Oxazolium-Derived Azomethine Ylides. External Oxazole Activation and Internal Dipole Trapping in the Synthesis of an Aziridinomitosene

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Intermolecular alkylation of the aziridinyl oxazole **20** using $PhSO_2CH_2CH_2OTf$ is possible despite the presence of potentially nucleophilic aziridine nitrogen. The resulting oxazolium salt **22** reacts with $BnNMe_3(+)CN(-)$ to produce the azomethine ylide **24b** via electrocyclic ring opening of an oxazoline **23b**. Internal cycloaddition affords **26** in 66% yield. After saponification and base-induced cleavage of the *N*-phenylsulfonylethyl group, conventional cyclization provides access to **33**. Deprotection and DDQ oxidation completes the synthesis of the aziridinomitosene derivative **9b**. The starting cis-disubstituted aziridine ester **16** can be prepared by the aza-Darzens reaction of **15** with *tert*-butyl chloroacetate.

Prior work in our laboratory has demonstrated the feasibility of pyrrole synthesis by intramolecular cycloaddition of azomethine ylides starting from oxazole precursors.[1−3] The key dipole intermediates **4a** or **4b** were generated from oxazolium salts **2** by nucleophilic activation using a hydride source (path a) or cyanide ion (path b). Both reactions proceed via a transient 4-oxazoline intermediate corresponding to **3a** or **3b**, and internal [2 + 3] cycloaddition results in the initial formation of dihydropyrroles **5a** or **5b**. Compared to the alternative method for generation of carbonyl-stabilized azomethine ylides from aziridines,[4] the oxazole approach has the advantage of considerably lower temperatures and greater tolerance for alkyl substituents on the ylide carbons.

In our initial studies, path a was more promising.[2] The resulting dihydropyrroles **5a** were difficult to purify due to facile double bond migration and aromatization, but isolation of the stable pyrrole **6** obtained by DDQ oxidation was relatively easy. Eventually, it was found that path b works better if an organic-soluble cyanide source, $BnNMe_3(+)$ $CN(-)$, is used as the nucleophile.[3] This procedure has the advantage that conversion from **5b** to **6** occurs spontaneously.[1,3,5] Both methods a and b have been used to prepare indoloquinones of general structure **7**, resulting from the DDQ oxidation of **6**.

The goal of the work described below was to explore an extension of the oxazolium salt activation method for the synthesis of indoloquinones belonging to the aziridinomitosene family.[6] Typical members of this series consist of a tetracyclic skeleton **8** with $X = OCH_3$ or NH_2 and contain a sensitive aziridine ring with $R = H$ or CH_3. The high solvolytic reactivity of the aziridine C(1)−N bond is responsible for the DNA cross-linking properties of the mitomycin antibiotics. This reactivity complicates synthetic strategies that target derivatives of **8**, and so far there is only one total synthesis of a natural aziridinomitosene (**8** with $R = H$ and $X = OCH_3$).[7] Several simpler analogues related to **8** have also been prepared in the course of synthetic studies,[8] including a C(10) ester **9a**.[8b] A similar structure **9b** was selected as our initial target to determine whether the ylide cycloaddition approach of Scheme 1 would tolerate an aziridinyl substituent as the R″ group. Assuming that the aziridinyl analogue of ylides **4a** or **4b** can be trapped internally by [2 + 3] cycloaddition, it should be possible to prepare the hydroxymethyl aziridine **10**, a logical precursor of **9b**, starting from a derivative of **1** where R″ is a suitably protected 2-aziridinyl substituent.

There was little reason to expect that the *N*-benzyl group in **9b** might serve as a removable protecting group in aziridinomitosene synthesis, given the sensitivity of the ring system.[9] On the other hand, the *N*-benzyl environment should allow a realistic test for the survivability of the aziridine group through the oxazolium salt activation and azomethine ylide generation sequence. Furthermore, the related *N*-benzyl aziridinomitosene **9a** is already known,[8b] and NMR and UV comparisons would

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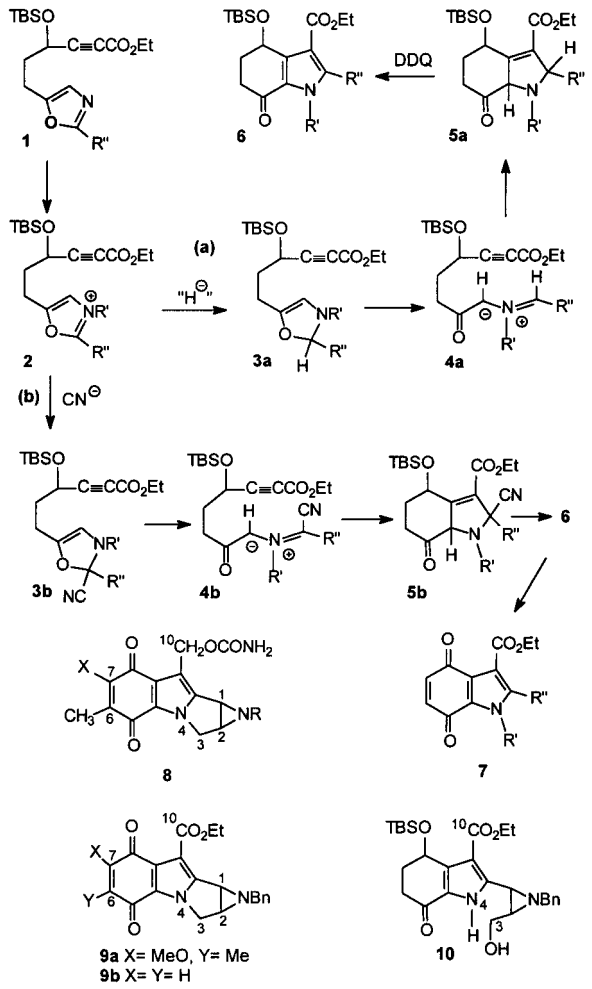
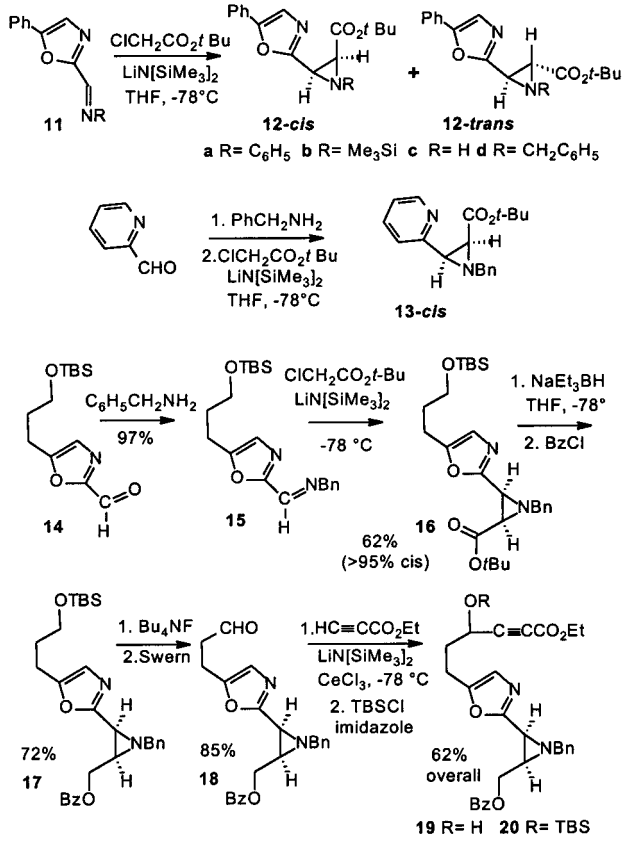
Scheme 1



help to establish structures for related aziridinomitosenes such as **9b**. The *N*-benzyl series was therefore adopted for the feasibility study as described below.

