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Studies Towards the Synthesis of Esperamicinone

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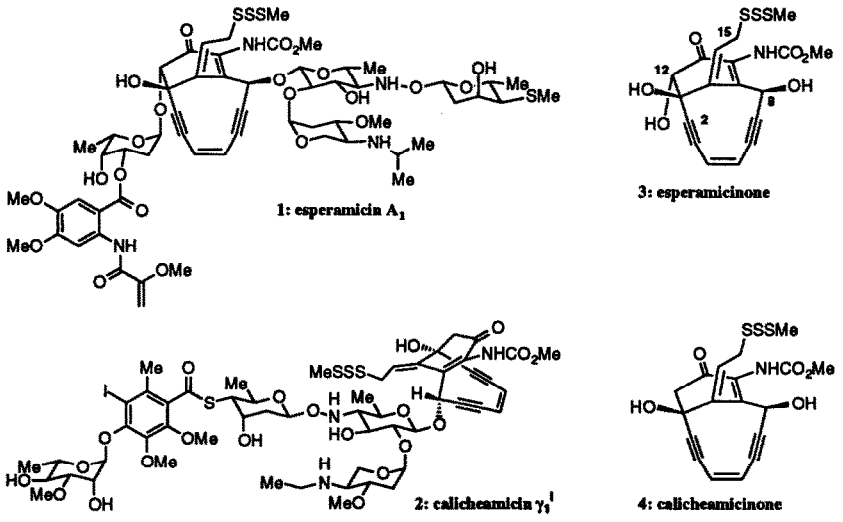
Abstract: A strategy is presented for the synthesis of esperamicinone (3), the aglycone of esperamicin A_1. The route is based on an asymmetric epoxidation of a quinone monoketal. Two approaches for the installation of the vinylogous urethane are described.

INTRODUCTION

Esperamicin A_1 (1, Scheme 1) is a member of the enediyne family of antitumor antibiotics[1] exhibiting activity against murine tumor models in the 100 ng / kg range.[2] The family of esperamicins were isolated from the bacteria *Actinomadura verrucosospora* and their structure elucidation was reported in 1987 by a Bristol Myers group.[3] Due to their extreme toxicity and highly unusual structure, these compounds represent challenging targets for total synthesis in which the usefulness of modern synthetic methods may be tested and perhaps expanded.

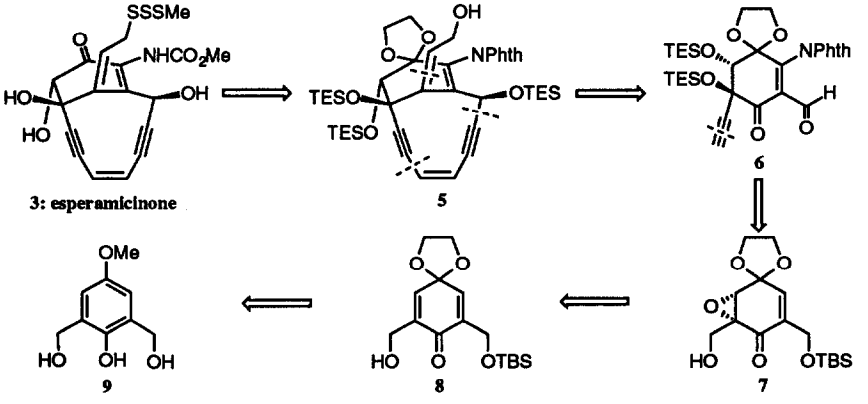


Scheme 1: Structures of esperamicin A_1 (1), calicheamicin γ_1^I (2) and their aglycones (3 and 4).

The closely related calicheamicin γ_1^I (**2**) has been the focus of much synthetic work which has culminated in syntheses of its aglycone,[4] its aryl tetrasaccharide[5] and recently of the entire natural product.[6] Synthetic efforts towards esperamicin A_1 (**1**) have mainly been concerned with the saccharide fragments,[7] with one report of an attempt at the synthesis of esperamicinone that delivered the wrong stereochemistry for the C-12 hydroxyl.[8] Danishefsky's approach[4a,b] to racemic calicheamicinone (**4**) involved elaboration of a protected *ortho*-quinone, while that of this group[4c,d] utilized an intramolecular nitrile oxide cycloaddition to construct the optically active functionalized core. While these strategies could be adapted to the synthesis of esperamicinone (**3**), a new approach to this molecule was sought, the essence of which is described below.

RETROSYNTHETIC ANALYSIS

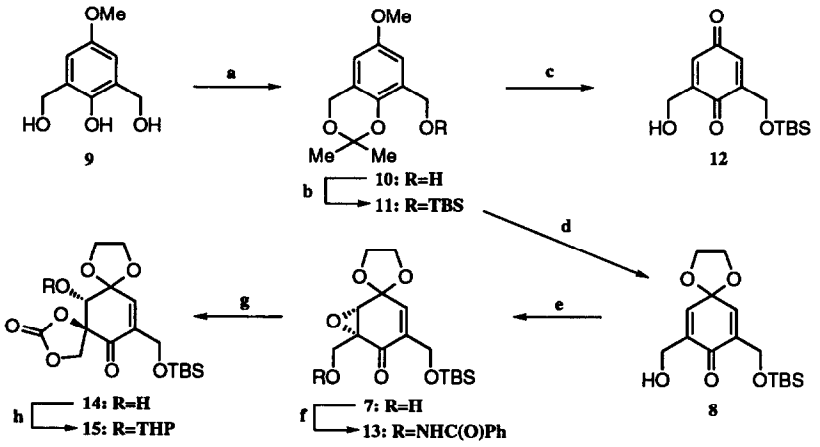
The newly conceived approach to esperamicinone is retrosynthetically depicted in Scheme 2. The similarity of esperamicinone (**3**) to calicheamicinone (**4**) allows advantage to be taken of previous synthetic work in the final stages. Thus, removal of the trisulfide unit and appropriate functional group protections lead from the targeted esperamicinone (**3**) to intermediate **5**. Disconnection of the enediyne ring and of the allylic alcohol as indicated in **5** leads to cyclohexenone **6** in which only two stereogenic centers remain. The *trans* diol system in **6** contains the extra hydroxyl group as compared to calicheamicinone (**4**) and could arise from a regioselective opening of an epoxide moiety. If the terminal alkyne could be generated from a primary hydroxyl group (and an appropriate one carbon fragment), then there exists an allylic alcohol as a template for Sharpless epoxidation[9] and, therefore, the possibility to introduce the required asymmetry. Thus **6** can be sequentially traced back to **7** and **8**. The conjugated enamine was anticipated to arise through a Michael addition of a nitrogen nucleophile to the enone **7** with appropriate trapping and reoxidation. The monoprotected quinone **8** was then traced back to the trihydroxy aromatic compound **9**, whose symmetry and accessibility endowed it with special attraction as a starting material.



Scheme 2: Retrosynthetic analysis of esperamicinone (3).

FIRST APPROACH. INTRODUCTION OF THE NITROGEN BY A 1,4-ADDITION TO AN ENONE

Beginning with the known triol **9**[10] (Scheme 3), the primary hydroxyl groups were first differentiated by ketalization (77 %) followed by silylation (100 %) under standard conditions to afford **11** *via* **10**. Expecting that selective protection of the less hindered carbonyl in **12** could be achieved, the latter compound was synthesized by oxidation (ammonium cerium(IV) nitrate) of **11** in aqueous acetonitrile (90 % yield). Although subsequent ketalization failed to provide useful amounts of the desired product (**8**), it was found that by conducting the oxidation with ethylene glycol as a co-solvent (ammonium cerium(IV) nitrate, 1,4-dioxane / ethylene glycol (1:1)), the desired monoprotected quinone (**8**) was obtained directly from **11** in high yield (82 %). Quinone monoketals are generally prepared by oxidation of phenols or by partial hydrolysis of *bis* ketals.[11] Formation of the ketone in this case is a result of acetonide collapse induced by oxidation of the aromatic ring. Simple addition and transketalization of ethylene glycol occurs to form the dioxolane, facilitated by acid catalysis under the reaction conditions.



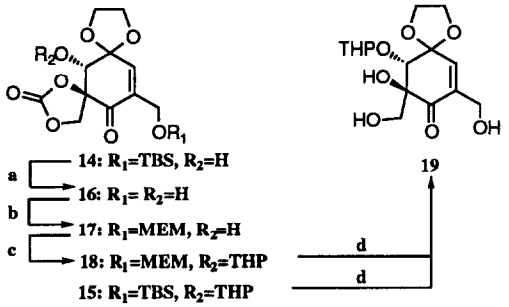
Scheme 3. Synthesis of key intermediate 15. Reagents and conditions: (a) 0.05 equiv of TsOH, $Me_2C(OMe)_2$ / acetone (2:1), 25 °C, 1.5 h then AcOH / H_2O (1:1), 16 h, 77 %; (b) 1.1 equiv of TBSCl, 1.5 equiv of imidazole, 0.05 equiv of DMAP, DMF, 25 °C, 1 h, 100 %; (c) 2.1 equiv of $Ce(NH_4)_2(NO_3)_6$, CH_3CN, 25 °C, 0.2 h, 90 %; (d) 2.05 equiv of $Ce(NH_4)_2(NO_3)_6$, ethylene glycol / 1,4-dioxane (1:1), 25 °C, 0.2 h, 82 %; (e) 0.1 equiv of $Ti(O^iPr)_4$, 0.125 equiv of DIPT, 2.0 equiv of ^{t}BuOOH, 4 Å M.S., CH_2Cl_2, 0 °C, 16 h, 87 %; (f) 1.1 equiv of PhNCO, 1.2 equiv of Et_3N, CH_2Cl_2, 25 °C, 1 h, 99 %; (g) 1.1 equiv of BF_3•OEt_2, CH_2Cl_2, 0 °C, 0.4 h then AcOH / H_2O (8:2), 25 °C, 0.3 h, 80 %; (h) 3.0 equiv of dihydropyran, 0.2 equiv of TsOH.pyr, CH_2Cl_2, 25 °C, 6 h, 81 %.

Sharpless epoxidation[9] of the resultant electron deficient alkene in **8** (Scheme 3) occurred without incident to afford epoxide **7** in 87 % yield and with acceptable levels of enantioselectivity (80 % *ee*).[12] To the best of

our knowledge, only one example of titanium catalyzed epoxidation of electron deficient alkenes had been reported prior to this work.[13] Two recrystallizations of the epoxide from heptane were sufficient to enhance the *ee* to greater than 95 %.[12]

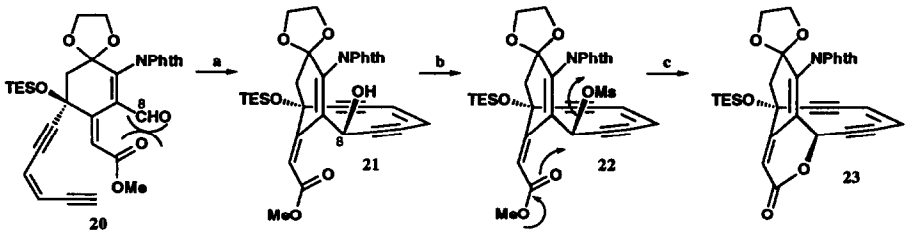
Epoxide opening was best effected using the procedure of Roush[14] (Scheme 3; 1. PhNCO, Et_3N, CH_2Cl_2, 99 %; 2. BF_3•OEt_2, CH_2Cl_2, then HOAc, H_2O, 80 % yield) which generated the hydroxy carbonate **14**. The resulting hindered secondary alcohol could be protected as an acetate (*vide infra*), or as a triethylsilyl (TES) or a tetrahydropyranyl (THP) ether (**15**), the latter being most useful despite the formation of a mixture of separable diastereomers (3:1 ratio, 81 % yield) due to its stability under the basic conditions used to remove the carbonate group. All subsequent studies described in this section were carried out with the major THP isomer.

The allylic ether present in **15** proved to be particularly labile as the chemistry presented in Scheme 4 demonstrates.



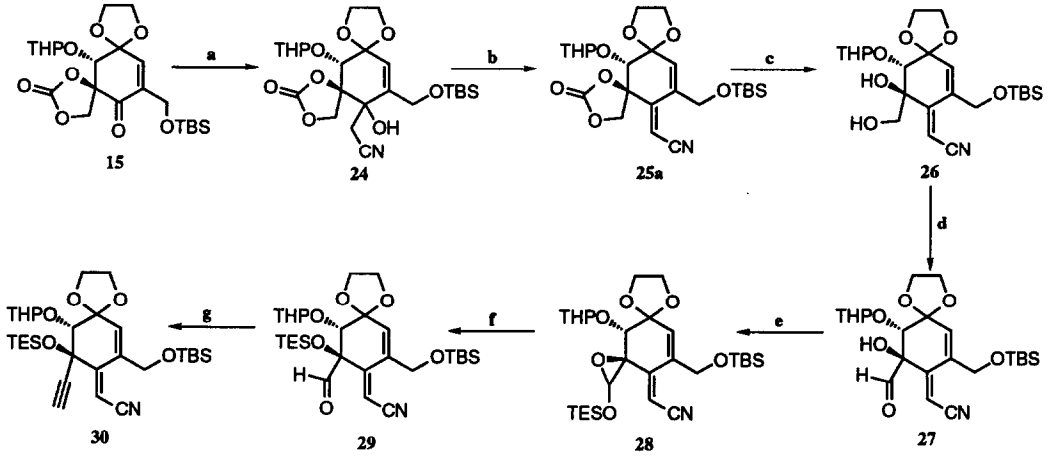
Scheme 4. Hydrolysis of carbonates 15 and 18. Reagents and conditions: (a) excess HF•pyr, THF, 0 °C, 0.3 h, 78 %; (b) 1.3 equiv of MEMCl, 1.8 equiv of $^{i}Pr_2EtN$, $ClCH_2CH_2Cl$, 80 °C, 1 h, 77 %; (c) 3.0 equiv of dihydropyran, 0.2 equiv of TsOH.pyr, $ClCH_2CH_2Cl$, 70 °C, 1.5 h, 86 %; (d) 4.0 equiv of NaOH, 1,4-dioxane / H_2O (3:2), 25 °C, 0.2 h, 73 %.

With ^{t}butyldimethylsilyl (TBS) or methoxyethoxymethyl (MEM) protection, hydrolysis through allylic displacement readily occurred with aqueous NaOH (**15** or **18** → **19**, 73 %). This prevented clean removal of the carbonate which was necessary for the generation of the alkyne. However, elaboration of the ketone by the requisite two carbon fragment led to the complete suppresion of this allylic lability. In extending the ketone, note was taken of problems that were encountered in our synthesis of calicheamicinone.[4c,d] Large steric interactions were encountered between an exocyclic acrylate unit and the C-8 center (Scheme 5, structure **20**). On closing the enediyne ring (**20** → **21**), the newly generated secondary hydroxyl at C-8 was thus obtained with the incorrect stereochemistry and inversion at this center required two additional steps (**21** → **23**). Consequently, a small replacement for the ester group was desired. The nitrile function (which is linear and possesses minimal steric bulk) was, therefore, selected as an ester surrogate.[15]



Scheme 5. Steric interactions in the synthesis of calicheamicinone.[4c,d] Reagents and conditions: (a) KHMDS, toluene, -90 °C, 50 % (b) MsCl, Et_3N, CH_2Cl_2, 0 °C (c) silica gel, pyr, CH_2Cl_2, 25 °C, 14 h, 85 % for two steps.

Extension was carried out in two steps (alkylation and dehydration) because Wittig, Peterson and Horner - Emmons reactions were ineffective and because a greater degree of control was expected during a separate dehydration step to influence the ratio of alkene isomers formed. The lithium anion of acetonitrile was generated with ^tBuLi[16] and condensed with ketone **15** to provide the adduct **24** (Scheme 6) as a single isomer (83 %). The facial selectivity of addition was not determined, but is presumed to be that derived from axial attack of the nucleophile to the ring conformation in which the secondary tetrahydropyranyl ether occupies an equatorial position.[17]



Scheme 6. Synthesis of model alkyne 30. Reagents and conditions: (a) 1.15 equiv of ^tBuLi, 1.25 equiv of CH_3CN, THF then **15**, -78 °C, 0.2 h, 83 %; (b) 1.3 equiv of $(CF_3CO)_2O$, 2.5 equiv of Et_3N, 0.1 equiv of DMAP, CH_2Cl_2, 25 °C, 0.5 h, 83 %; (c) 2.2 equiv of NaOH, 1,4-dioxane / H_2O (7:4), 25 °C, 5 h, 100 %; (d) 1.5 equiv of Dess-Martin periodinane, CH_2Cl_2, 25 °C, 4 h, 85 %; (e) 1.2 equiv of TESOTf, 1.5 equiv of 2,6-lutidine, CH_2Cl_2, 25 °C, 0.5 h, 74 %; (f) 10 equiv of TESOTf, 15 equiv of 2,6-lutidine, $ClCH_2CH_2Cl$, 70 °C, 1 h, 77 %; (g) 2.5 equiv of $(MeO)_2P(O)CHN_2$, 1.7 equiv of ^nBuLi, THF, -78 °C, 0.1 h then **29**, -78 → 0 °C, 40 %.

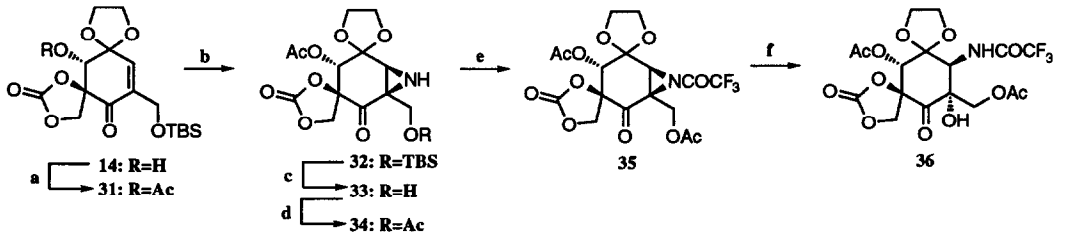
Dehydration of the tertiary allylic alcohol **24** with trifluoroacetic anhydride gave **25a,b** (Scheme 6; 83 %) as a 4:1 mixture of geometrical isomers with the desired isomer (**25a**) predominating. The geometry of the alkenes thus produced was deduced from the downfield shifts of the neighboring methylene proton signals

(^{1}H NMR) that are forced into close proximity with the nitrile group (mean values for the chemical shifts are: **25a**: 4.58 (carbonate CH_2), 4.71 (CH_2 OTBS) and **25b**: 4.74 (carbonate CH_2), 4.25 (CH_2 OTBS)).

The carbonate group could be cleanly removed from **25a** with aqueous NaOH to afford **26** in quantitative yield (Scheme 6). Dess-Martin oxidation[18] proved to be superior to other methods (e.g. SO_3-pyr[19], Swern[20]) for generation of the hydroxy aldehyde **27** from **26** (85 %). Attempted tertiary alcohol protection (TESOTf, 2,6-lutidine) gave the silyloxy epoxide **28** as the initial product (74 %), presumably due to the congested environment around the tertiary alcohol. Previous examples of isolable siloxy epoxides were prepared *via* the epoxidation of silyl enol ethers.[21] However, heating silyl lactol **28** with an excess of TESOTf caused collapse of the lactol, presumably through initial silylation of the epoxide, and produced the desired silyl ether **29** in good yield (77 %). Even though this protection could be carried out in a single step with excess reagents and prolonged reaction times, the two step process was more efficient.

Formation of the alkyne **30** from **29** (Scheme 6) was accomplished using the Seyferth reagent $(MeO)_2P(O)CHN_2$[22] and either ^{n}BuLi[23] or KO^{t}Bu[24] as base. The Corey-Fuchs method[25] was unsuccessful in this instance due to failure of aldehyde **29** to react with the ylid $Ph_3P{=}CBr_2$.

With the successful arrival at system **30**, focus was then shifted to methodology for the introduction of the enamine functionality which, as already mentioned, was intended to occur through a 1,4 addition of a nitrogen nucleophile (e. g. $TMSN_3$, PhthNSePh, or PhSeBr / CH_3CN) to the enone, followed by oxidation. Such reactions, however, with systems derived from **7** or **14** did not yield any of the desired products. Examination of the literature suggested that reaction of these enones with diphenylsulfilimine[26] (PhS=NH) could form the enamine directly.[27] However, this procedure, when applied to **31** gave, instead, the aziridine **32** (Scheme 7) in excellent yield (93 %) and as a single isomer. An X-ray crystallographic analysis of the crystalline diacetate **34** (ethyl acetate / petroleum ether, mp 154-156 °C) indicated that the aziridine was formed on the upper face of the enone (see ORTEP drawing, Figure 1). The formation of aziridines in the reactions of enones with sulfilimines has previously been noted[26b,27] but has received little synthetic attention.[28]



Scheme 7. Ring opening of aziridine 32. Reagents and conditions: (a) 1.2 equiv of AcCl, 1.3 equiv of DMAP, CH_2Cl_2, 25 °C, 0.5 h, 90 % (b) 2.0 equiv of $Ph_2S{=}NH$, C_6H_6, 55 °C, 1 h, 93 %; (c) excess HF•pyr, THF, 0 °C, 0.5 h; (d) 1.3 equiv of Ac_2O, 1.6 equiv of pyr, 0.1 equiv of DMAP, CH_2Cl_2, 25 °C, 0.5 h, 90 % for two steps; (e) 1.2 equiv of $(CF_3CO)_2O$, 1.5 equiv of Et_3N, 0.1 equiv of DMAP, CH_2Cl_2, 25 °C, 1 h; (f) 0.15 equiv of TsOH, THF / H_2O (10:1), 25 °C, 1 h, 80 % for two steps.

