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IMPROVED SYNTHESES OF THE FR900482 AND MITOMYCIN BENZAZOCINE RING CORE *VIA* MITSUNOBU CYCLIZATION

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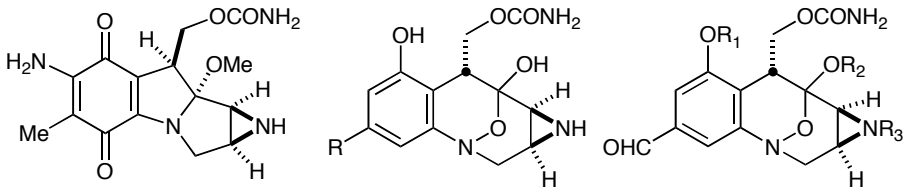
Abstract – An asymmetric synthesis of a highly functionalized benzazocine core of FR900482 and the mitomycins has been achieved in 20 and 19 steps, respectively. Key features of the synthesis include a highly chemoselective reduction of a nitro group and a Mitsunobu cyclization using either sulfonamides or carbamates. Removal of the protecting groups afforded the free benzazocine.

INTRODUCTION

Antitumor drugs restricting uncontrolled cellular growth by acting at the level of DNA replication and transcription are an important class of clinical agents.[1] Among these agents, mitomycin C (**1**) has been widely used in cancer chemotherapy for solid tumors for over 30 years despite its high hematotoxicity.[2] More recently, in the search for superior anticancer agents, Fujisawa Pharmaceutical Co isolated from the fermentation broth of *Streptomyces sandaensis* two new highly potent natural antitumor antibiotic alkaloids FR900482 (**2**) and FR66979 (**3**), which are structurally related to the mitomycins (Figure 1).[3] Similar to the mitomycins, studies on the mode of action of **2** and **3** have established that the cytotoxicity of these new agents derives from the formation of covalent DNA interstrand as well as DNA-protein cross-links both *in vitro* and *in vivo* as a result of the reactive mitosene intermediate generated upon reductive activation.[4] Semi-synthetic derivatives such as FK973 (**4**) and FK317[5] (**5**) were subsequently developed in the search for potentially superior clinical candidates.

Due to their potent antitumor activity, intriguing mode of action and densely functionalized structure, mitomycin C, FR900482 and congeners have attracted considerable interest from synthetic chemists. As a result, many original approaches to these compounds have been described in the literature resulting in a number of total syntheses of both the mitomycins[6] and FR900482 alkaloids.[7]



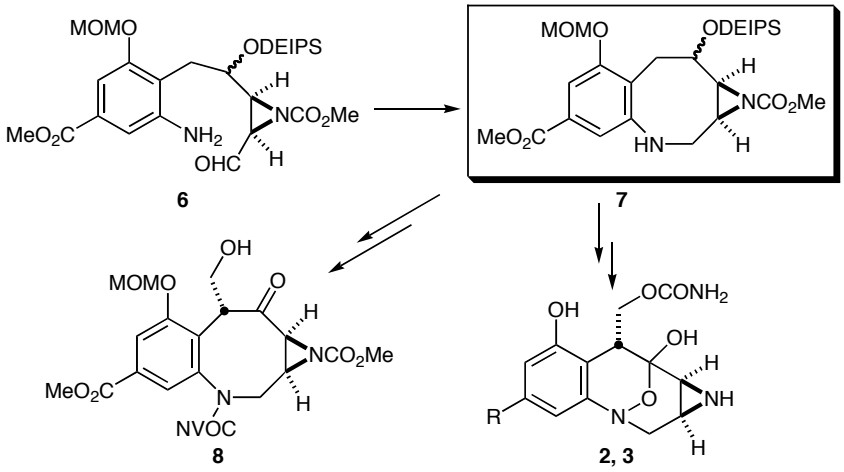
1, mitomycin C

2, FR900482, R=CHO
3, FR66979, R=CH_2OH

4, FK973, R_1=R_2=R_3=Ac
5, FK317, R_1=Me, R_2=R_3=Ac

Figure 1 Structure of mitomycin C, FR900482 and congeners

Most of the strategies that have been deployed rely upon the formation of the benzazocine ring system as a key intermediate, since, in principle, both the mitomycin and FR900482 frameworks can be accessed by varying the oxidation state of the benzazocine nitrogen.[8] New procedures for the synthesis of highly functionalized benzazocines are therefore of great interest. Synthetic efforts in our group were engaged and ultimately culminated in the concise enantioselective total synthesis of FR900482 (**2**) and FR66979 (**3**).[7d,g] A key intermediate in our synthesis was the aziridine containing benzazocine (**7**) that was subsequently used as a late stage intermediate in synthetic routes to **2** and **3** in addition to the photo-triggered mitosene progenitor (8)[9] (Scheme 1).



6 **7** **8** **2, 3**

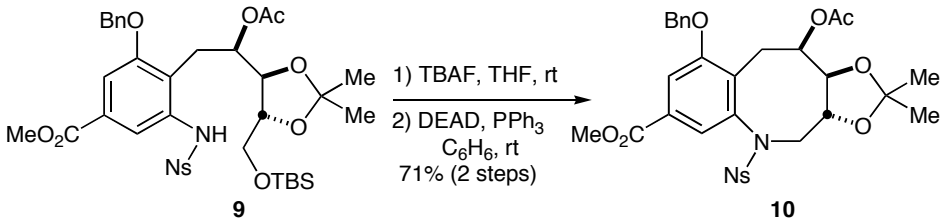
Scheme 1 Benzazocine (**7**) as FR900482/pro-mitosenes intermediate

RESULTS AND DISCUSSION

Compound (**7**) was obtained in moderate yield (50-70%) upon reductive amination of the anilinoaldehyde (**6**). Unfortunately, despite extensive optimization efforts, this reaction suffered from extensive dimerization upon scale up and therefore could only be carried out under dilute conditions (typically ~1 mM) and on a relatively small scale (200-300 mg). In order to address these shortcomings we envisioned

a new synthetic route to the benzazocine involving an intramolecular Mitsunobu[10] cyclization of a highly functionalized aziridine alcohol.

In 1995, Fukuyama and co-workers described the preparation of 2- and 4-nitrobenzenesulfonamides (Ns amide) and their use in Mitsunobu reactions for the synthesis of secondary amines, and later for the formation of macrocycles.[11] The value of this strategy was ultimately demonstrated in synthetic efforts towards the enantioselective total synthesis of FR900482 in which the ω-hydroxy-2-Ns amide (**9**) gave the benzazocine (**10**) in good yield *via* an intramolecular Mitsunobu cyclization (Scheme 2).[7h]



9 **10**

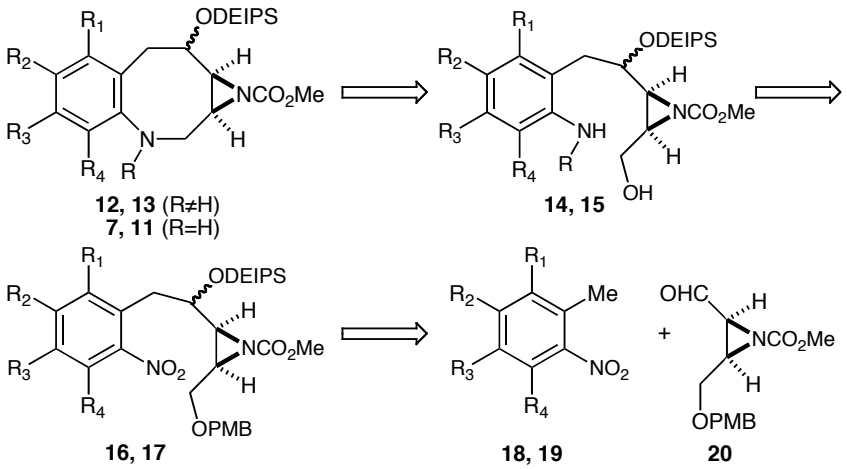
Scheme 2 Fukuyama's Mitsunobu cyclization

It should be mentioned that a similar strategy involving a Mitsunobu cyclization had been attempted in early synthetic efforts in our group utilizing a free aniline similar to **6**, but failed as a result of the lack of aniline activation.[12] With these observations in mind and in light of Fukuyama's successful cyclization, it became clear that the aniline nitrogen atom had to be substituted in a manner that would serve two purposes in our synthesis: (i) activation of the aniline through lowering the pK_a and, (ii) protection of the aniline during the oxidative removal of the *O*-pMB ether to furnish the corresponding alcohol. Herein, we report a synthesis of the core benzazocine ring system for both the FR900482 and mitomycin families of antitumor agents utilizing an intramolecular Mitsunobu cyclization of a highly functionalized aziridine alcohol with either a *N*-sulfonamide or *N*-carbamoyl moiety. Deprotection strategies to obtain the free anilines (**7**) and (**11**) will also be discussed.

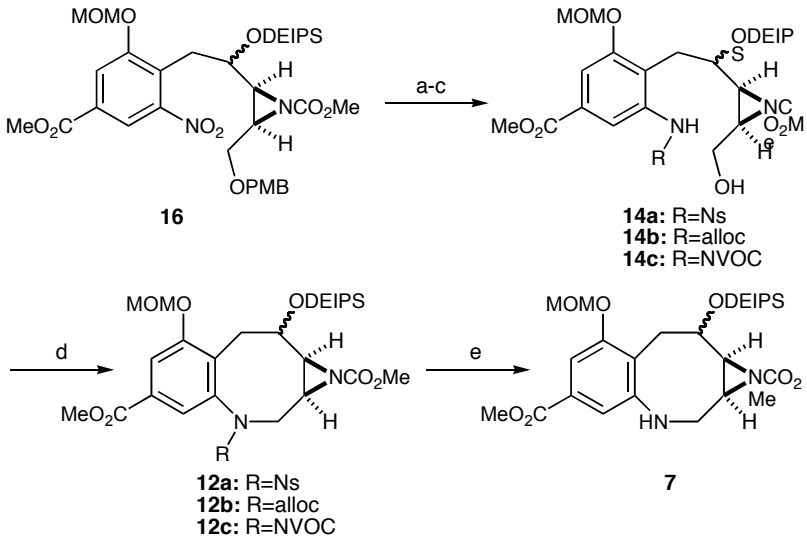
Our initial strategy for both the FR900482 and mitomycin series is outlined in Scheme 3. The nitro compounds (**16**) and (**17**), which would be prepared from coupling of the optically active aziridine (**20**)[13] and the appropriate nitrotoluene derivatives (**18**)[13] or (**19**),[14] would then be elaborated to the Mitsunobu precursors (**14**) and (**15**) in a three-step procedure. With **14** and **15** in hand, the Mitsunobu cyclization if successful, would afford the protected benzazocines (**12**) and (**13**) for both the FR900482 and mitomycin series.

Compound (**16**) was synthesized as previously described,[7g] as a mixture of diastereomers, which were separated by chromatography and subsequently processed independently. The first challenge was to effect the efficient and chemo-selective reduction of the nitro group of **16** in the presence of the pMB ether and

the sensitive aziridine. After extensive investigation, catalytic transfer hydrogenation[15] proved to be the most efficient method and cleanly afforded the desired aniline derivative in high yield. This is a notable improvement over the reduction conditions used by Fukuyama *et al*. on a similar substrate[7h] (20 min, 93% vs 52 h, 65%). Protection of the aniline as the corresponding nosyl (Ns) amide by treatment with 2-NsCl in pyridine followed by removal of the pMB group with DDQ afforded the desired alcohol (**14a**). Reaction of **14a** under standard Mitsunobu conditions (DEAD, Ph_3P, benzene) gave the desired benzazocine (**12a**) in 80% yield for both diastereomers (Scheme 4).



