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Published on Web 09/02/2006

# Studies on the Mechanism of Action of Prekinamycin, a Member of the Diazoparaquinone Family of Natural Products: Evidence for Both $sp^2$ Radical and Orthoquinonemethide Intermediates

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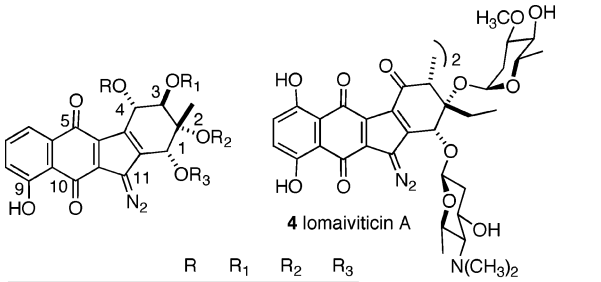
***Abstract:*** The putative reductive activation chemistry of the diazoparaquinone antibiotics was modeled with $Bu_3Sn-H$ and prekinamycin dimethyl ether along with prekinamycin itself. Reaction in various combinations of aromatic solvents, with and without the nucleophile benzylmercaptan present, led to isolation of both radical-trapping arene adducts and nucleophilic capture benzyl thioether products. On the basis of these product distribution studies, the intermediacies of, first, a cyclopentenyl radical and, next, an orthoquinonemethide electrophile are postulated.

## Introduction

The diazoparaquinone family of antibiotics, exemplified by its founding members kinamycin A−D (**1a**−**1d**),[1] recently has been enlarged by the discovery of the potent anticancer marine isolates lomaiviticins A (**4**) and B, Figure 1.[2] In addition to these species, at least 16 other kinamycins, all varying as per the alcohol acylation pattern and/or D-ring oxidation level, and the aromatic D-ring biosynthetic precursor prekinamycin (**5**) define this group of natural products.[3] The rarity of the diazo function in naturally occurring compounds is emphasized by the fact that only five other entries have been reported to date, as shown in Figure 2.[4] Whereas none of these species possesses the diazoparaquinone function characteristic of the kinamycins and lomaiviticins, they do display antitumor and/or antibiotic activity, presumably as a consequence of a reactive $N_2$ unit.[4b−f] However, it is the profound cytotoxic activity of the diazoparaquinone-containing compounds that has captivated the imagination of several groups, and preliminary mechanism-of-action hypotheses have been generated, Scheme 1.




| | | R | $R_1$ | $R_2$ | $R_3$ |
|---|---|---|---|---|---|
| **1a** | kinamycin A | H | Ac | Ac | Ac |
| **1b** | kinamycin B | H | H | Ac | H |
| **1c** | kinamycin C | Ac | Ac | H | Ac |
| **1d** | kinamycin D | H | Ac | H | Ac |
| **1e** | kinamycin E | H | H | H | Ac |
| **1f** | kinamycin F | H | H | H | H |
| **1g** | kinamycin G | Ac | Ac | COiPr | Ac |
| **1h** | kinamycin H | Ac | Ac | H | COiPr |
| **1i** | kinamycin I | Ac | COiPr | H | COiPr |
| **1j** | kinamycin J | Ac | Ac | Ac | Ac |
| **2a** | FL-120A | H | Ac | COiPr | Ac |
| **2b** | FL-120C | H | Ac | H | COiPr |
| **2c** | FL-120C' | H | Ac | H | COEt |
| **2d** | FL-120D' | H | H | H | COiPr |
| **2e** | FL-120B | H | 2,3-oxirane | | Ac |
| **2f** | FL-120B' | H | 2,3-oxirane | | COiPr |
| **3** | ketoanhydro -kinamycin | H | 2,3-oxirane | | 1-C=O |

***Figure 1.*** Diazoparaquinone-containing natural products.

(1) (a) Ito, S.; Matsuya, T.; Omura, S.; Otani, M.; Nakagawa, A.; Takeshima, H.; Iwai, Y.; Ohtani, M.; Hata, T. *J. Antibiot.* **1970**, *23*, 315−316. (b) Hata, T.; Omura, S.; Iwai, Y.; Nakagawa, A.; Otani, M.; Ito, S.; Matsuya, T. *J. Antibiot.* **1971**, *24*, 353−359. (c) Omura, S.; Nakagawa, A.; Yamada, H.; Hata, T.; Furusaki, A.; Watanabe, T. *Chem. Pharm. Bull.* **1973**, *21*, 931−940.

(2) He, H.; Ding, W.-D.; Bernan, V. S.; Richardson, A. D.; Ireland, C. M.; Greenstein, M.; Ellestad, G. A.; Carter, G. T. *J. Am. Chem. Soc.* **2001**, *123*, 5362−5363.

(3) (a) Gould, S. J.; Chen, J.; Cone, M. C.; Gore, M. P.; Melville, C. R.; Tamayo, N. *J. Org. Chem.* **1996**, *61*, 5720−5721. (b) Gould, S. J. *Chem Rev.* **1997**, *97*, 2499−2509 and references therein. (c) Marco-Contelles, J.; Molina, M. T. *Curr. Org. Chem.* **2003**, *7*, 1433−1442.

(4) (a) Isoprekinamycin: Proteau, P. J.; Li, Y.; Chen, J.; Williamson, R. T.; Gould, S. J.; Laufer, R. S.; Dmitrienko, G. I. *J. Am. Chem. Soc.* **2000**, *122*, 8325−8326. (b) Lagunamycin: Imae, K.; Nihei, Y.; Oka, M.; Yamasaki, T.; Konishi, M.; Oki, T. *J. Antibiot.* **1993**, *46*, 1031−1033. (c) Azaserine: Fusari, S. A.; Haskell, T. H.; Frohardt, R. P.; Bartz, Q. R. *J. Am. Chem. Soc.* **1954**, *76*, 2881−2883. (d) 6-Diazo-5-oxo-L-norleucine: Dion, H. W.; Fusari, S. A.; Jakubowski, Z. L.; Zora, J. G.; Bartz, Q. R. *J. Am. Chem. Soc.* **1956**, *78*, 3075−3077. (e) SF2415A2 and congeners: Gomi, S.; Ohuchi, S.; Sasaki, T.; Itoh, J.; Sezaki, M. *J. Antibiot.* **1987**, *40*, 740−749. (f) Fukuda, D. S.; Mynderse, J. S.; Baker, P. J.; Berry, D. M.; Boeck, L. D.; Yao, R. C.; Mertz, F. P.; Nakatsukasa, W. M.; Mabe, J.; Ott, J.; Counter, F. T.; Ensminger, P. W.; Allen, N. E.; Alborn, W. E., Jr.; Hobbes, J. N., Jr. *J. Antibiot.* **1990**, *43*, 623−633.


**10.1021/ja0642616 CCC: $33.50** 

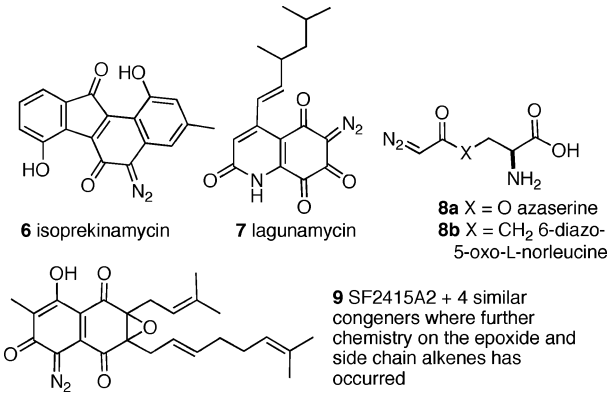
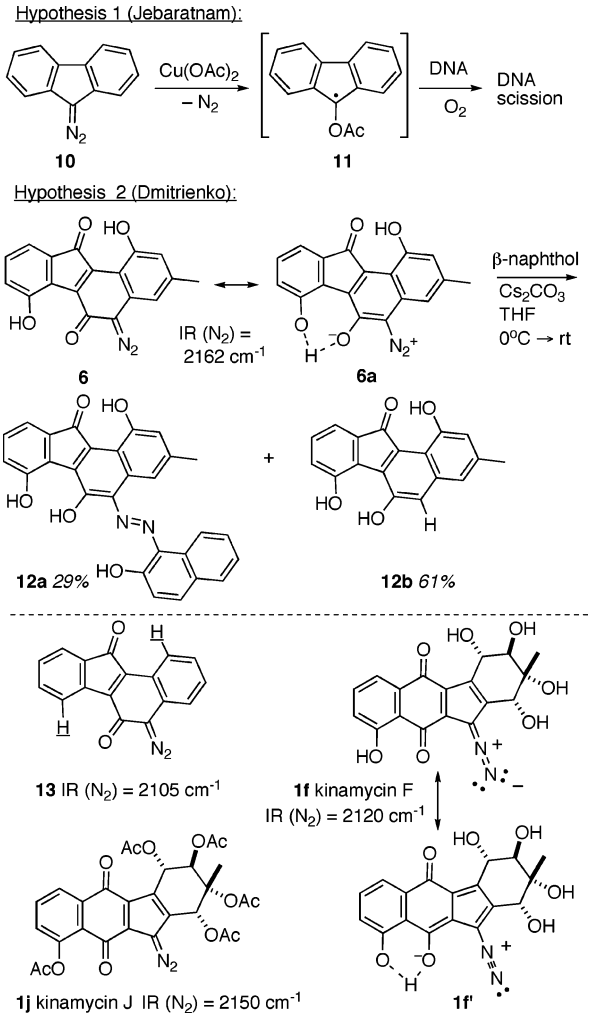



***Figure 2.*** Diazo-containing natural products lacking the paraquinone function.

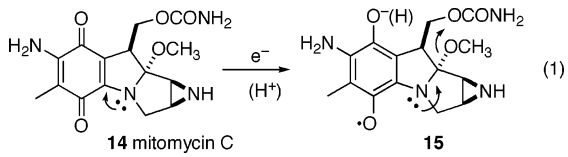
***Scheme 1.*** Previous Mechanistic Thinking on the Role of the Diazo Function in Reactions with Model Biological Targets




Jebaratnam and co-workers (Hypothesis 1) offered the first defined proposal based on the observation that the model compound diazofluorene (**10**) nicks plasmid DNA upon exposure to the oxidant $Cu(OAc)_2$.[5] They suggested that similar chemistry with the kinamycins and endogenous oxidants may lead to a reactive radical intermediate (cf. **11**) that could damage DNA via known oxygen-mediated pathways.[6] Later, Dmitrienko argued for an electrophilic intermediate on the basis of the facile alkylation of isoprekinamycin with $\beta$-naphthol (Hypothesis 2).[7] Central to this thesis is the observation that the deshydroxyl control **13** did not function similarly, a result which led to the proposal that internal hydrogen bonding is a key activator of **6** by virtue of rendering the $N_2$ function more diazonium-like and, hence, more electrophilic when compared with the diazo-like moiety of **13** (note the $N_2$ IR absorption for **6** vs that for **13**). Presumably, an extension of this proposition to the diazoparaquinones would lead to the expectation that kinamycin F (**1f**), for example, would react through the diazonium-like resonance form **1f′** with biologically relevant nucleophiles. However, one point of concern that may cloud this interpretation of diazoparaquinone reactivity emerges upon comparison of the $N_2$ stretching frequencies for the H-bond capable kinamycin F (**1f**) (2120 $cm^{-1}$) and the H-bond incapable derivative kinamycin J (**1j**) (2150 $cm^{-1}$).[1c] The fact that the H-bond incapable species has the higher (more diazonium-like) $N_2$ stretch frequency does not lend support to the Dmitrienko hypothesis, at least insofar as it applies to the diazoparaquinones.

A significant new clue regarding the biological mechanism of action of the diazoparaquinones might be found in He et al.'s lomaiviticin isolation/characterization studies, wherein the authors note that "An ongoing study showed that lomaiviticin A cleaved double-stranded DNA under reducing conditions".[2] The role that reductive activation might play in Jebaratnam's oxidative hypothesis or in Dmitrienko's electrophilic activation proposal remains unclear, especially since neither study included diazoparaquinone-bearing species. Thus, there may be room for consideration of alternative schemes through which the apparently reductively activated diazoparaquinone-containing natural products might elicit their striking cytotoxicity.

Much earlier work in the mitomycin field has led to formulation of the paradigm that a lone pair of electrons situated adjacent to a paraquinone function is sequestered by vinylogous resonance (e.g., **14**), but upon 1-electron reduction of the paraquinone, the lone pair is liberated and can participate in further chemistry, eq 1.[8]




(1)

Extending this line of reasoning to the diazoparaquinones leads to a similar proposition that entails formation of the 3-electron system **17a** by 1-electron reduction of **16**, Scheme 2. By reapportioning the 3-electron array as shown in the equivalent resonance form **17b**, a role for the diazo unit is revealed. Specifically, $\beta$-elimination of $N_2$ gas from the naphthalenolate moiety within **17c** can provide a new reactive intermediate, the $sp^2$ radical species **18**. The facility of this transform may in large measure depend on the tradeoff between the energetic penalty associated with the pyramidalization of C(11) required for alignment of the $\pi$ cloud with $\sigma^*_{C-N}$ and the energetic gain resulting from nitrogen gas expulsion. It is

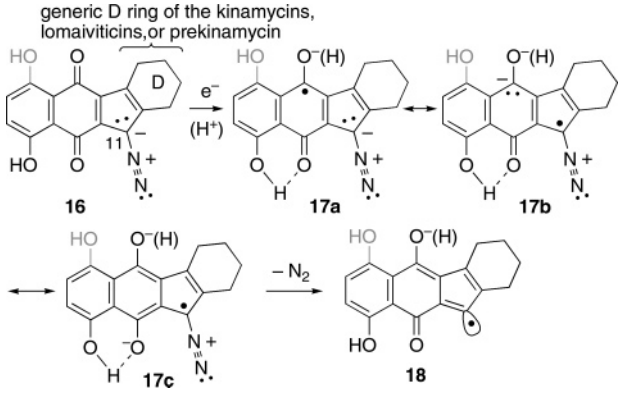
(5) Arya, D. P.; Jebaratnam, D. J. *J. Org. Chem.* **1995**, *60*, 3268−3269.

