Competing Pathways in the Azomethine Ylide Route to Indoloquinones: An Improved Procedure for the Generation of a Transient 4-Oxazoline from the Oxazolium Salt

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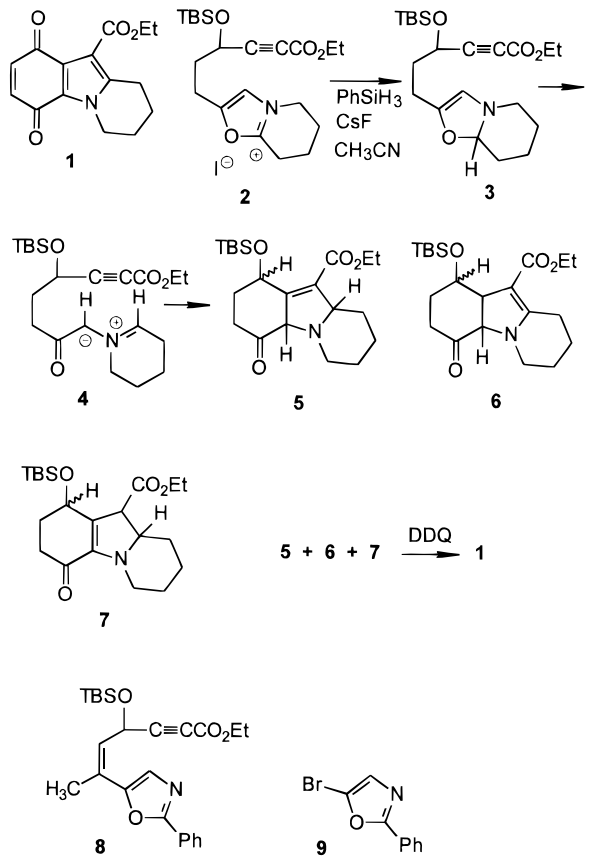
Azomethine ylide generation from the oxazolium salt **22** and $PhSiH_3$/CsF affords complex products derived from the initial cycloadduct **23** via three competing pathways. Colorless intermediates **24**−**27** have been detected, and their oxidation products **10**, **28**, and **29** have been identified. Nucleophilic activation of the oxazolium salt **22** is reported using the organic-soluble benzyltrimethylammonium cyanide. This variation affords the unstable cycloadduct **32,** which undergoes aromatization via a single pathway involving **24** and **27**, and DDQ oxidation gives the indoloquinone **10** in an improved 63% yield. Lower yields using $PhSiH_3$/CsF or NaCN activation methods are attributed to the heterogeneous conditions and interception of the azomethine ylide by unreacted oxazolium salt.

The indoloquinone nucleus is important as a subunit of the mitomycin family of antitumor agents.[1] This has stimulated numerous efforts to assemble bicyclic pyrrole derivatives and their precursors using azomethine ylide technology.[2] In a related report from our laboratory, it was demonstrated that indoloquinone **1** can be made by an internal 2 + 3 cycloaddition where the key azomethine ylide is formed by electrocyclic ring opening of an oxazoline precursor.[2h] Thus, an oxazolium salt **2** was reduced with $PhSiH_3$/CsF to generate the unstable 4-oxazoline **3** and spontaneous rearrangement gave the transient ylide **4** (Scheme 1). The product mixture from cycloaddition was complex, and we could not establish whether it contained the expected initial cycloadduct **5**, the double bond isomers or diastereomers (**6**, **7**, etc.), or other products derived from ylide decomposition. Fortunately, treatment of the product mixture with DDQ gave the stable and easily isolated quinone **1** in 41% overall yield from **3**. "Enolizable" azomethine ylides (those containing an α-C−H bond next to the iminium carbon) similar to **4** are difficult to intercept using the alternative of aziridine pyrolysis as the method for azomethine ylide generation. This is because high-temperature conditions promote competing side reactions that begin with enamine formation via deprotonation at the α-carbon.[3] We were therefore encouraged by the 41% yield in this difficult example via the oxazoline intermediate.

Scheme 1



In the course of experiments designed to optimize the indoloquinone synthesis, we had also explored a modified substrate **8** that could be prepared readily from 2-phenyl-5-bromooxazole (**9**)[4] as will be discussed shortly. The structural features of **8** were anticipated to improve efficiency and product recovery for several reasons. First, there is no possibility of enamine formation because the dipole corresponding to **4** would contain a simple phenyl group in place of the "enolizable" α-CH_2 group. Second, the *Z*-trisubstituted double bond in the tethered dipolarophile unit might improve the cycloaddition step by restricting tether geometry. The double bond should also facilitate aromatization in the DDQ step by decreasing

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(2) (a) Reviews: Lown, J. W. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, 1984; Chapter 1. Grigg, R.; Sidharan, V. *Adv. Cycloaddit. Chem.* **1993**, *3*, 161. (b) Hershenson, F. M. *J. Org. Chem.* **1975**, *40*, 1260. (c) Anderson, W. K.; Corey, P. F. *J. Org. Chem.* **1977**, *42*, 559. (d) Rebek, J., Jr.; Shaber, S. H.; Shue, Y. K.; Gehret, J. C.; Zimmerman, S. *J. Org. Chem.* **1984**, *49*, 5164. Rebek, J., Jr.; Shaber, S. H. *Heterocycles* **1981**, *16*, 1173. Rebek, J., Jr.; Gehret, J. C. E. *Tetrahedron Lett.* **1977**, 3027. (e) Vedejs, E.; Grissom, J. W. *J. Am. Chem. Soc.* **1988**, *110*, 3238. (f) Vedejs, E.; Grissom, J. W. *J. Org. Chem.* **1988**, *53*, 1876. (g) Vedejs, E.; Dax, S. L. *Tetrahedron Lett.* **1989**, *30*, 2627. (h) Vedejs, E.; Piotrowski, D. W. *J. Org. Chem.* **1993**, *58*, 1341−8. (i) Hutchison, D. R.; Nayyar, N. K.; Martinelli, M. J. *Tetrahedron Lett.* **1996**, *37*, 2887.

(3) Padwa, A.; Dean, D.; Oine, T. *J. Am. Chem. Soc.* **1975**, *97*, 2822; Dopp, D.; Nour-El-Din, A. M. *Tetrahedron Lett.* **1978**, *19*, 1463.

