Total Synthesis of Crystalline (±)-Fredericamycin A. Use of Radical Spirocyclization

Derrick L. J. Clive,* Yong Tao, Ahmad Khodabocus, Yong-Jin Wu, A. Gaëtan Angoh, Sharon M. Bennett, Christopher N. Boddy,[1] Luc Bordeleau, Dorit Kellner, Galit Kleiner,[2] Donald S. Middleton, Christopher J. Nichols,[2] Scott R. Richardson,[2] and Peter G. Vernon

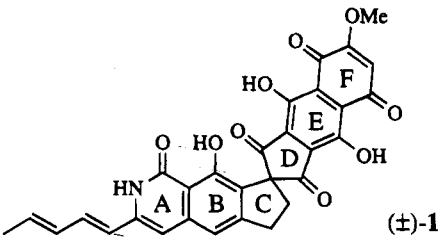
Contribution from the Department of Chemistry, University of Alberta, Edmonton, Alberta T6G 2G2, Canada

Received July 5, 1994[⊗]

Abstract: Crystalline (±)-fredericamycin A (**1**) was synthesized using, as a key step, 5-*exo*-digonal radical closure of selenide **55**. The selenide was generated from the corresponding ketone **54**, itself assembled from two components: aldehyde **29** and bromonaphthalene **48**. The product of the radical cyclization (**56**) was converted into spiro diketone **59**, and the pentadienyl chain was then formed by a Wittig reaction. Selective deprotection of ring A was accompanied by isomerization of the diene system to the required *E,E* geometry, and treatment with boron tribromide, followed by aqueous hydrolysis in the presence of air, effected selective demethylation and oxidation to (±)-**1**. The radical spirocyclization used in this synthesis is a general method.

Introduction

Fredericamycin A, an antitumor antibiotic with the unusual structure **1**,[3–6] has attracted much attention as a synthetic target.[7,8] The structure type—and shape—of **1** clearly distinguish



(±)-**1**

it from all other antitumor agents, and it is possible that the mode of action involves unusual features that might suggest new approaches for the design of anticancer drugs. Little is known about how fredericamycin A exerts its antitumor or antibiotic action,[6] although quite recent work has shown that the compound is an inhibitor of topoisomerases I and II.[6d]

The biosynthesis of fredericamycin A has been studied, at least to the extent of establishing that all the carbons, except that of the *O*-methyl group, are derived from acetate,[9] but the more difficult questions of how the spiro system is formed and whether the molecule is assembled in nature from one or from two chains have not been answered.

Viewed as a synthetic target, the extensive functionality and unique structure of fredericamycin A are sufficiently intricate that any successful approach would clearly need a fluent command of known reactions or the discovery of new ones. In retrospect, the large number of model studies[7] suggests that difficulties have quite generally been met, or anticipated, in attempts to synthesize the compound, and we ourselves found many unexpected problems in the routes we explored.

When we began, no synthesis of fredericamycin A had been accomplished, but during our work, Kelly and his collaborators reported[8a] what was to be the first and, for several years, the only synthesis. We describe here full details[8b] of our own synthesis of pure, recrystallized (±)-fredericamycin A, in which the spiro center was constructed by a radical process and the problem of controlling the geometry of the side chain double bonds was solved in an unexpected way. The isomer mixture **61** (see Scheme 13), which is an intermediate in our synthesis, has now also been reached by an independent free radical method[8c] and then taken on to the natural product. And, more recently, Julia has described[8d] a very different approach based on ionic reactions.

Model Studies. Our preliminary studies explored routes to spiro diketones resembling the central part of fredericamycin A. Guided by an extensive review[10] on the synthesis of compounds with quaternary carbons, we examined[7i] a number of standard approaches based on ionic reactions, but the difficulties we met convinced us—rightly or wrongly—that we were facing problems of a steric nature. Consequently, we switched our attention to radical processes; in some respects these are less sensitive to steric factors than ionic reactions and, for example, we could take advantage of the fact that addition of a carbon radical to a carbon–carbon double or triple bond has an early transition state.[11] Such a transition state is clearly ideal for generating a sterically congested center. This change in our plans was made in the early days of the modern development of synthetic radical chemistry, and once it had been made, we were quickly able to devise a general and flexible route to spiro compounds.[12] This approach, after much study and refinement, provided a route to the natural product.

⊗ Abstract published in *Advance ACS Abstracts,* November 1, 1994.

(1) High school research participant.

(2) Summer undergraduate research participant.

(3) Isolation: Pandey, R. C.; Toussaint, M. W.; Stroshane, R. M.; Kalita, C. C.; Aszalos, A. A.; Garretson, A. L.; Wei, T. T.; Byrne, K. M.; Geoghegan, R. F., Jr.; White, R. J. *J. Antibiot.* **1981**, *34*, 1389.

(4) Structure: Misra, R.; Pandey, R. C.; Silverton, J. V. *J. Am. Chem. Soc.* **1982**, *104*, 4478. Misra, R.; Pandey, R. C.; Hilton, B. D.; Roller, P. P.; Silverton, J. V. *J. Antibiot.* **1987**, *40*, 786.

(5) For a theoretical treatment of spiro compounds with orthogonal π-systems, see: Dürr, H.; Gleiter, R. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 559.

(6) Biological Properties: (a) Warnick-Pickle, D. J.; Byrne, K. M.; Pandey, R. C.; White, R. J. *J. Antibiot.* **1981**, *34*, 1402. (b) Misra, R. *J. Antibiot.* **1988**, *41*, 976. (c) Dalal, N. S.; Shi, X. *Biochemistry* **1989**, *28*, 748. (d) Latham, M. D.; King, C. K.; Gorycki, P.; Macdonald, T. L.; Ross, W. E. *Cancer Chemother. Pharmacol.* **1989**, *24*, 167. (e) Hilton, B. D.; Misra, R.; Zweier, J. L. *Biochemistry* **1986**, *25*, 5533.

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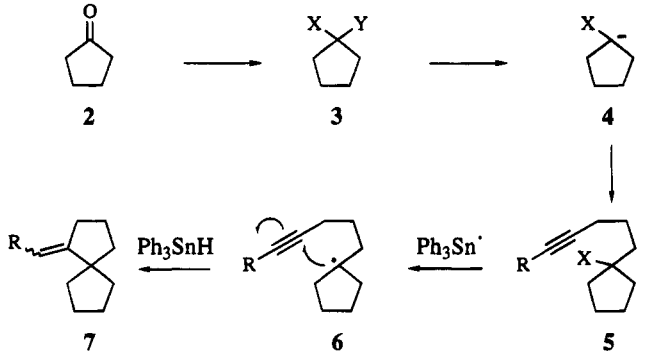
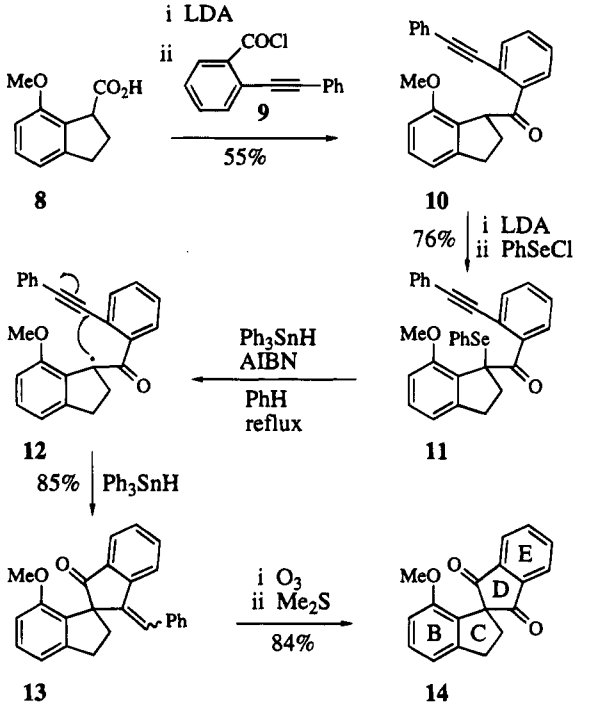
Scheme 1



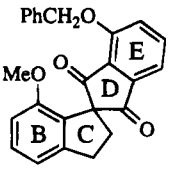
The principle of the radical spirocyclization is summarized in Scheme 1. The carbonyl carbon of a ketone is converted, via a derivative **3**, into a carbanion (**2** → **3** → **4**). This carbanion is then used to attach a chain with a suitably located triple bond (**4** → **5**), and finally, a radical is generated at the original carbonyl carbon by homolysis of the C–X bond. The radical closes onto the π-system to form a spirocyclic product (**6** → **7**). The groups X and Y have to be chosen so that one of them can be removed to form a carbanion and the other to form a carbon radical, and these conditions are easily satisfied by setting both X and Y equal to PhSe. The principle was easily reduced to practice and illustrated with a number of examples,[12] and it proved to represent a general and versatile route to compounds with quaternary centers, such as spiro carbocycles and spiro lactones.[12]

Scheme 2



A special feature of the radical spirocyclization is that the cyclization precursors can be assembled in a number of ways (see below), and once we had acquired some experience in making spiro compounds by radical cyclization, we tried to use it to prepare informative models of the central rings of fredericamycin A. Our first objective was the monomethoxy spiro diketone **14** (Scheme 2), and this was reached[7i] by the indicated route.

We next decided to prepare **15**, in which ring E has a single oxygen substituent, but of such a type that a second could probably be introduced by hydrogenolysis of the benzyl group followed by one of many standard methods for phenol oxidation.



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Accordingly, we prepared[7i] phenylseleno ketone **18** (Scheme 3). From that point, generation of the carbon radical and

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(8) Synthesis: (a) Kelly, T. R.; Bell, S. H.; Ohashi, N.; Armstrong-Chong, R. J. *J. Am. Chem. Soc.* **1988**, *110*, 6471. Kelly, T. R.; Ohashi, N.; Armstrong-Chong, R. J.; Bell, S. H. *J. Am. Chem. Soc.* **1988**, *108*, 7100. (b) Clive, D. L. J.; Tao, Y.; Khodabocus, A.; Wu, Y.-J.; Angoh, A. G.; Bennett, S. M.; Boddy, C. N.; Bordeleau, L.; Kellner, D.; Kleiner, G.; Middleton, D. S.; Nichols, C. J.; Richardson, S. R.; Vernon, P. G. *J. Chem. Soc., Chem. Commun.* **1992**, 1489. (c) Rama Rao, A. V.; Singh, A. K.; Venkateswara Rao, B.; Malla Reddy, K. *Tetrahedron Lett.* **1993**, *34*, 2665. (d) Saint-Jalmes, L.; Lila, C.; Xu, J. Z.; Moreau, L.; Pfeiffer, B.; Eck, G.; Pelsez, L.; Rolando, C.; Julia, M. *Bull Chem. Soc. Fr.* **1993**, *130*, 447.

