Synthesis of the namenamicin A–C disaccharide: towards the total synthesis of namenamicin

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Progress towards the total synthesis of namenamicin (**1**), the only enediyne antitumor antibiotic of marine origin, is reported. Two methods were investigated for the stereoselective introduction of the highly unusual quaternary C-4 center of the A-ring. Spirocyclic [3,3]-sigmatropic rearrangements of the thiocarbonates **6** and **10** gave products **7** and **11**, from processes involving approach of the sulfur atom solely to the α-faces of the substrates. The desired stereochemistry of the quaternary center was ultimately obtained by way of an intramolecular Michael addition of a xanthate anion derived from the α,β-unsaturated methyl ester **18**. Further functional group manipulations provided an olefin **25** which underwent dihydroxylation to give a mixture of diastereomeric diols **26**, allowing access to both potential diastereomers of the natural product. The A ring intermediate **29** was found to be a viable substrate of glycosidation with a glycosyl fluoride of the C ring aminosugar **30**, providing the protected A–C disaccharide subunit of **1**.

Introduction

The enediyne antitumor antibiotics have stimulated wide and ongoing interest due to their potent biological activities, unusual mode of action, and range of fascinating molecular architectures.[1] Recently isolated from an ascidian (*Polysyncraton lithostrotum*) off the coast of the Fiji island of Namenalala, namenamicin (**1**) is notably the only enediyne natural product of marine origin.[2,3] Remarkably, it shares many resemblances to its closest terrestrial counterparts, the calicheamicins[4] and esperamicins.[5] With an enediyne-bearing aglycon identical to that of the former, namenamicin **1** is an efficient, albeit moderately site selective, double standard DNA-cleaving agent with high *in vitro* cytotoxicity (IC_{50} = 3.5 ng ml^{-1}), *in vivo* antitumor activity (P388 leukemia model in mice) and potent antimicrobial activity.[2] Although its trisaccharide domain is reminiscent of esperamicin A_1, with an isopropyl aminosugar (C ring) and two unusual 6-deoxysugars (A and B rings), namenamicin's most striking feature is the unprecedented linkage between the A and B rings in which C-4 of the A ring is disubstituted with a methyl thioether and a two carbon fragment to which the B ring is appended at the C-7 oxygen. The poor availability of the natural product from the ascidian (less than 1 mg from 1 kg of frozen tissue, 0.0001% yield) has led to the suggestion that a symbiotically co-existing microorganism may be responsible for its biosynthesis. Although such an organism could lead to fermentation of the natural product (*e.g.* calicheamicins and esperamicins), thus providing sufficient material for further biological evaluation, none, as yet, has been reported. In addition, the small quantity of material available for structural determination precluded the degradation studies which would be needed for elucidation of the absolute stereochemistry at C-7. Thus, efforts towards the total synthesis of this intriguing molecule are strongly warranted.

Results and discussion

A retrosynthetic analysis of the molecule (Fig. 1) readily suggests that its trisaccharide segment could be constructed from the A ring, which would serve as a monosaccharide core. An *o*-nitrobenzyl glucosidic linkage would protect the reducing end of this unusual sugar for eventual photolytic deprotection and subsequent coupling to the suitably protected aglycon.[6] The two carbon fragment attached to the α-face of the A ring C-4 position would be masked as a vinyl substituent, eventually undergoing dihydroxylation and glycosylation of the C-7 hydroxy. Thus, a method was sought for the stereoselective introduction of the C-4 quaternary center, and two approaches were ultimately investigated.

Spirocyclic sigmatropic rearrangement approach

An initial strategy (Fig. 2) relied on a spirocyclic [3,3]-sigmatropic rearrangement of an appropriately substituted allylic alcohol to install the requisite functionality at C-4. Resembling a method developed by Fraser-Reid *et al.*[7] for the preparation of geminally di-substituted carbohydrates, it was envisaged that the thermal rearrangement of a thiocarbonyl intermediate should provide a product in which the sulfur atom would be bound to C-4.[8] The successful implementation of this approach would require the stereoselective introduction of the sulfur atom to the β-face of the sugar. This requirement seemed very feasible given the observation by Fraser-Reid and co-workers that allyl vinyl ethers derived from C-4 ketosugars underwent thermal rearrangement to give products resulting primarily from "β-folded" transition states. In this case, an allylic thiocarbonate *O*-ester **6** (Scheme 1) was designed to serve as a rearrangement substrate. Intermediate **6** was prepared from the disaccharide α-hydroxy ketone **2**, which, as an intermediate from our total synthesis of calicheamicin γ_1^I, was readily available and would serve as an excellent model with its *ethyl* (rather than requisite *isopropyl*) secondary amino group.[6] Wittig condensation of the ketone **2** with the stabilized ylide $Ph_3PC(H)CO_2Et$ provided the α,β-unsaturated ester **3** as a single geometric isomer (72% yield). Although not rigorously proven, the indicated stereochemistry of the newly formed double bond is that which is expected from an α-hydroxy directed Wittig condensation;[9] furthermore, the ester failed to lactonize with the neighboring C-3 hydroxy under the basic conditions required for removal of the FMOC carbamate (Et_2NH–THF, 25 °C). Silylation of the C-3 hydroxy group (TESOTf, iPr_2NEt)

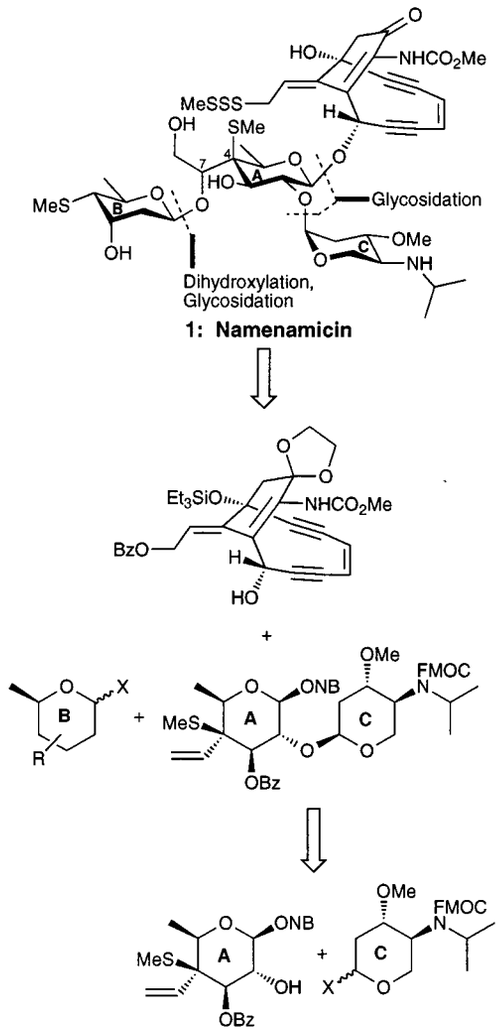


Fig. 1 Structure and retrosynthetic analysis of namenamicin (**1**). NB = *o*-nitrobenzyl; Bz = benzoyl; FMOC = (9*H*-fluoren-9-ylmethoxy)-carbonyl.

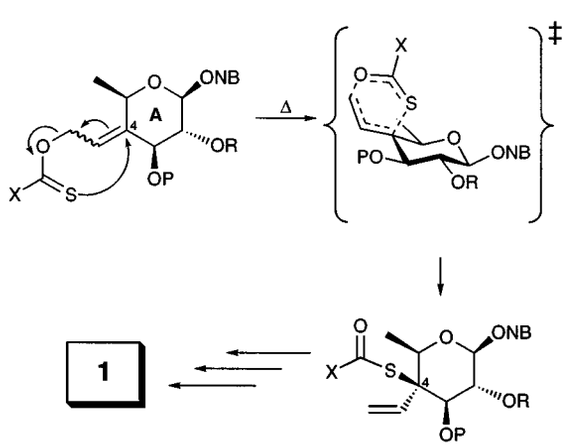
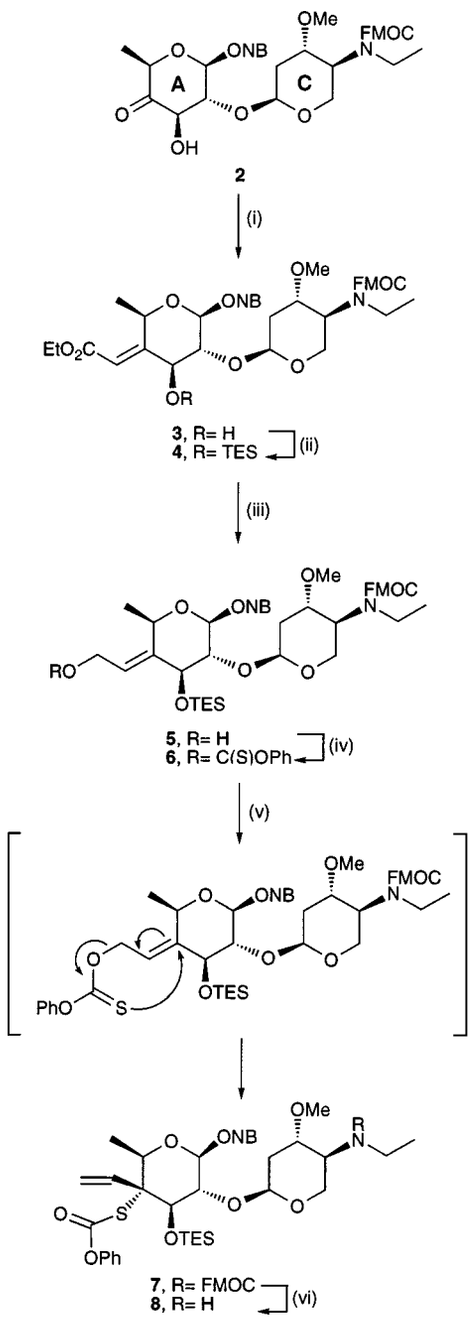


Fig. 2 Spirocyclic [3,3]-sigmatropic rearrangement proceeding through a "β-folded" transition state. P = protecting group; R = C-ring amino sugar (not shown for clarity); X = variable.

provided the protected compound **4** (90% yield) which was then treated with DIBAL to furnish the primary allylic alcohol **5** in good yield (80%). Subsequent treatment with Robins' reagent (PhOC(S)Cl) in the presence of pyridine gave the thiocarbonate **6** (99% yield).[10] After experimenting with several solvents and temperatures, it was found that the rearrangement proceeded best by simply heating the neat starting material at 170 °C for six minutes leading to the thiocarbonate product **7** as a single



Scheme 1 *Reagents and conditions*: (i) Ph_3PCO_2Et (2.0 equiv.), CH_3CN, 50 °C, 3 h, 72%; (ii) TESOTf (4.0 equiv.), iPr_2NEt (5.0 equiv.), CH_2Cl_2, 0 °C, 10 min, 75%; (iii) DIBAL (3.0 equiv.), CH_2Cl_2, −50 °C, 0.5 h, 80%; (iv) PhOC(S)Cl (2.0 equiv.), pyridine (1.5 equiv.), CH_2Cl_2, 25 °C, 1.5 h, 99%; (v) 170 °C, neat, 6 min, 75%, 100% de; (vi) Et_2NH–THF (1 : 3), 25 °C, 90%. FMOC = fluoren-9-ylmethyloxycarbonyl; NB = *o*-nitrobenzyl; TESOTf = triethylsilyl trifluoromethanesulfonate.

diastereoisomer and in good yield (75%). After cleavage of the FMOC group (which complicated NMR analysis at room temperature due to its hindered rotation), the free amine **8** was subjected to 2-D (ROESY) NMR analysis to determine the stereochemistry of the newly generated quaternary C-4 center (Fig. 3, structure **A**). Disappointingly, strong NOE's were detected between the C-2 axial hydrogen and the two *trans*-vinylic hydrogens, indicating that the terminal sulfur atom had approached the ring exclusively from the bottom (α) face of the molecule during the rearrangement. Considering the role of steric hindrance in governing the stereoselectivity of the reaction (Scheme 2), the neighboring C-3 triethylsilyl group of the allylic alcohol intermediate **4** was cleaved (HF·pyr) to provide a diol **9** in 75% yield. This compound **9** was selectively functional-

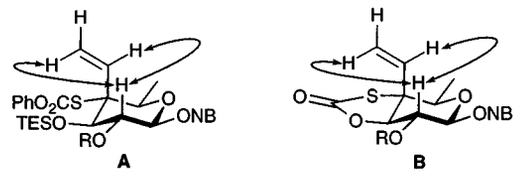
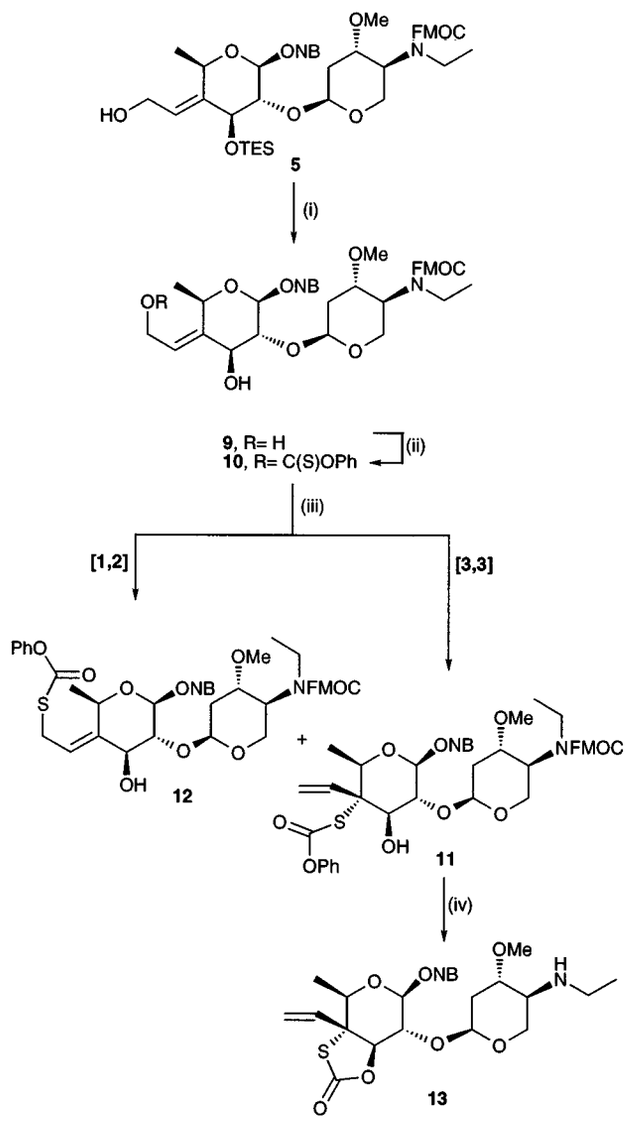


Fig. 3 Key NOE's (^{1}H–^{1}H ROESY, 600 MHz, 300 K) for structural determination of rearrangement products **7** (**A**) and **12** (**B**). R = C ring aminosugar (not shown for clarity).

