A Convergent Synthetic Route to (+)-Dynemicin A and Analogs of Wide Structural Variability

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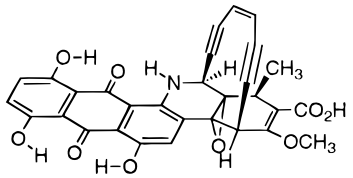
Abstract: An enantioselective synthetic route to (+)-dynemicin A (**1**) is described that involves as the key and final step the Diels−Alder cycloaddition of the quinone imine **6** with the isobenzofuran **107** followed by an oxidative workup to provide (+)-**1** in 40% yield. The synthetic route begins with the condensation of (−)-menthyl acetoacetate and *trans*-ethyl crotonate to form the crystalline cyclohexanedione **14**, which is then transformed to the enantiomerically pure quinone imine **6** in 23 steps with an average yield of 85% and an overall yield of 2−3%. Key features of this sequence include the coupling of the enol triflate **11** and the arylboronic acid **10** (90%), the thermal deprotection/internal amidation of the coupling product **18** (84%), the use of 2-chloropyridine as an economical alternative to 2,6-di-*tert*-butylpyridine to promote the reaction of the quinolone **9** and triflic anhydride (85%), the highly stereoselective addition of the (*Z*)-enediyne **31** to the quinoline **61** (89%), intramolecular acetylide addition within the acetylenic ketone **66** (94%), and oxidation of the phenol **76** with iodosobenzene to afford the quinone imine precursor **77** in 89% yield. Both the quinone imine and isobenzofuran components of the final coupling reaction can be varied, thus providing an ideal route for the preparation of a wide variety of dynemicin analogs.

Introduction and Retrosynthetic Analysis

Dynemicin A (**1**) is a recently isolated member of the enediyne family of natural products with potent in vitro and in vivo cytotoxicity against a variety of murine and human tumor cell lines.[1] Even among the highly unusual structures that define the enediyne antibiotics, dynemicin A (**1**) is distinctive. It is the only member of the series that contains an anthraquinone, a structural feature that is also common to the anthracycline antibiotics.[2] The anthraquinone is believed to function as an



Dynemicin A (**1**)

intercalating agent in the binding of **1** to DNA and as the initial site of reduction in the activation of **1** as a DNA-cleaving agent.[3] The latter activity is speculated to account for the antitumor properties of **1**. The anthraquinone lends an aesthetic quality to the dynemicins as well, for they are the only enediynes that are pigmented, violet in the solid state and deep blue in solution.

Dynemicin A is the only enediyne antibiotic, as the series is currently defined, that lacks carbohydrate residues. All other members of the class contain one or more carbohydrate residues, at least one of which is an aminoglycoside. As a consequence, each of the enediyne antibiotics is positively charged at physiological pH, with the exception of **1**, which, due to its carboxylic acid group, is anionic at pH 7. This distinction is correctly anticipated to have profound consequences in terms of DNA binding.

Other notable features of the dynemicin structure, with a perspective toward chemical synthesis, are the vinylogous carbonic acid ester of the A ring, the β-oriented methyl group, also of the A ring, and, most importantly, the contiguous enediyne and epoxide functional groups that bridge a common bicyclic ring system. These structural features, together with the potent antitumor activity of **1**, serve to define a challenging and important problem in chemical synthesis.

The first reports describing synthetic efforts relevant to dynemicin A (**1**), from the laboratories of Nicolaou,[4] Schreiber,[5] Magnus,[6] and Wender,[7] concerned important developments leading to the construction of analogs that contained the strained epoxy (*Z*)-enediyne component of **1**. The route employed by Schreiber et al.[5a,b] was extended in the first preparation of a

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(1) (a) Konishi, M.; Ohkuma, H.; Matsumoto, K.; Tsuno, T.; Kamei, H.; Miyaki, T.; Oki, T.; Kawaguchi, H.; VanDuyne, G. D.; Clardy, J. *J. Antibiot.* **1989**, *42*, 1449. (b) Konishi, M.; Ohkuma, H.; Tsuno, T.; Oki, T.; VanDuyne, G. D.; Clardy, J. *J. Am. Chem. Soc.* **1990**, *112*, 3715. (c) Shiomi, K.; Iinuma, H.; Naganawa, H.; Hamada, M.; Hattori, S.; Nakamura, H.; Takeuchi, T.; Iitaka, Y. *J. Antibiot.* **1990**, *43*, 1000. (d) Konishi, M.; Ohkuma, H.; Matsumoto, K.; Saitoh, K.; Miyaki, T.; Oki, T.; Kawaguchi, H. *J. Antibiot*. **1991**, *44*, 1300. (e) Kamei, H.; Nishiyama, Y.; Takahashi, A.; Yumiko, O.; Oki, T. *J. Antibiot*. **1991**, *44*, 1036. (f) Miyoshi-Saitoh, M.; Morisaki, N.; Tokiwa, Y.; Iwasaki, S.; Konishi, M.; Saitoh, K.; Oki, T. *J. Antibiot*. **1991**, *44*, 1037.

(2) (a) *Anthracycline Antibiotics*; El Khadem, H. S., Ed.; Academic: New York, 1982. (b) Recent Aspects in Anthracyclinone Chemistry. *Tetrahedron* **1984**, *40*, 4537. (c) *Anthracycline and Anthracenedione-Based Anticancer Agents*; Lown, J. W., Ed.; Elsevier: Amsterdam, 1988. (d) Fisher, J. F.; Aristoff, P. A. *Prog. Drug Res.* **1988**, *32*, 411.

(3) (a) Sugiura, Y.; Shiraki, T.; Konishi, M.; Oki, T. *Proc. Nat. Acad. Sci. U.S.A.* **1990**, *87*, 3831. (b) Semmelhack, M. F.; Gallagher, J.; Cohen, D. *Tetrahedron Lett*. **1990**, *31*, 1521. (c) Snyder, J. P.; Tipsword, G. E. *J. Am. Chem. Soc.* **1990**, *112*, 4040. (d) Shiraki, T.; Sugiura, Y. *Biochemistry* **1990**, *29*, 9795. (e) Sugiura, Y.; Arakawa, T.; Uesugi, M.; Shiraki, T.; Ohkuma, H.; Konishi, M. *Biochemistry* **1991**, *30*, 2989.

(4) Nicolaou, K. C.; Hwang, C.-K.; Smith, A. L.; Wendeborn, S. V. *J. Am. Chem. Soc.* **1990**, *112*, 7416.

(5) (a) Porco, J. A., Jr.; Schoenen, F. J.; Stout, T. J.; Clardy, J.; Schreiber, S. L. *J. Am. Chem. Soc.* **1990**, *112*, 7410. (b) Wood, J. L.; Porco, J. A., Jr.; Taunton, J.; Lee, A. Y.; Clardy, J.; Schreiber, S. L. *J. Am. Chem. Soc.* **1992**, *114*, 5898. (c) Taunton, J.; Wood, J. L.; Schreiber, S. L. *J. Am. Chem. Soc.* **1993**, *115*, 10378.

(6) Magnus, P.; Fortt, S. M. *J. Chem. Soc., Chem. Commun*. **1991**, 544.

(7) Wender, P. A.; Zercher, C. K. *J. Am. Chem. Soc.* **1991**, *113*, 2311.

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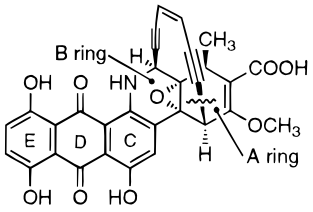
synthetic dynemicin, (±)-tri-*O*-methyldynemicin methyl ester.[5c] Contemporaneous with our own efforts toward the synthesis of the natural product itself, Danishefsky and co-workers have reported the development of an innovative strategy for the construction of the strained (*Z*)-enediyne functionality[8] of the dynemicins and have successfully applied this in a total synthesis of (±)-**1**.[9]

In this work, we describe in full our studies leading to an efficient, enantioselective synthetic route to (+)-**1**. The route we have developed has established the absolute configuration of natural dynemicin A [(+)-**1**] and has provided access to a wide variety of structural analogs of **1** by virtue of its late-stage convergence.[10] These structural analogs possess potent antitumor activity themselves and have enabled studies that have provided new insights into the mechanism of action of **1**.[10,11]

The exceptional reactivity of dynemicin A (**1**) enormously complicated the development of a route for its synthesis and, likely, its isolation from natural sources as well.[1a] Although the structural complexity of **1** alone is sufficient to define a challenging synthetic problem, reactivity considerations amplify the problem considerably from both strategic and operational points of view. It could be conjectured that any successful route to **1** (or any of the enediyne antibiotics) must follow a paradigm wherein those structural features responsible for the high reactivity of the final product are developed at as late a stage in the synthetic route as possible. The difficulty we faced in the initial stages of our synthetic planning was in the correct identification of the site of greatest reactivity within **1**. Influenced by our experience in synthetic studies of the highly reactive core structure of the enediyne antibiotic neocarzinostatin chromophore, we focused initially on the cyclic enediyne functionality of **1** and, accordingly, targeted this for retrosynthetic disconnection first. In the synthetic direction, we envisioned as a late-stage operation cyclization of the enediyne-containing ring by the formation of the σ bond indicated in the structure below.



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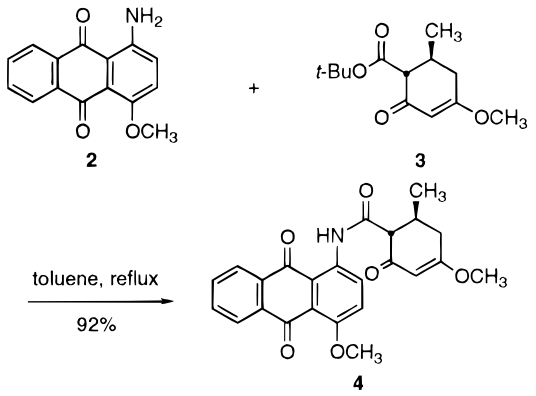
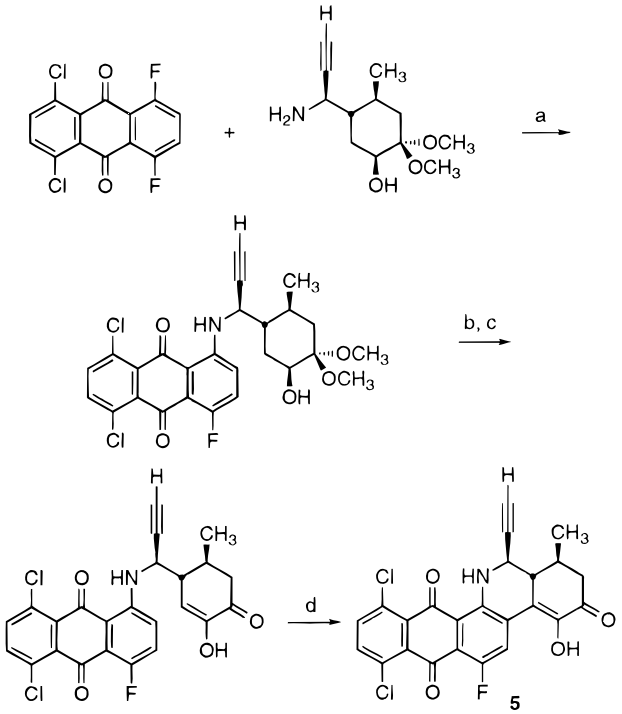
The targeting of related strategic bonds had proven viable for the construction of the core structures of the enediyne antibiotics calicheamicin,[12−14] esperamicin,[13,14] and neocarzinostatin chromophore[15] and, more recently, in syntheses of important analogs of the dynemicin structure.[4] Following retrosynthetic disconnection of the cyclic enediyne, our focus turned to assembly of the B ring by the joining of anthraquinone and A-ring fragments.



Our initial effort to execute this strategy was conducted in a model system and involved the coupling of the aminoanthraquinone **2** with the *tert*-butyl ester **3** (prepared in two steps from *tert*-butyl acetoacetate and *trans*-ethyl crotonate, vide infra) in a thermal condensation that was fashioned after the mechanistic studies of Witzeman on the transesterification of β-keto esters.[16] Although the coupling of the two components was quite efficient, this preliminary effort did not proceed further, due to our inability to close the B ring within the adduct **4** or any derivative of **4**.[17] Although the route was abandoned at this point, this preliminary venture was to greatly influence our final, successful synthetic plan.

A second attempt to construct the B ring by the coupling of anthraquinone and A-ring components was much more involved and proceeded as far as the pentacyclic intermediate **5** (Scheme 1).[17] Although we were able to close the B ring in this route by exploiting the propensity of anthraquinones to undergo nucleophilic addition to C-2 (as opposed to electrophilic attack at this site, the undoing of the first approach), the yield of both

Scheme 1



a. *i*-PrNH$_2$, DMF, 80 °C, 18%. b. PDC, CH_2Cl_2, 23 °C, 57%.
c. HCl, THF, reflux, 90%. d. Et_3N, DMF, 105 °C, 33%.

(8) Shair, M. D.; Yoon, T.-Y.; Danishefsky, S. J. *J. Org. Chem.* **1994**, *59*, 3755.

(9) (a) Shair, M. D.; Yoon, T.-Y.; Danishefsky, S. J. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1721. (b) Shair, M. D.; Yoon, T.-Y.; Mosny, K. K.; Chou, T. C.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1996**, *118*, 9509.

(10) Myers, A. G.; Fraley, M. E.; Tom, N. J.; Cohen, S. B.; Madar, D. J. *Chem. Biol.* **1995**, *2*, 33.

(11) Myers, A. G., Cohen, S. B., Tom, N. J., Madar, D. J., Fraley, M. E. *J. Am. Chem. Soc.* **1994**, *117*, 7574.

(12) Kende, A. S.; Smith, C. A. *Tetrahedron Lett.* **1988**, *29*, 4217.

(13) Schreiber, S. L.; Kiessling, L. L. *J. Am. Chem. Soc.* **1988**, *110*, 631.

(14) Danishefsky, S. J.; Mantlo, N. B.; Yamashita, D. S.; Schulte, G. *J. Am. Chem. Soc.* **1988**, *110*, 6890.

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

(16) (a) Witzeman, J. S. *Tetrahedron Lett.* **1990**, *31*, 1401. (b) Cohn, P. *Monatsh.* **1900**, *21*, 200. (c) Lapworth, A.; Hann, A. C. O. *J. Chem. Soc.* **1902**, *81*, 1499. (d) Carroll, M. F. *Proc. XIth Intern. Congr. Pure Applied Chem.* **1947**, *2*, 39. (e) Bader, A. R.; Cummings, L. O.; Vogel, H. A. *J. Am. Chem. Soc.* **1951**, *73*, 4195.

(17) Fraley, M. E. Ph.D. Thesis, California Institute of Technology, 1995.

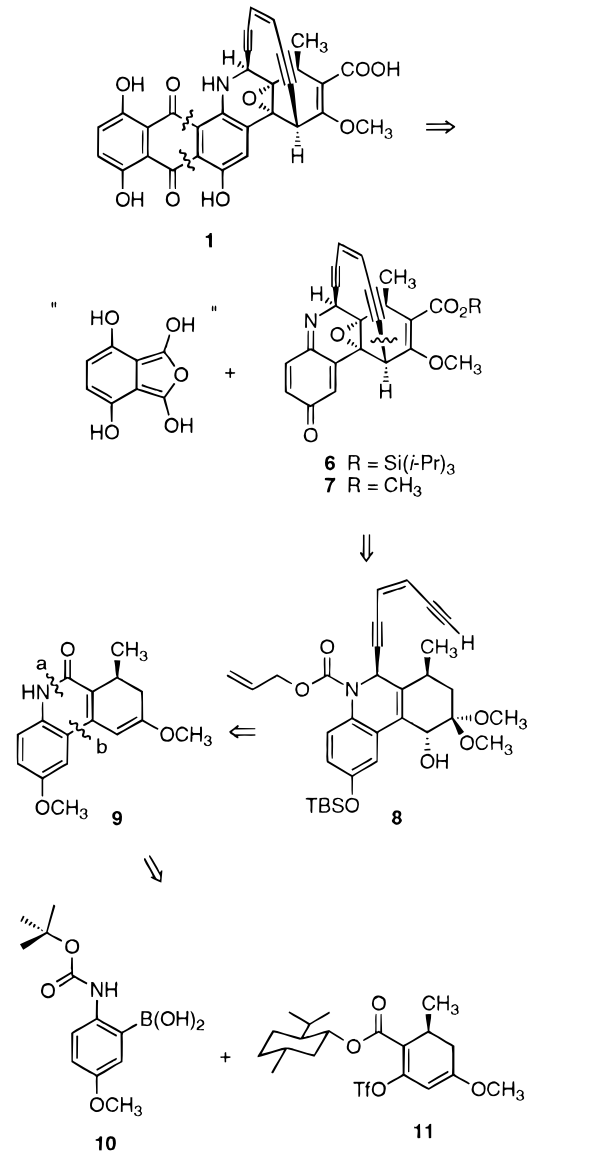
of the key steps that formed the B ring in this advanced model study was quite low. This was somewhat surprising, for simpler model studies of both steps had proceeded with much greater efficiencies. In both cases, the poor chemical yield was ascribed to competing reactions of the anthraquinone.

Contemporaneous observations in another synthetic project involving an anthraquinone[18] confirmed that even the simplest chemical transformations were capricious when conducted in the presence of an anthraquinone. In addition, anthraquinone-containing intermediates such as **5** were found to be poorly soluble and often decomposed on standing, features that, unavoidably, must emerge in the final stages of any successful route to **1**. Although cursory inspection might suggest that an intermediate such as **5** is far along a successful path to the dynemicins, we recognized the difficulty of such an endeavor and abandoned the route as impractical. Thus, by dint of experience we learned that the reactivity of the anthraquinone functional group virtually requires that it be introduced late in any successful synthetic scheme. Returning to our original premise, that the most reactive functional group must be introduced last, we modified our retrosynthetic plan to introduce the anthraquinone after construction of the strained epoxy (*Z*)-enediyne bridge.

With the benefit of retrospection, a new synthetic plan was devised wherein the anthraquinone would be introduced in the final step of the synthesis by a projected Diels−Alder addition reaction between a quinone imine such as **6** and a diene equivalent of tetrahydroxyisobenzofuran (Scheme 2). To our knowledge, the first use of an isobenzofuran−quinone Diels−Alder reaction for the construction of a complex anthraquinone was described by Kende et al. in synthetic studies of the anthracyclinones.[19] In implementing the isobenzofuran−quinone Diels−Alder strategy for the construction of **1**, it was necessary to develop a diene equivalent of 1,3,4,7-tetrahydroxyisobenzofuran that would undergo efficient Diels−Alder addition and, at the same time, would provide a cycloadduct that could be transformed into the anthraquinone under milder conditions and in fewer steps than allowed by existing methodology. This retrosynthetic plan held potentially enormous advantages over the prior strategies we had investigated, primarily due to its convergence. It reduced the problem of synthesizing **1** to the preparation of the quinone imine **6** and was particularly well suited for the preparation of dynemicin analogs. Although certain benzoquinone monoimines have been reported to be unstable,[20] we felt that the more complex quinone imine **6** would be a viable synthetic intermediate and, furthermore, that the electron-withdrawing nature of the quinone imine would serve to stabilize the reactive epoxide functionality. As detailed below, these projections proved to be correct.

Having defined the synthetic subgoal **6**, we could now return to our earlier retrosynthetic analysis wherein the cyclic enediyne was targeted for disconnection at the σ bond indicated in structure **6** to afford the synthetic precursor **8**. Implicit in the transformation of **8** to **6** was the oxidation of an electron-rich aromatic precursor to generate the quinone imine, as well as functional group modification within the A ring, according to our earlier strategy. It was further proposed that the quinolone **9** would serve as a key precursor for the synthesis of **8**. This

Scheme 2



analysis reduced the stereochemical complexity of **1** to a single stereogenic center, but brought with it the problem of stereocontrolled addition of the (*Z*)-enediyne group syn to the methyl group (vide infra). Finally, the quinolone **9** was disconnected retrosynthetically at bond a, by a proposed internal amidation of an amino ester, and then at bond b, by the palladium-catalyzed coupling of the arylboronic acid **10** and the enol triflate **11**. The successful realization of this synthetic plan is presented below.

Synthesis of (+)-Dynemicin A (1)

The first stage of the successful synthetic route to (+)-**1** involved the preparation of what would become the A ring of dynemicin A. The key constructive reaction selected for this purpose was a 3 + 3 condensation that forms a 1,3-cyclohexanedione as product (see structure **12**). This methodology, first described by von Schilling and Vorlünder in 1899,[21] involves the combination of a β-keto ester monoanion with an α,β-unsaturated ketone by sequential Michael addition[22] and Dieckman condensation[23] reactions. As it has been employed

(18) (a) Myers, A. G.; Dragovich, P. S. *J. Am. Chem. Soc.* **1992**, *114*, 5859. (b) Dragovich, P. S. Ph.D. Thesis, California Institute of Technology, 1993.

(19) Kende, A. S.; Curran, D. P.; Tsay, Y.-G.; Mills, J. E. *Tetrahedron Lett.* **1977**, 3537.

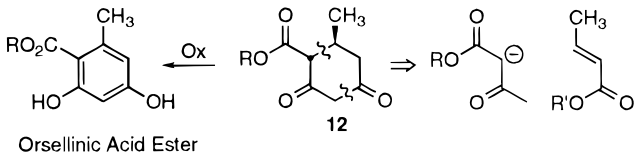
(20) (a) Swenton, J. S.; Shih, C.; Chen, C.-P.; Chou, C.-T. *J. Org. Chem.* **1990**, *55*, 2019. (b) Swenton, J. S.; Bonke, B. R.; Clark, W. M.; Chen, C.-P.; Martin, K. V. *J. Org. Chem.* **1990**, *55*, 2027.

(21) von Schilling, R.; Vorlünder, D. *Ann.* **1899**, *308*, 184.

(22) Michael, A. *J. Prakt. Chem.* **1887**, *35*, 349.

(23) Dieckmann, W. *Ber.* **1894**, *27*, 102.

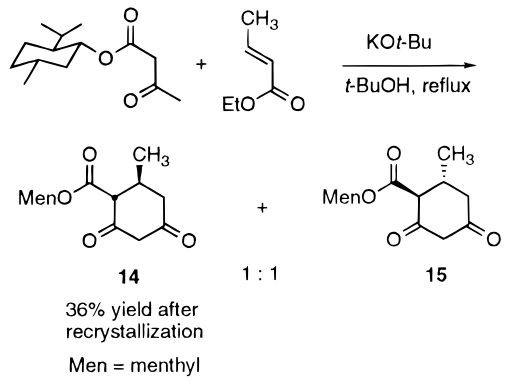
historically, the condensation reaction is typically followed by a two-electron oxidation step to provide an aromatic product, an orsellinic acid ester in the example shown below. We hoped



to avoid aromatization, and instead make use of the functionally rich 1,3-cyclohexanedione product **12** to prepare the enol triflate **11** for coupling with a dynemicin C-ring precursor (see Scheme 2). Also, because this step established the first stereogenic center in the synthesis, and that which ultimately controlled all others, we planned to explore asymmetric versions of the condensation reaction in order to achieve an enantioselective synthesis of dynemicin.

We first investigated the von Schilling−Vorlünder reaction[21] in racemic form. Optimal results were obtained when *tert*-butyl acetoacetate (1.05 equiv) and *trans*-ethyl crotonate (1 equiv) were combined as the condensation reagents along with potassium *tert*-butoxide (KO-*t*-Bu, 1.05 equiv) as base and *tert*-butyl alcohol as the solvent. After 1−1.5 h of heating at reflux, the potassium salt of the product began to crystallize from the reaction mixture and the reaction was complete within 2.5 h of heating. After an acidic aqueous workup and purification by recrystallization, the *tert*-butyl ester **13** was obtained in 87% yield. The keto−enol composition of **13** in solution was found to vary with concentration and solvent (^{1}H NMR analysis), with the diketo form favored in dilute solutions of chloroform-*d* ($\leq$1 mg/mL). On the basis of ^{1}H−^{1}H coupling constants, both the keto and enol forms of **13** exist with the methyl and ester groups in a trans relationship.

In order to bias the condensation reaction in an asymmetric fashion, we investigated the use of various acetoacetate esters derived from chiral alcohols. These were prepared by the thermal transesterification of *tert*-butyl acetoacetate with each alcohol, a transformation proposed to proceed via an acyl ketene intermediate.[16] For example, menthyl acetoacetate was prepared on a 500-g scale in 94% distilled yield by this method.[16b−e] Acetoacetate esters of fenchyl alcohol, borneol, and isoborneol were prepared similarly. The condensation of each of these β-keto esters with *trans*-ethyl crotonate revealed the menthyl ester to be the preferred substrate by virtue of the crystallinity of the reaction products. In the optimized procedure, the



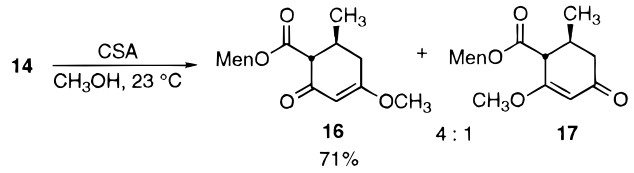
potassium salt of menthyl acetoacetate (1.04 equiv) was formed from 1.06 equiv of menthyl acetoacetate and 1.04 equiv of KO-*t*-Bu in *tert*-butyl alcohol at reflux. It was necessary to heat the resulting suspension in order to dissolve the enolate salt. Failing this, low yields of product were obtained in the subsequent condensation reaction. When largely dissolved, the enolate was treated with *trans*-ethyl crotonate (1 equiv) and the reaction mixture was heated at reflux for 2.5 h, followed by cooling and an acidic aqueous workup. The crude reaction mixture consisted of a 1:1 mixture of the two trans diastereoisomers **14** and **15**. Fortunately, the desired diastereomer (**14**) could be crystallized selectively from hot benzene, in about 36% combined yield for the condensation and crystallization steps. As with the *tert*-butyl ester **13**, the keto−enol composition of the menthyl ester **14** in solution varied with the solvent and concentration. The diketo form was favored in dilute solutions of chloroform-*d*, whereas a single enolic species was observed in dimethyl sulfoxide-d_6.[24]

Stereochemical assignments for the products of these reactions were established unequivocally by X-ray crystallography. Although crystals of **14** were unsuitable for X-ray analysis, the undesired diastereomer **15** did furnish suitable crystals when recrystallized from ethyl acetate−hexanes. The solid-state structure of **15** (see Supporting Information) verified that the menthyl ester and methyl groups were trans (previously established on the basis of ^{1}H−^{1}H coupling constants) and showed the less hindered carbonyl group of the 1,3-diketone to be in the enolic form. The stereochemistry of the desired diastereomer (**14**) was confirmed by X-ray crystallographic analysis of the product of the next synthetic step in the sequence (**16**) and by the eventual synthesis of (+)-**1**.