Scheme 3 Retrosynthesis of mitomycin/FR900482 benzazocines

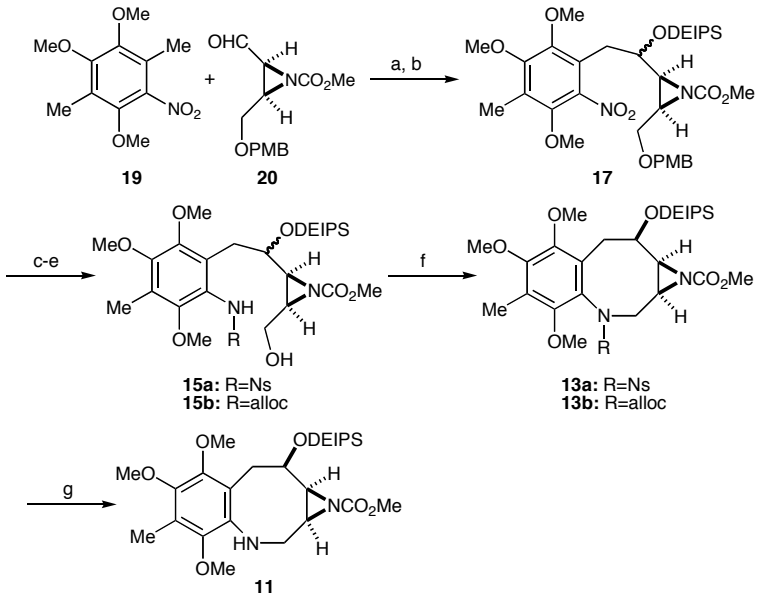


Scheme 4 Mitsunobu cyclization. Conditions: (a) 5% Pd-C 0.1 equiv, HCO_2NH_4 5 equiv, MeOH, rt, 20 min, 93%. (b) NsCl, pyridine, rt, 73% or RCOCl, $NaHCO_3$ aq, CH_2Cl_2, rt (R=alloc 80%, R=NVOC 78%). (c) DDQ, CH_2Cl_2:H_2O 15:1, rt, (R=Ns 73%, R=alloc 89%, R=NVOC 75%). (d) DEAD, Ph_3P, toluene, rt, (R=Ns 95%, R=NVOC 83%) or TMAD, PBu_3, toluene, rt (R=alloc 82%). (e) Cs_2CO_3, PhSH, MeCN, rt, 90%.

Interestingly, a more detailed investigation revealed that toluene was a slightly more effective solvent than benzene, resulting in a reduced reaction time (15 min) and slightly higher yield (95%). Using these optimized conditions, the cyclization was successfully performed on multigram scale. This result represents a considerable improvement over our previous cyclization route[7g] (15 min, 95% vs 72 h, 50-70%). Removal of the nosyl group using cesium carbonate and thiophenol[7h,16] cleanly afforded the benzazocine (**7**), which was spectroscopically identical to an authentic sample.[7g] Although the number of steps from **16** to **7** (5 steps) is identical to that of our reductive amination route, this procedure possesses several advantages including scale-up, short reaction times and ease of purification.

Having demonstrated the feasibility of the intramolecular Mitsunobu cyclization for the construction of the eight-membered ring, we then became interested in determining if this procedure could be applied to (i) groups other than a sulfonamide, such as carbamates and, (ii) synthesis of the core benzazocine (**13**) precursor to the mitomycins.

Reaction of the aniline derived from **16** with allyl or 6-nitroveratryl chloroformates and sodium hydrogen carbonate afforded the desired carbamates in high yield. Removal of the pMB group gave the alcohols (**14b,c)** (Scheme 4). Mitsunobu coupling using the DEAD/Ph_3P system gave the desired cyclized products (**12b,c)** that proved identical to a sample previously prepared.[9c] Interestingly, the cyclization of **14b** using the above conditions was much slower than for **14c** under similar condition and did not go to completion even after extended reaction time (40 h). Harsher conditions (90°C, 36 h, 79%) were required for efficient conversion to proceed. This observation likely reflects the higher pK_a of the carbamate group of **14b** as compared to **14c**.

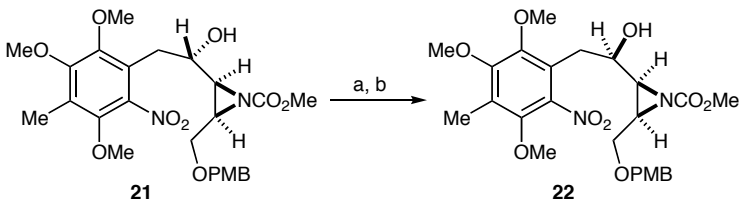


Scheme 5 Mitomycin benzazocine synthesis. Conditions: (a) NaHMDS, $ZnCl_2$, DMF, -45°C, 87%. (b) DEIPSCl, Im, CH_2Cl_2, rt, 89%. (c) 5% Pd-C 0.1 equiv, HCO_2NH_4 5 equiv, MeOH, rt, 80%. (d) NsCl, pyridine, rt, 79% or allocCl, $NaHCO_3$, CH_2Cl_2-H_2O, rt, 75%. (e) DDQ, CH_2Cl_2:H_2O 15;1, rt (R=Ns 87%, R=alloc 87%). (f) DEAD, Ph_3P, toluene, 70% (R=Ns) or TMAD, PBu_3, toluene, rt, 83% (R=alloc). (g) $Pd(Ph_3P)_4$ 5%, HCO_2H 4 equiv, THF, rt, 72%.

To overcome this reactivity problem we searched for alternative reagents for the Mitsunobu cyclization. A variety of Mitsunobu systems have been designed to allow for the use of nucleophiles possessing higher pKa values (pK_a=11-13).[17] Consequently, several reagents were screened and it was determined that the TMAD/PBu_3 system[18] allowed the cyclization of **14b** to proceed at room temperature in a reduced reaction time (6 h). This new approach to carbamate substituted benzazocines is two steps shorter than our previous synthesis[9c] and should allow the efficient preparation of various novel mitosene progenitors with alternative triggering mechanisms.

Finally, we turned our attention to utilizing this newly developed chemistry to construct the core benzazocine ring precursor to the mitomycins. Coupling of the nitrotoluene derivative (**19**) and the aziridine aldehyde (**20**) gave the desired alcohol as a 2:1 mixture of diastereomers, which were separated by column chromatography. Protection of the alcohols furnished the required precursor (**17**). Following the procedure used for the FR900482 series, we were pleased to find that the same sequence of reactions furnished the desired Mitsunobu products (**13a,b**) in all cases (Scheme 5).

As first observed for **14b**, the cyclization of the Alloc carbamate (**15b**) was noticeably slower than for the Ns amide (**15a**) and did not go to completion even after prolonged reaction time (24 h, 50% conversion). The use of TMAD/PBu_3, as before, proved to be a superior system for the Mitsunobu cyclization and provided **13b** much more efficiently (6 h, 83%). Although many similarities were observed with respect to the cyclization of intermediates in both the FR900482 and mitomycin series, we noticed several interesting differences. A surprising result was the stereochemical requirement for the Mitsunobu cyclization in the mitomycin series. It was found that the minor diastereomer of **15b** did not undergo cyclization even after prolonged heating in refluxing toluene. To rationalize this result, both diastereomers of **15b** were analyzed by molecular modeling. MM2 energy minimization showed that the C-N bond distance for the minor diastereomer (4.1 Å) was considerably greater than for the major diastereomer (3.0 Å) and likely accounts for the lack of reactivity. Fortunately, the minor diastereomer (**21**), obtained after coupling of **19** and **20**, could be easily converted in excellent yield to the major diastereomer (**22**) by Dess-Martin oxidation[19] to the corresponding ketone followed by reduction with $NaBH_3CN$ (Scheme 6).



Scheme 6 Epimerization. Conditions: (a) DMP, CH_2Cl_2, rt (b) $NaBH_3CN$, AcOH, CH_2Cl_2:MeOH 2:1, 4 °C, 95% (2 steps)

With an efficient method in hand for the construction of the requisite benzazocine ring, we then focused our efforts on the deprotection of the nitrogen position. Unfortunately, attempts to remove the Ns group of **13a** using a variety of conditions such as Cs_2CO_3/PhSH, $HSCH_2CO_2H/Et_3N$ or *n*-$PrNH_2$[20] failed to afford the desired benzazocine (**11**) even under forcing conditions. To the best of our knowledge this is the first example in which these conditions have failed to unmask a nosyl protected nitrogen. Alternatively, efforts to introduce a 2,4-dinitrosulfonamide[20b,21] moiety in an effort to facilitate the deprotection were also unsuccessful. In light of these results, we focused on the removal of the Alloc carbamate group in **13b**. Upon treatment of **13b** with tetrakis(triphenylphosphine)palladium in the presence of formic acid in THF[22] we were pleased to obtain the desired aniline (**11**) in 72% yield, whose data matched a sample prepared by an alternative procedure (unpublished result).

In conclusion, we have shown that the aziridine containing benzazocine ring precursor to the FR900482 and mitomycin alkaloids can be efficiently prepared by an intramolecular Mitsunobu reaction with either sulfonamides or carbamates. The free benzazocine could be obtained in each series. The use of benzazocine (**7**) to prepare stable and radioisotopically labeled FR900482 analogues as well as conversion of **13b** to achieve the first asymetric total synthesis of mitomycin K,[6c,d] A and C[6a,b] is currently being investigated and will be reported on in due course. In addition, this procedure, which is readily conducted on a preparative scale, provides access to gram quantities of various mitomycin and FR900482 analogues for biological testing.

EXPERIMENTAL

General Considerations. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ (^1H, 7.27; ^{13}C, 77.0 ppm) on Varian Inova-300 and Inova-400 spectrometers unless otherwise noted. When appropriate, the multiplicity of a signal is denoted as “br” to indicate the signal was broad. IR spectra were recorded on a Nicolet Avatar 320 spectrometer. MS spectra were obtained on a Fisons VG Autospec. Optical rotation values were measured using a Rudolph Research Autopol III automatic polarimeter referenced to the sodium D-line.

1,2,4-Trimethoxy-3,6-dimethyl-5-nitrobenzene (19)

To a solution of 1,3,4-trimethoxy-2,5-dimethylbenzene (20.0 g, 102 mmol) in acetic anhydride (400 mL) at 0°C was added cupric nitrate trihydrate (47.4 g, 204 mmol). After stirring for 45 min at rt, the reaction mixture was passed through a short plug of silica gel, eluted with EtOAc and the filtrate concentrated. The residual oil was dissolved in CH_2Cl_2 (200 mL), washed with sat. aq $NaHCO_3$ (150 mL) and brine (150 mL). The combined organics were dried over $MgSO_4$ and concentrated under reduced pressure. The

residue was purified by flash chromatography (90:10 hexanes:EtOAc) to afford **19** (24.0 g, 50%) as a yellow crystalline solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.14 (3H, s), 2.17 (3H, s), 3.76 (3H, s), 3.77 (3H, s), 3.82 (3H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 9.5, 10.6, 60.3, 60.5, 62.5, 122.3, 124.7, 142.9, 146.1, 147.6, 153.5. IR (NaCl neat) (cm^{-1}): 2997, 2942, 2854, 1571, 1532, 1471, 1370, 1253, 1094, 955. MS: m/z = 241 (100), 154 (90), 137 (72). HRMS (FAB+): m/z Calcd 241.0950 $(MH)^+$, Found 241.0954. mp: 26-27°C.