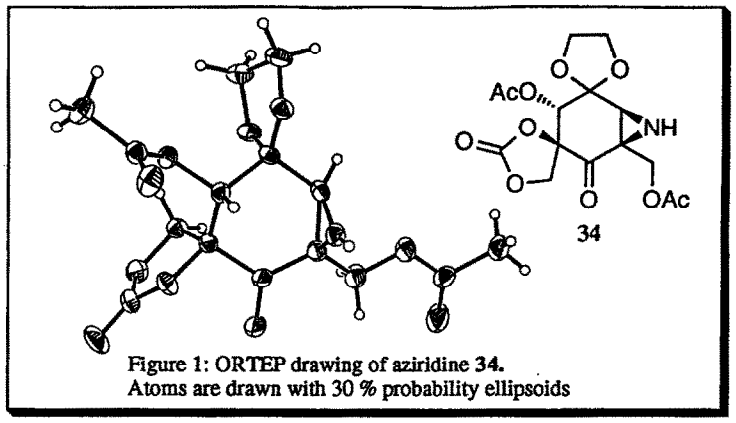
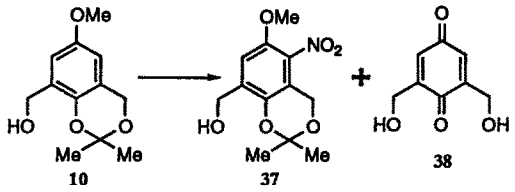


Figure 1: ORTEP drawing of aziridine **34**.
Atoms are drawn with 30 % probability ellipsoids

Treatment of this aziridine with electrophiles (e.g. phthaloyl dichloride) or protic or Lewis acids failed to cause rearrangement to the enamine. It was, however, possible to open the ring at the tertiary center with the assistance of a neighboring acetate group (Scheme 7, **34** → **35** → **36**; 80 % yield). Dehydration of **36** has, thus far, not been possible.

SECOND APPROACH. INSTALLMENT OF THE NITROGEN AT AN EARLY STAGE

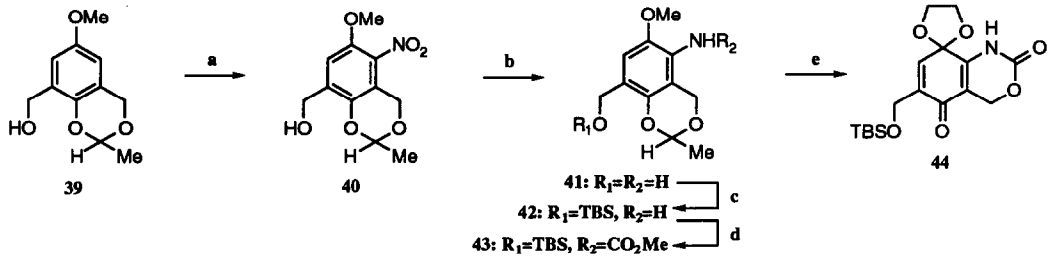
Pursuing a different strategy to the problem of enamine formation, consideration was given to introduction of the nitrogen at an early stage onto the aromatic ring. Thus, nitration of the hydroxy ketal **10** using nitric acid / acetic acid (Scheme 8) gave the nitro compound **37** but in only *ca* 25 % yield and with the major product being the quinone **38** (*ca* 60 %).[29]



Scheme 8. Attempted nitration of acetonide 10. Reagents and conditions: (a) 1.0 equiv of HNO_3, AcOH, 20 - 30 °C, 0.3 h, 37: 25 %, 38: 60 %.

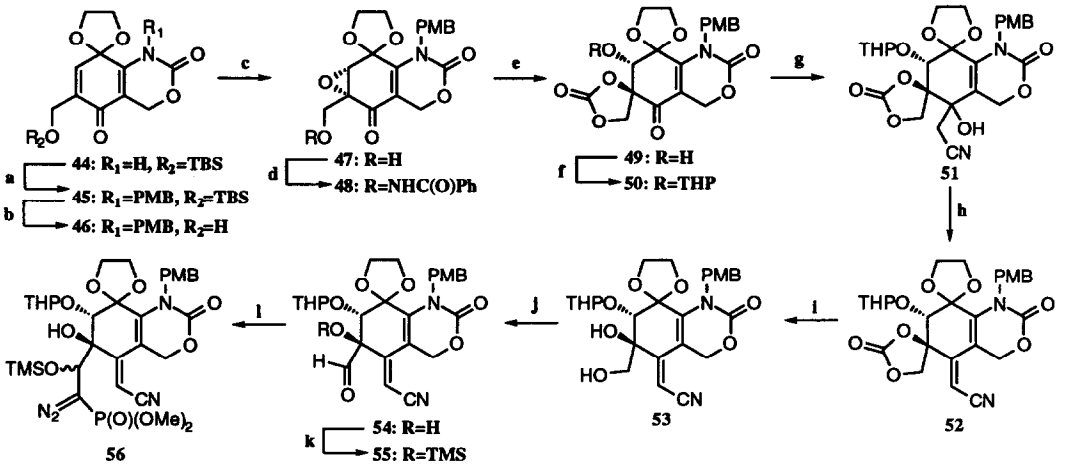
The oxidation process could be suppressed by employing a more stable ketal. With the cyclohexylidene ketal, the ratio of products was reversed and with the ethylidene ketal **39**, an excellent yield (91 %) of the nitro compound **40** was obtained as a single regioisomer (Scheme 9). Reduction of **40** to the aniline **41** was best effected with H_2 / PtO_2 (80 %) in the presence of a small amount of potassium carbonate to avoid benzylic hydrogenolysis, especially on a large scale. Silylation under standard conditions (**41** → **42**, 95 %) was followed by introduction of the urethane using phosgene and methanol (72 %) as methyl chloroformate proved to be too unreactive in this case. Oxidation (ammonium cerium(IV) nitrate, ethylene glycol / 1,4-dioxane (1:3))

of urethane **43** produced the desired monoprotected quinone **44** but only in 30 % yield. The primary hydroxyl group initially produced in this reaction, apparently cyclizes onto the urethane system during silica gel chromatography. This cyclization procedure is more convieniently realized prior to purification by stirring the material with silica gel in methylene chloride; most of the desired material may then be purified by crystallization. Although the yield of this process is rather modest, much functionality is being installed in this one step. Large amounts of urethane **43** can readily be prepared as chromatography may be avoided up to this stage.



Scheme 9. Synthesis of key intermediate 44. Reagents and conditions: (a) 1.0 equiv of HNO_3, AcOH, 20 - 30 °C, 0.3 h, 91 %; (b) H_2, 0.09 equiv of PtO_2, 0.08 equiv of K_2CO_3, MeOH, 25 °C, 6 h, 80 %; (c) 1.1 equiv of TBSCl, 1.4 equiv of imidazole, 0.05 equiv of DMAP, DMF, 25 °C, 3 h, 95 %; (d) 1.2 equiv of $COCl_2$, 4.0 equiv of Et_3N, 0.05 equiv of DMAP, CH_2Cl_2, 0 °C, 0.5 h then excess MeOH, 25 °C, 1 h, 72 % for two steps; (e) 2.0 equiv of $Ce(NH_4)_2(NO_3)_6$, ethylene glycol / 1,4-dioxane (1:3), 25 °C, 1.5 h, then silica gel, CH_2Cl_2, 25 °C, 16 h, 30 %.

Application of the chemistry developed for the introduction of the 1,2-diol and alkyne systems was next attempted (Scheme 10). Protection of the cyclic urethane **44** with a *p*-methoxybenzyl (PMB) group (90 %) followed by desilylation with HF•pyridine led to alcohol **46** (81 % overall yield) *via* intermediate **45**. Epoxidation of the allylic alcohol system in **46** using the Sharpless conditions furnished epoxide **47** (90 % yield, 80 % *ee*[12]). A single recrystallization from methanol (20 mL/g) gave optically pure material (60 % yield after crystallization, the optical purity was confirmed by ^1H NMR analysis of the *R*- Mosher ester derivative). Boron trifluoride induced epoxide opening *via* phenylurethane **48** proceeded smoothly to produce carbonate **49** in 81 % overall yield from **47**. Protection of the hydroxyl group in **49** as a tetrahydropyranyl ether under standard conditions (**49** → **50**; 90 % yield, 5:4 ratio of diastereomers) was followed by addition of the lithium anion of acetonitrile to afford hydroxynitrile **51** in 92 % yield as a single isomer of unassigned stereochemistry. Dehydration of **51** using acetic anhydride gave exclusively the desired geometrical isomer **52** after five days reaction time. Although aqueous NaOH attacked both the carbonate and the urethane functionalities in **52**, excellent selectivity for the carbonate group was observed with lithium hydride in ethylene glycol and THF[5b] (1:20) furnishing the 1,2-diol **53** in 90 % yield. Oxidation of the latter compound with the Dess-Martin reagent afforded the hydroxy aldehyde **54** in 90 % yield.

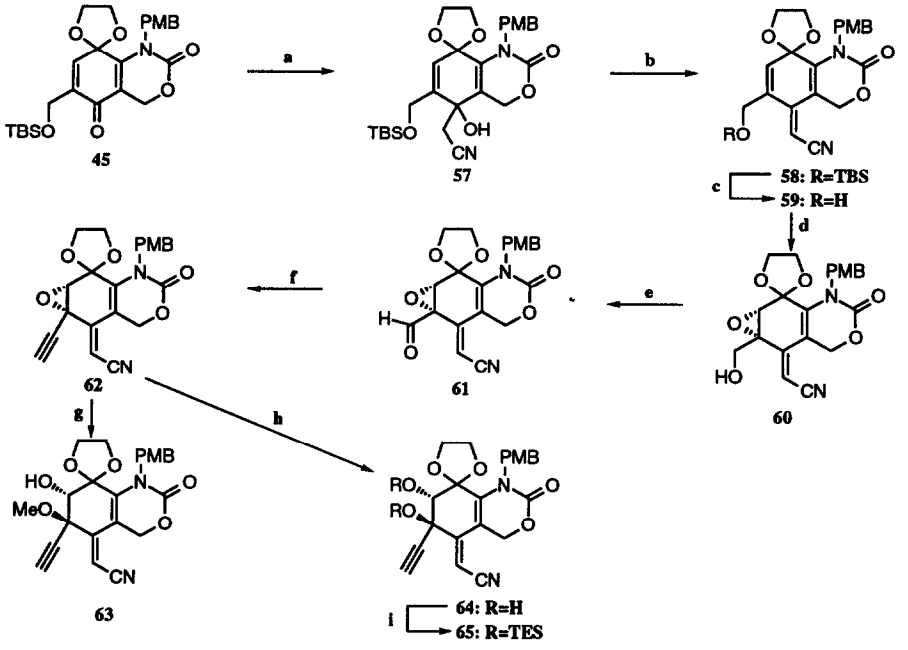


Scheme 10. Synthesis of adduct 56. Reagents and conditions: (a) 1.5 equiv of PMBBr, 2.0 equiv of K_2CO_3, DMF, 25 °C, 3.5 h, 90 %; (b) excess HF•pyr, THF, 0 °C, 0.4 h, 90 %; (c) 0.1 equiv of $Ti(O^iPr)_4$, 0.125 equiv of DIPT, 2.5 equiv of ^tBuOOH, 4 Å M.S., CH_2Cl_2, 0 °C, 16 h, 90 %; (d) 1.1 equiv of PhNCO, 1.3 equiv of Et_3N, CH_2Cl_2, 25 °C, 0.25 h, 94 %; (e) 1.1 equiv of BF_3•OEt_2, CH_2Cl_2, 0 °C, 0.3 h, then AcOH / H_2O (1:1), 25 °C, 0.6 h, 86 %; (f) 3.0 equiv of dihydropyran, 0.1 equiv of TsOH.pyr, $CHCl_3$, 60 °C, 16 h, 90 %; (g) 1.2 equiv of ^tBuLi, 1.3 equiv of CH_3CN, THF then **50**, -78 °C, 0.1 h, 92 %; (h) 1.3 equiv of Ac_2O, 1.6 equiv of Et_3N, 0.1 equiv of DMAP, CH_2Cl_2, 25 °C, 5 d, 82 %; (i) 1.0 equiv of LiH, ethylene glycol / THF (1:20), 25 °C, 1.5 h, 90 %; (j) 2.0 equiv of Dess-Martin periodinane, CH_3CN, 25 °C, 16 h, 90 %; (k) 10 equiv of TMSOTf, 15 equiv of 2,6-lutidine, $ClCH_2CH_2Cl$, 60 °C, 4.5 h, 60 %; (l) 1.4 equiv of $(MeO)_2P(O)CHN_2$, 1.3 equiv of ^nBuLi, THF, -78 °C, 0.1 h then **55**, -78 → 25 °C, 2 h.

Attempts to construct the acetylene unit onto **54** were unsuccessful (Scheme 10). Thus, even though the TES protected lactol analogous to **28** could be synthesized, albeit under more forcing conditions, its collapse to the protected tertiary alcohol was not possible without much decomposition. The TMS derivative **55** was, however, prepared (without observation of the protected lactol) in 60 % yield by exposure of **54** to TMSOTf under basic conditions. The subsequent reaction of **55** with dimethyl diazomethylphosphonate and ^nBuLi failed to produce the desired alkyne, leading instead to the diazo derivative **56**. Migration of the TMS group from the tertiary to the newly formed secondary hydroxy group is apparently preventing the Horner-Emmons pathway to the diazoalkene and hence to the targeted acetylene.

In order to circumvent the above complications, introduction of the acetylene prior to epoxide opening was examined (Scheme 11). Thus, the PMB protected urethane **45** was reacted with acetonitrile anion as described above to afford adduct **57** in 82 % yield. Exposure of **57** to trifluoroacetic anhydride in the presence of DMAP and Et_3N gave the unsaturated nitrile **58** as the major product (83 % yield, *ca* 10:1 ratio with its geometrical isomer). Desilylation of **58** with HF•pyridine under anhydrous conditions proceeded in excellent yield (96 %) to afford primary alcohol **59**. Asymmetric epoxidation of **59** under the Sharpless conditions proceeded rapidly and in good enantiomeric excess (86 % yield, 90 % *ee*[12]) furnishing epoxide **60**. Oxidation of **60** to aldehyde **61** was accomplished with the Dess-Martin reagent (99 % yield), and alkyne formation with $(MeO)_2P(O)CHN_2$ proceeded smoothly to afford compound **62** in 50 % yield. Solvolysis of alkynyl epoxides under acidic conditions has been reported to be both regio- and stereoselective.[30] In the event, treatment of epoxide **62** with sulfuric acid in methanol at 60 °C produced a single compound (**63**) and in 72 % yield. The regiochemistry of

63 was apparent from observation of two coupled doublets corresponding to the C*H* and O*H* of the secondary hydroxyl (^{1}H NMR). The stereochemical assignment was based on published precedent[30] and on the apparent absence of a second product. When the solvolysis was conducted in a mixture of 2 N aqueous sulfuric acid and ^{t}BuOH (1:1) at 90 °C, the corresponding diol (**64**) was formed in 60 % yield. The bis(TES) ether **65** was formed from **64** under standard conditions and in 95 % yield. It should be noted that in compounds **64** and **65** we now have all the necessary functionality in place for a final drive towards esperamicinone.



Scheme 11. Synthesis of diol 64. Reagents and conditions: (a) 1.15 equiv of ^{t}BuLi, 1.25 equiv of CH_3CN, THF, - 78 °C then **45**, 0.1 h, 82 %; (b) 1.2 equiv of $(CF_3CO)_2O$, 1.4 equiv of Et_3N, 0.1 equiv of DMAP, CH_2Cl_2, 25 °C, 0.25 h, 83 %; (c) excess HF•pyr, THF, 0 °C, 1 h, 96 %; (d) 0.1 equiv of $TiO(^iPr)_4$, 0.125 equiv of DIPT, 2.1 equiv of ^{t}BuOOH, 4 Å M.S., CH_2Cl_2, 0 °C, 16 h, 86 %; (e) 2.0 equiv of Dess-Martin periodinane, CH_2Cl_2, 25 °C, 36 h, 99 %; (f) 1.4 equiv of $(MeO)_2P(O)CHN_2$, 1.2 equiv of ^{n}BuLi, THF, 0.1 h, -78 °C, then **61**, 2.5 h, -78 → 0 °C, 50 %; (g) 13 equiv of H_2SO_4, MeOH, 65 °C, 1 h, 72 %; (h) 5 equiv of H_2SO_4, ^{t}BuOH / H_2O (1:1), 90 °C, 2.5 h, 60 %; (i) 3.1 equiv of TESOTf, 5.1 equiv of pyr, CH_2Cl_2, 25 °C, 1.5 h, 95 %.

CONCLUSION

Preliminary studies described in this article demonstrate the conversion of the readily available aromatic system **9** to a variety of highly functionalized intermediates suitable for potential elaboration to esperamicinone and related compounds. The most advanced intermediates are the aziridine **34**, urethane **36**, and acetylenes **64** and **65**. It is anticipated that after removal of the urethane from **65** and protecting group manipulation, completion of the synthesis could be accomplished in a similar manner to that described for calicheamicinone.

These and other related compounds may prove useful in the synthesis of enediyne systems and other compounds of medicinal interest.

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EXPERIMENTAL SECTION

General Techniques

All reactions were carried out under a dry argon atmosphere using freshly distilled solvents unless otherwise noted. Tetrahydrofuran and ethyl ether were distilled from sodium and benzophenone. Benzene, methylene chloride and toluene were distilled from calcium hydride. All other anhydrous solvents were purchased from Aldrich Chemical Company Inc. Amine bases were dried and stored over potassium hydroxide. Glassware was either oven dried (120 °C) or flame dried (0.05 torr) prior to use. Where necessary, compounds were dried by azeotropic removal of water with benzene or toluene under reduced pressure. Reactions were monitored by thin layer chromatography (TLC) on E. Merck silica gel plates (0.25 mm) and visualized using uv light (254 nm) and / or heating with *p*-anisaldehyde solution (340 mL ethanol, 9.2 mL *p*-anisaldehyde, 12.5 mL sulfuric acid and 3.75 mL acetic acid). Reaction temperatures were measured externally unless otherwise noted. Solvents used for work-up, chromatography, and recrystallizations were reagent grade from either Fisher Scientific or E. Merck. Reactions were worked-up by washing with saturated aqueous solutions of the salts indicated. Flash chromatography[31] was performed on E. Merck silica gel (60, particle size 0.040-0.063 mm). Yields refer to chromatographically and spectroscopically (^{1}H NMR) pure materials.

NMR spectra were recorded on a Bruker AMX-500 MHz spectrometer at ambient temperature. Chemical shifts are reported relative to the residual solvent peak. Multiplicities are designated as singlet (s), doublet (d), triplet (t), pseudo triplet (pt), quartet (q), multiplet (m), broad (b), apparent (app) or obstructed (obs). IR samples were prepared by evaporation of a solution of the compound in $CHCl_3$ or $CDCl_3$ onto a NaCl plate under a stream of argon. IR spectra were recorded on a Perkin Elmer 1600 series FT-IR spectrophotometer. Optical rotations were measured using a Perkin Elmer 241 polarimeter. High resolution mass spectra (HRMS) were recorded on a VG ZAB-ZSE mass spectrometer under Fast Atom Bombardment (FAB) conditions. Melting points were obtained with a Thomas Hoover Unimelt apparatus and are uncorrected. Microanalyses were performed at the Scripps Research Institute.

Abbreviations used in this paper are: TES = -$SiEt_3$, TBS = -Si^tBuMe_2, THP = tetrahydropyranyl-, Ts = *p*-$MePhSO_2$-, DMAP = *p*-(dimethylamino)pyridine, DIPT = di-isopropyl-D-tartrate, M.S. = molecular sieves, pyr = pyridine, MEM = methoxyethoxymethyl-, KHMDS = potassium bis(trimethylsilyl)amide, Ms = -SO_2Me, Tf = -SO_2CF_3, PMB = *p*-methoxybenzyl-, TMS = -$SiMe_3$.

