 12.3 Hz, 1 H)	40.0	0.01	0.0	2.63 (dd, *J* = 6.5, 13.0 Hz, 1 H)	40.0
2.80 (s, 3 H)	54.4	0.00	0.1	2.80 (s, 3 H)	54.3
3.88 (s, 1 H)	62.2	0.00	0.0	3.88 (s, 1 H)	62.2
4.07 (d, *J* = 5.2 Hz, 1 H)	67.4	0.00	0.0	4.07 (d, *J* = 5.5 Hz, 1 H)	67.4
4.59 (m, 1 H)	95.7	0.01	0.1	4.58 (m, 1 H)	95.6
6.32 (d, *J* = 3.9 Hz, 1 H)	107.2	0.01	0.0	6.31 (d, *J* = 4.1 Hz, 1 H)	107.2
6.91 (d, *J* = 3.9 Hz, 1 H)	113.8	0.01	0.0	6.90 (d, *J* = 4.1 Hz, 1 H)	113.8
	116.0	-	0.0		116.0
	124.1	-	0.0		124.1
	161.1	-	0.0		161.1
	161.4	-	0.0		161.4

[a]500 MHz; CD_3OD; 298 K. [b]125 MHz; CD_3OD, 298 K; [c]500 MHz; CD_3OD; 298 K; [d]125 MHz; CD_3OD, 298 K.

5. Domostoj, M., M.; Irving, E., Scheinmann, F.; Hale, K., J. *Org. Lett.* **2004**, *6*, 2615.

Experimental Procedures

(1*R,2*S**)-Acetic acid 2-(2,2,2-trichloroacetamide)-cyclopent-3-enyl ester (8).**



*Preparation of Trichloroacetimidate **10***

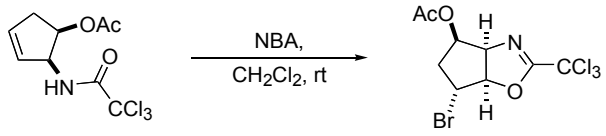
To a solution of (2*R**,4*S**)-acetic acid 4-hydroxycyclopent-2-enyl ester **9**[3] (5.0 g, 35.2 mmol) in CH_2Cl_2 (117 mL) was added, via syringe, DBU (1.58 mL, 10.6 mmol). The solution was cooled in an ice bath and Cl_3CCN (4.23 mL, 42.2 mmol) was added over 10-15 min, via syringe. The reaction mixture was stirred at 0 °C for 10 min then poured into saturated aqueous NH_4Cl (150 mL). The layers were separated and the aqueous layer extracted with CH_2Cl_2 (2 x 150 mL). The organic extracts were dried over Na_2SO_4 then concentrated under reduced pressure. The trichloroacetimidate **10** was then placed on a plug of SiO_2 (40 g) pretreated with acetone (200 mL) and eluted with hexanes/diethyl ether (9:1). The eluant was then concentrated under reduced pressure, to yield compound **10** (9.68 g, 96%) as a colorless oil: R_f = 0.27 (EtOAc/hexanes, 1:9); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.35 (s, 1 H), 6.25-6.23 (m, 1 H), 6.18-6.16 (m, 1 H), 5.71-5.70 (m, 1 H), 5.60-5.58 (m, 1 H), 2.98 (p, *J* = 7.5 Hz, 1 H), 2.06 (s, 3 H), 1.88 (dt, *J* = 4.0, 14.9 Hz, 1 H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 171.0, 162.4, 135.5, 134.0, 91.6, 81.5, 76.6, 37.2, 21.3.