Methyl (2*R*,3*S*)-2-((4-methoxybenzyloxy)methyl)-3-(1-hydroxy-2-(2,3,5-trimethoxy-4-methyl-6-nitro-phenyl)ethyl)aziridine-1-carboxylate (21, 22)

Prior to the reaction, compounds (**19**) (8.6 g, 36 mmol) and **20** (5.0 g, 18 mmol) were dehydrated three times by azeotropic distillation using anhydrous toluene and lastly dried under vacuum for 1 h before use. A solution of **20** in dry DMF (15 mL) was then added to freshly fused zinc chloride (2.9 g, 21.5 mmol). The resulting solution was stirred under argon for 1 h at rt. In a separate flask, NaHMDS (36 mL of a 1 M solution in THF, 36 mmol) was added dropwise to a solution of **19** in dry DMF (50 mL) cooled to -45°C. The mixture immediately turned deep red. To this solution was added dropwise the aziridine solution prepared above and the resulting mixture was stirred at -45°C until completion of the reaction by TLC analysis. The reaction mixture was quenched with sat. aq NH_4Cl (50 mL), allowed to warm to rt and H_2O (50 mL) was added. The aqueous phase was extracted with CH_2Cl_2 (5x150 mL), the combined organics dried over Na_2SO_4 and concentrated under reduced pressure. The crude oil was purified by flash column chromatography (60:40 hexanes:EtOAc) to afford the alcohol (8.3 g, 89%) as a pale yellow oil (2:1 mixture of separable diastereomers (**21**) and (**22**)). Major diastereomer: $[\alpha]_D^{20}$=-21.1° (*c*=1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.22 (3H, s), 2.60 (1H, dd, *J* = 8.0, 6.0 Hz), 2.83 (1H, q, *J* = 6.0 Hz), 2.92-3.03 (3H, m), 3.46 (1H, dd, *J* = 10.5, 7.5 Hz), 3.61-3.68 (1H, m), 3.70 (3H, s), 3.79 (3H, s), 3.81 (3H, s), 3.83 (3H, s), 3.85 (3H, s), 4.50 (2H, d, *J* = 1.5 Hz), 6.85 (2H, dt, *J* = 8.5, 2.5 Hz), 7.23 (2H, dt, *J* = 8.5, 2.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 9.7, 31.5, 39.8, 45.1, 53.7, 55.2, 60.2, 60.6, 62.5, 67.6, 69.6, 72.9, 113.8, 122.4, 125.9, 129.2, 129.5, 143.0, 146.2, 147.8, 153.3, 159.2, 162.9. IR (NaCl neat) (cm^{-1}): 3479, 3002, 2944, 2856, 1730, 1612, 1533, 1466, 1370, 1299, 1115, 755. MS: m/z = 521 (100), 493 (46), 491 (26), 474 (49). HRMS (FAB+): m/z Calcd 521.2135 $(MH)^+$, Found 521.2134.

Minor diastereomer: $[\alpha]_D^{20}$=+6.1° (*c*=1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.20 (3H, s), 2.45 (1H, d, *J* = 5.0 Hz), 2.64 (1H, t, *J* = 7.0 Hz), 2.78-2.95 (3H, m), 3.28 (1H, dd, *J* = 11.0, 5.0 Hz), 3.50 (1H, dd, *J* = 11.0, 7.0 Hz), 3.71-3.75 (1H, m), 3.76 (3H, s), 3.79 (3H, s), 3.81 (3H, s), 3.82 (3H, s), 3.83 (3H, s), 4.47 (1H, d, *J* = 11.5 Hz), 4.56 (1H, d, *J* = 11.5 Hz), 6.87 (2H, dt, *J* = 8.5, 2.5 Hz), 7.27 (2H, dt, *J* = 8.5, 2.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 9.7, 31.3, 41.4, 45.9, 54.0, 55.3, 60.2, 60.6, 62.6, 67.0, 69.5,

72.6, 113.8, 121.5, 126.5, 129.6, 130.0, 143.1, 146.3, 147.9, 153.5, 159.3, 163.4. IR (NaCl neat) (cm^{-1}): 3364, 3009, 2937, 2893, 1729, 1611, 1532, 1249, 1090, 1035. MS: m/z = 521(100), 493 (44), 491 (27), 474 (49), 154 (52), 137 (36). HRMS (FAB+): m/z Calcd 521.2135 $(MH)^+$, Found 521.2135.

Methyl (2*R*,3*S*)-2-((4-methoxybenzyloxy)methyl)-3-(1-(diethyl(isopropyl)silyloxy)-2-(2,3,5-trimethoxy-4-methyl-6-nitrophenyl)ethyl)aziridine-1-carboxylate (17)

To a solution of the alcohols (**21**) and (**22**) obtained above (5.2 g, 10.0 mmol) and imidazole (2.4 g, 35 mmol) in dry DCM (250 mL) was added dropwise chlorodiethylisopropylsilane (3.3 g, 20 mmol). The mixture was stirred at rt for 24 h. The reaction was quenched with sat. aq $NaHCO_3$, diluted with DCM and the layers separated. The aqueous layer was extracted with EtOAc (2x50 mL). The combined organics were washed with brine (50 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography (80:20 hexanes:EtOAc) to afford **17** as a pale yellow oil (6.15 g, 89%). Major diastereomer: $[\alpha]_D^{20}$=-19.9° (*c*=1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.42-0.65 (4H, m), 0.75-1.02 (13H, m), 2.21 (3H, s), 2.49 (1H, t, *J* = 6.0 Hz), 2.76 (1H, q, *J* = 6.0 Hz), 2.83-2.95 (2H, m), 3.61-3.77 (2H, m), 3.72 (3H, s), 3.78 (3H, s), 3.79 (3H, s), 3.81 (3H, s), 3.83 (3H, s), 4.11 (1H, dt, *J* = 10.0, 5.0 Hz), 4.53 (1H, d, *J* = 11.5 Hz), 4.66 (1H, d, *J* = 11.5 Hz), 6.88 (2H, d, *J* = 8.5 Hz), 7.32 (2H, *J* = 8.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 3.4, 3.6, 6.8, 6.9, 9.6, 12.7, 17.1, 33.1, 41.4, 45.0, 53.6, 55.2, 60.0, 60.5, 62.5, 67.5, 68.5, 72.5, 113.7, 122.8, 125.7, 129.5, 130.3, 143.4, 146.2, 148.2, 153.3, 159.2, 163.7. IR (NaCl neat) (cm^{-1}): 2943, 2875, 1731, 1612, 1533, 1464, 1290, 1114, 1093, 727. MS: m/z = 649 (100), 605 (20), 469 (22), 122 (90) . HRMS (FAB+): m/z Calcd 649.3156 $(MH)^+$, Found 649.3147.

General procedure for the nitro reduction

Methyl (2*R*,3*S*) 2-((4-methoxybenzyloxy)methyl)-3-(2-(2-amino-4-(methoxycarbonyl)-6-(methoxymethoxy) phenyl)-1-(diethyl(isopropyl)silyloxy)ethyl)aziridine-1-carboxylate

To a stirred suspension of **16** (3.36 g, 5.07 mmol) and 5% Pd-C (0.6 g) in dry MeOH (40 mL) was added anhydrous ammonium formate (1.6 g, 25.3 mmol) in one portion. The mixture was stirred at rt and monitored by TLC (50:50 hexanes:EtOAc). After complete consump-tion of the starting material (20-30 min), the catalyst was removed by filtration through a pad of celite and the filtrate was concentrated under reduced pressure. To the residue was added H_2O (40 mL) and the aqueous phase was extracted with DCM (2x40 mL). The combined organics were dried over $MgSO_4$ and concentrated under reduced pressure to afford clean aniline as a pale yellow oil (2.89 g, 90%) which was used without further purification. For

analytical purposes, the aniline was purified by flash column chromatography (60:40 hexanes:EtOAc). Major diastereomer: $[\alpha]_D^{20}$=-6.7° (*c*=1.53, $CHCl_3$).

^{1}H (300 MHz, $CDCl_3$): δ = 0.50 (4H, app sext, *J* = 7.5 Hz), 0.77-0.92 (13H, m), 2.53 (1H, dd, *J* = 6.0, 5.0 Hz), 2.76 (1H, q, *J* = 6.0 Hz), 2.97 (2H, d, *J* = 6.0 Hz), 3.45 (3H, s), 3.72 (3H, s), 3.74 (2H, d, *J* = 6.5 Hz), 3.81 (3H, s), 3.87 (3H, s), 4.15 (2H, br s), 4.26 (1H, q, *J* = 6.0 Hz), 4.51 (1H, d, *J* = 11.5 Hz), 4.61 (1H, d, *J* = 11.5 Hz), 5.16 (1H, d, *J* = 6.5 Hz), 5.19 (1H, d, *J* = 6.5 Hz), 6.88 (2H, dt, *J* = 8.5, 2.0 Hz), 7.03 (1H, d, *J* = 1.5 Hz), 7.12 (1H, d, *J* = 1.5 Hz), 7.29 (2H, dt, *J* = 8.5, 2.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 3.4, 3.5, 6.7, 6.8, 12.7, 17.1, 32.0, 40.8, 44.9, 52.0, 53.6, 55.2, 56.1, 67.7, 68.7, 72.8, 94.2, 104.3, 110.9, 113.8, 117.3, 129.4, 129.6, 129.8, 147.3, 156.0, 159.3, 163.8, 167.1. IR (NaCl neat) (cm^{-1}): 3449, 3376, 2952, 2875, 1720, 1584, 1513, 1437, 1343, 1298, 1240, 1077, 730. MS: m/z = 633 (88), 394 (34), 345 (20), 224 (66), 154 (26), 136 (35), 121 (100). HRMS (FAB+): m/z Calcd 633.3207 $(MH)^+$, Found 633.3221.

Minor diastereomer: $[\alpha]_D^{20}$=+23.8° (*c*=0.55, $CHCl_3$). ^{1}H (300 MHz, $CDCl_3$): δ = 0.46 (2H, q, *J* = 7.5 Hz), 0.61 (2H, q, *J* = 7.5 Hz), 0.78-0.98 (13H, m), 2.66 (1H, q, *J* = 8.0 Hz), 2.71-2.75 (1H, m), 2.81-2.85 (2H, m), 3.34 (3H, s), 3.35 (1H, dd, *J* = 11.5, 6.5 Hz), 3.45 (1H, dd, *J* = 11.5, 4.0 Hz), 3.74 (3H, s), 3.75-3.82 (1H, m), 3.80 (3H, s), 3.87 (3H, s), 4.12 (2H, br s), 4.53 (1H, d, *J* = 11.5 Hz), 4.64 (1H, d, *J* = 11.5 Hz), 5.06 (1H, d, *J* = 7.0 Hz), 5.09 (1H, d, *J* = 7.0 Hz), 6.87 (2H, dt, *J* = 9.0, 2.5 Hz), 7.07 (1H, s,), 7.14 (1H, s), 7.29 (2H, dt, *J* = 9.0, 2.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 3.5, 3.6, 6.8, 6.9, 12.8, 17.1, 17.2, 31.5, 41.3, 46.0, 51.9, 53.5, 55.2, 56.0, 67.2, 71.4, 72.2, 94.1, 104.6, 111.1, 113.7, 116.9, 129.2, 129.4, 129.9, 147.2, 156.0, 159.2, 163.5, 166.9. IR (NaCl neat) (cm^{-1}): 3435, 3368, 2952, 2875, 1720, 1513, 1240, 1065, 730. MS: m/z = 633 (10), 394 (10), 121 (100). HRMS (FAB+): m/z Calcd 633.3207 $(MH)^+$, Found 633.3221.