Preparation and selected data of Compounds

Acetonide 10. To a solution of triol **9** (74 g, 400 mmol) in acetone (370 mL) and 2,2-dimethoxypropane (740 mL) was added TsOH (3.8 g, 20.0 mmol) and the reaction mixture was stirred at 20 °C for 0.5 h. Further addition of TsOH (3.8 g) brought the reaction to completion after 1 h at which time the solution was neutralized by the addition of excess solid sodium bicarbonate. The mixture was concentrated under reduced pressure, diluted with ethyl ether (1000 mL) and washed with H_2O (4 × 200 mL). The solution was again concentrated under reduced pressure and acetic acid (24 mL, 50 % v/v aqueous solution) was added. The mixture was allowed to stand for 0.5 h before being diluted with ethyl ether (1000 mL), washed with $NaHCO_3$ (5 × 200 mL), NaCl (200 mL), dried ($MgSO_4$) and concentrated under reduced pressure to yield acetonide **10** (69.6 g, 77 %) as a white solid: White crystals (benzene), mp 82.5 - 83.0 °C; R_f = 0.35 (silica gel, 50 % ethyl ether in petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.77 (d, J = 2.9 Hz, 1 H, Ar), 6.44 (d, J = 2.9 Hz, 1 H, Ar), 4.81 (s, 2 H, ring benzylic CH_2), 4.62 (s, 2 H, CH_2OH), 3.74 (s, 3 H, OCH_3), 3.3-2.9 (bs, 1 H, OH), 1.53 (s, 6 H, acetonide); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.2, 142.8, 129.8, 119.9, 113.1, 108.5, 99.6, 61.3, 61.0, 55.7, 24.8; IR (film) ν_{max} 3418, 2993, 2941, 2858, 1612, 1480, 1378, 1283, 1245, 1199, 1145, 1051, 873 cm^{-1}; HRMS Calcd. for $C_{12}H_{16}O_4$ (M+Cs$^+$): 357.0103. Found: 357.0103.

Silyl ether 11. To a solution of **10** (19.7 g, 93.8 mmol) in DMF (188 mL) was added imidazole (9.6 g, 140 mmol), DMAP (507 mg, 4.70 mmol) and TBSCl (15.6 g, 103 mmol). The mixture was stirred at ambient temperature for 1 h before being diluted with ethyl ether (1000 mL), washed with 1 N HCl (2 × 300 mL), $NaHCO_3$ (300 mL), NaCl (300 mL) and dried ($MgSO_4$). The solution was concentrated under reduced pressure and placed under high vacuum (.03 torr, 24 h) to yield silyl ether **11** (30.4 g, 100 %) as an off white solid. The material can be recrystallized by dissolving it in ethanol (2 mL / g) and cooling to -20 °C for 24 h: White crystals (ethanol), mp 49.0 - 50.0 °C; R_f = 0.62 (silica gel, 20 % ethyl ether in petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.97 (d, J = 3.0 Hz, 1 H, Ar), 6.39 (d, J = 3.0 Hz, 1 H, Ar), 4.81 (s, 2 H, ring benzylic CH_2), 4.69 (s, 2 H, CH_2OTBS), 3.76 (s, 3 H, OCH_3), 1.51 (s, 6 H, acetonide), 0.96 (s, 9 H, Si^t*Bu*Me$_2$), 0.12 (s, 6 H, Si^{t}Bu*Me*$_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.2, 141.5, 130.7, 119.1, 111.5, 107.3, 99.1, 61.0, 59.5, 55.5, 25.9, 24.7, 18.4, -5.3; IR (film) ν_{max} 2949, 2856, 1612, 1477, 1379, 1247, 1145, 1114, 1058, 841, 779 cm^{-1}; HRMS Calcd. for $C_{18}H_{30}O_4Si$ (M+Cs$^+$): 471.0968. Found: 471.0968.

Quinone 12. To a solution of **11** (1.76 g, 5.21 mmol) in acetonitrile (60 mL) and H_2O (25 mL) was added ammonium cerium(IV) nitrate (5.97 g, 10.9 mmol). After 0.1 h the solution was diluted with ethyl ether (350 mL), washed with H_2O (100 mL), $NaHCO_3$ (2 × 100 mL), NaCl (100 mL) and dried ($MgSO_4$). The solution was filtered through a pad of silica gel and concentrated under reduced pressure to yield pure quinone **12** (1.32 g, 90 %): Yellow solid; R_f = 0.48 (silica gel, 50 % ethyl ether in petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.79 (dt, J = 2.6(d), 2.4(t) Hz, 1 H, vinyl CH), 6.75 (dt, J = 2.6(d), 2.0(t) Hz, 1 H, vinyl CH), 4.53 (app d, J = 2.4 Hz, 4 H, allylic CH_2), 2.40-2.35 (bs, 1 H, OH), 0.92 (s, 9 H, Si^t*Bu*Me$_2$), 0.09 (s, 6 H, Si^{t}Bu*Me*$_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 187.8, 187.6, 148.4, 146.9, 131.2, 130.8, 59.3, 59.0, 25.8, 18.2, -5.5; IR (film) ν_{max} 3444, 2932, 2858, 1852, 1465, 1406, 1288, 1258, 1166, 1115, 917, 842, 780 cm^{-1}; HRMS Calcd. for $C_{14}H_{22}O_4Si$ (M+Na$^+$): 305.1185. Found: 305.1179.

Quinone monoketal 8. To a solution of **11** (13.98 g, 41.36 mmol) in 1,4-dioxane (105 mL) and ethylene glycol (105 mL) was added ammonium cerium(IV) nitrate (46.5 g, 84.9 mmol). The mixture was stirred at ambient temperature for 0.2 h before being diluted with ethyl ether (500 mL), washed with H_2O (200 mL), $NaHCO_3$ (2 × 100 mL) and dried ($MgSO_4$). The solution was filtered through a pad of silica gel, washing with ethyl ether and concentrated under reduced pressure to give monoketal **8** (10.95 g, 82 %) as a yellow oil. A small sample of material was purified by flash chromatography (silica gel, 60 % ethyl ether in petroleum ether) for the purpose of data collection: Colorless oil; R_f = 0.28 (silica gel, 70 % ethyl ether in petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.66 (dt, *J* = 3.0(d), 2.2(t) Hz, 1 H, vinyl C*H*), 6.61 (dt, *J* = 3.0(d), 1.4(t) Hz, 1 H, vinyl C*H*), 4.41 (d, *J* = 1.4 Hz, 2 H, allylic CH_2), 4.37 (d, *J* = 2.2 Hz, 2 H, allylic CH_2), 4.18-4.15 (m, 4 H, ketal), 0.93 (s, 9 H, Si^t*Bu*Me$_2$), 0.09 (s, 6 H, Si^{t}Bu*Me*$_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 186.0, 138.7, 138.6, 137.7, 137.3, 99.2, 65.8, 60.5, 59.1, 25.9, 18.4, -5.4; IR (film) ν_{max} 3446, 2930, 2858, 1690, 1647, 1465, 1407, 1318, 1256, 1192, 1120, 1086, 969, 840, 779 cm^{-1}; HRMS Calcd. for $C_{16}H_{26}O_5Si$ (M+H$^+$): 327.1628. Found: 327.1630

Epoxide 7. A solution of allylic alcohol **8** (10.95 g, 33.6 mmol) in methylene chloride (54 mL) was stirred with pre-dried 4 Å molecular sieves (3.5 g) and di-isopropyl-D-tartrate (0.89 mL, 4.2 mmol) for 3 h at ambient temperature. The solution was cooled to -30 °C and titanium tetraisopropoxide (1.0 mL, 3.36 mmol) was added. The mixture was allowed to warm to -5 °C over 0.5 h before being recooled to -30 °C and treated with ^{t}butyl hydroperoxide (12.2 mL, *ca* 5.5 M in methylene chloride, 67.1 mmol). The reaction mixture was stirred for 14 h at 0 °C before being quenched with water (50 mL). The mixture was diluted with ethyl acetate (50 mL) and stirred for 1 h before being filtered through a pad of Celite®, washing with ethyl acetate (500 mL). The layers were separated and the organic phase was washed with $Na_2S_2O_4$ (2 × 250 mL, 15 % w/w aqueous solution), $NaHCO_3$ (200 mL), NaCl (100 mL) and dried ($MgSO_4$). Concentration under reduced pressure and purification by flash chromatography (silica gel, 50 → 60 % ethyl ether in petroleum ether) gave epoxide **7** (10.02 g, 87 %) which solidifies on standing. Optically pure material may be obtained by thrice recrystallizing from heptane (5 mL / g): White plates (heptane), mp 81.0 - 81.5 °C; R_f = 0.28 (silica gel, 70 % ethyl ether in petroleum ether); $[\alpha]_D^{25}$ +113.0 (c = 0.44, $CHCl_3$); ^{1}H NMR (500 MHz, C_6D_6) δ 6.62 (ddd, *J* = 2.9, 2.2, 2.1 Hz, 1 H, vinyl C*H*), 4.53 (dd, *J* = 16.1, 2.2 Hz, 1 H, allylic CH_2), 4.22 (dd, *J* = 16.1, 2.1 Hz, 1 H, allylic CH_2), 3.93-3.84 (bm, 2 H, CH_2OH), 3.65 (d, *J* = 2.9 Hz, 1 H, epoxide C*H*), 3.49-3.43 (m, 2 H, ketal), 3.39-3.36 (m, 2 H, ketal), 1.64 (bt, 1 H, O*H*), 0.88 (s, 9 H, Si^t*Bu*Me$_2$), -0.07 (s, 6 H, Si^{t}Bu*Me*$_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.9, 137.9, 135.4, 101.8, 66.1, 66.0, 59.1, 58.7, 58.5, 57.8, 25.8, 18.3, -5.5; IR (film) ν_{max} 3484, 2932, 2890, 2858, 1685, 1466, 1404, 1312, 1256, 1192, 1123, 985, 947, 842, 780 cm^{-1}; HRMS Calcd. for $C_{16}H_{26}O_6Si$ (M+Cs$^+$): 475.0553. Found: 475.0559. Anal. Calcd. for $C_{16}H_{26}O_6Si$: C, 56.12; H, 7.65. Found: C, 55.95; H, 7.70.

Urethane 13. To a solution of epoxide **7** (5.46 g, 16.0 mmol) in methylene chloride (53 mL) was added triethylamine (2.7 mL, 19.4 mmol) and phenyl isocyanate (1.9 mL, 17.5 mmol). After 1 h the reaction mixture was diluted with ethyl ether (200 mL) and washed with 1 N HCl (2 × 50 mL), $NaHCO_3$ (2 × 50 mL) and dried ($MgSO_4$). Concentration under reduced pressure and purification by flash chromatography (silica gel,

30 → 40 % ethyl ether in petroleum ether) yielded urethane **13** as a white foam (7.26 g, 99 %): Colorless oil; R_f = 0.34 (silica gel, 50 % ethyl ether in petroleum ether); $[\alpha]_D^{25}$ +82.0 (c = 4.37, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.37-7.35 (bm, 2 H, Ar), 7.31-7.27 (m, 2 H, Ar), 7.07-7.05 (m, 1 H, Ar), 6.87 (bs, 1 H, N*H*), 6.38 (dt, *J* = 2.8(d), 2.3(t) Hz, 1 H, vinyl C*H*), 4.70 (d, *J* = 12.5 Hz, 1 H, CH_2OC(O)NHPh), 4.54 (bd, *J* = 12.5 Hz, 1 H, CH_2OC(O)NHPh), 4.45 (dd, *J* = 16.4, 2.3 Hz, 1 H, allylic CH_2), 4.21 (dd, *J* = 16.4, 2.3 Hz, 1 H, allylic CH_2), 4.22-4.10 (m, 4 H, ketal), 3.72 (d, *J* = 2.8 Hz, 1 H, epoxide C*H*), 0.91 (s, 9 H, Si^t*Bu*Me_2), 0.07 (s, 6 H, Si^{t}Bu*Me*$_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.8, 152.5, 137.7, 137.4, 135.1, 129.0, 123.6, 118.6, 101.6, 66.1, 66.0, 60.1, 59.1, 58.5, 57.0, 25.8, 18.2, -5.5, -5.6; IR (film) ν_{max} 3335, 2953, 2890, 2857, 1738, 1686, 1602, 1539, 1446, 1316, 1218, 1120, 952, 841, 755 cm^{-1}; HRMS Calcd. for $C_{23}H_{31}O_7NSi$ ($M+Cs^+$): 594.0924. Found: 594.0931.

Carbonate 14. To a solution of urethane **13** (7.26 g, 15.7 mmol) in methylene chloride (80 mL) was added boron trifluoride etherate (2.1 mL, 17 mmol). After 0.3 h a solution of acetic acid (8 mL, 80 % v/v aqueous solution) in ethyl acetate (80 mL) was added and the mixture was stirred for a further 0.3 h. The reaction mixture was cautiously poured into a saturated aqueous solution of $NaHCO_3$ (300 mL) and stirred for 0.1 h. After dilution with ethyl ether (500 mL), the layers were separated and the organic phase was washed with $NaHCO_3$ (150 mL), NaCl (150 mL) and dried ($MgSO_4$). Concentration under reduced pressure and purification by flash chromatography (silica gel, 40 → 50 % ethyl ether in petroleum ether) gave carbonate **14** (4.85 g, 80 %): White solid (methylene chloride / petroleum ether), mp 115.0 - 115.5 °C; R_f = 0.33 (silica gel, 60 % ethyl ether in petroleum ether); $[\alpha]_D^{25}$ -6.1 (c = 1.57, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 6.77 (t, *J* = 2.1 Hz, 1 H, vinyl C*H*), 4.95 (d, *J* = 9.2 Hz, 1 H, carbonate CH_2), 4.42 (s, 1 H, C*H*OH), 4.38 (dd, *J* = 16.5, 2.1 Hz, 1 H, allylic CH_2), 4.33 (dd, *J* = 16.5, 2.1 Hz, 1 H, allylic CH_2), 4.33-4.30 (m, 1 H, ketal), 4.21-4.16 (m, 1 H, ketal), 4.15 (d, *J* = 9.2 Hz, 1 H, carbonate CH_2), 4.12-4.06 (m, 2 H, ketal), 3.95-3.75 (bs, 1 H, O*H*), 0.91 (s, 9 H, Si^t*Bu*Me_2), 0.08 (s, 6 H, Si^{t}Bu*Me*$_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.4, 154.6, 142.1, 138.9, 103.8, 85.1, 71.4, 71.3, 67.2, 67.1, 66.8, 59.0, 25.8, 18.2, -5.5; IR (film) ν_{max} 3455, 2953, 2894, 2858, 1814, 1695, 1469, 1391, 1329, 1258, 1095, 1066, 1027, 993, 951, 838, 778 cm^{-1}; HRMS Calcd. for $C_{17}H_{26}O_8Si$ ($M+Cs^+$): 519.0451. Found: 519.0459.

THP ether 15. To a solution of alcohol **14** (937 mg, 2.43 mmol) in methylene chloride (12 mL) was added dihydropyran (663 μL, 7.23 mmol) and PPTS (122 mg, 0.49 mmol). After 14 h at ambient temperature, the reaction mixture was diluted with ethyl acetate (40 mL), washed with $NaHCO_3$ (2 × 15 mL), NaCl (15 mL) and dried ($MgSO_4$). Concentration under reduced pressure and purification by flash chromatography (silica gel, 30 → 40 % ethyl ether in petroleum ether) yielded **15** (627 mg of the more polar isomer and 293 mg of the less polar isomer, 81 %).

15 (Less polar isomer): Colorless oil; R_f = 0.47 (silica gel, 50 % ethyl ether in petroleum ether); $[\alpha]_D^{25}$ -39.9 (c = 4.80, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 6.76 (t, *J* = 2.1 Hz, 1 H, vinyl C*H*), 4.91 (d, *J* = 9.3 Hz, 1 H, carbonate CH_2), 4.90-4.88 (m, 1 H, THP anomeric C*H*), 4.48 (s, 1 H, C*H*OTHP), 4.37 (dd, *J* = 16.4, 2.1 Hz, 1 H, allylic CH_2), 4.33 (dd, *J* = 16.4, 2.1 Hz, 1 H, allylic CH_2), 4.37-4.34 (m, 1 H, ketal), 4.20-4.16 (m, 1 H, ketal), 4.14 (d, *J* = 9.3 Hz, 1 H, carbonate CH_2), 4.12-4.04 (m, 2 H, ketal), 4.00-3.95 (m, 1 H, THP), 3.55-3.50 (m, 1 H, THP), 1.78-1.70 (m, 2 H, THP), 1.62-1.48 (m, 4 H,

THP), 0.89 (s, 9 H, Si^t*Bu*Me$_2$), 0.07 (s, 6 H, Si^{t}Bu*Me*$_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.5, 153.7, 142.7, 138.6, 104.0, 100.0, 85.5, 74.7, 67.6, 67.0, 66.7, 63.0, 58.9, 30.5, 25.8, 25.0, 19.3, 18.2, -5.5; IR (film) ν_{max} 2951, 2859, 1821, 1697, 1469, 1394, 1258, 1207, 1135, 1067, 953, 839 cm^{-1}; HRMS Calcd. for $C_{22}H_{34}O_9Si$ (M+Cs$^+$): 603.1026. Found: 603.1011.

15 (More polar isomer): White solid; R_f = 0.37 (silica gel, 50 % ethyl ether in petroleum ether); $[\alpha]_D^{25}$ +63.8 (c = 3.03, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.76 (t, *J* = 2.1 Hz, 1 H, vinyl C*H*), 5.11-5.09 (bm, 1 H, THP anomeric C*H*), 4.94 (d, *J* = 9.1 Hz, 1 H, carbonate C*H*$_2$), 4.49 (s, 1 H, C*H*OTHP), 4.37 (d, *J* = 2.1 Hz, 2 H, allylic C*H*$_2$), 4.23-4.19 (m, 1 H, ketal), 4.15 (d, *J* = 9.1 Hz, 1 H, carbonate C*H*$_2$), 4.17-4.11 (m, 1 H, ketal), 4.08-4.02 (m, 2 H, ketal), 3.94-3.88 (m, 1 H, THP), 3.60-3.54 (m, 1 H, THP), 1.80-1.52 (m, 6 H, THP), 0.91 (s, 9 H, Si^t*Bu*Me$_2$), 0.08 (s, 6 H, Si^{t}Bu*Me*$_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.6, 154.0, 142.3, 139.0, 105.0, 99.0, 84.1, 74.1, 67.6, 67.0, 66.2, 61.9, 59.0, 30.4, 25.8, 25.0, 18.4, 18.3, -5.4; IR (film) ν_{max} 2953, 2858, 1815, 1694, 1469, 1382, 1257, 1141, 1072, 1032, 951, 839 cm^{-1}; HRMS Calcd. for $C_{22}H_{34}O_9Si$ (M+Cs$^+$): 603.1026. Found: 603.1023. Anal. Calcd. for $C_{22}H_{34}O_9Si$: C, 56.15; H, 7.28. Found: C, 56.04; H, 7.46.

Diol 16. To a solution of silyl ether **14** (257 mg, 0.666 mmol) in THF (3.3 mL) in a polypropylene vessel at 0 °C was added hydrogen fluoride - pyridine (1.0 mL). The solution was stirred for 0.3 h, diluted with ethyl acetate (40 mL) and poured cautiously into $NaHCO_3$ (50 mL). After 0.1 h of stirring, the layers were separated and the organic phase was washed with NaCl (20 mL) and dried ($MgSO_4$). Concentration under reduced pressure and trituration with ethyl ether (2 × 10 mL) gave pure diol **16** (141 mg, 78 %): White solid. R_f = 0.41 (silica gel, ethyl acetate); ^{1}H NMR (500 MHz, acetone-d_6) δ 6.82 (t, *J* = 1.9 Hz, 1 H, vinyl C*H*), 5.68 (d, *J* = 5.7 Hz, 1 H, secondary O*H*), 4.89 (d, *J* = 9.1 Hz, 1 H, carbonate C*H*$_2$), 4.42 (d, *J* = 5.7 Hz, 1 H, C*H*OH), 4.35-4.31 (m, 1 H, ketal), 4.29-4.25 (m, 4 H, carbonate C*H*$_2$, C*H*$_2$OH and ketal), 4.20-4.09 (m, 3 H, ketal and primary O*H*); ^{13}C NMR (125 MHz, acetone-d_6) δ 192.9, 154.8, 142.8, 139.8, 105.0, 86.0, 71.8, 67.9, 67.2, 54.5; IR (film) ν_{max} 3282, 3020, 2921, 1812, 1692, 1381, 1127, 1071, 1030, 990, 954 cm^{-1}; HRMS Calcd. for $C_{11}H_{12}O_8$ (M+H$^+$): 273.0610. Found: 273.0607.

