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Synthesis of the First Photo-Triggered Pro-mitosene Based on FR-900482

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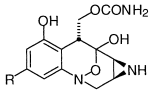
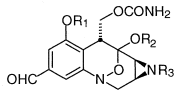
Abstract—A stereocontrolled synthesis of an eight-membered ring precursor to a photo-triggered mitosene is described.

Introduction

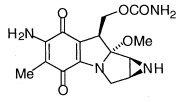
FR-900482 (**1**), and FR-66979 (**2**) are anti-tumor antibiotics that were obtained from the fermentation harvest of *Streptomyces sandaensis* No. 6897 at the Fujisawa Pharmaceutical Co. in Japan.[1–3] The triacetate derivative FK-973 (**3**)[4] and the recently disclosed drug candidate FK-317 (**4**),[5] both semi-synthetically derived from FR-900482, have shown highly promising anti-tumor activity in human clinical trials. FK-317, now in phase II clinical trials holds considerable promise to replace the structurally related and widely used anti-tumor drug mitomycin C (MMC, **6**).[2] In initial phase I clinical trials, patients treated with FK-973 exhibited vascular leak syndrome and this substance was subsequently withdrawn from clinical development. FK-317, on the other hand, was found not to induce vascular leak syndrome in patients and recently passed phase I clinical trials.[5]



1, FR-900482, R = CHO
2, FR-66979, R = CH_2OH



3, FK-973, R_1= R_2 = R_3 = Ac
4, FK-317, R_1 = Me, R_2 = R_3 = Ac
5, FR-70496, R_1 = Me, R_2 = OH, R_3 = Ac



6, mitomycin C (MMC)

Previous reports from the Fujisawa group have shown that FK-973 forms DNA–DNA interstrand cross-links and DNA–protein cross links in L1210 cells.[6] Similarly, FK-317 was shown to lead to the formation of DNA–DNA and DNA–protein cross-links in human non-small cell lung cancer cells (A549) and human colon cancer cells (SW-480 and SW-620) but requires deacetylation in vivo and in vitro to FR-70496 (**5**), for the expression of biochemical and cytotoxic activity.[5] In contrast to mitomycin C, FK-973 and FK-317 do not cause oxidative single strand scission of DNA.[6–9] The Fujisawa drugs have been shown to be a significantly less host toxic than mitomycin C and are approximately three-fold more potent. In addition, FK-317 has recently been shown to be more cytotoxic than adriamycin and *cis*-platin, drugs that are frequently used in the clinic.

It is well established that MMC is reductively activated to provide an electrophilic mitosene via the in situ bioreductive formation of a semi-quinone radical anion.[9] Non-specific oxidative damage to DNA and other cellular macromolecules mediated by MMC is a manifestation of superoxide production resulting from the reduction of molecular oxygen by the semi-quinone radical anion intermediates; subsequent Haber–Weiss/Fenton cycling produces hydroxyl radical and related highly reactive and diffusable oxidants capable of causing non-selective tissue damage.[10] The relatively low host toxicity of FK-973 and FK-317 in clinical trials relative to MMC may be correlated to the incapacity of these agents to cause indiscriminate oxidative damage to DNA and other healthy cellular targets. Since FK-973 and MMC both share the ability to cross-link DNA, it is very clear that the lack of oxidation chemistry inherent in FK-973 has not at all compromised its efficacy as an anti-tumor drug relative to MMC.

It has been demonstrated that FR-900482 (and by analogy, FR-66979, FK-973 and FK-317) undergo reductive activation in vitro to form the reactive mitosene derivative **9** (Scheme 1) which preferentially cross-links duplex DNA at $^{5'}CpG^{3'}$ steps.[7,8] The mechanism of reductive activation involves the thiol-mediated two-electron reduction of the N–O bond[11] in the presence of trace Fe(II) salts[8c] generating the transient ketone **7** which rapidly cyclizes to the

Keywords: mitosene; photochemical trigger; aziridine; FR-900482; anti-tumor antibiotic.

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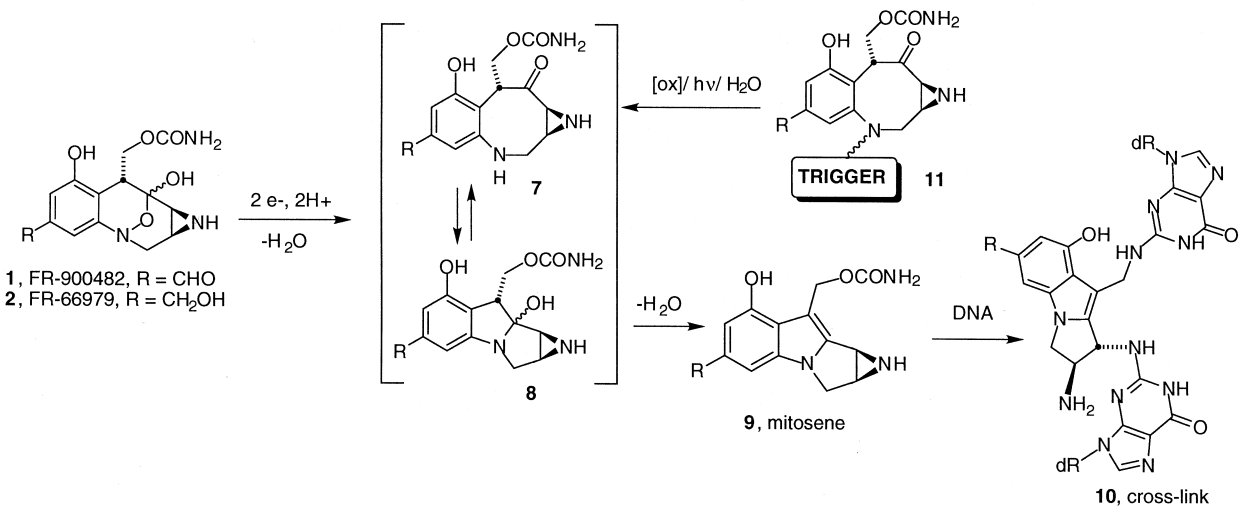


Scheme 1.

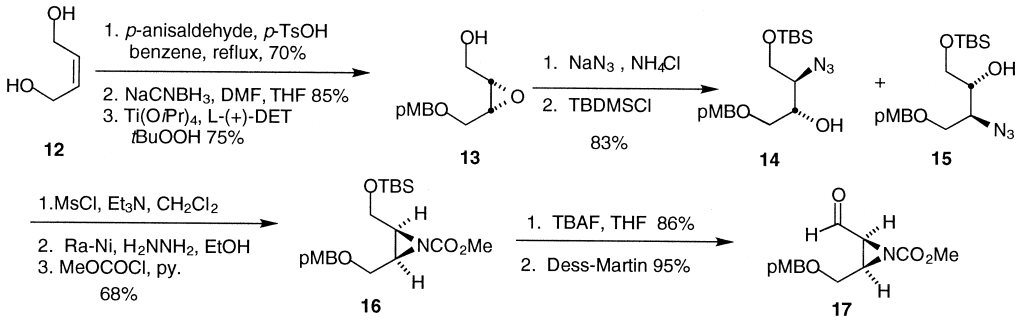
carbinolamines **8**. Expulsion of water has been inferred as the rate-determining step *enroute* to the electrophilic mitosene.[8d]

It can thus be seen that MMC, FR-900482 and congeners are actually naturally occurring clever 'pro-drugs' that must be reductively activated in vivo to expose the highly reactive electrophilic mitosene derivatives that are responsible for the biological activity displayed by these substances.[10] Our objectives in this area are aimed at exploiting the concept of latent triggering of pro-mitosenes by designing and synthesizing new masked mitosenes of the general structure **11** that can be triggered by alternative chemical and/or biochemical means. The ultimate goals of these strategies are to improve the tumor selectivity of such agents. Since many anti-tumor drugs display multiple modes of action such as, intercalation, oxidative scission of double- and single-stranded DNA, cross-linking, alkylation and membrane effects amongst others, the issue of chemical and biological selectivity is of paramount, fundamental importance to provide the next generation of highly effective and selective anti-tumor drugs.

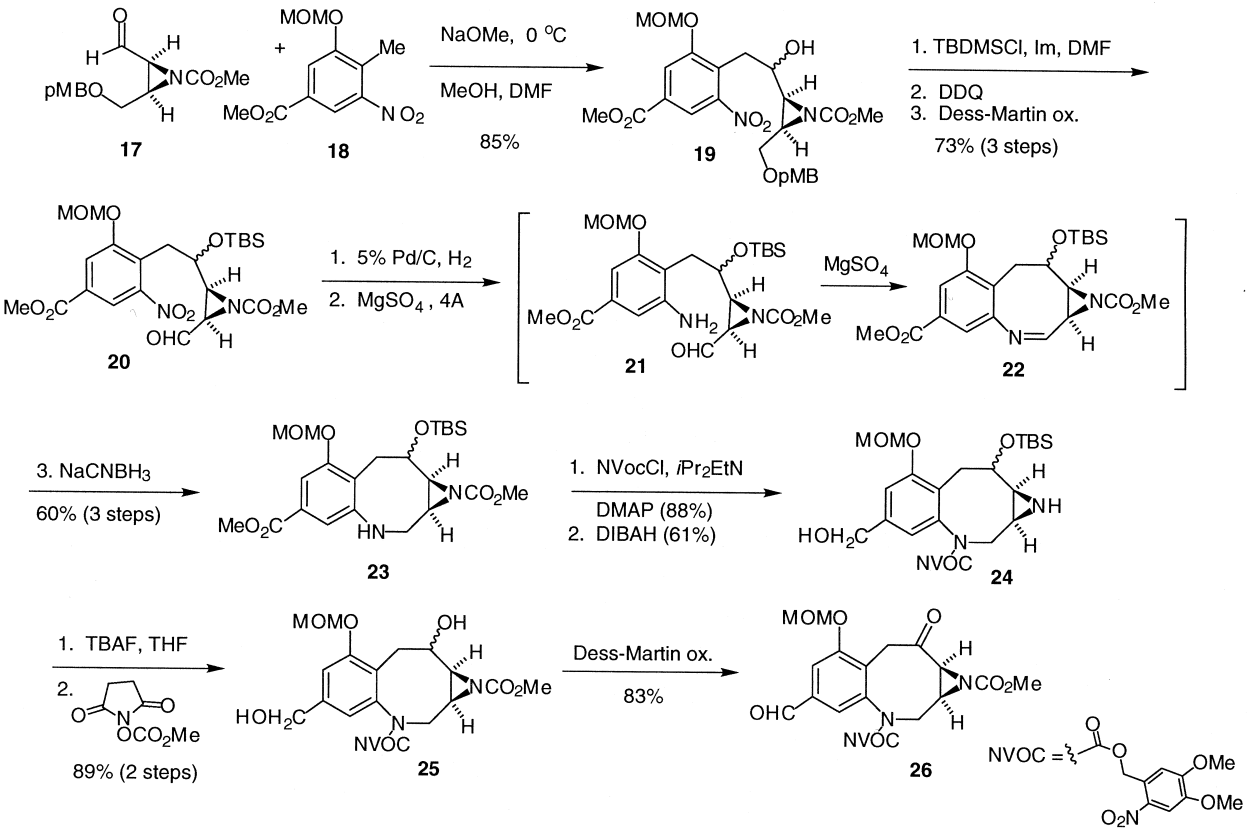
The unique structure of the Fujisawa drugs and their extraordinary anti-tumor activities have made these substances attractive synthetic targets. Several different approaches to the core nucleus of **1** have been published,[12] and three groups have successfully completed the syntheses of FR-900482.[13] In an attempt to design and synthesize molecules that mimic or combine the cross-linking activity of FR-900482, synthetic efforts in our labs have been focused on constructing a suitably masked activation cascade intermediate corresponding to **11** (Scheme 1) that is not reductively activated but that could, in principle, be triggered photochemically, oxidatively, or hydrolytically to form a reactive mitosene. As a first step toward testing this hypothesis, the synthesis of the first light-activated pro-mitosene is described herein.[14]

