Total Synthesis of the Duocarmycins

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Supporting Information

Experimental details and spectral data

General Considerations: All reactions were carried out in oven-dried glassware under a slight positive pressure of argon unless otherwise noted. ^1H NMR and ^{13}C NMR spectra were determined either on JEOL JNM-LA400 (^1H -NMR: 400 Hz, ^{13}C -NMR: 100 Hz) or on JEOL JNM-A500 (^1H NMR: 500 Hz, ^{13}C NMR: 125 Hz) instruments. Chemical shifts for ^1H NMR were reported in parts per million (ppm) downfield from tetramethylsilane as the internal standard and coupling constants are indicated in Hertz (Hz). The following abbreviations are used for spin multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and br = broad. Chemical shifts for ^{13}C NMR were reported in ppm, relative to the central line of the triplet at 77.0 ppm for deuteriochloroform. Infrared (IR) spectra were recorded on a JASCO FT/IR-410 Fourier Transform Infrared Spectrometer and are reported in wavenumbers (cm^{-1}). Where noted “neat”, the sample was loaded as a thin film on zinc-selenium plate. KBr disks were prepared by first grinding the sample with potassium bromide then pressing with a stainless-steel disc die assembly. High-resolution mass spectra (HRMS) were obtained on a JEOL JMS-GCmate in positive FAB ionization method, using Kanto Chemical PEG 600 matrix as the internal standard. Optical rotations were measured on a JASCO DIP-1000 digital polarimeter with a sodium lamp and reported as follows: $[\alpha]_{\lambda}^{t^{\circ}\text{C}}$ (c g/100 mL, solvent). Analytical thin layer chromatography (TLC) separations were performed on Merck precoated analytical plates, 0.25 mm thick, silica gel 60 F₂₄₅. Preparative TLC separations were performed on Merck analytical plates (0.25 or 0.50 mm thick) precoated with silica gel 60 F₂₅₄. Flash column

chromatography separations were performed on Kanto Chemical Silica Gel 60 (40-100 mesh) unless otherwise noted.

Solvents: Reagent grade solvents were used without any purification unless otherwise noted. “Dry” solvents generally refer to those with water content less than 10 ppm, prepared in the following manners. Methylene chloride, toluene and benzene were distilled from calcium hydride and stored over activated molecular sieves 4Å.^a Dehydrated tetrahydrofuran, diethyl ether and *N,N*-dimethylformamide were purchased from Kanto Chemicals Co., Inc. and were stored over activated molecular sieves 4Å. Dehydrated methanol, ethanol and acetonitrile were also purchased from Kanto Chemicals Co., Inc. and were stored over activated molecular sieves 3Å. Dimethyl sulfoxide was distilled from calcium hydride and was stored over activated molecular sieves 4Å. For use in copper-mediated aryl amination reactions, the aforementioned dimethyl sulfoxide was degassed *via* four to five cycles of freeze-pump-thaw sequence^b prior to use. When a large quantity of either dry methylene chloride or toluene were required, reagent grade solvent was first passed through a short column of basic alumina, then dried over activated molecular sieves 4Å. Typical water content of thus prepared solvents were less than 15 ppm.

Materials: Cuprous iodide and cesium acetate were purchased from Wako Pure Chemical Industries, Ltd. and were used as supplied. AD-mix- α and powdered potassium carbonate (–325 mesh) were purchased from Sigma-Aldrich Japan K.K. *n*-Butyllithium was purchased from Kanto Chemical Co., Inc. and was titrated against a known amount of phenylacetic acid in dry tetrahydrofuran. 2,2,2-Trichloroethyl chloroformate was distilled prior to use using a micro-distillation apparatus. Zinc powder “GR” (Particle size < 45 μm) was purchased from Merck KGaA, Germany, and was used as supplied.

^a Molecular sieves were “activated” in the following manner: A round-bottom flask containing molecular sieves was heated in a regular microwave for 2 min and the flask was immediately evacuated. When cooled to room temperature, the flask was backfilled with argon. The above procedure was repeated three times.

^b Typical procedure: To a round-bottom flask equipped with a three-way stopcock was added dry DMSO. With the cock closed, the flask was cooled to –78 °C. When all DMSO had solidified, the flask was evacuated and again closed, then warmed in warm water bath. Air bubbled off as DMSO melted. After repeating the above process for five times, the flask was finally backfilled with argon.

Methanesulfonic acid 4-nitrophenyl ester (25). A suspension of *p*-nitrophenol (64.0 g, 460 mmol) in dry methylene chloride (750 mL) in a 2-L round-bottom flask was cooled to 0 °C. Addition of triethylamine (67.0 mL, 483 mmol) resulted in formation of a yellow solution, to which methanesulfonyl chloride (38.0 mL, 483 mmol) was added dropwise *via* addition funnel over 15 min. The reaction mixture was warmed to room temperature and stirred for 3 h, after which time TLC (100% CH₂Cl₂) indicated complete consumption of the phenol. The resulting colorless solution was diluted with methylene chloride (300 mL), washed once with 1 *N* aqueous hydrochloric acid, saturated aqueous sodium bicarbonate, brine and dried over magnesium sulfate. The solvent was removed under reduced pressure and the remaining solid was recrystallized (EtOAc-Hex) to afford **25** as colorless plates (88.0 g, 406 mmol, 88%): m.p. 88.4-88.6 °C.

¹H NMR (400 MHz, CDCl₃): δ 8.31 (d, *J* = 9.0 Hz, 2H), 7.47 (d, *J* = 9.0 Hz, 2H), 3.27 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 153.2, 146.2, 125.7, 122.7, 38.2; IR (neat): 3115, 3084, 3039, 2945, 1616, 1588, 1521, 1487, 1373, 1347, 1205, 1166, 1155, 1113, 1008, 976, 863, 787, 751, 722, 685; Anal. Calcd. for C₇H₇NO₅S: C, 38.71; H, 3.25; N, 6.45; Found: C, 38.80; H, 3.13; N, 6.19.

Methanesulfonic acid 4-aminophenyl ester (26). A Parr pressure bomb was charged with **25** (68.2 g, 314 mmol), 350 mL of ethyl acetate and Raney nickel (W-2)^a in ethanol. The bomb was then pressurized with gaseous hydrogen (1400 psi) and stirred at room temperature for 24 h, after which time TLC (100% CH₂Cl₂) indicated complete consumption of the starting material. The resulting suspension was filtered through a pad of Celite[®] and the solvent was removed under reduced pressure to afford aniline **26** (61.4 g, quant.) as a white crystalline solid: m.p. 87.5-87.7 °C.

¹H NMR (400 MHz, CDCl₃): δ 7.05 (dd, *J* = 6.6, 2.2 Hz, 2H), 6.64 (d, *J* = 8.8 Hz, 2H), 3.65 (br s, 2H), 3.07 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 145.7, 141.1, 122.8, 115.6, 36.7; IR (KBr disk): 3481, 3386, 3229, 3032, 2938, 1631, 1601, 1504, 1337, 1328, 1296, 1190, 1168, 1149, 987, 879, 831, 778, 719, 686, 579, 521, 502; Anal. Calcd. for C₇H₉NO₃S: C, 44.91; H, 4.85; N, 7.48; Found: C, 44.79; H, 4.81; N, 7.45.

^a Billica, H. R.; Adkins, H. *Org. Synth., Coll. Vol. III* 181.

Methanesulfonic acid 4-amino-3,5-dibromophenyl ester (27). A 1-L round-bottom flask was charged with **26** (crude, 314 mmol), methanol (250 mL) and methylene chloride (300 mL). After cooling the solution to 0 °C, bromine (101 g, 628 mmol) was added dropwise *via* addition funnel over 20 min. The flask was let warm to room temperature over 30 min, after which time TLC (2:1 CH₂Cl₂-Hex) indicated complete consumption of the starting material. To the resulting slurry was cautiously added saturated aqueous sodium bicarbonate (750 mL). The mixture was then extracted three times with methylene chloride and the combined organic layers were washed twice with saturated aqueous sodium thiosulfate, once with brine and dried over sodium sulfate. Removal of the solvent under reduced pressure gave crude **27** as orange crystals (116 g). Recrystallization (EtOAc-Hex) gave **27** (94.5 g, 274 mmol, 87% from **25**) as pale beige needles: m.p. 84.0-84.2 °C.

¹H NMR (400 MHz, CDCl₃): δ 7.38 (s, 2H), 4.63 (br s, 2H), 3.14 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 141.7, 139.3, 125.6, 107.7, 37.2; IR (KBr disk): 3240, 3338, 3081, 3023, 2938, 1617, 1576, 1558, 1465, 1404, 1363, 1324, 1305, 1218, 1189, 1163, 1072, 967, 914, 877, 827, 789, 740, 706, 620, 539, 519, 503; Anal. Calcd. for C₇H₇Br₂NO₃S: C, 24.37; H, 2.05; N, 4.06; Found: C, 24.38; H, 2.12; N, 3.84.

Methanesulfonic acid 3,5-dibromo-4-iodophenyl ester (28). A 3-L three-necked round-bottom flask was charged with ice (500 g) and concentrated sulfuric acid (500 mL). To the stirred solution at 0 °C was added **27** (104 g, 301 mmol) in acetonitrile (500 mL) slowly *via* separatory funnel over 20 min. To the slurry thus formed was added sodium nitrite (37.4 g, 543 mmol) in cold water (300 mL) dropwise *via* separatory funnel over 20 min, while maintaining the temperature near 0 °C. The resulting clear solution was poured into a 5-L three-necked round-bottom flask containing a solution of potassium iodide (175 g, 1.05 mol) in water (500 mL). The resulting mixture was stirred vigorously with overhead mechanical stirrer for 45 min. The reaction mixture was then diluted with chloroform (1 L) and washed with water. The aqueous phase was back-extracted with chloroform and the combined organic layers were washed with saturated aqueous sodium carbonate, saturated aqueous sodium thiosulfate, then with brine and dried over magnesium sulfate. Removal of the solvent under reduced pressure gave **28** as analytically pure crystalline solid (132 g, 289 mmol, 96%). Further purification was possible by recrystallization (CH₂Cl₂-Hex) to afford **28** (119 g) as colorless needles: m.p. 111.3-111.5 °C.

¹H NMR (400 MHz, CDCl₃): δ 7.54 (s, 2H), 3.21 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 148.7, 131.7, 124.9, 108.3, 38.0; IR (KBr disk): 3118, 3072, 3034, 3012, 2932, 1569, 1549, 1396, 1350, 1245, 1208, 1163, 1104, 1008, 974, 925, 870, 859, 806, 759, 747, 730, 678, 552, 535, 512; Anal. Calcd. for C₆H₃Br₂IO: C, 18.44; H, 1.11; N, 0.00; Found: C, 18.31; H, 1.17; N, 0.00.

3,5-Dibromo-4-iodophenol (29). A 1-L three-necked round-bottom flask equipped with an overhead mechanical stirrer was charged with mesylate **28** (17.9 g, 39.3 mmol) and methylene chloride (200 mL). To the resulting solution was added potassium hydroxide (6.6 g, 118 mmol) in methanol (50 mL) and the slurry was stirred vigorously for 5 min at room temperature. After confirming the completion of reaction by TLC (10% EtOAc-Hex), 1 *N* aqueous hydrochloric acid (400 mL) was added. The resulting mixture was extracted three times with chloroform (100 mL each) and the combined organic layers were washed with brine then dried over sodium sulfate. Removal of the solvent under reduced pressure gave **29** as analytically pure crystalline solid (17.2 g, quant.). Recrystallization (CH₂Cl₂-MeOH) gave colorless needles: m.p. 153.5-153.9 °C.

¹H NMR (400 MHz, CDCl₃): δ 7.14 (s, 2H), 5.31 (s, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 156.4, 131.1, 119.1, 98.1; IR (KBr disk): 3289 (br), 3060, 1583, 1558, 1399, 1304, 1249, 1221, 1188, 1170, 1111, 905, 869, 855, 848, 828, 748, 666, 588; Anal. Calcd. for C₆H₃Br₂IO: C, 19.07; H, 0.80; N, 0.00; Found: C, 18.90; H, 0.89; N, 0.00.

3,5-Dibromo-4-iodophenol benzyl ether (3). A 500-mL round-bottom flask was charged with **29** (14.8 g, 39.3 mmol), dry *N,N*-dimethylformamide (120 mL) and powdered potassium carbonate (15.4 g, 118 mmol). To the resulting suspension stirred at room temperature was added benzyl bromide (4.9 mL, 39.3 mmol). The reaction was complete within 1 h (TLC: 10% EtOAc-PhH). The slurry was diluted with ether and hexanes (250 mL each) and washed with water. The aqueous phase was back-extracted twice with ether-hexanes and the combined organic layers were washed twice with water then with brine, and finally dried over sodium sulfate. Removal of the solvent under reduced pressure gave beige crystalline solid, which was recrystallized from ethanol to give **3** (16.2 g, 34.5 mmol, 88%) as fine colorless needles: m.p. 61.4-61.6 °C.

^1H NMR (400 MHz, CDCl_3): δ 7.38 (m, 5H), 7.24 (s, 2H), 5.01 (s, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 159.3, 135.4, 131.1, 128.7, 128.5, 127.5, 118.5, 98.2, 70.6; IR (neat): 3065, 3033, 2942, 2863, 1575, 1538, 1452, 1413, 1378, 1269, 1231, 1110, 1008, 903, 857, 833, 739, 695; Anal. Calcd. for $\text{C}_{13}\text{H}_9\text{Br}_2\text{IO}$: C, 33.37; H, 1.94; N, 0.00; Found: C, 33.09; H, 2.03; N, 0.00.