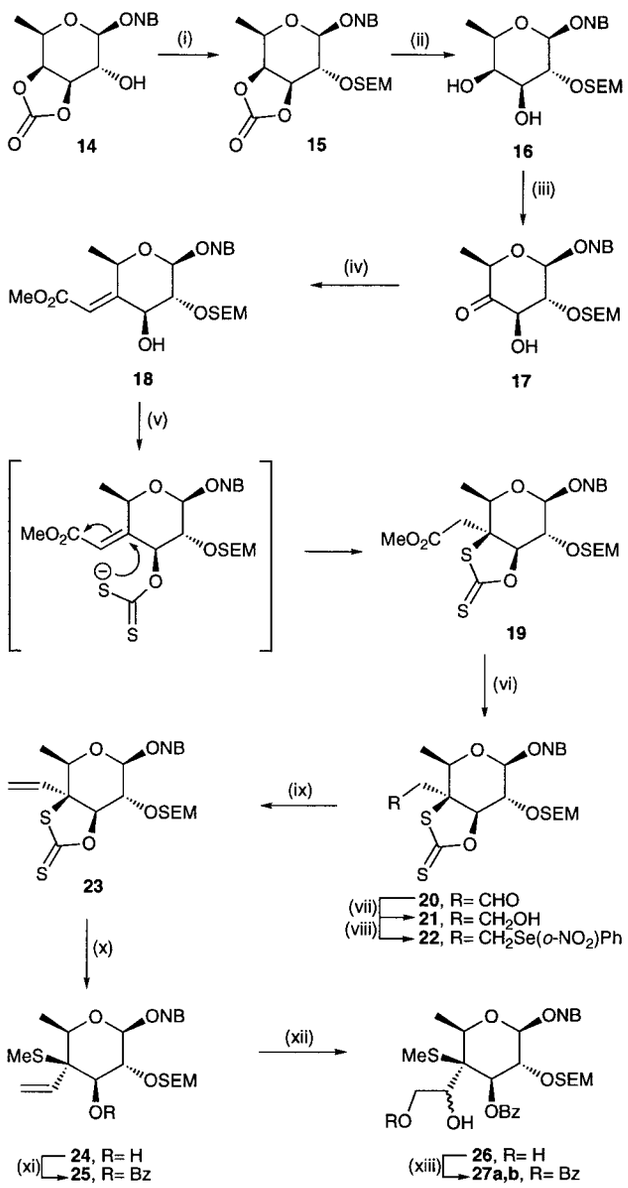


Scheme 2 *Reagents and conditions*: (i) HF·pyridine, THF, 0 °C, 1 h, 75%; (iii) PhOC(S)Cl (1.05 equiv.), pyridine (3.0 equiv.), CH_2Cl_2, 0 °C, 1.5 h, 84%; (iii) 100 °C, toluene, 1 h, 64% (51% of **11**, 13% of **12**); (iv) Et_2NH–THF (1 : 3), 90%.

ized at the primary position with Robins' reagent to furnish the thiocarbonate **10** (84%), which was subjected to the thermal rearrangement conditions. In this case, the reaction proceeded at lower temperature (100 °C, toluene) to yield a 4 : 1 mixture of isomers of identical mass. The major product (**11**) proved to be that which was obtained by the desired [3,3] process, while the 1D proton NMR spectrum of the minor product appeared similar to the starting material (a single, vinylic proton and allylic methylene), suggesting the monothiocarbonate product of a [1,2] rearrangement (**12**).[11] Treatment of the major product (**11**) with diethylamine removed the FMOC group and concomitant cyclization of the C-3 hydroxy of the A-ring with the thiocarbonate provided a cyclic monothiocarbonate (**13**). ROESY analysis of the disaccharide **13** (Fig. 3, structure **B**) showed strong NOE's between the C-2 axial hydrogen and the *trans* olefinic hydrogens, indicating that steric hindrance of the β-face of the sugar had no noticeable effect on the stereoselectivity of the rearrangement. Although the role of the olefin geometry of the starting material was briefly considered, the [3,3] sigmatropic rearrangement approach was ultimately abandoned in favor of one which would utilize the stereochemistry of the C-3 alcohol of the A-ring to direct the sulfur substituent to the same face of the molecule (Scheme 3).

Cyclic xanthate approach

Following the route first established for the synthesis of the calicheamicin γ_1^I oligosaccharide,[5] the peracetate of D-fucose (readily available in several steps from D-galactose)[12] was converted to the known cyclic carbonate **14** (Scheme 3). It was decided, for the sake of a more convergent synthesis, to introduce a protecting group to the C-2 hydroxy group which would be followed by the installation of the requisite C-4 quaternary center, deprotection of the C-2 alcohol, and subsequent glycosidation with the appropriate C ring glycosyl donor. Although silyl ethers (triethylsilyl or *tert*-butyldimethylsilyl) were readily installed at the C-2 position, cleavage of the 3,4-carbonate gave inseparable mixtures of products resulting from migration of the silicon groups. Instead, the SEM [2-(trimethylsilyl)ethoxymethyl] ether **15** was prepared (SEMCl, iPr$_2$NEt) in excellent yield (92%).[13] Cleavage of the carbonate upon treatment with catalytic sodium methoxide in methanol provided the diol **16** (99% yield) which underwent a regioselective oxidation of the C-4 alcohol *via* the brominolysis of an intermediate stannylene acetal[6,14] to provide the α-hydroxy ketone **17**. Condensation with the stabilized ylide $Ph_3PC(H)CO_2Me$ gave the α,β-unsaturated ester **18** as the single, expected, geometric isomer (63% yield for two steps). Recognizing the Michael acceptor capabilities of the unsaturated ester and the strong nucleophilicity of thiolate anions, it was reasoned that an addition of a sulfur nucleophile to C-4 would likely be a facile process. Furthermore, the C-3 hydroxy could provide the necessary asymmetric induction to allow its stereoselective introduction. Most gratifyingly, treatment of the alcohol **18** with sodium hydride (in the presence of a catalytic quantity of imidazole), followed by the addition of carbon disulfide, gave, in good yield (83%), the cyclic dithiocarbonate **19** resulting from conjugate addition of the intermediate xanthate ion. Elaboration of the two carbon fragment at C-4 to the requisite terminal olefin would require a sequence involving reduction of the ester to a primary alcohol followed by dehydration. Treatment of the ester **19** with DIBAL gave an aldehyde intermediate **20** which resisted further reduction, even after the addition of excess reagent and warming the reaction mixture. The inertness of the aldehyde under the reaction conditions may be attributed to a stable chelation complex involving the carbonyl oxygen, aluminum, and at least one of the sulfur atoms of the cyclic dithiocarbonate, which remained intact throughout the reduction. Nevertheless, the isolated aldehyde underwent facile reduction to the primary alcohol **21** by the action of sodium borohydride in methanol (91% for two steps). An *o*-nitrophenyl selenide derivative **22** of the primary alcohol **21** was prepared following the Grieco procedure,[15] and subsequent treatment with racemic 2-phenylsulfonyl-3-(phenyl)oxaziridine in the presence of pyridine effected its oxidation and elimination to afford the terminal olefin **23** (62% yield for two steps).[16] Notably, during oxidation of the intermediate selenide following the usual procedure (H_2O–THF),[17] concurrent oxidation of the xanthate moiety was effected to afford a mixture of diastereomeric *S*-oxides of the olefin **23**, as evidenced by doubling of the peaks in the proton NMR and a molecular ion corresponding to the incorporation of one additional oxygen atom. After several attempts to cleave the dithiocarbonate **23** under solvolytic and reductive conditions, it



Scheme 3 *Reagents and conditions*: (i) SEMCl (3.0 equiv.), iPr$_2$NEt (5.0 equiv.), CH_2Cl_2, 25 °C, 12 h, 92%; (ii) NaOMe (0.1 equiv.), MeOH, 25 °C, 20 min, 99%; (iii) Bu_2SnO (1.05 equiv.), MeOH, reflux, 1 h; Bu_3SnOMe (1.1 equiv.), Br_2 (1.0 equiv.), CH_2Cl_2, 25 °C; (iv) $Ph_3PC(H)CO_2Me$ (3.0 equiv.), CH_3CN, 65 °C, 3 h, 63% (two steps); (v) NaH (3.0 equiv.), imidazole (0.1 equiv.), THF, 0 °C, 10 min; CS_2 (1.5 equiv.), 25 °C, 20 min, 83%; (vi) DIBAL (2.0 equiv.), CH_2Cl_2, −78 °C, 0.5 h; (vii) $NaBH_4$ (2.0 equiv.), MeOH, 0 °C, 10 min, 91% (two steps); (viii) o-$NO_2PhSeCN$ (1.4 equiv.), Bu_3P (1.4 equiv.), THF, 25 °C, 20 min; 78%; (ix) *N*-phenylsulfonyloxaziridine (1.3 equiv.), pyridine (5.0 equiv.), CH_2Cl_2, 25 °C, 15 min, 79%; (x) MeCl (1.0 M in Et_2O, 9.0 equiv.), Et_2O–ethylenediamine (2:1), 0 °C, to 70 °C, 2 h, 80%; (xi) LHMDS (2.0 equiv.), BzCl (2.5 equiv.), THF, −78 °C to −20 °C, 1.5 h, 99%; (xii) OsO_4 (1.1 equiv.), pyridine, 25 °C, 3 h, 90%; (xiii) BzCN (1.5 equiv.), Et_3N (2.0 equiv.), CH_3CN, −20 °C, 20 min, 86% (72% **27a**, 14% **27b**). SEM = 2-(trimethylsilyl)ethoxymethyl; LHMDS = lithium hexamethyldisilazide; Bz = benzoyl.

was found that warming the starting material in the presence of methyl chloride (1.0 M diethyl ether) and ethylenediamine (0→70 °C) gave the product **24** resulting from methylation of the C-4 sulfur atom and liberation of the C-3 hydroxy (80% yield).[18] Anticipating the need to differentiate the C-2 from C-3 hydroxy groups, acylation of the alcohol **24** required the initial formation of the alkoxide anion (LHMDS, −78 °C) and its capture with benzoyl chloride to furnish the benzoate **25** (99% yield). Notably, even the most forcing of non-ionic conditions (acetic anhydride, 4-pyrrolidinopyridine, triethylamine sol-

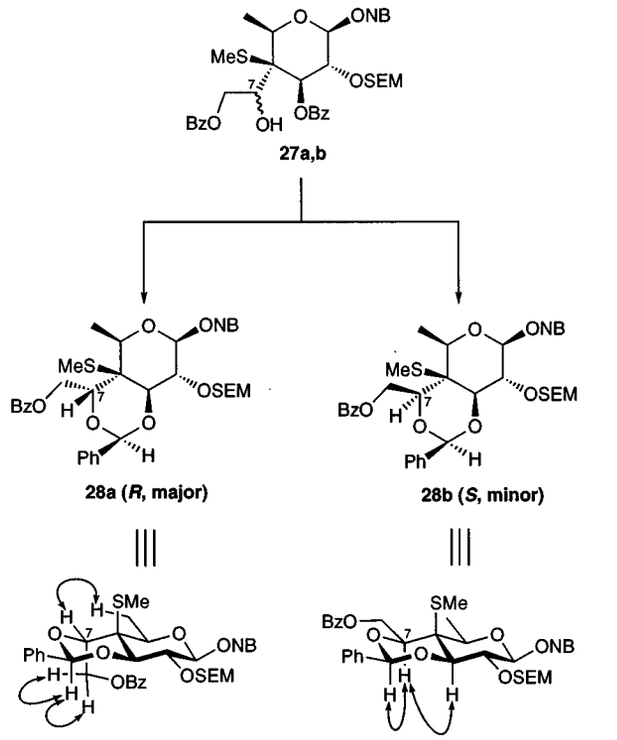
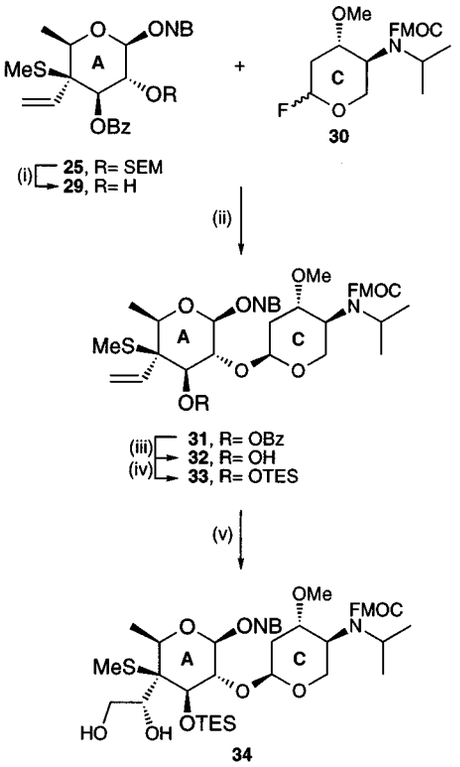


Fig. 4 Determination of C-7 stereochemistry of benzylidene derivatives **28a**,**b**. Arrows indicate key NOE's (^{1}H–^{1}H ROESY, 600 MHz, 300 K).

vent)[19] failed to acylate the C-3 alcohol. At this point, the conditions for dihydroxylation of the terminal olefin were explored. Of the catalytic methods available for the chemoselective dihydroxylation of olefins in the presence of thioethers, only the use of potassium ferricyanide as the terminal oxidant has been reported.[20] No reaction was observed under these conditions, both in the presence and absence of chiral ligands. Nevertheless, dihydroxylation of the olefin **25** was achieved following the classical Criegee protocol (OsO_4, pyridine) to give the diol **26** as an inseparable mixture of diastereoisomers (90% yield). Selective benzoylation of the primary alcohol (BzCN, Et_3N, −20 °C) furnished the diastereomeric dibenzoates **27a** and **27b** (86% yield, dr 5:1, respectively) which were readily separated on silica gel. After several unsuccessful attempts to prepare the Mosher ester derivatives of each of the alcohols **27a** and **27b**,[21] a plan was devised to determine the absolute stereochemistry of the C-7 center of both isomers (Fig. 4). Namely, derivatives **28a** and **28b** of both isomeric dibenzoates (**27a** and **27b**, respectively) were independently prepared in which the primary alcohols were protected as benzoate esters with the C-7 and C-3 hydroxy groups constrained in benzylidene acetal linkages. This was achieved through a sequence on each of the compounds (**27a**,**b**) involving simultaneous deprotection of both the primary and C-3 benzoates (NaOMe, MeOH), followed by selective re-benzoylation of the primary alcohol (BzCN, Et_3N, −20 °C) and formation of the benzylidene acetal (PhCH(OMe)$_2$, *p*-TsOH, benzene). The rigid *trans*-decalin-like systems **28a** and **28b** were each subjected to 2-D proton NMR analysis (^{1}H–^{1}H ROESY, 600 MHz, 300 K). In the case of the minor isomer (**28b**), strong NOE's were detected between the C-7 proton and both the C-3 and benzylidene protons, indicative of the 1,3-diaxial relationships expected for the *S* diastereoisomer. On the other hand, relatively weaker NOE's were observed for the benzylidene derived from the major alcohol (**28a**). These proved to be between the C-7 proton and the C-6 methyl protons, and between the benzylidene and α-benzoate (C-8) protons, indicative of the *R* isomer.

Ultimately, it was decided to access both diastereomeric



Scheme 4 *Reagents and conditions*: (i) CSA (0.1 equiv.), MeOH, 25 °C, 27 h, 87%; (ii) $AgClO_4$ (2.5 equiv.), $SnCl_2$ (2.5 equiv.), THF, −40 °C, 91% (based on 61% conversion); (iii) DIBAL (3.0 equiv.), CH_2Cl_2, −78 °C, 45 min, 94%; (iv) TESOTf, (2.0 equiv.), $i Pr_2NEt$ (3.0 equiv.), CH_2Cl_2, 0 °C, 0.5 h, 91%; (v) OsO_4 (1.0 equiv.), pyridine, 25 °C, 76%, 100% de. CSA = camphor-10-sulfonic acid.

alcohols at a later stage in the synthesis, allowing the olefin substituent of **25** to mask this functionality until a later point (Scheme 4). Thus, the C-2 alcohol would need to be released for glycosidation with the appropriate C-ring glycosyl donor. The usual conditions for deprotection of the SEM ether (TBAF–THF or TBAF–DMPU)[13b] gave only complex product mixtures, but acidic methanolysis (CSA, MeOH, 25 °C, 24 h) furnished the fully functionalized A ring glycosyl acceptor **29** in good yield (87%). The glycosidation of the alcohol **29** with the glycosyl fluoride of the C ring aminosugar **30**[22] (see Scheme 4) occurred readily following the Mukaiyama protocol.[6,23] Thus, upon exposure of the mixture to $AgClO_4$ and $SnCl_2$ in the presence of 4 Å molecular sieves (−40 °C), the disaccharide **31** was obtained as a single isomer (91% yield based on 61% conversion). The stereochemistry of the newly formed α-glycosidic linkage was confirmed by both the lack of large coupling constants ($J > 3$ Hz) for the anomeric proton of the 2-deoxy sugar to the neighboring (C-2) protons, and the lack of NOE's (^1H–^1H ROESY, 600 MHz, 25 °C) which would be expected between the same anomeric proton of a β-glycosidic linkage and any 1,3-diaxial protons. Anticipating the eventual need to selectively deprotect another benzoate, the C-3 benzoate of the A ring was cleaved with DIBAL to give the alcohol **32** (90% yield) which was re-protected (TESOTf, $i Pr_2EtN$) to give the triethylsilyl ether **33** (85% yield). In this case, dihydroxylation (OsO_4, pyridine) gave the diol **34** as a single diastereomer. Molecular modeling of the olefin substrate **33** suggests a single, low energy conformation about the sp^3–sp^2 bond between C-4 of the A ring and the vinyl substituent, with the *re* face of the olefin much less sterically hindered, thereby more exposed to the osmium oxidant than the *si* face. Thus, the absolute stereochemistry of C-7 of the diol **31** has tentatively been given the *R* assignment, in agreement with the stereochemistry determined for the major dihydroxylation product of the olefin **25**.