Results and Discussion

The aliphatic portion of the pro-drug model system was prepared from commercially available *cis*-2-butene-1,4-diol (**12**) (Scheme 2). Formation of the cyclic acetal with *p*-anisaldehyde and sodium cyanoborohydride reduction of the acetal gave the mono protected *cis*-diol in 60% yield over two steps. Sharpless epoxidation of the allylic alcohol gave epoxide **13** (75%) in approximately 94:6 *er*. Non-selective ring opening of **13** with sodium azide gave a mixture of the corresponding azido alcohols in a ~3:2 ratio (the mixture was not purified except for characterization purposes). Selective protection of the primary alcohols of gave a mixture of the corresponding O-TBS ethers **14** and **15** (83%, for the two steps).[15] Reduction of the azides with Raney Nickel and carbomethoxylation of the resulting



Scheme 2.



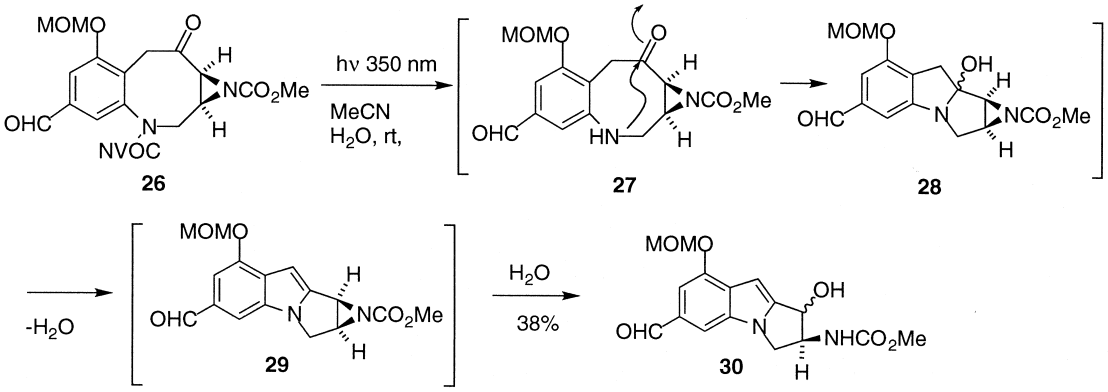
Scheme 3.

aziridine afforded **16** (88%, for the three steps). Removal of the O-TBS ether from **16** with tetra-*n*-butyl ammonium fluoride gave the corresponding alcohol (86% yield) which was converted to the corresponding aldehyde (**17**) with Dess–Martin periodinane[16] in 95% yield.

Following literature procedures, commercially available 3,5-dinitro-*p*-toluic acid was transformed into methyl 3-methoxymethyloxy-4-methyl-5-nitrobenzoate (**18**).[12b,12f,17] Deprotonation of nitro toluene **18** and nucleophilic addition[12a] to aldehyde **17** afforded the secondary alcohol **19** as a 4:1 mixture of diastereomers (85%) which were separated by chromatography and subsequently processed individually. The secondary alcohol was protected as the corresponding O-TBS ether (96%). The oxidative removal of the O-*p*-methoxybenzyl group[18] gave the primary alcohol (93%) which was subjected to Dess–Martin oxidation[16] to afford aldehyde **20** (82%) with an overall yield from **19** to **20** of 73%. Reduction of the nitro group was accomplished by catalytic hydrogenation to afford the labile aniline **21**.

As expected, cyclization of **21** to the eight-membered ring substance **23** proved difficult. It was found that cyclization was best accomplished by prior dehydration to the imine in the presence of $MgSO_4$ and 4 Å molecular sieves under dilute conditions (~0.002 M). After 24 h, the crude imine was reduced with $NaCNBH_3$ to give **23** in 60% overall yield from **20**. It should be noted that the imine-forming cyclization reaction is somewhat capricious with variable amounts of dimer derived from **22** being observed. Acylation of **23** with 6-nitroveratryl chloroformate (NVocCl) produced the corresponding carbamate (88%) as a mixture of conformational isomers (^{1}H NMR analysis).[20] Reduction of the methyl ester and removal of the carbomethoxy group in one step with DIBAH gave **24** (61%).[13b] It was observed that the TBS ether of **24** could be removed only via prior deprotection of the aziridine nitrogen atom. Thus, following decarbomethoxylation of the aziridine, the O-TBS ether was smoothly removed with TBAF to afford the corresponding diol. Selective re-protection of the aziridine gave **25** in 89% overall yield from **24**.[13b] Finally, Dess–Martin oxidation[16] of the primary and secondary alcohols produced keto-aldehyde **26** in 83% yield (Scheme 3).

With the 'pro-mitosene' model system (**26**) in hand, we examined removal of the NVOC group photochemically under various conditions to explore the proof-of-principle for the photochemical generation of a mitosene (Scheme 4). This was best effected by subjecting **26** (λ_{max}=345 nm, ϵ=6800; 295 nm, ϵ=7740; 238 nm, ϵ=17 300; 217 nm, ϵ=18 500, CH_3CN) to 350 nm irradiation for 24 h at room temperature in a 3:1 solution of CH_3CN/H_2O.[19] The sole isolable product was the ring-opened mitosene **30** as a 1:1 mixture of secondary alcohol diastereomers (38%). This substance must have arisen by the stepwise trans-annular cyclization of the secondary amine (**27**) on the ketone to give the tetracyclic carbinolamine **28** followed by dehydration to the mitosene **29**. This substance (**29**) proved too reactive to isolate from the aqueous milieu and we were



Scheme 4.

only able to obtain and characterize the water trapping adducts **30**.

Synthesis of **26** and the selective production of **30** from this material by photochemical activation demonstrates the viability of constructing novel 'pro-mitosene' derivatives which may find utility as new and selectively activated DNA–DNA and DNA–protein cross-linking agents and probes. Studies towards the synthesis of fully funtionalized photoactivated mitosenes and other non-reductively activated 'pro-mitosene' and related derivatives are under investigation in these laboratories and will be reported on in due course.

Experimental

General procedures

Unless otherwise noted materials were obtained from commercially available sources and used without further purification. Diethyl ether (Et_2O) and THF were distilled from sodium benzophenone ketyl under a nitrogen atmosphere. Methylene chloride, triethylamine, pyridine, acetonitrile, and methanol were distilled under a nitrogen atmosphere from calcium hydride. Dimethyl formamide was dried over activated 4 Å molecular sieves. All reactions involving hygroscopic substances were conducted with flame or oven dried glassware under an inert atmosphere (Ar) dried by passage of atmospheric gases through a column packed with $CaSO_4$. Filtrations of organic extracts were conducted with a cotton plug using gravity, and concentration of the resultant filtrate was performed under reduced pressure (aspirator) using a rotary evaporator. Chromatographic separations were performed with EM Science TLC plates (silica-gel 60, F_{254}, 20×20 cm×250 μm) or with EM Science 230–400 mesh silica gel using positive air pressure. Reactions and chromatographic fractions were monitored and analyzed with EM Science TLC plates. Visualization on TLC was achieved with ultraviolet light or heating of TLC plates submerged in a 5% solution of phosphomolybdic acid in 95% ethanol. Radial chromatography employed a Chromatotron Model 7954 using 2 or 4 mm silica plates as needed. Melting points were determined in open-ended capillary tubes with a Mel-Temp apparatus and are uncorrected. Infrared spectra were recorded on a Perkin–Elmer 1600 series FTIR as thin films from dichloromethane and are reported as λ_{max} in wavenumbers (cm^{-1}). Optical rotations were obtained on a Rudolph Research Autopol III automatic polarimeter at a wave length of 589 nm (sodium 'D' line) with a 1.0 dm cell with a volume of 1 mL. Specific rotations, $[\alpha]_D^{25}$ are reported at the specified temperature and concentration (*c*) given in grams per 100 mL in the specified solvent. Elemental analyses were performed by M-H-W Laboratories, Phoenix, AZ, and are accurate to within ±0.4% of the calculated values. High resolution mass spectra were obtained on a Fisons VG-7070 at University of California Riverside. Nuclear Magnetic Resonance (NMR) spectra were acquired using a Bruker AC-300 or JS-300 spectrometer.

4,7-Dihydro-2-(4-methoxyphenyl)-1,3-dioxepin. A mixture of *p*-anisaldehyde (136 g, 1.0 mol, 1.0 equiv.), *cis*-2-butene-1,4-diol (**12**) (105 g, 1.2 mol, 1.2 equiv.), and *p*-TsOH (0.20 g, 1.1 mmol, 0.11 mol%) in 450 mL of benzene was refluxed with azeotropic removal of water. After 1.5 days, the dark brown mixture was cooled to room temperature, diluted with 500 mL of benzene, washed sequentially with 3×125 mL H_2O and 1×200 mL sat. $NaCl_{(aq)}$. The organic solution was concentrated in vacuo, and the resulting oil was fractionally distilled under vacuum (1 mmHg, ~160°C) to yield 120 g (58% yield) of 4,7-dihydro-2-(4-methoxyphenyl)-1,3-dioxepin as a clear, colorless, viscous oil (>95% pure). R_f=0.50 (5:1 Hex/EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$) δ TMS: 3.79 (3H, s); 4.23 (2H, dd, *J*=1.7, 15.0 Hz); 4.36 (2H, dd, *J*=1.7, 15.0 Hz); 5.74 (2H, t, *J*=1.7 Hz); 5.81 (1H, s); 6.88 (2H, d, *J*=8.8 Hz); 7.43 (2H, d, *J*=8.8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ TMS: 55.2 (q), 64.3 (t), 101.9 (d), 113.4 (d), 127.6 (d), 129.9 (d), 131.1 (s), 159.6 (s). IR (NaCl, neat): 3030, 2938, 2855, 1613, 1586, 1513, 1445 cm^{-1}. Anal. calcd for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 69.68; H, 6.69.

