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Exploring the Chemistry of Epoxy Amides for the Synthesis of the 2"-*epi*-Diazepanone Core of Liposidomycins and Caprazamycins

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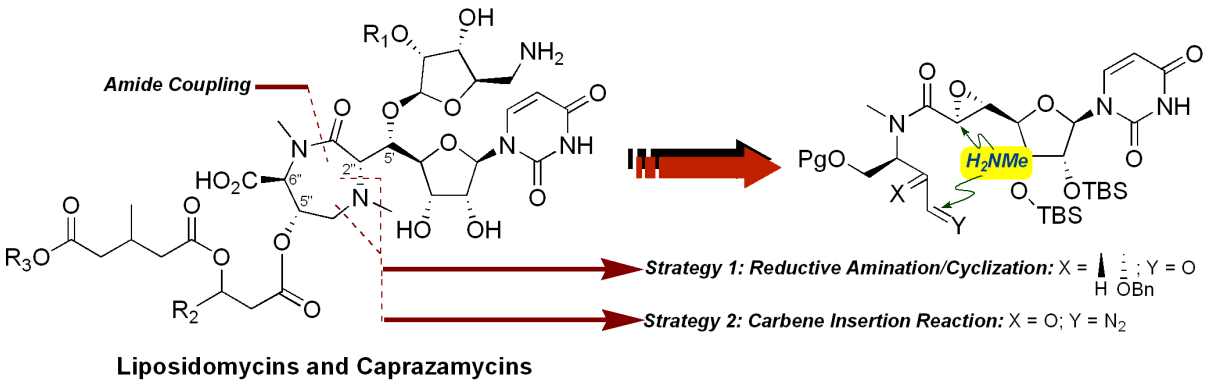


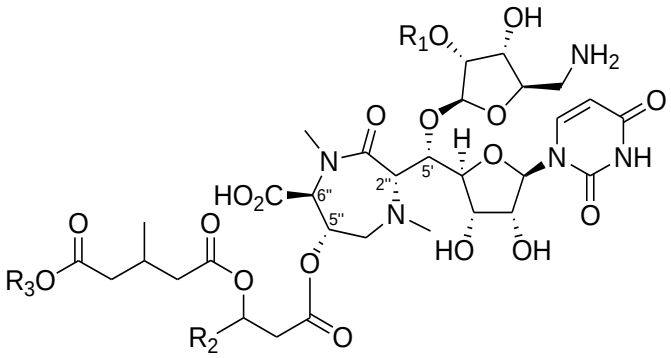
New synthetic strategies have been explored for the synthesis of the structural core of liposidomycins and caprazamycins, an intriguing class of complex nucleoside-type antibiotics. This structural core is comprised of a cyclic diazepanone system linked to an uridyl fragment. The various synthetic approaches have in common that they originate from an epoxyamide derived from uridine, obtained via reaction of uridyl aldehyde **19** with an amide stabilized sulfur ylide. Two different strategies were shown to be efficient in constructing the diazepanone ring system: a) a reductive amination of an epoxy aldehyde with N-methylamine with subsequent intramolecular oxirane ring opening; and b) a carbene insertion reaction of an acyclic diazoamine precursor.

1. Introduction

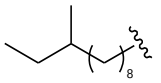
The liposidomycins[1] and caprazamycins[2] are unique nucleoside-type antibiotics isolated from *Streptomyces* belonging to the family of the complex nucleoside-type antibiotics.[3] Other notable members include muraymycins,[4] mureidomycins,[5] pacidamycins,[6] napsamycins,[7] and FR-900493.[8] These natural products (**1**-**6**, Figure 1) have elicited intense interest in the scientific community due to their antibiotic properties, which are characterized by an intriguing mechanism of action based on the inhibition of phospho-*N*-acetyl-muramoyl-pentapeptide-transferase (MraY),[9] also known as translocase I, an enzyme involved in the biosynthesis of the cell-wall of bacteria.[10] In addition to their striking antibiotic profiles,[11] their complex and unprecedented molecular architectures have appealed to synthetic chemists to investigate these molecules as synthetic targets[12] of great biological interest.[13] As a result, diverse synthetic approaches have been published and one total synthesis of the diazepanone system from the caprazamycins, termed caprazol, has recently been reported by Matsuda et al.[14]

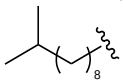
Our initial synthetic efforts towards the liposidomycins[15] were based on reactions of the *N*-indole epoxy amide[16] derived from uridine **7** with 1,3-diamines as bidentade nucleophiles as a means of constructing the diazepanone core in a straightforward and efficient manner to afford compounds of type **8**. In an attempt of extending this strategy to the fully functionalized system found in caprazol (**9**), the diazepanone core contained in the natural nucleosides would arise from two key disconnections at the amide and amine sites respectively, requiring a two-step process consisting of an amide bond formation (step 1) and an epoxide opening reaction (step 2). To this end, the advanced precursors *cis N*-indole epoxy amide **10** and diamine **11** were identified as key compounds to achieve this goal (Scheme 1).

Figure 1. Molecular Structures of Representative Members of Liposidomycins and Caprazamycins



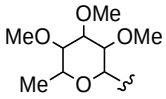
Liposidomycins:

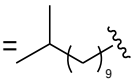
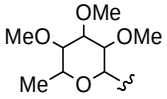
A-III (**1**): R_1 = H; R_2 =  ; R_3 = H

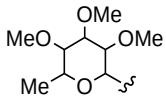
B (**2**): R_1 = SO_3H; R_2 =  ; R_3 = H

C (**3**): R_1 = SO_3H; R_2 =  ; R_3 = H

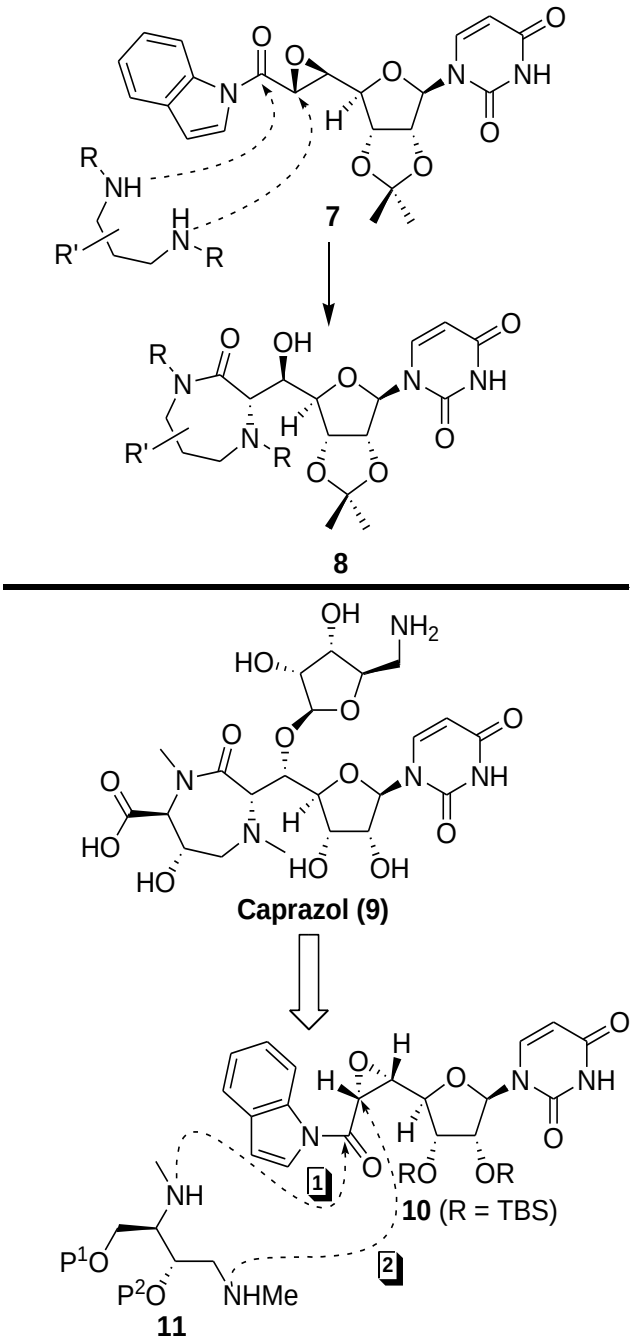
Caprazamycins:

A (**4**): R_1 = H; R_2 =  ; R_3 = 

B (**5**): R_1 = H; R_2 =  ; R_3 = 

C (**6**): R_1 = H; R_2 =  ; R_3 = 

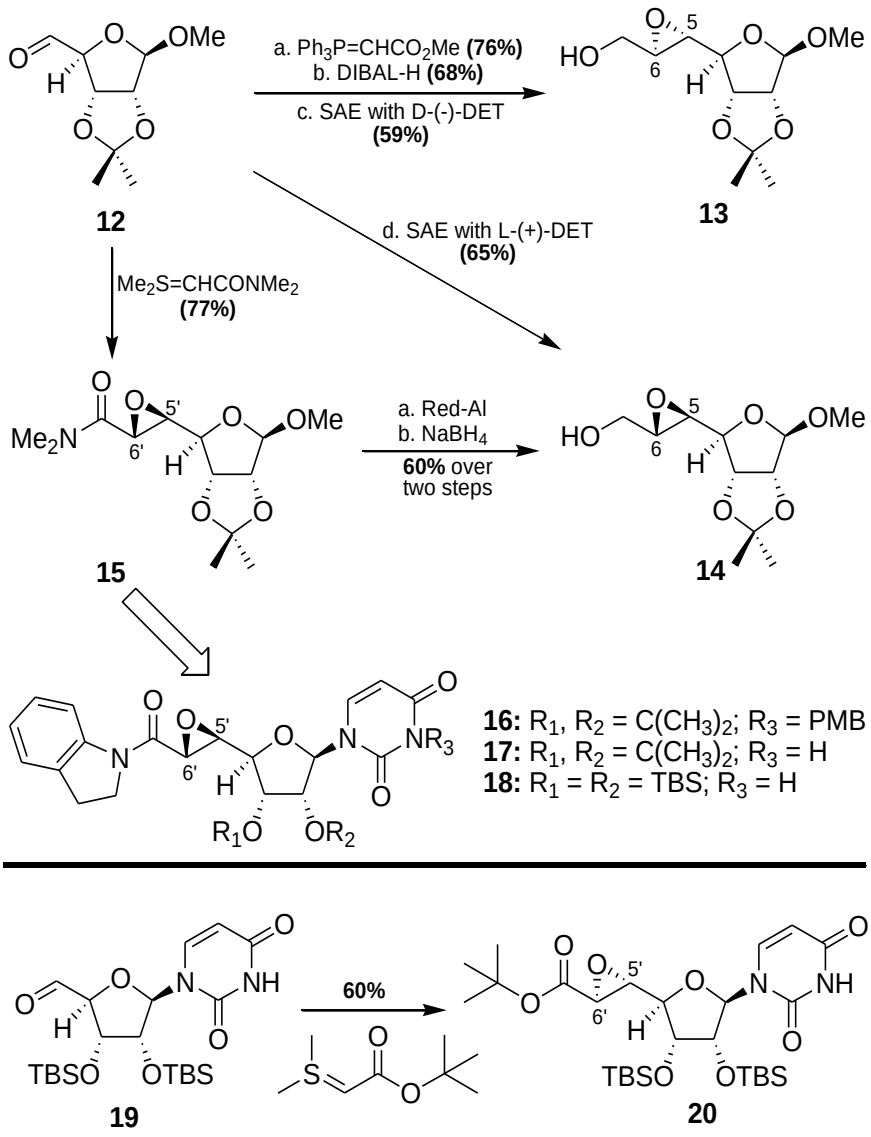
Scheme 1. Synthetic Strategy towards the Liposidomycin and Caprazamycin Antibiotics



For the assignment of configuration of the new chiral centres formed during the construction of the oxirane ring, we assumed the stereochemistry of epoxyamide **15,** demonstrated via Sharpless asymmetric epoxidations.[17] Thus, sequential reactions of aldehyde **12** to epoxy alcohols **13** and **14**[18] and comparison of the physical and spectroscopic properties of both epoxyalcohols with that obtained by reduction of epoxyamide **15** let us to establish the configurations at 5' and 6' positions as 5'-(*R*) and 6'-(*S*), which was supported by molecular

modeling studies of the starting aldehyde **12**.[19] As a consequence of these studies, we extended this stereochemical result to the epoxyamides derived from uridine, compounds **16-18**,[20] assuming a similar stereochemical outcome for the reactions of their corresponding aldehydes with the sulfur ylide, supported again by theoretical calculations of the starting aldehydes. However, recent studies, conducted by Ducho and coworkers,[21] have demonstrated by X-Ray analysis that the oxirane ring constructed via sulfur ylides (ex. compound **20**) resulted in the opposite stereochemistry with respect to that proposed by us (Scheme 2).