Another reason for selecting the *N*-benzyl target **9b** was that the *N*-alkyl environment allowed relatively easy access to cis-disubstituted aziridines using an aza-Darzens approach.[10] Wartskii had already shown that the enolate of *tert*-butyl chloroacetate converts PhN=CHPh into the cis-disubstituted aziridine if a lithium base is used for enolate generation.[10a] However, we found that the corresponding oxazole imine **11a** (prepared from 2-formyl-5-phenyloxazole;[11a] Scheme 2) produces a 1:1.7 cis:trans mixture, **12a-cis** and **12a-trans** (90%), under the Wartskii conditions. In the course of optimization studies, it was found that solvent changes could increase the proportion of the undesired trans isomer (cis:trans ratios toluene, 1:2.8; ether, 1:3.1; dimethoxyethane, 1:5.6) while a reaction in THF−HMPA produced a 1:1 isomer ratio. Changes in the aza-Darzens leaving group (bromo- vs chloroacetate) had no effect, so the effort to achieve better cis selectivity focused on changing the imine nitrogen substituent. Cainelli et al. have reported cis-selective aza-Darzens reactions using *N*-trimethylsilyl

Scheme 2



imines,[10b] but the oxazole derivative **11b** gave a cis:trans mixture (1.5:1 **12c-cis:12c-trans** in THF, 79% isolated after hydrolytic cleavage of the unstable *N*-trimethylsilylaziridines **12b-cis/trans**) in the reaction with *tert*-butyl chloroacetate/LiHMDS. On the other hand, the analogous *N*-benzyl imine **11d**[11a] afforded a single diastereomer according to NMR assay. Although the yield after chromatography was modest (70%), an evaluation of NMR data confirmed that the major product was the cis-diastereomer **12d-cis**: $J(2,3) = 6.6$ Hz. A similar result was observed starting from the benzylimine of pyridine-2-carbaldehyde[11b] (**13-cis** formed as the sole isomer detected by NMR assay, $J(2,3) = 7.0$ Hz), suggesting that this may be a general pattern of stereoselectivity for the aza-Darzens reaction of *N*-benzyl imines derived from heteroaromatic aldehydes.

On the basis of the encouraging model study, the same aza-Darzens procedure was used to prepare the starting materials required to test azomethine ylide cycloaddition methodology. Thus, the 5-substituted 2-formyloxazole **14**[12] was converted to the *N*-benzyl imine **15**. Treatment with *tert*-butyl chloroacetate and lithium hexamethyldisilazide gave a single major aziridine **16** after chromatography. According to NMR analysis, $J(2,3) = 6.6$ Hz, **16** is the desired cis-disubstituted aziridine.

Conversion of **16** into the benzoate ester **17** was accomplished after some difficulty by reduction ($NaEt_3BH$/THF) and treatment with benzoyl chloride. Lithium-based reducing agents were not suitable for this reduction, apparently due to competing aziridine ring opening. Deprotection of the silyl ether and Swern oxidation occurred without complications and allowed the preparation of a key aldehyde **18**. Following precedents from earlier model studies,[2] **18** was then treated with the cerium-

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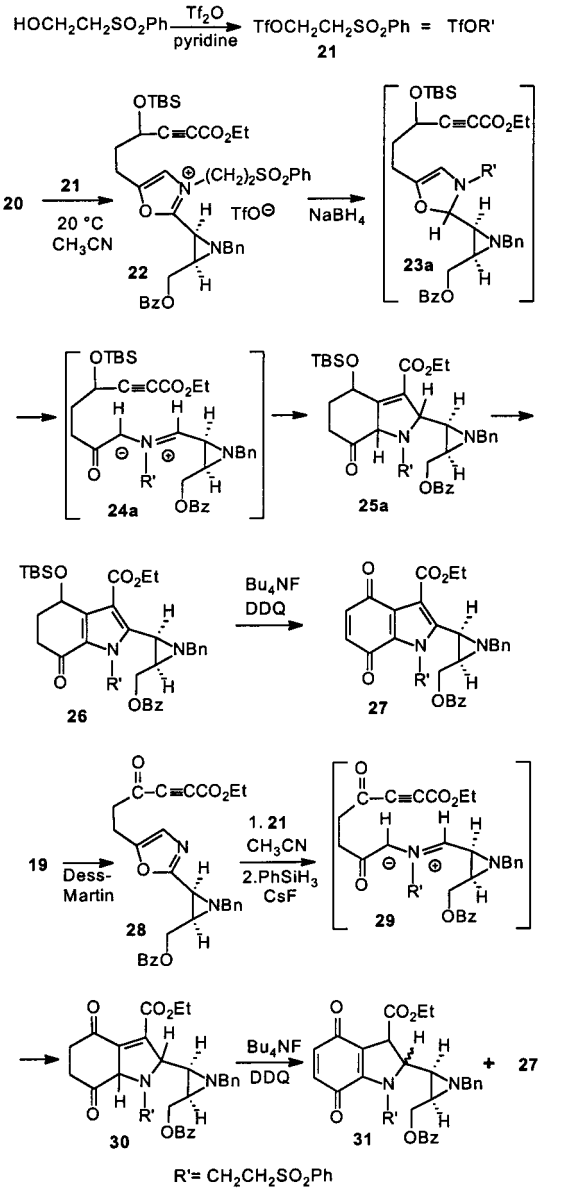
Scheme 3



modified ethyl propiolate anion followed by *O*-silylation of the alcohol **19** to give **20** (62% from **18**). Structure **20** contains the substituents required to evaluate azomethine ylide generation, as described in Scheme 3.

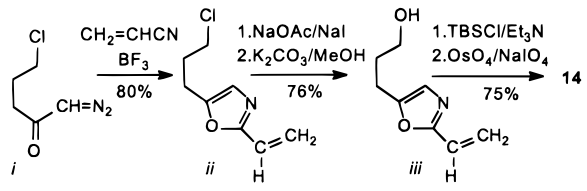
The intended conversions from **20** to a pyrrole **25** involve several challenging stages starting with the selective *N*-alkylation of oxazole nitrogen in the presence of aziridine nitrogen. Initially, we had imagined that this alkylation might be quite difficult because **20** contains a potentially nucleophilic aziridine nitrogen. On the other hand, the strained ring is expected to reduce the nucleophilic reactivity of the aziridine *N*-electron pair due to the same hybridization effect that decreases the basicity of aziridines compared to acyclic amines.[13] Furthermore, the cis-disubstituted aziridine ring should force the *N*-benzyl group into the less hindered orientation away from the C(2), C(3) substituents. This would place the unshared electron pair cis to the C(2), C(3) substituents, resulting in steric hindrance for aziridine *N*-alkylation. The combination of hybridization and steric factors might allow the direct *N*-alkylation of the oxazole nitrogen in **20** as required for oxazole activation.

Ultimately, it would be necessary to remove the *N*-alkyl group used to activate the oxazole because the unsubstituted nitrogen is required for eventual cyclization of ring C via closure of the C(3), N(4) bond. The initial experiments were therefore performed using triflate **21** (from the alcohol and triflic anhydride/pyridine, 86%) as a reagent that would introduce the potentially removable $PhSO_2(CH_2)_2$ group[14,15] at oxazole and, eventually, at pyrrole nitrogen. Reaction of **20** with **21** occurred at a reasonable rate in acetonitrile at room temperature and a promising downfield chemical shift was seen in the oxazole C-4 proton, suggesting that **22** may have been formed. However, the salt could not be purified to confirm the desired selectivity for oxazole rather than aziridine *N*-alkylation, or to prove that oxazole nitrogen had been alkylated rather than protonated. This structural uncertainty raised concerns when numerous attempts failed to convert the presumed oxazolium salt **22** into the desired cycloadducts **25a** or **26** (Scheme 3) via the reductive activation procedure of Scheme 1, path a.

The only hint of success using reductive activation came in an experiment where the salts obtained from **20** and **21** were reacted with $NaBH_4$ as the hydride source. The complex product mixture was treated with Bu_4NF to deprotect the alcohol, followed by DDQ oxidation to force conversion of the presumably unstable **25a** into the quinone **27**. Numerous products were detected by TLC assay, but one of the minor spots was relatively easy to separate, and its characteristic yellow color attracted closer scrutiny. The NMR and UV characteristics were those expected for an indoloquinone **27**, but the yield was only 2%!

An attempt was made to improve the efficiency of ylide trapping by increasing the electron demand in the dipolarophile. Thus, alcohol **19** was converted into the sensitive keto ester **28** by Dess−Martin oxidation (48%). Alkylation with $PhSO_2(CH_2)_2OTf$ in acetonitrile was performed as before, but reduction of the presumed oxazolium salt was carried out with the $PhSiH_3$/CsF reagent in the hope that it might be more tolerant of the presence of the acetylenic ketone, but the resulting mixture of products was again highly complex. The crude material was therefore treated with DDQ, and the product was assayed by TLC. This time, the reaction produced the yellow quinone **27** (3−5%), together with a second minor product that had a striking purple color. This proved to be a mixture of two diastereomers tentatively assigned the structure **31** (3−5%). The color as well as the UV spectrum (λ_{max} 534) is characteristic of an amino quinone of this type, and there is precedent in our model studies for the sequence of events leading

(12) Oxazole **14** was prepared from *i* and acrylonitrile via *ii* and *iii* following methods described in ref 2 for the corresponding sequence from *i* and acetonitrile.