(6) (a) Stubbe, J.; Kozarich, J. W. *Chem. Rev.* **1987**, *87*, 1107−1136. (b) Murphy, J. A.; Griffiths, J. *Nat. Prod. Rep.* **1993**, 551−564. (c) Dussy, A.; Meggars, E.; Giese, B. *J. Am. Chem. Soc.* **1998**, *120*, 7399−7403.

(7) Laufer, R. S.; Dmitrienko, G. I. *J. Am. Chem. Soc.* **2002**, *124*, 1854−1855.

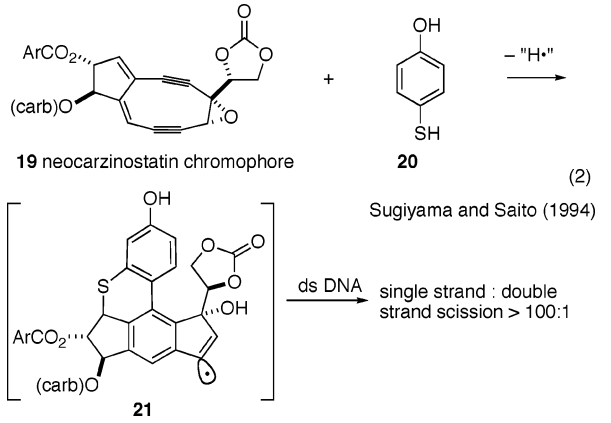
(8) (a) Danishefsky, S. J.; Schkeryantz, J. M. *Synlett* **1995**, 475−490. (b) Rajski, S. R.; Williams, R. M. *Chem. Rev.* **1998**, *98*, 2723−2795.

***Scheme 2.*** Proposal for the Generation of a C(11) $sp^2$ Radical from Diazoparaquinones via 1-Electron Reduction




not possible at this juncture to predict whether thermodynamics should trump kinetics for this process or vice versa, but if the former scenario pertains, then the net result is the transfer of the input electron into a carbon-bound radical at C(11). One significant consequence of this elimination reaction becomes apparent when considering the fate of the C(11) radical; it must, out of mechanistic necessity, switch its occupancy from a $\pi$ orbital to an $sp^2$ orbital. Thus, the diazoparaquinones may have evolved to incorporate a transduction mechanism that converts biologically accessible 1-electron (radical?) reductants into potentially much more reactive $sp^2$ carbon radicals.

The biological chemistry of DNA with $sp^2$ radicals in general,[6b] and cyclopentenyl $sp^2$ radicals in particular,[9] has been well documented, as exemplified in eq 2.[10] Given the dimeric structure of the lomaiviticins, the claim of double strand nicking may be rationalized by invoking two DNA-damaging events that each extend from the chemistry of a radical of the type **18** generated independently from each half.




In contrast to the neocarzinostatin chromophore chemistry **21** + DNA−H, diazoparaquinone/DNA chemistry has the potential to go beyond hydrogen abstraction/radical reactions (i.e., DNA• + $O_2$) in its capacity to inflict chemical damage on DNA. For example, rebound radical addition of DNA• with **22** might afford a covalent adduct **23**. An even more intriguing line of conjecture emerges upon consideration of the structural consequences of hydrogen abstraction by **18** to furnish the closed shell species **22**; a hydroxymethylacylfulvene subunit, which is the key electrophilic pharmacophore implicated in the potent cytotoxicity of the eponymous family of promising anticancer agents (cf. **26**),[11] is generated. By analogy with the chemistry of **26**, base alkylation by the electrophilic orthoquinonemethide **22**, as exemplified by the speculative depiction of a conjugate addition of guanosine N(7) with C(11),[8b] can provide an entirely independent and orthogonal avenue to introduce damage into DNA, **24** → **25**. N(7)-Alkylated guanosines are reported to undergo spontaneous depurination to furnish an abasic site.[12] The relative contributions (if any) of cyclopentenyl radical **18** and/or orthoquinonemethide **22** to the biological activity of the diazoparaquinones remain a matter of speculation, but it is possible that this rare diazoparaquinone chemical functionality has emerged through evolutionary pressure to act as an inducible (by 1-electron reduction) source of these two potentially lethal reactive intermediates. Interestingly, the isolation of the shunt metabolite seongomycin (**27**) from the fermentation broth of a prekinamycin-producing organism can be interpreted in terms of the transformation **16** → **22** (with an aromatic prekinamycin D-ring), and then trapping of **22** by *N*-acetyl cysteine and reoxidation of the derived hydroquinone.[13]

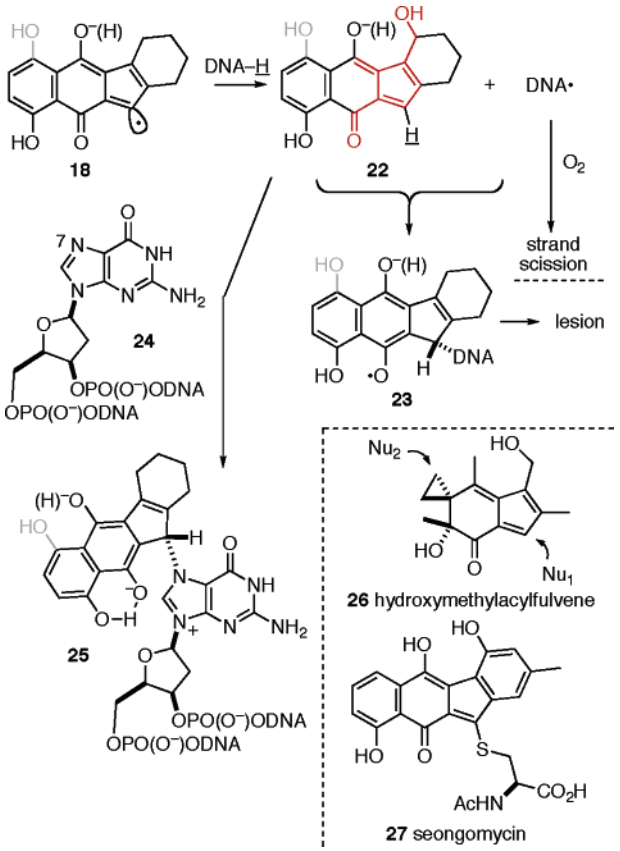
The exploration of these mechanistic hypotheses was undertaken using prekinamycin (**5**) and derived species with $Bu_3$-Sn−H as a model 1-electron reductant. These abiological conditions certainly limit the breadth of the conclusions that can be drawn, but they also arguably can serve to reveal the intrinsic chemistry of the diazoparaquinone function under reducing conditions regardless of the environment. Extrapolation from these studies to the biological chemistry of the lomaiviticins or kinamycins can be no more rigorous than argument-by-analogy, and a stronger connection will have to await the results of further experimentation in a relevant biological milieu. In the investigation to follow, evidence is presented that speaks to the core transforms of the mechanistic proposition offered in Schemes 2 and 3: formation of an $sp^2$ radical **18** from diazoparaquinones under 1-electron reductive conditions, and its subsequent conversion to a competent electrophile **22** by H-atom abstraction.

## Results and Discussion

Prekinamycin (**5**) was chosen as the starting point for these mechanistic studies, as it had the dual benefits of (1) embodying the key structural features of this family (diazoparaquinone, hydrogen-bond donors adjacent to the carbonyls) while at the same time (2) being readily accessible through synthesis.[14] The biological activity of prekinamycin apparently has not been reported, and so it is not possible to assess the validity of using these aromatic D-ring species as stand-ins for the oxidized D-ring kinamycins that do display potent cytotoxicity. In

(9) (a) Goldberg, I. H. *Acc. Chem. Res.* **1991**, *24*, 191−198. (b) Myers, A. G. *Tetrahedron Lett.* **1987**, *28*, 4493−4496.
(10) Sugiyama, H.; Fujiwara, T.; Saito, I. *Tetrahedron Lett.* **1994**, *35*, 8825−8828.
(11) (a) Woynarowski, J. M.; Napier, C.; Koester, S. K.; Chen, S.-F.; Troyer, D.; Chapman, W.; MacDonald, J. R. *Biochem. Pharmacol.* **1997**, *54*, 1181−1193. (b) Herzig, M. C. S.; Arnett, B.; MacDonald, J. R.; Woynarowski, J. M. *Biochem. Pharmacol.* **1999**, *58*, 217−225. (c) McMorris, T. C. *Bioorg. Med. Chem.* **1999**, *1*, 881−886.
(12) (a) Kushida, T.; Uesugi, M.; Sugiura, Y.; Kigoshi, H.; Tanaka, H.; Hirokawa, J.; Ojika, M.; Yamada, K. *J. Am. Chem. Soc.* **1994**, *116*, 479−486. (b) Hara, M.; Saitoh, Y.; Nakano, H. *Biochemistry* **1990**, *29*, 5676−5681. (c) Asai, A.; Saito, H.; Saitoh, Y. *Bioorg. Med. Chem.* **1997**, *5*, 723−729. (d) Hara, M.; Yoshida, M.; Nakano, H. *Biochemistry* **1990**, *29*, 10449−10455. (e) Sugiyama, H.; Furiwara, T.; Ura, A.; Tashiro, T.; Yamamoto, K.; Kawanishi, S.; Saito, I. *Chem. Res. Toxicol.* **1994**, *7*, 673−683.
(13) Carney, J. R.; Hong, S.-T.; Gould, S. J. *Tetrahedron Lett.* **1997**, *38*, 3139−3142.
(14) Hauser, F. M.; Zhou, M. *J. Org. Chem.* **1996**, *61*, 5722.

***Scheme 3.*** Speculative Pathways by Which Radical **18** Might Ultimately Lead to DNA Damage

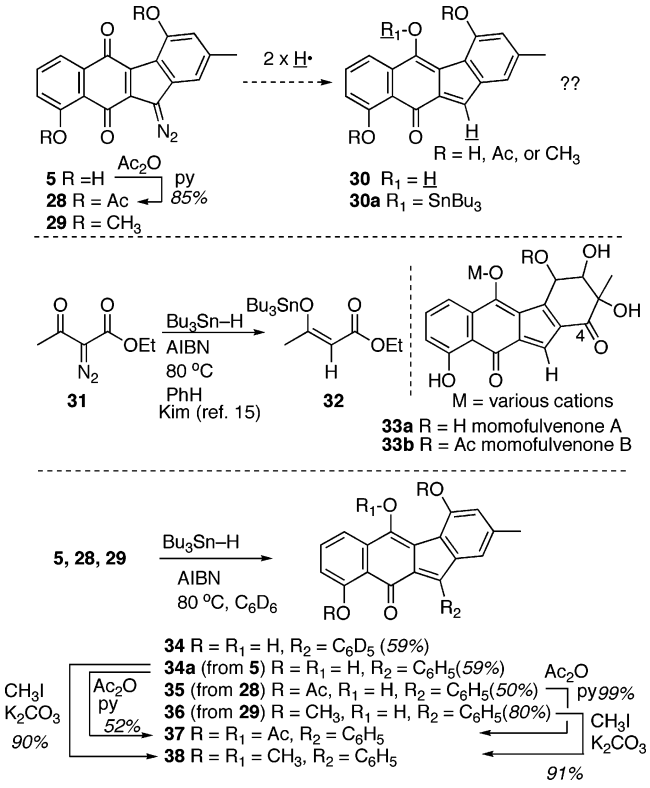



addition to the natural product itself, both the diacetate **28** and the dimethyl ether **29** were prepared in an attempt to both test the necessity of activation via hydrogen bonding to the carbonyl as per Dmitrienko's postulate, and to provide probe molecules whose solubility properties might make experimentation easier, Scheme 4. Both the dimethyl ether **29** and the diacetate **28** were prepared by Hauser as part of his prekinamycin synthesis work.[14] The initial experiments were designed to explore the simple question of whether the formal addition of $\underline{H}_2$ (as $Bu_3Sn-\underline{H}$, $\underline{H}^+$) would lead to an isolable orthoquinonemethide **30**. Cognizance of a report by Kim[15] that the diazoketone **31** reacted with the H•-equivalent reagent $Bu_3Sn-H$ to furnish the formal Sn−H addition product **32** stimulated thinking along similar lines with prekinamycin, **5** → **30a**. However, concerns about the stability/reactivity of a putative addition product **30a** could not be dismissed readily, especially in light of the disclosure that the related natural products, monofulvenones A (**33a**) and B (**33b**), decomposed within minutes upon addition of dilute acid.[16] Presumably, the protonated versions of **33a**/**33b** can express orthoquinonemethide reactivity to the detriment of isolation attempts. The question, then, is, will the aromatic D-ring of the desired kinamycin adduct **30a** mitigate its reactivity enough, compared with the potentially activating C(4) carbonyl of **33a**/**33b**, so that it could be isolated?