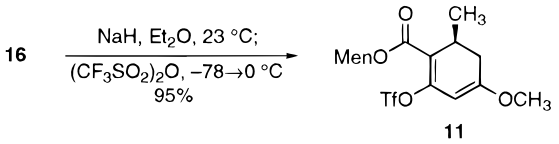
Because a 1:1 mixture of the two trans diastereomers **14** and **15** was produced in the condensation reaction, the menthyl "auxiliary" can be considered to have functioned as little more than a resolving agent. Nevertheless, this protocol proved to be quite effective for the large-scale production of **14**, with 100-g batches of crystalline **14** produced routinely from inexpensive starting materials. None of the other auxiliaries we examined offered the advantage of crystallinity exhibited by the menthyl ester, although fenchyl acetoacetate did offer an improved ratio of diastereomers (1.5:1, stereochemistry not determined). Modification of the crotonate ester component was also investigated as a means to improve the stereoselectivity of the condensation reaction with menthyl acetoacetate. Variously substituted aryl esters of crotonic acid were prepared and subjected to the cyclization reaction, with *o*-*tert*-butylphenyl emerging as the superior substrate, leading to a 1.5:1 mixture of cyclization products (67% combined yield) favoring the desired diastereomer (**14**). In practice, however, the benefits of this procedure did not outweigh the practicality of using commercial *trans*-ethyl crotonate in the condensation and so we adopted the latter, less selective reaction for the production of **14** on scale.

Stirring a methanolic solution of diketone **14** with camphorsulfonic acid (CSA) at 23 °C for 12 h led to the selective formation of the enol ether **16**, along with a lesser amount of the regioisomer **17** (ratio **16**:**17** ~4:1, respectively). The desired product (**16**) was cleanly separated from the minor regioisomer by flash column chromatography (71% yield from **14**). The minor regioisomer **17** could be resubjected to treatment with acidic methanol to return an apparently thermodynamic 4:1 distribution of **16** and **17**, respectively. ^{1}H NMR analysis of the product **16** showed that it was $\geq$95% trans (menthyl ester and methyl groups), but did contain a minor contaminant ($\leq$5%) that showed signals consistent with the cis stereoisomer. Upon slow evaporation of a dichloromethane−hexanes solution of **16**,

(24) Piskov, V. B.; Kasperovich, V. P. *Zh. Org. Khim.* **1985**, *21*, 1088. These authors report that the ^{1}H NMR of the methyl ester of **12** in dimethyl sulfoxide-d_6 showed two enol forms in a 6:1 ratio.

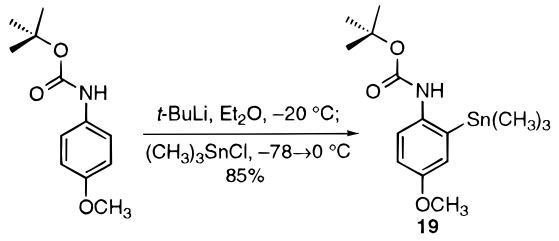


large prismatic crystals were deposited which proved suitable for X-ray crystallographic analysis. The crystals were uncontaminated with any cis isomer, and the X-ray structure (see Supporting Information) confirmed all stereochemical and regiochemical assignments. The presence of traces of the cis isomer in samples of **16** was inconsequential in the synthetic route, for both cis and trans isomers converged to the same product in the next step.

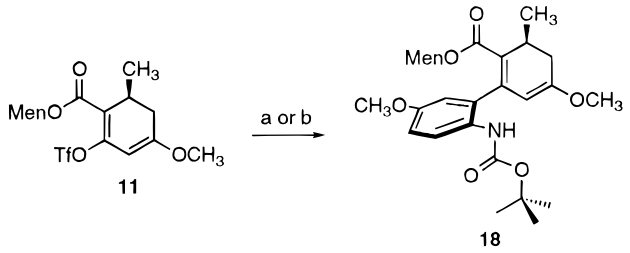


Deprotonation of the keto ester **16** with sodium hydride in ether and trapping of the resultant enolate with triflic anhydride (1.60 equiv) at −78 °C followed by warming to 0 °C afforded the corresponding enol triflate **11** as an oil in 95% yield. In large-scale preparations (≥10 g), **11** was not chromatographed, but was carried forward in crude form. Like many enol triflate derivatives, **11** was not suitable for storage and was therefore prepared immediately prior to its use in the subsequent coupling chemistry.

Two different protocols were developed for the coupling of the enol triflate **11** with an appropriate *tert*-butyl 2-metallo-4-methoxycarbanilate derivative to form the coupling product **18**. The first implemented was the Stille coupling[25] method and employed the 2-trimethylstannyl derivative **19** as the coupling partner. This arylstannane (**19**) was prepared in 85% yield by the dilithiation of *tert*-butyl 4-methoxycarbanilate (1 equiv) with *tert*-butyllithium (2.5 equiv) in ether at −20 °C, followed by trapping of the resultant dianion with trimethyltin chloride (2.5 equiv) at −78 °C.[26]

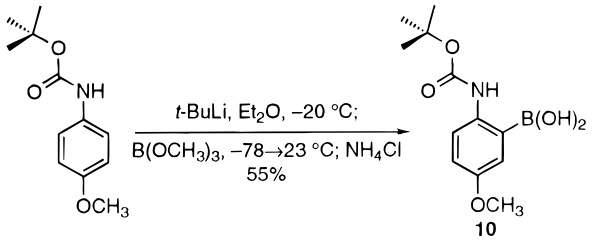


Heating a solution of the arylstannane **19** (1.05 equiv) and the enol triflate **11** (1 equiv) in the presence of tetrakis(triphenylphosphine)palladium(0) ($Pd(PPh_3)_4$, 0.05 equiv), cuprous iodide (0.04 equiv), 2,6-di-*tert*-butyl-4-methylphenol (0.018 equiv), and lithium chloride (4.4 equiv) in *p*-dioxane at reflux for 1 h afforded the coupling product **18** in 81% yield. A high barrier to rotation about the newly formed carbon−carbon bond was evident from the observation of two distinct sets of peaks, in approximately equal ratios, in both ^1H and ^{13}C NMR spectra, corresponding to atropisomeric forms of **18**.



a. **19**, $Pd(PPh_3)_4$, CuI, LiCl, BHT, *p*-dioxane, reflux, 81%. b. **10**, $Pd(PPh_3)_4$, Na_2CO_3, *p*-dioxane, reflux, 90%.

Although the Stille method was amenable to the preparation of multigram quantities of **18**, the expense and toxicity associated with the use of organotin reagents in the reaction led us to explore the Suzuki coupling protocol[27] as an alternative. Toward this end, the arylboronic acid **10** was synthesized in 55% yield by the trapping of dilithio *tert*-butyl 4-methylcarbanilate with trimethyl borate (−78 → 23 °C) followed by an acidic aqueous workup.



Heating a solution of the arylboronic acid **10** (1.1 equiv) and the enol triflate **11** (1 equiv) in *p*-dioxane in the presence of $Pd(PPh_3)_4$ (0.04 equiv) and sodium carbonate (1.4 equiv) at reflux for 45 min afforded the coupling product **18** in 90% yield. The Suzuki coupling protocol proved to be ideal for the large-scale synthesis of **18**; 25-g batches of crystalline **18** were routinely prepared by this method.

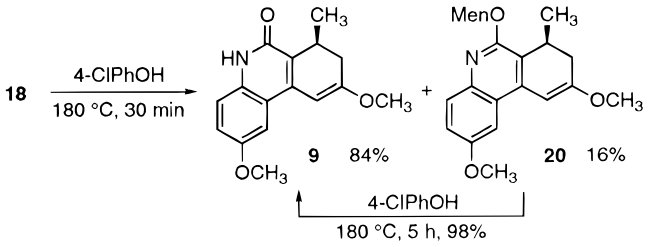
Deprotection of the *tert*-butyl carbamate group of **18** was investigated next in order to effect an internal amidation for the preparation of the key intermediate **9**. The deprotection and ring closure steps were conducted in a single operation. Although initial experiments established that the enol ether within **18** was not stable to strongly acidic conditions (e.g., trifluoroacetic acid in dichloromethane), by heating[28] **18** in the weakly acidic solvent 4-chlorophenol (180 °C, 30 min), the *tert*-butyl carbamate group was cleaved while preserving the enol ether function, affording the quinolone **9** in 84% yield. The menthyl quinolyl ether **20** was formed as a byproduct in this reaction (16%). This byproduct could be transformed into the desired product **9** in 98% yield by its resubjection to hot 4-chlorophenol (180 °C, 5 h). 4-Chlorophenol proved to be a nearly ideal solvent for the deprotection/amidation reaction and is believed to function as a mild Brönsted acid in the deprotection step. Preliminary experiments with aprotic solvents such as diphenyl ether showed a dramatic decrease in the rate of the deprotection reaction. When phenol itself was used as the solvent, the reaction was slower and was complicated by the formation of byproducts in which the solvent had been covalently incorporated into the substrate.

(25) (a) Scott, W. J.; Crisp, G. T.; Stille, J. K. *J. Am. Chem. Soc.* **1984**, *106*, 4630. (b) Liebeskind, L. S.; Fengl, R. W. *J. Org. Chem.* **1990**, *55*, 5359. (c) Gómez-Bengoa, E.; Echavarren, A. M. *J. Org. Chem.* **1991**, *56*, 3497.

(26) (a) Muchowski, J. M.; Venuti, M. C. *J. Org. Chem.* **1980**, *45*, 4798. (b) Stanetty, P.; Koller, H.; Mihovilovic, M. *J. Org. Chem.* **1992**, *57*, 6833.

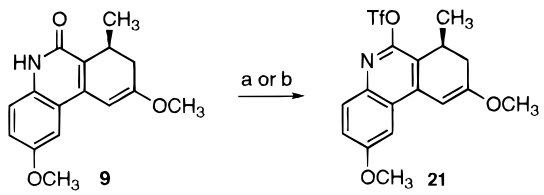
(27) (a) Miyaura, N.; Yanagi, T.; Suzuki, A. *Synth. Commun.* **1981**, *11*, 513. (b) Alo, B. I.; Kandil, A.; Patil, P. A.; Sharp, M. J.; Siddiqui, M. A.; Snieckus, V.; Josephy, P. D. *J. Org. Chem.* **1991**, *56*, 3763. (c) Yasuda, N.; Xavier, L.; Rieger, D. L.; Li, Y.; DeCamp, A. E.; Dolling, U.-H. *Tetrahedron Lett.* **1993**, *34*, 3211.

(28) (a) Wasserman, H. H.; Berger, G. D.; Cho, K. R. *Tetrahedron Lett.* **1982**, *23*, 465. (b) Rawal, V. H.; Jones, R. J.; Cava, M. P. *J. Org. Chem.* **1987**, *52*, 19.



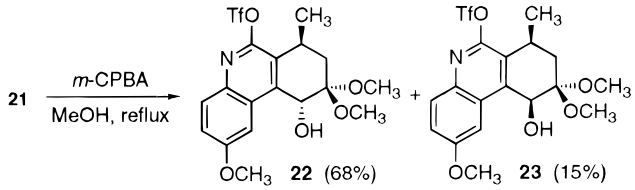
Having established an efficient route for the large-scale preparation of the key intermediate **9**, the next stage of our synthetic plan (**9** to **8**, Scheme 2) called for the stereoselective addition of the 6-carbon (*Z*)-enediyne bridge cis to the methyl group, as well as A-ring functionalization reactions. Toward this end, quinolone **9** was transformed into the corresponding quinolyl triflate derivative (**21**). Theoretically, this transformation allowed for the implementation of two different strategies for the introduction of the 6-carbons of the (*Z*)-enediyne group. The first involved a proposed coupling reaction of the (*Z*)-enediyne with the quinolyl triflate derivative followed by acylation/nucleophilic addition of hydride to the quinoline ring. This strategy was never explored, due to the successful implementation of the alternative strategy in which the ordering of steps was reversed; i.e., reduction of the quinolyl triflate to the corresponding quinoline was conducted first, followed by acylation/nucleophilic addition of the (*Z*)-enediyne group (Yamaguchi reaction).[29] At the planning stage, this versatility was felt to provide an important advantage for, a priori, the two different strategies were anticipated to produce opposite stereochemical outcomes, although this was never verified.

The quinolyl triflate **21** was prepared in 86% yield by treating **9** (1 equiv) with triflic anhydride (1.1 equiv) in the presence of 2,6-di-*tert*-butylpyridine (1.33 equiv) in dichloromethane at −78 °C, followed by warming to 23 °C. Although this protocol was quite effective for the preparation of **21**, the expense and poor availability of 2,6-di-*tert*-butylpyridine led us to search for an alternative base in the reaction (in the absence of a base, **9** was observed to decompose upon mixing with triflic anhydride). Other hindered amine bases such as 2,6-di-*tert*-butyl-4-methylpyridine, 2,6-lutidine, or *N*,*N*-diisopropylethylamine were found to lead to prolonged reaction times and incomplete conversions of **9**, presumably because the reaction of triflic anhydride with each base was competitive with its reaction with **9**.[30] We speculated that 2-chloropyridine might provide a viable alternative to the use of 2,6-di-*tert*-butylpyridine in this reaction by providing a comparable balance of weak basicity and relative inertness toward triflic anhydride. Treatment of the quinolone **9** with 2-chloropyridine (4 equiv) in the presence of triflic anhydride (2 equiv) at −78 °C, followed by warming to 23 °C, provided **21** in 85% yield. Thus, 2-chloropyridine was found to serve as a highly economical alternative to the use of 2,6-di-*tert*-butylpyridine in this particular application, and we speculate in others as well.



a. $(CF_3SO_2)_2O$, 2,6-di-*tert*-butylpyridine, −78→23 °C, 86%.
b. $(CF_3SO_2)_2O$, 2-chloropyridine, −78→23 °C, 85%.

Prior to the introduction of the (*Z*)-enediyne group, the A ring of **21** was further elaborated by oxidation of the enol ether.



This was accomplished by treating **21** with *m*-chloroperoxybenzoic acid (*m*-CPBA, 1.1 equiv) in methanol at reflux for 1 h to afford the α-oriented hydroxy dimethyl ketal **22** in 68% yield after purification by flash column chromatography and, in separate fractions, the *β*-oriented alcohol **23** (15% yield).

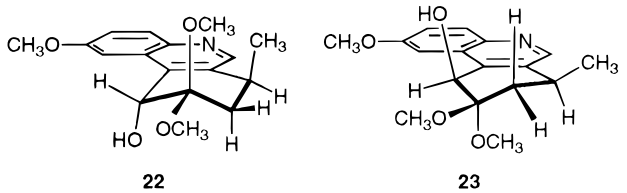
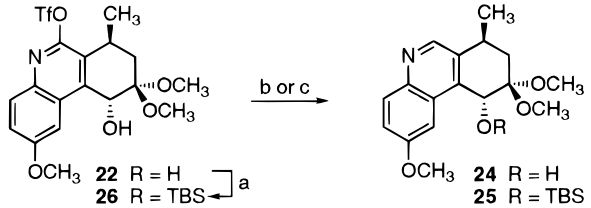


Figure 1. Proposed preferred conformations of α- and *β*-oriented alcohols **22** and **23**, respectively.

The stereochemistry of isomers **22** and **23** was assigned on the basis of $^1H-^1H$ coupling constants and the conformational analysis implicit within Figure 1. The two isomers are believed to adopt the two distinct half-chair conformations shown.

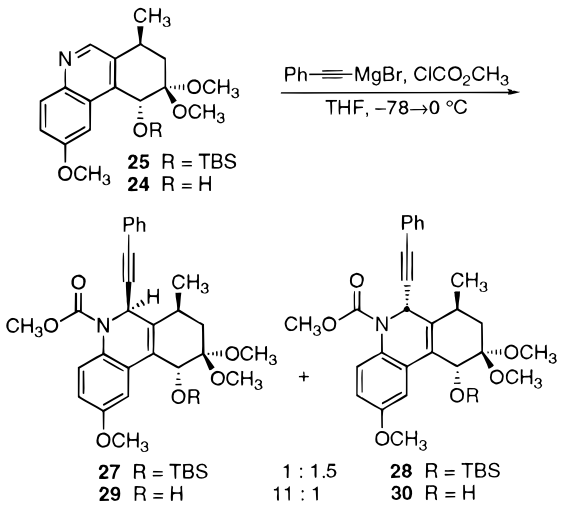
Of the two strategies for the introduction of the (*Z*)-enediyne group, that involving initial reduction of the quinolyl triflate to the corresponding quinoline followed by acetylide addition employing the method of Yamaguchi et al.[29] was investigated first. At this point in our research, the Yamaguchi protocol[29] for acetylide addition to an *N*-acylpyridinium intermediate had already proven to be highly successful in dynemicin synthetic studies reported by Nicolaou et al.[4] and Schreiber et al.[5a] In each of these precedents, the stereochemistry of the acetylide addition reaction had not been an issue. In the present case, the stereochemistry of the addition reaction was an overriding concern, where the desired product must result from addition of the acetylide to the same face of the *N*-acylquinolinium intermediate as that occupied by the methyl group, seemingly the less likely of the two alternatives.



a. TBSOTf, Et_3N, THF, −78→23 °C, 97%. b. $Pd(PPh_3)_4$, Et_3N, HCOOH, *p*-dioxane, reflux, (**24**) 97%. c. Bu_3SnH, LiCl, $Pd(PPh_3)_2Cl_2$, *p*-dioxane, reflux, (**25**) 80%.

Reductive cleavage of the triflate group of **22** to form the quinoline **24** was accomplished in 97% yield by heating **22** with formic acid (2.6 equiv), triethylamine (4.0 equiv), and a catalytic amount of $Pd(PPh_3)_4$ (0.04 equiv) in *p*-dioxane at reflux for 20 min.[31] The corresponding *tert*-butyldimethylsilyl ether **25** was also prepared as an alternative substrate for acetylide addition.

(29) Yamaguchi, R.; Nakazone, Y.; Kawanisi, M. *Tetrahedron Lett*. **1983**, *24*, 1801.
(30) Blinkley, R. W.; Ambrose, M. G. *J. Org. Chem*. **1983**, *48*, 1777.
(31) Cacchi, S.; Ciattini, P. G.; Morera, E.; Ortar, G. *Tetrahedron Lett*. **1986**, *27*, 5541.



In an initial model study, 1-(bromomagnesio)-2-phenylacetylene and the *tert*-butyldimethylsilyl ether **25** were combined in the presence of methyl chloroformate, affording the product of acetylide addition trans to the methyl group with modest selectivity (ratio **28**:**27** = 1.5:1, respectively, 48% yield), in accord with initial speculations. Surprisingly, when the same experiment was conducted with the free alcohol **24**, undoubtedly undergoing deprotonation in the reaction to form the corresponding magnesium alkoxide, the desired cis addition product was greatly favored (ratio **29**:**30** = 11:1, respectively, 32% yield). Although the efficiency of the acetylide addition was poor in this model study, this experiment was nevertheless critical for it revealed the presence of the free hydroxyl group (magnesium alkoxide) in the reaction as a means to obtain the desired stereochemistry in the addition.

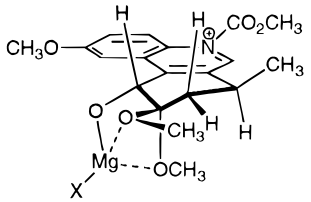


Figure 2. Proposed reactive conformation in the stereoselective Yamaguchi addition reaction.

This stereochemical outcome is believed to be due to the involvement of a reactive half-chair conformation in which the magnesium counterion of the intermediate alkoxide is chelated to one or both methoxyl oxygens, thereby placing the methyl group of **24** in a pseudoequatorial orientation (Figure 2). The preferred mode of acetylide addition then occurs along an axial-type trajectory cis to the methyl group, leading to a staggered arrangement of substituents in the product.

Stereochemical assignments for the products of the addition reaction (**29** and **30**) were based on $^1H-^1H$ NMR coupling constants, assisted by molecular modeling studies. Each diastereomeric product was predicted to occupy a different half-chair conformation on the basis of Monte Carlo conformational searches (MM2 force field, Figure 3). Assignments were made by comparing calculated $^1H-^1H$ coupling constants with observed values (see Supporting Information).

Encouraged by these results, yet recognizing the need to improve the efficiency of the addition reaction, we elected to pursue the incorporation of the entire (*Z*)-enediyne group employing the Yamaguchi protocol.[29] The monoprotected (*Z*)-enediyne **31** was prepared from (*Z*)-1,2-dichloroethylene

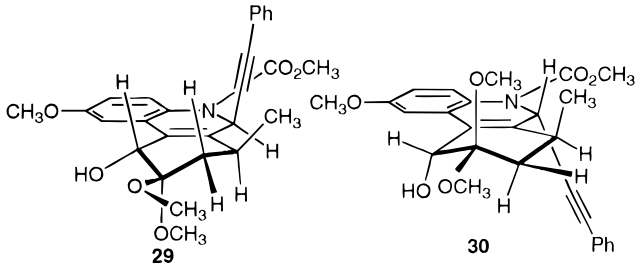
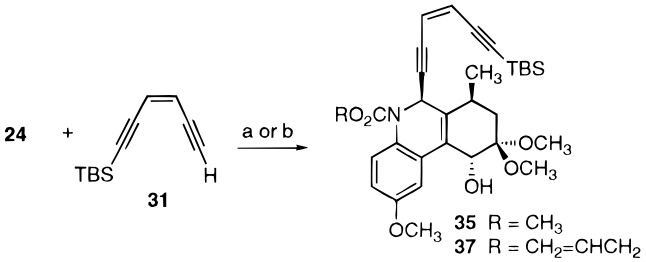


Figure 3. Conformational analysis of addition products **29** and **30**.

by sequential monocoupling reactions with (*tert*-butyldimethylsilyl)acetylene and (trimethylsilyl)acetylene, followed by selective cleavage of the trimethylsilyl ether protective group, in accord with known procedures (see Supporting Information).[12,13,32] Either ordering of the coupling steps was successful.

Deprotonation of the monoprotected (*Z*)-enediyne **31** with ethylmagnesium bromide in tetrahydrofuran (THF) at 50 °C for 30 min followed by cooling to 23 °C and addition of the resulting magnesium acetylide to a solution of the quinoline **24** and methyl chloroformate in THF at −5 °C afforded a 6:1 ratio of the diastereomeric addition products **35** (35%) and **36** (6%), respectively. Recognizing that the methyl carbamate protective group would be difficult, if not impossible, to remove at a late stage in the synthesis, we investigated the use of allyl chloroformate in the coupling reaction. In addition to the greater ease of cleavage of allyl carbamates[33] versus methyl carbamates, allyl chloroformate is a more reactive acylating agent. As a further modification to the experimental procedure, the substrate **24** was treated initially with ethylmagnesium bromide in THF at 0 °C in order to preform the magnesium alkoxide intermediate. These modifications led to a substantial improvement in the efficiency and stereoselectivity of the Yamaguchi reaction, providing the diastereomerically pure adduct **37** in 69% yield. A small amount (3%) of the undesired diastereomer **38** was also isolated in separate fractions. In solution, the conformational behavior of adducts **37** and **38** was found to parallel the phenylacetylide addition products **29** and **30** and, consequently, their stereochemistry was assigned analogously.



a. **31** + EtMgBr, THF, 50 °C; **24**, methyl chloroformate, –5 °C, 35% (β:α = 6:1). b. **31** + EtMgBr, THF, 0 °C→reflux; **24** + EtMgBr, allyl chloroformate, –78→0 °C, 69% (β:α = 23:1).

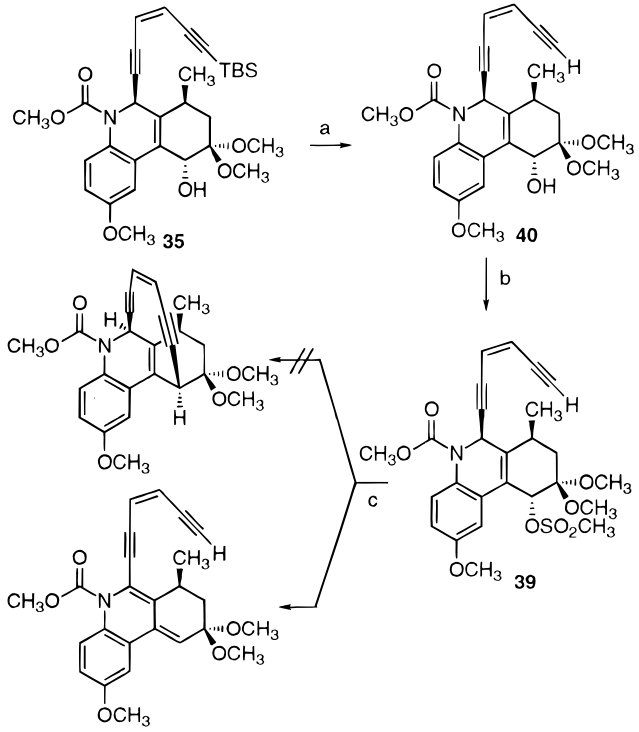
Although it was recognized at this point that the aryl methyl ether was not a suitable protective group to complete the synthesis because of the harsh conditions that would be required to reveal the phenol late in the synthetic route, we elected to address what were felt to be more pressing issues associated

(32) (a) Stephens, R. D.; Castro, C. E. *J. Org. Chem.* **1963**, *28*, 3313. (b) Guillerm, D.; Linstrumelle, G. *Tetrahedron Lett.* **1985**, *26*, 3811. (c) Vollhardt, K. P. C.; Winn, L. S. *Tetrahedron Lett.* **1985**, *26*, 709.

(33) (a) Four, P.; Guibe, F. *Tetrahedron Lett.* **1982**, *23*, 1825. (b) Guibe, F.; Dangles, O.; Balavoine, G. *Tetrahedron Lett.* **1986**, *27*, 2365. (c) Dangles, O.; Guibe, F.; Balavoine, G.; Lavielle, S.; Marquet, A. *J. Org. Chem.* **1987**, *52*, 4984.

with the closure of the strained (*Z*)-enediyne bridge and the further elaboration of the A ring before solving this problem.