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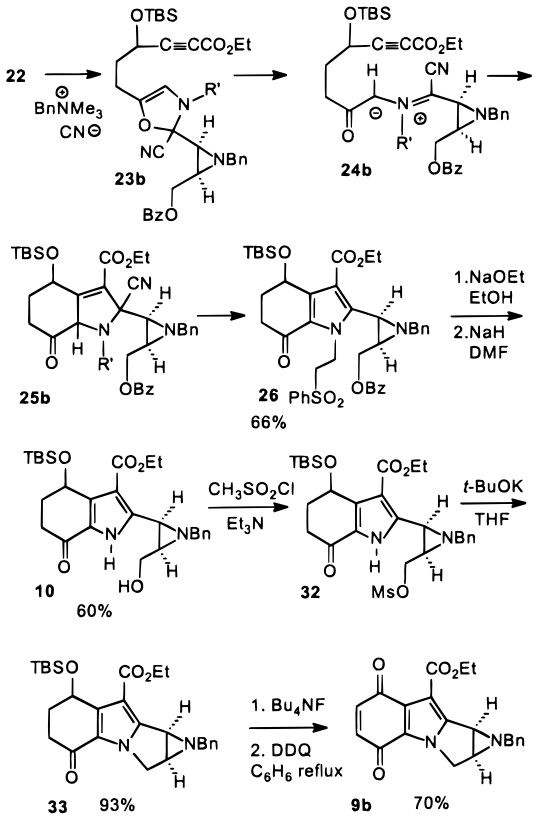
Scheme 4



to the purple quinone.[3] Presumably, **31** is formed from the cycloadduct **30** by initial double bond migration into the six-membered ring and subsequent oxidation, while **27** arises via initial aromatization to the pyrrole **26**, followed by oxidation of the six-membered ring.

The uncertainty regarding selective oxazole *N*-alkylation was resolved when improved conditions for oxazolium ion activation were developed using the crystalline, organic soluble cyanide source $BnNMe_3(+)CN(-)$ corresponding to path b, Scheme 1.[3] Formation of **22** in acetonitrile as before, followed by addition of a large excess of $BnNMe_3(+)CN(-)$ at room temperature resulted in the formation of a new product in 66% yield that proved to be the previously elusive pyrrole **26** (Scheme 4). Confirmation of the structure was obtained by treating **26** with Bu_4NF/DDQ to give the same yellow quinone **27** that had been isolated in low yield from the reductive activation experiments of Scheme 3. None of the purple quinone **31** was formed, as expected if the sequence from **22** to the dihydropyrrole **25b** is followed by spontaneous aromatization to **26**.[3] These observations also confirm that the ylide **24b** has been generated from **22** via an unstable 4-oxazoline **23b** (Scheme 4).

The overall yield of **26** (66% based on **20**) was sufficiently high to investigate further transformations to the aziridinomitosene skeleton. Saponification of the benzoate ester followed by base-induced cleavage of the $PhSO_2(CH_2)_2$ protecting group[14] gave the pyrrole alcohol **10**. Subsequent mesylate formation with CH_3SO_2Cl/Et_3N afforded **32** and base-induced cyclization produced the tetracyclic **33**. Finally, deprotection and DDQ oxidation gave the racemic aziridinomitosene **9b**, and the structure was established by comparison of UV and NMR characteristics with the closely related aziridinomitosene **9a** reported by Rapoport et al.[8b]

Summary

The experiments described above establish that intermolecular alkylation is selective for an oxazole nitrogen in the presence of an *N*-benzyl aziridine, and that the aziridine can survive the conditions required for azomethine ylide generation via a 4-oxazoline intermediate with subsequent intramolecular trapping by [2 + 3] cycloaddition. The 66% yield of **26** defines the lower limit for the selectivity for oxazole vs aziridine *N*-alkylation and reflects the combined influence of aziridine hybridization and substituent steric effects on nitrogen nucleophilicity in the three-membered ring.[13,16a] A convenient triflate reagent **21** for oxazole alkylation was developed in the course of this study. The crystalline triflate is easy to make and to store, and it should be useful for applications in nitrogen protection chemistry, judging from prior work with the less reactive phenylsulfonylethyl bromide.[14] Recent studies show that a variation of the azomethine ylide approach is possible where the oxazolium salt is formed via intramolecular alkylation.[16b] Further development of the azomethine ylide methodology for aziridinomitosene synthesis[17] will be reported in due course.

Experimental Section

5-Phenyloxazole-2-carboxaldehyde *N*-phenylimine (11a). 2-Formyl-5-phenyloxazole[11a] (382 mg, 2.2 mmol) was dissolved in 8 mL of dichloromethane. Excess magnesium sulfate (ca. 2 g) was added followed by aniline (202 μL, 2.2 mmol). After 24 h, the reaction was filtered through a pad of Celite and the solvent was removed (aspirator) to give 544 mg (99%) of imine **11a** as a yellow solid. Examination of the crude material by 200 MHz ^{1}H NMR showed exclusive formation of the imine. The crude material was sufficiently pure for further use. A sample of pure material was obtained by crystallization from hexane: mp 100−101.2 °C; HRMS 248.0965 (calcd for $C_{16}H_{12}N_2O$ 248.09500); IR (CCl_4, cm^{-1}) 1620 (C=N); 200 MHz NMR ($CDCl_3$, ppm) δ 8.42 (1H, s), 7.84−7.79 (2H, m), 7.58 (1H, s), 7.51−7.31 (8H, m).

***tert*-Butyl *cis*- and *trans*-2-(5-Phenyloxazol-2-yl)-*N*-phenylaziridinecarboxylate (12a-cis and 12a-trans).** Butyllithium (0.27 mL, 1.71 M in hexanes) was added dropwise to a solution of hexamethyldisilazane (98 μL, 0.47 mmol, Aldrich, distilled) in 5 mL of THF at −78 °C. After warming to room temperature over 15 min, the solution was re-cooled to −78 °C, and *tert*-butyl bromoacetate (63 μL, 0.39 mmol, Aldrich, neat) was added dropwise. After 15 min of stirring at −78 °C, a solution of oxazole *N*-phenylimine **11a** (39 mg, 0.16 mmol) in THF was added dropwise. The reaction was quenched at −78 °C with saturated ammonium chloride solution after 10 min, warmed to room temperature, diluted with water, extracted with dichloromethane, dried ($MgSO_4$), and filtered. After concentration (aspirator), the crude reaction mixture was analyzed by 200 MHz ^{1}H NMR to reveal a 1.8:1 trans:cis ratio. The residue was purified by flash chromatography on silica

(16) (a) The role of the *N*-benzyl group in the selective *N*-alkylation has been probed using analogues of **20** where Bn is replaced by H and OBz by iodide (see ref 16b for methodology to access the deprotected aziridines). Treatment of the NH aziridine with MeOTf in the presence of 2,6-di-*tert*-butyl-4-methylpyridine in deuterated aceonitrile gave ca. 25% of the *N*-methylaziridine as well as recovered starting material and decomposition products. Characteristic NMR shifts for oxazolium protons were also observed, indicating that the rates of oxazole and aziridine alkylation are similar in the absence of the *N*-benzyl substituent. (b) Vedejs, E.; Klapars, A.; Naidu, B. N.; Piotrowski, D. W. Tucci, F. C. *J. Am. Chem. Soc.* **2000**, *122*, 5401.

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gel (13 mm × 30 cm), 1:4 EtOAc/hexane eluent to afford 32 mg (58%) of *trans*-aziridine and 18 mg (32%) of *cis*-aziridine. **12a-trans**: analytical TLC on silica gel, 1:4 EtOAc/hexane, R_f = 0.32; HRMS 362.1616 (calcd for $C_{22}H_{22}N_2O_3$ 362.16306); IR (neat, cm^{-1}) 1730 (C=O), 200 MHz NMR ($CDCl_3$, ppm) δ 7.50−7.18 (8H, m), 7.01−6.94 (3H, m), 4.03 (1H, d, J = 2.5 Hz), 3.65 (1H, d, J = 2.5 Hz), 1.39 (9H, s). **12a-cis**: analytical TLC on silica gel, 1:4 EtOAc/hexane, R_f = 0.22; HRMS 362.1626 (calcd for $C_{22}H_{22}N_2O_3$ 362.16306), base peak = 261 amu; IR (neat, cm^{-1}) 1750 (C=O), 1150 (C−O); 200 MHz NMR ($CDCl_3$, ppm) δ 7.70−7.66 (2H, m), 7.44−7.07 (9H, m), 3.62 (1H, d, J = 6.5 Hz), 3.20 (1H, d, J = 6.5 Hz), 1.37 (9H, s).