(2R,3S)-2,3-Dihydroxy-3-phenylpropionic acid methyl ester^a (30). A 500-mL round-bottom flask was charged with methyl cinnamate (3.65 g, 22.5 mmol), *tert*-butyl alcohol (110 mL), water (110 mL), AD-mix- α (31.5 g) and methane sulfonamide (2.15 g, 22.5 mmol). The resulting orange, two-phase solution was stirred vigorously at room temperature. After 24 h, white precipitates had formed and TLC (5% MeOH-CH₂Cl₂) indicated the completion of reaction. Sodium sulfite (34 g, 27.0 mmol) was added in one portion and the resulting mixture was extracted three times with methylene chloride. The combined organic layers were washed with brine, dried over sodium sulfate and the solvent was removed under reduced pressure. Flash column chromatography (5% MeOH-CH₂Cl₂) afforded **30** (2.90 g, 14.8 mmol, 66%). Recrystallization (EtOAc-Hex) gave **30** as colorless needles: m.p. 83.9-84.3 °C. The enantiomeric excess was determined to be >99% using chiral HPLC.^{b,c}

¹H NMR (400 MHz, CDCl₃): δ 7.40-7.29 (m, 5H), 5.01-4.99 (m, 1H), 4.35 (s, 1H), 3.79 (s, 3H), 3.27 (s, 1H), 2.97 (d, J = 6.4 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 173.1, 139.9, 128.4, 128.0, 126.2, 74.7, 74.4, 52.8; IR (KBr disk): 3504, 3381 (br), 3092, 3066, 3032, 2952, 1714, 1492, 1457, 1436, 1398, 1370, 1324, 1301, 1275, 1227, 1200, 1112, 1082, 1050, 1027, 985, 937, 924, 884, 858, 766, 718, 704, 668, 575, 519; Anal. Calcd. for C₁₀H₁₂O₄: C, 61.22; H, 6.16; N, 0.00; Found: C, 60.97; H, 6.18; N, 0.00; $[\alpha]_D^{25}$ = +13° (c 0.36, CHCl₃).

^a Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* **1992**, 57, 2768.

^b Eluted with 20% *i*-PrOH-Hex at flow rate of 1 mL/min on Daicel Chemical Ind., Ltd. CHIRALCEL AD column (0.46 cm x 25 cm). Retention time: 2*R*,3*S* = 9.1 min, 2*S*,3*R* = 8.6 min.

^c Racemic diol was prepared by ruthenium-catalyzed dihydroxylation: Shing, T. K. M.; Tai, V. M. F.; Tam, E. K. W. *Angew. Chem. Int. Ed.* **1994**, 33, 2312.

(4*R*,5*S*)-2,2-Dimethyl-5-phenyl-1,3-dioxolane-4-carboxylic acid methyl ester (31). A 200-mL round-bottom flask was charged with **30** (2.52 g, 12.9 mmol), acetone (25 mL) and 2,2-dimethoxypropane (10 mL). *p*-Toluenesulfonic acid (12.2 mg, 64.2 μ mol) was added and the solution was stirred at room temperature for 3 h, after which time TLC (5% MeOH-CH₂Cl₂) indicated complete consumption of the starting material. Triethylamine was added and the solution was concentrated under reduced pressure. The resulting oil was taken up in ethyl acetate, washed with saturated aqueous sodium bicarbonate, brine, and dried over sodium sulfate. Removal of the solvent under reduced pressure afforded **31** as a colorless oil (2.94 g, 12.5 mmol, 97%).

¹H NMR (400 MHz, CDCl₃): δ 7.40-7.31 (m, 5H), 5.17 (d, J = 7.8 Hz, 1H), 4.36 (d, J = 7.8 Hz, 1H), 3.79 (s, 3H), 1.61 (s, 3H), 1.56 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 170.7, 137.6, 128.62, 128.58, 126.5, 111.6, 81.3, 80.7, 52.5, 26.9, 25.8; IR (neat): 3067, 3034, 2991, 2953, 2938, 1760, 1456, 1439, 1383, 1281, 1252, 1212, 1166, 1102, 1051, 1028, 990, 893, 850, 809, 760, 699; FABHRMS (PEG-600): m/z 236.1053 (M⁺, C₁₃H₁₆O₄ requires 236.1049); $[\alpha]_D^{25}$ = -20° (c 0.53, CHCl₃).

1-[(4*R*,5*S*)-2,2-Dimethyl-5-phenyl-[1,3]dioxolan-4-yl]-2-nitroethanol (32). Methyl ester **31** (2.94 g, 12.5 mmol) was dissolved in dry toluene (40 mL) and cooled to $-78\text{ }^\circ\text{C}$ in dry ice-acetone bath. DIBAL in toluene (1.0 M, 18.7 mL, 18.7 mmol) was added slowly *via* syringe. After stirring at $-78\text{ }^\circ\text{C}$ for 30 min, methanol (5 mL) was added and the reaction mixture was warmed to room temperature. Nitromethane (40 mL) was added to the slurry, followed by triethylamine (5.5 mL, 39.5 mmol). The mixture was stirred at room temperature for 1 h until TLC (25% EtOAc-Hex) indicated complete consumption of the aldehyde. The reaction was quenched with 1 *N* aqueous hydrochloric acid, extracted twice with ethyl acetate, washed with brine and dried over sodium sulfate. The solvent was removed under reduced pressure and the resulting solid was purified by flash column chromatography (15% EtOAc-Hex) to afford **32** as an amorphous solid (3.19 g, 11.9 mmol, 96%).

(20:3) mixture of diastereomers

^1H NMR (400 MHz, CDCl_3): δ 7.45-7.32 (m, 5H), 5.06 (d, $J = 8.4$ Hz, 0.15H), 4.99 (d, $J = 7.6$ Hz, 1H), 4.58-4.50 (m, 2H), 4.43-4.36 (m, 1H), 3.90 (dd, $J = 7.6, 6.4$ Hz, 1H), 3.73 (dd, $J = 8.4, 1.2$ Hz, 0.15H), 2.66 (d, $J = 4.8$ Hz, 1H), 2.65 (d, $J = 8.8$ Hz, 0.15H), 1.58 (s, 0.45H), 1.55 (s, 3H), 1.54 (s, 0.45H), 1.50 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 137.5, 128.9, 128.8, 127.2, 126.6, 110.3, 82.4, 80.9, 76.7, 69.8, 27.1, 26.9; IR (KBr disk): 3484 (br), 3445 (br), 3066, 3026, 2955, 2892, 2837, 1733, 1687, 1452, 1328, 1292, 1230, 1112, 1053, 1028, 939, 707, 668; Anal. Calcd. for $\text{C}_{13}\text{H}_{17}\text{NO}_6$: C, 58.42; H, 6.41; N, 5.24; Found: C, 58.25; H, 6.39; N, 5.12.

(4*S*,5*S*)-2,2-Dimethyl-4-(2-nitrovinyl)-5-phenyl-[1,3]dioxolane (4). A 200-mL round-bottom flask containing **32** (3.14 g, 11.8 mmol) in dry methylene chloride (60 mL) was cooled to 0 °C in an ice bath. To the solution was added methanesulfonyl chloride (1.0 mL, 12.9 mmol) followed by slow addition of triethylamine (3.5 mL, 24.8 mmol). After stirring for 5 min, TLC (10% EtOAc-Hex) indicated complete consumption of the starting material. The resulting pale yellow solution was diluted with ethyl acetate and washed with 1 *N* aqueous hydrochloric acid. The organic layer was then washed with saturated aqueous sodium bicarbonate, brine and dried over sodium sulfate. Removal of solvent under reduced pressure gave a residue, which was purified by flash column chromatography (5% EtOAc-Hex) to afford nitroalkene **4** (2.59 g, 10.4 mmol, 88%) as colorless crystals (plates): m.p. 60.4-61.2 °C.

¹H NMR (400 MHz, CDCl₃): δ 7.44-7.38 (m, 5H), 7.24-7.15 (m, 2H), 4.73 (d, *J* = 8.8 Hz, 1H), 4.44 (dd, *J* = 8.5, 1.2 Hz, 1H), 1.62 (s, 3H), 1.55 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 140.5, 136.5, 135.4, 129.1, 129.0, 126.5, 110.8, 82.7, 79.7, 27.0, 26.7; IR (KBr disk): 3138, 3098, 3066, 3033, 2991, 2935, 2870, 1659, 1525, 1495, 1456, 1373, 1354, 1323, 1274, 1225, 1171, 1125, 1042, 1026, 975, 945, 929, 890, 870, 818, 765, 757, 670, 641, 615, 515; Anal. Calcd. for C₁₃H₁₅NO₄: C, 62.64; H, 6.07; N, 5.62; Found: C, 62.40; H, 6.09; N, 5.62; [α]_D²⁵ = −73° (c 0.23, CHCl₃).

(4*S*,5*S*)-4-[(1*S*)-1-(4-Benzyloxy-2,6-dibromophenyl)-2-nitroethyl]-2,2-dimethyl-5-phenyl-[1,3]dioxolane (5).

A 500-mL three-necked round-bottom flask was warmed with a heat gun under vacuum to remove moisture, backfilled with argon, charged with aryl iodide **3** (6.77g, 15.8 mmol) and dry toluene (150 mL). The solution was cooled to -78°C and was treated with *n*-butyllithium in hexanes (1.60 M, 9.5 mL, 15.8 mmol). To the resulting slurry kept at -78°C was added nitroalkene **4** (3.58 g, 14.4 mmol) in toluene (100 mL) portionwise over 40 min. The reaction was complete when all of the nitroalkene had been added (TLC: 50% CH_2Cl_2 -Hex). To the solution at -78°C , 1 *N* aqueous hydrochloric acid was added and the mixture was warmed to room temperature, extracted with ethyl acetate, washed with saturated aqueous sodium bicarbonate, brine and dried over magnesium sulfate. The solvent was removed under reduced pressure and the resulting solid was subjected to flash column chromatography (3% EtOAc-Hex then 15% EtOAc-Hex) to afford **5** (5.45 g, 9.22 mmol, 64%) as a 10:1 mixture of diastereomers (1' epimers). Recrystallization from ethanol gave analytically pure **5** (4.18 g) as colorless needles: m.p. $114.5\text{--}115.5^\circ\text{C}$.

^1H NMR (400 MHz, CDCl_3): δ 7.43-7.35 (m, 5H), 7.21 (d, $J = 2.8$ Hz, 1H), 7.11-7.02 (m, 3H), 6.91-6.89 (m, 2H), 6.70 (d, $J = 2.8$ Hz, 1H), 5.25 (dd, $J = 13.2, 8.8$ Hz, 1H), 5.03 (dd, $J = 13.2, 4.8$ Hz, 1H), 4.96-4.80 (m, 5H), 1.58 (s, 6H); ^{13}C NMR (100 MHz, CDCl_3): δ 158.4, 136.3, 135.4, 128.73, 128.66, 128.5, 128.1, 127.9, 127.4, 127.0, 125.6, 123.2, 120.7, 119.6, 109.9, 82.2, 80.4, 75.7, 70.5, 47.4, 27.4, 26.8; IR (KBr disk): 3072, 3033, 2987, 2928, 2863, 1593, 1551, 1498, 1457, 1447, 1382, 1269, 1252, 1208, 1190, 1178, 1162, 1073, 1057, 1035, 1028, 1015, 918, 891, 857, 832, 761, 742, 699, 657, 547, 419; Anal. Calcd. for $\text{C}_{26}\text{H}_{25}\text{Br}_2\text{NO}_5$: C, 52.81; H, 4.26; N, 2.37; Found: C, 52.73; H, 4.32; N, 2.20; $[\alpha]_{\text{D}}^{25} = -61^\circ$ (c 0.50, CHCl_3).

(1*S*,2*S*,3*S*)-3-(4-Benzyloxy-2,6-dibromophenyl)-4-nitro-1-phenylbutane-1,2-diol (33).

A suspension of **5** (4.11 g, 6.95 mmol) in acetic acid (40 mL) and water (10 mL) was warmed to 100 °C. After 3 h, TLC (25% EtOAc-Hex) indicated complete consumption of the starting material. The resulting clear solution was concentrated under reduced pressure, taken up in ethyl acetate, poured cautiously into saturated aqueous sodium bicarbonate and extracted twice with ethyl acetate. The combined organic layers were washed with brine and dried over sodium sulfate. Removal of the solvent under reduced pressure afforded crude diol **33** (3.82 g, quant.). Further purification was performed on 20 mg of the crude diol for molecular analysis (preparative TLC: 30% EtOAc-Hex).

¹H NMR (400 MHz, CDCl₃): δ 7.41-7.36 (m, 5H), 7.31-7.19 (m, 7H), 5.16 (dd, *J* = 13.2, 5.6 Hz, 1H), 5.08 (dd, *J* = 13.2, 7.6 Hz, 1H), 5.01 (s, 2H), 4.89-4.83 (m, 1H), 4.70-4.65 (m, 1H), 4.43-4.42 (m, 1H), 2.54 (d, *J* = 7.6 Hz, 1H), 2.50 (d, *J* = 5.2 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 158.5, 140.9, 135.4, 128.9, 128.8, 128.5, 128.4, 127.8, 127.6, 127.4, 125.7, 122.6, 121.3, 119.8, 76.0, 74.3, 72.5, 70.6, 47.6; IR (KBr disk): 3524 (br), 3471, 3092, 3066, 3026, 1591, 1550, 1497, 1448, 1398, 1378, 1271, 1254, 1223, 1025, 836, 750, 733, 698; FABHRMS (PEG-600): *m/z* 548.9863 (M+H, C₂₃H₂₁Br₂NO₅ requires 548.9786); [α]_D²⁵ = -24° (c 1.01, CHCl₃).