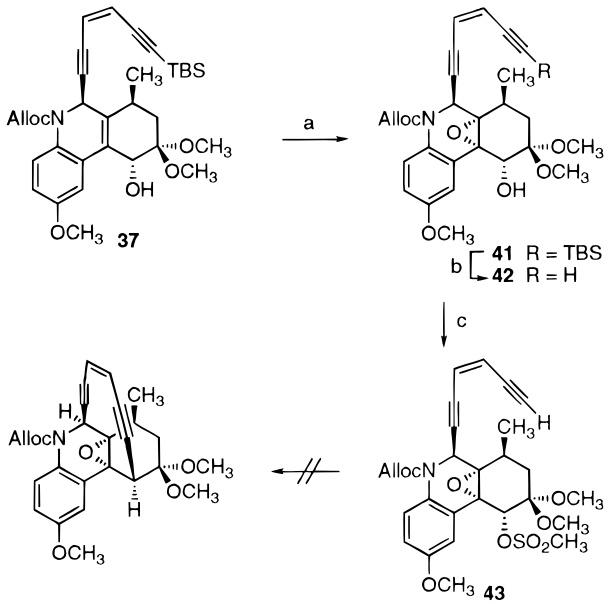
The first problem we addressed was the development of conditions to cyclize the strained ring containing the (*Z*)-enediyne. We initially attempted to bring about an intramolecular acetylide displacement within an appropriately activated derivative of **35**. Toward this end, the allylic mesylate **39** was prepared by deprotection of **35** with tetra-*n*-butylammonium fluoride (TBAF) in THF at 0 °C followed by the slow addition of methanesulfonic anhydride to a solution of the resultant alkynol **40** and triethylamine in dichloromethane at 0 °C. However, it soon became apparent that the allylic mesylate **39** was exceedingly sensitive toward base, for all attempts to induce an intramolecular displacement reaction within **39** led instead to the diene arising from 1,4-elimination.



a. *n*-Bu_4NF, THF, 0 °C, 100%. b. $(CH_3SO_2)_2O$, Et_3N, CH_2Cl_2, 0 °C, 84%. c. base (e.g., $LiN(TMS)_2$).

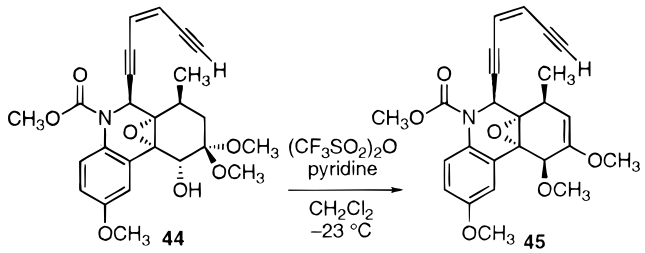
In an effort to prevent elimination and, at the same time, to advance the synthetic route, the tetrasubstituted olefin within the allyloxy carbamate-protected substrate **37** was epoxidized with *m*-CPBA in a biphasic mixture of dichloromethane and pH 7 aqueous phosphate buffer solution at 0 °C for 23 h to provide the α-epoxide **41** in 71% yield. It was necessary to conduct this reaction at 0 °C for at elevated temperatures epoxidation of the allyl group occurred competitively. Deprotection and mesylation, as before, then provided the epoxy mesylate **43**. Unfortunately, this substrate proved to be unreactive in the presence of a wide range of bases, as well as combinations of bases and metal salts that were explored in an effort to induce cyclization.

Efforts to prepare the corresponding epoxy triflate derivative from the epoxy alcohol **44** using excess triflic anhydride and



a. *m*-CPBA, CH_2Cl_2, pH 7 buffer, 0 °C, 71%. b. *n*-Bu_4NF, THF, 0 °C, 89%. c. CH_3SO_2Cl, Et_3N, CH_2Cl_2, 23 °C, 76%.

pyridine led to 1,2-migration of a methoxyl group (presumed *β*) with concomitant proton loss to form the enol ether **45**. Attempts to prepare an α-oriented halide derivative from the epoxy alcohol were also unsuccessful.

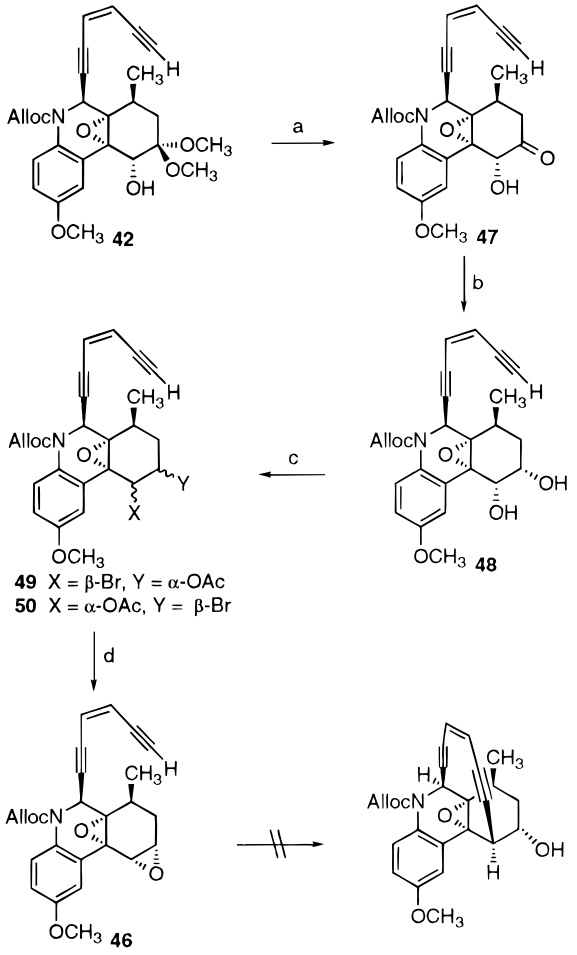


The failure of the mesylate **43** to undergo base-induced intramolecular displacement was perhaps not surprising in light of the generally poor reactivity of acetylide anions in S_N2 displacement chemistry. An important exception to this generalization is the Lewis acid-assisted opening of epoxides by acetylide anions, as described by Yamaguchi and Hirao.[34] With this in mind, the highly strained bis-epoxide **46** was prepared as shown in Scheme 3. The key step in this sequence involved the double-inversion protocol of Moffatt[35] and Sharpless[36] to transform the diol **48** into the bis-epoxide **46**. Unfortunately, all attempts to induce cyclization of **46** were either nonproductive or led to decomposition of the substrate.

Unsuccessful in cyclization attempts using a direct displacement strategy, we turned to now well-established methodology for the preparation of strained cyclic (*Z*)-enediynes, by the intramolecular addition of an acetylide anion to a carbonyl group. This type of closure reaction had proven highly successful in the synthesis of calicheamicin derivatives,[12,14] in our own work on the preparation of the neocarzinostatin chromophore core structure,[15] and, of greater relevance, in model studies of the dynemicin core by Nicolaou and co-workers.[4] The intramolecular acetylide addition reaction was anticipated to proceed with equal or greater efficiency in the case at hand than in the latter model studies, for the carbonyl group of the substrate **51** is nonenolizable. This strategy necessitated an additional step to deoxygenate the bridgehead hydroxyl group of the cyclization product, but this problem had already been solved by Nicolaou et al.[4] in an ingenious use of Barton's

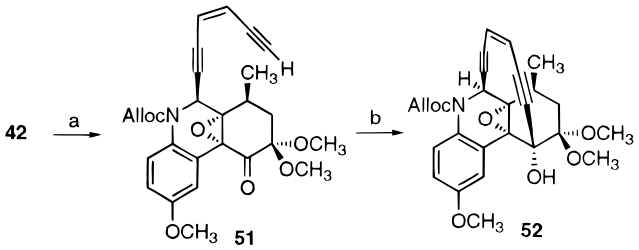
(34) Yamaguchi, M.; Hirao, I. *Tetrahedron Lett*. **1983**, *24*, 391.
(35) (a) Greenberg, S.; Moffatt, J. G. *J. Am. Chem. Soc*. **1973**, *95*, 4016. (b) Russell, A. F.; Greenberg, S.; Moffatt, J. G. *J. Am. Chem. Soc*. **1973**, *95*, 4025.
(36) Sharpless, K. B.; Kolb, H. C. *Tetrahedron* **1992**, *48*, 10515.
(37) (a) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574. (b) Barton, D. H. R.; Subramanian, R. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1718.

Scheme 3



a. HCl, H_2O, THF, 23 °C, 91%. b. $NaBH_4$, EtOH, 23 °C, 92%. c. $CH_3C(OCH_3)_3$, PPTS, CH_2Cl_2, 23 °C; CH_3COBr, Et_3N, CH_2Cl_2, 23 °C, 77%. d. K_2CO_3, MeOH, 23 °C, 79%.

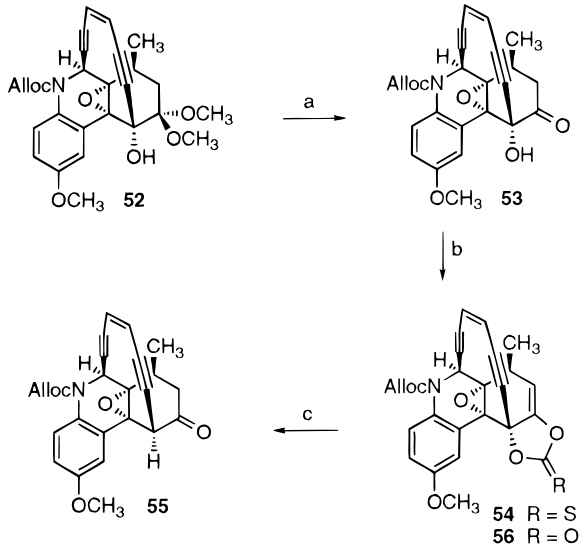
deoxygenation protocol[37] within the context of a dynemicin-like substrate containing a strained (*Z*)-enediyne.



a. $(COCl)_2$, DMSO, CH_2Cl_2, −40 °C; Et_3N, −78→0 °C, 90%.
b. $LiN(TMS)_2$, $CeCl_3$, THF, −78 °C, 72%.

Oxidation of the hydroxy dimethyl ketal **42** using a Swern protocol[38] provided the cyclization substrate **51** in 90% yield. Treatment of a solution of **51** in THF at −78 °C with lithium *N*,*N*-bis(trimethylsilyl)amide ($LiN(TMS)_2$, 1.1 equiv) afforded the cyclization product **52** in modest yield (≤50%). In keeping with a prior observation in neocarzinostatin synthetic studies,[15] we found that the efficiency of this transformation was substantially improved (72% yield) when the substrate was stirred with anhydrous cerium(III) chloride (4.9 equiv) at 23 °C prior to the addition of base. Unlike the cyclization products in neocarzinostatin synthetic studies, the cyclic (*Z*)-enediyne **52** proved to be quite stable to chromatography, routine manipulations, and storage.

Further elaboration of the A ring within the cyclization product **52** was initiated by the hydrolysis of the dimethyl ketal group using *p*-toluenesulfonic acid monohydrate (*p*-TsOH, 1.6 equiv) in acetone at 23 °C to furnish the hydroxy ketone **53** (72%). Preparatory to deoxygenation of the bridgehead alcohol



a. *p*-TsOH•H_2O, acetone, 23 °C, 72%. b. 1,1′-thiocarbonyldiimidazole, DMAP, CH_2Cl_2, reflux, 92%. c. Bu_3SnH, AIBN, toluene, 70 °C, 60%.

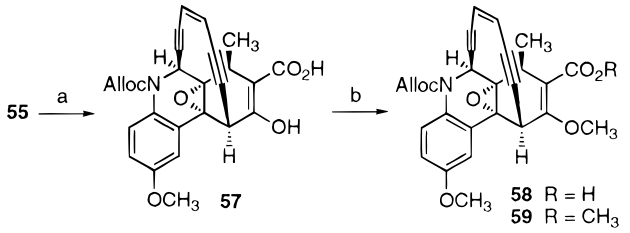
following the precedent of Nicolaou et al.,[4] the hydroxy ketone **53** was treated with 1,1′-(thiocarbonyl)diimidazole and 4-(dimethylamino)pyridine (DMAP) in refluxing dichloromethane, producing the cyclic thionocarbonate **54** in 92% yield. This product, in which the ketone had apparently undergone enolization followed by internal acylation, had not been anticipated but nevertheless proved to be viable as a substrate for Barton deoxygenation. Heating a solution of the cyclic thionocarbonate **54** with tributyltin hydride (1.7 equiv) and azobis(isobutyronitrile) (AIBN, 0.8 equiv) in toluene at 70 °C for 10 min afforded the deoxygenated ketone **55** as a colorless oil in 60% yield. The primary byproduct in this reaction was the cyclic carbonate **56**, whose formation was later traced to the presence of trace quantities of molecular oxygen in the reaction mixture (vide infra).

Having successfully prepared the ketone **55**, we explored the final A-ring functionalization reactions, α-carboxylation of the ketone followed by *O*-methylation (enol oxygen) of the resulting *β*-keto acid, prior to solving the aryl methyl ether protective group problem. This seemingly simple sequence proved to be the single most difficult transformation in the entire synthetic route. Initial studies showed that attempted enolization of the ketone **55** with a variety of bases ($LiN(TMS)_2$, lithium diisopropylamide (LDA), lithium tetramethylpiperdide (LTMP), potassium *N*,*N*-bis(trimethylsilyl)amide ($KN(TMS)_2$), or KO-*t*-Bu) resulted in complete destruction of the substrate, even at −100 °C. Efforts to trap the enolate in situ with an electrophile such as methyl cyanoformate,[39] also at −100 °C, led to decomposition as well. We speculated that alkali metal enolates derived from **55** underwent spontaneous decomposition, perhaps by transannular addition to the epoxide followed by Bergman

(38) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165.

(39) Mander, L. N.; Sethi, S. P. *Tetrahedron Lett.* **1983**, *24*, 5425.

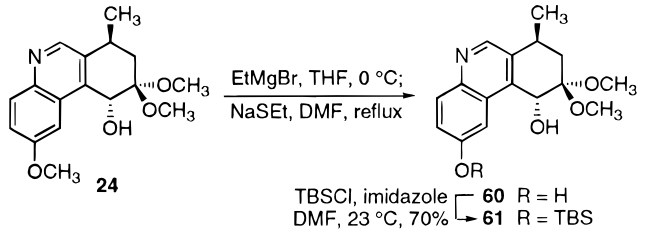
cyclization[40] of the (*Z*)-enediyne group. After extensive experimentation, we found that carboxylation via a presumed magnesium enolate, using conditions first disclosed by Matsumura et al.[41] and extensively elaborated by Rathke et al.,[42] was highly effective when applied to the substrate **55**. Thus, treatment of the ketone **55** with magnesium bromide (2.5 equiv) and triethylamine (15 equiv) in acetonitrile at 23 °C under an atmosphere of carbon dioxide efficiently formed the vinylogous carbonic acid **57** in high yield, as determined by ^{1}H NMR analysis of the crude reaction mixture. The yield of this



a. $MgBr_2$, CO_2, Et_3N, CH_3CN, 23 °C. b. CH_2N_2, CH_3OH, 23 °C.

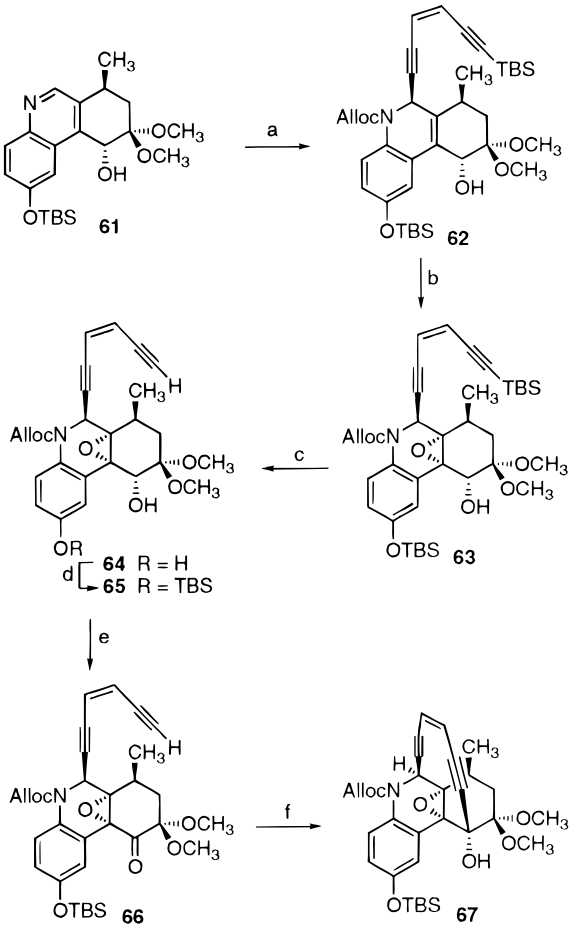
transformation was difficult to assess accurately, for the product underwent spontaneous decarboxylation upon aqueous workup and concentration and, therefore, could not be purified. Initially, we had planned to methylate both the enol and carboxylate oxygens and then saponify the methyl ester to furnish the desired acid **58**. However, bis-methylation of **57** proved not to be straightforward (20−30% yield using excess diazomethane in methanol) and initial efforts to saponify the methyl ester within the product **59** resulted in rapid decomposition of the substrate. We eventually solved this problem by selective methylation of the enol(ate) oxygen in the presence of the carboxylate group. Because this transformation proved to be exceedingly sensitive, requiring exact adherence to a carefully defined protocol, we elected to optimize the reaction on the actual substrate that would be used to prepare dynemicin A (**1**), that is to say, after solving the aryl methyl ether protective group problem.

The most appropriate point for cleavage of the aryl methyl ether was deemed to be prior to the introduction of the sensitive (*Z*)-enediyne group, at the stage of the quinoline **24**. In an initial survey of demethylation conditions, we found that many standard nucleophilic reagents for this purpose (sodium cyanide in refluxing dimethyl sulfoxide, lithium chloride in refluxing *N*,*N*-dimethylformamide (DMF), sodium ethyl mercaptide in refluxing DMF)[43] induced decomposition of the substrate and/or competitive demethylation of the dimethyl ketal group. Further experimentation revealed that nucleophilic cleavage of the dimethyl ketal group could be abolished, or at least minimized, by the initial treatment of the quinoline **24** with ethylmagnesium bromide (1.1 equiv) in THF at 0 °C. Treatment of the resultant magnesium alkoxide with an excess of sodium ethyl mercaptide (3 equiv) in DMF followed by removal of the more volatile solvent, THF, and heating of the resultant slurry at reflux for 1.5 h afforded the phenol **60** in 71% yield.



Selective protection of the phenolic hydroxyl group with *tert*-butyldimethylsilyl chloride (1.3 equiv) and imidazole (2.6 equiv) in DMF at 23 °C for 2 h then afforded the aryl silyl ether **61** (91%). On scales larger than 5 g, the quinoline **24** was directly transformed into the aryl silyl ether **61** without purification of the intermediate phenol (70% yield).

Scheme 4



a. EtMgBr, THF, 0 °C; (*Z*)-BrMgC≡CCH=CHC≡CTBS, allyl chloroformate, −78→0 °C, 89% (β:α ≥ 25:1). b. *m*-CPBA, CH_2Cl_2, pH 7 buffer, 0 °C, 88%. c. *n*-Bu_4NF, THF, 0 °C, 100%. d. TBSCl, imidazole, DMF, 23 °C, 96%. e. $(COCl)_2$, DMSO, CH_2Cl_2, −40 °C; Et_3N, −78→0 °C, 92%. f. $KN(TMS)_2$, $CeCl_3$, THF, −78 °C, 94%.

The same sequence of steps described above for the elaboration of the aryl methyl ether **24** was then followed, with certain procedural modifications for improved chemical efficiency, using the aryl silyl ether **61** as starting material (Scheme 4). Thus, treatment of the aryl silyl ether **61** with ethylmagnesium bromide (0.9 equiv) in THF at 0 °C afforded the corresponding magnesium alkoxide, which was combined with the magnesium acetylide derived from the (*Z*)-enediyne **31** (2.0 equiv) and allyl chloroformate (1.6 equiv) to afford the cis adduct **62** in 89% yield (9-g scale, ≥25:1 diastereoselectivity).

(40) (a) Jones, R. R.; Bergman, R. G. *J. Am. Chem. Soc.* **1972**, *94*, 660. (b) Bergman, R. G. *Acc. Chem. Res.* **1973**, *6*, 25. (c) Lockhart, T. P.; Comita, P. B.; Bergman, R. G. *J. Am. Chem. Soc.* **1981**, *103*, 4082. (d) Lockhart, T. P.; Bergman, R. G. *J. Am. Chem. Soc.* **1981**, *103*, 4091.

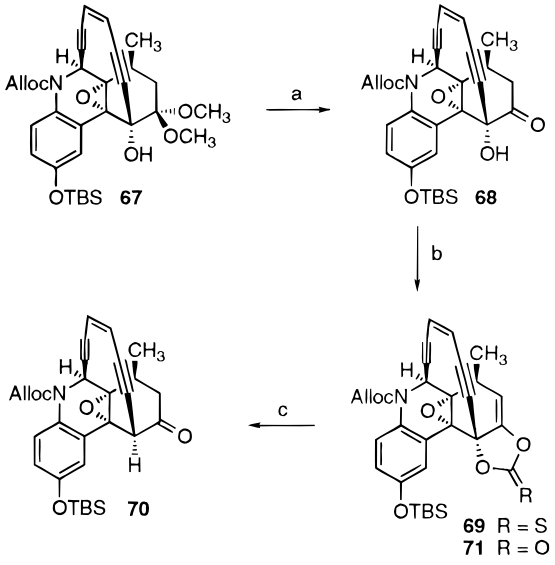
(41) Matsumura, N.; Yagyu, Y.; Imoto, E. *Nippon Kaguku Kaishi* **1977**, 1344.

(42) Tirpak, R. E.; Olsen, R. S.; Rathke, M. W. *J. Org. Chem.* **1985**, *50*, 4877.

(43) (a) Feutrill, G. I.; Mirrington, R. N. *Tetrahedron Lett.* **1970**, 1327. (b) Feutrill, G. I.; Mirrington, R. N. *Aust. J. Chem.* **1972**, *25*, 1719. (c) Feutrill, G. I.; Mirrington, R. N. *Aust. J. Chem.* **1972**, *25*, 1731. (d) McCarthy, J. R.; Moore, J. L.; Cregge, R. J. *Tetrahedron Lett.* **1978**, 5183. (e) Bernard, A. M.; Ghiani, M. R.; Piras, P. P.; Rivoldini, A. *Synthesis* **1989**, 287.

Selective epoxidation of the tetrasubstituted olefin within **62**, as before, afforded the α-epoxide **63** in 88% yield. Treatment of **63** with TBAF (2 equiv) in THF at 0 °C for 15 min led to cleavage of both *tert*-butyldimethylsilyl groups to afford the phenol **64** in quantitative yield. Reprotection of the phenolic hydroxyl group was accomplished in 96% yield by the treatment of **64** with imidazole and *tert*-butyldimethylsilyl chloride in DMF at 23 °C. Oxidation of the product **65** using a Swern protocol,[38] as before, produced the corresponding ketone **66** in 92% yield. Intermediates **64**, **65**, and **66**, containing the (desilylated) acyclic (*Z*)-enediyne functional group, were not stable to storage and were processed immediately.

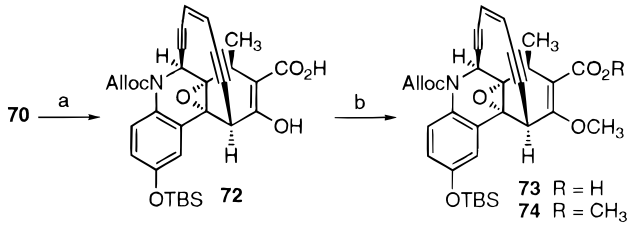
Surprisingly, when the ketone **66** was treated with $LiN(TMS)_2$ in the presence of anhydrous cerium(III) chloride, following the cyclization protocol previously developed for the aryl methyl ether substrate **51**, only slight conversion to the ring-closed product **67** was observed. However, by using 1.1 equiv of $KN(TMS)_2$ as base in the presence of anhydrous cerium(III) chloride (3 equiv, THF, −78 °C), the cyclic product was formed with remarkable efficiency (94% yield). Unlike its acyclic (*Z*)-enediyne precursors, the cyclic product **67** was found to be quite stable to storage in neat form.



a. *p*-TsOH•H_2O, acetone, 23 °C, 83%. b. 1,1'-thiocarbonyldiimidazole, DMAP, CH_2Cl_2, reflux, 85%. c. Bu_3SnH, AIBN, toluene, 70 °C, 97%.

Hydrolysis of the dimethyl ketal group of **67** was accomplished as before, in 83% yield. Reaction of the product (**68**) with 1,1′-(thiocarbonyl)diimidazole (7 equiv) and DMAP (4 equiv) in dichloromethane at reflux for 21 h then afforded the cyclic thionocarbonate **69** in 85% yield. Reductive cleavage of the cyclic thionocarbonate was then brought about by heating a solution of **69** with tributyltin hydride and a catalytic amount of AIBN in deoxygenated toluene at 70 °C for 30 min, affording the ketone **70** in 97% yield. Experiments with this substrate (**69**) revealed the importance of thorough deoxygenation of the reaction mixture in order to avoid formation of the carbonate byproduct **71**.

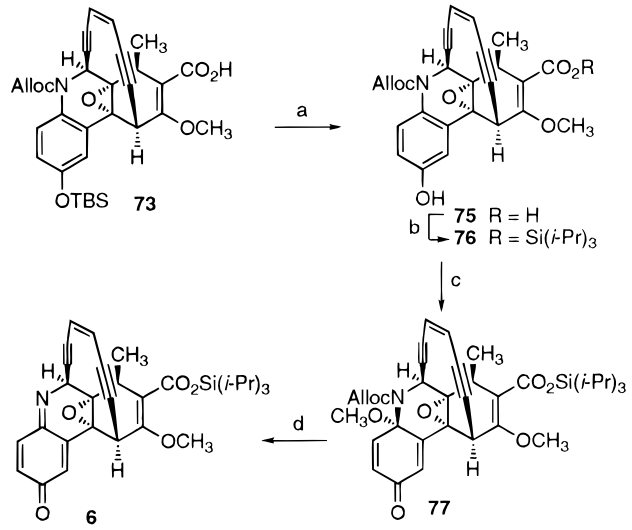
Application of the Rathke[42] carboxylation conditions to the ketone **70** then provided the vinylogous acid **72**. Like the carbonic acid **57**, product **72** underwent spontaneous decarboxylation upon concentration or purification. For this reason, **72** was prepared immediately prior to use, with brief storing at 0 °C in an ethereal solution (ca. 0.2 M). Conditions for the selective methylation of the enolate oxygen of the dianion derived from the carboxylation product **72** were developed by



a. $MgBr_2$, CO_2, Et_3N, CH_3CN, 23 °C. b. KO*t*-Bu, Et_2O, −78 °C; $CF_3SO_3CH_3$, toluene, −20 °C, 54%.

systematic experimentation modifying the base, solvent, methylating agent, and the temperature and duration of the reaction.