***tert*-Butyl *cis*- and *trans*-2-(5-Phenyloxazol-2-yl)aziridinecarboxylate (12c-cis and 12c-trans).** Butyllithium (2.0 mL, 1.68 M in hexanes) was added dropwise to a solution of hexamethyldisilazane (0.7 mL, 3.33 mmol, Aldrich, distilled) in 5 mL of THF at −78 °C. After warming to room temperature over 15 min, the solution was cooled to 0 °C, and a solution of 2-formyl-5-phenyloxazole (524 mg, 3.03 mmol) in 1.5 mL of THF was added. The solution was allowed to warm to room temperature over 1 h to form **11b**. In a separate flask, butyllithium (5.4 mL, 1.68 M in hexanes) was added dropwise to a solution of hexamethyldisilazane (1.9 mL, 9.08 mmol) in 20 mL of THF at −78 °C. After warming to room temperature over 15 min, *tert*-butyl chloroacetate (1.3 mL, 9.08 mmol, Aldrich, neat) was added dropwise. After 15 min of stirring at −78 °C, the previously prepared solution of N-TMS imine **11b** was added dropwise. The reaction was warmed to room temperature after 1 h, quenched with water, extracted with ether, dried ($MgSO_4$), and filtered. After removal of solvent (aspirator), the residue was purified by flash chromatography on silica gel 1:2 EtOAc/hexane eluent, to afford 357 mg (41%) *cis*-aziridine and 162 mg (19%) *trans*-aziridine. **12c-cis**: analytical TLC on silica gel, 3:2 EtOAc/hexane, R_f = 0.32; HRMS 286.1317 (calcd for $C_{16}H_{18}N_2O_3$ 286.13174); 200 MHz NMR ($CDCl_3$, ppm) δ 7.72−7.32 (5H, m), 7.28 (1H, s), 3.34 (1H, dd, J = 5.9, 8.4 Hz), 2.90 (1H, dd, J = 5.9, 9.1 Hz), 2.10 (1H, dd, J = 8.4, 9.1 Hz), 1.33 (9H, s). **12c-trans**: analytical TLC on silica gel, 3:2 EtOAc/hexane, R_f = 0.57; 200 MHz NMR ($CDCl_3$, ppm) δ 7.72−7.31 (5H, m), 7.27 (1H, s), 3.41 (1H, dd, J = 2.4, 9.8 Hz), 3.05 (1H, dd, J = 2.42.4, 8.4 Hz), 1.90 (1H, dd, J = 8.4, 9.8 Hz), 1.51 (9H, s).

5-Phenyloxazole-2-carboxaldehyde *N*-benzylimine (11d). 2-Formyl-5-phenyloxazole (322 mg, 1.86 mmol) was dissolved in 8 mL of dichloromethane. Excess magnesium sulfate (ca. 2 g) was added to the solution followed by the addition of benzylamine (203 μL, 1.86 mmol). After 24 h, the reaction was filtered through a pad of Celite, and the solvent was removed (aspirator) to give 483 mg (99%) of imine **11d** as a yellow solid. Examination of the crude material by 200 MHz ^{1}H NMR showed exclusive formation of the imine. The crude material was sufficiently pure for further use. Pure material was obtained as yellow needles by crystallization from ethyl acetate/hexane: mp 91−92 °C; HRMS 262.1107 (calcd for $C_{17}H_{14}N_2O$ 262.11063), base peak = 91 amu; IR (CCl_4, cm^{-1}) 1630 (C=N); 200 MHz NMR ($CDCl_3$, ppm) δ 8.25 (1H, t, J = 1.5 Hz), 7.78−7.73 (2H, m), 7.49−7.33 (9H, m), 4.94 (2H, d, J = 1.5 Hz).

***tert*-Butyl *cis*-2-(5-Phenyloxazol-2-yl)-*N*-benzylaziridinecarboxylate (12d-cis).** Butyllithium (0.44 mL, 1.7 M in hexanes) was added dropwise to a solution of hexamethyldisilazane (156 μL, 0.74 mmol, Aldrich, distilled) in 5 mL of THF at −78 °C. After warming to room temperature over 15 min, the solution was re-cooled to −78 °C, and *tert*-butyl chloroacetate (106 μL, 0.74 mmol, Aldrich, neat) was added dropwise. After 15 min of stirring at −78 °C, a solution of *N*-benzylimine **11d** (65 mg, 0.25 mmol) in THF was added dropwise. The reaction was warmed to room temperature after 10 min, quenched with water, extracted with dichloromethane, dried ($MgSO_4$), and filtered. After removal of solvent (aspirator), the residue was purified by flash chromatography on silica gel (15 mm × 40 cm), 1:2 EtOAc/hexane eluent, to afford 65 mg (70%) of aziridine **12d-cis** as an oil: analytical TLC on silica gel, 1:2 EtOAc/hexane, R_f = 0.24. Pure material was obtained by crystallization from hexane: mp 112.5−113.5 °C; HRMS 376.1778 (calcd for $C_{23}H_{24}N_2O_3$ 376.17871), base peak = 275 amu; IR (CCl_4, cm^{-1}) 1753 (C=O), 1715 (C=O), 1170 (C−O); 200 MHz NMR ($CDCl_3$, ppm) δ 7.65−7.50 (2H, m), 7.46−7.27 (9H, m), 3.92 (1H, d, J = 15.8 Hz), 3.83 (1H, d, J = 15.8 Hz), 3.06 (1H, d, J = 6.6 Hz), 2.63 (1H, d, J = 6.6 Hz), 1.32 (9H, s).

***tert*-Butyl *cis*-2-(2-Pyridyl)-*N*-benzylaziridinecarboxylate (13-cis).** Butyllithium (1.7 mL, 1.64 M in hexanes) was added dropwise to a solution of hexamethyldisilazane (574 μL, 2.72 mmol, Aldrich, distilled) in 10 mL of THF at −78 °C. After warming to room temperature over 15 min, the solution was re-cooled to −78 °C, and *tert*-butyl chloroacetate (389 μL, 2.72 mmol, Aldrich, neat) was added dropwise. After 15 min of stirring at −78 °C, a solution of 2-pyridine carbaldehyde[11b] *N*-benzylimine (178 mg, 0.91 mmol) in THF was added dropwise. The reaction was warmed to room temperature after 30 min, quenched with water, extracted with dichloromethane, dried ($MgSO_4$), and filtered. After removal of solvent (aspirator), the residue was purified by flash chromatography on silica gel, 1:2 EtOAc/hexane eluent, to afford 140 mg (50%) of the *cis*-aziridine **13-cis** as a solid: analytical TLC on silica gel, 1:2 EtOAc/hexane, R_f = 0.14. Pure material was obtained by crystallization from hexane: mp 67.5−68.5 °C; HRMS 311.1778 (calcd for $C_{19}H_{22}N_2O_2$, M + 1); base peak = 209 amu; IR (CCl_4, cm^{-1}) 1745 (C=O); 200 MHz NMR ($CDCl_3$, ppm) δ 8.48−8.45 (1H, m), 7.65−7.09 (8H, m), 3.99 (1H, d, J = 13.7 Hz), 3.61 (1H, d, J = 13.7 Hz), 3.18 (1H, d, J = 7.0 Hz), 2.65 (1H, d, J = 7.0 Hz), 1.20 (9H, s).

Synthesis of 2-Formyl-5-(3′-*tert*-butyldimethylsiloxypropyl)oxazole (14). 2-Vinyl-5-(3′-chloropropyl)oxazole was prepared following the procedure for 2-methyl-5-(3′-chloropropyl)oxazole reported in ref 2, substituting acrylonitrile for acetonitrile. The product was purified by distillation to afford 80% of 2-vinyl-5-(3′-chloropropyl)oxazole as a clear liquid: bp 70−73 °C, 1.0 mmHg, short path; HRMS 171.0447 (calcd for $C_8H_{10}ClNO$), base peak = 108 amu; IR (neat, cm^{-1}) 1600 (C=N); 200 MHz NMR ($CDCl_3$, ppm) δ 6.82 (1H, s), 6.55 (1H, dd, J = 11.2, 17.7 Hz), 6.10 (1H, dd, J = 1.1, 17.7 Hz), 5.58 (1H, dd, J = 1.1, 11.2 Hz), 3.59 (2H, t, J = 6.3 Hz), 2.86 (2H, t, J = 7.1 Hz), 2.20−2.06 (2H, m).