(4) Kashima, C.; Arao, H. *Synthesis* **1989**, 873.

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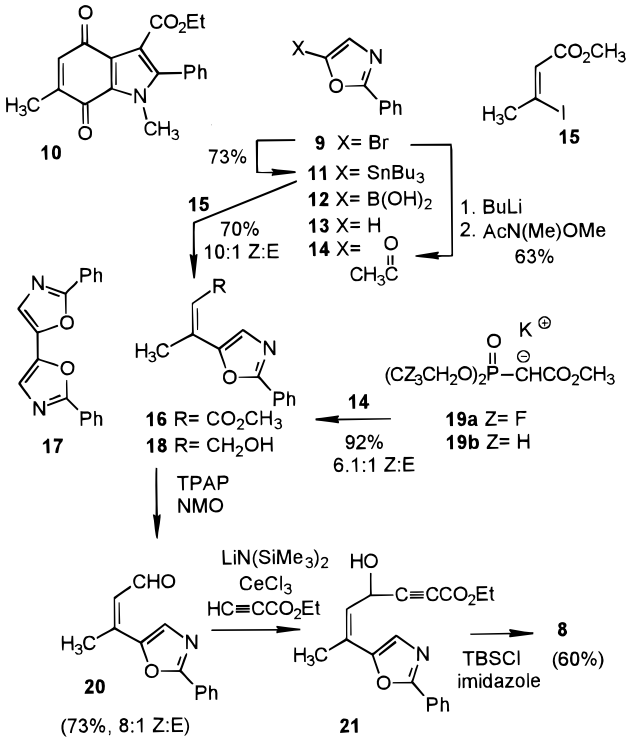
Scheme 2



the number of oxidative events needed to convert the initial 2 + 3 cycloadduct into a quinone. Finally, the 2-phenyl substituent in **8** was expected to serve as an easily detected label for the corresponding carbon in the event that iminium C−N bond cleavage in the derived dipole proved to be a factor in material recovery. When the above considerations were evaluated in preliminary experiments, we were surprised to find new complications instead of the expected yield improvement using the original CsF/$PhSiH_3$ activation procedure. Fortunately, key intermediates in the azomethine ylide cycloaddition process could be partially separated and identified. This has produced a better understanding of risk factors in the oxazolium activation−cycloaddition−aromatization sequence from **8** to the corresponding indoloquinone **10**. A more reliable procedure for stabilized azomethine ylide generation from oxazolium salts has been developed in the course of this study. As described below, undesired side reactions are minimized when the soluble benzyltrimethylammonium cyanide is used as the nucleophile in the oxazolium activation step.

Our first objective was to devise a stereoselective route to **8**. In the first approach, 5-bromo-2-phenyloxazole (**9**) was converted via lithiation and stannylation into the tributyltin derivative **11** (73%), and the latter was subjected to Stille coupling with methyl (*Z*)-3-iodocrotonate (**15**) (Scheme 2).[5] Depending on the conditions, some loss of enoate geometry occurred in the coupling step leading to the desired **16**. The use of $PdCl_2(CH_3CN)_2$ in DMF gave the best *Z*:*E* ratio (20:1; 50%), but better yields were obtained with other palladium sources, and the $Pd_2(dba)_3$/trifurylphosphine procedure[6] in DMF gave a good compromise of selectivity (10:1 *Z*:*E*) and yield (70% of **16** isolated). However, purification was not easy because the coupling reactions also produced destannylated side products including 2-phenyloxazole (**13**) as well as a second contaminant assigned the bis-oxazole structure **17** based on NMR and exact mass data (ca. 5−10% total **13** + **17**). Separation of the mixture was best performed later, after DIBAL reduction of the initial products, to give the alcohol **18**. The latter could be separated from the destannylated byproducts by flash chromatography. A similar approach based on the Suzuki coupling[7] of an oxazoleboronic acid **12** was also explored briefly. This resulted in clean coupling in the best experiments, but the method was difficult to optimize because **12** could not be obtained as a homogeneous substance, presumably due to the variable presence of boronic anhydrides. A simpler, more reliable route to **16** was desired.

An acceptable procedure was found using the Gennari−Still variant of the Horner−Emmons reaction,[8] starting from the ketone **14** (prepared in 84% yield from 5-bromo-2-phenyloxazole by lithiation and trapping with the Weinreb amide).[9] Reaction of **14** with **19a** gave a mixture of **16** and the undesired *E*-isomer (92% yield), and a 6.1:1 *Z*:*E* ratio was demonstrated on a preparative scale. On the other hand, the conventional Horner−Emmons reagent **19b** produced largely the undesired *E*-isomer of **16** (14:1 *E*:*Z*, 84%).[10]

The 5-acyloxazole **16** proved to be somewhat light sensitive, and *Z*/*E* equilibration was noted upon storage. Therefore, the mixture of isomers was converted to the relatively stable alcohol **18** (86%, 6.1:1 *Z*:*E*; DIBAL). Oxidation to the enal **20** was performed using the TPAP method,[11] and purification by flash chromatography resulted in some improvement in the *Z*:*E* ratio to 8:1 (74% isolated). The aldehyde was also light sensitive, so **20** was immediately treated with the cerium-modified lithiopropiolate reagent.[2h,12] The resulting acetylenic alcohol **21** was converted to the desired TBS ether **8**, and separation of nearly all of the residual E-alkane and contaminants was possible at this stage by flash chromatography to give **8** with 20:1 *Z*:*E*, 60% overall yield, based on **20**.