The answer, unfortunately, is no. Treatment of **5** with $Bu_3SnH$/AIBN in $C_6D_6$ at 80 °C did not lead to detection of any product, even as a minor component, that possessed the

(15) Kim, S.; Cho, J. R. *Bull. Korean Chem. Soc.* **1993**, *14*, 664−665.
(16) Volkmann, C.; Rössner, E.; Metzler, M.; Zähner, H.; Zeeck, A. *Liebigs Ann.* **1995**, 1169−1172.

***Scheme 4.*** Preliminary Experiments to Probe the Formal 1-Electron Reduction Chemistry of Prekinamycin and Derivatives



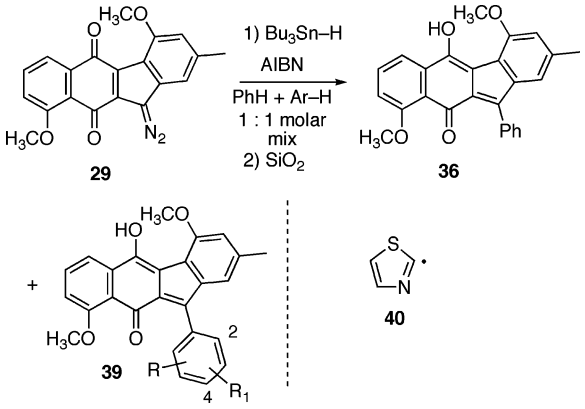

orthoquinonemethide unit of **30**/**30a**, Scheme 4. In fact, a single compound was formed in good yield, but initial examination of its $^1H$ NMR spectrum generated more puzzlement than illumination. All of the peaks of the A−B−C−D ring platform were identifiable and present, but the identity of the attachment at C(11) was not apparent. In what was to be the first of several surprises with the reductive chemistry of **5**, further spectroscopic analysis revealed the unequivocal presence of solvent deuteriobenzene attached to this reactive center, **34**. Given the rather modest reactivity of benzene, this result implied that the reductive conditions with **5** were generating some type of highly reactive intermediate, and at this juncture none of the obvious candidates—carbene, carbocation (or electrophilic orthoquinonemethide equivalent), or radical—could be ruled out. Control experiments with substrate **29** as indicated in Table 1 did provide some guidance in that they (a) demand the presence of all radical generating ingredients and (b) exclude the possibility that either a purely thermally or a photochemically generated species is involved.

The crude product mixtures were purified via $SiO_2$ chromatography to furnish pure **34a** from **5**, **35** from **28**, and **36** from **29**. Despite much effort with modified conditions of reaction, workup, or purification, no tin-bearing species (cf. **34a** with $R_1 = Bu_3Sn$; compare **32**) could be isolated. Attempts to prepare

***Table 1.*** Control Experiments with the Dimethyl Ether **29**

| entry | light | heat | $Bu_3Sn-H$ | AIBN | result |
|---|---|---|---|---|---|
| 1 | X | X | X | X | 80% **36** |
| 2 | | X | X | X | 79% **36** |
| 3 | X | | X | X | recovered **29** |
| 4 | X | X | | X | recovered **29** |
| 5 | X | X | X | | recovered **29** |

***Table 2.*** Relative Reactivity of Electron-Rich and Electron-Deficient Arene Solvents with **29** under Radical-Generating Conditions




| | ArH | | yield **36** + | | | **40** | |
|---|---|---|---|---|---|---|---|
| | R | $R_1$ | **39**(%)[a] | rel. rate[a,b] | *o*:*m*:*p* | rel rate[b,d] | *o*:*m*:*p* |
| *a* | $CH_3$ | H | 43 ± 3 | 2.2 ± 0.1 | 62:23:15 | 2.1 | 69:23:17 |
| *b* | Cl | H | 64 ± 6 | 1.5 ± 0.2 | 48:32:20 | 0.9 | 49:33:19 |
| *c* | CN | H | 67 ± 5 | 2.1 ± 0.3 | 43:25:32 | 2.0 | 56:18:26 |
| *d* | $OCH_3$ | H | 68 ± 11 | 3.1 ± 0.7 | 72:16:12 | 2.2 | 63:14:23 |
| *e* | $CH_3$ | $CH_3$ | 52 ± 11 | 4.0 ± 0.9 | 50:50:0[c] | | |
| *f* | $OCH_3$ | $OCH_3$ | 75 ± 10 | 4.2 ± 1.5 | 31:69:0[c] | | |
| *g* | CN | CN | 69 ± 7 | 6.1 ± 0.5[e] | 24:76:0[c] | | |

[a] Quintuple measurements with standard deviation. [b] Rate relative to benzene. [c] Ratio of 2,4-:2,6-:3,5- adducts. [d] Data from ref 20. [e] Extrapolated from the results of 1:9 and 1:13 ratios of 1,3-dicyanobenzene to benzene solvent due to solubility constraints.

a more stable version of **34a** ($R_1$ = $SnPh_3$ or $Si(TMS)_3$) with $Ph_3SnH$ or $TMS_3SiH$ did not provide any benefit in this regard. Both the diacetate **28** and the dimethyl ether **29** performed similarly under these reductive tin conditions, leading to the respective phenyl adducts in good yields. The higher yield of adduct **36** with the dimethyl ether **29** can be attributed to ease of chromatographic purification of the product compared to **34a** or **35**, both of which streaked on $SiO_2$. All of the subsequent chemistry was conducted with **29** for this reason. The ability to hydrogen-bond to the carbonyl (**5** vs **29**) apparently has no significant bearing of the facility of this chemistry.

Identifying the reactive intermediate, generated upon reduction of **29**, which participates in C−C bond formation with benzene, became the focus of the next series of experiments. A priori, a C(11) carbene seemed the least likely candidate given the type of products formed and the results of the control experiments; thus, distinguishing between the remaining two possibilities, a C(11) radical or a C(11) electrophile (ortho-quinonemethide ≈ secondary carbocation), was of paramount concern. The use of aryl substituent effects in the context of a Hammet-type study provided one avenue to probe this question. Toward this end, the prekinamycin dimethyl ether substrate **29** was exposed to the usual mixture of $Bu_3SnH$ and AIBN in a variety of equimolar mixtures of benzene and other substituted aromatic solvents, Table 2. Absolute chemical yields of the benzene adduct **36** and the substituted arene analogues **39** were recorded, as were ortho:meta:para ratios (or other substituent ratios, as appropriate). Standard Hammet (para) substituent constants $\sigma$ were used for this analysis, which necessitated normalizing the raw data.[17]

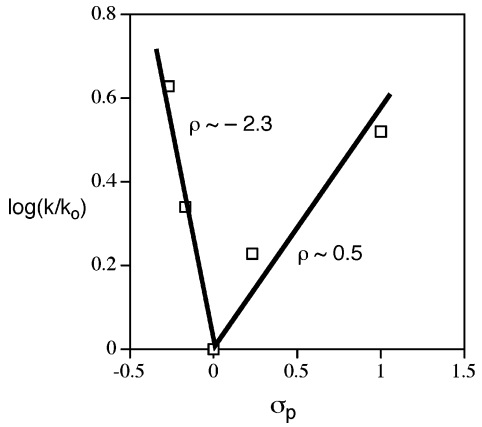



***Figure 3.*** Hammett study of the reaction between **29** and arene solvents under radical-generating conditions.

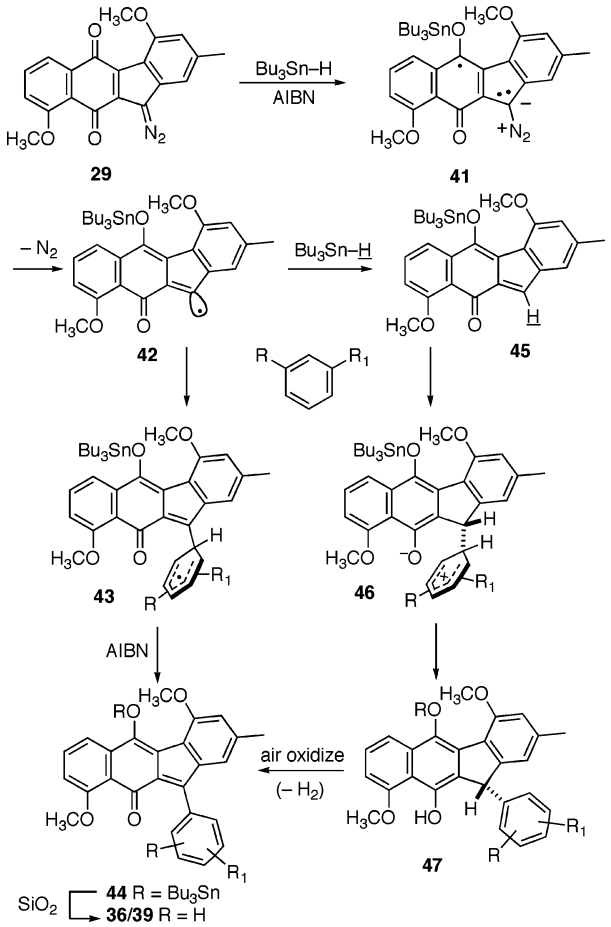
The undeniable dogleg exposed by graphing the data from entries *a*−*d* of Table 2 against $\sigma$ (see Figure 3) provides little support for a hypothesis that depends on a C(11) cationic intermediate for C−C bond formation to the arene. That any non-hydrogen substituent on the arene accelerates adduct formation is reinforced by the dual substituent entries *e*−*g* of Table 2, where a rough additivity in rates is seen for 1,3-dimethyl, 1−3-dimethoxy, and 1,3-dicyanobenzene compared to that for the corresponding monsubstituted species. The facts that (1) 1,3-dicyanobenzene is the most reactive arene solvent examined and (2) this electron-deficient arene is closely followed in relative reactivity by the electron-rich 1,3-dimethoxybenzene argue perhaps the most persuasively against adduct formation via an electrophilic orthoquinonemethide intermediate. However, these observations, in and of themselves, do not permit the rigorous exclusion of this species from further consideration if it were perhaps just a minor player with the more electron-rich arenes (vide infra).

Therefore, by process of elimination, the mechanistic picture for conversion of **29** into **36**/**39** or, by extension, that for the similar conversion of **5** into **34a** can be refined substantially to include a prominent role for direct $sp^2$ radical addition to the arene solvent,[18] Scheme 5. Thus, the data presented in Table 2 are consistent with a sequence whereby $sp^2$ radical **42**, generated by formal 1-electron reduction of **29** with loss of $N_2$, adds directly to the arene ring of the solvent to furnish a transient cyclohexadienyl radical-containing adduct **43**. Despite the fact that the transformation is run under globally reducing conditions, the apparent oxidation of this radical by AIBN itself to reformulate the aryl ring of product **44** is not unexpected, as

(17) $\sigma$ values from: Hammett, L. P. *J. Am. Chem. Soc.* **1937**, *59*, 96−103. The raw [**39**]/[**36**] values were (1) divided by 1/6 to compensate for the six equivalent positions of benzene, and (2) multiplied by the % para product from Table 2.

(18) (a) Dannley, R. L.; Gregg, E. C., Jr.; Phelps, R. E.; Coleman, C. B. *J. Am. Chem. Soc.* **1954**, *76*, 445−448. (b) Dannley, R. L.; Gregg, E. C., Jr. *J. Am. Chem. Soc.* **1954**, *76*, 2997−3000. (c) Kryger, R. G.; Lorand, J. P.; Stevens, N. R.; Herron, N. R. *J. Am. Chem. Soc.* **1977**, *99*, 7589−7600. (d) Madhavan, V.; Schuler, R. H.; Fessenden, R. W. *J. Am. Chem. Soc.* **1978**, *100*, 888−893. (e) Traynham, J. G. *Chem. Rev.* **1979**, *79*, 323−330. (f) Scaiano, J. C.; Stewart, L. C. *J. Am. Chem. Soc.* **1983**, *105*, 3609−3614. (g) Crich, D.; Hwang, J.-T. *J. Org. Chem.* **1998**, *63*, 2765−2770. (h) Martínez-Barrasa, V.; García de Viedma, A.; Burgos, C.; Alvarez-Builla, J. *Org. Lett.* **2000**, *2*, 3933−3935. (i) Núñez, A.; Sánchez, A.; Burgos, C.; Alvarez-Builla, J. *Tetrahedron* **2004**, *60*, 6217−6224. (j) McLoughlin, P. T. F.; Clyne, M. A.; Aldabbagh, F. *Tetrahedron* **2004**, *60*, 8065−8071. (k) Liu, J.-a.; Petzold, C. J.; Ramirez-Arizmendi, L. E.; Perez, J.; Kenttämaa, H. *J. Am. Chem. Soc.* **2005**, *127*, 12758−12759.

***Scheme 5.*** Mechanistic Proposal for the Formation of Arene Adducts **36/39** from Diazoparaquinone **29**

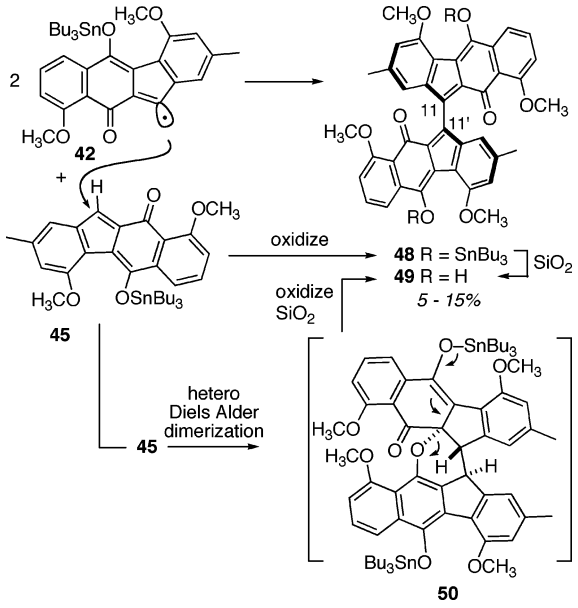



per the work of Beckwith et al.[19] Workup via $SiO_2$ chromatography then provides the detected product(s) **36**/**39**.