(2S)-2-(4-Benzyloxy-2,6-dibromophenyl)-3-nitropropan-1-ol (34). A solution of **33** (3.80 g, 6.90 mmol) in tetrahydrofuran (35 mL) was cooled to 0 °C and was treated with orthoperiodic acid (1.89 g, 8.28 mmol). The suspension that initially formed turned to milky solution within 5 min, after which time TLC (25% EtOAc-Hex) indicated complete consumption of the diol. The reaction mixture was then cooled to -78 °C and chilled methanol (20 mL) was added, followed by sodium borohydride (1.30 g, 34.5 mmol). After stirring at -78 °C for 5 min, the completion of reaction was confirmed by TLC (50% EtOAc-Hex). The reaction mixture was then let warm to room temperature, quenched with 1 *N* aqueous hydrochloric acid and extracted twice with ethyl acetate. The combined organic layers were washed with saturated aqueous sodium bicarbonate, brine and dried over sodium sulfate. Removal of the solvent under reduced pressure followed by flash column chromatography (25% EtOAc-Hex) gave **34** (2.76 g, 6.24 mmol, 90%, >98% ee^a) as a colorless amorphous solid.

¹H NMR (400 MHz, CDCl₃): δ 7.43-7.35 (m, 5H), 7.26 (t, *J* = 1.2 Hz, 1H), 7.18 (d, *J* = 2.8 Hz, 1H), 5.07 (dd, *J* = 6.0, 2.4 Hz, 2H), 5.01 (s, 2H), 4.79 (td, *J* = 6.8, 2.0 Hz, 1H), 4.16 (dd, *J* = 10.8, 9.2 Hz, 1H), 4.02 (dd, *J* = 10.8, 6.4 Hz, 1H), 1.70 (s, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 158.4, 135.4, 128.7, 128.5, 128.4, 127.5, 127.3, 122.4, 121.0, 120.0, 75.4, 70.6, 62.0, 46.4; IR (neat): 3371 (br), 3069, 2898, 1591, 1551, 1498, 1445, 1382, 1276, 1254, 1172, 1066, 1036, 1027, 984, 911, 734, 694, 637, 607; FABHRMS (PEG-600): *m/z* 442.9355 (M⁺, C₁₆H₁₅Br₂NO₄ requires 442.9368); [α]_D²⁵ = -21° (c 1.23, CHCl₃).

^a The enantiomeric excess was determined by Mosher's method: Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512.

(2S)-N-(2-Nitrobenzenesulfonyl)-3-amino-2-(4-benzyloxy-2,6-dibromophenyl)-

propanol (35). To a 200-mL round-bottom flask equipped with a reflux condenser were added **34** (2.56 g, 5.75 mmol), iron powder (3.21 g, 57.5 mmol), ferrous chloride (730 mg, 5.75 mmol), 95% ethanol (50 mL) and 1 *N* aqueous hydrochloric acid (5 mL). The apparatus was flushed with argon and the mixture was heated to reflux. The reaction was complete within 2 h (TLC: 5% MeOH-CH₂Cl₂). The mixture was cooled to room temperature, filtered through Celite® and rinsed with methanol. The filtrate was then basified with aqueous sodium hydroxide. The resulting green mass was filtered away with Celite® and rinsed thoroughly with methanol. The filtrate was concentrated under reduced pressure to give crude amino-alcohol, to which were added methylene chloride (50 mL), saturated aqueous sodium bicarbonate (5 mL), and *o*-nitrobenzenesulfonyl chloride (1.27 g, 5.75 mmol). After stirring vigorously at room temperature for 5 min, TLC (20% MeOH-CH₂Cl₂) indicated complete consumption of the amino-alcohol. The mixture was extracted with ethyl acetate, washed with 1 *N* aqueous hydrochloric acid, saturated aqueous sodium bicarbonate, brine and dried over sodium sulfate. The crude nosylamide **35** obtained after removal of the solvent (3.42 g, 5.70 mmol, quant.) was analytically pure.

¹H NMR (400 MHz, CDCl₃): δ 8.12-8.09 (m, 1H), 7.83-7.81 (m, 1H), 7.72-7.68 (m, 2H), 7.44-7.36 (m, 5H), 7.15 (d, *J* = 2.8 Hz, 1H), 7.07 (d, *J* = 2.8 Hz, 1H), 5.64 (t, *J* = 6.0 Hz, 1H), 4.98 (s, 2H), 4.19-4.13 (m, 1H), 4.04 (td, *J* = 7.2, 6.0 Hz, 1H), 3.99-3.94 (m, 1H), 3.87-3.75 (m, 2H), 1.64 (t, *J* = 5.2 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 157.8, 147.4, 136.6, 135.5, 133.5, 133.3, 132.9, 130.8, 130.2, 128.6, 128.3, 127.4, 125.3, 122.2, 120.9, 119.1, 70.3, 62.7, 48.7, 44.0; IR (neat): 3553 (br), 3360 (br), 3093, 3028, 2885, 1591, 1538, 1497, 1447, 1361, 1259, 1223, 1165, 1125, 1024, 910, 854, 783, 738, 697, 654, 586; FABHRMS (PEG-600): *m/z* 597.9386 (M⁺, C₂₂H₂₀Br₂N₂O₆S requires 597.9409); [α]_D²⁵ = +41° (c 0.062, CHCl₃).

(2S)-3-Benzylamino-2-(4-benzyloxy-2,6-dibromophenyl)-propan-1-ol (6). To a solution of **35** (5.13 mmol) in dry *N,N*-dimethylformamide (30 mL) were added powdered potassium carbonate (4.24 g, 30.8 mol) and benzyl bromide (609 μL , 5.13 mmol). The mixture was stirred at room temperature for 1 h, after which time TLC indicated complete consumption of the nosylamide (10% EtOAc-PhH). To the mixture was then added thiophenol (1.6 mL, 15.4 mmol). After stirring at room temperature for 1 h, the reaction mixture was diluted with ethyl acetate, washed four times with 5% aqueous sodium chloride, once with brine and dried over sodium sulfate. The solvent was removed under reduced pressure and the remaining residue was subjected to flash column chromatography (25% EtOAc-Hex then 5% MeOH- CH_2Cl_2) to give **6** (1.91 g, 3.78 mmol, 74%) as a colorless oil.

^1H NMR (400 MHz, CDCl_3): δ 7.40-7.28 (m, 10H), 7.23 (d, $J = 2.4$ Hz, 1H), 7.14 (d, $J = 2.4$ Hz, 1H), 4.99 (s, 2H), 4.55 (t, $J = 10.0$ Hz, 1H), 4.05-3.97 (m, 1H), 3.91 (d, $J = 12.8$ Hz, 1H), 3.83 (d, $J = 12.8$ Hz, 1H), 3.82-3.78 (m, 1H), 3.69 (dd, $J = 12.0, 10.8$ Hz, 1H), 3.08-3.03 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 157.6, 139.1, 135.7, 130.8, 128.7, 128.6, 128.4, 128.3, 127.9, 127.5, 127.3, 122.3, 121.0, 119.3, 70.5, 65.3, 53.5, 51.3, 47.9; IR (neat): 3312 (br), 3060, 3030, 2869, 1592, 1540, 1496, 1448, 1379, 1264, 1025, 911, 849, 835, 734, 697; FABHRMS (PEG-600): m/z 503.0103 (M^+ , $\text{C}_{23}\text{H}_{23}\text{Br}_2\text{NO}_2$ requires 503.0096); $[\alpha]_{\text{D}}^{25} = -2^\circ$ (c 0.28, CHCl_3).

(3S)-1-Benzyl-6-benzyloxy-4-bromo-3-hydroxymethylindoline (36). A 20-mL round-bottom flask was charged with **6** (1.91 g, 3.78 mmol), cuprous iodide (144 mg, 756 μmol) and cesium acetate^a (1.03 g, 5.36 mmol). The flask was evacuated and backfilled with argon (balloon). Freshly degassed dry dimethyl sulfoxide (10 mL) was added to the flask. The resulting clear, deep blue-green solution was stirred under argon atmosphere for 24 h, without taking TLC. The resulting deep blue solution was diluted with ethyl acetate and washed with a mixture of aqueous ammonium hydroxide and 5% aqueous sodium chloride. The aqueous phase was back-extracted twice with ethyl acetate. The combined organic layers were washed with 5% aqueous sodium chloride, brine and dried over sodium sulfate. The solvent was removed under reduced pressure and the remaining residue was purified by flash column chromatography (100% CH_2Cl_2) to afford analytically pure **36** (1.07 g, 2.52 mmol, 67%) as a colorless solid. Recrystallization (CH_2Cl_2 -Hex) gave fine colorless needles: m.p. 113.3-115.4 $^\circ\text{C}$.

^1H NMR (400 MHz, CDCl_3): δ 7.37-7.26 (m, 10H), 6.40 (d, $J = 2.0$ Hz, 1H), 6.05 (d, $J = 2.0$ Hz, 1H), 4.96 (s, 2H), 4.33 (d, $J = 14.8$ Hz, 1H), 4.14 (d, $J = 14.8$ Hz, 1H), 3.89-3.85 (m, 1H), 3.78-3.72 (m, 1H), 3.56 (dd, $J = 9.2, 2.4$ Hz, 1H), 3.47 (t, $J = 9.2$ Hz, 1H), 3.41-3.35 (m, 1H), 1.46 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 160.6, 154.5, 137.4, 136.6, 128.60, 128.55, 128.0, 127.6, 127.5, 127.3, 121.4, 119.4, 105.7, 94.2, 70.3, 63.2, 55.9, 52.3, 43.9; IR (neat): 3369 (br), 3068, 3035, 2930, 2854, 1616, 1572, 1490, 1453, 1383, 1345, 1343, 1294, 1184, 1110, 1027, 957, 814, 735, 698; Anal. Calcd. for $\text{C}_{23}\text{H}_{22}\text{BrNO}_2$: C, 65.10; H, 5.23; N, 3.30; Found: C, 64.82; H, 5.39; N, 3.03; $[\alpha]_{\text{D}}^{25} = -6^\circ$ (c 0.30, CHCl_3).

^a Transferred in a plastic bag filled with argon to prevent rapid absorption of moisture.

(3S)-1-Benzyl-6-benzyloxy-4-bromo-3-(*tert*-butyldimethylsilyloxymethyl)indoline

(7). A 10-mL round-bottom flask was charged with **36** (702 mg, 1.66 mmol), imidazole (170 mg, 2.49 mmol) and *t*-butyldimethylchlorosilane (275 mg, 1.82 mmol). Dry *N,N*-dimethylformamide (1 mL) was added and the solution was stirred for 10 min at room temperature, after which time TLC (25% EtOAc-Hex) indicated complete consumption of the starting material. The reaction mixture was diluted with ethyl acetate, washed four times with water and then with brine. The organic layer was dried over sodium sulfate and the solvent was removed under reduced pressure. The resulting oil was purified by flash column chromatography (3% EtOAc-Hex) to give analytically pure **7** (932 mg, quant.) as a colorless oil.

^1H NMR (400 MHz, CDCl_3): δ 7.37-7.26 (m, 10H), 6.39 (d, $J = 2.0$ Hz, 1H), 6.04 (d, $J = 2.0$ Hz, 1H), 4.94 (s, 2H), 4.34 (d, $J = 15.0$ Hz, 1H), 4.12 (d, $J = 15.0$ Hz, 1H), 3.94-3.91 (m, 1H), 3.62 (d, $J = 7.6$ Hz, 1H), 3.55-3.50 (m, 1H), 3.40-3.33 (m, 2H), 0.89 (s, 9H), 0.06 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 160.5, 154.4, 137.6, 136.7, 128.5, 127.9, 127.6, 127.5, 127.2, 122.1, 119.4, 105.3, 94.0, 70.2, 62.7, 55.6, 52.2, 44.2, 25.9, 18.3, -5.2, -5.4; IR (neat): 3087, 3063, 3031, 2952, 2928, 2855, 1618, 1573, 1496, 1470, 1454, 1378, 1357, 1337, 1290, 1255, 1190, 1115, 1082, 1027, 959, 836, 814, 777, 735, 697, 666, 624, 578; FABHRMS (PEG-600): m/z 537.1682 (M^+ , $\text{C}_{29}\text{H}_{36}\text{BrNO}_2\text{Si}$ requires 537.1699); $[\alpha]_{\text{D}}^{25} = -11^\circ$ (c 0.44, CHCl_3).

2-Aminomalonic acid dimethyl ester^a (37). A 1-L round-bottom flask were charged with dimethyl malonate (50 mL, 436 mmol), acetic acid (75 mL, 1.31 mol) and water (100 mL) and cooled to 0 °C in an ice-bath. With stirring, sodium nitrite (90.2 g, 1.31 mol) was added portionwise over 1 h, while maintaining the internal temperature near 0 °C. The flask was removed from ice-bath upon completion of the addition and the mixture was stirred at room temperature. After 3 h, water was added and the mixture was extracted four times with diethyl ether. The combined ether layers were cautiously treated with an equal volume of saturated aqueous sodium bicarbonate. Solid sodium bicarbonate was then added until the aqueous layer turned to yellow. The ether layer was dried over sodium sulfate and concentrated under reduced pressure to give crude oxime. A Parr pressure bomb was charged with 10% palladium on charcoal^b (1.8 g) and crude oxime in ethanol (300 mL). The bomb was then pressurized with gaseous hydrogen (max. 1400 psi) and stirred for 12 h. The reaction mixture was filtered through a pad of Celite® and rinsed thoroughly with ethanol. Removal of the solvent under reduced pressure gave analytically pure **37** (58.3 g, 397 mmol, 91%) as a colorless oil.

¹H NMR (400 MHz, CDCl₃): δ 4.23 (s, 1H), 3.80 (s, 6H), 2.00 (s, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 170.0, 58.4, 53.0; IR (neat): 3330 (br), 2959, 1751, 1436, 1260; FABHRMS (PEG-600): *m/z* 147.0529 (M⁺, C₅H₉NO₄ requires 147.0532).

^a Zambito, A. J.; Howe, E. E. *Org. Synth., Coll. Vol. V* 373; Hartung, W. H.; Beaujon, J. H. R.; Cocolas, G. *Org. Synth., Coll. Vol. V* 376.

^b Purchased from Kawaken Fine Chemicals Co., Ltd. Type: AD (wet).