Scheme 5



a. 3HF•Et_3N, CH_3CN, 23 °C, 91%. b. TIPSOTf, imidazole, THF, 0 °C, 69%. c. PhIO, CH_3OH, 23 °C, 89%. d. Bu_3SnH, $Pd(PPh_3)_2Cl_2$, CH_2Cl_2, H_2O, 23 °C, 78%.

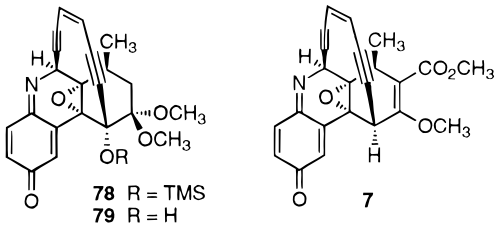
The optimum procedure involved the addition of a solution of the freshly prepared vinylogous carbonic acid **72** to a suspension of KO-*t*-Bu (4 equiv) in ether at −78 °C followed by transfer of the resulting mixture to a solution of freshly distilled methyl trifluoromethanesulfonate (5 equiv) in toluene at −20 °C and further reaction at −20 °C for 30 min. The vinylogous carbonic acid **73** was obtained in 54% yield for the two-step carboxylation/methylation sequence. A small amount of the bis-methylated product **74** was also isolated (10−15%).

Completion of the synthesis of the quinone imine **6** (Scheme 5) was accomplished by a sequence involving the initial cleavage of the silyl ether within **73** using triethylamine trihydrofluoride (91% yield) followed by selective protection of the carboxylic acid group of the resulting product (**75**) with triisopropylsilyl trifluoromethanesulfonate and imidazole in THF at 0 °C to provide the silyl ester **76** in 69% yield, as well as a small amount of recovered carboxylic acid **75** (ca. 15%). Oxidation of the electron-rich aromatic ring of the product silyl ester (**76**) with iodosobenzene (1.8 equiv) in methanol at 23 °C for 40 min provided the protected quinone imine **77** in 89% yield.[44] Treatment of **77** with 1.1 equiv of tributyltin hydride and a catalytic amount of bis(triphenylphosphine)palladium(II) chloride in wet dichloromethane then afforded the quinone imine **6** as a waxy yellow semisolid in 78% yield.[33] This intermediate proved to be stable to chromatography on silica gel, to routine manipulations, and to storage.

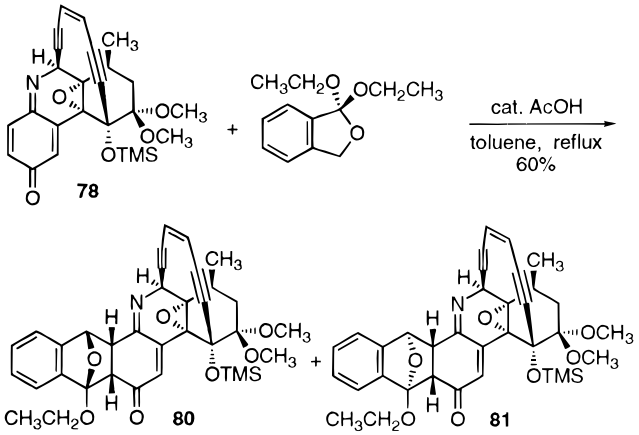
In addition to the quinone imine **6**, the direct precursor of dynemicin A (**1**), the quinone imines **78**, **79**, and **7** were prepared

(44) Barret, R.; Daudon, M. *Tetrahedron Lett.* **1991**, *32*, 2133.

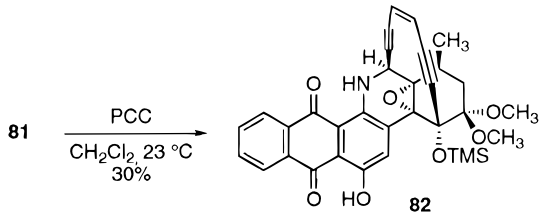
(60−80% yield) from the corresponding aromatic precursors by the same series of steps described for **6** and were useful in model studies for the synthesis of the anthraquinone moiety of **1** and for the preparation of dynemicin analogs.



The viability of using a Diels−Alder cycloaddition reaction to append an anthraquinone to each of the synthetic quinone imines described above was investigated initially in the 15,18-dideoxydynemicin series, using 1,1-diethoxyphthalan as a precursor to the unstable Diels−Alder diene 1-ethoxyisobenzofuran.[45] Because the quinone imines **78** and **79** were more readily accessible than the dynemicin A precursor **6**, they were investigated first in model studies. Heating a solution of the quinone imine **78** with excess 1,1-diethoxyphthalan (22 equiv) and glacial acetic acid (1.6 equiv) in toluene at reflux for 20 min afforded a 1:1 mixture of endo and exo Diels−Alder adducts **80** and **81**, respectively, in 60% yield. Both adducts



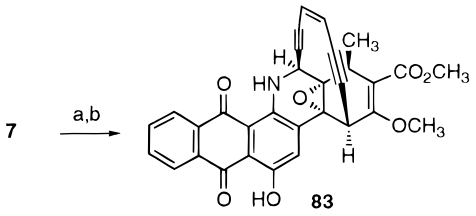
are believed to arise from addition of the isobenzofuran intermediate to the less hindered α-face of the quinone imine and with the regiochemistry shown. When the exo adduct **81** was stirred with excess pyridinium chlorochromate (PCC, 11 equiv) in dichloromethane at 23 °C, the deep red anthraquinone **82** was produced in 30% yield. By a similar sequence, the



quinone imine **7** was transformed into dideoxydynemicin methyl ester (**83**) in 6% yield. The low yields obtained in these transformations are believed to be due, in part, to oxidative decomposition of the products under the reaction conditions.

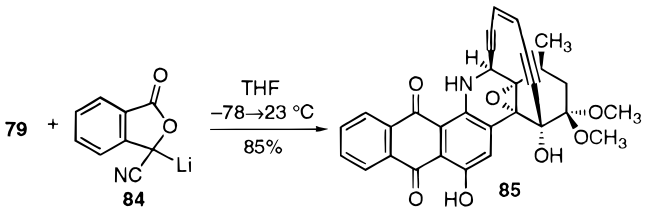
A far superior route to these dideoxydynemicin analogs involved a conjugate addition−enolate trapping strategy that

(45) Contreras, L.; Slemon, C. E.; MacLean, D. B. *Tetrahedron Lett.* **1978**, 4237.



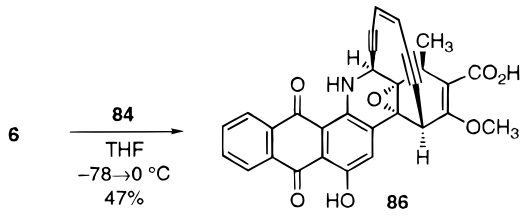
a. 1,1-diethoxyphthalan, cat. AcOH, toluene, reflux. b. PCC, CH_2Cl_2, 23 °C, 6%.

was first described by Kraus and Sugimoto.[46] Addition of a solution of the lithiated cyanophthalide intermediate **84**[47] (2.5 equiv) in THF at −78 °C to a solution of the quinone imine **79** (1 equiv) in THF at −78 °C followed by slow warming to 23 °C provided the anthraquinone **85** in 85% yield after two chromatographic purifications, initially using silica gel and then Sephadex LH-20. Upon slow evaporation of a methanolic solution of **85**, violet crystals were deposited which proved

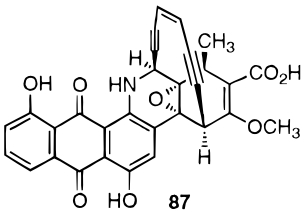


suitable for X-ray crystallographic analysis. The X-ray structure (Figure 4) confirmed all stereochemical assignments made earlier. This is the third X-ray structure of a dynemicin reported (dynemicin A triacetate[1b] and deoxydynemicin A[1c] were the first and the second to appear, respectively) and only the second high-quality structure. The dideoxyanthraquinone is found to be more nearly planar in this structure than the anthraquinones in the prior structures, and the A ring adopts a half-chair conformation rather than a boat-like conformation.

The same sequence provided dideoxydynemicin methyl ester (**83**) from the quinone imine **7** (58%) and dideoxydynemicin (**86**) from the quinone imine **6** (47%). Dideoxydynemicin (**86**)



has not as yet been reported as a natural product, but the monodeoxy derivative **87** was recently identified as a component of a fermentation broth from the microorganism *Micromonospora chersina*.[1c]



(46) Kraus, G. A.; Sugimoto, H. *Tetrahedron Lett.* **1978**, 2263.

(47) (a) Freskos, J. N.; Morrow, G. W.; Swenton, J. S. *J. Org. Chem.* **1985**, *50*, 805. (b) Okazaki, K.; Nomura, K.; Yoshii, E. *Synth. Commun.* **1987**, *17*, 1021.

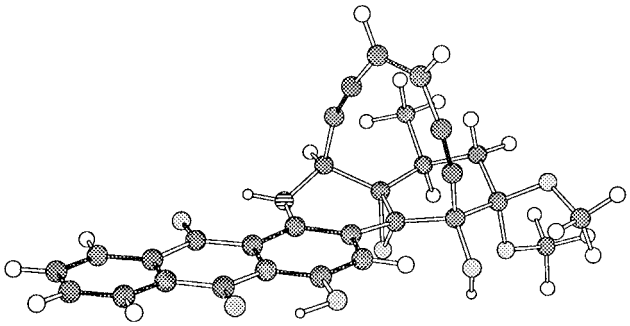
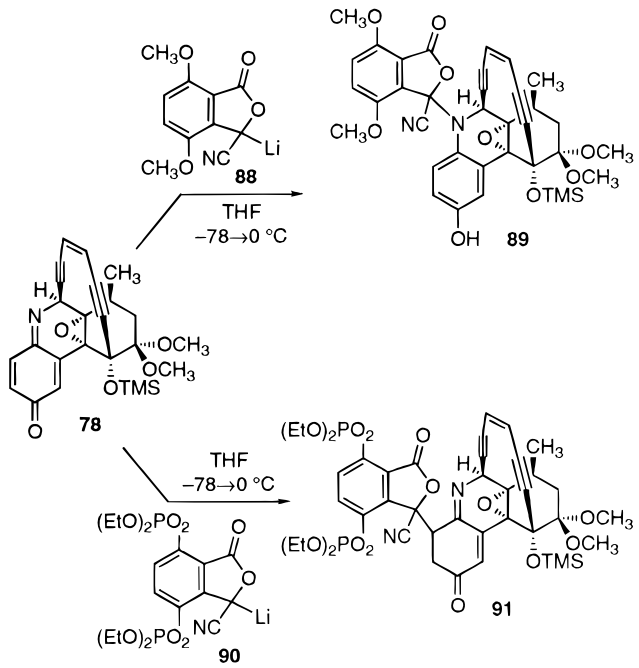


Figure 4. X-ray crystal structure of dynemicin analog **85**.

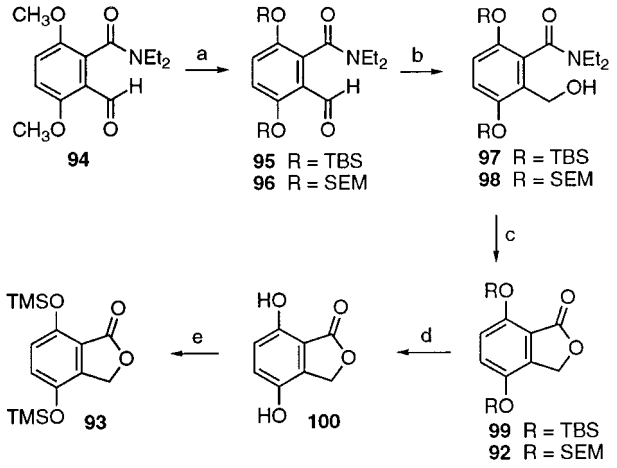
Although the cyanophthalide addition methodology was highly effective for the synthesis of dideoxydynemicin analogs, this chemistry was not successful in the preparation of the more highly oxygenated anthraquinone of dynemicin A. For example, the reaction of the quinone imine **78** with the lithiated



dimethoxycyanophthalide **88** afforded the aniline derivative **89** by C−N bond formation, whereas reaction of **78** with the lithiated cyanophthalide bisphosphate **90** gave rise to the Michael addition product **91** (stereochemistry not determined). Neither the product **91** nor its putative enolate precursor could be transformed into the desired anthraquinone.

Unsuccessful in implementing a conjugate addition/enolate capture sequence for anthraquinone formation, we returned to the original Diels−Alder cycloaddition strategy which, ideally, would employ a protected form of 1,3,4,7-tetrahydroxyisobenzofuran as the diene. However, literature precedent suggested that such an isobenzofuran intermediate would not undergo efficient Diels−Alder addition, even if it could be prepared, a nontrivial synthetic problem in its own right.[48] It has been shown, for example, that 1,3-bis((trimethylsilyl)oxy)isobenzofuran is unstable at temperatures above −20 °C and is unreactive toward a range of dienophiles at this temperature.[49] In general, 1,3-disubstituted isobenzofurans react efficiently only with exceptionally reactive dienes such as benzyne.[50] For this reason,

Scheme 6

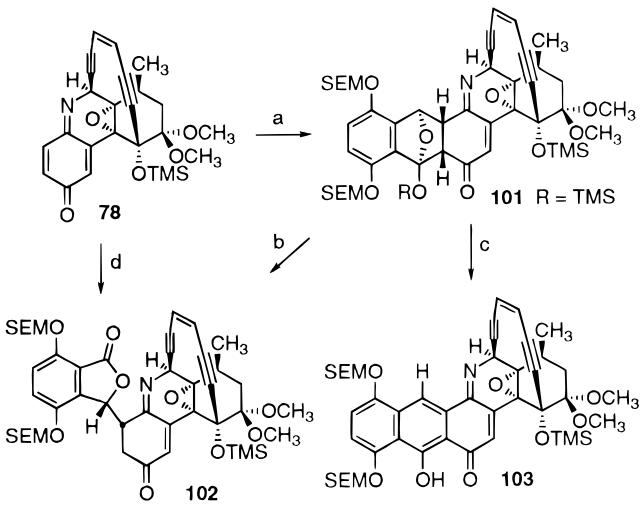


a. BBr_3,CH_2Cl_2, −78→23 °C; TBSCl, imidazole, DMF, 23 °C, 94% (R = TBS). b. $NaBH_4$, EtOH, 0 °C, 97% (R = TBS). $NaBH_4$, EtOH, 23 °C, 92% (R = SEM). c. 1,3,5-trimethylbenzene, reflux, 59% (R = TBS). cat. K_2CO_3, 1,3,5-trimethylbenzene, reflux, 81% (R = SEM). d. 3HF•Et_3N, CH_3CN, 23 °C, 96% (R = TBS). H_2SO_4, THF, CH_3OH, 23 °C, 98% (R = SEM). e. $[(CH_3)_3Si]_2NH$, cat. H_2SO_4, THF, reflux, 100%.

and in the interest of synthetic accessibility, the synthetic plan was modified to incorporate a protected form of the less substituted diene 1,4,7-trihydroxyisobenzofuran followed by a 2-electron oxidation step to form the anthraquinone. This type of isobenzofuran intermediate was readily prepared by deprotonation of phthalide substrates such as **92** and **93**, followed by trapping of the resultant enolate with a silylating agent.[51] The phthalides **92** and **93** were prepared as shown in Scheme 6.[52]

In an early model study, the phthalide **92** was treated with a solution of $LiN(TMS)_2$ in THF at −78 °C, followed by trapping of the resultant enolate with chlorotrimethylsilane at −78 °C. Addition of the quinone imine **78** (limiting reagent, 2.7-fold molar excess of the phthalide) at −78 °C followed by rapid warming of the resultant solution to reflux then afforded the exo-oriented cycloadduct **101** in 32% yield. To the best of our knowledge, this represents the first successful use of a protected 1,4,7-trihydroxyisobenzofuran in a Diels−Alder cycloaddition reaction. This cycloadduct proved to be an exceedingly sensitive compound, readily undergoing cleavage to form the phthalide **102** upon attempted desilylation with triethylamine trihydrofluoride and triethylamine. This result was reminiscent of transformations occurring within the tetracycline antibiotics[53] and suggested that the failure of earlier attempts to prepare anthraquinones in this series employing a conjugate addition−enolate capture sequence (vide supra) might have suffered from unfavorable thermodynamics in the Dieckman closure step. Consistent with this proposal, addition of the lithium enolate derived from the phthalide **92** to the quinone imine **78** produced the Michael adduct **102** as the major component of a 1.3:1 diastereomeric product mixture (64% yield). Further experimentation revealed that ring cleavage of the sensitive cycloadduct **101** could be avoided by treatment of the crude Diels−Alder adduct **101** with triethylamine trihydrofluoride in acetonitrile

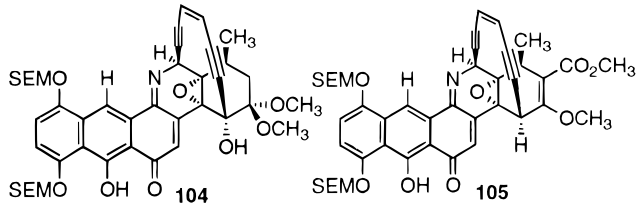
(48) Rodrigo, R. *Tetrahedron* **1988**, *44*, 2093.
(49) (a) Troll, T.; Schmid, K. *Tetrahedron Lett.* **1984**, *25*, 2981. (b) Tobia, D.; Rickborn, B. *J. Org. Chem.* **1987**, *52*, 2611.
(50) Crump, S. L.; Netka, J.; Rickborn, B. *J. Org. Chem.* **1985**, *50*, 2746.
(51) Bloomer, J. L.; Lankin, M. E. *Tetrahedron Lett.* **1992**, *33*, 2769.
(52) (a) de Silva, S. O.; Reed, J. N.; Snieckus, V. *Tetrahedron Lett.* **1978**, 5099. (b) de Silva, S. O.; Watanabe, M.; Snieckus, V. *J. Org. Chem.* **1979**, *44*, 4802. (c) Sibi, M. P.; Altintas, N.; Snieckus, V. *Tetrahedron* **1984**, *40*, 4593.
(53) (a) Waller, C. W.; Hutchings, B. L.; Broschard, R. W.; Goldman, A. A.; Stein, W. J.; Wolf, C. F.; Williams, J. H. *J. Am. Chem. Soc.* **1952**, *74*, 4981. (b) Stephens, C. R.; Conover, L. H.; Pasternack, R.; Hochstein, F. A.; Moreland, W. T.; Regna, P. P.; Pilgrim, F. J.; Brunings, K. J.; Woodward, R. B. *J. Am. Chem. Soc.* **1954**, *76*, 3568.



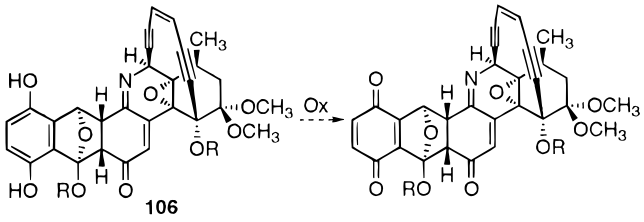
a. **92**, $LiN(TMS)_2$, THF, –78 °C; TMSCl, –78 °C; **78**, –78 °C→reflux, 32%. b. $3HF•Et_3N$, Et_3N, CH_3CN, 23 °C, 100%. c. $3HF•Et_3N$, silica gel, CH_3CN, 44%. d. **92**, $LiN(TMS)_2$, THF, –78 °C; **78**, –78→0 °C, 64% (1.3:1 mixture of diastereomers).

at 23 °C, and then silica gel, thereby affording the dark red naphthalenol derivative **103** in 44% yield.

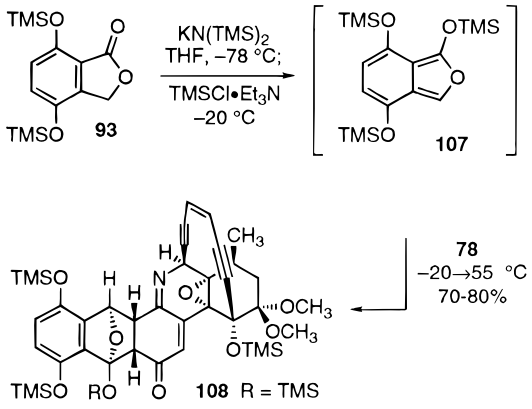
Although the naphthalenol **103** was formally separated from the desired anthraquinone by a single 2-electron oxidation step, a large series of oxidants, including Fremy's salt, PCC, pyridinium dichromate, chromium trioxide, ozone, hydrogen peroxide, singlet oxygen, triplet oxygen,[9] ceric ammonium nitrate, iodosobenzene, dimethyldioxirane, 2,3-dichloro-4,5-dicyano-1,4-benzoquinone, and lead tetraacetate, failed to bring about this transformation. Similar efforts to convert the naphthalenols **104** and **105** (prepared from the quinone imines **79** and **7**, respectively) into the corresponding anthraquinones were also unsuccessful.



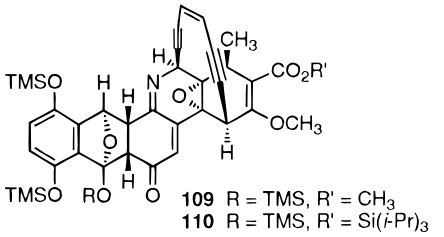
In considering the oxidation problem from a different standpoint, it was recognized that if the left-most ring of the Diels–Alder adduct **101**, formally a hydroquinone derivative, was transformed into the corresponding quinone, the resultant intermediate would lie at the same level of oxidation as the desired anthraquinone, removed from that product only by the opening of the bicyclic ketal and tautomerization. In order to implement such a strategy, it was necessary to reveal the hydroquinone (see structure **106**) from the Diels–Alder adduct before cleavage of the sensitive bicyclic ketal occurred. This required the use of an isobenzofuran precursor with highly labile protective groups, for which the bis-trimethylsilyl ether **93** appeared ideally suited.



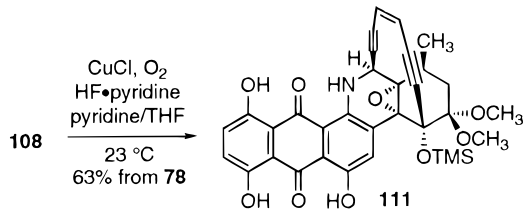
Treatment of the phthalide **93** with $KN(TMS)_2$ at –78 °C, followed by addition of an excess of a chlorotrimethylsilane–triethylamine complex, and warming of the resulting solution to –20 °C produced 1,4,7-tris((trimethylsilyl)oxy)isobenzofuran (**107**) as evidenced by the fact that addition of the quinone imine **78** at –20 °C, followed by rapid warming of the resultant solution to 55 °C, afforded the sensitive exo-oriented Diels–Alder adduct **108** in 70–80% yield (based on ^1H NMR analysis



of the crude reaction mixture integrating against dichloromethane added as an internal standard). In a similar manner, the Diels–Alder adducts **109** and **110** were prepared from the quinone imines **7** and **6**, respectively.



With Diels–Alder adducts **108**–**110** in hand, a range of conditions for in situ desilylation and oxidation was explored to reveal the desired anthraquinones. The cycloadduct **108** was used in initial model studies because it was the most easily prepared. Hydrogen fluoride–pyridine and triethylamine trihydrofluoride were employed as mild desilylating agents in conjunction with a wide variety of oxidants. Thin-layer chromatographic (TLC) analysis proved to be exceedingly sensitive in detecting the formation of the anthraquinone in these reactions for the anthraquinone formed a distinct blue spot with a characteristic R_f value. Several of the oxidants investigated



did, in fact, afford the desired anthraquinone, to include cuprous chloride–dioxygen,[54] iron(III) chloride–dioxygen, iron(II) chloride tetrahydrate–dioxygen, copper tetrafluoroborate–dioxygen, iodobenzene(bistrifluoroacetate), pyridinium chlorochromate,

(54) (a) Karpov, V. V.; Khidekel, M. L. *Zh. Org. Khim.* **1967**, *3*, 1669. (b) Orlando, C. M., Jr. *J. Org. Chem.* **1968**, *33*, 2516. (c) Radel, R. J.; Sullivan, J. M.; Hatfield, J. D. *Ind. Eng. Chem. Prod. Res. Dev.* **1982**, *21*, 566.

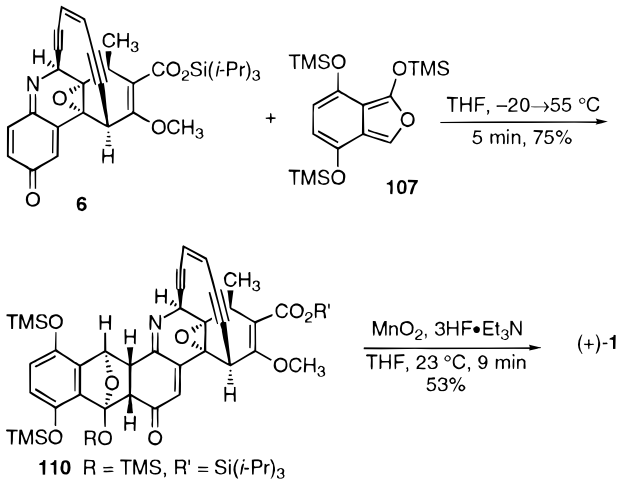
manganese acetate, and manganese dioxide.[55] Of these, cuprous chloride (4 equiv) in the presence of excess hydrogen fluoride−pyridine and a positive flow of oxygen formed the dynemicin analog **111** with particularly high efficiency (63% yield from **78**).

When these conditions were applied to the Diels−Alder adducts **109** and **110**, dynemicin methyl ester **112** and dynemicin A (**1**) were formed in 12% and 14% yields, respectively. Extensive experimentation failed to improve the efficiency of these reactions and revealed that the adduct **108** was a somewhat misleading model system. Reinvestigation of the aforementioned series of reaction conditions using the substrates **109** and **110** showed that the optimum conditions for anthraquinone formation for these substrates involved the use of manganese dioxide as the oxidant in the presence of triethylamine trihydrofluoride. The latter reaction conditions also induced concomitant removal of the triisopropylsilyl ester protective group of the substrate **110**, thus affording dynemicin A (**1**) directly in ∼25% yield on scales of a few milligrams.

