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Internal Azomethine Ylide Cycloaddition Methodology for Access to the Substitution Pattern of Aziridinomitosene A

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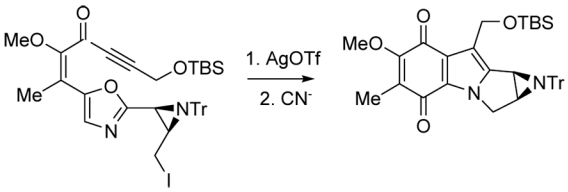
Abstract



Highly substituted, tethered alkyne dipolarophiles participate in the internal 2 + 3 cycloaddition with azomethine ylides generated by treatment of oxazolium salts with cyanide ion. Starting from oxazole **26**, a sequence of *N*-methylation, cyanide addition, and electrocyclic ring opening of a 4-oxazoline intermediate affords the indoloquinone **31** in a one-pot process. A similar reaction from the protected alkynol derivative **25** affords the sensitive, but isolable enone **32**, and subsequent oxidation affords **31** and the deprotected quinine alcohol **34**. Related azomethine cycloaddition methodology via intramolecular oxazolium salt formation from **43** or **46** is also demonstrated, and allows the synthesis of quinone **45** and derived structures having the substitution pattern of aziridinomitosene A. Removal of the *N*-trityl protecting group could not be achieved without aziridine cleavage.

Introduction

Enantiocontrolled synthesis of aziridinomitosenes has been a challenging problem over many years.[1–7] Prior reports from our laboratory describe a potential solution, illustrated by the synthesis of non-racemic quinones **1–3** related to aziridinomitosene A (**4**), but lacking the C (7) methoxy group (Scheme 1).[5c] The approach uses an intramolecular azomethine ylide cycloaddition to assemble the tetracyclic aziridinomitosene core in a sequence that begins with conversion of an oxazole **5** into the oxazolium salt **6**. Cyanide addition then forms a labile 4-oxazoline intermediate **7** and electrocyclic ring opening occurs to generate the transient azomethine ylide **8**. Intramolecular cycloaddition to **9** proceeds with yields of ca. 60% or better when R^1 = H or Me and R^2 = trityl, but becomes less efficient when R^2 = Me (30–40% yield). Our continuing efforts to prepare aziridinomitosene A (**4**) using similar methodology have therefore focused on the *N*-trityl series to learn whether a late stage detritylation may be possible in the highly sensitive environment. Although detritylation could not be accomplished without aziridine cleavage, the studies described below demonstrate access to relevant methoxy-substituted indoloquinones and reveal reaction pathways not encountered previously. The total synthesis of racemic **4** by Jiminez and Dong in 1999 remains the only route to the fully functionalized molecule.[8]

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Methods and Results

Our azomethine ylide cycloaddition approach to **4** requires a 2,5-disubstituted oxazole intermediate **10** (Y, Z= O, H or Y=Z=O). Introduction of the acetylenic dipolarophile subunit via alkynyl anion addition to the aldehyde **11** borrows from prior work, but the current route features a more direct method for sidechain assembly from **12** based on lithiation at the oxazole C(5) position, metal exchange via **13**, and palladium catalyzed coupling with enol triflate **14**-*E*. The latter was easily prepared by deprotonation of the β-keto ester **15**[9] with various bases and enolate quenching with *N*-phenylbistriflimide (Table 1).[10] As expected, the *E:Z* ratio of **14** increased with the coordinating ability of the enolate counterion (Li>Na<K, entries 1–3), but enolate reactivity decreased markedly. The best compromise of yield and *E:Z* ratio was obtained using LiH as the base (entry 6; 65% yield, 93:7 *E:Z*), although the reaction was very slow and required seven days at rt for good conversion. The isomers were assigned from the methyl ^{1}H NMR chemical shifts, assuming a greater downfield shift for **14**-*Z* (δ = 2.36 ppm) compared to **14**-*E* (δ = 2.18 ppm) due to proximity of the methyl and ester groups.[11]

With access to the enol triflate **14**-*E* established, the oxazole coupling and azomethine ylide cycloaddition were investigated in a model system (Scheme 2). Metallated oxazoles were obtained from 2-phenyloxazole **16**[12] via deprotonation (BuLi/TMEDA)[13] or from the 5-bromo derivative **17**[14] by lithium halogen exchange. The intermediate lithiooxazole **18** was then quenched with Bu_3SnCl to afford the stannane **19** (84% isolated),[15] or with anhydrous $ZnCl_2$ to generate **20** *in situ*. Starting from **16**, a preliminary test of the Negishi coupling[16] of **20** was performed using $Pd_2(dba)_3/PPh_3$ with 1.1 equiv of a 1:1 mixture of the enol triflates **14**-*E* and **14**-*Z*. After 15h at rt, the enoate **21** was obtained in a modest 36% overall yield, but with a promising 9:1 ratio of *E:Z* isomers suggesting higher reactivity for the *E*-isomer. Enoate **21** was also prepared by Stille coupling.[17] Thus, **20** was heated at 65 °C with 1.1 equiv of **14** (57:43 *E:Z* mixture) in the presence of $Pd_2(dba)_3$ and trifurylphosphine.[18] This gave **21** in 84% yield, but with a lower E:Z ratio (3:1). On the other hand, when enriched **14**-*E* (>95:5 *E:Z*, 1.3 equiv) was used, the desired enoate **21** was obtained in >95% yield as the sole product.

Next, the tethered alkyne required for the cycloaddition was installed. Enoate **21** was converted to the enal **23** (71% overall) by DIBAL reduction to the allylic alcohol **22** and oxidation with TPAP-NMO.[19] Installation of the alkyne dipolarophile was then accomplished by addition of $LiC{\equiv}CCH_2OTBS$ to give an intermediate alcohol **24** and protection afforded the TBS ether **25** (73% from **23**). Alternatively, oxidation of **24** gave the ynone **26** (57% from **23**).

With cycloaddition precursors **25** and **26** in hand, generation of the azomethine ylide and subsequent [3 + 2] cycloaddition could be explored (Scheme 3). Enone **26** was studied first because the expected cycloadduct would be at the desired quinone oxidation state. Thus, the oxazole nitrogen of **26** was alkylated selectively with MeOTf (CH_3CN, 48 h). The resulting oxazolium salt **27** was added to excess $BnMe_3N^+ CN^-$ at 0 °C to form the transient 4-oxazoline **28**, followed by electrocyclic ring opening to the azomethine ylide **29** and subsequent [3 + 2] cycloaddition to **30**.[5a,5c,15] Spontaneous elimination of HCN then produced the indoloquinone **31**, isolated in 40% overall yield from the oxazole **26**.

Focus then turned to the protected diol oxazole **25** as the cycloaddition precursor (Scheme 3). Alkylation of **25** with MeOTf as before and the usual treatment with cyanide ion initiated the cycloaddition sequence. Despite initial concerns about the stability of the desired cycloadduct **32**, the substance could be purified by chromatography on silica gel (47% yield), although some decomposition was noted. Structure **32** was confirmed, and the aromatic tautomer **33** was ruled out by ^{1}H and ^{13}C NMR evidence, including the characteristic enone ^{13}C signal at δ 179.5 ppm.

Oxidation of **32** proceeded smoothly using 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ),[15] and allowed conversion of the crude cycloaddition product to the more stable quinone oxidation state. Partial deprotection occurred as well, and the product was obtained as a 7:1 mixture of **31**:**34** (95% combined from oxazole **25** without purification of **32**). Several other oxidations[20] were also effective (Table 2), although partial deprotection of the primary OTBS ether occurred in entries 1–3. On the other hand, the combination of various oxidants with stronger bases for the oxidation step[5c] resulted in conversion to the protected quinone **31**, although in somewhat lower yield. Presumably, these reactions proceed via the phenoxide anion derived from **33**.

As shown in Scheme 3, the methoxy enone substitution pattern corresponding to the aziridinomitosene A quinone is fully compatible with the azomethine ylide cycloaddition step. Indeed, better yields were obtained from **25** and from **26** compared to related cycloadditions studied previously in our laboratory. Furthermore, the potentially troublesome non-aromatized intermediate **32** could be handled with minimal complications using the *in situ* oxidation approach. With these encouraging results in hand, we sought to apply similar methodology to the synthesis of aziridinomitosene A (**4**) according to the retrosynthesis shown in Scheme 1.

The aziridinyl oxazole **12** was prepared starting with the addition of lithiated oxazole borane **35**[21] to *N*-trityl-*O*-allylserinal **36**[5c] (Scheme 4). This gave **37** as an inseparable 6:1 diastereomer mixture (84%), but the major isomer could be purified after aziridine formation under Mitsunobu conditions. Based on the vicinal coupling constant J= 6.1 Hz for the aziridine methine protons, the major aziridine (65%) was assigned the *cis* stereochemistry **38**. This result was expected from previous studies using 5-substituted oxazoles,[5c] and provides the basis for assigning the stereochemistry of **37**. Allyl deprotection using zirconocene generated *in situ*[22] followed by iodide formation following a modified Mitsunobu procedure[23] then gave the desired **12**.

Compared to the lithiation of oxazole **16** used in the model system (Scheme 2), the corresponding reaction of **12** must contend with the potentially sensitive iodomethylaziridine subunit. Although lithium-iodine exchange or oligomerization of **16** were potential concerns, it was anticipated that steric shielding in the cis-fused, trityl substituted aziridine would discourage intermolecular events involving either the primary iodide or the aziridine moieties, and that sp^2 hybridization and adjacent heteroatoms would favor the lithiated oxazole. Fortunately, **12** was deprotonated cleanly with LDA/TMEDA[13] at −78 °C (Scheme 4) without any additional precautions compared to the model system. The resulting anion **13** was stirred with freshly fused $ZnCl_2$ to generate **39**, followed by Negishi coupling[16] with triflate **14** (1.1 equiv of *E*-**14**) to give ester **40** in 70% overall yield from oxazole **12**. The corresponding Stille coupling[17] was investigated briefly, but **40** was obtained in a lower 56% yield from **12**.

To install the alkyne necessary for [3 + 2] cycloaddition, ester **40** was converted to aldehyde **11** by the usual two-step reduction/oxidation procedure via alcohol **41** (65%). Addition of $LiC{\equiv}CCH_2OTBS$ to **11** then gave an intermediate alcohol **42** that was oxidized to ketone **43** in 70% overall yield.

The key [3+2] cycloaddition could now be explored starting with ketone **43**. This approach is the most direct route to the tetracyclic aziridinomitosene core, and it is also the safest route because it avoids the hydroquinone oxidation state corresponding to solvolytically reactive leucoaziridino-mitosenes. Best results were obtained using the crystallized benzene complex of AgOTf[24] for iodine activation and intramolecular *N*-alkylation. Conversion of **43** to the oxazolium salt **44** was monitored by ^1H NMR spectroscopy in C_6D_6 and was complete after 3 h. Subsequent azomethine ylide generation was then performed by addition of **44** to excess $BnMe_3N^+ CN^-$ in CH_3CN at rt, the same procedure used in the model study. A transient yellow

color was observed that faded within seconds, presumably due to the formation and subsequent reactions of the azomethine ylide. After 2 h at rt, the desired tetracyclic aziridinomitosene **45** was indeed isolated. A single experiment gave **45** in 33% yield, but this result was never reproduced despite much effort. The crucial variables could not be identified and yields in the 10–27% range were more typical, and unknown byproducts were formed that could not be isolated.

Because the cycloaddition from ketone **43** was too unpredictable for scaleup, an alternative route from alcohol **42** was explored after protection as the TBS ether **46** (78% over the two steps from **11**; Scheme 5). Intramolecular alkylation and ylide generation were then performed as before using the purified AgOTf-benzene complex.[24] Following the same procedure used in Scheme 4 and in prior studies, the intermediate oxazolium salt **47** was added to $BnMe_3N^+$ CN^- (4 equiv) in CH_3CN at rt and the transient color of ylide **48** appeared as usual. However, the isolated product proved to be **50** (33%, 2:1 dr) and not the expected enone **49**. The formula of **50** was deduced using ESMS (*m/z*= **49** + HCN), and the connectivity was established by NMR spectroscopy. Furthermore, the ^{13}C NMR spectrum showed CN peaks at δ = 117.0 and 117.1 ppm for the two diastereomers and the ^1H NMR spectrum contained two signals for the C(6) methine hydrogens at δ = 3.30 ppm and δ = 3.26 ppm as quartets, consistent with structure **50**. Analogous cyanide adducts were not observed starting from the ketone **44**, nor in the model study from either **25** or **26**. Furthermore, nucleophilic addition at C(7) in mitomycin-derived quinones is reported to follow an addition/elimination pathway.[25] On the other hand, simple addition of cyanide to a vinylogous ester has been reported in an unrelated substrate.[26]

Even though the product was not the desired vinylogous ester **49**, oxidation of the cycloaddition product mixture containing **50** was nonetheless attempted in the hope that elimination of HCN might generate **49** *in situ* and that enolization and subsequent oxidation would afford the desired quinone **45**. However, treatment with KHMDS/NCS at −78 °C gave **45** in a marginal 17% yield from **46**.

In an attempt to prevent formation of the cyanide adduct **50**, azomethine ylide generation was performed with 1.0 equiv of $BnMe_3N^+$ CN^- instead of the excess used earlier (Scheme 6). This experiment gave a low yield (<10%) of the quinone **45**, but neither **49** nor **50** was detected by NMR. On the other hand, a mass corresponding to **50** (*m/z*= **49** + HCN) did appear in the electrospray mass spectrum of the crude product, suggesting that isomers of **50** had been formed. Structure **51** resulting from simple iodide-cyanide exchange was ruled out based on disappearance of the oxazole proton in the NMR spectrum, but further characterization of the sensitive product mixture was difficult. Eventually, partially enriched fractions of two new products were obtained by chromatography on NEt_3 buffered silica gel that proved to be two diastereomers **53** resulting from the desired [2+3] cycloaddition of azomethine ylide **52**, but without the usual elimination of HCN. Varying amounts of decomposition products were also observed during attempts to purify **53** by chromatography, including a structure that is tentatively assigned as the expected adduct **49** from MS and NMR evidence. However, enriched samples of **49** were never obtained, nor could either isomer of **53** be isolated without contamination. Structure **53** is consistent with the upfield chemical shift of the aziridine protons (δ = 2.15, 2.59 ppm and δ = 2.34, 2.79 ppm) compared to δ = 2.89 and 3.03 ppm for the analogous protons of **45**. However, decisive evidence for **53** proved elusive until yet another unexpected product was isolated during attempts to aromatize **53** to **45**.

Oxidation of **53** using base/NCS, DDQ, or TBAF/Pd-C/O_2 gave extensive degradation along with traces of **45**. However, treatment of crude **53** with HF-pyridine/O_2[20] and added NEt_3 to prevent aziridine cleavage produced a separable mixture of highly colored quinones (Scheme 6), including quinone alcohol **54** as well as the silyl ether **45**. A deep red quinone was also isolated, and was assigned structure **55**, corresponding to oxidation without HCN elimination.

