Oxazole Activation for Azomethine Ylide Trapping: Singly and Doubly Tethered Substrates

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Bicyclic oxazolium salts **18**, **24**, **37**, and **44** can be generated from tethered haloalkyloxazoles by internal alkylation. Reductive alkylation of the oxazolium salts using CsF/$PhSiH_3$ converts the salts initially into the corresponding 4-oxazoline derivatives. Subsequent electrocyclic ring opening generates stabilized azomethine ylides that can be trapped by suitable dipolarophiles. Intermolecular dipole trapping followed by DDQ oxidation affords the ring-fused pyrroles **22** and **26**. When tethered alkynoates are used for internal dipole trapping, the adducts **38** and **45** can be obtained by a similar reductive activation sequence, followed by DDQ workup. Effective procedures for the internal oxazole N-alkylation step are described using an acetonitrile–trifluoroethanol solvent system. Also, an improved method for the generation of the dichlorocerium derivative of ethyl propiolate and intermolecular trapping by an aldehyde is reported.

Beginning with studies first reported in 1986, we have demonstrated that 4-oxazolines **2** and the derived azomethine ylides **3** can be generated by the addition of nucleophiles to oxazolium salts **1**.[1] Good results are obtained using fluoride-activated silicon nucleophiles $PhSiH_3$/CsF or Me_3SiCN/CsF to produce **2** with Z = H or Z = CN, respectively. Subsequent electrocyclic ring opening[1,2] occurs at room temperature or below when R_5 is aryl, alkyl, alkoxy, or H and converts **2** into the stabilized azomethine ylide **3**. Conventional trapping with a dipolarophile such as dimethyl acetylenedicarboxylate (DMAD) is then possible and leads to the dihydropyrrole **4**. Further conversion into the pyrrole **5** is spontaneous if Z = CN.[1b] In the case where Z = H, much of the dihydropyrrole **4** survives until workup, but it is difficult to isolate because of competing double-bond isomerization and aromatization. For that reason, product isolation is best performed at the pyrrole stage, after deliberate aromatization of the mixture with DDQ.

The above studies were initiated with the goal of finding a highly convergent route from simple oxazoles to indoloquinones belonging to the mitosene family.[3] The typical mitosene skeleton **6** requires three additional rings, two of which can be derived from the obvious "handles" R_5 and R_2 in the pyrrole **5**. The third ring is the troublesome aziridine subunit that has foiled many (but not all)[3b] attempts at the synthesis of mitosenes and mitomycins. Although it is too early to discuss our plans for the aziridine, the essentials of a highly convergent approach to the carbon skeleton of mitosenes can now be summarized. The plan depends on internal N-alkylation of an oxazole **7** to generate the oxazolium salt **8**. This structure is suitably activated for conversion into the azomethine ylide **9** via a 4-oxazoline intermediate and for subsequent internal dipole trapping. A model study for the latter transformation was recently reported from our laboratory.[4] Thus, an oxazolium salt prepared by the intermolecular N-alkylation of **11** was converted into **14** via the 4-oxazoline **12**. Aromatization with DDQ produced the indoloquinone **15** in 32% overall yield based on the oxazole precursor **11**. We can now report extensions of this technology to include several variants of the intramolecular N-alkylation suggested in the generalized scheme from **7** to **8**. Eventually, this conversion will have to be performed in the presence of heteroatom functionality (implied by Y in the drawings) that is synthetically equivalent to the mitosene aziridine ring.

Internal N-alkylation of oxazoles to form oxazolium salts has been known for some time,[5] and the necessary 2-(haloalkyl)oxazole precursors can be prepared easily from 2-(lithiomethyl)oxazoles by alkylation.[6] Thus, a model compound 2-methyl-5-phenyloxazole (**16**)[7] was deprotonated with *n*-butyllithium, and the lithium derivative was treated with $I(CH_2)_3Cl$ to afford **17**. The chloride **17** was not sufficiently reactive to form an oxazolium salt efficiently, but internal N-alkylation occurred upon heating with NaI/CH_3CN to give **18** (90% isolated). No problems were encountered with the subsequent generation of a bicyclic oxazoline **19**. Thus, reduction of **18** using the $PhSiH_3$/CsF reagent[1] in the presence of DMAD gave a mixture of **21** and **22**. To simplify product isolation, the mixture was aromatized with DDQ, resulting in a 70% overall yield of **22** from **18**.

A similar route was used to prepare **26**, a substance that contains the dihydropyrrolizine subunit that is also present in the mitosenes. The key steps could be accomplished as planned, but this route was more demanding and required additional optimization. The internal alkylation

(1) (a) Vedejs, E.; Grissom, J. W. *J. Am. Chem. Soc.* **1986**, *108*, 6433. (b) Vedejs, E.; Grissom, J. W. *J. Org. Chem.* **1988**, *53*, 1838. Vedejs, E.; Grissom, J. W. *J. Org. Chem.* **1988**, *53*, 1882. Vedejs, E.; Grissom, J. W. *J. Am. Chem. Soc.* **1988**, *110*, 3238. (c) Piotrowski, D. Ph.D. Dissertation, University of Wisconsin, 1991.

(2) Baldwin, J. E.; Pudussery, R. G.; Qureshi, A. K.; Sklarz, B. *J. Am. Chem. Soc.* **1968**, *90*, 5325.

(3) (a) For earlier studies dealing with azomethine ylide approaches to mitosenes, see: Hershenson, F. M. *J. Org. Chem.* **1975**, *40*, 1260. Rebek, J.; Shabar, S. H.; Shue, Y.-K.; Gehret, J.-C.; Zimmerman, S. *J. Org. Chem.* **1984**, *49*, 5164. Rebek, J.; Shaber, S. H. *Heterocycles* **1981**, *16*, 1173. Rebek, J.; Gehret, J.-C. E. *Tetrahedron Lett.* **1977**, *19*, 3027. Anderson, W. K.; Corey, P. F. *J. Org. Chem.* **1977**, *42*, 559. (b) Fukuyama, T.; Nakatsubo, F.; Cocuzza, A. J.; Kishi, Y. *Tetrahedron Lett.* **1977**, 4295. Kishi, Y.; Nakatsubo, F.; Cocuzza, A. J.; Keeley, D. E. *J. Am. Chem. Soc.* **1977**, *99*, 4835. Kishi, Y.; Nakatsubo, F.; Fukuyama, T.; Cocuzza, A. J. *J. Am. Chem. Soc.* **1977**, *99*, 8115. Fukuyama, T.; Yang, L. *Tetrahedron Lett.* **1986**, *27*, 6299. Fukuyama, T.; Yang, L. *J. Am. Chem. Soc.* **1987**, *109*, 7881. Fukuyama, T.; Yang, L. *J. Am. Chem. Soc.* **1989**, *111*, 8303.

(4) Vedejs, E.; Dax, S. L. *Tetrahedron Lett.* **1989**, *30*, 2627.

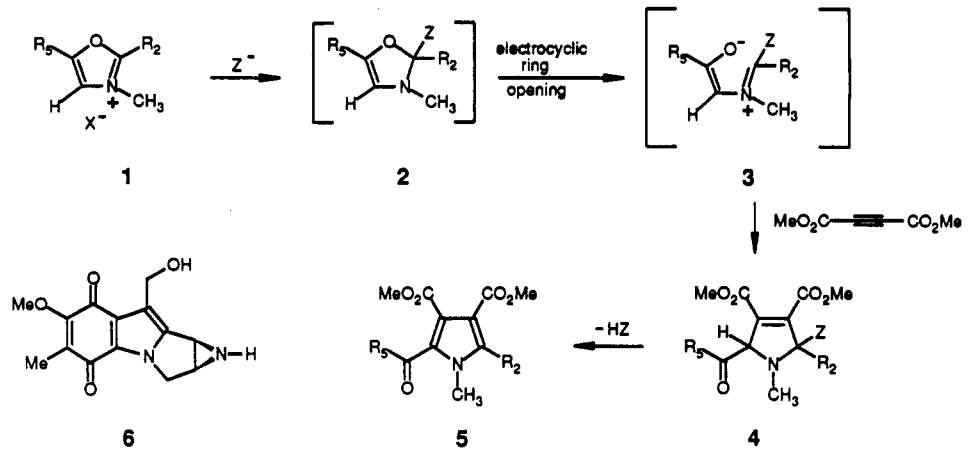
(5) Good, R. H.; Jones, G. *J. Chem. Soc. C* **1970**, 1938.