Overman Rearrangement

In a flask equipped with a reflux condenser, trichloroacetimidate **10** was dissolved in xylenes (350 ml) then heated at reflux for 18 h. The contents were then cooled, concentrated under reduced pressure, and purified by flash chromatography (EtOAc/hexanes, 1:5) to yield **8** (7.84 g, 78%) as a white solid: mp 67-70 °C; R_f 0.26 (EtOAc/hexanes, 1:4); IR (film) υ_{max} 3318, 1710, 1532, 1371, 1257, 1242, 835, 825 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.84 (d, *J* = 6.7 Hz, 1 H), 6.01-5.98 (m, 1 H), 5.74-5.72 (m, 1 H), 5.48-5.45 (m, 1 H), 5.07-5.03 (m, 1 H), 2.82-2.75 (m, 1 H), 2.49-2.44 (m, 1 H), 2.04 (s, 3 H); ^{13}C NMR

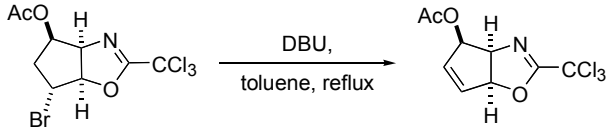
(125 MHz, $CDCl_3$) δ 169.9, 161.5, 133.3, 128.6, 92.7, 72.1, 57.4, 38.3, 21.0; HRMS-ESI calcd for $C_9H_{10}NO_3Na^{35}Cl_3$ $[M+Na]^+$ 307.9624, found: 307.9622.

(3a*,4*R,6*R**,6a*R**)-Acetic acid 6-bromo-2-trichloromethyl-4,5,6,6a-tetrahydro-3a*H*-cyclopentaoxazol-4-yl ester (11).**



To a solution of **8** (5.41 g, 18.9 mmol) in CH_2Cl_2 (63 mL) was added *N*-bromoacetamide (3.65 g, 26.4 mmol) in one portion. The reaction mixture was heated at reflux for 16 h, cooled to rt, then treated with more *N*-bromoacetamide (1.30 g, 9.4 mmol). The reaction mixture was heated for an additional 8 h at reflux, then cooled to rt and diluted with CH_2Cl_2 (75 mL), sequentially washed with aqueous Na_2SO_3 (30 ml) and brine (30 ml), then dried over Na_2SO_4. The organic extracts were concentrated under reduced pressure and the solid residue purified by flash chromatography (EtOAc/hexanes, 1:8) to yield **11** (5.21 g, 76%) as a white solid: mp 94-95 ˚C; R_f = 0.46 (EtOAc/hexanes, 1:4); IR (film) υ_{max} 2993, 2956, 2935, 1742, 1664, 1236, 989, 791 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.59-5.53 (m, 1 H), 5.40 (d, *J* = 7.5 Hz, 1 H), 5.13 (t, *J* = 7.0 Hz, 1 H), 4.42 (d, *J* = 3.5 Hz, 1 H), 2.48-2.43 (m, 1 H), 2.28-2.21 (m, 1 H), 2.11 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 162.5, 92.5, 86.0, 74.5, 70.7, 46.4, 37.3, 20.9; HRMS-ESI calcd for $C_9H_{10}O_3N^{79}Br^{35}Cl_3$ $[M+H]^+$ 363.89041, found: 363.89025.

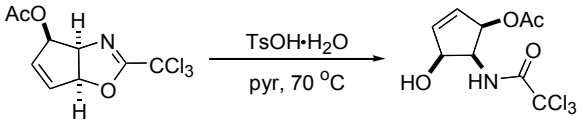
(3aS*,4R*,6aS*)-Acetic acid 2-trichloromethyl-4,6a-dihydro-3aH-cyclopentaoxazol-4-yl ester (12).



A solution of **11** (1.55 g, 4.24 mmol) and DBU (1.6 mL, 10.6 mmol) in toluene (14.1 mL) was heated at reflux for 3 h then cooled to rt. The solid precipitate was filtered on a Büchner funnel and the filter cake washed with toluene (2 x 50 mL). The combined filtrates were sequentially washed with saturated aqueous NH_4Cl (30 mL) and brine (20 mL), then dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by flash chromatography (EtOAc/hexanes, 1:5) to yield **12**