2-Vinyl-5-(3′-acetoxypropyl)oxazole: Sodium acetate (5.67 g, 68.4 mmol), sodium iodide (3.18 g, 21.2 mmol), and 2-vinyl-5-(3′-chloropropyl)oxazole (5.87 g, 34.2 mmol) were mixed in 44 mL 1:1 HMPA/THF, and the suspension was heated at 65 °C. After 36 h, water was added. The solution was extracted with ether and with ethyl acetate. The combined organic layers were washed with water and brine, dried ($MgSO_4$), and filtered. After removal of solvent (aspirator), the residue was purified by flash chromatography on silica gel, EtOAc/hexane (gradient 0:1−1:2) eluent, to afford 5.07 g (76%) of 2-vinyl-5-(3′acetoxypropyl)oxazole as an oil: analytical TLC on silica gel, 1:2 EtOAc/hexane, R_f = 0.25; M^+ calcd for $C_{10}H_{13}NO_3$ 195.08952, found 195.0896, error = 0 ppm, base peak = 135 amu; IR (neat, cm^{-1}) 1745 (C=O), 1600 (C=N), 1240 (C−O); 200 MHz NMR ($CDCl_3$, ppm) δ 6.69 (1H, t, J = 0.9 Hz), 6.55 (1H, dd, J = 11.2, 17.7 Hz), 6.09 (1H, dd, J = 1.1, 17.7 Hz), 5.56 (1H, dd, J = 1.1, 11.1 Hz), 4.14 (2H, t, J = 6.3 Hz), 2.76 (2H, dt, J = 0.8, 6.8 Hz), 2.08−1.94 (5H, overlapping m and s).

2-Vinyl-5-(3′-hydroxypropyl)oxazole: Potassium carbonate (3.10 g, 22.3 mmol) was added to a solution of 2-vinyl-5-(3′-acetoxypropyl)oxazole (3.96 g, 20.3 mmol) in 100 mL of methanol and 5 mL of water. After 1 h, the solution was concentrated and then extracted with ethyl acetate, dried ($MgSO_4$), and filtered. After removal of solvent (aspirator), the residue was purified by flash chromatography on silica gel, EtOAc/hexane (0:1−1:1) eluent, to afford 1.86 g (60%) of the title alcohol as an oil: analytical TLC on silica gel, 1:1 EtOAc/hexane, R_f = 0.15; HRMS 153.0800 (calcd for $C_8H_{11}NO_2$ 153.07898), base peak = 108 amu; IR (neat, cm^{-1}) 3400 (O−H), 1600 (C=N); 200 MHz NMR ($CDCl_3$, ppm) δ 6.78 (1H, t, J = 1.0 Hz), 6.56 (1H, dd, J = 11.2, 17.7 Hz), 6.09 (1H, dd, J = 1.1, 17.7 Hz), 5.56 (1H, dd, J = 1.1, 11.2 Hz), 3.72 (2H, t, J = 6.3 Hz), 2.79 (2H, t, J = 7.4 Hz), 1.99−1.86 (3H, overlapping m and br s).

2-Formyl-5-(3′-*tert*-butyldimethylsiloxypropyl)oxazole (**14**): *tert*-Butyldimethylsilyl chloride (0.83 g, 5.52 mmol) was added to a solution of 2-vinyl-5-(3′-hydroxypropyl)oxazole (0.77 g, 5.02 mmol), triethylamine (0.84 mL, 6.02 mmol), and a catalytic amount of DMAP (approximately 15 mg) in dichloromethane at 0 °C. After warming to room temperature, the reaction was stirred for 24 h. The reaction mixture was poured into water, extracted with dichloromethane, dried ($MgSO_4$), and filtered. After removal of solvent (aspirator), the residue was purified by flash chromatography on silica gel, EtOAc/hexane (0:1−1:4) eluent, to afford 1.30 g (97%) of 2-vinyl-5-(3′-*tert*-butyldimethyl-siloxypropyl)oxazole, sufficiently pure for use in the next step.

A catalytic amount of osmium tetroxide (30 mg, Merck) was added to a solution of 2-vinyl-5-(3′-*tert*-butyldimethylsiloxypropyl)oxazole (1.30 g, 4.86 mmol) in 20 mL of THF and 15 mL water. After 5 min, sodium metaperiodate (2.34 g, 10.94 mmol, Aldrich) was added portionwise over 1 h. After 24 h, the mixture was diluted with water, extracted with ethyl acetate, dried ($MgSO_4$), and filtered. After removal of solvent (aspirator), the residue was purified by flash chromatography on silica gel (15 mm × 35 cm), EtOAc/hexane (gradient; 0:1−1:4) eluent, to afford 976 mg (75%) of **14** as an oil: analytical TLC on silica gel, 1:4 EtOAc/hexane, R_f = 0.20; HRMS 269.1463 (calcd for $C_{13}H_{23}NO_3Si$ 269.14471), base peak = 212 amu; IR (neat, cm^{-1}) 1711 (C=O); 200 MHz NMR ($CDCl_3$, ppm) δ 9.66 (1H, s), 7.07 (1H, s), 3.65 (2H, t, J = 5.8 Hz), 2.85 (2H, t, J = 8.1 Hz), 1.97−1.86 (2H, m), 0.87 (9H, s), 0.03 (6H, s).

***tert*-Butyl *cis*-3-[5-(3′-*tert*-butyldimethylsiloxypropyl)-oxazol-2-yl]-*N*-benzylaziridine-2-carboxylate (16).** The 2-formyloxazole TBS ether **14** (2.26 g, 8.39 mmol) was dissolved in 50 mL of dichloromethane. Excess $MgSO_4$ (approximately 4 g) was added followed by the addition of benzylamine (0.93 mL, 8.47 mmol, Aldrich, distilled). After 24 h, the mixture was filtered through a pad of Celite and concentrated (aspirator). Residual solvent and benzylamine were removed in vacuo (1 mmHg) to give 2.92 g (97%) of *N*-benzylimine **15** as an oil. The crude material was sufficiently pure for use in the next step.

Butyllithium (4.94 mL, 1.51 M in hexanes) was added dropwise to a solution of hexamethyldisilazane (1.20 g, 7.46 mmol, Aldrich, distilled) in 60 mL of dry THF at −78 °C. After warming to room temperature over 15 min, the solution was re-cooled to −78 °C, and a solution of *tert*-butyl chloroacetate (1.123 g, 7.46 mmol, Aldrich) in 10 mL of THF was added dropwise. After 30 min of stirring at −78 °C, a solution of *N*-benzylimine **15** (0.889 g, 2.48 mmol) in 15 mL of THF was added dropwise. The orange reaction mixture was warmed to room temperature after 35 min, and the resulting yellow solution was quenched with water, extracted with ether, dried ($MgSO_4$), and filtered. After removal of solvent (aspirator), the residue was purified by flash chromatography on silica gel (15 mm × 35 cm), 1:2 EtOAc/hexane eluent, to afford a forerun of byproducts (ca. 0.5 g) followed by a more polar fraction, 0.725 g (62%) of *cis*-aziridine **16** as an oil: analytical TLC on silica gel, 1:2 EtOAc/hexane, R_f = 0.26; HRMS 472.2754 (calcd for $C_{26}H_{40}N_2O_4Si$ 472.27560); IR (neat, cm^{-1}) 1745 (C=O), 1725 (C=O); 200 MHz NMR ($CDCl_3$, ppm) δ 7.45−7.27 (5H, m), 6.68 (1H, t, J = 1.0 Hz), 3.89 (1H, d, J = 14.1 Hz), 3.77 (1H, d, J = 13.9 Hz), 3.63 (2H, t, J = 6.1 Hz), 2.98 (1H, d, J = 6.6 Hz), 2.71 (2H, t, J = 7.5 Hz), 2.55 (1H, d, J = 6.6 Hz), 1.89−1.76 (2H, m), 1.37 (9H, s), 0.89 (9H, s), 0.04 (6H, s).

Oxazolyl Aziridine Benzoate Ester 17. *cis*-3-[5-(3′-*tert*-Butyldimethylsiloxypropyl)oxazol-2-yl]-*N*-benzylaziridine-2-methanol: A solution of sodium triethylborohydride (1.7 mL, 1.0 M in THF, Aldrich) was added dropwise to a solution of oxazole aziridine ester **16** (319 mg, 0.68 mmol) in 15 mL of THF at −78 °C. After warming to room temperature over 20 min, the reaction was quenched with methanol (2 mL). After evaporation (aspirator), the residue was purified by flash chromatography on silica gel (15 mm × 40 cm), EtOAc/hexane (0:1−1:0) eluent, to afford 226 mg (83%) of the aziridine alcohol as an oil: analytical TLC on silica gel, 1:1 EtOAc/hexane, R_f = 0.21; HRMS 403.2407 (calcd for $C_{22}H_{34}N_2O_3Si$, M + 1); IR (neat, cm^{-1}) 3400 (O−H); 200 MHz NMR ($CDCl_3$, ppm) δ 7.40−7.26 (5H, m), 6.64 (1H, s), 4.00−3.80 (1H, m), 3.88 (1H, d, J = 13.5 Hz), 3.65−3.50 (1H, m), 3.64 (2H, t, J = 6.0 Hz), 3.60 (1H, br s), 3.56 (1H, d, J = 13.4 Hz), 2.75−2.67 (3H, d, overlapping d and t, J = 6.4 Hz and J = 7.8 Hz), 2.36−2.27 (1H, m), 1.90−1.80 (2H, m), 0.90 (9H, s), 0.05 (6H, s).