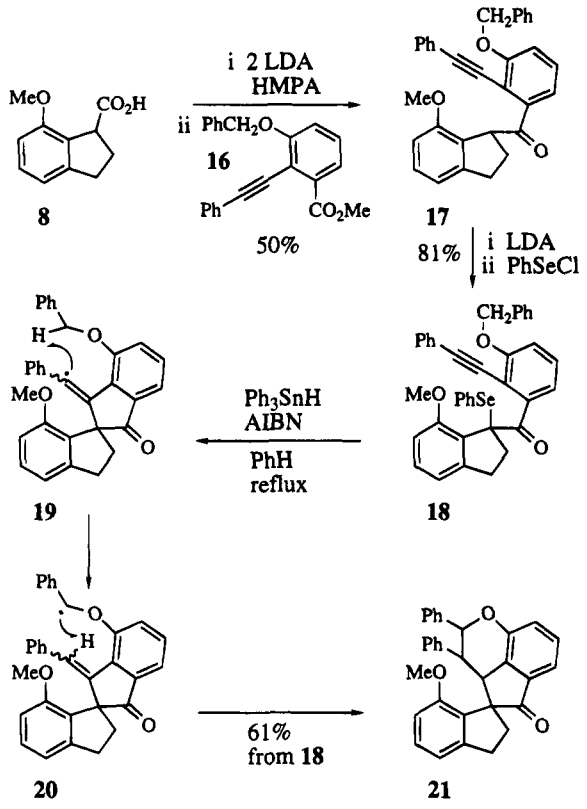
(9) Byrne, K. M.; Hilton, B. D.; White, R. J.; Misra, R.; Pandey, R. C. *Biochemistry* **1985**, *24*, 478.

(10) Martin, S. F. *Tetrahedron* **1980**, *36*, 419.

(11) Beckwith, A. L. J. *Tetrahedron* **1981**, *37*, 3073.

(12) Set, L.; Cheshire, D. R.; Clive, D. L. J. *J. Chem. Soc., Chem. Commun.* **1985**, 1205.

Scheme 3



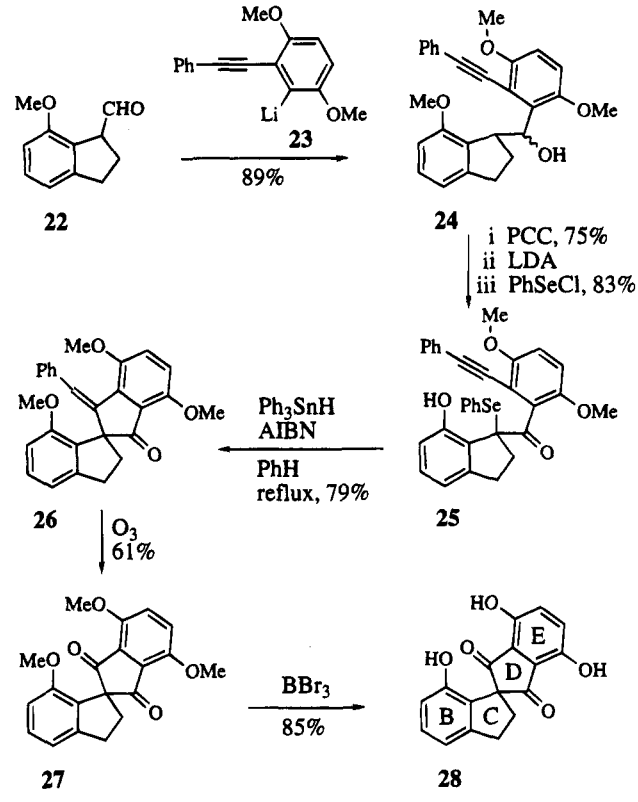
cyclization (**18** → **19**) proceeded normally but the intermediate vinyl radical **19** underwent 1,7 intramolecular hydrogen transfer to form a new radical (**19** → **20**). This, in turn, cyclized by a 6-*endo*-trigonal path so that the observed product was **21**, isolated as a mixture of two diastereoisomers. The intramolecular hydrogen transfer is a very easy process, and even when the stannane was added in one portion, rather than by slow addition, it was possible to isolate the major and minor isomers of **21** in yields of 89% and 5.8%, respectively.

Intramolecular hydrogen transfer has, of course, been developed into a useful technique for synthetic radical chemistry,[13] but at the time we did these experiments, the process was not well-known and for us it was a nuisance. The result did, however, serve to reveal a limitation to our method of spirocyclization and indicated that any protecting groups close to the acetylenic radical acceptor (*cf.* **17** in Scheme 3) should not have easily abstractable hydrogens. On this basis, then, we were able to redefine our model study in terms of the sequence shown in Scheme 4. The details of that work (in which we took the opportunity to introduce a second oxygen substituent into ring E) have been published elsewhere;[7u] here only the following points need be made: the C−H bond of a methoxy group is stronger than the benzylic C−H bond of a benzyl ether[14] (*cf.* **19**, Scheme 3), and so the use of *O*-methyl ethers, as here, should suppress the intramolecular hydrogen transfer seen in the preceding model study. This indeed turned out to be the case, and the spirocyclization **25** → **26** worked well. The best conditions involve adding all of the stannane and the initiator in one portion at the beginning of the experiment. This procedure differs from the high-dilution technique often found essential in radical cyclizations. In contrast, our previous radical

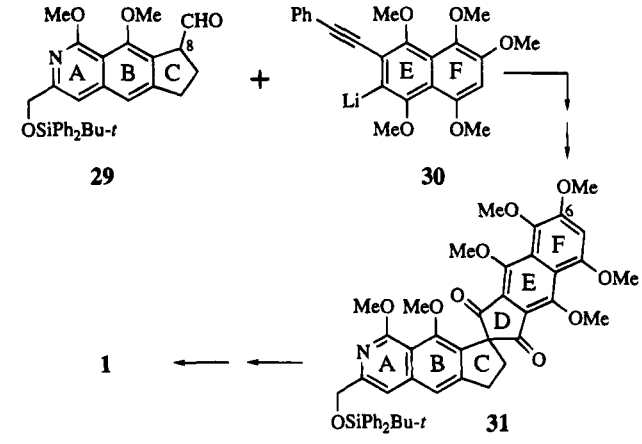
(13) E.g.: Curran, D. P.; Abraham, A. C.; Liu, H. *J. Org. Chem.* **1991**, *56*, 4335 and references therein.

(14) Merényi, R.; Janousek, Z.; Viehe, H. G. In *Substituent Effects in Radical Chemistry*; Viehe, H. G., Janousek, Z., Merényi, R., Eds.; Reidel Publishing Co.: Dordrecht, The Netherlands, 1986; p 301.

Scheme 4



Scheme 5



spirocyclization (Scheme 2) that had also involved an α-keto radical[15] worked well (85% yield) by the standard high-dilution method.

Formulation of the Synthetic Plan. At this point, we were in a position to identify a potential synthetic route to fredericamycin A. In our most advanced model study (Scheme 4), we had combined the two subunits **22** and **23** to produce the fully protected spiro diketone **27** and the corresponding deprotected material (**28**). Direct extrapolation of this model work to fredericamycin A can be expressed in the terms of Scheme 5. Instead of an indanyl carboxaldehyde (**22**) and a lithiated benzene (**23**), we would need an isoquinoline-derived carboxaldehyde (**29**) and a lithiated naphthalene (**30**), respectively. Our general methodology should then lead first to the protected spiro diketone **31** and, eventually, to fredericamycin A itself (**31** → **1**).

Extending the model work in this way does, however, disguise a number of problems. Besides the obvious fact that synthetic

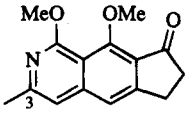
(15) Clive, D. L. J.; Cheshire, D. R. *J. Chem. Soc., Chem. Commun.* **1987**, 1520.

routes to the subunits **29** and **30** would have to be developed, the most significant feature of Scheme 5 is that the advanced intermediate **31** has seven *O*-methyl groups while the target natural product has just one. Consequently, a method would be required for selective deprotection and, failing that, a different choice of protecting groups would become necessary.

Exclusive use of *O*-methyl groups was considered first for a number of reasons: analogy with the model study of Scheme 4, probable simplification of routes to the subunits **29** and **30**, avoidance of intramolecular hydrogen transfer in the spirocyclization, and—equally important—the fact that some possibilities for selective deprotection were easy to recognize. For example, all the methyl groups could, perhaps, be removed and then the required one replaced, some guidance being available in the literature for this last remethylation.[16] Alternatively, ceric ammonium nitrate should serve to oxidize ring F (*cf.* **31**) to a quinone, leaving the C-6 methoxy group in place;[7v,17,18] reduction and acetylation of the resulting hydroquinone would set the stage for a second application of ceric ammonium nitrate that would then deprotect ring E. We suspected that removal of the *O*-methyl group of ring A (see **31**) could be achieved by the action of acid but were unsure of how to deprotect ring B. More detailed planning did not seem warranted at this stage, and use of the all-methyl series would certainly give us valuable experience—which we would need if it became necessary to repeat the sequence with a better choice of protecting groups. As things turned out, *O*-methyl groups proved to be an admirable choice and they were, in any case, largely forced on us by difficulties in attaching other groups to the naphthalenic precursors of **30**.

As far as construction of the pentadienyl side chain is concerned, the fact is that we did not give it much attention at this stage because a number of powerful methods were available to handle the task—at least in principle. When we actually came to this part of the synthesis, we quickly found that the problem is not simple, but fortunately the problem unexpectedly disappeared. Our plans, as implied by Scheme 5, called for introducing the pentadienyl chain before final deprotection. This choice restricts the conditions that may be used for deprotection but delays the need to handle a sensitive hydroquinone system.

Synthesis of the ABC Subunit (29). In order to practice constructing the rare cyclopent[*g*]isoquinolinone structure represented by **29**, we made compound **32**, using a route that we



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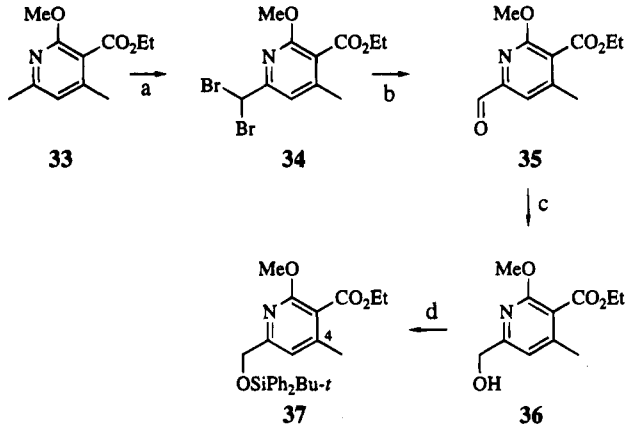
have reported elsewhere.[7s] The approach was developed quite quickly; however, making an analogue with functionality at the C(3) methyl (*cf.* **32** and **29**) took a great deal of time and effort. Several different routes were explored, but eventually, the method used for **32** was successfully modified as shown in (Scheme 6 and 7).