Methyl (2*R*,3*S*)-2-((4-methoxybenzyloxy)methyl)-3-(2-(2-amino-3,5,6-trimethoxy-4-methylphenyl)-1-(diethyl(isopropyl)silyloxy)ethyl)aziridine-1-carboxylate

The experiment was carried out by the general procedure for the nitro reduction with **17** (0.72 g, 1.08 mmol), 5% Pd-C (0.13 g) and anhydrous ammonium formate (0.35 g, 5.57 mmol) in dry MeOH (6 mL). The crude product was purified by flash column chromatography (70:30 hexanes:EtOAc) to yield the aniline (0.53 g, 80%) as a pale yellow oil. Major diastereomer: $[\alpha]_D^{20}$=-7.3° (*c*=5.6, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.48 (4H, app sext, *J* = 8.0 Hz), 0.77-0.92 (13H, m), 2.17 (3H, s), 2.60 (1H, dd, *J* = 6.0, 5.0 Hz), 2.75 (1H, q, *J* = 6.0 Hz), 2.88 (2H, d, *J* = 7.0 Hz), 3.59-3.68 (2H, m), 3.67 (3H, s), 3.70 (3H, s), 3.73 (3H, s), 3.77 (3H, s), 3.80 (3H, s), 4.04 (2H, br s), 4.15 (1H, q, *J* = 6.0 Hz), 4.51 (1H, d, *J* = 11.5 Hz), 4.61 (1H, d, *J* = 11.5 Hz), 6.87 (2H, d, *J* = 8.5 Hz), 7.29 (2H, d, *J* = 8.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 3.4, 3.5, 6.7, 6.8, 9.2, 12.6, 17.1, 32.1, 41.0, 45.0, 53.5, 55.1, 59.3, 40.2, 60.2, 67.5,

69.6, 72.6, 113.6, 115.4, 123.0, 129.5, 129.9, 135.9, 141.6, 143.1, 148.2, 159.1, 163.8. IR (NaCl neat) (cm^{-1}): 3436, 3361, 2952, 1731, 1613, 1513, 1464, 1248, 1090, 1014, 821, 730. MS: m/z = 618 (100), 380 (24), 210 (46), 180 (17). HRMS (FAB+): m/z Calcd 618.3336 $(MH)^+$, Found 618.3361.

General procedure for the nosylation

Methyl (2*R*,3*S*)-2-((4-methoxybenzyloxy)methyl)-3-(1-diethyl(isopropyl)silyloxy)-2-(4-(methoxycarbonyl) -2-(methoxymethoxy)-6-(2-nitrophenylsulfonamido) phenyl)ethyl)aziridine-1-carboxylate

To a stirred solution of aniline derived from **16** (0.06 g, 0.095 mmol) in dry pyridine (0.4 mL) was added 2-nitrobenzenesulfonyl chloride (0.084 g, 0.38 mmol) portion wise over 20 min. After the end of the addition, the reaction was stirred at rt and monitored by TLC until complete consumption of the starting material. The reaction mixture was diluted with EtOAc and washed with brine (5 mL), 1N HCl (5 mL) and brine (5 mL). The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography (70:30 hexanes:EtOAc) to afford the sulfonamide as a pale yellow oil (0.056 g, 73%). Major diastereomer: $[\alpha]_D^{20}$=-6.4° (*c*=0.56, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.39 (2H, m), 0.48 (2H, q, *J* = 7.5 Hz), 0.69-0.86 (13H, m), 2.54 (1H, dd, *J* = 13.5, 11.0 Hz), 2.73 (1H, t, *J* = 6.5 Hz), 2.80 (1H, q, *J* = 6.0 Hz), 2.86 (1H, dd, *J* = 13.5, *J* = 3.5 Hz), 3.33 (3H, s), 3.50 (2H, m), 3.65-3.70 (1H, m), 3.67 (3H, s), 3.80 (3H, s), 3.93 (3H, s), 4.48 (1H, d, *J* = 11.5 Hz), 4.57 (1H, d, *J* = 11.5 Hz), 5.07 (2H, s), 6.86 (2H, dt, *J* = 8.5, 2.0 Hz), 7.24 (2H, dt, *J* = 8.5, 2.0 Hz), 7.55 (1H, dt, *J* = 7.5, 1.0 Hz), 7.60 (1H, d, *J* = 1.5 Hz), 7.70 (1H, dt, *J* = 7.5, 1.5 Hz), 7.74 (1H, dd, *J* = 7.5, 1.5 Hz), 7.95 (1H, dd, *J* = 8.0, 1.5 Hz), 7.97 (1H, d, *J* = 1.5 Hz), 8.83 (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 3.3, 3.4, 6.4, 6.6, 12.6, 16.9, 17.0, 31.3, 41.0, 45.6, 52.3, 53.7, 55.2, 56.1, 67.5, 69.0, 72.7, 94.4, 112.4, 113.7, 122.1, 125.9, 128.0, 129.5, 129.6, 129.8, 130.6, 132.5, 133.5, 133.7, 137.1, 147.8, 155.1, 159.3, 163.0, 166.3. IR (NaCl neat) (cm^{-1}): 3269, 2954, 1726, 1543, 1306, 1244, 1174, 1087, 1061, 732. MS: m/z = 818 (8), 307 (19), 154 (68) 137 (48), 121 (100). HRMS (FAB+): m/z Calcd 818.2990 $(MH)^+$, Found 818.2980.

Methyl (2*R*,3*S*)-2-((4-methoxybenzyloxy)methyl)-3-(1-(diethyl(isopropyl)silyloxy)-2-(2,3,5-trimethoxy-4-methyl-6-(2-nitrophenylsulfonamido)phenyl) ethyl)aziridine-1-carboxylate

The experiment was carried out by the general procedure for nosylation with the aniline derived from **17** (0.120 g, 0.19 mmol), 2-nitrobenzenesulfonyl chloride (0.172 g, 0.77 mmol) in dry pyridine (1 mL). The crude product was purified by flash column chromatography (70:30 hexanes:EtOAc) to afford the sulfonamide as a pale yellow oil (0.118 g, 79%). Major diastereomer: $[\alpha]_D^{20}$=+17.7° (*c*=1.0, $CHCl_3$). ^1H

NMR (400 MHz, $CDCl_3$): δ = 0.40-0.54 (4H, m), 0.75-0.91 (13H, m), 2.09 (3H, s), 2.61 (1H, t, *J* = 6.5 Hz), 2.69 (1H, dt, *J* = 7.0, 4.5 Hz), 2.78 (1H, dd, *J* = 13.5, 9.0 Hz), 2.96 (1H, dd, *J* = 13.5, 5.0 Hz), 3.36 (3H, s), 3.48-3.55 (2H, m), 3.66 (3H, s), 3.71 (3H, s), 3.73 (3H, s) 3.77 (3H, s), 3.80-3.83 (1H, m), 4.47 (1H, d, *J* = 11.5 Hz), 4.59 (1H, d, *J* = 11.5 Hz), 6.83 (2H, d, *J* = 8.5 Hz), 7.24 (2H, d, *J* = 8.5 Hz), 7.62 (1H, dt, *J* = 7.5, 1.5 Hz), 7.67 (1H, dt, *J* = 7.5, 1.5 Hz), 7.77 (1H, s), 7.89 (1H, dd, *J* = 9.0, 1.5 Hz), 7.97 (1H, dd, *J* = 9.0, 1.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 3.3, 6.7, 9.5, 12.8, 17.0, 17.3, 29.6, 33.0, 40.9, 45.2, 53.6, 55.1, 59.4, 59.7, 60.1, 67.5, 69.8, 72.5, 113.6, 124.3, 124.8, 125.0, 125.2, 128.5, 129.4, 129.9, 130.3, 131.0, 132.3, 132.8, 135.4, 136.4, 147.6, 151.3, 151.9, 159.1, 163.5. IR (NaCl neat) (cm^{-1}): 3319, 2930, 1728, 1542, 1464, 1409, 1251, 1172, 1082, 732. MS: m/z = 804 (15), 618 (89), 574 (15), 472 (13), 380 (100), 376 (55), 330 (22), 234 (30). HRMS (FAB+): m/z Calcd 804.3197, Found 804.3191.

General procedure for carbamate formation

Methyl (2*R*,3*S*)-2-((4-methoxybenzyloxy)methyl)-3-(2-(2-(allyloxycarbonyl)-4-(methoxycarbonyl)-6- (methoxymethoxy)phenyl)-1-(diethyl(isopropyl)-silyloxy)ethyl)aziridine-1-carboxylate)

To a stirred solution of aniline derived from **16** (0.180 g, 0.284 mmol) and allyl chloroformate (90 μL, 0.852 mmol) in DCM (5 mL) was added sat. aq $NaHCO_3$ (0.8 mL). The reaction was vigorously stirred at rt and monitored by TLC until complete consumption of the starting material. The reaction mixture was diluted with EtOAc and brine (10 mL) was added. The phases were separated and the aqueous phase was extracted with EtOAc (3x10 mL). The combined organics were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography (70:30 hexanes:EtOAc) to afford the carbamate as a colorless oil (0.163 g, 80%). Major diastereomer: $[\alpha]_D^{25}$=+7.9° (*c*=1.07, $CHCl_3$)**.** ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.37-0.45 (2H, m), 0.51 (2H, q, *J* = 8.0 Hz), 0.71-0.90 (13H, m), 2.64 (1H, t, *J* = 6.0 Hz), 2.80 (1H, q, *J* = 6.0 Hz), 2.91 (1H, dd, *J* = 14.0, 10.0 Hz), 3.21 (1H, dd, *J* = 14.0, 3.0 Hz), 3.41 (3H, s), 3.58 (1H, dd, *J* = 10.5, 5.5 Hz), 3.66 (1H, dd, *J* = 10.5, 6.5 Hz), 3.76 (3H, s), 3.80 (3H, s), 3.89 (3H, s), 4.05 (1H, ddd, *J* = 9.0, 5.0, 3.0 Hz), 4.51 (1H, d, *J* = 11.5 Hz), 4.60 (1H, d, *J* = 11.5 Hz), 4.62-4.74 (2H, m), 5.17 (2H, s), 5.25 (1H, dd, *J* = 10.5, 1.5 Hz), 5.36 (1H, app dq, *J* = 17.0, 1.5 Hz), 5.98 (1H, m), 6.87 (2H, dt, *J* = 8.5, 2.0 Hz), 7.26 (2H, dt, *J* = 8.5, 2.0 Hz), 7.49 (1H, d, *J* = 1.5 Hz), 7.93 (1H, br s), 8.15 (1H, br s). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 3.8, 7.0, 7.2, 13.1, 17.5, 32.6, 41.4, 45.7, 52.6, 54.2, 55.7, 56.6, 66.3, 67.9, 70.0, 73.2, 94.9, 110.4, 114.2, 117.6, 118.4, 124.2, 129.9, 130.1, 130.2, 133.0, 139.0, 154.1, 155.7, 159.8, 164.0, 167.1. IR (NaCl neat) (cm^{-1}): 3358, 2952, 1732, 1589, 1436, 1249, 1214, 1083, 1018, 728. MS: m/z = 717 (100), 404 (28), 154 (100). HRMS (FAB+): m/z Calcd 717.3418 $(MH)^+$, Found 717.3436.