(6) Lipshutz, B. L.; Hungate, R. W. *J. Org. Chem.* **1981**, *46*, 1410.

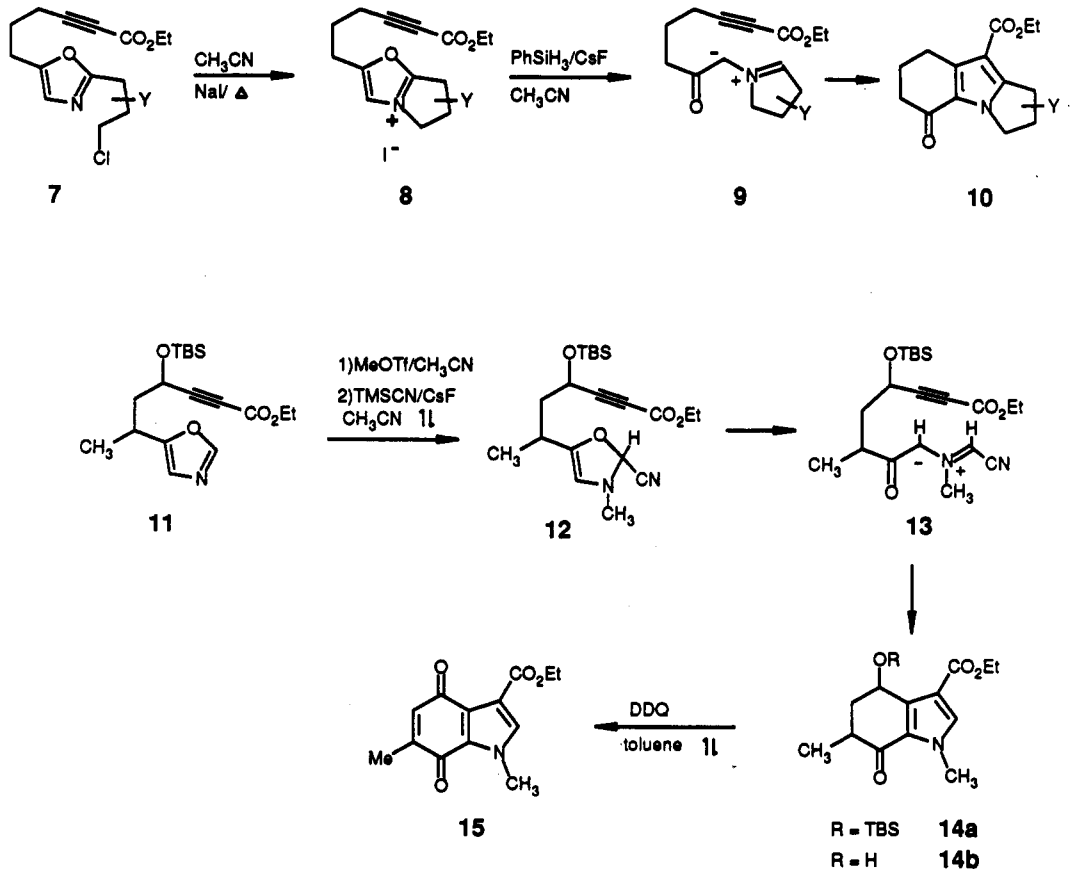
(7) Kondrat'eva, G. Ya.; Chzhi-Khen, K. *J. Gen. Chem. USSR* **1962**, *32*, 2315.

0022-3263/93/1958-1341$04.00/0

Scheme I



Scheme II



proved to be especially difficult. Heating **23** in acetonitrile with NaI present gave only 37% of the oxazolium salt **24**, in contrast to the 6-membered ring example from **17** to **18** where a 90% yield was realized. Eventually, it was found that a 2:3 mixture of acetonitrile/trifluoroethanol[8] gave better results (60% of **24** isolated after 66 h at reflux). Ylide generation from **24** followed the same procedure as before and gave **26** in 45% yield after the DDQ oxidation. No further attempt was made to optimize this model system.

The above experiments show that the internal alkylation approach is viable for the generation of both the 6- and the 5-membered oxazolium salts. Two recent papers by Hassner et al. describe similar findings with an analogue of **22**.[9] These workers were able to generate **27** in solution and to convert it into an azomethine ylide using cyanide as the nucleophilic activating agent. However, the 5-membered oxazolium salt **28** could not be obtained, and the authors concluded that the strain inherent in this bicyclic ring system may be too large. Fortunately, this is not the case in our series, and the synthetic problem can be solved by optimizing the conditions for internal alkylation as described above for the preparation of **24**.

Having demonstrated internal N-alkylation as well as internal dipole trapping, we turned to more complex examples where both of the intramolecular processes would have to occur in succession. These studies were also designed to explore more versatile techniques for oxazole

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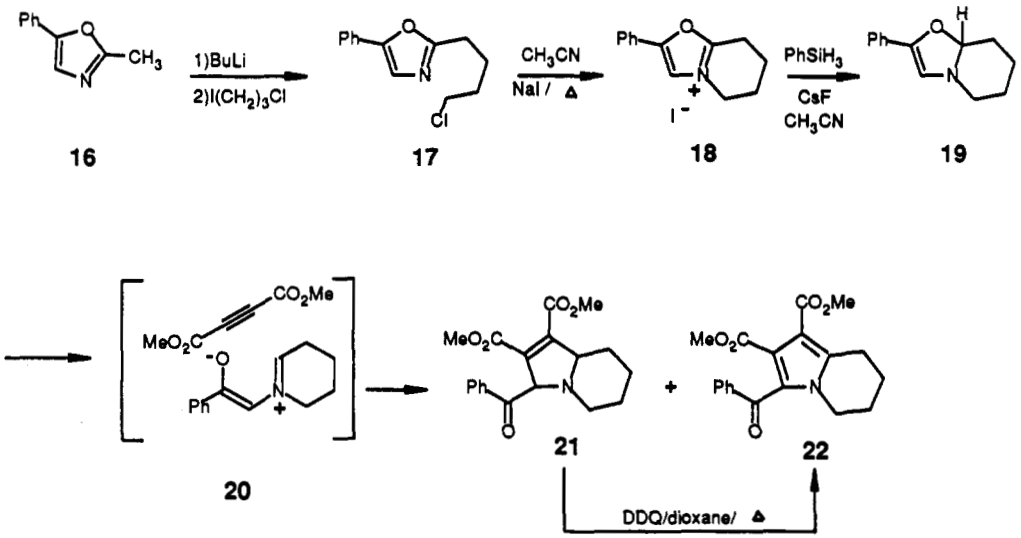
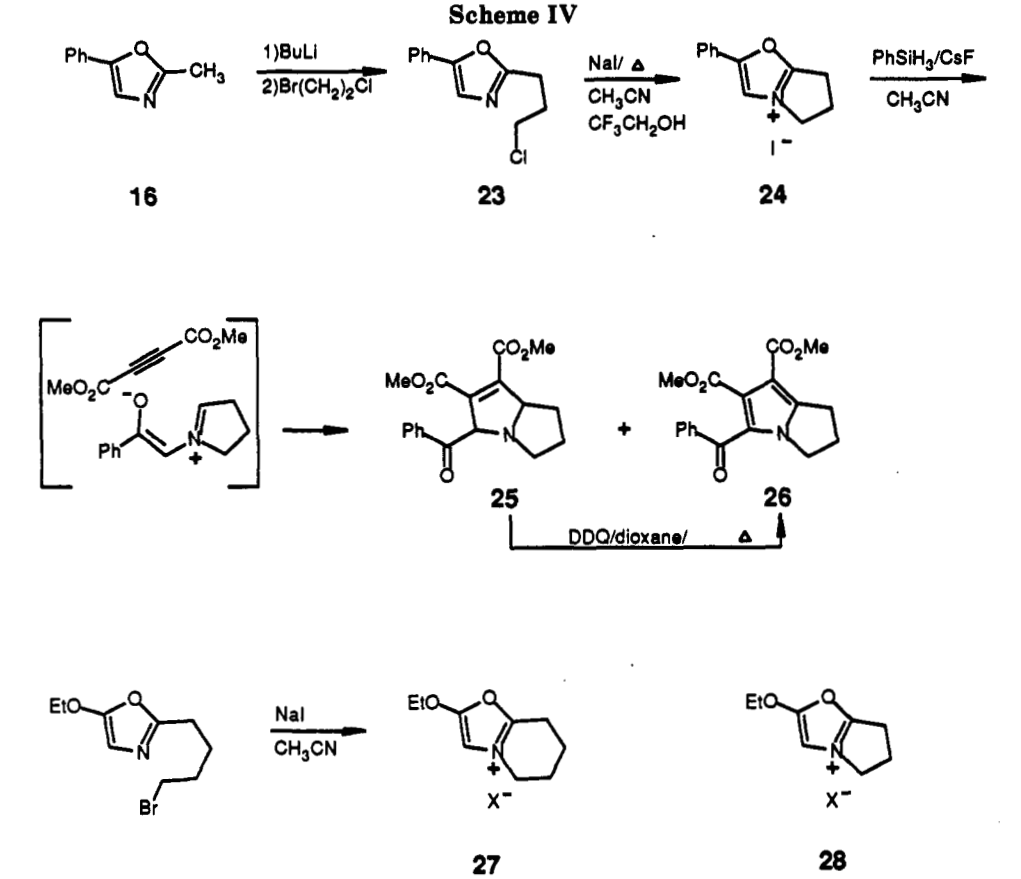
(9) Hassner, A.; Fischer, B. *Tetrahedron Lett.* **1990**, *31*, 7213. Hassner, A.; Fischer, B. *J. Org. Chem.* **1992**, *57*, 3070.