We could now address the key optimization issues in the cycloaddition−aromatization−oxidation sequence. Alkylation of **8** using methyl triflate gave a noncrystalline oxazolium salt **22** to set the stage for generation of the critical 4-oxazoline intermediate. The first experiments explored the same reductive activation method ($PhSiH_3$/CsF) used earlier for conversion of **2** into **1**. Clear indications were obtained that ylide formation and internal cycloaddition to give **23** had occurred, but the product mixtures were complex and air sensitive. Even a brief exposure to air resulted in the formation of intensely colored products. One of these proved to be the expected indoloquinone **10** (yellow), but the yield was low and variable. Three other colored products were formed, and TLC analysis detected several labile, colorless precursors. Chromatographic separation of the crude product gave fractions enriched in the colored substances, including two purple quinones **28a,b** and a deep red

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(7) Suzuki, A. *Pure Appl. Chem.* **1991**, *63*, 419. Miyaura, N.; Yanagi, T.; Suzuki, A. *Synth. Commun.* **1981**, *11*, 513.
(8) Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405.
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(10) The stabilized ylide $Ph_3P{=}CHCO_2CH_3$ produced a 1:10 *Z*:*E* product ratio in methanol at 65 °C (29% yield).
(11) (a) Griffith, W. P.; Ley, S. *Aldrichim. Acta* **1990**, *23*, 13. (b) Griffith, W. P.; Jolliffe, J. M.; Ley, S. *Synth. Commun.* **1992**, *22*, 1967.
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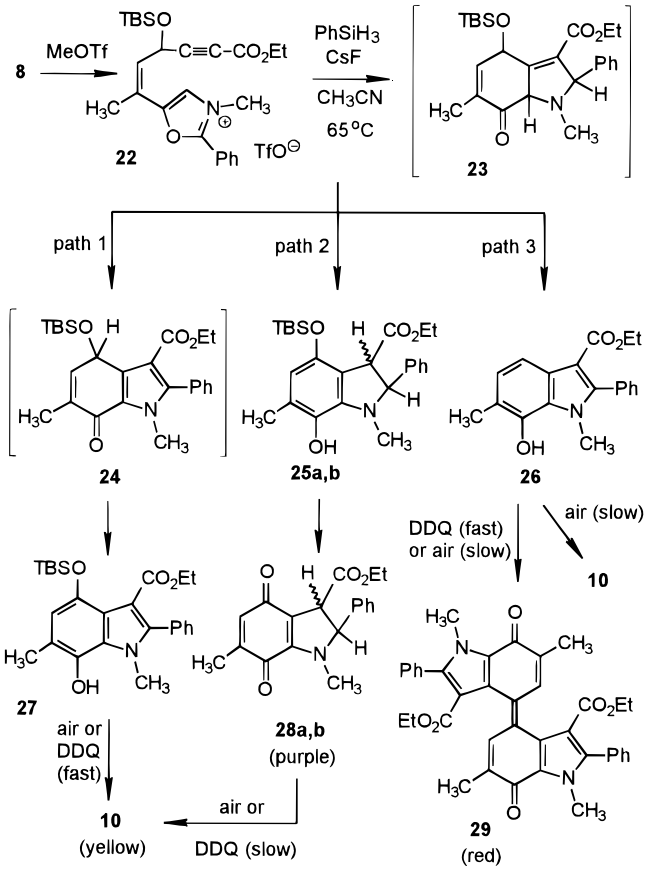
Scheme 3



compound **29** whose structure was understood only after X-ray quality crystals became available.

All of the colored products of the reaction have been traced to the formation of five unstable, colorless intermediates **24**, **25a,b**, **26**, and **27**. Knowing these structures, it is easy to see how individual susbtances might arise from the initially expected **23**. However, it was difficult to reach structural and mechanistic conclusions. One complicating factor was that **23** was never detected among the products, but the main problem was that all of the colorless intermediates are sensitive to air oxidation and most of them were never obtained free of contaminants or decomposition products. In any case, it is now clear that there are three competing pathways from **23**, as outlined in Scheme 3, one of which (path 1, via **24** and **27**) leads efficiently to **10**. The two other pathways (path 2, via **25a,b** and **28a,b**; path 3, via **26**) can also produce **10**, depending on the conditions of subsequent oxidation, but these pathways also produce the purple and red products **28a,b** (path 2) and **29** (path 3), respectively. After the complexities were understood, it was realized that path 2 can be forced to **10**, while path 3 affords **10** and the red product **29** from a common intermediate **26**, depending on the conditions. Neither **10** nor **29** are capable of producing any of the other products under conditions encountered during this study. A description of how these conclusions were reached is presented below, starting with structure assignments for the intensely colored products.

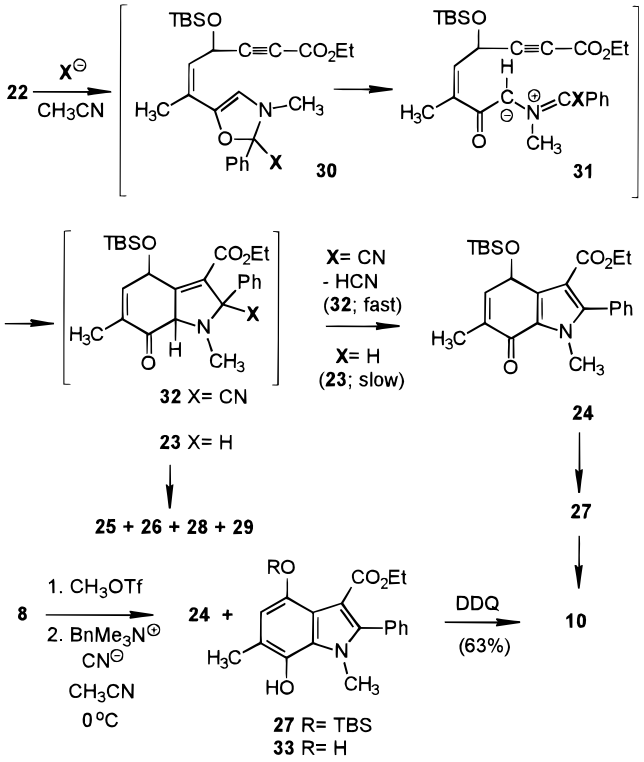
The purple quinones could be separated from each other (minor, unknown contaminants could not be removed completely) and were identified as the diastereomers **28a** and **28b** on the basis of a combination of NMR and UV evidence. The chromophore (λ_{max} 558 nm) is characteristic of this ring system and the β-amino quinone environment.[13] Furthermore, the NMR spectra indicate the presence of mutually coupled, vicinal methine protons in each diastereomer, as well as the characteristic quinone C−H signal (δ 6.38 and 6.39 ppm), split into a quartet (J = 1.5 Hz) by long-range coupling to the vinylic methyl group. Treatment of the purple quinones with DDQ or prolonged exposure to air resulted in slow conversion into the yellow quinone **10**, consistent with the conclusion that **10** and **28** have the same bicyclic skeleton and substitution pattern and differ only in the level of oxidation. On the other hand, it became clear that the quinone diastereomers **28a,b** are not the primary precursors of **10**. Furthermore, the DDQ experiments with **28a,b** did not produce the red product, nor was the latter detected in control experiments starting from purified **10** and DDQ.