If the orthoquinonemethide **45** *is* formed from **42** by hydrogen abstraction from $Bu_3SnH$, it is unclear at this point whether this electrophile plays any productive (even if only minor) role in adduct formation, at least with the electron-rich arene solvents. The overall chemical yields of the arene adducts ranged from 52 to 80%, leaving as an open question the fate of the remainder of the starting material. The diversion of **42** to the orthoquinonemethide **45** may account for some of the consumed **29**, as this species apparently does not participate in direct adduct formation with the electron-deficient arenes (vide infra). With electron-rich arenes, however, some minor involvement of Friedel–Crafts-type alkylation with **45** may occur to give the reduced hydroquinone adduct **47**, which can suffer air-induced oxidation to intercept **44** en route to the observed product **39**. If this electrophile mechanistic channel were expressed, the oxidation/hydrolysis sequence that forms **39** from **47** might just as reasonably be reversed (i.e., hydrolysis and then oxidation).

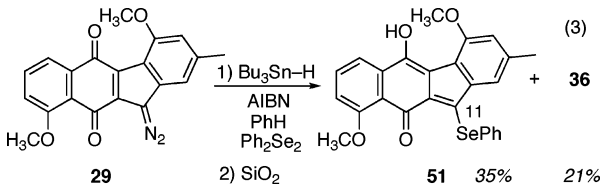
The conclusion regarding the prominence of radical addition chemistry over orthoquinonemethide chemistry only pertains to reactions with an aromatic solvent nucleophile. Extrapolating to a biological milieu, where much more potent nucleophilic partners for putative orthoquinonemethide **45** are present, would not seem warranted. Studies to be discussed shortly do provide

***Scheme 6.*** Plausible Routes to the C(11)–C(11′) Dimer **49**




some insight into this question about the role of **45** under such circumstances (vide infra). Further support for the radical-as-key-intermediate hypothesis in these arene additions can be garnered from two observations: (1) similar relative rates and similar ortho:meta:para ratios for thiazole-derived radical **40** addition to substituted arenes have been recorded by Dou (see Table 2),[20] and (2) small and variable amounts of the C(11) dimer **49** were isolated from many of the runs, Scheme 6. The formation of **49** is difficult to explain without invoking the intermediacy of radical **42**, either by direct dimerization or through participation of the derived but undetected orthoquinonemethide, **42** + **45** → **48** or **45** + **45** → **50** → **49**.

A few more attempts to trap radical **42** with other radical-reactive reagents were explored, eq 3. Standard reaction of **29**/$Bu_3SnH$/AIBN in the presence of $Ph_2Se_2$ led to formation of the C(11) selenium adduct **51** along with the benzene addition product **36**. Attempts to perform the tin hydride-mediated reduction of **29** in non-aromatic solvents were uniformly unrewarding, as reaction in either THF, 1,4-dioxane, $CCl_4$, $CH_3CN$, EtOH, or $Cl_3CH$ returned only unreacted starting material. These observations, taken together, may point to a defined role for the aromatic solvent in either promoting the formation of, or possibly stabilizing, the $sp^2$ radical by $\pi$-complexation.




So, if *some* orthoquinonemethide **45** is formed from **42**, what is its fate? This question was probed through two different types of experiments featuring either (1) variation of the $Bu_3SnH$/substrate ratio or, independently, (2) examination of the product distribution when nucleophiles that are better than arene rings are present. The partitioning of radical **42** into either the arene

(19) Beckwith, A. L. J.; Bowry, V. W.; Bowman, W. R.; Mann, E.; Parr, J.; Storey, J. M. D. *Angew. Chem., Int. Ed.* **2004**, *43*, 95–98 and references therein.

(20) Vernin, G.; Jauffred, R.; Ricard, C.; Dou, H. J. M.; Metzger, J. *J. Chem. Soc., Perkin Trans. 2* **1972**, 1145–1150.

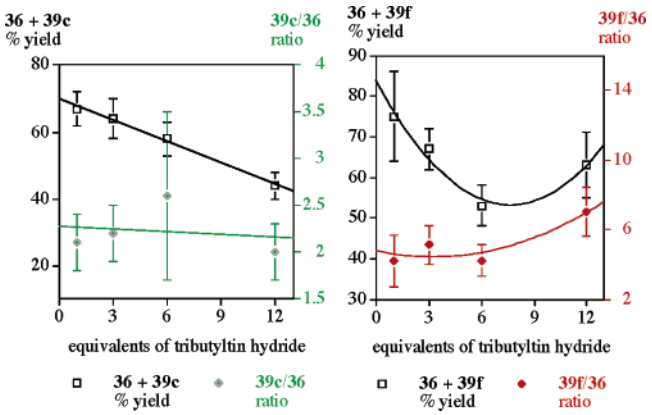


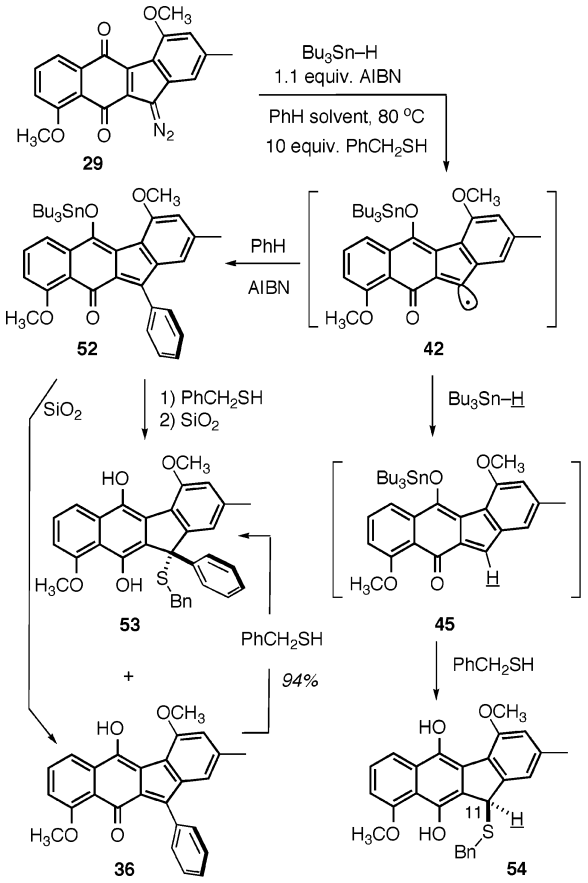

***Figure 4.*** Yield and ratio of aromatic trapping products **39c**/**36** (left) and **39f**/**36** (right) upon increasing [$Bu_3SnH$]. All data points result from averaging quadruplicate or pentuplicate measurements.

adduct **43** or the putative orthoquinonemethide **45** should be responsive to the tin hydride concentration if the mechanistic model detailed in Scheme 5 is applicable. In the case of an electron-deficient solvent, any orthoquinonemethide **45** so formed would not lead to adduct formation, and thus the overall yield of adducts **36**/**39**, which can only derive from **42**, should decrease as [$Bu_3SnH$] increases. This hypothesis was tested by exposing a 1:1 molar mixture of PhH and PhCN to **29**/AIBN/(varying) $Bu_3SnH$ at 80 °C, Figure 4 (left). The data obtained from these studies support this interpretation, as the overall yield of arene adducts decreases linearly with increasing [$Bu_3SnH$] over the range 1−12 equiv of the tin reagent. Verification of the expectation that adduct formation derives only from radical **42** and not orthoquinonemethide **45** for these non-electron-rich arenes can be seen by examining the **39c**/**36** ratio as a function of [$Bu_3SnH$]; this ratio remains constant within experimental error, indicating no change in mechanism as tin hydride concentration increases.

This situation changes noticeably when an electron-rich aromatic solvent, 1,3-dimethoxybenzene, is used in place of PhCN, Figure 4 (right). For these experiments, the overall yield of arene adducts **39f** + **36** decreases roughly monotonically at lower tin hydride concentration, but then this trend reverses at the highest [$Bu_3SnH$] examined, where the yield of total arene adducts actually *increases*. Could the orthoquinonemethide **45** now be playing a role in adduct formation (**45** → **46** → **47** → **39f**, cf. Scheme 5) with this more nucleophilic solvent? Evidence in support of this hypothesis can be found by examining the ratio of arene adducts **39f**/**36** as a function of tin hydride concentration; unlike the electron-deficient PhCN trials, the ratio favoring the electron-rich adduct **39f** increases at high [$Bu_3SnH$]. These observations are entirely consistent with incursion of the orthoquinonemethide reaction channel to some extent in (electron-rich) arene adduct formation. Thus, it appears that both reactive intermediates, the $sp^2$ radical **42** and the orthoquinonemethide **45**, are generated sequentially upon formal 1-electron reduction of diazoparaquinone **29**, and both species can be trapped if the appropriate complementary reaction partners are present.

The last series of experiments were designed to probe the question of whether the orthoquinonemethide **45** might be coaxed into playing a bigger role in product formation if a reagent much more nucleophilic than a methoxyaromatic solvent were included in the reaction mixture. In fact, these trials begin

***Scheme 7.*** Thiol Adduct Formation in the Reductive Activation of Diazoparaquinone **29**

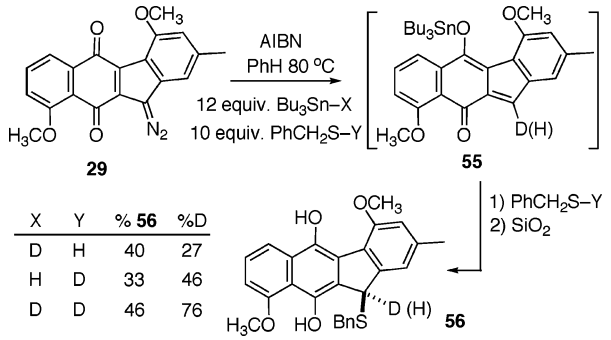



| equiv. $Bu_3Sn$–H | total yield | **53** (%) | **36** (%) | **54** (%) |
|---|---|---|---|---|
| 1.1 | *83%* | *22%* | *15%* | *46%* |
| 12 | *90%* | *23%* | *10%* | *57%* |

control: no $Bu_3Sn$–H / AIBN, no reaction

to speak to the question of relevance to the chemistry of diazoparaquinones in a biological setting, where nucleophiles such as thiols and amines (cf. Scheme 3) might participate in adduct formation. Inclusion of benzylmercaptan in the reaction solution provided the means to test these ideas (Scheme 7). Treatment of a solution of diazoparaquinone **29**, either 1.1 or 12 equiv of $Bu_3SnH$, and 10 equiv of $PhCH_2SH$ in benzene solvent at reflux with 1.1 equiv of AIBN in benzene led to results which encouraged the point of view that the orthoquinonemethide **45** may, in fact, be a major player in the chemistry of diazoparaquinones under 1-electron reducing conditions as long as suitable nucleophile partners are present. Thus, the products of direct radical **42** addition to benzene, **36** and **53**, are formed in a combined yield of 37% with 1.1 equiv of $Bu_3SnH$, and in a combined 33% yield with 12 equiv of $Bu_3SnH$. That **52** precedes **53** is suggested by the independent synthesis of **53** from **36** and $PhCH_2SH$. So, if approximately one-third of the starting diazoparaquinone can be accounted for by the direct radical addition pathway under these experimental conditions, where is the other two-thirds going? It was gratifying to see that about half of the starting material was converted into the C(11) benzylmercaptan adduct **54**, a species that retains the C(11) hydrogen as well. The hydroquinone **54** was moderately

***Scheme 8.*** Deuterium-Labeling Experiments with Diazoparaquinone **29** and $Bu_3SnD$ and/or $PhCH_2SD$




| X | Y | % **56** | %D |
|---|---|---|---|
| D | H | 40 | 27 |
| H | D | 33 | 46 |
| D | D | 46 | 76 |

sensitive to quinone formation via air oxidation, but careful handling under a $N_2$ atmosphere reduced this unwanted side reaction to almost undetectable levels. The most concise explanation for the formation of this benzylmercaptan adduct involves reaction through the orthoquinonemethide electrophile **45**, where now the much greater nucleophilicity of the thiol, compared with that of aromatic solvents, provides a ready trap for this reactive entity. No evidence for the dimerization product **49** was forthcoming from these thiol-containing runs. In a critical control experiment, refluxing a solution of diazoparaquinone **29** with 100 equiv of benzylmercaptan in benzene led to absolutely no evidence for chemical reaction, and **29** could be recovered unchanged from this test. The incorporation of radical-generating (reducing) reagents appears to be an inescapable requirement for reaction. The lack of direct nucleophilic addition between the thiol and the diazo function of **29** does not lend support to the nucleophilic activation mechanism of Dmitrienko (Scheme 1), although the claimed H-bond activation within **6** is absent in **29**. To probe this point further, the H-bond capable species prekinamycin (**5**) itself was subjected to the same control—exposure to 100 equiv of $PhCH_2SH$ in refluxing benzene—to the same end; no evidence for chemical reaction was detected, and **5** could be recovered unchanged.