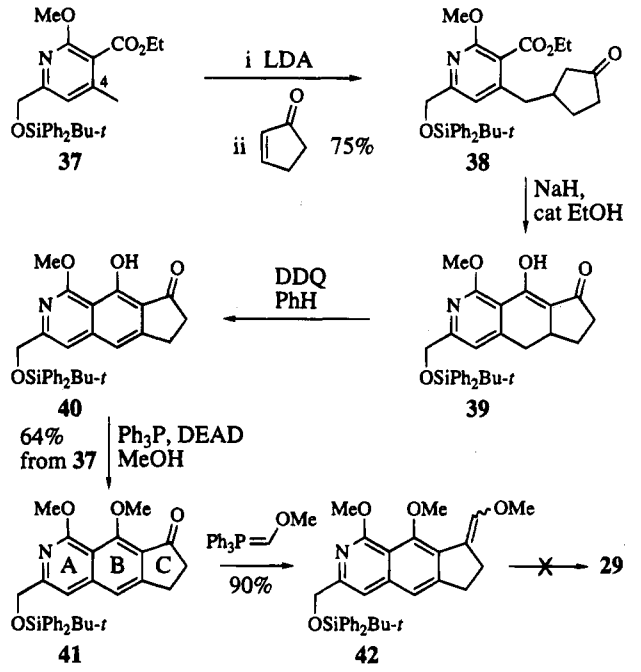
Treatment of the dimethylpyridine ester **33**, which is readily and cheaply made[7s] in large quantities, with *N*-bromosuccinimide took an unexpected but most helpful course, as the geminal dibromide **34** was formed. We had been prepared to use a product in which each of the two methyl groups of **33** had been monobrominated, but the dibromide **34** was much better for the job in hand. Geminal free radical halogenation of dimethylpyridines is not a general procedure; usually, for polymethyl arenes, the course of halogenation depends on the experimental conditions and on the nature and relative positions of the other substituents,[19] and so we were fortunate that the present reaction worked quite well. Hydrolysis to an aldehyde, reduction to an alcohol, and protection (**34** → **35** → **36** → **37**) proceeded without incident. As in the earlier study (i.e., the preparation of **32**), the methyl group at C-4 of **37** was easily deprotonated with LDA, and the resulting carbanion underwent smooth conjugate addition to cyclopentenone (**37** → **38**, Scheme 7). Base-catalyzed cyclization gave β-diketone **39**, which exists largely in its enolized form, and dehydrogenation then gave naphthol **40**.

Scheme 6[a]



[a] (a) NBS, CCl_4, reflux. (b) $AgNO_3$, H_2O–THF, room temperature. (c) $NaBH_4$, EtOH; 60% from **33**. (d) *t*-$BuPh_2SiCl$, DMAP; 97%.

Scheme 7



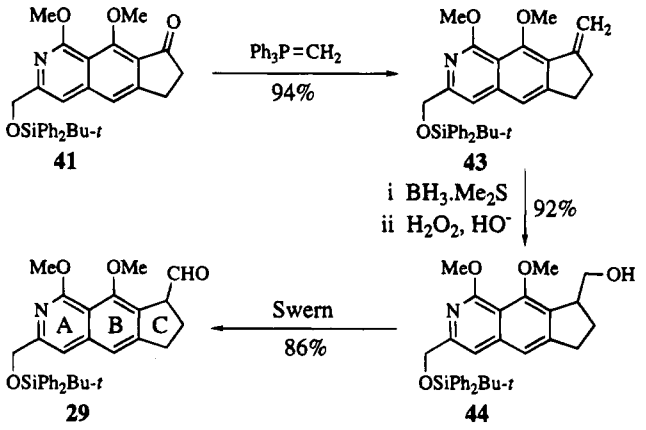
(16) *Cf.*: Kelly, T. R.; Saha, J. K.; Whittle, R. R. *J. Org. Chem.* **1985**, *50*, 3680. Kelly, T. R. *Tetrahedron Lett.* **1978**, 1387.

(17) *Cf.*: Keinan, E.; Eren, D. *J. Org. Chem.* **1987**, *52*, 3872.

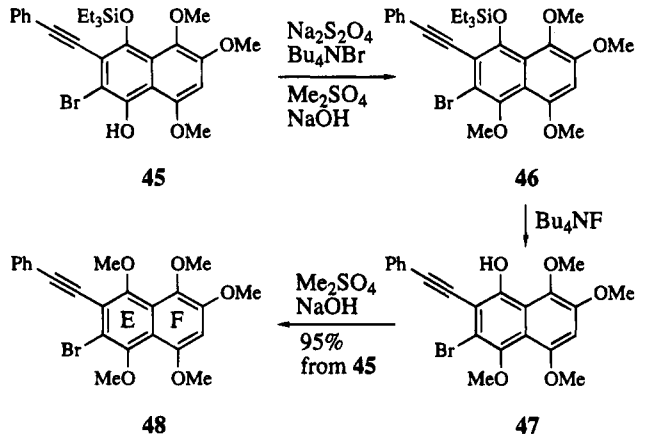
(18) Model studies on selective deprotection: Clive, D. L. J.; Middleton, D. S. *Isr. J. Chem.* **1991**, *31*, 211.

(19) For a discussion of the chlorination and bromination of heteroaryl- and arylmethanes, see: Khanna, R. K.; Armstrong, B.; Cui, H.; Tanko, J. M. *J. Am. Chem. Soc.* **1992**, *114*, 6003. Box, V. G.; Yiannikouros, G. P. *Heterocycles* **1990**, *31*, 1261. Newkome, G. R.; Kiefer, G. E.; Xia, Y.-J.; Gupta, V. K. *Synthesis* **1984**, 676. Offermann, W.; Vögtle, F. *Synthesis* **1977**, 272. Friedrich, S. S.; Friedrich, E. C.; Andrews, L. J.; Keefer, R. M. *J. Org. Chem.* **1969**, *34*, 900. Offermann, W.; Vögtle, F. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 464.

Scheme 8



Scheme 9

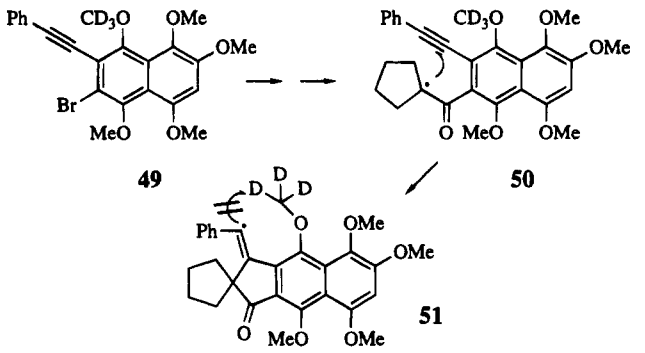


We experienced some difficulty in methylating the naphthol and could obtain an acceptable yield only by using a Mitsunobu reaction[20,21] (**40** → **41**, Scheme 7).

Homologation of **41** was first tried using a Wittig reagent to form the enol ethers **42** (see Scheme 7). However, hydrolysis to aldehyde **29** was not possible without damaging other parts of the molecule. Fortunately, this problem was quickly solved. Use of a different Wittig reagent—methylenetriphenylphosphorane—gave olefin **43** (Scheme 8). This material was easily hydroborated to alcohol **44**, and that, in turn, yielded the required aldehyde **29** on Swern oxidation. All three steps were very efficient. We now had the ABC ring system in hand and could concentrate our full effort on the preparation of the lithiated naphthalene **30** (see Scheme 5).

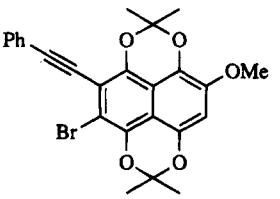
Synthesis of the EF Subunit (48). Preparation of bromide **48** (see Scheme 9), from which the lithiated naphthalene **30** was to be generated, proved an extremely troublesome task. It was the most time-consuming part of the synthesis, and it required a resolute effort to find a convenient route. Although the details of this work have been described elsewhere,[22] the last few steps are shown in Scheme 9 in order to explain some features that offered a certain amount of reassuring flexibility to our synthetic plan. As indicated in the scheme, the ring E

Scheme 10



oxygens are protected sequentially (**45** → **46** and then **47** → **48**); consequently, they need not bear the same type of protecting group. This opportunity was made use of in one of our model studies,[23] where they were protected as in **49** (see Scheme 10) simply by substituting trideuteromethyl *p*-toluenesulfonate for dimethyl sulfate in the last step (*cf.* **47** → **48**). In the case of **49**, the operation of isotope effects after the first stage of the radical closure dramatically suppressed[23] (see **51**, curly arrow) an unwanted intramolecular hydrogen transfer which was observed in the absence of the heavy isotope[23,24] and which we could not circumvent in any other way. We did, of course, try to generate the nondeuterated versions of radicals **50** and **51** at a low temperature, but those attempts were not successful. In the fredericamycin A synthesis itself, however, formation of the corresponding radicals at room temperature (see later) was easily achieved and the desired product was obtained in an acceptable yield. Accordingly, there was then no need to make use of an isotopically improved protecting group.

We had, in addition, tried unsuccessfully to make bromide **52**—an EF subunit which would have let us avoid the hydrogen transfer problem altogether.



52

Linking of the EF and ABC Subunits and Radical Spirocyclization. With aldehyde **29** and bromide **48** in hand, the next step was to link the two subunits together. Halogen–metal exchange smoothly converted the bromide into the desired organolithium **30**, but in all our early attempts—and there were many—the organolithium gave very little (often less than 10%) of the desired coupling product **53** (Scheme 11). By contrast, **30** reacted[22] efficiently (89% yield) with cyclopentanecarboxaldehyde. We resorted to a number of standard procedures to try and improve matters: replacement of the C-8 hydrogen of **29** (see Scheme 5 for numbering) by deuterium or of the lithium by cerium, zirconium, or titanium did not help, and we even went so far as to investigate a substantial change in the synthetic plan; however, we eventually discovered a curious fact: bromide **48**—from which the organolithium is made—contains a trace contaminant that inhibits[25] the desired coupling. This contaminant is not evident in 400 MHz proton NMR spectra, but when the bromide is further purified shortly before use, by crystal-

(20) Bittner, S.; Yassaf, Y. *Chem. Ind. (London)* **1975**, 281. Manhas, M. S.; Hoffman, W. H.; Lal, B.; Bose, A. K. *J. Chem. Soc., Perkin Trans. 1* **1975**, 461.