Separation of individual components from the CsF/$PhSiH_3$ cycloadduct mixture prior to oxidation was difficult as already mentioned. We did succeed in isolating nearly colorless fractions by chromatography that were enriched in some of the intermediates. One of these fractions contained saturated methine and ester signals in the ^{1}H NMR spectrum consistent with the structure **25a,b** (mixture of diastereomers; ca. 15% recovery). The spectrum was unusual in that the ^{1}H NMR signals for N−CH_3 and aromatic C−CH_3 signals of both diastereomers were broad, indicating slow exchange of rotamers or tautomers on the NMR time scale. The structure was assigned on the basis of the facile conversion from **25a,b** to **28a,b** upon DDQ or air oxidation.

Other fractions contained intermediate **26** as the major component, along with a precursor of **10** that was later identified as **27**. On one occasion, a small fraction of **26** was obtained nearly free of contaminants, and the resulting NMR spectrum was helpful in the assignment of structure. This result was not duplicated in other runs, and the yield (estimated at 20%) is not accurately known. Intermediate **26** was initially recognized in chromatography fractions by the appearance of distinct new aromatic signals in the ^{1}H NMR spectrum (mutually coupled doublets at δ 7.67 and 6.99 ppm, J = 8.3 Hz). In the purified sample, the *t*-$BuMe_2Si$ ^{1}H NMR absorptions were missing and so was the signal corresponding to the methine hydrogen next to OTBS in the starting **8**. This evidence suggested that elimination of the oxygen substituent from the initial cycloadduct had taken place to generate a nonaromatic trienone (not shown) that had tautomerized to give the phenol **26**. When fractions containing **26** were exposed to air or to DDQ, an intense red color developed over time. Starting with the purified sample of **26**, a DDQ experiment conducted in the presence of air afforded a ca. 2:3 ratio of the yellow quinone **10** and the red product **29**. In another experiment, treatment of **26** with DDQ in the absence of air and using deoxygenated solvents afforded **29** with only traces of **10**. Thus, atmospheric oxygen is implicated in the conversion from **26** to **10** while either oxidant (DDQ or atmospheric oxygen) leads to **29**. The NMR spectra of **29** could not be fully interpreted, and crystallization was problematic due to the marginal crystal size of this sparingly soluble substance. However, a small amount of material was obtained that was suitable for X-ray

(13) A related purple quinone containing a donor amine nitrogen β to quinone carbonyl has been described; the corresponding indoloquinone is yellow: Shaw, K. J.; Luly, J. R.; Rapoport, H. *J. Org. Chem.* **1985**, *50*, 4515.

Scheme 4



diffraction. The resulting structure **29** is consistent with oxidative dimerization of **26** according to one of the pathways reported for 7-hydroxyindole[14a] and for a 6,7-dihydroxy analog.[14b] Together with ^{1}H NMR data, this evidence is taken as confirmation of the structure assigned to **26**.

Despite much effort, the $PhSiH_3$/CsF activation method gave no more than 30% recovery of the yellow quinone **10**. These reactions were difficult to reproduce, and the yield of the desired quinone was lower than that (41%) obtained earlier in the preparation of the related quinone **1**.[1] Attention was therefore turned to the alternative activation method using cyanide anion as the nucleophile.[1,2f,g,15] Initially, this also proved to be disappointing. Thus, treatment of **22** with Me_3SiCN/CsF according to the method originally worked out for the direct synthesis of pyrroles[2f] gave a mixture of products. Oxidative workup with DDQ afforded **10** in 20−25% yield and with poor mass recovery. Essentially identical results were obtained using the oxazolium salt activation conditions reported by Hassner and Fischer (NaCN in acetonitrile).[15] While these procedures were no better than the $PhSiH_3$/CsF method, they did provide an important insight. Exposure of the crude cycloaddition products to air did not produce the purple quinones **28a,b** or the red dimer **29**, nor could we detect the phenols **25a,b** or **26** in these experiments.

As shown in Scheme 4, cyanide ion converts the oxazolium salt **22** into an initial adduct **32** via the oxazoline **30** and the ylide **31**. On the basis of prior studies, the 2-cyanopyrroline **32** should undergo spontaneous aromatization to a pyrrole **24**. Evidently, this intermediate is not on the pathway to **26** or to the purple quinones **28a,b**. Products of imine CN cleavage at the stage of dipole **31** were also not found. On the other hand, the mass recovery was still low in spite of the apparent simplification in reaction pathways compared to the $PhSiH_3$ experiments. These results convinced us that the number of competing pathways after cycloaddition was not the reason for low material recovery and that azomethine ylide generation and trapping is the problem step.

Much of our previous optimization work had been predicated on the assumption that it is important to keep the azomethine ylide concentration at a minimum. Dimerization of azomethine ylides is known,[16] and this could easily lead to highly polar products that might account for the missing material. Both the $PhSiH_3$/CsF and TMSCN/CsF procedures probably generate the dipole under high dilution conditions because the activating agent (CsF) is only slightly soluble in the acetonitrile medium. The heterogeneous conditions appeared to be well-suited for minimizing ylide concentration, and they had been shown to work well with relatively simple substrates. On the other hand, no direct evidence for ylide dimerization had been obtained, and other potential complications had to be considered. If ylide self-condensation is not the problem, then an alternative source of polar side products could be the 2 + 3 cycloaddition of the azomethine ylide with the oxazolium ion acting as a dipolarophile (for example, **31** + **22**). We could find no direct oxazolium ion precedent for this possibility, but it suggested a very different approach to optimization that was easily tested. If it is necessary to minimize the concentration of oxazolium ion, then a high concentration of cyanide ion might be sufficient to force the salt **22** to the oxazoline **30** and to the cycloadduct **32**. Depending on the relative rates and potential reversibility of several steps (nucleophilic addition from **22** to **30**; electrocyclic ring opening from **30** to **31**; cycloaddition from **31** to **32**), it might be possible to minimize the risk of side reactions involving **22** simply by using a more soluble cyanide source.