The isolation of a reaction product **54** that still retained a presumably tin hydride-donated hydrogen at C(11) leads to the obvious labeling experiment with $Bu_3SnD$, Scheme 8. Not so obvious was the result when diazoparaquinone **29** was combined with 12 equiv of the tin deuteride and 10 equiv of $PhCH_2SH$ in refluxing benzene; the expected C(11) benzylthiolated hydroquinone product **56** was isolated in good yield, but with only 27% deuterium incorporation at C(11) ($^1$H NMR analysis). The unexpectedly high proton count in **56** was partially explained by rerunning the labeling experiment with $PhCH_2SD$ as the source of deuterium. In this instance, the hydroquinone **56** was formed with 46% deuterium incorporation at C(11). As controls, heating a mixture of either $Bu_3SnD/PhCH_2SH$ or, independently, $Bu_3SnH/PhCH_2SD$ in benzene with AIBN present did not lead to any deuterium crossover. Finally, it was comforting to note that when both $Bu_3SnD$ and $PhCH_2SD$ were used simultaneously, the deuterium count in the product **56** (76%) matched the sum of the deuterium incorporations of the two single-deuterium source experiments. The origin of the remaining ~25% of protium in the double-deuterium source experiment remains a mystery, although $PhC\underline{H}_2SH$ may be a likely candidate. No further labeling studies were pursued to probe this point.

## Conclusions

In summary, the results described herein provide a comprehensive picture of the chemistry that unfolds when a diazoparaquinone-containing species, prekinamycin dimethyl ether (**29**), is treated with the formal 1-electron reductant $Bu_3SnH$/AIBN. Evidence in support of a mechanistic sequence involving first a C(11) $sp^2$ radical and then an electrophilic orthoquinonemethide has been obtained. The radical intermediate is a competent partner for additions with either electron-deficient or electron-rich arenes, whereas the subsequent orthoquinone species will react with both electron-rich arenes and an alkanethiol. The relevance of this chemistry to the larger question of kinamycin/lomaiviticin mechanism of action remains to be established, but at the very least, these results speak to the intrinsic chemistry available to diazoparaquinone-containing species under reducing conditions, and they hint at plausible reaction chemistry within a biological milieu.

## Experimental Section

**General Procedure 1. Phenylation of Prekinamycin and Derivatives.** AIBN (1.1 equiv) in benzene (0.06 M) was added via syringe pump addition over a period of 1 h to a stirring solution of diazoparaquinones **5**, **28**, or **29** (1 equiv) and $Bu_3SnH$ (1.1 equiv) in benzene (0.06 M) at 80 °C. When the addition was complete, the reaction solution was allowed to cool to room temperature. After reaching room temperature the reaction mixture was concentrated in vacuo. The resulting residue was purified by flash chromatography on $SiO_2$ using the specified eluent.

**General Procedure 2. Aromatic Solvent Competition Experiments.** AIBN (1.1 equiv) in an equimolar solution of benzene and the indicated aromatic solvent (0.06 M) was added via syringe pump addition over a period of 1 h to a stirring solution of diazoparaquinone **29** (1 equiv) and $Bu_3SnH$ (1.1 equiv) also in an equimolar solution of benzene and the indicated aromatic solvent (0.06 M) at 80 °C. When the addition was complete, the reaction solution was allowed to cool to room temperature. After reaching room temperature the reaction mixture was diluted with $CH_2Cl_2$, poured onto a $SiO_2$ column, and purified by eluting with $CH_2Cl_2$ with an increasing percentage of either EtOAc or acetone from 0% to 10%. Purification furnished the clean benzene-trapped product **36** and in most cases a mixture of ortho, meta, and para or the 2,4- and 2,6-regioisomers of the given substituted aromatic trapped product **39a**−**g**. Relative rates were quantified by product mass comparison of the substituted aromatic adducts **39** vs the benzene addition product **36**. Isolation of analytical samples of pure ortho, meta, or para (or the 2,4- or 2,6-regioisomers) from chromatography permitted $^1$H NMR identification. In cases where isomer separation was not achieved, the ratios were determined by inspection of $^1$H NMR spectra of the mixtures.

**General Procedure 3. Aromatic Solvent Competition Experiments with Varying Equivalents of Tin.** General Procedure 2 was used, varying only in the equivalents of $Bu_3SnH$ used as indicated in Figure 4.

**4,5,9-Trihydroxy-2-methyl-11-phenyl-benzo[*b*]fluoren-10-one (34a).** Following General Procedure 1, prekinamycin (**5**) (18 mg, 0.057 mmol) was converted into benzo[*b*]fluorenone **34a** (12.3 mg, 59%): mp 260 °C (dec); IR (neat): 3409, 1585 cm$^{-1}$. Presumably due to the partial free radical nature of **34a** analogous to kinobscurinone,[21] **34a** appears to be "NMR silent", exhibiting neither a $^1$H- nor a $^{13}$C NMR signature; ESI m/z relative intensity 391($MNa^+$ 100); TOFHRMS (+ESI) Calcd for $C_{24}H_{16}O_4Na$: 391.0946, Found 391.0947.

**Acetic Acid 9-Acetoxy-11-diazo-2-methyl-5,10-dioxo-10,11-dihydro-5H-benzo[*b*]fluoren-4-yl ester (28).** Pyridine (3.6 mL, 28 mmol)

(21) Gould, S. J.; Melville, C. R. *Tetrahedron Lett.* **1997**, *38*, 1473−1476.

and $Ac_2O$ (3.6 mL, 44 mmol) were sequentially added to a mixture of **5** (150 mg, 0.471 mmol) and DMAP (6.0 mg, 0.05 mmol) in $CH_2Cl_2$ (15.0 mL) at room temperature. The dark purple mixture was stirred at room temperature for 2 days, turning to a dark red color. At this time, the reaction solution was diluted with saturated aqueous $NaHCO_3$ (50 mL) and $CH_2Cl_2$ (30 mL). The layers were separated, and the aqueous layer was extracted with $CH_2Cl_2$ (3 × 10 mL). The combined organic layers were washed with water and brine, dried over $Na_2SO_4$, filtered, and concentrated. The resulting dark red solid was purified by flash chromatography on silica gel eluting with $CH_2Cl_2$/EtOAc (99:1) to yield the di-acetate (**28**) as a red solid (156 mg, 85%): mp 205 °C (dec); IR (neat): 3365, 2924, 2102, 1766 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 8.17 (d, $J$ = 7.8 Hz, 1H), 7.72 (t, $J$ = 7.9 Hz, 1H), 7.30 (d, $J$ = 7.9 Hz, 1H), 7.20 (s, 1H), 6.89 (s, 1H), 2.57 (s, 3H), 2.47 (s, 3H), 2.46 (s, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 180.0, 177.6, 171.0, 170.0, 150.0, 147.6, 139.7, 137.7, 137.2, 136.7, 136.4, 135.2, 129.0, 126.4, 126.0, 124.3, 122.3, 121.9, 116.9, 22.1, 21.9, 21.6; ESI m/z relative intensity 425 ($MNa^+$ 72); TOFHRMS (+ESI) Calcd for $C_{22}H_{15}N_2O_6Na$: 425.0750, Found 425.0738.

**Acetic Acid 9-Acetoxy-5-hydroxy-2-methyl-10-oxo-11-phenyl-10H-benzo[*b*]fluoren-4-yl Ester (35).** Following General Procedure 1, diazoparaquinone **28** (17.5 mg, 0.044 mmol) was converted into benzo[*b*]fluorenone **35** (9.8 mg, 50%): mp 200 °C (dec); IR (neat): 3330, 1789, 1766 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 9.39 (s, 1H), 7.88 (d, $J$ = 7.9 Hz, 1H), 7.56 (t, $J$ = 8.0 Hz, 2H), 7.55 (d, $J$ = 7.7 Hz, 1H), 7.41−7.50 (m, 3H), 7.06 (d, $J$ = 8.0 Hz, 1H), 7.06 (s, 1H), 7.05 (s, 1H), 2.51 (s, 3H), 2.36 (s, 3H), 2.32 (s, 3H), $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 180.2, 170.2, 166.9, 151.3, 149.9, 147.9, 144.4, 143.3, 138.5, 135.7, 133.9, 133.8, 129.7, 128.8, 128.7, 128.2, 126.5, 125.4, 123.3, 123.2, 123.0, 122.6, 114.6, 21.7, 21.6, 21.3; ESI m/z relative intensity 475 ($MNa^+$ 100); TOFHRMS (+ESI) Calcd for $C_{28}H_{20}O_6Na$: 475.1158, Found 475.1142.

**5-Hydroxy-4,9-dimethoxy-2-methyl-11-phenyl-benzo[*b*]fluoren-10-one (36).** Following General Procedure 1, diazoquinone **29** (10.5 mg, 0.032 mmol) was converted into benzo[*b*]fluorenone **36** (10.0 mg, 79%): mp 220 °C (dec); IR (neat): 3181, 1633 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 10.76 (s, 1H), 7.58 (d, $J$ = 7.6 Hz, 1H), 7.56 (d, $J$ = 6.8 Hz, 2H), 7.48 (t, $J$ = 8.2 Hz, 1H), 7.45 (t, $J$ = 7.1 Hz, 2H), 7.39 (d, $J$ = 7.2 Hz, 1H), 7.00 (d, $J$ = 8.4 Hz, 1H), 6.81 (s, 1H), 6.67 (s, 1H), 4.09 (s, 3H), 3.90 (s, 3H), 2.32 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 182.0, 161.8, 151.9, 151.1, 146.6, 144.3, 138.7, 136.9, 135.0, 134.6, 130.0, 129.4, 128.4, 128.2, 128.1, 120.0, 119.2, 117.8, 115.0, 114.9, 115.2, 56.9, 56.6, 22.2; ESI m/z relative intensity 497 ($MH^+$ 50); TOFHRMS (+ESI) Calcd for $C_{26}H_{21}O_4$: 397.1440, Found 397.1443.

**Acetic Acid 4,5-Diacetoxy-2-methyl-10-oxo-11-phenyl-10H-benzo-[*b*]fluoren-9-yl Ester (37). From 34a.** Pyridine (0.26 mL, 3.1 mmol) and $Ac_2O$ (0.31 mL, 3.1 mmol) were added sequentially to a mixture of **34a** (11.0 mg, 0.031 mmol) and DMAP (1.0 mg, 0.008 mmol) in $CH_2Cl_2$ (1.0 mL) at room temperature. The dark purple mixture was stirred at room temperature for 30 min, turning to a dark red/orange color. At this time, the reaction solution was diluted with saturated aqueous $NaHCO_3$ (10 mL) and $CH_2Cl_2$ (10 mL). The layers were separated, and the aqueous layer was extracted with $CH_2Cl_2$ (3 × 10 mL). The combined organic layers were washed with water and brine, dried over $Na_2SO_4$, filtered, and concentrated. The resulting dark red solid was purified by flash chromatography on silica gel ($CH_2Cl_2$) to yield the triacetate **37** as a bright orange solid (8.1 mg, 52%).

**From 35.** Pyridine (0.070 mL, 0.90 mmol) and $Ac_2O$ (0.85 mL, 0.90 mmol) were sequentially added to a mixture of **35** (4.0 mg, 0.90 mmol) and DMAP (1.0 mg, 0.008 mmol) in $CH_2Cl_2$ (1.0 mL) at room temperature. The dark red mixture was stirred at room temperature for 30 min, changing to a dark red/orange color. At this time, the reaction solution was diluted with saturated aqueous $NaHCO_3$ (10 mL) and $CH_2Cl_2$ (10 mL). The layers were separated, and the aqueous layer was extracted with $CH_2Cl_2$ (3 × 10 mL). The combined organic layers were washed with water and brine, dried over $Na_2SO_4$, filtered, and concentrated. The resulting dark red solid was purified by flash chromatography on silica gel ($CH_2Cl_2$). The triacetate **37** was obtained as a orange solid (4.4 mg, 99%): mp 195 °C (dec); IR (neat): 1769, 1635 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 7.59 (d, $J$ = 7.8 Hz, 1H), 7.58 (d, $J$ = 7.3 Hz, 1H), 7.47−7.52 (m, 4H), 7.39 (d, $J$ = 8.3 Hz, 1H), 7.01 (d, $J$ = 7.7 Hz, 1H), 6.99 (s, 1H), 6.80 (s, 1H), 2.53 (s, 3H), 2.43 (s, 3H), 2.31 (s, 6H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 179.4, 169.6, 168.7, 167.6, 154.6, 151.4, 145.9, 145.2, 142.0, 141.1, 136.5, 133.8, 132.8, 129.4, 129.3, 129.3, 128.9, 128.0, 125.9, 125.3, 124.8, 124.2, 123.7, 121.8, 21.3, 21.2, 21.1, 20.9; ESI m/z relative intensity 517 ($MNa^+$ 100); TOFHRMS (+ESI) Calcd for $C_{30}H_{22}O_7Na$: 517.1263, Found 517.1245.

**4,5,9-Trimethoxy-2-methyl-11-phenyl-benzo[*b*]fluoren-10-one (38). From 34a.** Methyl iodide (0.042 mL, 0.68 mmol) was added to a mixture of **34a** (25.0 mg, 0.068 mmol) and $K_2CO_3$ (93.0 mg, 0.068 mmol) in DMF (2.0 mL) at room temperature. The dark purple mixture was stirred at room temperature for 12 h, turning to a dark red color. The reaction solution was then diluted with saturated aqueous $NH_4Cl$ (10 mL) and $Et_2O$ (10 mL). The layers were separated, and the aqueous layer was extracted with $Et_2O$ (3 × 10 mL). The combined organic layers were washed with water and brine, dried over $Na_2SO_4$, filtered, and concentrated. The resulting light red solid was purified by flash chromatography on silica gel ($CH_2Cl_2$). The trimethyl ether **38** was obtained as a bright red solid (11.5 mg, 41%).