(*Z*)-4-[(4-Methoxyyphenyl)methoxy]-2-buten-1-ol. The acetal (4,7-dihydro-2-(4-methoxyphenyl)-1,3-dioxepin) prepared as described above (11.8 g, 57.2 mmol, 1 equiv.) and 180 mL of dry DMF were added to a 1 L flask. A solution of $NaCNBH_3$ (10.6 g, 168.7 mmol, 3 equiv.) and TFA (22.7 mL, 294.6 mmol, 5 equiv.) in 90 mL of dry DMF (prepared at 0°C) was transferred via cannula into the flask under negative pressure at ambient temperature. The

resulting solution was stirred 2.0 h until TLC analysis (1:1 EtOAc/Hex) showed the reaction to be complete. The reaction was quenched by dropwise addition of 1 M $NaOH_{(aq)}$ until the solution reached a pH equal to 7. Following concentration in vacuo, the resulting oil was redissolved in 200 mL of CH_2Cl_2 and washed with 2×100 mL H_2O and 1×150 mL sat. $NaCl_{(aq)}$. The solution was dried over $MgSO_4$, filtered, concentrated, and dried under vacuum for 12 h. The crude oil was purified by distillation using a kugelrohr apparatus (~1 mmHg, 160°C) to yield 10.0 g of the allylic alcohol (85% yield) as a clear colorless oil (>95% pure). R_f=0.40 1:1 Hex/EtOAc. ^{1}H NMR (300 MHz, $CDCl_3$) δ TMS: 2.04 (1H, br, D_2O exch.); 3.78 (3H, s); 4.04 (2H, d, J=6.0 Hz); 4.14 (2H, d, J=6.0 Hz); 4.44 (2H, s); 5.76 (2H, m); 6.86 (2H, d, J=8.6 Hz); 7.23 (2H, d, J=8.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ TMS: 55.2 (q), 58.7 (t), 65.3 (t), 72.1 (t), 113.8 (d), 128.4 (d), 129.5 (d), 129.9 (s), 132.3 (d), 159.3 (s). IR (NaCl, neat): 3406, 3022, 2934, 2860, 1613, 1586, 1513, 1464 cm^{-1}. Anal. calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 68.94; H, 7.56.

(2*S*-*cis*)-3-[[(4-Methoxyphenyl)methoxy]methyl]-oxiranemethanol (13). Freshly distilled CH_2Cl_2 (200 mL) was added to a 1 L three-neck round bottom flask and cooled to −24°C before addition of 5 g of powdered 4 Å molecular sieves. Next, freshly distilled (+)-diethyl-L-tartrate (8.2 mL, 48.5 mmol, 1.3 equiv.), freshly distilled titanium isopropoxide (12.2 mL, 41.0 mmol, 1.1 equiv.), and 3.0 M *tert*-butyl hydroperoxide in toluene (25 mL, 74.6 mmol, 2.0 equiv.) were added to the flask. The mixture was stirred for 30 min to let the catalyst age. The allylic alcohol ((*Z*)-4-[(4-methoxyyphenyl)methoxy]-2-buten-1-ol) prepared as described above (7.5 g, 36.0 mmol, 1.0 equiv.) in ~10 mL of CH_2Cl_2 (dried over 4 Å molecular sieves) was added dropwise to the mixture over 20 min. The reaction was stirred at −24°C for 2 days. After TLC analysis (1:1 Hex/EtOAc) showed no sign of starting material, the reaction was placed on a −45°C acetonitrile/CO_2 bath and quenched with 100 mL of 10% aqueous tartaric acid. The two-phase solution was stirred with a mechanical stirrer for 30 min and then allowed to warm to room temp over 1 h. Approximately 200 mL of water was added to the mixture, and the aqueous solution was extracted. During the extraction, the emulsion due to the molecular sieves was removed by filtering the aqueous solution through a cotton plug. The combined organic extracts were dried over $MgSO_4$ and immediately passed through a Celite pad. The concentrated oil was dissolved in 150 mL Et_2O and cooled to 0°C on an ice bath. Next, 50 mL of 1 M $NaOH_{(aq)}$, pre-cooled to 0°C, was added to the organic solution. The biphasic mixture was stirred vigorously for 1.5 h. The organic layer was separated, washed with 1×H_2O, and 1×sat. $NaCl_{(aq)}$, and dried over Na_2SO_4. The resulting oil was dried overnight under vacuum. Crystalization of the product from Et_2O at −33°C afforded 6.05 g (75% yield) of epoxide **13** as a white solid (>95% pure). R_f=0.31 (1:1 Hex/EtOAc) $[\alpha]_D^{25}$=−25.5 (c=1.0, $CHCl_3$). R_f=0.31 (1:1 Hex/EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$) δ TMS: 2.04 (1H, br, D_2O exch.); 3.22–3.28 (2H, m); 3.62 (1H, dd, J=5.0, 11.0 Hz); 3.71 (1H, dd, J=5.9, 11.0 Hz); 3.65–3.80 (2H, m); 3.80 (3H, s); 4.46 (1H, d, J=11.4 Hz); 4.55 (1H, d, J=11.4 Hz); 6.87 (2H, d, J=8.6 Hz); 7.26 (2H, d, J=8.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ TMS: 54.7 (d); 55.2 (q); 55.6 (d); 60.7 (t); 67.7 (t); 73.1 (t); 113.9 (d); 129.4 (s); 129.5 (d); 159.4 (s). IR (NaCl, neat): 3424, 2935, 1612, 1585, 1513, 1463 cm^{-1}. Anal. calcd for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 64.49; H, 7.10.

Mosher ester of epoxide 13. Alcohol **13** (~0.10 mmol, 1.0 equiv.) and 500 μL of CH_2Cl_2 were added to a 10 mL conical flask. The solution was stirred until the alcohol had completely dissolved, and DMAP (1.0 equiv.) and Et_3N (4.0 equiv.) were added. After stirring for another 2 min, (+)-MTPA-Cl (1.2 equiv.) was added to the solution. An immediate change to orange was seen, and the reaction was stirred until the reaction was complete by TLC analysis (4:1 Hex/EtOAc). The excess acid chloride was quenched by the addition of dimethylaminopropylamine (5.0 equiv.), and the mixture was stirred for another 15 min. The mixture was concentrated and passed through a short plug of silica gel (4:1 Hex/EtOAc). The crude oil was analyzed by ^{19}F NMR without further purification. R_f=0.60 (4:1 Hex/EtOAc). ^{19}F NMR (282 MHz, $CDCl_3$) (ref CF_3CH_2OH −80 ppm) δ TMS: −74.54 (CF_3); −74.60 (CF_3). 87% *ee* (±2% *ee*).

[*S*-(*R*,*S*)]-2-Azido-4-[(4-methoxyphenyl)methoxy]-1,3-butanediol and [*R*-(*R*,*S*)]-3-azido-4-[(4-methoxyphenyl)-methoxy]-1,2-butanediol. Epoxide **13** (1.52 g, 6.78 mmol, 1.0 equiv.), NH_4Cl (0.72 g, 13.5 mmol, 2.0 equiv.), NaN_3 (2.20 g, 33.9 mmol, 5.0 equiv.), 40 mL $CH_3OCH_2CH_2OH$, and 5 mL distilled H_2O were added to a 100 mL flask. The stirred reaction mixture was heated at reflux for 4 h when TLC analysis (EtOAc) showed complete loss of starting material. The cooled mixture was concentrated in vacuo. The resulting orange solid was dissolved in EtOAc, passed through a short plug of silica gel using EtOAc as eluant, concentrated, and dried overnight under vacuum. The cloudy orange oil was used without further purification. For analytical purposes, the mixture of regioisomers was further purified (>95% pure) by silica gel column chromatography (EtOAc). R_f=0.56; 0.47 (EtOAc). Mixture of isomers: ^{1}H NMR (300 MHz, $CDCl_3$) δ TMS: 2.1–2.3 (1H, br, D_2O exch.); 2.4–2.7 (1H, br, D_2O exch.); 3.52 (1H, d, J=1.8 Hz); 3.53 (1H, d, J=2.3 Hz); 3.59 (1/2H, m); 3.64 (1/2H, d, J=5.0 Hz); 3.71 (1/2H, d, J=5.1 Hz); 3.77 (3/2H, m); 3.79 (3H, s); 3.82 (1/2H, d, J=4.8 Hz); 3.94 (1/2H, q, J=4.3 Hz); 4.47 (1H, s); 4.49 (1H, s); 6.87 (2H, d, J=8.6 Hz); 7.24 (2H, d, J=8.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ TMS: Major isomer, 55.2 (q), 62.6 (t), 64.1 (d), 70.6 (d), 70.7 (t), 73.2 (t), 113.9 (d), 129.3 (s), 129.5 (d), 159.4 (s). Minor isomer, 55.2 (q), 62.2 (d), 63.6 (t), 69.8 (t), 71.8 (d), 73.2 (t), 113.9 (d), 129.3 (s), 129.4 (d), 159.4 (s). IR (NaCl, neat): 3410, 2935, 2865, 2104, 1612, 1586, 1514, 1464 cm^{-1}. Anal. calcd for the mixture $C_{12}H_{17}N_3O_4$: C, 53.92; H, 6.41; N, 15.72. Found: C, 53.71; H, 6.36; N, 15.49.

[*S*-(*R*,*S*)]-3-Azido-4-[[(1,1-dimethlethyl)dimethylsilyl]oxy]-1-[(4-methoxyphenyl)methoxy]-2-butanol (14) and [*R*-(*R*,*S*)]-3-azido-1-[[(1,1-dimethlethyl)dimethylsilyl]oxy]-4-[(4-methoxyphenyl)methoxy]-2-butanol (15). The diol (as a mixture of isomers) from the previous reaction (1.15 g, 4.31 mmol, 1.0 equiv.), and 17 mL of CH_2Cl_2 were added to a 50 mL conical flask. The stirred mixture was cooled on an ice bath for 10 min when Et_3N (1.20 mL,

8.62 mmol, 2.0 equiv.), TBSCl (943 mg, 6.25 mmol, 1.4 equiv.), and DMAP (53 mg, 0.43 mmol, 0.1 equiv.) were added. After stirring for 1 h, the mixture was placed in the refrigerator at 4°C. After 15.5 h, TLC analysis of the crude reaction mixture (EtOAc) showed complete loss of starting material. The reaction mixture was concentrated in vacuo and passed through a short plug of silica gel using 4:1 Hex/EtOAc as eluant to yield 1.60 g (90% from **13**) of **14** and **15** as a cloudy orange oil which was used without further purification. For analytical purposes, the mixture was further purified (>95% pure) by silica gel column chromatography (4:1 Hex/EtOAc). Mixture of isomers: R_f=0.34; 0.27 (1:1 Hex/ EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$) δ TMS: 0.05 (1.5H, s); 0.06 (1.5H, s); 0.08 (3H, s); 0.88 (4.5 H, s); 0.89 (4.5H, s); 2.5 (1H, br, D_2O exch.); 3.78 (3H, s); 3.46–3.92 (6H, m); 4.47 (1H, s); 4.50 (1H, s); 6.87 (2H, d, J=8.6 Hz); 7.23 (1H, d, J=8.6 Hz); 7.26 (1H, d, J=8.6 Hz). IR (NaCl, neat): 3424, 3005, 2935, 2838, 2103, 1613, 1586, 1514 cm^{-1}. Anal. calcd for $C_{18}H_{31}N_3O_4Si$: C, 56.66; H, 8.19; N, 11.01. Found: C, 56.48; H, 7.89; N, 10.79.