Methyl (2*S*,3*R*)-2-(2-(2-((4,5-dimethoxy-2-nitrobenzyloxy)carbonyl)-4-(methoxycarbonyl)-6-(methoxymethoxy)phenyl)-1-(diethyl(isopropyl) silyloxy)ethyl)-3-((4-methoxybenzyloxy)-methyl)aziridine-1-carboxylate

The experiment was carried out by the general procedure for carbamate formation with the aniline derived from **16** (0.062 g, 0.098 mmol) and 6-nitroveratryl chloroformate (0.081 g, 0.294 mmol) in CH_2Cl_2 (0.7 mL) and sat. aq $NaHCO_3$ (0.3 mL). The crude product was purified by flash column chromatography (60:40 hexanes:EtOAc) to afford the carbamate (0.066 g, 78%) as a pale yellow oil. Major diastereomer: $[\alpha]_D^{20}$=-5.9° (*c*=1.65, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.41 (2H, m), 0.49 (2H, q, *J* = 7.5 Hz), 0.70-0.83 (13H, m), 2.63 (1H, t, *J* = 6.0 Hz), 2.80 (1H, q, *J* = 6.0 Hz), 2.92 (1H, dd, *J* = 13.5, 10.0 Hz), 3.21 (1H, dd, *J* = 14.0, 3.0 Hz), 3.40 (3H, s), 3.57 (1H, dd, *J* = 10.5, 5.5 Hz), 3.64 (1H, dd, *J* = 10.5, 6.5 Hz), 3.74 (3H, s), 3.78 (3H, s), 3.90 (3H, s), 3.95 (6H, br s), 4.01-4.10 (1H, m), 4.47 (1H, d, *J* = 11.5 Hz), 4.56 (1H, d, *J* = 11.5 Hz), 5.17 (2H, s), 5.60 (2H, s), 6.83 (2H, d, *J* = 8.5 Hz), 7.04 (1H, br s), 7.22 (2H, d, *J* = 8.5 Hz), 7.51 (1H, d, *J* = 1.0 Hz), 7.71 (1H, s), 8.03 (1H, br s), 8.07 (1H, br s). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 3.5, 6.7, 6.8, 12.8, 17.1, 17.2, 32.4, 41.0, 45.4, 52.3, 53.9, 55.3, 56.2, 56.4, 56.5, 62.8, 64.0, 67.5, 69.5, 72.8, 94.4, 108.1, 108.2, 110.3, 110.6, 110.9, 113.7, 127.5, 129.4, 129.6, 132.2, 138.1, 139.9, 148.1, 153.4, 155.2, 159.2, 163.4, 166.4. IR (NaCl neat) (cm^{-1}): 3362, 2953, 1727, 1520, 1277, 1068. MS: m/z = 872 (5), 196 (20), 121 (100). HRMS (FAB+): m/z Calcd 872.3637 (MH)+, Found 872.3650.

Methyl (2*R*,3*S*)-2-((4-methoxybenzyloxy)methyl)-3-(2-(2-(allyloxycarbonyl)-3,5,6-trimethoxy-4-methylphenyl)-1-(diethyl(isopropyl)silyloxy) ethyl)aziridine-1-carboxylate

The experiment was carried out by the general procedure for carbamate formation with the aniline derived from **16** (0.25 g, 0.40 mmol) and allyl chloroformate (68 μL, 0.80 mmol) in CH_2Cl_2 (2 mL) and sat. aq $NaHCO_3$ (0.8 mL). The crude product was purified by flash column chromatography (70:30 hexanes:EtOAc) to afford the carbamate (0.21 g, 75%) as a colorless oil. Major diastereomer: $[\alpha]_D^{25}$=-3.1° (*c*=3.0, $CHCl_3$)**.** ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.49 (4H, app sext, *J* = 8.0 Hz), 0.75-0.94 (13H, m), 2.15 (3H, s), 2.56 (1H, t, *J* = 6.0 Hz), 2.68 (1H, q, *J* = 6.0 Hz), 2.85 (1H, dd, *J* = 13.0, 9.0 Hz), 2.98 (1H, dd, *J* = 13.5, 4.5 Hz), 3.52-3.57 (2H, m), 3.65 (3H, s), 3.69 (3H, s), 3.72 (3H, s), 3.73 (3H, s), 3.77 (3H, s), 3.98 (1H, br s), 4.45 (1H, d, *J* = 11.5 Hz), 4.59 (1H, d, *J* = 11.5 Hz), 4.62-4.68 (2H, m), 5.18 (1H, d, *J* = 10.0 Hz), 5.31 (1H, d, *J* = 16.5 Hz), 5.93 (1H, m), 6.83 (2H, d, *J* = 7.0 Hz), 6.99 (1H, br s), 7.24 (2H, d, *J* = 6.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 3.4, 3.5, 6.7, 6.8, 12.7, 17.1, 32.9, 41.0, 53.7, 55.2, 59.9, 60.2, 65.8, 67.4, 70.0, 72.5, 113.7, 117.2, 124.3, 126.5, 129.4,129.9, 133.0, 147.6, 150.4, 150.9, 154.6, 159.2, 163.8**.** IR (NaCl neat) (cm^{-1}): 3330, 2939, 1724, 1613, 1513, 1465, 1228, 1090, 757, 729. MS: m/z = 703 (100), 464 (22), 452 (33), 415 (27), 318 (32), 294 (53), 253 (58), 221 (36). HRMS

(FAB+): m/z Calcd 703.3626 $(MH)^+$, Found 703.3613.

General procedure for the PMB deprotection

Methyl (2*S*,3*R*)-2-(diethyl(isopropyl)silyloxy)-2-(4-(methoxycarbonyl)-2-methoxymethoxy-6-(2-nitrophenylsulfonamido)phenyl)ethyl)-3-(hydroxymethyl)aziridine-1-carboxylate (14a)

To a stirred solution of sulfonamide derived from **16** (4.29 g, 5.25 mmol) in 15:1 solution of DCM-H_2O (50 mL) was added DDQ (1.55 g, 6.83 mmol) in one portion. The reaction mixture immediately turned green and over the course of 1.5 h the mixture turned brown-orange. After 2 h, the reaction mixture was passed through a short pad of activated alumina using 10:1 DCM:MeOH as eluant. The filtrate was concentrated under reduced pressure and the crude product was purified by flash column chromatography (40:60 hexanes:EtOAc) to afford the alcohol (**14a**) (3.55 g, 97%). Major diastereomer: $[\alpha]_D^{20}$=-15.1° (*c*=0.9, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.41 (2H, m), 0.50 (2H, q, *J* = 8.0 Hz), 0.66-0.91, (13H, m), 1.75 (1H, br s), 2.60 (1H, dd, *J* = 13.5, 10.5 Hz), 2.78 (1H, dd, *J* = 6.0, 5.5 Hz), 2.79 (1H, dd, *J* = 6.0, *J* = 5.5 Hz), 2.92 (1H, dd, *J* = 13.5, 3.5 Hz), 3.40 (3H, s), 3.60-3.68 (1H, m), 3.69 (3H, s), 3.84-3.94 (2H, m), 3.93 (3H, s), 5.13 (1H, d, *J* = 7.0 Hz), 5.18 (1H, d, *J* = 7.0 Hz), 7.57 (1H, dt, *J* = 7.5, 1.5 Hz), 7.62 (1H, d, *J* = 1.5 Hz), 7.71 (1H, dt, *J* = 8.0, 1.5 Hz), 7.77 (1H, dd, *J* = 8.0, 1.5 Hz), 7.94 (1H, d, *J* = 1.5 Hz), 7.95 (1H, dd, *J* = 8.0, 1.5 Hz), 8.80 (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 3.4, 3.5, 6.5, 6.6, 12.7, 16.9, 31.3, 43.1, 46.3, 52.4, 53.8, 56.3, 60.2, 69.3, 94.5, 112.5, 122.1, 125.8, 127.9, 129.9, 130.7, 132.5, 133.5, 133.8, 137.0, 147.8, 155.2, 163.1, 166.3. IR (NaCl neat) (cm^{-1}): 3515, 3265, 2954, 1725, 1543, 1308, 1240, 1061, 1010, 732. MS: m/z = 698 (100), 512 (17), 154 (85) 136 (60), 129 (35). HRMS (FAB+): m/z Calcd 698.2415 $(MH)^+$, Found 698.2389.

Methyl (2*S*,3*R*) 2-(2-(2-allyloxycarbonyl-4-methoxycarbonyl-6-(methoxymethoxy)phenyl)-1-(diethyl(isopropyl)silyloxy)ethyl)-3-(hydroxymethyl)aziridine-1-carboxylate (14b)

The experiment was carried out by the general procedure for the PMB deprotection with the alloc carbamate (0.160 g, 0.223 mmol), DDQ (0.061 g, 0.268 mmol) in 15:1 CH_2Cl_2-H_2O (3 mL). The crude product was purified by flash chromatography (60:40 petroleum ether:EtOAc) to yield **14b** as a colorless oil (0.118 g, 89 %). Major diastereomer: $[\alpha]_D^{20}$=+3.1° (*c*=0.65, $CHCl_3$)**.** ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.42 (2H, m), 0.52 (2H, q, *J* = 8.0 Hz), 0.73-0.89 (13H, m), 1.97 (1H, br s), 2.73 (1H, t, *J* = 6.0 Hz), 2.78 (1H, q, *J* = 6.0 Hz), 2.93 (1H, dd, *J* = 13.5, 10.0 Hz), 3.24 (1H, dd, *J* = 14.0, 3.0 Hz), 3.45 (3H, s), 3.77 (3H, s), 3.78-3.87 (2H, m), 3.89 (3H, s), 4.15 (1H, ddd, *J* = 9.0, 5.5, 3.0 Hz), 4.69 (2H, m), 5.20-5.29 (3H, m), 5.38 (1H, dt, *J* = 17.5, 1.5 Hz), 5.99 (1H, m), 7.50 (1H, s), 7.93 (1H, br s), 8.15 (1H, br s). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 3.4, 6.6, 6.7, 12.7, 17.0, 22.6, 29.7, 32.1, 43.0, 46.1, 52.2, 53.9, 56.3, 60.2, 65.9,

69.8, 94.4, 94.5, 110.0, 117.1, 118.0, 123.6, 129.7, 132.5, 138.5, 153.6, 155.2, 163.6, 166.7. IR (NaCl neat) (cm^{-1}): 3500, 3366, 2953, 1728, 1590, 1436, 1215, 1038, 1017. MS: m/z = 597 (100), 565 (30), 307 (49), 288 (32). HRMS (FAB+): m/z Calcd 597.2843 $(MH)^+$, Found 597.2832.

Methyl (2*S*,3*R*)-2-(2-(2-((4,5-dimethoxy-2-nitrobenzyloxy)carbonyl)-4-(methoxycarbonyl)-6-(methoxymethoxy)phenyl)-1-(diethyl(isopropyl)-silyloxy)ethyl)-3-(hydroxymethyl)aziridine-1-carboxylate (14c)

The experiment was carried out by the general procedure for the PMB deprotection with the NVOC carbamate (0.064 g, 0.073 mmol), DDQ (0.020 g, 0.088 mmol) in 15:1 CH_2Cl_2-H_2O (0.7 mL). The crude product was purified by flash chromatography (40:60 hexanes: EtOAc) to yield **14c** as a yellow oil (0.041 g, 75 %). Major diastereomer: $[\alpha]_D^{20}$=-14° (*c*=0.1, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.39 (2H, m), 0.50 (2H, q, *J* = 8.0 Hz), 0.72-0.85 (13H, m), 2.17 (1H, br s), 2.68 (1H, t, *J* = 6.0 Hz), 2.77 (1H, q, *J* = 6.0 Hz), 2.96 (1H, br t, *J* = 11.5 Hz), 3.22 (1H, dd, *J* = 14.0, 3.0 Hz), 3.45 (3H, s), 3.72 (3H, s), 3.82-3.90 (3H, m), 3.88 (3H, s), 3.93-4.00 (3H, m), 3.96 (3H, s), 4.21 (1H, dt, *J* = 10.5, 5.0 Hz), 5,22 (1H, d, *J* = 6.5 Hz), 5.24 (1H, d, *J* = 6.5 Hz), 5.61 (2H, s), 7.07 (1H, br s), 7.52 (1H, d, *J* = 1.0 Hz), 7.72 (1H, s), 8.09 (1H, br s). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 3.3, 3.4, 6.5, 6.7, 12.7, 16.9, 32.1, 42.6, 45.8, 52.2, 53.9, 56.3, 56.4, 60.2, 64.0, 69.5, 94.5, 108.2, 110.2, 111.1, 117.2, 123.7, 127.3, 129.7, 138.2, 140.0, 148.3, 153.5, 155.3, 163.5, 166.5 IR (NaCl neat) (cm^{-1}): 3512, 3361, 2953, 1727, 1587, 1522, 1326, 1278, 1214, 1067, 756. MS: m/z = 752 (12), 196 (100), 154 (29), 136 (24). HRMS (FAB+): m/z Calcd 752.3062 $(MH)^+$, Found 752.3053.