Scheme III



Scheme IV



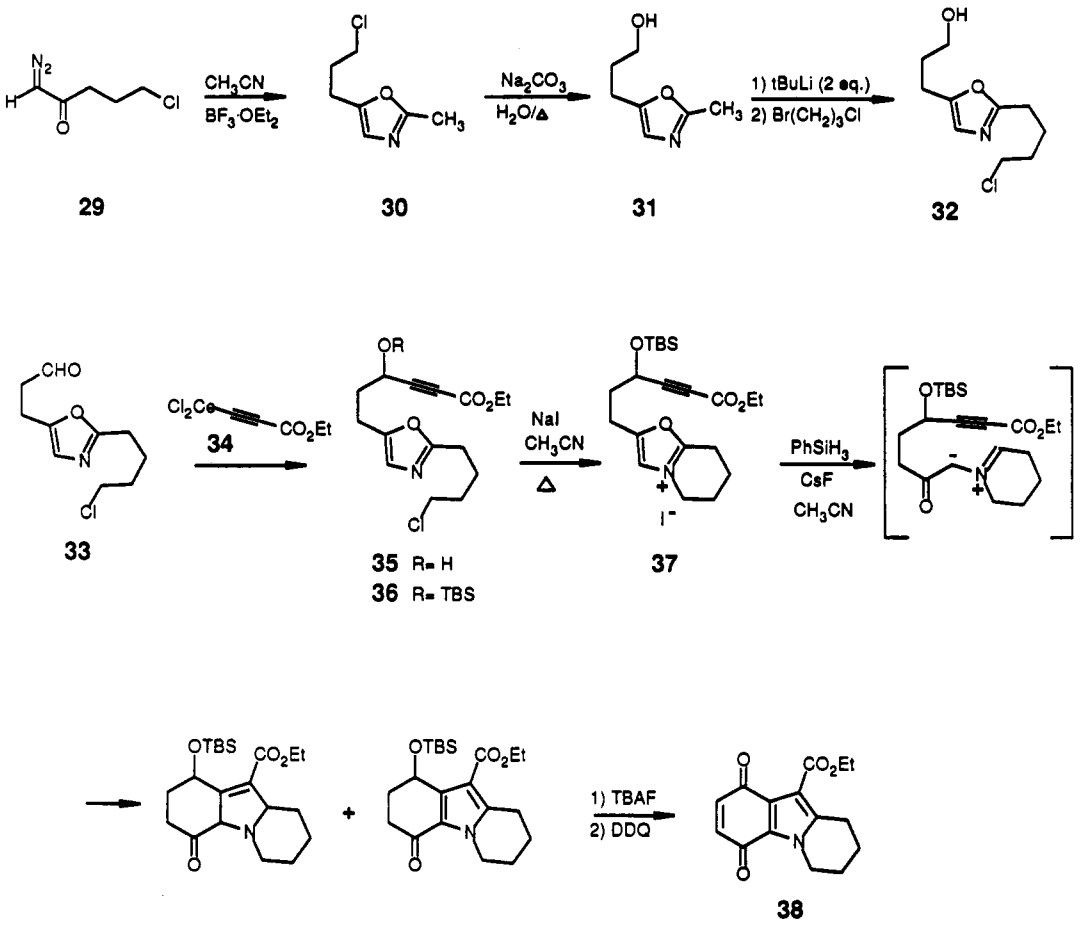
functionalization that would provide access to relatively complex 2,5-disubstituted oxazoles. Among the reported oxazole syntheses,[10] we have found that the method of Doyle et al. and Ibata et al. offers the best combination of practicality and generality for synthesis of 2,5-disubstituted oxazoles.[11] Thus, reaction of the diazo ketone **29** (available from 4-chlorobutyroyl chloride and diazomethane) with acetonitrile in the presence of boron trifluoride etherate gave **30** in 82% yield. Conversion to alcohol **31** by a simple solvolysis reaction using refluxing aqueous sodium carbonate (62% **31** isolated) followed by alkylation of the dilithio derivative produced **32** in 75% yield, and Swern oxidation afforded the aldehyde **33** (73% isolated).

At this stage, connection of the tethered acetylenic dipolarophile was necessary. In our previous study, we had found that simple nonactivated alkynes are not reactive enough to intercept the oxazoline-derived azomethine ylides in acceptable yield. An acetylenic ester **36** is required for practical results in the internal [2 + 3]

(10) For reviews on oxazoles see: (a) Turchi, I. J.; Dewar, M. J. S. *Chem. Rev.* **1975**, *75*, 389. (b) Turchi, I. J. In *Oxazoles*; Turchi, I. J., Ed.; Wiley: New York, 1986; Vol. 45, pp 1–341. (c) Lakhan, R.; Ternai, B. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Boulton, A. J., Eds.; Academic: New York, 1974; Vol. 17, pp 99–211.

(11) (a) Doyle, M. P.; Oppenhuizen, M.; Elliot, R. C.; Boelkins, M. R. *Tetrahedron Lett.* **1978**, 2247. Doyle, M. P.; Burho, W. E.; Davidson, J. G.; Elliot, R. C.; Hoekstra, J. W.; Oppenhuizen, M. *J. Org. Chem.* **1980**, *45*, 3657. (b) Ibata, T.; Sato, R. *Chem. Lett.* **1978**, 1129. Ibata, T.; Sato, R. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 3597.

Scheme V



cycloaddition, but addition of propiolate anion to aldehydes is experimentally demanding. We had previously used the reagent obtained from cerium trichloride and C-lithiated propiolate ester ($LiC{\equiv}CCO_2Et$).[4,12] The original procedure was to add the lithio propiolate via cooled cannula at −78 °C to a suspension of $CeCl_3$ in THF, but this technique was difficult to control, and the reaction with **33** gave no more than 50% yield of the alkynol **35**. After some effort, we were able to obtain much better results using an in situ method, similar to a procedure described for internal acetylide–aldehyde addition by Myers et al.[13] Thus, a mixture of ethyl propiolate and anhydrous $CeCl_3$ was treated with lithium hexamethyldisilazide in THF (1 h, −78 °C), and the oxazole aldehyde **33** was then added slowly. This simple technique gave **35** in 95% yield after chromatography. The yield was considerably improved, and the difficult cold cannula transfer step was avoided.

Next, it was necessary to convert alkynol **35** into the required oxazolium salt **37**. This was accomplished by protection of **35** as the *tert*-butyldimethylsilyl ether **36** followed by treatment with sodium iodide in refluxing acetonitrile. In typical preparative experiments, the salt **37** was not isolated because ylide generation proceeded without problems using the crude material. However, ^1H NMR evidence consistent with the structure **37** was obtained and confirmed the presence of the characteristic C-4 oxazolium proton at δ 7.65 ppm. Since the internal N-alkylation requires heating in acetonitrile, we were initially concerned that internal [2 + 4] cycloaddition might compete with the internal alkylation by analogy to the 5-substituted oxazoles studied by Jacobi et al. in refluxing toluene.[14] However, no evidence for this potential complication was detected in refluxing acetonitrile.