2-Benzyloxycarbonylamino-2-methylmalonic acid dimethyl ester (38). A solution of **37** (3.53 g, 24.0 mmol) in dry methylene chloride (90 mL) was treated with benzyl chloroformate (3.42 mL, 24.0 mmol) and pyridine (1.94 mL, 24.0 mmol). The reaction was complete within 5 min (TLC: 50% EtOAc-Hex). The solution was poured into 1 *N* aqueous hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium bicarbonate, brine and dried over sodium sulfate. Removal of the solvent under reduced pressure gave **38** (6.47 g, 23.0 mmol, 96%) as a colorless oil.

^1H NMR (400 MHz, CDCl_3): δ 7.36-7.26 (m, 5H), 5.86 (d, $J = 6.8$ Hz, 1H), 5.13 (s, 2H), 5.06 (d, $J = 7.8$ Hz, 1H), 3.8 (s, 6H); ^{13}C NMR (100 MHz, CDCl_3): δ 166.7, 155.4, 135.9, 128.6, 128.3, 128.2, 67.5, 57.5, 53.5; IR (neat): 3375 (br), 3034, 2957, 1733, 1516, 1456, 1436, 1346, 1291, 1220, 1162, 1070, 1018, 912, 777, 744, 700; FABHRMS (PEG-600): m/z 281.0910 (M^+ , $\text{C}_{13}\text{H}_{15}\text{NO}_6$ requires 281.0899).

2-Benzyloxycarbonylamino-2-methylmalonic acid dimethyl ester (39). A solution of sodium methoxide was prepared in a 500-mL three-necked round-bottom flask by dissolving sodium metal (635 mg, 27.6 mmol) in dry methanol (50 mL). The flask was then equipped with a reflux condenser and a solution of **38** (6.47 g, 23.0 mmol) in dry methanol (50 mL) was added. Methyl iodide (2.9 mL, 46.0 mmol) was added *via* addition funnel over 2 h while stirring at 50 °C. When all methyl iodide had been added, TLC (25% EtOAc-Hex, developed twice) indicated complete consumption of the starting material. The reaction mixture was concentrated and the resulting residue was acidified with 1 *N* aqueous hydrochloric acid, extracted with ethyl acetate, washed with saturated aqueous sodium bicarbonate, brine and dried over sodium sulfate. Evaporation of the solvent under reduced pressure gave **39** (5.19 g, 17.5 mmol, 76%) as a colorless oil.

^1H NMR (400 MHz, CDCl_3): δ 7.38-7.30 (m, 5H), 6.20 (s, 1H), 5.10 (s, 2H), 3.78 (s, 6H), 1.78 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 169.1, 154.5, 136.1, 128.5, 128.2, 128.1, 67.0, 63.1, 53.5, 21.5; IR (neat): 3378, 3028, 2956, 1743, 1499, 1447, 1374, 1271, 1208, 1119, 1063, 879; FABHRMS (PEG-600): m/z 295.1064 (M^+ , $\text{C}_{14}\text{H}_{17}\text{NO}_6$ requires 295.1056).

(2R)-2-Benzyloxycarbonylamino-2-methylmalonic acid monomethyl ester (40). A 500-mL beaker equipped with an overhead mechanical stirrer was charged with **39** (10.0 g, 33.8 mmol), acetone (30 mL) and aqueous phosphate buffer (300 mL, pH 7.5). To the solution was added PLE^a (780 mg), and the resulting suspension was stirred vigorously at room temperature. The pH was maintained between 7.5 to 8.5 by adding 1 *N* sodium hydroxide from time to time (total: 34 mL, 34 mmol). The reaction was monitored by TLC (5:4:1 toluene-HCO₂Et-HCO₂H). After three days, the mixture was filtered through a pad of Celite[®] with aid of ethyl acetate and the filtrate was concentrated. The remaining residue was acidified with 1 *N* aqueous hydrochloric acid, shaken with ethyl acetate and the emulsion was again filtered through a pad of Celite[®]. The aqueous phase was extracted with ethyl acetate and the combined organic layers were washed with brine and dried over sodium sulfate. Evaporation of solvent under reduced pressure gave analytically pure **40** (10 g, quant., 94% ee^b) as a viscous oil. Recrystallization (EtOAc-Hex) gave optically pure **40** (4 g, >98% ee^b) as a colorless amorphous solid: m.p. 121.7-122.9 °C.

¹H NMR (400 MHz, *d*₆-DMSO): δ 7.48 (s, 1H), 7.38-7.28 (m, 5H), 5.02 (s, 2H), 3.62 (s, 3H), 1.55 (s, 3H); ¹³C NMR (100 MHz, CD₃OD): δ 171.4, 171.0, 138.0, 129.4, 129.1, 128.8, 67.6, 64.4, 53.5, 21.9; IR (KBr disk): 3351, 3038 (br), 1738, 1663, 1525, 1445, 1379, 1297, 1204, 1119, 1075, 971, 920, 900; FABHRMS (PEG-600): *m/z* 281.0884 (M⁺, C₁₃H₁₅NO₆ requires 281.0899); Anal. Calcd. for C₁₃H₁₅NO₆: C, 55.51; H, 5.38; N, 4.98. Found: C, 55.21; H, 5.41; N, 4.92; [α]_D²⁵ = +18° (c 0.87, CHCl₃).

^a PLE = Porcine Liver Lipase. Amano Enzyme Co., Inc. (Activity: 6000 unit/g).

^b The enantiomeric excess was determined by coupling with chiral phenethylamine of known configuration:

(4S)-2-Benzyloxy-4-methoxycarbonyl-4-methyl-5-oxo-4,5-dihydro-oxazole (8). A 200-mL round-bottom flask was charged with **40** (907 mg, 3.23 mmol) and triphosgene (479 mg, 1.61 mmol). After filling the flask with argon, dry ethyl acetate (61 mL) was added. The flask was cooled to 0 °C and triethylamine (900 μ L, 6.46 mmol) was added. The flask was removed from the bath and warmed to room temperature. After 5 min, TLC^a (5:4:1 toluene-HCO₂Et-HCO₂H) indicated the completion of reaction. The mixture was again cooled in ice-bath for complete precipitation of the salt. The suspension was filtered through a pad of basic alumina and Celite[®] with aid of dry ethyl acetate. The filtrate was concentrated under reduced pressure and the resulting residue was taken up in dry benzene and the solvent was again removed under reduced pressure to give analytically pure azlactone **8** (880 mg, quant.) as a colorless oil.^b

¹H NMR (400 MHz, CDCl₃): δ 7.36-7.19 (m, 5H), 5.38 (s, 2H), 3.69 (s, 3H), 1.61 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 172.4, 167.0, 159.6, 133.5, 129.0, 128.6, 128.5, 73.1, 72.2, 53.4, 20.6; IR (neat): 3035, 2956, 1842, 1756, 1681, 1602, 1456, 1320, 1262, 1167, 1130, 1068, 981, 730, 697; FABHRMS (PEG-600): m/z 263.0796 (C₁₃H₁₃NO₅ requires 263.0794); $[\alpha]_D^{25} = -39^\circ$ (c 0.56, CHCl₃).

^a TLC sample was treated with methanol and was developed as dimethyl ester **39**.

^b Azlactone was relatively unstable and easily hydrolyzed upon exposure to moisture.

(2R)-3-[(3S)-1-Benzyl-6-benzyloxy-3-(*tert*-butyldimethylsilyloxymethyl)-2,3-dihydro-1*H*-indol-4-yl]-2-benzyloxycarbonylamino-2-methyl-3-oxo-propionic acid methyl ester (9). A dry 10-mL round-bottom flask was charged with **7** (581 mg, 1.08 mmol) and dry tetrahydrofuran (3.6 mL). The flask was cooled to $-78\text{ }^{\circ}\text{C}$ in dry ice-hexane bath and *n*-butyllithium in hexanes (1.51 M, 714 μL , 1.08 mmol) was added. The lithiated indoline was then cannulated into a 50-mL round-bottom flask containing a solution of azlactone **8** (526 mg, 2.00 mmol) in dry toluene (17 mL) at $-78\text{ }^{\circ}\text{C}$. The resulting bright yellow solution was stirred at $-78\text{ }^{\circ}\text{C}$ for 1 h. The mixture was diluted with diethyl ether and quenched with 1 *N* aqueous hydrochloric acid. The organic layer was washed with saturated aqueous sodium bicarbonate, brine and dried over sodium sulfate. Flash column chromatography (3~5% EtOAc-Hex) gave **9** (586 mg, 811 μmol , 75%) as a bright yellow oil.

^1H NMR (400 MHz, CDCl_3): δ 7.35-7.23 (m, 13H), 7.11 (br s, 2H), 6.42 (s, 1H), 6.21 (d, $J = 1.6\text{ Hz}$, 1H), 5.09 (d, $J = 12.4\text{ Hz}$, 1H), 4.93 (d, $J = 12.2\text{ Hz}$, 1H), 4.88 (d, $J = 11.5\text{ Hz}$, 1H), 4.90 (br s, 1H), 4.87 (br s, 1H), 4.35 (d, $J = 15.6\text{ Hz}$, 1H), 4.16 (d, $J = 15.6\text{ Hz}$, 1H), 3.94 (m, 1H), 3.83-3.70 (m, 1H), 3.71 (s, 3H), 3.67 (s, 1H), 3.33 (t, $J = 8.4\text{ Hz}$, 1H), 3.18 (t, $J = 12.0\text{ Hz}$, 1H), 1.82 (s, 3H), 0.85 (s, 9H), 0.04 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 192.8, 171.2, 159.1, 155.0, 153.8, 137.8, 136.8, 136.5, 130.8, 128.6, 128.5, 128.4, 127.90, 127.87, 127.6, 127.5, 127.3, 127.2, 125.7, 101.5, 99.2, 70.1, 66.9, 66.5, 63.0, 56.2, 53.6, 52.4, 43.4, 26.0, 22.4, 18.3, -5.2 , -5.4 ; IR (neat): 3318 (br), 3063, 3032, 2952, 2928, 2855, 1721, 1643, 1601, 1496, 1454, 1437, 1361, 1260, 1219, 1177, 1142, 1115, 1082, 1054, 1029, 836, 775, 736, 698; FABHRMS (PEG-600): m/z 722.3365 (M^+ , $\text{C}_{42}\text{H}_{50}\text{N}_2\text{O}_7\text{Si}$ requires 722.3387); $[\alpha]_{\text{D}}^{25} = -35^{\circ}$ (c 0.29, CHCl_3).

(2*R*)-3-[(3*S*)-1-Benzyl-6-benzyloxy-5-bromo-3-(*tert*-butyldimethylsilyloxymethyl)-2,3-dihydro-1*H*-indol-4-yl]-2-benzyloxycarbonylamino-2-methyl-3-oxo-propionic acid methyl ester (41**).** To a solution of **9** (170 mg, 235 μmol) in *N,N*-dimethylformamide (500 μL) was added *N*-bromosuccinimide (41.9 mg, 235 μmol) in *N,N*-dimethylformamide (470 μL). The solution was stirred for 5 min, after which time TLC (50% CH_2Cl_2 -Hex) indicated complete consumption of the starting material. Aqueous sodium thiosulfate and 5% aqueous sodium chloride were added and the mixture was extracted with ethyl acetate. The organic layer was washed three times with 5% aqueous sodium chloride then with brine and dried over sodium sulfate. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography (15% EtOAc-Hex) to give **41** (155 mg, 193 μmol , 82%) as a colorless oil.

^1H NMR (400 MHz, CDCl_3): δ 7.42-7.21 (m, 15H), 6.05 (s, 1H), 5.91 (s, 1H), 5.05-4.83 (m, 4H), 4.31 (d, $J = 15.4$ Hz, 1H), 4.12 (d, $J = 15.4$ Hz, 1H), 3.77 (s, 3H), 3.57-3.49 (m, 2H), 3.41-3.36 (m, 3H), 2.00 (s, 3H), 0.83 (s, 9H), -0.03 (s, 3H), -0.06 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 168.8, 154.8, 153.4, 137.4, 136.4, 128.7, 128.6, 128.49, 128.46, 128.3, 128.1, 128.0, 127.9, 127.5, 127.4, 127.1, 127.04, 126.99, 94.6, 71.2, 66.8, 64.9, 64.0, 56.3, 53.3, 52.1, 43.1, 43.0, 25.9, 18.3, -5.3 , -5.5 ; IR (neat): 3418 (br), 3039, 2953, 2850, 1730, 1595, 1497, 1455, 1374, 1272, 1118, 1066, 1008, 837, 777, 734, 698; FABHRMS (PEG-600): m/z 800.2478 (M^+ , $\text{C}_{42}\text{H}_{49}\text{BrN}_2\text{O}_7\text{Si}$ requires 800.2492); $[\alpha]_{\text{D}}^{25} = +16^\circ$ (c 0.68, CHCl_3).

(2*R*,8*S*)-6-Benzyl-4-benzyloxy-8-(*tert*-butyldimethylsilyloxymethyl)-2-methyl-1-oxo-1,2,3,6,7,8-hexahydro-3,6-diaza-*as*-indacene-2,3-dicarboxylic acid 3-benzyl ester 2-methyl ester (10**).** A 10-mL test tube was charged with **41** (155 mg, 193 μmol), cuprous iodide (37 mg, 386 μmol) and cesium acetate^a (180 mg, 938 μmol). The flask was fitted with a rubber septum, evacuated and then backfilled with argon (balloon). Freshly degassed dry dimethyl sulfoxide (400 μL) was added, giving transparent pale brown solution. After stirring at room temperature for 3 h, TLC (5% EtOAc-PhH) indicated complete consumption of the starting material. The mixture was diluted with diethyl ether and washed with water. The aqueous phase was extracted five times with diethyl ether and the combined organic layers were dried over sodium sulfate. Flash column chromatography (15% EtOAc-Hex) gave **10** (139 mg, quant.) as an orange solid.