Scheme 2. Established Configurations for Epoxyamides **16**-**18** and Corrected Configuration by Ducho *et al*



Ducho *et al, Tetrahedron: Asymmetry*, **2010**, *21*, 763-766

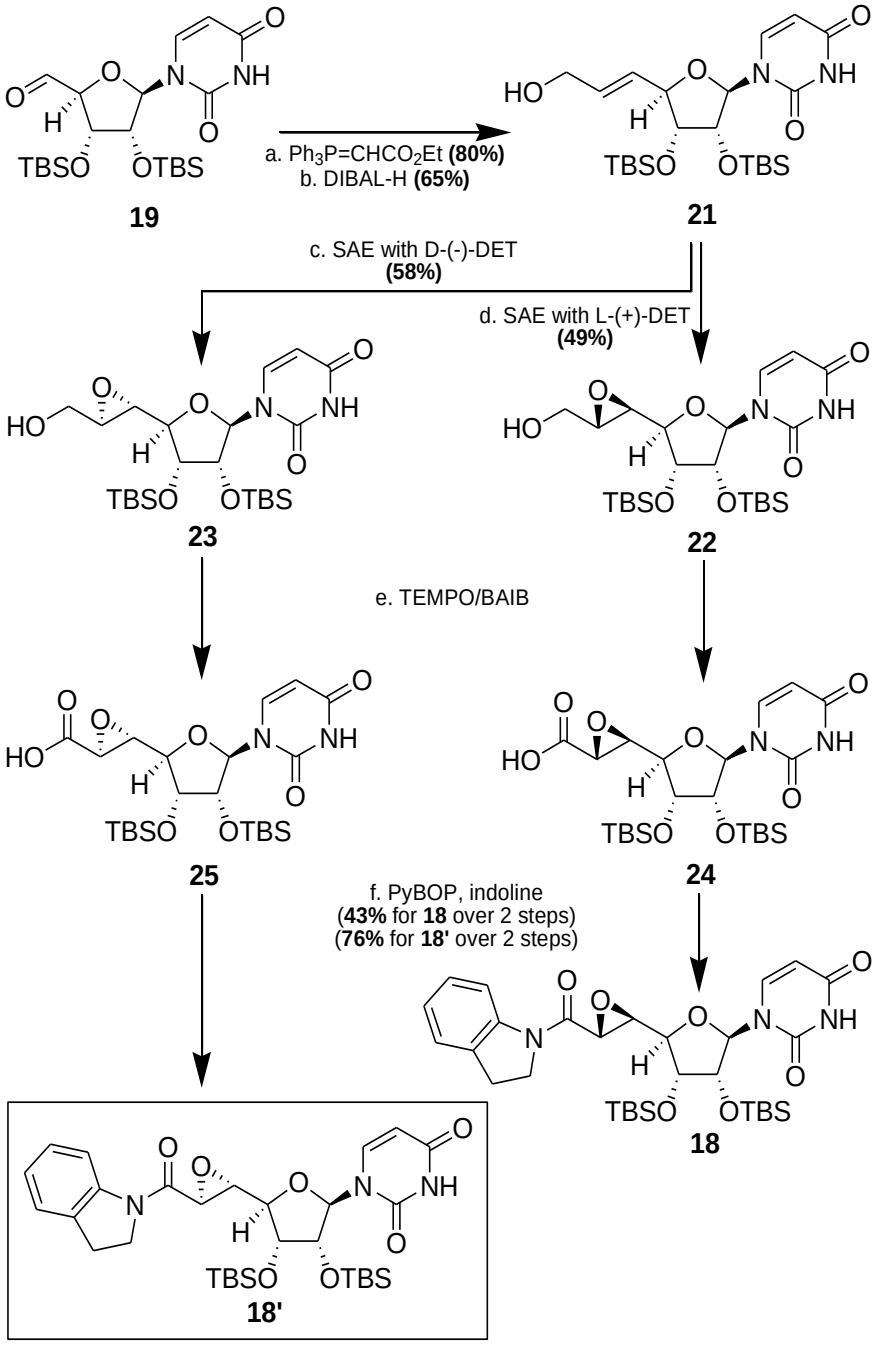
In the present article, we wish to report our synthetic efforts directed to the construction of key diazepanone ring found in this class of antibiotics, including the establishment of the absolute configurations of the synthesized epoxyamides, precursors of the diazepanonic derivatives. The successful generation of a fully functionalized diazepanone core occurred in this family of complex nucleosides should serve as the basis for an eventual total synthesis of the natural antibiotics.

2. Results and Discussion

2.1. Establishment of the Absolute Configuration of Epoxyamides. For this first objective, we prepared allylic alcohol **21** from aldehyde **19**, via a Wittig reaction followed by DIBAL reduction of the resulting α,β-unsaturated ester. Then, **21** was subjected to Sharpless asymmetric epoxidations by treatment with (+)-Diethyl L-tartrate [(+)-DET] and (-)-Diethyl D-tartrate [(-)-DET] respectively, in the presence of Ti(O*i*Pr)$_4$ and TBHP to provide epoxyalcohols **22** and **23** in 59 and 65% yields. With both epoxyalcohols in hand, we initially tried the transformation of epoxyamide **18** to its corresponding epoxyalcohol by the action of Super-H,[22] but this reaction proved to be unsuccessful and provided a complex mixture of decomposition products. This result compelled us to transform epxyalcohols **22** and **23** to the corresponding *N*-indoline epoxyamides. This conversion was undertaken by oxidation of **22** and **23** to the epoxy acids **24** and **25** by the action of TEMPO/BAIB[23] in the presence of water, followed by coupling with indoline assisted by PyBOP [Benzotriazol-1-yloxy-tri(pyrrolidino)phosphonium hexafluorophosphate][24] to give epoxyamides **18** and **18'**. Inspection of their corresponding ^{1}H NMR spectra and comparison with that obtained from the resulting epoxyamide via the sulfur ylide revealed that the ^{1}H NMR spectra of **18'**, obtained from **25**, matched completely with the spectra obtained through the sulfur ylide chemistry. This finding corroborates the stereochemical assignment accomplished by Ducho

et al., and consequently, the initial stereochemical assignment, proposed by us in previous articles is not correct (Scheme 3).

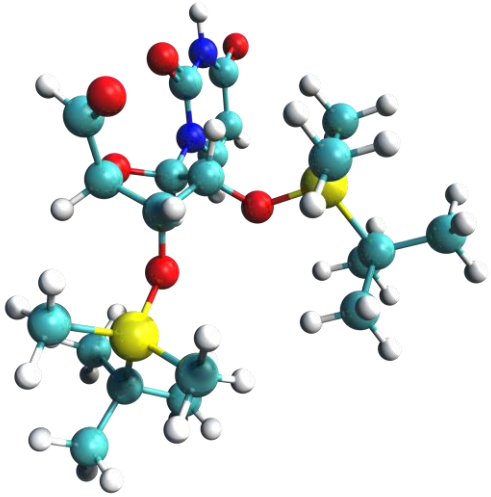
Scheme 3. Synthetic Studies for the Establishment of Configuration of Epoxyamide **18**.



Interestingly, molecular modeling studies performed for aldehyde **19**[25] revealed a preference for a conformational arrangement, depicted in Figure 2, in which the carbonyl group is perpendicular with respect to the C-O bond of the furanoside ring. According to this, the preferential attack of a nucleophile should take place at the *re* face to form the epoxide

with the stereochemistry initially proposed and should be in agreement with the prediction of the Felkin-Ahn model.[26] However, this theoretical observation does not correspond with the experimental result obtained. We propose that the uracil heterocycle is playing an essential role in directing the nucleophylic attack from the opposite face of the aldehyde with respect to the model´s prediction.

Figure 2. Preferred Conformation of Aldehyde **19**



2. Synthetic Studies towards the Diazepanone Ring System. The following step in this study was to establish new methodologies capable of installing the complete functionality found in the diazepanonic system of the liposidomycins and caprazamycins. To this aim, we investigated *N*-allyl amides as potentially useful acyclic precursors of the cyclic diazepanone derivatives, supported by our previous studies[15] based on epoxidation of the double bond. An extension of this reaction to the more functionalized *N*-allyl amide could lead us to the desired diazepanone system via cyclization with *N*-methylamine. Thus, allyl amine **27**[27] was chosen as a suitable starting point. Direct displacement of this amine to the *N*-indole amide **26**, prepared from **18'** by treatment with DDQ,[20] was unsuccessful resulting in starting amide. This result forced us to introduce an additional step consisting of the hydrolysis of *N*-indole amide **26** to the corresponding acid, which was accomplished by treatment with LiOH to give the epoxy acid **25** in 89% yield, followed by coupling with amine **27** by the action of

EDCI/HOBt to give amide **29** in 52% yield. However, when epoxidation of the double bond was attempted by use of *m*CPBA, the expected diepoxide was not obtained, only recovered starting material. Other oxidative agents such as DMDO,[28] or methyl(trifluoromethyl)dioxirane[29] were similarly unsuccessful. Since more simple *N*-allylamides were oxidized by the action of peracids, the lack of reactivity of the double bond to oxidative agents found in this case was adscribed to steric factors, which led us to consider allylamine **28**. In this case, direct displascement of the indole moiety was possible, providing amide **30** in a reasonable good yield (62%). On the other hand, coupling of acid **25** with **28** afforded also **30** but in a surprising poor yield (35%). Then, we proceeded with the epoxidation reaction by treatment of **30** with peracids or dioxiranes. Disappointingly, the result was no formation of the desired diepoxide (Scheme 4, part A). Additional attempts of epoxidation assisted by the hydroxyl group, such as Sharpless epoxidation or methods mediated by $VO(acac)_2$,[30] were similarly unsuccessful.

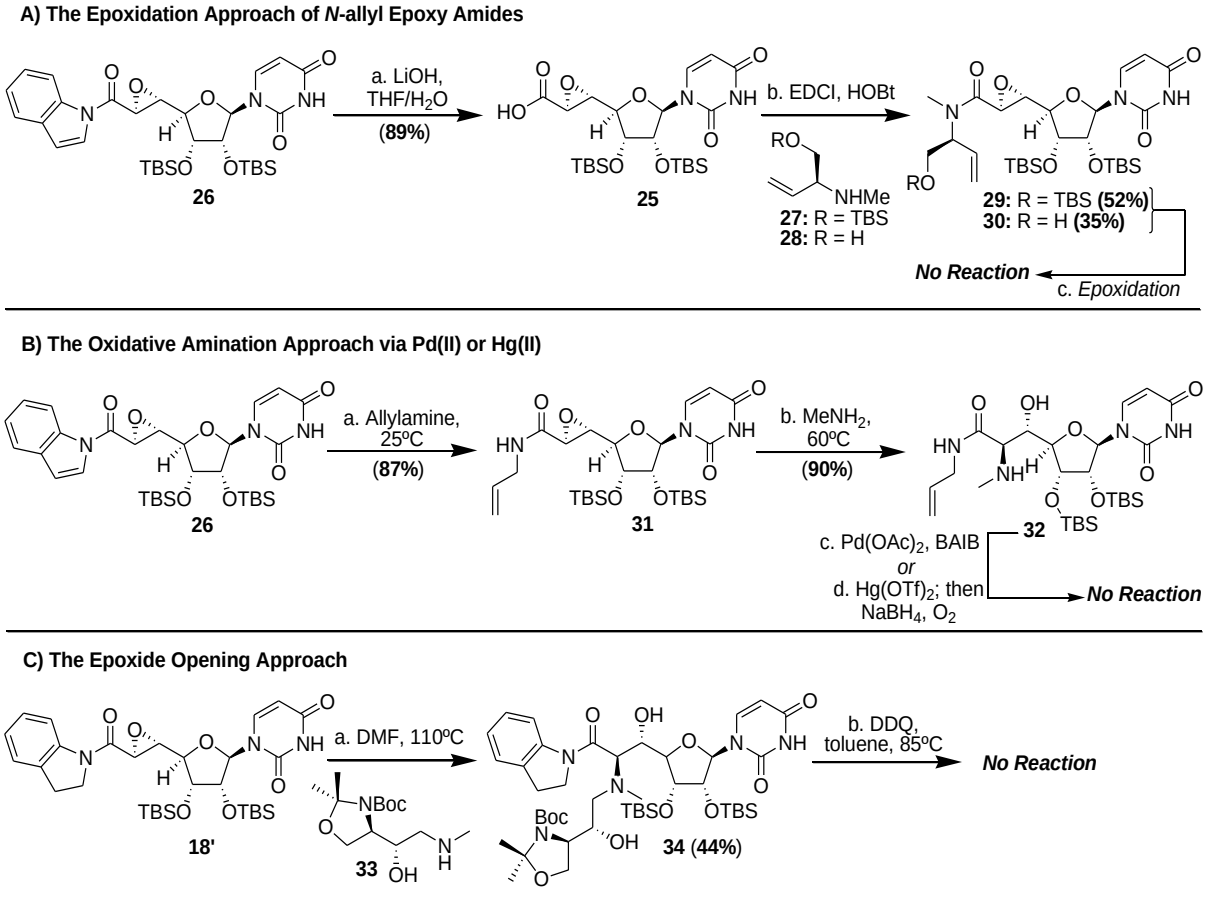
Given the challenges, we considered *N*-allyl amide **31**, readily prepared from *N*-indole amide **26** in 87% yield by smooth treatment with allylamine, to investigate new cyclizations procedures. Thus, after epoxide opening with methylamine, to provide amino alcohol **32**, we attempted various procedures to accomplish the cyclization process. These new strategies required activation of the olefinic group, for which procedures based on Sharpless asymmetric dihydroxylation,[31] or cyclizations assisted by palladium (II) or mercury (II) were considered. In the first case, treatment of **32** with ADmixβ resulted in no reaction, only recovered starting material. More interesting and promising seemed to be the procedures based on the use of palladium (II)[32] or mercury (II)[33] followed by oxidative work-ups. However, treatment of **32** with $Pd(OAc)_2$ and $Hg(OTf)_2$ respectively followed by oxidative work up with BAIB for the first case and $O_2/NaBH_4$ for the second, resulted again in no formation of the desired

products, obtaining only complex mixtures of decomposition products instead (Scheme 4, part B).

Due to the synthetic hurdles encountered in the functionalization of the amine fragment linked to the uridyl derivative, it seemed clear that such functionalization must be done prior to the assembly to the uridine moiety. On the other hand, we deemed of interest to introduce the amine fragment by opening of the oxirane ring instead of an earlier formation of the amide. This new strategy therefore commenced with the installation of the acyclic amine, already possessing the required functionzalition and stereochemistry, via oxirane ring opening. For this installation, the amino alcohol **33** was reacted with epoxide **18'** by heating in DMF to obtain compound **34** in 44% yield. Oxidation of the *N*-indoline amide to its corresponding *N*-indole should provide a suitable compound that could be cyclized via intramolecular attack by the amine group present in the molecule. However, oxidation of **34** with DDQ did not furnish the coveted indole derivative (Scheme 4, part C).