Conversion of oxazolium salt **37** into a cyclic azomethine ylide followed by [2 + 3] cycloaddition was possible using the same methods described for the synthesis of **22**. An acetonitrile solution of **37** was treated with $PhSiH_3/CsF$ to generate the dipole as before. This procedure afforded a mixture of cycloadducts containing dihydropyrrole double-bond isomers, aromatized products, and partially desilylated products due to the presence of CsF. It was therefore necessary to complete the desilylation process by treatment of the product mixture with excess tetrabutylammonium fluoride (TBAF) and then to aromatize the crude mixture in the usual way with DDQ in refluxing toluene. The result was a 41% overall yield of the indoloquinone **38** based on the oxazole **36**. Due to the complexity of the initial cycloaddition product mixture, the exact sequence of events from **37** to **38** cannot be specified. However, it is likely to involve DDQ oxidation of the deprotected secondary hydroxyl group to a ketone, followed by tautomerization to a hydroquinone and further oxidation to the indoloquinone derivative **38**. This product is a 6-membered ring analog of the carbon skeleton present in mitosenes.[3]

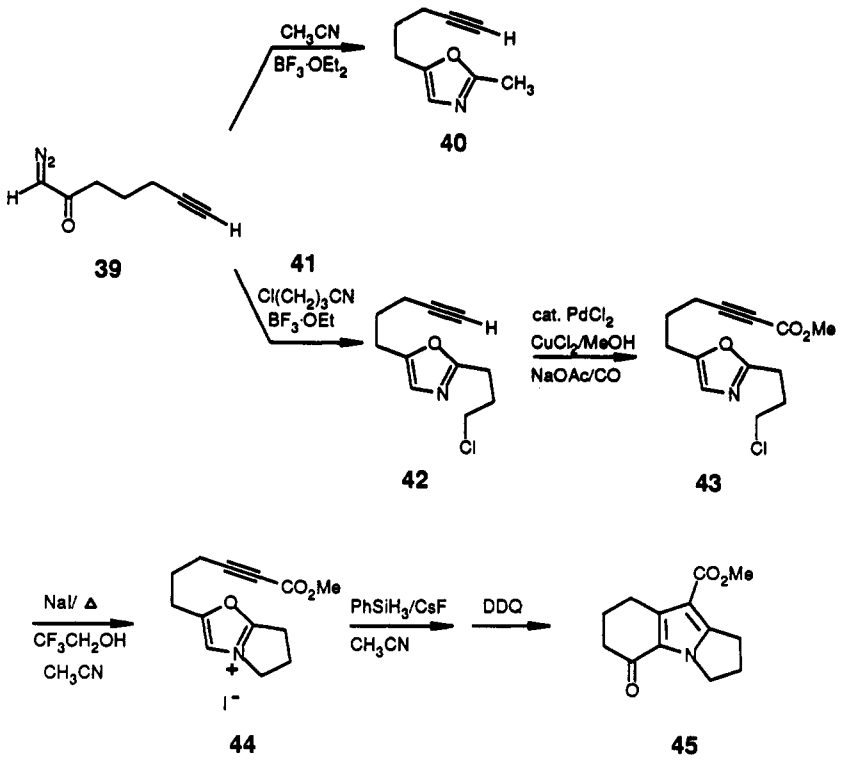
One final sequence was investigated to evaluate the feasibility of a [2 + 3] cycloaddition approach to the

(12) Takeda, K.; Yano, S.; Sato, M.; Yoshii, E. *J. Org. Chem.* **1987**, *52*, 4137.

(13) Myers, A. G.; Harrington, P. M.; Kuo, E. Y. *J. Am. Chem. Soc.* **1991**, *113*, 694.

(14) Jacobi, P. A.; Walker, D. G.; Odeh, I. M. A. *J. Org. Chem.* **1981**, *46*, 2065.

Scheme VI



pyrrolo[1,2-*a*]indoloquinone nucleus of mitosenes. Synthesis of this ring system requires the more demanding internal N-alkylation to form **44**, a 5-membered oxazolium salt precursor of the azomethine ylide. This study was begun before the propiolate anion addition technique had been optimized, so an alternative approach to oxazoles containing a tethered acetylenic ester was investigated. A practical solution was found by extension of the Doyle–Ibata oxazole synthesis[11] to a diazo ketone containing an acetylene group. Thus, 5-hexynoyl chloride was reacted with excess diazomethane to afford **39**. When an acetonitrile solution of **39** was treated with boron trifluoride etherate, a 69% yield of 2-methyl-5-(4′-pentynyl)oxazole (**40**) was obtained. In principle, this substance could have been converted into the required halide **42** using the alkylation strategy described earlier. However, it was found that 4-chlorobutyronitrile also reacted with **39** to give a 59% yield of the appropriately substituted oxazole **42**, and this highly convergent route was used without further optimization.

The next problem was to convert the terminal alkyne into a more potent dipolarophile. Attempts to carboxylate oxazole alkyne **42** using a variety of bases ($NaNH_2/NH_3$, BuLi, MeLi, or MeMgBr) failed due to competing deprotonation of the 2-methyl group. However, Tsuji et al.[15] have shown that simple acetylenic esters can be prepared via an oxidative carbonylation procedure. The mild conditions (catalytic $PdCl_2/CuCl_2$/NaOAc/MeOH; carbon monoxide at atmospheric pressure) tolerate a variety of functional groups, including hydroxy, amino, or carbomethoxy.[16] Accordingly, when oxazole alkyne **42** was subjected to these reaction conditions, a 68% yield of the acetylenic ester **43** was obtained.

Ester **43** is a suitable starting material for internal N-alkylation and internal azomethine ylide cycloaddition. Thus, an acetonitrile solution of **43** and sodium iodide was heated under reflux for 18 h to give the oxazolium salt **44**. Isolation of the salt in pure form was not achieved, but ^1H NMR analysis showed the C-4 oxazolium proton at the expected downfield shift of δ 7.87 ppm. The crude **44** was then treated with $PhSiH_3/CsF$ in acetonitrile followed by the usual DDQ oxidation to give a 48% yield of the desired cycloadduct **45**. The structural assignment of the pyrrolotetrahydroindolone **45** is based on the UV spectrum (λ_{max} = 288 nm, ϵ = 25 500) and on characteristic NMR data (see Experimental Section).

During attempts to optimize this reaction, reducing agents other than $PhSiH_3/CsF$ were examined for the conversion of oxazolium salt **44** to the 4-oxazoline. The advantage of $PhSiH_3/CsF$ over many other hydride donors is that overreduction of the 4-oxazoline or of the derived dipole is minimized. This problem becomes especially severe with reducing agents that have Lewis acid character or for reducing agents that are used in protic solvents ($NaBH_4$ or $NaCNBH_3$ in methanol). However, sodium borohydride had not been tested under aprotic conditions. This simpler variation appeared worth investigating and was tested with one of the less demanding substrates (**18**). The reaction worked well when the oxazolium salt **18** was treated with $NaBH_4$ in acetonitrile containing 3 equiv of DMAD. After oxidation with DDQ, a 68% yield of indolizine **22** was isolated. This result compares favorably with the use of $PhSiH_3/CsF$ which gave a 70% yield. Similarly, the bicyclic oxazolium salt **44** could be converted into the dipole when $NaBH_4$ was used as the reductant, but the yield was 40%, significantly lower than with the original $PhSiH_3/CsF$ procedure for this specific case.

In conclusion, we have shown that 2,5-disubstituted oxazoles can be converted into bicyclic or tricyclic pyrrole derivatives that are structurally related to the mitosenes. The synthesis of structures **38** and **45** demonstrates the

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(16) Abdulganeeva, S. A.; Erzhanov, K. B. *J. Org. Chem. USSR* **1988**, *24*, 1598. Arcadi, A.; Bernocchi, E.; Burini, A.; Cacchi, S.; Marinelli, F.; Pietroni, B. *Tetrahedron* **1988**, *44*, 481. Crimmins, M. T.; Mascarella, S. W.; De Loach, J. A. *J. Org. Chem.* **1984**, *49*, 3033.

following key transformations: (1) elaboration of suitably functionalized side chains at oxazole C_2 and C_5, (2) internal N-alkylation to form the oxazolium salt, and (3) conversion into the azomethine ylide required for internal cycloaddition. The longest route from commercially available materials consists of eight isolated intermediates. Similar, highly convergent strategy with aziridine-containing intermediates is currently under investigation.