¹H NMR (400 MHz, CDCl₃): δ 7.40-7.24 (m, 15H), 6.38 (s, 1H), 5.21 (d, J = 12.0 Hz, 1H), 5.07 (d, J = 12.0 Hz, 1H), 5.06 (d, J = 12.0 Hz, 1H), 5.00 (d, J = 12.0 Hz, 1H), 4.27 (d, J = 15.2 Hz, 1H), 4.20 (d, J = 15.6 Hz, 1H), 3.81 (dd, J = 9.2, 4.0 Hz, 1H), 3.68-3.65 (m, 2H), 3.57 (dd, J = 9.6, 8.0 Hz, 1H), 3.45 (s, 3H), 3.41 (d, J = 6.0 Hz, 1H), 1.75 (s, 3H), 0.81 (s, 9H), 0.01 (s, 3H), -0.05 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 195.4, 167.4, 152.2, 151.7, 149.1, 137.7, 136.8, 135.7, 129.0, 128.62, 128.61, 128.51, 128.49, 128.36, 128.29, 127.8, 127.7, 127.6, 127.4, 127.3, 121.2, 119.5, 103.2, 74.5, 71.7, 67.8, 63.1, 56.9, 53.1, 52.9, 42.6, 25.9, 20.6, 18.2, -5.2, -5.4; IR (neat): 3066, 3034, 2953, 2926, 2856, 1761, 1747, 1714, 1624, 1598, 1498, 1454, 1407, 1338, 1291, 1256, 1214, 1153, 1117, 1082, 1005, 836, 777, 753, 697; FABHRMS (PEG-600): m/z 720.3226 (M^+ , C₄₂H₄₈N₂O₇Si requires 720.3231); $[\alpha]_D^{25}$ = +160° (c 1.11, CHCl₃).

^a Transferred in a plastic bag filled with argon to prevent rapid absorption of moisture.

(2*R*,8*S*)-4-Benzoyloxy-8-(*tert*-butyldimethylsilyloxy)-2-methyl-1-oxo-1,2,3,6,7,8-hexahydro-3,6-diaza-*as*-indacene-2,3,6-tricarboxylic acid 3-benzyl ester 2-methyl ester 6-(2,2,2-trichloroethyl) ester (42). A 10-mL Pyrex tube with a screw cap was charged with **10** (139 mg, 193 μmol), sodium bicarbonate (32.4 mg, 386 μmol) and dry acetonitrile (2 mL). The tube was purged with argon and 2,2,2-trichloroethyl chloroformate (53 μL , 386 μmol) was added. The tube was capped and heated to 70 $^\circ\text{C}$ for 2 h, after which time TLC (2:1 CH_2Cl_2 -Hex, developed twice) indicated complete consumption of the starting material. The reaction mixture was concentrated under reduced pressure and the resulting residue was directly purified by flash column chromatography (15% EtOAc-Hex) to give **42** (108 mg, 136 μmol , 70%) as a colorless film.

^1H NMR (400 MHz, CDCl_3): δ 8.06 (s, 1H), 7.50 (d, $J = 7.6$ Hz, 1H), 7.46-7.32 (m, 9H), 5.25-5.12 (m, 3H), 5.06 (d, $J = 12.0$ Hz, 1H), 4.93 (d, $J = 12.0$ Hz, 1H), 4.80 (d, $J = 12.0$ Hz, 1H), 4.36 (td, $J = 11.2, 2.8$ Hz, 1H), 4.15-4.69 (m, 1H), 3.85 (dd, $J = 10.0, 3.6$ Hz, 1H), 3.81-3.75 (m, 1H), 3.73-3.67 (m, 1H), 3.45 (s, 3H), 1.77 (s, 3H), 0.74 (s, 9H), -0.05 (s, 3H), -0.20 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3): δ 195.0, 166.9, 151.4, 148.9, 141.8, 138.9, 136.3, 135.4, 128.60, 128.57, 128.51, 128.3, 128.0, 127.7, 127.5, 127.4, 120.4, 109.7, 74.7, 71.7, 68.1, 63.6, 53.0, 52.1, 41.4, 25.6, 20.6, 17.9, -5.4 , -5.7 ; IR (neat): 2953, 2863, 1751, 1717, 1505, 1436, 1387, 1324, 1257, 1210, 1159, 1138, 1066, 837, 785, 753, 698; FABHRMS (PEG-600): m/z 804.1824 (M^+ , $\text{C}_{38}\text{H}_{43}\text{Cl}_3\text{N}_2\text{O}_9\text{Si}$ requires 804.1803); $[\alpha]_{\text{D}}^{25} = +103^\circ$ (c 0.29, CHCl_3).

(2*R*,8*S*)-4-Benzoyloxy-8-(*tert*-butyldimethylsilyloxymethyl)-2-methyl-1-oxo-1,2,3,6,7,8-hexahydro-3,6-diaza-*as*-indacene-2,3-dicarboxylic acid 3-benzyl ester 2-methyl ester (11**).** A 10-mL test tube was charged with **42** (108 mg, 136 μmol), tetrahydrofuran (400 μL), zinc powder (267 mg, 4.08 mmol) and 1 M aqueous potassium dihydrogen phosphate (80 μL). The suspension was stirred vigorously at room temperature for 1 h, after which time TLC (25% EtOAc-Hex) indicated complete consumption of the starting material. The reaction mixture was diluted with ethyl acetate, filtered through a pad of Celite[®], washed with saturated aqueous sodium bicarbonate, brine and dried over sodium sulfate. Removal of the solvent followed by flash column chromatography (15~20% EtOAc-Hex) gave **11** (59.5 mg, 94.2 μmol , 69%) as a yellow solid.

¹H NMR (400 MHz, CDCl₃): δ 7.45 (d, J = 7.2 Hz, 2H), 7.37-7.29 (m, 8H), 6.61 (s, 1H), 5.21 (d, J = 12.4 Hz, 1H), 5.14 (d, J = 12.4 Hz, 1H), 5.09 (d, J = 5.2 Hz, 1H), 5.06 (d, J = 5.2 Hz, 1H), 3.82 (dd, J = 9.6, 4.0 Hz, 1H), 3.77-3.69 (m, 2H), 3.64-3.59 (m, 1H), 3.54 (dd, J = 9.6, 8.4 Hz, 1H), 3.41 (s, 3H), 1.76 (s, 3H), 0.83 (s, 9H), 0.03 (s, 3H), -0.04 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 195.2, 167.4, 151.7, 149.1, 136.8, 135.6, 135.3, 128.6, 128.54, 128.52, 128.3, 127.9, 127.2, 121.2, 119.3, 105.6, 74.5, 71.7, 67.9, 63.0, 52.9, 50.5, 44.2, 25.8, 20.7, 18.2, -5.2, -5.4; IR (neat): 3392 (br), 2953, 2857, 1761, 1743, 1734, 1713, 1623, 1505, 1456, 1404, 1387, 1338, 1290, 1213, 1155, 1117, 1084, 1028, 836, 777, 740, 698, 560; FABHRMS (PEG-600): m/z 630.2767 (M⁺, C₃₅H₄₂N₂O₇Si requires 630.2761); $[\alpha]_{\text{D}}^{25}$ = +166° (c 0.26, CHCl₃).

2-Bromo-3,4,5-trimethoxybenzaldehyde (15). A 500-mL round-bottom flask was charged with 3,4,5-trimethoxybenzaldehyde (7.00 g, 35.7 mmol), methylene chloride (150 mL) and acetic acid (200 μL). The flask was cooled to $0\text{ }^\circ\text{C}$ in an ice-bath and bromine (1.84 mL, 35.7 mmol) in methylene chloride (10 mL) was added dropwise *via* addition funnel over 15 min. After stirring at $0\text{ }^\circ\text{C}$ for 30 min, aqueous sodium thiosulfate was added and the mixture was extracted three times with methylene chloride. The combined organic layers were washed with saturated aqueous sodium bicarbonate, brine and dried over sodium sulfate. Removal of the solvent under reduced pressure gave a solid, which was recrystallized (EtOAc-Hex) to give **15** (8.55 g, 31.1 mmol, 87%) as colorless needles: $67.5\text{--}69.2\text{ }^\circ\text{C}$.

^1H NMR (400 MHz, CDCl_3): δ 10.31 (d, $J = 4.8\text{ Hz}$, 1H), 7.31 (s, 1H), 3.99 (s, 3H), 3.920 (s, 3H), 3.915 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 191.0, 153.0, 150.8, 148.7, 128.8, 115.6, 107.4, 61.2, 61.1, 56.2; IR (KBr disk): 3003, 2981, 2944, 2867, 1690, 1579, 1564, 1481, 1452, 1428, 1405, 1385, 1331, 1286, 1246, 1199, 1166, 1107, 1045, 1006, 981, 922, 860, 818, 775, 728, 646, 586; Anal. Calcd. for $\text{C}_{10}\text{H}_{11}\text{BrO}_4$: C, 43.66; H, 4.03; N, 0.00; Found: C, 43.61; H, 4.10; N, 0.00.

2-Benzyloxycarbonylamino-3-(2-bromo-3,4,5-trimethoxyphenyl)acrylic acid methyl ester (17). A 300-mL round-bottom flask was charged with **15** (3.54 g, 12.8 mmol), *N*-benzyloxycarbonyl-dimethoxyphosphoryl-glycine methyl ester^a (4.52 g, 13.6 mmol) and methylene chloride (75 mL). The flask was cooled to 0 °C in an ice-bath and 1,1,3,3-tetramethylguanidine (1.92 mL, 15.4 mmol) was added, giving a pale yellow solution. The reaction mixture was warmed to room temperature and stirred for three days, after which time TLC (25% EtOAc-Hex) indicated complete consumption of the starting material. To the solution was added 1 *N* aqueous hydrochloric acid, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium bicarbonate, brine and dried over sodium sulfate. The solvent was removed under reduced pressure. Recrystallization from chloroform gave **17** (5.95 g, 12.4 mmol, 97%) as a colorless amorphous solid: m.p. 119.5-120.8 °C.

¹H NMR (400 MHz, CDCl₃): δ 7.43 (s, 1H), 7.33-7.29 (m, 5H), 6.89 (s, 1H), 6.44 (s, 1H), 5.09 (s, 2H), 3.89 (s, 3H), 3.87 (s, 3H), 3.85 (s, 3H), 3.57 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 165.3, 153.7, 152.4, 151.0, 143.6, 135.8, 129.40, 129.35, 128.5, 128.41, 128.35, 125.5, 111.9, 108.1, 67.5, 61.1, 61.0, 55.8, 52.9; IR (neat): 3310 (br), 2941, 2850, 1723, 1643, 1559, 1480, 1391, 1334, 1255, 1139, 1107, 1055, 926, 824; Anal. Calcd. for C₂₁H₂₂BrNO₇: C, 52.51; H, 4.62; N, 2.92; Found: C, 52.32; H, 4.62; N, 2.81.

^a Schmidt, U.; Lieberknecht, A.; Wild, J. *Synthesis* **1984**, 53.

1-Benzyloxycarbonyl-5,6,7-trimethoxy-1H-indole-2-carboxylic acid methyl ester (18).

A 20-mL round-bottom flask was charged with **17** (1.02 g, 2.13 mmol), cuprous iodide (606 mg, 3.18 mmol) and cesium acetate^a (2.73 g, 14.2 mmol). The flask was evacuated then backfilled with argon. Freshly degassed dry dimethyl sulfoxide (5 mL) was added and the resulting yellow solution was stirred under argon atmosphere (balloon) for 24 h, after which time TLC (25% EtOAc-Hex) indicated complete consumption of the starting material. The reaction mixture was poured into dilute aqueous ammonium hydroxide solution and extracted twice with ethyl acetate. The combined organic layers were washed with water, brine and dried over sodium sulfate. Upon removal of the solvent, analytically pure **18** (830 mg, 2.08 mmol, 98%) was obtained as colorless crystals. Further purification was possible by recrystallization from methanol: m.p. 101.0-103.1 °C.

¹H NMR (400 MHz, CDCl₃): δ 7.50-7.48 (m, 2H), 7.41-7.35 (m, 3H), 7.12 (s, 1H), 6.80 (s, 1H), 5.47 (s, 2H), 3.91 (s, 3H), 3.89 (s, 3H), 3.85 (s, 3H), 3.82 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 160.8, 152.6, 150.6, 142.0, 139.6, 134.2, 128.7, 128.5, 128.3, 127.4, 126.4, 122.4, 111.8, 98.0, 70.6, 61.0, 55.9, 51.8; IR (neat): 2941, 2834, 1769, 1715, 1576, 1541, 1487, 1460, 1428, 1382, 1235, 1160, 1123, 1076, 1057, 998, 995, 909, 841, 755, 699; Anal. Calcd. for C₂₁H₂₁NO₇: C, 63.15; H, 5.30; N, 3.51; Found: C, 62.86; H, 5.33; N, 3.38.

^a Transferred in a plastic bag filled with argon to prevent rapid absorption of moisture.

5,6,7-Trimethoxy-1*H*-indole-2-carboxylic acid methyl ester (43). A 200-mL round-bottom flask was charged with **18** (3.26 g, 8.17 mmol), 2.5% palladium on charcoal^a (4.0 g), ethyl acetate (40 mL) and ethanol (10 mL). The flask was then purged with hydrogen gas (balloon) and stirred at room temperature for 3 h, after which time TLC (25% EtOAc-Hex) indicated complete consumption of the starting material. The mixture was filtered through a pad of Celite[®] with aid of ethyl acetate. Removal of the solvent under reduced pressure provided analytically pure **43** (2.14 g, 8.08 mmol, 99%) as a colorless amorphous solid. Recrystallization (EtOAc-Hex) afforded fine colorless needles: m.p. 105.8-106.3 °C.