MEM ether 17. To a solution of diol **16** (137 mg, 0.504 mmol) in 1,2-dichloroethane (2.5 mL) was added diisopropylethylamine (158 μL, 0.907 mmol) and MEM chloride (75 μL, 0.65 mmol) and the mixture was refluxed for 1 h. After cooling to ambient temperature the solution was diluted with ethyl acetate (40 mL), washed with 1 N HCl (15 mL), $NaHCO_3$ (15 mL) and NaCl (15 mL). The aqueous phases were extracted with methylene chloride (50 mL) and the combined organic phase was dried ($MgSO_4$). Concentration under reduced pressure and purification by flash chromatography (silica gel, 20 % acetone in chloroform) gave pure MEM ether **17** (140 mg, 77 %): White solid; R_f = 0.23 (silica gel, 20 % acetone in chloroform); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.78 (t, *J* = 1.7 Hz, 1 H, vinyl C*H*), 4.92 (d, *J* = 9.2 Hz, 1 H, carbonate C*H*$_2$), 4.74, (s, 2 H, OC*H*$_2$O), 4.39 (d, *J* = 5.4 Hz, 1 H, C*H*OH), 4.31-4.26 (m, 1 H, ketal), 4.26 (d, *J* = 1.7 Hz, 2 H, allylic C*H*$_2$), 4.16 (d, *J* = 5.4 Hz, 1 H, O*H*), 4.14 (d, *J* = 9.2 Hz, 1 H, carbonate C*H*$_2$), 4.18-4.13 (m, 1 H, ketal), 4.10-4.04 (m, 2 H, ketal), 3.69-3.66 (m, 2 H, MEM OC*H*$_2$CH$_2$O), 3.55-3.52 (m, 2 H, MEM OCH$_2$C*H*$_2$O), 3.36 (s, 3 H, OC*H*$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.2, 154.4, 143.6, 136.0, 103.7, 95.4, 85.0, 71.6, 71.0, 67.2, 67.1, 66.9, 66.7, 63.0, 59.0; IR (film) ν_{max} 3414, 2892,

1807, 1699, 1470, 1374, 1090, 1057 cm^{-1}; HRMS Calcd. for $C_{15}H_{20}O_{10}$ ($M+Na^+$): 383.0954. Found: 383.0960.

THP ether 18. To a solution of alcohol **17** (140 mg, 0.39 mmol) in 1,2-dichloroethane (1.9 mL) was added dihydropyran (106 μL, 1.17 mmol) and PPTS (20 mg) and the mixture was heated at 70 °C for 1.5 h. After cooling to ambient temperature the mixture was diluted with ethyl acetate (40 mL), washed with $NaHCO_3$ (15 mL), NaCl (15 mL) and dried ($MgSO_4$). Concentration under reduced pressure and purification by flash chromatography (silica gel, 80 % ethyl ether in petroleum ether then ethyl ether) gave the less polar isomer (49 mg) and the more polar isomer (99 mg) (86 % total yield of **18**).
18 (More polar isomer): Colorless oil; R_f = 0.36 (silica gel, ethyl ether); ^1H NMR (500 MHz, $CDCl_3$) δ 6.78 (t, J = 1.7 Hz, 1 H, vinyl C*H*), 5.11-5.09 (m, 1 H, THP anomeric C*H*), 4.94 (d, J = 9.1 Hz, 1 H, carbonate CH_2), 4.77, (s, 2 H, OCH_2O), 4.50 (s, 1 H, C*H*OTHP), 4.29 (d, J = 1.7 Hz, 2 H, allylic CH_2), 4.17 (d, J = 9.1 Hz, 1 H, carbonate CH_2), 4.21-4.10 (m, 2 H, ketal), 4.09-4.01 (m, 2 H, ketal), 3.93-3.88 (m, 1 H, THP), 3.70-3.68 (m, 2 H, MEM OCH_2CH_2O), 3.59-3.54 (m, 3 H, MEM OCH_2CH_2O and THP), 3.39 (s, 3 H, OCH_3), 1.80-1.50 (m, 6 H, THP); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.3, 154.0, 143.6, 136.2, 104.9, 99.0, 95.5, 84.1, 73.9, 71.6, 67.5, 67.2, 67.0, 66.2, 62.9, 61.9, 59.1, 30.4, 25.0, 18.4; IR (film) ν_{max} 2945, 2894, 1816, 1696, 1469, 1378, 1063, 956 cm^{-1}; HRMS Calcd. for $C_{20}H_{28}O_{11}$ ($M+Na^+$): 467.1529. Found: 467.1540.

Triol 19. To a solution of carbonate **18** (80 mg, 18 μmol) in 1,4-dioxane (2.0 mL) and water (1.0 mL) was added sodium hydroxide (80 μL, 1 N aqueous solution, 80 μmol). After 0.2 h the mixture was diluted with ethyl acetate (50 mL), washed with H_2O (20 mL), NaCl (20 mL) and dried ($MgSO_4$). Concentration under reduced pressure and purification by flash chromatography (silica gel, ethyl acetate) gave triol **19** (32 mg, 73 %): Colorless oil; R_f = 0.19 (silica gel, ethyl acetate); ^1H NMR (500 MHz, $CDCl_3$) δ 6.55 (t, J = 1.5 Hz, 1 H, vinyl C*H*), 4.65 (bs, 1 H, tertiary O*H*), 4.64-4.62 (m, 1 H, THP anomeric C*H*), 4.39 (dd, J = 15.0, 1.5 Hz, 1 H, allylic CH_2), 4.32 (dd, J = 15.0, 1.5 Hz, 1 H, allylic CH_2), 4.20-4.02 (m, 5 H, ketal and THP), 4.12 (s, 1 H, C*H*OTHP), 3.97 (d, J = 11.8 Hz, 1 H, CH_2OH), 3.82 (d, J = 11.8 Hz, 1 H, CH_2OH), 3.55-3.49 (m, 1 H, THP), 3.0-2.8 (bs, 1 H, O*H*), 2.4-2.1 (bs, 1 H, O*H*), 1.90-1.50 (m, 6 H, THP); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.9, 139.2, 138.9, 104.5, 102.6, 82.5, 78.7, 67.0, 65.8, 65.2, 64.8, 59.9, 31.1, 24.6, 20.8; IR (film) ν_{max} 3418, 2945, 1686, 1445, 1385, 1353, 1123, 1029, 974, 912 cm^{-1}; HRMS Calcd. for $C_{15}H_{22}O_8$ ($M+Na^+$): 353.1212. Found: 353.1204.

Acetonitrile adduct 24. To a solution of ^{t}butyl lithium (154 μL, 1.7 M in pentane, 262 μmol) in THF (2.3 mL) at -78 °C was added acetonitrile (15 μL, 0.29 mmol). After 90 s, a solution of ketone **15** (107 mg, 0.23 mmol) in THF (0.5 mL) was added *via* cannula. After a further 0.1 h, the reaction was quenched by the addition of a saturated solution of ammonium chloride and the mixture was warmed to ambient temperature. The mixture was diluted with ethyl acetate (50 mL), the aqueous phase was separated and the organic layer was washed with NaCl (20 mL) and dried ($MgSO_4$). Concentration under reduced pressure and purification by flash chromatography (silica gel, 60 % ethyl ether in petroleum ether) gave adduct **24** (96 mg, 83 %): Colorless oil; R_f = 0.22 (silica gel, 60 % ethyl ether in petroleum ether); $[\alpha]_D^{25}$ +96.5 (c = 1.57,

$CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 5.54 (s, 1 H, O*H*), 5.54 (app s, 1 H, vinyl C*H*), 4.99-4.97 (m, 1 H, THP anomeric C*H*), 4.91 (d, *J* = 8.6 Hz, 1 H, carbonate CH_2), 4.75 (dd, *J* = 13.1, 1.3 Hz, 1 H, CH_2OTBS), 4.40 (d, *J* = 8.6 Hz, 1 H, carbonate CH_2), 4.37 (s, 1 H, C*H*OTHP), 4.28 (dd, *J* = 13.1, 0.8 Hz, 1 H, CH_2OTBS), 4.15-4.06 (m, 2 H, THP and/or ketal), 3.99-3.84 (m, 3 H, THP and/or ketal), 3.60-3.55 (m, 1 H, THP), 3.17 (d, *J* = 16.8 Hz, 1 H, CH_2CN), 2.92 (d, *J* = 16.8 Hz, 1 H, CH_2CN), 1.8-1.5 (m, 6 H, THP), 0.90 (s, 9 H, Si^t*Bu*Me_2), 0.14 (s, 3 H, Si^{t}Bu*Me*$_2$), 0.12 (s, 3 H, Si^{t}Bu*Me*$_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.2, 136.7, 127.4, 116.6, 105.3, 98.7, 87.3, 75.8, 72.8, 66.7, 65.7, 65.0, 64.8, 61.8, 30.3, 26.9, 25.6, 24.9, 18.2, 18.0, -5.6, -5.7; IR (film) ν_{max} 3385, 2950, 2892, 2859, 2254, 1808, 1468, 1391, 1257, 1184, 1075, 1030, 960, 838, 778, 732 cm^{-1}; HRMS Calcd. for $C_{24}H_{37}O_9NSi$ ($M+H^+$): 512.2316. Found: 512.2320.

Alkenes 25a and 25b. To a solution of adduct **24** (506 mg, 0.99 mmol) in methylene chloride (5 mL) was added triethylamine (343 μL, 2.48 mmol), DMAP (12 mg, 0.1 mmol) and trifluoroacetic anhydride (182 μL, 1.29 mmol). After 0.5 h, the reaction mixture was diluted with ethyl ether (50 mL), washed with 1 N HCl (2 × 20 mL), $NaHCO_3$ (20 mL), NaCl (20 mL) and dried ($MgSO_4$). Concentration under reduced pressure and purification by flash chromatography (silica, 40 → 50 % ethyl ether in petroleum ether) gave compound **25a** (450 mg, 91 %). Further elution with 70 % ethyl ether in petroleum ether gave the isomer **25b** (30 mg, 6%).

25a: Colorless oil; R_f = 0.54 (silica gel, 5 % acetone in chloroform); $[\alpha]_D^{25}$ +129.7 (c = 1.59, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 6.11 (ddd, *J* = 1.9, 1.7, 1.4 Hz, 1 H, ring vinyl C*H*), 5.74 (d, *J* = 1.4 Hz, 1 H, C*H*CN), 5.20 (d, *J* = 8.9 Hz, 1 H, carbonate CH_2), 5.04-5.01 (m, 1 H, THP anomeric C*H*), 4.82 (dd, *J* = 14.9, 1.9 Hz, 1 H, CH_2OTBS), 4.60 (dd, *J* = 14.9, 1.7 Hz, 1 H, CH_2OTBS), 4.31 (s, 1 H, C*H*OTHP), 4.18-4.10 (m, 2 H, THP and/or ketal), 4.00-3.90 (m, 3 H, THP and/or ketal), 3.96 (d, *J* = 8.9 Hz, 1 H, carbonate CH_2), 3.59-3.54 (m, 1 H, THP), 1.8-1.5 (m, 6 H THP), 0.91 (s, 9 H, Si^t*Bu*Me_2), 0.11 (s, 3 H, Si^{t}Bu*Me*$_2$), 0.11 (s, 3 H, Si^{t}Bu*Me*$_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.4, 151.4, 135.1, 131.6, 116.2, 105.1, 98.9, 93.5, 83.9, 74.7, 69.6, 66.8, 65.1, 62.0, 61.5, 30.3, 25.8, 25.0, 18.3, -5.4, -5.5; IR (film) ν_{max} 3061, 2951, 2894, 2858, 2218, 1820, 1598, 1469, 1382, 1257, 1203, 1145, 1078, 1035, 955, 910, 837, 780, 733 cm^{-1}; HRMS Calcd. for $C_{24}H_{35}O_8NSi$ ($M+Cs^+$): 626.1186. Found: 626.1191.

25b: Colorless oil; R_f = 0.24 (silica gel, 60 % ethyl ether in petroleum ether); $[\alpha]_D^{25}$ +40.9 (c = 3.97, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 6.06-6.05 (m, 1 H, ring vinyl C*H*), 5.70 (s, 1 H, C*H*CN), 5.30 (d, *J* = 8.8 Hz, 1 H, carbonate CH_2), 5.12-5.10 (m, 1 H, THP anomeric C*H*), 4.35 (s, 1 H, C*H*OTHP), 4.26 (dd, *J* = 13.7, 1.4 Hz, 1 H, CH_2OTBS), 4.23 (dd, *J* = 13.7, 1.4 Hz, 1 H, CH_2OTBS), 4.17 (d, *J* = 8.8 Hz, 1 H, carbonate CH_2), 4.15-4.08 (m, 2 H, ketal), 4.03-3.93 (m, 3 H, THP and ketal), 3.59-3.54 (m, 1 H, THP), 1.8-1.5 (m, 6 H, THP), 0.89 (s, 9 H, Si^t*Bu*Me_2), 0.07 (s, 6 H, Si^{t}Bu*Me*$_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.5, 153.3, 135.3, 133.3, 114.7, 104.9, 98.7, 96.5, 82.9, 74.1, 70.7, 66.8, 65.3, 62.1, 61.9, 30.4, 25.7, 24.9, 18.3, -5.4; IR (film) ν_{max} 3061, 2951, 2893, 2858, 2216, 1818, 1591, 1470, 1382, 1253, 1204, 1152, 1077, 1034, 954, 840, 780, 732 cm^{-1}; HRMS Calcd. for $C_{24}H_{35}O_8NSi$ ($M+H^+$): 494.2210. Found: 494.2210.

Diol 26. To a solution of carbonate **25a** (450 mg, 0.91 mmol) in dioxane (3.5 mL) was added sodium hydroxide (2 mL, 1 N aqueous solution, 2.0 mmol). After stirring for 1 h at ambient temperature, the reaction mixture was diluted with ethyl acetate (50 mL), washed with H_2O (2 × 20 mL), NaCl (20 mL) and dried ($MgSO_4$). Concentration under reduced pressure and purification by flash chromatography (silica, 60 % ethyl ether in petroleum ether) gave diol **26** (400 mg, 94 %): Colorless oil; R_f = 0.60 (silica gel, 80 % ethyl ether in petroleum ether); $[\alpha]_D^{25}$ +138.2 (c = 5.03, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 6.05 (ddd, *J* = 2.1, 1.8, 1.3 Hz, 1 H, ring vinyl C*H*), 5.93 (d, *J* = 1.3 Hz, 1 H, C*H*CN), 5.04 (s, 1 H, tertiary O*H*), 4.92 (dd, *J* = 15.3, 2.1 Hz, 1 H, CH_2OTBS), 4.51 (dd, *J* = 15.3, 1.8 Hz, 1 H, CH_2OTBS), 4.46-4.43 (m, 1 H, THP anomeric C*H*), 4.12-3.93 (m, 5 H, THP and ketal), 3.89 (s, 1 H, C*H*OTHP), 3.73 (d, *J* = 11.6 Hz, 1 H, CH_2OH), 3.56 (d, *J* = 11.6 Hz, 1 H, CH_2OH), 3.54-3.49 (m, 1 H, THP), 2.5-2.4 (bs, 1 H, CH$_2$O*H*), 1.89-1.77 (m, 2 H, THP), 1.60-1.45 (m, 4 H, THP), 0.90 (s, 9 H, Si*t*-*Bu*Me$_2$), 0.08 (s, 3 H, Si*t*BuM*e*$_2$), 0.08 (s, 3 H, Si*t*BuM*e*$_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.2, 137.3, 128.6, 117.7, 104.7, 103.8, 94.2, 85.2, 76.0, 67.0, 66.5, 66.2, 65.6, 61.5, 31.4, 25.8, 24.6, 21.4, 18.2, -5.5, -5.5; IR (film) ν_{max} 3405, 2950, 2859, 2213, 1592, 1465, 1404, 1359, 1257, 1206, 1126, 1071, 1034, 973, 838, 780, 733 cm^{-1}; HRMS Calcd. for $C_{23}H_{37}O_7NSi$ (M+Cs$^+$): 600.1394. Found: 600.1411. Anal. Calcd. for $C_{23}H_{37}O_7NSi$: C, 59.11; H, 7.92; N, 3.00. Found: C, 59.43; H, 7.70; N, 2.87.

Aldehyde 27. To a solution of diol **26** (330 mg, 0.71 mmol) in methylene chloride (3.5 mL) was added Dess-Martin periodinane (450 mg, 1.07 mmol) and the reaction mixture was stirred for 48 h at ambient temperature. The mixture was diluted with ethyl ether (50 mL), filtered through a pad of silica gel, concentrated under reduced pressure and purified by flash chromatography (silica gel, 30 → 40 % ethyl ether in petroleum ether) to yield aldehyde **27** as a clear oil (310 mg, 94 %): White solid; R_f = 0.61 (silica gel, 60 % ethyl ether in petroleum ether); $[\alpha]_D^{25}$ +112.6 (c = 1.35, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 9.58 (s, 1 H, C*H*O), 6.21 (ddd, *J* = 2.1, 1.8, 1.3 Hz, 1 H, ring vinyl C*H*), 5.94 (d, *J* = 1.3 Hz, 1 H, C*H*CN), 5.54 (s, 1 H, tertiary O*H*), 4.96 (dd, *J* = 15.3, 2.1 Hz, 1 H, CH_2OTBS), 4.60 (dd, *J* = 15.3, 1.8 Hz, 1 H, CH_2OTBS), 4.56 (dd, *J* = 6.8, 2.3 Hz, 1 H, THP anomeric C*H*), 4.14-3.99 (m, 5 H, THP and ketal), 4.02 (s, 1 H, C*H*OTHP), 3.60-3.55 (m, 1 H, THP), 1.87-1.76 (m, 2 H, THP), 1.64-1.51 (m, 4 H, THP), 0.93 (s, 9 H, Si*t*-*Bu*Me$_2$), 0.12 (s, 3 H, Si*t*BuM*e*$_2$), 0.12 (s, 3 H, Si*t*BuM*e*$_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.5, 150.4, 137.2, 130.4, 117.3, 104.4, 102.8, 95.4, 85.9, 81.6, 67.1, 66.3, 65.4, 61.5, 31.2, 25.9, 24.7, 20.6, 18.3, -5.4, -5.5; IR (film) ν_{max} 3337, 3057, 2950, 2859, 2214, 1733, 1591, 1466, 1356, 1259, 1202, 1126, 1033, 957, 837, 780 cm^{-1}; HRMS Calcd. for $C_{23}H_{35}O_7NSi$ (M+Cs$^+$): 598.1237. Found: 598.1234.

Silyloxy epoxide 28. To a solution of hydroxy aldehyde **27** (65 mg, 0.14 mmol) in 1,2-dichloroethane (700 μL) was added 2,6-lutidine (17 μL, 0.21 mmol) and TESOTf (38 μL, 0.17 mmol). After 0.5 h, the reaction mixture was diluted with ethyl ether (20 mL), washed with $CuSO_4$ (5 mL), $NaHCO_3$ (5 mL) and dried ($MgSO_4$). Concentration under reduced pressure and purification by flash chromatograpy (silica gel, 10 → 15 % ethyl ether in petroleum ether) gave silyl lactol **28** (62 mg, 77 %): Colorless oil; R_f = 0.48 (silica gel, 30 % ethyl ether in petroleum ether); $[\alpha]_D^{25}$ +86.2 (c = 2.53, $CHCl_3$); ^1H NMR (500 MHz, C_6D_6) δ 6.42 (ddd, *J* = 2.0, 1.8, 1.3 Hz, 1 H, ring vinyl C*H*), 5.74 (d, *J* = 1.3 Hz, 1 H, C*H*CN),

5.40 (s, 1 H, C*H*OTES), 5.10-5.08 (m, 1 H, THP anomeric C*H*), 5.03 (dd, *J* = 15.2, 2.0 Hz, 1 H, C*H*$_2$OTBS), 4.85 (dd, *J* = 15.2, 1.8 Hz, 1 H, C*H*$_2$OTBS), 4.38 (s, 1 H, C*H*OTHP), 4.28-4.22 (m, 1 H, ketal or THP), 3.61-3.44 (m, 5 H, ketal and THP), 1.80-1.69 (m, 1 H, THP), 1.53-1.24 (m, 5 H, THP), 0.95 (s, 9 H, Si*t*-*Bu*Me$_2$), 0.92 (t, *J* = 8.0 Hz, 9 H, Si(CH$_2$C*H*$_3$)$_3$), 0.55 (q, *J* = 8.0 Hz, 6 H, Si(C*H*$_2$CH$_3$)$_3$), 0.08 (s, 3 H, Si^{t}Bu*Me*$_2$), 0.06 (s, 3 H, Si^{t}Bu*Me*$_2$); ^{13}C NMR (125 MHz, C_6D_6) δ 147.2, 137.9, 131.3, 117.8, 107.2, 98.4, 94.5, 79.0, 73.3, 66.4, 65.7, 65.2, 62.2, 60.9, 30.7, 26.1, 25.7, 18.7, 18.5, 6.6, 4.8, -5.4; IR (film) ν_{max} 3054, 2952, 2883, 2211, 1590, 1464, 1412, 1256, 1191, 1123, 1038, 961, 835, 781, 742 cm^{-1}; LRMS Calcd. for $C_{29}H_{49}O_7NSi_2$ (M+Cs$^+$): 712. Found: 712.