[*S*-(*R*,*S*)]-3-Azido-4-[[(1,1-dimethlethyl)dimethylsilyl]oxy]-1-[(4-methoxyphenyl)methoxy]-methanesulfonate-2-butanol and [*R*-(*R*,*S*)]-3-azido-1-[[(1,1-dimethlethyl)dimethylsilyl]oxy]-4-[(4-methoxyphenyl)methoxy]-methanesulfonate-2-butanol. Alcohols **14** and **15** (15.8 g, 41.4 mmol, 1.0 equiv.) and 414 mL of CH_2Cl_2 were added to a 1 L conical flask. The stirred solution was placed on an ice bath for 15 min when Et_3N (17.3 mL, 124.1 mmol, 3.0 equiv.) was added. The mixture was stirred for another 5 min when methanesulfonyl chloride (4.8 mL, 62.0 mmol, 1.5 equiv.) was added to the flask dropwise over a minute. After 30 min, TLC analysis (2:1:2 CH_2Cl_2/Et_2O/Hex) of the reaction showed complete loss of the starting material. To the reaction mixture was added 200 mL of sat $NaHCO_{3(aq)}$, and the bilayer solution was stirred vigorously for 10 min. Following the addition of 100 mL of H_2O, the two layers were separated. The aqueous layer was extracted with 2×150 mL EtOAc, and the combined organic layers were washed with 1×200 mL sat $NaCl_{(aq)}$, and dried over Na_2SO_4. The reaction mixture was concentrated in vacuo and passed through a short plug of silica gel using 4:1 Hex/EtOAc as eluant to yield 19.0 g (96% yield) of the product as a light yellow oil which was used without further purification. For analytical purposes, the mixture was further purified (>95% pure) by column chromatography (10:1:10 CH_2Cl_2/Et_2O/Hex). Mixture of isomers: R_f=0.44 (2:1:2 CH_2Cl_2/Et_2O/Hex). ^{1}H NMR (300 MHz, $CDCl_3$) δ TMS: 0.03, 0.05, 0.06 (6H, s); 0.86, 0.87 (9H, s); 3.04, 3.05 (3H, s); 3.79 (3H, s); 3.64-3.88 (6H, m); 4.47, 4.48 (2H, ABq, J=11.4 Hz); 4.70, 4.80 (1H, q, J=5 Hz); 6.86, 6.87 (2H, d, J=8.6 Hz); 7.22, 7.25 (2H, d, J=8.6 Hz). IR (NaCl, neat): 2955, 2932, 2108, 1613, 1515, 1465 cm^{-1}. Anal. calcd for $C_{19}H_{33}N_3O_6SSi$: C, 49.65; H, 7.24; N, 9.14. Found: C, 49.86; H, 7.06; N, 8.98.

(2*S*-*cis*)-Methyl ester 2-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]methyl]-3-[(4-methoxypheny)methoxylmethyl]-1-aziridinecarboxylic acid (16). The mesylate compound described above (19.0 g, 41.3 mmol, 1 equiv.) and 440 mL of EtOH were added to a 1 L flask. To the resulting solution was added hydrazine monohydrate (34.3 mL, 707.1 mmol, 17.1 equiv.) followed by approximately 3 g of Raney Nickel. The reaction mixture was stirred for 3 h under argon atmosphere when TLC analysis (1:1 EtOAc/Hex) showed the reaction to be complete. The reaction was filtered through a pad of Celite with EtOH and concentrated. The resulting oil was dissolved in 400 mL of EtOAc and washed with 1×$NaCl_{(aq)}$ and dried over Na_2SO_4. The mixture was filtered, concentrated, and placed under vacuum for 12 h. The clear yellow oil was dissolved in 300 mL of CH_2Cl_2 and cooled on an ice bath for ~15 min while stirring. Pyridine (10.0 mL, 20.8 mmol, 3.1 equiv.) was added to the mixture, and the mixture was stirred for another 5 min when methyl chloroformate (6.4 mL, 82.8 mmol, 2.0 equiv.) was added dropwise over 2 min. The reaction was stirred for 20 min when TLC analysis showed a complete loss of the unprotected aziridine (R_f=0.73 10:1 CH_2Cl_2/MeOH). To the reaction mixture was added 300 mL sat $NaHCO_{3(aq)}$, and the bilayer was stirred vigorously for 10 min. The two layers were separated. The aqueous layer was extracted with 2×150 mL EtOAc, and the combined organic layers were washed 1×200 mL sat $NaCl_{(aq)}$. The organic layer was dried over Na_2SO_4, filtered, and concentrated. The crude oil was purified by column chromatography (4:1 Hex/EtOAc) to yield 15.0 g (88% overall yield from **14** and **15**) of **16** as a light yellow oil (>95% pure). $[\alpha]_D^{25}$=+9.6 (c=2.1, $CHCl_3$). R_f=0.50 (2:1 hexane/EtOAc). ^{1}H NMR (500 MHz, $CDCl_3$) δ TMS: 0.03 (3H, s); 0.05 (3H, s); 0.86 (9H, s); 2.69 (1H, dd, J=6.0, 6.0 Hz); 2.77 (1H, dd, J=6.0, 6.0 Hz); 3.55 (1H, dd, J=5.5, 11.2 Hz); 3.58 (1H, dd, J=6.3, 11.2 Hz); 3.60 (1H, dd, J=6.1, 11.4 Hz); 3.71 (3H, s); 3.77 (1H, dd, J=5.9, 11.4 Hz); 3.78 (3H, s); 4.46 (1H, d, J=11.5 Hz); 4.59 (1H, d, J=11.5 Hz); 6.85 (2H, d, J=8.6 Hz); 7.26 (2H, d, J=8.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ TMS: −5.4 (q); −5.3 (q); 18.2 (s); 25.7 (q); 40.4 (d); 41.8 (d); 53.5 (q); 55.1 (q); 61.2 (t); 67.1 (t); 72.4 (t); 113.7 (d); 129.4 (d); 129.9 (s); 159.2 (s); 163.5 (s). IR (NaCl, neat): 3436, 3001, 2954, 2931, 1732, 1613, 1514, 1464, 1439 cm^{-1}. Anal. calcd for $C_{20}H_{33}NO_5Si$: C, 60.73; H, 8.41; N, 3.54. Found: C, 60.60; H, 8.62; N, 3.45.

(2*S*-*cis*)-Methyl ester 2-(hydroxymethyl)-3-[(4-methoxypheny)methoxylmethyl]-1-aziridinecarboxylic acid. Aziridine **16** (2.02 g, 5.1 mmol, 1.0 equiv.) and 50 mL of THF were added to a 200 mL flask. The stirred solution was cooled on an ice bath for 15 min, and 1 M TBAF in THF (6.1 mL, 6.1 mmol, 1.2 equiv.) was added. After 30 min, the reaction was complete by TLC analysis (4:1 Hex/EtOAc). The reaction mixture was removed from the ice bath, quenched by the addition of 25 mL sat $NH_4Cl_{(aq)}$, and stirred vigorously for 5 min. The THF was evaporated, and the aqueous solution was diluted with 25 mL H_2O and extracted with Et_2O (5×30 mL). The combined organic layers were dried over Na_2SO_4 overnight. The filtered solution was concentrated, and the resulting oil was purified by column chromatography (2:1 CH_2Cl_2/Et_2O) to yield 1.24 g (86% yield) of the alcohol as light yellow oil (>95% pure). $[\alpha]_D^{25}$=+36.6 (c=1.3, $CHCl_3$). R_f=0.21 (2:1 CH_2Cl_2/Et_2O). ^{1}H NMR (300 MHz, $CDCl_3$) δ TMS: 2.37 (1H, br, D_2O exch.); 2.81 (2H, m); 3.40 (1H, dd, J=7.2, 10.7 Hz); 3.51 (1H, m); 3.70 (3H, s); 3.78 (3H, s); 3.82 (1H, m); 3.84 (1H, dd, J=5.5, 10.7 Hz); 4.44 (1H, d, J=11.4 Hz); 4.52 (1H, d, J=11.4 Hz); 6.86 (2H, d, J=8.7 Hz); 7.23 (2H, d,

J=8.7 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ TMS: 39.5 (d); 41.5 (d); 53.7 (q); 55.2 (q); 60.5 (t); 67.4 (t); 73.0 (t); 113.9 (d); 129.2 (s); 129.6 (d); 159.5 (s); 163.2 (s). IR (NaCl, neat): 3430, 3003, 2955, 1728, 1613, 1586, 1514, 1440 cm^{-1}. Anal. calcd for $C_{14}H_{19}NO_5$: C, 59.78; H, 6.81; N, 4.98. Found: C, 59.80; H, 7.02; N, 4.82.

(2*S*-*cis*)-Methyl ester 2-formyl-3-[(4-methoxypheny)-methoxylmethyl]-1-aziridinecarboxylic acid (17). The alcohol described above (1.29 g, 4.58 mmol, 1.0 equiv.) and 45 mL CH_2Cl_2 were added to a 200 mL flask. The mixture was stirred for 5 min when Dess–Martin reagent[16] (3.5 g, 7.3 mmol, 1.6 equiv.) was added to the flask in one portion. The mixture was stirred for 2.5 h when TLC analysis (2:1 CH_2Cl_2/Et_2O) showed complete loss of starting material. The reaction mixture was dissolved in 150 mL Et_2O and poured into a solution of 150 mL sat $NaHCO_{3(aq)}$ with seven-fold excess of $Na_2S_2O_3{\cdot}5H_2O$ (9.0 g). The biphasic mixture was vigorously stirred for 15 min while the milky color of the organic layer slowly disappeared The two layers were separated. The organic layer was washed with 1×25 mL sat $NaHCO_{3(aq)}$ and 1×25 mL H_2O. The combined aqueous layers were back extracted with 5×30 mL Et_2O. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The crude oil was purified by column chromatography (1.5:1 Hex/EtOAc) to yield 1.20 g (92% yield) of **17** as a clear colorless oil (>95% pure). $[\alpha]_D^{25}$=−80.6 (c=1.3, $CHCl_3$). R_f=0.60 (2:1 CH_2Cl_2/Et_2O). ^{1}H NMR (300 MHz, $CDCl_3$) δ TMS: 3.04 (1H, ddd, J=4.3, 4.4, 6.9 Hz); 3.10 (1H, dd, J=4.5, 6.9 Hz); 3.64 (1H, dd, J=4.3, 11.2 Hz); 3.73 (1H, dd, J=4.4, 11.2 Hz); 3.75 (3H, s); 3.78 (3H, s); 4.45 (1H, d, J=11.5 Hz); 4.47 (1H, d, J=11.5 Hz); 6.85 (2H, d, J=8.7 Hz); 7.19 (2H, d, J=8.7 Hz); 9.31 (1H, d, J=4.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ TMS: 43.5 (d); 44.7 (d); 54.1 (q); 55.2 (q); 65.8 (q); 73.0 (q); 113.9 (d); 129.2 (s); 129.5 (d); 159.4 (s); 161.8 (s); 196.3 (d). IR (NaCl, neat): 3006, 2953, 2834, 1719, 1612, 1586, 1513, 1438 cm^{-1}. Anal. calcd for $C_{14}H_{17}NO_5$: C, 60.21; H, 6.14; N, 5.02. Found: C, 60.45; H, 6.21; N, 4.96.