¹H NMR (400 MHz, CDCl₃): δ 8.90 (s, 1H), 7.10 (d, *J* = 2.4 Hz, 1H), 6.82 (s, 1H), 4.07 (s, 3H), 3.930 (s, 3H), 3.926 (s, 3H), 3.90 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 162.2, 150.2, 140.6, 138.9, 126.9, 126.6, 123.1, 108.9, 97.8, 61.5, 61.1, 56.3, 51.9; IR (KBr disk): 3319, 2945, 2838, 1711, 1578, 1534, 1499, 1468, 1437, 1352, 1301, 1255, 1232, 1197, 1146, 1113, 1092, 1041, 998, 952, 931, 898, 845, 769, 758; Anal. Calcd. for C₁₃H₁₅NO₅: C, 58.86; H, 5.70; N, 5.28; Found: C, 58.59; H, 5.76; N, 5.19.

^a Purchased from Kawaken Fine Chemicals Co., Ltd. Type: PH (wet).

5,6,7-Trimethoxy-1*H*-indole-2-carboxylic acid (44).^a To a solution of **43** (1.57 g, 5.92 mmol) in methanol (30 mL) was added 3 *N* aqueous potassium hydroxide (10 mL). The solution was heated to reflux for 1 h, after which time TLC (5:4:1 toluene-HCO₂Et-HCO₂H) indicated complete consumption of the starting material. The mixture was concentrated, poured into 1 *N* aqueous hydrochloric acid, extracted three times with ethyl acetate, washed with brine and dried over sodium sulfate. Removal of the solvent followed by recrystallization (EtOAc only) gave **44** (1.52 g, 5.25 mmol, 89%) as fine colorless needles: m.p. 224.3-226.5 °C.

¹H NMR (400 MHz, *d*₆-DMSO): δ 12.73 (s, 1H), 11.56 (s, 1H), 7.00 (s, 1H), 6.89 (s, 1H), 3.88 (s, 3H), 3.77 (s, 3H), 3.76 (s, 3H); ¹³C NMR (100 MHz, *d*₆-DMSO): δ 162.5, 149.2, 140.2, 139.3, 128.5, 126.7, 123.0, 108.3, 98.0, 61.1, 60.9, 55.9; IR (KBr disk): 3281, 2994, 2933, 2837, 1653, 1539, 1504, 1442, 1429, 1405, 1374, 1341, 1305, 1263, 1230, 1197, 1150, 1110, 1090, 1040, 993, 908, 841, 777, 764; Anal. Calcd. for C₁₂H₁₃NO₅: C, 57.37; H, 5.22; N, 5.48; Found: C, 57.20; H, 5.38; N, 5.48.

^a Fukuda, Y.; Nakatani, K.; Ito, Y.; Terashima, S. *Tetrahedron Lett.* **1990**, *31*, 6699.

5,6,7-Trimethoxy-1H-indole-2-carbonyl chloride (12). To a suspension of **44** (95.6 mg, 381 μmol) in dry toluene (1.3 mL) was added thionyl chloride (140 μL , 1.90 mmol) followed by *N,N*-dimethylformamide (4 μL). The solution was warmed to $70\text{ }^\circ\text{C}$ for 20 min. The reaction mixture was concentrated under reduced pressure to give crude **12** (115 mg, quant.) as a pale yellow solid.

(2*R*,8*S*)-4-Benzoyloxy-8-(*tert*-butyldimethylsilyloxymethyl)-2-methyl-1-oxo-6-(5,6,7-trimethoxy-1*H*-indole-2-carbonyl)-1,2,3,6,7,8-hexahydro-3,6-diaza-*as*-indacene-2,3-dicarboxylic acid 3-benzyl ester 2-methyl ester (45). A 10-mL test tube was charged with **11** (55.6 mg, 88.1 μ mol) and dry methylene chloride (600 μ L). The tube was cooled to 0 °C in an ice-bath and pyridine (14 μ L, 176 μ mol) was added, followed by **12** (35.7 mg, 132 μ mol) in dry methylene chloride (300 μ L). TLC (25% EtOAc-Hex) indicated complete consumption of the starting material after 10 min. 1 *N* Aqueous hydrochloric acid was added and the mixture was extracted with methylene chloride. The organic phase was washed with saturated aqueous sodium bicarbonate, brine and dried over sodium sulfate. The solvent was removed under reduced pressure. Flash column chromatography using disposable Pasteur pipette (CH₂Cl₂ only) afforded **45** (68.5 mg, 79.3 μ mol, 90%) as a yellow solid.

¹H NMR (400 MHz, CDCl₃): δ 9.39 (s, 1H), 8.63 (s, 1H), 7.52 (d, *J* = 7.2 Hz, 2H), 7.40-7.33 (m, 8H), 6.97 (d, *J* = 2.0 Hz, 1H), 6.86 (s, 1H), 5.28 (d, *J* = 12.4 Hz, 1H), 5.22 (dd, *J* = 11.6, 6.0 Hz, 2H), 5.07 (d, *J* = 12.4 Hz, 1H), 4.72 (dd, *J* = 10.0, 2.4 Hz, 1H), 4.49 (t, *J* = 10.0 Hz, 1H), 4.08 (s, 3H), 3.98-3.90 (m, 2H), 3.95 (s, 3H), 3.92 (s, 3H), 3.73-3.67 (m, 1H), 3.46 (s, 3H), 1.80 (s, 3H), 0.74 (s, 9H), -0.07 (s, 3H), -0.18 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 195.0, 167.0, 160.1, 151.4, 150.2, 148.5, 143.3, 140.6, 139.4, 138.9, 136.4, 135.4, 129.8, 128.62, 128.57, 128.52, 128.4, 128.0, 127.6, 125.6, 123.7, 122.6, 119.9, 112.3, 106.5, 97.7, 74.8, 71.7, 68.2, 63.7, 61.5, 61.1, 56.3, 54.2, 53.0, 42.6, 25.7, 20.6, 18.0, -5.4, -5.6; IR (neat): 3272 (br), 2953, 2928, 2857, 1765, 1716, 1627, 1558, 1525, 1495, 1464, 1423, 1387, 1311, 1220, 1165, 1114, 837, 777, 750, 698; FABHRMS (PEG-600): *m/z* 863.3442 (M⁺, C₄₇H₅₃N₃O₁₁Si requires 863.3449); $[\alpha]_D^{25}$ = +113° (c 0.88, CHCl₃).

(2*R*,8*S*)-4-Benzoyloxy-8-hydroxymethyl-2-methyl-1-oxo-6-(5,6,7-trimethoxy-1*H*-indole-2-carbonyl)-1,2,3,6,7,8-hexahydro-3,6-diaza-*as*-indacene-2,3-dicarboxylic acid 3-benzyl ester 2-methyl ester (46). To a solution of **45** (56.4 mg, 65.3 μmol) in dry tetrahydrofuran (550 μL) was added 1 M tetrabutylammonium fluoride in tetrahydrofuran (98 μL , 98 μmol). After stirring at room temperature for 30 min, TLC (50% EtOAc-Hex) indicated complete consumption of the starting material. The reaction mixture was diluted with ethyl acetate and washed with saturated aqueous ammonium chloride. The aqueous phase was extracted with ethyl acetate and the combined organic layers were washed with brine then dried over sodium sulfate. Removal of the solvent followed by preparative TLC (50% EtOAc-Hex) gave **46** (37.2 mg, 49.6 μmol , 76%) as a yellow solid.

^1H NMR (400 MHz, CDCl_3): δ 9.39 (s, 1H), 8.62 (s, 1H), 7.51 (d, $J = 6.8$ Hz, 2H), 7.40-7.33 (m, 8H), 6.98 (d, $J = 2.4$ Hz, 1H), 6.83 (s, 1H), 5.28-5.19 (m, 3H), 5.10 (d, $J = 12.9$ Hz, 1H), 4.65 (dd, $J = 10.5, 3.2$ Hz, 1H), 4.56 (t, $J = 10.3$ Hz, 1H), 4.07 (s, 3H), 3.98-3.92 (m, 2H), 3.94 (s, 3H), 3.90 (s, 3H), 3.76-3.68 (m, 1H), 3.47 (s, 3H), 1.80 (s, 3H), 1.64 (br s, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 195.6, 166.8, 160.3, 151.3, 150.2, 148.7, 142.9, 140.6, 139.7, 138.8, 136.2, 135.2, 129.4, 128.57, 128.55, 128.51, 128.4, 128.0, 127.6, 125.6, 123.6, 121.6, 119.9, 112.2, 106.8, 97.6, 74.8, 71.5, 68.2, 64.3, 61.5, 61.1, 56.2, 54.4, 53.1, 42.7, 20.6; IR (neat): 3466 (br), 3257 (br), 2944, 2837, 1764, 1717, 1623, 1494, 1426, 1390, 1310, 1216, 1165, 1119, 1075, 1044, 991, 887, 830, 748, 701; FABHRMS (PEG-600): m/z 749.2591 (M^+ , $\text{C}_{41}\text{H}_{39}\text{N}_3\text{O}_{11}$ requires 749.2585); $[\alpha]_{\text{D}}^{25} = +145^\circ$ (c 0.99, CHCl_3).

(2*R*,8*S*)-4-Benzoyloxy-8-methanesulfonyloxymethyl-2-methyl-1-oxo-6-(5,6,7-trimethoxy-1*H*-indole-2-carbonyl)-1,2,3,6,7,8-hexahydro-3,6-diaza-*as*-indacene-2,3-dicarboxylic acid 3-benzyl ester 2-methyl ester (47**).** To a solution of **46** (36.8 mg, 49.1 μmol) in pyridine (250 μL) was added methanesulfonyl chloride (5.6 mg, 49.1 μmol). After stirring at room temperature for 10 min, TLC (50% EtOAc-Hex then 100% CH_2Cl_2) indicated complete consumption of the starting material. The reaction mixture was concentrated under reduced pressure and the resulting residue was taken up in ethyl acetate, washed three times with 1 *N* aqueous hydrochloric acid, once with saturated aqueous sodium bicarbonate, brine and dried over sodium sulfate. The solvent was removed under reduced pressure and the resulting solid was passed through a short plug of silica with 1% MeOH- CH_2Cl_2 to give **47** (35.7 mg, 43.1 μmol , 88%) as a yellow solid.

^1H NMR (400 MHz, CDCl_3): δ 9.31 (s, 1H), 8.51 (s, 1H), 7.44 (d, $J = 7.1$ Hz, 2H), 7.33-7.24 (m, 8H), 6.90 (d, $J = 2.2$ Hz, 1H), 6.79 (s, 1H), 5.21 (d, $J = 11.2$ Hz, 2H), 5.15 (d, $J = 12.4$ Hz, 1H), 5.01 (d, $J = 12.4$ Hz, 1H), 4.61 (dd, $J = 10.8, 3.6$ Hz, 1H), 4.56-4.52 (m, 2H), 4.26 (dd, $J = 10.0, 8.4$ Hz, 1H), 4.15-4.09 (m, 1H), 4.00 (s, 3H), 3.87 (s, 3H), 3.84 (s, 3H), 3.39 (s, 3H), 2.90 (s, 3H), 1.74 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 195.2, 166.6, 160.3, 151.2, 150.3, 149.3, 143.1, 140.7, 140.0, 138.8, 136.0, 135.2, 129.0, 128.59, 128.55, 128.53, 128.47, 128.1, 127.6, 125.7, 123.6, 119.9, 118.0, 112.1, 107.0, 97.7, 74.9, 71.5, 69.5, 68.2, 61.4, 61.1, 56.2, 53.9, 53.1, 39.8, 37.2, 20.6; IR (neat): 2936, 2850, 1760, 1714, 1628, 1495, 1494, 1456, 1423, 1394, 1340, 1309, 1220, 1173, 1112, 1071, 1044, 978, 953, 845, 748, 699; FABHRMS (PEG-600): m/z 827.2346 (M^+ , $\text{C}_{42}\text{H}_{41}\text{N}_3\text{O}_{13}\text{S}$ requires 827.2360); $[\alpha]_{\text{D}}^{25} = +102^\circ$ (c 1.26, CHCl_3).

(2*R*,8*S*)-4-Hydroxy-8-methanesulfonyloxymethyl-2-methyl-1-oxo-6-(5,6,7-trimethoxy-1*H*-indole-2-carbonyl)-1,2,3,6,7,8-hexahydro-3,6-diaza-*as*-indacene-2-carboxylic acid methyl ester (13**).^a** A 10-mL test tube was charged with **47** (34.2 mg, 41.3 μmol) and 10% palladium on charcoal^b (ca. 10 mg). After purging the tube with argon, ethyl acetate (300 μL) and ethanol (200 μL) were added. The tube was then purged with gaseous hydrogen (balloon) and stirred at room temperature for 8 h, after which time TLC (80% EtOAc-Hex) indicated complete consumption of the starting material. The reaction mixture was filtered through a pad of Celite[®] with aid of methylene chloride and the solvent was removed under reduced pressure to afford **13** (21.6 mg, 35.8 μmol , 87%) as a yellow film.

¹H NMR (400 MHz, CDCl_3): δ 9.58 (s, 1H), 8.51 (s, 1H), 6.97 (s, 1H), 6.82 (s, 1H), 5.58 (s, 1H), 4.77 (dd, $J = 10.4, 3.6$ Hz, 1H), 4.58 (d, $J = 6.8$ Hz, 2H), 4.37 (t, $J = 9.2$ Hz, 1H), 4.10 (s, 3H+1H), 3.95 (s, 3H), 3.91 (s, 3H), 3.68 (s, 3H), 3.02 (s, 3H), 1.68 (s, 3H); ¹³C NMR (100 MHz, CDCl_3): δ 196.5, 168.9, 160.4, 149.9, 143.9, 140.5, 138.2, 137.4, 128.5, 125.6, 123.1, 116.7, 115.2, 112.2, 107.7, 97.5, 70.9, 70.4, 61.2, 60.9, 55.9, 53.9, 53.1, 39.6, 36.7, 29.4, 21.6; IR (neat): 3330 (br), 2927, 2853, 1743, 1695, 1586, 1527, 1504, 1464, 1447, 1430, 1391, 1357, 1308, 1246, 1224, 1197, 1174, 1112, 1049, 952, 878, 849, 826, 795, 745, 574, 528; FABHRMS (PEG-600): m/z 603.1552 ($\text{C}_{27}\text{H}_{29}\text{N}_3\text{O}_{11}\text{S}$ requires 603.1523); $[\alpha]_{\text{D}}^{25} = +90^\circ$ (c 0.65, CHCl_3).