Benzoyl chloride (139 μL, 1.25 mmol, Mallinckrodt) was added to a solution of the aziridine alcohol from the preceding step (420 mg, 1.04 mmol), triethylamine (218 μL, 1.56 mmol), and a catalytic amount of DMAP (ca. 10 mg) in 20 mL of dichloromethane at 0 °C. After slowly warming to room temperature over 2 h, the solution was stirred for an additional 10 h. The reaction was quenched with water, extracted with dichloromethane, dried ($MgSO_4$), and filtered. After removal of solvent (aspirator), the residue was purified by flash chromatography on silica gel (15 mm × 40 cm), 1:2 EtOAc/hexane eluent, to afford 459 mg (87%) of the aziridinemethanol benzoate **17** as an oil: analytical TLC on silica gel, 1:2 EtOAc/hexane, R_f = 0.29; HRMS 506.2590 (calcd for $C_{29}H_{38}N_2O_4Si$ 506.26007), base peak = 105 amu; IR (neat, cm^{-1}) 1725 (C=O), 1240 (C−O); 200 MHz NMR ($CDCl_3$, ppm) δ 7.89−7.81 (2H, m), 7.57−7.22 (8H, m), 6.70 (1H, s), 4.57 (1H, dd, J = 5.2, 11.8 Hz), 4.47 (1H, dd, J = 7.5, 11.8 Hz), 4.07 (1H, d, J = 13.4 Hz), 3.62 (2H, t, J = 6.0 Hz), 3.41 (1H, d, J = 13.4 Hz), 2.95 (1H, d, J = 6.4 Hz), 2.71 (2H, t, J = 7.5 Hz), 2.52−2.43 (1H, m), 1.89−1.76 (2H, m), 0.89 (9H, s), 0.04 (6H, s).

Conversion of 17 to the Aldehyde 18. A solution of tetrabutylammonium fluoride (0.88 mL, 1.0 M in THF, Petrarch) was added dropwise to a solution of oxazole aziridine **17** (444 mg, 0.88 mmol) in 20 mL of THF. After 1 h, the reaction was diluted with ethyl acetate and water, extracted with ethyl acetate, dried ($MgSO_4$), and filtered. After removal of solvent (aspirator), the residue was purified by flash chromatography on silica gel (15 mm × 40 cm), EtOAc eluent, to afford 303 mg (88%) of deprotected alcohol as an oil: analytical TLC on silica gel, EtOAc, R_f = 0.30; HRMS 392.1725 (calcd for $C_{23}H_{24}N_2O_4$ 392.17358), base peak = 105 amu; IR (neat, cm^{-1}) 3400 (O−H), 1718 (C=O); 200 MHz NMR ($CDCl_3$, ppm) δ 7.85−7.81 (2H, m), 7.57−7.23 (8H, m), 6.72 (1H, s), 4.56 (1H, dd, J = 5.4, 11.8 Hz), 4.45 (1H, dd, J = 7.4, 11.8 Hz), 4.07 (1H, d, J = 13.4 Hz), 3.65 (2H, t, J = 5.4 Hz), 3.43 (1H, d, J = 13.3 Hz), 2.97 (1H, d, J = 6.4 Hz), 2.74 (2H, t, J = 7.4 Hz), 2.53−2.44 (1H, m), 1.95−1.81 (2H, m), 1.65 (1H, br s).

DMSO (1.2 mL, 16.6 mmol) was added dropwise to a solution of oxalyl chloride (760 μL, 8.7 mmol) in 50 mL of dichloromethane at −78 °C. After 20 min, a solution of deprotected alcohol, prepared as described above, (1.31 g, 3.33 mmol) in 20 mL of dichloromethane was added, dropwise via cannula. After 40 min, triethylamine (1.9 mL, 13.3 mmol) was added and the solution was warmed to room temperature. The reaction was quenched with water, extracted with dichloromethane, dried ($MgSO_4$), and filtered. After removal of solvent (aspirator), the residue was purified by flash chromatography on silica gel (17 mm × 35 cm), 1:1 EtOAc/hexane eluent, to afford 1.10 g (85%) of oxazole aldehyde **18** as an amorphous solid: analytical TLC on silica gel, EtOAc, R_f = 0.48; HRMS 390.1580 (calcd for $C_{23}H_{22}N_2O_4$ 390.15796), base peak = 105 amu; IR (CCl_4, cm^{-1}) 2820 (aldehyde C−H), 2715 (aldehyde C−H), 1725 (C=O); 200 MHz NMR ($CDCl_3$, ppm) δ 9.79 (1H, s), 7.85−7.81 (2H, m), 7.58−7.20 (8H, m), 6.73 (1H, s), 4.56 (1H, dd, J = 5.4, 11.8 Hz), 4.43 (1H, dd, J = 7.4, 11.8 Hz), 4.06 (1H, d, J = 13.3 Hz), 3.44 (1H, d, J = 13.3 Hz), 3.01−2.94 (3H, m), 2.76 (2H, t, J = 6.6 Hz), 2.54−2.44 (1H, m).

Alkynoate Alcohol TBS Ether 20. Ceric chloride, 3.53 g (9.0 mmol) ($CeCl_3 \cdot 7H_2O$ ground to a powder and dried (1 mm) and 140 °C for 5 h), was suspended in 45 mL of dry THF under nitrogen at 0 °C and stirred 15 h at room temperature to make a slurry. In a separate flask, butyllithium (3.3 mL, 2.42 M in hexane) was added dropwise to a solution of hexamethyldisilazane (1.31 g, 8.1 mmol) in 30 mL of THF at − 78 °C. The resulting LiHMDS solution was warmed to room temperature over 15 min. Ethyl propiolate (Aldrich, 0.780 g, was then added dropwise by syringe to the previously prepared $CeCl_3$/THF suspension at −78 °C, followed by dropwise cannula transfer of the LiHMDS solution. The resulting yellow mixture was and

stirred 0.5 h at −78 °C. A solution of aldehyde **18** (0.837 g, 2.15 mmol) in 20 mL of THF was then added dropwise via cannula and stirred for 0.5 h. The reaction was quenched with water, extracted with ethyl acetate, washed with brine, dried ($MgSO_4$), and filtered. After removal of solvent (aspirator), the crude alcohol **19** was obtained as an oil (1.05 g).

tert-Butyldimethylsilyl chloride (0.486 g, 3.23 mmol, Petrarch) was added to a solution of the crude alkynol **19** (1.05 g) from above and imidazole (0.366 g, 5.38 mmol) in 15 mL of DMF at room temperature. After 12 h, the mixture was poured into water, extracted with ethyl acetate, dried ($MgSO_4$), and evaporated (aspirator). The residue was purified by flash chromatography on silica gel (13 mm × 20 cm) using 1:2 EtOAc/hexane to afford 0.80 g of **20** as an oil (62% from **18**): analytical TLC on silica gel, 1:1 EtOAc/hexane, R_f = 0.50; HRMS 602.2806 (calcd for $C_{34}H_{42}N_2O_6Si$ 602.28119), base peak = 105 amu; IR (CCl_4, cm^{-1}) 2238 (C═C), 1723 (C═O); 200 MHz NMR ($CDCl_3$, ppm) δ 7.89−7.81 (2H, m), 7.57−7.22 (8H, m), 6.72 (1H, s), 4.61−4.38 (3H, m), 4.24 (2H, q, J = 7.1 Hz), 4.07 (1H, d, J = 13.2 Hz), 3.42 (1H, d, J = 13.4 Hz), 2.95 (1H, d, J = 6.4 Hz), 2.81 (2H, t, J = 7.7 Hz), 2.53−2.43 (1H, m), 2.10−1.99 (2H, m), 1.31 (3H, t, J = 7.1 Hz), 0.91 (9H, s), 0.16 (3H, s), 0.11 (3H, s).

2-(Phenylsulfonyl)ethyl trifluoromethanesulfonate (21). Triflic anhydride (551 μL, 3.27 mmol, Aldrich) was added dropwise to a solution of pyridine (287 μL, 3.55 mmol) in 20 mL of dichloromethane at −20 °C to give a white suspension. After 10 min, a solution of 2-(phenylsulfonyl)ethanol[18] (508 mg, 2.73 mmol) in dichloromethane was added dropwise to the above suspension. The mixture was warmed to room temperature over 30 min, filtered through a plug of coarse silica gel (25 mm × 15 cm) with ether, and concentrated (aspirator). Pure material was obtained by crystallization from carbon tetrachloride to afford 749 mg (86%) of 2-(phenylsulfonyl)ethyl triflate **21** as white needles: mp 63−64 °C; HRMS 317.9845 (calcd for $C_9H_9F_3O_5S_2$ 317.98431), base peak = 125 amu; IR ($CHCl_3$, cm^{-1}) 1330 (SO_2), 1145 (SO_2); 200 MHz NMR ($CDCl_3$, ppm) δ 7.97−7.92 (2H, m), 7.74−7.59 (3H, m), 4.83 (2H, t, J = 6.2 Hz), 3.61 (2H, t, J = 6.2 Hz).