Conclusion

A method for the synthesis of the unusual A ring thiosugar of namenamicin (**1**) and its elaboration to the A–C disaccharide of this novel natural product has been achieved. Two approaches were studied for the introduction of the requisite quaternary (C-4) center of the A-ring. While the spirocyclic [3,3] sigmatropic rearrangement of an allylic thiocarbonate proceeded with stereoselectivity *counter* to that which could be expected from literature precedent,[6] the C-4 sulfur substituent was introduced with the desired stereochemistry by way of an intramolecular conjugate addition of a xanthate anion. Further manipulations of the functionalities within the cyclic dithiocarbonate thus obtained gave way to the A-ring alcohol **29**, which served as an excellent glycosyl acceptor toward the aminosugar fluoride **30**. Continuing studies directed towards the total synthesis of **1** are in progress.

Experimental

General experimental techniques

NMR spectra were recorded on Bruker DRX-600 or AMX-500 instruments. The following abbreviations were used to explain the multiplicities: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; b, broad; at, apparent triplet; obs, obscured. Coupling constants are given in Hz. IR spectra were recorded on a Perkin-Elmer 1600 series FT-IR spectrophotometer. Optical rotations were recorded 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.

All reactions were monitored by thin-layer chromatography carried out on 0.25 mm E. Merck silica gel plates (60F-254), using UV light, ethanolic *p*-anisaldehyde solution as developing agent. E. Merck silica gel (60, particle size 0.040–0.063 mm) was used for flash column chromatography. Tetrahydrofuran (THF) and diethyl ether were distilled from sodium–benzophenone and methylene chloride, benzene and toluene were distilled from calcium hydride.

All reactions were carried out under an argon atmosphere with anhydrous, freshly distilled solvents under anhydrous conditions, unless otherwise noted. Yields refer to chromatographically and spectroscopically (^1H NMR) homogeneous materials, unless otherwise stated.

[5-{5-[Ethyl(9*H*-fluoren-9-ylmethoxycarbonyl)amino]-4-methoxytetrahydropyran-2-yloxy}-4-hydroxy-2-methyl-6-(2-nitrobenzyloxy)tetrahydropyran-3-ylidene]acetic acid ethyl ester 3

To a solution of the ketone **2** (1.02 g, 1.5 mmol) in dry CH_3CN (7.5 mL) was added ethyl (triphenylphosphoranylidene)acetate (1.05 g, 3.0 mmol) and the resulting solution was heated at 50 °C under argon for 3 h. The reaction mixture was diluted with ethyl acetate (70 mL) and washed with saturated aqueous NH_4Cl (2 × 50 mL), H_2O (2 × 50 mL), and brine (2 × 50 mL). The organic phase was dried ($MgSO_4$), concentrated and purified by flash column chromatography (silica gel, 50% ethyl acetate in hexanes) to afford the ester **3** (0.807 g, 72%) as a white foam. **3**: $R_f = 0.60$ (silica, 80% ethyl acetate in hexanes); $[a]_D^{22} = -57.6$ (*c* 0.87, $CHCl_3$); IR (thin film) ν_{max} 3407, 2935, 2361, 1700, 1526, 1451, 1341, 1276 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6, 350 K) δ 8.00 (d, *J* 8.3, 1 H, nitrobenzyl Ar), 7.83 (d, *J* 7.4, 2 H, FMOC Ar), 7.77 (d, *J* 7.8, 1 H, nitrobenzyl Ar), 7.70 (m, 1 H, nitrobenzyl Ar), 7.58 (dd, *J* 9.8, 7.6, 2 H, FMOC Ar), 7.52–7.49 (m, 1 H, nitrobenzyl Ar), 7.39–7.37 (m, 2 H, FMOC, Ar), 7.30–7.27 (m, 2 H, FMOC Ar), 5.94 (dd, *J* 1.7, 1.6, 1 H, C*H*CO_2Et), 5.52 (d, *J* 5.6, 1 H, A-1), 5.23 (dd, *J* 6.9, 1.9, 1 H, H-3), 5.22 (b s, 1 H, C-1), 5.13, 4.87 (doublets, *J* 14.4, 1 H each, nitrobenzyl CH_2), 4.70 (d, *J* 6.1), 4.37–4.30 (m, 2 H, FMOC CH_2), 4.22 (dd, *J* 6.1, 6.0, 1 H, FMOC benzylic), 4.18 (dd, *J* 5.6, 5.4, 1 H), 4.12 (q, *J* 7.0, 2 H, $CO_2CH_2CH_3$), 3.80 (t,

J 6.4, 1 H), 3.70 (b s, 1 H, C-3), 3.15 (s, 3 H, OCH_3), 2.78 (b s, 1 H, C-4), 2.32 (m, 1 H, C-2 eq), 1.44 (d, 6.8, 3 H, A-6), 1.39 (m, 1 H, C-2 ax), 1.22 (t, *J* 7.0, 3 H, $CO_2CH_2CH_3$), 0.67 (b s, 3 H, NCH_2CH_3); ^{13}C NMR (600 MHz, DMSO-d_6, 350 K) δ 164.58, 160.51, 143.60, 140.49, 133.14, 133.03, 128.64, 128.09, 127.06, 126.50, 124.36, 123.81, 119.50, 114.14, 101.78, 96.03, 92.21, 83.25, 71.95, 70.86, 69.62, 65.67, 59.29, 54.54, 54.29, 46.56, 34.44, 21.06, 13.79, 13.57; HRMS (FAB) Calc. for $C_{40}H_{46}O_{12}N_2$ (M + Cs): 879.2105, found 879.2082.

[5-{5-[Ethyl(9*H*-fluoren-9-ylmethoxycarbonyl)amino]-4-methoxytetrahydropyran-2-yloxy}-2-methyl-6-(2-nitrobenzyloxy)-4-(triethylsilyloxy)tetrahydropyran-3-ylidene]acetate acid ethyl ester 4

To a solution of the ester **3** (795 mg, 1.06 mmol) in CH_2Cl_2 (20 mL) at 0 °C under argon was added *N*,*N*-diisopropylethylamine (0.93 mL, 5.32 mmol) followed by triethylsilyl trifluoromethanesulfonate (0.96 mL, 4.24 mmol). After 10 min, the reaction mixture was diluted with ethyl acetate (100 mL) and washed with saturated aqueous $NaHCO_3$ (100 mL) and brine (100 mL). The organic layer was dried ($MgSO_4$), concentrated under reduced pressure and purified by flash column chromatography (25% ethyl acetate in hexanes) to give the silyl ether **4** (685 mg, 75%) as a white foam. **4**: $R_f = 0.69$ (silica, 70% ethyl acetate in hexanes); $[a]_D^{22} = -52.9$ (*c* 0.17, $CHCl_3$); IR (thin film) ν_{max} 2932, 2359, 1698, 1526, 1456, 1339, 1222, 1158 cm^{-1}; ^{1}H NMR (600 MHz DMSO-d_6, 350 K) δ 8.00 (d, *J* 8.1, 1 H, nitrobenzyl Ar), 7.83 (d, *J* 7.6, 2 H, FMOC Ar), 7.77 (d, *J* 7.7, 1 H, aromatic), 7.69 (dd, *J* 7.4, 7.2, 1 H, nitrobenzyl Ar), 7.63 (dd, *J* 7.5, 7.4, 1 H, nitrobenzyl Ar), 7.58 (dd, *J* 8.5, 7.9, 2 H, FMOC Ar), 7.51 (t, *J* 7.1, 1 H, nitrobenzyl Ar), 7.38 (dd, *J* 7.4, 7.3, 2 H, FMOC Ar), 7.32–7.27 (m, 2 H, FMOC Ar), 5.93 (s, 1 H, C*H*CO_2Et), 5.19 (dq, *J* 6.5, 1.2, 1 H, A-5), 5.11 (b s, 1 H, C-1), 5.10, 4.91 (doublets, *J* 14.5, 1 H each, nitrobenzyl CH_2), 4.53 (d, *J* 6.0, 1 H, A-1), 4.37–4.31 (m, 2 H, FMOC CH_2), 4.29 (d, *J* 2.1, 1 H, A-3), 4.22 (t, *J* 5.9, 1 H, FMOC benzylic), 4.13 (q, *J* 7.1, 2 H, $CO_2CH_2CH_3$), 3.80 (dd, *J* 5.8, 2.7, 1 H, A-2), 3.69 (b m, 3 H, C-3, C-5, C-5′), 3.22 (m, 1 H, C-4), 3.15 (s, 3 H, OCH_3), 2.82 (b m, 2 H, NCH_2), 2.23 (m, 1 H, C-2 eq), 1.45 (d, *J* 6.6, 3 H, A-6), 1.24 (obs m, 1 H, C-2 ax), 1.23 (t, *J* 7.0, 3 H, $CO_2CH_2CH_3$), 0.94 (t, *J* 7.9, 9 H, $Si(CH_2CH_3)_3$), 0.75–0.60 (m, 9 H, $Si(CH_2CH_3)_3$, NCH_2CH_3); ^{13}C NMR (600 MHz, DMSO-d_6, 350 K) δ 174.34, 164.31, 158.10, 154.63, 143.60, 140.49, 133.15, 133.10, 128.65, 128.10, 127.06, 126.51, 124.34, 123.81, 119.50, 116.54, 111.46, 101.56, 94.57, 78.73, 78.17, 73.74, 70.92, 66.00, 59.54, 54.57, 46.56, 34.48, 21.01, 13.80, 13.55, 6.14, 6.02, 5.40, 3.95; HRMS (FAB) Calc. for $C_{46}H_{60}O_{12}N_2Si$ (M + Cs): 993.2970, found 993.2928.

***N*-Ethyl-*N*-{6-[5-(2-hydroxyethylidene)-6-methyl-2-(2-nitrobenzyloxy)-4-(triethylsilyloxy)tetrahydropyran-3-yloxy]-4-methoxytetrahydropyran-3-yl}carbamic acid 9*H*-fluoren-9-ylmethyl ester 5**

DIBAL (1.0 M in CH_2Cl_2, 1.95 mL) was added dropwise to a solution of the ester **4** (560 mg, 0.65 mmol) in CH_2Cl_2 (5.0 mL) at −50 °C. After 45 min without warming, the reaction was quenched with the addition of ethyl acetate (1.0 mL) and the solution poured into a rapidly stirred mixture of saturated aqueous sodium potassium tartrate and saturated aqueous $NaHCO_3$ (1 : 1, 30 mL), washing with CH_2Cl_2. After 40 min, the clear organic phase was removed, dried (Na_2SO_4), concentrated under reduced pressure, and purified by flash column chromatography (50% ethyl acetate in hexanes) to give the alcohol **5** (425 mg, 80%) as a colorless oil. **5**: $R_f = 0.45$ (silica, 60% ethyl acetate in hexanes); $[a]_D^{22} = -48.3$ (*c* 0.59, $CHCl_3$); IR (thin film) ν_{max} 3404, 2933, 2345, 1691, 1640, 1526, 1342, 1281, 1163, 1148, 1097, 1056, 1016 cm^{-1}; ^{1}H NMR (600 MHz, DMSO-d_6, 350 K) δ 8.00 (d, *J* 7.9, 1 H, nitrobenzyl Ar), 7.83 (d, *J* 7.5, 2 H, FMOC Ar), 7.78 (d, *J* 7.7, 1 H, nitrobenzyl Ar), 7.69 (dd, *J* 7.3, 7.3, 1 H, nitrobenzyl Ar), 7.58 (dd, *J* 8.1, 8.0, 2 H, FMOC Ar), 7.51 (t, *J* 7.3, 1 H, nitrobenzyl Ar), 7.38 (dd, *J* 7.5, 7.4, 2 H, FMOC Ar), 7.31–7.28 (m, 2 H, FMOC Ar), 5.68 (s, 1 H, C*H* vinylic), 5.55 (dd, *J* 5.6, 5.4, 1 H, O*H*), 5.09 (b s, 1 H, C-1), 5.08, 4.90 (doublets, *J* 14.6, 1 H each, nitrobenzyl CH_2), 4.64 (q, *J* 6.3, 1 H, A-5), 4.46 (d, *J* 6.0, 1 H, A-1), 4.37–4.31 (m, 2 H, FMOC CH_2), 4.22 (t, *J* 5.8, 1 H, FMOC benzylic), 4.11 (b s, 1 H, A-3), 4.04 (dd, *J* 14.0, 7.1, 1 H, C*H*OH), 3.93 (dd, *J* 13.9, 4.9, 1 H, C*H*′OH), 3.72 (dd, *J* 5.8, 1.7, 1 H, A-2), 3.72–3.58 (m, 3 H, C-3, C-5, C-5′), 3.22 (m, 1 H, C-4), 3.15 (s, 3 H, OCH_3), 2.82 (b m, 2 H, NCH_2), 2.21 (b d, *J* 10.4, 1 H, C-2 eq), 1.45 (m, 1 H, C-2 ax), 1.33 (d, *J* 6.6, 3 H, A-6), 0.94 (t, *J* 7.9, 9 H, $Si(CH_2CH_3)_3$), 0.66 (b s, 3 H, NCH_2CH_3), 0.62 (q, *J* 7.9, 6 H, $Si(CH_2CH_3)_3$); ^{13}C NMR (600 MHz, $CDCl_3$) δ 154.63, 146.89, 143.60, 140.49, 136.94, 133.17, 133.10, 128.63, 128.04, 127.06, 126.72, 126.50, 124.33, 123.80, 119.49, 101.55, 101.39, 94.29, 92.22, 78.84, 74.78, 70.97, 70.10, 65.90, 56.42, 54.55, 46.56, 34.60, 21.66, 13.80, 6.10, 5.40, 4.06; HRMS (FAB) Calc. for $C_{44}H_{58}O_{11}N_2Si$ (M + Cs): 951.2864, found 951.2889.

Thiocarbonic acid *S*-[5-{5-[ethyl(9*H*-fluoren-9-ylmethoxycarbonyl)amino]-4-methoxytetrahydropyran-2-yloxy}-2-methyl-6-(2-nitrobenzyloxy)-4-(triethylsilyloxy)-3-vinyltetrahydropyran-3-yl] ester *O*-phenyl ester 7

To a solution of the alcohol **5** (73 mg, 0.089 mmol) in CH_2Cl_2 (0.60 mL) at room temperature was added pyridine (0.03 mL, 0.36 mmol) followed by phenyl thionochloroformate (*O*-phenyl chlorothioformate, PhOC(S)Cl) (0.02 mL, 0.14 mmol). The solution was stirred under argon for 45 min, diluted with ethyl acetate (50 mL), washed with saturated aqueous $NaHCO_3$ (50 mL) and brine (50 mL). The organic layer was dried (Na_2SO_4), concentrated under reduced pressure, and purified by flash column chromatography (25% ethyl acetate in hexanes) to give the thiocarbonate **6** (85 mg, 99%): oil; $R_f = 0.35$ (30% ethyl acetate in hexanes). HRMS (FAB) Calc. for $C_{51}H_{62}O_{12}N_2SSi$ (M + Cs): 1087.2847, found 1087.2875. The product **6** was used immediately in the next step.