After all the discouranging results encountered in pursuit of the diazepanonic system, we decided to revisit the strategy based on the early formation of the amide with the requisite of introducing an amine with the required functionalization. For this purpose amine **35**[35] was selected as a preferred candidate to address this synthetic challenge. Direct introduction of the amine from epoxyamide **26** was not possible, which compelled us to introduce it via coupling with epoxyacid **25** by the action of BOP [Benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate][24] to obtain complex epoxyamide **36** in 65% yield. Selective deprotection of the primary silylether was successfully performed by treatment of **36** with CSA to afford alcohol **37** in a good 88% yield. This compound offered diverse possibilities for chemical transformations and was amenable to a cyclization reaction, taking advantage of the presence of the oxirane ring.

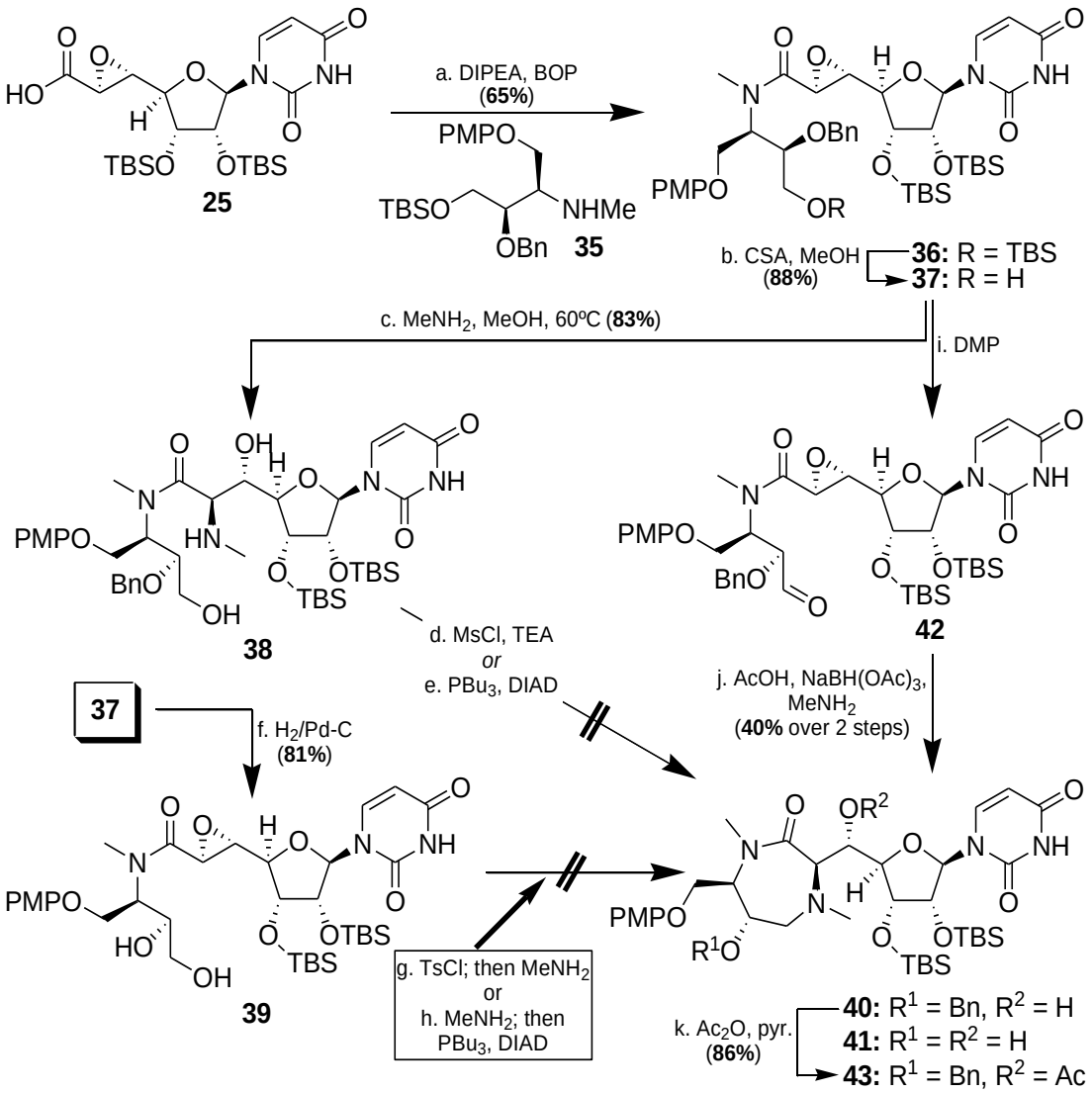
Scheme 4. Synthetic Studies towards the Complex Diazepanone System



Thus, we initiated a series of chemical screenings with the introduction of a good leaving group at this position. However, an initial attempt at introducing a sulfonate group did not work. As an alternative, introduction of the amine group was performed by treatment of **37** with methylamine. The oxirane ring opened product, amino alcohol **38**, was then subjected to an intramolecular Mitsunobu-type reaction that should have formed compound **40**. Again, the result was unsuccessfull, resulting in recovered starting material. Considering that steric hindrance present in these molecules one could rationalize these discouraging results, thus we decided to remove the benzyl protecting group, which was undertaken by catalytic hydrogenation to give the dihydroxy amide **39**. From this point, the introduction of a leaving group at the terminal hydroxyl group or a Mitsunobu reaction was feasible. With this advanced acyclic product in hand, the cyclization was attempted again by the action of methylamine, disappointingly the reaction did not work as desired, resulting in the formation of a complex mixture of products, not detecting the formation of **41** (Scheme 5).

In our continuing quest to establish a strategy to prepare the fully functionalized diazepanone, we determined that a few other approaches were left to be attempted. To this end, we considered a cyclization via reductive amination of an aldehyde with concomitant intramolecular epoxide opening by the resulting amine. In the event, the aldehyde **42** was obtained by oxidation of alcohol **37** with Dess-Martin periodinane,[36] which was not isolated and allowed to react with methylamine in the presence of $NaBH(OAc)_3$. The result was the preparation of the cyclic diazepanone system **40** in a modest, albeit reasonable, 40% yield over two steps. Acetylation of **40** was carried out to support the structure of the diazepanonic ring system, providing the acetyl derivative **43** (Scheme 5).

Scheme 5. Synthesis of the Complex Diazepanone System. I. The Reductive Amination/Cyclization Strategy.

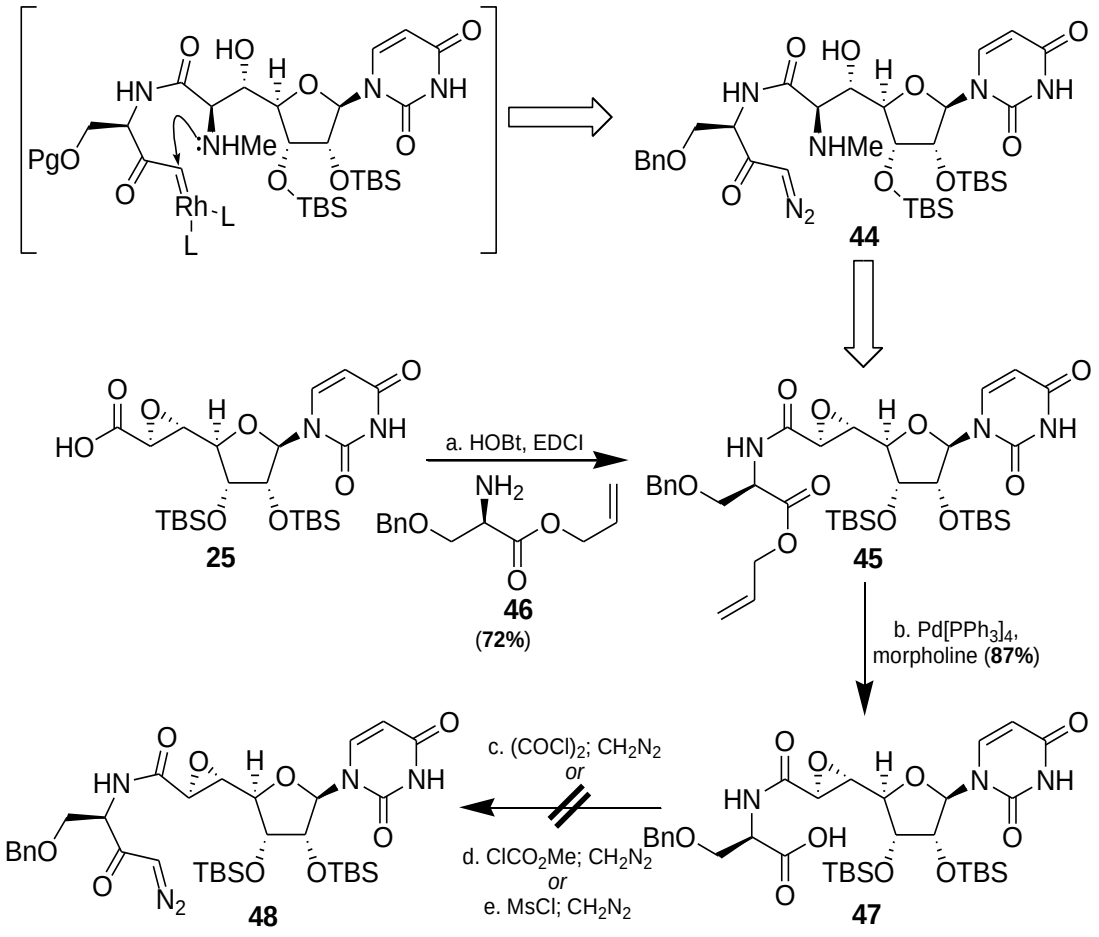


Finally, another approach was explored based on a carbene insertion process for the construction of the cyclic diazepanone core. This carbene insertion reaction would consist of an intramolecular NH trapping by the carbenoid species, depicted in Scheme 6, produced from an amino diazo derivative, represented by compound **44**, and mediated by the action of rhodium (II) acetate.[37] For this new route, we considered the ester **45** as a potential precursor for the introduction of the diazo functionality. Thus, we prepared the compound **45** by coupling epoxy acid **25** with allyl ester **46**[38] by the assistance of EDCI/HOBt to provide amide **45** in 72% yield. After allyl ester deprotection by the action of palladium (0), the corresponding epoxy acid **47** was subjected to conventional methods[39] for the introduction of the diazo group. Oddly, treatment of **47** with oxalyl chloride to give the acid chloride followed by reaction with freshly prepared diazomethane did not produce diazo derivative **48**. In addition, utilization of mesylchloride for activation of the acid, a method recently reported that proved to be efficient for hindered acids,[40] did not give the desired product (Scheme 6).

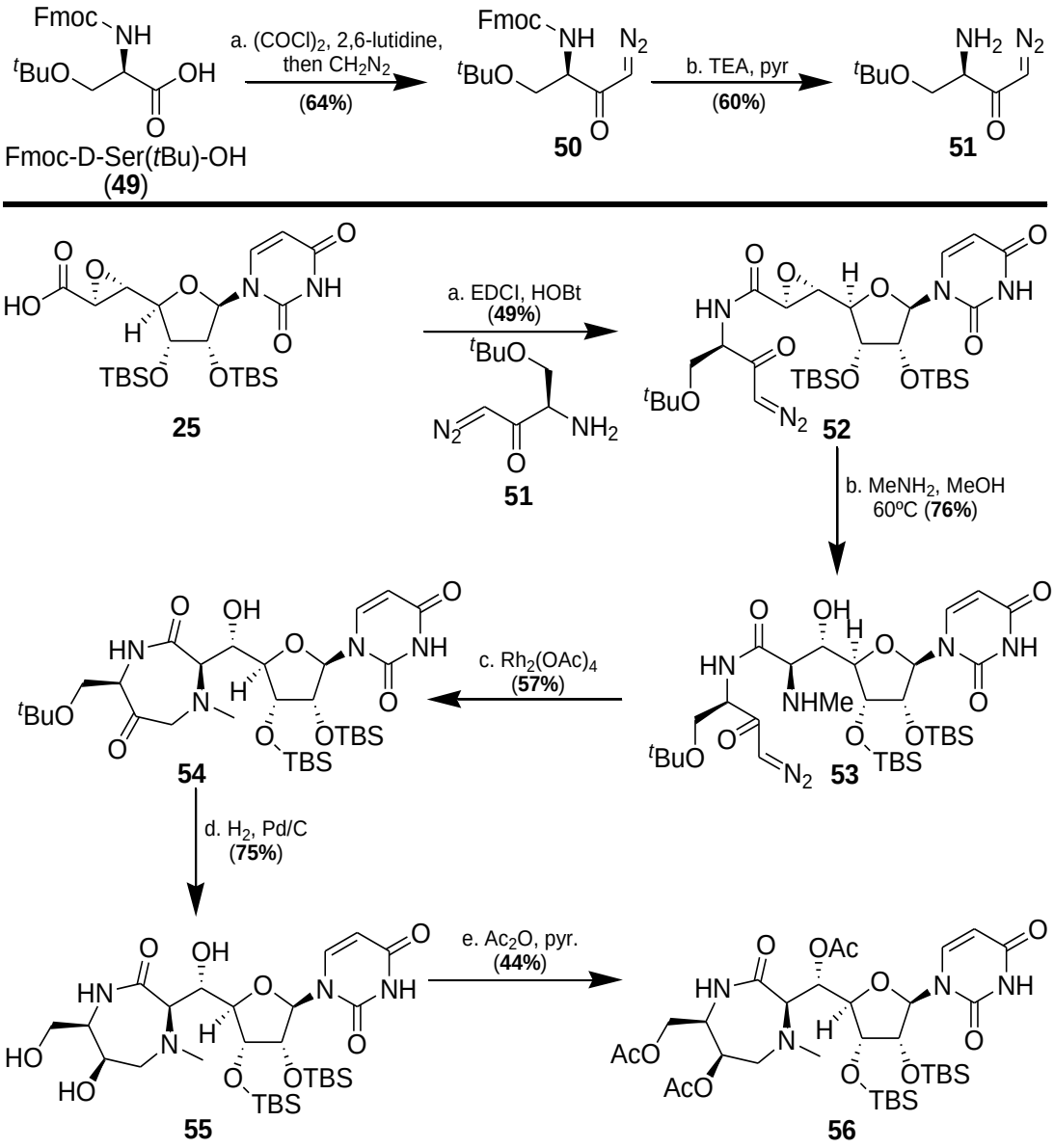
These results forced us to introduce the diazo group prior to the coupling with the uridyl derivative. To this aim, diazo compound **51** was prepared from commercially available serine Fmoc-D-Ser(*t*Bu)-OH (**49**) in two steps that included diazo coupling, through the acid chloride intermediate, to give diazo ketone **50**, followed by Fmoc deprotection. The acid **25** was coupled with diazoketone **51** by treatment with EDCI/HOBt to provide epoxy diazo amide **52** in 49% yield. Subsequent reaction of **52** with *N*-methylamine afforded the corresponding epoxide opened product, amino diazo derivative **53**, in 76% yield. This product represents a key compound for investigation of the utility of this new synthetic approach for the liposidomycins and related complex nucleosides. Gratifyingly, when **53** was subjected to the action of a catalytic amount of $Rh_2(OAc)_4$ in CH_2Cl_2 at 25ºC, formation of a new product was detected. After purification and NMR analysis, the new product was determined to be the cyclic ketone **54**, obtained in 57% yield. Catalytic hydrogenation using Pd-C provided a