The transformation of the Diels−Alder adduct **110** to dynemicin A (**1**) with manganese dioxide−triethylamine trihydrofluoride was optimized by careful monitoring of the reaction. HPLC analysis established that dynemicin A (**1**) was not stable to the reaction conditions. In a representative experiment, the following yields of dynemicin A (**1**) were measured at the indicated time points: 45% (6 min), 49% (15 min), 18% (30 min). The isolated yield of **1** (total reaction period 30 min) in this case was 16%. Visual inspection of the reaction mixture provided an equally valuable and simpler means of monitoring the reaction. In the experiment described, telling color changes occurred throughout the course of the reaction: the reaction mixture was violet at 6 min, deep blue at 15 min, and gray at 30 min. This visual indicator proved to be a valuable tool in the optimization of the reaction, with best results observed by quenching the reaction mixture when it was deep blue.

Optimal conditions for the preparation of dynemicin A (**1**) are as follows. Treatment of a solution of the phthalide **93** (5 equiv) in THF at −78 °C with $KN(TMS)_2$ (5.1 equiv) for 25 min, followed by the addition of excess chlorotrimethylsilane (9 equiv) and warming of the resulting solution to −20 °C for 1 min, provided the isobenzofuran **107**. This intermediate was not characterized but was treated directly with a solution of the quinone imine **6** (1 equiv) at −20 °C, followed by heating of the reaction mixture at 55 °C for 5 min and concentration of the resulting solution in vacuo to provide the Diels−Alder adduct **110** in 75% yield (based on ^{1}H NMR analysis of the crude product integrating against dichloromethane added as an internal standard). Excess activated manganese dioxide and triethylamine trihydrofluoride (1:1 molar ratio, ∼70 equiv) were added to a solution of the crude Diels−Alder adduct **110** in THF, and the resulting mixture was stirred at 23 °C until a deep blue color was obtained (9 min). At this point, the reaction suspension was loaded directly onto a short column of Sephadex LH-20 and the solumn was eluted with 30% acetonitrile in methanol. Concentration of appropriate column fractions and further purification of the product by column chromatography using Sephadex LH-20 (20% acetonitrile in methanol) afforded pure dynemicin A (**1**) as a violet solid in 53% yield (15.4 mg) from the intermediate **110** (40% yield from the quinone imine **6**).

Synthetic dynemicin A (**1**) was shown to be identical to an authentic sample of the natural product[56] by ^{1}H NMR and UV−vis spectroscopic analysis, reverse-phase HPLC analysis (co-injection), TLC analysis in several solvent systems (co-spotting), and circular dichroism. The latter showed that the synthetic sample of **1** possessed the natural stereochemical configuration and thereby established for the first time the absolute configuration of natural **1** as 2*S*,3*S*,4*S*,7*R*,8*R*. In addition to spectroscopic and analytical data, synthetic **1** was shown to be the same as the natural product by a DNA cleavage analysis using a 3′-^{32}P-end-labeled 193-base pair restriction fragment (*Eco* RI/*Ssp* I) from the plasmid pBR322 (GSH, NADPH, or NADH activation).[10,11] In pure form, dynemicin A (**1**) exhibited good stability; low-temperature (−20 °C) storage in the solid state led to only trace decomposition over a 6-month period as assayed by spectroscopy and DNA-cleaving analyses.



The synthetic route described has provided (+)-dynemicin A (**1**) in 24 linear steps and 1−2% chemical yield from the optically pure diketone **14**. More than 25 mg of pure dynemicin A (**1**) have been prepared by this route. In addition, a wide variety of novel structural analogs of **1** have been prepared by modification of the convergent route described and have been shown to possess distinct and interesting DNA-cleavage properties.[57]

Experimental Section

General Procedure. All reactions were performed in flame-dried round-bottomed or modified Schlenk (Kjeldahl shape) flasks fitted with rubber septa under a positive pressure of argon, unless otherwise noted. Air- and moisture-sensitive liquids and solutions were transferred via syringe or stainless steel cannula. Where necessary (so noted), solutions were deoxygenated by alternate evacuation for 10−15 s and flushing with argon (≥5 iterations) or by freeze−pump−thaw cycles (≥3 iterations). Organic solutions were concentrated by rotary evaporation below 30 °C at ca. 25 Torr (water aspirator). Analytical and preparative thin-layer chromatography were performed using glass plates precoated with 0.25 mm 230−400 mesh silica gel impregnated with a fluorescent indicator (254 nm). Thin-layer chromatography plates were visualized by exposure to ultraviolet light and/or by immersion in an acidic staining solution (*p*-anisaldehyde or ceric ammonium molybdinate) followed by heating on a hot plate. Flash column chromatography was performed as described by Still et al.,[58] employing 230−400 mesh silica gel.

Materials. Commercial reagents and solvents were used as received with the following exceptions. Tetrahydrofuran and ether were distilled from sodium benzophenone ketyl. Methanol was distilled from magnesium turnings. Dichloromethane, chlorotrimethylsilane, *N*,*N*-diisopropylethylamine, triethylamine, hexamethyldisilazane, toluene, benzene, *tert*-butyl alcohol, and acetonitrile were distilled from calcium

(55) (a) Fatiadi, A. J. *Synthesis* **1976**, 65. (b) Fatiadi, A. J. *Synthesis* **1976**, 133.

(56) Authentic sample of (+)-dynemicin A (**1**) was obtained from Bristol-Myers Squibb.

(57) Manuscript in preparation.

(58) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

(59) Kofron, W. G.; Baclawski, L. M. *J. Org. Chem.* **1976**, *41*, 1879.

hydride. Dimethyl sulfoxide was distilled from calcium hydride at reduced pressure and was stored over 4 Å molecular sieves. Methanesulfonyl chloride was distilled from phosphorus pentoxide at atmospheric pressure. Triflic anhydride and trimethylsilyl trifluoromethanesulfonate were stored in the glovebox in round-bottomed flasks fitted with polycarbonate or glass stoppers. Methyl trifluoromethanesulfonate was prepared and distilled at atmospheric pressure immediately prior to use. Copper(I) iodide was purified by continuous extraction (24 h) with tetrahydrofuran in a Soxhlet apparatus. The molarity of *n*-butyllithium solutions was determined by titration using diphenylacetic acid as an indicator[59] (average of three determinations).

Instrumentation. Infrared spectra are referenced to a polystyrene standard. Data are presented as follows: frequency of adsorption (cm^{-1}), intensity of adsorption (vs = very strong, s = strong, m = medium, w = weak, vw = very weak, br = broad, sh = shoulder), and assignment. Proton magnetic resonance (^{1}H NMR) spectra were recorded at 500, 400, or 300 MHz; chemical shifts are expressed in parts per million (δ scale) downfield from tetramethylsilane and are referenced to residual protium in the NMR solvent ($CHCl_3$, δ 7.26; C_6HD_5, δ 7.20, CD_2HOD, δ 3.30; $CD_3S(O)CD_2H$, δ 2.49; $(CD_3)(CD_2H)NCDO$, δ 2.74). Data are presented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, m = multiplet and/or multiple resonances, app = apparent, br = broad), integration, and coupling constant in hertz. ^{13}C NMR spectra were recorded at 125 or 100 MHz; chemical shifts are referenced to the carbon signal for the solvent ($CDCl_3$, δ 77.0; C_6D_6, δ 128.0; CD_2Cl_2, δ 53.8; CD_3OD, δ 49.0; $(CD_3)_2SO$, δ 39.5). High-performance liquid chromatography (HPLC) was conducted using a Beckman Ultrasphere (C_{18}, 5 μm) reverse phase HPLC column. Optical rotations were determined at 589 nm (sodium lamp). High-resolution mass spectra were obtained from the University of California, Riverside, Mass Spectrometry Facility, the Midwest Center for Mass Spectrometry at the University of Nebraska—Lincoln, or the Caltech Mass Spectrometry Center. X-ray crystallography was performed by Dr. Joseph Ziller at the University of California—Irvine or by the Beckman Institute Center for X-ray crystallography at Caltech. Combustion analyses were obtained by Dr. Fenton Harvey at Caltech or by Quantitative Technologies, Inc. Melting points are uncorrected.

(1*R*,3*R*,4*S*)-*p*-Menth-3-yl Acetoacetate. A solution of (−)-menthol (250 g, 1.60 mol, 1 equiv) and *tert*-butyl acetoacetate (265 mL, 1.60 mol, 1 equiv) in toluene (350 mL) was heated at reflux for 12 h and then was cooled to 23 °C. Volatiles were removed in vacuo, and toluene (200 mL) was added to the residue. The resulting solution was heated at reflux for 14 h and then was cooled to 23 °C. The cooled reaction mixture was concentrated in vacuo, and the residue was purified by distillation under reduced pressure (bp 90 °C, 0.030 mmHg) to afford (1*R*,3*R*,4*S*)-*p*-menth-3-yl acetoacetate as a viscous pale yellow oil (365 g, 95%): R_f 0.66, 40% ethyl acetate−hexanes; ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.19 (s, 1H), 4.95 (s, 1H), 4.73 (td, 1H, J = 10.9, 4.4 Hz), 3.43 (s, 2H), 2.26 (s, 3H), 2.02 (m, 1H), 1.87 (m, 1H), 1.68 (m, 2H), 1.42 (m, 2H), 1.05 (m, 2H), 0.91 (d, 3H, J = 4.8 Hz), 0.89 (d, 3H, J = 5.4 Hz), 0.83 (m, 1H), 0.76 (d, 3H, J = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.5, 166.6, 75.4, 50.4, 46.8, 40.6, 34.0, 31.3, 29.9, 26.0, 23.2, 21.9, 20.6, 16.0; FTIR (neat), cm^{-1} 1733 (s, C═O), 1713 (s, C═O); $[\alpha]^{22}_D$ ($CHCl_3$), −123.7, c = 1.69; HRMS (FAB) *m/z* calcd for $C_{14}H_{24}O_3$ $(M)^+$ 240.1725, found 240.1737. Anal. Calcd for $C_{14}H_{24}O_3$: C, 69.96; H, 10.06. Found: C, 70.10; H, 10.16.

Diketone 14. A 2-L, 3-necked round-bottomed flask, fitted with a reflux condenser, a mechanical stirrer, and a glass stopper, was charged with *tert*-butyl alcohol (300 mL) and potassium *tert*-butoxide (68.7 g, 612 mmol, 1.04 equiv). The glass stopper was removed, and with efficient mechanical stirring, (1*R*,3*R*,4*S*)-*p*-menth-3-yl acetoacetate (150 g, 624 mmol, 1.06 equiv) was added rapidly to the yellow slurry. The open neck of the reaction flask was fitted with a 100-mL addition funnel containing *trans*-ethyl crotonate (73.2 mL, 588 mmol, 1 equiv). The largely solid reaction mixture was heated at reflux with a heating mantle for 45 min. At this point, *trans*-ethyl crotonate was added to the refluxing, dark yellow slurry over 15 min via the addition funnel. The addition funnel was replaced with a glass stopper, and heating at reflux was continued. Solids were observed to dissolve within 1 h after addition of *trans*-ethyl crotonate; the product began to crystallize from solution after about 1.5 h. After a total reflux period of 2.5 h (from addition of *trans*-ethyl crotonate), heating was discontinued and the reaction mixture was allowed to cool to 23 °C. The cooled reaction mixture was partitioned between aqueous sulfuric acid solution (5% v/v, 500 mL) and dichloromethane (600 mL). The aqueous layer was separated and extracted further with two 600-mL portions of dichloromethane. The combined organic layers were dried over sodium sulfate and then were concentrated. The solid residue was dissolved in boiling benzene (ca. 600 mL), and the resulting solution was allowed to cool slowly to 23 °C whereupon the diketone **14** crystallized as a white powder (mp 180−181 °C, 64.5 g, 36%). To isolate the diastereomeric diketone **15**, the mother liquor was concentrated and the solid residue was dissolved in boiling ethyl acetate (ca. 200 mL). Hexanes (50 mL) was added to the hot solution, and the mixture was allowed to cool to 23 °C. Further cooling to −20 °C induced crystallization of the diketone **15** over a period of 12 h (mp 140−141 °C, 45 g, 25%). **14**: R_f 0.17, 5% methanol−dichloromethane; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.79 (td, 1H, J = 10.9, 4.2 Hz), 3.63 (d, 1H, J = 17.2 Hz), 3.40 (d, 1H, J = 17.2 Hz), 3.30 (dd, 1H, J = 8.4, 0.9 Hz), 2.80 (ddd, 1H, J = 15.5, 4.4, 1.1 Hz), 2.60 (m, 1H), 2.39 (ddd, 1H, J = 15.5, 9.1, 1.1 Hz), 2.05 (m, 1H), 1.90 (m, 1H), 1.70 (m, 2H), 1.50 (m, 1H), 1.40 (m, 1H), 1.10 (d, 3H, J = 6.7 Hz), 1.00 (m, 2H), 0.92 (d, 3H, J = 5.7 Hz), 0.90 (d, 3H, J = 6.8 Hz), 0.85 (m, 1H), 0.78 (d, 3H, J = 6.9 Hz); ^{13}C NMR (100 MHz, $(CD_3)_2SO_2$) δ 192.9, 177.7, 169.9, 102.7, 73.7, 59.7, 46.2, 40.3, 35.4, 33.6, 31.4, 30.7, 25.3, 22.7, 21.8, 20.4, 18.9, 15.9; FTIR (neat), cm^{-1} 1724 (s, C═O), 1608 (s, C═O); $[\alpha]^{22}_D$ (CH_3OH), +66.9, c = 0.77; HRMS (EI) *m/z* calcd for $C_{18}H_{29}O_4$ $(MH)^+$ 309.2066, found 309.2081. Anal. Calcd for $C_{18}H_{28}O_4$: C, 70.10; H, 9.15. Found: C, 70.05; H, 9.24. **15**: R_f 0.17, 5% methanol−dichloromethane; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.80 (td, 1H, J = 11.0, 4.4 Hz), 3.62 (d, 1H, J = 17.2 Hz), 3.40 (d, 1H, J = 17.2 Hz), 3.31 (d, 1H, J = 8.3 Hz), 2.79 (dd, 1H, J = 15.4, 4.4 Hz), 2.61 (m, 1H), 2.39 (dd, 1H, J = 15.8, 9.2 Hz), 2.05 (m, 1H), 1.85 (m, 1H), 1.68 (m, 2H), 1.51 (m, 1H), 1.40 (m, 1H), 1.09 (d, 3H, J = 7.0 Hz), 1.04 (m, 2H), 0.91 (d, 3H, J = 7.4 Hz), 0.89 (d, 3H, J = 7.5 Hz), 0.86 (m, 1H), 0.77 (d, 3H, J = 7.0 Hz).

Enol Methyl Ether 16. A solution of the diketone **14** (24.0 g, 77.8 mmol, 1 equiv) in methanol (300 mL) was treated with camphorsulfonic acid (0.80 g, 3.9 mmol, 0.05 equiv), and the resulting solution was stirred at 23 °C for 12 h. The reaction mixture was neutralized by the addition of solid potassium carbonate (1.08 g, 7.81 mmol, 0.100 equiv), the resulting suspension was filtered, and the filtrate was concentrated. The residue was concentrated from toluene (2 × 15 mL) and then was purified by flash column chromatography (20% ethyl acetate in hexanes) to afford the enol methyl ether **16** as a white solid (mp 78−80 °C, 17.9 g, 71%). The regioisomeric enol methyl ether **17** was isolated in separate fractions and was resubjected to the reaction conditions to establish the equilibrium mixture of enol methyl ethers, in which the desired product **16** is strongly favored (ratio 4:1). **16**: R_f 0.49, 40% ethyl acetate−hexanes; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.38 (d, 1H, J = 1.3 Hz), 4.76 (td, 1H, J = 10.9, 4.4 Hz), 3.70 (s, 3H), 2.98 (d, 1H, J = 11.3 Hz), 2.59 (m, 1H), 2.47 (dd, 1H, J = 17.3, 4.8 Hz), 2.19 (ddd, 1H, J = 17.3, 10.5, 1.4 Hz), 2.05 (m, 2H), 1.65 (m, 2H), 1.50 (m, 1H), 1.40 (m, 1H), 1.08 (d, 3H, J = 6.5 Hz), 1.00 (m, 2H), 0.91 (d, 3H, J = 1.9 Hz), 0.89 (d, 3H, J = 2.5 Hz), 0.85 (m, 1H), 0.79 (d, 3H, J = 9.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.0, 177.1, 169.8, 101.2, 75.1, 61.0, 55.7, 46.8, 40.5, 35.7, 34.2, 31.4, 31.3, 25.8, 23.0, 21.9, 20.7, 19.5, 15.8; FTIR (neat), cm^{-1} 1733 (s, C═O), 1657 (s, α,β-unsaturated C═O), 1607 (vs, C═C); $[\alpha]^{22}_D$ ($CHCl_3$), +159.0, c = 0.98; HRMS (EI) *m/z* calcd for $C_{19}H_{30}O_4$ $(MH)^+$ 323.2222, found 323.2228. Anal. Calcd for $C_{19}H_{30}O_4$: C, 70.77; H, 9.38. Found: C, 70.66; H, 9.60. **17**: R_f 0.38, 40% ethyl acetate−hexanes; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.39 (d, 1H, J = 1.3 Hz), 4.71 (td, 1H, J = 10.9, 4.4 Hz), 3.62 (s, 3H), 3.06 (dd, 1H, J = 7.5, 1.2 Hz), 2.55 (m, 1H), 2.45 (dd, 1H, J = 16.5, 3.9 Hz), 2.03 (d, 1H, J = 8.0 Hz), 1.97 (m, 1H), 1.86 (m, 1H), 1.62 (m, 2H), 1.45 (m, 1H), 1.37 (m, 1H), 1.03 (d, 3H, J = 6.6 Hz), 0.92 (m, 2H), 0.88 (d, 3H, J = 1.8 Hz), 0.84 (d, 3H, J = 2.5 Hz), 0.81 (m, 1H), 0.75 (d, 3H, J = 9.8 Hz).

Enol Triflate 11. A solution of the enol methyl ether **16** (35.5 g, 110 mmol, 1 equiv) in ether (300 mL) was transferred by cannula over 15 min to a stirring suspension of sodium hydride (3.96 g, 165 mmol, 1.50 equiv) in ether (100 mL) at 0 °C. The resulting slurry was allowed to warm to 23 °C over approximately 10 min and was stirred at that

temperature for 5 h. Excess sodium hydride was quenched by the addition of 10-μL aliquots of water to the suspension at 30-min intervals until such point as gas evolution was no longer evident. The reaction mixture was then cooled to −78 °C, and triflic anhydride (29.6 mL, 176 mmol, 1.60 equiv) was added by syringe over 10 min. Upon completion of the latter addition, the reaction mixture was placed in an ice bath and was stirred for 30 min. The product solution was partitioned between aqueous phosphate buffer solution (pH 7, 0.05 M in sodium hydrogen phosphate and 0.05 M in potassium dihydrogen phosphate, 400 mL) and ether (400 mL). The aqueous layer was separated and extracted further with ether (2 × 400 mL). The combined organic layers were dried over sodium sulfate and then were concentrated. The residue was purified by flash column chromatography (10% ethyl acetate in hexanes) to afford the enol triflate **11** as a pale yellow oil (47.3 g, 95%). Due to its instability to storage, product **11** was typically carried directly on to the next step in the sequence. In addition, for large scale reactions (≥10 g), product **11** was used without purification: R_f 0.49, 15% ethyl acetate−hexanes; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.88 (s, 1H), 4.85 (td, 1H, J = 10.9, 4.3 Hz), 3.70 (s, 3H), 3.06 (m, 1H), 2.81 (ddd, 1H, J = 17.1, 8.1, 2.2 Hz), 2.10 (m, 1H), 2.05 (m, 1H), 1.95 (m, 1H), 1.70 (m, 2H), 1.50 (m, 1H), 1.45 (m, 1H), 1.10 (d, 3H, J = 7.0 Hz), 1.05 (m, 2H), 0.91 (d, 3H, J = 4.9 Hz), 0.90 (partially obscured m, 1H), 0.88 (d, 3H, J = 5.4 Hz), 0.75 (d, 3H, J = 7.0 Hz); ^{13}C NMR (100 MHz, C_6D_6) δ 167.0, 163.6, 150.8, 119.2 (q, 1C, J = 318 Hz), 115.3, 90.6, 75.2, 55.4, 47.0, 41.1, 34.5, 34.1, 31.8, 29.5, 26.3, 23.5, 22.1, 21.0, 17.2, 16.2; FTIR (neat), cm^{-1} 1693 (m, C═O), 1582 (s, C═C).

***tert*-Butyl 4-Methoxy-2-(trimethylstannyl)carbanilate (19).** A solution of *tert*-butyllithium in pentane (1.70 M, 148 mL, 251 mmol, 2.50 equiv) was added via cannula to a solution of *tert*-butyl 4-methoxycarbanilate (22.4 g, 100 mmol, 1 equiv) in ether (500 mL) at −20 °C, producing a cloudy yellow solution. After being stirred at −20 °C for 5 h, the reaction mixture was cooled to −78 °C and a solution of trimethyltin chloride (50.0 g, 251 mmol, 2.50 equiv) in ether (50 mL) was added via cannula. After the addition, the reaction mixture was warmed to −20 °C and was stirred at that temperature for 30 min, then was stirred in an ice bath for 30 min. The product solution was partitioned between aqueous phosphate buffer solution (pH 7, 0.05 M in sodium hydrogen phosphate and 0.05 M in potassium dihydrogen phosphate, 600 mL) and ether (400 mL). The aqueous layer was separated and extracted further with ether (2 × 400 mL). The combined organic layers were dried over sodium sulfate and were concentrated. The product was purified by flash column chromatography (15% ethyl acetate in hexanes) to afford *tert*-butyl 4-methoxy-2-(trimethylstannyl)-carbanilate (**19**) as a yellow oil (33.3 g, 85%): R_f 0.33, 15% ethyl acetate−hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, 1H, J = 8.6 Hz), 6.95 (d, 1H, J = 3.0 Hz), 6.83 (dd, 1H, J = 8.6, 3.0 Hz), 6.13 (br s, 1H), 3.79 (s, 3H), 1.49 (s, 9H), 0.32 (s, 9H); FTIR (neat), cm^{-1} 3324 (br, NH), 1702 (s, C═O); HRMS (FAB) *m/z* calcd for $C_{15}H_{25}NO_3Sn$ $(M)^+$ 387.0856, found 387.0835.

***tert*-Butyl 2-Borono-4-methoxycarbanilate (10).** A solution of *tert*-butyllithium in pentane (1.70 M, 200 mL, 340 mmol, 2.50 equiv) was added via cannula to a solution of *tert*-butyl 4-methoxycarbanilate (30.4 g, 136 mmol, 1 equiv) in ether (500 mL) at −20 °C, producing a cloudy yellow solution. After the solution was stirred at −20 °C for 5 h, trimethyl borate (46.3 mL, 408 mmol, 3.00 equiv) was added. The resulting viscous solution was swirled manually for 5 min, was allowed to warm to 23 °C, and was held at that temperature for 12 h. The product solution was partitioned between saturated aqueous ammonium chloride solution (500 mL) and ethyl acetate (500 mL). The aqueous layer was separated and extracted further with ethyl acetate (2 × 500 mL). The combined organic layers were dried over sodium sulfate and were concentrated. The product was purified by flash column chromatography (2.5% methanol in dichloromethane initially, grading to 10% methanol in dichloromethane) to provide the *tert*-butyl 2-borono-4-methoxycarbanilate (**10**) as a yellow powder (19.9 g, 55%): R_f 0.43, 10% methanol−dichloromethane; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.05 (br s, 1H), 7.62 (br d, 1H, J = 8.4 Hz), 7.40 (br s, 1H), 6.91 (dd, 1H, J = 8.8, 2.8 Hz), 3.80 (s, 3H), 3.49 (s, 2H), 1.38 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.3, 154.7, 135.9, 124.2, 119.2, 118.1, 116.7, 82.6, 55.4, 28.3; FTIR (neat), cm^{-1} 3328 (br s, NH), 1696 (s, C═O); HRMS (FAB) *m/z* calcd for $C_{12}H_{19}NO_5B$ $(MH)^+$ 267.1393, found 267.1395.

Coupling Product 18. From *tert*-Butyl 4-Methoxy-2-((trimethylsilyl)stannyl)carbanilate (19). Tetrakis(triphenylphosphine)palladium-(0) (1.50 g, 1.30 mmol, 0.050 equiv) and copper(I) iodide (200 mg, 1.05 mmol, 0.04 equiv) were added sequentially to a deoxygenated solution of the enol triflate **11** (11.2 g, 24.6 mmol, 1 equiv), *tert*-butyl 4-methoxy-2-(trimethylstannyl)carbanilate (**19**, 10.4 g, 26.8 mmol, 1.05 equiv), lithium chloride (3.40 g, 112 mmol, 4.40 equiv), and 2,6-di-*tert*-butyl-4-methylphenol (100 mg, 450 μmol, 0.018 equiv) in *p*-dioxane (200 mL). The resulting solution was deoxygenated further by alternate vacuum/argon-purge cycles (5×). The deoxygenated reaction mixture was heated at reflux for 1 h, causing the solution to turn from yellow to black. After being cooled to 23 °C, the product solution was filtered through a pad of Celite and the filtrate was concentrated in vacuo. The residue was dissolved in ethyl acetate (500 mL) and was washed sequentially with aqueous phosphate buffer solution (pH 7, 0.05 M in sodium hydrogen phosphate and 0.05 M in potassium dihydrogen phosphate, 2 × 300 mL) and saturated aqueous sodium chloride solution (300 mL). The organic layer was dried over sodium sulfate and was concentrated. The crude product was dissolved in boiling ethyl acetate (400 mL), and hexanes (100 mL) was added to the hot solution. Slow cooling to 23 °C induced crystallization of the product; further cooling to −20 °C produced additional crystals. The crystals were isolated by filtration. The mother liquor was concentrated and was purified by flash column chromatography (15% ethyl acetate in hexanes), followed by recrystallization (ethyl acetate−hexanes, as above). The combined yield of crystalline coupling product **18** was 10.5 g (81%).