The high field chemical shifts of the aziridine protons at δ = 2.64 and 2.96 ppm suggested the same sp^3 environment at C(9a) as seen in **53**. With a mass corresponding to **54** + CN + OH and strong NMR evidence for the HO and CH_2OH subunits (one exchangeable proton, singlet at δ = 4.03 ppm; a second exchangeable proton at δ = 4.65 ppm as a doublet of doublets coupled to the C(10) methylene protons). Eventually, X-ray quality crystals were obtained and the structure was confirmed.

For preparative purposes, it was best to oxidize the crude cycloaddition mixture obtained from **46** by activation with AgOTf-benzene complex[24] followed by 1.0 equiv of $BnMe_3N^+$ CN^-. Without separation, the resulting mixture was treated with HF-pyridine/O_2[20] and NEt_3 to give 34% of **45** + **54** combined, together with 14% of **55**. Similar experiments with partially purified **53** were less efficient overall, but did provide evidence that only one of the two diastereomers of **53** undergoes elimination of HCN while the other oxidizes to **55**. The combined 48% yield of tetracyclic adducts is not far from the range of yields obtained using simpler cycloaddition substrates, but the 34% recovery of useful quinones (**45**+**54**) was less than desired. Some solace was taken by considering the dramatic change in structure and the number of transformations to **45** in the one pot procedure starting from oxazole **46**.

The last steps potentially leading to aziridinomitosene A require introduction of the carbamate and removal of the trityl protecting group. When tetracycle **45** was subjected to reductive detritylation conditions with Et_3SiH/MsOH at −40 °C desilylation to **54** proved faster than detritylation.[27] The TBS ether in **45** was therefore removed with NEt_3/HF-pyr, and the alcohol **54** was converted to carbamates **56** and **57** using standard methods (Scheme 7).[28] Treatment of **56** with Et_3SiH/MsOH at 0 °C followed by cleavage of the trichloroacyl group with K_2CO_3 afforded a product mixture having a major ESMS peak at *m/z*= 358 amu corresponding to the ring opened amino alcohol **59** + Na. Another peak at *m/z*= 275 amu was assigned to the cation **60** resulting from heterolysis of the carbamate, identical to ESMS data reported previously for **59**.[29] A small peak at *m/z*= 340 amu, the mass expected for aziridinomitosene A (**4**) + Na, was also observed in samples of the crude product mixture. However, **4** was not detected by NMR comparison with a spectrum of authentic material, and was not present above the detection threshold level of ca. 2–3%. Treatment of the carbamate **57** with Et_3SiH/MsOH also gave the amino alcohol **59** according to ESMS assay, although the mass corresponding to **4** was not detected in this case.[29]

In view of the above results, the reductive detritylation procedure was re-optimized in an attempt to lower the temperature threshold. Using the stronger acid TfOH together with the more potent hydride source triphenylsilane allowed detritylation of simpler model structures (for example, (*R*)-benzyl 1-tritylaziridine-2-carboxylate) as low as −40 °C with 1.0 equiv of each reagent over a time scale of 0.5–15 h. However, when the new procedure (15 h at −40 °C and workup with pH 10.3 buffer) was applied to **57**, ESMS assay (*m/z*= 600 amu, **58** + Na) indicated formation of the *N*-trityl amino alcohol **58** as the main component in a 3:1 mixture with the amino alcohol **59**. The *N*-trityl amino alcohol was not purified, but structure **58** is consistent with the ESMS data and ^1H NMR evidence for the intact *N*-trityl group, new C(6) methyl signals at δ = 1.94 and δ = 1.90 ppm in a 3:1 ratio, as well as new downfield methine signals. Tentatively, we interpret the methyl signals as evidence for diastereomeric amino alcohols from aziridine cleavage as reported for **59**. When 2 equiv of TfOH and 2 equiv of $HSiPh_3$ were used for the deprotection of **57** at −40 °C, only the amino alcohol **59** was recovered (ca. 5:1 dr by NMR), and the structure was confirmed by comparison with literature MS and NMR data.[29,30]

The deprotection studies of **57** are consistent with rapid C(1)-N heterolysis due to the activating effect of the indoloquinone nitrogen. This was no surprise given the long history of DNA alkylation involving similar events, and in particular, the studies by Kohn *et al* with

aziridinomitosenes B, C, and D.[31] Nevertheless, there was reason to think that deprotection might be possible. Thus, earlier efforts in our laboratory had succeeded in the detritylation of **61** to **62** using iPr$_3$SiH/MsOH.[27b] Evidently, the vinylogous carbamate C=O group of the ester substituent in **62** is an important stabilizing factor, but we had imagined (hoped) that the vinylogous amide (quinone) carbonyls of **57** would be at least as effective. This has proven not to be the case.

Conclusions

Indoloquinone **31** was obtained in excellent yield using internal azomethine ylide cycloaddition methodology starting from the oxazole **25** when the sensitive intermediate cycloadduct **32** was oxidized without isolation. The ketone substrate **26** gave lower yields of **31** using the analogous oxazolium salt activation with cyanide ion. Similar routes to the tetracyclic quinone **45** encountered complications due to cyanide addition at the stage of the vinylogous ketone **49**. Furthermore, two unexpectedly stable cycloadduct diastereomers **53** were encountered, and only one diastereomer could be converted into the desired quinone **45** after oxidation. The presence of a sensitive aziridine in all of the tetracyclic intermediates raises complications throughout the late stages of this sequence, but the challenge was met until the very last stage, the reductive *N*-trityl cleavage. This transformation has been achieved in a related system (**61**), but could not be demonstrated on a preparative scale with **57** due to aziridine ring opening.

We were well aware that *N*-trityl cleavage as the last step would be exceptionally challenging. This risk was accepted for two reasons. First, one of the goals of the study was to better define the limits of what chemistry is possible in the presence of the solvolytically sensitive aziridines. Second, the bulky *N*-trityl group is helpful at the stage of oxazolium salt formation using AgOTf. When smaller substituents are present at the aziridine nitrogen, activation of the iodide results in competing internal alkylation of oxazole nitrogen and intermolecular displacement by the same cyanide ion that is necessary to generate the azomethine ylide for the cycloaddition. At this point, it is clear that a different protecting group for aziridine nitrogen will be needed that is compatible with the internal oxazole alkylation/cyanide activation sequence.

Experimental

(*E*)-Methyl 2-methoxy-3-(trifluoromethylsulfonyloxy)but-2-enoate (14)

To a suspension of LiH (81.0 mg, 10.2 mmol) in THF (28 mL) at −78 °C was added a solution of **15**[9] in THF (1 mL) dropwise over 5 min. After stirring at −78 °C for 1 h, a solution of *N*-phenyl-bis(trifluoromethanesulfonimide) (2.43 g, 6.80 mmol) in THF (6 mL) was added dropwise over 5 min. The resulting solution was stirred at −78 °C for 1 h then warmed to rt and stirred for 7 d. The yellow solution was poured into H_2O (100 mL) and extracted with Et_2O. The combined organic extracts were washed with a 10% citric acid solution, dried ($MgSO_4$), filtered, and solvents were removed (aspirator). The residue was purified by flash chromatography on silica gel (50 mm × 15 cm, 10% Et_2O/hexanes, 50 mL fractions) to yield 1.23 g (65%) of triflate **14** as a volatile clear oil as an inseparable 93:7 ratio of *E:Z* isomers (^{1}H NMR analysis), analytical TLC on silica gel 60 F254, 10% Et_2O/hexanes, Rf = 0.3. Molecular ion (M+Na) calculated for $C_7H_9F_3NaO_6S$: 300.9970; found *m/z* = 300.9963, error = 2 ppm; IR (neat, cm^{-1}) 1735, C=O, 1424; 500 MHz ^{1}H NMR ($CDCl_3$, ppm) major *E*-isomer: δ 3.87 (3H, s) 3.70 (3H, s) 2.18 (3H, s). The presence of the minor *Z*-isomer was deduced from methyl integrals at δ 3.88 (0.07H, s) 3.71 (0.07H, s) 2.36 (0.07H, s). ^{13}C NMR (125 MHz, $CDCl_3$, ppm) *E*-isomer δ 161.5, 146.8, 142.4, 118.5 (q, 318 Hz), 60.5, 52.5, 15.8. *Z*-isomer δ 163.2, 147.1, 142.5, 118.5 (q, 318 Hz), 60.4, 52.7, 17.2.

Preparation of (*E*)-methyl 2-methoxy-3-(2-phenyloxazol-5-yl)but-2-enoate (21) by Negishi coupling between 17 and 14

5-Bromo-2-phenyloxazole[14] (**17**) (151 mg, 0.673 mmol) in THF (3 mL) was cooled to −78 °C and *n*-BuLi (1.67 M solution in hexanes, 0.50 mL, 0.84 mmol) was added dropwise over 2 min. After stirring at −78 °C for 10 min, $ZnCl_2$ (1.0 M solution in THF, 2.7 mL, 2.7 mmol) was added and the yellow solution was allowed to warm to rt over 25 min. In a separate flask, Pd_2dba_3 (60.0 mg, 0.0655 mmol) and PPh_3 (38.0 mg, 0.0145 mmol) were dissolved in THF (2 mL) and stirred at rt 20 min. Triflate **14** (205 mg, 0.737 mmol of a 1:1 ratio of *E/Z*-**14**) in THF (1 mL) was added dropwise at rt and the resulting green solution was stirred at rt for 10 min. The previously made organozinc was added via cannula dropwise over 5 min followed by a THF rinse (1 mL). After stirring at rt for 15 h, the solution was poured into saturated aqueous NH_4Cl (10 mL) and extracted with Et_2O. The combined organic extracts were dried ($MgSO_4$), filtered, and solvents were removed (aspirator). The yellow oil was purified by flash column chromatography on silica gel (30 mm × 16 cm, 15% EtOAc/hexanes, 30 mL fractions) to yield 66 mg (36%) of ester **21** as a light yellow oil in an inseparable 93:7 ratio of *E:Z* isomers, analytical TLC on silica gel 60 F254, 15% EtOAc/hexanes, Rf = 0.2. Molecular ion (M+H) calculated for $C_{15}H_{16}NO_4$: 274.1079; found *m/z* = 274.1070, error = 3 ppm; IR (neat, cm^{-1}) 1729, C=O, 1644; for major *E*-**21**: 400 MHz ^1H NMR ($CDCl_3$, ppm) δ 8.01-7.95 (2H, m) 7.48-7.43 (3H, m) 7.18 (1H, s) 3.82 (3H, s) 3.71 (3H, s) 2.10 (3H, s). The presence of the minor *Z*-isomer was deduced from methyl integrals at δ 3.88 (0.24H, s) 3.72 (0.24H, s) 2.46 (0.24H, s). ^{13}C NMR of the major *E*-**21** (100 MHz, $CDCl_3$, ppm) δ 165.1, 161.2, 149.1, 144.6, 130.6, 129.0, 127.4, 127.0, 126.4, 112.9, 58.6, 52.6, 13.7.

Preparation of 21 by Negishi coupling between 16 and 14

To a solution of 2-phenyloxazole **16**[12] (32.0 mg, 0.220 mmol) in THF (1.5 mL) at −78 °C was added TMEDA (0.33 mL, 2.20 mmol, distilled over solid Na) and *n*-BuLi (1.30 M solution in hexanes, 0.19 mL, 0.242 mmol) dropwise over 5 min. After stirring at −78 °C for 1 h, $ZnCl_2$ (1.12 M in THF, 0.79 mL, 0.880 mmol) was added dropwise then the cooling bath was removed and the organozinc solution was allowed to warm to rt. In a separate flask, Pd_2dba_3 (20.1 mg, 0.0220 mmol) and PPh_3 (23.0 mg, 0.0880 mmol) was dissolved in THF (0.5 mL) and stirred at rt 20 min. Triflate **14** (71.1 mg, 0.255 mmol of a >95:5 ratio of *E/Z*-**14**) in THF (0.5 mL) was added dropwise and the resulting green solution was stirred at rt for 25 min. The previously made organozinc was added via cannula dropwise over 5 min followed by a THF rinse (0.5mL). After stirring at rt for 15 h, the solution was poured into saturated aqueous NH_4Cl and extracted with Et_2O. The combined organic extracts were dried ($MgSO_4$), filtered, and solvents were removed (aspirator). The yellow oil was purified by preparatory TLC on silica gel (20 cm × 20 cm × 1000 μm, 15% EtOAc/hexanes eluent) to give 28.3 mg (47%) of **21** as a light yellow oil in a >95:5 ratio of *E:Z* isomers.

Preparation of 21 by Stille coupling of 19 and 14

To a suspension of $Pd_2(dba)_3$ (123 mg, 0.134 mmol) and trifurylphosphine (125 mg, 0.537 mmol) in DMF (4 mL) that was stirred at rt 20 min was added a solution of triflate **14** (478 mg, 1.48 mmol of a >95:5 ratio of *E/Z*-**14**) in DMF (4 mL, including cannula and flask washings) via cannula dropwise. The dark purple solution was allowed to stir at rt 20 min then a solution of stannane **19**[15] (583 mg, 1.34 mmol) in DMF (5 mL, including cannula and flask washings) was added via cannula dropwise. The reaction was heated to 65 °C and stirred 15 h. After cooling to rt, the green solution was poured into saturated aqueous NH_4Cl (30 mL) and extracted with Et_2O. The combined organic extracts were washed with H_2O and brine, dried ($MgSO_4$), and the solvents were removed (aspirator). The yellow oil was purified by flash column chromatography on silica gel (40 mm × 15 cm, 15% EtOAc/hexanes, 40 mL

fractions) to yield 0.367 g (>99%) of ester **21** as a light yellow oil in a >95:5 ratio of *E:Z* isomers identical to previously made material.

(*E*)-2-Methoxy-3-(2-phenyloxazol-5-yl)but-2-en-1-ol (22)

To a solution of ester **21** (158 mg, 0.578 mmol) in toluene (6 mL) at −78 °C was added DIBAL-H (20 wt % solution in toluene, 1.80 mL, 2.17 mmol) dropwise over 5 min. After stirring at −78 °C for 2 h, the cooling bath was removed and 6 mL of Et_2O was added followed by 6 mL of saturated aqueous sodium potassium tartrate (Rochelle's Salt). The biphasic solution was vigorously stirred at rt for 1 h, then the mixture was extracted with Et_2O. The combined organic extracts were dried ($MgSO_4$), filtered, and solvents were removed (aspirator). The off white solid was purified by flash column chromatography on silica gel (20 mm × 15 cm, 3:1 Et_2O/hexanes, 11 mL fractions) to yield 0.134 g (94%) of alcohol **22** as white solid, analytical TLC on silica gel 60 F254, 3:1 Et_2O/hexanes, Rf = 0.3. Pure material was obtained by crystallization in EtOAc/hexanes as white rods, mp = 97 – 99 °C. Molecular ion (M+H) calculated for $C_{14}H_{16}NO_3$: 246.1130; found *m/z* = 246.1119, error = 4 ppm; IR (neat, cm^{-1}) 3263, OH, 1642; 400 MHz ^1H NMR ($CDCl_3$, ppm) δ 7.98-7.93 (2H, m) 7.44-7.41 (3H, m) 6.97 (1H, s) 4.59 (2H, d, *J*=5.9 Hz) 3.83 (3H, s) 2.93 (1H, t, *J*=5.9 Hz) 1.93 (3H, s). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 160.8, 153.5, 151.1, 130.4, 129.0, 127.3, 126.2, 125.3, 107.8, 58.3, 56.9, 13.4.