Methyl (2*S*,3*R*)-2-(1-(diethyl(isopropyl)silyloxy)-2-(2,3,5-trimethoxy-4-methyl-6-(2-nitrophenyl-sulfonamido)phenyl)ethyl)-3-(hydroxymethyl)-aziridine-1-carboxylate (15a)

The experiment was carried out by the general procedure for the PMB deprotection with the Ns sulfonamide (0.052 g, 0.065 mmol), DDQ (0.02 g, 0.084 mmol) in 15:1 CH_2Cl_2-H_2O (0.8 mL). The crude product was purified by flash column chromatography (50:50 hexanes:EtOAc) to afford the alcohol (**15a**) (0.039 g, 87%) as a colorless oil. Major diastereomer: $[\alpha]_D^{25}$=+24.2° (*c*=1.6, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.45-0.63 (4H, m), 0.81-0.95 (13H, m), 2.07 (3H, s), 2.69 (2H, m), 2.91 (1H, dd, *J* = 13.0, 8.5 Hz), 3.08 (1H, dd, *J* = 13.5, 5.5 Hz), 3.32 (3H, s), 3.65 (3H, s), 3.74 (3H, s), 3.78 (3H, s), 3.83-3.89 (1H, m), 4.00 (1H, m), 7.64 (1H, td, *J* = 7.5, 1.5 Hz), 7.68 (1H, td, *J* = 7.5, 1.5 Hz), 7.79, (1H, s), 7.90 (1H, dd, *J* = 9.0, 1.5 Hz), 7.98 (1H, dd, *J* = 9.0, 1.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 3.6, 3.7, 6.8, 9.5, 13.0, 17.1, 33.0, 42.4, 45.8, 53.7, 59.4, 59.8, 60.3, 70.3, 124.4, 124.6, 124.9, 128.5, 131.1, 132.4,

132.8, 135.4, 147.5, 147.7, 151.3, 151.8, 163.5. IR (NaCl neat) (cm^{-1}): 3319, 3099, 2940, 2877, 1727, 1694, 1514, 1464, 1382, 1296, 1079, 1016, 733, 653. MS: m/z = 684 (20), 498 (100), 454 (25), 380 (39), 352 (46), 210 (26). HRMS (FAB+): m/z Calcd 684.2622 $(MH)^+$, Found 684.2615.

(2*S*,3*R*)-Methyl 2-(2-(2-allyloxycarbonyl-3,5,6-trimethoxy-4-methylphenyl)-1-(diethyl(isopropyl)silyl oxy)ethyl)-3-(hydroxymethyl)aziridine-1-carboxylate (15b)

The experiment was carried out by the general procedure for PMB deprotection with PMB ether (0.19 g, 0.26 mmol) and DDQ (0.80 g, 0.34 mmol) in 15:1 CH_2Cl_2-H_2O (3 mL). The crude product was purified by flash column chromatography (50:50 hexanes:EtOAc) to afford the alcohol (**15b**) (0.13 g, 87%) as a colorless oil. Major diastereomer: $[\alpha]_D^{25}$=-13.6° (*c*=1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.50 (2H, q, *J* = 7.5 Hz), 0.56 (2H, q, *J* = 7.5 Hz), 0.81-0.98 (13H, m) 1.97 (1H, br s), 2.15 (3H, s), 2.61-2.67 (2H, m), 2.91 (2H, dd, *J* = 13.5, 8.0 Hz), 3.00 (1H, dd, *J* = 13.5, 5.5 Hz), 3.65 (3H, s), 3.67 (3H, s), 3.74 (3H, s), 3.78 (3H, s), 3.80 (1H, d, *J* = 2.0 Hz), 4.08-4.13 (1H, m), 4.63 (2H, d, *J* = 2.0 Hz), 5.20 (1H, d, *J* = 10.0 Hz), 5.34 (1H, d, *J* = 17.0 Hz), 5.95 (1H, m), 6.91 (1H, br s). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 3.8, 3.9, 4.1, 6.9, 7.0, 9.7, 13.1, 13.3, 17.4, 33.2, 43.1, 46.0, 54.0, 60.1, 60.5, 63.4, 66.1, 70.5, 94.6, 108.8, 117.7, 124.7, 126.6, 133.1, 147.9 150.8, 151.2, 163.9. IR (NaCl neat) (cm^{-1}): 3346, 2942, 2877, 1728, 1602, 1504, 1464, 1230, 1090, 1045, 728. MS: m/z = 583 (43), 464 (41), 379 (36), 362 (70), 253 (75), 236 (100), 194 (48), 147 (75), 129 (78). HRMS (FAB+): m/z Calcd 583.3050, Found 583.3034.

General procedure for the Mitsunobu cyclization

Method A (DEAD/Ph_3P):

Methyl (3*S*,4*R*)-5-(diethyl(isopropyl)silyloxy)-7-methoxymethoxy-1-(2-nitrophenylsulfonyl)-(3,4)-[*N*-(methoxycarbonyl)aziridino]-1,2,3,4,5,6-hexahydrobenzo[*b*]azocine-9-carboxylate (12a)

To a stirred solution of **14a** (0.10 g, 0.143 mmol) and triphenylphosphine (0.068 g, 0.258 mmol) in dry toluene (7 mL) was added DEAD (94 μL of a 40% solution in toluene, 0.215 mmol). The mixture was stirred at rt and monitored by TLC until complete consumption of the starting material (30 min). The reaction mixture was concentrated under reduced pressure and the residue was purified by flash column chromatography (70:30 hexanes:EtOAc) to afford the benzazocine (**12a**) (0.092 g, 95%) as a white foam. Major diastereomer: $[\alpha]_D^{20}$=-9.1° (*c*=1.44, $CHCl_3$) Note: ^{1}H NMR and ^{13}C NMR are reported as a mixture of rotamers at both room temperature and 323K. ^{1}H NMR (300 MHz, DMSO, 393K): δ = 0.52 (2H, q, *J* = 8.0 Hz), 0.68 (2H, q *J* = 8.0 Hz), 0.92-1.04 (13H, m), 2.58 (1H, dd, *J* = 6.5, 3.5 Hz), 2.65 (1H, dd, *J* = 6.5, 3.5 Hz), 2.62-2.69 (1H, m), 2.90-3.03 (1H, m), 3.465 ((2/3)3H, s), 3.47 ((1/3)3H, s), 3.64

((2/3)3H, s), 3.67 ((1/3)3H, s), 3.79 ((1/4)3H, s), 3.80 ((3/4)3H, s), 4.00-4.27 (3H, m), 4.46 (1H, app p, *J* = 4.5 Hz), 5.28 (1H, d, *J* = 6.5 Hz), 5.31 (1H, d, *J* = 6.5 Hz), 7.10 ((1/3)H, d, *J* = 1.5 Hz), 7.14 ((2/3)H, d, *J* = 1.5 Hz), 7.63 ((1/3)H, d, *J* = 1.5 Hz), 7.66 ((2/3)H, d, *J* = 1.5 Hz), 7.74-7.94 (4H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 3.5, 6.9, 12.7, 17.1, 30.6, 40.3, 46.3, 51.8, 52.2, 53.6, 56.4, 94.6, 114.7, 124.0, 124.4, 131.2, 132.4, 132.5, 133.8, 139.2, 147.9, 155.8, 163.7, 165.6. IR (NaCl neat) (cm^{-1}): 2954, 2876, 1727, 1545, 1437, 1372, 1297, 1243, 1077, 730. MS: m/z = 680 (100), 636 (41), 494 (23), 348 (42), 154 (59), 136 (57). HRMS (FAB+): m/z Calcd 680.2309 $(MH)^+$, Found 680.2310.

Methyl (3*S*,4*R*)-1-((4,5-dimethoxy-2-nitrobenzyloxy) carbonyl)-5-(diethyl(isopropyl)silyloxy)-7-methoxy methoxy-(3,4)-[*N*-(methoxycarbonyl)aziridino]-1,2,3,4,5,6-hexahydrobenzo[1,2-*b*]-azocine-9-carboxylate (12c)

The experiment was carried out by the general procedure for the Mitsunobu cyclization (method A) with **14c** (0.021 g, 0.028 mmol), DEAD (7 μL, 0.042 mmol) and Ph_3P (0.013 g, 0.05 mmol) in dry toluene (0.5 mL). The crude product was purified by PTLC (30:70 petroleum ether:EtOAc) to afford the benzazocine (**12c**) (0.017 g, 83%) as a pale yellow oil. Major diastereomer: $[\alpha]_D^{20}$=+45.2° (*c*=1.3, $CHCl_3$)**.** ^{1}H NMR (300 MHz, DMSO, 393 K): δ = 0.65-0.75 (4H, m), 0.96-1.02 (13H, m), 2.67 (1H, br s), 2.86 (4H, br s), 2.98 (1H, br s), 3.47 (3H, s), 3.62 (3H, s), 3.80 (3H, s), 3.86 (3H, s), 3.87 (3H, s), 3.92 (1H, t, *J* = 4.0 Hz), 4.35 (1H, br s), 5.28 (1H, d, *J* = 7.0 Hz), 5.32 (1H, d, *J* = 6.5 Hz), 5.41 (2H, s), 6.93 (1H, br s), 7.46 (1H, d, *J* = 2.0 Hz), 7.63 (1H, d, *J* = 1.5 Hz), 7.65 (1H, s). ^{13}C NMR (75 MHz, $CDCl_3$) (note: at room temperature, this compound exists as an equilibrating mixture of conformational isomers of the alloc urethane on the NMR time scale): δ = 3.5, 3.6, 7.0, 7.0, 12.7, 17.2, 17.2, 29.3, 29.5, 40.4, 47.6, 48.5, 52.2, 52.4, 53.5, 53.6, 53.6, 56.2, 56.4, 64.5, 64.8, 70.4, 94.3, 107.8, 108.2, 113.6, 122.1, 128.5, 130.6, 131.3, 138.6, 142.1, 147.4, 153.4, 153.9, 155.7, 164.1, 165.6. IR (NaCl neat) (cm^{-1}): 2951, 1725, 1581, 1522, 1438. MS: m/z = 734 (15), 196 (100), 154 (22). HRMS (FAB+): m/z Calcd 734.2956 $(MH)^+$, Found 734.2941.

Methyl (3*R*,4*S*)-5-(diethyl(isopropyl)silyloxy)-7,8,10-trimethoxy-9-methyl-1-(2-nitrophenylsulfonyl)-[*N*-(methoxycarbonyl)aziridino]-1,2,3,4,5,6-hexahydrobenzo[*b*]azocine (13a)

The experiment was carried out by the general procedure for the Mitsunobu cyclization (method A) with alcohol (**15a**) (0.04 g, 0.057 mmol), DEAD (14 μL, 0.086 mmol) and triphenylphosphine (0.027 g, 0.10 mmol) in dry toluene (2.5 mL). The crude product was purified by flash column chromatography (80:20 hexanes:EtOAc) to afford the benzazocine **13a** (0.026 g, 70%) as a colorless oil. Major diastereomer: $[\alpha]_D^{25}$= +4.8° (*c*=1.0, $CHCl_3$)**.** ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.65 (4H, m), 0.79-0.85 (2H, m),

0.92-0.97 (17H, m), 2.09 (3H, s), 2.35-2.40 (2H, m), 2.70 (1H, dd, *J* = 13.5, 9.5 Hz), 2.97 (1H, dd, *J* = 13.5, 4.5 Hz), 3.29 (1H, s), 3.64 (3H, s), 3.68 (3H, s), 3.81 (6H, s), 3.88 (1H, d, *J* = 2.5 Hz), 3.91 (1H, s), 4.06-4.16 (2H, m), 4.49 (2H, dd, *J* = 14.5, 5.0 Hz), 7.50-7.55 (2H, m), 7.58-7.64 (2H, m), 7.89 (1H, dd, *J* = 9.0, 1.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 3.4, 3.5, 7.0, 10.2, 12.7, 14.4, 17.2, 31.4, 40.0, 45.9, 50.4, 53.5, 60.1, 60.5, 60.8, 69.4, 123.5, 124.4, 127.0, 128.3, 130.9, 131.0, 132.1, 133.2, 133.3, 147.0, 148.1, 152.7, 153.2, 153.9**.** IR (NaCl neat) (cm^{-1}): 3450, 3314, 2926, 1731, 1545, 1463, 1372, 1260, 942, 731. MS: m/z = 666 (100), 622 (50), 480 (84), 436 (45), 334 (70) 234 (37), 221 (42). HRMS (FAB+): m/z Calcd 666.2516 $(MH)^+$, Found 666.2498.