Experimental Section

2-(3′-Chloropropyl)-5-phenyloxazole (23). 2-Methyl-5-phenyloxazole (**16**)[7] (320 mg, 2.0 mmol) was dissolved in 10 mL of THF and cooled to −78 °C. Butyllithium (1.3 mL, 1.7 M in hexanes) was added dropwise to give a deep red solution. After 20 min, a solution of 1-bromo-2-chloroethane (502 μL, 6.03 mmol, Aldrich) in 5 mL of THF was added dropwise. The reaction was allowed to warm to room temperature over 0.5 h and stirred for an additional 12 h. The reaction was quenched with water and extracted with dichloromethane (3 × 20 mL). The combined organic phases were washed with $Na_2S_2O_3$ solution (2 × 5 mL), dried ($MgSO_4$), and filtered. After removal of solvent (aspirator), the residue was purified by flash chromatography on silica gel, 1:5 EtOAc/hexane eluent, to afford 39 mg of recovered 2-methyl-5-phenyloxazole (**16**) and 195 mg (44%; 50% based on recovered starting material) of the oxazole **23** as a yellow oil which solidified; analytical TLC on silica gel, 1:4 EtOAc/hexane, R_f = 0.16. Pure material was obtained by sublimation (50–100 °C, 0.9 mm), mp 28.5–29.5 °C: molecular ion calcd for $C_{12}H_{12}ClNO$ 221.060 81, found m/e = 221.0606, error = 1 ppm; base peak = 159 amu; IR (CCl_4, cm^{-1}) 1550, C=N; 200-MHz NMR ($CDCl_3$, ppm) δ 7.62–7.57 (2 H, m), 7.44–7.29 (3 H, m), 7.22 (1 H, s), 3.67 (2 H, t, J = 6.3 Hz), 3.01 (2 H, t, J = 7.2 Hz), 2.32–2.26 (2 H, m).

5-Membered Oxazolium Iodide 24. 2-(3′-Chloropropyl)-5-phenyloxazole (**23**) (123 mg, 0.55 mmol) was dissolved in 1.5 mL of 2,2,2-trifluoroethanol and added via cannula to a suspension of flame-dried NaI (749 mg, 5.00 mmol) in 3.5 mL of 2,2,2-trifluoroethanol. An additional 4 mL of 2,2,2-trifluoroethanol was added along with 6 mL of dry acetonitrile. The solution was heated under reflux. After 66 h, the solvent was removed in vacuo. The residue was taken up in dichloromethane, filtered through a pad of Celite, and concentrated. The residue was dissolved in ethanol, and ether was added until a solid precipitated. Vacuum filtration afforded 104 mg (60%) of the oxazolium iodide **24** as a yellow powder sufficiently pure for the next step. Pure material was obtained by crystallization from ethanol/ether, mp 170 °C dec: 200 MHz NMR ($CDCl_3$, ppm) δ 8.62 (1 H, s), 7.73–7.42 (5 H, m), 4.67 (2 H, t, J = 7.8 Hz), 3.62 (2 H, t, J = 7.3 Hz), 3.10–2.95 (2 H, m). Anal. Calcd: C, 46.03; H, 3.86. Found: C, 45.83; H, 3.85.

Dihydropyrrolizine 26. The crude oxazolium iodide **24** (72 mg, 0.23 mmol), phenylsilane (38 mg, 0.35 mmol, Petrarch), and dimethyl acetylenedicarboxylate (DMAD) (99 mg, 0.69 mmol, Aldrich) were dissolved in 2 mL of dry acetonitrile and added via cannula to a suspension of flame-dried cesium fluoride (95 mg, 0.62 mmol, Aldrich) in 4 mL of dry acetonitrile. After vigorous stirring for 2 h at room temperature, the solvent was removed (aspirator) and the residue was purified by flash chromatography on silica gel, 1:2 EtOAc/hexane eluent, to give an inseparable mixture of tetrahydropyrrolizines **25** and the dihydropyrrolizine **26**.

A dioxane solution of the dihydropyrrolizine **26** and the tetrahydropyrrolizines **25** was added via cannula to DDQ (58 mg, 0.25 mmol, Aldrich) in 7 mL of dioxane, and the mixture was heated under reflux for 12 h. The solution was diluted with ether and washed with 5% NaOH (3 × 10 mL), and the organic layer was dried ($MgSO_4$). Solvent removal (aspirator) afforded 34 mg (45%) of 5-benzoyl-2,3-dihydro-1*H*-pyrrolizine-6,7-dicarboxylic acid dimethyl ester (**26**); analytical TLC on silica gel, 1:1 EtOAc/hexane, R_f = 0.36. Pure material was obtained by crystallization from ethyl acetate/hexane, mp 114–115 °C: molecular ion calcd for $C_{18}H_{17}NO_5$ 327.110 63, found m/e = 327.1117, error = 3 ppm; IR (CH_2Cl_2, cm^{-1}) 1740, C=O; 1710, C=O; 1640, C=O; 200-MHz NMR ($CDCl_3$, ppm) δ 7.71–7.67 (2 H, m), 7.57–7.39 (3 H, m), 4.38 (2 H, t, J = 7.2 Hz), 3.79 (3 H, s), 3.25 (3 H, s), 3.13 (2 H, t, J = 7.6 Hz), 2.65–2.50 (2 H, m).

2-(4′-Chlorobutyl)-5-phenyloxazole (17). 2-Methyl-5-phenyloxazole (**16**)[7] (1.02 g, 6.42 mmol) was dissolved in 30 mL of THF and cooled to −100 °C (ether/liquid N_2). Butyllithium (4.4 mL, 1.61 M in hexanes) was added dropwise to give a deep red solution. The mixture was warmed to −78 °C, and 1-chloro-3-iodopropane (1.44 g, 7.06 mmol, neat, Aldrich) was added dropwise. After being warmed to room temperature over 2 h, the reaction was quenched with water and extracted with ether (3 × 30 mL). The combined organic layers were dried ($MgSO_4$) and filtered. After removal of solvent (aspirator), the residue was purified by flash chromatography on silica gel, 1:4 EtOAc/hexane eluent, to afford 1.14 g (75%) of the oxazole **17** as a yellow solid; analytical TLC on silica gel, 2:1 EtOAc/hexane, R_f = 0.28. Pure material was obtained by sublimation (50–100 °C, 0.9 mm), mp 34–35 °C: molecular ion calcd for $C_{13}H_{14}ClNO$ 235.038 45, found m/e = 235.0759, error = 2 ppm; base peak = 172 amu; IR (CCl_4, cm^{-1}) 1570, C=N; 200-MHz NMR ($CDCl_3$, ppm) δ 7.64–7.59 (2 H, m), 7.46–7.26 (3 H, m), 7.22 (1 H, s), 3.59 (2 H, t, J = 6.3 Hz), 2.88 (2 H, t, J = 7.0 Hz), 2.04–1.87 (4 H, m).

6-Membered Oxazolium Iodide 18. 2-(4′-Chlorobutyl)-5-phenyloxazole (**17**) (943 mg, 4.0 mmol) in 5 mL of dry acetonitrile was added via cannula to a saturated solution of sodium iodide in 25 mL of acetonitrile. The suspension was heated under reflux for 3 h and cooled to room temperature, and the solvent was removed (aspirator). The residue was taken up in dichloromethane and filtered and the solvent removed (aspirator) to give an orange solid. The solid was washed twice with 20 mL of ether and dried in vacuo to afford 1.18 g (90%) of the oxazolium iodide **18** as a light yellow powder, sufficiently pure for the next step. A pure sample was obtained by crystallization from dichloromethane/ether, mp 221–222 °C: molecular ion calcd for $C_{13}H_{14}INO$ 327.012 27, found m/e = 327.0115, error = 2 ppm; M − 127, 200.1072, error = 2 ppm; base peak = 200 amu; IR (CCl_4, cm^{-1}) 2900, CH; 200-MHz NMR ($CDCl_3$, ppm) δ 8.73 (1 H, s), 7.77–7.72 (2 H, m), 7.48–7.40 (3 H, m), 4.54 (2 H, t, J = 5.8 Hz), 3.36 (2 H, t, J = 6.0 Hz), 2.36–2.19 (4 H, m).