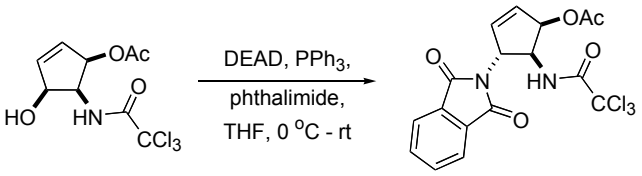
(1.07 g, 89%) as a white solid: mp 75-77 °C; R_f = 0.27 (EtOAc/hexanes, 1:4); IR (film) υ_{max} 1741, 1723, 1512, 1223, 1061, 822 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.18-6.13 (m, 2 H), 5.76 (dt, *J* = 1.3, 5.1 Hz, 1 H), 5.65 (dd, *J* = 1.6, 7.4 Hz, 1 H), 5.05 (t, *J* = 7.0 Hz, 1 H), 2.10 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 161.9, 136.3, 131.1, 89.3, 86.8, 77.9, 69.6, 20.8; HRMS-ESI calcd for $C_9H_9O_3N^{35}Cl_3$ $[M+H]^+$ 283.96425, found: 283.96412.

(1*R,4*S**,5*S**)-Acetic acid 4-hydroxy-5-(2,2,2-trichloroacetamide)-cyclopent-2-enyl ester (7).**



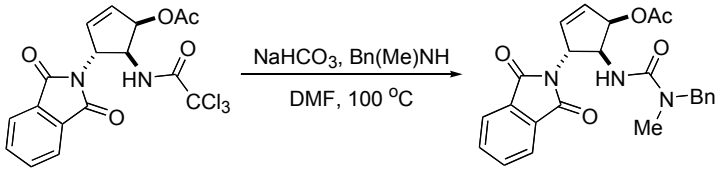
A solution of **12** (424 mg, 1.49 mmol) and *p*-toluenesulfonic acid (24.4 mg, 1.28 mmol) in pyridine (12.9 mL) and water (3.2 mL) was heated at 70 °C for 2 h, then cooled to rt and diluted with water (30 mL) and saturated aqueous $NaHCO_3$ (30 mL). The resulting mixture was extracted with diethyl ether (3 x 50 mL) and the combined organic extracts sequentially washed with 5% aqueous $CuSO_4$ (2 x 30 mL), water (30 mL), brine (30 mL) and then dried over Na_2SO_4. Concentration under reduced pressure provided a crude residue which was purified by flash chromatography (EtOAc/hexanes, 1:2) to yield **7** (420 mg, 93%) as a white solid: mp 76-78 °C; R_f = 0.14 (EtOAc/hexanes, 1:2); IR (film) υ_{max} 3398, 3070, 2935, 1720, 1510, 1235, 1054, 821 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.38 (d, *J* = 6.8 Hz, 1 H), 6.32 (dd, *J* = 2.6, 6.0 Hz, 1 H), 6.22 (dd, *J* = 2.5, 6.0 Hz, 1 H), 5.62 (dd, *J* = 2.5, 6.2 Hz, 1 H), 4.72-4.69 (m, 1 H), 4.38 (q, *J* = 6.4 Hz, 1 H), 2.48 (d, *J* = 7.7 Hz, 1 H), 2.04 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.0, 162.1, 137.8, 133.6, 92.6, 74.4, 72.9, 53.2, 21.1; HRMS-ESI calcd for $C_9H_{10}O_4N^{35}Cl_3Na$ $[M+Na]^+$ 323.95676, found: 323.95657.

(1*R,4*R**,5*S**)-Acetic acid 4-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-5-(2,2,2-trichloroacetamide)-cyclopent-2-enyl ester (13).**