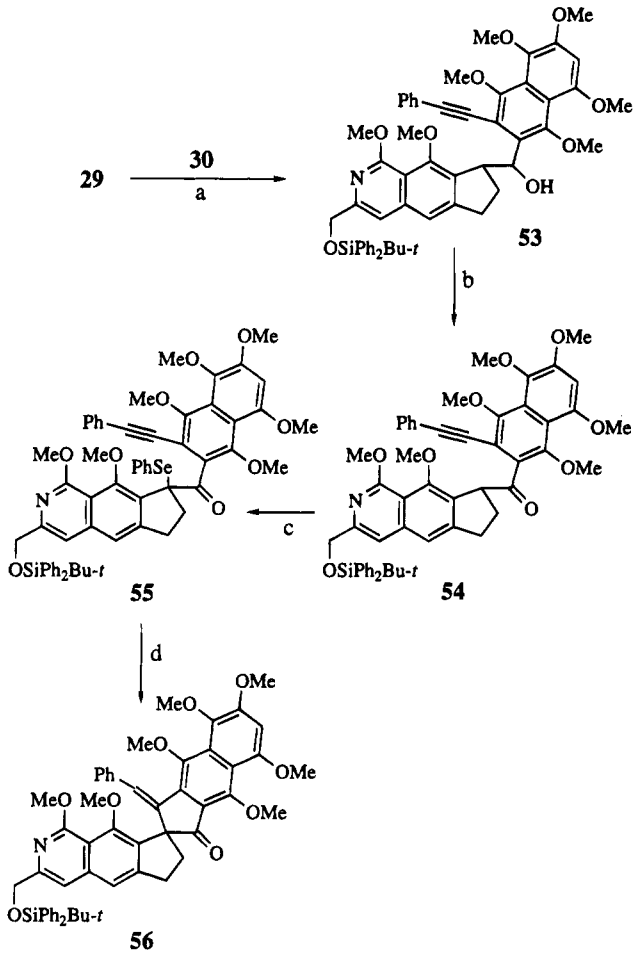
(21) We also prepared the corresponding benzyl-, triethylsilyl-, and *tert*-butyldimethylsilyl-protected derivatives [*cf.*: Clive, D. L. J.; Kellner, D. *Tetrahedron Lett.* **1991**, *32*, 7159] as well as the methoxymethyl ether.

(22) Clive, D. L. J.; Khodabocus, A.; Vernon, P. G.; Angoh, A. G.; Bordeleau, L.; Middleton, D. S.; Lowe, C.; Kellner, D. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1433. [Diagram **1** in this reference is incorrectly drawn and should be as diagram **1** here. The methoxy group in Scheme 1 of this reference is also in the wrong position.]

(23) Clive, D. L. J.; Khodabocus, A.; Cantin, M.; Tao, Y. *J. Chem. Soc., Chem. Commun.* **1991**, 1755. Clive, D. L. J.; Cantin, M.; Khodabocus, A.; Kong, X.; Tao, Y. *Tetrahedron* **1993**, *49*, 7917.

(24) Deuterated protecting groups have been used to simplify NMR spectra: Thiem, J.; Mohn, H.; Heesing, A. *Synthesis* **1985**, 775.

Scheme 11[a]

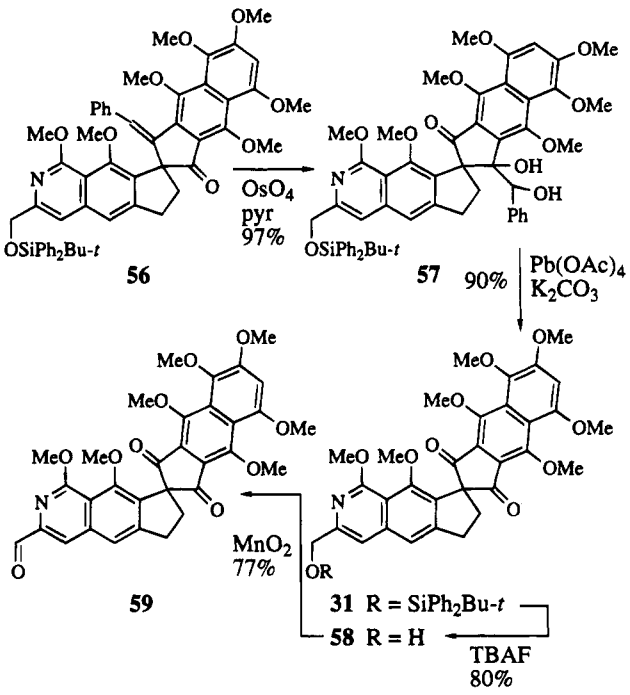


[a] (a) THF–Et_2O; 65%. (b) Ph_3BiCO_3, PhMe–pyridine, 80 °C; 80%. (c) LDA, BuLi, PhSeCl; 70%. (d) Ph_3SnH, Et_3B, air, room temperature; 50%.

lization or rechromatography, then the coupled alcohol **53** can be isolated in 68% yield (as a single isomer). Oxidation to ketone **54** was achieved after a brief delay; manganese dioxide does not work well, but the transformation is easily and efficiently accomplished with triphenylbismuth carbonate.[26]

Introduction of a phenylseleno group would give the starting material (**55**) for radical spirocyclization, but it was to be some time before that radical process could be tried because our early attempts at phenylselenylation, using standard conditions (LDA, PhSeCl), gave unpromising and erratic results. Attempts to use the derived trimethylsilyl enol ether were also unsuccessful. Eventually, however, we found out how to introduce the selenium unit in good yield. The ketone is treated with 1 equiv of LDA, and then 1 equiv of butyllithium is added before introduction of phenylselenyl chloride. By following this experimental procedure, it was possible to isolate the required selenide in 70% yield, provided that the reaction mixture is maintained below room temperature during workup. Once the selenide is pure, it is quite easy to handle. Treatment with triphenyltin hydride at room temperature, and in the presence of triethylborane[27] and air, served to generate the desired radical, which cyclized to afford spiro ketone **56**. This crucial experiment was done twice on a gram scale and gave the product as a single isomer in 50% or greater yield.[28] In earlier model work (Scheme 10), we had tried unsuccessfully to generate a similar radical at room temperature. Here, however, the radical to be formed is not only adjacent to a carbonyl but is also benzylic, and so room temperature conditions worked. For this reason, we did not have to make use of deuterium isotope effects in order to get an acceptable yield of spirocyclic product **56**.[29]

Scheme 12



Modification of the Spiro System 56 and Completion of the Synthesis. The next task was to cleave the exocyclic double bond of **56** (Scheme 12). This cleavage was very troublesome, until we realized that the concentration of osmium tetroxide must be quite high in order to increase the rate of hydroxylation relative to some undesired processes that also occur. When the reaction is done under appropriate conditions, it is almost quantitative and we isolate one diol only (**56** → **57**). Cleavage of the diol with lead tetraacetate was straightforward, and we were almost ready to attach the dienyl side chain. To prepare for this, the silicon group was removed and the resulting alcohol was oxidized to an aldehyde (**31** → **58** → **59**), both steps being very efficient under standard conditions (tetrabutylammonium fluoride followed by manganese dioxide).

Examination of the literature suggested that the Wittig reagent derived from phosphonium salt **60**[30] (Scheme 13) should be tried for construction of the pentadienyl side chain. This reagent gives *E,E* dienes with aliphatic aldehydes[30] but does not appear to have been used with aromatic compounds. In our case, a

(25) We had wondered whether traces of a palladium species (originating from one of the steps in the preparation of **48**) were responsible, but attempted coupling of **30** in the presence of 1,2-bis(phenylphosphino)ethane also failed. *Cf.*: Chuang, C.-P.; Gallucci, J. C.; Hart, D. J.; Hoffman, C. *J. Org. Chem.* **1988**, *53*, 3218.

(26) Barton, D. H. R.; Kitchin, J. P.; Lester, D. J.; Motherwell, W. B.; Papoula, M. T. B. *Tetrahedron Suppl. (No. 1)* **1981**, *37*, 73.

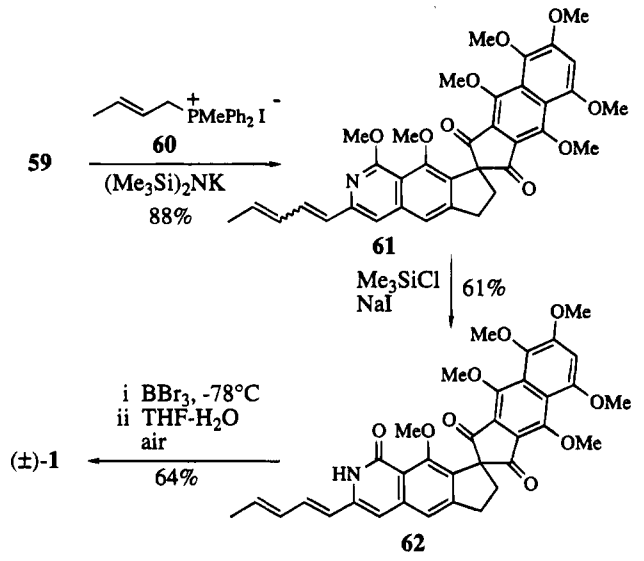
(27) Nozaki, K.; Oshima, K.; Utimoto, K. *Tetrahedron Lett.* **1988**, *29*, 6125. Nozaki, K.; Oshima, K.; Utimoto, K. *J. Am. Chem. Soc.* **1987**, *109*, 2547. Barton, D. H. R.; Jang, D. O.; Jaszberenyi, J. Cs. *Tetrahedron Lett.* **1990**, *31*, 4681.

(28) We did not examine the reaction mixture for the presence of another geometrical isomer. The cyclization can be done thermally in refluxing PhH.

(29) In some of our studies on the preparation of spiro compounds related to **56**, we have found that a phenylthio group is sometimes easier to introduce than a phenylseleno group and appears to serve as well for the radical spirocyclization.

(30) (a) *Cf.*: Vedejs, E.; Ahmad, S. *Tetrahedron Lett.* **1988**, *29*, 2291 and references therein. (b) Huang, W.; Xiao, W.; Wang, J. *Youji Huaxue* **1986**, 376; *Chem. Abstr.* **1987**, *106*, 138113c. Related reagents with the same substitution pattern on phosphorus show poor stereoselectivity with benzaldehyde.

Scheme 13



diene was easily formed with a reagent made by treating the phosphonium salt with potassium hexamethyldisilazide but it was a mixture (*ca.* 10:1) of geometrical isomers (**61**). We were unable to separate them chromatographically, and so we decided to continue our synthesis in the hope of resolving the problem at a later stage. Further experiments would, in any event, give valuable information about the crucial business of selective deprotection.