single alcohol which was tentatively assigned as compound **55**. Inspection of its NMR spectra indicated the loss of the tert-butyl ether group, most likely occurring during the hydrogenation reaction due to the acidic character of the employed catalyst. Finally, compound **55** was peracetylated by treatment with acetic anhydride in pyridine to provide tri-O-acetyl derivative **56** (Scheme 7).

Scheme 6. Towards the Synthesis of Diazo Ketone **48**.

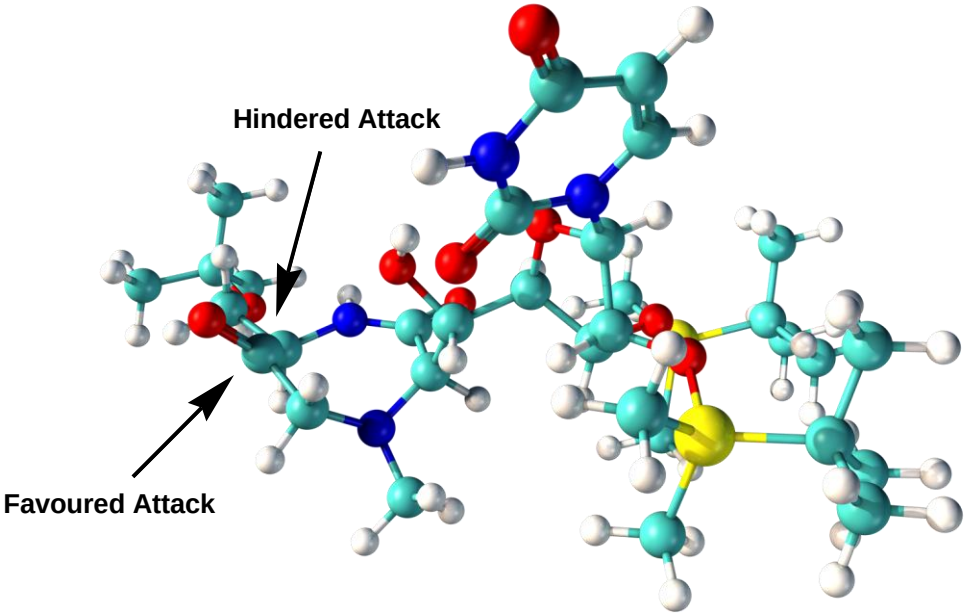


Scheme 7. Synthesis of the Complex Diazepanone System. II. The Diazo Strategy.



In order to gain insight into the stereochemical outcome of the reduction step and to assign the correct stereochemistry for the reduction product **55**, we undertook theoretical calculations of compound **54**. The study revealed a conformation (Figure 3), in which the β-face of the ketone displayed steric hindrance due to the presence of the hydroxyl group, while on the α-face an equatorial attack of a hydrogen appeared to be favoured, thus allowing us to predict and justify the configuration indicated.

Figure 3. Preferred Conformation of Ketone **54**



3. Conclusions

In conclusion, the synthetic results described herein show promise for the construction of the diazepanone ring system contained in the liposidomycins and caprazamycins antibiotics. Thus, an extensive synthetic study based on the use of epoxy amides, obtained via sulfur ylides, has been carried out, demonstrating the synthetic potential of this methodology for the construction of the diazepanonic system contained in these natural products. The application of these synthetic methodologies to the corresponding *cis* epoxide should allow for the synthesis of the diazepanone system with the proper functional groups and correct stereochemistry. Synthetic efforts in this direction are currently being explored in our laboratories.

4. Experimental

General Techniques. All reactions were carried out under an argon atmosphere with dry, freshly distilled solvents under anhydrous conditions, unless otherwise noted. Tetrahydrofuran (THF) and ethyl ether (ether) were distilled from sodium benzophenone, and methylene chloride (CH_2Cl_2), benzene (PhH), and toluene from calcium hydride. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials, unless otherwise stated. All solutions used in workup procedures were saturated unless otherwise noted. All reagents were purchased at highest commercial quality and used without further purification unless otherwise stated.

All reactions were monitored by thin-layer chromatography carried out on 0.25 mm silica gel plates (60F-254) using UV light as visualizing agent and 7% ethanolic phosphomolybdic acid or *p*-anisaldehyde solution and heat as developing agents. Silica gel (60, particle size 0.040-0.063 mm) was used for flash column chromatography. Preparative thin-layer chromatography (PTLC) separations were carried out on 0.25, 0.50 or 1 mm silica gel plates (60F-254).

NMR spectra were recorded on a 400 MHz instrument and calibrated using residual undeuterated solvent as an internal reference. The following abbreviations were used to explain the multiplicities: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; band, several overlapping signals; b, broad. Optical rotations were recorded on a polarimeter. High resolution mass spectra (HRMS) were recorded on a mass spectrometer under fast atom bombardment (FAB) conditions in a *m*-nitrobenzyl alcohol (NBA) matrix.

Allylic alcohol 21. A solution of aldehyde **19** (500 mg, 1.06 mmol, 1.0 equiv) in CH_2Cl_2 (10 mL) was treated with the phosphorous ylide $Ph_3P{=}CHCO_2Et$ (738 mg, 2.12 mmol, 2.0 equiv) at 25ºC. After stirring at this temperature for 8 h, the reaction mixture was concentrated under reduced pressure and the resulting crude purified by flash column chromatography (silica gel, 30% EtOAc in hexanes) to obtain the corresponding α,β-

unsaturated ester (458 mg, 80%) as a white solid: R_f = 0.43 (silica gel, 30% EtOAc in hexanes); m. p. = 62-64ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.06 (s, 3 H), 0.07 (s, 3 H), 0.09 (s, 3 H), 0.13 (s, 3 H), 0.90 (s, 9 H), 0.91 (s, 9 H), 1.31 (t, J = 7.1 Hz, 3 H), 3.38 (dd, J = 6.8, 4.1 Hz, 1 H), 4.19 (dd, J = 4.0, 2.7 Hz, 1 H), 4.25 (dc, J = 7.1, 3.8 Hz, 2 H), 4.63 (dt, J = 6.2, 1.6 Hz, 1 H), 5.71 (d, J = 2.7 Hz, 1 H), 5.79 (dd, J = 8.1, 2.2 Hz, 1 H), 6.15 (dd, J = 15.7, 1.7 Hz, 1 H), 6.97 (dd, J = 15.7, 5.7 Hz, 1 H), 7.33 (d, J = 8.2 Hz, 1 H), 9.42 (bs, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = -4.8, -4.7, -4.5, -4.2, 14.2, 18.0, 18.1, 25.7, 25.8, 60.8, 75.0, 75.2, 81.9, 91.8, 102.5, 123.3, 139.6, 143.1, 150.0, 163.3, 165.6. Then, a solution of DIBAL in CH_2Cl_2 (1.0 M, 2.1 mL, 2.1 mmol, 2.5 equiv) was dropwise added to a solution of the α,β-unsaturated ester (458 mg, 0.84 mmol) in CH_2Cl_2 (8 mL) at -78ºC. After 0.5 h at this temperature, the reaction mixture was treated with MeOH (1 mL) followed by EtOAc (5 mL). After 10 min, a saturated aqueous Na-K tartrate solution was added and the resulting mixture was diluted with EtOAc and allowed to reach room temperature. After vigorous stirring for 1 h, the biphasic system was separated, the aqueous phase extracted with EtOAc and the combined organic solution was dried ($MgSO_4$), filtered and concentrated. Purification by flash column chromatography (silica gel, 50% AcOEt in hexanes) afforded allylic alcohol **21** (272 mg, 65%) as a colorless oil: R_f = 0.63 (silica gel, 50% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.06 (s, 3 H), 0.07 (s, 3 H), 0.09 (s, 3 H), 0.11 (s, 3 H), 0.90 (s, 9 H), 0.91 (s, 9 H), 1.75 (bs,1 H), 3.81 (dd, J = 5.7, 4.2 Hz, 1 H), 4.22-4.27 (m, 2 H), 4.27-4.31 (m, 1 H), 4.50 (dd, J = 7.3, 6.1 Hz, 1 H), 5.62 (d, J = 3.4 Hz, 1 H), 5.76 (dd, J = 8.1, 2.0 Hz, 1 H), 5.83 (ddt, J = 15.4, 7.8, 1.7 Hz, 1 H), 6.03 (ddt, J = 15.4, 4.6, 0.9 Hz, 1 H), 7.37 (d, J = 8.2 Hz, 1 H), 8.86 (bs, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = -4.8, -4.7, -4.5, -4.2, 18.0, 18.1, 25.7, 25.8, 62.4, 74.9, 75.5, 84.2, 92.1, 102.2, 126.8, 134.9, 140.4, 150.0, 162.9; FAB HRMS (NBA): *m/e* 499.2656, $M+H^+$ calcd for $C_{23}H_{42}N_2O_6Si_2$ 499.2660.

Epoxy Alcohol 22. A solution of titanium tetraisopropoxide (11 μL, 0.037 mmol, 0.25 equiv) and 4Å molecular sieves (35 mg) in CH_2Cl_2 (3 mL) was added L-(+)-DET (7.0 μL, 0.037 mmol, 0.25 equiv) at -23ºC. After 15 min at this temperature, a solution of allylic alcohol **21** (75 mg, 0.150 mmol, 1.0 equiv) in CH_2Cl_2 (2.5 mL) was added dropwise, followed by the addition, after additional 30 min, of TBHP (5.5 M solution in decane, 40 μL, 0.225 mmol, 1.5 equiv) at -23ºC. After 24 h at this temperature, the reaction mixture was filtered and the filtrate was diluted with EtOAc and washed with a saturated aqueous solution of sodium sulphate. After decantation, the aqueous phase was extracted with EtOAc, and the combined organic layer was dried ($MgSO_4$), filtered and concentrated. The resulting crude product was purified by flash column chromatography (silica gel, 2.5% MeOH in CH_2Cl_2) to obtain epoxy alcohol **22** (38 mg, 49% yield) as a colorless oil: R_f = 0.30 (silica gel, 2.5% MeOH in CH_2Cl_2); $[\alpha]_D^{22}$ -21.5 (*c* 0.2, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.03 (s, 3 H), 0.06 (s, 3 H), 0.09 (s, 3 H), 0.10 (s, 3 H), 0.87 (s, 9 H), 0.91 (s, 9 H), 3.17 (dt, *J* = 3.9, 2.6 Hz, 1 H), 3.34 (dd, *J* = 4.2, 2.4 Hz, 1 H), 3.75 (dd, *J* = 12.9, 4.0 Hz, 1 H), 3.94 (ddd, *J* = 9.8, 4.7, 2.1 Hz, 1 H), 4.09 (dd, *J* = 4.2, 2.9 Hz, 1 H), 4.45 (dd, *J* = 5.8, 4.2 Hz, 1 H), 5.69 (d, *J* = 5.8 Hz, 1 H), 5.78 (dd, *J* = 8.1, 2.2 Hz, 1 H), 7.39 (d, *J* = 8.2 Hz, 1 H), 9.11 (bs, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = -4.9, -4.7, -4.6, -4.3, 17.9, 18.1, 25.8, 54.4, 57.1, 60.9, 72.1, 74.1, 83.4, 84.2, 91.2, 102.7, 141.4, 150.3, 163.0; FAB HRMS (NBA): *m/e* 515.2612, $M+H^+$ calcd for $C_{23}H_{42}N_2O_7Si_2$ 515.2609.