The thiocarbonate *O*-ester **6** was azeotroped to dryness from benzene (5 mL), and the neat compound placed under an atmosphere of argon and heated at 170 °C for 6 min. After cooling to room temperature, the material was taken up in CH_2Cl_2 (2 mL) and checked for completion. The solution was concentrated and the residue purified by flash column chromatography (silica, 30% ethyl acetate in hexanes) to give the monothiocarbonate *S*-ester **7** (68 mg, 80%) as an oil. **7**: $R_f = 0.49$ (silica, 40% ethyl acetate in hexanes); $[a]_D^{22} = -48.2$ (*c* 2.09, $CHCl_3$); IR (thin film) ν_{max} 3410, 2955, 2868, 2360, 1698, 1526, 1453, 1422, 1366, 1090 cm^{-1}; ^{1}H NMR (600 MHz, DMSO-d_6, 350 K) δ 7.98 (d, *J* 8.1, 1 H, nitrobenzyl Ar), 7.83–7.79 (m, 3 H, aromatic), 7.69 (dd, *J* 7.6, 7.2, 1 H, nitrobenzyl Ar), 7.58 (dd, *J* 7.1, 7.0, 2 H, aromatic), 7.50 (dd, *J* 7.7, 7.3, 1 H, nitrobenzyl Ar), 7.48–7.45 (m, 2 H, aromatic), 7.37 (dd, *J* 7.4, 7.3, 2 H, aromatic), 7.32 (t, *J* 7.4, 1 H, aromatic), 7.30–7.27 (m, 2 H, aromatic), 7.16 (d, *J* 7.6, 2 H, aromatic), 5.98 (dd, *J* 17.7, 11.5, 1 H, C*H*=CH_2), 5.52 (d, *J* 11.5, 1 H, *cis*-*H*CH′=CH), 5.39 (d, *J* 17.7, 1 H, *trans*-HC*H*=CH), 5.12 (b s, 1 H, C-1), 5.09, 5.00 (doublets, *J* 14.5, 1 H each, nitrobenzyl CH_2), 4.59 (d, *J* 7.9, 1 H, A-1), 4.53 (d, *J* 8.7, 1 H, A-3), 4.41 (q, *J* 6.3, 1 H, A-5), 4.40–4.33 (m, 2 H, FMOC CH_2), 4.22 (t, *J* 6.0, 1 H, FMOC benzylic), 3.82 (b m, 1 H, one of C-3, C-5, or C-5′), 3.73 (b m, 1 H, one of C-3, C-5, or C-5′), 3.57 (t, *J* 8.3, 1 H, A-2), 3.17 (s, 3 H, OCH_3), 2.82 (b m, 2 H, NCH_2), 2.28 (b d, *J* 12.5, 1 H, C-2 eq), 1.42 (m, 1 H, C-2 ax), 1.28 (d, *J* 6.3, 3 H, A-6), 0.99 (t, *J* 7.9, 9 H, $Si(CH_2CH_3)_3$), 0.74 (q, *J* 7.9, 6 H, $Si(CH_2CH_3)_3$), 0.70–0.66 (b m, 3 H, NCH_2CH_3); ^{13}C NMR (600 MHz, DMSO-d_6, 350 K) δ 168.65, 159.55, 156.35, 151.63, 148.70, 145.33, 142.22, 134.75, 134.69, 133.15, 131.13, 130.68, 129.82, 128.77, 128.23, 127.92, 126.05, 125.44, 122.48, 122.43, 121.20, 102.61, 99.32, 80.04, 77.26, 72.90, 71.26, 68.06, 67.53, 65.80, 63.96, 61.13, 56.25,

48.31, 36.54, 29.27, 16.95, 15.51, 8.01, 6.60, 5.73; HRMS (FAB) Calc. for $C_5H_{62}O_{12}N_2SSi$ (M + Cs): 1087.2847, found 1087.297.

Thiocarbonic acid *S*-[5-(5-ethylamino-4-methoxytetrahydropyran-2-yloxy)-4-hydroxy-2-methyl-6-(2-nitrobenzyloxy)-4-triethylsilyloxy-3-vinyltetrahydropyran-3-yl] ester *O*-phenyl ester 8

A solution of the carbamate **7** (21 mg, 0.022 mmol) in a mixture of THF (0.6 mL) and ethylenediamine (0.2 mL) was stirred at room temperature for 2 h. The solvent was removed under reduced pressure, and the residue purified by preparative TLC (0.5 mm silica, 20 cm × 20 cm, 50% ethyl acetate in hexanes) to give the amine **8** (15 mg, 90%) as an oil. **8**: $R_f = 0.15$ (silica, 50% ethyl acetate in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (d, *J* 7.5, 1 H, nitrobenzyl Ar), 7.86 (d, *J* 7.5, 1 H, nitrobenzyl Ar), 7.53 (t, *J* 7.5, 1 H, nitrobenzyl Ar), 7.31 (t, *J* 8.0, 3 H, aromatic), 7.17 (t, *J* 7.5, 1 H, phenyl), 7.02 (d, *J* 8.0, 2 H, phenyl), 5.93 (dd, *J* 18.0, 11.5, 1 H, C*H*=CH$_2$), 5.37 (d, *J* 11.5, 1 H, *cis*-(*H*)CH=CH), 5.27 (d, *J* 18.0, 1 H, *trans*-(H)C*H′*=CH), 5.19 (d, *J* 15.0, 1 H, benzylic), 5.06 (b s, 1 H, C-1), 4.93 (d, *J* 15.0, 1 H, benzylic), 4.49 (d, *J* 8.5, 1 H, A-1), 4.45–4.42 (m, 2 H, A-3, A-5), 3.58 (dd, *J* 8.5, 8.0, 1 H, A-2), 3.52 (b m, 1 H, C-4), 3.40–3.33 (m, 2 H, C-3, C-5), 3.24 (s, 3 H, OC*H*$_3$), 2.53 (b m, 1 H, C-5′), 2.40 (b m, 2 H, NC*H*$_2$CH$_3$), 2.15 (m, 1 H, C-2 eq), 1.45 (m, 1 H, C-2 ax), 1.26 (d, *J* 6.0, 3 H, A-6), 0.92–0.88 (m, 12 H, NCH$_2$C*H*$_3$, Si(CH$_2$C*H*$_3$)$_3$), 0.66 (q, *J* 8.0, 6 H, Si(C*H*$_2$CH$_3$)$_3$); HRMS (FAB) Calc. for $C_{36}H_{52}O_{10}N_2SSi$ (M + Cs): 865.2166, found 865.2187.

***N*-Ethyl-*N*-{6-[4-hydroxy-5-(2-hydroxyethylidene)-6-methyl-2-(2-nitrobenzyloxy)tetrahydropyran-3-yloxy]-4-methoxytetrahydropyran-3-yl}carbamic acid 9*H*-fluoren-9-ylmethyl ester 9**

To a solution of the alcohol **4** (68 mg, 0.08 mmol) in THF (0.90 mL) in a small, plastic vial at 0 °C was added HF·pyridine complex (0.05 mL). The solution was stirred for 1 h without warming, and poured into a mixture of saturated aqueous $NaHCO_3$ (15 mL) and ethyl acetate (15 mL). The organic layer was washed with brine (20 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Flash column chromatography (90% ethyl acetate in hexanes) provided the pure diol **9** (41 mg, 75%) as an oil. **9**: $R_f = 0.31$ (silica, 100% ethyl acetate); $[\alpha]_D^{23} = -16.0$ (*c* 0.48, $CHCl_3$); IR (thin film) ν_{max} 3405, 2934, 2362, 1694, 1526, 1450, 1423, 1336, 1259, 1145, 1058, 981 cm^{-1}; ^{1}H NMR (600 MHz, DMSO-d_6, 350 K) δ 8.00 (d, *J* 8.1, 1 H, nitrobenzyl Ar), 7.83 (d, *J* 7.9, 2 H, FMOC Ar), 7.78 (d, *J* 7.9, 1 H, aromatic), 7.69 (dd, *J* 7.5, 7.0, 1 H, aromatic), 7.64 (d, *J* 7.5, 1 H, aromatic), 7.58 (dd, *J* 9.0, 8.0, 1 H, aromatic), 7.51 (t, *J* 8.0, 1 H, aromatic), 7.41–7.37 (m, 2 H, aromatic), 7.32–7.27 (m, 2 H, aromatic), 5.58 (dd, *J* 6.3, 5.6, 1 H, C*H* vinylic), 5.19 (s, 1 H, C-1), 5.09 (d, *J* 14.6, 1 H, nitrobenzyl benzylic), 4.95 (d, *J* 5.7, 1 H, O*H*), 4.88 (d, *J* 14.6, 1 H, nitrobenzyl benzylic), 4.62 (q, *J* 6.2, 1 H, A-5), 4.54 (d, *J* 6.4, 1 H, A-1), 4.42–4.32 (m, 2 H, FMOC C*H*$_2$), 4.34 (d, *J* 6.0, 1 H, *H*CH′OH), 4.22 (dd, *J* 6.0, 5.9, 1 H, FMOC benzylic), 3.96–3.70 (m, 3 H, C-3, C-5, C-5′), 3.68 (dd, *J* 6.1, 4.9, 1 H, HC*H′*OH), 3.15 (s, 3 H, OC*H*$_3$), 2.82 (m, 2 H, C*H*$_2$N), 2.26 (b m, 1 H, C-2 eq), 1.38 (m, 1 H, C-2 ax), 1.33 (d, *J* 6.2, 3 H, A-6), 0.61 (b m, 3 H, C*H*$_3$CH$_2$N); ^{13}C NMR (600 MHz, DMSO-d_6, 350 K) δ 159.61, 154.67, 154.23, 143.59, 140.48, 138.20, 133.12, 128.62, 128.04, 127.06, 126.67, 124.36, 123.79, 119.50, 95.21, 73.29, 71.02, 70.09, 65.71, 56.58, 54.53, 46.62, 46.56, 34.58, 21.81; HRMS (FAB) Calc. for $C_{38}H_{44}O_{11}N_2$ (M + Cs): 837.1999, found 837.1979.

7-(5-Ethylamino-4-methoxytetrahydropyran-2-yloxy)-4-methyl-6-(2-nitrobenzyloxy)-3a-vinyltetrahydro[1,3]oxathiolo[4,5-*c*]-pyran-2-one 13

To a solution of the diol **9** (39 mg, 0.06 mmol) in CH_2Cl_2 (0.70 mL) at 0 °C was added pyridine (0.013 mL, 0.17 mmol) and phenyl thionochloroformate (0.01 mL, 0.072 mmol). After 1.5 h at 0 °C, the reaction mixture was diluted with ethyl acetate (15 mL) and washed with saturated aqueous $NaHCO_3$ (20 mL) and brine (20 mL). The organic layer was dried (Na_2SO_4), concentrated under reduced pressure, and purified by flash column chromatography (silica, 40% ethyl acetate in hexanes) to give the thiocarbonate **10** (39 mg, 84%), which was used immediately in the next step. $R_f = 0.38$ (silica, 60% ethyl acetate in hexanes); HRMS (FAB) Calc. for $C_{45}H_{48}O_{12}N_2S$ (M + Cs): 973.1982, found 973.1959.

A solution of the thiocarbonate **10** (39 mg, 0.046 mmol) in toluene (15 mL) was heated at 100 °C under argon for 1 h. The solvent was removed under reduced pressure and the residue purified by preparative TLC (silica, 60% ethyl acetate in hexanes) to give the major isomer **11** (20 mg, 51%) and a minor, more polar isomer **12** (5 mg, 13%). The major product **11** was used immediately in the next step. Major isomer **11**: $R_f = 042$ (silica, 60% ethyl acetate in hexanes); HRMS (FAB) Calc. for $C_{45}H_{48}O_{12}N_2S$ (M + Cs): 973.1982, found 973.2011. Minor isomer **12**: $R_f = 0.26$ (silica, 60% ethyl acetate in hexanes); HRMS (FAB) Calc. for $C_{45}H_{48}O_{12}N_2S$ (M + Cs): 973.1982, found 973.2008.

The major product from the rearrangement step **11** (15 mg, 0.018 mmol) was dissolved in THF–diethylamine (0.6 mL, 2 : 1) and stirred at 25 °C under argon for 2 h. The reaction mixture was concentrated under reduced pressure and purified by preparative TLC (silica, 80% ethyl acetate in hexanes) to give the free base **13** (8.5 mg, 90%) as an oil. **13**: $R_f = 0.18$ (silica, 80% ethyl acetate in hexanes); $[\alpha]_D^{22} = -24.3$ (*c* 0.40, $CHCl_3$); IR (thin film) ν_{max} 2926, 2359, 1755, 1526, 1342, 1047 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.11 (dd, *J* 8.2, 1.1, 1 H, aromatic), 7.94 (d, *J* 7.6, 1 H, aromatic), 7.67 (ddd, *J* 7.6, 7.6, 1.2, 1 H, aromatic), 7.45 (dd, *J* 8.3, 7.3, 1 H, aromatic), 6.23 (dd, *J* 16.8, 10.7, 1 H, C*H*=CH$_2$), 5.85 (d, *J* 16.8, 1 H, *trans*-*H*CH′=CH), 5.65 (d, *J* 10.7, 1 H, *cis*-HC*H′*=CH), 5.34, 5.15 (doublets, *J* 15.0, benzylic), 5.13 (m, 1 H, C-1), 4.74 (d, *J* 7.0, 1 H, A-1), 4.37 (d, *J* 10.9, 1 H, A-3), 4.12–4.05 (m, 2 H, A-5, A-2), 3.69–3.62 (m, 3 H, C-3, C-5, C-5′), 3.33 (s, 3 H, OC*H*$_3$), 2.70–2.66 (m, 1 H, C-4), 2.56–2.53 (m, 2 H, C*H*$_2$N), 2.25 (ddd, *J* 13.0, 4.6, 1.8, 1 H, C-2 eq), 1.52 (m, 1 H, C-2 ax), 1.18 (d, *J* 6.4, 3 H, A-6), 1.04 (t, *J* 7.1, 3 H, C*H*$_3$CH$_2$N); ^{13}C NMR (600 MHz, $CDCl_3$) δ 134.08, 133.72, 130.39, 129.505, 128.13, 124.76, 123.68, 102.19, 97.71, 89.49, 79.63, 78.30, 78.17, 77.94, 74.23, 72.16, 68.16, 65.60, 58.62, 56.11, 41.66, 33.61, 29.69, 17.73; HRMS (FAB) Calc. for $C_{24}H_{32}O_9N_2S$ (M + Cs): 525.1907, found 525.1915.

4-Methyl-6-(2-nitrobenzyloxy)-7-[2-(trimethylsilyl)ethoxymethoxy]tetrahydro[1,3]dioxolo[4,5-*c*]pyran-2-one 15

To a solution of the alcohol **14** (26.9 g, 83 mmol) in dry CH_2Cl_2 (41 mL) at 0 °C was added *N*,*N*-diisopropylethylamine (72 mL, 414 mmol) followed by SEM chloride (44 mL, 248 mmol). The reaction mixture was stirred at room temperature for 12 h followed by dilution with ethyl acetate (450 mL). The organic phase was washed with H_2O (400 mL), saturated aqueous $NaHCO_3$ (400 mL), and brine (400 mL) then dried (Na_2SO_4). Concentration under reduced pressure followed by flash column chromatography (silica gel, 35% ethyl acetate in hexanes) provided the SEM ether **15** (34.7 g, 92%) as white plates. **15**: $R_f = 0.28$ (silica, 40% ethyl acetate in hexanes); $[\alpha]_D^{23} = +51.3$ (*c* 2.66, $CHCl_3$); IR (thin film) ν_{max} 2952, 2894, 1805, 1527, 1343, 1249 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.08 (dd, *J* 8.2, 1.1, 1 H, aromatic), 7.79 (dd, *J* 7.5, 0.6, 1 H, aromatic), 7.65 (ddd, *J* 7.5, 1.2, 1 H, aromatic), 7.45 (ddd, *J* 7.5, 1.1, 1 H, aromatic), 5.24 (d, *J* 15.0, 1 H, benzylic), 5.03 (d, *J* 15.0, 1 H, benzylic), 4.86 (d, *J* 6.8, 1 H, OC*H*$_2$O), 4.79 (d, *J* 6.8, 1 H, OC*H*$_2$O), 4.78 (d, *J* 5.0, 1 H, H-1), 4.76 (dd, *J* 7.8, 4.7, 1 H, H-3), 4.61 (dd, *J* 7.8, 1.9, 1 H, H-4), 4.00 (dq, *J* 6.6, 1.8, 1 H, H-5), 3.95 (dd, *J* 5.0, 4.7, 1 H, H-2), 3.71, 3.60 (multiplets, 1 H each, OC*H*$_2$CH$_2$SiMe$_3$), 1.41 (d, *J* 6.6, 3 H, H-6), 0.95 (m, 2 H,

CH_2SiMe_3), 0.00 (s, 9 H, $Si(CH_3)_3$); ^{13}C NMR (600 MHz, $CDCl_3$) δ 153.98, 153.83, 146.96, 133.89, 128.90, 128.16, 124.66, 100.19, 94.74, 76.71, 76.52, 73.24, 67.59, 67.02, 65.85, 17.86, 16.42, −1.50; HRMS (FAB) Calc. for $C_{20}H_{29}O_9NSi$ (M + Cs): 588.0666, found 588.0651.