From *tert*-Butyl 2-Borono-4-methoxycarbanilate (10). Tetrakis-(triphenylphosphine)palladium(0) (2.78 g, 2.40 mmol, 0.036 equiv) was added to a deoxygenated mixture of aqueous sodium carbonate solution (2.0 M, 48.5 mL, 97.0 mmol, 1.45 equiv) and a solution of the enol triflate **11** (30.4 g, 66.9 mmol, 1 equiv) and *tert*-butyl 2-borono-4-methoxycarbanilate (**10**, 19.9 g, 74.3 mmol, 1.11 equiv) in *p*-dioxane (220 mL). The reaction mixture was deoxygenated further by alternate vacuum/argon-purge cycles (5×) and then was heated at reflux for 45 min. The product mixture was cooled to 23 °C and was concentrated to half the original volume in vacuo. The concentrated product solution was partitioned between water (400 mL) and ethyl acetate (400 mL). The aqueous layer was separated and extracted further with ethyl acetate (2 × 400 mL). The combined organic layers were dried over sodium sulfate and were concentrated. The product was purified by flash column chromatography (10% ethyl acetate in hexanes initially, grading to 20% ethyl acetate in hexanes) and then by recrystallization [ethyl acetate (800 mL) and hexanes (150 mL)], affording the coupling product **18** after two crops of crystals (mp 141−142 °C, 31.9 g, 90%): R_f 0.33, 15% ethyl acetate−hexanes; ^{1}H NMR (300 MHz, $CDCl_3$, 1:1 mixture of atropisomers) δ 7.76 (br s, 1H), 6.81, 6.79 (m, 1H), 6.54, 6.48 (d, 1H, J = 2.9 Hz), 6.27, 6.19 (br s, 1H), 4.89, 4.87 (d, 1H, J = 2.1 Hz), 4.49 (m, 1H), 3.76, 3.75 (s, 3H), 3.62 (s, 3H), 3.16, 2.98 (m, 1H), 2.85, 2.80 (m, 1H), 2.13, 2.07 (app d, 1H, J = 1.7 Hz), 1.85, 1.82 (m, 1H), 1.75, 1.70 (m, 1H), 1.65−1.52 (m, 2H), 1.47, 1.46 (s, 9H), 1.35 (m, 2H), 1.20 (m, 3H), 0.90 (m, 2H), 0.80 (m, 6H), 0.75 (m, 1H), 0.65 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 1:1 mixture of atropisomers) δ 166.9, 166.2, 162.6, 162.4, 155.5, 155.3, 153.2, 153.1, 142.2, 141.7, 135.4, 134.8, 127.8, 127.7, 123.4, 123.3, 121.9, 121.0, 113.0, 112.5, 112.4, 96.9, 96.6, 79.7, 79.5, 73.9, 73.5, 55.3, 55.1, 46.5, 40.2, 40.1, 34.5, 34.1, 34.0, 31.2, 31.0, 29.8, 29.1, 28.2, 25.8, 25.4, 22.9, 22.6, 21.8, 20.8, 20.7, 17.8, 17.6, 15.9, 15.5; FTIR (neat), cm^{-1} 1693 (m, C═O); $[\alpha]^{22}_D$ ($CHCl_3$), +9.2, c = 1.50; HRMS (EI) *m/z* calcd for $C_{31}H_{46}NO_6$ $(MH)^+$ 528.3325, found 528.3308. Anal. Calcd for $C_{31}H_{45}NO_6$: C, 70.56; H, 8.59; N, 2.65. Found: C, 70.92; H, 8.58; N, 2.54.

Quinolone 9. A deoxygenated, solid mixture of the coupling product **18** (23.5 g, 44.5 mmol) and 4-chlorophenol (ca. 400 g) was heated at 180 °C for 30 min, whereupon all solids dissolved. The product solution was cooled to 23 °C, and 4-chlorophenol was removed by distillation under high vacuum. The residue was purified by flash column chromatography (dichloromethane initially, grading to 10% methanol in dichloromethane) to afford the quinolone **9** as a yellow solid (mp 153−157 °C, 10.2 g, 84%). The byproduct quinolyl ether **20** was isolated in separate fractions and could be converted to the

desired product **9** by resubjection to the reaction conditions (5 h, 98%). **9**: R_f 0.27, ethyl acetate; ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.80 (br s, 1H), 7.33 (d, 1H, J = 8.8 Hz), 7.17 (d, 1H, J = 2.6 Hz), 7.11 (dd, 1H, J = 8.8, 2.6 Hz), 5.86 (d, 1H, J = 1.9 Hz), 3.88 (s, 3H), 3.87 (s, 3H), 3.54 (quin, 1H, J = 7.1 Hz), 2.83 (ddd, 1H, J = 16.7, 8.1, 2.1 Hz), 2.19 (d, 1H, J = 16.9 Hz), 1.16 (d, 3H, J = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.6, 162.44, 154.7, 139.7, 132.6, 123.7, 118.8, 117.6 (2C), 105.9, 88.8, 55.9, 55.3, 34.2, 26.4, 17.4; FTIR (dichloromethane solution cell), cm^{-1} 3392 (w, NH), 1655 (s, C=O); $[\alpha]^{22}_D$ ($CHCl_3$), −61.3, c = 0.69; HRMS (FAB) *m/z* calcd for $C_{16}H_{18}NO_3$ $(MH)^+$ 272.1287, found 272.1293. **20**: R_f 0.50, 15% ethyl acetate−hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, 1H, J = 8.8 Hz), 7.24 (m, 2H), 6.02 (d, 1H, J = 2.0 Hz), 5.33 (td, 1H, J = 10.5, 4.0 Hz), 3.93 (s, 3H), 3.87 (s, 3H), 3.43 (quin, 1H, J = 7.0 Hz), 2.86 (ddd, 1H, J = 16.7, 7.9, 2.2 Hz), 2.36 (m, 1H), 2.18 (dd, 1H, J = 17.9, 1.1 Hz), 2.05 (m, 1H), 1.73 (m, 2H), 1.62 (m, 1H), 1.55 (m, 1H), 1.21 (m, 1H), 1.13 (d, 3H, J = 7.0 Hz), 1.05 (m, 1H), 0.94 (d, 3H, J = 6.6 Hz), 0.92 (d, 3H, J = 7.5 Hz), 0.85 (m, 1H), 0.83 (d, 3H, J = 7.0 Hz).

Quinolyl Triflate 21. Using 2,6-Di-*tert*-butylpyridine as Base. Triflic anhydride (3.80 mL, 22.4 mmol, 1.10 equiv) was added via syringe to a suspension the quinolone **9** (5.52 g, 20.3 mmol, 1 equiv) and 2,6-di-*tert*-butylpyridine (6.10 mL, 27.1 mmol, 1.33 equiv) in dichloromethane (400 mL) at −78 °C. The cold suspension was allowed to warm to 23 °C over 30 min and was stirred at that temperature for 15 min. Solids were observed to dissolve as the reaction proceeded. The reaction mixture was poured into aqueous phosphate buffer solution (pH 7, 0.05 M in sodium hydrogen phosphate and 0.05 M in potassium dihydrogen phosphate, 200 mL). The aqueous layer was separated and extracted further with two 200-mL portions of dichloromethane. The combined organic layers were dried over sodium sulfate and were concentrated in vacuo. The residue was purified by flash column chromatography (40% dichloromethane in hexanes) to provide the quinolyl triflate **21** as an off-white solid (7.09 g, 86%).

Using 2-Chloropyridine as Base. Triflic anhydride (24.3 mL, 144 mmol, 2.00 equiv) was added via syringe to a suspension the quinolone **9** (19.5 g, 71.9 mmol, 1 equiv) and 2-chloropyridine (27.2 mL, 287 mmol, 4.00 equiv) in dichloromethane (750 mL) at −78 °C. The cold suspension was allowed to warm to 23 °C over 30 min and was stirred at that temperature for 15 min. Solids were observed to dissolve as the reaction proceeded. The reaction mixture was poured into aqueous phosphate buffer solution (pH 7, 0.05 M in sodium hydrogen phosphate and 0.05 M in potassium dihydrogen phosphate, 500 mL). The aqueous layer was separated and extracted further with dichloromethane (2 × 300 mL). The combined organic layers were dried over sodium sulfate and were concentrated in vacuo. The residue was purified by flash column chromatography (40% dichloromethane in hexanes) to provide the quinolyl triflate **21** as an off-white solid (mp 129.5−130.5 °C, 24.6 g, 85%): R_f 0.37, 40% dichloromethane−hexanes; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 (d, 1H, J = 9.2 Hz), 7.35 (dd, 1H, J = 9.2, 2.7 Hz), 7.20 (d, 1H, J = 2.7 Hz), 6.09 (d, 1H, J = 1.9 Hz), 3.96 (s, 3H), 3.91 (s, 3H), 3.39 (quin, 1H, J = 7.1 Hz), 2.92 (ddd, 1H, J = 16.7, 7.7, 2.1 Hz), 2.28 (dd, 1H, J = 17.4, 0.7 Hz), 1.21 (d, 3H, J = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.5, 158.0, 151.2, 142.9, 140.7, 130.5, 125.1, 121.5, 118.7 (q, 1C, J = 319 Hz), 117.9, 101.8, 89.6, 55.5, 55.4, 34.0, 27.1, 18.3; FTIR (neat), cm^{-1} 1622 (m, C=C); $[\alpha]^{22}_D$ ($CHCl_3$), −28.0, c = 0.95; HRMS (FAB) *m/z* calcd for $C_{17}H_{16}NO_5SF_3$ $(M)^+$ 403.0701, found 403.0679. Anal. Calcd for $C_{17}H_{16}NO_5SF_3$: C, 50.62; H, 4.00; N, 3.47. Found: C, 50.56; H, 3.87; N, 3.30.

α-Hydroxy Dimethyl Ketal 22. A solution of the quinolyl triflate **21** (17.7 g, 43.9 mmol, 1 equiv) and *m*-chloroperoxybenzoic acid (70% w/w, 21.6 g, 87.8 mmol, 2.00 equiv) in methanol (600 mL) was heated at reflux for 45 min. After being cooled to 23 °C, the reaction solution was partitioned between a 1:1 mixture of saturated aqueous sodium bicarbonate solution and saturated aqueous sodium thiosulfate solution (600 mL) and dichloromethane (500 mL). The aqueous layer was separated and extracted further with dichloromethane (2 × 500 mL). The combined organic layers were dried over sodium sulfate and were concentrated. The residue was purified by flash column chromatography (25% ethyl acetate in hexanes initially, grading to 60% ethyl acetate in hexanes) to afford separately the α-hydroxy dimethyl ketal **22** as a yellow foam (13.5 g, 68%) and the β-hydroxy dimethyl ketal **23** as a yellow foam (3.17 g, 16%). **22**: R_f 0.24, 40% ethyl acetate−hexanes; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (d, 1H, J = 9.0 Hz), 7.44 (d, 1H, J = 2.6 Hz), 7.36 (dd, 1H, J = 9.1, 2.7 Hz), 5.18 (app t, 1H, J = 1.9 Hz), 3.98 (s, 3H), 3.49 (s, 3H), 3.36 (td, 1H, J = 7.1, 1.7 Hz), 3.30 (s, 3H), 2.72 (d, 1H, J = 2.4 Hz), 2.25 (dd, 1H, J = 14.2, 6.8 Hz), 2.09 (dt, 1H, J = 14.2, 1.7 Hz), 1.47 (d, 3H, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.8, 151.4, 143.0, 139.8, 130.2, 128.7, 125.1, 121.9, 118.6 (q, 1C, J = 319 Hz), 102.5, 100.0, 64.2, 55.5, 48.6, 48.2, 30.2, 28.6, 20.9; FTIR (neat), cm^{-1} 3484 (br, OH); $[\alpha]^{22}_D$ ($CHCl_3$), −11.6, c = 1.16; HRMS (FAB) *m/z* calcd for $C_{18}H_{21}NO_7SF_3$ $(MH)^+$ 452.0991, found 452.0984. Anal. Calcd for $C_{18}H_{20}NO_7SF_3$: C, 47.89; H, 4.47; N, 3.10. Found: C, 47.94; H, 4.60; N, 2.84. **23**: R_f 0.23, 40% ethyl acetate−hexanes: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (d, 1H, J = 9.1 Hz), 7.44 (d, 1H, J = 2.7 Hz), 7.36 (dd, 1H, J = 9.1 Hz, 2.7 Hz), 5.18 (app t, 1H, J = 2.0 Hz), 3.98 (s, 3H), 3.44 (s, 3H), 3.21 (br quin, 1H, J = 7.1 Hz), 3.21 (s, 3H), 2.70 (br d, 1H, J = 2.4 Hz), 2.37 (ddd, 1H, J = 14.2, 7.2, 2.0 Hz), 1.93 (dd, 1H, J = 14.2, 10.0 Hz), 1.43 (d, 3H, J = 6.7 Hz).

Quinolyl Methyl Ether 24. Tetrakis(triphenylphosphine)palladium-(0) (778 mg, 673 μmol, 0.040 equiv) was added to a deoxygenated solution of the α-hydroxy dimethyl ketal **22** (7.60 g, 16.8 mmol, 1 equiv) and triethylamine (9.40 mL, 67.3 mmol, 4.00 equiv) in *p*-dioxane (300 mL) at 23 °C. The resulting solution was deoxygenated further by alternate vacuum/argon-purge cycles (5×). Formic acid (1.70 mL, 43.8 mmol, 2.63 equiv) was added slowly over 5 min via syringe, and the resulting solution was heated at reflux for 20 min and then was allowed to cool to 23 °C. The reaction mixture was partitioned between saturated aqueous sodium chloride solution (300 mL) and ethyl acetate (300 mL). The aqueous layer was separated and extracted further with ethyl acetate (2 × 300 mL). The combined organic layers were dried over sodium sulfate and were concentrated in vacuo. The residue was purified by flash column chromatography (ether initially, grading to 20% ethyl acetate in ether) to provide the quinolyl methyl ether **24** as a white foam (mp 135−136 °C, 4.94 g, 97%): R_f 0.12, 50% ethyl acetate−hexanes; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.68 (s, 1H), 7.97 (d, 1H, J = 9.2 Hz), 7.51 (d, 1H, J = 2.7 Hz), 7.31 (dd, 1H, J = 9.2, 2.7 Hz), 5.24 (br d, 1H, J = 4.5 Hz), 3.97 (s, 3H), 3.48 (s, 3H), 3.35 (s, 3H), 3.28 (m, 1H), 2.95 (br d, 1H, J = 4.4 Hz), 2.31 (dd, 1H, J = 14.3, 6.6 Hz), 1.91 (ddd, 1H, J = 14.1, 4.1, 1.1 Hz), 1.48 (d, 3H, J = 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.1, 148.6, 143.0, 137.3, 133.3, 131.1, 128.2, 120.4, 102.5, 100.0, 66.1, 55.5, 49.3, 48.3, 32.2, 30.0, 22.7; FTIR (neat), cm^{-1} 3286 (br, OH); $[\alpha]^{22}_D$ ($CHCl_3$), +5.2, c = 0.54; HRMS (FAB) *m/z* calcd for $C_{17}H_{22}NO_4$ $(MH)^+$ 304.1549, found 304.1549. Anal. Calcd for $C_{17}H_{21}NO_4$: C, 67.31; H, 6.98; N, 4.62. Found: C, 67.40; H, 6.83; N, 4.43.

Quinolyl Alcohol 60. A solution of ethylmagnesium bromide in tetrahydrofuran (1.0 M, 8.9 mL, 8.9 mmol, 1.1 equiv) was added by syringe to a solution of the quinolyl methyl ether **24** (2.46 g, 8.10 mmol, 1 equiv) in tetrahydrofuran (5 mL) at −78 °C. The reaction flask was transferred to an ice bath for 10 min and then was cooled to −78 °C. A 100-mL flame-dried Schlenk-type flask was charged with sodium hydride (1.17 g, 48.7 mmol, 6.00 equiv), and *N*,*N*-dimethylformamide (20 mL) was added to the hydride powder cautiously over 5 min. The resulting slurry was cooled to 0 °C, and ethanethiol (1.80 mL, 24.3 mmol, 3.00 equiv) was added dropwise over 15 min by syringe, causing vigorous gas evolution. After the gas evolution had subsided, the reaction flask was removed from the ice bath and was stirred at 23 °C for 10 min. The solution of magnesium alkoxide prepared above was then added to the slurry of sodium ethanethiolate via cannula over 5 min. The more volatile solvent, tetrahydrofuran, was removed in vacuo, and the reaction mixture was heated at reflux for 1.5 h. The resulting thick, brown slurry was cooled to 23 °C and was partitioned between saturated aqueous ammonium chloride solution (500 mL) and ethyl acetate (500 mL). The aqueous layer was separated and extracted sequentially with ethyl acetate (500 mL) and 20% methanol in dichloromethane (500 mL). The aqueous layer was then neutralized by the addition of aqueous hydrochloric acid solution (1 N, 100 mL) and was extracted with ethyl acetate (2 × 500 mL). The combined organic layers were dried over sodium sulfate and were concentrated in vacuo. The residue was purified by flash column chromatography (2.5% methanol in dichloromethane initially, grading to 5% methanol in dichloromethane) to afford the quinolyl alcohol **60** as a yellow solid (1.66 g, 71%). For large scale reactions, the crude product was used

without chromatographic purification: R_f 0.39, 5% methanol−dichloromethane; ^{1}H NMR (300 MHz, CD_3OD) δ 8.51 (s, 1H), 7.83 (d, 1H, J = 9.2 Hz), 7.50 (d, 1H, J = 2.8 Hz), 7.25 (dd, 1H, J = 9.6, 2.8 Hz), 5.12 (m, 1H), 3.44 (s, 3H), 3.26 (m, 1H), 3.21 (s, 3H), 2.27 (dd, 1H, J = 14.4, 7.6 Hz), 1.97 (d, 1H, J = 14.8 Hz), 1.43 (d, 3H, J = 7.2 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ 157.7, 149.2, 142.4, 139.6, 134.8, 130.8, 130.1, 121.8, 106.2, 102.0, 65.4, 48.9, 48.4, 31.6, 31.0, 23.7; FTIR (neat), cm^{-1} 3200 (br, OH); $[\alpha]^{22}_D$ (CH_3OH), +11.5, c = 0.33; HRMS (FAB) *m/z* calcd for $C_{16}H_{19}NO_4$ $(M)^+$ 290.1392, found 290.1374.

Quinolyl Silyl Ether 61. Imidazole (1.01 g, 14.8 mmol, 2.60 equiv) and *tert*-butyldimethylsilyl chloride (1.11 g, 7.39 mmol, 1.30 equiv) were added sequentially to a solution of the quinolyl alcohol **60** (1.64 g, 5.69 mmol, 1 equiv) in *N*,*N*-dimethylformamide (10 mL) at 23 °C. After being stirred for 1 h at 23 °C, the reaction mixture was partitioned between water (100 mL) and ethyl acetate (100 mL). The aqueous layer was separated and extracted further with two 100-mL portions of ethyl acetate. The combined organic layers were dried over sodium sulfate and were concentrated. The residue was purified by flash column chromatography (30% ethyl acetate in hexanes) to afford the quinolyl silyl ether **61** as a light yellow foam (2.10 g, 91%): R_f 0.35, 40% ethyl acetate−hexanes; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.66 (s, 1H), 7.94 (d, 1H, J = 9.0 Hz), 7.57 (d, 1H, J = 2.6 Hz), 7.23 (dd, 1H, J = 9.0, 2.6 Hz), 5.18 (br s, 1H), 3.46 (s, 3H), 3.33 (s, 3H), 3.27 (m, 1H), 2.80 (d, 1H, J = 4.3 Hz), 2.30 (dd, 1H, J = 14.2, 6.5 Hz), 1.90 (ddd, 1H, J = 14.2, 4.1, 1.3 Hz), 1.47 (d, 3H, J = 7.3 Hz) 1.03 (s, 9H), 0.28 (s, 3H), 0.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.2, 149.0, 143.0, 137.2, 133.1, 131.0, 128.2, 124.0, 111.3, 100.0, 65.8, 49.2, 48.2, 32.1, 30.0, 25.7, 22.6, 18.3, −4.3; FTIR (neat), cm^{-1} 3177 (br OH); $[\alpha]^{22}_D$ ($CHCl_3$), +1.7, c = 1.20; HRMS (FAB) *m/z* calcd for $C_{22}H_{34}NO_4Si$ $(MH)^+$ 404.2257, found 404.2242. Anal. Calcd for $C_{22}H_{33}NO_4Si$: C, 65.47; H, 8.24; N, 3.47. Found: C, 65.32; H, 8.13; N, 3.35.

Addition Product 62. A solution of ethylmagnesium bromide in tetrahydrofuran (1.0 M, 13.6 mL, 13.6 mmol, 0.901 equiv) was added to a solution of the quinolyl silyl ether **61** (6.10 g, 15.1 mmol, 1 equiv) in tetrahydrofuran (30 mL) at −78 °C. The reaction mixture was stirred in an ice bath for 10 min and then was cooled to −78 °C. In a separate flask, a solution of ethylmagnesium bromide in tetrahydrofuran (1.0 M, 22.7 mL, 22.7 mmol, 1.50 equiv) was added to a solution of *tert*-butyl[(*Z*)-3-hexene-1,5-diynyl]dimethylsilane (**31**, 5.75 g, 30.2 mmol, 2.00 equiv) in tetrahydrofuran (20 mL) at 0 °C. The resulting solution was warmed to 23 °C and then was heated briefly to reflux with a heat gun. After the latter solution had cooled to 23 °C, it was transferred via cannula over 3 min to the cold solution (−78 °C) of magnesium alkoxide prepared above. Allyl chloroformate (2.60 mL, 24.5 mmol, 1.62 equiv) was added to the reaction mixture, and the resulting solution was warmed to 0 °C and was stirred at that temperature for 2 h. The product solution was partitioned between aqueous phosphate buffer solution (pH 7, 0.05 M in sodium hydrogen phosphate and 0.05 M in potassium dihydrogen phosphate, 150 mL) and ethyl acetate (150 mL). The aqueous layer was separated and extracted further with ethyl acetate (2 × 150 mL). The combined organic layers were dried over sodium sulfate and were concentrated. The residue was purified by flash column chromatography (10% ethyl acetate in hexanes initially, grading to 20% ethyl acetate in hexanes) to afford the addition product **62** as a light yellow foam (9.16 g, 89%): R_f 0.22, 20% ethyl acetate−hexanes; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 (br s, 1H), 6.93 (d, 1H, J = 2.7 Hz), 6.70 (dd, 1H, J = 8.8, 2.6 Hz), 5.95 (m, 1H), 5.90 (br s, 1H), 5.71 (d, 1H, J = 11.1 Hz), 5.61 (dd, 1H, J = 11.1, 1.9 Hz), 5.35 (br d, 1H, J = 17.5 Hz), 5.22 (br d, 1H, J = 10.5 Hz), 4.75 (br m, 1H), 4.72 (dd, 1H, J = 8.5, 2.0 Hz), 4.62 (br m, 1H), 3.43 (s, 3H), 3.34 (s, 3H), 2.59 (m, 1H), 2.37 (br m, 1H), 2.14 (dd, 1H, J = 14.2, 5.2 Hz), 1.61 (dd, 1H, J = 14.3, 8.3 Hz), 1.31 (d, 3H, J = 7.2 Hz), 0.99 (s, 9H), 0.96 (s, 9H), 0.22 (s, 3H), 0.21 (s, 3H), 0.14 (s, 6H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 153.3, 152.7, 138.0, 132.9, 129.1, 128.9, 128.6, 125.7, 120.0, 119.9, 118.7, 118.3, 116.5, 102.8, 101.8, 99.1, 94.8, 80.7, 68.8, 67.4, 50.8, 48.5, 47.7, 35.9, 33.0, 26.4, 26.0, 19.2, 18.6, 16.9, −4.1, −4.4; FTIR (neat), cm^{-1} 3472 (br, OH), 2249 (w, C≡C), 2144 (w, C≡C), 1700 (vs, C═O); $[\alpha]^{22}_D$ ($CHCl_3$), +368.7, c = 1.10; HRMS (FAB) *m/z* calcd for $C_{38}H_{55}NO_6Si_2$ $(M)^+$ 677.3568, found 677.3575. Anal. Calcd for $C_{38}H_{55}NO_6Si_2$: C, 67.32; H, 8.18; N, 2.07. Found: C, 67.39; H, 8.30; N, 1.78.

Epoxide 63. *m*-Chloroperoxybenzoic acid (70% w/w, 4.74 g, 19.2 mmol, 1.50 equiv) was added to a biphasic mixture of a solution of the addition product **62** (8.70 g, 12.8 mmol, 1 equiv) in dichloromethane (200 mL) and aqueous phosphate buffer solution (pH 7, 0.05 M in sodium hydrogen phosphate and 0.05 M in potassium dihydrogen phosphate, 200 mL) at 0 °C. The biphasic mixture was stirred at 0 °C for 12 h. A second portion of *m*-chloroperoxybenzoic acid (70% w/w, 4.74 g, 19.2 mmol, 1.50 equiv) was added, and the reaction mixture was stirred at 0 °C for an additional 7 h. The product solution was poured into a 1:1 mixture of saturated aqueous sodium bicarbonate solution and saturated aqueous sodium thiosulfate solution (300 mL). The aqueous layer was separated and extracted further with dichloromethane (2 × 250 mL). The combined organic layers were dried over sodium sulfate and were concentrated. The residue was purified by flash column chromatography (20% ethyl acetate in hexanes) to provide the epoxide **63** as a yellow foam (7.61 g, 85%): R_f 0.23, 20% ethyl acetate−hexanes; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23 (d, 1H, J = 2.7 Hz), 7.14 (br d, 1H, J = 8.2 Hz), 6.77 (dd, 1H, J = 8.1, 2.3 Hz), 5.87 (m, 1H), 5.84 (br s, 1H), 5.74 (d, 1H, J = 11.2 Hz), 5.53 (br d, 1H, J = 11.9 Hz), 5.29 (m, 2H), 4.68 (m, 1H), 4.64 (d, 1H, J = 10.7 Hz), 4.52 (m, 1H), 3.41 (s, 3H), 3.28 (s, 3H), 2.92 (br d, 1H, J = 10.0 Hz), 2.35 (m, 1H), 1.96 (dd, 1H, J = 14.3, 4.2 Hz), 1.50 (dd, 1H, J = 14.3, 10.7 Hz), 1.46 (d, 3H, J = 7.4 Hz), 0.99 (s, 9H), 0.97 (s, 9H), 0.24 (s, 3H), 0.23 (s, 3H), 0.14 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.9, 152.9, 132.2, 129.6, 128.5, 128.2, 120.0, 119.6, 119.3, 118.9, 117.3, 102.1, 101.6, 98.4, 92.4, 82.0, 75.9, 69.9, 66.7, 62.9, 50.6, 48.4, 46.1, 36.7, 30.3, 26.0, 25.6, 18.1, 17.6, 16.5, −4.4, −4.7; FTIR (neat), cm^{-1} 3554 (sh w, OH), 3475 (br, w, OH), 2255 (w, C≡C), 2140 (w, C≡C), 1712 (vs, C═O); $[\alpha]^{22}_D$ ($CHCl_3$), +90.4, c = 1.14, HRMS (FAB) *m/z* calcd for $C_{38}H_{55}NO_7Si_2$ $(M)^+$ 693.3517, found 693.3487. Anal. Calcd for $C_{38}H_{55}NO_7Si_2$: C, 65.76; H, 7.99; N, 2.02. Found: C, 65.44; H, 8.11; N, 1.86.