(*E*)-2-Methoxy-3-(2-phenyloxazol-5-yl)but-2-enal (23)

A solution of alcohol **22** (268 mg, 1.09 mmol), *N*-methyl morpholine *N*-oxide (NMO) (269 mg, 2.30 mmol), and molecular sieves (activated powder, 4Å, 1.34 g) in CH_2Cl_2 (14 mL) was stirred at rt for 30 min. Tetrapropylammonium perruthenate (TPAP) (77.0 mg, 0.219 mmol) was then added and the resulting black solution was stirred at rt 1 h then filtered through a silica gel plug eluting with 250 mL of a 1:1 acetone/hexanes solution. Solvents were removed (aspirator) and the light yellow solid was purified by flash column chromatography on silica gel (30 mm × 16 cm, 40% Et_2O/hexanes, 12 mL fractions) to yield 0.200 g (75%) of aldehyde **23** as a light yellow solid, analytical TLC on silica gel 60 F254, 40% Et_2O/hexanes, Rf = 0.3. Pure material was obtained by crystallization in hexanes as light yellow needles, mp = 77 – 80 °C. Molecular ion (M+H) calculated for $C_{14}H_{14}NO_3$: 244.0974; found *m/z* = 244.0966, error = 3 ppm; IR (neat, cm^{-1}) 1665 C=O; 500 MHz ^1H NMR ($CDCl_3$, ppm) δ 10.19 (1H, s) 8.06-8.02 (2H, m) 7.52-7.47 (3H, m) 7.34 (1H, s) 3.83 (3H, s) 2.29 (3H, s). ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 187.1, 163.6, 151.9, 148.2, 131.4, 131.3, 129.4, 129.2, 126.9, 126.8, 60.3, 13.4.

(*E*)-7-(tert-Butyldimethylsilyloxy)-3-methoxy-2-(2-phenyloxazol-5-yl)hept-2-en-5-yn-4-one (26)

To a solution of *tert*-butyldimethylsilyl propargyl ether[32] (33.0 mg, 0.193 mmol) in THF (1.0 mL) at −40 °C was added *n*-BuLi (0.374 M solution in hexanes, 0.52 mL, 0.193 mmol) dropwise over 5 min. After stirring at −42 °C for 1 h, a solution of aldehyde **23** (26.0 mg, 0.107 mmol) in THF (1.0 mL, including cannula and flask washings) was added dropwise via cannula and the reaction was stirred an additional 2 h at −42 °C then the cooling bath was removed and 2 mL of saturated aqueous sodium bicarbonate was added. After stirring at rt 10 min, the solution was poured into brine and extracted with CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4), filtered, and solvents were removed (aspirator). To the crude alcohol from above in CH_2Cl_2 (2 mL) was added NMO (26.0 mg, 0.225 mmol) and molecular sieves (activated powder, 4Å,120 mg) and the mixture was stirred at rt 20 min. TPAP (8.0 mg, 0.021 mmol) was added in one portion and the black solution was stirred an additional 1 h at rt then filtered through a silica gel plug (2 cm × 5 cm) and eluted with 50 mL of a 1:1 hexanes/acetone solution. Solvents were removed (aspirator) and the yellow foam was purified by preparatory TLC on silica gel (20 cm × 20 cm × 1000 μm, 20% EtOAc/hexanes eluent) to give 25.0 mg (57%) of **26** as a yellow foam, analytical TLC on silica gel 60 F254, 20% EtOAc/hexanes, Rf

= 0.3. Molecular ion (M+H) calculated for $C_{23}H_{30}NO_4Si$: 412.1944; found *m/z* = 412.1935, error = 2 ppm; IR (neat, cm^{-1}) 1640 C=O; 500 MHz ^1H NMR ($CDCl_3$, ppm) δ 8.05-8.01 (2H, m) 7.49 (1H, s) 7.47-7.44 (3H, m) 4.33 (2H, s) 3.75 (3H, s) 2.22 (3H, s) 0.84 (9H, s) 0.03 (6H, s). ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 174.8, 162.1, 151.0, 148.4, 130.9, 130.5, 129.1, 127.2, 126.8, 120.3, 92.4, 84.3, 59.9, 51.7, 25.9, 18.4, 15.4, −5.2.

(*E*)-5-(4,7-Bis(*tert*-butyldimethylsilyloxy)-3-methoxyhept-2-en-5-yn-2-yl)-2-phenyloxazole (25)

To a solution of *tert*-butyldimethylsilyl propargyl ether[32] (252 mg, 1.48 mmol) in THF (1.5 mL) at −78 °C was added *n*-BuLi (1.47 M solution in hexanes, 1.01 mL, 1.48 mmol) dropwise over 5 min. The solution was allowed to stir at −78 °C for 1 h then a solution of aldehyde **23** (200 mg, 0.822 mmol) in THF (0.5 mL, including cannula and flask washings) was added dropwise via cannula and the reaction was allowed to slowly warm to −42 °C over 20 minutes. The light yellow solution was stirred at −42 °C for 2 h then the cooling bath was removed and 2 mL of saturated aqueous sodium bicarbonate was added. After stirring at rt 10 min, the solution was poured into brine and extracted with CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4), filtered, and solvents were removed (aspirator). The crude alcohol from above was dissolved in CH_2Cl_2 (2 mL) and *tert*-butyldimethylsilyl chloride (151 mg, 1.00 mmol) was added followed by imidazole (84.0 mg, 1.23 mmol). The suspension was stirred for 15 h at rt and then poured into brine and extracted with CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4), filtered, and solvents were removed (aspirator). The clear oil was purified by flash column chromatography on silica gel (40 mm × 15 cm, 20% Et_2O/hexanes, 15 mL fractions) to yield 0.318 g (73%) of oxazole **23** as a clear oil, analytical TLC on silica gel 60 F254, 20% Et_2O/hexanes, Rf = 0.5. Molecular ion (M+Na) calcd for $C_{29}H_{45}NNaO_4Si_2$: 550.2785; found *m/z* = 550.2777, error = 1 ppm; IR (neat, cm^{-1}) 1638; 400 MHz ^1H NMR ($CDCl_3$, ppm) δ 8.09-8.02 (2H, m) 7.49-7.42 (3H, m) 7.07 (1H, s) 5.80 (1H, t, *J*=1.8 Hz) 4.38 (2H, d, *J*=1.8 Hz) 3.99 (3H, s) 2.03 (3H, s) 0.89 (9H, s) 0.88 (9H, s) 0.11 (6H, s) 0.09 (3H, s) 0.05 (3H, s). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 161.2, 152.7, 150.6, 130.4, 129.0, 127.7, 126.4, 126.3, 107.5, 84.3, 83.8, 61.2, 59.9, 52.0, 26.0, 25.9, 18.4, 14.1, −4.6, −4.8, −5.0.

Azomethine ylide cycloaddition to form 4-(*tert*-butyldimethylsilyloxy)-3-((*tert*-butyldimethylsilyloxy)methyl)-5-methoxy-1,6-dimethyl-2-phenyl-1*H*-indol-7(4*H*)-one (31)

To a solution of ynone oxazole **26** (10.0 mg, 0.0243 mmol) in freshly distilled CH_3CH_2CN (0.5 ml, stirred over activated 4 Å molecular sieves, distilled over CaH_2, and distilled again over P_2O_5) and molecular sieves (activated 4 Å, 7 beads) was added MeOTf (4 μL, 0.0365 mmol). The clear solution was allowed to stir at rt 15 h. MeOTf (4 μL, 0.0592 mmol) was added and the light brown solution was stirred an additional 15 h at rt. Salt formation was indicated by TLC analysis of reaction mixture, Rf = 0.0 and by mass spectroscopy with molecular ion (M+) calculated for $C_{24}H_{32}NO_4Si$: 426, found *m/z* = 426. The oxazolium salt was transferred to a solution of $BnMe_3N^+$ CN^- (9.0 mg, 0.054 mmol) in freshly distilled CH_3CH_2CN (2.0 mL, including cannula and flask washings, stirred over activated 4 Å molecular sieves, distilled over CaH_2, and distilled again over P_2O_5) at 0 °C via cannula dropwise over 5 minutes. The reaction was stirred at 0 °C for 10 min then the cooling bath was removed and the light orange solution was stirred at rt for 15 h. The orange solution was poured into brine and extracted with Et_2O. The combined organic extracts were dried ($MgSO_4$), filtered, and solvents were removed (aspirator) to yield a light orange oil. The orange oil was purified by preparative TLC on silica gel (20 cm × 20 cm × 1000 μm, 15% EtOAc/hexanes eluent) to give 4.0 mg (40%) of **31** as an orange oil. Molecular ion (M+Na) calculated for $C_{24}H_{31}NNaO_4Si$: 448.1920; found *m/z* = 448.1922, error = 1 ppm; IR (neat, cm^{-1}) 1661 C=O, 1640 C=O, 1609; UV (CH_3OH, nm) 266 (ε 33000), 347 (ε 8500), 448 (ε 4400). 500 MHz ^1H NMR ($CDCl_3$, ppm) δ 7.50-7.42 (5H, m) 4.67 (2H, s) 4.00 (3H, s) 3.80 (3H, s) 2.00 (3H, s)

0.86 (9H, s) 0.05 (3H, s). ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 179.9, 179.6, 156.9, 141.9, 130.8, 129.4, 129.3, 129.3, 129.3, 128.7, 122.5, 121.9, 61.3, 55.6, 34.4, 26.2, 18.8, 9.0, −5.1.

Cycloaddition from protected akynol 25 to pyrroloenone 32

A solution of oxazole **25** (48.0 mg, 0.0909 mmol) and molecular sieves (activated 4 Å, 200 mg) in CH_3CN (2 mL, stirred over activated 4 Å molecular sieves, distilled over CaH_2, and distilled again over P_2O_5) was stirred at rt for 15 min. MeOTf (15 μL, 0.136 mmol) was added and the solution was allowed to stir at rt for 15 h. MeOTf (15 μL, 0.136 mmol) again was added and the solution stirred at rt an addition 15 h. Salt formation was indicated by TLC analysis of reaction mixture, Rf = 0.0, and by mass spectroscopy with molecular ion (M+) calculated for $C_{30}H_{48}NO_4Si_2$: 542, found *m/z* = 542. The newly formed oxazolium salt was added to a solution of $BnMe_3N^+$ CN^- (35.0 mg, 0.200 mmol) in CH_3CN (2 mL, including cannula and flask washings), stirred over activated 4 Å molecular sieves, distilled over CaH_2, and distilled again over P_2O_5) at 0 °C via cannula dropwise over 5 min. The reaction was stirred at 0 °C for 10 min then warmed to rt and stirred for 2 h. The orange solution was poured into pH 5.8 buffer (15 mL) and extracted with Et_2O. The combined organic extracts were dried ($MgSO_4$), filtered, and solvents were removed (aspirator). The orange oil was purified by preparative TLC on silica gel (20 cm × 20 cm × 1000 μm, 20% EtOAc/hexanes eluent) to give 23.0 mg (47%) of **32** as a white solid, analytical TLC on silica gel 60 F254, 20% EtOAc/hexanes, Rf = 0.6. Pure material was obtained by crystallization in hexanes as off-white rods, mp = 72 – 74 °C. Molecular ion (M+Na) calculated for $C_{30}H_{47}NNaO_4Si_2$: 564.2941; found *m/z* = 564.2939, error = 0 ppm; IR (neat, cm^{-1}) 1638; 500 MHz ^{1}H NMR ($CDCl_3$, ppm) δ 7.48-7.40 (3H, m) 7.38-7.36 (2H, m) 5.81 (1H, s) 4.86 (1H, AB, *J*=11.2 Hz) 4.26 (1H, AB, *J*=11.2 Hz) 4.08 (3H, s) 3.84 (3H, s) 1.86 (3H, s) 0.90 (9H, s) 0.86 (9H, s) 0.05 (3H, s) 0.04 (3H, s) −0.08 (3H, s) −0.46 (3H, s). ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 179.5, 165.9, 139.7, 130.7, 130.5, 128.7, 128.6, 128.5, 125.3, 120.4, 116.1, 61.7, 56.9, 56.4, 33.9, 26.2, 25.9, 18.7, 18.5, 7.9, −4.0, −4.1, −5.1, −5.2.

Preparation of 31 and 3-(hydroxymethyl)-5-methoxy-1,6-dimethyl-2-phenyl-1*H*-indole-4,7-dione (34) from 25

To a solution of oxazole **25** (25.0 mg, 0.0474 mmol) in CH_3CN (0.6 ml, stirred over activated 4 Å molecular sieves, distilled over CaH_2, and distilled again over P_2O_5) and molecular sieves (activated 4 Å, 150 mg) was added MeOTf (14 μL, 0.0592 mmol). The clear solution was allowed to stir at rt 15 h. MeOTf (7 μL, 0.0592 mmol) was added and the light brown solution was stirred an additional 15 h at rt. The oxazolium salt was transferred to a solution of $BnMe_3N^+$ CN^- (18.0 mg, 0.104 mmol) in CH_3CN (4.5 mL, including cannula and flask washings, stirred over activated 4 Å molecular sieves, distilled over CaH_2, and distilled again over P_2O_5) at 0 °C via cannula dropwise over 5 minutes. The reaction was stirred at 0 °C for 10 min then the cooling bath was removed and the light orange solution was stirred at rt for 2 h. The orange solution was poured into pH 5.8 buffer (15 mL) and extracted with Et_2O. The combined organic extracts were dried ($MgSO_4$), filtered, and solvents were removed (aspirator) to yield a light orange oil. The crude oil from above was dissolved in benzene (1.0 mL) and DDQ (22.0 mg, 0.0948 mmol) was added in one portion. The dark black solution was stirred at rt for 2 h then poured into Et_2O:H_2O:1 M NaOH (10 mL: 10 mL: 1 mL) and extracted with Et_2O. The combined organic extracts were dried ($MgSO_4$), filtered, and solvents were removed (aspirator). The orange oil was purified by preparative TLC on silica gel (20 cm × 20 cm × 1000 μm, 15% EtOAc/hexanes eluent) to give 16.8 mg of **31** as an orange oil and 1.7 mg of **34** as an orange solid (95% combined yield), analytical TLC on silica gel 60 F254, 15% EtOAc/hexanes, Rf = 0.5 (silyl ether) and Rf = 0.2 (alcohol). For alcohol **34**: Pure material was obtained by crystallization in EtOAc/hexanes as orange needles, mp = 119 – 121°C. Molecular ion (M+Na) calculated for $C_{18}H_{17}NNaO_4$: 334.1055; found *m/z* = 334.1055, error = 0 ppm; IR (neat, cm^{-1}) 3425 OH, 1731 C=O, 1638 C=O; 500 MHz ^{1}H NMR ($CDCl_3$, ppm) δ 7.52-7.46 (3H,

m) 7.31-7.29 (2H, m) 4.51 (2H, d, *J*=7.1 Hz) 4.19 (1H, t, *J*=7.1 Hz) 4.03 (3H, s) 3.79 (3H, s) 2.02 (3H, s). ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 181.2, 179.5, 156.6, 139.5, 130.7, 130.2, 129.9, 129.6, 129.1, 128.6, 124.1, 122.8, 61.4, 56.4, 34.3, 9.2.