To a cooled (0 °C) solution of **7** (1.50 g, 5.0 mmol), PPh_3 (1.95 g, 7.4 mmol) and phthalimide (1.09 g, 7.4 mmol) in THF (45mL) was added over 5 min, via cannula, DEAD (1.72 g, 9.9 mmol) in THF (5 mL). The reaction mixture was warmed to rt and stirred for 24 h before the volatiles components were removed under reduced pressure. The residual oil was purified by flash chromatography (EtOAc/toluene, 1:30) to yield **13** (1.95 g, 91%) as a white solid: mp 186-189 °C; R_f = 0.21 (EtOAc/hexanes, 1:2); IR (film) υ_{max} 3325, 3207, 3060, 1774, 1739, 1715, 1525, 1388, 1237, 717 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.84 (dd, *J* = 3.0, 5.4 Hz, 2 H), 7.73 (dd, *J* = 3.0, 5.4 Hz, 2 H), 7.29 (d, *J* = 8.0 Hz, 1 H), 6.25 (dd, *J* = 2.6, 5.5 Hz, 1 H), 6.18 (dd, *J* = 1.7, 6.1 Hz, 1 H), 5.78-5.76 (m, 1 H), 5.42-5.41 (m, 1 H), 5.01 (q, *J* = 8.1 Hz, 1 H), 2.13 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.7, 168.0, 162.3, 136.8, 134.5, 132.0, 130.4, 123.8, 92.3, 75.6, 59.1, 55.4, 21.0; HRMS-ESI calcd for $C_{17}H_{13}O_5N_2{}^{35}Cl_3Na$ $[M+Na]^+$ 452.97823, found: 452.97793.

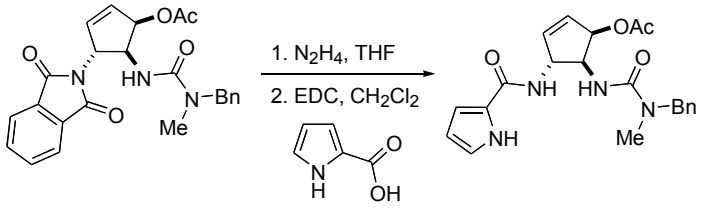
(1*R,4*R**,5*S**)-Acetic acid 5-(3-benzyl-3-methyl-ureido)-4-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-cyclopent-2-enyl ester (14, R = Bn).**



To a solution of **13** (1.0 g, 2.32 mmol) in DMF (23 mL) was sequentially added, powdered $NaHCO_3$ (0.973 g, 11.58 mmol) and *N*-benzylmethylamine (0.39 mL, 3.01 mmol) via syringe. The rapidly stirred heterogeneous mixture was then submerged in a preheated oil bath (100 °C) for 40 min before being allowed to cool to rt. The contents of the flask were poured into cold (0 °C) aqueous HCl (0.5 M, 30 mL), and then extracted with EtOAc (3 x 75 mL). The combined organic extracts were sequentially

washed with water (20 mL), brine (20 mL) then dried over Na_2SO_4 and concentrated under reduced pressure. The residual oil was purified by flash chromatography (EtOAc/hexanes, 1:1) to yield **14** (675 mg, 68%) as a white solid: mp 185-187 °C; R_f = 0.23 (EtOAc/hexanes, 1:1); IR (film) υ_{max} 3438, 3031, 2922, 1772, 1734, 1713, 1652, 1520, 1388, 1374, 1236, 720 cm^{-1}; ^1H NMR (400 MHz, acetone-d_6) δ 7.88-7.83 (m, 4 H), 7.30-7.26 (m, 2 H), 7.23-7.19 (m, 1 H), 7.16 (d, *J* = 7.1 Hz, 2 H), 6.28 (dd, *J* = 1.7, 6.3 Hz, 1 H), 6.12 (dt, *J* = 2.8, 6.0 Hz, 1 H), 5.82 (d, *J* = 9.0 Hz, 1 H), 5.65 (dq, *J* = 1.2, 6.0 Hz, 1 H), 5.30-5.27 (m, 1 H), 5.18-5.12 (m, 1 H), 4.47 (d, *J* = 15.8, 1 H), 4.33 (d, *J* = 15.8 Hz, 1 H), 2.82 (s, 3 H), 2.01 (s, 3 H); ^{13}C NMR (100 MHz, acetone-d_6) δ 170.6, 168.8, 158.7, 139.7, 138.8, 135.2, 133.3, 130.7, 129.4, 128.3, 127.9, 123.9, 76.4, 60.2, 55.9, 52.4, 34.4, 21.0; HRMS-ESI calcd for $C_{24}H_{23}O_5N_3Na$ $[M+Na]^+$ 456.15299, found: 456.15254.