Aldehyde 29. To a solution of protected lactol **28** (50 mg, 86 μmol) in 1,2-dichloroethane (4.3 mL) was added 2,6-lutidine (151 μL, 1.29 mmol), and TESOTf (195 μL, 0.86 mmol) and the mixture was placed in an oil bath at 70 °C. After 1 h the mixture was cooled, diluted with ethyl ether (40 mL), washed with $CuSO_4$ (10 mL), $NaHCO_3$ (10 mL) and dried ($MgSO_4$). Concentration under reduced pressure and purification by preparative TLC (silica gel, 30 % ethyl ether in petroleum ether) gave the silyl ether **29** (37 mg, 74 %): Colorless oil; R_f = 0.58 (silica gel, 30 % ethyl ether in petroleum ether); $[\alpha]_D^{25}$ +161.8 (c = 0.50, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.40 (s, 1 H, C*H*O), 6.19 (ddd, *J* = 2.2, 1.9, 1.2 Hz, 1 H, ring vinyl C*H*), 5.58 (d, *J* = 1.2 Hz, 1 H, C*H*CN), 5.27 (pt, *J* = 5.4 Hz, 1 H, THP anomeric C*H*), 5.04 (dd, *J* = 15.6, 2.2 Hz, 1 H, C*H*$_2$OTBS), 4.56 (dd, *J* = 15.6, 1.9 Hz, 1 H, C*H*$_2$OTBS), 4.20-4.15 (m, 1 H, ketal), 4.12-4.06 (m, 3 H, ketal), 4.04 (s, 1 H, C*H*OTHP), 3.65-3.61 (m, 2 H, THP), 1.96-1.90 (m, 2 H, THP), 1.65-1.53 (m, 4 H, THP), 0.96 (t, *J* = 8.0 Hz, 9 H, Si(CH$_2$C*H*$_3$)$_3$), 0.93 (s, 9 H, Si*t*-*Bu*Me$_2$), 0.60 (q, *J* = 8.0 Hz, 6 H, Si(C*H*$_2$CH$_3$)$_3$), 0.13 (s, 3 H, Si^{t}Bu*Me*$_2$), 0.13 (s, 3 H, Si^{t}Bu*Me*$_2$); ^{13}C NMR (125 MHz, C_6D_6) δ 191.8, 149.8, 139.2, 131.1, 116.3, 108.9, 102.9, 93.2, 87.5, 86.0, 66.3, 65.5, 62.1, 61.4, 34.4, 32.4, 25.6, 20.8, 18.1, 6.7, 4.4, -5.7, -5.8; IR (film) ν_{max} 2954, 2877, 2218, 1733, 1462, 1377, 1254, 1151, 1103, 1043, 838, 779, 743 cm^{-1}; HRMS Calcd. for $C_{29}H_{49}O_7NSi_2$ (M+Cs$^+$): 712.2102. Found: 712.2111.

Alkyne 30. To a solution of dimethyl diazomethylphosphonate (12 μL, 100 μmol) in THF (0.5 mL) at -78 °C was added ^{n}butyl lithium (27 μL, 2.5 M in hexane, 64 μmol). After 0.1 h, a solution of **29** (23 mg, 40 μmol) in THF (0.5 mL) was added. The reaction mixture was allowed to warm to -5 °C over 1.5 h before being quenched with a saturated solution of ammonium chloride (5 mL) and diluted with ethyl ether (20 mL). The layers were separated and the organic phase was washed with $NaHCO_3$ (5 mL) and dried ($MgSO_4$). Concentration under reduced pressure and purification by preparative TLC (30 % ethyl ether in petroleum ether) gave pure alkyne **30** (9 mg, 40 %): Colorless oil; R_f = 0.60 (silica gel, 30 % ethyl ether in petroleum ether); $[\alpha]_D^{25}$ +139 (c = 0.27, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.14 (ddd, *J* = 2.1, 1.9, 1.3 Hz, 1 H, ring vinyl C*H*), 5.67 (d, *J* = 1.3 Hz, 1 H, C*H*CN), 5.21 (pt, *J* = 5.3 Hz, 1 H, THP anomeric C*H*), 4.91 (dd, *J* = 15.2, 2.1 Hz, 1 H, C*H*$_2$OTBS), 4.53 (dd, *J* = 15.2, 1.9 Hz, 1 H, C*H*$_2$OTBS), 4.22-4.18 (m, 2 H, ketal), 4.15-4.10 (m, 1 H, ketal), 4.04-3.99 (m, 1 H, ketal), 3.75 (s, 1 H, C*H*OTHP), 3.64-3.60 (m, 2 H, THP), 2.54 (s, 1 H, CC*H*), 1.98-1.90 (m, 2 H, THP), 1.65-1.52 (m, 4 H, THP), 0.96 (t, *J* = 8.0 Hz, 9 H, Si(CH$_2$C*H*$_3$)$_3$), 0.92 (s, 9 H, Si*t*-*Bu*Me$_2$), 0.60 (q, *J* = 8.0 Hz, 6 H, Si(C*H*$_2$CH$_3$)$_3$), 0.11 (s, 3 H, Si^{t}Bu*Me*$_2$), 0.11 (s, 3 H, Si^{t}Bu*Me*$_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.5,

137.7, 131.1, 116.4, 108.8, 102.7, 91.2, 84.7, 80.9, 76.6, 76.2, 75.7, 67.1, 65.0, 62.5, 61.6, 34.5, 32.5, 25.8, 20.6, 18.3, 6.8, 4.4, -5.4, -5.4; IR (film) ν_{max} 3311, 3274, 2954, 2877, 2219, 2116, 1462, 1259, 1101, 1041, 838, 779, 742 cm^{-1}; HRMS Calcd. for $C_{30}H_{49}O_6NSi_2$ ($M+H^+$): 576.3177. Found: 576.3180.

Acetate 31. To a solution of secondary alcohol **14** (415 mg, 1.08 mmol) in methylene chloride (2.2 mL) was added DMAP (171 mg, 1.40 mmol) and acetyl chloride (97 μL, 1.30 mmol) and the reaction mixture was stirred for 0.5 h at ambient temperature. The mixture was diluted with ethyl ether (30 mL), washed with 1 N HCl (10 mL), $NaHCO_3$ (10 mL) and dried ($MgSO_4$). Concentration under reduced pressure and purification by flash chromatography (silica gel, 50 → 60 % ethyl ether in petroleum ether) gave acetate **31** (414 mg, 90 %): White crystals (methylene chloride / petroleum ether), mp 137.5 - 138.0 °C; R_f = 0.39 (silica gel, 80 % ethyl ether in petroleum ether); $[\alpha]_D^{25}$ +3.1 (c = 1.07, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 6.81 (t, *J* = 2.1 Hz, 1 H, vinyl C*H*), 5.80 (s, 1 H, C*H*OAc), 4.85 (d, *J* = 9.5 Hz, 1 H, carbonate C*H*$_2$), 4.40 (dd, *J* = 16.8, 2.1 Hz, 1 H, allylic C*H*$_2$), 4.36 (dd, *J* = 16.8, 2.1 Hz, 1 H, allylic C*H*$_2$), 4.22 (d, *J* = 9.5 Hz, 1 H, carbonate C*H*$_2$), 4.19-4.12 (m, 2 H, ketal), 4.09-3.99 (m, 2 H, ketal), 2.18 (s, 3 H, acetate), 0.91 (s, 9 H, Si*t*-*Bu*Me$_2$), 0.09 (s, 3 H, Si*t*-Bu*Me*$_2$), 0.09 (s, 3 H, Si*t*-Bu*Me*$_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.2, 168.4, 153.2, 141.5, 139.1, 103.5, 83.0, 69.3, 67.5, 66.8, 66.4, 58.9, 25.8, 20.6, 18.3, -5.5, -5.5; IR (film) ν_{max} 2951, 2856, 1823, 1763, 1692, 1468, 1376, 1327, 1262, 1223, 1143, 1107, 1061, 1030, 998, 951, 836, 782 cm^{-1}; HRMS Calcd. for $C_{19}H_{28}O_9Si$ ($M+H^+$): 429.1581. Found: 429.1580.

Aziridine 32. To a solution of enone **31** (424 mg, 0.99 mmol) in benzene (5.0 mL) was added diphenylsulfilimine (398 mg, 1.98 mmol) and the mixture was heated at 55 °C for 1 h before being cooled, concentrated under reduced pressure and purified by flash chromatography (silica gel, 80 % ethyl ether in petroleum ether) to yield aziridine **32** (410 mg, 93 %): White crystals (methylene chloride / petroleum ether), mp 168.0 - 168.5 °C; R_f = 0.31 (silica gel, 80 % ethyl ether in petroleum ether); $[\alpha]_D^{25}$ +9.4 (c = 0.34, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 6.16 (s, 1 H, C*H*OAc), 4.70 (d, *J* = 9.3 Hz, 1 H, carbonate C*H*$_2$), 4.20 (d, *J* = 9.3 Hz, 1 H, carbonate C*H*$_2$), 4.15-4.03 (m, 4 H, ketal), 4.10 (d, *J* = 11.1 Hz, 1 H, C*H*$_2$OTBS), 4.00 (d, *J* = 11.1 Hz, 1 H, C*H*$_2$OTBS), 2.73 (s, 1 H, aziridine C*H*), 2.14 (s, 3 H, acetate), 2.0 (bs, 1 H, N*H*), 0.87 (s, 9 H, Si*t*-*Bu*Me$_2$), 0.08 (s, 3 H, Si*t*-Bu*Me*$_2$), 0.07 (s, 3 H, Si*t*-Bu*Me*$_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.7, 168.2, 153.4, 106.5, 83.0, 68.1, 67.5, 66.9, 66.6, 56.2, 45.1, 40.1, 25.7, 20.7, 18.1, -5.5, -5.5; IR (film) ν_{max} 3288, 2953, 2859, 1820, 1762, 1732, 1470, 1374, 1219, 1163, 1100, 1061, 909, 838, 782, 733 cm^{-1}; HRMS Calcd. for $C_{19}H_{29}O_9NSi$ ($M+H^+$): 444.1690. Found: 444.1690. Anal. Calcd. for $C_{19}H_{29}O_9NSi$: C, 51.45; H, 6.59; N, 3.16. Found: C, 51.42; H, 6.59; N, 3.15.

Alcohol 33. To a solution of silyl ether **32** (390 mg, 0.88 mmol) in THF (4.4 mL) in a polypropylene vessel at 0 °C was added hydrogen fluoride - pyridine (1.3 mL). The cooling bath was removed and after 0.25 h the mixture was poured cautiously into $NaHCO_3$ (60 mL), diluted with ethyl acetate (120 mL) and stirred for 0.1 h. The layers were separated and the organic phase was washed with $NaHCO_3$ (40 mL), NaCl (40 mL) and dried ($MgSO_4$). The solution was concentrated under reduced pressure to a small volume and petroleum ether (15 mL) was added dropwise. The white solid was collected by filtration (270

mg): White crystals (ethyl acetate); mp 179.5 - 181.0 °C (dec); R_f = 0.29 (silica gel, ethyl acetate); $[\alpha]_D^{25}$ +15.3 (c = 0.7, $CHCl_3$); ^1H NMR (500 MHz, DMSO-d_6) δ 5.72 (bs, 1 H, C*H*OAc), 5.11 (t, *J* = 5.9 Hz, 1 H, O*H*), 4.64 (d, *J* = 9.6 Hz, 1 H, carbonate C*H*$_2$), 4.40 (d, *J* = 9.6 Hz, 1 H, carbonate C*H*$_2$), 4.15-3.98 (m, 5 H, ketal and C*H*$_2$OH), 3.41-3.34 (bm, 1 H, C*H*$_2$OH), 3.26 (bd, *J* = 7.6 Hz, 1 H, N*H*), 2.82 (bd, *J* = 7.6 Hz, 1 H, aziridine C*H*), 2.14 (s, 3 H, acetate); ^{13}C NMR (125 MHz, DMSO-d_6) δ 199.1, 169.0, 153.2, 105.8, 83.3, 66.9, 66.1, 66.1, 57.4, 45.0, 41.0, 20.4; IR (film) ν_{max} 3335, 3264, 2965, 2902, 1795, 1752, 1483, 1427, 1379, 1328, 1220, 1176, 1056, 1022, 969 cm^{-1}; HRMS Calcd. for $C_{13}H_{15}O_9N$ (M+Cs^+): 461.9801. Found: 461.9809.

Acetate 34. To a solution of alcohol **33** (270 mg, 0.88 mmol) in methylene chloride (4.1 mL) was added pyridine (106 μL, 1.41 mmol), DMAP (10 mg, 0.09 mmol) and acetic anhydride (101 μL, 1.14 mmol). The reaction mixture was stirred for 0.5 h before being diluted with ethyl acetate (50 mL), washed with 1 N HCl (2 × 20 mL), $NaHCO_3$ (20 mL), NaCl (20 mL) and dried ($MgSO_4$). The solution was concentrated under reduced pressure to a small volume and petroleum ether was added dropwise. The white solid (**34**) was collected by filtration (294 mg, 90 % for two steps): White crystals (ethyl acetate / petroleum ether); mp 154.0 - 156.0 °C; R_f = 0.41 (silica gel, ethyl acetate); $[\alpha]_D^{25}$ +7.75 (c = 2.34, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 6.02 (s, 1 H, C*H*OAc), 4.68 (d, *J* = 9.4 Hz, 1 H, carbonate C*H*$_2$), 4.56 (d, *J* = 12.2 Hz, 1 H, C*H*$_2$OAc), 4.27 (bd, *J* = 12.2 Hz, 1 H, C*H*$_2$OAc), 4.21 (d, *J* = 9.4 Hz, 1 H, carbonate C*H*$_2$), 4.15-4.00 (m, 4 H, ketal), 2.88 (s, 1 H, aziridine C*H*), 2.13 (s, 3 H, acetate), 2.2-2.0 (bs, 1 H, N*H*), 2.07 (s, 3 H, acetate); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.8, 170.5, 168.4, 153.3, 105.8, 82.9, 67.9, 67.0, 66.6, 61.2, 43.5, 42.5, 20.6; IR (film) ν_{max} 3288, 2990, 2903, 1816, 1750, 1474, 1432, 1374, 1221, 1166, 1060, 912, 731 cm^{-1}; HRMS Calcd. for $C_{15}H_{17}O_{10}N$ (M+Cs^+): 503.9907. Found: 503.9910.

Trifluoroacetate 35. To a solution of aziridine **34** (429 mg, 1.16 mmol) in methylene chloride (5.8 mL) was added triethylamine (242 μL, 1.74 mmol), DMAP (14 mg, 0.12 mmol), and trifluoroacetic anhydride (196 μL, 1.41 mmol). The reaction mixture was stirred for 1 h before being diluted with ethyl acetate (50 mL), washed with 1 N HCl (10 mL), $NaHCO_3$ (10 mL), NaCl (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The unstable product was immediately subjected to the following reaction. A small sample was purified by flash chromatography (silica gel, 20 % acetone in chloroform) for the purpose of data collection: Colorless oil; R_f = 0.55 (silica gel, 30 % acetone in chloroform); ^1H NMR (500 MHz, C_6D_6) δ 5.57 (s, 1 H, C*H*OAc), 4.45 (q, *J* = 1.3 Hz, 1 H, aziridine C*H*), 4.04 (s, 2 H, C*H*$_2$OAc), 3.89 (d, *J* = 9.6 Hz, 1 H, carbonate C*H*$_2$), 3.74 (d, *J* = 9.6 Hz, 1 H, carbonate C*H*$_2$), 3.31-3.14 (m, 4 H, ketal), 1.55 (s, 3 H, acetate), 1.41 (s, 3 H, acetate); ^{13}C NMR (125 MHz, C_6D_6) δ 194.1, 169.5, 167.5, 152.6, 104.2, 89.4, 82.2, 72.8, 71.1, 67.4, 67.4, 66.1, 63.3, 53.5, 29.4, 19.5; IR (film) ν_{max} 2967, 2915, 1823, 1756, 1701, 1379, 1216, 1168, 1064, 757 cm^{-1}; HRMS Calcd. for $C_{17}H_{16}O_{11}NF_3$ (M+H^+): 468.0754. Found: 468.0750.

Tertiary alcohol 36. To a sample of crude aziridine **35** (530 mg), in THF (5 mL) and water (0.5 mL) was added TsOH (30 mg, 0.16 mmol). After stirring for 1 h, the reaction mixture was diluted with ethyl acetate (50 mL), washed with $NaHCO_3$ (10 mL), NaCl (10 mL) and dried ($MgSO_4$). Concentration

under reduced pressure and purification by flash chromatography (silica gel, 20 → 30 % acetone in chloroform) yielded **36** (449 mg, 80 % for two steps): Colorless oil; R_f = 0.23 (silica gel, 30 % acetone in chloroform); $[\alpha]_D^{25}$ +70.9 (c = 0.74, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.50 (d, *J* = 9.6 Hz, 1 H, N*H*), 5.97 (s, 1 H, C*H*OAc), 4.92 (bs, 1 H, tertiary O*H*), 4.73 (d, *J* = 9.3 Hz, 1 H, carbonate C*H*2), 4.59 (d, *J* = 9.3 Hz, 1 H, carbonate C*H*2), 4.44 (d, *J* = 9.6 Hz, 1 H, C*H*NHCOCF3), 4.37 (d, *J* = 11.9 Hz, 1 H, C*H*2OAc), 4.25 (d, *J* = 11.9 Hz, 1 H, C*H*2OAc), 4.14-4.02 (m, 4 H, ketal), 2.17 (s, 3 H, acetate), 2.06 (s, 3 H, acetate); ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.7, 170.4, 169.0, 157.8 (app d, *J* = 37.9 Hz), 152.8, 116.8, 114.5, 112.2, 105.0, 82.9, 75.8, 69.1, 67.5, 67.1, 66.0, 63.8, 53.2, 30.9, 29.1, 20.5, 20.5; IR (film) ν_{max} 3326, 3106, 2978, 2907, 1816, 1730, 1547, 1377, 1218, 1165, 1065, 913, 733 cm^{-1}; HRMS Calcd. for $C_{17}H_{18}O_{12}NF_3$ ($M+H^+$): 486.0859. Found: 486.0860.

Ketal 39. To a solution of **9** (220 g, 1.20 mol) in benzene (2.4 L) was added anhydrous copper sulfate (48 g, 300 mmol), acetaldehyde (134 mL, 2.40 mol) and Amberlyst-15 (22 g). The mixture was stirred at ambient temperature for 5 h before being filtered and concentrated under reduced pressure. Acetic acid (460 mL) and water (200 mL) were added and the mixture was left to stand for 14 h. The mixture was then diluted with ethyl ether (2.0 L), washed with 2 N NaOH (4 × 500 mL) and NaCl (500 mL). The aqueous phases were extracted with methylene chloride (2 × 500mL) and the combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The solid was recrystallized from methylene chloride (350 mL) and petroleum ether (500 mL) to give ketal **39** (174 g). A second crop yielded a further 32.2 g (87 % total yield): White crystals (ethyl ether); mp 99 - 100 °C; R_f = 0.46 (silica gel, 80 % ethyl ether in petroleum ether); ^1H NMR (500 MHz, $CDCl_3$) δ 6.77 (d, *J* = 2.9 Hz, 1 H, Ar), 6.42 (d, *J* = 2.9 Hz, 1 H, Ar), 5.14 (q, *J* = 5.1 Hz, 1 H, OC*H*O), 4.97 (d, *J* = 14.6 Hz, 1 H, ring benzylic C*H*2), 4.78 (d, *J* = 14.6 Hz, 1 H, ring benzylic C*H*2), 4.65 (d, *J* = 13.1 Hz, 1 H, C*H*2OH), 4.62 (d, *J* = 13.1 Hz, 1 H, C*H*2OH), 3.74 (s, 3 H, OC*H*3), 2.30 (s, 1 H, O*H*), 1.54 (d, *J* = 5.1 Hz, 3 H, CHC*H*3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.6, 144.5, 129.4, 121.1, 112.8, 108.6, 97.0, 66.3, 60.9, 55.6, 20.6; IR (film) ν_{max} 3449, 2942, 2867, 1611, 1481, 1404, 1220, 1102, 1048 cm^{-1}; HRMS Calcd. for $C_{11}H_{14}O_4$ ($M+Cs^+$): 342.9946. Found: 342.9952.