Tetrahydroindolizine 22. Procedure A: Reduction with $PhSiH_3$/CsF. The oxazolium iodide **18** (75 mg, 0.23 mmol), phenylsilane (38 mg, 0.35 mmol, Petrarch), and dimethyl acetylenedicarboxylate (DMAD) (99 mg, 0.69 mmol, Aldrich) were dissolved in 2 mL of dry acetonitrile and added via cannula to a suspension of flame-dried cesium fluoride (95 mg, 0.62 mmol, Aldrich) in 4 mL of dry acetonitrile. After vigorous stirring for 2 h at room temperature, the solvent was removed (aspirator) and the residue was purified by flash chromatography on silica gel, 2:5 EtOAc/hexane eluent, to give an inseparable mixture of hexahydroindolizines **21** and the trahydroindolizine **22**.

A dioxane solution of tetrahydroindolizine **22** and the hexahydroindolizines **21** was added via cannula to 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (51 mg, 0.24 mmol, Aldrich) in 5 mL of dioxane, and the mixture was heated under reflux for 12 h. The solution was diluted with 15 mL of ether and extracted with 5% NaOH (3 × 10 mL), and the organic layer was dried ($MgSO_4$). Solvent removal (aspirator) afforded 55 mg (70%) of 3-benzoyl-5,6,7,8-tetrahydro-1,2-indolizinedicarboxylic acid dimethyl ester (**22**) as an off-white powder; analytical TLC on silica gel, 1:1 EtOAc/hexane, R_f = 0.41. Pure material was obtained by crystallization from ethyl acetate/hexane, mp 134–135 °C: molecular ion calcd for $C_{19}H_{19}NO_5$ 341.126 28, found m/e = 341.1284, error = 6 ppm; M − 32, 309.1031, error = 10 ppm; base peak = 309 amu; IR (CCl_4, cm^{-1}) 1725, C=O; 1700, C=O; 1625, C=O; 200-MHz NMR ($CDCl_3$, ppm) δ 7.73–7.69 (2 H, m), 7.54–7.38 (3 H, m), 4.26 (2 H, t, J = 5.5 Hz), 3.77 (3 H, s), 3.19 (3 H, s), 3.13 (2 H, t, J = 6.4 Hz), 2.00–1.89 (4 H, m).

Procedure B: Reduction with $NaBH_4$. The oxazolium iodide **18** (77 mg, 0.24 mmol) was dissolved in 6 mL of dry acetonitrile. Dimethyl acetylenedicarboxylate (DMAD) (87 μL, 0.71 mmol, Aldrich) was added. Solid sodium borohydride (9 mg, 0.24 mmol, Aldrich) was added, followed by the addition of 200 μL of methanol, which resulted in gas evolution. After being stirred for 10 min at room temperature, the reaction was quenched with water, extracted with dichloromethane (3 × 15 mL), dried ($MgSO_4$), and filtered. After removal of solvent (aspirator), the residue was dissolved in dioxane. The solution of the crude

reaction mixture was added via cannula to DDQ (64 mg, 0.28 mmol, Aldrich) in 5 mL of dioxane, and the mixture was heated under reflux for 12 h. After cooling, the solution was diluted with 15 mL of ether and extracted with 5% KOH (3 × 10 mL). The organic layer was dried ($MgSO_4$) and filtered. Solvent removal (aspirator) afforded 55 mg (68%) of 3-benzoyl-5,6,7,8-tetrahydro-1,2-indolizinedicarboxylic acid dimethyl ester (**22**) as an off-white powder.

2-Methyl-5-(3′-chloropropyl)oxazole (30). The diazo ketone **29**[17] (4.14 g, 2.8 mmol) was dissolved in 4 mL of dry acetonitrile. The yellow solution was added dropwise via cannula to a solution of boron trifluoride etherate (7.0 mL, 5.7 mmol) in 20 mL of dry acetonitrile at 0 °C. After complete gas evolution, the solution was warmed to room temperature and stirred for 1 h. The mixture was poured into ether and washed once with 1 M NaOH solution. The organic layer was dried ($MgSO_4$), filtered, and concentrated (aspirator). Distillation of the product afforded 3.67 g (82%) of 2-methyl-5-(3′-chloropropyl)oxazole (**30**) as a clear liquid, bp 110–113 °C, 10 mm, short path; analytical TLC on silica gel, 1:4 EtOAc/hexane, R_f = 0.19: molecular ion calcd for $C_7H_{10}ClNO$ 159.045 15, found m/e = 159.0448, error = 2 ppm; IR (neat, cm^{-1}) 1625, C=N; 200-MHz NMR ($CDCl_3$, ppm) δ 6.65 (1 H, s), 3.57 (2 H, t, J = 6.3 Hz), 2.80 (2 H, t, J = 7.3 Hz), 2.41 (3 H, s), 2.16–2.06 (2 H, m).

2-Methyl-5-(3′-hydroxypropyl)oxazole (31). 2-Methyl-5-(3′-chloropropyl)oxazole (**30**) (1.69 g, 10.6 mmol) was added to approximately 10 mL of saturated sodium carbonate solution and heated under reflux for 12 h. After being cooled to room temperature, the reaction mixture was extracted with dichloromethane (3 × 20 mL), dried ($MgSO_4$), filtered, and concentrated (aspirator). Distillation of the product afforded 0.92 g (62%) of 2-methyloxazole alcohol **31** as a clear, colorless liquid, bp 110–111 °C, 1.0 mm, short path; analytical TLC on silica gel, 3:2 EtOAc/hexane, R_f = 0.11: molecular ion calcd for $C_7H_{11}NO_2$ 141.078 98, found m/e = 141.0790, error = 0 ppm; IR (neat, cm^{-1}) 3300, OH; 1575, C=N; 200-MHz NMR ($CDCl_3$, ppm) δ 6.61 (1 H, s), 3.80 (2 H, t, J = 6.3 Hz), 2.73 (2 H, t, J = 7.8 Hz), 2.41 (3 H, s), 2.04 (1 H, bs), 1.96–1.82 (2 H, m).

2-(4′-Chlorobutyl)-5-(3″-hydroxypropyl)oxazole (32). *tert*-Butyllithium (6.0 mL, 1.7 M in pentane) was added dropwise to a solution of crude oxazole alcohol **31** (695 mg, 4.9 mmol) in 20 mL of THF at −78 °C to give a yellow suspension. After 30 min, 1-bromo-3-chloropropane (1.46 mL, 14.8 mmol, neat, Aldrich) was added dropwise to give a clear yellow solution. The solution was warmed to room temperature over 2 h, quenched with water, extracted with ethyl acetate (3 × 20 mL), dried ($MgSO_4$), and filtered. After removal of solvent (aspirator), the residue was purified by flash chromatography on silica gel (17 mm × 35 cm), EtOAc/hexane (1:2–1:0) eluent, to afford 799 mg (75%) of the oxazole alcohol **32** as an oil and 69 mg of recovered starting oxazole alcohol **31**; analytical TLC on silica gel, EtOAc, R_f = 0.29: molecular ion calcd for $C_{10}H_{16}ClNO_2$ 217.087 00, found m/e = 217.0877, error = 3 ppm; base peak = 182 amu; IR (neat, cm^{-1}) 3350, OH; 200-MHz NMR ($CDCl_3$, ppm) δ 6.63 (1 H, s), 3.70 (2 H, t, J = 6.0 Hz), 3.56 (2 H, t, J = 6.0 Hz), 2.79–2.70 (4 H, overlapping t, J = 6.0 and 6.0), 1.96–1.82 (6 H, m), 1.69 (1 H, br s).