Treatment of the isomer mixture with iodotrimethylsilane, which was generated *in situ* from the silyl chloride and sodium iodide,[31] resulted in exclusive deprotection of the ring A oxygen. The product was obtained in 61% yield as a very nicely crystalline material, but to our initial disappointment, the 400 MHz proton NMR spectrum showed that we were dealing with a mixture of geometrical isomers, and again we were unable to effect any chromatographic separation. After a time, we began to wonder whether the crystals were actually pure but suffered isomerization in deuterochloroform. With this suspicion in mind, we quickly discovered that compound **62** is very sensitive[32] to visible light; our crystalline product was indeed pure, but it rapidly isomerized during preparation of the NMR sample unless the solution was made up with protection from light. The preparation of compound **62** is done under normal laboratory lighting, and it is possible that, as the compound crystallizes, a mobile equilibrium among the geometrical isomers continuously shifts in favor of the desired *E,E* isomer. However, we have not sought experimental evidence on this point.[33]

Finally, exposure of the partially deprotected material (**62**) to boron tribromide at a low temperature served to remove five—and the correct five—of the remaining *O*-methyl groups.[34,35] We presume that the intermediate product was some type of boron ester, and this was hydrolyzed in aqueous tetrahydrofuran[36] and oxidized by air to fredericamycin A. The synthetic material was purified by flash chromatography and then recrystallized by slow evaporation from a solution made up in a mixture of chloroform, methanol, and acetic acid. The dark red crystalline product (64%) was indistinguishable [by ^{1}H NMR (400 MHz), ^{13}C NMR (100.64 MHz), FABMS, and TLC (silica TLC plate, 87:3:3 chloroform–methanol–acetic acid; RP-18 silica TLC plate, 70:30:1 methanol–water–acetic acid] from a sample of the natural product.

Experimental Section

General Procedures. Unless stated to the contrary, the following conditions apply. Reactions were carried out under a slight static pressure of argon that had been purified by passage through a column (3.5 × 42 cm) of R-311 catalyst[37] and then through a similar column of Drierite. Glassware was dried in an oven for at least 3 h before use (120 °C) and either cooled in a desiccator over Drierite or assembled quickly, sealed with rubber septa, and allowed to cool under a slight static pressure of argon. Reaction mixtures were stirred by Teflon-coated magnetic stirring bars.

Solvents for chromatography and extractions were distilled before use.

Products were isolated from solution by evaporation under water-aspirator vacuum at, or below, room temperature, using a rotary evaporator.

Microliter syringes were washed with water and acetone, using a suction device to draw the solvents through. Then air was sucked through for 1 min. The solution to be dispensed was drawn up and expelled, and this operation was repeated several times before drawing up the sample to be used. Cannula transfers were always done under slight pressure (argon), not by suction.

Melting points were determined on a Kofler block melting point apparatus.

Commercial thin layer chromatography (TLC) plates (silica gel, Merck 60F-254) were used. Spots were detected by spraying the plate with a solution of phosphomolybdic acid,[38] followed by charring on a hot plate or by examination under UV light. Silica gel for flash chromatography was Merck type 60 (230–400 mesh).

Dry solvents were prepared under an inert atmosphere and transferred by syringe or cannula. Dry tetrahydrofuran (THF) and diethyl ether were distilled from sodium and benzophenone ketyl. Dry PhH was distilled from sodium. Dry Et_3N, CH_2Cl_2, MeOH, MeCN, and pyridine were distilled from CaH_2. Commercial (Aldrich) solutions of *n*-BuLi and MeLi were assumed to have the stated molarity. Petroleum ether refers to the fraction boiling at 60–90 °C.

FTIR measurements were made as casts from the specified solvent using potassium bromide plates.

The symbols s′, d′, t′, and q′ used for ^{13}C NMR signals indicate zero, one, two, or three attached hydrogens, respectively.

Mass spectra were recorded with a AEI Model MS-12, MS-50, or MS9 (modified) or Kratos MS50 (modified) mass spectrometer.

Microanalyses were performed by the microanalytical laboratory of this department.

Preparation of the Ring ABC Subunit (29). Ethyl 6-(Hydroxymethyl)-2-methoxy-4-methyl-3-pyridinecarboxylate (36). NBS (13.95 g, 78.4 mmol) and AIBN (5 mg) were added to a solution of ethyl 2-methoxy-4,6-dimethyl-3-pyridinecarboxylate (**33**) (7.79 g, 37.4 mmol) in dry CCl_4 (160 mL), and the mixture was refluxed in an oil bath and irradiated with a 300 W tungsten lamp for 3 h, by which time no NBS remained at the bottom of the flask. The yellow mixture was cooled and filtered, the insoluble material being washed with hexane. Evaporation of the filtrate gave the crude dibromide **34**, which should be used promptly for the next step.

In another experiment, dibromide **34** was purified by flash chromatography over silica gel, using 1:19 EtOAc–hexane, and obtained as

(31) Morita, T.; Okamoto, Y.; Sakurai, H. *J. Chem. Soc., Chem. Commun.* **1978**, 874. Olah, G.; Narang, S. C.; Gupta, B. G. B.; Malhotra, R. *Synthesis* **1979**, 61.

(32) Fortunately, this tendency is not shared, at least to such a significant degree, by fredericamycin A.

(33) Iodine is liberated in the deprotection of ring A, which is done without protection from light. The stage at which isomerization occurs was not established.

(34) Review of ether cleavage: Bhatt, M. V.; Kulkarni, S. U. *Synthesis* **1983**, 249. Selective demethylations with boron trichloride: Carvahlo, C. F.; Sargent, M. V. J. *Chem. Soc., Chem. Commun.* **1984**, 227.

(35) We also treated the fully protected isomer mixture **61** with boron tribromide, but the result (of a single experiment) was not encouraging. Under the conditions we used, deprotection was incomplete and we believe that only the EF rings were deprotected.

(36) *Cf.*: Fisher, M. J.; Chow, K.; Villalobos, A.; Danishefsky, S. J. *J. Org. Chem.* **1991**, *56*, 2900.

(37) Supplied by Chemical Dynamics Corp., South Plainfield, NJ.

(38) Phosphomolybdic acid (15 g) and ceric ammonium sulfate (2.5 g) dissolved in a mixture of water (985 mL) and concentrated sulfuric acid (15 mL).

an oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.39 (t, J = 7.0 Hz, 3 H), 2.32 (s, 3 H), 4.00 (s, 3 H), 4.43 (q, J = 7.0 Hz, 2 H), 6.50 (s, 1 H), 7.16 (s, 1 H); exact mass *m/z* calcd for $C_{11}H_{13}{}^{79}Br^{81}BrNO_3$ 366.9241, found 3666.9208.

The above crude material was dissolved in THF (160 mL), and a solution of $AgNO_3$ (18.7 g, 100 mmol) in water (55 mL) was added dropwise with stirring (protection from light). Stirring was continued overnight, and the resulting precipitate was filtered off. The filtrate was evaporated at room temperature, and the residue was extracted with Et_2O (3 × 100 mL). The organic extract was washed with brine, dried ($MgSO_4$), and evaporated to afford the crude aldehyde **35**. All silver-containing residues should be discarded promptly (*explosion danger*).

In another experiment, aldehyde **35** was purified by flash chromatography over silica gel, using 1:9 EtOAc−hexane, and obtained as an oil: FTIR ($CHCl_3$ cast) 1733, 1718 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.39 (t, J = 7.0 Hz, 3 H), 3.39 (s, 3 H), 4.04 (s, 3 H), 4.43 (q, J = 7 Hz, 2 H), 7.42 (s, 1 H), 9.95 (s, 1 H); exact mass *m/z* calcd for $C_{11}H_{13}NO_4$ 223.0844, found 223.0845.

$NaBH_4$ (2.1 g, 55.5 mmol) was added in small portions to a stirred and cooled (0 °C) solution of the above crude aldehyde **35** in absolute EtOH (110 mL) (argon atmosphere). After 1 h, reaction was complete (TLC control, silica, 2:3 EtOAc−hexane). Most of the EtOH was evaporated at room temperature, and the residue was partitioned between water and Et_2O. The organic extract was washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (5 × 20 cm), using 2:3 EtOAc−hexane, gave pure (^{1}H NMR, 300 MHz) **36** (5.02 g, 60% overall): FTIR (CH_2Cl_2 cast) 3445, 1729 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.38 (t, J = 7.2 Hz, 3 H), 2.30 (s, 3 H), 3.56 (t, J = 4.6 Hz, 1 H), 3.95 (s, 3 H), 4.39 (q, J = 7.2 Hz, 2 H), 4.62 (d, J = 4.6 Hz, 2 H), 6.72 (s, 1 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 14.14 (q′), 19.12 (q′), 53.80 (q′), 61.35 (t′), 63.87 (t′), 114.51 (d′), 115.79 (s′), 148.29 (s′), 157.74 (s′), 160.36 (s′), 166.88 (s′); exact mass *m/z* calcd for $C_{11}H_{15}NO_4$ 225.1001, found 225.0999. Anal. Calcd for $C_{11}H_{15}NO_4$: C, 58.66; H, 6.71; N, 6.22. Found: C, 58.51; H, 6.64; N, 6.17. Alcohol **36** can be stored in the refrigerator.

Ethyl 6-[[[(1,1-Dimethylethyl)diphenylsilyl]oxy]methyl]-2-methoxy-4-methyl-3-pyridinecarboxylate (37). *t*-$BuPh_2SiCl$ (4.16 g, 15.15 mmol) in dry CH_2Cl_2 (7 mL plus 2 mL as a rinse) was added dropwise to a stirred and cooled (0 °C) solution of alcohol **36** (3.10 g, 13.77 mmol) and DMAP (1.85 g) in dry CH_2Cl_2 (50 mL). The cold bath was left in place but not recharged, and the mixture was stirred overnight. Water (50 mL) was added, and the organic layer was washed with dilute hydrochloric acid (1 M, 20 mL), saturated aqueous $NaHCO_3$ (1 × 20 mL), water (1 × 20 mL), and brine (1 × 20 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (5 × 15 cm), using 3:47 EtOAc−hexane, gave pure (TLC, silica, 3:47 EtOAc−hexane) **37** (6.2 g, 97%) as a white solid: FTIR ($CHCl_3$ cast) 1791 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.13 (s, 9 H), 1.38 (t, J = 7.0 Hz, 3 H), 2.36 (s, 3 H), 3.84 (s, 3 H), 4.39 (q, J = 7.0 Hz, 2 H), 4.73 (s, 2 H), 7.09 (s, 1 H), 7.38 (m, 6 H), 7.70 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 14.243 (q′), 19.32 (s′), 19.42 (q′), 26.67 (q′), 53.67 (q′), 61.22 (t′), 66.30 (t′), 114.38 (d′), 115.51 (s′), 127.78 (d′), 129.79 (d′), 133.24 (s′), 135.50 (d′), 147.89 (s′), 159.24 (s′), 160.15 (s′), 167.24 (s′); exact mass *m/z* calcd for $C_{23}H_{24}NO_4$ (M − *t*-Bu) 406.1474, found 406.1484. Anal. Calcd for $C_{27}H_{33}NO_4Si$: C, 69.94; H, 7.17; N, 3.02. Found: C, 70.16; H, 3.37; N, 3.06.