Epoxy alcohol 23. Epoxy alcohol **23** (48 mg, 58%) was obtained from allylic alcohol **21** (80 mg, 0.160 mmol) according to the same procedure described above for **22** but using D-(-)-DET. **[23]:** colorless oil; R_f = 0.30 (silica gel, 2.5% MeOH in CH_2Cl_2); $[\alpha]_D^{22}$ +32.9 (*c* 0.3, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.08 (s, 6 H), 0.12 (s, 3 H), 0.13 (s, 3 H), 0.89 (s, 9 H), 0.93 (s, 9 H), 1.72 (bs, 1 H), 3.31 (dd, *J* = 2.3, 1.1 Hz, 1 H), 3.36 (dt, *J* = 3.3, 2.3 Hz, 1 H), 3.76 (dd, *J* = 13.0, 3.4 Hz, 1 H), 4.04 (dd, *J* = 13.0, 2.2 Hz, 1 H), 4.07-4.12 (m, 2 H), 4.31

(dd, *J* = 4.0, 1.2 Hz, 1 H), 5.76 (dd, *J* = 8.2, 2.3 Hz, 1 H), 5.87 (d, *J* = 3.7 Hz, 1 H), 7.79 (d, *J* = 8.2 Hz, 1 H), 8.55 (bs, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = -4.9, -4.7, -4.6, -4.4, 18.0, 18.1, 25.7, 25.8, 54.3, 55.6, 60.2, 73.4, 75.3, 79.5, 88.6, 102.5, 139.8, 150.2, 162.8; FAB HRMS (NBA): *m/e* 515.2615, $M+H^+$ calcd for $C_{23}H_{42}N_2O_7Si_2$ 515.2609.

Epoxy Amide 18. To a solution of epoxy alcohol **22** (132 mg, 0.256 mmol) in acetonitrile:H_2O (4 mL, 1:1) was added BAIB (495 mg, 1.536 mmol, 6.0 equiv) and the crude mixture treated with TEMPO (32 mg, 0.205 mmol, 0.8 equiv) at 25ºC. After stirring for 40 min at this temperature, the reaction mixture was diluted with EtOAc and washed with a saturated aqueous $Na_2S_2O_3$ solution. The aqueous layer was extracted with EtOAc and the combined organic layer washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The resulting epoxy acid **24** was used for the next step without further purification. A solution of crude epoxy acid **24** (~ 0.256 mmol) in DMF (10 mL) was treated with DIPEA (92 μL, 0.524 mmol, 2.0 equiv) at 25ºC. After stirring for 10 min, indoline (44 μL, 0.393 mmol, 1.5 equiv) and PyBOP (163 mg, 0.315 mmol, 1.2 equiv) were added and the resulting mixture was stirred at 25ºC for 12 h. After this time, the reaction mixture was diluted with Et_2O and the resulting organic solution washed with a saturated aqueous NH_4Cl solution. After separation of both phases, the organic layer was washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 10% → 50% AcOEt in hexanes) to obtain epoxy amide **18** (68 mg, 43% yield over two steps) as a colorless oil: R_f = 0.50 (silica gel, 50% EtOAc in hexanes); $[\alpha]_D^{22}$ -11.3 (*c* 0.2, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) □ δ = 0.03 (s, 3 H), 0.07 (s, 3 H), 0.13 (s, 6 H), 0.88 (s, 9 H), 0.93 (s, 9 H), 3.25 (t, *J* = 8.3 Hz, 2 H), 3.56 (dd, *J* = 5.2, 0.8 Hz, 1 H), 3.68 (d, *J* = 1.0 Hz, 1 H), 4.00 (dd, *J* = 5.3, 2.8 Hz, 1 H), 4.12-4.15 (m, 1 H), 4.15-4.22 (m, 1 H), 4.22-4.28 (m, 1 H), 4.44-4.48 (m, 1 H), 5.75-5.79 (m, 2 H), 7.06 (t, *J* = 7.1 Hz, 1 H), 7.21 (t, *J* = 6.4 Hz, 2 H), 7.37 (d, *J* = 8.1 Hz, 1 H), 8.17 (d, *J* = 8.2 Hz, 1 H),

8.64 (bs, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = -4.8, -4.7, -4.6, -4.4, 17.9, 18.1, 25.7, 25.8, 28.2, 47.2, 52.9, 56.8, 72.9, 74.0, 84.1, 90.8, 102.8, 117.4, 124.7, 127.7, 131.0, 141.0, 142.3, 150.0, 162.7, 163.8; FAB HRMS (NBA): *m/e* 630.3025, $M+H^+$ calcd for $C_{31}H_{47}N_3O_7Si_2$ 630.3031.

Epoxy Amide 18'. Synthesis of epoxy amide **18'** (44 mg, 76% yield over two steps) was achieved from epoxy alcohol **23** (48 mg, 0.092 mmol) in exactly same manner as described above for epoxy amide **18'** through epoxy acid **25**. Physical and spectroscopic properties of **18'** were exactly the same as epoxy amide obtained via sulphur ylides as reported by us elsewhere.[20]

Epoxy acid 25. To a solution of epoxy amide **26** (300 mg, 0.48 mmol, 1.0 equiv) in THF (10 mL) was added a 0.1 M aqueous LiOH solution (11.9 mL, 1.19 mmol, 2.5 equiv) dropwise during 15 min at 0 ºC. After 5 min, the reaction mixture was diluted with EtOAc (15 mL) and both phases were separated. The aqueous layer was washed with EtOAc and acidified with Amberlyst-15 until pH 5. Then, the solution was extracted with EtOAc and the combined organic extracts were concentrated *in vacuo* to obtain crude epoxy acid **25** (225 mg, 89%) which did not require further purification and was used in the next step: R_f = 0.10 (silica gel, 50% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.03 (s, 3 H), 0.04 (s, 3 H), 0.10 (s, 3 H), 0.11 (s, 3 H), 0.86 (s, 9 H), 0.91 (s, 9 H), 3.46 (bs, 1 H), 3.64 (d, *J* = 1.6 Hz, 1 H), 4.05 (dd, *J* = 4.3, 4.3 Hz, 1 H), 4.09-4.13 (m, 1 H), 4.33 (d, *J* = 4.3 Hz, 1 H), 5.78 (d, *J* = 8.1 Hz, 1 H), 5.88 (d, *J* = 4.8 Hz, 1 H), 7.68 (d, *J* = 8.1 Hz, 1 H), 9.33 (bs, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = -4.9, -4.7, -4.4, 17.9, 18.1, 25.7, 25.8, 50.0, 57.2, 73.3, 75.0, 78.8, 88.3, 102.7, 139.8, 163.7, 172.0, 176.4; FAB HRMS (NBA): *m/e* 551.2225, $M+Na^+$ calcd for $C_{23}H_{40}N_2O_8Si_2$ 551.2221.

Epoxyamide 29 from Epoxy Acid 25. Epoxy acid **25** (194 mg, 0.37 mmol, 1.0 equiv) was dissolved in dry CH_2Cl_2 (10 mL) and treated with HOBt (61 mg, 0.44 mmol, 1.2 equiv) at room temperature. After stirring for 5 min, EDCI (87 mg, 0.44 mmol, 1.2 equiv) was added to the reaction mixture, which was stirred for 45 min, prior to the addition to a solution of **27** (103 mg, 0.48 mmol, 1.3 equiv) in CH_2Cl_2 (5 mL). The mixed system was stirred for 12 h, after which, aqueous 15% NH_3 solution (0.3 mL) was added and the resulting mixture was diluted with Et_2O and washed with a saturated aqueous NH_4Cl solution. The layers were separated and the aqueous phase was extracted with Et_2O. The combined organic solution was dried ($MgSO_4$), filtered and concentrated. Purification by flash column chromatography (silica gel, 20% EtOAc, 10% MeOH in hexanes) afforded epoxyamide **29** (138 mg, 52%) as a colorless oil: R_f = 0.39 (silica gel, 20% EtOAc, 10% MeOH in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) (mixture of rotamers in a 1:1 ratio) δ = -0.01 (s, 1.5 H), 0.01 (s, 1.5 H), 0.02 (s, 3 H), 0.03 (s, 3 H), 0.04 (s, 3 H), 0.09 (s, 3 H), 0.10 (s, 3 H), 0.82 (s, 4.5 H), 0.83 (s, 4.5 H), 0.84 (s, 4.5 H), 0.85 (s, 4.5 H), 0.89 (s, 4.5 H), 0.90 (s, 4.5 H), 2.84 (s, 1.5 H), 3.0 (s, 1.5 H), 3.32 (s, 0.5 H), 3.34 (s, 0.5 H), 3.69-3.78 (m, 2 H), 3.79 (d, J = 2.1 Hz, 0.5 H), 3.93 (d, J = 2.1 Hz, 0.5 H), 4.05-4.30 (m, 3 H), 4.48-4.53 (m, 1 H), 5.14-5.32 (m, 2 H), 5.70-5.80 (m, 1 H), 5.97 (d, J = 5.9 Hz, 0.5 H), 6.02 (d, J = 5.9 Hz, 0.5 H), 7.73 (d, J = 8.1 Hz, 1 H), 8.42 (bs, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) (mixture of rotamers in a 1:1 ratio) δ = -5.6, -5.55, -5.5, -5.4, -4.8, -4.7, -4.6, -4.4, -4.3, 14.0, 18.0, 18.1, 18.2, 23.0, 23.8, 25.7, 25.8, 25.9, 28.5, 28.9, 30.4, 31.4, 32.0, 36.5, 38.8, 51.3, 51.9, 58.3, 60.3, 61.8, 62.6, 68.2, 71.0, 71.1, 71.9, 72.5, 75.1, 75.9, 81.2, 82.8, 89.2, 89.6, 101.8, 102.3, 118.5, 119.3, 128.8, 130.9, 131.7, 132.4, 140.8, 141.0, 150.0, 150.2, 162.6, 162.8, 168.8, 170.0; FAB HRMS (NBA): *m/e* 726.3996, $M+H^+$ calcd for $C_{34}H_{63}N_3O_8Si_3$ 726.4001.

Epoxyamide 30 from Epoxy Amide 26. A solution of epoxyamide **26** (66 mg, 0.106 mmol, 1.0 equiv) in acetonitrile (3 mL) was treated with allylamine **28** (16.1 mg, 0.159 mmol,

1.5 equiv) at 25ºC. Then, the reaction mixture was heated at 80ºC for 36 h. After this time, the crude mixture was concentrated under reduced pressure and purified by flash column chromatography (silica gel, 40% EtOAc, 5% MeOH in hexanes) to obtain epoxyamide **30** (40 mg, 62%) as a white foam: R_f = 0.21 (silica gel, 40% EtOAc, 5% MeOH in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) (mixture of rotamers in a 1:1 ratio) δ = -0.08 (s, 1.5 H), -0.04 (s, 1.5 H), -0.02 (s, 3 H), 0.04 (s, 3 H), 0.05 (s, 1.5 H), 0.06 (s, 1.5 H), 0.78 (s, 4.5 H), 0.79 (s, 4.5 H), 0.84 (s, 4.5 H), 0.85 (s, 4.5 H), 2.82 (s, 1.5 H), 2.97 (s, 1.5 H), 3.28 (s, 0.5 H), 3.36 (s, 0.5 H), 3.63-3.79 (m, 3 H), 3.99-4.27 (m, 3 H), 4.72 (bs, 0.5 H), 5.07 (bs, 0.5 H), 5.11-5.26 (m, 2 H), 5.61-5.73 (m, 1 H), 5.87 (d, J = 4.8 Hz, 0.5 H), 5.90 (d, J = 4.8 Hz, 0.5 H), 7.61 (d, J = 8.1 Hz, 0.5 H), 7.66 (d, J = 8.1 Hz, 0.5 H), 9.08 (bs, 1 H); ^{13}C NMR (100 MHz, DMSO-d_6) (mixture of rotamers in a 1:1 ratio) δ = -4.8, -4.7, -4.3, -4.2, -4.1, 18.1, 18.2, 18.3, 26.0, 26.2, 29.0, 31.0, 51.4, 52.0, 55.4, 58.0, 60.9, 61.1, 70.8, 71.3, 73.7, 74.1, 74.9, 75.2, 85.0, 85.2, 86.4, 86.6, 103.3, 117.7, 118.9, 134.0, 134.1, 140.2, 140.4, 151.3, 151.4, 163.3, 163.4, 167.9, 168.2; FAB HRMS (NBA): *m/e* 612.3138, $M+H^+$ calcd for $C_{28}H_{49}N_3O_8Si_2$ 612.3136.

Epoxyamide 30 from Epoxy Acid 25. Epoxy acid **25** (142 mg, 0.268 mmol, 1.0 equiv) and amine **28** (41 mg, 0.403 mmol, 1.5 equiv) were subjected to the action of HOBt (44 mg, 0.322 mmol, 1.2 equiv) and EDCI (63 mg, 0.322 mmol, 1.2 equiv) under the same conditions as described above for **29** to obtain epoxyamide **30** (57 mg, 35%) which showed identical physical and spectroscopic properties as described above for this compound.