3-[(4′-Chlorobutyl)oxazol-2-yl]propanal (33). DMSO (1.26 mL, 17.7 mmol, Aldrich) was added dropwise to a solution of oxalyl chloride (805 μL, 9.2 mmol, Aldrich) in 25 mL of dichloromethane at −78 °C. After 20 min, a solution of oxazole alcohol **32** (773 mg, 3.5 mmol) in dichloromethane was added dropwise via cannula. After 40 min, triethylamine (2.0 mL, 14.2 mmol) was added, and the solution was warmed to room temperature. Water was added, and the mixture was extracted with dichloromethane (3 × 30 mL), dried ($MgSO_4$), and filtered. After removal of solvent (aspirator), the residue was purified by flash chromatography on silica gel (15 mm × 35 cm), 1:1 EtOAc/hexane eluent, to afford 556 mg (73%) of oxazole aldehyde **33** as an oil; analytical TLC on silica gel, EtOAc, R_f = 0.46: molecular ion calcd for $C_{10}H_{14}ClNO_2$ 215.071 35, found m/e = 215.0708, error = 2 ppm; base peak = 152 amu; IR (neat, cm^{-1}) 1720, C=O; 200-MHz NMR ($CDCl_3$, ppm) δ 9.83 (1 H, t, J = 1.0 Hz), 6.64 (1 H, t, J = 0.8 Hz), 3.57 (2 H, t, J = 6.2 Hz), 2.97 (2 H, t, J = 7.3 Hz), 2.85–2.72 (4 H, overlapping dt and t, J = 1.1, 6.2, and 7.3), 1.92–1.86 (4 H, m).

[2-(4′-Chlorobutyl)oxazol-5-yl]alkynol 35. $CeCl_3 \cdot 7H_2O$ (1.95 g, 5.2 mmol, Aldrich) was dried in vacuo (1 mm) at 140 °C for 2 h and then suspended in 20 mL of THF and stirred for 12 h. In a separate flask, *n*-butyllithium (2.8 mL, 1.63 M in hexane) was added dropwise to a solution of hexamethyldisilazane (964 μL, 4.5 mmol, Aldrich) in 10 mL of THF at −78 °C. After being warmed to room temperature over 15 min, the solution was added dropwise to the previously prepared $CeCl_3$/THF suspension containing ethyl propiolate (463 μL, 4.5 mmol, Aldrich) at −78 °C and stirred for 1 h. A solution of oxazole aldehyde **33** (548 mg, 2.5 mmol) in THF was added dropwise via cannula and stirred for 1 h. The reaction was quenched with water, extracted with ether (3 × 30 mL), dried ($MgSO_4$), and filtered. After removal of solvent (aspirator), the residue was purified by flash chromatography on silica gel (15 mm × 35 cm), 1:1 EtOAc/hexane eluent, to afford 759 mg (95%) of the alkynol **35** as an oil; analytical TLC on silica gel, 3:2 EtOAc/hexane, R_f = 0.18: molecular ion calcd for $C_{15}H_{20}ClNO_4$ 313.108 09, found m/e = 313.1086, error = 2 ppm; M − 63 ($-C_2H_4Cl$), 250.1057, error = 9 ppm; IR (neat, cm^{-1}) 3300, OH; 2234, C≡C; 1712, C=O; 200-MHz NMR ($CDCl_3$, ppm) δ 6.68 (1 H, s), 4.54 (1 H, q, J = 4.2 Hz), 4.25 (2 H, q, J = 7.2 Hz), 3.57 (2 H, t, J = 6.2 Hz), 3.38 (1 H, d, J = 3.9 Hz), 2.84 (2 H, t, J = 7.5 Hz), 2.77 (2 H, t, J = 7.0 Hz), 2.09 (2 H, dt, J = 7.5, 7.0 Hz), 2.00–1.83 (4 H, m), 1.32 (3 H, t, J = 7.2 Hz).

[2-(4′-Chlorobutyl)oxazol-5-yl]alkyne TBS Ether 36. *tert*-Butyldimethylsilyl trifluoromethanesulfonate (582 μL, 2.8 mmol, Petrarch) was added dropwise to a solution of oxazolylalkynol **35** (725 mg, 2.3 mmol) and diisopropylethylamine (604 μL, 3.5 mmol, Aldrich) in 30 mL of dichloromethane at −78 °C. The reaction was allowed to warm slowly to room temperature. After 12 h, the mixture was poured into water, extracted with dichloromethane (3 × 20 mL), dried ($MgSO_4$), and filtered. After removal of solvent (aspirator), the residue was purified by flash chromatography on silica gel (15 mm × 35 cm), 1:4 EtOAc/hexane eluent, to afford 879 mg (91%) of oxazolylalkyne TBS ether **36** as an oil; analytical TLC on silica gel, 1:1 EtOAc/hexane, R_f = 0.48: molecular ion calcd for $C_{21}H_{34}ClNO_4Si$ 427.194 58, found m/e = 427.1935, error = 2 ppm; M − 57, 370.1254, error = 3 ppm; IR (neat, cm^{-1}) 2240, C≡C; 1718, C=O; 200-MHz NMR ($CDCl_3$, ppm) δ 6.62 (1 H, s), 4.49 (1 H, t, J = 6.2 Hz), 4.20 (2 H, q, J = 7.2 Hz), 3.54 (2 H, t, J = 6.2 Hz), 2.38 (2 H, t, J = 7.2 Hz), 2.73 (2 H, t, J = 6.7 Hz), 2.02 (2 H, dt, J = 6.5, 7.1 Hz), 1.91–1.84 (4 H, m), 1.29 (3 H, t, J = 7.2 Hz), 0.88 (9 H, s), 0.14 (3 H, s), 0.09 (3 H, s).

Pyrido[1,2-*a*]indoloquinone 38. Oxazole **36** (38 mg, 0.09 mmol) and NaI (67 mg, 0.45 mmol) were dissolved in 5 mL of dry acetonitrile and heated under reflux for 10 h. The solvent was removed (aspirator). The residue was taken up in dichloromethane, filtered through a plug of Celite, and concentrated. Examination of the crude oxazolium salt **37** by 200-MHz ^1H NMR revealed the C-4 oxazole proton at δ 7.65 ($\Delta\delta$ 1.03).

The crude oxazolium salt **37** and phenylsilane (17 μL, 0.13 mmol, Petrarch) were dissolved in 3 mL of dry acetonitrile and added via cannula to flame-dried CsF (41 mg, 0.27 mmol, Aldrich) in 2 mL of dry acetonitrile. After being stirred at room temperature for 24 h, the reaction was filtered and concentrated to give a brown oil. The crude oil was dissolved in THF and treated with tetrabutylammonium fluoride (approximately 100 μL, 1.0 M in THF, Aldrich) and stirred for 12 h. The solution was concentrated and purified by plug filtration chromatography on silica gel, 1:1 EtOAc/hexane eluent, to give 12 mg of an inseparable mixture of pyrrole and pyrrolines.

The mixture of pyrrole and pyrrolines (12 mg) was dissolved in 5 mL of toluene along with DDQ (33 mg, 0.14 mmol, Aldrich) and heated under reflux for 1.5 h. 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 10 mg (41% overall) of the pyrido[1,2-*a*]indoloquinone **38** as a yellow solid; analytical TLC on silica gel, 1:1 EtOAc/hexane, R_f = 0.51. Pure material was obtained as orange needles by crystallization from ether/hexane, mp 144 °C dec: molecular ion calcd for $C_{15}H_{15}NO_4$ 273.100 07, found m/e = 273.0996, error = 2 ppm; base peak = 227 amu; IR (CCl_4, cm^{-1}) 1704, C=O; 1668,

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C=O; 1656, C=O; UV (MeOH, λ_{max}) 422 nm, ϵ = 2200; 330 nm, ϵ = 3200, 244 nm, ϵ = 14 130; 200-MHz NMR ($CDCl_3$, ppm) δ 6.58 (1 H, d, J = 10.2 Hz), 6.50 (1 H, d, J = 10.2 Hz), 4.39 (2 H, t, J = 6.0 Hz), 4.37 (2 H, q, J = 7.1 Hz), 3.09 (2 H, t, J = 6.5 Hz), 2.05–1.85 (4 H, m), 1.40 (3 H, t, J = 7.1 Hz).