A promising reagent was found in the crystalline, organic-soluble benzyltrimethylammonium cyanide ($BnMe_3NCN$).[17] From the first experiments, it was clear that this salt induced qualitatively much faster reactions starting from the usual oxazolium precursor **22**, suggesting that the conversion of **22** to **30** had been rate-limiting under the heterogeneous conditions with TMSCN/CsF or NaCN. Best results were obtained using 2.2 equiv of this reagent in acetonitrile or dichloromethane. To further minimize the concentration of oxazolium salt, **22** was added dropwise to the cyanide solution. This instantly produced a purple color, but the color faded rapidly and is probably due to the transient appearance of the ylide **31** (X= CN). Oxidative workup with DDQ afforded a single quinone product **10** in a much improved yield after chromatographic purification, 63% overall from the oxazole **12**. The reaction could be performed at temperatures as low as −22 °C, but there was no yield advantage over treatment at 0 °C to room temperature in acetonitrile or dichloromethane, 1−2 h total reaction time. By comparison, typical Me_3SiCN/CsF reactions were very slow at room temperature (ca. 15% conversion after 18

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(15) Hassner, A.; Fischer, B. *J. Org. Chem.* **1992**, *57*, 3070.

(16) Huisgen, R.; Scheer, G.; Huber, H. *Tetrahedron Lett.* **1966**, *7*, 397. Vedejs, E.; Dax, S.; Martinez, G. R.; McClure, C. K. *J. Org. Chem.* **1987**, *52*, 3470.

(17) (a) Sugimoto, N.; Fujita, T.; Noboru, S.; Ayada, A. *Chem. Pharm. Bull.* **1962**, *10*, 427.

h), and prolonged heating was necessary to obtain modest (30−40%) yields of the cycloadducts.

A welcome benefit of the $BnMe_3NCN$ activation method was encountered upon examining the intermediates of an experiment conducted at −25 to −20 °C without DDQ treatment. Chromatographic purification afforded three fractions enriched in colorless intermediates. Exposure to air produced the yellow quinone **10**, but it was possible to obtain meaningful NMR spectra of the precursors. Prior to chromatography, the products consisted largely of two isomeric substances by TLC assay. According to NMR spectroscopy, one of the isomers was the ketopyrrole **24** and the other was the corresponding hydroquinone tautomer **27** that had been encountered earlier (as a contaminant in fractions containing the phenol **26** from $PhSiH_3$ experiments). Thus, characteristic ^1H signals for **24** were present at δ 1.93, 5.6−5.62, and 6.68−6.7 ppm in a 3:1:1 ratio, indicating that the original alkene and allylic methine subunits were still intact. Evidence for **27** included a phenolic proton at δ 4.48 ppm, and indications that a plane of symmetry was present (simple *O*-ethyl quartet; equivalent CH_3Si groups). In the course of chromatographic purification, **24** and **27** were partially transformed into the third substance containing an additional phenolic signal at δ 10.83 ppm, tentatively assigned as the hydroquinone **33**. This substance was especially sensitive to oxidation, and it was obtained in fractions that also contained the yellow quinone **10**. Exposure of **33** to air resulted in rapid conversion to **10**, while **24** and **27** were oxidized more slowly. No trace of the red product **29**, the purple quinones **28a,b**, or their precursors **26** or **25a,b** was found in these experiments using the soluble $BnMe_3NCN$ as the activating agent. The material balance was comparable to the best that we have seen in any previous example involving nucleophilic activation of oxazolium salts.

Conclusion

Efficient ylide generation and intramolecular cycloaddition (**31** to **32** to **24**) is demonstrated under conditions where the concentration of the oxazolium salt **22** is kept to a minimum. This is easy to do using the soluble $BnMe_3NCN$ as a nucleophilic cyanide source. Variable substrate-dependent yields as well as material recovery and reproducibility problems in the other activation methods ($PhSiH_3$/CsF; TMSCN/CsF; NaCN) are attributed partly to the heterogeneous conditions and partly to subtle differences in the relative rates of the competing reactions involving the azomethine ylide. Reductive activation of the oxazolium salt via **23** encounters multiple decomposition pathways because there is no easy path from **23** to **24**, but these complications are not the main reason for low yields.

The major complicating factor in the oxazolium route to azomethine ylides appears to involve the reaction between the oxazolium salt and the azomethine ylide (**22** + **31**). No specific products of this hypothetical process have been identified, but the use of $BnMe_3NCN$ and the resulting high concentration of nucleophilic cyanide improves the yield and simplifies the product mixture, presumably by minimizing the concentration of **22**. Applications of this newly optimized methodology to the synthesis of more complex indoloquinones are under investigation. It is too early to comment on this work in detail, but we have obtained good yields of indoloquinones starting with analogous substrates that lack the *Z*-double bond subunit present in **8**.[11] The geometrical constraint imposed by the (*Z*)-alkene appears not to be important for the azomethine ylide cycloaddition. Furthermore, aromatization of the 6-membered ring is no problem once the crucial intermediate **24** is produced. Rapid conversion from the dihydropyrrole **32** to the pyrrole stage (**24**) is the key to efficient formation of the desired indoloquinone **10** according to path 1, Scheme 3. Once this stage is reached, the other aromatization steps occur smoothly in the presence of DDQ.

Experimental Section

General Methods. All reactions were carried out under nitrogen. Solvents were dried as follows: diethyl ether and tetrahydrofuran were distilled from sodium/benzophenone; dichloromethane was distilled from P_2O_5; acetonitrile was distilled first from P_2O_5 followed by distillation from K_2CO_3 and was stored over 3 Å sieves; dimethylformamide was distilled from $MgSO_4$ and stored over 4 Å sieves; triethylamine was distilled from CaH_2 and stored over KOH; pyridine was distilled from KOH and stored over 4 Å sieves; DMSO was distilled from CaH_2 and stored over 3 Å sieves.