Aminoalcohol (37)

To a solution of the oxazole (1.74 g, 25.2 mmol) in 100 mL of anhydrous THF at rt was added BH_3-THF (1.0 M solution in THF, Aldrich, fresh bottle, 26.5 mL, 26.5 mmol). After stirring at rt for 1h, the colorless solution was cooled to −78 °C, and *n*BuLi (1.52 M solution in hexanes, 17.4 mL, 26.5 mmol) was added dropwise over 30 min. The colorless solution was stirred at −78 °C for 1.5 h, and then a solution of the aldehyde **36**[5c] (9.36 g, 25.2 mmol) in anhydrous THF (75 mL, including cannula and flask washings) was added via cannula dropwise over 30 min. The resulting pale yellow solution was stirred at −78 °C for 1.5 h, and then quenched with 200 mL of 5% AcOH in EtOH. The cooling bath was removed, and the reaction mixture was allowed to warm to rt. After stirring at rt for 24 h, the colorless solution was concentrated by rotary evaporation, poured into ether, and washed with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with ether, all organic extracts were combined, dried (Na_2SO_4), and concentrated by rotary evaporation. The crude material contained a 6:1 dr ratio, as determined by ^{1}H NMR assay. The residue was purified by flash chromatography on silica gel (5.5×20 cm, 900 mL of 1:1 hexane/ether then 900 mL of 2:1 hexane/acetone eluent, 20 mL fractions). Fractions 52–67 gave 9.21 g (84%) of the alcohol **37** with 12:1 dr (NMR analysis) as a white foam, analytical TLC on silica gel 60 F254, 2:1 hexane/EtOAc, Rf= 0.2. Molecular ion ($M+Na^+$) calcd for $C_{28}H_{28}N_2NaO_3$: 463.19980; found (electrospray) *m/z*= 463.2019, error= 5 ppm; base peak= 243 amu; IR (neat, cm^{-1}) 3342, O-H; 1571; 400 MHz NMR ($CDCl_3$, ppm), major diastereomer, δ 7.62 (1H, d, *J*= 0.7 Hz) 7.56-7.51 (6H, m) 7.30-7.24 (6H, m) 7.22-7.16 (3H, m) 7.07 (1H, s) 5.77-5.62 (1H, m) 5.16-5.03 (2H, m) 4.58 (2H, d, *J*= 5.1 Hz) 3.60-3.50 (2H, m) 3.36-3.29 (1H, m) 2.85 (1H, dd, *J*= 9.5, 2.9 Hz) 2.82-2.50 (1H, s) 2.41 (1H, dd, *J*= 9.5, 6.6 Hz). In addition, signals for the minor (8%) diastereomer were resolved at 7.62-7.58 (1H, m) 6.99 (1H, s), 4.02 (1H, dd, *J*= 8.8, 3.7 Hz) 3.91 (1H, d, *J*= 8.8 Hz) 3.68-3.65 (2H, m) 3.26-3.19 (1H, s) 3.18 (1H, dd, *J*= 9.5, 2.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, ppm), major diastereomer, δ 164.3, 146.4, 138.8, 134.1, 128.6, 128.0, 126.9, 126.6, 117.0, 71.8, 70.9, 69.3, 69.1, 54.9.

2-[(2*S*,3*R*)-3-Allyloxymethyl-1-trityl-aziridin-2-yl] oxazole 38 from aminoalcohol 37

To a solution of alcohol **37** (9.21 g, 20.9 mmol) and Ph_3P (8.22 g, 31.3 mmol) in 150 mL of anhydrous THF was added diethyl azodicarboxylate (4.8 mL, 30.7 mmol) dropwise over 10 min. The cooling bath was removed and the reaction mixture was allowed to warm to rt. After stirring at rt for 14 h, the yellow solution was concentrated to approximately 10 mL by rotary evaporation and then passed through a 5×10 cm^2 plug of silica and the plug was washed with 1:1 hexane/EtOAc. The filtrate was concentrated by rotary evaporation and purified by flash chromatography on silica gel (5×20 cm, 2:1 hexane/Et_2O eluent, 1×300 mL then 20 mL fractions). Fractions 14–24 were concentrated to yield product. Fractions 25–63 were concentrated by rotary evaporation and the residue was purified by another flash chromatography on silica gel under the same conditions. Fractions 18–36 were combined with the original 14–24 to give 5.7 g (65%) of **38** with >95% dr (NMR analysis) as a white foam, analytical TLC on silica gel 60 F254, 5:1 hexane/EtOAc, Rf= 0.1. Molecular ion ($M+Na^+$) calcd for $C_{28}H_{26}N_2NaO_2$: 445.18920; found *m/z*= 445.1880, error= 3 ppm; base peak= 243 amu; IR (neat, cm^{-1}) 1596; 1574; 300 MHz NMR ($CDCl_3$, ppm) δ 7.66 (1H, d, *J*= 0.8 Hz) 7.56-7.48 (6H, m) 7.30-7.17 (9H, m) 7.15 (1H, d, *J*= 0.8 Hz) 5.71 (1H, dddd, *J*= 17.0, 10.4, 5.5, 5.5 Hz) 5.14-5.04 (2H, m) 4.01 (1H, dd, *J*= 10.4, 4.9 Hz) 3.78 (2H, ddd, *J*= 5.5, 1.4, 1.4 Hz) 3.72 (1H, dd, *J*= 10.4, 7.1 Hz) 2.56 (1H, d, *J*= 6.1 Hz) 1.98 (1H, ddd, *J*= 7.1, 6.0, 4.9 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 161.7, 143.5, 138.6, 134.4, 129.4, 127.7, 127.5, 126.9, 116.9, 75.0, 71.8, 68.1, 38.6, 32.2.

Allyl ether cleavage from 38; (2*S*,3*R*)-2-(oxazol-2-yl)-3-hydroxymethyl-1-tritylaziridine

A solution of zirconocene dichloride (Aldrich, 2.63 g, 8.99 mmol) in 40 mL of anhydrous THF was cooled to −78 °C, and *n*BuLi (1.56 M solution in hexanes, 11.5 mL, 17.9 mmol) was added dropwise over 30 min. After the resulting yellow solution was stirred at −78 °C for 1 h, a solution of the allyl ether **38** (2.48 g, 5.87 mmol) in anhydrous THF (30 mL, including cannula and flask washings) was added dropwise via cannula. The yellow solution was stirred at −78 °C for 5 min, the cooling bath was removed, and the reaction mixture was allowed to warm to rt. After 1 h at rt, the resulting dark brown solution was cooled to 0 °C, and 30 mL of saturated aqueous NH_4Cl was added. The pale yellow suspension was stirred at rt for 3 h and then filtered through Celite (3□5 cm) with ether (200 mL). The filtrate was washed with brine, dried (Na_2SO_4), and concentrated by rotary evaporation. The residue was purified by flash chromatography on silica gel (5□17 cm, 3:2 hexane/EtOAc eluent, 20 mL fractions). Fractions 16–46 gave 2.22 g (98%) of the product as a colorless foam, analytical TLC on silica gel 60, 1:1 hexane/EtOAc, Rf= 0.3. Molecular ion ($M+Na^+$) calcd for $C_{25}H_{22}N_2NaO_2$: 405.15790; found *m/z*= 405.1582, error= 1 ppm; IR (neat, cm^{-1}) 3379, O-H; 1574; 300 MHz NMR ($CDCl_3$, ppm) δ 7.67 (1H, d, *J*= 0.8 Hz) 7.58-7.51 (6H, m) 7.34-7.20 (9H, m) 7.15 (1H, d, *J*= 0.8 Hz) 4.13 (1H, ddd, *J*= 12.1, 6.3, 4.1 Hz) 4.01-3.83 (2H, m) 2.38 (1H, d, *J*= 6.0 Hz) 2.02-1.94 (1H, m). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 162.4, 143.6, 139.2, 129.3, 127.8, 127.0, 127.0, 74.9, 61.1, 39.4, 31.6.

(2*S*,3*R*)-2-(Oxazol-2-yl)-3-iodomethyl-1-tritylaziridine (12)

A solution of Ph_3P (2.28 g, 8.7 mmol) in 40 mL of anhydrous toluene was cooled to 0 °C, and diethyl azodicarboxylate (Aldrich, 1.3 mL, 8.12 mmol) was added, followed by a solution of the alcohol prepared above (2.22 g, 5.8 mmol) in anhydrous toluene (40 mL, including cannula and flask washings), followed by MeI (0.54 mL, 8.7 mmol). After stirring the resulting white suspension at 0 °C for 5 min, the cooling bath was removed, and the reaction mixture was heated at 70 °C for 2 h. The precipitate gradually dissolved forming a mixture of a pale yellow solution and a few drops of brown oil, which was concentrated by rotary evaporation. The residue was dissolved in 5 mL of CH_2Cl_2 and purified by flash chromatography on silica gel (4.5 × 15 cm, 5:1 hexane/ethyl acetate, 20 mL fractions). Fractions 9–31 were concentrated by rotary evaporation and purified by another flash chromatography on silica gel (4.5 × 15 cm, 10:1 hexane/ethyl acetate, 20 mL fractions). Fractions 9–22 gave 2.78 g (97%, 95% for 2 steps) of the pure product as a colorless foam, analytical TLC on silica gel 60, 5:1 hexane/ethyl acetate eluent, Rf= 0.3. Molecular ion ($M+Na^+$) calcd for $C_{25}H_{21}IN_2NaO$: 515.05990; found *m/z*= 515.0600, error= 0 ppm; IR (neat, cm^{-1}) 1574; 300 MHz NMR ($CDCl_3$, ppm) δ 7.70 (1H, d, *J*= 0.8 Hz) 7.55-7.48 (6H, m) 7.32-7.20 (9H, m) 7.19 (1H, d, *J*= 0.8 Hz) 3.68 (1H, dd, *J*= 9.9, 4.7 Hz) 3.55 (1H, dd, *J*= 9.9, 9.4 Hz) 2.60 (1H, d, *J*= 6.0 Hz) 2.11 (1H, ddd, *J*= 9.4, 6.0, 4.7 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 160.5, 143.3, 139.0, 129.2, 127.8, 127.8, 127.1, 75.4, 41.5, 34.9, 3.2.

Preparation of (*E*)-methyl 3-(2-((2*S*,3*R*)-3-(iodomethyl)-1-tritylaziridin-2-yl)oxazol-5-yl)-2-methoxybut-2-enoate (40) from 12

To a solution of diisopropyl amine (153 μL, 1.09 mmol) in THF (3 mL) at 0 °C was added *n*-BuLi (1.53M solution in hexanes, 0.69 mL, 1.04 mmol) dropwise over 5 min. After stirring at 0 °C for 30 min, theLDA solution was transferred via cannula dropwise over 20 min to a stirred solution of oxazole **12** (0.466 g, 0.946 mmol) and TMEDA (1.43 mL, 9.46 mmol, distilled over solid Na) in THF (3 mL) at −78 °C. After stirring the resulting yellow solution at −78 °C for 1 h, $ZnCl_2$ (1.5 M in THF, 2.52 mL, 3.78 mmol) was added dropwise then the cooling bath was removed and the organozinc solution was allowed to warm to rt.

In a separate flask, Pd_2dba_3 (87.0 mg, 0.0946 mmol) and PPh_3 (99.0 mg, 0.378 mmol) was dissolved in THF (2.5 mL) and stirred at rt 25 min. Triflate **14** (305 mg, 1.10 mmol of a >95:5

ratio of *E/Z*-**14**) in THF (2.5 mL) was added dropwise and the resulting green solution was stirred at rt for 25 min. The previously made organozinc was added via cannula dropwise over 5 min. After stirring at rt for 15 h, the solution was poured into saturated aqueous NH_4Cl (20 mL) and extracted with Et_2O (3 × 40 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and solvents were removed (aspirator). The yellow oil was purified by flash column chromatography on silica gel (40 mm × 16 cm, 5:1 hexanes/EtOAc, 30 mL fractions) to yield 0.408 g (70%) of ester **40** as a colorless solid, analytical TLC on silica gel 60 F254, 5:1 EtOAc/hexanes, Rf = 0.3. Pure material was obtained by crystallization in EtOAc/hexanes as clear rods, mp = 125 – 127 °C. Molecular ion (M+Na) calculated for $C_{31}H_{29}IN_2NaO_4$: 643.1070; found *m/z* = 643.1077, error = 1 ppm; IR (neat, cm^{-1}) 1729 C=O; 400 MHz ^1H NMR ($CDCl_3$, ppm) δ 7.50-7.49 (6H, m) 7.30-7.21 (9H, m) 7.10 (1H, s) 3.75 (3H, s) 3.69 (3H, s) 3.70-3.66 (1H, m) 3.53 (1H, dd, *J*=9.9Hz, 9.2 Hz) 2.53 (1H, d, *J*=5.9 Hz) 2.13-2.07 (1H, m) 2.07 (3H, s). ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 165.0, 160.0, 149.7, 144.6, 143.5, 129.5, 128.0, 127.4, 126.2, 112.9, 75.6, 58.6, 52.6, 41.9, 35.3, 13.8, 3.3.