Ethyl 6-[[[(1,1-Dimethylethyl)diphenylsilyl]oxy]methyl]-2-methoxy-4-[(3-oxocyclopentyl)methyl]-3-pyridinecarboxylate (38). LDA was prepared by dropwise addition of BuLi (6.5 mL, 1.6 M solution in hexanes, 10.37 mmol) to a stirred and cooled (0 °C) solution of *i*-Pr_2NH (1.82 mL, 12.96 mmol) in THF (15 mL). The solution was stirred for 15 min at 0 °C, cooled to −78 °C, and then added *dropwise* (over *ca.* 10 min) via a short, thin cannula (argon pressure) to a stirred and cooled (−78 °C) solution of pyridine **37** (4.0 g, 8.64 mmol) in THF (60 mL). Stirring at −78 °C was continued for 30 min, and then a precooled (−78 °C) solution of freshly distilled 2-cyclopentenone (17.28 mL, 1.45 mmol) in THF (15 mL) was added dropwise by cannula. Stirring was continued for 30 min with the cold bath in place, and then, saturated aqueous NH_4Cl (50 mL) was added and the mixture was extracted with Et_2O (3 × 100 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (4 × 20 cm), using 3:17 EtOAc−hexane, gave **38** (3.54 g, 75%) as a pure (^{1}H NMR, 300 MHz) oil: FTIR (CH_2Cl_2 cast) 1743, 1732 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.13 (s, 9 H), 1.38 (t, J = 7.0 Hz, 3 H), 1.55−1.72 (m, 1 H), 1.92 (ddd, J = 1.1, 10.0, 18.0 Hz, 1 H), 2.14−2.60 (m, 5 H), 2.70−2.86 (m, 2 H), 3.86 (s, 3 H), 4.40 (q, J = 7.0 Hz, 2 H), 4.75 (s, 2 H), 7.10 (s, 1 H), 7.31−7.50 (m, 6 H), 7.70 (dd, J = 1.4, 7.8 Hz, 4 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 14.27 (q′), 19.35 (s′), 26.88 (q′), 29.21 (t′), 37.70 (d′), 38.25 (t′), 38.43 (t′), 44.89 (t′), 53.78 (q′), 61.47 (t′), 66.30 (t′), 113.27 (d′), 115.58 (s′), 127.81 (d′), 129.87 (d′), 133.20 (s′), 135.48 (d′), 149.53 (s′), 159.62 (s′), 160.32 (s′), 167.21 (s′), 218.161 (s′); exact mass *m/z* calcd for $C_{30}H_{34}NO_4Si$ (M − OC_2H_5) 500.2257, found 500.2256. Anal. Calcd for $C_{32}H_{39}NO_5Si$: C, 70.43; H, 7.20; N, 2.57. Found: C, 70.52; H, 7.23; N, 2.56.

When carried out on one-third of the above scale, the yield was 83%.

3-[[[(1,1-Dimethylethyl)diphenylsilyl]oxy]methyl]-6,7-dihydro-1,9-dimethoxy-8*H*-cyclopent[*g*]isoquinolin-8-one (41). A solution of keto ester **38** (7.59 g, 13.91 mmol) in THF (25 mL plus 10 mL as a rinse) was added dropwise to a stirred and cooled (0 °C) suspension of NaH (60% w/w in oil, 1.67 g, 41.78 mmol) in THF (280 mL). Absolute EtOH (1.2 mL, 16.97 mmol) was added dropwise, and stirring at 0 °C was continued for 3 h (TLC control, silica, 1:3 EtOAc−hexane). Saturated aqueous NH_4Cl solution (40 mL) was added slowly, and the mixture was acidified with 1 N hydrochloric acid to pH 5−6. The mixture, which must be acidic, was partitioned between water (100 mL) and EtOAc (2 × 125 mL), and the organic extract was washed with brine (2 × 200 mL), dried ($MgSO_4$), and evaporated to give the crude β-diketone **39** as a yellow oil. The material was used directly in the next step.

In another experiment, the material was purified by flash chromatography over silica gel, using first 3:17 EtOAc−CH_2Cl_2 and then 1:19 MeOH−CH_2Cl_2, to afford pure (^{1}H NMR, 200 MHz) **39**: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.88−3.4 (m, 17 H), 4.05 (s, 3 H), 4.9 (s, 2 H), 7.28 (s, 1 H), 7.52−7.70 (m, 6 H), 7.82−7.98 (m, 4 H).

DDQ (2.9 g, 12.86 mmol) was added in small portions to a stirred solution of the above crude β-diketone in PhH (280 mL). Stirring at room temperature was continued for 30 min, and the mixture was filtered through a tightly-packed column (5 × 10 cm) of Celite, covered with a thin layer of silica gel, using PhH to wash through all yellow material. The column should be packed dry under vacuum and pressed down well. Evaporation of the solvent gave hydroxy ketone **40** as a yellow solid, which can be stored in the refrigerator.

In another experiment, the crude hydroxy ketone **40** was washed with 1:1 Et_2O−hexane until the solid became white. The resulting material was dried in vacuum to afford a white foam: FTIR (CH_2Cl_2 cast) 3360, 1708 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.17 (s, 9 H), 2.73−2.81 (m, 2 H), 3.15−3.22 (m, 2 H), 4.09 (s, 3 H), 4.83 (br s, 2 H), 7.23 (s, 1 H), 7.34−7.47 (m, 7 H), 7.63 (br d, J = 7.5 Hz, 4 H), 10.72 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100.614 MHz) δ 19.37 (s′), 25.38 (t′), 26.90 (q′), 36.46 (t′), 54.03 (q′), 66.26 (t′), 107.29 (s′), 110.28 (d′), 113.97 (d′), 118.82 (s′), 127.77 (d′), 129.78 (d′), 133.29 (s′), 135.51 (d′), 146.19 (s′), 153.99 (s′), 155.32 (s′), 157.45 (s′), 161.98 (s′), 207.16 (s′); mass (FAB) *m/z* calcd for $C_{30}H_{32}NO_4Si$ (M + 1) 498, found 498.

DEAD (5.93 mL, 37.98 mmol) was added dropwise to a stirred and cooled (−78 °C) solution of Ph_3P (10.9 g, 41.6 mmol) in THF (260 mL). The mixture was stirred at −78 °C for 30 min, by which time a precipitate had formed, and then dry MeOH (50.23 mL, 1.78 mmol) was added dropwise. Stirring (−78 °C) was continued until all the solids had dissolved (*ca.* 15 min), and then a solution of the above crude hydroxy ketone **40** in THF (50 mL plus 10 mL as a rinse) was added dropwise. The cold bath was left in place but not recharged, and stirring was continued overnight. Evaporation of the solvent and flash chromatography of the residue over silica gel (5 × 20 cm), using 1:4 EtOAc−hexane, gave pure (^{1}H NMR, 200 MHz) **41** (4.45 g, 64% overall) as a cream solid: mp 153−155 °C (from EtOAc−hexane); FTIR (CH_2Cl_2 cast) 1712 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.17 (s, 9 H), 2.71−2.80 (m, 2 H), 3.15−3.27 (m, 2 H), 4.02 (s, 3 H), 4.08 (s, 3 H), 4.83 (d, J = 0.8 Hz, 2 H), 7.34−7.48 (m, 7 H), 7.49 (br s, 1 H), 7.74 (dd, J = 7.5, 1.0 Hz, 4 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 19.41 (s′), 25.17 (t′), 26.94 (q′), 37.32 (t′), 54.01 (q′), 63.16 (q′), 66.29 (t′), 109.46 (d′), 112.85 (s′), 118.82 (d′), 126.13 (s′), 127.80 (d′),

129.80 (d'), 133.36 (s'), 135.55 (d'), 145.64 (s'), 154.62 (s'), 158.71 (s'), 161.99 (s'), 203.34 (s); exact mass *m/z* calcd for $C_{27}H_{24}NO_4Si$ (M − C_4H_9) 454.1474, found 454.1474. Anal. Calcd for $C_{31}H_{33}NO_4Si$: C, 72.77; H, 6.50; N, 2.74. Found: C, 72.51; H, 6.48; N, 2.68. Ketone **41** is the most stable compound of the above series and can be stored.

3-[[[(1,1-Dimethylethyl)diphenylsilyl]oxy]methyl]-7,8-dihydro-1,9-dimethoxy-8-methylene-6*H*-cyclopent[*g*]isoquinoline (43). *t*-BuOK (4.15 g, 36.98 mmol) was added in one portion to a stirred suspension of methyltriphenylphosphonium bromide (12.98 g, 36.33 mmol) in dry THF (130 mL). The resulting yellow suspension was stirred for 30 min and then ketone **41** (6.33 g, 12.33 mmol) in dry THF (20 mL plus 5 mL as a rinse) was added dropwise. The mixture turned from yellow to dark brown. Stirring at room temperature was continued for a further 30 min, and water (150 mL) was then added. The mixture was extracted with Et_2O (3 × 50 mL), and the combined organic extracts were washed with brine and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (5.5 × 20 cm), using 1:20 EtOAc−hexane, gave pure (^{1}H NMR, 200 MHz) **43** (6.30 g, 94%): mp 137−138 °C (from 1:5 EtOAc−hexane); FTIR (CH_2Cl_2 cast) 1635, 1618 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.17 (s, 9 H), 2.78−2.89 (m, 2 H), 3.02−3.11 (br t, *J* = 6.9 Hz, 2 H), 3.88 (s, 3 H), 4.04 (s, 3 H), 4.83 (s, 2 H), 5.31 (dd, *J* = 1.8, 4.1 Hz, 1 H), 6.09 (dd, *J* = 1.9, 4.1 Hz, 1 H), 7.32−7.47 (m, 8 H), 7.72−7.82 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 19.43 (s'), 26.96 (q'), 29.91 (t'), 32.74 (t'), 53.77 (q'), 60.59 (q'), 66.39 (t'), 109.20 (t'), 110.06 (d'), 112.85 (s'), 118.28 (d'), 127.75 (d'), 129.71 (d'), 131.11 (s'), 133.57 (s'), 135.60 (d'), 142.16 (s'), 147.46 (s'), 151.34 (s'), 154.53 (s'), 160.00 (s'); exact mass *m/z* calcd for $C_{32}H_{35}NO_3Si$ 509.2386, found 509.2379. Anal. Calcd for $C_{32}H_{35}NO_3Si$: C, 75.40; H, 6.92; N, 2.75. Found: C, 75.49; H, 7.10; N, 2.66.