Aziridinyl Indoloquinone via Borohydride Ylide Generation (27). Oxazole **20** (89 mg, 0.15 mmol) and 2-(phenylsulfonyl)ethyl triflate (**21**) (52 mg, 0.16 mmol) were dissolved in 5 mL of dry acetonitrile and stirred at room temperature for 34 h. Solid sodium borohydride (11 mg, 0.28 mmol, Aldrich) was added to give a yellow solution. After 1 h of stirring at room temperature, the reaction was diluted with ethyl acetate and water, extracted with ethyl acetate, dried ($MgSO_4$), filtered, and concentrated (aspirator) to give a white foam. The foam was purified by plug filtration chromatography on silica gel, 2:5 EtOAc/hexane eluent, to give 68 mg of a mixture that was dissolved in 5 mL of THF and treated with excess TBAF (0.3 mL, 1.0 mL in THF, Petrarch). After 12 h, water was added, and the solution was extracted with ethyl acetate, dried ($MgSO_4$), filtered, and concentrated (aspirator). Residual solvent was removed in vacuo (1 mm) to give a brown foam.

The brown foam was dissolved in 5 mL of THF along with DDQ (101 mg, 0.45 mmol) and refluxed for 1.5 h. After removal of solvent (aspirator), the residue was purified by flash chromatography on silica gel (13 mm × 30 cm), 1:1 EtOAc/hexane eluent, to afford 8 mg of impure yellow quinone **27**. Repurification by preparative thin-layer chromatography on silica gel; 1:1 EtOAc/hexane eluent (two elutions) afforded 2 mg (2%) of quinone **27** as a yellow amorphous solid: analytical TLC on silica gel, 1:1 EtOAc/hexane, R_f = 0.36; HRMS 561.1350 (calcd for $C_{36}H_{32}N_2O_8S - C_7H_7$), base peak = 125 amu; IR (CCl_4, cm^{-1}) 1727, C═O; 1670, C═O; 1654, C═O; UV (MeOH, λ_{max} (nm)) 288 (ϵ = 10 400), 220 (ϵ = 27 860), broadened shoulder 400; 200 MHz NMR ($CDCl_3$, ppm) δ 7.84−7.79 (2H, m), 7.70−7.24 (13H, m), 6.54 (1H, d, J = 10.4 Hz), 6.45 (1H, d, J = 10.3 Hz), 5.10−4.90 (1H, m), 4.76−4.68 (1H, m), 4.67 (1H, d, J = 13.0 Hz), 4.40−4.25 (2H, m), 4.13 (1H, dd, J = 5.0, 12.0 Hz), 3.95−3.65 (3H, m), 3.20 (1H, d, J = 6.2 Hz), 3.04 (1H, d, J = 13.1 Hz), 2.52−2.46 (1H, m), 1.35 (3H, t, J = 7.2 Hz).

Ynone Ester 28. Dess−Martin periodinane[19] (579 mg, 1.37 mmol) was added to a solution of oxazole alkynol **19** (214 mg, 0.44 mmol) in 25 mL of dichloromethane. After 30 min, saturated aqueous $NaHCO_3$ and excess $Na_2S_2O_3$ were added to the reaction mixture. After the solids were dissolved the mixture was extracted with dichloromethane. The combined organic layers were washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$), and filtered. After removal of solvent (aspirator), the residue was purified by flash chromatography on silica gel (13 mm × 20 cm), 2:3 EtOAc/hexane eluent, to afford 102 mg (48%) of **28** as an oil: analytical TLC on silica gel, 1:1 EtOAc/hexane, R_f = 0.26; HRMS 368.1135 (calcd $C_{28}H_{26}N_2O_6 - C_8H_8N$), base peak = 105 amu; IR (CCl_4, cm^{-1}) 1724 (C═O), 1695 (C═O); 200 MHz NMR ($CDCl_3$, ppm) δ 7.86−7.81 (2H, m), 7.58−7.22 (8H, m), 6.75 (1H, s), 4.56 (1H, dd, J = 5.4, 11.8 Hz), 4.42 (1H, dd, J = 7.4, 11.8 Hz), 4.30 (2H, q, J = 7.2 Hz), 4.07 (1H, d, J = 13.3 Hz), 3.43 (1H, d, J = 13.3 Hz), 3.04−2.99 (4H, m), 2.95 (1H, d, J = 6.4 Hz), 2.54−2.44 (1H, m), 1.33 (3H, t, J = 7.1 Hz).

Purple Quinone (31). Alkynyl ketone **28** (102 mg, 0.21 mmol) and 2-(phenylsulfonyl)ethyl triflate (**21**) (75 mg, 0.23 mmol) were dissolved in 6 mL of dry acetonitrile and stirred at room temperature for 48 h. Phenyl silane (39 μL, 0.31 mmol) was added to the solution of the crude oxazolium salt, and then the solution was added via cannula to flame-dried CsF (approximately 60 mg) in 2 mL of dry acetonitrile. After 15 h of stirring at room temperature, the reaction was filtered through a plug of Celite and concentrated (aspirator). The crude oil was dissolved in 8 mL of THF along with DDQ (63 mg, 0.28 mmol) and refluxed for 1 h. After removal of solvent (aspirator), the residue was purified by flash chromatography on silica gel (13 mm × 20 cm), 1:1 EtOAc/hexane eluent, to afford 12 mg of a yellow zone containing **27** and 12 mg of a purple zone containing product **31**. The products were purified further by preparative thin-layer chromatography on silica gel, 1:1 EtOAc/hexane, to afford **27** (analytical TLC on silica gel, 1:1 EtOAc/hexane, R_f = 0.36, identical to material prepared from oxazole **20**) and the purple quinone **31** (analytical TLC on silica gel, 1:1 EtOAc/hexane, R_f = 0.29; UV (MeOH, λ_{max} (nm)) 534 (ϵ = 470), 272 (ϵ = 5650), 220 (ϵ = 17 064); partial 270 MHz NMR ($CDCl_3$, ppm) δ 6.53 (1H, d, J = 10.1 Hz), 6.37 (1H, d, 10.1 Hz), 4.44 (1H, dd, J = 5.6, 11.7 Hz), 4.31 (1H, dd, J = 7.1, 11.7 Hz), 3.78 (1H, d, J = 12.7 Hz), 3.38 (1H, d, J = 12.7 Hz), 2.33−2.24 (1H, m).

Internal Azomethine Ylide Cycloaddition to Form 26. To a solution of aziridinyl oxazole **20** (527 mg, 0.88 mmol) in dry acetonitrile (25 mL) was added **21** (318 mg, 1.00 mmol), and this mixture was stirred at room temperature under N_2 for 48 h. Then, a solution of $BnMe_3NCN$ (385 mg, 2.19 mmol) in dry acetonitrile (15 mL) was slowly added via cannula. The resulting yellow gold solution was stirred for 1 h at room temperature and then poured into an aqueous 1% $NaHCO_3$ solution. The mixture was extracted with ethyl acetate (50 mL), the organic layer was separated and washed succesively with H_2O and brine. After drying over $MgSO_4$, the solution was filtered, and the solvent was removed (aspirator). The residue was chromatographed on silica gel with 2:1 hexane: ethyl acetate to yield 446 mg (66%) of **26** as a white foam: 1:1 mixture of diastereomers; R_f = 0.56 (2:1 hexane/ethyl acetate); ^{1}H NMR ($CDCl_3$, 300 MHz, ppm) δ 7.95−7.85 (2H, m); 7.65−7.46 (8H, m), 7.35−7.22 (5H, m), 5.46−5.43 (1H, m), 5.28−5.08 (1H, m), 4.87 (0.5H, d, J = 12.0 Hz), 4.86 (0.5H, d, J = 12.6 Hz), 4.63−4.78 (1H, m), 4.46−4.16 (3H, m), 4.09−3.83 (1H, m), 3.70−3.51 (1.5H, m), 3.39 (0.5H, dd, J = 11.5, 8.4 Hz), 3.16 (0.5 H, d, J = 6.3 Hz), 3.11 (0.5H, d, J = 6.3 Hz), 3.01−2.88 (2H, m), 2.52−2.45 (1H, m), 2.35−2.26 (1H, m), 2.25−2.03 (2H, m), 1.38 (1.5H, t, J = 7.3 Hz), 1.39 (1.5H, t, J = 7.3 Hz), 0.84 (4.5H, s), 0.79 (4.5H, s), 0.16 (1.5H, s), 0.14 (1.5H, s), 0.02 (1.5H, s), −0.06 (1.5H, s); IR (neat, cm^{-1}) 2949, 1703, 1667; HRMS 770.3029 (calcd for $C_{42}H_{50}N_2O_8SSi$ 770.3057).