[2*S*-(2α,3α)]-Methyl ester 2-[1-hydroxy-2-[4-(methoxy-carbonyl)-2-(methoxymethoxy)-6-nitrophenyl]ethyl]-3-[[(4-methoxyphenyl)methoxy]methyl]-1-aziridinecar-boxylic acid (19). Compound **18** (4.69 g, 18.4 mmol, 2.0 equiv.) and 20 mL of DMF were added to a 50 mL flask. The stirred mixture was cooled on an ice bath for 20 min when 0.5 M NaOMe in MeOH (1.8 mL, 0.9 mmol, 0.1 equiv.) was added. The clear solution immediately turned dark purple. After the addition of base, **17** (2.58 g, 9.2 mmol, 1.0 equiv.) in 10 mL of DMF was added to the reaction mixture in 1 mL aliquots every 5 min. After the additions were complete (50 min), the reaction was stirred for another 3.5 h and quenched with 35 mL of sat $NH_4Cl_{(aq)}$. After 10 min, the reaction was diluted with 20 mL water, and the aqueous mixture was extracted with 6×50 mL Et_2O, 1×25 mL CH_2Cl_2, and 1×25 mL EtOAc. The combined organic extracts were washed with 1×45 mL sat $NaCl_{(aq)}$, dried over Na_2SO_4, filtered and concentrated. The crude oil was purified by column chromatography (1:1 Hex/EtOAc) to yield 4.2 g (85–90% yield) of **19** as a yellow oil (4:1 mixture of separable diastereomers) (>95% pure).

Major diastereomer **19**: $[\alpha]_D^{25}$=−38.4 (c=1.3, $CHCl_3$). R_f=0.50 (2:1 CH_2Cl_2/Et_2O). ^{1}H NMR (300 MHz, $CDCl_3$) δ TMS: 2.65 (1H, dd, J=6.5, 8.4 Hz); 2.80 (1H, ddd, J=5.7, 6.5, 7.9 Hz); 2.98 (1H, br, D_2O exch.); 3.33 (1H, dd, J=7.9, 10.5 Hz); 3.40 (2H, m); 3.42 (3H, s); 3.60 (1H, m); 3.64 (3H, s); 3.76 (3H, s); 3.85 (1H, dd, J=5.7, 10.5 Hz); 3.92 (3H, s); 4.41 (1H, d, J=11.5 Hz); 4.46 (1H, d, J=11.5 Hz); 5.25 (2H, app. sing.); 6.79 (2H, d, J=8.6 Hz); 7.17 (2H, d, J=8.6 Hz); 7.91 (1H, d, J=1.5 Hz); 8.10 (1H, d, J=1.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ TMS: 30.4 (t), 39.2 (d), 44.8 (d), 52.4 (q), 53.5 (q), 54.9 (q), 56.3 (q), 67.3 (t), 69.1 (d), 72.7 (t), 94.7 (t), 113.6 (d), 117.6 (d), 118.1 (d), 126.8 (s), 128.8 (s), 129.4 (d), 129.7 (s), 151.5 (s), 156.0 (s), 159.2 (s), 162.7 (s), 164.7 (s). IR (NaCl, neat): 3509, 2956, 2923, 2854, 1728, 1613, 1538, 1514, 1438 cm^{-1}. Anal. for the mixture of diastereo-mers: calcd for $C_{25}H_{30}N_2O_{11}$: C, 56.18; H, 5.66; N, 5.24. Found: C, 55.93; H, 5.83; N, 5.04.

Minor diastereomer **19**: $[\alpha]_D^{25}$=+14.2 (c=1.3, $CHCl_3$). R_f=0.45 (2:1 CH_2Cl_2/Et_2O). ^{1}H NMR (300 MHz, $CDCl_3$) δ TMS: 2.33 (1H, br, D_2O exch.); 2.66 (1H, dd, J=6.8, 6.8 Hz); 2.81 (1H, ddd, J=5.2, 6.5, 6.8 Hz); 3.20 (1H, dd, J=5.2, 13.4 Hz); 3.36 (2H, m); 3.41 (3H, s); 3.50 (1H, dd, J=6.5, 11.0 Hz); 3.73 (3H, s); 3.78 (3H, s); 3.84 (1H, m); 3.92 (3H, s); 4.43 (1H, d, J=11.4 Hz); 4.50 (1H, d, J=11.4 Hz); 5.21 (2H, app. sing.); 6.84 (2H, d, J=8.6 Hz); 7.21 (2H, d, J=8.6 Hz); 7.92 (1H, d, J=1.5 Hz); 8.08 (1H, d, J=1.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ TMS: 30.9 (t), 41.3 (d), 45.8 (d), 52.7 (q), 53.9 (q), 55.2 (q), 56.6 (q), 66.9 (t), 68.9 (d), 72.6 (t), 95.0 (t), 113.8 (d), 118.0 (d), 118.5 (d), 126.3 (s), 129.4 (d), 129.7 (s), 130.3 (s), 151.5 (s), 156.3 (s), 159.3 (s), 163.3 (s), 164.7 (s). IR (NaCl, neat): 3509, 2956, 2855, 1728, 1613, 1538, 1514, 1438 cm^{-1}.

[2*S*-(2α,3α)]-Methyl ester 2-[1-[[(1,1-dimethylethyl)di-methylsilyl]oxy]-2-[4-(methoxycarbonyl)-2-(methoxy-methoxy)-6-nitrophenyl]ethyl]-3-[[(4-methoxyphenyl)-methoxy]methyl]-1-aziridinecarboxylic acid. Compound **19** (337 mg, 0.70 mmol, 1.0 equiv.), and 350 μL of DMF were added to a 10 mL conical flask. Once **19** had completely dissolved, imidazole (167 mg, 2.46 mmol, 3.5 equiv.), and TBSCl (212 mg, 1.41 mmol, 2.0 equiv.) were added to the flask. After stirring for 24 h, TLC analysis (1:1 Hex/EtOAc) of the crude reaction showed complete loss of starting material, and the reaction was diluted with 15 mL Et_2O. The organic solution was washed with 10 mL water, and the two layers were separated. The aqueous layer was back extracted with 6×15 mL Et_2O. The combined organic layers were washed with 15 mL sat $NaCl_{(aq)}$, dried over Na_2SO_4, filtered, and concentrated. The crude oil was purified by column chromatography (1.5:1 Hex/EtOAc) to give 437 mg (96% yield) of product as a clear yellow oil (>95% pure).

Major diastereomer: $[\alpha]_D^{25}$=−27.6 (c=1.6, $CHCl_3$). R_f=0.50 (1:1 Hex/EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$) δ TMS: −0.40 (3H, s); −0.11 (3H, s); 0.69 (9H, s); 2.59 (1H, dd, J=5.5, 6.3 Hz); 2.74 (1H, ddd, J=4.6, 6.3, 6.8 Hz); 3.22 (1H, dd, J=4.8, 13.5 Hz); 3.41 (1H, dd, J=9.0, 13.5 Hz); 3.43 (3H, s); 3.60 (1H, dd, J=6.8, 11.0 Hz); 3.68 (3H, s); 3.68 (1H, dd, J=4.6, 11.0 Hz); 3.77 (3H, s); 3.91 (3H, s);

4.12 (1H, ddd, *J*=4.8, 5.5, 9.0 Hz); 4.50 (1H, d, *J*=11.4 Hz); 4.60 (1H, d, *J*=11.4 Hz); 5.21 (2H, app. sing.); 6.85 (2H, d, *J*=8.5 Hz); 7.27 (2H, d, *J*=8.5 Hz); 7.90 (1H, d, *J*=1.5 Hz); 8.06 (1H, d, *J*=1.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ TMS: −0.53 (q), −0.48 (q), 17.8 (s), 25.6 (q), 32.2 (t), 41.1 (d), 45.1 (d), 52.6 (q), 53.6 (q), 55.2 (q), 56.6 (q), 67.3 (t), 68.0 (d), 72.5 (t), 94.9 (t), 113.7 (d), 117.6 (d), 118.4 (d), 127.3 (s), 129.5 (d), 129.9 (s), 130.0 (s), 151.7 (s), 156.6 (s), 159.2 (s), 163.5 (s), 164.9 (s). IR (NaCl, neat): 3001, 2954, 2856, 1731, 1613, 1537, 1514, 1438 cm^{-1}. Anal. for the mixture of diastereomers: calcd for $C_{31}H_{44}N_2O_{11}Si$: C, 57.39; H, 6.84; N, 4.32. Found: C, 57.50; H, 6.91; N, 4.50.

Minor diastereomer: $[\alpha]_D^{25}$=+10.5 (*c*=1.1, $CHCl_3$). R_f=0.5 (1:1 Hex/EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$) δ TMS: −0.31 (3H, s); 0.03 (3H, s); 0.80 (9H, s); 2.61 (1H, ddd, *J*=4.4, 6.7, 7.1 Hz); 2.69 (1H, dd, *J*=6.7, 8.5 Hz); 2.98 (1H, dd, *J*=4.4, 11.1 Hz); 3.11 (1H, dd, *J*=6.6, 13.2 Hz); 3.19 (1H, dd, *J*=7.1, 11.1 Hz); 3.23 (1H, dd, *J*=7.6, 13.2 Hz); 3.39 (3H, s); 3.69 (3H, s); 3.77 (3H, s); 3.79 (1H, m); 3.91 (3H, s); 4.40 (1H, d, *J*=11.5 Hz); 4.50 (1H, d, *J*=11.5 Hz); 5.17 (2H, apparent singlet); 6.82 (2H, d, *J*=8.6 Hz); 7.18 (2H, d, *J*=8.6 Hz); 7.87 (1H, d, *J*=1.5 Hz); 8.01 (1H, d, *J*=1.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ TMS: −5.3 (q), −4.8 (q), 17.7 (s), 25.6 (q), 31.8 (t), 40.9 (d), 46.0 (d), 52.6 (q), 53.4 (q), 55.1 (q), 56.5 (q), 66.9 (t), 70.3 (d), 72.1 (t), 94.7 (t), 113.6 (d), 117.4 (d), 118.2 (d), 126.1 (s), 129.4 (d), 129.6 (s), 130.1 (s), 151.5 (s), 156.6 (s), 159.1 (s), 163.2 (s), 164.6 (s). IR (NaCl, neat): 2964, 1732, 1614, 1538, 1514, 1438 cm^{-1}.