(1*R,4*R**,5*S**)-Acetic acid 5-(3-benzyl-3-methyl-ureido)-4-[(1 H-pyrrole-2-carbonyl)-amino]-cyclopent-2-enyl ester (15).**



*Hydrazinolysis of **14***

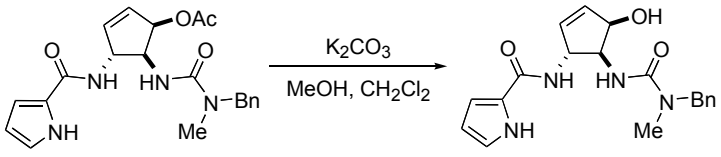
A solution of **14** (474 mg, 1.09 mmol) in THF (11.0 mL) was treated with a solution of hydrazine (69.9 mg, 2.18 mmol) in THF (2.0 mL), via syringe. After stirring at rt for 4 h, the white heterogeneous solution was treated with aqueous HCl (1.0 M, 4.0 mL) and stirred for an additional 3 h. The pH of the now homogenous solution was adjusted to 10 with saturated aqueous Na_2CO_3 and then extracted with $CHCl_3$ (3 x 40 mL). The combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4 and concentrated under reduced pressure to yield the primary amine (**19**, not shown) (330 mg) as a yellow oil; IR (film) υ_{max} 3360, 3309, 3061, 3028, 2926, 1734, 1639, 1522, 1372, 1237, 1024 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.25 (t, *J* = 7.2 Hz, 2 H), 7.18 (d, *J* = 7.2 Hz, 1 H), 7.14 (d, *J* = 7.2 Hz, 2 H),

5.91 (dd, *J* = 1.4, 6.1 Hz, 1 H), 5.85-5.83 (m, 1 H), 5.36 (d, *J* = 5.4 Hz, 1 H), 4.93 (d, *J* = 8.2 Hz, 1 H), 4.42 (dd, *J* = 16.2, 20.5 Hz, 2 H), 4.01 (q, *J* = 8.1 Hz, 1 H), 3.73 (d, *J* = 5.3 Hz, 1 H), 2.85 (s, 3 H), 1.92 (bs, 2 H), 1.79 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.8, 158.2, 142.5, 137.5, 128.7, 128.4, 127.3, 126.8, 77.0, 62.7, 61.0, 52.2, 34.6, 20.7; HRMS-ESI calcd for $C_{16}H_{21}O_3N_3Na$ $[M+Na]^+$ 326.14751, found: 326.14735.

EDC-Mediated Coupling of Amine

The crude amine **19** was dissolved in CH_2Cl_2 (11.0 mL) and sequentially treated with 1*H*-pyrrole-2-carboxylic acid (146 mg, 1.3 mmol) and EDC (252 mg, 1.3 mmol). After stirring for 24 h, the reaction mixture was concentrated, under reduced pressure, to 25% of its original volume and the concentrate purified by flash chromatography (CH_2Cl_2/MeOH, 30:1) to yield **15** (370 mg, 85%) as a white solid: R_f = 0.43 (EtOAc); IR (film) υ_{max} 3323, 3258, 3163, 3064, 3028, 2925, 1727, 1635, 1616, 1584, 1532, 1338, 1236, 1027, 749 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.5 (s, 1 H), 8.19 (d, *J* = 8.2 Hz, 1 H), 7.26 (t, *J* = 7.3 Hz, 2 H), 7.21 (d, *J* = 6.8 Hz, 1 H), 7.16 (d, *J* = 7.3 Hz, 2 H), 6.87 (s, 1 H), 6.83 (d, *J* = 2.2 Hz, 1 H), 6.60 (d, *J* = 8.2 Hz, 1 H), 6.09 (d, *J* = 4.2 Hz, 2 H), 5.98-5.96 (m, 1 H), 5.55 (d, *J* = 4.6 Hz, 1 H), 5.22 (d, *J* = 6.8 Hz, 1 H), 4.53 (d, *J* = 15.8 Hz, 1 H), 4.40 (t, *J* = 6.9 Hz, 1 H), 4.31 (d, *J* = 15.7 Hz, 1 H), 2.74 (s, 3 H), 1.97 (s, 3 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.8, 160.9, 157.8, 140.8, 138.6, 129.0, 128.3, 127.1, 126.8, 125.9, 121.4, 110.4, 108.6, 74.6, 57.4, 56.6, 51.1, 33.7, 20.8; HRMS-ESI calcd for $C_{21}H_{24}O_4N_4Na$ $[M+Na]^+$ 419.16898, found: 419.16857.