3-[[[(1,1-Dimethylethyl)diphenylsilyl]oxy]methyl]-7,8-dihydro-1,9-dimethoxy-6*H*-cyclopent[*g*]isoquinoline-8-methanol (44). Borane−dimethyl sulfide complex (8.7 mL, 2 M in THF, 17.4 mmol) was added dropwise to a stirred and cooled (0 °C) solution of olefin **43** (2.21 g, 4.34 mmol) in THF (43 mL). The mixture was stirred for an additional 3 h at 0 °C, and aqueous NaOH (21.7 mL, 2 M, 43.4 mmol) was then added dropwise with stirring (H_2 evolution), followed by H_2O_2 (30%, 22 mL, 217 mmol). The cold bath was removed, and the mixture was stirred vigorously for 1 h, diluted with water (40 mL), and extracted with EtOAc (3 × 40 mL). The combined organic extracts were washed with brine (2 × 70 mL) and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (5 × 15 cm), using 1:1 EtOAc−hexane, gave pure (TLC, silica, 1:1 EtOAc−hexane) **44** (2.09 g, 91%) as a white foam. Yields were consistently in the range 88−92%. Compound **44**: FTIR (CH_2Cl_2 cast) 3440, 1630 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.16 (s, 9 H), 1.94−2.09 (m, 1 H), 2.24−2.41 (m, 1 H), 2.78 (br, 1 H), 2.92−3.21 (m, 2 H), 3.63−3.76 (m, 1 H), 3.84 (br d, *J* = 6 Hz, 2 H), 3.90 (s, 3 H), 4.04 (s, 3 H), 4.83 (s, 2 H), 7.32−7.48 (m, 8 H), 7.77 (br d, 4 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 19.45 (s'), 26.96 (q'), 28.88 (t'), 31.49 (t'), 46.19 (d'), 53.80 (q'), 62.23 (q'), 66.19 (t'), 66.38 (t'), 110.19 (d'), 112.12 (s'), 118.47 (d'), 127.77 (d'), 129.73 (d'), 133.59 (s'), 133.64 (s'), 135.47 (s'), 135.62 (d'), 142.14 (s'), 149.72 (s'), 151.07 (s'), 153.22 (s'), 159.21 (s'); exact mass *m/z* calcd for $C_{32}H_{37}NO_4Si$ 527.2491, found 527.2477. Anal. Calcd for $C_{32}H_{37}NO_4Si$: C, 72.83; H, 7.07; N, 2.65. Found: C, 72.93; H, 7.18; N, 2.58.

3-[[[(1,1-Dimethylethyl)diphenylsilyl]oxy]methyl]-7,8-dihydro-1,9-dimethoxy-6*H*-cyclopent[*g*]isoquinoline-8-carboxaldehyde (29). Dry DMSO (450 μL, 6.30 mmol) was added dropwise to a stirred and cooled (−78 °C) solution of $(COCl)_2$ (275 μL, 3.15 mmol) in CH_2Cl_2 (30 mL) under argon. After 10 min, a solution of alcohol **44** (1.510 g, 2.87 mmol) in CH_2Cl_2 (10 mL plus 5 mL as a rinse) was added dropwise over *ca.* 30 min. Stirring at −78 °C was continued for 30 min, and then Et_3N (2.0 mL, 14.50 mmol) was added dropwise. Stirring was continued for 20 min, the cold bath was removed, and stirring was continued for 30 min. Brine (30 mL) was added, and the mixture was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic extracts were washed with brine (2 × 30 mL) and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (2.5 × 15 cm), using 1:6 EtOAc−hexane, gave pure (^{1}H NMR, 200 MHz) **29** (1.31 g, 86%) as a colorless foam, which should be stored in a refrigerator and used within a week: FTIR (CH_2Cl_2, cast) 1726 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.15 (s, 9 H), 2.25−2.36 (m, 1 H), 2.40−2.52 (m, 1 H), 3.04−3.21 (m, 2 H), 3.77 (s, 3 H), 4.04 (s, 3 H), 4.17−4.25 (m, 1 H), 4.84 (s, 2 H), 7.33−7.45 (m, 8 H), 7.72−7.78 (m, 4 H), 9.77 (d, *J* = 3.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100.614 Hz) δ 19.39 (s'), 26.15 (t'), 26.90 (q'), 32.20 (t'), 53.79 (q'), 55.48 (d'), 61.92 (q'), 66.29 (t'), 110.15 (d'), 112.11 (s'), 118.38 (d'), 127.72 (d'), 129.69 (d'), 133.49 (s'), 133.54 (s'), 135.56 (d'), 142.69 (s'), 149.03 (s'), 151.60 (s'), 159.29 (s'), 199.55 (d'); exact mass *m/z* calcd for $C_{32}H_{35}NO_4Si$ 525.2335, found 525.2332.

Preparation of the EF Unit (48). The procedure is described in ref 22, but we have improved some of the steps and the modifications are given in the supplementary material.

Coupling of the ABC (29) and EF (48) Units and Elaboration into Fredericamycin A. 3-[[[(1,1-Dimethylethyl)diphenylsilyl]oxy]-methyl]-7,8-dihydro-1,9-dimethoxy-α-[1,4,5,6,8-pentamethoxy-3-(phenylethynyl)-2-naphthalenyl]-6*H*-cyclopent[*g*]isoquinoline-8-methanol (53). In this experiment, it is essential to use very pure bromonaphthalene **48**. The material should be subjected to flash chromatography until it is bright canary yellow, and a small scale (*ca.* 50 mg) coupling should be attempted as a check before doing the experiment on a large scale.

Pure bromonaphthalene **48** (1.12 g, 2.45 mmol) was dissolved in dry THF (18 mL). The solution was diluted with an equal volume of dry Et_2O and cooled to −78 °C (argon atmosphere). BuLi (2.0 mL, 1.5 M solution in hexanes, 2.94 mmol) was added dropwise (over *ca.* 1 min), and stirring was continued for 5 min at −78 °C. A solution of aldehyde **29** (1.80 g, 3.43 mmol) in dry Et_2O (18 mL plus 2 mL as a rinse) was then injected by syringe over *ca.* 2 min, and stirring at −78 °C was continued for 45 min. The cold bath was removed, and after 15 min, saturated aqueous NH_4Cl (*ca.* 250 mL) was added. The mixture was extracted with EtOAc (1 × 200 mL), the layers were separated, and the aqueous phase was extracted with EtOAc (1 × 100 mL). The combined organic phases were washed with brine (1 × 50 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (2.5 × 20 cm) with 3:7 EtOAc−hexane gave pure (TLC, silica, 2:3 EtOAc−hexane; ^{1}H NMR, 200 MHz) **53** as a light yellow foam (1.45 g, 65%). Only a single isomer was isolated.

Some of the starting aldehyde (*ca.* 500 mg) was recovered from the flash chromatography. The experiment has been done with 200 mg to 1.5 g of bromonaphthalene to give yields of 62−68%.

Compound **53**: FTIR (CH_2Cl_2 cast) 3500, 1630, 1600, 1570, 1353, 1344 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.15 (s, 9 H), 2.11−2.27 (m, 1 H), 2.78 (dd, *J* = 7.5, 12.8 Hz, 1 H), 2.86 (dd, *J* = 8.2, 16.5 Hz, 1 H), 3.09−3.20 (m, 1 H), 3.57 (s, 3 H), 3.75 (s, 3 H), 3.83 (s, 6 H), 3.85 (s, 3 H), 3.91 (s, 3 H), 4.02 (s, 3 H), 4.08 (t, *J* = 7.4 Hz, 1 H), 4.69 (br d, *J* = 9.6 Hz, 1 H, signal disappeared in the presence of D_2O), 4.83 (s, 2 H), 5.55 (dd, *J* = 7.4, 9.6 Hz, 1 H, signal simplified to a doublet in the presence of D_2O), 6.77 (s, 1 H), 7.11 (br s, 1 H), 7.22−7.47 (m, 12 H), 7.71−7.82 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 19.45 (s'), 26.97 (q'), 29.28 (t'), 31.33 (t'), 51.05 (d'), 53.24 (q'), 56.80 (q'), 57.48 (q'), 61.55 (q'), 61.76 (q'), 61.99 (q'), 63.09 (q'), 66.42 (t'), 73.19 (d'), 84.50 (s'), 98.29 (s'), 99.20 (d'), 110.15 (d'), 112.27 (s'), 115.57 (s'), 116.78 (s'), 117.82 (d'), 123.49 (s'), 125.62 (s'), 127.75 (d'), 128.16 (d'), 128.21 (d'), 129.69 (d'), 130.05 (s'), 131.31 (d'), 133.72 (d'), 135.07 (s'), 135.60 (d'), 137.29 (s'), 142.17 (s'), 150.16 (s'), 150.24 (s'), 150.42 (s'), 150.88 (s'), 152.84 (s'), 154.16 (s'), 154.26 (s'), 159.42 (s'); exact mass *m/z* calcd for $C_{55}H_{57}NO_9Si$ 903.3802, found 903.3804.

[3-[[[(1,1-Dimethylethyl)diphenylsilyl]oxy]methyl]-7,8-dihydro-1,9-dimethoxy-6*H*-cyclopent[*g*]isoquinolin-8-yl][1,4,5,6,8-pentamethoxy-3-(phenylethynyl)-2-naphthalenyl]methanone (54). Ph_3BiCO_3[26,39] (2.80 g, 5.62 mmol) was added to a vigorously stirred solution of alcohol **53** (1.45 g, 1.605 mmol) in a mixture of toluene (75 mL) and pyridine (5 mL). The mixture was heated at 80 °C under argon for 48 h (TLC control, silica, 7:13 EtOAc−hexane; two developments). The mixture was then filtered through a pad of silica (3 × 4 cm), using EtOAc. Evaporation of the filtrate and flash chromatography of the residue over silica gel (2.5 × 20 cm), using 3:7 EtOAc−hexane, gave pure (^{1}H NMR, 200 MHz; TLC, silica, 2:3 EtOAc−hexane) **54** (1.16 g, 80%) as a yellow foam. In another

(39) Preparation of triphenylbismuth dichloride: Wittig, G.; Clauss, K. *Justus Liebigs Ann. Chem.* **1952**, *578*, 136.

experiment, using a 24 h reaction period, the yield was 88%. Compound **54**: FTIR ($CHCl_3$, cast) 1702, 1635, 1599, 1572, 1357, 1344 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.16 (s, 9 H), 2.25–2.41 (m, 1 H), 2.61 (dd, J = 7.2, 12.4 Hz, 1 H), 2.95 (dd, J = 8.1, 16.0 Hz, 1 H), 3.18–3.30 (m, 1 H), 3.88 (s, 3 H), 3.89 (s, 3 H), 3.91 (s, 3 H), 4.03 (s, 3 H), 4.04 (s, 3 H), 4.05 (s, 6 H), 4.87 (s, 2 H), 5.26 (d, J = 9.0 Hz, 1 H), 6.82 (s, 1 H), 7.23–7.33 (m, 3 H), 7.33–7.41 (m, 10 H), 7.72–7.82 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 19.47 (s′), 26.99 (q′), 30.12 (t′), 32.23 (t′), 53.59 (d′), 56.42 (q′), 56.82 (q′), 56.97 (q′), 62.18 (q′), 62.29 (q′), 64.29 (q′), 66.47 (s′), 83.86 (s′), 97.66 (s′), 98.20 (d′), 110.35 (d′), 112.46 (s′), 113.76 (s′), 116.58 (s′), 117.67 (d′), 123.23 (s′), 126.71 (s′), 127.78 (d′), 128.21 (d′), 128.41 (d′), 129.71 (d′), 131.70 (d′), 131.92 (s′), 132.48 (s′), 133.71 (s′), 133.76 (s′), 135.64 (d′), 137.15 (s′), 142.62 (s′), 149.64 (s′), 150.12 (s′), 150.80 (s′), 151.46 (s′), 153.77 (s′), 154.36 (s′), 154.57 (s′), 159.55 (s′), 203.87 (s′); exact mass m/z calcd for $C_{55}H_{55}NO_9Si$ 902.36458, found 901.36595.