[2*S*-(2α,3α)]-Methyl ester 2-[1-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-2-[4-(methoxycarbonyl)-2-(methoxymethoxy)-6-nitrophenyl]ethyl]-3-(hydroxymethyl)-1-aziridinecarboxylic acid. The silyl ether described above (205 mg, 0.32 mmol, 1.0 equiv.), 2.7 mL of CH_2Cl_2, and 150 μL of H_2O were added to a 25 mL flask. After stirring for 5 min, DDQ (93 mg, 0.41 mmol, 1.3 equiv.) was added to the mixture in one portion. The reaction mixture immediately turned dark green, and over the course of the next 1.5 h, the mixture slowly turned bright orange. After 1.5 h, the crude reaction mixture was passed through a short plug of activated alumina using 10:1 CH_2Cl_2/MeOH as eluant. After concentration in vacuo, the crude oil was purified by column chromatography (1:1 Hex/EtOAc) to give 160 mg (93% yield) of product as a clear orange oil (>95% pure).

Major diastereomer: $[\alpha]_D^{25}$=−55.6 (*c*=1.2, CH_2Cl_2). R_f=0.30 (1:1 Hex/EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$) δ TMS: −0.34 (3H, s); −0.06 (3H, s); 0.73 (9H, s); 1.95 (1H, br, D_2O exch.); 2.61 (1H, dd, *J*=5.7, 6.2 Hz); 2.72 (1H, ddd, *J*=4.5, 6.4, 6.4 Hz); 3.26 (1H, dd, *J*=5.1, 13.4 Hz); 3.42 (1H, dd, *J*=8.8, 13.4 Hz); 3.49 (3H, s); 3.67 (3H, s); 3.90 (2H, m); 3.92 (3H, s); 4.25 (1H, ddd, *J*=5.1, 5.7, 8.8 Hz); 5.27 (1H, d, *J*=6.9 Hz); 5.29 (1H, d, *J*=6.9 Hz); 7.92 (1H, d, *J*=1.5 Hz); 8.09 (1H, d, *J*=1.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ TMS: −5.2 (q), −4.9 (q), 17.8 (s); 25.5 (q); 32.3 (t); 42.9 (d)45.9 (d); 52.6 (q); 53.7 (q); 56.6 (q); 60.2 (t); 68.1 (d); 95.0 (t); 117.6 (d); 118.4 (d); 127.0 (s); 129.9 (s); 151.6 (s); 156.6 (s); 163.5 (s); 164.8 (s). IR (NaCl, neat): 3510, 2955, 2856, 1730, 1540, 1438 cm^{-1}. Anal. for the mixture of diastereomers: calcd for $C_{23}H_{36}N_2O_{10}Si$: C, 52.26; H, 6.86; N, 5.30. Found: C, 52.22; H, 6.66; N, 5.19.

Minor diastereomer: $[\alpha]_D^{25}$=+8.8 (*c*=2.8, CH_2Cl_2). R_f=0.30 (1:1 Hex/EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$) δ TMS: −0.24 (3H, s); 0.02 (3H, s); 0.82 (9H, s); 1.78 (1H, br, D_2O exch.); 2.56 (1H, ddd, *J*=4.4, 6.6, 6.7 Hz); 2.74 (1H, dd, *J*=6.6, 8.7 Hz); 3.13 (3H, m); 3.25 (1H, dd, *J*=7.2, 13.2 Hz); 3.47 (3H, s); 3.68 (3H, s); 3.90 (1H, m); 3.92 (3H, s); 5.27 (1H, d, *J*=7.0 Hz); 5.29 (1H, d, *J*=7.0 Hz); 7.92 (1H, d, *J*=1.5 Hz); 8.05 (1H, d, *J*=1.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ TMS: −5.3 (q), −4.8 (q), 17.7 (s), 25.5 (q), 31.9 (t), 42.8 (d), 46.9 (d), 52.6 (q), 53.4 (q), 56.6 (q), 60.0 (t), 70.0 (d), 94.9 (t), 117.4 (d), 118.1 (d), 125.9 (s), 130.2 (s), 151.5 (s), 156.6 (s), 163.3 (s), 164.6 (s). IR (NaCl, neat): 3503, 2954, 2857, 1732, 1538, 1438 cm^{-1}.

[2*S*-(2α,3α)]-Methyl ester 2-[1-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-2-[4-(methoxycarbonyl)-2-(methoxymethoxy)-6-nitrophenyl]ethyl]-3-formyl-1-aziridinecarboxylic acid (20). The alcohol described in the previous experiment (98 mg, 0.18 mmol, 1.0 equiv.), and 1.5 mL of CH_2Cl_2 were added to a 25 mL flask. The mixture was stirred for 5 min and Dess–Martin reagent[16] (118 mg, 0.32 mmol, 1.8 equiv.) was added to the flask in one portion. After stirring for 2.5 h, the cloudy white mixture was diluted in 10 mL Et_2O and poured into a solution of 20 mL sat $NaHCO_{3(aq)}$ with 8.0 equiv. of $Na_2S_2O_3{\cdot}5H_2O$ (435 mg). The milky biphasic mixture turned clear after 15 min of vigorous stirring. The two layers were separated, and the organic layer was washed with 1×10 mL $NaHCO_{3(aq)}$, and 1×10 mL H_2O. The combined aqueous layers were extracted with 3×15 mL Et_2O. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The crude oil was purified by flash chromatography (2:1 Hex/EtOAc) to give 81 mg (82% yield) of **20** as a clear colorless oil (>95% pure).

Major diastereomer **20**: $[\alpha]_D^{25}$=+5.4 (*c*=1.1, CH_2Cl_2). R_f=0.42 (1:1 Hex/EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$) δ TMS: −0.18 (3H, s); 0.00 (3H, s); 0.76 (9H, s); 2.79 (1H, dd, *J*=3.5, 6.8 Hz); 3.00 (1H, dd, *J*=4.6, 6.8 Hz); 3.14 (1H, dd, *J*=6.8, 13.2 Hz); 3.23 (1H, dd, *J*=7.4, 13.2 Hz); 3.49 (3H, s); 3.68 (3H, s); 3.92 (3H, s); 4.50 (1H, ddd, *J*=3.5, 6.8, 7.4 Hz); 5.30 (2H, s); 7.94 (1H, d, *J*=1.5 Hz); 8.12 (1H, d, *J*=1.5 Hz); 9.50 (1H, d, *J*=4.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ TMS: −5.3 (q), −4.7 (q), 17.9 (s), 25.6 (q), 32.1 (t), 45.1 (d), 48.7 (d), 52.7 (q), 53.9 (q), 56.7 (q), 67.7 (d), 94.9 (t), 118.0 (d), 118.4 (d), 125.8 (s), 130.4 (s), 151.2 (s), 156.7 (s), 161.9 (s), 164.6 (s), 196.9 (d). IR (NaCl, neat): 2962, 2863, 1730, 1537, 1437 cm^{-1}. Anal. for the mixture of diastereomers: calcd for $C_{23}H_{34}N_2O_{10}Si$: C, 52.46; H, 6.51; N, 5.32. Found: C, 52.64; H, 6.61; N, 5.30.

Minor diastereomer **20**: $[\alpha]_D^{25}$=+112 (*c*=2.0, CH_2Cl_2). R_f=0.42 (1:1 Hex/EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$) δ TMS: −0.23 (3H, s); 0.08 (3H, s); 0.85 (9H, s); 3.01 (2H, m); 3.05 (1H, dd, *J*=6.7, 13.3 Hz); 3.23 (1H, dd, *J*=7.3, 13.3 Hz); 3.47 (3H, s); 3.72 (3H, s); 3.93 (3H, s); 3.96 (1H, m); 5.26 (1H, d, *J*=7.0 Hz); 5.28 (1H, d, *J*=7.0 Hz); 7.91 (1H, d, *J*=1.5 Hz); 8.06 (1H, d, *J*=1.5 Hz); 8.95 (1H, d, *J*=5.5 Hz). ^{13}C NMR (75 MHz, CDCl3) δ TMS: −5.3 (q), −4.8 (q), 17.7 (s), 25.5 (q), 31.7 (t), 45.6 (d), 48.7 (d), 52.6

(q), 53.8 (q), 56.6 (q), 69.7 (d), 94.8 (t), 117.6 (d), 118.3 (d), 125.1 (s), 130.5 (s), 151.4 (s), 156.3 (s), 161.4 (s), 164.5 (s), 195.0 (d). IR (NaCl, neat): 2956, 2858, 1732, 1538, 1439 cm^{-1}.

(1a*S*,9a*S*)-Dimethyl ester 9-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-1a,2,3,8,9,9a-hexahydro-7-(methoxymethoxy)-1H-azirino[2,3-*c*][1]benzazocine-1,5-dicarboxylic acid (23). 40 mL of MeOH, freshly distilled from CaH_2, was added to a 100 mL flask. The stirred solution was degassed with H_2 for 30 min using a 20 gauge needle connected directly to a H_2 cylinder. The flask was then flushed with argon, and 5% Pd/C (200 mg, 0.095 mmol, 0.25 equiv.) was added in one portion. The mixture was degassed with H_2 for another 30 min and then kept under H_2 for another 30 min. Nitroaldehyde **20** (200 mg, 0.38 mmol, 1.0 equiv.) in 2 mL of MeOH was added to the mixture dropwise over 1 min. After 8 min, TLC analysis (1:1 Hex/EtOAc) of the reaction showed complete loss of **20**. The reaction was diluted with MeOH and passed through a short pad of Celite using MeOH, and the filtrate was concentrated in vacuo. The residue was filtered through a short plug of Celite using CH_2Cl_2, and the filtrate was concentrated again. The residue was dissolved in 200 mL of CH_2Cl_2. Activated 4 Å molecular sieves (~30 pieces) and $MgSO_4$ (2 g) were added to the solution. The stirred mixture was heated to reflux for 24–36 h. The cooled mixture was filtered through a pad of Celite using 10:1 CH_2Cl_2/MeOH (500 mL). The filtrate was concentrated, and the residue was immediately dissolved in solution of 2:1 CH_2Cl_2/MeOH (12 mL). After the mixture was cooled on an ice bath for 10 min, $NaCNBH_3$ (23 mg, 0.38 mmol, 1.0 equiv.) and TFA (29 μL, 0.38 mmol, 1.0 equiv.) were added in one portion. After 4 min, TLC analysis of the reaction (1:1 Hex/EtOAc) showed no signs of the starting material, and the reaction was quenched with 30 mL sat $NaHCO_{3(aq)}$. The two layers were separated, and the aqueous layer was extracted with 3×CH_2Cl_2. The combined organic layers were washed with 1×sat $NaCl_{(aq)}$, dried over Na_2SO_4, filtered, concentrated, and purified by radial silica PTLC (4 mm plate, 2:1 Hex/EtOAc) to give 110 mg (40–60% yield from **20**) of **23** as a clear yellow oil (>95% pure).