Phenol 64. A solution of tetrabutylammonium fluoride in tetrahydrofuran (1.0 M, 9.50 mL, 9.50 mmol, 2.00 equiv) was added to a solution of the epoxide **63** (3.30 g, 4.75 mmol, 1 equiv) in tetrahydrofuran (100 mL) at 0 °C. After being stirred at 0 °C for 10 min, the reaction mixture was partitioned between aqueous phosphate buffer solution (pH 7, 0.05 M in sodium hydrogen phosphate and 0.05 M in potassium dihydrogen phosphate, 150 mL) and dichloromethane (150 mL). The aqueous layer was separated and extracted further with dichloromethane (2 × 150 mL). The combined organic layers were dried over sodium sulfate and were concentrated. The residue was purified by flash column chromatography (60% ethyl acetate in hexanes) to afford the phenol **64** as a yellow foam (2.21 g, 100%): R_f 0.30, 40% ethyl acetate−hexanes; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (d, 1H, J = 2.7 Hz), 7.16 (d, 1H, J = 8.6 Hz), 6.77 (dd, 1H, J = 8.7, 2.7 Hz), 5.87 (s, 1H), 5.84 (br s, 1H), 5.81 (m, 1H), 5.68 (br s, 2H), 5.19 (m, 2H), 4.70 (br m, obscured, 1H), 4.70 (d, 1H, J = 11.0 Hz), 4.52 (br dd, 1H, J = 13.7, 4.4 Hz), 3.38 (s, 3H), 3.24 (s, 3H), 3.18 (br d, 1H, J = 11.1 Hz), 3.16 (d, 1H, J = 0.9 Hz), 2.32 (m, 1H), 1.95 (dd, 1H, J = 14.6, 4.2 Hz), 1.56 (br dd, 1H, J = 14.2, 11.9 Hz), 1.46 (d, 3H, J = 7.5 Hz); ^{13}C (100 MHz, $CDCl_3$) δ 155.5, 153.9, 132.0, 128.7, 128.6 (2C), 120.2, 119.5, 117.5, 115.2, 115.0, 98.5, 92.3, 85.1, 81.9, 80.2, 75.7, 70.2, 67.1, 63.1, 50.7, 48.4, 46.3, 36.7, 30.2, 17.3; FTIR (neat), cm^{-1} 3395 (br s, OH), 3297 (m, C≡CH), 2252 (w, C≡C), 2094 (w, C≡C), 1694 (vs, C═O); $[\alpha]^{22}_D$ ($CHCl_3$), +286.7, c = 0.45; HRMS (FAB) *m/z* calcd for $C_{26}H_{27}NO_7$ $(M)^+$ 465.1788, found 465.1794.

***tert*-Butyldimethylsilyl Phenyl Ether 65.** A solution of the phenol **64** (6.10 g, 13.1 mmol, 1 equiv) in *N*,*N*-dimethylformamide (80 mL) at 23 °C was treated sequentially with imidazole (2.32 g, 34.1 mmol, 2.60 equiv) and *tert*-butyldimethylsilyl chloride (2.60 g, 17.0 mmol, 1.30 equiv). After being stirred at 23 °C for 1 h, the reaction solution was partitioned between water (300 mL) and ethyl acetate (300 mL). The aqueous layer was separated and extracted further with two 300-mL portions of ethyl acetate. The combined organic layers were dried over sodium sulfate and were concentrated. The residue was purified by flash column chromatography (20% ethyl acetate in hexanes) to provide the *tert*-butyldimethylsilyl phenyl ether **65** as a yellow foam (7.27 g, 96%): R_f 0.25, 20% ethyl acetate−hexanes; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23 (d, 1H, J = 2.7 Hz), 7.14 (br d, 1H, J = 8.2 Hz),

6.76 (dd, 1H, J = 8.6, 2.3 Hz), 5.87 (m, 1H), 5.83 (br s, 1H), 5.70 (dd, 1H, J = 1.11, 1.6 Hz), 5.66 (br d, 1H, J = 11.3 Hz), 5.19 (m, 2H), 4.67 (m, 1H), 4.64 (d, 1H, J = 10.9 Hz), 4.50 (br dd, 1H, J = 13.0, 4.1 Hz), 3.41 (s, 3H), 3.27 (s, 3H), 3.16 (d, 1H, J = 1.7 Hz), 2.94 (br d, 1H, J = 10.5 Hz), 2.34 (m, 1H), 1.95 (dd, 1H, J = 14.5, 4.3 Hz), 1.57 (dd, 1H, J = 14.4, 11.3 Hz), 1.46 (d, 3H, J = 7.6 Hz), 0.98 (s, 9H), 0.23 (s, 3H), 0.22 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.0, 153.0, 132.2, 129.7, 128.6, 128.2, 120.3, 119.7, 119.3 (2C), 117.4, 98.4, 92.6, 84.8, 81.9, 80.4, 76.0, 70.1, 66.8, 62.9, 50.7, 48.4, 46.1, 36.8, 30.3, 25.7, 18.2, 17.3, −4.4; FTIR (neat), cm^{-1} 3552 (sh, w, OH), 3474 (br, m, OH), 3298 (m, C≡CH), 2252 (w, C≡C), 2090 (w, C≡C), 1711 (vs, C═O); $[\alpha]^{22}_D$ ($CHCl_3$), +230.2, c = 0.41; HRMS (FAB) *m/z* calcd for $C_{32}H_{41}NO_7Si$ $(M)^+$ 579.2652, found 579.2633. Anal. Calcd for $C_{32}H_{41}NO_7Si$: C, 66.29; H, 7.13; N, 2.42. Found: C, 65.99; H, 7.09; N, 2.31.

Ketone 66. Dimethyl sulfoxide (4.22 mL, 59.5 mmol, 15.0 equiv) was added to a solution of oxalyl chloride (3.46 mL, 39.7 mmol, 10.0 equiv) in dichloromethane (75 mL) at −78 °C. After the resulting solution was stirred at −78 °C for 20 min, a solution of the *tert*-butyldimethylsilyl phenyl ether **65** (2.30 g, 3.97 mmol, 1 equiv) in dichloromethane (75 mL) was added over 10 min via cannula. The reaction mixture was warmed to −40 °C and was held at that temperature for 10 h. The reaction mixture was then cooled to −78 °C, triethylamine (16.6 mL, 119 mmol, 30.0 equiv) was added, and the resulting solution was stirred in an ice bath for 30 min. The product solution was poured into aqueous phosphate buffer solution (pH 7, 0.05 M in sodium hydrogen phosphate and 0.05 M in potassium dihydrogen phosphate, 150 mL). The aqueous layer was separated and extracted further with dichloromethane (2 × 150 mL). The combined organic layers were dried over sodium sulfate and were concentrated. The residue was purified by flash column chromatography (2% ethyl acetate in dichloromethane initially, grading to 5% ethyl acetate in dichloromethane) to afford the ketone **66** as a light brown foam (2.10 g, 92%). Due to its instability to storage, product **66** was typically carried directly on to the next step in the sequence: R_f 0.51, 5% ethyl acetate−dichloromethane; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (d, 1H, J = 2.6 Hz), 7.17 (br d, 1H, J = 8.3 Hz), 6.80 (dd, 1H, J = 8.6, 2.5 Hz), 5.86 (m, 1H), 5.82 (br s, 1H), 5.68 (br s, 2H), 5.20 (m, 2H), 4.67 (br dd, 1H, J = 13.0, 4.7 Hz), 4.52 (br d, 1H, J = 13.4 Hz), 3.29 (s, 3H), 3.28 (s, 3H), 3.14 (d, 1H, J = 1.0 Hz), 2.77 (m, 1H), 2.19 (dd, 1H, J = 14.0, 6.1 Hz), 1.98 (dd, 1H, J = 14.0, 3.2 Hz), 1.51 (d, 3H, J = 7.5 Hz), 0.96 (s, 9H), 0.22 (s, 3H), 0.22 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.5, 154.9, 152.9, 132.0, 129.9, 128.6, 123.8, 120.3 (2C), 120.1, 119.8, 117.6, 97.8, 91.6, 85.0, 82.7, 80.1, 77.3, 66.9, 58.4, 49.7 (2C), 47.2, 35.6, 30.6, 25.6, 19.2, 18.1, −4.5; FTIR (neat), cm^{-1} 3297 (m, C≡CH), 2094 (w, C≡C), 1713 (vs, C═O).

Cyclization Product 67. A suspension of anhydrous cerium(III) chloride (1.70 g, 6.90 mmol, 4.93 equiv) and the ketone **66** (810 mg, 1.40 mmol, 1 equiv) in tetrahydrofuran (30 mL) was stirred at 23 °C for 30 min. The suspension was then cooled to −78 °C, and a solution of potassium *N*,*N*-bis(trimethylsilyl)amide in toluene (0.5 M, 4.50 mL, 2.25 mmol, 1.61 equiv) was added dropwise over 5 min causing the yellow suspension to turn initially light brown, darkening to a deep gray-brown. The reaction flask was transferred to an ice bath, and saturated aqueous ammonium chloride solution (150 mL) was added carefully. The biphasic mixture was extracted with ethyl acetate (3 × 150 mL). The combined organic layers were dried over sodium sulfate and were concentrated. The residue was purified by flash column chromatography (25% ethyl acetate in hexanes) to afford the cyclization product **67** as a pale yellow foam (761 mg, 94%): R_f 0.14, 20% ethyl acetate−hexanes; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (d, 1H, J = 2.7 Hz), 7.11 (br s, 1H), 6.73 (dd, 1H, J = 8.6, 2.7 Hz), 5.85 (m, 1H), 5.78 (d, 1H, J = 10.0 Hz), 5.70 (br s, 1H), 5.65 (dd, 1H, J = 9.9, 1.6 Hz), 5.20 (m, 2H), 4.68 (br dd, 1H, J = 13.2, 5.2 Hz), 4.58 (br m, 1H), 3.51 (s, 3H), 3.49 (s, 1H), 3.36 (s, 3H), 2.50 (m, 1H), 2.07 (m, 2H), 1.40 (d, 3H, J = 7.3 Hz), 0.96 (s, 9H), 0.21 (s, 3H), 0.19 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.7, 152.1, 132.1, 130.2, 129.5, 126.9, 123.9, 122.5 (2C), 119.2, 117.5, 100.5, 100.3, 94.8, 93.5, 89.7, 77.6, 73.6, 67.1, 66.8, 51.6, 50.0, 47.0, 36.8, 30.6, 25.8, 18.2, 17.4, −4.4, −4.5; FTIR (neat), cm^{-1} 3465 (br, m, OH), 2280 (w, C≡C), 2192 (w, C≡C), 1705 (vs, C═O); $[\alpha]^{22}_D$ ($CHCl_3$), +579.8, c = 0.48; HRMS (FAB) *m/z* calcd for $C_{32}H_{39}NO_7Si$ $(M)^+$ 577.2496, found 577.2527. Anal. Calcd for $C_{32}H_{39}NO_7Si$: C, 66.53; H, 6.80; N, 2.42. Found: C, 66.60; H, 6.89; N, 2.14.

Hydroxy Ketone 68. A solution of the cyclization product **67** (5.43 g, 9.40 mmol, 1 equiv) in acetone (300 mL) was stirred with *p*-toluenesulfonic acid monohydrate (7.15 g, 37.6 mmol, 4.00 equiv) at 23 °C for 2 h. The reaction solution was partitioned between saturated aqueous sodium bicarbonate solution (300 mL) and ethyl acetate (300 mL). The aqueous layer was separated and extracted further with ethyl acetate (2 × 300 mL). The combined organic layers were dried over sodium sulfate and were concentrated. The residue was purified by flash column chromatography (25% ethyl acetate in hexanes) to afford the hydroxy ketone **68** as a pale yellow foam (4.03 g, 81%): R_f 0.52, 40% ethyl acetate−hexanes; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 (d, 1H, J = 2.7 Hz), 7.19 (br d, 1H, J = 8.7 Hz), 6.80 (dd, 1H, J = 8.7, 2.7 Hz), 5.95 (m, 1H), 5.87 (d, 1H, J = 9.8 Hz), 5.79 (dd, 1H, J = 10.3, 1.5 Hz), 5.78 (br s, 1H), 5.21 (m, 2H), 4.69 (s, 1H), 4.65 (m, 1H), 4.58 (br m, 1H), 3.00 (m, 1H), 2.90 (m, 2H), 1.54 (d, 3H, J = 7.1 Hz), 0.97 (s, 9H), 0.21 (s, 3H), 0.21 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.7, 154.7, 152.7, 131.9, 130.1, 127.5, 127.1, 123.9, 123.4, 121.9, 120.0, 117.6, 97.9, 95.7, 94.3, 91.0, 74.5, 74.3, 70.8, 66.8, 48.3, 41.0, 33.8, 25.7, 19.8, 18.2, −4.5, −4.6; FTIR (neat), cm^{-1} 3420 (br, m, OH), 2280 (w, C≡C), 2187 (w, C≡C), 1714 (vs, C═O); $[\alpha]^{22}_D$ ($CHCl_3$), +904.6, c = 0.35; HRMS (FAB) *m/z* calcd for $C_{30}H_{33}NO_6Si$ $(M)^+$ 531.2077, found 531.2106. Anal. Calcd for $C_{30}H_{33}NO_6Si$: C, 67.77; H, 6.26; N, 2.63. Found: C, 68.11; H, 6.36; N, 2.33.

Thionocarbonate 69. (Thiocarbonyl)diimidazole (4.19 g, 23.5 mmol, 5.00 equiv) and 4-(dimethylamino)pyridine (862 mg, 7.05 mmol, 3.00 equiv) were added sequentially to a solution of the hydroxy ketone **68** (1.25 g, 2.35 mmol, 1 equiv) in dichloromethane (100 mL) at 23 °C. The reaction mixture was heated at a gentle reflux for 7 h. A second portion of (thiocarbonyl)diimidazole (838 mg, 4.70 mmol, 2.00 equiv) and 4-(dimethylamino)pyridine (287 mg, 2.35 mmol, 1 equiv) was added, and the reaction mixture was heated at a gentle reflux for an additional 14 h. The reaction mixture was then cooled to 23 °C, and volatiles were removed in vacuo. The residue was purified by flash column chromatography (30% hexanes in dichloromethane) to afford the thionocarbonate **69** as an off-white foam (1.15 g, 85%): R_f 0.44, dichloromethane; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (d, 1H, J = 2.7 Hz), 7.23 (br s, 1H), 6.86 (dd, 1H, J = 8.8, 2.7 Hz), 5.95 (m, 1H), 5.83 (d, 1H, J = 10.0 Hz), 5.78 (br s, 1H), 5.77 (dd, 1H, J = 10.3, 1.3 Hz), 5.57 (d, 1H, J = 6.7 Hz), 5.21 (m, 2H), 4.70 (br dd, 1H, J = 14.4, 7.2 Hz), 4.62 (br d, 1H, J = 15.2 Hz), 3.44 (quin, 1H, J = 7.3 Hz), 1.44 (d, 3H, J = 7.5 Hz), 0.99 (s, 9H), 0.26 (s, 3H), 0.25 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.3, 154.8, 153.2, 142.9, 131.8, 129.3, 127.8, 125.8, 125.0, 122.6, 120.8, 120.2, 117.8, 105.9, 95.4, 94.8, 94.6, 90.5, 81.6, 71.5, 67.1, 65.7, 47.6, 34.6, 25.7, 18.3, 17.6, −4.4, −4.5; FTIR (neat), cm^{-1} 2280 (w, C≡C), 2195 (w, C≡C), 1724 (sh, s, C═S), 1714 (vs, C═O); $[\alpha]^{22}_D$ ($CHCl_3$), +750.7, c = 0.43; HRMS (FAB) *m/z* calcd for $C_{31}H_{31}NO_6SiS$ $(M)^+$ 573.1641, found 573.1660. Anal. Calcd for $C_{31}H_{31}NO_6SSi$: C, 64.90; H, 5.45; N, 2.44. Found: C, 64.57; H, 5.66; N, 2.37.

Ketone 70. Tributyltin hydride (722 μL, 2.68 mmol, 1.40 equiv) and azobis(isobutyronitrile) (75.0 mg, 457 μmol, 0.238 equiv) were added sequentially to a solution of the thionocarbonate **69** (1.10 g, 1.92 mmol, 1 equiv) in toluene (75 mL). The resulting pale yellow solution was deoxygenated by three consecutive freeze−pump−thaw cycles; then the reaction vessel was placed in an oil bath preheated to 70 °C. The reaction mixture was heated at 70 °C for 30 min and then was allowed to cool to 23 °C. Volatiles were removed in vacuo. The residue was purified by flash column chromatography (dichloromethane initially, then 1% ethyl acetate in dichloromethane) to furnish the ketone **70** as an off-white foam (957 mg, 97%): R_f 0.21, dichloromethane; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22 (br s, 1H), 6.89 (d, 1H, J = 2.6 Hz), 6.81 (dd, 1H, J = 8.7, 2.6 Hz), 5.90 (m, 1H), 5.77 (dd, 1H, J = 9.7, 1.5 Hz), 5.70 (dd, 1H, J = 9.5, 0.4 Hz), 5.70 (br s, 1H), 5.22 (m, 2H), 4.75 (br dd, 1H, J = 14.6, 7.2 Hz), 4.60 (br d, 1H, J = 15.2 Hz), 4.21 (d, 1H, J = 0.9 Hz), 3.07 (m, 1H), 2.85 (dd, 1H, J = 16.8, 8.1 Hz), 2.50 (dd, 1H, J = 17.2, 3.4 Hz), 1.51 (d, 3H, J = 7.5 Hz), 0.96 (s, 9H), 0.18 (s, 3H), 0.17 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.5, 154.6, 152.9, 131.9, 139.7, 128.5, 127.7, 124.0, 123.6, 120.2, 117.9, 117.7, 96.2, 95.1, 91.3, 91.2, 72.1, 67.0, 63.8, 47.9, 43.5, 42.9,

32.6, 25.7, 20.4, 18.2, −4.4, −4.5; FTIR (neat), cm^{-1} 2280 (w, C≡C), 2192 (w, C≡C), 1714 (vs, C═O); $[\alpha]^{22}_D$ ($CHCl_3$), +816.7, $c = 0.66$; HRMS (FAB) *m/z* calcd for $C_{30}H_{33}NO_5Si$ $(M)^+$ 515.2128, found 515.2119. Anal. Calcd for $C_{30}H_{33}NO_5Si$: C, 69.87; H, 6.45; N, 2.72. Found: C, 69.54; H, 6.70; N, 2.58.

Enol Methyl Ether Acid 73. Triethylamine (405 μL, 2.91 mmol, 15.0 equiv) was added to a solution of the ketone **70** (100 mg, 194 μmol, 1 equiv) and magnesium bromide (89.0 mg, 485 μmol, 2.50 equiv) in acetonitrile (4 mL) at 23 °C under an atmosphere of carbon dioxide. After being stirred for 1 h at 23 °C, the reaction solution was concentrated in vacuo. The residue was partitioned between aqueous hydrochloric acid solution (1 N, 10 mL) and ether (10 mL). The aqueous layer was separated and extracted further with ether (2 × 10 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (25 mL), were dried over sodium sulfate, and were concentrated at 0 °C to a volume of ca. 1 mL. The concentrated ethereal solution of the β-keto acid **72** was transferred via cannula to a suspension of potassium *tert*-butoxide (87.0 mg, 776 μmol, 4.00 equiv) in ether (500 μL) at −78 °C. The transfer was quantitated with additional ether (1.5 mL). The reaction mixture was stirred at −78 °C for 2 min and then was transferred via cannula over 5 min to a solution of freshly distilled methyl trifluoromethanesulfonate (110 μL, 970 μmol, 5.00 equiv) in toluene (5 mL) at −20 °C. The transfer was quantitated with additional toluene (2 mL). The reaction mixture was stirred at −20 °C for 30 min. Excess methyl trifluoromethanesulfonate was quenched by the sequential addition of triethylamine (3 mL) and methanol (6 mL). The product solution was partitioned between aqueous hydrochloric acid solution (1 N, 25 mL) and dichloromethane (25 mL). The aqueous layer was separated and extracted further with dichloromethane (2 × 25 mL). The combined organic layers were dried over sodium sulfate and were concentrated. The product was purified by flash column chromatography (25% ethyl acetate in hexanes initially, and then 50% ethyl acetate in hexanes, then ethyl acetate) to afford the enol methyl ether acid **73** as a pale yellow foam (61 mg, 54%) and the enol methyl ether methyl ester **74** (18 mg, 16%). **73**: R_f 0.61, ethyl acetate; ^{1}H NMR (300 MHz, C_6D_6) δ 7.35 (br s, 1H), 7.11 (d, 1H $J = 2.6$ Hz), 6.78 (dd, 1H $J = 8.7$, 2.6 Hz), 6.11 (br s, 1H), 5.66 (m, 1H), 5.11 (br d, 1H, $J = 16.3$ Hz), 5.08 (s, 2H), 4.94 (br d, 1H, $J = 10.4$ Hz), 4.57 (dd, 1H, $J = 13.6$, 5.3 Hz), 4.48 (dd, 1H, $J = 13.4$, 5.0 Hz), 4.15 (q, 1H, $J = 7.1$ Hz), 3.93 (s, 1H), 2.85 (s, 3H), 1.49 (d, 3H, $J = 7.1$ Hz), 1.02 (s, 9H), 0.17 (s, 3H), 0.16 (s, 3H); ^{13}C (100 MHz, $CDCl_3$) δ 164.7, 155.6, 154.6, 152.9, 132.0, 130.0, 128.4, 127.9, 124.2, 123.3, 120.1, 117.9 (2C), 115.5, 96.3, 95.6, 91.0, 90.8, 71.1, 67.1, 63.5, 58.0, 47.5, 35.4, 31.6, 25.8, 18.3, 18.2, −4.2, −4.4; FTIR (neat), cm^{-1} 3274 (br, COOH), 2279 (w, C≡C), 2197 (w, C≡C), 1714 (vs, C═O); $[\alpha]^{22}_D$ ($CHCl_3$), +565.4, $c = 0.40$; HRMS (FAB) *m/z* calcd for $C_{32}H_{35}NO_7Si$ $(M)^+$ 573.2183, found 573.2200. **74**: R_f 0.48, 40% ethyl acetate−hexanes; ^{1}H NMR (400 MHz, C_6D_6) δ 7.35 (br s, 1H), 7.16 (d, 1H, $J = 2.4$ Hz), 6.79 (dd, 1H, $J = 8.5$, 2.4 Hz), 6.18 (br s, 1H), 5.65 (m, 1H), 5.13 (dd, 1H, $J = 9.8$, 1.5 Hz), 5.10 (br d obscured, 1H), 5.07 (dd, 1H, $J = 9.5$, 0.4 Hz), 4.93 (br d, 1H, $J = 10.7$ Hz), 4.57 (br dd, 1H, $J = 13.2$, 5.1 Hz), 4.49 (br dd, 1H, $J = 13.4$, 5.0 Hz), 4.11 (br s, 1H), 3.97 (br m, 1H), 3.49 (s, 3H), 3.43 (s, 3H), 1.47 (d, 3H, $J = 6.6$ Hz), 1.01 (s, 9H), 0.15 (s, 3H), 0.14 (s, 3H); ^{13}C (100 MHz, $CDCl_3$) δ 166.4, 155.8, 154.8, 152.8, 132.0, 129.8, 129.0, 127.8, 124.0, 123.2, 119.9, 118.1, 117.7, 115.2, 98.4, 95.2, 91.1, 89.6, 70.9, 66.9, 63.5, 59.1, 51.7, 47.5, 36.1, 33.6, 25.7, 18.4, 18.3, −4.3, −4.4; FTIR (neat), cm^{-1} 2280 (w, C≡C), 2197 (w, C≡C), 1711 (vs, C═O); $[\alpha]^{22}_D$ ($CHCl_3$), +690.5, $c = 0.68$; HRMS (FAB) *m/z* calcd for $C_{33}H_{37}NO_7Si$ $(M)^+$ 587.2339, found 587.2332.

Phenol Acid 75. Triethylamine trihydrofluoride (0.10 mL, 0.62 mmol, 3.5 equiv) was added to a solution of the enol methyl ether acid **73** (100 mg, 0.174 mmol, 1 equiv) in acetonitrile (5 mL) in a polypropylene test tube. The reaction mixture was stirred at 23 °C for 2 h and then was partitioned between aqueous hydrochloric acid solution (0.1 N, 10 mL) and dichloromethane (10 mL). The aqueous layer was separated and extracted further with two 10-mL portions of dichloromethane. The combined organic layers were dried over sodium sulfate and were concentrated to a volume of ca. 1 mL (concentration to dryness leads to decomposition of the crude product). The resulting solution was immediately purified by flash column chromatography (5% methanol in dichloromethane, then 10% methanol in dichloromethane) to provide the phenol acid **75** as a light yellow foam (72 mg, 91%): R_f 0.26, 10% methanol−dichloromethane; ^{1}H NMR (500 MHz, $CDCl_3$, 70 °C) δ 7.13 (d, 1H, $J = 8.6$ Hz), 6.67 (br d, 1H, $J = 8.6$ Hz), 6.50 (br s, 1H), 5.99 (m, 1H), 5.68 (dd, 1H, $J = 10.1$, 1.2 Hz), 5.66 (dd, 1H, $J = 8.8$, 1.1 Hz), 5.57 (br s, 1H), 5.39 (app d, 1H, $J = 17.2$ Hz), 5.29 (app d, 1H, $J = 10.5$ Hz), 4.82 (br dd, 1H, $J = 13.1$, 4.8 Hz), 4.72 (br dd, 1H, $J = 13.3$, 5.5 Hz), 4.58 (br s, 1H), 3.94 (s, 3H), 3.83 (m, 1H), 1.42 (d, 3H, $J = 7.2$ Hz); ^{13}C (100 MHz, $CDCl_3$, 40 °C) δ 165.6, 156.1, 155.7, 154.3, 131.9, 128.0, 127.8, 127.5, 123.7 (2C), 118.9, 118.4, 113.6, 112.2, 95.8, 94.2, 91.4, 90.5, 71.0, 67.5, 64.2, 57.0, 48.1, 35.4, 30.3, 18.4; FTIR (neat), cm^{-1} 3690−2400 (br, m, COOH), 3324 (m, OH), 2251 (w, C≡C), 2190 (w, C≡C), 1710 (vs, NC═O), 1689 (vs, C═O); $[\alpha]^{22}_D$ ($CHCl_3$), +868.4, $c = 0.19$; HRMS (FAB) *m/z* calcd for $C_{26}H_{21}NO_7$ $(M)^+$ 459.1318, found 459.1325.