^a Fukuda, Y.; Nakatani, K.; Ito, Y.; Terashima, S. *Tetrahedron Lett.* **1990**, 31, 6699.

^b Purchased from Kawaken Fine Chemicals Co., Ltd. Type: PH (dry).

(+)-Duocarmycin A (1). A 10-mL test tube was charged with **13** (10.7 mg, 17.7 μmol) and cesium carbonate (40 mg, 123 μmol). After adding some dry benzene, the tube was evacuated and backfilled with argon. To the tube was then added dry acetonitrile (1.8 mL, 0.01 M). The resulting pale yellow suspension was stirred at room temperature. After 30 min, TLC (50% EtOAc-Hex) indicated complete consumption of the starting material. The reaction mixture was diluted with ethyl acetate (4 mL) and filtered through a pad of Celite[®]. The filtrate was then washed with 5% aqueous sodium chloride and the aqueous phase was back-extracted with ethyl acetate. The combined organic layers were washed with brine and dried over sodium sulfate. Removal of the solvent under reduced pressure provided analytically pure (+)-duocarmycin A (**1**) (6.9 mg, 13.6 μmol , 77%) as a yellow solid. Further purification was possible by passing through a short plug of silica packed in a disposable Pasteur pipette.

¹H NMR (400 MHz, CDCl₃): δ 9.24 (s, 1H), 7.18 (s, 1H), 6.94 (d, $J = 2.4$ Hz, 1H), 6.78 (s, 1H), 6.03 (s, 1H), 4.45, 4.41 (AB in ABX, $J_{AB} = 10.5$ Hz, $J_{AX} = 4.7$ Hz, $J_{BX} < 1$ Hz, 2H), 4.08 (s, 3H), 3.94 (s, 3H), 3.89 (s, 3H), 3.75 (s, 3H), 3.05 (m, 1H), 2.25 (dd, $J = 7.6, 3.9$ Hz, 1H), 1.67 (s, 3H), 1.29 (t, $J = 4.5$ Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 194.7, 179.7, 167.9, 165.0, 164.3, 161.1, 150.6, 141.3, 138.8, 128.0, 126.6, 123.2, 113.2, 112.2, 108.1, 97.6, 71.0, 61.5, 61.2, 56.3, 55.3, 53.5, 30.6, 22.3, 22.0, 21.2; IR (neat): 3310 (br), 2933, 2851, 1745, 1680, 1631, 1565, 1526, 1492, 1465, 1448, 1385, 1304, 1275, 1200, 1165, 1114, 1049, 955, 906, 890, 865, 826, 752, 715; FABHRMS (PEG-600): m/z 507.1644 (M^+ , C₂₆H₂₅N₃O₉ requires 507.1642); $[\alpha]_D^{25} = +288^\circ$ (c 0.075, MeOH)^a.

^a Lit. $[\alpha]_D^{25} = +282^\circ$ (c 0.1, MeOH): see reference 1.

(Z)-3-[(3S)-1-Benzyl-6-benzyloxy-3-(tert-butyldimethylsilyloxymethyl)-2,3-dihydro-1H-indol-4-yl]-2-benzyloxycarbonylaminoacrylic acid methyl ester (21). A 10-mL Pyrex tube with screw cap was charged with **19** (71.8 mg, 123 μmol), *N*-benzyloxycarbonyl-dehydroalanine methyl ester (**20**)^a (43.2 mg, 184 μmol), palladium acetate (1.4 mg, 6.15 μmol) and tri-*o*-tolylphosphine (5.2 mg, 17.2 μmol). The tube was fitted with a rubber septum and purged with argon. After adding dry acetonitrile (400 μL), the solution was degassed *via* four freeze-pump-thaw cycles. Finally, triethylamine (34 μL , 246 μmol) was added and the rubber septum was exchanged with a screw cap under argon atmosphere. The sealed tube was then heated to 90 $^\circ\text{C}$ for 4 h, after which time TLC (25% EtOAc-Hex) indicated complete consumption of indoline **19**. The reaction mixture was diluted with ethyl acetate, washed with 1 *N* aqueous hydrochloric acid, saturated aqueous sodium bicarbonate, brine and dried over sodium sulfate. The solution was concentrated and the resulting residue was subjected to flash column chromatography (5%~10% EtOAc-Hex) to afford **21** (61.0 mg, 88.0 μmol , 72%) as a yellow solid.

^1H NMR (500 MHz, CDCl_3): δ 7.29-7.20 (m, 15 H), 7.17 (s, 1H), 6.51 (s, 1H), 6.36 (s, 1H), 6.08 (s, 1H), 5.09 (d, $J = 12.5$ Hz, 1H), 5.05 (d, $J = 12.5$ Hz, 1H), 4.82 (s, 2H), 4.32 (d, $J = 16.0$ Hz, 1H), 4.06 (d, $J = 16.0$ Hz, 1H), 3.76 (s, 3H), 3.60-3.57 (m, 1H), 3.50 (d, $J = 9.0$ Hz, 1H), 3.41 (t, $J = 9.5$ Hz, 1H), 3.36-3.31 (m, 1H), 3.26 (t, $J = 8.5$ Hz, 1H), 0.82 (s, 9H), -0.02 (s, 3H), -0.04 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3): δ 165.4, 159.8, 153.8, 137.7, 136.9, 135.7, 130.3, 128.44, 128.39, 128.10, 128.07, 127.8, 127.6, 127.5, 127.1, 126.8, 125.4, 123.6, 100.9, 96.3, 69.9, 67.4, 64.4, 56.1, 52.43, 52.36, 42.5, 25.8, 18.2, -5.4, -5.5; IR (neat): 3340, 2928, 2850, 1718, 1601, 1496, 1454, 1436, 1362, 1340, 1260, 1219, 1176, 1142, 1115, 1083, 1049, 1029, 836, 776, 737, 698; FABHRMS (PEG-600): m/z 692.3274 (M^+ , $\text{C}_{41}\text{H}_{48}\text{N}_2\text{O}_6\text{Si}$ requires 692.3282); $[\alpha]_{\text{D}}^{25} = +61^\circ$ (c 0.35, CHCl_3).

^a Kolar, A. J.; Olsen, R. K *Synthesis* **1977**, 457.

(Z)-3-[(3S)-1-Benzyl-6-benzyloxy-5-bromo-3-(*tert*-butyldimethylsilyloxymethyl)-2,3-dihydro-1*H*-indol-4-yl]-2-benzyloxycarbonylaminoacrylic acid methyl ester (48**).**

To a solution of **21** (142 mg, 205 μmol) in *N,N*-dimethylformamide (400 μL) was added *N*-bromosuccinimide (36.5 mg, 205 μmol) in *N,N*-dimethylformamide (375 μL). The solution was stirred for 5 min, after which time TLC (50% CH_2Cl_2 -Hex) indicated the completion of reaction. The reaction mixture was diluted with ethyl acetate and washed three times with 5% aqueous sodium chloride, once with saturated aqueous sodium bicarbonate, brine and dried over sodium sulfate. Removal of the solvent followed by flash column chromatography (10% EtOAc-Hex) gave **48** (130 mg, 168 μmol , 82%) as a colorless film.

^1H NMR (500 MHz, CDCl_3): δ 7.41-7.23 (m, 15H), 7.03 (s, 1H), 6.28 (s, 1H), 6.05 (s, 1H), 5.05 (d, $J = 8.0$ Hz, 2H), 5.01 (s, 2H), 4.28 (d, $J = 15.0$ Hz, 1H), 4.13 (d, $J = 15.0$ Hz, 1H), 3.82 (s, 3H), 3.55 (dd, $J = 10.0, 4.5$ Hz, 1H), 3.46 (d, $J = 9.0$ Hz, 1H), 3.40 (t, $J = 5.5$ Hz, 1H), 3.22-3.13 (m, 2H), 0.82 (s, 9H), -0.02 (s, 3H), -0.04 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3): δ 164.6, 155.8, 153.3, 152.7, 137.6, 136.7, 135.8, 131.8, 128.6, 128.53, 128.50, 128.34, 128.26, 127.9, 127.6, 127.3, 127.1, 125.8, 121.5, 99.0, 94.1, 71.0, 67.4, 63.7, 56.1, 52.6, 52.4, 43.3, 25.9, 25.7, 18.3, -5.4 , -5.5 ; IR (neat): 2951, 2929, 2855, 1734, 1594, 1453, 1359, 1259, 1219, 1150, 1113, 1082, 836, 778, 737, 697; FABHRMS (PEG-600): m/z 770.2366 (M^+ , $\text{C}_{41}\text{H}_{47}\text{BrN}_2\text{O}_6\text{Si}$ requires 770.2387); $[\alpha]_{\text{D}}^{25} = +27^\circ$ (c 1.03, CHCl_3).

(8S)-4-Benzyloxy-8-(*tert*-butyldimethylsilanyloxymethyl)-3,6,7,8-tetrahydro-3,6-diaza-*as*-indacene-2,3,6-tricarboxylic acid 3-benzyl ester 2-methyl ester 6-(2,2,2-trichloro-ethyl) ester (49). A 10-mL Pyrex tube with a screw cap was charged with **22** (76.8 mg, 111 μmol), sodium bicarbonate (19.0 mg, 222 μmol) and dry acetonitrile (900 μL). The tube was purged with argon and 2,2,2-trichloroethyl chloroformate (47.1 mg, 222 μmol) was added. The tube was capped and heated to 70 $^\circ\text{C}$ for 20 min, after which time TLC (10% EtOAc-Hex, developed four times) indicated complete consumption of the starting material. The reaction mixture was concentrated under reduced pressure and the resulting residue was directly purified by flash column chromatography (8~10% EtOAc-Hex) to give **49** (64.9 mg, 84.9 μmol , 77%) as a colorless film.

^1H NMR (500 MHz, CDCl_3): δ 7.77 (s, 1H), 7.47-7.28 (m, 9H), 7.20-7.18 (m, 2H), 5.15 (s, 2H), 5.00 (s, 2H), 4.91 (d, $J = 12.0$ Hz, 1H), 4.82 (d, $J = 12.0$ Hz, 1H), 4.26-4.16 (m, 2H), 3.92 (dd, $J = 9.5, 5.5$ Hz, 1H), 3.83 (s, 3H), 3.74-3.68 (m, 1H), 3.60 (t, $J = 9.0$ Hz, 1H), 0.87 (s, 9H), 0.04 (s, 3H), -0.02 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 160.9, 152.7, 151.1, 145.8, 137.8, 136.1, 134.3, 128.6, 128.63, 128.58, 128.50, 128.44, 128.42, 124.3, 115.2, 109.6, 97.6, 95.5, 74.7, 71.1, 70.5, 65.5, 52.2, 51.9, 42.4, 29.7, 18.3, -5.3, -5.5; IR (neat): 3033, 2953, 2928, 2856, 1772, 1720, 1597, 1539, 1498, 1456, 1429, 1387, 1329, 1230, 1171, 1137, 1093, 1039, 1006, 836; FABHRMS (PEG-600): m/z 774.1696 (M^+ , $\text{C}_{37}\text{H}_{41}\text{Cl}_3\text{N}_2\text{O}_8\text{Si}$ requires 774.1698); $[\alpha]_{\text{D}}^{25} = -6^\circ$ (c 0.38, CHCl_3).

(8*S*)-4-Benzoyloxy-8-(*tert*-butyldimethylsilanyloxymethyl)-3,6,7,8-tetrahydro-3,6-diaza-*as*-indacene-2,3-dicarboxylic acid 3-benzyl ester 2-methyl ester (23**).** A 10-mL test tube was charged with **49** (64.9 mg, 84.9 μ mol), tetrahydrofuran (1 mL), zinc powder (111 mg, 1.70 mmol) and 1 M aqueous potassium dihydrogen phosphate (200 μ L). The suspension was stirred vigorously at room temperature and TLC (25% EtOAc-Hex then 2x 10% EtOAc-Hex) indicated complete consumption of the starting material after 1 h. The reaction mixture was diluted with ethyl acetate, filtered through a pad of Celite[®], washed with saturated aqueous sodium bicarbonate, brine and dried over sodium sulfate. Removal of the solvent under reduced pressure followed by flash column chromatography (10~20% EtOAc-Hex) gave **23** (29.7 mg, 49.4 μ mol, 58%) as a yellow solid.

¹H NMR (400 MHz, CDCl₃): δ 7.43-7.31 (m, 5H), 7.28-7.20 (m, 5H), 7.12 (s, 1H), 6.39 (s, 1H), 5.03 (s, 2H), 5.02 (s, 2H), 3.89-3.85 (m, 1H), 3.82 (s, 3H), 3.72-3.58 (m, 3H), 3.51-3.48 (m, 1H), 2.70 (br s, 1H), 0.90 (s, 9H), 0.05 (s, 3H), 0.03 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 161.2, 153.1, 147.3, 145.9, 136.5, 134.6, 128.6, 128.4, 128.2, 128.0, 125.4, 123.7, 112.3, 109.8, 95.4, 70.9, 70.3, 65.2, 52.0, 51.0, 45.3, 26.0, 18.4, -5.2, -5.4; IR (neat): 3373 (br), 2953, 2928, 2854, 1771, 1718, 1653, 1539, 1496, 1436, 1387, 1332, 1240, 1165, 1133, 1117, 1096, 835, 777, 751, 739, 697; FABHRMS (PEG-600): m/z 600.2640 (M⁺, C₃₄H₄₀N₂O₆Si requires 600.2656); $[\alpha]_D^{25} = +4^\circ$ (c 0.70, CHCl₃).