[2*S*-(2α,3α)]-Methyl ester 2-[2-[2-amino-4-(methoxycarbonyl)-6-(methoxymethoxy)phenyl]-1-[[(1,1-dimethylethyl)dimethylsilyl]oxy]ethyl]-3-formyl-1-aziridinecarboxylic acid (21). Major diastereomer **21**: R_f=0.43 (1:1 Hex/EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$) δ TMS: −0.13 (3H, s); 0.10 (3H, s); 0.82 (9H, s); 2.69 (1H, dd, *J*=6.5, 13.8 Hz); 2.82 (1H, dd, *J*=7.8, 13.7 Hz); 2.88 (1H, dd, *J*=2.6, 6.9 Hz); 3.05 (1H, dd, *J*=4.0, 6.9 Hz); 3.47 (3H, s); 3.73 (3H, s); 3.84 (3H, s); 3.89 (2H, br, D_2O exch.); 4.44 (1H, m); 5.21 (2H, s); 7.03 (1H, d, *J*=1.4 Hz); 7.11 (1H, d, *J*=1.4 Hz); 9.54 (1H, d, *J*=4.0 Hz). IR (NaCl, neat): 3466, 3381, 2954, 2857, 1718, 1586, 1437 cm^{-1}.

Intermediate imine (22). Major diastereomer **22**: R_f=0.49 (1:1 Hex/EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$) δ TMS: 0.07 (3H, s); 0.18 (3H, s); 0.96 (9H, s); 2.29 (1H, dd, *J*=11.0, 12.9 Hz); 2.56 (1H, dd, *J*=5.9, 5.9 Hz); 2.86 (1H, d, *J*=6.0 Hz); 3.00 (1H, dd, *J*=4.3, 12.9 Hz); 3.46 (3H, s); 3.73 (3H, s); 3.87 (3H, s); 4.28 (1H, ddd, *J*=4.5, 6.0, 10.7 Hz); 5.22 (1H, d, *J*=6.9 Hz); 5.28 (1H, d, *J*=6.9 Hz); 7.36 (1H, d, *J*=1.4 Hz); 7.50 (1H, d, *J*=1.4 Hz); 8.09 (1H, s).

(1a*S*,9a*S*)-Dimethyl ester 9-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-1a,2,3,8,9,9a-hexahydro-7-(methoxymethoxy)-1H-azirino[2,3-*c*][1]benzazocine-1,5-dicarboxylic acid (23). Major diastereomer **23**: $[\alpha]_D^{25}$=+48.9 (*c*=0.9, CH_2Cl_2). R_f=0.42 (1:1 Hex/EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$) δ TMS: 0.15 (3H, s); 0.17 (3H, s); 0.94 (9H, s); 2.52 (2H, m); 2.84 (1H, dd, *J*=10.5, 13.9 Hz); 3.18 (1H, dd, *J*=5.3, 13.9 Hz); 3.46 (3H, s); 3.59 (1H, m); 3.67 (3H, s); 3.78 (1H, m); 3.84 (3H, s); 4.06 (1H, br, D_2O exch.); 4.47 (1H, ddd, *J*=5.3, 5.3, 5.3 Hz); 5.19 (1H, d, *J*=6.6 Hz); 5.23 (1H, d, *J*=6.6 Hz); 7.04 (1H, d, *J*=1.5 Hz); 7.18 (1H, d, *J*=1.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ TMS: −5.1 (q), −4.9 (q), 18.4 (s), 25.8 (q), 31.0 (t), 41.4 (d), 43.0 (d), 47.3 (t), 52.0 (q), 53.3 (q), 56.3 (q), 69.0 (d), 94.3 (t), 105.3 (d), 114.3 (d), 118.3 (s), 129.4 (s), 148.3 (s), 156.2 (s), 163.9 (s), 166.8 (s). IR (NaCl, neat): 3394, 2952, 2855, 1724, 1587, 1438 cm^{-1}. Mass spectrum (ES+) *m/z*: 481 (M+H). Anal. for the mixture of diastereomers: calcd for $C_{23}H_{36}N_2O_7Si$: C, 57.48; H, 7.55; N, 5.83. Found: C, 57.77; H, 7.86; N 5.64.

Minor diastereomer **23**: $[\alpha]_D^{25}$=+127 (*c*=0.9, CH_2Cl_2). R_f=0.50 (1:1 Hex/EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$) δ TMS: 0.10 (3H, s); 0.11 (3H, s); 0.92 (9H, s); 2.58 (1H, m); 2.66 (1H, dd, *J*=5.1, 6.9 Hz); 3.06 (1H, dd, *J*=8.7, 15.0 Hz); 3.12 (1H, d, *J*=4.5 Hz); 3.13 (1H, d, *J*=4.5 Hz); 3.45 (3H, s); 3.62 (1H, dd, *J*=3.6, 8.1 Hz); 3.66 (3H, s); 3.83 (1H, br, D_2O exch.); 3.84 (3H, s); 4.23 (1H, ddd, *J*=4.5, 4.5, 4.5 Hz); 5.16 (1H, d, *J*=6.6 Hz); 5.19 (1H, d, *J*=6.6 Hz); 7.07 (1H, d, *J*=1.5 Hz); 7.30 (1H, d, *J*=1.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ TMS: −5.0 (q), −4.9 (q), 18.2 (s), 25.7 (q), 33.5 (t), 40.2 (d), 48.2 (t), 48.4 (d), 52.0 (q), 53.4 (q), 56.2 (q), 72.9 (d), 94.6 (t), 107.7 (d), 115.6 (d), 123.3 (s), 129.0 (s), 149.3 (s), 156.4 (s), 163.3 (s), 166.8 (s). IR (NaCl, neat): 3387, 2953, 2856, 1724, 1585, 1437 cm^{-1}. Mass spectrum (ES+) *m/z*: 481 (M+H).

(1a*S*,9a*S*)-3-[(4,5-Dimethoxy-2-nitrophenyl)methyl] 1,5 dimethyl ester 9-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-1a,2,3,8,9,9a-hexahydro-7-(methoxymethoxy)-1H-azirino[2,3-*c*][1]benzazocine-1,3,5(2H)-tricarboxylic acid. Compound **23** (140 mg, 290 μmol, 1.0 equiv.) and 3.5 mL of CH_2Cl_2 were added to a 25 mL conical flask. The solution was stirred for 3 min when *N*,*N*-diisopropylethylamine (152 μL, 870 μmol, 3.0 equiv.), 6-nitroveratryl chloroformate (200 mg, 730 μmol, 2.5 equiv.), and DMAP (36 mg, 290 μmol, 1.0 equiv.) were added. After 4 h, TLC analysis (1:1 Hex/EtOAc) of the reaction showed no starting material. The reaction was diluted with 15 mL sat $NaHCO_{3(aq)}$ and extracted with 3×EtOAc. The combined organic layers were washed with 1×sat $NaCl_{(aq)}$, dried over Na_2SO_4, filtered, concentrated, and purified using radial silica gel PTLC (2:1 Hex/EtOAc, 2 mm plate) to give 185 mg (88% yield) of product as a clear yellow oil.

Major diastereomer: $[\alpha]_D^{25}$=+26.9 (*c*=1.2, CH_2Cl_2). R_f=0.40 (1:1 Hex/EtOAc). ^{1}H NMR (300 MHz, d_6-DMSO, 383 K) δ TMS: 0.12 (3H, s); 0.14 (3H, s); 0.88 (9H, s); 2.68 (2H, br); 2.88 (2H, s); 2.93 (1H, br); 3.07 (1H, br); 3.46 (3H, s); 3.62 (3H, s); 3.80 (3H, br); 3.86 (3H, s); 3.87 (3H, s); 4.34 (1H, br); 5.29 (2H, s); 5.41 (2H, s); 6.92

(1H, s); 7.46 (1H, d, J=1.5 Hz); 7.63 (1H, d, J=1.5 Hz); 7.65 (1H, s). IR (NaCl, neat): 2953, 2856, 1726, 1581, 1522, 1440 cm^{-1}. Mass spectrum (ES+) m/z (relative intensity): 720 (M+H) (100%). Exact mass: (FAB) calcd for $C_{33}H_{46}N_3O_{13}Si$ 720.2799. Found: 720.2786. Anal. calcd for $C_{33}H_{45}N_3O_{13}Si$: C, 55.06; H, 6.30; N, 5.84. Found: C, 54.93; H, 6.48; N, 5.66.

(1a*S*,9a*S*)-3-[(4,5-Dimethoxy-2-nitrophenyl)methyl] 5-methanol-9-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-1a,2,3,8,9,9a-hexahydro-7-(methoxymethoxy)-1H-azirino[2,3-*c*][1]benzazocine-3-carboxylic acid (24). Nitroveratryl carbamate described above (76 mg, 0.105 mmol, 1.0 equiv.) and 1.5 mL CH_2Cl_2 were added to a 25 mL round bottom flask. The stirred solution was cooled to −78°C on a CO_2/acetone bath for 10 min when 1.0 M DIBAL in hexane (528 μL, 0.528 mmol, 5.5 equiv.) was added in dropwise portions with 5 min between each addition. After 5 h, the reaction was quenched at −78°C by the addition of one drop of MeOH and two drops of sat $NaCl_{(aq)}$. After removing from the bath and coming to room temperature, the solution was filtered through a short plug of Celite with CH_2Cl_2. The two layers were separated, and the aqueous layer was extracted with 3×CH_2Cl_2. The combined organic layers were dried over Na_2SO_4. The solution was filtered, concentrated, and purified by radial silica gel PTLC (2 mm plate, 22:1 CH_2Cl_2/MeOH) to give 39 mg (61% yield) of aziridine **24** as a clear yellow oil.

Major diastereomer: $[\alpha]_D^{25}$=+25.4 (c=2.6, CH_2Cl_2). R_f=0.41 (10:1 CH_2Cl_2/MeOH). ^{1}H NMR (300 MHz, d_6-DMSO, 373 K) δ TMS: 0.12 (3H, s); 0.13 (3H, s); 0.91 (9H, s); 2.02 (2H, s); 2.86 (2H, s); 2.93 (2H, s); 3.45 (3H, s); 3.83 (3H, s); 3.87 (3H, s); 4.28 (1H, s); 4.46 (2H, s); 4.71 (1H, s, D_2O exch.); 5.19 (1H, d, J=6.6 Hz); 5.22 (1H, d, J=6.6 Hz); 5.41 (2H, s); 6.81 (1H, s); 7.03 (2H, s); 7.66 (1H, s). IR (NaCl, neat): 3368, 2954, 2856, 1713, 1582, 1524, 1441 cm^{-1}. Mass spectrum (ES+) m/z (relative intensity): 634 (M+H, 100%). Exact mass: (FAB) calcd for $C_{30}H_{44}N_3O_{10}Si$: 634.2796. Found: 634.2760. Anal. calcd for $C_{30}H_{43}N_3O_{10}Si$: C, 56.85; H, 6.84; N, 6.63. Found: C, 56.53; H, 7.07; N, 6.37.