Alkynyl Diazo Ketone 39. An ethanol-free ethereal solution of diazomethane was generated from Diazald (21.0 g, 97.5 mmol, Aldrich) and KOH (5.9 g, 105.2 mmol) with 2'-ethoxy-2-ethoxyethanol (Aldrich) as the cosolvent. An ether solution of 5-hexynoyl chloride[18] (5.09 g, 39.0 mmol) was added dropwise via Teflon cannula to the diazomethane solution at 0 °C. After 2 h, the solution was concentrated by vigorous N_2 flow. Residual solvent was removed in vacuo (1 mm). The crude material was sufficiently pure for the next step: molecular ion calcd for $C_7H_8N_2O$ 136.063 70, found m/e = 136.0654, error = 12 ppm; M − 41 (−CHN_2), 95.0518; base peak = 95.0518 amu; IR (neat, cm^{-1}) 3300, ≡CH; 2230, C≡C; 2100, C=N_2; 200-MHz NMR ($CDCl_3$, ppm) δ 5.25 (1 H, br s), 2.49 (2 H, t, J = 6.2 Hz), 2.25 (2 H, dt, J = 2.5, 7.8 Hz), 1.98 (1 H, t, J = 2.5 Hz), 1.90–1.70 (2 H, m).

2-Methyl-5-(4'-pentynyl)oxazole (40). The crude diazo ketone **39** (270 mg, 2.0 mmol) was dissolved in dry acetonitrile and added to a solution of boron trifluoride etherate (0.29 mL, 2.4 mmol, Aldrich) in 5 mL of dry acetonitrile at 0 °C. After gas evolution was complete, the solution was warmed to room temperature and stirred for an additional 1 h. The reaction mixture was diluted with ether and washed twice with 1 N KOH solution. The combined aqueous layers were back-extracted with ether (2 × 20 mL). The combined organic layers were 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/hexane (1:5–1:3), to afford 203 mg (69%) of the oxazolyl alkyne **40** as a light yellow oil; analytical TLC on silica gel, 1:1 EtOAc/hexane, R_f = 0.48: molecular ion calcd for $C_9H_{11}NO$ 149.084 08; found m/e = 149.0836, error = 3 ppm; IR (neat, cm^{-1}) 3300, ≡CH; 2120, C≡C; 1580, C=N; 200 MHz NMR ($CDCl_3$, ppm) δ 6.63 (1 H, s), 2.74 (2 H, t, J = 7.5 Hz), 2.41 (3 H, s), 2.26 (2 H, dt, J = 2.6, 7.0 Hz), 2.00 (1 H, t, J = 2.6 Hz), 1.93–1.78 (2 H, m).

2-(3'-Chloropropyl)-5-(4'-pentynyl)oxazole (42). The crude diazo ketone **39** (530 mg, 3.9 mmol) was dissolved in 1.5 mL of 4-chlorobutyronitrile (Fluka) and added dropwise via cannula to a solution of boron trifluoride etherate (0.58 mL, 4.7 mmol, Aldrich) in 5 mL of 4-chlorobutyronitrile at 0 °C. After gas evolution was complete, the reaction was warmed to room temperature and stirred for 12 h. The mixture was diluted with ether and washed twice with 1 N KOH solution. As recommended by Doyle et al.,[11a] concentrated HCl (about 20 mL) was added dropwise with minimal mixing to extract the oxazole. The aqueous layer was neutralized with KOH solution and extracted with ether (3 × 20 mL), and the organics were dried ($MgSO_4$) and evaporated (aspirator) to a brown oil. The excess 4-chlorobutyronitrile was carefully distilled away (40 °C/0.01 mm). The residue was purified by flash chromatography on silica (15 mm × 40 cm), 1:3 EtOAc/hexane eluent, to afford 493 mg (59%) of alkynyloxazole **42** as an orange oil; analytical TLC on silica gel, 3:2 ether/hexane, R_f = 0.35: molecular ion calcd for $C_{11}H_{14}ClNO$ 211.038 45, found m/e = 211.0382, error = 1 ppm; IR (neat, cm^{-1}) 3300, ≡CH; 2100, C≡C; 1585, C=N; 200-MHz NMR ($CDCl_3$, ppm) δ 6.66 (1 H, s), 3.64 (2 H, t, J = 6.4 Hz), 2.90 (2 H, t, J = 7.3 Hz), 2.75 (2 H, t, J = 7.4 Hz), 2.30–2.17 (4 H, m), 2.00 (1 H, t, J = 2.6 Hz), 1.98–1.82 (2 H, m).

2-(3'-Chloropropyl)oxazolyl Acetylenic Ester 43. Anhydrous $CuCl_2$ (119 mg, 0.89 mmol, Baker), anhydrous sodium acetate (73 mg, 0.89 mmol, MCB), and catalytic $PdCl_2$ (approximately 10 mg, Alfa) were mixed in 8 mL of methanol to give a green, heterogeneous solution. After 5 min, a solution of oxazolyl alkyne **42** (94 mg, 0.44 mmol) in 2 mL of methanol was added. A rubber balloon filled with carbon monoxide was attached to the flask. After 2 h, the reaction stalled; extra $PdCl_2$ (approximately 5 mg) was added. After a total of 3.5 h, the reaction mixture was diluted with dichloromethane, washed once with concd ammonium hydroxide solution, dried ($MgSO_4$), and filtered. After removal of solvent (aspirator), the residue was purified by flash chromatography on silica gel (15 mm × 40 cm), 2:3 EtOAc/hexane eluent, to afford 80 mg (67%) of the alkyne ester **43** as an oil; analytical TLC on silica gel, 1;1 EtOAc/hexane, R_f = 0.42: molecular ion calcd for $C_{13}H_{16}ClNO_3$ 269.08191, found m/e = 269.0817, error = 1 ppm; M − 49 (−CH_2Cl), 220.0957, error = 7 ppm; base peak = 220 amu; IR (neat, cm^{-1}) 2230, C≡C; 1720, C=O; 1585, C=N; 200-MHz NMR ($CDCl_3$, ppm) δ 6.67 (1 H, s), 3.77 (3 H, s), 3.64 (2 H, t, J = 6.3 Hz), 2.90 (2 H, t, J = 7.3 Hz), 2.38 (2 H, t, J = 7.4 Hz), 2.40 (2 H, t, J = 7.0 Hz), 2.31–2.16 (2 H, m), 1.98–1.84 (2 H, m).

Pyrrolo[1,2-a]indolone 45. The oxazole **43** (55 mg, 0.20 mmol) and flame-dried NaI (190 mg, 1.27 mmol) were dissolved in 5 mL of dry acetonitrile and heated under reflux for 18 h. After removal of solvent (aspirator), the residue was taken up in dichloromethane, filtered through a plug of Celite, and concentrated. Examination of the crude oxazolium salt **44** by 200-MHz ^1H NMR reveals the C-4 oxazole proton at δ 7.87 ($\Delta\delta$ 1.20).

The crude oxazolium salt **44** (73 mg, 0.20 mmol) and phenylsilane (38 μL, 0.31 mmol, Petrarch) were dissolved in 4 mL of dry acetonitrile and added via cannula to flame-dried CsF (126 mg, 0.83 mmol, Aldrich) in 1 mL of dry acetonitrile. After 8 h, the solution was concentrated (aspirator), and the residue was purified by flash chromatography on silica gel (15 mm × 40 cm), EtOAc/hexane (1:2–1:1) eluent, to afford 23 mg (48%) of the pyrroloindolone **45**; analytical TLC on silica gel, 1:1 EtOAc/hexane, R_f = 0.43. Pure material was obtained by crystallization from hexane, mp 89.7–90 °C: molecular ion calcd for $C_{13}H_{15}NO_3$ 233.105 16, found m/e = 233.1055, error = 1 ppm; M − 15 (−CH_3), 218.0811, error = 3 ppm; IR (CCl_4, cm^{-1}) 1730, C=O; 1670, C=O; UV (MeOH, λ_{max}) 288 nm, ϵ = 25 470; 230 nm, ϵ = 26 415; 200-MHz NMR ($CDCl_3$, ppm) δ 4.27 (2 H, t, J = 7.2 Hz), 3.80 (3 H, s), 3.10–2.98 (4 H, overlapping t, J = 7.5 and 6.0 Hz), 2.56–2.43 (4 H, m), 2.12–2.05 (2 H, m).

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Supplementary Material Available: ^1H NMR spectra of key products and procedures and characterization data for preparation of **11**, **12**, **14**, and **15** based on the Jacobi oxazole synthesis[19] (20 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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