(*E*)-3-(2-((2*S*,3*R*)-3-(Iodomethyl)-1-tritylaziridin-2-yl)oxazol-5-yl)-2-methoxybut-2-enal (11)

To a solution of ester **40** (0.958 g, 1.54 mmol) in toluene (25 mL) at −78 °C was added DIBAL-H (20% wt solution, 4.8 mL, 5.79 mmol) dropwise. After stirring the resulting yellow solution for 2 h at −78 °C, the cooling bath was removed and 25 mL of Et_2O was added followed by 25 mL of saturated aqueous sodium potassium tartrate (Rochelle's Salt). The mixture was vigorously stirred for 1 h, then the mixture was extracted with Et_2O. The combined organic extracts were dried ($MgSO_4$), filtered, and solvents were removed (aspirator) to give 0.719 g (79%) of **41** as a white foam that was sufficiently pure for the next reaction without further purification, analytical TLC on silica gel 60 F254, 30% EtOAc/hexanes, Rf = 0.2. A solution of the alcohol from above (185 mg, 0.312 mmol), *N*-methyl morpholine *N*-oxide (77.0 mg, 0.655 mmol), and molecular sieves (activated powder, 4Å, 360 mg) in CH_2Cl_2 (5 mL) was stirred at rt. After stirring at rt 30 min, TPAP (22.0 mg, 0.0624 mmol) was added in one portion. After stirring at rt 1 h, the black solution was filtered through a silica gel plug eluting with 150 mL of a 1:1 acetone/hexanes solution. Solvents were removed (aspirator) and the light yellow solid was purified by flash column chromatography on silica gel (30 mm × 15 cm, 2:1 hexanes/Et_2O, 20 mL fractions) to yield 0.150 g (82%) of aldehyde **11** as a light yellow foam, analytical TLC on silica gel 60 F254, 2:1 hexanes/Et_2O, Rf = 0.3. Molecular ion (M+Na) calculated for $C_{30}H_{27}IN_2NaO_3$: 613.0964; found *m/z* = 613.0959, error = 1 ppm; IR (neat, cm^{-1}) 1673 C=O; 500 MHz ^1H NMR ($CDCl_3$, ppm) δ 9.99 (1H, s) 7.53-7.51 (6H, m) 7.30-7.27 (6H, m) 7.27 (1H, s) 7.25-7.22 (3H, m) 3.80 (3H, s) 3.68 (1H, dd, *J*=9.8 Hz, 4.4 Hz) 3.50 (1H, dd, *J*=9.8 Hz, 9.8 Hz) 2.57 (1H, d, *J*=5.9 Hz) 2.24 (3H, s) 2.19-2.15 (1H, m). ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 187.0, 162.4, 152.2, 148.6, 143.3, 130.2, 129.5, 129.4, 128.1, 127.4, 75.7, 60.1, 42.0, 35.1, 15.3, 3.2.

(*E*)-7-(*tert*-Butyldimethylsilyloxy)-2-(2-((2*S*,3*R*)-3-(iodomethyl)-1-tritylaziridin-2-yl)oxazol-5-yl)-3-methoxyhept-2-en-5-yn-4-one (43)

To a solution of *tert*-butyldimethylsilyl propargyl ether[32] (213 mg, 1.25 mmol) in THF (8 mL) at −78 °C was added *n*-BuLi (1.53 M solution in hexanes, 0.82 mL, 1.25 mmol) dropwise over 5 min. The clear solution was stirred for 1 h at −78 °C, then a solution of aldehyde **11** (370 mg, 0.627 mmol) in THF (5 mL including flask and cannula washings) was added via cannula dropwise over 5 min. The resulting yellow solution was warmed to −42 °C and stirred for 2 h at −42 °C. The cooling bath was then removed and 10 mL of saturated aqueous sodium bicarbonate was added. After stirring at rt 10 min, the solution was poured into H_2O and extracted with Et_2O. The combined organic extracts were dried ($MgSO_4$), filtered, and solvents were removed (aspirator).

The crude alcohol **42** from above, *N*-methyl morpholine *N*-oxide (154 mg, 1.32 mmol), and molecular sieves (activated powder, 4 Å, 1.40 g) in CH_2Cl_2 (13 mL) was stirred at rt for 30 min. TPAP (44.0 mg, 0.125 mmol) was then added in one portion and the black solution was stirred at rt 1 h. The black solution was then filtered through a silica gel plug eluting with 100 mL of a 1:1 acetone/hexanes solution. Solvents were removed (aspirator) and the light yellow solid was purified by flash column chromatography on silica gel (40 mm × 17 cm, 20% EtOAc/hexanes, 25 mL fractions) to yield 0.335 g (70%) of ketone **43** as a light yellow foam, analytical TLC on silica gel 60 F254, 20% EtOAc/hexanes, Rf = 0.4. Molecular ion (M+Na) calculated for $C_{39}H_{43}IN_2NaO_4Si$: 781.1934; found *m/z* = 781.1932, error = 0 ppm; IR (neat, cm^{-1}) 1648 C=O; 500 MHz ^1H NMR ($CDCl_3$, ppm) δ 7.57 (1H, s) 7.53-7.51 (6H, m) 7.29-7.26 (6H, m) 7.23-7.22 (3H, m) 4.38 (1H, AB, *J*=17.6 Hz) 4.36 (1H, AB, *J*=17.6 Hz) 3.75 (3H, s) 3.66 (1H, dd, *J*=9.8 Hz, 4.9 Hz) 3.50 (1H, dd, *J*=9.8 Hz, 9.0 Hz) 2.56 (1H, d, *J*=5.9 Hz) 2.19 (3H, s) 2.13-2.09 (1H, m) 0.89 (9H, s) 0.10 (6H, s). ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 174.7, 161.1, 150.5, 148.9, 143.5, 129.9, 129.5, 128.0, 127.3, 120.0, 92.7, 84.3, 75.6, 60.1, 51.9, 41.9, 35.2, 25.9, 18.4, 15.3, 3.4, −5.0.

Cycloaddition from ketone 43; isolation of 45

To a nitrogen flushed dry NMR tube was added AgOTf·1/2 benzene[24] (10.0 mg, 0.0343 mmol) and C_6D_6 (0.25 mL) and then ketone **43** (20.0 mg, 0.0264 mmol) in C_6D_6 (0.2 mL including cannula and flask washings) via cannula and set in the dark. After 135 min, ^1H NMR showed no starting oxazole **43** and oxazolium salt formation was indicated by characteristic changes in the chemical shift of the oxazole hydrogen from δ = 7.67 ppm (C_6D_6) to 8.55 ppm (C_6D_6), and this solution was transferred via syringe equipped with a syringe filter to a solution of $BnMe_3N^+$ CN^- (19.0 mg, 0.106 mmol) in freshly distilled CH_3CN (1.0 mL including NMR tube washings, stirred over activated 4 Å molecular sieves, distilled over CaH_2, and distilled again over P_2O_5) at rt over 5 min. The dark orange solution was stirred at rt for 2 h, then poured into H_2O:brine and extracted with Et_2O. The combined organic extracts were dried ($MgSO_4$), filtered, and solvents were removed (aspirator). The orange oil was purified by preparative TLC on silica gel (20 cm × 20 cm × 1000 μm pretreated with NEt_3 vapor for 30 min, 5:1 hexanes/EtOAc with 2% NEt_3 eluent) to give 5.4 mg (33%) of tetracycle **45** as an orange oil, analytical TLC on silica gel 60 F254, 40% EtOAc/hexanes, Rf = 0.7; $[\alpha]_D^{23}$ −12.5 (*c* 0.04, EtOAc). Molecular ion (M+Na) calculated for $C_{39}H_{42}N_2NaO_4Si$: 653.2812; found *m/z* = 653.2808, error = 1 ppm; IR (neat, cm^{-1}) 1657 C=O, 1642 C=O; UV (CH_3OH, nm) 286 (ε 1100) 350 (ε 600) 433 (ε 450). 500 MHz ^1H NMR ($CDCl_3$, ppm) δ 7.45-7.44 (6H, m) 7.31-7.22 (9H, m) 5.14 (1H, AB, *J*=14.2 Hz) 4.92 (1H, AB, *J*=14.2 Hz) 4.55 (1H, d, *J*=13.8 Hz) 4.10 (1H, dd, *J*=13.8 Hz, 3.9 Hz) 4.00 (3H, s) 3.03 (1H, d, *J*=4.9 Hz) 2.89 (1H, dd, *J*=4.9 Hz, 3.9 Hz) 1.97 (3H, s) 0.81 (9H, s) 0.01 (3H, s) −0.05 (3H, s). ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 179.9, 179.0, 157.4, 141.7, 129.4, 128.4, 128.1, 128.0, 127.3, 127.2, 123.0, 120.3, 74.4, 61.4, 58.9, 50.2, 41.9, 35.4, 26.3, 18.7, 8.7, −5.2, −5.2.

5-((*E*)-4,7-Bis(*tert*-butyldimethylsilyloxy)-3-methoxyhept-2-en-5-yn-2-yl)-2-((2*S*,3*R*)-3-(iodomethyl)-1-tritylaziridin-2-yl)oxazole (46)

To a solution of *tert*-butyldimethylsilyl propargyl ether[32] (251 mg, 1.47 mmol) in THF (10 mL) at −78 °C was added *n*-BuLi (1.47 M solution in hexanes, 1.0 mL, 1.47 mmol) dropwise over 5 min. After stirring the clear solution for 1 h at −78 °C, a solution of aldehyde **11** (435 mg, 0.737 mmol) in THF (5 mL including cannula washings) was added via cannula dropwise over 5 min. The resulting yellow solution was warmed to −42 °C and stirred for 2 h. The cooling bath was then removed and 10 mL of saturated aqueous sodium bicarbonate was added and stirred at rt 10 min. The resulting light yellow solution was poured into brine and extracted with Et_2O. The combined organic extracts were dried ($MgSO_4$), filtered, and solvents were removed (aspirator). The crude alcohol from above was dissolved in CH_2Cl_2 (15 mL) and *tert*-butyldimethylsilyl chloride (222 mg, 1.47 mmol) was added followed by imidazole (125

mg, 1.84 mmol). After stirring for 15 h at rt, the reaction was poured into H_2O (20 mL) and extracted wth CH_2Cl_2 (3 × 30 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and solvents were removed (aspirator). The clear oil was purified by flash column chromatography on silica gel (50 mm × 16 cm, 10% EtOAc/hexanes, 40 mL fractions) to yield 0.500 g (78%) of oxazole **46** as an inseparable 1:1 mixture of diastereomers as a white foam, analytical TLC on silica gel 60 F254, 10% EtOAc/hexanes, Rf = 0.2. Molecular ion (M+Na) calculated for $C_{45}H_{59}IN_2NaO_4Si_2$: 897.2956; found *m/z* = 897.2947, error = 1 ppm; IR (neat, cm^{-1}) 1638; 400 MHz ^1H NMR ($CDCl_3$, ppm); overlapping diastereomer signals given as a sum of individual isomer values, δ 7.53-7.51 (12H, m) 7.29-7.19 (18H, m) 7.02 (1H, s) 7.00 (1H, s) 5.69 (1H, t, *J*=1.8 Hz) 5.67 (1H, t, *J*=1.8 Hz) 4.38 (2H, d, *J*=1.8 Hz) 4.34 (2H, 2, *J*=1.8 Hz) 3.98 (3H, s) 3.97 (3H, s) 3.70-3.66 (2H, m) 3.59-3.53 (2H, m) 2.57-2.54 (2H, m) 2.16-2.06 (2H, m) 2.00 (3H, s) 1.99 (3H, s) 0.90 (9H, s) 0.89 (9H, s) 0.88 (18H, s) 0.11 (3H, s) 0.11 (3H, s) 0.09 (6H, s) 0.08 (3H, s) 0.07 (3H, s) 0.03 (3H, s) 0.02 (3H, s). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 159.9, 159.7, 152.5, 152.5, 151.0, 151.0, 143.5, 143.5, 129.5, 129.5, 128.0, 128.0, 127.3, 127.3, 125.6, 125.5, 107.4, 107.2, 84.4, 84.4, 83.7, 83.7, 75.7, 75.6, 61.1, 61.0, 59.9, 59.8, 52.0, 52.0, 41.8, 41.7, 35.3, 35.2, 26.0, 26.0, 18.4, 18.4, 18.3, 14.2, 14.1, 3.5, 3.5, −4.4, −4.5, −4.7, −4.7, −4.9, −4.9.

Cyanide adduct 50 via azomethine ylide generation from 46

To a solution of AgOTf·1/2 benzene[24] (8.0 mg, 0.026 mmol) in C_6D_6 (0.2 mL) in a dry, nitrogen flushed NMR tube was added a solution of oxazole **46** (24 mg, 0.027 mmol) in C_6D_6 (0.4 mL including cannula and flask washings) via cannula. After sitting in the dark for 3.5 h at rt, ^1H NMR showed no starting oxazole **46** and oxazolium salt formation was indicated by characteristic changes in the chemical shift of the oxazole hydrogens from δ = 7.01 ppm and 6.99 ppm (CD_2Cl_2) to 7.77 ppm and 7.73 ppm (CD_2Cl_2), and the brown solution was transferred via syringe equipped with a syringe filter to a solution of $BnMe_3N^+$ CN^- (19 mg, 0.11 mmol) in freshly distilled CH_3CN (1.0 mL including NMR tube washings, stirred over activated 4 Å molecular sieves, distilled over CaH_2, and distilled again over P_2O_5) at 0 °C over 5 min. After stirring the orange solution at 0 °C for 30 min the reaction was warmed to rt over 10 minutes and stirred for an additional 30 min. The dark solution was poured into H_2O:brine and extracted with EtOAc. The combined organic extracts were dried ($MgSO_4$), filtered, and solvents were removed (aspirator). The brown oil was purified by preparative TLC on silica gel (20 cm × 20 cm × 1000 μm pretreated with NEt_3 vapor for 30 min, 5:1 hexanes/EtOAc with 2% NEt_3 eluent) to give 6.9 mg (33%) of tetracycle **50** as a white solid in a 3:2 mixture (^1H NMR analysis) of inseparable diastereomers, analytical TLC on silica gel 60 F254 pretreated with NEt_3 vapor, 5:1 hexanes/EtOAc with 2% NEt_3, Rf = 0.6. Molecular ion (M +Na) calculated for $C_{46}H_{59}N_3NaO_4Si_2$: 796.3942; found *m/z* = 796.3962, error = 3 ppm; IR (neat, cm^{-1}) 1659 C=O; 500 MHz ^1H NMR ($CDCl_3$, ppm) overlapping diastereomer signals given as a sum of individual isomer values, δ 7.48-7.44 (10H, m) 7.30-7.21 (15H, m) 5.36 (1H, s) 5.36 (0.6H, s) 4.77 (1H, AB, *J*=12.0 Hz) 4.74 (0.6H, AB, *J*=12.5 Hz) 4.68 (0.6H, AB, *J*=12.5 Hz) 4.64 (1H, AB, *J*=12.0 Hz) 4.63 (0.6H, d, *J*=13.2 Hz) 4.56 (1H, d, *J*=13.2 Hz) 4.18-4.13 (1.6H, m) 3.59 (3H, s) 3.57 (2H, s) 3.30 (0.6H, q, *J*=7.1 Hz) 3.26 (1H, q, *J*=6.8 Hz) 2.91-2.88 (2.6H, m) 2.81 (0.6H, d, *J*=4.9 Hz) 1.44 (3H, d, *J*=6.8 Hz) 1.42 (2H, d, *J*=7.1 Hz) 0.89 (6H, s) 0.86 (9H, s) 0.84 (6H, s) 0.80 (9H, s) 0.25 (1.8H, s) 0.17 (3H, s) 0.06 (1.8H, s) 0.05 (3H, s) −0.01 (1.8H, s) −0.05 (1.8H, s) −0.06 (3H, s) −0.16 (3H, s). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 184.6, 184.5, 144.1, 143.9, 132.3, 132.3, 129.4, 129.3, 128.0, 127.3, 127.3, 123.8, 123.3, 117.1, 117.0, 116.3, 116.3, 83.9, 83.8, 77.4, 74.5, 74.2, 63.0, 62.7, 57.5, 56.9, 53.1, 50.8, 50.6, 45.1, 45.0, 43.1, 41.9, 35.1, 34.7, 29.9, 29.9, 26.2, 26.1, 25.7, 25.7, 18.5, 18.4, 8.9, 8.8, −4.2, −4.3, −4.7, −4.8, −5.0, −5.1, −5.2, −5.4.