(18) Hartung, W. H.; Simonoff, R. *Org. React.* **1953**, *7*, 263.

(19) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4156.

Conversion of 26 to Tetracyclic Ketone 32. Sodium (14 mg) was added to a flask containing absolute ethanol (15 mL), at room temperature and under N_2. The mixture was stirred until all sodium had been dissolved. A solution of **26** (200 mg, 0.26 mmol) in absolute ethanol (5 mL) was added, and the resulting mixture was stirred for 8 h. The reaction was then diluted with H_2O and extracted with ethyl acetate. The organic phase was washed with brine and dried ($MgSO_4$). After filtration and evaporation (aspirator) the residue was chromatographed on silica gel with 2:1 hexane:ethyl acetate to yield the saponified alcohol, 148 mg (86%), as a white foam, consisting of a 1:1 mixture of diastereomers: $R_f = 0.35$ (2:1 hexane/ethyl acetate); IR (neat, cm^{-1}) 3467, 1716, 1663; HRMS 666.2794 (calcd for $C_{35}H_{46}N_2O_7SSi$ 666.2795); 300 MHz NMR ($CDCl_3$, ppm) δ 7.98−7.89 (2H, m), 7.69−7.30 (8H, m), 5.45−5.40 (1H, m), 5.30−5.00 (1H, br) 4.85−4.63 (2H, m), 4.47−4.35 (1H, m), 4.28−4.16 (1H, m), 3.96−3.59 (2H, m), 3.43−3.35 (1H, m), 3.21−3.14 (1H, m), 3.09−2.85 (3H, m), 2.33−2.26 (2H, m), 2.07−2.04 (2H, m), 1.80−1.55 (1H, m), 1.37 (1.5H, t, $J = 6.2$ Hz), 1.35 (1.5H, t, $J = 6.2$ Hz), 0.83 (4.5H, s), 0.78 (4.5H, s), 0.15 (1.5H, s), 0.10 (1.5H, s), 0.02 (1.5H, s), −0.09 (1.5H, s).

Sodium hydride (18 mg of a 60% suspension in oil; 0.43 mmol) was placed in a 10-mL round-bottomed flask fitted with a rubber septum under N_2. Dry hexane (2 mL) was added via syringe, and the suspension was stirred for 15 min. Stirring was stopped, and the solids were allowed to settle. The supernatant liquid was carefully removed with a syringe, and dry hexane (2 mL) was again added via syringe. This operation was repeated once more. To the washed solid, dry DMF (5 mL) was added, and the resulting suspension was cooled to 0 °C. A solution of the saponification product from above (140 mg, 0.21 mmol) in DMF (1 mL) was slowly added via cannula. The resulting mixture was stirred for 1 h at 0 °C. H_2O (5 mL) was slowly added via syringe followed by ethyl acetate (20 mL). The organic layer was then successively washed with H_2O and brine, dried ($MgSO_4$), and evaporated (aspirator). The residue was chromatographed on silica gel with 2:1 hexane:ethyl acetate, yielding 74 mg (70%) of alcohol **10** as a white foam, 1:1 mixture of diastereomers, $R_f = 0.48$ (1:1 hexane/ethyl acetate), sufficiently pure for the next step.

To a solution containing **10** (105 mg, 0.21 mmol) and triethylamine (49 μL, 0.35 mmol) in CH_2Cl_2 (10 mL), under N_2 and at 0 °C, was added mesyl chloride (23 μL, 0.30 mmol). The resulting mixture was stirred for 2 h at 0 °C, then diluted with ethyl ether, and washed with H_2O and brine. The organic layer was dried ($MgSO_4$) and evaporated (aspirator) to yield 121 mg of the mesylate **32** as a yellow oil.

The mesylate **32** (121 mg) was dissolved in THF (40 mL), and potassium *tert*-butoxide (30 mg, 0.25 mmol) was added. This mixture was stirred for 2 h under N_2, and then partitioned between ethyl acetate and brine. The organic phase was washed with H_2 and brine, dried ($MgSO_4$), and evaporated (aspirator). The residue was chromatographed on silica gel with 2:1 hexane/ethyl acetate to yield 93 mg (93% from **10**) of tetracyclic **33** as a 1:1 mixture of diastereomers: $R_f = 0.41$ (2:1 hexane/ethyl acetate); IR (neat, cm^{-1}) 2936, 1716, 1663; HRMS 480.2414 (calcd for $C_{27}H_{36}O_4N_2Si$ 480.2444); 300 MHz NMR ($CDCl_3$, ppm) δ 7.36−7.26 (5H, m), 5.43 (0.5H, t, $J = 2.7$ Hz), 5.41 (0.5H, t, $J = 2.7$ Hz), 4.44 (0.5H, d, $J = 13.8$ Hz), 4.40 (0.5H, d, $J = 13.2$ Hz), 4.36−4.11 (3H, m), 3.65 (1H, s), 3.66 (1H, AB q $J = 13.8$ Hz), 3.45 (0.5H, d, $J = 4.8$ Hz), 3.41 (0.5H, d, $J = 4.5$ Hz), 3.11 (t, $J = 4.5$ Hz), 3.03−2.89 (1H, m), 2.33 (0.5H, t, $J = 3.0$ Hz), 2.28 (0.5H, t, $J = 3.0$ Hz), 2.14−2.10 (2H, m), 1.28−1.22 (3H, m), 0.85 (9H, s), 0.20 (1.5H, s), 0.05 (1.5H, s), 0.04 (1.5H, s), 0.01 (1.5H, s).

Deprotection of 33 and DDQ Oxidation to 9b. A solution of **33** (53 mg, 0.11 mmol) in THF (6 mL) under N_2 was prepared, and tetrabutylammonium fluoride (500 μL of a 1.0 M solution in THF; 0.50 mmol) was added via syringe. The resulting mixture was stirred at room temperature for 2 h, and water (10 mL) was added. The reaction mixture was extracted with ethyl acetate, and the organic layer was washed with H_2O and brine, dried ($MgSO_4$), and evaporated (aspirator). The residue was chromatographed on silica gel with 1:1 hexane/ethyl acetate to yield 35 mg (87%) of the desilylated alcohol as an oil: 1:1 diastereomeric mixture; $R_f = 0.19$ (1:1 hexane/ethyl acetate); IR (neat, cm^{-1}) 3405, 3006, 1662; HRMS 366.1577 (calcd for $C_{21}H_{22}N_2O_4$ 366.1579); 300 MHz NMR ($CDCl_3$, ppm) δ 7.35−7.26 (5H, m), 5.52 (1H, s), 5.13−5.09 (1H, m), 4.44 (1H, d, $J = 13.5$ Hz), 4.30−4.19 (2H, m), 4.20 (1H, dd, $J = 13.8$, 3.9 Hz), 3.82 (1H, d, $J = 13.5$ Hz), 3.65 (2H, AB q, $J = 13.8$ Hz), 3.37 (1H, d, $J = 4.8$) 3.14 (1H, t, $J = 4.8$ Hz), 2.64−2.57 (1H, m), 2.48−2.37 (2H, m), 2.10−2.06 (1H, m), 1.19 (1.5H, t, $J = 7.2$ Hz), 1.21 (0.5H, t, $J = 7.2$ Hz).

The alcohol from above (5.6 mg, 0.015 mmol) was dissolved in benzene (400 μL), under N_2 with stirring. DDQ (10 mg, 0.046 mmol) was then added, and the mixture was refluxed for 1 h and then cooled to room temperature. The solvent was removed (aspirator), and the residue was filtered through a short column of silica gel with ethyl acetate. After solvent removal, 4.4 mg (80%) of **9b** was obtained as a yellow amorphous solid: $R_f = 0.38$ (1:1 hexane/ethyl acetate); 300 MHz NMR ($CDCl_3$, ppm) δ 7.40−7.25 (5H, m), 6.63 (1H, d, $J = 9.9$ Hz), 6.53 (1H, d, $J = 9.9$ Hz), 4.47 (1H, d, $J = 14.1$ Hz), 4.35−4.22 (3H, m), 3.69 (2H, s), 3.51 (1H, d, $J = 4.2$ Hz), 3.21 (1H, t, $J = 4.2$ Hz), 1.26 (3H, t, $J = 6.9$ Hz); IR (neat, cm^{-1}) 2936, 1716, 1663; HRMS 362.1250 (calcd for $C_{21}H_{18}N_2O_4$ 362.1267); UV (MeOH, λ_{max} (nm)) = 250 ($\epsilon = 11\,400$), 406 ($\epsilon = 1340$).

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Supporting Information Available: NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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