2-Methyl-6-(2-nitrobenzyloxy)-5-[2-(trimethylsilyl)ethoxymethoxy]tetrahydropyran-3,4-diol 16

To a solution of the carbonate **15** (26.7 g, 58.6 mmol) in anhydrous MeOH (535 mL) was added NaOMe (0.5 M in MeOH, 23 mL, 11.7 mmol). After 20 min at room temperature, Amberlyst R-15 resin (3 g) was added in small portions until the solution reached neutrality. Filtration followed by concentration of the filtrate under reduced pressure provided the diol **16** (25.1 g, 99%) as a colorless oil. **16**: $R_f = 0.36$ (silica, 70% ethyl acetate in hexanes); $[\alpha]_D^{23} = +46.8$ (*c* 1.52, $CHCl_3$); IR (thin film) ν_{max} 3422, 2952, 2361, 1684, 1526, 1341, 1062, 859 cm^{-1} ^1H NMR (600 MHz, $CDCl_3$) δ 8.05 (dd, *J* 8.1, 1.1, 1 H, aromatic), 7.82 (d, *J* 7.8, 1 H, aromatic), 7.63 (ddd, *J* 7.4, 1.09, 1 H, aromatic), 7.42 (dd, *J* 7.4, 1.1, 1 H, aromatic), 5.27 (d, *J* 15.0, 1 H, benzylic), 5.07 (d, *J* 15.0, 1 H benzylic), 4.89 (d, *J* 6.7, 1 H, OCH_2O), 4.74 (d, *J* 6.7, 1 H, OCH_2O), 4.45 (d, *J* 7.4, 1 H, H-1), 4.40 (d, *J* 1.2, CHO*H*), 3.84 (m, 1 H, $OCH_2CH_2SiMe_3$), 3.78 (s, 1 H, CHO*H*), 3.65 (q, 1 H, *J* 6.5, 1 H, H-5), 3.61–3.53 (m, 4 H, $OCH_2CH_2SiMe_3$, H-2, H-3, H-4), 1.38 (d, *J* 6.48, 3 H, H-6), 0.99 (m, 2 H, CH_2SiMe_3), 0.01 (s, 9 H, $Si(CH_3)_3$); ^{13}C NMR (600 MHz, $CDCl_3$) δ 148.08, 135.31, 134.45, 129.78, 128.89, 125.50, 102.27, 97.53, 82.52, 73.75, 71.69, 71.19, 68.61, 67.23, 18.98, 17.13, −0.65; HRMS (FAB) Calc. for $C_{19}H_{31}O_8NSi$ (M + Cs): 562.0873, found 562.0861.

4-Hydroxy-2-methyl-6-(2-nitrobenzyloxy)-5-[2-(trimethylsilyl)-ethoxymethoxy]tetrahydropyran-3-one 17

A mixture of the diol **16** (3.49 g, 8.13 mmol) and dibutyltin oxide (2.12 g, 8.52 mmol) in dry methanol (120 mL) was vigorously refluxed for 1 h. After cooling to room temperature, the clear solution was concentrated *in vacuo* and azeotroped to dryness several times from benzene. After taking up the residue in CH_2Cl_2 (120 mL) and adding tributyltin methoxide (2.57 mL, 8.93 mmol), the pale yellow solution was tritiated by the dropwise addition of a 1 M solution of Br_2 in CH_2Cl_2 (*ca.* 8 mL) until the orange color persisted without fading. The solution was diluted with ethyl acetate (600 mL) and the organic phase washed with saturated aqueous $NaHCO_3$ (2 × 200 mL) and brine (200 mL). After drying ($MgSO_4$) and filtering through a pad of Celite, the filtrate was concentrated under reduced pressure to give a residue which was dissolved in acetonitrile (500 mL). The solution was washed with hexanes (2 × 500 mL) and concentrated to give the crude ketone **17** as an oil, which was used in the next step without further purification. A small portion (50 mg) of the crude material was purified by flash column chromatography (silica gel, 30% ethyl acetate in hexanes) for analytical characterization. **17**: $R_f = 0.31$ (silica, 40% ethyl acetate in hexanes); $[\alpha]_D^{23} = +20.9$ (*c* 2.0, $CHCl_3$); IR (thin film) ν_{max} 3448, 2955, 2355, 1737, 1520, 1337, 1243, 1055, 844 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.10 (dd, *J* 8.2, 1.2, 1 H, aromatic), 7.83 (dd, *J* 7.2, 0.6, 1 H, aromatic), 7.66 (ddd, *J* 7.8, 7.6, 1.1, 1 H, aromatic), 7.46 (ddd, *J* 8.2, 7.8, 1.0, 1 H, aromatic), 5.31, 5.13 (doublets, *J* 15.1, 1 H each, benzylic), 4.92 (m, 3 H, H-1, OCH_2O), 4.30 (dd, *J* 9.3, 2.5, 1 H, H-3), 4.15 (q, *J* 6.5, 1 H, H-5), 3.82 (m, 2 H, H-2, $OCH_2CH_2SiMe_3$), 3.76 (d, *J* 2.5, 1 H, O*H*), 3.63 (m, 1 H, $OCH_2CH_2SiMe_3$), 1.39 (d, *J* 6.5, 3 H, H-6), 0.93 (m, 2 H, $OCH_2CH_2SiMe_3$), −0.01 (s, 9 H, $Si(CH_3)_3$); ^{13}C NMR (600 MHz, $CDCl_3$) δ 203.29, 133.97, 133.81, 128.78, 128.70, 128.23, 124.79, 101.44, 95.14, 82.09, 76.85, 73.23, 67.87, 65.84, 17.95, 14.29, −1.52; HRMS (FAB) Calc. for $C_{19}H_{29}O_8NSi$ (M + Na): 450.1560, found 450.1572.

{4-Hydroxy-2-methyl-6-(2-nitrobenzyloxy)-5-[2-(trimethylsilyl)-ethoxymethoxy]tetrahydropyran-3-ylidene}acetic acid methyl ester 18

To a solution of the crude ketone **17** (3.44 g) in acetonitrile (170 mL) was added methyl (triphenylphosphoranylidene)acetate (8.0 g, 23.9 mmol) and the resulting solution was heated at 65 °C for 3 h. After concentrating the reaction mixture under reduced pressure, the solid phosphine oxide was removed by filtration, washed with diethyl ether (100 mL) and the filtrate concentrated and purified by flash column chromatography (silica gel, 20% to 30% ethyl acetate in hexanes) to give the ester **18** (2.48 g, 63% for two steps) as a colorless oil. **18**: $R_f = 0.40$ (silica, 40% ethyl acetate in hexanes); $[\alpha]_D^{23} = -7.1$ (*c* 2.73, $CHCl_3$); IR (thin film) ν_{max} 3441, 2949, 2362, 1716, 1529, 1342, 1225 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.07 (dd, *J* 8.1, 1.1, 1 H, aromatic), 7.77 (d, *J* 8.1, 1 H, aromatic), 7.64 (ddd, *J* 7.7, 7.4, 1.2, 1 H, aromatic), 7.46 (ddd, *J* 7.8, 7.4, 1.5, 1 H, aromatic), 6.05 (dd, *J* 1.9, 1.8, 1 H, $CHCO_2CH_3$), 5.42 (dq, *J* 7.0, 1.8, 1 H, H-5), 5.26 (d, *J* 15.0, 1 H, benzylic), 5.00 (d, *J* 15.0, 1 H, benzylic), 4.85 (d, *J* 7.0, 1 H, H-1), 4.77 (two doublets, *J* 5.5, 2 H, OCH_2O), 4.23 (ddd, *J* 5.6, 5.5, 1.9, 1 H, H-3), 3.89 (dd, *J* 7.0, 5.5, 1 H, H-2), 3.67 (m, 1 H, $OCH_2CH_2SiMe_3$), 3.71 (s, 3 H, CO_2CH_3), 3.67 (d, *J* 5.6, 1 H, CHO*H*), 3.61 (m, 1 H, $OCH_2CH_2SiMe_3$), 1.56 (d, *J* 7.0, 3 H, H-6), 0.95 (m, 2 H, $OCH_2CH_2Si(CH_3)_3$), 0.01 (s, 9 H, $Si(CH_3)_3$); ^{13}C NMR (500 MHz, $CDCl_3$) δ 165.9, 159.1, 147.3, 134.1, 133.6, 128.9, 128.2, 124.8, 115.0, 102.9, 95.6, 81.7, 72.09, 72.02, 66.90, 66.19, 51.35, 21.93, 18.06, −1.54; HRMS (FAB) Calc. for $C_{22}H_{33}O_9NSi$ (M + Cs): 616.0979, found 616.0971.

{4-Methyl-6-(2-nitrobenzyloxy)-2-thioxo-7-[2-(trimethylsilyl)-ethoxymethoxy]tetrahydro[1,3]oxathiolo[4,5-*c*]pyran-3a-yl}-acetic acid methyl ester 19

Imidazole (28 mg, 0.39 mmol) was added to a solution of the ester **18** (1.90 g, 3.93 mmol) in THF (67 mL) under argon and the resulting solution cooled to 0 °C. Sodium hydride (60% dispersion in mineral oil, 470 mg, 11.8 mmol) was added to the reaction mixture and the resulting orange-colored mixture stirred at 0 °C for 10 min followed by the dropwise addition of CS_2 (0.36 mL, 5.90 mmol). After ten minutes, the ice bath was removed and the reaction mixture stirred at room temperature for 20 min then carefully poured into a mixture of aqueous 2% (v/v) HCl (150 mL) and Et_2O (50 mL) with rapid stirring. The aqueous phase was washed with diethyl ether (100 mL) and the combined organic extracts washed with brine (100 mL) and dried (Na_2SO_4). Concentration under reduced pressure followed by flash column chromatography (20% ethyl acetate in hexanes) provided the cyclic xanthate **19** (1.83 g, 83%) as an oil. **19**: $R_f = 0.40$ (silica, 40% ethyl acetate in hexanes); $[\alpha]_D^{23} = -15.1$ (*c* 2.93, $CHCl_3$); IR (thin film) ν_{max} 2953, 2894, 1732, 1614, 1578, 1527, 1437, 1343, 1199, 1048 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.11 (dd, *J* 8.2, 1.2, 1 H, aromatic), 7.83 (d, *J* 7.8, 1 H, aromatic), 7.66 (ddd, *J* 7.8, 7.6, 1.2, 1 H, aromatic), 7.46 (ddd, 8.2, 7.8, 1.1, 1 H, aromatic), 5.40 (d, *J* 7.85, 1 H, H-1), 5.30 5.10 (doublets, *J* 15.1, 1 H each, benzylic), 4.98, 4.79 (doublets, *J* 6.7, 1 H each, OCH_2O), 4.62 (d, *J* 8.2, 1 H, H-3), 4.17 (q, *J* 6.3, 1 H, H-5), 4.08 (dd, *J* 8.2, 7.9, 1 H, H-2), 3.92 (m, 1 H, $OCH_2CH_2SiMe_3$), 3.74 (s, 3 H, CO_2CH_3), 3.54 (m, 1 H, $OCH_2CH_2SiMe_3$), 3.09, 2.84 (doublets, *J* 16.5, 1 H, each, $CH_2CO_2CH_3$), 1.31 (d, *J* 6.3, 3 H, H-6), 1.07, 0.92 (two × ddd, *J* 12.0, 8.3, 5.2, 1 H, each, $OCH_2CH_2Si(CH_3)_3$), 0.01 (s, 9 H, $Si(CH_3)_3$); ^{13}C NMR (600 MHz, $CDCl_3$) δ 207.90, 169.27, 146.81, 133.96, 128.57, 128.18, 124.78, 101.55, 94.97, 92.24, 73.91, 69.30, 67.99, 67.97, 67.82, 65.97, 52.42, 40.33, 18.91, 17.90, −1.42; HRMS (FAB) Calc. for $C_{23}H_{33}O_9NS_2Si$ (M + Cs): 692.0420, found 692.0442.

{4-Methyl-6-(2-nitrobenzyloxy)-2-thioxo-7-[2-trimethylsilyl)-ethoxymethoxy]tetrahydro[1,3]oxathiolo[4,5-*c*]pyran-3a-yl}-acetaldehyde 20

DIBAL (1.0 M in CH_2Cl_2, 25.3 mL) was added dropwise to a

solution of the ester **19** (7.07 g, 12.63 mmol) in CH_2Cl_2 (360 mL) under argon at −78 °C. After 0.3 h, the reaction was quenched with the addition of ethyl acetate (20 mL) then poured into a 1:1 mixture of saturated aqueous $NaHCO_3$ and saturated aqueous sodium potassium tartrate (400 mL) and stirred at room temperature for 1 h. The organic layer was removed and the aqueous layer washed with CH_2Cl_2 (100 mL). The combined organic phases were dried (Na_2SO_4) and concentrated under reduced pressure. The crude aldehyde **20** was used in the next step without purification, and a portion (50 mg) of the crude material was purified by flash column chromatography (30% ethyl acetate in hexanes) for analytical purposes. **20**: colorless oil, $R_f = 0.35$ (silica, 40% ethyl acetate in hexanes); $[\alpha]_D^{23} = -16.2$ (*c* 2.85, $CHCl_3$); IR (thin film) ν_{max} 2953, 2891, 1719, 1527, 1342, 1248, 1202 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 9.71 (s, 1 H, CH_2CHO), 8.11 (dd, *J* 13.9, 1.1, 1 H, aromatic), 7.83 (d, *J* 7.84, 1 H, aromatic), 7.66 (ddd, *J* 8.3, 7.8, 1.2, 1 H, aromatic), 7.47 (ddd, *J* 8.3, 7.8, 1.0, 1 H, aromatic), 5.31 (d, *J* 15.1, 1 H, benzylic), 5.14 (d, *J* 7.8, 1 H, H-1), 5.12 (d, *J* 15.1, 1 H, benzylic), 4.98, 4.69 (doublets, *J* 6.7, 1 H each OCH_2O), 4.69 (d, *J* 8.2, 1 H, H-3), 4.29 (q, *J* 6.4, 1 H, H-5), 4.09 (dd, *J* 8.2, 7.8, 1 H, H-2), 3.90, 3.53 (multiplets, 1 H each, $OCH_2CH_2Si(CH_3)_3$), 3.23 (d, *J* 20.0, 1 H, CH_2CHO), 3.08 (dd, *J* 20.0, 0.8, 1 H, CH_2CHO), 1.28 (d, *J* 6.4, 3 H, H-6), 1.07, 0.92 (2 × ddd, *J* 12.0, 6.8, 5.2, 1 H each, $CH_2Si(CH_3)_3$), 0.01 (s, 9 H, $Si(CH_3)_3$); ^{13}C NMR (600 MHz, $CDCl_3$) δ 207.57, 197.57, 146.88, 133.94, 128.62, 128.23, 124.80, 101.52, 94.97, 93.07, 92.69, 73.84, 69.21, 67.83, 67.68, 65.98, 49.55, 18.93, 17.90, −1.42; HRMS (FAB) Calc. for $C_{21}H_{33}O_8NSSi$ (M + Cs): 662.0315, found 662.0330.

3a-(2-Hydroxyethyl)-4-methyl-6-(2-nitrobenzyloxy)-7-[2-(trimethylsilyl)ethoxymethoxy]tetrahydro[1,3]oxathiolo[4,5-*c*]pyran-2-thione 21

$NaBH_4$ (956 mg, 25.3 mmol) was added to a solution of the crude aldehyde **20** (7.0 g) in MeOH (360 mL) at 0 °C. After 10 min, the reaction mixture was poured into chilled 2% (v/v) HCl (300 mL) and extracted with diethyl ether (2 × 400 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (150 mL) and brine (150 mL) then dried (Na_2SO_4), concentrated under reduced pressure and purified by flash column chromatography (50% ethyl acetate in hexanes) to give the alcohol **21** (6.1 g, 91% for two steps) as a white foam. **21**: $R_f = 0.43$ (silica, 60% ethyl acetate in hexanes); $[\alpha]_D^{23} = +18.7$ (*c* 1.43, $CHCl_3$); IR (thin film) ν_{max} 3450, 2952, 2880, 2362, 1523, 1342, 1197, 1047, 860, 834 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.10 (dd, *J* 8.0, 1.1, 1 H, aromatic), 7.84 (dd, *J* 7.8, 0.7, 1 H, aromatic), 7.66 (ddd, *J* 8.0, 7.6, 1.1, 1 H, aromatic), 7.45 (ddd, *J* 8.0, 7.6, 1.1, 1 H aromatic), 5.30 (d, *J* 15.0, 1 H, benzylic), 5.16 (d, *J* 7.7, 1 H, H-1), 5.10 (d, *J* 15.0, 1 H, benzylic), 4.96, 4.79 (doublets, *J* 6.6, 1 H each, OCH_2O), 4.56 (d, *J* 8.0, 1 H, H-3), 4.03 (m, 2 H, H-2, H-5), 3.89 (m, 3 H, CH_2OH), 3.89 (obs bddd, *J* 11.7, 9.6, 5.6, 1 H, $OCH_2CH_2Si(CH_3)_3$), 3.56 (ddd, *J* 11.7, 9.6, 5.6, 1 H, $OCH_2CH_2Si(CH_3)_3$), 2.25, 2.07 (multiplets, 1 H each, CH_2CH_2OH), 1.33 (d, *J* 6.2, 3 H, H-6), 1.06, 0.09 (multiplets, 1 H each, $CH_2Si(CH_3)_3$), 0.01 (s, 9 H, $Si(CH_3)_3$); ^{13}C NMR (600 MHz, $CDCl_3$) δ 146.93, 133.97, 133.91, 128.76, 128.21, 124.75, 101.69, 95.03, 93.44, 74.28, 70.75, 69.42, 67.76, 66.01, 58.52, 40.08, 19.04, 17.91, −1.41; HRMS (FAB) Calc. for $C_{22}H_{33}O_8NS_2Si$ (M + Cs): 664.0471, found 588.0651.