NCS oxidation of 50 to indoloquinone 45

To a solution of AgOTf·1/2 benzene[24] (23.0 mg, 0.0778 mmol) in CH_2Cl_2 (0.25 mL) in a dry, nitrogen flushed NMR tube was added a solution of oxazole **46** (34.0 mg, 0.0389 mmol) in CD_2Cl_2 (0.45 mL including cannula and flask washings) via cannula. After 1 h at rt, shielded from light, ^{1}H NMR showed no starting oxazole **46** and the brown solution was transferred via syringe equipped with a syringe filter to a solution of $BnMe_3N^+$ CN^- (27.0 mg, 0.156 mmol) in CD_3CN (2.0 mL including NMR tube washings) at 0 °C over 5 min. The orange solution was warmed to rt over 5 min then stirred an addition 1 h at rt. The dark solution was poured into H_2O:brine (20 mL, 1:1 v:v) and extracted with EtOAc (3 × 15 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and solvents were removed (aspirator). To the crude product obtained above in THF (0.6 mL) at −78 °C was added KHMDS (0.30 mL of a 0.258 M solution in THF, 0.0778 mmol) and stirred at −78 °C for 30 min. NCS (0.34 mL of a 0.232 M solution in THF, 0.0778 mmol) was added and stirred an additional 25 min at −78 °C. After warming to rt over 15 min, the orange solution was poured into H_2O and extracted with EtOAc. The combined organic extracts were dried ($MgSO_4$), filtered, and solvents were removed. The orange oil was purified by preparative TLC on silica gel (20 cm × 20 cm × 1000 μm pretreated with NEt_3 vapor for 30 min, 5:1 hexanes/EtOAc with 2% NEt_3 eluent) to give 4.1 mg (17% over 2 steps) of tetracycle **45** as an orange oil identical to the material described above by ^{1}H NMR.

Azomethine ylide cycloaddition from bis-TBS protected diol 46; isolation of 54 and 55 and detection of 53

To a solution of AgOTf·1/2 benzene[24] (13.5 mg, 0.0457 mmol) in CD_2Cl_2 (0.2 mL) in a dry, nitrogen flushed NMR tube was added a solution of oxazole **46** (40.0 mg, 0.0457 mmol) in CD_2Cl_2 (0.4 mL including cannula and flask washings) via cannula. After sitting in the dark for 1 h at rt, ^{1}H NMR showed no starting oxazole **46** and oxazolium salt formation was indicated by characteristic changes in the chemical shift of the oxazole hydrogens from δ = 7.01 ppm and 6.99 ppm (CD_2Cl_2) to 7.77 ppm and 7.73 ppm (CD_2Cl_2), and this solution was transferred via syringe equipped with a syringe filter to a solution of $BnMe_3N^+$ CN^- (8.0 mg, 0.0457 mmol) in CH_2Cl_2 (2.0 mL including NMR tube washings) at 0 °C over 5 min. After stirring the orange solution at 0 °C for 1 h, H_2O (2 mL) was added and the solution was poured into H_2O and extracted with CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4), filtered, and solvents were removed (aspirator) to yield crude **53** as a 1:1 ratio of diastereomers. In preparative work, this mixture was used without further purification to minimize decomposition, but chromatography allowed isolation of small amounts of partially purified material for spectroscopy. Preparative TLC on silica gel 60 F254, 5:1 hexanes/EtOAc 2% NEt_3, Rf = 0.4 (20 cm × 20 cm × 1000 μm, 5:1 hexanes/EtOAc 2% NEt_3 eluent) gave the less polar diastereomer of **53**; ESMS molecular ion (M + Na) calculated for $C_{46}H_{59}N_3NaO_4Si_2$: 796.4; found *m/z* = 796.4; partial 500 MHz ^{1}H NMR ($CDCl_3$, ppm) δ 7.41-7.40 (6H, m) and 7.31-7.20 (9H, m) for the *N*-Tr group, 5.77 (1H, s) for the C*H*-OTBS hydrogen, 4.60 (1H, dd, *J*=14.6 Hz, 2.0 Hz) and 4.48 (1H, dd, *J*=14.6 Hz, 2.7 Hz) for the CH_2OTBS hydrogens, 3.98 (3H, s) for the OCH_3 hydrogens, 3.60 (1H, d, *J*=13.4 Hz) and 3.49 (1H, dd, *J*=13.4 Hz, 2.2 Hz) for the N-CH_2-CHNTr hydrogens, 2.59 (1H, d, *J*=4.6 Hz) and 2.15 (1H, dd, *J*=4.6 Hz, 2.2 Hz) for the aziridine hydrogens, 1.79 (3H, s) for the C-6 CH_3 hydrogens. ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 117.4 for the CN. For the more polar diastereomer, Rf = 0.2, partial purification by preparative TLC on buffered silica gel as above gave peaks in the 500 MHz ^{1}H NMR ($CDCl_3$, ppm) δ 7.59-7.57 (6H, m) and 7.31-7.19 (9H, m) for the *N*-Tr group, 5.31 (1H, s) for the C*H*-OTBS hydrogen, 4.50 (1H, d, *J*=13.2 Hz) and 4.38 (1H, dd, *J*=13.2 Hz, 2.2 Hz) for the CH_2OTBS hydrogens, 3.92 (3H, s) for the OCH_3 hydrogens, 2.79 (1H, d, *J*=5.4 Hz) and 2.35 (1H, dd, *J*=5.4 Hz, 3.4 Hz) for the aziridine hydrogens, 1.70 (3H, s) for the C-6 CH_3 hydrogens. If the chromatography was attempted without NEt_3 buffer in the eluent, then increased decomposition was observed, tentatively to give ca. 10% conversion to **49** according to ESMS

data (*m/z*= 747 amu; **49** + H) and proton chemical shifts of δ 5.06 (s, CH adjacent to OTBS), 4.83 (AB q, *J*=11.9 Hz) and 4.69 (AB q, *J*=11.9 Hz for methylene adjacent to OTBS), 4.09 (s, OMe), 2.87 (d, *J*=4.9 Hz) and 2.83 (dd, *J*=4.9 Hz, 3.6 Hz) for the aziridine protons, and 1.84 (s, Me). For preparative purposes, NEt_3 (0.16 mL, 1.14 mmol) was added to the crude cycloadduct from above in CH_3CN (7 mL) and the mixture was placed under an atmosphere of O_2 (balloon). The reaction was stirred at rt 10 min and HF-pyr (0.18 mL of a 3.9 M solution in CH_3CN, 0.702 mmol) was then added. After stirring at rt 16 h under O_2, the dark red solution was poured into $NaHCO_3$ (20 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and solvents were removed (aspirator). The red oil was purified by preparative TLC on silica gel (20 cm × 20 cm × 1000 μm, 50% EtOAc/hexanes eluent) to give 3.8 mg (16%) of alcohol **54** as an orange solid, 5.2 mg (18%) of **45** as an orange oil, and 3.5 mg (14%) of **55** as a red solid (total of 48% cylclized material), analytical TLC on silica gel 60 F254, 40% EtOAc/hexanes, for **54** Rf = 0.4. Pure **54** obtained by crystallization in EtOAc/hexanes as orange needles, MP = >200 °C (decomposes). Molecular ion (M^+) calculated for $C_{33}H_{28}N_2O_4$: 516.2049; found *m/z* = 516.2051, error = 0 ppm; IR (neat, cm^{-1}) 3417 OH, 1640 C=O, 1600 C=O; 500 MHz ^1H NMR ($CDCl_3$, ppm) δ 7.43-7.42 (6H, m) 7.32-7.29 (6H, m) 7.27-7.24 (3H, m) 4.78 (1H, dd, *J*=13.9 Hz, 6.1 Hz) 4.61 (1H, dd, *J*=13.9 Hz, 8.1 Hz) 4.54 (1H, d, *J*=13.9 Hz) 4.15 (1H, dd, 13.9 Hz, 3.9 Hz) 4.03 (3H, s) 3.90 (1H, dd, *J*=8.1 Hz, 6.1 Hz) 2.89 (1H, dd, 4.9 Hz, 3.9 Hz) 2.84 (1H, d, *J*=4.9 Hz) 1.99 (3H, s). ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 180.9, 178.9, 157.5, 144.1, 140.8, 129.3, 129.1, 128.3, 128.1, 127.5, 125.0, 119.5, 74.5, 61.5, 56.7, 50.5, 42.6, 33.9, 8.9. For **55**, analytical TLC on silica gel 60 F254, 40% EtOAc/hexanes Rf = 0.2. Pure **55** was obtained by crystallization in EtOAc/hexanes as fine red needles, MP = 165-168 °C (dec). Molecular ion (M+Na) calculated for $C_{34}H_{29}N_3NaO_5$: 582.2005; found *m/z* = 582.2007, error = 0 ppm; IR (neat, cm^{-1}) 3415 OH, 1650 C=O, 1574 C=O; 500 MHz ^1H NMR ($CDCl_3$, ppm) δ 7.58-7.57 (6H, m) 7.33-7.30 (6H, m) 7.27-7.23 (3H, m) 4.65 (1H, dd, *J*=11.7 Hz, 2.4 Hz) 4.27 (1H, dd, *J*=11.7 Hz, 2.4 Hz) 4.12 (1H, d, *J*=12.2 Hz) 4.05 (3H, s) 4.03 (1H, s) 3.84 (1H, dd, *J*=11.7 Hz, 11.7 Hz) 3.66 (1H, dd, *J*=12.2 Hz, 4.4 Hz) 2.96 (1H, d, *J*=5.4 Hz) 2.64 (1H, broad dd, *J* obsc) 1.89 (3H, s). ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 182.3, 179.3, 158.3, 152.8, 143.5, 129.6, 128.1, 127.5, 126.0, 121.4, 116.7, 82.8, 75.9, 64.3, 61.8, 52.7, 45.6, 41.1, 8.6.

Preparation of (1*S*, 2,*S*)-9-hydroxymethyl-2,3-dihydro-7-methoxy-6-methyl-1,2-(*N*-tritylaziridino)-1*H*-pyrrolo[1,2-a]indole (54) from 45

To a solution of tetracycle **45** (8.0 mg, 0.013 mmol) in CH_3CN (0.6 mL) at rt was added NEt_3 (11 μL, 0.076 mmol) dropwise. HF·pyr (10 μL of a 3.9 M solution in CH_3CN, 0.039 mmol) was added dropwise and stirred at rt for 15 h. The dark orange solution was poured into brine (20 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and solvents were removed (aspirator). The orange oil was was purified by preparative TLC on silica gel (20 cm × 20 cm × 1000 μm pretreated with NEt_3 vapor for 30 min, 30% EtOAc/hexanes with 2% NEt_3 eluent) to give 4.9 mg (75%) of alcohol **54** as an orange solid identical to the material described above by ^1H NMR.

Carbamoylation of 54 and analytical scale detritylation

To a solution of alcohol **54** (3.8 mg, 0.0074 mmol) in CH_2Cl_2 (0.5 mL) cooled to −78 °C was added trichloroacetyl isocyanate (18 μL of a 0.42 M solution in CH_2Cl_2, 0.0076 mmol) dropwise. After stirring at −78 °C for 1 h, the reaction was warmed to rt over 20 min and then stirred an additional 1 h. The orange solution was poured into H_2O (8 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and solvents were removed (aspirator). The unstable orange oil was purified by preparative TLC on silica gel (20 cm × 20 cm × 250 μm pretreated with NEt_3 vapor for 30 min, 100% EtOAc with 2% NEt_3 eluent) to give 4.0 mg (80%) of **56** as an orange oil that was quickly used in the following reaction to minimize decomposition; analytical TLC on silica gel 60 F254 pretreated

with NEt_3 vapor, 100% EtOAc with 2% NEt_3 eluent, Rf = 0.2. Molecular ion (M+Na) *m/z* calculated for $C_{36}H_{28}Cl_3N_3NaO_6$: 726.1; found 726.1. Partial 500 MHz ^{1}H NMR ($CDCl_3$, ppm) δ 7.44-7.43 (6H, m) and 7.31-7.23 (9H, m) for the *N*-Tr group, 5.47 (2H, s) for the C*H*$_2$-O hydrogens, 4.58 (1H, d, *J*=13.9 Hz) and 4.15 (1H, dd, *J*=13.9 Hz, 3.9 Hz) for the N-C*H*$_2$-NTr hydrogens, 4.05 (3H, s) for the OC*H*$_3$ hydrogens, 3.14 (1H, d, *J*=6.1 Hz) and 2.90 (1H, dd, *J*=6.1 Hz, 3.9 Hz) for the aziridine hydrogens, 1.98 (3H, s) for the C-6 C*H*$_3$ hydrogens. To a solution of crude **56** from above (1.0 mg, 0.0014 mmol) in CH_2Cl_2 (0.4 mL) at 0 °C was added triethylsilane (7 μL of a 0.629 M solution in CH_2Cl_2, 0.043 mmol) followed by methansulfonic acid (8 μL of a 0.514 M solution in CH_2Cl_2, 0.043 mmol). After stirring the orange solution at 0 °C for 25 min NEt_3 (4 μL, 0.030 mmol) was added and stirred an addition 25 min at 0 °C. 0.2 mL of a 5% K_2CO_3 aqueous solution in MeOH (1:1, v:v) was added and the reaction was allowed to warm to rt and stir an addition 1 h. Formation of known amino alcohol **59**[29] was indicated by the molecular ion (M+Na) for $C_{15}H_{17}N_3NaO_6$: 358.1, together with a weak mass peak corresponding to aziridinomitosene A[8] (**4**), molecular ion (M+Na) for $C_{15}H_{15}N_3NaO_5$: 340.1. Characteristic signals to support the formation of **4** could not be found in the NMR spectrum.