Allyl (3*R*,4*S*)-5-(diethyl(isopropyl)silyloxy)-7,8,10-trimethoxy-9-methyl-[*N*-(methoxycarbonyl)-aziridino] -3,4,5,6-tetrahydrobenzo[*b*]azocine-1(2*H*)-carboxylate (13b)

The experiment was carried out by the general procedure for the Mitsunobu cyclization (method A) with alcohol (**15b**) (0.180 g, 0.31 mmol), TMAD (0.081 g, 0.56 mmol) and tributylphosphine (140 μL, 0.56 mmol) in dry toluene (12 mL). The solution immediately turned deep purple and slowly changed to a light brown color as the reaction progressed. The crude product was purified by flash column chromatography (80:20 hexanes:EtOAc) to afford the benzazocine (**13b**) (0.142 g, 81%) as a colorless oil. Major diastereomer: $[\alpha]_D^{25}$=+28.1° (*c*=1.2, $CHCl_3$) **Note:** ^{1}H NMR and ^{13}C NMR spectra are reported as a 1.4:1 mixture of rotamers at room temperature. At 323K onset of coalescence was observed. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.70-0.91 (m), 1.04-1.10 (m), 1.26 (d, *J* = 3.0 Hz), 2.18 (s), 2.17 (s), 2.42 (m), 2.52, (dd, *J* = 8.5, 2.0 Hz), 2.57, (dd, *J* = 9.0, 2.0 Hz), 2.73 (dd, *J* = 9.5, 3.0 Hz), 2.89 (d, *J* = 1.5 Hz), 2.91 (d, *J* = 3.0 Hz), 3.28, (dd, *J* = 7.5, 1.5 Hz), 3.32 (dd, *J* = 7.0, 1.5 Hz), 3.60 (d, *J* = 1.5 Hz), 3.66 (s), 3.69 (s), 3.73 (d, *J* = 1.5 Hz), 3.83 (s), 3.84 (s), 3.85 (s), 4.10 (m), 4.54 (dq, *J* = 9.5, 1.5 Hz), 4.64 (dt, *J* = 8.0, 1.5 Hz), 4.68 (dt, *J* = 9.0, 1.5 Hz), 4.76 (dd, *J* = 19.0, 3.5 Hz), 4.86 (dd, *J* = 19.0, 3.5 Hz), 5.04 (t, *J* = 1.5 Hz), 5.08 (dq, *J* = 11.0, 1.5 Hz), 5.13 (q, *J* = 5.0, 1.5 Hz), 5.23 (dq, *J* = 14.5, 1.5 Hz), 5.39 (m), 5.81 (m), 6.01 (m). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 3.7, 3.9, 7.3, 9.7, 9.8, 13.0, 17.5, 29.5, 29.7, 40.7, 40.9, 47.5, 47.6, 47.9, 53.7, 53.8, 60.3, 60.4, 60.6, 60.8, 61.0, 66.3, 66.7, 71.8, 71.9, 117.2, 117.5, 122.9, 124.8 125.1, 129.7, 130.6, 132.2, 133.0, 133.3, 147.4, 151.8, 155.2, 164.6, 164.9, 168.3, 168.5, 168.7. IR (NaCl neat) (cm^{-1}): 2951, 2876, 1730, 1710, 1467, 1245, 1094, 721. MS: m/z = 565 (100), 521 (48), 421 (26), 334 (17), 221 (20), 136 (10). HRMS (FAB+): m/z Calcd 565.2945 $(MH)^+$, Found 565.2935.

Method B (TMAD/PBu_3):

Methyl (3*S*,4*R*)-1-(allylloxycarbonyl)-5-(diethyl (isopropyl)silyloxy)-7-methoxymethoxy-(3,4)-[*N*-(methoxycarbonyl)aziridino]-1,2,3,4,5,6-hexahydrobenzo[1,2-*b*]azocine-9-carboxylate (12b)

To a solution of **14b** (0.036 g, 0.06 mmol) and tributylphosphine (26 μL, 0.102 mmol) in dry toluene (1.5

mL) was added TMAD (0.016 g, 0.09 mmol). The solution immediately turned yellow and slowly changed to a white cloudy color as the reaction progressed. The mixture was stirred under argon at rt and monitored by TLC until complete consumption of the starting material (6 h). The reaction mixture was concentrated under reduced pressure and the residue was purified by flash column chromatography (70:30 hexanes:EtOAc) to afford the benzazocine (**12b**) (0.028 g, 82%) as a colorless oil. Major diastereomer: $[\alpha]_D^{25}$=+26.1° (*c*= 0.67, $CHCl_3$)**.** ^{1}H NMR (300 MHz, DMSO, 393 K): δ = 0.66-0.75 (4H, m), 0.95-1.04 (13H, m), 2.63-2.71 (2H, m), 2.82-3.07 (4H, m), 3.48 (3H, s), 3.66 (3H, s), 3.75-3.86 (1H, m), 3.87 (3H, s), 4.06-4.20 (1H, br s), 4.33-4.42 (1H, m), 4.56 ((3/4)H, d, *J* = 5.0 Hz), 4.62 ((1/4)H, d, *J* = 5.0 Hz), 5.13-5.23 (1H, m), 5.27 (1H, d, *J* = 6.5 Hz), 5.31 (1H, d, *J* = 6.5 Hz), 5.89 (1H, m), 7.41 (1H, d, *J* = 1.5 Hz), 7.62 (1H, d, *J* = 1.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) (note: at room temperature, this compound exists as an equilibrating mixture of conformational isomers of the alloc urethane on the NMR time scale): δ = 3.4, 3.5, 7.0, 12.7, 17.2, 29.2, 29.4, 38.8, 40.4, 45.9, 47.2, 48.4, 49.7, 52.2, 52.3, 53.5, 53.6, 56.3, 66.2, 66.7, 70.2, 94.4, 94.8, 113.0, 113.5, 113.8, 116.9, 117.2, 117.7, 122.6, 123.0, 130.3, 130.8, 131.5, 131.8, 132.4, 132.6, 142.1, 142.5, 154.5, 154.9, 155.0, 155.5, 155.8, 156.0, 164.3, 166.0. IR (NaCl neat) (cm^{-1}): 2953, 1727, 1583, 1437, 1240, 1105, 730. MS: m/z = 579 (84), 307 (29), 154 (100), 137 (69). HRMS (FAB+): m/z Calcd 579.2738 $(MH)^+$, Found 579.2737.

General procedure for the nosyl deprotection:

Methyl (3*S*,4*R*)-5-(diethyl(isopropyl)silyloxy)-7-methoxymethoxy-(3,4)-[*N*-(methoxycarbonyl)-aziridino]-1,2,3,4,5,6-hexahydrobenzo[*b*]azocine-9-carboxylate (7)

To a solution of **12a** (0.62 g, 0.91 mmol) in dry MeCN (15 mL) were successively added thiophenol (106 μL, 1.03 mmol) and cesium carbonate (0.875 g, 2.68 mmol). The reaction mixture immediately turned yellow and after 1 h the solution was partitioned between EtOAc and 10% citric acid. The organic phase was washed with brine (10 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography (70:30 hexanes:EtOAc) to afford the benzazocine (**7**) as a pale yellow oil (0.397 g, 88%). Major diastereomer: $[\alpha]_D^{20}$=+60.6° (*c*=1.2, $CHCl_3$). ^{1}H NMR (400 MHz, C_6D_6): δ = 0.74-0.86 (4H, m), 1.08-1.19 (13H, m), 2.10 (1H, m), 2.20 (1H, t, *J* = 6.0 Hz), 2.94 (1H, dt, *J* = 13.5, 10.5 Hz), 3.15 (3H, s), 3.18-3.25 (1H, m), 3.35 (1H, dd, *J* = 13.5, 6.0 Hz), 3.36 (3H, s), 3.40-3.48 (1H, m), 3.52 (3H, s), 4.66 (1H, dt, *J* = 12.5, 6.0 Hz), 4.87 (1H, d, *J* = 6.5 Hz), 4.90 (1H, d, *J* = 6.5 Hz), 7.05 (1H, d, *J* = 1.5 Hz), 7.61 (1H, d, *J* = 1.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 3.4, 3.5, 7.0, 12.9, 17.2, 31.3, 41.3, 43.0, 47.3, 52.1, 53.4, 56.2, 68.7, 94.3, 105.3, 114.2, 118.3, 129.4, 148.3, 156.1, 163.9, 166.8. IR (NaCl neat) cm^{-1}: 3380, 2953, 1724, 1587, 1437. MS: m/z = 495 (100), 451 (40), 393 (46), 349 (59), 248 (42), 204 (75), 136 (76). HRMS (FAB+): m/z Calcd 495.2527 $(MH)^+$, Found 495.2524.

General procedure for the alloc deprotection

To a solution of **12a** (0.159 g, 0.159 mmol) in dry THF (10 mL) were successively added acetic acid (46 μL, 0.795 mmol), triphenylphosphine (0.042 g, 0.159 mmol) and tetrakis (triphenylphosphine)palladium (0.046 g, 40 μmol). The reaction mixture was stirred at rt for 20 min and was diluted with Et_2O (15 mL). The organic phase was washed with $NaHCO_3$ (10 mL) then brine (10 mL). The combined organics were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography (70:30 hexanes:EtOAc) to afford the benzazocine (**7**) (0.063 g, 81%) as a pale yellow oil.

(3*R*,4*S*)-5-(Diethyl(isopropyl)silyloxy)-7,8,10-trimethoxy-9-methyl-(3,4)-[*N*-(methoxycarbonyl)-aziridino]-1,2,3,4,5,6-hexahydrobenzo[*b*]azocine (11)

The experiment was carried out by the general procedure for the alloc deprotection with benzazocine (**13b**) (0.025 g, 0.035 mmol), acetic acid (6 μL, 0.14 mmol) and tetrakis(triphenylphosphine)palladium (0.02 g, 1.8 μmol) in dry THF (0.3 mL). The crude product was purified by column chromatography (70:30 hexanes:EtOAc) to afford the benzazocine (**11**) (0.013 g, 72%) as a white solid. Major diastereomer: $[\alpha]_D^{25}$=+38.1° (*c*=0.21, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.72-0.79 (4H, m), 1.02-1.09 (13H, m), 2.17 (3H, s), 2.51-2.57 (2H, m), 2.82 (1H, dd, *J* = 13.5, 10.0 Hz), 3.13 (1H, dd, *J* = 14.0, 6.0 Hz), 3.44-3.64 (1H, m), 3.67 (3H, s), 3.68 (3H, s), 3.76 (3H, s), 3.83 (3H, s), 3.79-3.86 (1H, m), 4.51 (1H, dt, *J* = 10.5, 5.5 Hz), 4.60 (1H, br s). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 3.5, 3.6, 7.1, 9.5, 13.0, 17.3, 31.8, 41.5, 42.9, 46.5, 53.3, 59.8, 60.2, 60.5, 69.0, 115.5, 122.9, 136.7, 142.8, 143.5, 148.0, 163.8. IR (NaCl neat) (cm^{-1}): 3390, 2952, 2875, 1730, 1490, 1464, 1293, 1229, 1090, 730. MS: m/z = 480 (100), 394 (13), 307 (30), 289 (14), 154 (95), 136 (72). HRMS (FAB+): m/z Calcd 480.2656 $(MH)^+$, Found 480.2649. mp = 131-133°C.