**From 36.** Methyl iodide (0.031 mL, 0.50 mmol) was added to a mixture of **36** (20.0 mg, 0.050 mmol) and $K_2CO_3$ (69.0 mg, 0.050 mmol) in DMF (1.0 mL) at room temperature. The dark red mixture was stirred at room temperature for 12 h, turning to a light red color. The reaction was then diluted with saturated aqueous $NH_4Cl$ (10 mL) and $Et_2O$ (10 mL). The layers were separated, and the aqueous layer was extracted with $Et_2O$ (3 × 10 mL). The combined organic layers were washed with water and brine, dried over $Na_2SO_4$, filtered, and concentrated. The resulting light red solid was purified by flash chromatography on silica gel ($CH_2Cl_2$). The trimethyl ether **38** was obtained as a bright red solid (12.0 mg, 59%): mp 210 °C (dec); IR (neat): 1643 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7.50−7.60 (m, 2H), 7.40−7.50 (m, 5H), 6.96 (dd, $J$ = 6.7, 2.7 Hz, 1H), 6.76 (s, 1H), 6.59 (s, 1H), 4.02 (s, 3H), 3.96 (s, 3H), 3.89 (s, 3H), 2.32 (s, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 181.5, 161.6, 155.2, 153.0, 151.7, 145.3, 140.3, 138.7, 134.3, 134.2, 130.1, 129.2, 128.3, 127.8, 126.8, 121.4, 118.3, 118.2, 117.4, 113.9, 113.6, 63.9, 56.1, 55.9, 21.7; ESI m/z relative intensity 411 ($MH^+$ 100); TOFHRMS (+ESI) Calcd for $C_{27}H_{22}O_4$: 411.1596, Found 411.1596.

**5-Hydroxy-4,9-dimethoxy-2-methyl-11-*p*-tolyl-benzo[*b*]fluoren-10-one (39a).** Following General Procedure 2, diazoparaquinone **29** (20.0 mg, 0.060 mmol) was converted into a 2:1 mixture of benzo[*b*]-fluorenone **39a** (ortho:meta:para = 62:23:15) (7.4 mg, 30%) and benzo-[*b*]fluorenone **36** (3.6 mg, 15%). Note that the 2.2:1 ratio of **39a** to **36** that is reported in Table 2 reflects the average of five independent runs. (Ortho:meta:para mixture) IR (neat): 3190, 1633 $cm^{-1}$; ortho isomer: $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 10.64 (s, 1H), 7.60 (d, $J$ = 7.9 Hz, 1H), 7.50 (t, $J$ = 8.1 Hz, 1H), 7.22−7.36 (m, 3H), 7.19 (d, $J$ = 7.3 Hz, 1H), 7.01 (d, $J$ = 8.3 Hz, 1H), 6.69 (s, 1H), 6.54 (s, 1H), 4.11 (s, 3H), 3.89 (s, 3H), 2.31 (s, 3H), 2.16 (s, 3H); (ortho:meta:para mixture) $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 10.76 (s, 0.4H, meta, para), 10.68 (s, 0.6H, *o*) 7.60 (d, $J$ = 7.7 Hz, 0.5H), 7.59 (d, $J$ = 7.4 Hz, 0.5H), 7.47−7.51 (m, 1H), 7.33−7.36 (m, 1H), 7.22−7.30 (m, 2H), 7.19 (d, $J$ = 6.8 Hz, 1H), 7.01 (d, $J$ = 8.3 Hz, 1H), 6.85 (s, 0.25H), 6.79 (s, 0.25H), 6.69 (s, 1H), 6.54 (s, 0.5H), 4.11 (s, 1.8H, *o*), 4.10 (s, 1.2H, meta, para), 3.90 (s, 1.2H, meta, para) 3.89 (s, 1.8H, *o*), 2.35 (s, 1.8H, meta, para), 2.31 (s, 1.8H, *o*), 2.16 (s, 3H); (ortho:meta:para mixture) $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 181.5, 161.3, 151.5, 150.6, 145.9, 144.2, 138.5, 136.7, 136.5, 135.1, 134.0, 129.9, 129.5, 128.5, 127.6, 126.6, 125.4, 121.3, 119.4, 118.9, 118.6, 117.4, 114.6, 114.4, 111.1, 56.53,

56.5, 56.5, 21.8, 21.7, 19.9; ESI m/z relative intensity 411 ($MH^+$ 30); TOFHRMS (+ESI) Calcd for $C_{27}H_{22}O_4$: 411.1596, Found 411.1611.

**11-(4-Chlorophenyl)-5-hydroxy-4,9-dimethoxy-2-methyl-benzo[*b*]fluoren-10-one (39b).** Following General Procedure 2, diazoparaquinone **29** (20.0 mg, 0.060 mmol) was converted into a 1.8:1 mixture of benzo[*b*]fluorenone **39b** (ortho:meta:para = 48:32:20) (9.5 mg, 37%) and benzo[*b*]fluorenone **36** (5.0 mg, 21%). Note that the 1.5:1 ratio of **39b** to **36** that is reported in Table 2 reflects the average of five independent runs. **39b** isomers were separated via preparative TLC (20% EtOAc in benzene). Ortho isomer: mp 280 °C (dec); IR (neat): 3178, 1630 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 10.76 (s, 1H), 7.60 (d, $J$ = 7.8 Hz, 1H), 7.50 (m, 2H), 7.33 (m, 3H), 7.02 (d, $J$ = 8.2 Hz, 1H), 6.69 (s, 1H), 6.58 (s, 1H), 4.11 (s, 3H), 3.90 (s, 3H), 2.33 (s, 3H). Meta isomer: mp 260 °C (dec); IR (neat): 3378, 1630 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 10.82 (s, 1H), 7.60 (d, $J$ = 8.2 Hz, 1H), 7.51 (m, 2H), 7.44 (d, $J$ = 6.8 Hz, 1H), 7.38 (t, $J$ = 7.8 Hz, 1H), 7.37 (s, 1H), 7.30 (d, $J$ = 8.3 Hz, 1H), 6.75 (s, 1H), 6.71 (s, 1H), 4.12 (s, 3H), 3.91 (s, 3H), 2.36 (s, 3H). Para isomer: mp 240 °C (dec); IR (neat): 3166, 1631 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 10.81 (s, 1H), 7.60 (d, $J$ = 8.4 Hz, 1H), 7.52 (d, $J$ = 8.6 Hz, 2H), 7.50 (t, $J$ = 8.2 Hz, 1H), 7.42 (d, 8.6 Hz, 2H), 7.30 (d, $J$ = 8.4 Hz, 1H), 6.79 (s, 1H), 6.71 (s, 1H), 4.12 (s, 3H), 3.92 (s, 3H), 2.35 (s, 3H); (ortho:meta:para mixture) $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 181.6, 181.5, 181.3, 161.3, 151.5, 151.4, 151.3, 151.1, 144.5, 143.5, 143.3, 142.3, 138.5, 136.6, 136.5, 136.4, 134.1, 133.8, 133.7, 133.2, 131.1, 130.7, 130.3, 129.5, 129.2, 129.1, 128.9, 128.3, 128.1, 127.9, 126.5, 121.1, 119.6, 119.5, 119.3, 118.5, 118.4, 118.3, 117.5, 114.7, 114.4, 114.2, 111.2, 111.1, 56.6, 56.5, 56.2, 56.1, 21.8, 21.7; ESI m/z relative intensity 431 ($MH^+$ 100); TOFHRMS (+ESI) Calcd for $C_{26}H_{20}O_4Cl$: 431.1050, Found 431.1060.

**4-(5-Hydroxy-4,9-dimethoxy-2-methyl-10-oxo-10H-benzo[*b*]fluoren-11-yl)benzonitrile (39c).** Following General Procedure 2, diazoparaquinone **29** (20.0 mg, 0.060 mmol) was converted into a 2.2:1 mixture of benzo[*b*]fluorenone **39c** (ortho:meta:para = 43:25:32) (13.0 mg, 51%) and benzo[*b*]fluorenone **36** (5.6 mg, 23%). Note that the 2.1:1 ratio of **39c** to **36** that is reported in Table 2 reflects the average of five independent runs. **39c** isomers were separated via preparative TLC (20% EtOAc in benzene). Ortho isomer: mp 265 °C (dec); IR (neat): 3394, 2232, 1631 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 10.87 (s, 1H), 7.77 (d, $J$ = 7.6 Hz, 1H), 7.66 (t, $J$ = 7.7 Hz, 1H), 7.61 (d, $J$ = 7.9 Hz, 1H), 7.52 (t, $J$ = 8.2 Hz, 1H), 7.49 (d, $J$ = 7.8 Hz, 1H), 7.46 (t, $J$ = 7.7 Hz, 1H), 7.03 (d, $J$ = 8.2 Hz, 1H), 6.71 (s, 1H), 6.58 (s, 1H), 4.13 (s, 3H), 3.92 (s, 3H), 2.34 (s, 3H). Meta isomer: mp 265 °C (dec); IR (neat): 3412, 2216, 1633 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 10.88 (s, 1H), 7.82 (d, $J$ = 8.0 Hz, 1H), 7.81 (s, 1H), 7.67 (d, $J$ = 7.7 Hz, 1H), 7.61 (d, $J$ = 7.8 Hz, 1H), 7.54 (t, $J$ = 8.0 Hz, 1H) 7.47 (t, $J$ = 8.1 Hz, 1H), 7.04 (d, $J$ = 7.7 Hz, 1H), 6.72 (s, 1H), 6.70 (s, 1H), 4.13 (s, 3H), 3.93 (s, 3H), 2.37 (s, 3H). Para isomer: mp 265 °C (dec); IR (neat): 3412, 2223, 1631 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 10.92 (s, 1H), 7.73 (d, $J$ = 8.4 Hz, 2H), 7.66 (d, $J$ = 8.5 Hz, 2H), 7.61 (d, $J$ = 7.8 Hz, 1H), 7.52 (t, $J$ = 8.2 Hz, 1H), 7.04 (d, $J$ = 8.3 Hz, 1H), 6.72 (s, 1H), 6.71 (s, 1H), 4.13 (s, 3H), 3.92 (s, 3H), 2.36 (s, 3H); (ortho:meta:para mixture) $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 181.7, 181.6, 181.4, 161.5, 161.4, 152.4, 152.1, 151.6, 151.5, 143.1, 143.0, 142.9, 139.9, 139.6, 138.7, 138.6, 138.5, 136.4, 136.3, 136.2, 134.4, 133.0, 132.9, 132.3, 131.7, 131.5, 130.8, 130.4, 130.0, 129.7, 128.8, 127.9, 121.0, 119.5, 118.3, 118.1, 118.0, 117.9, 117.8, 115.2, 114.4, 114.3, 114.2, 113.1, 112.1, 111.4, 111.3, 111.3, 56.6, 56.5, 56.3, 56.3, 56.2, 21.8; ESI m/z relative intensity 444 ($MNa^+$ 100); TOFHRMS (+ESI) Calcd for $C_{27}H_{19}NO_4Na$: 444.1212, Found 444.1215.

**5-Hydroxy-4,9-dimethoxy-11-(4-methoxyphenyl)-2-methyl-benzo[*b*]fluoren-10-one (39d).** Following General Procedure 2, diazoparaquinone **29** (20.0 mg, 0.060 mmol) was converted into a 3.2:1 mixture of benzo[*b*]fluorenone **39d** (ortho:meta:para = 76:16:12) (14.5 mg, 57%) and benzo[*b*]fluorenone **36** (4.3 mg, 18%). Note that the 3.1:1 ratio of **39d** to **36** that is reported in Table 2 reflects the average of five independent runs. Ortho isomer: mp 210 °C (dec); IR (neat): 3182, 1632 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 10.70 (s, 1H), 7.58, (d, $J$ = 7.9 Hz, 1H), 7.48 (t, $J$ = 8.1 Hz, 1H), 7.36 (t, $J$ = 7.6 Hz, 1H), 7.34 (d, $J$ = 7.7 Hz, 1H), 7.03 (t, $J$ = 7.5 Hz, 1H), 7.01 (d, $J$ = 8.2 Hz, 1H), 7.0 (d, $J$ = 8.3 Hz, 1H), 6.66 (s, 1H), 6.65 (s, 1H), 4.10 (s, 3H), 3.89 (s, 3H), 3.73 (s, 3H), 2.32 (s, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 181.3, 161.2, 157.4, 151.4, 150.4, 144.0, 142.8, 138.1, 136.5, 133.8, 130.7, 130.0, 129.2, 124.3, 121.6, 120.4, 119.4, 118.7, 117.3, 114.7, 114.6, 111.3, 110.9, 56.5, 56.1, 55.7, 21.8. Meta:para isomer: IR (neat): 3178, 2216, 1622 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 10.78 (s, 0.43H, *p*), 10.76 (s, 0.57H, *m*), 7.59 (d, $J$ = 7.3 Hz, 1H), 7.58 (d, $J$ = 8.4 Hz, 1H), 7.49 (t, $J$ = 8.0 Hz, 1H), 7.37 (t, $J$ = 8.0 Hz, 1H), 7.14 (d, $J$ = 7.6 Hz, 0.5H), 6.98−7.06 (m, 2H), 6.93 (d, $J$ = 8.6 Hz, 0.5H), 6.88 (s, 0.5H), 6.82 (s, 0.5H), 6.69 (s, 1H), 4.10 (s, 3H), 3.91 (s, 3H), 3.88 (s, 1.5H), 3.88 (s, 1.5H), 2.35 (s, 1.5H), 2.34 (s, 1.5H); IR (neat): 3412, 2223, 1631 $cm^{-1}$; $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 181.6, 181.3, 161.4, 161.2, 159.6, 159.2, 157.4, 151.4, 150.8, 150.4, 150.2, 149.4, 146.2, 145.8, 144.0, 142.8, 138.6, 138.2, 136.5, 136.4, 136.2, 136.1, 134.0, 133.8, 133.7, 131.2, 130.7, 130.0, 129.2, 128.9, 128.7, 128.3, 126.6, 124.3, 122.1, 122.0, 121.7, 121.6, 120.4, 119.8, 119.4, 118.9, 118.8, 118.7, 117.4, 117.3, 114.8, 114.7, 114.6, 114.4, 113.7, 113.6, 113.2, 111.3, 111.1, 110.9, 110.5, 56.5, 56.4, 56.1, 56.0, 55.7, 55.3, 55.2, 21.8, 21.7; ESI m/z relative intensity 449 ($MNa^+$ 85); TOFHRMS (+ESI) Calcd for $C_{27}H_{22}O_5Na$: 449.1365, Found 449.1346.