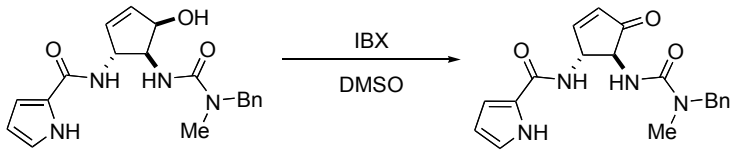
(1*R,4*R**,5*S**)-1*H*-Pyrrole-2-carboxylic acid [5-(3-benzyl-3-methyl-ureido)-4-hydroxy-cyclopent-2-enyl]-amide (20, not shown).**



To a solution of **15** (45.3 mg, 0.114 mmol) in a mixture of MeOH and CH_2Cl_2 (1:1, 1.2 mL) was added solid K_2CO_3 (3.2 mg, 0.023 mmol). The reaction mixture was stirred at rt for 4 h then diluted with

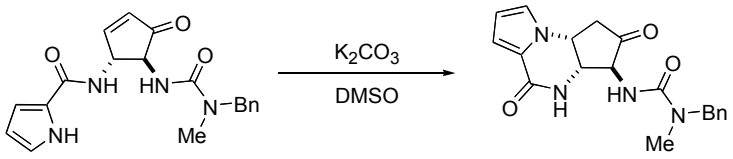
CH_2Cl_2 (10 ml) and placed on a pad of silica gel eluting with CH_2Cl_2-MeOH (20:1). The elutant was concentrated under reduced pressure to yield the title compound **20** (40.2 mg, 99%) as a white solid: mp 212 °C (dec.); R_f = 0.14 (CH_2Cl_2/MeOH, 19:1); IR (film) υ_{max} 3277, 3060, 3028, 2928, 1628, 1559, 1527, 1409, 1044, 741 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 11.5, (s, 1 H), 8.15 (d, *J* = 8.0 Hz, 1 H), 7.29-7.18 (m, 5 H), 6.89, (s, 1 H), 6.86 (s, 1 H), 6.14-6.10 (m, 2 H). 6.00-5.98 (m, 1 H), 5.89 (dd, *J* = 0.92, 5.8 Hz, 1 H), 5.12 (t, *J* = 7.3 Hz, 1 H), 4.77 (d, *J* = 7.1 Hz, 1 H), 4.49 (t, *J* = 6.0 Hz, 1 H), 4.44 (s, 2 H), 4.17 (q, *J* = 6.8 Hz, 1 H), 2.78 (s, 3 H), ; ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.0, 158.3, 138.6, 136.4, 133.9, 128.4, 127.4, 126.9, 126.3, 121.4, 110.4, 108.7, 71.8, 58.9, 57.8, 51.3, 33.8; HRMS-ESI calcd for $C_{19}H_{22}O_3N_4Na$ $[M+Na]^+$ 377.15841, found: 377.15823.

(1*R,5*S**)-1*H*-Pyrrole-2-carboxylic acid [5-(3-benzyl-3-methyl-ureido)-4-oxo-cyclopent-2-enyl]-amide (6).**