Methyl (*Z*)-3-(2′-Phenyloxazol-5′-yl)-(*Z*)-2-butenoate 16 by the Still−Gennari Method. To a suspension of bis(2,2,2-trifluoroethyl) [(methoxycarbonyl)methyl]phosphonate[8] (2.97 g, 9.33 mmol) and 18-crown-6 (10.3 g, 38.9 mmol, Aldrich, recrystallized from dry acetonitrile) in 40 mL of THF was added KHMDS (9.92 mL, 0.94 M in THF). The mixture was stirred at room temperature for 0.5 h and then cooled to −40 °C. To this mixture was added 2-phenyl-5-acetyloxazole (**14**)[9] in 5 mL of THF cooled to −40 °C via cannula. The mixture was stirred for 7 h at −40 °C followed by 8 h at −20 °C. The solution was then allowed to warm to 0 °C over a 4 h period and was partitioned between ether (50 mL) and H_2O (50 mL). The organic layer was washed with H_2O (50 mL) and brine (50 mL), dried ($MgSO_4$), and filtered. After removal of solvent (aspirator), the residue (2.99 g) was purified by flash column chromatography on silica gel (10 × 4 cm); 1:5.7 EtOAc/hexane eluent; fraction volume of 5 mL after an initial fraction of 125 mL. Fractions 6−18 contained 2.11 g of white solid. The material was crystallized from hexanes to afford 1.86 g (92%) methyl 3-(2′-phenyl oxazol-5-yl)-2-butenoate **16** as a 6.1:1, *Z*:*E* mixture of isomers that was used in subsequent transformations. For analytical purposes, 190 mg of this material was repurified by flash chromatography on silica gel (15 × 4 cm), 1:9 EtOAc/hexane eluent, to yield 124 mg of **16** as a solid. Pure material was obtained by crystallization from hexane: mp 69−70 °C; white needles; analytical TLC on silica gel, 1:5.6 EtOAc/hexane, $Rf = 0.33$; molecular ion calcd for $C_{14}H_{13}NO_3$ 243.089 52 found m/e 243.0895, error = 0 ppm; base peak = 140 amu; IR (CCl_4, cm^{-1}) 1725, C=O; 200 MHz NMR ($CDCl_3$, ppm) δ 8.14−8.04 (3H, m) 7.50−7.46 (3H, m) 5.87 (1H, q, $J = 1.4$ Hz) 3.77 (3H, s) 2.32 (3H, d, $J = 1.4$ Hz).

The *E*-isomer of **16** was prepared by a conventional Horner−Emmons synthesis from $(CH_3O)_2POCH_2CO_2CH_3$ by the same procedure as given above. This reaction produced a 1:14 *Z*:*E* ratio according to NMR assay, 84% yield. Methyl (*E*)-3-(2′-phenyloxazol-5′-yl)-(*Z*)-2-butenoate: analytical TLC on silica gel, 1:5.6 EtOAc/hexane, $Rf = 0.29$. Pure material was obtained by crystallization from hexane: mp 105.5−106.5 °C; white needles; molecular ion calcd for $C_{14}H_{13}NO_3$ 243.089 52, found *m*/*e* 243.0903, error = 3 ppm; base peak = 140 amu; IR (CCl_4, cm^{-1}) 1718, C=O; 200 MHz NMR ($CDCl_3$, ppm) δ 8.11−8.06 (2H, m) 7.50−7.40 (4H, m) 6.46 (1H, q, $J = 1.3$ Hz) 3.79 (3H, s) 2.50 (3 H, d, $J = 1.3$ Hz).

(*Z*)-3-(2′-Phenyloxazole-5′-yl)-2-butenol (18). The 6.1:1 *Z*:*E* mixture of esters **16** (1.925 g, 7.913 mmol) was dissolved in THF and cooled to −78 °C. Dibal (19.78 mL, 1 M in hexane, Aldrich) was added, and the mixture was stirred at −78 °C for 30 min. The cooling bath was removed and the solution diluted with 20 mL of Et_2O. A spatula tip of Rochelle's salt was added followed by the addition of a saturated solution of

Rochelle's salt. The aqueous layer was extracted with Et_2O (40 mL). The combined organic layer was dried ($MgSO_4$) and filtered. After removal of solvent, the residue (1.71 g) of yellow oil was purified by flash chromatography on silica gel (5 × 5 cm) 1:1.5 EtOAc/hexane eluent, fractions of 5 mL after an initial fraction of 100 mL. Fractions 2−5 contained 163 mg of recovered ester **16**. Fractions 14−28 contained 1.47 g (6.82 mmol, 86%) of 3-(2′-phenyloxazol-5-yl)but-2-enol **(18)** (6.1:1, *Z*:*E*), sufficiently pure for the next step. For analytical purposes, 64 mg of the product was repurified by preparative layer chromatography on silica gel (20 × 20 × 0.1 cm), 1:4 THF/hexane eluent; to afford 42 mg of the Z isomer as the leading zone. (*Z*)-3-(2′-phenyloxazol-5′-yl)but-2-enol **(18)**: analytical TLC on silica gel, 1:4 THF/hexane, $Rf = 0.13$; molecular ion calcd for $C_{13}H_{13}NO_2$ 215.094 64, found *m*/*e* 215.0945, error = 1 ppm; base peak = 172 amu; IR (CCl_4, cm^{-1}) 3347, OH; 300 MHz NMR ($CDCl_3$, ppm) δ 8.04−8.00 (2H, m) 7.49−7.44 (3H, m) 7.10 (1H, s) 5.76−5.72 (1H, m) 4.65−4.61 (2H, m) 2.10−2.09 (3H, m) 1.91 (1H, t, $J = 5.8$ Hz). ^{13}C NMR (75.4 MHz, $CDCl_3$, ppm) δ 161.2, 150.9, 130.5, 129.6, 128.8, 127.0, 126.5, 126.2, 122.6, 60.3, 20.6.