**11-(3,5-Dimethylphenyl)-5-hydroxy-4,9-dimethoxy-2-methyl-benzo[*b*]fluoren-10-one (39e).** Following General Procedure 2, diazoparaquinone **29** (20.0 mg, 0.060 mmol) was converted into a 3.1:1 mixture of benzo[*b*]fluorenone **39e** (2:4:5 = 50:50:0) (11.5 mg, 44%) and benzo[*b*]fluorenone **36** (3.4 mg, 14%). Note that the 4.0:1 ratio of **39e** to **36** that is reported in Table 2 reflects the average of five independent runs. **39e** isomers were separated via preparative TLC (1% EtOAc in $CH_2Cl_2$). 2,4-Dimethyl isomer: mp 220 °C (dec); IR (neat): 3195, 1633 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 10.67 (s, 1H), 7.59 (d, $J$ = 7.3 Hz, 1H), 7.49 (t, $J$ = 8.0 Hz, 1H), 7.12 (s, 1H), 7.09 (d, $J$ = 7.7 Hz, 1H), 7.05 (d, $J$ = 7.7 Hz, 1H), 7.00 (d, $J$ = 8.2 Hz, 1H), 6.68 (s, 1H), 6.58 (s, 1H), 4.11 (s, 3H), 3.89 (s, 3H), 2.37 (s, 3H), 2.30 (s, 3H), 2.13 (s, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 181.5, 161.3, 151.4, 150.4, 146.1, 144.3, 138.4, 137.1, 136.5, 136.5, 133.9, 131.9, 130.8, 129.9, 128.4, 126.1, 121.4, 119.4, 118.6, 117.3, 114.5, 114.4, 111.1, 56.5, 56.1, 21.7, 21.3, 19.8; 2,6-dimethyl isomer: mp 250 °C (dec); IR (neat): 3194, 1633 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 10.64 (s, 1H), 7.60 (d, $J$ = 7.5 Hz, 1H), 7.49 (t, $J$ = 7.8 Hz, 1H), 7.18 (t, $J$ = 8.1 Hz, 1H), 7.10 (d, $J$ = 7.6 Hz, 2H), 7.01 (d, $J$ = 8.1 Hz, 1H), 6.69 (s, 1H), 6.45 (s, 1H), 4.12 (s, 3H), 3.89 (s, 3H), 2.30 (s, 3H), 2.04 (s, 6H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 181.5, 161.3, 151.5, 150.3, 145.9, 143.3, 138.6, 136.6, 135.9, 134.8, 134.0, 130.8, 130.0, 127.1, 127.0, 121.1, 119.5, 118.0, 117.3, 114.5, 111.2, 56.4, 56.1, 20.7 20.1; ESI m/z relative intensity 425 ($MH^+$ 50); TOFHRMS (+ESI) Calcd for $C_{28}H_{25}O_4$: 425.1753, Found 425.1740.

**11-(3,5-Dimethoxyphenyl)-5-hydroxy-4,9-dimethoxy-2-methyl-benzo[*b*]fluoren-10-one (39f).** Following General Procedure 2, diazoparaquinone **29** (20.0 mg, 0.060 mmol) was converted into a 4.2:1 mixture of benzo[*b*]fluorenone **39f** (2,4-:2,6-;3,5- = 31:69:0) (16.2 mg, 59%) and benzo[*b*]fluorenone **36** (3.4 mg, 14%). Note that the 4.2:1 ratio of **39f** to **36** that is reported in Table 2 reflects the average of five independent runs. 2,4-Dimethoxy isomer: mp 190 °C (dec); IR (neat): 3195, 1633 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 10.68 (s, 1H), 7.57 (d, $J$ = 7.6 Hz, 1H), 7.46 (t, $J$ = 8.2 Hz, 1H), 7.31 (d, $J$ = 8.9 Hz, 1H), 6.99 (d, $J$ = 8.3 Hz, 1H), 6.70 (s, 1H), 6.65 (s, 1H), 6.59 (m, 2H), 4.08 (s, 3H), 3.89 (s, 3H), 3.87 (s, 3H), 3.72 (s, 3H), 2.32 (s, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 181.3, 161.2, 160.9, 158.9, 151.4, 150.0, 144.1, 142.8, 138.0, 136.5, 133.6, 131.5, 128.3, 121.8, 119.5, 118.8, 117.2, 116.8, 114.7, 114.5, 110.9, 104.5, 99.0, 56.5, 56.1, 55.6, 55.4, 21.8; 2,6-dimethoxy isomer: mp 180 °C (dec); IR (neat): 3190, 1633 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 10.80 (s, 1H), 7.58 (d, $J$ = 8.1 Hz, 1H), 7.47 (t, $J$ = 8.1 Hz, 1H), 7.30 (t, $J$ = 8.3 Hz, 1H), 6.99 (d,

$J$ = 8.2 Hz, 1H), 6.65 (d, $J$ = 8.5 Hz, 2H) 6.64 (s, 1H), 6.57 (s, 1H), 4.08 (s, 3H), 3.89 (s, 3H), 3.68 (s, 6H), 2.30 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 181.1, 161.1, 158.5, 151.5, 150.0. 144.0, 130.4, 138.1, 136.7, 136.3, 133.6, 129.1, 121.6, 119.5, 118.5, 117.2, 114.9, 114.5, 113.7, 113.3, 110.9, 110.6, 104.3, 56.2, 56.1, 56.0, 21.8; ESI m/z relative intensity 457 ($MH^+$ 30); TOFHRMS (+ESI) Calcd for $C_{28}H_{25}O_6$: 457.1651, Found 457.1653.

**5-(5-Hydroxy-4,9-dimethoxy-2-methyl-10-oxo-10H-benzo[*b*]fluoren-11-yl)isophthalonitrile (39g).** Due to the insolubility of 1,3-dicyanobenzene in benzene at 80 °C, the following experiment was run at a 13:1 ratio of benzene:1,3-dicyanobenzene. Solid AIBN (11.0 mg, 0.066 mmol) was added portionwise over a period of 1 h to a stirring solution of diazoparaquinone **29** (20.0 mg, 0.060 mmol), 1,3-dicyanobenzene (0.11 g, 0.86 mmol), and $Bu_3SnH$ (0.018 mL, 0.066 mmol) in benzene (1.0 mL, 11 mmol) at 80 °C. When the addition was complete, the reaction solution was allowed to cool to room temperature. After reaching room temperature the reaction mixture was diluted with $CH_2Cl_2$ and purified with flash column chromatography, eluting with an increasing percentage of EtOAc from 0% to 10% in $CH_2Cl_2$. Purification furnished a 1:2.2 mixture of benzo[*b*]fluorenone **39g** (2,4-:2,6-;3,5- = 24:76:0) (6.5 mg, 24%) and benzo[*b*]fluorenone **36** (12.4 mg, 52%). The ratio of **39g**:**36**, extrapolated to equimolar amounts of benzene and 1,3-dicyanobenzene, is calculated to be 6.0:1. Note that the 6.1:1 ratio of **39g** to **36** that is reported in Table 2 reflects the average of five independent runs. **39g** isomers were separated via preparative TLC (20% EtOAc in benzene). 2,4-Dicyano isomer: mp 270 °C (dec); IR (neat): 3213, 2526, 1633 $cm^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 10.97 (s, 1H), 8.04 (s, 1H), 7.91 (d, $J$ = 8.1 Hz, 1H), 7.63 (d, $J$ = 8.1 Hz, 1H), 7.61 (d, $J$ = 7.3 Hz, 1H), 7.53 (t, $J$ = 8.1 Hz, 1H), 7.06 (d, $J$ = 8.1 Hz, 1H), 6.72 (s, 1H), 6.54 (s, 1H), 4.13 (s, 3H), 3.93 (s, 3H), 2.35 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 181.4, 161.5, 153.7, 151.7, 144.6, 141.8, 138.9, 137.4, 136.2, 136.2, 135.3, 134.8, 131.4, 131.3, 120.58, 119.6, 118.1, 117.2, 117.1, 116.2, 115.6, 115.0, 114.0, 112.3, 111.5, 56.6, 56.3, 21.8; 2,6-isomer: mp 290 °C (dec); IR (neat): 3213, 2238, 1631 $cm^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 10.99 (s, 1H), 7.96 (d, $J$ = 8.0 Hz, 1H), 7.62 (d, $J$ = 8.2 Hz, 1H), 7.60 (t, $J$ = 7.9 Hz, 1H), 7.53 (d, $J$ = 8.2 Hz, 1H), 7.06 (d, $J$ = 8.4 Hz, 2H) 6.72 (s, 1H), 6.48 (s, 1H), 4.13 (s, 3H), 3.93 (s, 3H), 2.34 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 161.5, 153.9, 151.7, 144.4, 141.5, 138.8, 136.5, 136.3, 135.0, 134.8, 132.2, 131.9, 128.4, 120.5, 119.6, 118.2, 117.1, 116.4, 115.5, 115.0, 114.1, 111.6, 56.6, 56.4, 21.9; ESI m/z relative intensity 469 ($MNa^+$ 100); TOFHRMS (+ESI) Calcd for $C_{28}H_{18}N_2O_4Na$: 469.1164, Found 469.1156.

**C(11) Dimer of 5-Hydroxy-4,9-dimethoxy-2-methyl-benzo[*b*]-fluoren-10-one (49).** Following General Procedure 2, in many of the solvent competition experiments aimed at converting diazoparaquinone **29** (20 mg, 0.06 mmol) to the aromatic solvent-trapped adducts (**36** + **39a**−**g**), the dimeric species (**49**) was isolated as a minor product (0−3.3 mg, 0−15%): mp 210 °C (dec); IR (neat): 3414, 2921, 1626 $cm^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 10.64 (s, 1H), 7.59 (d, $J$ = 7.9 Hz, 1H), 7.47 (t, $J$ = 8.17 Hz, 1H), 6.96 (d, $J$ = 7.7 Hz, 1H), 6.62 (d, $J$ = 8.1 Hz, 1H), 4.10 (s, 3H), 3.83 (s, 3H), 2.23 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 180.8, 161.2, 151.6, 150.2, 142.7, 141.2, 138.3, 136.7, 133.8, 131.1, 121.3, 120.2, 118.3, 117.3, 115.0, 114.4, 111.1, 56.5, 56.1, 21.8; ESI m/z relative intensity 639 ($MH^+$ 100); TOFHRMS (+ESI) Calcd for $C_{40}H_{31}O_8$: 639.2019, Found 639.2047.

**5-Hydroxy-4,9-dimethoxy-2-methyl-11-phenylselanyl-benzo[*b*]-fluoren-10-one (51).** A solution of AIBN (11.0 mg, 0.067 mmol) in benzene (1 mL) was added over the period of 1 h to a stirring solution of diazoparaquinone **29** (20 mg, 0.06 mmol), $Bu_3SnH$ (0.018 mL, 0.067 mmol), and diphenyl diselenide (0.112 mg, 0.36 mmol) at 80 °C. The light red mixture turned to a dark red/purple color upon addition of AIBN. When the addition was complete, the reaction solution was allowed to cool to room temperature. After reaching room temperature the reaction mixture was diluted with $CH_2Cl_2$ and poured onto a $AgNO_3$ impregnated silica gel column (silica gel column chromatography alone was insufficient for separation) and purified by eluting with $CH_2Cl_2$ with an increasing percentage of EtOAc from 0% to 10%. Purification furnished the benzene-trapped adduct **36** (5.0 mg, 21%), and the phenylselenide-trapped adduct **51** (10 mg, 35%): mp 162 °C (dec); IR (neat): 3414, 2919, 1631, 1607, 1583 $cm^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 10.42 (s, 1H), 7.80 (d, $J$ = 7.0 Hz, 1H), 7.62 (d, $J$ = 8.3 Hz, 2H), 7.52 (t, $J$ = 8.1 Hz, 1H), 7.44 (t, $J$ = 7.2 Hz, 1H), 7.35 (t, $J$ = 7.1 Hz, 2H), 7.06 (d, $J$ = 8.2 Hz, 1H), 6.53 (s, 1H), 5.75 (s, 1H), 4.03 (s, 3H), 4.02 (s, 3H), 1.96 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 180.6, 161.3, 151.1, 147.6, 143.8, 142.4, 137.4, 136.4, 136.3, 133.7, 131.7, 129.1, 128.9, 128.7, 121.3, 120.1, 117.2, 113.6, 113.5, 113.4, 110.9, 56.4, 56.1, 21.7; ESI m/z relative intensity 477 ($MH^+$ 100); TOFHRMS (+ESI) Calcd for $C_{26}H_{21}O_4Se$: 477.0605, Found 477.0615.