4-Methyl-6-(2-nitrobenzyloxy)-3a-[2-(2-nitrophenylselanyl)-ethyl]-7-[2-(trimethylsilyl)ethoxymethoxy]tetrahydro[1,3]-oxathiolo[4,5-*c*]pyran-2-thione 22

To a solution of the alcohol **21** (5.24 g, 9.86 mmol) in THF (100 mL) was added *o*-nitrophenyl selenocyanate (3.13 g, 13.8 mmol). Tributylphosphine (3.44 mL, 13.8 mmol) was added dropwise at room temperature and the resulting dark brown-black solution was stirred for 20 min. The reaction mixture was then diluted with Et_2O (500 mL) and washed with saturated aqueous $NaHCO_3$ (250 mL). The aqueous layer was then washed with Et_2O (100 mL) and the combined organic layers washed with brine (200 mL), dried (Na_2SO_4), concentrated under reduced pressure, and purified by flash column chromatography (silica gel, 40% hexanes then 20% hexanes in CH_2Cl_2 then 100% CH_2Cl_2) to give the selenide **22** (6.4 g, 78%) as a yellow, powdery solid. **22**: $R_f = 0.42$ (silica, 40% ethyl acetate in hexanes); $[\alpha]_D^{23} = +44.3$ (*c* 2.42, $CHCl_3$); IR (thin film) ν_{max} 2955, 2896, 2355, 1519, 1331, 1196, 1040 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.28 (dd, *J* 8.3, 1.2, 1 H, aromatic), 8.07 (d, *J* 8.2, 1 H, aromatic), 7.82 (d, *J* 7.9, 1 H, aromatic), 7.64 (dd, *J* 10.0, 7.6, 1 H, aromatic), 7.56 (ddd, *J* 7.9, 7.1, 1.3, 1 H, aromatic), 7.49 (d, *J* 8.1, 1 H, aromatic), 7.46 (dd, *J* 7.8, 7.7, 1 H, aromatic), 7.36 (ddd, *J* 9.2, 8.3, 1.1, 1 H, aromatic), 5.27, 5.11 (doublets, *J* 14.7, 1 H each, benzylic), 4.95 (d, *J* 6.5, 1 H, OCH_2O), 4.87 (d, *J* 7.5, 1 H, H-1), 4.82 (d, *J* 6.5, 1 H, OCH_2O), 4.56 (d, *J* 7.6, 1 H, H-3), 4.04 (dd, *J* 7.6, 7.5, 1 H, H-2), 3.88 (ddd, *J* 15.2, 9.8, 5.4, 1 H, $OCH_2CH_2Si(CH_3)_3$), 3.82 (q, *J* 6.3, 1 H, H-5), 3.61 (ddd, *J* 15.2, 9.8, 5.4, 1 H, $OCH_2CH_2Si(CH_3)_3$), 3.14, 3.01 (multiplets, 1 H each, CH_2SeAr), 2.29, 2.19 (multiplets, 1 H each, CH_2CH_2SeAr), 1.33 (d, *J* 6.3, 3 H, H-6), 1.05, 0.95 (multiplets, 1 H each, $CH_2Si(CH_3)_3$), 0.01 (s, 9 H, $Si(CH_3)_3$); ^{13}C NMR (600 MHz, $CDCl_3$) δ 134.00, 133.71, 131.52, 129.20, 128.90, 128.37, 126.55, 126.11, 124.72, 101.84, 95.32, 93.83, 74.59, 71.77, 70.34, 67.80, 66.21, 38.64, 19.94, 19.28, 18.06, −1.37; HRMS (FAB) Calc. for $C_{28}H_{36}O_9N_2S_2SeSi$ (M + Cs): 842.9911, found 848.9879.

4-Methyl-6-(2-nitrobenzyloxy)-7-[2-(trimethylsilyl)ethoxymethoxy]-3a-vinyltetrahydro[1,3]oxathiolo[4,5-*c*]pyran-2-thione 23

To a solution of the selenide **22** (6.4 g, 8.9 mmol) in CH_2Cl_2 (89 mL) was added pyridine (3.6 mL, 44.7 mmol) followed by 2-phenylsulfonyl-3-(phenyl)oxaziridine (2.85 g, 11.6 mmol). The resulting solution was stirred at room temperature for 15 min then diluted with diethyl ether (400 mL) and washed with saturated aqueous $NaHCO_3$ (300 mL) and brine (300 mL). The organic layer was dried (Na_2SO_4), concentrated under reduced pressure, and purified by flash column chromatography (silica gel, hexanes then 10% ethyl acetate then 20% ethyl acetate in hexanes) to give the olefin **23** (3.63 g, 79%) as an oil. **23**: $R_f = 0.35$ (silica, 30% ethyl acetate in hexanes); $[\alpha]_D^{23} = +19.0$ (*c* 2.51, $CHCl_3$); IR (thin film) ν_{max} 2955, 2896, 2344, 1531, 1337, 1196; 1044 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.10 (dd, *J* 8.2, 1.2, 1 H, aromatic), 7.83 (d, *J* 7.9, 1 H, aromatic), 7.66 (ddd, *J* 7.9, 7.6, 1.1, 1 H, aromatic), 7.45 (dd, *J* 8.2, 7.3, 1 H, aromatic), 5.82 (dd, *J* 16.8, 10.4, 1 H, $CH{=}CH_2$), 5.67 (d, *J* 16.8, 1 H, *trans*-CH=C(*H*)H), 5.48 (d, *J* 10.4, 1 H, *cis*-CH=C(*H*)H), 5.31, 5.11 (doublets, *J* 15.1, 1 H each, benzylic), 4.97 (d, *J* 6.6, 1 H, OCH_2O), 5.83 (d, *J* 7.9, 1 H, H-1), 4.79 (d, *J* 6.6, 1 H, OCH_2O), 4.59 (d, *J* 8.1, 1 H, H-3), 4.09 (dd, *J* 8.1, 7.9, 1 H, H-2), 3.90 (ddd, *J* 11.9, 9.6, 5.3, 1 H, $OCH_2CH_2Si(CH_3)_3$), 3.82 (q, *J* 6.3, 1 H, H-5), 3.55 (ddd, *J* 11.8, 9.6, 5.6, 1 H, $OCH_2CH_2Si(CH_3)_3$), 1.25 (d, *J* 6.3, 3 H, H-6), 1.06, 0.92 2 × ddd, *J* 13.6, 11.9, 5.3, 1 H each, $CH_2Si(CH_3)_3$), 0.01 (s, 9 H, $Si(CH_3)_3$); ^{13}C NMR (600 MHz, $CDCl_3$) δ 146.89, 135.06, 133.93, 133.87, 128.71, 128.25, 124.77, 119.69, 101.80, 95.02, 93.44, 93.42, 73.75, 71.64, 71.35, 67.85, 66.01, 18.63, 17.88, −1.42; HRMS (FAB) Calc. for $C_{22}H_{31}O_7NS_2Si$ (M + Cs): 646.0366, found 646.0395.

2-Methyl-3-methylsulfanyl-6-(2-nitrobenzyloxy)-5-[2-(trimethylsilyl)ethoxymethoxy]-3-vinyltetrahydropyran-4-ol 24

The xanthate **23** (3.03 g, 5.90 mmol) was taken up in a 1.0 M solution of MeCl in Et_2O (54 mL, 54 mmol of MeCl) and cooled to 0 °C under an argon atmosphere. Ethylenediamine (25 mL) was added dropwise to the solution. The reaction mixture was stirred at room temperature for 30 min, then heated at 70 °C for 2 h and finally poured into a mixture of 2%

(v/v) HCl (400 mL) and Et_2O (100 mL). The aqueous layer was washed with Et_2O (100 mL), and the combined organic layers washed with saturated aqueous $NaHCO_3$ (200 mL) and brine (200 mL), dried (Na_2SO_4) and concentrated. Purification of the residue by flash column chromatography (20% ethyl acetate in hexanes) gave the alcohol **24** (2.03 g, 80%) as an oil. **24**: $R_f = 0.50$ (silica, 40% ethyl acetate in hexanes); $[\alpha]_D^{23} = -11.3$ (*c* 2.26, $CHCl_3$); IR (thin film) ν_{max} 3441, 2948, 2360, 1252, 1340, 1246, 758 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.06 (dd, *J* 8.2, 1.0, 1 H, aromatic), 7.83 (d, *J* 7.8, 1 H, aromatic), 7.64 (ddd, *J* 7.8, 7.6, 1.0, 1 H, aromatic), 7.44 (ddd, *J* 8.4, 7.8, 0.94, 1 H, aromatic), 5.70 (dd, *J* 17.6, 11.1, 1 H, C*H*=CH_2), 5.47 (dd, *J* 17.6, 1.0, 1 H, *trans*-C(*H*)H=CH), 5.39 (dd, *J* 11.1, 1.0, 1 H, *cis*-C(*H*)H=CH), 5.26, 5.05 (doublets, *J* 15.1, 1 H each, benzylic), 4.92, 4.84 (doublets, *J* 6.6, 1 H each, OCH_2O), 4.46 (d, *J* 7.5, 1 H, H-1), 3.94 (dd, *J* 8.9, 7.5, 1 H, H-2), 3.85 (dd, *J* 8.9, 2.7, 1 H, H-3), 3.83 (m, 1 H, OC$H_2$$CH_2Si(CH_3)_3$), 3.71 (d, *J* 2.7, 1 H, CHO*H*), 3.62 (m, 1 H, OC$H_2$$CH_2Si(CH_3)_3$), 3.50 (q, *J* 6.3, 1 H, H-5), 1.39 (d, *J* 6.3, 3 H, H-6), 0.98 (m, 2 H, OCH_2CH_2-$Si(CH_3)_3$), −0.01 (s, 9 H, $Si(CH_3)_3$); ^{13}C NMR (600 MHz, $CDCl_3$) δ 147.20, 136.25, 134.47, 133.56, 128.93, 127.99, 124.62, 118.44, 102.38, 96.68, 82.11, 75.07, 67.70, 66.40, 62.35, 59.87, 18.16, 15.64, 13.57, −2.21; HRMS (FAB) Calc. for $C_{22}H_{35}O_7NSSi$ (M × Cs): 508.1801, found 508.1815.

Benzoic acid 2-methyl-3-methylsulfanyl-6-(2-nitrobenzyloxy)-5-[2-(trimethylsilyl)ethoxymethoxy]-3-vinyltetrahydropyran-4-yl ester 25

To a solution of the alcohol **24** (2.33 g, 4.59 mmol) in THF (26 mL) at −78 °C under argon was added LHMDS (1.0 M in THF, 9.18 mL). After 10 min at the same temperature, benzoyl chloride (1.33 mL, 11.48 mmol) was added dropwise to the reaction mixture, which was then allowed to warm over 1.5 h to −20 °C. The reaction was quenched with the addition of saturated aqueous NH_4Cl (5 mL) and diluted with Et_2O (100 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ (100 mL), brine (100 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Purification by flash column chromatography (15% ethyl acetate in hexanes) gave the benzoate **25** (2.71 g, 100%) as an oil. **25**: $R_f = 0.51$ (silica, 40% ethyl acetate in hexanes); $[\alpha]_D^{23} = +1.88$ (*c* 2.55, $CHCl_3$); IR (thin film) ν_{max} 2948, 2348, 1722, 1528, 1269, 1092, 1055 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.10–8.09 (m, 3 H, aromatic), 7.89 (dd, *J* 7.8, 0.7, 1 H, aromatic), 7.65 (ddd, *J* 7.8, 7.7, 1.1, 1 H, aromatic), 7.57 (at, *J* 7.4, 1 H, aromatic), 7.47–7.41 (m, 3 H, aromatic), 5.70 (d, *J* 9.4, 1 H, H-3), 5.65 (dd, *J* 17.7, 11.2, 1 H, C*H*=CH_2), 5.42 (d, *J* 17.7, 1 H, *trans*-C(*H*)H=CH), 5.33 (d, *J* 15.3, 1 H, benzylic), 5.29 (d, *J* 11.2, 1 H, *cis*-C(*H*)H=CH), 5.09 (d, *J* 15.3, 1 H, benzylic), 4.87 (d, *J* 6.8, 1 H, OCH_2O), 4.74 (d, *J* 6.8, 1 H, OCH_2O), 4.64 (d, *J* 7.7, 1 H, H-1), 4.39 (dd, *J* 9.4, 7.7, 1 H, H-2), 3.64 (q, *J* 6.2, 1 H, H-5), 3.28 (m, 2 H, OCH_2-$CH_2Si(CH_3)_3$), 2.21 (s, 3 H, SCH_3), 1.40 (d, *J* 6.2, 3 H, H-6), 0.61, 0.43 (2 × ddd, *J* 13.6, 10.4, 6.7, 1 H each, OCH_2CH_2-$Si(CH_3)_3$), −0.02 (s, 9 H, $Si(CH_3)_3$); ^{13}C NMR (600 MHz, $CDCl_3$) δ 165.76, 135.52, 134.47, 133.77, 133.23, 130.57, 129.98, 129.78, 128.80, 128.54, 127.94, 124.67, 118.89, 103.22, 95.93, 77.29, 75.78, 67.47, 65.99, 60.21, 17.59, 15.56, 13.20, −1.99; HRMS (FAB) Calc. for $C_{29}H_{39}O_8NSSi$ (M + Cs): 722.1220, found 722.1237.

Benzoates 27a,b

To a solution of the olefin **25** (104 mg, 0.18 mmol) in pyridine (2.5 mL) was added solid OsO_4 (49 mg, 0.19 mmol). The solution was stirred for 3.5 h at 25 °C, then poured into an aqueous solution of 10% $Na_2S_2O_3$ and stirred at room temperature for 2 h. The mixture was diluted with ethyl acetate (100 mL) and the organic layer washed with aqueous HCl (10% v/v, 2 × 100 mL), saturated aqueous $NaHCO_3$ (100 mL), and brine (100 mL). The organic layer was dried (Na_2SO_4), concentrated under reduced pressure, and purified by flash column chromatography (silica, 60% ethyl acetate in hexanes) to give the diols **26** (99 mg, 90%) as an inseparable mixture of diastereoisomers, which were used immediately in the next step.

To a solution of the diols **26** (99 mg, 0.15 mmol) in dry CH_3CN (1.1 mL) was added Et_3N (0.04 mL, 0.34 mmol), and the resulting solution cooled at −20 °C. A solution of benzoyl cyanide in CH_3CN (0.5 M, 0.48 mL, 0.24 mmol) was then added dropwise, and the reaction mixture stirred without warming for 20 min. The solution was then diluted with ethyl acetate (20 mL), and washed with saturated aqueous $NaHCO_3$ (20 mL) and brine (20 mL). The organic layer was dried (Na_2SO_4), concentrated under reduced pressure, and the products separated by flash column chromatography (silica, hexanes to 25% ethyl acetate in hexanes) to afford the major (less polar) and minor (more polar) dibenzoates **27a** (79 mg, 72%) and **27b** (15 mg, 14%), respectively, as white foams.

27a: $R_f = 0.27$ (silica, 30% ethyl acetate in hexanes); $[\alpha]_D^{23} = -18.4$ (*c* 1.84, $CHCl_2$); IR (thin film) ν_{max} 2955, 2364, 2344, 1718, 1526, 1340, 1273, 111 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.16 (dd, *J* 8.1, 1.0, 2 H, phenyl), 8.10 (dd, *J* 8.2, 1.1, 1 H, nitrobenzyl Ar), 7.99 (dd, *J* 8.1, 1.2, 2 H, phenyl), 7.88 (d, *J* 7.6, 1 H, nitrobenzyl Ar), 7.67–7.62 (m, 2 H, aromatic), 7.55–7.49 (m, 3 H, aromatic), 7.45 (dd, *J* 8.1, 7.4, 1 H, nitrobenzyl Ar), 7.40 (dd, *J* 8.0, 7.7, 2 H, phenyl), 5.79 (d, *J* 9.4, 1 H, H-3), 5.32, 5.10 (doublets, *J* 15.2, 1 H each, benzylic), 5.00 (d, *J* 11.8, 1 H, *H*CH′OBz), 4.87, 4.78 (doublets, *J* 6.7, 1 H each, OCH_2O), 4.61 (d, *J* 7.7, 1 H, H-1), 4.54 (dd, *J* 11.8, 8.5, 1 H, HC*H′*OBz), 4.43 (dd, *J* 9.4, 7.8, 1 H, H-2), 4.16 (q, *J* 6.3, 1 H, H-5), 3.99 (dd, *J* 7.2, 5.0, 1 H, C*H*OH), 3.66 (d, *J* 5.0, 1 H, O*H*), 3.36–3.28 (m, 2 H, OC$H_2$$CH_2Si(CH_3)_3$), 2.28 (s, 3 H, SC$H_3$), 1.50 (d, *J* 6.3, 3 H, H-6), 0.69–0.64, 0.55–0.50 (multiplets, 1 H each, $OCH_2CH_2Si(CH_3)_3$), −0.02 (s, 9 H, $Si(CH_3)_3$); ^{13}C NMR (600 MHz, $CDCl_3$) δ 168.15, 167.54, 147.92, 135.21, 134.79, 134.58, 133.99, 131.23, 130.69, 129.79, 129.65, 129.46, 128.90, 125.58, 103.83, 96.75, 78.67, 77.38, 72.20, 71.02, 68.38, 67.85, 66.85, 59.12, 27.69, 18.71, 14.44, 12.85, −0.90; HRMS (FAB) Calc. for $C_{36}H_{45}O_{11}NSSi$ (M + Cs): 860.1537, found 860.1514.