Nitrobenzene derivative 40. To a solution of ketal **39** (213 g, 1.01 mol) in acetic acid (1.0 L) was added nitric acid (71 mL, 15.8 M) in a dropwise fashion over a period of 0.2 h. A large exotherm at the midpoint of the addition was controlled with an ice bath such that the internal temperature did not exceed 30 °C. Shortly after completion of the addition, the product precipitated. The mixture was stirred for a further 0.2 h and filtered. The solid was washed with H_2O (1.5 L) and the mother liquor was further diluted with H_2O (1 L) and cooled to -20 °C for 4 h. A second crop of product was thus recovered, washed with H_2O (1 L) and the combined solid was dried *in vacuo* to give **40** (233 g, 90 %). The material can be recrystallized from methylene chloride (10mL / g) and petroleum ether (20 mL / g): Yellow crystals (methylene chloride), mp 145.5 - 146.0 °C; R_f = 0.36 (silica gel, 80 % ethyl ether in petroleum ether); ^1H NMR (500 MHz, $CDCl_3$) δ 7.08 (s, 1 H, Ar), 5.17 (q, *J* = 5.1 Hz, 1 H, OC*H*O), 5.02 (d, *J* = 15.8 Hz, 1 H, ring benzylic C*H*2), 4.79 (d, *J* = 15.8 Hz, 1 H, ring benzylic C*H*2), 4.74 (d, *J* = 14.5 Hz, 1 H, C*H*2OH), 4.70 (d, *J* = 14.5 Hz, 1 H, C*H*2OH), 3.89 (s, 3 H, OC*H*3), 2.11 (bs, 1 H, O*H*), 1.56 (d, *J* = 5.1 Hz, 3 H,

$CHCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.2, 143.6, 136.2, 133.3, 115.2, 111.2, 97.3, 64.1, 60.0, 57.0, 20.5; IR (film) ν_{max} 3518, 2901, 1610, 1600, 1518, 1459, 1407, 1348, 1293, 1227, 1093 cm^{-1}; HRMS Calcd. for $C_{11}H_{13}NO_6$ ($M+Cs^+$): 387.9797. Found: 387.9800. Anal. Calcd. for $C_{11}H_{13}NO_6$: C, 51.77; H, 5.13; N, 5.49. Found: C, 51.92; H, 5.11; N, 5.26.

Aniline derivative 41. To a solution of **40** (61 g, 240 mmol) in methanol (2.8 L) was added potassium carbonate (2.8 g, 20 mmol) and platinum oxide (500 mg, 22 mmol). The vessel was evacuated (20 torr) and flushed with argon three times. The reaction mixture was then stirred vigorously under an atmosphere of hydrogen (1 - 2 atm) until TLC analysis (ethyl ether) indicated that the reaction was complete. The mixture was filtered through a pad of silica gel and concentrated under reduced pressure. Crystallization from ethyl acetate (300 mL) gave aniline derivative **41** as an off white solid (43 g, 80 %): White solid (ethyl acetate / petroleum ether); mp 125.5 - 126.0 °C; $R_f = 0.33$ (silica gel, ethyl ether); ^1H NMR (500 MHz, $CDCl_3$) δ 6.69 (s, 1 H, Ar), 5.09 (q, $J = 5.1$ Hz, 1 H, $OCHO$), 4.79 (d, $J = 14.2$ Hz, 1 H, ring benzylic CH_2), 4.72 (d, $J = 14.2$ Hz, 1 H, ring benzylic CH_2), 4.61 (d, $J = 12.3$ Hz, 1 H, CH_2OH), 4.56 (d, $J = 12.3$ Hz, 1 H, CH_2OH), 3.81 (s, 3 H, OCH_3), 3.8-2.5 (bs, 3 H, NH_2 and OH), 1.55 (d, $J = 5.1$ Hz, 3 H, $CHCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.2, 140.8, 131.5, 117.0, 110.1, 107.0, 96.4, 63.7, 60.8, 56.1, 20.6; IR (film) ν_{max} 3308, 3223, 2905, 2843, 1627, 1496, 1457, 1407, 1358, 1305, 1259, 1157, 1100, 1038, 906, 849 cm^{-1}; HRMS Calcd. for $C_{11}H_{15}NO_4$ (M^+): 225.1001. Found: 225.1000.

Silyl ether 42. To a solution of alcohol **41** (23.4 g, 104 mmol) in DMF (350 mL) was added imidazole (9.90 g, 146 mmol), DMAP (635 mg, 5.2 mmol) and TBSCl (17.26 g, 114 mmol). The mixture was left to stand for 3 h before being quenched with anhydrous methanol (30 mL). After 0.25 h, the reaction mixture was diluted with ethyl ether (1 L), washed with H_2O (500 mL), $NaHCO_3$ (500 mL) and dried ($MgSO_4$). The mixture was concentrated under reduced pressure and placed under high vacuum (0.03 torr) for 36 h to yield crude silyl ether **42** (37.0 g, 100 %) as an off white solid. A small sample was purified by flash chromatography (silica gel, 40 → 50 % ethyl ether in petroleum ether) for the purpose of data collection: White crystals (neat); mp 65 - 67.5 °C; $R_f = 0.26$ (silica gel, 40 % ethyl ether in petroleum ether); ^1H NMR (500 MHz, $CDCl_3$) δ 6.86 (s, 1 H, Ar), 5.05 (q, $J = 5.1$ Hz, 1 H, $OCHO$), 4.79 (d, $J = 14.1$ Hz, 1 H, ring benzylic CH_2), 4.73 (d, $J = 14.1$ Hz, 1 H, ring benzylic CH_2), 4.70 (d, $J = 13.0$ Hz, 1 H, CH_2OTBS), 4.65 (d, $J = 13.0$ Hz, 1 H, CH_2OTBS), 3.82 (s, 3 H, OCH_3), 3.7-3.4 (bs, 2 H, NH_2), 1.53 (d, $J = 5.1$ Hz, 3 H, $CHCH_3$) 0.95 (s, 9 H, Si^tBuMe_2), 0.11 (s, 6 H, Si^tBuMe_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.8, 141.1, 130.4, 117.7, 108.9, 106.8, 96.2, 63.7, 59.3, 56.0, 26.0, 20.6, 18.4, -5.2; IR (film) ν_{max} 3454, 3366, 2934, 2856, 1628, 1497, 1464, 1406, 1364, 1263, 1156, 1103, 1045, 910, 841, 778 cm^{-1}; HRMS Calcd. for $C_{17}H_{29}NO_4Si$ (M^+): 339.1866. Found: 339.1870.

Urethane 43. To a solution of crude amine **42** (37.0 g, 104 mmol) in methylene chloride (350 mL) was added triethylamine (57.9 mL, 416 mmol), and DMAP (635 mg, 5.2 mmol) and the mixture was cooled to 0 °C. Phosgene (65 mL, 1.93 M in toluene, 125 mmol) was cautiously added and the reaction mixture was allowed to warm to ambient temperature. After 1 h, methanol (50 mL) was added and the reaction mixture was left to stand for 0.5 h before being diluted with ethyl ether (1 L), washed with 1 N HCl (2 × 300 mL),

$NaHCO_3$ (300 mL), NaCl (300 mL) and dried ($MgSO_4$). The mixture was concentrated under reduced pressure and placed under high vacuum (0.03 torr) until the residue solidified. The solid was dissolved in the minimum amount of methylene chloride (*ca* 30 mL) and petroleum ether (100 mL) was added. After cooling to -20 °C for 24 h, the product was filtered (27.42 g) and the mother liquor was concentrated under reduced pressure and purified by flash chromatography (silica gel, 30 % ethyl ether in petroleum ether) to yield a further 2.11 g of urethane **43** (72 % for two steps): Colorless rhombohedral crystals (ethyl ether and petroleum ether); mp 85.5 - 86.0 °C; R_f = 0.74 (silica gel, 70 % ethyl ether in petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.00 (s, 1 H, Ar), 6.4-6.3 (bs, 1 H, N*H*), 5.17 (q, *J* = 5.0 Hz, 1 H, OC*H*O), 5.00 (bd, *J* = 14.7 Hz, 1 H, ring benzylic CH_2), 4.71 (d, *J* = 14.7 Hz, 1 H, ring benzylic CH_2), 4.71 (s, 2 H, CH_2OTBS), 3.79 (s, 3 H, OCH_3), 3.74 (s, 3 H, OCH_3), 1.52 (d, *J* = 5.0 Hz, 3 H, CHCH_3), 0.96 (s, 9 H, Si^t*Bu*Me$_2$), 0.11 (s, 6 H, Si^{t}Bu*Me*$_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.1, 146.6, 142.9, 127.1, 119.8, 117.9, 108.0, 96.7, 65.1, 59.4, 55.8, 52.7, 25.9, 20.7, 18.4, -5.3; IR (film) ν_{max} 3314, 2950, 2857, 1734, 1614, 1511, 1463, 1408, 1352, 1252, 1079, 907, 842, 777 cm^{-1}; HRMS Calcd. for $C_{19}H_{31}NO_6Si$ (M+Cs$^+$): 530.0975. Found: 530.0965. Anal. Calcd. for $C_{19}H_{31}NO_6Si$: C, 57.4; H, 7.86; N, 3.52. Found: C, 57.18; H, 8.17; N, 3.30.

Quinone monoketal 44. To a solution of **43** (27.4 g, 69.0 mmol) in 1,4-dioxane (260 mL) and ethylene glycol (86 mL) at 0 °C was added ammonium cerium(IV) nitrate (75.7 g, 138 mmol). After 0.2 h the cooling bath was removed and stirring continued for a further 0.25 h. The mixture was then left to stand for a further 1.5 h before being diluted with ethyl ether (1200 mL) and washed with H_2O (300 mL). The aqueous phase was extracted with ethyl ether (300 mL) and the combined organic phases were washed with $NaHCO_3$ (3 × 300 mL), NaCl (300 mL) and dried ($MgSO_4$). After concentration under reduced pressure the residue was redissolved in methylene chloride (200 mL) and silica gel (60 g) was added. The slurry was stirred for 14 h before being filtered and concentrated under reduced pressure. Crystallization from benzene (50 mL) yielded compound **44** (5.44 g). Purification of the mother liquor by flash chromatography (silica gel, 40 → 60 → 70 % ethyl ether in petroleum ether) yielded a further 2.16 g of **44** (30 %): White crystals (benzene); mp 178 - 179 °C (dec); R_f = 0.58 (silica gel, ethyl ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.65 (bs, 1 H, N*H*), 6.59 (t, *J* = 2.2 Hz, 1 H, vinyl C*H*), 5.15 (s, 2 H, cyclic allylic CH_2), 4.42 (d, *J* = 2.2 Hz, 2 H, CH_2OTBS), 4.40-4.35 (m, 2 H, ketal), 4.26-4.21 (m, 2 H, ketal), 0.92 (s, 9 H, Si^t*Bu*Me$_2$), 0.09 (s, 6 H, Si^{t}Bu*Me*$_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 181.2, 151.3, 145.7, 137.2, 132.1, 107.5, 97.4, 66.2, 65.7, 59.1, 25.9, 18.4, -5.4; IR (film) ν_{max} 3234, 3162, 2953, 1739, 1698, 1636, 1480, 1415, 1333, 1255, 1222, 1131, 1052 cm^{-1}; HRMS Calcd. for $C_{17}H_{25}O_6NSi$ (M+Cs$^+$): 500.0505. Found: 500.0503.

PMB urethane 45. To a solution of amide **44** (3.45 g, 9.4 mmol) in DMF (47 mL) was added finely ground potassium carbonate (2.59 g, 18.8 mmol) and *p*-methoxybenzyl bromide (7.05 mL, 2 M solution in benzene, 14.1 mmol). The reaction mixture was was stirred for 3.5 h before being diluted with ethyl acetate (250 mL), washed with H_2O (50 mL), NaCl (50 mL) and dried ($MgSO_4$). Concentration under reduced pressure and purification by flash chromatography (silica gel, 40 → 50 % ethyl ether in petroleum ether) yielded **45** (4.12 g, 90 %): Colorless oil; R_f = 0.53 (silica gel, 70 % ethyl ether in petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.7 Hz, 2 H, Ar), 6.84 (d, *J* = 8.7 Hz, 2 H, Ar), 6.64 (t, *J* = 2.2 Hz, 1 H, vinyl C*H*), 4.94 (s, 2 H, benzylic CH_2 or cyclic allylic CH_2), 4.91 (s, 2 H, benzylic CH_2 or cyclic

allylic CH_2), 4.44 (d, J = 2.2 Hz, 2 H, CH_2OTBS), 4.29-4.21 (m, 4 H, ketal), 3.78 (s, 3 H, OCH_3), 0.93 (s, 9 H, Si^t*Bu*Me$_2$), 0.09 (s, 6 H, Si^{t}Bu*Me*$_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 181.4, 158.9, 152.3, 145.7, 135.4, 132.0, 129.6, 128.5, 113.8, 113.6, 99.8, 64.4, 62.0, 58.7, 55.2, 47.8, 25.8, 18.3, -5.4; IR ($CHCl_3$) ν_{max} 1738, 1689, 1635, 1514, 1418, 1248, 1162, 1132 cm^{-1}; HRMS Calcd. for $C_{25}H_{33}O_7NSi$ (M+Cs$^+$): 620.1081. Found: 620.1075.

Allylic alcohol 46. To a solution of silyl ether **45** (2.48 g, 5.09 mmol) in THF (20 mL) in a polypropylene vessel at 0 °C was added hydrogen fluoride - pyridine (7.6 mL) portionwise over 0.2 h. After 1 h the mixture was poured cautiously into a saturated solution of $NaHCO_3$ (250 mL) and diluted with ethyl acetate (250 mL). After stirring for 0.1 h, the layers were separated and the organic phase was washed with $NaHCO_3$ (50 mL) and NaCl (100 mL). The aqueous phases were extracted with methylene chloride (2 × 100 mL) and the combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was dissolved in methylene chloride (20 mL) and pure alcohol **46** (1.76 g, 93 %) was precipitated by the dropwise addition of petroleum ether (40 mL): White crystals (toluene); mp 155.5 - 156.5 °C (prior yellowing); R_f = 0.33 (silica gel, 20 % acetone in chloroform); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (d, J = 8.7 Hz, 2 H, Ar), 6.84 (d, J = 8.7 Hz, 2 H, Ar), 6.59 (t, J = 1.6 Hz, 1 H, vinyl C*H*), 4.94 (s, 2 H, benzylic CH_2 or cyclic allylic CH_2), 4.89 (s, 2 H, benzylic CH_2 or cyclic allylic CH_2), 4.40 (d, J = 1.6 Hz, 2 H, CH_2OH), 4.31-4.20 (m, 4 H, ketal), 3.78 (s, 3 H, OCH_3), 2.3-2.2 (bs, 1 H, O*H*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 181.9, 158.9, 152.3, 145.9, 134.5, 133.3, 129.4, 128.5, 113.8, 113.5, 99.5, 64.5, 62.0, 59.5, 55.2, 47.8; IR (film) ν_{max} 3438, 2909, 1728, 1690, 1634, 1513, 1415, 1246, 1162, 1135, 732 cm^{-1}; HRMS Calcd. for $C_{19}H_{19}NO_7$ (M+Cs$^+$): 506.0216. Found: 506.0214. Anal. Calcd. for $C_{19}H_{19}NO_7$: C, 61.12; H, 5.13; N, 3.75. Found: C, 61.11; H, 5.00; N, 3.86.

Epoxide 47. A solution of allylic alcohol **46** (1.75 g, 4.69 mmol) in methylene chloride (7.2 mL) was stirred with pre-dried 4Å molecular sieves (530 mg) and di-isopropyl-D-tartrate (65 μL, 0.59 mmol) for 4 h. The mixture was cooled to -30 °C, treated with titanium tetraisopropoxide (73 μL, 0.47 mmol) and allowed to warm to -3 °C over 0.5 h. The mixture was then re-cooled to -20 °C and treated with ^{t}butyl hydroperoxide (2.15 mL, *ca* 5.5 M in methylene chloride, 11.8 mmol). The reaction mixture was stirred for 14 h at 0 °C before being quenched with H_2O (10 mL), diluted with ethyl acetate (10 mL) and stirred for 1 h. The mixture was filtered through a pad of Celite® and further diluted with ethyl acetate (150 mL). The layers were separated and the organic phase was washed with $Na_2S_2O_4$ (2 × 50 mL, 15 % w/w aqueous solution), $NaHCO_3$ (50 mL), NaCl (50 mL) and dried ($MgSO_4$). Concentration under reduced pressure and purification by flash chromatography (silica gel, 10 → 20 % acetone in methylene chloride) gave pure epoxide **47** (1.64 g, 90 %) as a white foam: White crystals (methanol); mp 166.0 - 166.5 °C; R_f = 0.37 (silica gel, 20 % acetone in chloroform); $[\alpha]_D^{25}$ -41.7 (c = 1.10, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 (d, J = 8.7 Hz, 2 H, Ar), 6.85 (d, J = 8.7 Hz, 2 H, Ar), 4.92 (app d, J = 14.2 Hz, 2 H, benzylic CH_2 and allylic CH_2), 4.72 (d, J = 15.1 Hz, 1 H, benzylic CH_2 or allylic CH_2), 4.69 (d, J = 13.9 Hz, 1 H, benzylic CH_2 or allylic CH_2), 4.45-4.33 (m, 3 H, ketal), 4.25-4.17 (m, 1 H, ketal), 4.15 (bd, J = 13.5 Hz, 1 H, CH_2OH), 4.05 (bd, J = 13.5 Hz, 1 H, CH_2OH), 3.79 (s, 3 H, OCH_3), 3.77 (s, 1 H, epoxide C*H*), 2.0-1.9 (bs, 1 H, O*H*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 188.8, 159.1, 152.3, 145.0, 129.1, 128.7, 114.0, 113.3,

102.3, 65.2, 65.0, 62.2, 58.6, 58.0, 55.7, 55.3, 48.6; IR (film) ν_{max} 3557, 2912, 1737, 1662, 1513, 1412, 1246, 1158, 1076, 1025, 750 cm^{-1}; HRMS Calcd. for $C_{19}H_{19}O_8N$ (M+Cs^+): 522.0165. Found: 522.0179.

Urethane 48. To a solution of epoxy alcohol **47** (862 mg, 2.20 mmol) in methylene chloride (11 mL) was added triethylamine (400 µL, 2.86 mmol) and phenyl isocyanate (265 µL, 2.42 mmol). After 0.1 h the reaction mixture was diluted with ethyl acetate (100 mL) and washed with 1 N HCl (2 × 30 mL), $NaHCO_3$ (30 mL), NaCl (30 mL) and dried ($MgSO_4$). Concentration under reduced pressure and purification by flash chromatography (silica gel, 80 % ethyl ether in petroleum ether then ethyl ether) yielded pure urethane **48** (1.06 g, 94 %) as a white foam: White crystals (methylene chloride and ethyl ether); mp 161.0 - 164.0 °C (prior yellowing); R_f = 0.43 (silica gel, ethyl ether); $[\alpha]_D^{25}$ -18.4 (c = 0.99, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.38-7.34 (m, 1 H, Ph), 7.33-7.29 (m, 3 H, Ph), 7.23 (d, *J* = 8.7 Hz, 2 H, PMB Ar), 7.10-7.06 (m, 1 H, Ph), 6.85 (bs, 1 H, N*H*), 6.85 (d, *J* = 8.7 Hz, 2 H, PMB Ar), 4.94 (d, *J* = 13.9 Hz, 1 H, benzylic C*H*$_2$, C*H*$_2$OC(O)NHPh or allylic C*H*$_2$), 4.91 (d, *J* = 14.0 Hz, 1 H, benzylic C*H*$_2$, C*H*$_2$OC(O)NHPh or allylic C*H*$_2$), 4.77 (d, *J* = 12.6 Hz, 1 H, benzylic C*H*$_2$, C*H*$_2$OC(O)NHPh or allylic C*H*$_2$), 4.71 (d, *J* = 14.0 Hz, 1 H, benzylic C*H*$_2$, C*H*$_2$OC(O)NHPh or allylic C*H*$_2$), 4.70 (d, *J* = 13.9 Hz, 1 H, benzylic C*H*$_2$, C*H*$_2$OC(O)NHPh or allylic C*H*$_2$), 4.53 (bd, *J* = 12.6 Hz, 1 H, benzylic C*H*$_2$, C*H*$_2$OC(O)NHPh or allylic C*H*$_2$), 4.41-4.30 (m, 3 H, ketal), 4.21-4.16 (m, 1 H, ketal), 3.80 (s, 1 H, epoxide C*H*), 3.78 (s, 3 H, OC*H*$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 186.9, 159.0, 152.5, 152.2, 144.7, 137.3, 129.1, 129.0, 128.6, 123.8, 118.6, 113.9, 113.1, 102.0, 65.2, 65.0, 62.2, 59.8, 57.0, 55.2, 48.5; IR (film) ν_{max} 3338, 2964, 2910, 1735, 1665, 1605, 1537, 1515, 1444, 1413, 1384, 1348, 1315, 1219, 1160, 1095, 1065, 1025, 908, 731 cm^{-1}; HRMS Calcd. for $C_{26}H_{24}O_9N_2$ (M+Cs^+): 641.0536. Found: 641.0555.