(1*S*,2,*S*)-9-Carbamoyloxymethyl-2,3-dihydro-7-methoxy-6-methyl-1,2-(*N*-tritylaziridino)-1*H*-pyrrolo[1,2-a]indole (57)

To the tetracyclic alcohol **54** (2.8 mg, 0.0050 mmol) in CH_2Cl_2 (0.5 mL) at −78 °C was added trichloroacetyl isocyante (13 μL of a 0.42 M solution in CH_2Cl_2, 0.054 mmol) and the reaction was stirred at −78 °C for 1 h. The reaction was allowed to warm to rt over 20 min then stirred an additional 1 h. Next, 0.5 mL of a 5% K_2CO_3 aqueous solution in MeOH (1:1, v:v) was added and the reaction was stirred vigorously at rt. After stirring vigorously at rt for 3 h, the biphasic solution was poured into H_2O (5 mL) and extracted with CH_2Cl_2 (3 × 7 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and solvents were removed (aspirator). The orange solid was purified by preparative TLC on silica gel (20 cm × 20 cm × 250 μm pretreated with NEt_3 vapor for 30 min, 100% EtOAc with 2% NEt_3 eluent) to give 2.0 mg (67%) of **57** as an orange solid, analytical TLC on silica gel 60 F254 pretreated with NEt_3 vapor, 100% EtOAc with 2% NEt_3 eluent, Rf = 0.6. Molecular ion (M+Na) calculated for $C_{34}H_{29}N_3NaO_5$: *m/ z* = 582.2; found 582.2; IR (neat, cm^{-1}) 3465 NH, 3346 NH, 1725 C=O, 1659 C=O, 1642 C=O; 500 MHz ^{1}H NMR ($CDCl_3$, ppm) δ 7.46-7.45 (6H, m) 7.32-7.24 (9H, m) 5.36 (1H, AB, *J*=13.4 Hz) 5.31 (1H, AB, *J*=13.4 Hz) 4.57 (1H, d, *J*=13.7 Hz) 4.19 (2H, bs) 4.14 (1H, dd, *J*=13.7 Hz, 3.9 Hz) 4.03 (3H, s) 2.98 (1H, d, *J*=4.8 Hz) 2.88 (1H, dd, *J*=4.8 Hz, 3.9 Hz) 1.97 (3H, s). ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 179.6, 179.0, 157.5, 156.7, 142.4, 129.4, 128.2, 128.1, 127.8, 127.5, 123.8, 113.7, 106.5, 74.6, 61.5, 59.1, 50.4, 42.3, 34.8, 8.8.

Detritylation of 57; detection of 58 and isolation of 59

To a solution of **57** (2.7 mg, 0.0048 mmol) and triphenylsilane (78 μL of a 0.0614 M solution in CH_2Cl_2, 0.0048 mmol) in CH_2Cl_2 (0.45 mL) cooled to −78 °C was added triflic acid (0.5 μL, 0.0048 mmol). The reaction was allowed to stir at −78 °C for 5 min then slowly warmed to −40 °C over 30 min and stirred an addition 15 h at −40 °C. To the orange solution was added pH 10.3 buffer (0.2 mL) cooled to 0 °C. The biphasic solution was warmed to rt and extracted with CH_2Cl_2 (5 × 1 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and solvents were removed (aspirator). The orange solid was purified by preparative TLC on silica gel (20 cm × 20 cm × 250 μm, 10:1 CH_2Cl_2:MeOH eluent) to give 2.0 mg (72%) of **58** as a 3:1 mixture of diastereomers as an orange solid, analytical TLC on silica gel 60 F254, 10:1 CH_2Cl_2:MeOH, Rf = 0.63 for the less polar major diastereomer and Rf = 0.60 for the more polar minor diastereomer. Molecular ion (M+Na) calculated for $C_{34}H_{31}N_3NaO_6$: *m/z*= 600.2, found 600.2. Partial 500 MHz ^{1}H NMR ($CDCl_3$, ppm) δ 7.60 (6H, m) and 7.32-7.22 (9H, m) for the *N*-Tr group, 5.02 (1H, AB, *J*=12.2 Hz) and 5.01 (1H, AB, *J*=12.2 Hz) for the C*H*$_2$OC(O)NH$_2$ hydrogens, 4.60 (2H, br s) for the C(O)N*H*$_2$ hydrogens, 4.52 (1H, dd, *J*=12.4 Hz, 7.7

Hz) for one of the N-CH_2-CHNTr hydrogen, 4.00 (3H, s) for the OCH_3 hydrogens, 3.25 (1H, d, *J*=5.1 Hz) for the C*H*-OH hydrogen, 1.94 (3H, s) for the C-6 CH_3 hydrogens.

To a solution of amino alcohol **58** (2.0 mg, 0.0035 mmol) prepared above in CH_2Cl_2 (0.3 mL) at 0 °C was added triethylsilane (11 μL of a 0.628 M solution in CH_2Cl_2, 0.0069 mmol) and trifluoroacetic acid (12 μL of a 0.573 M solution in CH_2Cl_2, 0.0069 mmol). After stirring the orange solution at 0 °C for 30 min, diisopropylethylamine (2 μL, 0.010 mmol) was added and stirred at 0 °C for an additional 30 min. Solvents were removed (aspirator) and the orange solid was purified by preparative TLC on silica gel (20 cm × 20 cm × 250 μm, 10:1 CH_2Cl_2:MeOH eluent) to give 1.0 mg (83%) of amino alcohol **59** identical by ^{1}H NMR and mass spectrometry comparisons with literature data.[29,30]

Alternatively, a solution of tetracycle **57** (2.0 mg, 0.0036 mmol) and triphenylsilane (109 μL of a 0.0653 M solution in CH_2Cl_2, 0.0071 mmol) in CH_2Cl_2 (0.40 mL) cooled to −78 °C was treated with triflic acid (0.6 μL, 0.0071 mmol). The reaction was allowed to stir at −78 °C for 5 min and then was slowly warmed to −40 °C over 30 min and stirred an addition 15 h at −40 °C. To the orange solution was added DIEA (2 μL, 0.011 mmol) and the mixture was stirred at −40 °C for an additional 30 min. Solvents were then removed (aspirator) and the orange solid was purified by preparative TLC on silica gel as above to give 1.0 mg (83%) of amino alcohol **59**.[29]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENT

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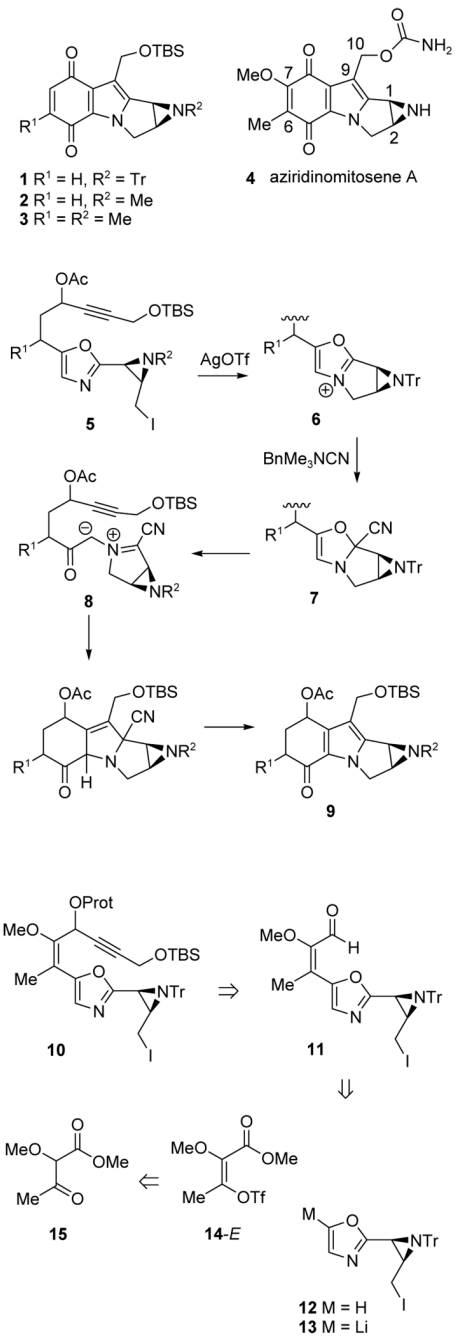
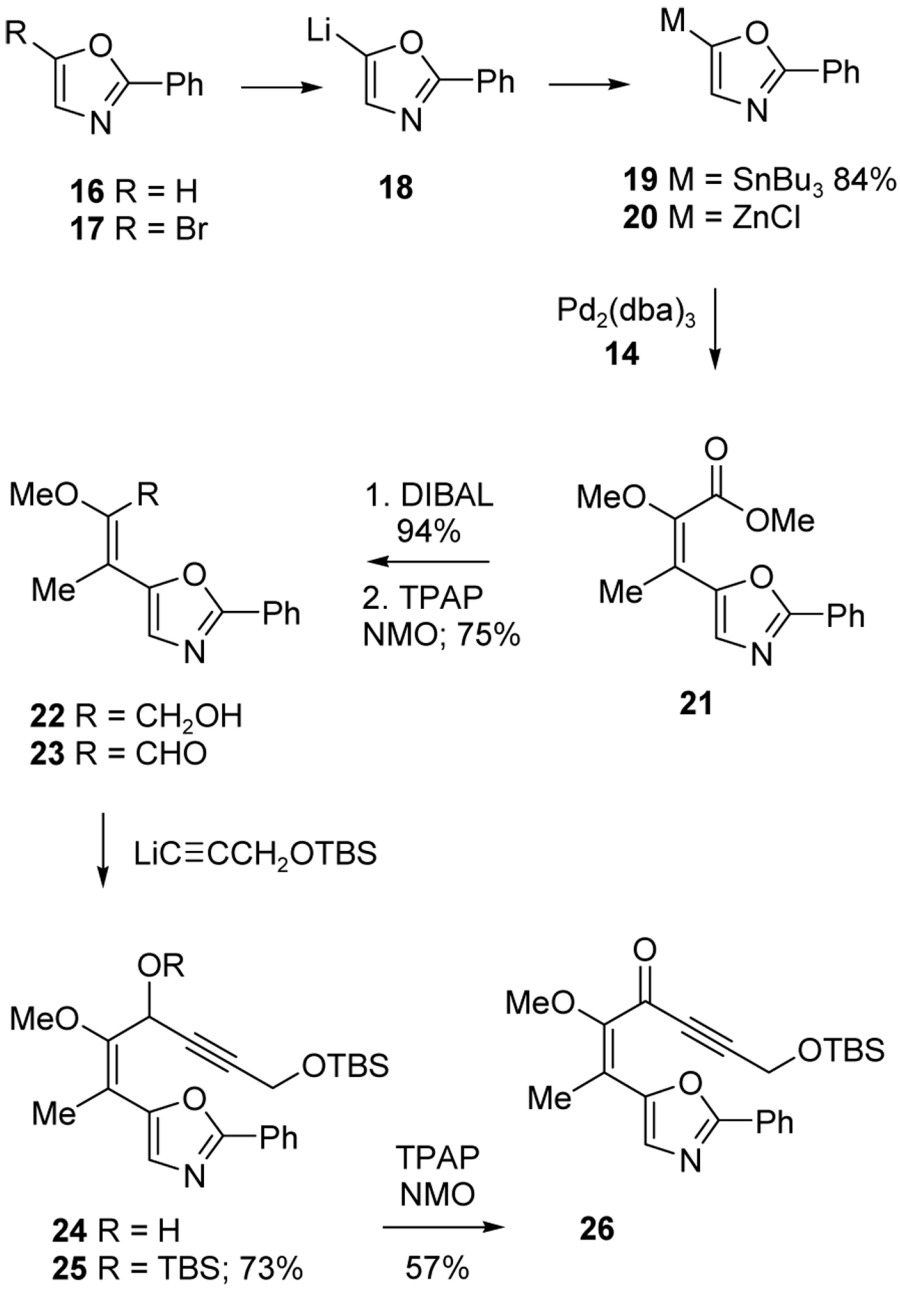


Scheme 1.



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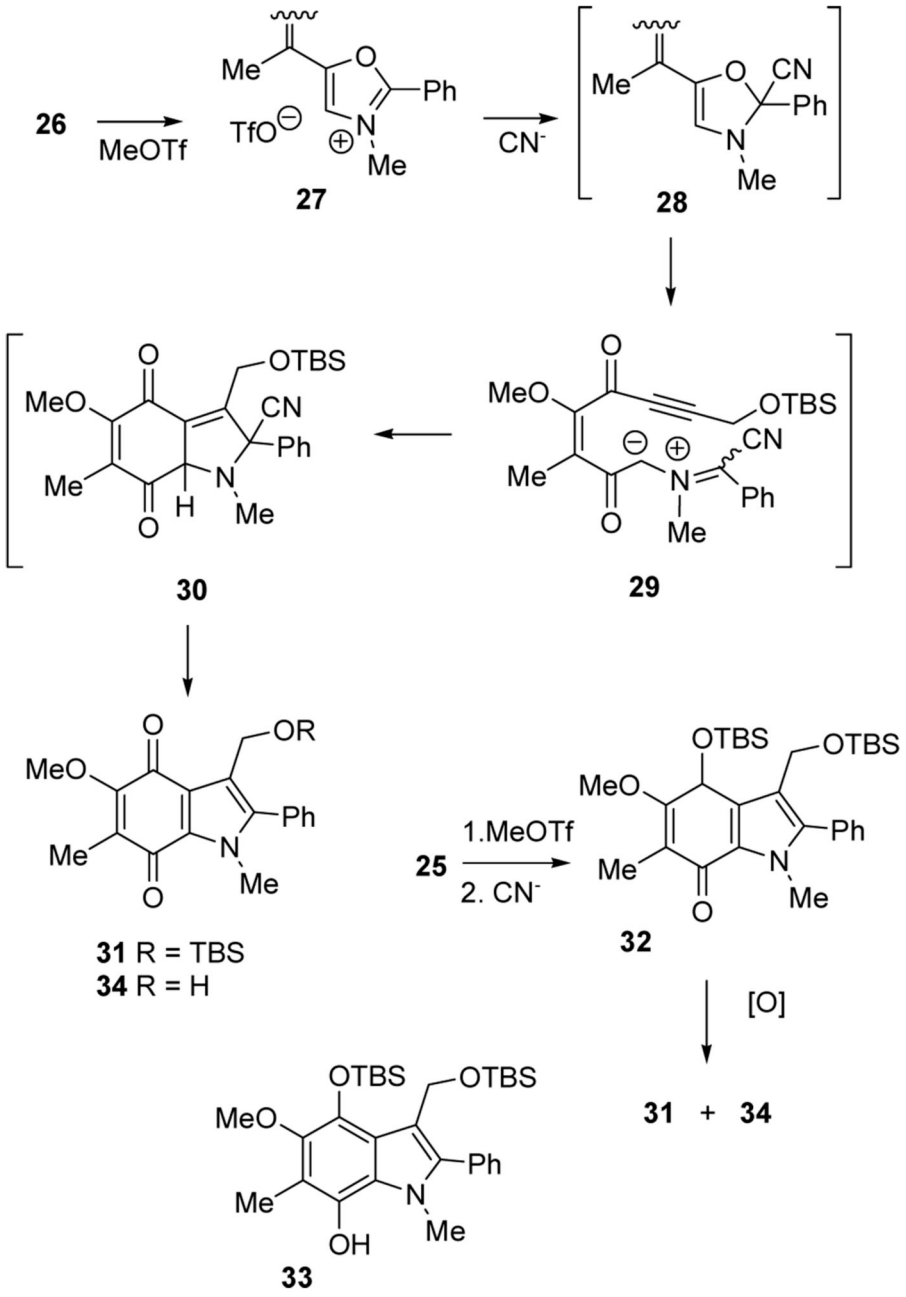