27b: $R_f = 0.21$ (silica, 30% ethyl acetate in hexanes); $[\alpha]_D^{23} = -9.3$ (*c* 0.74, $CHCl_3$); IR (thin film) ν_{max} 2953, 2362, 2342, 1723, 1526, 1450, 1271, 1068 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.13 (d, *J* 7.5, 2 H, phenyl), 8.10 (d, *J* 8.1, 1 H, aromatic), 8.01 (d, *J* 7.4, 2 H, phenyl), 7.87 (d, *J* 7.7, 1 H, aromatic), 7.65 (dd, *J* 7.5, 7.4, 1 H, aromatic), 7.61 (at, *J* 7.4, 1 H, aromatic), 7.56 (at, *J* 7.4, 1 H, aromatic), 7.49 (at, *J* 7.7, 2 H, phenyl), 7.45–7.42 (m, 3 H, aromatic), 5.79 (d, *J* 9.5, 1 H, H-3), 5.34, 5.10 (doublets, *J* 15.2, 1 H each, benzylic), 4.88 (d, *J* 7.5, 1 H, *H*CH′OBz), 4.87, 4.74 (doublets, *J* 6.8, 1 H each, OCH_2O), 4.64 (d, *J* 7.6, 1 H, H-1), 4.41 (dd, *J* 11.7, 7.5, 1 H, HC*H′*OBz), 4.30 (dd, *J* 9.5, 7.6, 1 H, H-2), 4.08 (q, *J* 6.3, 1 H, H-5), 4.03 (d, *J* 11.1, 1 H, C*H*OH), 3.32–3.25 (m, 2 H, OCH_2-$CH_2Si(CH_3)_3$), 3.17 (b s, 1 H, O*H*), 2.42 (s, 3 H, SCH_3), 1.51 (d, *J* 6.3, 3 H, H-6), 0.65–0.60, 0.49–0.44 (multiplets, 1 H each, $OCH_2CH_2Si(CH_3)_3$), −0.25 (s, 9 H, $Si(CH_3)_3$); ^{13}C NMR (600 MHz, $CDCl_3$) δ 165.67, 134.29, 133.77, 133.65, 133.24, 130.15, 129.76, 129.58, 129.25, 128.83, 128.73, 128.39, 128.05, 124.75, 102.90, 95.82, 93.08, 78.67, 77.67, 74.83, 72.85, 69.76, 67.50, 66.05, 60.37, 17.61, 16.71, 13.11, −1.76; HRMS (FAB) Calc. for $C_{36}H_{45}O_{11}NSSi$ (M + Cs): 840.1537, found 860.1507.

Benzylidenes 28a,b

To a solution of the dibenzoate (**27a**) (32 mg, 0.044 mmol) in MeOH (0.50 mL) was added a methanolic solution of sodium methoxide (0.5 M, 0.018 mL, 0.008 mmol) and the solution stirred at room temperature for 0.5 h. The reaction was quenched with the addition of aqueous hydrochloric acid (2% v/v, 0.02 mL), followed by triethylamine (0.02 mL). The solution was concentrated under reduced pressure and the residue

purified by flash column chromatography (silica, 50% ethyl acetate in hexanes) to give a triol intermediate (18 mg, 83%) which was immediately used in the next step. Triol derived from major diastereomer (**27a**): R_f = (0.65, 80% ethyl acetate in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (d, *J* 7.5, 1 H, aromatic), 7.63 (t, *J* 7.5, 1 H, aromatic), 7.45 (dd, *J* 7.5, 7.0, 1 H, aromatic), 5.26, 5.04 (doublets, *J* 15.0, 1 H each, benzylic), 4.87, 4.75 (doublets, *J* 6.5, 1 H each, OCH_2O), 4.70 (d, *J* 3.0, 1 H, O*H*), 4.56 (d, *J* 8.5, 1 H, H-1), 4.05 (dd, *J* 9.5, 3.0, 1 H, H-7), 3.84–3.57 (m, 7 H, H-2, H-3, OCH_2CH$_2$Si, CH_2OH), 2.42 (s, 3 H, SCH_3), 1.37 (d, *J* 6.5, 3 H, H-6), 0.99–0.91 (m, 2 H, CH_2Si), −0.02 (s, 9 H, Si(CH_3)$_3$).

The triol derived from the minor isomer (**27b**) was prepared following the same method described for the preparation of the triol derived from the major isomer (**27a**): R_f = (0.51, 80% ethyl acetate in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (dd, *J* 8.1, 1.1, 1 H, aromatic), 7.77 (d, *J* 7.8, 1 H, aromatic), 7.63 (ddd, *J* 7.7, 7.6, 1.2, 1 H, aromatic), 7.45 (dd, *J* 7.4, 6.9, 1 H, aromatic), 5.26, 5.05 (doublets, *J* 15.0, 1 H each, benzylic), 4.90, 4.80 (doublets, *J* 6.6, 1 H each, OCH_2O), 4.52 (b s, 1 H, O*H*), 4.43 (d, *J* 7.6, 1 H, H-1), 4.11 (b d, *J* 11.8, 1 H, C*H*(H′)OH), 4.03 (q, *J* 6.4, 1 H, H-5), 3.90 (b d, *J* 9.4, 1 H, H-3), 3.83–3.80 (m, 1 H, OCH_2CH$_2$Si), 3.76 (b t, *J* 5.8, 1 H, CH(*H′*)OH), 3.65 (dd, *J* 9.3, 7.7, 1 H, H-2), 3.28 (b d, *J* 7.0, 1 H, H-7), 2.30 (s, 3 H, SCH_3), 1.44 (d, *J* 6.4, 3 H, H-6), 1.02–0.88 (m, 2 H, CH_2Si), −0.01 (s, 9 H, Si(CH_3)$_3$).

Each of the triols derived from isomeric dibenzoates **27a** and **27b** were benzoylated following the procedure described for the preparation of **27a** and **27b** from the mixture of diols **26**. Monobenzoate derived from major dibenzoate (**27a**): ^{1} H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, *J* 8.16, 1 H, aromatic), 8.08–8.04 (m, 2 H, aromatic), 7.80 (d, *J* 7.0, 1 H, aromatic), 7.66–7.57 (m, 2 H, aromatic), 7.46–7.43 (m, 3 H, aromatic), 5.28, 5.05 (doublets, *J* 15.0, 1 H each, benzylic), 4.90, 4.77 (doublets, *J* 6.7, 1 H each, OCH_2O), 4.59 (d, *J* 2.2, 1 H, O*H*), 4.43 (d, *J* 7.5, 1 H, H-1), 4.27 (b s, 2 H, CH_2OBz), 3.79–3.57 (m, 6 H, H-2, H-3, H-5, OCH_2CH$_2$Si, H-7), 2.46 (s, 3 H, SCH_3), 1.44 (d, *J* 6.4, 3 H, H-6), 1.00–0.86 (m, 2 H, CH_2Si), −0.02 (s, 9 H, Si(CH_3)$_3$). Monobenzoate derived from the minor dibenzoate (**27b**): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (m, 3 H, aromatic), 7.82 (d, *J* 7.5, 1 H, nitrobenzyl Ar), 7.64 (t, *J* 7.5, 1 H, nitrobenzyl Ar), 7.59 (t, *J* 7.5, 1 H, nitrobenzyl Ar), 7.46 (dd, *J* 8.0, 7.5, 2 H, phenyl), 7.46 (obs t, *J* 8.0, 1 H, nitrobenzyl Ar), 5.28, 5.06 (doublets, *J* 15.0, 1 H each, benzylic), 4.91, 4.83 (doublets, *J* 6.5, 1 H each, OCH_2O), 4.81 (d, *J* 1.0, 1 H, O*H*), 4.65 (dd, *J* 12.0, 8.0, 1 H, C*H*OBz), 4.46 (d, *J* 8.0, 1 H, H-1), 4.32 (b d, *J* 8.0, 1 H, H-7), 4.05 (dd, *J* 9.5, 3.0, 1 H, H-3), 4.04 (q, *J* 6.5, 1 H, H-5), 3.88 (d, *J* 3.0, 1 H, O*H*), 3.86–3.81 (m, 2 H, H-2, OCH_2CH$_2$Si), 3.61 (m, 1 H, OCH_2CH$_2$Si), 1.46 (d, *J* 6.5, 3 H, H-6), 0.96 (m, 2 H, CH_2Si), −0.01 (s, 9 H, Si(CH_3)$_3$).

To the monobenzoate derived from **27a** (5.0 mg, 0.008 mmol) in benzene (5 mL) was added a solution of PTSA (monohydrate) in H_2O (0.07 M, 0.02 mL, 0.002 mmol) followed by benzaldehyde dimethyl acetal (0.012 mL, 0.08 mmol) and the mixture was heated at reflux with a Dean–Stark trap for 30 min. After cooling, triethylamine (0.1 mL) was added, and the solution was concentrated under reduced pressure to give a residue which was purified by preparative TLC (silica, 0.25 mm, 10 cm × 10 cm, 20% ethyl acetate in hexanes) to give the benzylidene **28a**.

28a: oil, R_f = 0.24 (silica, 20% ethyl acetate in hexanes); $[\alpha]_D^{23}$ = +8.6 (*c* 0.07, $CHCl_3$); IR (thin film) ν_{max} 2922, 2850, 2362, 2344, 1718, 1527, 1271, 1025, 859 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.10 (d, *J* 8.1, 1 H, nitrobenzyl Ar), 8.05 (d, *J* 7.4, 2 H, phenyl), 7.94 (d, *J* 7.7, 1 H, nitrobenzyl), 7.66 (at, *J* 7.4, 1 H, nitrobenzyl Ar), 7.59 (dd, *J* 7.7, 7.4, 1 H, nitrobenzyl Ar), 7.50 (dd, *J* 7.8, 4.0, 2 H, phenyl), 7.47–7.44 (m, 4 H, phenyl), 7.34–7.32 (m, 2 H, phenyl), 6.12 (s, 1 H, PhC*H*), 5.33 (d, *J* 15.1, 1 H, nitrobenzyl benzylic), 5.21 (dd, *J* 11.8, 9.2, 1 H, C*H*OBz), 5.10 (d, *J* 15.1, 1 H, nitrobenzyl benzylic), 4.93, 4.90 (doublets, *J* 6.3, 1 H, OCH_2O), 4.57 (obs dd, *J* 9.2, 4.1, 1 H, C(*H′*)OBz), 4.56 (d, *J* 7.4, 1 H, H-1), 4.46 (dd, *J* 12.0, 4.1, C(*H*)CH$_2$OBz), 4.28 (dd, *J* 9.2, 7.4, 1 H, H-2), 4.20 (d, *J* 9.2, 1 H, H-3), 3.67 (q, *J* 6.3, 1 H, H-5), 3.64–3.60 (m, 2 H, OCH_2-CH$_2$Si(CH$_3$)$_3$), 2.43 (s, 3 H, SCH_3), 1.46 (d, *J* 6.3, 3 H, H-6), −0.18 (s, 9 H, Si(CH_3)$_3$); HRMS (FAB) Calc. for $C_{36}H_{45}O_{10}$-NSSi (M + Cs): 844.158, found 844.1553.

The benzylidene **28b** was prepared in the same manner as **28a**. **28b**: oil, R_f = 0.32 (silica, 20% ethyl acetate in hexanes); $[\alpha]_D^{23}$ = +16.7 (*c* 0.18, $CHCl_3$); IR (thin film) ν_{max} 2921, 2848, 2360, 2342, 1721, 1526, 1342, 1268, 1061, 1025 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.10 (d, *J* 8.2, 1 H, nitrobenzyl Ar), 8.07 (d, *J* 7.2, 2 H, phenyl), 7.96 (d, *J* 7.5, 1 H, nitrobenzyl Ar), 7.66 (dd, *J* 7.8, 7.5, 1 H, nitrobenzyl Ar), 7.57 (at, *J* 7.4, 1 H, nitrobenzyl Ar), 7.48–7.43 (m, 5 H, phenyl), 7.36–7.35 (m, 3 H, phenyl), 5.71 (s, 1 H, C*H*Ph), 5.33, 5.12 (doublets, *J* 15.3, 1 H each, nitrobenzyl benzylic), 5.04 (dd, *J* 12.6, 1.6, 1 H C(*H*)OBz), 4.96, 4.93 (doublets, *J* 6.6, 1 H each, OCH_2O), 4.66 (d, *J* 7.3, 1 H, H-1), 4.64 (dd, *J* 12.6, 5.8, 1 H, C(*H′*)OBz), 4.53 (dd, *J* 9.9, 7.3, 1 H, H-2), 4.22 (d, *J* 5.8, 1.6, C*H*CH$_2$OBz), 3.93 (d, *J* 9.8, 1 H, H-3), 3.68–3.64 (m, 3 H, H-5, OCH_2CH$_2$-Si(CH$_3$)$_3$), 2.54 (s, 3 H, SCH_3), 0.87–0.83 (m, 2 H, CH_2Si(CH$_3$)$_3$), −0.15 (s, 9 H, Si(CH_3)$_3$); HRMS (FAB) Calc. for $C_{36}H_{45}O_{10}$NSSi (M + Cs): 844.1588, found 844.1557.

Benzoic acid 5-hydroxy-2-methyl-3-methylsulfanyl-6-(2-nitrobenzyloxy)-3-vinyltetrahydropyran-4-yl ester 29

To a solution of the SEM ether **25** (2.68 g, 4.54 mmol) in methanol (72 mL) was added camphorsulfonic acid (105 mg, 0.45 mmol) and the resulting solution was stirred at room temperature under argon for 27 h. Triethylamine (1 mL) was added to the reaction mixture, which was then concentrated under reduced pressure. The residue was taken up in ethyl acetate (100 mL) and washed with saturated aqueous $NaHCO_3$ (100 mL) and brine (100 mL). The organic phase was dried (Na_2SO_4), concentrated under reduced pressure, and purified by flash column chromatography (100% hexanes to 25% ethyl acetate in hexanes) to give the alcohol **29** (1.81 g, 87%) as a white foam. **29**: R_f = 0.63 (silica, 40% ethyl acetate in hexanes); $[\alpha]_D^{23}$ = −21.7 (*c* 1.25, $CHCl_3$); IR (thin film) ν_{max} 3472, 2919, 1713, 1520, 1337, 1273, 1093, 1067, 1041 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.06 (m, 3 H, aromatic), 7.87 (d, *J* 7.9, 1 H, aromatic), 7.63 (ddd, *J* 7.8, 7.6, 1.2, 1 H, aromatic), 7.58 (t, *J* 7.45, 1 H, aromatic), 7.46 (m, 3 H, aromatic), 5.67 (m, 2 H, C*H*=CH$_2$, *cis*-C(*H*)H=CH), 5.40 (d, *J* 17.7, 1 H, *trans*-C(*H*)H=CH), 5.30 (d, *J* 10.9, 1 H, H-3), 5.29, 5.11 (doublets, *J* 14.9, 1 H each, benzylic), 4.57 (d, *J* 7.7, 1 H, H-1), 4.40 (ddd, *J* 10.9, 7.7, 3.6, 1 H, H-2), 3.66 (q, *J* 6.3, 1 H, H-5), 2.23 (s, 3 H, SCH_3), 1.42 (d, *J* 6.3, 3 H, H-6); ^{13}C NMR (600 MHz, $CDCl_3$) δ 135.59, 134.01, 133.63, 133.32, 129.92, 129.62, 129.08, 128.50, 128.18, 124.62, 118.68, 103.38, 78.12, 76.09, 72.08, 67.71, 59.70, 15.63, 13.21; HRMS (FAB) Calc. for $C_{23}H_{25}O_7NS$ (M + Cs): 592.0406, found 592.0426.