Carbonate 49. To a solution of epoxy urethane **48** (1.06 g, 2.02 mmoL) in methylene chloride (10 mL) at 0 °C was added boron trifluoride etherate (281 µL, 2.22 mmoL) and the mixture was allowed to warm to ambient temperature. After 0.3 h, acetic acid (1.0 mL, 50 % v/v aqueous solution) and ethyl acetate (10 mL) were added and the mixture was stirred for a further 0.6 h. The mixture was diluted with ethyl acetate (100 mL), washed with H_2O (20 mL), $NaHCO_3$ (2 × 20 mL) and NaCl (20 mL). The aqueous phases were extracted with methylene chloride (2 × 20 mL) and the combined organic phases were dried ($MgSO_4$). Concentration under reduced pressure and purification by flash chromatography (silica gel, 10 → 20 % acetone in chloroform) gave carbonate **49** (771 mg, 86 %): White crystals (methylene chloride / ethyl ether); mp 115 - 135 °C; R_f = 0.75 (silica gel, ethyl acetate); $[\alpha]_D^{25}$ +100.7 (c = 0.87, $CHCl_3$); ^1H NMR (500 MHz, DMSO-d_6) δ 7.17 (d, *J* = 8.7 Hz, 2 H, Ar), 7.01 (d, *J* = 6.1 Hz, 1 H, O*H*), 6.86 (d, *J* = 8.7 Hz, 2 H, Ar), 4.99 (d, *J* = 14.0 Hz, 1 H, benzylic C*H*$_2$ or allylic C*H*$_2$), 4.79 (d, *J* = 14.0 Hz, 1 H, benzylic C*H*$_2$ or allylic C*H*$_2$), 4.75 (d, *J* = 9.0 Hz, 1 H, carbonate C*H*$_2$), 4.69 (d, *J* = 15.9 Hz, 1 H, benzylic C*H*$_2$ or allylic C*H*$_2$), 4.65 (d, *J* = 15.9 Hz, 1 H, benzylic C*H*$_2$ or allylic C*H*$_2$), 4.52 (d, *J* = 9.0 Hz, 1 H, carbonate C*H*$_2$), 4.50 (d, *J* = 6.1 Hz, 1 H, C*H*OH), 4.39-4.25 (m, 2 H, ketal), 4.09-4.04 (m, 2 H, ketal), 3.72 (s, 3 H, OC*H*$_3$); ^{13}C NMR (125 MHz, DMSO-d_6) δ 187.1, 158.2, 153.9, 151.4, 150.0, 129.4, 127.8, 113.6, 105.2, 83.9, 79.2, 72.7, 67.6, 67.4, 66.6, 62.0, 55.0, 48.5; IR (film) ν_{max} 3404, 2967, 2914, 2838, 1806, 1738, 1671, 1627, 1512, 1409, 1382, 1347, 1243, 1173, 1087, 1056, 947, 752 cm^{-1}; HRMS Calcd.

for $C_{20}H_{19}O_{10}N$ ($M+Na^+$): 456.0907. Found: 456.0903. Anal. Calcd. for $C_{20}H_{19}O_{10}N$: C, 55.43; H, 4.42; N, 3.23. Found: C, 55.19; H, 4.08; N, 3.17.

THP ether 50. To a solution of alcohol **49** (759 mg, 1.75 mmol) in chloroform (8.8 mL) was added dihydropyran (480 μL, 5.25 mmol) and PPTS (44 mg, 0.18 mmol) and the mixture heated at reflux for 16 h. After cooling to ambient temperature, the mixture was diluted with ethyl acetate (100 mL) and washed with $NaHCO_3$ (30 mL), NaCl (30 mL) and dried ($MgSO_4$). After concentration under reduced pressure, the solid was triturated with ethyl ether (2 × 20 mL) and purified by flash chromatography (silica gel, 2.5 → 5 % acetone in methylene chloride) to yield the less polar isomer (456 mg) and the more polar isomer (367 mg), (90 % total yield of **50**).

50 (Less polar isomer): White crystals (methylene chloride / ethyl ether); mp 195.0 - 197.5 (dec); R_f = 0.40 (silica gel, 5 % acetone in chloroform); $[\alpha]_D^{25}$ +104.8 (c = 1.47, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.19 (d, *J* = 8.7 Hz, 2 H, Ar), 6.84 (d, *J* = 8.7 Hz, 2 H, Ar), 5.06 (d, *J* = 14.2 Hz, 1 H, benzylic C*H*$_2$ or allylic C*H*$_2$), 4.90 (d, *J* = 15.0 Hz, 1 H, benzylic C*H*$_2$ or allylic C*H*$_2$), 4.90 (d, *J* = 9.1 Hz, 1 H, carbonate C*H*$_2$), 4.75-4.69 (m, 2 H, THP anomeric C*H* and ketal), 4.66 (d, *J* = 15.0 Hz, 1 H, benzylic C*H*$_2$ or allylic C*H*$_2$), 4.63 (d, *J* = 14.2 Hz, 1 H, benzylic C*H*$_2$ or allylic C*H*$_2$), 4.62 (s, 1 H, C*H*OTHP), 4.46-4.42 (m, 1 H, ketal), 4.28 (d, *J* = 9.1 Hz, 1 H, carbonate C*H*$_2$), 4.20-4.12 (m, 2 H, ketal), 4.05-4.00 (m, 1 H, THP), 3.79 (s, 3 H, OC*H*$_3$), 3.54-3.47 (m, 1 H, THP), 1.9-1.5 (m, 6 H, THP); ^{13}C NMR (125 MHz, $CDCl_3$) δ 186.1, 159.1, 153.3, 151.5, 151.2, 128.7, 128.5, 114.0, 113.6, 105.1, 102.4, 83.8, 78.0, 68.0, 67.5, 67.3, 65.9, 61.5, 55.2, 49.0, 31.4, 24.8, 21.2; IR (film) ν_{max} 2944, 2859, 1816, 1745, 1674, 1628, 1513, 1408, 1245, 1171, 1062, 1034, 952 cm^{-1}; HRMS Calcd. for $C_{25}H_{27}O_{11}N$ ($M+Cs^+$): 650.0638. Found: 650.0629.

50 (More polar isomer): White crystals (methylene chloride / ethyl ether); mp 184.0 - 185.5 °C (dec); R_f = 0.28 (silica gel, 5 % acetone in chloroform); $[\alpha]_D^{25}$ +19.0 (c = 0.97, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.17 (d, *J* = 8.7 Hz, 2 H, Ar), 6.85 (d, *J* = 8.7 Hz, 2 H, Ar), 4.98 (d, *J* = 14.2 Hz, 1 H, benzylic C*H*$_2$ or allylic C*H*$_2$), 4.90 (obs, 1 H, THP anomeric C*H*), 4.89 (d, *J* = 15.2 Hz, 1 H, benzylic C*H*$_2$ or allylic C*H*$_2$), 4.83 (d, *J* = 9.0 Hz, 1 H, carbonate C*H*$_2$), 4.77 (d, *J* = 14.2 Hz, 1 H, benzylic C*H*$_2$ or allylic C*H*$_2$), 4.76 (d, *J* = 15.2 Hz, 1 H, benzylic C*H*$_2$ or allylic C*H*$_2$), 4.53 (s, 1 H, C*H*OTHP), 4.40-4.26 (m, 3 H, ketal and carbonate C*H*$_2$), 4.17-4.08 (m, 2 H, ketal), 3.93-3.88 (m, 1 H, THP), 3.79 (s, 3 H, OC*H*$_3$), 3.60-3.55 (m, 1 H, THP), 1.85-1.72 (m, 2 H, THP), 1.65-1.53 (m, 4 H, THP); ^{13}C NMR (125 MHz, $CDCl_3$) δ 186.5, 159.0, 153.6, 151.6, 151.1, 128.4, 128.2, 114.0, 106.1, 100.8, 82.5, 78.0, 67.6, 67.4, 67.3, 63.3, 61.8, 55.2, 49.1, 30.9, 24.6, 19.3; IR (film) ν_{max} 2949, 1813, 1745, 1671, 1629, 1513, 1410, 1246, 1172, 1065, 1036, 952 cm^{-1}; HRMS Calcd. for $C_{25}H_{27}O_{11}N$ ($M+Cs^+$): 650.0638. Found: 650.0621.

Acetonitrile adduct 51. To a solution of ^{t}butyl lithium (382 μL, 1.7 M in pentane, 0.65 mmol) in THF (2.7 mL) at -78 °C was added acetonitrile (37 μL, 0.70 mmol). After 90 s, the solution was transferred rapidly *via* cannula to a solution of ketone **50** (more polar isomer) (280 mg, 0.54 mmol) in THF (5.4 mL) at -78 °C. After 0.1 h, the reaction was quenched by the addition of a saturated solution of NH_4Cl (5 mL), H_2O (5 mL) and ethyl acetate (5 mL). After warming to ambient temperature, the mixture was diluted with ethyl

acetate (70 mL) and the layers were separated. The organic phase was washed with NaCl (30 mL) and dried ($MgSO_4$). Concentration under reduced pressure and purification by flash chromatography (silica gel, 10 → 20 % acetone in chloroform) gave adduct **51** (279 mg, 92 %): White solid; R_f = 0.30 (silica gel, 20 % acetone in chloroform); $[\alpha]_D^{25}$ -37.8 (c = 1.95, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20 (d, *J* = 8.7 Hz, 2 H, Ar), 6.84 (d, *J* = 8.7 Hz, 2 H, Ar), 4.96 (d, *J* = 9.2 Hz, 1 H, carbonate C*H*$_2$), 4.79 (d, *J* = 14.1 Hz, 1 H, benzylic C*H*$_2$ or allylic C*H*$_2$), 4.78-4.76 (m, 1 H, THP anomeric C*H*), 4.70 (d, *J* = 15.1 Hz, 1 H, benzylic C*H*$_2$ or allylic C*H*$_2$), 4.69 (d, *J* = 14.1 Hz, 1 H, benzylic C*H*$_2$ or allylic C*H*$_2$), 4.68 (d, *J* = 9.2 Hz, 1 H, carbonate C*H*$_2$), 4.62 (d, *J* = 15.1 Hz, 1 H, benzylic C*H*$_2$ or allylic C*H*$_2$), 4.35-4.30 (m, 3 H, C*H*OTHP, O*H* and/or ketal), 4.22-4.12 (m, 3 H, O*H* and/or ketal), 3.96-3.91 (m, 1 H, THP), 3.79 (s, 3 H, OC*H*3) 3.58-3.54 (m, 1 H, THP), 3.07 (d, *J* = 17.1 Hz, 1 H, C*H*$_2$CN), 2.90 (d, *J* = 17.1 Hz, 1 H, C*H*$_2$CN), 1.86-1.75 (m, 2 H, THP), 1.65-1.53 (m, 4 H, THP); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.8, 154.7, 154.6, 134.0, 128.9, 128.2, 128.1, 118.4, 116.1, 113.8, 106.2, 101.5, 86.7, 78.1, 73.2, 67.2, 66.8, 65.6, 63.8, 62.5, 55.2, 47.7, 31.2, 26.3, 24.7, 19.7; IR (film) ν_{max} 3382, 2925, 2248, 1808, 1723, 1512, 1246, 1179, 1070, 1032 cm^{-1}. HRMS Calcd. for $C_{27}H_{30}O_{11}N_2$ (M+Na$^+$): 581.1747. Found: 581.1760.

Acrylonitrile 52. To a solution of tertiary alcohol **51** (217 mg, 0.389 mmol) in methylene chloride (3.9 mL) was added triethylamine (174 μL, 1.21 mmol), DMAP (4.8 mg, 0.04 mmol) and acetic anhydride (48 μL, 0.51 mmol). The mixture was left to stand for 5 d before being diluted with ethyl acetate (40 mL), washed with 1 N HCl (15 mL), $NaHCO_3$ (15 mL), NaCl (15 mL) and dried ($MgSO_4$). Concentration under reduced pressure and purification by flash chromatography (silica gel, 5 % acetone in chloroform) yielded **52** (172 mg, 82 %): Colorless oil; R_f = 0.48 (silica gel, 10 % acetone in chloroform); $[\alpha]_D^{25}$ -133 (c = 4.35, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.18 (d, *J* = 8.7 Hz, 2 H, Ar), 6.86 (d, *J* = 8.7 Hz, 2 H, Ar), 5.63 (s, 1 H, C*H*CN), 5.27 (d, *J* = 14.1 Hz, 1 H, allylic C*H*$_2$), 5.11 (d, *J* = 9.1 Hz, 1 H, carbonate C*H*$_2$), 5.01 (d, *J* = 14.1 Hz, 1 H, allylic C*H*$_2$), 4.85 (d, *J* = 14.9 Hz, 1 H, benzylic C*H*$_2$), 4.85-4.83 (m, 1 H, THP anomeric C*H*), 4.78 (d, *J* = 14.9 Hz, 1 H, benzylic C*H*$_2$), 4.43-4.38 (m, 1 H, ketal), 4.30 (s, 1 H, C*H*OTHP), 4.26-4.22 (m, 1 H, ketal), 4.20-4.11 (m, 2 H, ketal), 4.17 (d, *J* = 9.1 Hz, 1 H, carbonate C*H*$_2$), 3.97-3.93 (m, 1 H, THP), 3.80 (s, 3 H, OC*H*3), 3.59-3.55 (m, 1 H, THP), 1.82-1.76 (m, 2 H, THP), 1.65-1.55 (m, 4 H, THP); ^{13}C NMR (125 MHz, $CDCl_3$) δ 128.5, 122.1, 114.1, 92.7, 78.9, 69.4, 67.0, 63.9, 63.4, 55.3, 48.3, 47.2, 31.2, 24.7, 19.7; IR (film) ν_{max} 2925, 2854, 2213, 1817, 1736, 1613, 1513, 1376, 1246, 1178, 1069, 1034, 950 cm^{-1}. HRMS Calcd. for $C_{27}H_{28}O_{10}N_2$ (M+Na$^+$): 563.1642. Found: 563.1660.

Diol 53. To a solution of carbonate **52** (131 mg, 0.25 mmol) in THF (2.5 mL) and ethylene glycol (125 μL) was added lithium hydride (2.0 mg, 0.25 mmol). The reaction mixture was stirred for 1.25 h before being diluted with ethyl acetate (45 mL), washed with H_2O (2 × 10 mL), NaCl (10 mL) and dried ($MgSO_4$). Concentration under reduced pressure and purification by flash chromatography (silica gel, 5 → 10 % acetone in chloroform) gave diol **53** (100 mg, 80 %): White solid; R_f = 0.54 (silica gel, 20 % acetone in chloroform); $[\alpha]_D^{25}$ -128 (c = 3.45, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.18 (d, *J* = 8.6 Hz, 2 H, Ar), 6.84 (d, *J* = 8.6 Hz, 2 H, Ar), 5.88 (s, 1 H, C*H*CN), 5.39 (d, *J* = 13.9 Hz, 1 H, allylic C*H*$_2$), 5.29 (s, 1 H, THP anomeric C*H*), 4.92 (d, *J* = 13.9 Hz, 1 H, allylic C*H*$_2$), 4.82 (d, *J* = 15.2 Hz, 1 H,

benzylic C*H*$_2$), 4.70 (d, *J* = 15.2 Hz, 1 H, benzylic C*H*$_2$), 4.47-4.45 (m, 1 H, ketal), 4.36-4.34 (m, 1 H, ketal), 4.17-4.07 (m, 3 H, ketal and THP), 3.95 (s, 1 H, C*H*OTHP), 3.78 (s, 3 H, OC*H*$_3$), 3.75 (bd, *J* = 11.7 Hz, 1 H, C*H*$_2$OH), 3.72-3.68 (bm, 1 H, C*H*$_2$OH), 3.57-3.53 (m, 1 H, THP), 2.40 (bs, 1 H, O*H*), 1.92-1.85 (m, 1 H, THP), 1.83-1.75 (m, 1 H, THP), 1.62-1.50 (m, 4 H, THP); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.8, 153.5, 153.4, 138.4, 129.5, 128.1, 117.5, 115.8, 113.9, 106.0, 103.7, 93.6, 87.3, 74.7, 67.6, 66.7, 66.6, 65.4, 63.6, 55.2, 47.6, 31.6, 24.4, 21.4; IR (film) ν_{max} 3368, 3063, 2950, 2866, 2209, 1730, 1615, 1513, 1421, 1368, 1246, 1180, 1121, 1030, 953, 912, 864, 732 cm^{-1}; HRMS Calcd. for $C_{26}H_{30}O_9N_2$ (M+H$^+$): 515.2030. Found: 515.2048.

Aldehyde 54. To a solution of diol **53** (87 mg, 0.17 mmol) in acetonitrile (1.7 mL) was added Dess-Martin periodinane (144 mg, 0.338 mmol) and the mixture was stirred for 30 h. After dilution with ethyl acetate (40 mL) the mixture was filtered through a pad of silica gel, concentrated under reduced pressure and purified by flash chromatography (silica gel, 3 → 5 % acetone in chloroform) to yield hydroxy aldehyde **54** (81 mg, 93 %): Colorless oil; R_f = 0.56 (silica gel, 10 % acetone in chloroform); ^{1}H NMR (500 MHz, C_6D_6) δ 9.55 (s, 1 H, C*H*O), 7.29 (d, *J* = 8.7 Hz, 2 H, Ar), 6.82 (d, *J* = 8.7 Hz, 2 H, Ar), 5.68 (s, 1 H, C*H*CN), 5.38 (d, *J* = 14.2 Hz, 1 H, allylic C*H*$_2$), 4.82 (d, *J* = 15.2 Hz, 1 H, benzylic C*H*$_2$), 4.71 (d, *J* = 15.2 Hz, 1 H, benzylic C*H*$_2$), 4.50 (d, *J* = 14.2 Hz, 1 H, allylic C*H*$_2$), 4.03 (dd, *J* = 6.5, 2.8 Hz, 1 H, THP anomeric C*H*), 3.66-3.61 (m, 1 H, ketal), 3.59-3.54 (m, 1 H, ketal), 3.51 (s, 1 H, C*H*OTHP), 3.42-3.27 (m, 3 H, ketal and THP), 3.30 (s, 3 H, OC*H*$_3$), 3.12-3.05 (m, 1 H, THP), 1.4-0.9 (m, 6 H, THP); IR (film) ν_{max} 3315, 3059, 2925, 2860, 2211, 1733, 1615, 1513, 1436, 1372, 1246, 1183, 1121, 1029, 952, 913, 814, 731 cm^{-1}; LRMS Calcd. for $C_{26}H_{28}O_9N_2$ (M+Cs$^+$): 645. Found: 645.

TMS ether 55. To a solution of hydroxy aldehyde **54** (21 mg, 41 μmol) in 1,2-dichloroethane (4 mL) was added 2,6-lutidine (72 μL, 620 μmol) and TMSOTf (79 μL, 410 μmol). The mixture was heated at 70 °C for 4.5 h before being cooled, diluted with ethyl ether (50 mL), washed with $CuSO_4$ (20 mL), $NaHCO_3$ (20 mL) and dried ($MgSO_4$). Concentration under reduced pressure and purification by flash chromatography (silica gel, 10 % ethyl acetate in toluene) gave pure silyl ether **55** (14 mg, 60 %): Colorless oil; R_f = 0.29 (silica gel, 70 % ethyl ether in petroleum ether); ^{1}H NMR (500 MHz, C_6D_6) δ 9.61 (s, 1 H, C*H*O), 7.25 (d, *J* = 8.7 Hz, 2 H, Ar), 6.79 (d, *J* = 8.7 Hz, 2 H, Ar), 5.32 (s, 1 H, C*H*CN), 5.08 (d, *J* = 14.0 Hz, 1 H, allylic C*H*$_2$), 4.85 (d, *J* = 15.1 Hz, 1 H, benzylic C*H*$_2$), 4.75 (d, *J* = 15.1 Hz, 1 H, benzylic C*H*$_2$), 4.60 (d, *J* = 14.0 Hz, 1 H, allylic C*H*$_2$), 4.24 (dd, *J* = 8.5, 2.2 Hz, 1 H, THP anomeric C*H*), 3.93 (s, 1 H, C*H*OTHP), 3.74-3.68 (m, 1 H, ketal), 3.58-3.54 (m, 1 H, ketal), 3.30-3.24 (m, 3 H, ketal and THP), 3.29 (s, 3 H, OC*H*$_3$), 3.03-2.96 (m, 1 H, THP), 1.4-0.9 (m, 6 H, THP), 0.34 (s, 9 H, TMS); IR (film) ν_{max} 2929, 2856, 2211, 1734, 1616, 1513, 1424, 1376, 1247, 1180, 1118, 1035, 946, 910, 847 cm^{-1}; HRMS Calcd. for $C_{29}H_{36}O_9N_2Si$ (M+Na$^+$): 607.2088. Found: 607.2080.