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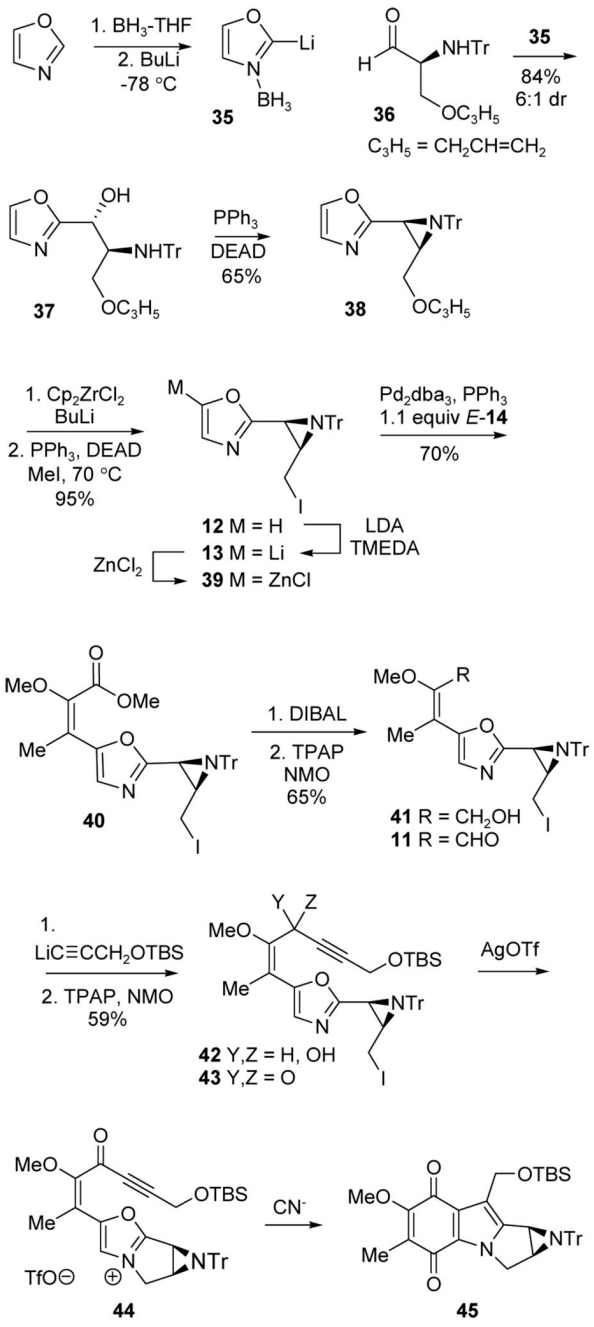

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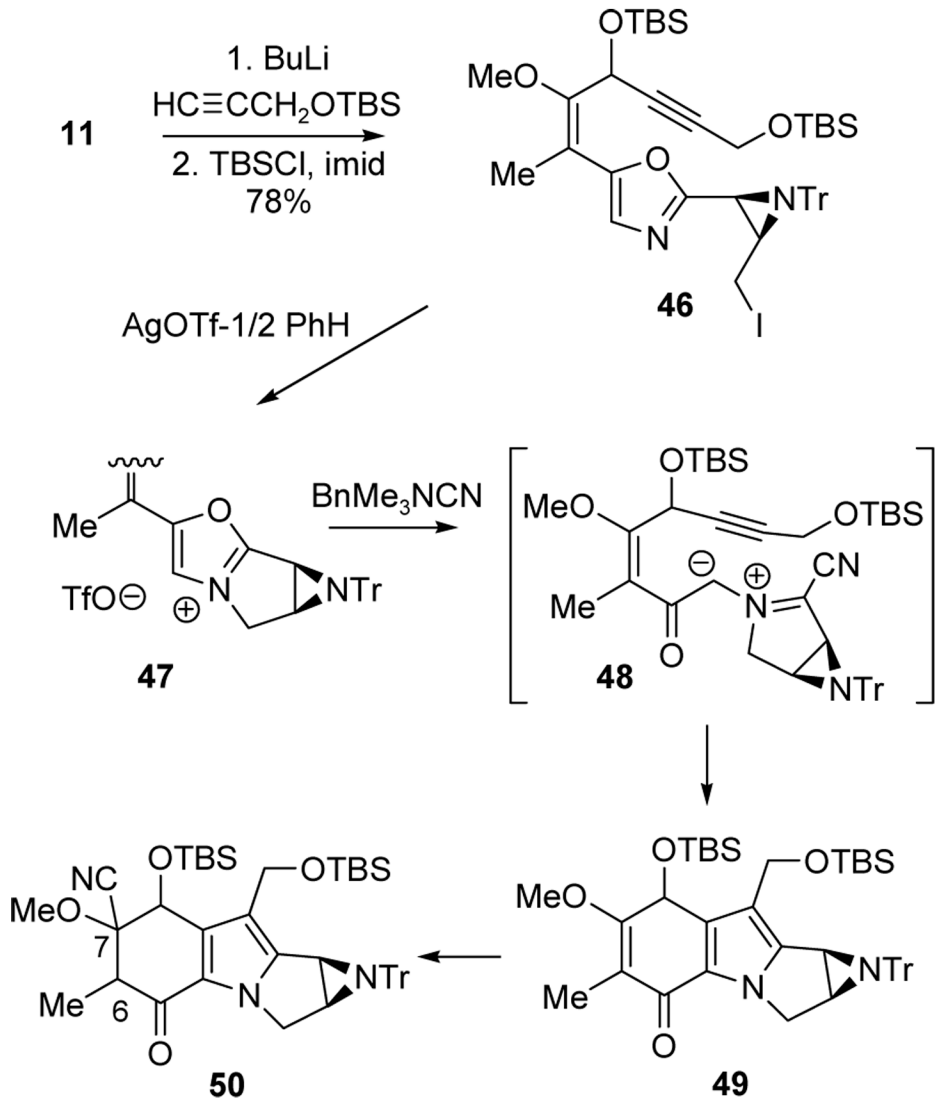

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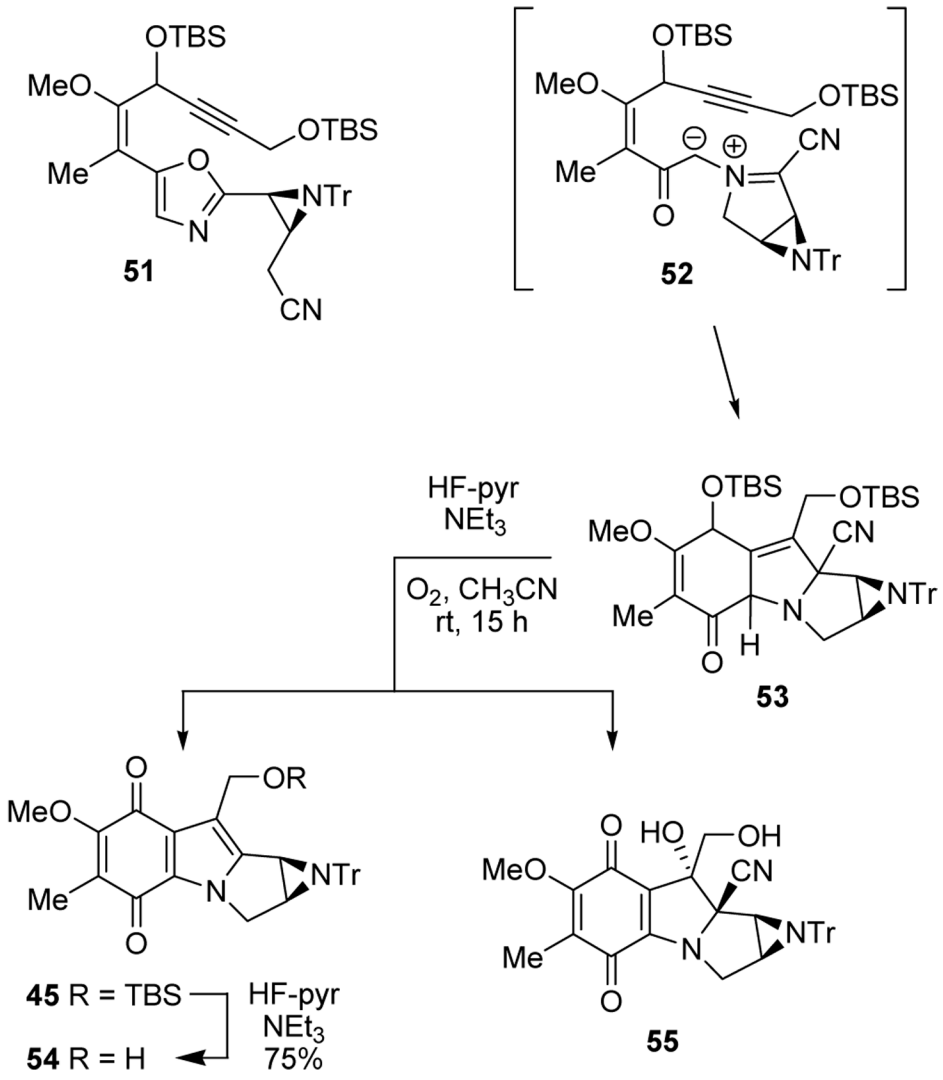

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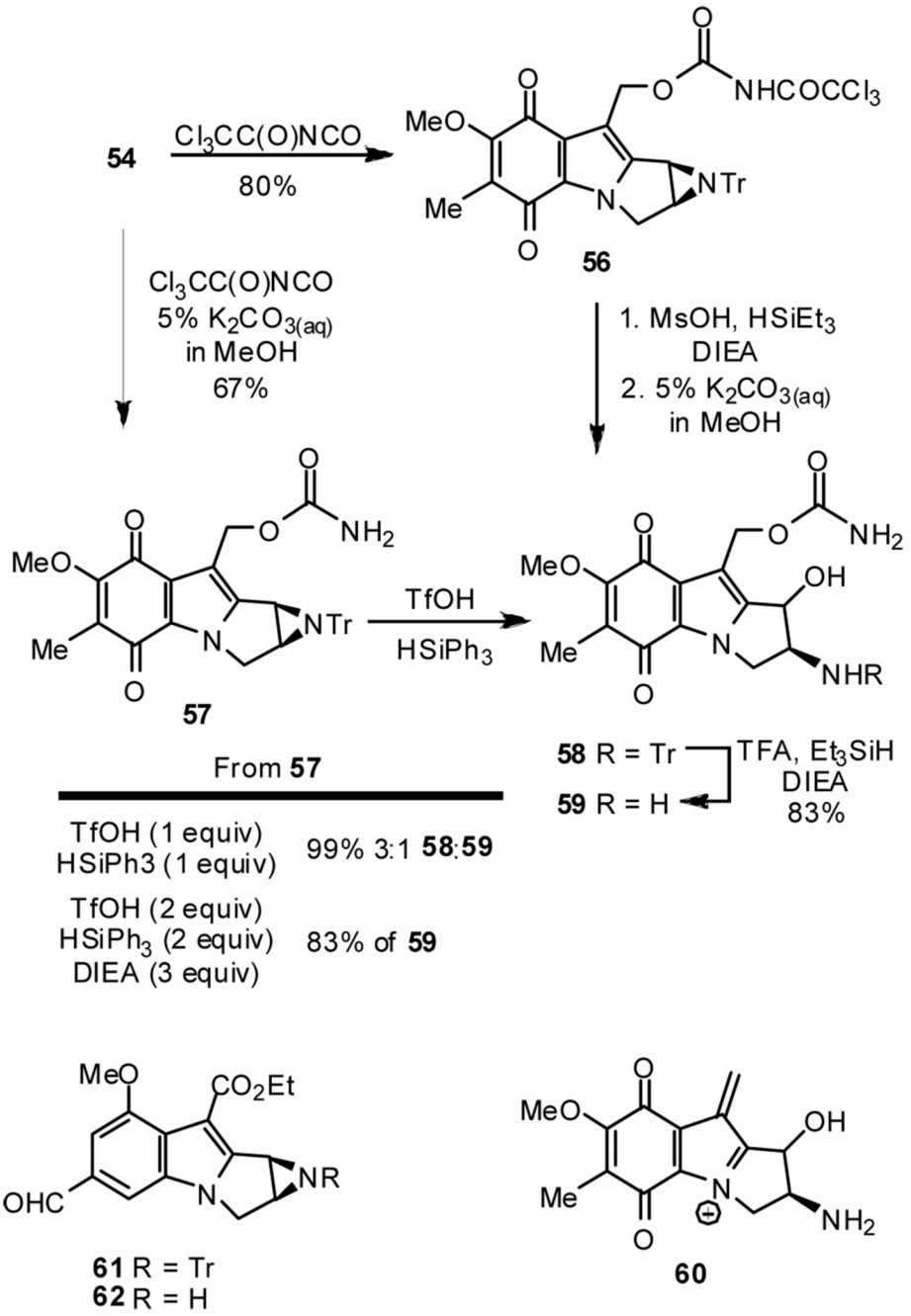

Scheme 7.

Table 1

Conversion of **15** to enol triflate **14**.[a]

entry	base	Time	Yield	*E:Z*
1	KHMDS	15 h	63%	25:75
2	NaHMDS	15 h	61%	40:60
3	LiHMDS	7 d	28%	>95:5
4	NaH	15 h	72%	54:46
5	MesLi	4 d	20%	>95:5
6	LiH	7 d	65%	93:7

[a]Enolate generated in THF at −78 °C, *N*-phenylbistriflimide added and warmed to and stirred (time: see table).

Table 2

Oxidation of **32** to quinones **31** and **34**.

Entry	[O]	Temp	time	yield	Products
1	DDQ	rt	2 h	95%[a]	7:1 **31:34**
2	TBAF, O_2, Pd/C	rt	15 h	88%[a]	4:1 **31:34**
3	HF-pyr, O_2, NEt_3	rt	15 h	99%[b]	3:2 **31:34**
4	KHMDS; then NCS	−78 ° C	10 min	72%[b]	**31**
5	DBU and NCS	0–20 ° C	1 h	84%[b]	**31**
6	Phosphazene,[c] NCS	rt	15 h	56%[b]	**31**
7	KHMDS; PhSeCl	−78 ° C to rt	10 min	74%[b]	**31**
8	KHMDS; PhI(OAc)	−78–20 ° C	1 h	69%[b]	**31**

[a] Isolated combined yield of **31** and **34** from crude **32**

[b] Purified **32** used.

[c] Phosphazene base P_1-*t*-Bu.