(8S)-4-Benzoyloxy-8-(*tert*-butyldimethylsilyloxymethyl)-6-(5,6,7-trimethoxy-1*H*-indole-2-carbonyl)-3,6,7,8-tetrahydro-3,6-diaza-*as*-indacene-2,3-dicarboxylic acid 3-benzyl ester 2-methyl ester (50**).** A 10-mL test tube was charged with **23** (29.7 mg, 49.4 μ mol) and dry methylene chloride (1 mL). The tube was cooled to 0 °C in an ice-bath and pyridine (8 μ L, 98.8 μ mol) was added, followed by **12** (16.0 mg, 59.3 μ mol) in dry methylene chloride (500 μ L). TLC (25% EtOAc-Hex) indicated complete consumption of the starting material after 10 min. 1 *N* Aqueous hydrochloric acid was added and the mixture was extracted with methylene chloride. The organic phase was washed with saturated aqueous sodium bicarbonate, brine and dried over sodium sulfate. Removal of the solvent under reduced pressure followed by flash column chromatography using disposable Pasteur pipette (25% EtOAc-Hex) afforded **50** (34.4 mg, 41.2 μ mol, 83%) as a colorless solid.

^1H NMR (500 MHz, CDCl_3): δ 9.49 (s, 1H), 8.27 (s, 1H), 7.48 (d, $J = 7.5$ Hz, 2H), 7.40-7.32 (m, 2H), 7.29-7.25 (m, 4H), 7.21-7.19 (m, 3H), 6.93 (s, 1H), 6.85 (s, 1H), 5.18 (s, 2H), 5.01 (s, 2H), 4.59 (t, $J = 9.5$ Hz, 1H), 4.52 (dd, $J = 10.5, 2.4$ Hz, 1H), 4.14-4.08 (m, 1H), 4.06 (s, 3H), 3.98-3.89 (m, 1H), 3.94 (s, 3H), 3.91 (s, 3H), 3.83 (s, 3H), 3.64 (t, $J = 9.0$ Hz, 1H), 0.86 (s, 9H), 0.02 (s, 3H), -0.04 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3): δ 160.9, 159.9, 152.6, 150.1, 145.3, 140.4, 139.5, 138.9, 136.2, 134.3, 130.4, 128.63, 128.56, 128.50, 128.44, 128.35, 125.6, 125.4, 123.8, 116.2, 109.7, 106.1, 100.2, 97.8, 71.1, 70.5, 65.5, 61.5, 61.1, 56.3, 54.2, 52.2, 43.6, 29.7, 25.9, 18.3, -5.3 , -5.5 ; IR (neat): 2952, 2929, 2855, 1772, 1718, 1612, 1527, 1495, 1464, 1419, 1387, 1312, 1228, 1172, 1112, 1051, 1004, 836, 752, 697; FABHRMS (PEG-600): m/z 833.3356 (M^+ , $\text{C}_{46}\text{H}_{51}\text{N}_3\text{O}_{10}\text{Si}$ requires 833.3344); $[\alpha]_{\text{D}}^{25} = +14^\circ$ (c 0.83, CHCl_3).

(8S)-4-Benzoyloxy-8-hydroxymethyl-6-(5,6,7-trimethoxy-1*H*-indole-2-carbonyl)-3,6,7,8-tetrahydro-3,6-diaza-*as*-indacene-2,3-dicarboxylic acid 3-benzyl ester 2-methyl ester (51**).** To a solution of **50** (34.4 mg, 41.2 μmol) in dry tetrahydrofuran (500 μL) was added 1 M tetrabutylammonium fluoride in tetrahydrofuran (49.5 μL , 49.5 μmol). After stirring at room temperature for 30 min, TLC (50% EtOAc-Hex) indicated complete consumption of the starting material. The reaction mixture was diluted with ethyl acetate and washed with saturated aqueous ammonium chloride. The aqueous phase was extracted with ethyl acetate and the combined organic layers were washed with brine then dried over sodium sulfate. Removal of the solvent under reduced pressure followed by preparative TLC (25~60% EtOAc-Hex) gave **51** (25.3 mg, 35.1 μmol , 85%) as a colorless solid.

^1H NMR (500 MHz, CDCl_3): δ 9.48 (s, 1H), 8.23 (s, 1H), 7.45 (d, $J = 7.0$ Hz, 2H), 7.39-7.33 (m, 3H), 7.29-7.28 (m, 3H), 7.20-7.18 (m, 2H), 7.18 (s, 1H), 6.92 (d, $J = 2.5$ Hz, 1H), 6.80 (s, 1H), 5.14 (s, 2H), 5.01 (s, 2H), 4.60 (t, $J = 9.0$ Hz, 1H), 4.53 (dd, $J = 10.5, 3.5$ Hz, 1H), 4.07 (s, 3H), 3.99-3.87 (m, 3H), 3.94 (s, 3H), 3.91 (s, 3H), 3.84 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3): δ 160.8, 159.9, 152.6, 150.1, 145.5, 140.4, 139.84, 138.85, 136.2, 134.3, 130.2, 128.67, 128.57, 128.52, 128.44, 128.43, 128.39, 128.34, 125.6, 125.4, 123.7, 123.5, 115.1, 109.1, 106.4, 100.2, 97.8, 71.1, 70.6, 64.6, 61.5, 61.1, 56.3, 54.1, 52.2, 43.1; IR (neat): 3464 (br), 2937, 1771, 1717, 1611, 1526, 1494, 1439, 1418, 1385, 1311, 1232, 1171, 1137, 1108, 1046, 832, 751, 698; FABHRMS (PEG-600): m/z 719.2485 (M^+ , $\text{C}_{40}\text{H}_{37}\text{N}_3\text{O}_{10}$ requires 719.2479); $[\alpha]_{\text{D}}^{25} = +2^\circ$ (c 0.49, CHCl_3).

4-Benzoyloxy-8-methanesulfonyloxymethyl-6-(5,6,7-trimethoxy-1*H*-indole-2-carbonyl)-3,6,7,8-tetrahydro-3,6-diaza-*as*-indacene-2,3-dicarboxylic acid 3-benzyl ester 2-methyl ester (52**).** To a solution of **51** (11.6 mg, 19.4 μmol) in pyridine (130 μL) was added methanesulfonyl chloride (2.7 mg, 23.3 μmol). After stirring at room temperature for 10 min, TLC (5% MeOH-CH₂Cl₂) indicated complete consumption of the starting material. The reaction mixture was concentrated and the resulting residue was taken up in ethyl acetate, washed three times with 1 *N* aqueous hydrochloric acid, once with saturated aqueous sodium bicarbonate, brine and dried over sodium sulfate. The solvent was removed under reduced pressure and the residue was purified by preparative TLC (MeOH-CH₂Cl₂) to give **52** (10.7 mg, 13.4 μmol , 88%) as a white solid.

¹H NMR (500 MHz, CDCl₃): δ 9.40 (s, 1H), 8.22 (s, 1H), 7.48 (d, *J* = 7.0 Hz, 2H), 7.42-7.34 (m, 3H), 7.30-7.29 (m, 3H), 7.21-7.19 (m, 2H), 7.18 (s, 1H), 6.94 (d, *J* = 2.5 Hz, 1H), 6.87 (s, 1H), 5.18 (d, *J* = 2.5 Hz, 2H), 5.02 (s, 2H), 4.68 (dd, *J* = 11.0, 9.5 Hz, 1H), 4.60-4.55 (m, 2H), 4.23 (dd, *J* = 10.5, 9.0 Hz, 1H), 4.13-4.09 (m, 1H), 4.07 (s, 3H), 3.94 (s, 3H), 3.92 (s, 3H), 3.85 (s, 3H), 2.94 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 160.7, 160.0, 152.4, 150.2, 146.1, 140.6, 139.9, 138.9, 135.9, 134.1, 129.8, 128.9, 128.7, 128.6, 128.5, 125.54, 125.51, 123.6, 123.4, 112.4, 108.3, 106.4, 99.9, 97.7, 71.1, 70.8, 70.0, 61.5, 61.1, 56.3, 53.9, 52.3, 40.7, 37.7; IR (neat): 2942, 1772, 1718, 1616, 1525, 1496, 1419, 1358, 1312, 1233, 1174, 1112, 955, 827, 747, 698; FABHRMS (PEG-600): *m/z* 797.2272 (M⁺, C₄₁H₃₉N₃O₁₂S requires 797.2254); $[\alpha]_{\text{D}}^{25}$ = +8° (c 0.54, MeOH).

(8S)-4-Hydroxy-8-methanesulfonyloxymethyl-6-(5,6,7-trimethoxy-1*H*-indole-2-carbonyl)-3,6,7,8-tetrahydro-3,6-diaza-*as*-indacene-2-carboxylic acid methyl ester (24). A 10-mL test tube was charged with **52** (8.9 mg, 11.2 μmol) and 10% palladium on charcoal^a (*ca.* 20 mg). After purging the tube with argon, ethyl acetate (200 μL) and ethanol (100 μL) were added. The tube was then purged with gaseous hydrogen (balloon) and stirred at room temperature for 10 min, after which time TLC (5% $\text{MeOH-CH}_2\text{Cl}_2$) indicated complete consumption of the starting material. The reaction mixture was filtered through a pad of Celite[®] with aid of methylene chloride and the solvent was removed under reduced pressure to afford **24** (5.2 mg, 9.02 μmol , 81%) as a colorless film.

¹H NMR (400 MHz, CDCl_3): δ 9.57 (s, 1H), 9.33 (s, 1H), 8.28 (s, 1H), 7.24 (s, 1H), 7.13 (d, $J = 2.4$ Hz, 1H), 6.98 (d, $J = 2.4$ Hz, 1H), 6.87 (s, 1H), 4.72-4.67 (m, 1H), 4.64-4.57 (m, 2H), 4.25 (t, $J = 10.0$ Hz, 1H), 4.18 (s, 3H), 4.13-4.08 (m, 1H), 3.97 (s, 3H), 3.96 (s, 3H), 3.93 (s, 3H), 2.94 (s, 3H); ¹³C NMR (100 MHz, CD_3OD): δ 163.6, 162.3, 151.0, 145.5, 141.5, 132.0, 129.7, 127.9, 127.1, 125.6, 125.3, 123.5, 107.8, 107.1, 101.6, 99.3, 72.1, 61.9, 61.7, 56.8, 55.8, 52.3, 48.8, 48.6, 48.4, 41.7, 37.2; IR (neat): 3437 (br), 3355 (br), 3013, 2937, 2847, 1717, 1597, 1527, 1496, 1436, 1391, 1356, 1316, 1259, 1220, 1174, 1110, 1048, 999, 954, 846, 745; FABHRMS (PEG-600): m/z 573.1447 (M^+ , $\text{C}_{26}\text{H}_{27}\text{N}_3\text{O}_{10}\text{S}$ requires 573.1417); $[\alpha]_{\text{D}}^{25} = +4^\circ$ (c 0.25, MeOH).

^a Purchased from Kawaken Fine Chemicals Co., Ltd. Type: PH (dry).

(+)-Duocarmycin SA (2). A 10-mL test tube was charged with **24** (3.4 mg, 5.90 μmol) and cesium carbonate (15.8 mg, 48.5 μmol). After adding some dry benzene, the tube was evacuated and backfilled with argon. To the tube was then added dry acetonitrile (600 μL , 0.01 M) and the resulting colorless suspension was stirred at room temperature. After 1 h, the color had turned to pale yellow and TLC (5% MeOH-CH₂Cl₂) indicated complete consumption of the starting material. The reaction mixture was diluted with ethyl acetate (4 mL) and filtered through a pad of Celite[®]. The filtrate was then washed with 5% aqueous sodium chloride and the aqueous phase was back-extracted with ethyl acetate. The combined organic layers were washed with brine and dried over sodium sulfate. The solvent was removed under reduced pressure. Preparative TLC (5% MeOH-CH₂Cl₂) provided (+)-duocarmycin SA (**2**) (2.6 mg, 5.45 μmol , 92%) as a yellow solid.

¹H NMR (500 MHz, CDCl₃): δ 9.87 (s, 1H), 9.25 (s, 1H), 7.02 (s, 1H), 6.94 (d, J = 2.2 Hz, 1H), 6.78 (s, 1H), 6.61 (d, J = 2.2 Hz, 1H), 4.46 (dd, J = 10.4, 4.9 Hz, 1H), 4.38 (d, J = 10.4 Hz, 1H), 4.08 (s, 3H), 3.94 (s, 3H), 3.91 (s, 3H), 3.89 (s, 3H), 2.80-2.77 (m, 1H), 1.77-1.74 (m, 1H).^a ¹³C NMR (125 MHz, CDCl₃): δ 177.8, 161.5, 161.1, 160.9, 150.5, 141.1, 138.9, 131.6, 129.8, 128.4, 126.7, 126.4, 123.2, 112.6, 107.8, 107.6, 97.7, 61.5, 61.2, 56.3, 54.8, 52.1, 31.3, 25.9, 23.5; IR (neat): 3249 (br), 3002, 2937, 2848, 1633, 1520, 1492, 1465, 1428, 1387, 1303, 1265, 1206, 1140, 1109, 1048, 1001, 941, 862; FABHRMS (PEG-600): m/z 477.1534 (M⁺, C₂₅H₂₃N₃O₇ requires 477.1536); $[\alpha]_{\text{D}}^{25}$ = +178° (c 0.03, MeOH).^b

^a A peak corresponding to proton on the cyclopropane (lit. 1.54 ppm) was obscured by H₂O peak (1.56 ppm).

^b Lit. $[\alpha]_{\text{D}}^{25}$ = +180° (c 0.1, MeOH): see reference 2.