Epoxyamide 31. A solution of epoxyamide **26** (150 mg, 0.239 mmol, 1.0 equiv) in acetonitrile (5 mL) was treated with allylamine (59 µL, 0.764 mmol, 3.2 equiv) at 25ºC for 7 h. After this time, the reaction mixture was diluted with toluene and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 45% EtOAc, 5% MeOH in hexanes) furnished epoxyamide **31** (118 mg, 87%) as a colorless oil: R_f = 0.50

(silica gel, 50% EtOAc, 5% MeOH in hexanes); $[\alpha]_D^{22}$ +11.3 (*c* 0.4, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.05 (s, 3 H), 0.09 (s, 3 H), 0.10 (s, 6 H), 0.86 (s, 9 H), 0.90 (s, 9 H), 3.26 (d, *J* = 2.1 Hz, 1H), 3.63 (d, *J* = 2.1 Hz, 1H), 3.86-3.91 (m, 2 H), 4.05 (d, 2 H), 4.30 (d, *J* = 2.7 Hz, 1 H), 5.14-5.20 (m, 2 H), 5.71-5.85 (m, 3 H), 6.22 (d, *J* = 5.9 Hz, 1 H), 7.59 (d, *J* = 8.1 Hz, 1 H), 8.80 (bs, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = -4.9, -4.8, -4.7, -4.4, 17.9, 18.1, 25.6, 25.7, 41.3, 52.4, 58.0, 73.2, 75.0, 78.8, 88.8, 102.6, 117.1, 133.2, 139.4, 150.1, 162.9, 166.8; FAB HRMS (NBA): *m/e* 590.2690, $M+Na^+$ calcd for $C_{26}H_{45}N_3O_7Si_2$ 590.2694.

Amino Alcohol 32. To a solution of epoxyamide **31** (61 mg, 0.107 mmol, 1.0 equiv) in MeOH (3 mL) was added an aqueous $MeNH_2$ solution (40% w/v solution, 0.17 mL, 2.15 mmol, 20.0 equiv). Then, the reaction mixture was heated at 60ºC for 36 h. After this time, the crude mixture was allowed to reach room temperature and concentrated under reduced pressure. The resulting crude product was subjected to purification by flash column chromatography (silica gel, 45% EtOAc, 5% MeOH in hexanes) to obtain amino alcohol **32** (58 mg, 90%) as a colorless oil: R_f = 0.31 (silica gel, 60% EtOAc, 5% MeOH in hexanes); $[\alpha]_D^{22}$ +3.3 (*c* 0.12, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.02 (s, 3 H), 0.03 (s, 3 H), 0.05 (s, 3 H), 0.06 (s, 3 H), 0.85 (s, 9 H), 0.87 (s, 9 H), 2.43 (s, 3 H), 3.25 (bs, 1 H), 3.88-3.93 (m, 3 H), 4.12 (d, *J* = 3.8 Hz, 1H), 4.17 (dd, *J* = 4.3, 3.8 Hz, 1H), 4.29 (d, *J* = 4.8, 4.3 Hz, 1 H), 5.12-5.21 (m, 2 H), 5.72 (d, *J* = 8.1 Hz, 1 H), 5.76 (d, *J* = 4.8 Hz, 1 H), 5.77-5.87 (m, 1 H), 7.69 (bs, 1 H), 8.03 (d, *J* = 8.1 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = -4.8, -4.7, -4.6, -4.5, 17.9, 18.0, 25.8, 34.5, 41.5, 63.1, 70.5, 72.2, 74.7, 84.1, 90.2, 102.3, 116.6, 133.6, 141.6, 150.5, 163.3, 174.0; FAB HRMS (NBA): *m/e* 599.3293, $M+H^+$ calcd for $C_{27}H_{50}N_4O_7Si_2$ 599.3296.

Amide 34. To a solution of epoxyamide **18'** (160 mg, 0.253 mmol, 1.0 equiv) in DMF (5 mL) was added a solution of amino alcohol **33** (73 mg, 0.265 mmol, 1.05 equiv) in DMF (2

mL) at 25ºC. Then, the reaction mixture was heated at 110ºC for 48 h. After this time, the crude mixture was concentrated under reduced pressure and purified by flash column chromatography (silica gel, 40% EtOAc in hexanes) to obtain amide **34** (100 mg, 44%) as a colorless oil: R_f = 0.25 (silica gel, 40% EtOAc, 5% MeOH in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ = -0.03 (s, 3 H), 0.02 (s, 3 H), 0.08 (s, 3 H), 0.10 (s, 3 H), 0.82 (s, 9 H), 0.89 (s, 9 H), 1.43 (s, 15 H), 2.46-2.72 (m, 4 H), 3.15-3.24 (m, 3 H), 3.61-4.54 (m, 11 H), 5.66 (d, J = 6.5 Hz, 1 H), 5.75 (dd, J = 8.1, 1.6 Hz, 1 H), 7.01-7.22 (m, 3 H), 7.77 (d, J = 8.1 Hz, 1 H), 8.17-8.21 (m, 1 H), 8.84 (bs, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = -4.9, -4.8, -4.6, -4.5, -4.4 17.9, 18.1, 25.7, 25.8, 25.9, 28.1, 28.3, 29.7, 47.9, 58.5, 71.8, 73.3, 85.2, 91.2, 102.7, 117.6, 124.5, 124.6, 124.7, 124.8, 127.4, 127.7, 131.7, 141.9, 142.2, 150.5, 163.1, 164.8; FAB HRMS (NBA): *m/e* 904.4918, $M+H^+$ calcd for $C_{44}H_{73}N_5O_{11}Si_2$ 904.4923.

Epoxyamide 36 from Epoxy Acid 25. Epoxy acid **25** (453 mg, 0.856 mmol, 1.0 equiv) was dissolved in dry DMF (10 mL) and treated with DIPEA (0.29 mL, 1.71 mmol, 2.0 equiv) at room temperature. After stirring for 5 min, a solution of amine **35** (458 mg, 1.03 mmol, 1.2 equiv) in DMF (4 mL) was added. After additional stirring for 5 min, the mixed system was treated with BOP (464 mg, 1.03 mmol, 1.2 equiv) and stirred for 12 h. After this time, a saturated aqueous NH_4Cl solution was added followed by dilution with EtOAc. The layers were separated and the aqueous phase was extracted with EtOAc. The combined organic solution was dried ($MgSO_4$), filtered and concentrated. Purification by flash column chromatography (silica gel, 35% EtOAc in hexanes) afforded epoxyamide **36** (529 mg, 65%) as a colorless oil: R_f = 0.70 (silica gel, 50% EtOAc in hexanes); $[\alpha]_D^{22}$ +27.8 (c 0.2, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) (mixture of rotamers in a 1:1 ratio) δ = 0.02 (s, 3 H), 0.03 (s, 3 H), 0.04 (s, 3 H), 0.09 (s, 3 H), 0.10 (s, 3 H), 0.11 (s, 3 H), 0.85 (s, 4.5 H), 0.86 (s, 4.5 H), 0.88 (s, 9 H), 0.89 (s, 4.5 H), 0.90 (s, 4.5 H), 2.93 (s, 1.5 H), 3.14 (s, 1.5 H), 3.32 (d, J = 2.1 Hz, 1 H), 3.41 (d, J = 2.1 Hz, 1 H), 3.65-3.80 (m, 3 H), 3.72 (s, 1.5 H), 3.74 (s, 1.5 H), 3.96

(d, *J* = 2.1 Hz, 1 H), 4.01-4.15 (m, 3 H), 4.19-4.44 (m, 2 H), 4.49 (d, *J* = 11.3 Hz, 1 H), 4.73 (d, *J* = 11.3 Hz, 1 H), 5.59 (dd, *J* = 8.1, 1.6 Hz, 0.5 H), 5.76 (dd, *J* = 8.1, 1.6 Hz, 0.5 H), 5.88 (d, *J* = 4.8 Hz, 0.5 H), 5.95 (d, *J* = 4.8 Hz, 0.5 H), 6.74-6.80 (m, 4 H), 7.27-7.34 (m, 5 H), 7.68 (d, *J* = 8.1 Hz, 0.5 H), 7.73 (d, *J* = 8.1 Hz, 0.5 H), 9.14 (bs, 0.5 H), 9.25 (bs, 0.5 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = -5.5, -5.4, 4.9, -4.8, -4.7, -4.5, 17.8, 18.0, 18.2, 18.3, 25.6, 25.7, 25.8, 29.6, 50.0, 50.4, 55.6, 56.8, 56.9, 63.2, 65.5, 65.9, 72.9, 73.5, 74.7, 75.0, 78.2, 78.4, 78.8, 79.1, 87.7, 87.9, 102.7, 102.9, 114.6, 114.7, 115.3, 115.4, 127.7, 127.9, 128.0, 128.1, 128.3, 128.6, 137.1, 137.9, 139.4, 139.5, 150.3, 150.4, 152.1, 152.4, 153.9, 154.2, 163.1, 166.7, 167.5; FAB HRMS (NBA): *m/e* 956.4951, $M+H^+$ calcd for $C_{48}H_{77}N_3O_{11}Si_3$ 956.4944.

Hydroxy Epoxyamide 37. Epoxyamide **36** (355 mg, 0.371 mmol, 1.0 equiv) was dissolved in CH_2Cl_2:MeOH (1:1, 10 mL), the solution was cooled to 0ºC, and CSA (0.15 mg, 0.63 mmol, 1.7 equiv) was added. The mixture was stirred for 4 h, allowing to reach room temperature. Then, TEA (87 μL, 0.63 mmol, 1.7 equiv) was added and, after 5 min, the solvents were removed under reduced pressure. Flash column chromatography (silica gel, 60% EtOAc in hexanes) furnished alcohol **37** (275 mg, 88%) as a colorless oil: R_f = 0.51 (silica gel, 80% EtOAc in hexanes); $[\alpha]_D^{22}$ +9.2 (*c* 0.2, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) (mixture of rotamers in a 1:1 ratio) δ = 0.02 (s, 3 H), 0.07 (s, 3 H), 0.09 (s, 3 H), 0.10 (s, 3 H), 0.81 (s, 4.5 H), 0.83 (s, 4.5 H), 0.88 (s, 4.5 H), 0.89 (s, 4.5 H), 2.86 (s, 1.5 H), 3.15 (s, 1.5 H), 3.28 (d, *J* = 2.1 Hz, 1 H), 3.36 (d, *J* = 2.1 Hz, 1 H), 3.32-3.38 (m, 1 H), 3.86-3.89 (m, 1 H), 3.71-3.73 (m, 1 H), 3.71 (s, 1.5 H), 3.74 (s, 1.5 H), 3.84 (d, *J* = 2.1 Hz, 1 H), 4.03-4.25 (m, 5 H), 4.29 (s, 1 H), 4.47-4.70 (m, 2 H), 5.68-5.73 (m, 1 H), 5.94-5.96 (m, 1 H), 6.70-6.81 (m, 4 H), 7.27-7.33 (m, 5 H), 7.60 (d, *J* = 8.6 Hz, 0.5 H), 7.67 (d, *J* = 8.6 Hz, 0.5 H), 9.10 (bs, 0.5 H), 9.33 (bs, 0.5 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = -5.0, -4.8, -4.6, -4.5, 17.8, 18.0, 25.6, 25.7, 28.7, 29.6, 50.3, 50.7, 54.4, 55.6, 56.9, 57.7, 58.4, 59.9, 65.9, 66.3, 72.2, 73.5, 73.9, 74.4, 74.7, 76.2, 79.1, 79.8, 86.9, 87.6, 102.9, 103.0, 114.6, 114.7, 115.2, 115.4, 128.0, 128.1,

128.5, 128.7, 136.7, 137.4, 139.4, 139.6, 150.5, 152.0, 152.2, 153.9, 154.1, 163.0, 168.0; FAB HRMS (NBA): *m/e* 865.4045, $M+Na^+$ calcd for $C_{42}H_{63}N_3O_{11}Si_2$ 865.4052.

Amino diol 38. To a solution of epoxide **37** (153 mg, 0.182 mmol, 1.0 equiv) in MeOH (3 mL) was added a 40% aqueous $MeNH_2$ solution (0.21 mL, 2.73 mmol, 15.0 equiv) and the resulting reaction mixture was heated at 60ºC for 7 h. After this time, the solvents were removed under reduced pressure and the crude product was purified by flash column chromatography (silica gel, 80% EtOAc, 5% MeOH in hexanes) to obtain amino diol **38** (131 mg, 83%) as a colorless oil: R_f = 0.58 (silica gel, 80% EtOAc, 5% MeOH in hexanes); $[\alpha]_D^{22}$ +4.3 (*c* 0.1, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) (mixture of rotamers in a 1:1 ratio) δ = -0.01 (s, 1.5 H), 0.01 (s, 1.5 H), 0.02 (s, 3 H), 0.05 (s, 3 H), 0.07 (s, 3 H), 0.82 (s, 4.5 H), 0.84 (s, 4.5 H), 0.88 (s, 9 H), 2.28 (s, 1.5 H), 2.39 (s, 1.5 H), 2.77 (s, 1.5 H), 2.99 (s, 1.5 H), 3.49-3.62 (m, 2 H), 3.66 (s, 1.5 H), 3.64-3.71 (m, 1 H), 3.73 (s, 1.5 H), 3.84-3.90 (m, 2 H), 4.05-4.25 (m, 5 H), 4.41 (s, 1 H), 4.42-4.76 (m, 2 H), 5.26 (d, *J* = 8.1 Hz, 0.5 H), 5.48 (d, *J* = 4.3 Hz, 0.5 H), 5.68 (d, *J* = 8.1 Hz, 0.5 H), 5.84 (d, *J* = 4.3 Hz, 0.5 H), 6.70-6.79 (m, 4 H), 7.26-7.33 (m, 5 H), 7.54 (d, *J* = 8.1 Hz, 0.5 H), 7.75 (d, *J* = 8.1 Hz, 0.5 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = -5.1, -4.8, -4.7, -4.6, -4.5, 17.8, 17.9, 18.0, 25.7, 25.8, 28.8, 29.6, 34.4, 55.6, 55.7, 57.7, 59.8, 61.0, 66.0, 67.5, 71.4, 71.7, 72.1, 72.9, 73.2, 75.0, 76.4, 83.9, 88.4, 102.1, 102.3, 114.6, 114.7, 115.1, 115.2, 127.9, 128.1, 128.2, 128.4, 128.6, 137.2, 137.6, 140.4, 150.3, 150.5, 152.3, 154.0, 154.2, 163.1, 163.2; FAB HRMS (NBA): *m/e* 896.4427, $M+Na^+$ calcd for $C_{43}H_{68}N_4O_{11}Si_2$ 896.4422.