Benzoic acid 5-{5-[(9*H*-fluoren-9-ylmethoxycarbonyl)isopropylamino]-4-methoxytetrahydropyran-2-yloxy}-2-methyl-3-methylsulfanyl-6-(2-nitrobenzyloxy)-3-vinyltetrahydropyran-4-yl ester 31

The alcohol **29** (118 mg, 0.26 mmol) and fluoride **30** (158 mg, 0.38 mmol) were combined, azeotroped to dryness several times from benzene and left under vacuum for 3 h. $AgClO_4$ (187 mg, 0.90 mmol) and $SnCl_2$ (169 mg, 0.90 mmol) were combined in another flask, azeotroped to dryness from benzene, suspended in dry THF (3.3 mL) and treated with powdered, activated 4 Å molecular sieves (500 mg). The mixture of alcohol **29** and fluoride **30** in dry THF (3.3 mL) was added dropwise *via* syringe to the flask containing the molecular sieves at −45 °C under argon. After 5 h at −45 °C, the reaction mixture was diluted

with Et_2O (30 mL) and filtered through a short plug of Celite. The organic phase was washed with saturated aqueous $NaHCO_3$ (2 × 50 mL), brine (2 × 50 mL), dried (Na_2SO_4) and concentrated. Flash column chromatography (100% hexanes to 45% Et_2O in hexanes) gave recovered alcohol **29** (39 mg) and disaccharide **31** (135 mg, 91% based on 61% conversion) as a white foam. **31**: $R_f = 0.30$ (silica, 40% ethyl acetate in hexanes); $[\alpha]_D^{23} = -25.8$ (*c* 3.28, $CHCl_3$); IR (thin film) ν_{max} 3414, 2941, 2359, 2341, 1718, 1684, 1526, 1449, 1267 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6, 350 K) δ 8.00 (m, 3 H, aromatic), 7.85 (d, *J* 7.7, 1 H, aromatic), 7.81 (d, *J* 7.6, 2 H, aromatic), 7.72 (dd, *J* 7.8, 7.5, 1 H, aromatic), 7.68 (ddd, *J* 7.5, 7.4, 1.1, 1 H, aromatic), 7.57–7.51 (m, 5 H, aromatic), 7.35 (ddd, *J* 7.5, 7.4, 3.3, 2 H, aromatic), 7.29–7.24 (m, 2 H, aromatic), 5.73 (d, *J* 9.3, 1 H, A-3), 5.68 (dd, *J* 17.7, 11.2, 1 H, C(*H*)=CH_2), 5.35 (d, *J* 17.7, 1 H, *trans*-C(*H*)H=CH), 5.29 (d, *J* 11.2, 1 H, *cis*-C(*H*)H=CH), 5.12, 5.02 (doublets, *J* 14.7, 1 H each, nitrobenzyl benzylic), 4.94 (b s, 1 H, C-1), 4.81 (d, *J* 7.6, 1 H, A-1), 4.40 (b s, 3 H, FMOC CH_2), 4.35 (b dd, 1 H, FMOC benzylic), 4.23–4.19 (m, 2 H, A-2, one of C-3, C-5, or C-5′), 3.91 (b s, 1 H, one of C-3, C-5, or C-5′), 3.87 (q, *J* 6.3, 1 H, A-5), 3.70 (b s, 1 H, one of C-3, C-5, or C-5′), 3.41 (b s, 1 H, C-4), 2.88 (s, 3 H, OCH_3), 2.17 (s, 3 H, SCH_3), 1.76 (b d, 1 H, C-2 eq), 1.23 (d, *J* 6.3, 3 H, A-6), 1.01 (b ddd, 1 H, C-2 ax), 0.84, 0.68 (broad singlets, 3 H each, CH(CH_3)$_2$); ^{13}C NMR (600 MHz, DMSO-d_6, 350 K) δ 164.67, 146.65, 143.66, 140.51, 135.33, 133.24, 133.15, 129.50, 128.87, 128.84, 128.78, 128.57, 128.20, 127.97, 126.99, 126.45, 124.91, 124.24, 123.78, 119.47, 117.93, 100.83, 98.31, 78.25, 76.66, 74.22, 74.13, 70.87, 66.01, 65.35, 59.64, 56.23, 46.47, 46.01, 34.69, 20.01, 19.50, 14.94, 12.07; HRMS (FAB) Calc. for $C_{47}H_{52}O_{11}N_2S$ (M + Cs): 985.2346, found 985.2381.

N-{6-[4-Hydroxy-6-methyl-5-methylsulfanyl-2-(2-nitrobenzyloxy)-5-vinyltetrahydropyran-3-yloxy]-4-methoxytetrahydropyran-3-yl}-*N*-isopropylcarbamic acid 9*H*-fluoren-9-ylmethyl ester 32

To a solution of the benzoate **31** (208 mg, 0.24 mmol) in CH_2Cl_2 (2.4 mL) at −78 °C was added DIBAL (1.0 M in CH_2Cl_2, 0.61 mL) dropwise. After 15 min, the reaction was quenched with the addition of ethyl acetate (5 mL) and poured into a mixture (1 : 1, v/v) of saturated aqueous $NaHCO_3$ and saturated aqueous Rochelle's salt (50 mL). After stirring at room temperature for 45 min, the organic layer was removed and dried (Na_2SO_4). Concentration under reduced pressure and flash column chromatography (silica gel, 40% ethyl acetate in hexanes) provided the alcohol **32** (172 mg, 94%) as an oil. **32**: $R_f = 0.39$ (silica, 50% ethyl acetate in hexanes); $[\alpha]_D^{23} = -41.6$ (*c* 1.80, $CHCl_3$); IR (thin film) ν_{max} 2928, 1718, 1685, 1526, 1449, 1341, 1291, 1061 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6, 350 K) δ 7.99 (b d, *J* 7.6, 1 H, aromatic), 7.85 (d, *J* 7.7, 1 H, aromatic), 7.82 (d, *J* 7.5, 2 H, aromatic), 7.70 (dd, *J* 5.8, 3.4, 1 H, aromatic), 7.65 (dd, *J* 5.5, 3.3, 1 H, aromatic), 7.57 (dd, *J* 14.7, 7.3, 1 H, aromatic), 7.50 (b dd, *J* 7.2, 1 H, aromatic), 7.31–7.26 (m, 2 H, aromatic), 5.67 (dd, *J* 17.7, 10.3, 1 H, C(*H*)=CH_2) 5.37 (d, *J* 17.7, 1 H, *trans*-C(*H*)H=CH), 5.34 (b s, 1 H, A-1), 5.33 (d, *J* 10.3, 1 H, *cis*-C(*H*)H=CH), 5.07 (b s, 1 H, C-1), 5.05, 4.98 (doublets, *J* 15.0, 1 H each, nitrobenzyl benzylic), 4.51 (dd, *J* 5.3, 3.5, 1 H, A-3), 4.34 (b s, 2 H, FMOC CH_2), 4.27 (b dd, 1 H, FMOC benzylic), 4.16 (dd, *J* 5.7, 5.4, 1 H, one of C-3, C-5, or C-5′), 4.15 (dd, *J* 5.4, 5.2, 1 H, A-2), 4.03 (b s, 1 H, one of C-3, C-5, or C-5′), 3.90 (d, *J* 3.5, 1 H, O*H*), 3.55 (q, *J* 6.3, 1 H, A-5), 3.46 (b s, 1 H, C-4), 3.15 (s, 3 H, OCH_3), 2.11 (s, 3 H, SCH_3), 1.64 (m, 1 H, C-2 eq), 1.18 (d, *J* 6.3, 3 H, A-6), 0.85, 0.63 (broad singlets, 3 H each, CH(CH_3)$_2$); ^{13}C NMR (600 MHz, DMSO-d_6, 350 K) δ 146.55, 140.55, 133.59, 133.19, 131.50, 130.99, 128.42, 128.19, 127.86, 127.04, 126.50, 119.51, 117.50, 100.95, 97.89, 78.74, 76.46, 73.73, 71.08, 67.24, 59.79, 59.40, 56.63, 46.57, 37.94, 29.56, 28.01, 23.03, 21.88, 15.16, 12.32, 10.34; HRMS (FAB) Calc. for $C_{40}H_{48}O_{10}N_2S$ (M + Cs): 881.2084, found 881.2098.

N-Isopropyl-*N*-{4-methoxy-6-[6-methyl-5-methylsulfanyl-2-(2-nitrobenzyloxy)-4-(triethylsilyloxy)-5-vinyltetrahydropyran-3-yloxy]tetrahydropyran-3-yl}carbamic acid 9*H*-fluoren-9-ylmethyl ester 33

To a solution of the alcohol **32** (90 mg, 0.12 mmol) in CH_2Cl_2 (1.4 mL) at 0 °C were added *N*,*N*-diisopropylethylamine (0.13 mL, 0.75 mmol) and triethylsilyl trifluoromethanesulfonate (0.11 mL, 0.48 mmol). After 30 min at 0 °C, the reaction mixture was diluted with ethyl acetate (30 mL) and washed with saturated aqueous $NaHCO_3$ (20 mL), H_2O (20 mmLl) and brine (20 mL). The organic layer was dried (Na_2SO_4), concentrated under reduced pressure and purified by flash column chromatography (silica gel, 25% ethyl acetate in hexanes) to give the silyl ether **33** (94 mg, 91%) as an oil. **33**: $R_f = 0.58$ (silica, 40% ethyl acetate in hexanes); $[\alpha]_D^{23} = -36.3$ (*c* = 0.65, $CHCl_3$); IR (thin film) ν_{max} 2958, 2361, 2343, 1685, 1526, 1508, 1458, 1306, 1123, 1099, 1058 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6, 350 K) δ 7.98 (d, *J* 7.9, 1 H, nitrobenzyl Ar), 7.84–7.81 (m, 3 H, 2 × FMOC Ar, nitrobenzyl Ar), 7.71 (at, *J* 7.3, 1 H, nitrobenzyl Ar), 7.57 (dd, *J* 9.5, 8.1, 2 H, FMOC Ar), 7.50 (dd, *J* 7.5, 7.4, 1 H, nitrobenzyl Ar), 7.37 (ddd, *J* 9.8, 7.3, 2.7, 2 H, FMOC Ar), 7.29 (dd, *J* 8.5, 7.7, 2 H, FMOC Ar), 5.71 (dd, *J* 17.5, 11.0, 1 H, C(*H*)=CH_2), 5.43 (d, *J* 11.0, 1 H, *cis*-C(*H*)H=CH), 5.39 (d, *J* 17.5, 1 H, *trans*-C(*H*)H=CH), 5.12 (b s, 1 H, C-1), 5.06, 4.99 (doublets, *J* 14.9, 1 H each, nitrobenzyl benzylic), 4.59 (b s, 1 H, A-1), 4.41 (b s, 1 H, FMOC benzylic), 4.35–4.32 (m, 2 H, FMOC CH_2), 4.21 (dd, *J* 5.6, 5.5, 1 H, one of C-3, C-5 or C-5′), 4.04–4.00 (m, 2 H, A-2, A-3), 3.90 (b s, 1 H, one of C-3, C-5 or C-5′), 3.71 (q, *J* 6.3, 1 H, H-5), 3.46 (b s, 1 H, one of C-3, C-5, or C-5′), 3.13 (s, 3 H, OCH_3), 2.29 (b d, *J* 9.5, 1 H, C-4), 2.14 (s, 3 H, SCH_3), 1.43 (b ddd, *J* 13.8, 10.0, 3.8, 1 H, C-2 ax), 1.25 (b s, 1 H, C-2 eq), 1.11 (d, *J* 6.3, 3 H, A-6), 0.95 (t, *J* 7.9, 9 H, Si(CH$_2$CH_3)$_3$), 0.90–0.82 (b s, 3 H, CH(CH_3)), 0.67 (t, *J* 7.9, 6 H, Si(CH_2CH$_3$)$_3$), 0.72–0.64 (obs, 3 H, CH(CH_3)′); ^{13}C NMR (60 MHz, DMSO-d_6, 350 K) δ 146.62, 143.69, 140.53, 137.33, 133.51, 133.07, 128.56, 127.85, 127.01, 126.47, 124.25, 123.71, 119.47, 100.96, 97.78, 81.96, 72.68, 65.33, 60.58, 59.62, 56.38, 46.58, 65.33, 60.58, 59.62, 56.38, 46.58, 35.04, 19.98, 15.07, 12.17, 6.32, 4.80; HRMS (FAB) Calc. for $C_{48}H_{62}O_{10}N_2SSi$ (M + Cs): 995.2949, found 995.2909.

N-{6-[5-(1,2-Dihydroxyethyl)-6-methyl-5-methylsulfanyl-2-(2-nitrobenzyloxy)-4-(triethylsilyloxy)tetrahydropyran-3-yloxy]-4-methoxytetrahydropyran-3-yl}-*N*-isopropylcarbamic acid 9*H*-fluoren-9-ylmethyl ester 34

Solid OsO_4 (35 mg, 0.14 mmol) was added to a solution of the olefin **33** (104 mg, 0.12 mmol) in dry pyridine (3.0 mL). After 1.5 h at room temperature, $Na_2S_2O_3$ (10% in H_2O, 20 mL) was added to the reaction mixture, which was stirred an additional 1 h at room temperature. The organic layer was diluted with ethyl acetate (50 mL) and washed with HCl (10% in H_2O, 2 × 50 mL), saturated aqueous $NaHCO_3$ (2 × 50 mL), and brine (50 mL). The organic phase was dried (Na_2SO_4), concentrated under reduced pressure and purified by flash column chromatography to give the diol **34** (76 mg, 71%) as a white foam. **34**: $R_f = 0.26$ (silica, 40% ethyl acetate in hexanes); $[\alpha]_D^{23} = -56$ (*c* 0.39, $CHCl_3$); IR (thin film) ν_{max} 3445, 2956, 1683, 1652, 1526, 1456, 1340, 1308, 1051 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6, 350 K) δ 7.98 (d, *J* 7.9, 1 H, aromatic), 7.82 (d, *J* 7.5, 3 H, aromatic), 7.70 (dd, *J* 7.4, 6.8, 1 H, aromatic), 7.58 (dd, *J* 8.0, 7.9, 2 H, aromatic), 7.50 (dd, *J* 7.7, 7.6, 1 H, aromatic), 7.36 (ddd, *J* 9.8, 7.2,, 2.5, 2 H, aromatic), 7.29 (d, *J* 7.5, 1 H, aromatic), 7.27 (d, *J* 7.3, 1 H, aromatic), 5.11 (b s, 1 H, C-1), 5.02, 4.94 (doublets, *J* 14.9, 1 H each, nitrobenzyl benzylic), 4.56 (d, *J* 4.8, 1 H), 4.48–4.38 (m, 2 H), 4.44 (d, *J* 7.4, 1 H, A-1), 4.31 (d, *J* 8.8, 1 H, C(*H*)HOH), 4.21 (at, *J* 5.4, 1 H, one of C-3, C-5, or

C-5′), 4.07–3.97 (m, 2 H), 3.97 (dd, *J* 5.8, 1 H), 3.90 (b s, 1 H, one of C-3, C-5, or C-5′), 3.82 (q, *J* 6.3, 1 H, A-5), 3.53 (b dd, 1 H, one of C-3, C-5, or C-5′), 3.47 (b s, 1 H, C-4), 3.13 (s, 3 H, OCH_3), 2.31 (m, 1 H, C-2 ax), 2.17 (s, 3 H, SCH_3), 1.98 (d, *J* 2.3, 1 H, O*H*), 1.43 (b ddd, 1 H, C-2 eq), 1.14 (d, *J* 6.3, 3 H, A-6), 0.98 (t, *J* 9.0, 9 H, $Si(CH_2CH_3)_3$), 0.78–0.62 (m, 12 H, $Si(CH_2CH_3)_3$, $CH(CH_3)_2$); ^{13}C NMR (600 MHz, DMSO-d_6, 350 K) δ 146.68, 143.70, 140.54, 133.57, 133.01, 128.67, 127.81, 127.01, 126.64, 124.26, 123.66, 119.48, 101.19, 97.75, 78.25, 71.45, 71.24, 69.80, 65.70, 65.32, 63.82, 61.74, 59.62, 58.45, 56.43, 46.60, 35.13, 19.99, 19.56, 17.42, 11.19, 6.41, 4.78, 4.50; HRMS (FAB) Calc. for $C_{46}H_{64}O_{12}N_2SSi$ (M + Cs): 1029.3004, found 1029.2963.

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