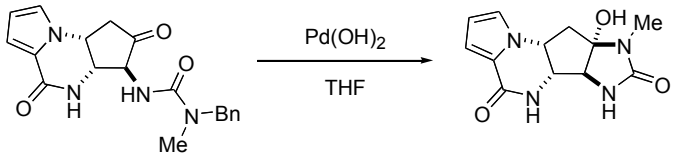
A solution of the allylic alcohol previously described (57.7 mg, 0.163 mmol) and IBX (91.7 mg, 0.327 mmol) in DMSO (2.7 mL) was stirred at rt for 8 h, diluted with EtOAc (100 mL) then washed with water (3x10 mL) and brine (10 mL). The organic extracts were dried over Na_2SO_4, concentrated under reduced pressure and the residue purified by flash chromatography (CH_2Cl_2/MeOH, 19:1) to yield **6** (52.8 mg, 92%) as a white solid: mp 209 °C (dec.); R_f 0.20 (CH_2Cl_2/MeOH, 19:1); IR (film) υ_{max} 3319, 3280, 2923, 1721, 1635, 1581, 1563, 1527, 1407, 1394, 1338, 1304, 1028, 762 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 8.42 (d, *J* = 8.8 Hz, 1 H), 7.52 (dd, *J* = 2.0, 6.2 Hz, 1 H), 7.23 (t, *J* = 7.5 Hz, 2 H), 7.24 (d, *J* = 7.2 Hz, 1 H), 7.20 (d, *J* = 7.2 Hz, 2 H), 7.16 (d, *J* = 7.3 Hz, 1 H), 6.88 (d, *J* = 1.0 Hz, 1 H), 6.78 (s, 1 H), 6.33 (dd, *J* = 1.9, 6.2 Hz, 1 H), 6.10 (dd, *J* = 2.4, 3.4 Hz, 1 H), 5.31-5.27 (m, 1 H), 4.39 (dd, *J* = 15.8, 24.1 Hz, 2 H), 3.94 (dd, *J* = 3.8, 7.2 Hz, 1 H), 2.73 (s, 3 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 203.2, 161.2, 160.6, 157.5, 138.4, 132.1, 128.4, 127.2, 126.8, 125.9, 121.7, 110.1, 108.6, 61.5, 54.7, 51.0, 33.6; HRMS-ESI calcd for $C_{19}H_{20}O_3N_4Na$ $[M+Na]^+$ 375.14276, found: 375.14264.

(3*S,3a*R**,8b*R**)-(1-Benzyl-3-(2,5-dioxo-2,3,3a,4,5,8b-hexahydro-1*H*-4,8a-diaza-*as*-indacen-3-yl)-1-methylurea (16).**



A suspension of **6** (50.0 mg, 0.14 mmol) and K_2CO_3 (2.0 mg, 0.014 mmol) in DMSO (2.8 mL) was submerged in a preheated oil bath (100 °C) and stirred for 1 h. The reaction mixture was then cooled to rt, diluted with EtOAc (50 mL) and sequentially washed with water (2x10 mL) and brine (10 mL). The organic extracts were dried (Na_2SO_4), concentrated under reduced pressure and the crude residue purified by flash chromatography (CH_2Cl_2/MeOH, 19:1) to yield **16** (23.8 mg, 48%) as a white solid: mp 174 °C (dec.); R_f 0.17 (CH_2Cl_2/MeOH, 19:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33-7.23 (m, 4 H), 7.19 (d, *J* = 7.1 Hz, 2 H), 6.99 (dd, *J* = 1.1, 3.9 Hz, 1 H), 6.82-6.81 (m, 1 H), 6.32, (dd, *J* = 3.0, 3.8 Hz, 1 H), 5.78 (bs, 1 H), 4.85-4.76 (m, 1 H), 4.68-4.64 (m, 1 H), 4.56 (d, *J* = 16.2 Hz, 1 H), 4.39 (d, *J* = 16.2 Hz, 1 H), 3.47 (t, *J* = 6.8 Hz, 1 H), 3.22 (dd, *J* = 6.7, 18.7 Hz, 1 H), 3.07 (d, *J* = 18.7 Hz, 1 H), 3.01 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.0, 160.4, 157.7, 137.6, 128.8, 127.4, 127.1, 123.5, 123.1, 115.6, 111.9, 62.3, 55.9, 52.0, 50.8, 42.5, 34.3; HRMS-ESI calcd for $C_{19}H_{21}O_3N_4$ [M+H] 353.16082, found: 353.15958.