(1a*S*,9a*S*)-3-[(4,5-Dimethoxy-2-nitrophenyl)methyl] 5-methanol-1a,2,3,8,9,9a-hexahydro-7-(methoxymethoxy)-9-hydroxy-1H-azirino[2,3-*c*][1]benzazocine-3-carboxylic acid. Compound **24** (50 mg, 0.079 mol, 1.0 equiv.) and 1 mL THF were added to a 10 mL conical flask. The solution was stirred for 5 min on an ice bath when 1.0 M TBAF in THF (135 μL, 0.135 mmol, 1.65 equiv.) was added dropwise over 1 min. After the addition was complete, the reaction was allowed to warm to room temp. After 4 h, TLC analysis (10:1 CH_2Cl_2/MeOH) showed no sign of starting material. The reaction was diluted with water, and the THF was removed in vacuo. The aqueous solution was extracted with 3×EtOAc. The combined organic layers were dried over Na_2SO_4, filtered, concentrated, and purified by radial silica gel PTLC (2 mm plate, 10:1 CH_2Cl_2/MeOH) to give 35 mg (85% yield) of the diol as a foamy yellow oil. The unstable diol was immediately taken on to the next step without further purification.

Major diastereomer: R_f=0.23 (10:1 CH_2Cl_2/MeOH). IR (NaCl, neat): 3429 br, 3314 br, 2928, 2854, 1704, 1581, 1524, 1440 cm^{-1}. Mass spectrum (ES+) m/z (relative intensity): 520 (M+H, 100%).

(1a*S*,9a*S*)-3-[(4,5-Dimethoxy-2-nitrophenyl)methyl] 1-methyl ester 5-methanol-1a,2,3,8,9,9a-hexahydro-7-(methoxymethoxy)-9-hydroxy-1H-azirino[2,3-*c*][1]benzazocine-1,3(2H)-dicarboxylic acid (25). The diol described above (15 mg, 29 μmol, 1.0 equiv.) and 300 μL pyridine were added to a 10 mL flask. After stirring for 5 min, *N*-((methoxy)carbonyloxy)succinimide (5 mg, 29 μmol, 1.0 equiv.) was added in one portion. After 2.5 h, TLC analysis (10:1 CH_2Cl_2/MeOH) showed complete loss of starting material, and the reaction was diluted with water and sat $NH_4Cl_{(aq)}$. The aqueous solution was extracted with 3×EtOAc. The combined organic layers were washed with 1×sat $NaHCO_{3(aq)}$ and 1×sat $NaCl_{(aq)}$, dried over Na_2SO_4, filtered, concentrated, and purified by radial silica gel PTLC (10:1 CH_2Cl_2/MeOH, 2 mm plate) to give 14 mg (89% yield from **24**) of **25** as a foamy yellow oil.

Major diastereomer: $[\alpha]_D^{25}$=+30.6 (c=1.5, CH_2Cl_2). R_f=0.38 (10:1 CH_2Cl_2/MeOH). ^{1}H NMR (300 MHz, d_6-DMSO, 378 K) δ TMS: 2.64 (2H, s); 2.84 (2H, s); 2.91 (2H, s); 3.44 (3H, s); 3.62 (3H, s); 3.78 (3H, s); 3.85 (3H, s); 4.06 (1H, s); 4.41 (1H, br, D_2O exch.); 4.45 (2H, s); 4.72 (1H, D_2O exch.); 5.21 (2H, s); 5.37 (2H, s); 6.81 (1H, s); 6.90 (1H, s); 7.03 (1H, s); 7.65 (1H, s). IR (NaCl, neat): 3741, 2954, 2852, 1731, 1715, 1614, 1582, 1520, 1442 cm^{-1}. Mass spectrum (ES+) m/z (relative intensity): 578 (M+H, 100%). Exact mass: (FAB) calcd for $C_{26}H_{32}N_3O_{12}$: 578.1986. Found: 578.1954. Anal. calcd for $C_{26}H_{32}N_3O_{12}\cdot 0.6H_2O$: C, 53.07; H, 5.51; N, 7.14. Found: C, 53.39; H, 5.71; N, 6.75.

(1a*S*-*cis*)-3-[(4,5-Dimethoxy-2-nitrophenyl)methyl] 1-methyl ester 5-formyl-1a,8,9,9a-tetrahydro-7-(methoxymethoxy)-9-oxo-1H-azirino[2,3-*c*][1]benzazocine-1,3(2H)-dicarboxylic acid (26). Diol **25** (35 mg, 62 μmol, 1.0 equiv.) and 600 μL CH_2Cl_2 were added to a 10 mL conical flask. The solution was stirred for 5 min when Dess–Martin periodinane[16] (68 mg, 160 μmol, 2.6 equiv.) was added in one portion. The reaction immediately became cloudy and white. After 1.5 h, additional amounts of Dess–Martin reagent (55 mg) and 150 μL CH_2Cl_2 were added to the reaction. After another 0.5 h, TLC analysis (10:1 CH_2Cl_2/MeOH) showed no sign of staring material. The reaction was diluted with Et_2O and added to a solution of sat $NaHCO_{3(aq)}$ and $NaS_2O_3\cdot 5H_2O$ (123 mg, 8 equiv.). The biphasic mixture was vigorously stirred for 15 min. The organic layer was diluted with EtOAc and separated from the aqueous layer. The organic layer was washed with 1×sat $NaHCO_{3(aq)}$ and 1×H_2O. The combined aqueous layers were back extracted with 2×EtOAc. The combined organic layers were dried over Na_2SO_4, filtered, concentrated, and purified using radial silica gel PTLC (2 mm plate, 2:1 CH_2Cl_2/Et_2O) to give 28 mg (83% yield) of ketone **26** as a clear foamy oil.

Major diastereomer: $[\alpha]_D^{25}$=−40.3 (c=1.3, CH_2Cl_2). R_f=0.80 (10:1 CH_2Cl_2/MeOH). ^{1}H NMR (300 MHz, d_6-DMSO, 378 K) δ TMS: 2.91 (4H, s); 3.37 (1H, s); 3.38 (1H, s); 3.44 (3H, s); 3.60 (3H, s); 3.76 (3H, s); 3.85 (3H, s); 5.34 (4H, m); 6.82 (1H, s); 7.27 (1H, s); 7.58 (1H, s); 7.63

(1H, s); 9.93 (1H, s). IR (NaCl, neat): 2954, 2847, 1729, 1702, 1581, 1521, 1443 cm^{-1}. UV λ_{max} (CH_3CN) nm (ϵ): 345 (6800), 298 (7740), 238 (18 500). Mass spectrum (FAB) *m/z* (relative intensity): 574 (M+H, 100%). Exact mass: (FAB) calcd for $C_{26}H_{28}N_3O_{12}$: 574.1673. Found: 574.1702.

(2*S*)-Methyl ester [6-formyl-2,3-dihydro-1-hydroxy-8-(methoxymethoxy)-1H-pyrrolo[1,2-*a*]indol-2-yl]-carbamic acid (30). Ketone **26** (15 mg, 26 μmol, 1.0 equiv.), 3 mL CH_3CN, and 1 mL H_2O were added to a 5 mL pyrex tube. The test tube was placed in a 50 mL pyrex test tube. The 50 mL tube was stoppered and placed in a Rayonet™ photochemical reactor and exposed to 350 nm light. Over the course of the reaction, the solution slowly turned dark orange. After 24 h, the reaction mixture was removed from the photo reactor, and the CH_3CN was removed in vacuo. The resulting aqueous solution was diluted with water and extracted with 3×EtOAc. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated. The orange residue was purified by PTLC to yield 3.0 mg of **30** (38% yield) as brown solids in a 1:1 mixture of isomers. The stereochemistry was tentatively assigned by ^1H NMR correlation with similar diastereomers.[21]

trans-Diastereomer: $[\alpha]_D^{25}=+15.2$ (c=0.25, CH_2Cl_2). R_f=0.42 (20:20:1 CH_2Cl_2/Et_2O/MeOH). ^1H NMR (300 MHz, $CDCl_3$) δ TMS: 2.34 (1H, br, D_2O exch.); 3.52 (3H, s); 3.74 (3H, s); 3.92 (1H, dd, J=8.0, 10.0 Hz); 4.55 (1H, dd, J=8.0, 10.0 Hz); 4.88 (1H, m); 5.19 (1H, d, J=4.8 Hz); 5.34 (1H, d, J=6.6 Hz); 5.37 (1H, d, J=6.6 Hz); 5.70 (1H, d, J=7.2 Hz); 6.65 (1H, s); 7.23 (1H, d, J=1.2 Hz); 7.41 (1H, d, J=1.2 Hz); 9.88 (1H, s). IR (NaCl, neat): 3354, 2956, 2923, 1716, 1682, 1558, 1538, 1456 cm^{-1}. ^{13}C NMR (75 MHz, $CDCl_3$) δ TMS: 47.9 (t), 52.6 (d), 56.3 (q), 56.5 (q), 66.6 (d), 77.1 (s), 94.1 (d), 94.5 (t), 102.2 (d), 109.4 (d), 127.8 (s), 132.3 (s), 133.5 (s), 144.9 (s), 151.2 (s), 192.0 (d). Mass spectrum (ES+) *m/z* (relative intensity): 335 (M+H, 100%). Exact mass: (FAB) calcd for $C_{16}H_{19}N_2O_6$: 335.1243. Found: 335.1229.

cis-Diastereomer: $[\alpha]_D^{25}=-21.6$ (c=0.25, CH_2Cl_2). R_f=0.27 (20:20:1 CH_2Cl_2/Et_2O/MeOH). ^1H NMR (300 MHz, $CDCl_3$) δ TMS: 2.81 (1H, br, D_2O exch.); 3.53 (3H, s); 3.73 (3H, s); 3.93 (1H, m); 4.61 (2H, m); 5.06 (1H, br, D_2O exch.); 5.22 (1H, d, J=3.9 Hz); 5.35 (2H, s); 6.64 (1H, s); 7.25 (1H, d, J=1.2 Hz); 7.45 (1H, d, J=1.2 Hz); 9.93 (1H, s). IR (NaCl, neat): 3332, 2923, 2852, 1704, 1682, 1568, 1532, 1455 cm^{-1}. ^{13}C NMR (75 MHz, $CDCl_3$) δ TMS: 48.4 (t), 52.7 (d), 56.3 (q), 63.3 (q), 74.2 (d), 77.1 (s), 94.0 (d), 94.9 (t), 103.3 (d), 108.5 (d), 128.7 (s), 132.4 (s), 133.6 (s), 145.2 (s), 151.2 (s), 191.8 (d). Mass spectrum (ES+) *m/z* (relative intensity): 335 (M+H, 100%). Exact mass: (FAB) calcd for $C_{16}H_{19}N_2O_6$: 335.1243. Found: 335.1244.

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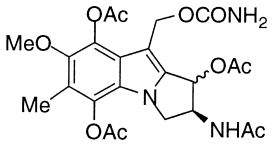
19. A control experiment where, incubation of **29** in the dark for 24 h in 3:1 CH_3CN/H_2O at room temperature led to no detectable loss of the starting material.

20. From this point forward, only the major diastereomer series was carried through.

21. The stereochemistry of tetraacetates *i* and *ii* has previously been determined: Egbertson, M. S. PhD Dissertation, Yale University, 1989.



i, cis

ii, trans