Phenol Silyl Ester 76. Imidazole (33 mg, 0.49 mmol, 5.0 equiv) and triisopropylsilyl trifluoromethanesulfonate (53 μL, 0.20 mmol, 2.0 equiv) were added sequentially to a solution of the phenol acid **75** (45 mg, 98 μmol, 1 equiv) in tetrahydrofuran (5 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min and then was partitioned between aqueous phosphate buffer solution (pH 7, 0.05 M in sodium hydrogen phosphate and 0.05 M in potassium dihydrogen phosphate, 10 mL) and ethyl acetate (10 mL). The aqueous layer was separated and extracted further with ethyl acetate (2 × 10 mL). The combined organic layers were dried over sodium sulfate and were concentrated. The residue was purified by flash column chromatography (30% ethyl acetate in hexanes initially, grading to 40% ethyl acetate in hexanes) to the phenol silyl ester **76** as an off-white foam (41 mg, 69%): R_f 0.40, 40% ethyl acetate−hexanes; ^{1}H NMR (400 MHz, $CDCl_3$, 60 °C) δ 7.27 (br s, 1H), 6.98 (d, 1H, $J = 2.4$ Hz), 6.75 (dd, 1H, $J = 8.8$, 2.8 Hz), 5.92 (m, 1H), 5.74 (d, 1H, $J = 10.0$ Hz), 5.66 (d, 1H, $J = 8.8$ Hz), 5.28 (br d, 1H, $J = 17.1$ Hz), 5.20 (br d, 1H, $J = 10.5$ Hz), 5.02 (br s, 1H), 4.71 (br dd, 1H, $J = 13.6$, 5.3 Hz), 4.62 (br dd, 1H, $J = 13.1$, 4.8 Hz), 4.18 (br s, 1H), 3.83 (s, 3H), 3.74 (q, 1H, $J = 7.0$ Hz), 1.45 (d, 3H, $J = 7.5$ Hz), 1.37 (m, 3H), 1.12 (d, 18H, $J = 7.5$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$, 60 °C) δ 165.5, 156.0, 154.6, 153.0, 132.2, 129.7, 129.6, 127.9, 124.1, 123.2, 117.9, 116.7, 115.5, 113.6, 98.8, 95.6, 91.2, 89.8, 71.1, 67.0, 63.6, 58.6, 47.9, 36.7, 33.6, 18.5, 17.9, 12.3; FTIR (neat), cm^{-1} 3385 (m, OH), 2197 (w, C≡C), 1697 (vs, NC═O), 1677 (vs, C═O); $[\alpha]^{22}_D$ ($CHCl_3$), +771.0, $c = 0.31$.

Protected Quinone Imine 77. Iodosobenzene (35 mg, 0.16 mmol, 1.6 equiv) was added to a solution of the phenol silyl ester **76** (62 mg, 0.10 mmol, 1 equiv) in methanol (5 mL). The reaction mixture was stirred at 23 °C for 50 min. An additional portion of iodosobenzene (9 mg, 0.04 mmol, 0.4 equiv) was added, and the resulting solution was stirred at 23 °C for 30 min. The product solution was partitioned between a 1:1 mixture of saturated aqueous sodium bicarbonate solution and saturated aqueous sodium thiosulfate solution (30 mL) and ethyl acetate (30 mL). The aqueous layer was separated and extracted further with two 30-mL portions of ethyl acetate. The combined organic layers were dried over sodium sulfate and were concentrated. The residue was purified by flash column chromatography (25% ethyl acetate in hexanes initially, grading to 30% ethyl acetate in hexanes) to afford the protected quinone imine **77** as a pale yellow foam (58 mg, 89%): R_f 0.39, 30% ethyl acetate−hexanes; ^{1}H NMR (500 MHz, C_6D_6, 65 °C) δ 7.58 (br s, 1H), 6.77 (d, 1H, $J = 1.5$ Hz), 6.26 (dd, 1H, $J = 10.4$, 1.5 Hz), 6.04 (br s, 1H), 5.74 (m, 1H), 5.28 (s, 2H), 5.19 (app d, 1H, $J = 17.4$ Hz), 5.04 (app d, 1H, $J = 10.4$ Hz), 4.62 (br dd, 1H, $J = 13.3$, 5.3 Hz), 4.47 (br dd, 1H, $J = 13.0$, 4.5 Hz), 4.01 (q, 1H, $J = 7.2$ Hz), 3.71 (s, 1H), 3.55 (s, 3H), 3.05 (s, 3H), 1.51 (d, 3H, $J = 7.2$ Hz), 1.42 (m, 3H), 1.22 (d, 18H, $J = 7.2$ Hz); ^{13}C NMR (125 MHz, C_6D_6, 65 °C) δ 183.2, 165.5, 155.6, 147.2, 143.4, 133.9, 132.5, 128.6, 128.2, 124.2, 123.0, 117.7, 116.8, 99.1, 96.9, 90.5, 90.1, 83.3, 67.0, 65.0, 64.7, 58.4, 51.2, 47.6, 37.4, 33.8, 18.0, 17.8, 12.5; FTIR (neat), cm^{-1} 2193 (w, C≡C), 1700 (vs, NC═O), 1671 (vs, C═O); $[\alpha]^{22}_D$ ($CHCl_3$), +732.5, $c = 0.32$; HRMS (FAB) *m/z* calcd for $C_{36}H_{44}NO_8Si$ $(MH)^+$ 646.2836, found 646.2805.

Quinone Imine 6. Tributyltin hydride (34.0 μL, 126 μmol, 1.10 equiv) was injected into a deoxygenated suspension of the protected quinone imine **77** (74.0 mg, 114 μmol, 1 equiv), bis(triphenylphosphine)palladium(II) chloride (40 mg, 57 μmol, 0.5 equiv), and water (75 μL) in dichloromethane (5 mL) at 23 °C. The reaction mixture

was stirred for 10 min at 23 °C and then was concentrated to a volume of ca. 1 mL. The resulting slurry was loaded directly onto a column of flash-grade silica gel prepared with 20% ethyl acetate in hexanes. The product was eluted with 20% ethyl acetate in hexanes initially, grading to 30% ethyl acetate in hexanes, to provide, after concentration of appropriate fractions, the quinone imine **6** as a yellow waxy semisolid (48 mg, 78%): R_f 0.23, 20% ethyl acetate−hexanes; ^{1}H NMR (300 MHz, C_6D_6) δ 6.81 (d, 1H, J = 10.0 Hz), 6.44 (d, 1H, J = 2.0 Hz), 6.04 (dd, 1H, J = 10.0, 2.0 Hz), 5.19 (dd, 1H J = 10.0, 1.5 Hz), 5.13 (dd, 1H, J = 10.0, 1.4 Hz), 5.03 (d, 1H, J = 1.4 Hz), 3.91 (q, 1H, J = 7.5 Hz), 3.61 (s, 1H), 3.49 (s, 3H), 1.47 (d, 3H, J = 7.3 Hz), 1.39 (m, 3H), 1.19 (d, 18H, J = 7.2 Hz); ^{13}C NMR (100 MHz, C_6D_6) δ 185.9, 166.0, 161.5, 155.2, 141.2, 137.4, 131.7, 127.0, 123.9, 123.2, 116.8, 99.2, 97.4, 89.3, 88.4, 64.0, 63.3, 58.3, 52.7, 36.7, 31.6, 19.1, 18.1, 12.4; FTIR (neat), cm^{-1} 2280 (vw, C≡C), 2193 (vw, C≡C), 1652 (vs, C═O); $[\alpha]^{20}_D$ (C_6H_6), +1,149, c = 0.500; HRMS (FAB) *m/z* calcd for $C_{31}H_{38}NO_5Si$ $(M+3H)^+$ 532.2519, found 532.2529.

2-Formyl-3,6-bis(*tert*-butyldimethylsiloxy)benzoic Acid *N*,*N*-Diethylamide (95). A solution of boron tribromide in dichloromethane (1.0 M, 42.2 mL, 42.4 mmol, 5.00 equiv) was added via cannula to a solution of 2-formyl-3,6-dimethoxybenzoic acid *N*,*N*-diethylamide (**94**, 2.25 g, 8.48 mmol, 1 equiv) in dichloromethane (45 mL) at −78 °C. The reaction mixture was stirred at −78 °C with slow warming over 12 h to 23 °C. The resulting suspension was then carefully poured into water (150 mL). The aqueous layer was separated and extracted further with two 150-mL portions of ethyl acetate. The combined organic layers were dried over sodium sulfate and were concentrated to afford 2-formyl-3,6-dihydroxybenzoic acid *N*,*N*-diethylamide as an orange solid which was used in the next step without chromatographic purification: R_f 0.20, 50% ethyl acetate−hexanes; ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.10 (s, 1H), 9.78 (s, 1H), 8.02 (br s, 1H), 6.91 (d, 1H, J = 9.2 Hz), 6.74 (d, 1H, J = 8.8 Hz), 3.42 (br m, 4H), 1.20 (br m, 6H).

Imidazole (4.62g, 67.8 mmol, 8.00 equiv) and *tert*-butyldimethylsilyl chloride (5.11g, 33.9 mmol, 4.00 equiv) were added sequentially to a solution of 2-formyl-3,6-dihydroxybenzoic acid *N*,*N*-diethylamide in *N*,*N*-dimethylformamide (50 mL) at 23 °C. The reaction mixture was stirred at 23 °C for 2 h and then was partitioned between water (50 mL) and ethyl acetate (50 mL). The aqueous layer was separated and extracted further with two 50-mL portions of ethyl acetate. The combined organic layers were dried over sodium sulfate and were concentrated. The residue was purified by flash column chromatography (10% ethyl acetate in hexanes) to afford 2-formyl-3,6-bis(*tert*-butyldimethylsiloxy)benzoic acid *N*,*N*-diethylamide (**95**) as a white solid (mp 122−125 °C, 3.69 g, 94%): R_f 0.35, 20% ethyl acetate−hexanes; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.38 (s, 1H), 6.93 (d, 1H, J = 8.7 Hz), 6.74 (d, 1H, J = 8.7 Hz), 3.81 (m, 1H), 3.28 (m, 1H), 3.08 (m, 2H), 1.37 (t, 3H, J = 7.1 Hz), 1.02 (t, 3H, J = 7.1 Hz), 1.00 (s, 9H), 0.95 (s, 9H), 0.26 (s, 3H), 0.25 (s, 3H), 0.21 (s, 3H), 0.19 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.7, 166.7, 153.2, 145.8, 129.7, 126.0, 124.5, 120.4, 42.6, 38.8, 25.7, 25.6, 18.3, 18.1, 13.4, 12.2, −4.1, −4.2, −4.4, −4.6; FTIR (neat), cm^{-1} 1686 (m, C═O), 1637 (s, NC═O); HRMS (FAB) *m/z* calcd for $C_{24}H_{44}NO_4Si_2$ $(MH)^+$ 466.2809, found 466.2802. Anal. Calcd for $C_{24}H_{43}NO_4Si_2$: C, 61.89; H, 9.30; N, 3.01. Found: C, 61.95; H, 9.68; N, 2.89.

2-(Hydroxymethyl)-3,6-bis(*tert*-butyldimethylsiloxy)benzoic Acid *N*,*N*-Diethylamide (97). Sodium borohydride (2.23 g, 59.0 mmol, 5.00 equiv) was added to an ice-cold solution of 2-formyl-3,6-bis(*tert*-butyldimethylsiloxy)benzoic acid *N*,*N*-diethylamide (**95**, 5.50 g, 11.8 mmol, 1 equiv) in absolute ethanol (75 mL). The reaction mixture was stirred at 0 °C for 4 h and then was carefully partitioned between saturated aqueous ammonium chloride solution (200 mL) and ethyl acetate (200 mL). The aqueous layer was separated and extracted further with ethyl acetate (2 × 200 mL). The combined organic layers were dried over saturated sodium sulfate and then were concentrated in vacuo to provide 2-(hydroxymethyl)-3,6-bis(*tert*-butyldimethylsiloxy)benzoic acid *N*,*N*-diethylamide (**97**) as a white solid (mp 90−92 °C, 5.36 g, 97%): R_f 0.47, 25% ethyl acetate−hexanes; ^{1}H NMR (300 MHz, C_6D_6) δ 6.77 (d, 1H, J = 8.7 Hz), 6.66 (d, 1H, J = 8.7 Hz), 5.10 (t, 1H, J = 11.6 Hz), 4.58 (dd, 1H, J = 11.8, 2.4 Hz), 3.75 (dd, 1H, J = 11.4, 2.4 Hz), 3.60 (m, 1H), 3.15 (m, 2H), 2.85 (m, 1H), 1.12 (t, 3H, J = 7.1 Hz), 1.08 (s, 9H), 1.03 (s, 9H), 0.74 (t, 3H, J = 7.1 Hz), 0.29 (s, 3H), 0.20 (s, 3H), 0.20 (s, 3H), 0.18 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.3, 148.0, 144.9, 130.2, 129.8, 119.8, 119.0, 58.2, 43.2, 39.6, 25.7, 25.6, 18.2, 18.0, 13.9, 13.1, −4.2, −4.2, −4.5, −4.6; FTIR (neat), cm^{-1} 3435 (br, OH), 1617 (s, C═O); HRMS (FAB) *m/z* calcd for $C_{24}H_{46}NO_4Si_2$ $(MH)^+$ 468.2965, found 468.2968. Anal. Calcd for $C_{24}H_{45}NO_4Si_2$: C, 61.62; H, 9.70; N, 2.99. Found: C, 61.77; H, 9.84; N, 3.21.

2-(Hydroxymethyl)-3,6-bis[[2-(trimethylsilyl)ethoxy]methoxy]-benzoic Acid *N*,*N*-Diethylamide (98). Sodium borohydride (272 mg, 7.19 mmol, 4.99 equiv) was added to an ice-cold solution of 2-formyl-3,6-bis[[2-(trimethylsilyl)ethoxy]methoxy]benzoic acid *N*,*N*-diethylamide (**96**, 718 mg, 1.44 mmol, 1 equiv) in absolute ethanol (15 mL). The reaction mixture was stirred for 3 h at 0 °C and then was partitioned between half-saturated aqueous sodium chloride solution (100 mL) and ethyl acetate (70 mL). The aqueous layer was separated and extracted further with ethyl acetate (2 × 70 mL). The combined organic layers were dried over sodium sulfate and were concentrated. The residue was purified by flash column chromatography (50% ethyl acetate in hexanes) to provide 2-(hydroxymethyl)-3,6-bis[[2-(trimethylsilyl)-ethoxy]methoxy]benzoic acid *N*,*N*-diethylamide (**98**) as a colorless oil (660 mg, 92%): R_f 0.15, 40% ethyl acetate−hexanes; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.09 (d, 1H, J = 9.1 Hz), 7.05 (d, 1H, J = 9.1 Hz), 5.21 (m, 2H), 5.13 (m, 2H), 4.61 (d, 1H, J = 12.1 Hz), 4.44 (d, 1H, J = 12.1 Hz), 3.73 (m, 4H), 3.59 (q, 2H, J = 7.1 Hz), 3.20 (m, 2H), 2.90 (br s, 1H), 1.26 (t, 3H, J = 7.1 Hz), 1.06 (t, 3H, J = 7.1 Hz), 0.98−0.91 (m, 4H), −0.01 (s, 18H); FTIR (neat), cm^{-1} 3445 (br, OH), 1615 (vs, NC═O); HRMS (CI) *m/z* calcd for $C_{24}H_{46}NO_6Si_2$ $(MH)^+$ 500.2864, found 500.2837.

4,7-Bis(*tert*-butyldimethylsiloxy)phthalide (99). A solution of 2-(hydroxymethyl)-3,6-bis(*tert*-butyldimethylsiloxy)benzoic acid *N*,*N*-diethylamide (**97**, 8.10 g, 17.3 mmol, 1 equiv) in 1,3,5-trimethylbenzene (75 mL) was heated at reflux for 10 h. The reaction mixture was cooled to 23 °C and then was concentrated in vacuo. The residue was purified by flash column chromatography (hexanes initially, grading to 10% ethyl acetate in hexanes) to provide 4,7-bis(*tert*-butyldimethylsiloxy)-phthalide (**99**) as a white solid (mp 92−94 °C, 4.03 g, 59%): R_f 0.45, 10% ethyl acetate−hexanes; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.90 (d, 1H, J = 8.6 Hz), 6.73 (d, 1H, J = 8.6 Hz), 5.10 (s, 2H), 1.03 (s, 9H), 0.98 (s, 9H), 0.23 (s, 6H), 0.21 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4, 148.8, 143.6, 137.9, 125.0, 121.1, 116.8, 66.6, 25.5, 25.4, 18.2, 17.9, −4.5, −4.7; FTIR (neat), cm^{-1} 1764 (s, C═O); HRMS (CI) *m/z* calcd for $C_{20}H_{35}O_4Si_2$ $(MH)^+$ 395.2074, found 395.2062. Anal. Calcd for $C_{20}H_{34}O_4Si_2$: C, 60.87; H, 8.68. Found: C, 60.53; H, 8.54.

4,7-Bis[[2-(trimethylsilyl)ethoxyl]methoxy]phthalide (92). A suspension of 2-(hydroxymethyl)-3,6-bis[[2-(trimethylsilyl)ethoxy]-methoxy]benzoic acid *N*,*N*-diethylamide (**98**, 695 mg, 1.39 mmol, 1 equiv) and potassium carbonate (10 mg, 0.07 mmol, 0.05 equiv) in 1,3,5-trimethylbenzene (30 mL) was heated at reflux for 80 min. The reaction mixture was cooled to 23 °C and then was concentrated in vacuo. The residue was purified by flash column chromatography (30% ethyl acetate in hexanes) to provide 4,7-bis[[2-(trimethylsilyl)ethoxyl]methoxy]phthalide (**92**) as a white solid (mp 80.0−81.5 °C, 481 mg, 81%): R_f 0.53, 40% ethyl acetate−hexanes; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (d, 1H, J = 8.9 Hz), 7.16 (d, 1H, J = 8.9 Hz), 5.35 (s, 2H), 5.22 (s, 2H), 5.20 (s, 2H), 3.78 (m, 4H), 0.95 (m, 4H), 0.00 (s, 9H), −0.01 (s, 9H); FTIR (neat), cm^{-1} 1765 (vs, C═O); HRMS (CI) *m/z* calcd for $C_{20}H_{38}NO_6Si_2$ $(MNH_4)^+$ 444.2238, found 444.2213.

4,7-Dihydroxyphthalide (100). From 4,7-Bis(*tert*-butyldimethylsiloxy)phthalide (99). Triethylamine trihydrofluoride (2 mL, 12.3 mmol, 1.27 equiv) was added to a solution of 4,7-bis(*tert*-butyldimethylsiloxy)phthalide (**99**, 3.80 g, 9.63 mmol, 1 equiv) in acetonitrile (40 mL) in a polypropylene test tube. The reaction mixture was stirred at 23 °C for 2 h and then was partitioned between aqueous potassium dihydrogen phosphate solution (1.0 M, pH 5, 100 mL) and ethyl acetate (100 mL). The aqueous layer was separated and extracted further with two 100-mL portions of ethyl acetate. The combined organic layers were dried over sodium sulfate and were concentrated to afford 4,7-dihydroxyphthalide (**100**) as a tan solid (1.53 g, 96%).

From 4,7-Bis[[2-(trimethylsilyl)ethoxyl]methoxy]phthalide (92). A solution of concentrated sulfuric acid (4.0 mL, 75 mmol, 15 equiv) in methanol (50 mL) at 23 °C was added to a solution of 4,7-bis[[2-(trimethylsilyl)ethoxyl]methoxy]phthalide (**92**, 2.148 g, 5.034 mmol, 1 equiv) in tetrahydrofuran (50 mL) at 23 °C. The reaction mixture

was stirred for 2 h at 23 °C. The product solution was poured carefully into a separatory funnel containing saturated aqueous sodium bicarbonate solution (200 mL), saturated aqueous sodium chloride solution (150 mL), and ethyl acetate (100 mL). The aqueous layer was separated and extracted further with ethyl acetate (2 × 100 mL). The combined organic layers were dried over sodium sulfate and were concentrated to provide 4,7-dihydroxyphthalide (**100**) as an off-white solid (mp 229−231 °C, 821 mg, 98%): R_f 0.14, 40% ethyl acetate−hexanes; ^{1}H NMR (300 MHz, CD_3OD) δ 6.94 (d, 1H, J = 8.4 Hz), 6.72 (d, 1H, J = 8.4 Hz), 5.20 (s, 2H); ^{13}C (100 MHz, $CDCl_3$) δ 172.8, 151.0, 145.6, 134.3, 124.0, 117.6, 112.8, 69.2; FTIR (KBr pellet), cm^{-1} 3310 (br, OH), 3130 (br, OH), 1725 (s, C═O); HRMS (EI) *m/z* calcd for $C_8H_6O_4$ $(M)^+$ 166.0266, found 166.0264.

4,7-Bis(trimethylsiloxy)phthalide (93). A suspension of 4,7-dihydroxyphthalide (**100**, 46 mg, 0.28 mmol, 1 equiv) in a mixture of hexamethyldisilazane (1.0 mL, 4.7 mmol, 17 equiv), concentrated sulfuric acid (1.0 μL, 19 μmol, 68 μequiv), and tetrahydrofuran (2 mL) was heated at reflux for 30 min. The reaction mixture was cooled to 23 °C and then was filtered through Celite. The filtrate was concentrated in vacuo to afford 4,7-bis(trimethylsiloxy)phthalide (**93**) as a moisture-sensitive pale yellow oil (86 mg, 100%). Due to its instability to storage, the product was typically prepared immediately prior to its use in the next step in the sequence. ^{1}H NMR (300 MHz, C_6D_6) δ 6.68 (d, 1H, J = 8.6 Hz), 6.63 (d, 1H, J = 8.6 Hz), 4.63 (s, 2H), 0.35 (s, 9H), 0.07 (s, 9H); ^{13}C (100 MHz, C_6D_6) δ 168.4, 149.0, 143.9, 138.7, 125.2, 121.8, 118.0, 66.5, 0.18.

(+)-Dynemicin A (1). A solution of potassium *N*,*N*-bis(trimethylsilyl)amide in toluene (0.5 M, 732 μL, 366 μmol, 5.10 equiv) was added to a deoxygenated solution of 4,7-bis(trimethylsiloxy)phthalide (**93**, 111 mg, 359 μmol, 5.00 equiv, dried by azeotropic distillation with toluene, 1 mL) in tetrahydrofuran (3 mL) at −78 °C, and the resulting bright yellow solution was stirred at −78 °C for 25 min. Chlorotrimethylsilane (82.0 μL, 646 μmol, 9.00 equiv) was then added. The reaction mixture was warmed to −20 °C for 1 min, whereupon the bright yellow solution became colorless. At this point, a solution of the quinone imine **6** (38.0 mg, 71.7 μmol, 1 equiv) in tetrahydrofuran (1.5 mL) was transferred to the cold reaction mixture. The resulting solution was heated at 55 °C for 5 min, was cooled to 23 °C, and was concentrated to afford a yellow solid. ^{1}H NMR analysis of the crude product revealed that the desired Diels−Alder addition product **110** had been formed cleanly, in ∼75% yield, on the basis of integration against dichloromethane added as an internal standard. The crude product was carried on to the next step in the sequence immediately and without purification: ^{1}H NMR (400 MHz, C_6D_6, unobscured protons) δ 6.84 (s, 1H), 5.73 (s, 1H), 5.37 (dd, 1H, J = 9.9, 1.5 Hz), 5.29 (dd, 1H, J = 10.2, 1.5 Hz), 4.95 (d, 1H, J = 1.1 Hz), 3.92 (br s, 1H), 3.85 (q, 1H, J = 7.0 Hz), 3.54 (s, 3H), 3.25 (d, 1H, J = 7.7 Hz), 2.94 (d, 1H, J = 7.5 Hz), 1.51 (d, 3H, J = 7.4 Hz), 1.44 (m, 3H), 1.23 (d, 18H, J = 7.7 Hz).

To a solution of the crude product from above in tetrahydrofuran (10 mL) at 23 °C were added sequentially activated manganese dioxide (350 mg, 4.03 mmol) and triethylamine trihydrofluoride (600 μL, 3.68 mmol). The suspension became red upon addition of triethylamine trihydrofluoride. After being stirred for 1 min at 23 °C, the reaction suspension was reddish-violet, at 5 min it was violet, and shortly thereafter it became deep blue. After being stirred at 23 °C for 9 min (from the point of addition of triethylamine trihydrofluoride), the deep blue reaction suspension was applied to the top of a column of lipophilic Sephadex LH-20 loaded with 20% acetonitrile in methanol. Dynemicin A eluted as a dark blue band. Overlapping fractions were collected and repurified on Sephadex LH-20 (20% acetonitrile in methanol, adding dimethyl sulfoxide (2 mL) during loading to improve solubility, two sequential columns, 50 mm diameter). Fractions containing pure **1** were pooled and concentrated to afford (+)-dynemicin A as a violet solid (15.4 mg, 53%, 40% over two steps): R_f 0.37, ethyl acetate, 0.21, 30% methyl ethyl ketone−*p*-xylene; ^{1}H NMR (400 MHz, $(CD_3)_2SO_2$) δ 13.19 (br s, 1H), 12.78 (br s, 1H), 12.28 (br s, 1H), 9.86 (br d, 1H, J = 3.9 Hz), 8.00 (s, 1H), 7.37 (d, 1H, J = 9.2 Hz), 7.35 (d, 1H, J = 8.3 Hz), 6.08 (br d, 1H, J = 10.1 Hz), 6.04 (br d, 1H, J = 10.1 Hz), 5.05 (br d, 1H, J = 3.9 Hz), 4.85 (br s, 1H), 3.80 (s, 3H), 3.55 (br q, 1H, J = 7.0 Hz), 1.25 (d, 3H, J = 7.0 Hz); ^{1}H NMR (400 MHz, $(CD_3)_2NCDO$) δ 13.20 (br s, 1H), 12.55 (br s, 2H), 10.06 (d, 1H, J = 4.0 Hz), 8.11 (s, 1H), 7.42 (d, 1H, J = 9.2 Hz), 7.37 (d, 1H, J = 8.3 Hz), 6.17 (dd, 1H, J = 9.7, 1.3 Hz), 6.13 (dd, 1H, J = 10.0, 1.8 Hz), 5.26 (d, 1H, J = 3.1 Hz), 5.05 (br s, 1H), 3.98 (s, 3H), 3.74 (br q, 1H, J = 7.0 Hz), 1.41 (d, 3H, J = 7.0 Hz); FTIR (neat), cm^{-1} 3686−2730 (br, m, COOH), 3405 (br, m, OH), 1750−1500 (br, m, C═O), 1642 (m, C═O); HRMS (FAB) *m/z* calcd for $C_{30}H_{19}NO_9$ $(M)^+$ 537.1060, found 537.1034.

Supporting Information Available: Experimental details of compounds prepared in this paper (43 pages). See any current masthead page for ordering and Internet access information.

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