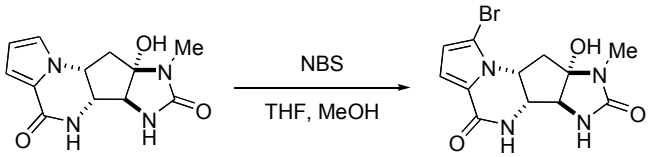
(±)-Debromoagelastatin A.



A round-bottom flask charged with **16** (17.7 mg, 0.050mmol), $Pd(OH)_2$/C (7.1 mg, 20% dry basis) and THF (1.0 mL) was flushed with N_2 then placed under an atmosphere of H_2 (1 atm). After stirring at rt for 24 h, the reaction mixture was diluted with methanol (5 mL), filtered through a plug of Celite and concentrated under reduced pressure. The resulting residue was purified by preparative thin-layer chromatography (SiO_2, 1.0 mm), eluting with EtOAc-MeOH (6:1) to yield **18** (8.0 mg, 61%) as a white

solid: mp 242-244 °C {lit.[6] mp 242.5-244 °C}; R_f = 0.34 (CH_2Cl_2/MeOH, 7:1); IR (film) υ_{max} 3303, 2924, 2852, 1689, 1678, 1660, 1551, 1473, 1452, 1415, 1376, 1300, 1072, 753 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 7.02 (dd *J* = 1.5, 2.3 Hz, 1 H), 6.88 (dd, *J* = 1.4, 3.9 Hz, 1 H), 6.23 (dd, *J* = 2.6, 3.8 Hz, 1 H), 4.65 (dt, *J* = 5.9, 9.9 Hz, 1 H), 4.00 (d, *J* = 4.8 Hz, 1 H), 3.80 (s, 1 H), 2.79 (s, 3 H), 2.61 (dd, *J* = 6.4, 13.3 Hz, 1 H), 2.28 (dd, *J* = 10.3, 13.3 Hz, 1 H); ^{13}C NMR (500 MHz, CD_3OD) δ 162.1, 161.3, 125.6, 122.9, 115.4, 111.1, 95.8, 68.0, 62.9, 55.6, 41.6, 24.2; HRMS-ESI calcd for $C_{12}H_{15}N_4O_3$ [M+H] 263.1144, found: 263.1143.

(±)-Agelastatin A (1).



To a cooled (0 °C) solution of **18** (6.4 mg, 0.024 mmol) in THF (1.8 mL) and MeOH (0.8 mL) was added NBS (3.9 mg, 0.022 mmol) in one portion. The reaction was warmed to rt, stirred for 16 h and then the reaction mixture was concentrated under reduced pressure. The residue was purified by preparative thin-layer chromatography (SiO_2, 1.0 mm), eluting with CH_2Cl_2-MeOH (7:1), to yield (±)-agelastatin A (**1**) (6.2 mg, 75%) as a white solid: mp 193 °C (dec.) {lit.[7] mp 193 °C (dec.)}; R_f = 0.38 (CH_2Cl_2/MeOH, 7:1); ^1H NMR (500 MHz, CD_3OD) δ 6.91 (d, *J* = 3.9 Hz, 1 H), 6.32 (d, *J* = 3.9 Hz, 1 H), 4.59 (m, 1 H), 4.07 (d, *J* = 5.2 Hz, 1 H), 3.88 (s, 1 H), 2.80 (s, 3 H), 2.64 (dd, *J* = 6.0, 12.3 Hz, 1 H), 2.09 (t, *J* = 12.9 Hz, 1 H); ^{13}C NMR (500 MHz, CD_3OD) δ 161.4, 161.1, 124.1, 116.0, 113.8, 107.2, 95.7, 67.4, 62.2, 54.4, 40.0, 24.2; HRMS-ESI calcd for $C_{12}H_{14}N_4O_3{}^{79}Br$ [M+H] 341.0249, found: 341.0260.

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6. Ichikawa, Y.; Yamaoka, T.; Nakano, K.; Kotsuki, H. *Org. Lett.* **2007**, *9*, 2989.