**11-Benzylsulfanyl-4,9-dimethoxy-2-methyl-11-phenyl-benzo[*b*]-fluorene-5,10-diol (53), and 11-Benzylsulfanyl-4,9-dimethoxy-2-methyl-11H-benzo[*b*]fluorene-5,10-diol (54).** A Solution of AIBN (11.0 mg, 0.067 mmol) in benzene (1 mL) was added over the period of 1 h to a stirring solution of diazoparaquinone **29** (20 mg, 0.06 mmol), $Bu_3SnH$ (0.018 mL, 0.067 mmol, 1.1 equiv) (or 12 equiv), and benzyl mercaptan (0.077 mL, 0.6 mmol) at 80 °C. The light red mixture turned to a dark red color upon addition of AIBN. When the addition was complete, the reaction solution was allowed to cool to room temperature. After reaching room temperature the reaction mixture was diluted with $CH_2Cl_2$ and poured onto a silica gel column and purified by eluting with hexanes/$CH_2Cl_2$ (1:1) followed by $CH_2Cl_2$ with an increasing percentage of EtOAc from 0% to 5%. Oxidation of the air-sensitive hydroquinone **54** was minimized during purification by employing $N_2$ purged solvents and using low-pressure $N_2$ gas for the chromatography. Purification furnished the benzene-trapped adduct **36** (3.5 mg, 15%), the benzene/benzyl mercaptan-trapped adduct **53** (6.7 mg, 22%) and the benzyl mercaptan-trapped adduct **54** (12.5 mg, 46%). **53**: mp 260 °C (dec); IR (neat): 3378, 3307, 2922, 1644, 1610 $cm^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 9.85 (s, 1H), 9.12 (s, 1H) 7.95 (d, $J$ = 8.5 Hz, 1H), 7.50 (d, $J$ = 8.6 Hz, 2H), 7.33 (t, $J$ = 7.8 Hz, 1H), 7.19−7.27 (m, 3H), 6.94−7.04 (m, 5H), 6.91 (s, 1H), 6.79 (d, $J$ = 7.7 Hz, 1H), 6.65 (s, 1H), 4.16 (s, 3H), 3.96 (s, 3H), 3.25 (d, $J$ = 12.6 Hz, 1H), 3.14 (d, $J$ = 12.6 Hz, 1H), 2.30 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 156.5, 152.6, 151.0, 143.5, 141.4, 139.8, 138.9, 137.6, 128.8, 128.3, 128.1, 127.7, 126.9, 126.8, 126.2, 126.0, 125.0, 123.8, 120.4, 120.2, 116.7, 115.8, 111.3, 104.9, 64.0, 56.5, 55.8, 34.4, 29.7; ESI m/z relative intensity 543 ($MNa^+$ 40); TOFHRMS (+ESI) Calcd for $C_{33}H_{28}O_4SNa$: 543.1606, Found 543.1647; **54**: mp 160 °C (dec); IR (neat): 3389, 3311, 2921, 1611, 1580 $cm^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 9.64 (s, 1H), 9.26 (s, 1H), 7.86 (d, $J$ = 8.5 Hz, 1H), 7.26 (t, $J$ = 7.8 Hz, 1H), 6.89−7.03 (m, 6H), 6.76 (d, $J$ = 7.6 Hz, 1H), 6.62 (s, 1H), 5.05 (s, 1H), 4.02 (s, 3H), 3.99 (s, 3H), 3.40 (d, $J$ = 12.9 Hz, 1H), 3.22 (d, $J$ = 12.9 Hz, 1H), 2.32 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 156.3, 151.3, 147.4, 143.5, 139.3, 139.1, 138.4, 128.9, 128.0, 127.9, 126.3, 125.1, 124.8, 122.6, 120.8, 120.3, 116.8, 115.3, 111.3, 104.9, 56.5, 56.0, 48.0, 33.5, 29.7; ESI m/z relative intensity 467 ($MNa^+$ 95); TOFHRMS (+ESI) Calcd for $C_{27}H_{24}O_4SNa$: 467.1293, Found 467.1301.

**Control Experiment: Benzyl Mercaptan Addition to Diazoparaquinone 29 with No Radical-Generating Ingredients.** Benzyl mercaptan (0.019 mL, 0.15 mmol) was added to a stirring solution of diazoparaquinone **29** (5.0 mg, 0.015 mmol) at 80 °C. The light red mixture was stirred at 80 °C for 1 h. Following 1 h of stirring, the reaction solution was allowed to cool to room temperature. After reaching room temperature the reaction mixture was diluted with $CH_2Cl_2$ and poured onto a silica gel column and purified by eluting with hexanes/$CH_2Cl_2$ (1:1), followed by $CH_2Cl_2$ with an increasing percentage of EtOAc from 0% to 5%. Purification provided diazoparaquinone **29** (4.7 mg, 94%) unchanged.

**Control Experiment: Benzyl Mercaptan Addition to Prekinamycin (5) with No Radical-Generating Ingredients.** Benzyl mercaptan (0.015 mL, 0.12 mmol) was added to a stirring solution of prekinamycin (**5**) (3.7 mg, 0.012 mmol) at 80 °C. The dark purple/

brown mixture was stirred at 80 °C for 1 h. Following 1 h of stirring, the reaction solution was allowed to cool to room temperature. After reaching room temperature the reaction mixture was diluted with $CH_2Cl_2$ and poured onto a silica gel column and purified by eluting with hexanes/$CH_2Cl_2$ (1:1), followed by $CH_2Cl_2$ with an increasing percentage of EtOAc from 0% to 5%. Purification provided prekinamycin (**5**) (3.7 mg, 100%) unchanged.

**11-Benzylsulfanyl-4,9-dimethoxy-2-methyl-11-phenyl-benzo[*b*]-fluorene-5,10-diol (53) from Benzene-Trapped Adduct (36).** Benzyl mercaptan (0.100 mL, 0.80 mmol) was added to a stirring solution of benzene-trapped adduct **36** (3.0 mg, 0.008 mmol) at 80 °C. The bright red solution turned to a dark red solution over the 2 h of stirring at 80 °C. Upon consumption of the starting material by TLC, the reaction solution was allowed to cool to room temperature. After reaching room temperature the reaction mixture was diluted with $CH_2Cl_2$ and poured onto a silica gel column and purified by eluting with hexanes/$CH_2Cl_2$ (1:1), followed by $CH_2Cl_2$ with an increasing percentage of EtOAc from 0% to 5%. Purification afforded benzyl mercaptan addition product **53** (3.7 mg, 94%).

**Deuterium-Labeling Experiment: $PhCH_2SD/Bu_3SnH/AIBN$.** A solution of AIBN (11.0 mg, 0.067 mmol) in benzene (1 mL) was added over the period of 1 h to a stirring solution of diazoparaquinone **29** (20 mg, 0.06 mmol), $Bu_3SnH$ (0.018 mL, 0.067 mmol), and $PhCH_2SD$ (0.077 mL, 0.6 mmol) at 80 °C. The light red mixture turned to a dark red color upon addition of AIBN. When the addition was complete, the reaction solution was allowed to cool to room temperature. After reaching room temperature the reaction mixture was diluted with $CH_2Cl_2$ and poured onto a silica gel column and purified by eluting with hexanes/$CH_2Cl_2$ (1:1), followed by $CH_2Cl_2$ with an increasing percentage of EtOAc from 0% to 5%. Purification furnished benzyl mercaptan-trapped adduct **54** (33% by $^1$H NMR) with 46% deuterium incorporation at C(11). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 9.64 (s, 1H), 9.26 (s, 1H), 7.86 (d, $J$ = 8.5 Hz, 1H), 7.26 (t, $J$ = 7.8 Hz, 1H), 6.89−7.03 (m, 6H), 6.76 (d, $J$ = 7.6 Hz, 1H), 6.62 (s, 1H), 5.05 (s, 0.54H), 4.02 (s, 3H), 3.99 (s, 3H), 3.40 (d, $J$ = 12.9 Hz, 1H), 3.22 (d, $J$ = 12.9 Hz, 1H), 2.32 (s, 3H).

**Deuterium-Labeling Experiment: $PhCH_2SH/Bu_3SnD/AIBN$.** A solution of AIBN (11.0 mg, 0.067 mmol) in benzene (1 mL) was added over the period of 1 h to a stirring solution of diazoparaquinone **29** (20 mg, 0.06 mmol), $Bu_3SnD$ (0.018 mL, 0.067 mmol), and $PhCH_2SH$ (0.077 mL, 0.6 mmol) at 80 °C. The light red mixture turned to a dark brown color upon addition of AIBN. When the addition was complete, the reaction solution was allowed to cool to room temperature. After reaching room temperature the reaction mixture was diluted with $CH_2Cl_2$ and poured onto a silica gel column and purified by eluting with hexanes/$CH_2Cl_2$ (1:1), followed by $CH_2Cl_2$ with an increasing percentage of EtOAc from 0% to 5%. Purification furnished benzyl mercaptan-trapped adduct **54** (40% by $^1$H NMR) with 27% deuterium incorporation at C(11). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 9.64 (s, 1H), 9.26 (s, 1H), 7.86 (d, $J$ = 8.5 Hz, 1H), 7.26 (t, $J$ = 7.8 Hz, 1H), 6.89−7.03 (m, 6H), 6.76 (d, $J$ = 7.6 Hz, 1H), 6.62 (s, 1H), 5.05 (s, 0.73H), 4.02 (s, 3H), 3.99 (s, 3H), 3.40 (d, $J$ = 12.9 Hz, 1H), 3.22 (d, $J$ = 12.9 Hz, 1H), 2.32 (s, 3H).

**Deuterium-Labeling Experiment: $PhCH_2SD/Bu_3SnD/AIBN$.** A solution of AIBN (11.0 mg, 0.067 mmol) in benzene (1 mL) was added over the period of 1 h to a stirring solution of diazoparaquinone **29** (20 mg, 0.06 mmol), $Bu_3SnD$ (0.018 mL, 0.067 mmol), and $PhCH_2SD$ (0.077 mL, 0.6 mmol) at 80 °C. The light red mixture turned to a dark brown color upon addition of AIBN. When the addition was complete, the reaction solution was allowed to cool to room temperature. After reaching room temperature the reaction mixture was diluted with $CH_2Cl_2$ and poured onto a silica gel column and purified by eluting with hexanes/$CH_2Cl_2$ (1:1) followed $CH_2Cl_2$ with an increasing percentage of EtOAc from 0% to 5%. Purification furnished benzyl mercaptan-trapped adduct **54** (46% by $^1$H NMR) with 76% deuterium incorporation at C(11). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 9.64 (s, 1H), 9.26 (s, 1H), 7.86 (d, $J$ = 8.5 Hz, 1H), 7.26 (t, $J$ = 7.8 Hz, 1H), 6.89−7.03 (m, 6H), 6.76 (d, $J$ = 7.6 Hz, 1H), 6.62 (s, 1H), 5.05 (s, 0.24H), 4.02 (s, 3H), 3.99 (s, 3H), 3.40 (d, $J$ = 12.9 Hz, 1H), 3.22 (d, $J$ = 12.9 Hz, 1H), 2.32 (s, 3H).

**Deuterium-Crossover Control Experiment: $PhCH_2SD/Bu_3SnH/AIBN$.** AIBN (12.0 mg, 0.073 mmol), $PhCH_2SD$ (0.010 mL, 0.073 mmol), and $Bu_3SnH$ (0.020 mL, 0.073 mmol) were dissolved in $d_6$-benzene (1 mL) and inspected by $^1$H NMR, and it was noted that a triplet at 1.43 ppm ($PhCH_2S\underline{H}$) was absent. The reaction solution was then heated at 80 °C for 1 h. After 1 h at 80 °C, close inspection of the $^1$H NMR spectrum did not provide any evidence for a signal at 1.43 ppm.

**Deuterium-Crossover Control Experiment: $Bu_3SnD/PhCH_2SH/AIBN$.** AIBN (12.0 mg, 0.073 mmol), $Bu_3SnD$ (0.020 mL, 0.073 mmol), and $PhCH_2SH$ (0.010 mL, 0.073 mmol) were dissolved in $d_6$-benzene (1 mL) and inspected by $^1$H NMR, and the presence of a triplet at 1.43 ppm (1H) ($PhCH_2S\underline{H}$) was noted. The reaction solution was then heated at 80 °C for 1 h. After 1 h at 80 °C, close inspection of the $^1$H NMR spectrum revealed that the triplet at 1.43 ppm remained and had not diminished in intensity.

**Acknowledgment.** Financial support from the National Institutes of Health, General Medical Sciences Division (GM 37861) is gratefully acknowledged.

**Note Added after ASAP Publication.** There were missing nitrogen, hydrogen, and complete compound labels in Scheme 2 published ASAP August 29, 2006; the corrected version was published ASAP September 6, 2006.

**Supporting Information Available:** Copies of $^1$H and $^{13}$C NMR spectra for **34a**, **35**, **37**, **38**, **39a**−**g**, **49**, **51**, **53**, and **54** as proof of purity. This material is available free of charge via the Internet at http://pubs.acs.org.

JA0642616