Acetonitrile adduct 57. To a solution of ^{t}butyl lithium (2.07 mL, 1.7 M in pentane, 3.52 mmol) in THF (25 mL) at -78 °C was added acetonitrile (200 μL, 3.83 mmol). After stirring for 90 s, a solution of ketone **45** (1.49 g, 3.06 mmol) in THF (2 × 3mL) was added and the reaction mixture was stirred for a further 0.1 h before being quenched with a saturated solution of ammonium chloride. The mixture was warmed to

ambient temperature and diluted with ethyl acetate (200 mL). The layers were separated and the organic phase was washed with NaCl (40 mL) and dried ($MgSO_4$). Concentration under reduced pressure and purification by flash chromatography (silica gel, 70 % ethyl ether in petroleum ether) yielded adduct **57** (1.32 g, 82 %): Colorless oil; R_f = 0.29 (silica gel, 80 % ethyl ether in petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.7 Hz, 2 H, Ar), 6.82 (d, *J* = 8.7 Hz, 2 H, Ar), 5.93 (dd, *J* = 1.4, 1.1 Hz, 1 H, vinyl C*H*), 4.91 (d, *J* = 13.5 Hz, 1 H, benzylic CH_2 or cyclic allylic CH_2), 4.84 (d, *J* = 15.2 Hz, 1 H, benzylic CH_2 or cyclic allylic CH_2), 4.75 (d, *J* = 15.2 Hz, 1 H, benzylic CH_2 or cyclic allylic CH_2), 4.75 (s, 1 H, tertiary O*H*), 4.64 (d, *J* = 13.5 Hz, 1 H, benzylic CH_2 or cyclic allylic CH_2), 4.50 (dd, *J* = 13.5, 1.4 Hz, 1 H, CH_2OTBS), 4.38 (dd, *J* = 13.5, 1.1 Hz, 1 H, CH_2OTBS), 4.19-4.05 (m, 4 H, ketal), 3.76 (s, 3 H, OCH_3), 2.84 (d, *J* = 16.7 Hz, 1 H, CH_2CN), 2.75 (d, *J* = 16.7 Hz, 1 H, CH_2CN), 0.91 (s, 9 H, Si*t*-*Bu*Me$_2$), 0.12 (s, 3 H, Si*t*-Bu*Me*$_2$), 0.12 (s, 3 H, Si*t*-Bu*Me*$_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.6, 154.6, 137.2, 132.2, 130.3, 128.5, 123.7, 121.0, 115.6, 113.7, 100.0, 69.3, 64.2, 63.8, 62.9, 62.1, 55.1, 47.6, 29.0, 25.7, 18.1, -5.6; IR (film) ν_{max} 3383, 2953, 2858, 1702, 1613, 1513, 1463, 1375, 1248, 1147, 1111, 1048, 965, 838, 779, 732 cm^{-1}; HRMS Calcd. for $C_{27}H_{36}O_7N_2Si$ (M+H$^+$): 529.2370. Found: 529.2370.

Alkenes 58a and 58b. To a solution of alcohol **57** (1.32 g, 2.50 mmol) in methylene chloride (12.5 mL) was added triethylamine (487 μL, 3.5 mmol), DMAP (31 mg, 0.25 mmol) and trifluoroacetic anhydride (424 μL, 3.0 mmol). After 0.25 h the reaction mixture was diluted with ethyl acetate (150 mL), washed with 1 N HCl (40 mL), $NaHCO_3$ (40 mL), NaCl (40 mL) and dried ($MgSO_4$). Concentration under reduced pressure and purification by flash chromatography (silica gel, 1 % acetone in chloroform) yielded **58a** (960 mg, 75 %) and **58b** (100 mg, 8 %).

58a: Colorless oil; R_f = 0.58 (silica gel, 5 % acetone in chloroform); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.7 Hz, 2 H, Ar), 6.85 (d, *J* = 8.7 Hz, 2 H, Ar), 6.20 (bs, 1 H, ring vinyl C*H*), 5.48 (s, 1 H, C*H*CN), 5.27 (s, 2 H, cyclic allylic CH_2), 4.87 (s, 2 H, benzylic CH_2), 4.37 (d, *J* = 1.3 Hz, 2 H, CH_2OTBS), 4.24-4.19 (m, 4 H, ketal), 3.79 (s, 3 H, OCH_3), 0.92 (s, 9 H, Si*t*-*Bu*Me$_2$), 0.10 (s, 6 H, Si*t*-Bu*Me*$_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.8, 153.1, 143.4, 137.7, 132.7, 129.9, 128.6, 126.4, 117.5, 114.9, 113.8, 100.4, 92.0, 64.0, 63.9, 61.6, 55.1, 47.9, 25.7, 18.1, -5.4; IR (film) ν_{max} 3057, 2954, 2930, 2901, 2856, 2206, 1735, 1614, 1513, 1382, 1249, 1170, 1144, 963, 840, 778, 733 cm^{-1}; HRMS Calcd. for $C_{27}H_{34}O_6N_2Si$ (M+H$^+$): 511.2264. Found: 511.2260.

58b: White crystals (ether); mp 144.5 - 147.5 °C (prior yellowing); R_f = 0.51 (silica gel, 5 % acetone in chloroform); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.7 Hz, 2 H, Ar), 6.84 (d, *J* = 8.7 Hz, 2 H, Ar), 6.47 (dt, *J* = 2.0(t), 1.3(d) Hz, 1 H, ring vinyl C*H*), 5.08 (d, *J* = 1.3 Hz, 1 H, C*H*CN), 4.89 (s, 2 H, benzylic C*H*2 or cyclic allylic CH_2), 4.85 (d, *J* = 2.0 Hz, 2 H, CH_2OTBS), 4.82 (s, 2 H, benzylic C*H*2 or cyclic allylic CH_2), 4.26-4.16 (m, 4 H, ketal), 3.78 (s, 3 H, OCH_3), 0.95 (s, 9 H, Si*t*-*Bu*Me$_2$), 0.14 (s, 6 H, Si*t*-Bu*Me*$_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.9, 152.6, 142.3, 136.5, 132.6, 129.9, 128.7, 126.3, 117.6, 113.8, 113.6, 100.4, 90.7, 64.0, 63.4, 61.2, 55.3, 48.0, 25.8, 18.3, -5.4; IR (film) ν_{max} 3056, 2954, 2930, 2901, 2856, 2206, 1731, 1618, 1513, 1384, 1248, 1170, 1143, 1056, 960, 838 cm^{-1}; HRMS Calcd. for $C_{27}H_{34}O_6N_2Si$ (M+H$^+$): 511.2264. Found: 511.2260. Anal. Calcd. for $C_{27}H_{34}O_6N_2Si$: C, 63.51; H, 6.71; N, 5.49. Found: C, 63.30; H, 6.75; N, 5.48.

Allylic alcohol 59. To a solution of silyl ether **58** (242 mg, 0.475 mmol) in THF (4.8 mL) in a polypropylene vessel at 0 °C was added hydrogen fluoride - pyridine (710 µL). After 1 h the mixture was poured cautiously into a saturated solution of $NaHCO_3$ (100 mL) and diluted with ethyl acetate (200 mL). After stirring for 0.1 h, the layers were separated and the organic phase was washed with $NaHCO_3$ (50 mL), NaCl (50 mL) and dried ($MgSO_4$). Concentration under reduced pressure and purification by flash chromatography (silica gel, methylene chloride, then 70 % ethyl acetate in petroleum ether) yielded allylic alcohol **59** (181 mg, 96 %): White solid; R_f = 0.45 (silica gel, ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.7 Hz, 2 H, Ar), 6.84 (d, *J* = 8.7 Hz, 2 H, Ar), 6.19 (s, 1 H, ring vinyl C*H*), 5.57 (s, 1 H, C*H*CN), 5.26 (s, 2 H, cyclic allylic CH_2), 4.84 (s, 2 H, benzylic CH_2), 4.35 (d, *J* = 5.7 Hz, 2 H, CH_2OH), 4.26-4.17 (m, 4 H, ketal), 3.78 (s, 3 H, OC*H*3), 2.56 (t, *J* = 5.7 Hz, 1 H, O*H*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.9, 153.4, 143.2, 137.5, 132.8, 129.8, 128.7, 128.6, 127.2, 117.6, 115.1, 113.9, 100.3, 92.9, 64.1, 64.0, 61.5, 55.2, 48.0; IR (film) ν_{max} 3455, 3058, 2965, 2906, 2839, 2207, 1723, 1615, 1512, 1432, 1381, 1294, 1246, 1169, 1094, 1031, 960, 911, 814, 731 cm^{-1}; HRMS Calcd. for $C_{21}H_{20}O_6N_2$ (M+H$^+$): 397.1400. Found: 397.1400.

Epoxide 60. A suspension of allylic alcohol **59** (460 mg, 1.16 mmol) in methylene chloride (2.0 mL) was stirred with pre-dried 4 Å molecular sieves (140 mg) and di-isopropyl-D-tartrate (31 µL, 0.145 mmol) for 4 h. The mixture was cooled to -30 °C and treated with titanium tetraisopropoxide (35 µL, 0.116 mmol). The mixture was allowed to warm to -5 °C over 0.5 h before being re-cooled to -10 °C and treated with ^{t}butyl hydroperoxide (422 µL, *ca* 5.5 M in methylene chloride, 2.32 mmol). The reaction mixture was stirred for 14 h at 0 °C before being quenched with H_2O (2 mL), diluted with ethyl acetate (5 mL) and stirred for 1 h. The mixture was filtered through a pad of Celite® and further diluted with ethyl acetate (100 mL). The layers were separated and the organic phase was washed with $Na_2S_2O_4$ (2 × 30 mL, 15 % w/w aqueous solution), $NaHCO_3$ (30 mL), NaCl (30 mL) and dried ($MgSO_4$). Concentration under reduced pressure and purification by flash chromatography (silica gel, 70 % ethyl acetate in petroleum ether) gave pure epoxide **60** (410 mg, 86 %): White solid; R_f = 0.45 (silica gel, ethyl acetate); $[\alpha]_D^{25}$ -298 (c = 0.99, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.7 Hz, 2 H, Ar), 6.85 (d, *J* = 8.7 Hz, 2 H, Ar), 5.66 (s, 1 H, C*H*CN), 5.06 (d, *J* = 13.9 Hz, 1 H, allylic CH_2), 4.97 (d, *J* = 13.9 Hz, 1 H, allylic CH_2), 4.92 (d, *J* = 15.0 Hz, 1 H, benzylic CH_2), 4.54 (d, *J* = 15.0 Hz, 1 H, benzylic CH_2), 4.38-4.27 (m, 3 H, ketal), 4.22-4.17 (m, 1 H, ketal), 4.15 (d, *J* = 12.7 Hz, 1 H, CH_2OH), 3.85 (d, *J* = 12.7 Hz, 1 H, CH_2OH), 3.79 (s, 3 H, OC*H*3), 3.62, (s, 1 H, epoxide C*H*), 2.4-2.3 (bs, 1 H, O*H*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.0, 153.1, 149.1, 136.2, 129.4, 128.7, 116.4, 114.7, 113.9, 103.3, 95.6, 64.8, 60.7, 60.3, 57.6, 55.7, 55.2, 48.6; IR (film) ν_{max} 3450, 3069, 2963, 2910, 2214, 1725, 1628, 1512, 1425, 1378, 1290, 1245, 1161, 1023, 910, 817, 730 cm^{-1}; HRMS Calcd. for $C_{21}H_{20}O_7N_2$ (M+H$^+$): 413.1349. Found: 413.1350.

Aldehyde 61. To a solution of epoxy alcohol **60** (410 mg, 0.955 mmol) in methylene chloride (10 mL) was added Dess-Martin periodinane (844 mg, 1.91 mmol) and the mixture was stirred at ambient temperature for 36 h. The mixture was filtered through a pad of Celite®, concentrated under reduced pressure and purified by flash chromatography (silica gel, 70 → 80 % ethyl acetate in petroleum ether) to yield

aldehyde **61** (404 mg, 99 %): White solid; R_f = 0.41 (silica gel, ethyl acetate); ^{1}H NMR (500 MHz, C_6D_6) δ 8.33 (s, 1 H, C*H*O), 7.26 (d, *J* = 8.6 Hz, 2 H, Ar), 6.74 (d, *J* = 8.6 Hz, 2 H, Ar), 5.61 (s, 1 H, C*H*CN), 5.02 (d, *J* = 14.9 Hz, 1 H, allylic CH_2), 4.79 (d, *J* = 14.1 Hz, 1 H, benzylic CH_2), 4.65 (d, *J* = 14.1 Hz, 1 H, benzylic CH_2), 4.36 (d, *J* = 14.9 Hz, 1 H, allylic CH_2), 3.30-3.10 (m, 4 H, ketal), 3.27 (s, 3 H, OCH_3), 2.91, (s, 1 H, epoxide C*H*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.6, 159.2, 153.1, 143.1, 135.4, 129.2, 128.8, 116.2, 115.2, 114.1, 114.0, 99.0, 65.2, 65.1, 64.9, 64.6, 57.1, 56.5, 55.3, 53.7, 48.8, 29.2; IR (film) ν_{max} 3439, 3075, 2911, 2839, 2214, 1729, 1626, 1513, 1425, 1380, 1246, 1159, 1023, 944, 816, 755 cm^{-1}.

Alkyne 62. To a solution of dimethyl diazomethylphosphonate, (52 mg, 0.35 mmol) in THF (2.0 mL) at -78 °C was added ^{n}butyl lithium (119 μL, 2.5 M in hexane, 298 μmol). After 0.1 h, a solution of aldehyde **61** (101 mg, 0.246 mmol) in THF (0.6 mL) was added *via* cannula. After a further 0.25 h the mixture was allowed to warm to 0 °C over 3 h and quenched with a saturated aqueous solution of NH_4Cl. The mixture was diluted with ethyl acetate (60 mL) and the layers were separated. The organic phase was washed with NaCl (20 mL) and dried ($MgSO_4$). Concentration under reduced pressure and purification by flash chromatography (silica gel, 50 % ethyl acetate in petroleum ether) yielded alkyne **62** (50 mg, 57 % accounting for 13 mg of recovered starting material): White solid; R_f = 0.40 (silica gel, ethyl ether); $[\alpha]_D^{25}$ -279.0 (c = 0.13, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.6 Hz, 2 H, Ar), 6.85 (d, *J* = 8.6 Hz, 2 H, Ar), 6.15 (s, 1 H, C*H*CN), 5.09 (d, *J* = 14.0 Hz, 1 H, allylic CH_2), 4.96 (d, *J* = 14.0 Hz, 1 H, allylic CH_2), 4.92 (d, *J* = 15.0 Hz, 1 H, benzylic CH_2), 4.52 (d, *J* = 15.0 Hz, 1 H, benzylic CH_2), 4.38-4.33 (m, 3 H, ketal), 4.27-4.20 (m, 1 H, ketal), 3.82 (s, 1 H, epoxide C*H*), 3.79 (s, 3 H, OCH_3), 2.78 (s, 1 H, CC*H*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.1, 152.7, 147.0, 135.9, 129.3, 128.8, 116.2, 114.0, 113.3, 102.8, 97.6, 77.9, 75.5, 65.0, 64.6, 59.8, 55.2, 50.8, 48.6; IR (film) ν_{max} 3270, 3016, 2912, 2839, 2215, 2128, 1733, 1629, 1514, 1421, 1380, 1247, 1150, 1019, 755 cm^{-1}; HRMS Calcd. for $C_{22}H_{18}O_6N_2$ (M+H$^+$): 407.1243. Found: 407.1240.

Methyl ether 63. To a solution of epoxide **62** (11 mg, 27 μmol) in methanol (0.5 mL) was added sulfuric acid (10 μL, 36 N) and the solution heated at 60 °C for 1 h. After cooling to ambient temperature, the solution was diluted with ethyl acetate (40 mL), washed with $NaHCO_3$ (15 mL), NaCl (15 mL) and dried ($MgSO_4$). Concentration under reduced pressure and purification by flash chromatography (silica gel, 80 % ethyl ether in petroleum ether then ethyl ether) gave methyl ether **63** (8.5 mg, 72 %): Colorless oil; R_f = 0.36 (silica gel, ethyl ether); ^{1}H NMR (500 MHz, C_6D_6) δ 7.26 (d, *J* = 8.7 Hz, 2 H, Ar), 6.76 (d, *J* = 8.7 Hz, 2 H, Ar), 5.61 (s, 1 H, C*H*CN), 5.00 (d, *J* = 15.1 Hz, 1 H, benzylic CH_2 or allylic CH_2), 4.90 (d, *J* = 13.6 Hz, 1 H, benzylic CH_2 or allylic CH_2), 4.84 (d, *J* = 13.6 Hz, 1 H, benzylic CH_2 or allylic CH_2), 4.65 (d, *J* = 15.1 Hz, 1 H, benzylic CH_2 or allylic CH_2), 3.70 (d, *J* = 2.5 Hz, 1 H, C*H*OH), 3.29 (s, 3 H, PMB OCH_3), 3.24-3.18 (m, 2 H, ketal), 3.08-3.03 (m, 1 H, ketal), 2.99-2.93 (m, 1 H, ketal), 2.91 (s, 3 H, tertiary OCH_3), 2.45 (d, *J* = 2.5 Hz, 1 H, O*H*), 2.07 (s, 1 H, CC*H*); ^{13}C NMR (125 MHz, C_6D_6) δ 159.2, 152.9, 150.3, 137.3, 130.1, 128.7, 127.9, 116.3, 113.8, 111.8, 104.5, 96.7, 79.0, 78.7, 77.9, 73.6, 64.3, 64.2, 63.7, 54.4, 52.4, 47.7; IR (film) ν_{max} 3445, 3263, 2925, 2855, 2214, 2114, 1726, 1620, 1513,

1458, 1422, 1376, 1246, 1179, 1089, 1023 cm^{-1}; HRMS Calcd. for $C_{23}H_{22}O_7N_2$ ($M+H^+$): 439.1505. Found: 439.1512.

Diol 64. To a solution of epoxide **62** (50 mg, 0.12 mmol) in ^{t}butanol (600 µL) was added sulfuric acid (600 µL, 2 N aqueous solution, 0.60 mmol). The vessel was evacuated (20 torr) and flushed with argon three times. The reaction mixture was then heated under argon at 90 °C for 1.5 h before being cooled to ambient temperature and diluted with ethyl acetate (30 mL). The mixture was washed with $NaHCO_3$ (15 mL), NaCl (15 mL) and dried ($MgSO_4$). Concentration under reduced pressure and purification by flash chromatography (silica gel, ethyl ether, then ethyl acetate) yielded epoxide **62** (26 mg) and diol **64** (16 mg) (65 % based on recovered starting material): White solid; R_f = 0.48 (silica gel, ethyl acetate); $[\alpha]_D^{25}$ -141.4 (c = 0.42, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.7 Hz, 2 H, Ar), 6.86 (d, *J* = 8.7 Hz, 2 H, Ar), 5.94 (s, 1 H, C*H*CN), 5.12 (d, *J* = 13.6 Hz, 1 H, allylic CH_2), 5.07 (d, *J* = 13.6 Hz, 1 H, allylic CH_2), 4.91 (d, *J* = 15.0 Hz, 1 H, benzylic CH_2), 4.76 (d, *J* = 15.0 Hz, 1 H, benzylic CH_2), 4.36-4.30 (m, 2 H, ketal), 4.23-4.17 (m, 2 H, ketal), 3.82 (d, *J* = 9.2 Hz, 1 H, C*H*OH), 3.80 (s, 3 H, OCH_3), 3.63 (bs, 1 H, tertiary O*H*), 2.87 (d, *J* = 9.2 Hz, 1 H, CHO*H*), 2.64 (s, 1 H, CC*H*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.0, 153.3, 151.3, 138.5, 129.5, 128.7, 128.5, 116.7, 114.0, 104.7, 93.5, 79.5, 78.9, 76.4, 71.5, 67.3, 65.8, 64.2, 55.3, 48.0; IR (film) ν_{max} 3422, 3280, 2924, 2854, 2214, 2114, 1714, 1617, 1513, 1377, 1246, 1179, 1024 cm^{-1}; HRMS Calcd. for $C_{22}H_{20}O_7N_2$ ($M+H^+$): 425.1349. Found: 425.1350.

Bis silyl ether 65. To a solution of diol **64** (16 mg, 35 µmol) in methylene chloride (500 µL) was added pyridine (14 µL, 180 µmol) and TESOTf (24 µL, 110 µmol). After 1.5 h the reaction mixture was diluted with ethyl ether (30 mL), washed with $CuSO_4$ (10 mL), $NaHCO_3$ (10 mL) and dried ($MgSO_4$). Concentration under reduced pressure and purification by flash chromatography (silica gel, 30 → 40 % ethyl ether in petroleum ether) gave bis silyl ether **65** (24 mg, 98 %): Colorless oil; R_f = 0.33 (silica gel, 40 % ethyl ether in petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.7 Hz, 2 H, Ar), 6.83 (d, *J* = 8.7 Hz, 2 H, Ar), 5.93 (s, 1 H, C*H*CN), 5.24 (d, *J* = 13.7 Hz, 1 H, allylic CH_2), 4.93 (d, *J* = 13.7 Hz, 1 H, allylic CH_2), 4.92 (d, *J* = 15.0 Hz, 1 H, benzylic CH_2), 4.81 (d, *J* = 15.0 Hz, 1 H, benzylic CH_2), 4.11-4.01 (m, 4 H, ketal), 3.79 (s, 4 H, OCH_3 and C*H*OTES), 2.79 (s, 1 H, CC*H*), 0.96-0.90 (m, 18 H, Si(CH_2CH_3)$_3$), 0.66-0.60 (m, 12 H, Si(CH_2CH_3)$_3$); IR (film) ν_{max} 3267, 2955, 2912, 2879, 2211, 2114, 1733, 1616, 1513, 1459, 1417, 1376, 1245, 1176, 1136, 1012, 740 cm^{-1}; HRMS Calcd. for $C_{34}H_{48}O_7N_2Si_2$ ($M+H^+$): 653.3078. Found: 653.3080.

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