(*Z*)-3-(2′-Phenyloxazol-5′-yl)but-2-enal (20). To a mixture of butenols **18** (6.1:1, *Z*:*E*; 1.41 g, 6.54 mmol) in 20 mL of CH_2Cl_2 was added 3.72 g of 4 Å powdered molecular sieves and *N*-methylmorpholine *N*-oxide (1.15 g, 9.81 mmol, Aldrich). The mixture was cooled to 0 °C, and tetrapropylammonium perruthenate[12] (TPAP, 103 mg, 0.327 mmol, Aldrich) was added in portions. TLC analysis after 2 h showed that starting material was still present. An additional portion of TPAP (20 mg, 0.0634 mmol) was added, and the reaction was stirred for an additional 30 min. The solution was filtered through a 2 in. plug of celite and a 0.5 in. layer of silica gel with CH_2Cl_2. After removal of solvent (aspirator), the residue (1.37 g) was purified by flash chromatography on silica gel (7.5 × 5 cm), 1:2:7 EtOAc/dichloromethane/hexane eluent, fractions of 5 mL after an initial fraction of 50 mL. Fractions 22−35 contained 1.03 g (73%) of an 8:1 *Z*:*E* mixture of aldehyde **20**. Fractions 36−42 contained an additional 47 mg of the *E* aldehyde. A 27 mg portion of material was repurified by preparative layer chromatography on silica gel (20 × 20 × 0.1 cm), 1:4 THF/hexane eluent to yield 22 mg of *Z* aldehyde **20**: analytical TLC on silica gel, 1:4 THF/hexane, $Rf = 0.32$. Pure material was obtained by crystallization from hexane: mp 114.5−115.5 °C; white needles; molecular ion calcd for $C_{13}H_{11}NO_2$ 213.078 98, found *m*/*e* 213.0767, error = 10 ppm; base peak = 110 amu; IR (CCl_4, cm^{-1}) 1670, C=O; 300 MHz NMR ($CDCl_3$, ppm) δ 10.52 (1H, d, $J = 8.3$ Hz) 8.06−8.02 (2H, m) 7.51−7.45 (4H, m) 5.97 (1H, dd, $J = 8.3$, 1.1 Hz) 2.29 (3H, d, $J = 1.1$ Hz); ^{13}C NMR (75.4 MHz, $CDCl_3$, ppm) δ 192.2, 163.9, 149.6, 139.6, 131.9, 131.4, 129.0, 128.0, 126.9, 126.3, 21.6.

Ethyl (*Z*)-4-Hydroxy-6-(2′-phenyloxazol-5′-yl)hept-5-en-3-ynoate (21). To $CeCl_3$ (2.89 g, 11.7 mmol, Aldrich, dried 4 h at 135 °C/0.5 torr) was added 60 mL of THF, and the mixture was stirred of 24 h. In a separate flask, HMDS (1.98 mL, 9.38 mmol, Aldrich, distilled) was added to 45 mL of THF. The mixture was cooled to −78 °C. *n*-BuLi (5.90 mL, 1.63 M in hexane, Aldrich) was added, and the solution was stirred for 45 min and added via cannula (5 min) to the $CeCl_3$ solution to which ethyl propiolate (0.95 mL, 9.38 mmol, Lancaster Synthesis, distilled) had been added. The resulting deep rust-colored solution was stirred at −78 °C for 1.5 h. In a separate flask, the aldehyde **20** (1.00 g, 4.69 mmol, 8:1 *Z*:*E*, azeotropically dried with 2 × 20 mL portions of benzene) was dissolved in 5 mL of THF. The solution was cooled to −78 °C and added dropwise via cannula to the $CeCl_3$ solution. After 2 h, the cooling bath was removed, and saturated NH_4Cl (15 mL) was added. The solution was extracted with Et_2O (3 × 40 mL, with additions of brine and hexane to break emulsions). The combined organic layer was dried ($MgSO_4$) and concentrated to give 1.63 g of yellow oil. The residue was purified by flash column chromatography on silica gel (15 × 4 cm) 1:2.3 EtOAc/hexane eluent, fractions of 5 mL after an initial fraction of 150 mL. Fractions 1−4 contained 39 mg of the trimethylsilyl-protected alkynyl alcohol. Fractions 7−12 contained 25 mg of a mixture of compounds containing unreacted starting material, oxazole alcohol **18**, and unidentified products. Fractions 15−30 contained 1.29 g of the *Z* enynol **21** contaminated by another substance, tentatively believed to result from conjugate addition of propiolate to **21** (10:1 by 1H NMR, 88% combined yield). This material was sufficiently pure for the next step. An analytical sample was obtained from a 38 mg of the sample by preparative layer chromatography on silica gel (20 × 20 × 0.1 cm), 1:4 THF/hexane eluent, to yield 32 mg of pure Z enynol **21**: analytical TLC on silica gel, 1:4 THF/hexane, $Rf = 0.15$; molecular ion calcd for $C_{18}H_{17}NO_4$: 311.115 72, found *m*/*e* 311.1143, error = 5 ppm; base peak = 105 amu; IR (CCl_4, cm^{-1}) 1718, C=O; 300 MHz NMR ($CDCl_3$, ppm) δ 8.04−8.01 (2H, m) 7.47−7.43 (3H, m) 7.22 (1H, s) 5.74 (1H, d, $J = 8.2$ Hz) 5.56 (1H, dq, $J = 8.2$, 1.2 Hz) 4.20 (2H, q, $J = 7.0$ Hz) 3.0−2.6 (1H, br) 2.09 (3H, d, $J = 1.2$ Hz) 1.26 (3H, t, $J = 7.0$ Hz); ^{13}C NMR (75.4 MHz, $CDCl_3$, ppm) δ 161.9, 153.2, 149.7, 130.8, 128.9, 128.0, 126.8, 126.5, 126.0, 125.6, 86.0, 76.4, 62.2, 59.3, 20.7, 14.0.

Ethyl (*Z*)-4-(*tert*-Butyldimethylsiloxy)-6-(2′-phenyloxazol-5′-yl)hept-5-en-3-ynoate (8). To 260 mg (0. 830 mmol) of the contaminated alcohol **21** from above in 4 mL of CH_2Cl_2 was added *tert*-butyldimethylchlorosilane (163 mg, 1.09 mmol, Aldrich) followed immediately by imidazole (73 mg, 1.09 mmol, Aldrich). Within 1 min, the reaction had turned cloudy in appearance. After 12 h, the mixture was filtered through a 1 in. plug of Celite. After removal of solvent (aspirator), the residue was purified by flash chromatography on silica gel (12 × 2 cm), 1:2:17 EtOAc/dichloromethane/hexane eluent, fractions of 5 mL after an initial fraction of 75 mL. Fractions 5−25 contained 241 mg (68%) of the (*Z*)-*tert*-butyldimethylsilyl-protected alkynyl alcohol **8**. The contaminants (tentatively, derived from the conjugate addition product from the propiolate step and from the *E*-isomer of **8**) eluted in later fractions, but were not obtained pure . Analytical data for **8**: TLC on silica gel, 1:9 EtOAc/hexane, $Rf = 0.17$; molecular ion calcd for $C_{24}H_{31}NO_4Si$ 425.202 21, found *m*/*e* 425.2016, error = 1 ppm; base peak = 105 amu; IR(CCl_4, cm^{-1}) 1709, C=O; 300 MHz NMR (CD_2Cl_2, ppm) δ 8.09−8.05 (2H, m) 7.51−7.48 (3H, m) 7.22 (1H, s) 5.80 (1H, d, $J = 7.9$ Hz) 5.60 (1H, dq, $J = 7.9$, 1.1 Hz) 4.18 (2H, q, $J = 7.2$ Hz) 2.13−2.12 (3H, m) 1.25 (3H, t, $J = 7.2$ Hz) 0.91 (9H, s) 0.14 (3H, s) 0.12 (3H, s); ^{13}C NMR (75.4 MHz, CD_2Cl_2, ppm) δ 162.1, 153.7, 150.4, 131.0, 129.3, 128.3, 128.2, 127.6, 126.8, 123.9, 86.8, 76.2, 62.4, 60.9, 25.8, 20.8, 18/5, 14.2, −4.5, −4.6.