Epoxy diol 39. To a solution of epoxy alcohol **37** (103 mg, 0.122 mmol, 1.0 equiv) in MeOH (5 mL) was added 10%Pd/C (103 mg). The reaction was allowed to proceed under an atmosphere of H_2 at 25ºC for 30 min, after which no starting benzyl ether was detected by TLC. The mixture was filtered through Celite and the clear solution was concentrated under

reduced pressure. The resulting crude product was purified by flash column chromatography (silica gel, 80% EtOAc in hexanes) to give epoxy diol **39** (74 mg, 81%) as a colorless oil: R_f = 0.24 (silica gel, 80% EtOAc in hexanes); $[\alpha]_D^{22}$ +23.3 (*c* 0.3, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) (mixture of rotamers in a 1:1 ratio) δ = -0.08 (s, 1.5 H), -0.01 (s, 1.5 H), 0.02 (s, 1.5 H), 0.04 (s, 1.5 H), 0.07 (s, 3 H), 0.09 (s, 1.5 H), 0.11 (s, 1.5 H), 0.80 (s, 4.5 H), 0.84 (s, 4.5 H), 0.87 (s, 4.5 H), 0.89 (s, 4.5 H), 2.98 (s, 1.5 H), 3.16 (s, 1.5 H), 3.35 (d, *J* = 1.6 Hz, 0.5 H), 3.42 (d, *J* = 1.6 Hz, 0.5 H), 3.54-3.66 (m, 2 H), 3.69 (s, 1.5 H), 3.72 (s, 1.5 H), 3.85-3.92 (m, 2 H), 4.06-4.57 (m, 6 H), 4.41 (s, 1 H), 5.66-5.75 (m, 1 H), 5.91 (d, *J* = 4.8 Hz, 0.5 H), 5.95 (d, *J* = 4.8 Hz, 0.5 H), 6.74-6.79 (m, 4 H), 7.62 (d, *J* = 8.1 Hz, 0.5 H), 7.68 (d, *J* = 8.1 Hz, 0.5 H), 9.49 (bs, 0.5 H), 9.52 (bs, 0.5 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = -4.7, -4.5, -4.4, 17.8, 17.9, 18.0, 25.6, 25.8, 29.6, 50.3, 50.7, 55.6, 57.0, 63.2, 66.0, 66.4, 69.5, 70.0, 71.4, 73.4, 74.0, 74.3, 74.8, 75.3, 79.0, 79.9, 86.2, 86.9, 88.0, 89.8, 101.9, 102.8, 103.1, 114.6, 115.3, 115.5, 139.5, 139.8, 150.4, 150.7, 152.1, 152.2, 154.2, 163.3, 163.9, 168.0; FAB HRMS (NBA): *m/e* 775.3530, $M+Na^+$ calcd for $C_{35}H_{57}N_3O_{11}Si_2$ 775.3533.

Diazepanone 40. To a solution of alcohol **37** (104 mg, 0.123 mmol, 1.0 equiv) in CH_2Cl_2 (5 mL) was added solid $NaHCO_3$ (83 mg, 0.988 mmol, 8.0 equiv). The mixture was cooled to 0ºC and then Dess-Martin periodinane (DMP) (122 mg, 0.28 mmol, 2.25 equiv) was added in one portion. After stirring for 1 h at 0ºC, TLC revealed depletion of starting material and formation of aldehyde **42**. The reaction mixture was then diluted with EtOAc and treated with a saturated aqueous $NaHCO_3$. After stirring for additional 20 min, both phases were separated and the organic layer was washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The resulting crude aldehyde was then used for the next step without further purification. A solution of crude aldehyde **42** in EtOAc (9 mL) in the presence of 4Å MS was treated with a solution of methylamine (2.0 M in THF, 93 μL, 0.185 mmol, 1.5 equiv), glacial AcOH (92 μL) and $NaBH(OAc)_3$ (110 mg, 0.494 mmol, 4.0 equiv)

at 25ºC. After stirring for 48 h at this temperature, the crude mixture was filtered through a celite pad, diluted with EtOAc and washed with a saturated aqueous $NaHCO_3$. The organic solution was then washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 40% EtOAc in hexanes) to obtain diazepanone **40** (42 mg, 40% over two steps from **37**) as a white foam: R_f = 0.56 (silica gel, 60% EtOAc in hexanes); $[\alpha]_D^{22}$ +66.7 (*c* 0.6, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ = -0.02 (s, 3 H), 0.01 (s, 3 H), 0.06 (s, 3 H), 0.07 (s, 3 H), 0.83 (s, 9 H), 0.88 (s, 9 H), 2.54 (s, 3 H), 3.14 (s, 3 H), 3.41-3.46 (m, 1 H), 3.73 (s, 3 H), 3.67-3.81 (m, 4 H), 4.03-4.23 (m, 5 H), 4.42 (bs, 1 H), 4.57 (d, *J* = 11.3 Hz, 1 H), 4.60 (d, *J* = 11.3 Hz, 1 H), 5.61 (d, *J* = 8.1 Hz, 1 H), 5.73 (d, *J* = 2.7 Hz, 1 H), 6.64-6.75 (m, 4 H), 7.23-7.35 (m, 5 H), 8.00 (d, *J* = 8.1 Hz, 1 H), 8.35 (bs, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = -4.9, -4.7, -4.4, 17.9, 18.0, 25.7, 25.8, 29.6, 37.0, 38.9, 50.3, 55.6, 63.7, 69.9, 71.0, 72.1, 74.5, 75.7, 82.9, 88.3, 102.0, 114.5, 114.8, 127.2, 127.8, 128.5, 140.9, 150.2, 152.1, 153.9, 163.4; FAB HRMS (NBA): *m/e* 877.4222, $M+Na^+$ calcd for $C_{43}H_{66}N_4O_{10}Si_2$ 877.4215.

Acetyl Diazepanone 43. A solution of diazepanone **40** (20 mg, 0.023 mmol, 1.0 equiv) in pyridine (3 mL) was treated with Ac_2O (44 μL, 0.47 mmol, 20.0 equiv) and 4-DMAP (2.9 mg) at 25ºC. After stirring for 24 h, the crude mixture was concentrated under reduced pressure and the crude product purified by flash column chromatography (silica gel, 50% EtOAc in hexanes) to obtain acetyl diazepanone **40** (18 mg, 86%) as a colorless oil: R_f = 0.22 (silica gel, 60% EtOAc in hexanes); $[\alpha]_D^{22}$ +25.8 (*c* 0.2, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ = -0.16 (s, 3 H), -0.08 (s, 3 H), 0.06 (s, 3 H), 0.08 (s, 3 H), 0.78 (s, 9 H), 0.90 (s, 9 H), 2.04 (s, 3 H), 2.52 (s, 3 H), 3.10 (s, 3 H), 3.42-3.48 (m, 1 H), 3.61-3.64 (m, 2 H), 3.73 (s, 3 H), 3.72-3.76 (m, 1 H), 3.97-4.01 (m, 1 H), 4.09-4.15 (m, 2 H), 4.25-4.33 (m, 2 H), 4.54-4.63 (m, 3 H), 5.60 (d, *J* = 8.1 Hz, 1 H), 5.62 (d, *J* = 2.1 Hz, 1 H), 5.89 (d, *J* = 7.5 Hz, 1 H), 6.63 (d, *J* = 9.1 Hz, 1 H), 6.72 (d, *J* = 9.1 Hz, 1 H), 7.27-7.34 (m, 5 H), 7.40 (d, *J* = 8.1 Hz, 1

H), 8.07 (bs, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = -5.3, -4.9, -4.7, -4.5, 17.9, 18.0, 20.9, 23.6, 25.5, 25.6, 28.8, 29.6, 38.6, 54.0, 60.7, 65.7, 68.2, 71.3, 102.2, 128.7, 130.7, 147.2, 148.0, 162.4, 167.5, 169.4; FAB HRMS (NBA): *m/e* 919.4325, $M+Na^+$ calcd for $C_{45}H_{68}N_4O_{11}Si_2$ 919.4321.

Epoxyamide 45 from Epoxy Acid 25. Epoxy acid **25** (336 mg, 0.635 mmol, 1.0 equiv) was dissolved in dry CH_2Cl_2 (12 mL) and treated with HOBt (105 mg, 0.76 mmol, 1.2 equiv) at room temperature. After stirring for 5 min, EDCI (149 mg, 0.76 mmol, 1.2 equiv) was added to the reaction mixture, which was stirred for 45 min, prior to the addition of a solution of **46** (224 mg, 0.953 mmol, 1.5 equiv) in CH_2Cl_2 (5 mL). The mixed system was stirred for 2 h, after which, aqueous 15% NH_3 solution (0.2 mL) was added and the resulting mixture was diluted with Et_2O and washed with a saturated aqueous NH_4Cl solution. The layers were separated and the aqueous phase was extracted with Et_2O. The combined organic solution was dried ($MgSO_4$), filtered and concentrated. Purification by flash column chromatography (silica gel, 20% EtOAc, 10% MeOH in hexanes) afforded epoxyamide **45** (340 mg, 72%) as a yellow oil: R_f = 0.50 (silica gel, 30% EtOAc, 10% MeOH in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.04 (s, 3 H), 0.05 (s, 3 H), 0.10 (s, 6 H), 0.86 (s, 9 H), 0.99 (s, 9 H), 3.35 (s, 1 H), 3.63 (d, *J* = 2.1 Hz, 1 H), 3.69 (dd, *J* = 9.7, 2.7 Hz, 1 H), 3.95 (dd, *J* = 9.7, 2.7 Hz, 1 H), 4.03 (dd, *J* = 4.8, 4.3 Hz, 1 H), 4.10 (dd, *J* = 4.3 Hz, 1 H), 4.31 (d, *J* = 4.3 Hz, 1 H), 4.47 (d, *J* = 11.8 Hz, 1 H), 4.55 (d, *J* = 11.8 Hz, 1 H), 4.61 (d, *J* = 5.4 Hz, 2 H), 4.73-4.76 (m, 1 H), 5.21-5.31 (m, 2 H), 5.75 (dd, *J* = 8.1, 2.1 Hz, 1 H), 5.79-5.87 (m, 1 H), 5.89 (d, *J* = 4.8 Hz, 1 H), 6.98 (d, *J* = 8.6 Hz, 1 H), 7.26-7.34 (m, 5 H), 7.61 (d, *J* = 8.1 Hz, 1 H), 8.74 (bs, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = -4.9, -4.7, -4.5, 17.9, 18.1, 25.6, 25.7, 52.0, 57.8, 66.3, 69.2, 73.3, 75.0, 78.8, 88.1, 102.8, 119.0, 127.7, 128.0, 128.5, 131.3, 137.2, 139.3, 150.2, 162.8, 163.3, 167.1; FAB HRMS (NBA): *m/e* 768.3319, $M+Na^+$ calcd for $C_{36}H_{55}N_3O_{10}Si_2$ 768.3324.

Epoxy Acid 47. A solution of epoxy amide **45** (337 mg, 0.45 mmol, 1.0 equiv) in THF (15 mL) was treated with morpholine (0.39 mL, 4.51 mmol, 10.0 equiv) and $Pd[PPh_3]_4$ (78 mg, 0.067 mmol, 0.15 equiv) at 25ºC. After stirring for 1 h, the reaction mixture was diluted Et_2O and the resulting solution washed with a 0.5 M aqueous citric acid solution twice and brine. The layers were separated and the organic solution was dried ($MgSO_4$), filtered and concentrated. Purification by flash column chromatography (silica gel, 10% MeOH in CH_2Cl_2) afforded epoxy acid **47** (277 mg, 87%) as a yellow oil: R_f = 0.25 (silica gel, 10% MeOH in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.05 (s, 6 H), 0.10 (s, 6 H), 0.86 (s, 9 H), 0.89 (s, 9 H), 3.36 (s, 1 H), 3.61 (d, *J* = 2.1 Hz, 1 H), 3.73 (dd, *J* = 9.7, 3.2 Hz, 1 H), 3.97 (dd, *J* = 9.7, 3.2 Hz, 1 H), 4.04 (dd, *J* = 4.8, 4.3 Hz, 1 H), 4.12 (dd, *J* = 4.3, 3.8 Hz, 1 H), 4.30 (d, *J* = 3.8 Hz, 1 H), 4.53 (s, 2 H), 4.73-4.75 (m, 1 H), 5.78 (d, *J* = 8.1 Hz, 1 H), 5.90 (d, *J* = 4.8 Hz, 1 H), 7.27-7.71 (m, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = -4.8, -4.6, -4.4, 19.2, 26.0, 30.1, 52.9, 58.3, 71.3, 74.0, 75.1, 79.8, 88.2, 103.9, 128.5, 128.6, 129.6, 129.7, 134.1, 139.8, 151.1, 163.9, 167.4, 172.3; FAB HRMS (NBA): *m/e* 728.3015, $M+Na^+$ calcd for $C_{33}H_{51}N_3O_{10}Si_2$ 728.3011.