Procedure for the alcohol epimerization

To a stirred solution of the alcohol (**21**) (3.0 g, 5.8 mmol) in dry DCM (200 mL) was added DMP (2.97 g, 7.0 mmol) in one portion. The reaction was stirred at rt and monitored by TLC until complete consumption of the starting material (2 h). The reaction was diluted with Et_2O (200 mL) and a solution of aqueous $Na_2S_2O_3$ was added. The reaction mixture was vigorously stirred until the solution becomes clear. The phases were separated and the aqueous phase was extracted with EtOAc (3x10 mL). The combined organics were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash column chromatography (70:30 hexanes:EtOAc) to afford the ketone as a pale yellow oil (2.9 g, 97%). $[\alpha]_D^{25}$=-44.6° (*c*=1.3, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.24 (3H, s), 3.05 (1H, dd, *J* = 12.5, 5.5 Hz), 3.40 (1H, d, *J* = 7.0 Hz), 3.53 (1H, dd, *J* = 11.0, 5.5 Hz), 3.63 (1H, dd, *J* = 11.0, 5.5 Hz),

3.77 (3H, s), 3.78 (3H, s), 3.81 (3H, s), 3.83 (3H, s), 3.84 (3H, s), 3.92 (2H, d, *J* = 8.5 Hz), 4.50 (1H, d, *J* = 11.5 Hz), 4.53 (1H, d, *J* = 8.5 Hz), 6.87 (2H, d, *J* = 8.5 Hz), 7.28 (2H, d, *J* = 8.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 9.8, 39.0, 43.1, 44.1, 54.1, 55.3, 60.2, 60.6, 62.6, 66.3, 72.9, 113.9, 119.3, 127.2, 129.7, 129.8, 142.3, 146.8, 153.8, 159.4, 162.0, 198.9. MS: m/z = 519 (100), 503 (90), 460 (15), 307 (35), 154 (85), 137 (70). HRMS (FAB+): m/z Calcd 519.1979 $(MH)^+$, Found 519.1964.

A stirred solution of the ketone (2.0 g, 3.9 mmol) in DCM:MeOH 2:1 (300 mL) was cooled to 0°C with an ice bath for 15 min. $NaBH_3CN$ (0.73 g, 11.6 mmol) and acetic acid (0.66 mL, 11.6 mmol) were then added sequentially. The reaction mixture was stirred at 5°C and monitored by TLC (50:50 hexanes:EtOAc) until complete consumption of the starting material. The reaction was quenched with sat. aq $NaHCO_3$ (100 mL). The phases were separated and the aqueous phase was extracted with DCM (3x100 mL). The combined organics were washed with brine (100 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash column chromatography (70:30 hexanes:EtOAc) to afford the alcohol (**22**) as a pale yellow oil (1.97 g, 98%).

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REFERENCES

1. For reviews on DNA cross-linking agents see: M. Gniazdowski and C. Cera, *Chem. Rev*., 1996, **96**, 619; S. R. Rajski and R. M. Williams, *Chem. Rev*., 1998, **98**, 2723; S. E. Wolkenberg and D. L. Boger, *Chem. Rev*., 2002, **102**, 2477. For recent reviews about DNA cancer chemotherapy, see: L. H. Hurley, *Nat. Rev. Cancer*, 2002, **2**, 188; S. M. Nelson, L. R. Ferguson, and W. A. Denny, *Cell & Chromosome*, 2004, 3:2.
2. W. A. Denny, 'Cancer Chemotherapeutic Agents,' ed. by W. A. Foye, American Chemical Society, Washington DC, 1995, pp. 491-493.
3. M. Iwami, S. Kiyoto, H. Terano, M. Kohsaka, H. Aoki, and H. Imanaka, *J. Antibiotics*, 1987, **40**, 589; S. Kiyoto, T. Shibata, M. Yamashita, T. Komori, M. Okuhara, H. Terano, M. Kohsaka, H. Aoki, and H. Imanaka, *J. Antibiotics*, 1987, **40**, 594; K. Shimomura, O. Hirai, T. Mizota, S. Matsumoto, J. Mori, F. Shibayama, and H. Kikuchi, *J. Antibiotics*, 1987, **40**, 600; O. Hirai, K. Shimomura, T. Mizota, S. Matsumoto, J. Mori, and H. Kikuchi, *J. Antibiotics*, 1987, **40**, 607; I. Uchida, S. Takase, H. Kayakiri, S. Kiyoto, M. Hashimoto, T. Tada, S. Koda, and Y. Morimoto, *J. Am. Chem. Soc*., 1987, **109**, 4108; H. Terano, S. Takase, J. Hosoda, and M. Kohsaka, *J. Antibiotics*, 1989, **42**, 145.

4. R. M. Williams, S. R. Rajski, and S. B. Rollins, *Chem. Biol.*, 1997, **4**, 127 and references therein.
5. R. M. Williams and P. Ducept, *Biochemistry*, 2003, **42**, 14696 and references therein.
6. For racemic total syntheses of mitomycin, see: Y. Kishi, *J. Nat. Prod.*, 1979, **42**, 549; T. Fukuyama and L. Yang, *J. Am. Chem. Soc.*, 1989, **111**, 8303; J. W. Benbow, G. K. Schulte, and S. J. Danishefsky, *Angew. Chem., Int. Ed. Engl.*, 1992, **31**, 915; Z. Wang and L. Jimenez, *Tetrahedron Lett.*, 1996, **37**, 6049. For reviews of mitomycin syntheses, see: W. A. Remers and B. S. Lynegar, 'Recent Progress in the Chemical Synthesis of Antibiotics,' ed. by G. Lukacs and M. Ohmo, Springer-Verlag, New York, 1990, pp. 415-445; M. Kasai and M. Kono, *Synlett*, 1992, 778.
7. For total syntheses of FR900482 and FR66979, see: T. Fukuyama, L. Xu, and S. Goto, *J. Am. Chem. Soc.*, 1992, **114**, 383; J. M. Schkeryantz and S. J. Danishefsky, *J. Am. Chem. Soc.*, 1995, **117**, 4722; T. Katoh, E. Itoh, Y. Yoshino, and S. Terashima, *Tetrahedron*, 1997, **53**, 10229; T. C. Judd and R. M. Williams, *Angew. Chem. Int. Ed.*, 2002, **41**, 4683; M. Suzuki, M. Kambe, H. Tokuyama, and T. Fukuyama, *Angew. Chem. Int. Ed.*, 2002, **41**, 4686; R. Ducray and M. Cuifolini, *Angew. Chem. Int. Ed.*, 2002, **41**, 4688; T. C. Judd and R. M. Williams, *J. Org. Chem.*, 2004, **69**, 2825; M. Suzuki, M. Kambe, H. Tokuyama, and T. Fukuyama, *J. Org. Chem.*, 2004, **69**, 2831. For formal syntheses of FR900482, see: I. M. Fellows, D. E. Kaelin Jr., and S. F. Martin, *J. Am. Chem. Soc.*, 2000, **122**, 10781; M. R. Paleo, N. Aurrecoechea, K.-Y. Jung, and H. Rapoport, *J. Org. Chem.*, 2003, **68**, 130.
8. For synthetic routes to FR900482 utilizing benzazocines, see ref 7 as well as: N. Yasuda and R. M. Williams, *Tetrahedron Lett.*, 1989, **30**, 3397; M. A. Ciufolini, M. Chen, D. P. Lovett, and M. V. Deaton, *Tetrahedron Lett.*, 1997, **38**, 4355; M. Kambe, E. Arai, M. Suzuki, H. Tokuyama, and T. Fukuyama, *Org. Lett.*, 2001, **3**, 2575; N. Papaioannou, C. A. Evans, J. T. Blank, and S. J. Miller, *Org. Lett.*, 2001, **3**, 2879; T. J. Greshock and R. L. Funk, *J. Am. Chem. Soc.*, 2002, **124**, 754; M. K. Ameriks and B. M. Trost, *Org. Lett.*, 2004, **6**, 1745.
9. S. B. Rollins and R. M. Williams, *Tetrahedron Lett.*, 1997, **38**, 4033; S. B. Rollins, T. C. Judd, and R. M. Williams, *Tetrahedron*, 2000, **56**, 521; T. C. Judd and R. M. Williams, *Org. Lett.*, 2002, **4**, 3711.
10. O. Mitsunobu, *Synthesis*, 1981, 1; O. Mitsunobu, 'Comprehensive Organic Synthesis,' Vol. 6, ed. by B. M. Trost and I. Fleming, Pergamon Press, Oxford, 1991, pp. 65-101.
11. For a review of Ns chemistry, see: T. Kan and T. Fukuyama, *Chem. Commun.*, 2004, 353; T. W. Greene and P. G. M. Wuts, 'Protective Groups in Organic Synthesis, 3rd edition,' John Wiley & Sons, Inc., New York, 1999, p. 609.
12. S. B. Rollins, Ph.D. thesis, Colorado State University, 1997.
13. R. M. Williams, S. B. Rollins, and T. C. Judd, *Tetrahedron*, 2000, **56**, 521.
14. L. F. Fieser and M. I. Ardao, *J. Am. Chem. Soc.*, 1956, **78**, 774; S. Iyer and L. S. Liebeskind, *J. Am. Chem. Soc.*, 1987, **109**, 2759.

15. S. Ram and R. E. Ehrenkaufer, *Tetrahedron Lett.*, 1984, **25**, 3415.
16. T. Fukuyama, M. Cheung, C.-K. Jow, Y. Hidai, and T. Kan, *Tetrahedron Lett.*, 1997, **38**, 5831.
17. R. Dembinski, *Eur. J. Org. Chem.*, 2004, 2763.
18. T. Tsunoda, J. Otsuka, Y. Yamamiya, and S. Itô, *Chem. Lett.*, 1994, 539; T. Tsunoda, M. Nagaku, C. Nagino, Y. Kawamura, R. Ozaki, H. Hioki, and S. Itô, *Tetrahedron Lett.*, 1995, **36**, 2531.
19. D. B. Dess and J. C. Martin, *J. Org. Chem.*, 1983, **48**, 4155; D. B. Dess and J. C. Martin, *J. Am. Chem. Soc.*, 1991, **113**, 7277; R. E. Ireland and L. Liu, *J. Org. Chem.*, 1993, **58**, 2899.
20. T. Fukuyama, C.-K. Jow, and M. Cheung, *Tetrahedron Lett.*, 1995, **36**, 6373; T. Fukuyama, M. Cheung, C.-K. Jow, Y. Hidai, and T. Kan, *Tetrahedron Lett.*, 1997, **38**, 5831; T. Fukuyama, M. Cheung, and T. Kan, *Synlett*, 1999, 1301.
21. T. Messeri, D. D. Sternbach, and N. C. O. Tomkinson, *Tetrahedron Lett.*, 1998, **39**, 1669; T. Messeri, D. D. Sternbach, and N. C. O. Tomkinson, *Tetrahedron Lett.*, 1998, **39**, 1673.
22. I. Minami, Y. Ohashi, I. Shimizu, and J. Tsuji, *Tetrahedron Lett.*, 1985, **26**, 244.