Benzyltrimethylammonium Cyanide.[17] A small variation of the literature method was used as follows. Benzyltrimethylammonium methoxide (17.9 g, 40 wt %, Aldrich) was diluted with 25 mL of methanol. Gaseous HCl was added to the solution at 0 °C. After 30 min the solution was concentrated and the resulting residue crystallized twice from acetonitrile. The resulting white plates were collected by removing the solvent by cannula and dried in the presence of P_2O_5 under vacuum for 3 days to afford 5.33 g (73%) of the chloride salt as a hygroscopic white solid. Benzyltrimethylammonium chloride (2.75 g, 14.8 mmol) was dissolved in 25 mL of methanol. The solution was added to a solution of NaCN in 80 mL of methanol via cannula and rinsed with an additional 8 mL portion of methanol. The resulting mixture turned cloudy rapidly. After 1.5 h, the solution was filtered through a 10 cm plug of Celite and concentrated. The residue was crystallized from acetonitrile and the solvent removed by cannula. The resulting white plates were dried with a N_2 stream and then in a vacuum desiccator over P_2O_5 for 3 d to afford 1.71 g (66%) of benzyltrimethylammonium cyanide as a hygroscopic white solid.

Yellow Quinone 10: 1-Methyl-2-phenyl-3-carbethoxy-6-methyl-4,7-indoloquinone. Oxazole **8** (290 mg, 0.680 mmol) was dried by azeotropic distillation with benzene (1 × 10 mL), and 150 mg of powdered 3Å molecular sieves was added followed by 7 mL of acetonitrile. The mixture was stirred for 10 min followed by the addition of methyl triflate (96 μL, 0.849 mmol, Aldrich) and stirring for 10 h at room temperature. TLC analysis indicated a small amount of unreacted oxazole **8** present. An additional portion of methyl triflate (20 μL, 0.177 mmol) was added and the reaction stirred 24 h more at room temperature. Stirring was discontinued, and the solution was transferred by cannula away from the

molecular sieves. The sieve dust was washed with acetonitrile (2 × 7 mL). The combined acetonitrile portions were concentrated with a N_2 flow. The resulting solid was washed with hexane (3 × 10 mL) under N_2, with the hexane washes being removed by cannula away from the salt. The resulting white solid was dried with a N_2 flow. A standard solution of oxazolium salt was prepared by dissolving the salt in 20.0 mL of acetonitrile (0.680 mmol/20.0 mL). A portion of the resulting stock solution (5 mL, 0.0846 mmol) was removed and concentrated with N_2 flow to a volume of 1 mL. In a separate flask, benzyltrimethylammonium cyanide (32.8 mg, 0.186 mmol) from above was stirred for several minutes with 8 mL of acetonitrile. To the solution of benzyltrimethylammonium cyanide at 0 °C was added the 1 mL solution of oxazolium salt via cannula, washed in with an additional 0.5 mL portion of acetonitrile. The resulting mixture instantly turned purple and then lightened to yellow. The solution was stirred for 2 h at room temperature and was then partitioned between hexane (20 mL)/pH 5.8 buffer (20 mL, KH_2PO_4/K_2HPO_4). The aqueous layer was extracted with hexane (3 × 20 mL). The combined organic layer was dried ($MgSO_4$) and filtered. After removal of solvent (aspirator), the resulting rust-colored solid was dissolved in 2 mL of benzene, and DDQ (38 mg, 0.169 mmol, Sigma, recrystallized from EtOH) was added. After 8 h at rt, the solution was partitioned between Et_2O (10 mL)/H_2O (10 mL), and NaOH (1 mL, 1 N) was added. The organic layer was washed with brine (10 mL), dried ($MgSO_4$), and filtered. After removal of solvent (aspirator), the residue was purified by flash chromatography on silica gel (16 × 2 cm), 1:4 EtOAc/hexane eluent (fractions 6−15, fraction volume of 5 mL after an initial fraction of 75 mL; the initial fraction from the flash column contained 6 mg of material consisting largely of impure **27**. Fractions 6−15 were concentrated to afford 17 mg of yellow quinone **10** (63% yield): analytical TLC on silica gel, 1:4 EtOAc/hexane, $Rf = 0.15$. Pure material was obtained by crystallization from hexane: mp 115.2−116.2 °C; fine yellow needles; molecular ion calcd for $C_{19}H_{17}NO_4$ 323.11572, found m/e = 323.1159, error = 1 ppm; base peak = 279 amu; IR (CCl_4, cm^{-1}) 1651, C═O; 1720, C=O; 300 MHz NMR ($CDCl_3$, ppm) δ 7.47−7.44 (3H, m) 7.35−7.31 (2H, m) 6.47 (1H, q, J = 1.6 Hz) 4.15 (2H, q, J = 7.0 Hz) 3.78 (3H, s) 2.08 (3H, d, J = 1.6 Hz) 1.07 (3H, t, J = 7.0 Hz). ^{13}C NMR (5.4 MHz, CD_2Cl_2, ppm) δ 182.1, 179.2, 164.1, 145.6, 142.9, 134.4, 130.5, 129.9, 129.3, 128.8, 128.7, 124.0, 114.6, 61.2, 34.4, 15.7, 13.9; UV (MeOH) λ_{max} 260 (ϵ = 23 863), 330 (ϵ = 2886), 420 (ϵ = 1656).

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Supporting Information Available: Preparation and characterization of **9**, **11**, **14**, **28a,b**, and **29**; preparation of **16** and **17** by Stille coupling; partial characterization of unstable intermediates on the pathways to **10**, **28a,b**, and **29**; X-ray data tables for **29**; NMR spectra of products and key intermediates (34 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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