Diazo Ketone 50. A solution of Fmoc-D-Ser(*t*Bu)-OH (**49**) (1.2 g, 3.13 mmol, 1.0 equiv) in CH_2Cl_2 (60 mL) was treated with 2,6-lutidine (0.44 mL, 3.76 mmol, 1.2 equiv) and $(COCl)_2$ (0.29 mL, 3.44 mmol, 1.1 equiv) at -15ºC. After stirring for 4 h at this temperature, the solvent was removed under reduced pressure and the crude mixture was dissolved in THF (40 mL) and cooled at -20ºC. Then, an ethereal solution of freshly prepared CH_2N_2 (31.3 mmol, 10.0 equiv) was dropwise added at -20ºC and the reaction mixture was stirred for 45 min. After this time, it was checked depletion of starting amino acid derivative by TLC and the reaction was quenched by addition of several drops of acetic acid. The resulting organic solution was washed twice with a saturated aqueous $NaHCO_3$ solution and brine, the layers

were separated and the organic solution was dried ($MgSO_4$), filtered and concentrated. Purification by flash column chromatography (silica gel, 50% EtOAc in hexanes) afforded diazo ketone **50** (820 mg, 64%) as a white solid, together with the methyl ester (Fmoc-D-Ser(*t*Bu)-OMe) (359 mg, 29%). [**50**]: R_f = 0.65 (silica gel, 50% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.14 (s, 9 H), 3.42-3.45 (m, 1 H), 3.72-3.76 (m, 1 H), 4.19-4.26 (m, 2 H), 4.39-4.43 (m, 1 H), 4.51-4.55 (m, 1 H), 5.37 (bs, 1 H), 5.60 (d, J = 7.5 Hz, 1 H), 7.29-7.33 (m, 2 H), 7.36-7.41 (m, 2 H), 7.55-7.61 (m, 2 H), 7.74-7.76 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 27.3, 47.3, 54.1, 58.4, 61.6, 66.7, 73.7, 120.0, 124.9, 125.1, 127.0, 127.1, 127.7, 141.3, 143.6, 155.9, 192.8.

Amino Diazo Ketone 51. Diazo Ketone **50** (373 mg, 0.915 mmol, 1.0 equiv) was dissolved in pyridine (9 mL) and treated with TEA (3.2 mL, 22.9 mmol, 25.0 equiv) at 25ºC. The reaction mixture was stirred for 12 h, after which the solvents were removed under reduced pressure. The crude product was then subjected to purification by flash column chromatography (silica gel, 10% MeOH in CH_2Cl_2) to obtain amino diazo ketone **51** (101.5 mg, 60%) as a yellow oil: R_f = 0.39 (silica gel, 10% MeOH in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.13 (s, 9 H), 2.12 (bs, 2 H), 3.39-3.41 (m, 1 H), 3.47-3.51 (m, 2 H), 5.76 (bs, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 27.1, 54.0, 56.1, 58.9, 63.8, 73.4, 196.1.

Diazo Epoxy Amide 52. Epoxy acid **25** (178 mg, 0.34 mmol, 1.0 equiv) was dissolved in dry CH_2Cl_2 (6 mL) and treated with HOBt (56 mg, 0.404 mmol, 1.2 equiv) at room temperature. After stirring for 5 min, EDCI (79 mg, 0.404 mmol, 1.2 equiv) was added to the reaction mixture, which was stirred for 45 min, prior to the addition of a solution of **51** (72 mg, 0.39 mmol, 1.15 equiv) in CH_2Cl_2 (3 mL). The mixed system was stirred for 1 h, after which, aqueous 15% NH_3 solution (0.2 mL) was added and the resulting mixture was diluted with Et_2O and washed with a saturated aqueous NH_4Cl solution. The layers were separated

and the aqueous phase was extracted with Et_2O. The combined organic solution was dried ($MgSO_4$), filtered and concentrated. Purification by flash column chromatography (silica gel, 70% EtOAc in hexanes) afforded diazo epoxyamide **52** (114 mg, 49%) as a yellow oil: R_f = 0.39 (silica gel, 70% EtOAc in hexanes); $[\alpha]_D^{22}$ +11.1 (*c* 0.3, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) (mixture of rotamers in a 1:1 ratio) δ = 0.02 (s, 1.5 H), 0.04 (s, 1.5 H), 0.05 (s, 1.5 H), 0.09 (s, 1.5 H), 0.10 (s, 3 H), 0.11 (s, 3 H), 0.85 (s, 9 H), 0.89 (s, 9 H), 1.13 (s, 4.5 H), 1.15 (s, 4.5 H), 3.26 (s, 0.5 H), 3.33 (s, 0.5 H), 3.40-3.47 (m, 1 H), 3.66-3.71 (m, 1 H), 3.63 (d, *J* = 2.1 Hz, 0.5 H), 3.64 (d, *J* = 2.1 Hz, 0.5 H), 4.02-4.11 (m, 2 H), 4.30 (d, *J* = 4.8 Hz, 0.5 H), 4.32 (d, *J* = 4.8 Hz, 0.5 H), 4.53 (bs, 1 H), 5.47 (bs, 0.5 H), 5.54 (bs, 0.5 H), 5.73 (d, *J* = 8.1 Hz, 0.5 H), 5.74 (d, *J* = 8.1 Hz, 0.5 H), 5.83 (d, *J* = 4.8 Hz, 0.5 H), 5.87 (d, *J* = 4.8 Hz, 0.5 H), 7.11 (d, *J* = 7.0 Hz, 1 H), 7.60 (d, *J* = 8.1 Hz, 0.5 H), 7.62 (d, *J* = 8.1 Hz, 0.5 H), 8.93 (d, *J* = 4.8 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = -4.9, -4.8, -4.5, -4.4, 17.9, 18.0, 25.6, 25.7, 27.3, 51.9, 52.1, 54.8, 56.1, 57.8, 61.6, 73.1, 73.3, 73.8, 73.9, 74.9, 75.1, 78.4, 78.8, 88.1, 88.6, 102.7, 139.3, 150.2, 163.0, 167.0, 191.1; FAB HRMS (NBA): *m/e* 718.3272, $M+Na^+$ calcd for $C_{31}H_{53}N_5O_9Si_2$ 718.3280.

Diazo Amino Alcohol 53. To a solution of diazo epoxy amide **52** (72 mg, 0.103 mmol, 1.0 equiv) in MeOH (3 mL) was added a 40% aqueous $MeNH_2$ solution (80 μL, 1.03 mmol, 10.0 equiv) and the resulting reaction mixture was heated at 60ºC for 12 h. After this time, the solvents were removed under reduced pressure and the crude product was purified by flash column chromatography (silica gel, 10% MeOH in CH_2Cl_2) to obtain diazo amino alcohol **53** (57 mg, 76%) as a yellow oil: R_f = 0.44 (silica gel, 10% MeOH in CH_2Cl_2); $[\alpha]_D^{22}$ +4.9 (*c* 0.5, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) (mixture of rotamers in a 1:1 ratio) δ = -0.02 (s, 3 H), 0.00 (s, 3 H), 0.03 (s, 6 H), 0.82 (s, 9 H), 0.85 (s, 9 H), 1.13 (s, 9 H), 2.37 (s, 1.5 H), 2.42 (s, 1.5 H), 3.19 (d, *J* = 8.6 Hz, 0.5 H), 3.24 (d, *J* = 8.6 Hz, 0.5 H), 3.45-3.51 (m, 1 H), 3.66-3.73 (m, 1 H), 3.77 (d, *J* = 8.6 Hz, 0.5 H), 3.87 (d, *J* = 8.6 Hz, 0.5 H), 4.13 (s, 1 H), 4.24-

4.32 (m, 2 H), 4.54 (bs, 1 H), 5.67-5.75 (m, 3 H), 7.91 (d, J = 8.1 Hz, 0.5 H), 7.97 (d, J = 8.1 Hz, 0.5 H), 8.12 (d, J = 8.1 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = -4.9, -4.8, -4.7, -4.6, 17.9, 25.7, 25.8, 27.2, 34.4, 34.5, 54.5, 57.0, 61.3, 61.5, 63.7, 64.2, 70.5, 70.9, 72.2, 72.5, 73.8, 74.4, 74.6, 84.0, 84.3, 90.2, 90.4, 102.2, 141.6, 141.8, 150.6, 163.6, 174.1, 191.8, 192.3; FAB HRMS (NBA): *m/e* 727.3876, $M+H^+$ calcd for $C_{32}H_{58}N_6O_9Si_2$ 727.3882.

Diazepanodione 54. Amino Diazo Ketone **53** (42 mg, 0.058 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (5 mL) and treated with $Rh_2(OAc)_4$ (2.6 mg, 0.0058 mmol, 0.1 equiv) at 25ºC. After stirring for 2 h, TLC revealed depletion of starting diazo. Then, the solvent was removed under reduced pressure and the crude product was purified by flash column chromatography (silica gel, 70% EtOAc, 5% MeOH in hexanes) to obtain compound **54** (23 mg, 57%) as a colorless oil: R_f = 0.46 (silica gel, 70% EtOAc, 5% MeOH in hexanes); $[\alpha]_D^{22}$ +5.7 (*c* 0.5, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.07 (s, 3 H), 0.09 (s, 3 H), 0.14 (s, 6 H), 0.88 (s, 9 H), 0.89 (s, 9 H), 1.23 (s, 9 H), 2.51 (s, 3 H), 3.64 (s, 1 H), 3.78 (d, J = 5.4 Hz, 0.5 H), 4.04-4.24 (m, 7 H), 4.45 (d, J = 5.4 Hz, 1 H), 5.78 (s, 1 H), 5.94 (d, J = 8.1 Hz, 1 H), 6.12 (bs, 1 H), 7.98 (d, J = 8.1 Hz, 1 H), 9.63 (bs, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = -5.1, -4.9, -4.7, -4.4, -4.1, 18.0, 18.2, 25.8, 25.9, 35.3, 59.1, 59.9, 66.8, 69.0, 69.3, 71.6, 72.6, 73.9, 75.1, 75.7, 77.7, 102.2, 103.5, 140.8, 149.5, 168.0, 171.4, 173.9, 191.5; FAB HRMS (NBA): *m/e* 721.3636, $M+Na^+$ calcd for $C_{32}H_{58}N_4O_9Si_2$ 721.3640.

Triol 55. To a solution of diazepanodione **54** (21 mg, 0.033 mmol, 1.0 equiv) in MeOH (2 mL) was added 10%Pd/C (21 mg). The reaction was allowed to proceed under an atmosphere of H_2 at 25ºC for 12 h. After this time, the mixture was filtered through Celite, the solid washed with MeOH (3 x 3 mL) and the clear solution was concentrated under reduced pressure. The resulting crude product was purified by flash column chromatography (silica gel, 85% EtOAc, 5% MeOH in hexanes) to give triol **55** (14.5 mg, 75%) as a white foam: R_f =

0.47 (silica gel, 85% EtOAc, 5% MeOH in hexanes); $[\alpha]_D^{22}$ +8.6 (*c* 0.5, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ = -0.01 (s, 3 H), 0.02 (s, 3 H), 0.05 (s, 3 H), 0.06 (s, 3 H), 0.85 (s, 9 H), 0.88 (s, 9 H), 2.57 (s, 3 H), 3.16 (d, *J* = 10.2 Hz, 1 H), 3.62-3.65 (m, 2 H), 3.78-3.92 (m, 4 H), 4.10-4.13 (m, 3 H), 4.22 (dd, *J* = 5.9, 4.8 Hz, 1 H), 4.31 (s, 1 H), 5.56 (bs, 1 H), 5.75 (d, *J* = 8.1 Hz, 1 H), 6.00 (d, *J* = 5.9 Hz, 1 H), 7.00 (bs, 1 H), 8.23 (d, *J* = 8.1 Hz, 1 H), 8.95 (bs, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = -4.9, -4.8, -4.6, 17.8, 17.9, 18.0, 25.7, 25.8, 43.9, 51.4, 60.8, 61.5, 68.5, 71.9, 72.7, 74.2, 75.5, 83.3, 88.0, 102.4, 141.1, 150.5, 163.5, 174.5; FAB HRMS (NBA): *m/e* 667.3185, $M+Na^+$ calcd for $C_{28}H_{52}N_4O_9Si_2$ 667.3171.

Triacetyl Diazepanone 56. A solution of diazepanone **55** (12.5 mg, 0.019 mmol, 1.0 equiv) in pyridine (1.5 mL) was treated with Ac_2O (73 μL, 0.775 mmol, 40.0 equiv) at 25ºC. After stirring for 48 h, the crude mixture was concentrated under reduced pressure and the crude product purified by flash column chromatography (silica gel, 65% EtOAc, 5% MeOH in hexanes) to obtain tri-O-acetyl diazepanone **56** (6.5 mg, 44%) as a colorless oil: R_f = 0.47 (silica gel, 30% EtOAc, 5% MeOH in hexanes); $[\alpha]_D^{22}$ +12.5 (*c* 0.1, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.00 (s, 3 H), 0.05 (s, 3 H), 0.08 (s, 6 H), 0.87 (s, 9 H), 0.88 (s, 9 H), 2.08 (s, 3 H), 2.48 (s, 3 H), 2.53 (s, 3 H), 2.58 (s, 3 H), 3.50 (d, *J* = 9.7 Hz, 1 H), 3.65-4.32 (m, 7 H), 4.60 (bs, 1 H), 4.91-4.96 (m, 1 H), 5.40 (d, *J* = 9.7 Hz, 1 H), 5.77 (d, *J* = 8.1 Hz, 1 H), 5.89 (d, *J* = 3.8 Hz, 1 H), 7.87 (d, *J* = 8.1 Hz, 1 H), 8.34 (bs, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = -4.7, -4.6, -4.3, 14.9, 18.4, 22.8, 26.7, 26.8, 29.8, 30.1, 39.3, 55.8, 62.3, 66.1, 68.5, 68.8, 72.1, 72.9, 82.5, 98.5, 103.2, 128.7, 131.7, 150.5, 164.1, 168.3, 171.2, 173.5; FAB HRMS (NBA): *m/e* 793.3492, $M+Na^+$ calcd for $C_{34}H_{58}N_4O_{12}Si_2$ 793.3487.

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Supporting Information Available: Theoretical calculations data and ^{1}H- and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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