[3-[[[(1,1-Dimethylethyl)diphenylsilyl]oxy]methyl]-7,8-dihydro-1,9-dimethoxy-8-(phenylseleno)-6*H*-cyclopent[*g*]isoquinolin-8-yl]-[1,4,5,6,8-pentamethoxy-3-(phenylethynyl)-2-naphthalenyl]methanone (55). For this experiment, it is best to dry the starting ketone overnight under a diffusion pump vacuum. Our impression is that, if EtOAc is used for purification (flash chromatography) of the starting ketone, then the EtOAc is difficult to remove. Accordingly, we sometimes used 1:8 acetone–hexane for the chromatography. The first time this experiment is tried it should be done on a small scale (less than 100 mg of **54**).

BuLi (2.1 mL, 1.5 M in hexanes, 3.126 mmol) was added to a stirred and cooled (−78 °C) solution of *i*-Pr_2NH (480 μL, 3.428 mmol) in dry THF (15 mL). After about 15 min, a solution of ketone **54** (1.408 g, 1.563 mmol) in THF (15 mL) was injected over *ca.* 2 min to produce a brown solution. Stirring was continued for *ca.* 1 h and then more BuLi (1.05 mL, 1.56 mmol) was added. After a further 10 min at −78 °C, a precooled (−78 °C) solution of PhSeCl (1.496 g, 7.815 mmol) in dry THF (5.0 mL plus 1.0 mL as a rinse) was added by narrow cannula (under a positive pressure of argon) over *ca.* 1 min. The brown color faded rapidly. Saturated aqueous NH_4Cl (30 mL) was added *ca.* 5 min after the end of the addition, and the mixture was then shaken with EtOAc (100 mL). The aqueous phase was extracted with EtOAc (2 × 50 mL), and all the organic extracts were combined, washed with brine (1 × 50 mL), dried ($MgSO_4$), and evaporated, using a water bath at room temperature and a rotary evaporator fitted with a dry ice condenser. *It is most important to avoid warming the solution.* By having the rotating flask just splashed with water from the water bath, the evaporating solution is always below room temperature. Flash chromatography of the residue over silica gel (3 × 20 cm), using 3:7 EtOAc–hexane, and evaporation as just described gave pure (^1H NMR, 200 MHz; TLC, silica, 3:7 EtOAc–hexane) **55** (1.100 g, 70%) as a yellow foam. The flash chromatography should be done quickly, and delay between the various operations is best avoided. Yields ranged from 62% (100 mg of starting material) to 73% (600 mg of starting material). Compound **55**: FTIR ($CHCl_3$, cast) 1695, 1623, 1599, 1566, 1356, 1344 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.16 (s, 9 H), 2.46–2.58 (m, 1 H), 2.58–2.70 (m, 1 H), 2.77–2.88 (m, 1 H), 2.88–3.00 (m, 1 H), 3.56 (br s, 3 H), 3.60 (s, 3 H), 3.79 (s, 3 H), 3.88 (s, 3 H), 3.89 (s, 3 H), 3.95 (s, 3 H), 4.00 (s, 3 H), 4.80 (br s, 2 H), 6.69 (s, 1 H), 7.06–7.16 (m, 3 H), 7.18–7.35 (m, 5 H), 7.35–7.50 (m, 8 H), 7.55–7.61 (m, 2 H), 7.72–7.81 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 19.45 (s′), 26.98 (q′), 31.37 (t′), 38.69 (t′), 53.18 (q′), 56.68 (q′), 58.12 (q′), 61.99 (q′), 62.10 (q′), 63.17 (q′), 63.51 (q′), 66.42 (s′), 67.08 (s′), 84.91 (s′), 97.68 (s′), 100.29 (d′), 109.92 (d′), 112.31 (s′), 114.39 (s′), 116.52 (d′), 116.75 (s′), 123.69 (s′), 126.33 (s′), 127.76 (d′), 128.11 (d′), 128.22 (d′), 128.38 (d′), 128.72 (d′), 129.24 (s′), 129.74 (d′), 130.79 (s′), 131.82 (d′), 133.62 (s′), 133.66 (s′), 134.38 (s′), 135.61 (d′), 137.46 (s′), 137.73 (d′), 142.86 (s′), 149.01 (s′), 149.48 (s′), 150.92 (s′), 151.00 (s′), 153.65 (s′), 154.13 (s′), 155.43 (s′), 159.41 (s′), 202.14 (s′). We could not obtain a satisfactory mass spectrum.

3′-[[[(1,1-Dimethylethyl)diphenylsilyl]oxy]methyl]-6′,7′-dihydro-1′,4,5,6,8,9,9′-heptamethoxy-3-(phenylmethylene)spiro[2*H*-benz[*f*]-indene-2,8′-[8*H*]cyclopent[*g*]isoquinolin]-1(3*H*)-one (56). Ph_3SnH (2.0 mL, 7.83 mmol) was added to a stirred solution of phenylseleno ketone **55** (4.03 g, 3.80 mmol) in a mixture of dry PhH (160 mL) and hexane (37 mL; distilled without protection from the atmosphere) contained in an open round-bottomed flask. A solution of Et_3B in hexane (1.0 M, 3.8 mL) was added, and stirring at room temperature in the air was continued for 10 min (TLC control, silica, 1:2 EtOAc–hexane). The reaction mixture was then applied directly to the top of a flash chromatography column made up with silica gel (4 × 20 cm) and 1:3 EtOAc–hexane. Elution of the column with 1:3 EtOAc–hexane gave a solution of the desired product. The solution was evaporated to a small volume, the residue was dissolved in Et_2O (*ca.* 20 mL), and then hexane (*ca.* 20 mL) was added. The solution was allowed to stand at room temperature to afford **56** (1.65 g, 50%) as a pure (^1H NMR, 400 MHz) solid: mp 205–207 °C (from 1:1 Et_2O-hexane); FTIR (CH_2Cl_2, cast) 1708, 1625, 1596, 1569, 1363, 1342 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.17 (s, 9 H), 2.34–2.45 (m, 2 H), 2.55–2.66 (m, 1 H), 3.26–3.38 (m, 1 H), 3.46 (br s, 3 H), 3.90 (s, 3 H), 3.91 (s, 3 H), 3.96 (s, 3 H), 3.97 (s, 3 H), 4.02 (s, 3 H), 4.08 (s, 3 H), 4.83 (q, J = 15.0 Hz, 2 H), 6.76 (s, 1 H), 6.81 (br d, J = 7.0 Hz, 2 H), 6.96–7.10 (m, 3 H), 7.31–7.48 (m, 8 H), 7.73–7.82 (m, 4 H), 8.42 (s, 1 H); ^{13}C NMR (75.469 MHz, $CDCl_3$) δ 19.44 (t′), 26.98 (q′), 31.99 (t′), 36.04 (s′), 53.53 (q′), 56.65 (q′), 57.23 (q′), 60.71 (q′), 62.25 (q′), 62.35 (q′), 62.75 (q′), 64.35 (s′), 66.39 (t′), 97.20 (d′), 110.33 (d′), 112.23 (s′), 117.92 (s′), 118.22 (d′), 121.83 (s′), 126.53 (d′), 127.75 (d′), 129.10 (d′), 129.70 (d′), 129.91 (d′), 130.83 (s′), 133.55 (s′), 133.70 (s′), 135.61 (d′), 137.07 (s′), 137.52 (s′), 139.97 (s′), 142.06 (s′), 142.71 (s′), 147.81 (s′), 150.51 (s′), 150.68 (s′), 152.76 (s′), 152.99 (s′), 154.13 (s′), 156.85 (s′), 159.31 (s′), 204.64 (s′); mass (HRFAB) m/z calcd for $C_{55}H_{56}O_9NSi$ (M + 1) 902.37, found 902.52. Anal. Calcd for $C_{55}H_{55}O_9NSi$: C, 73.23; H, 6.15; N, 1.55. Found: C, 73.46; H, 6.22; N, 1.52.

We formed the impression that the radical cyclization product is unstable in CH_2Cl_2, if kept in this solvent for more than about 45 min.

3′-[[[(1,1-Dimethylethyl)diphenylsilyl]oxy]methyl]-6′,7′-dihydro-3-hydroxy-3-(hydroxyphenylmethyl)-1′,4,5,6,8,9,9′-heptamethoxyspiro-[2*H*-benz[*f*]indene-2,8′-[8*H*]cyclopent[*g*]isoquinolin]-1(3*H*)-one (57). The radical cyclization product **56** (one isomer, 440 mg, 0.489 mmol) was added to a freshly prepared solution of OsO_4 (879 mg, 3.425 mmol) in bench pyridine (50 mL), and the solution was stirred at room temperature for 4 h (TLC control was not very helpful because there is no change in R_f, but the spot representing the product is whitish when the plate is examined in UV light). The mixture was diluted with EtOAc (100 mL) and washed successively with saturated aqueous $NaHSO_3$ (1 × 50 mL), 2 N hydrochloric acid (2 × 100 mL), and brine (1 × 40 mL), dried (Na_2SO_4), and evaporated at room temperature. Flash chromatography of the residue over silica gel (3 × 20 cm), using 2:3 EtOAc–hexane, gave pure (^1H NMR, 400 MHz) **57** as a yellow glassy solid (435 mg, 95%), which was a single isomer.

The dihydroxylation must be done using an excess of OsO_4 so that reaction is complete quickly; the starting material decomposes during the reaction, and this can be a serious problem if the reaction is run under conditions (1–4 equiv of OsO_4) in which it takes appreciably more than 2 or 3 h.

Compound **57**: FTIR (CH_2Cl_2, cast) 3400, 1720, 1626, 1599, 1564, 1369, 1342 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.18 (s, 9 H), 2.39 (ddd, J = 2.7, 11.7, 20.3 Hz, 1 H), 2.62 (dd, J = 7.7, 12.0 Hz, 1 H), 2.94 (dd, J = 8.4, 15.8 Hz, 1 H), 3.42 (br s, 3 H), 3.54 (s, 3 H), 3.52–3.63 (m, 1 H), 3.81 (br s, 1 H, signal becomes smaller in the presence of D_2O), 3.97 (s, 3 H), 4.03 (s, 3 H), 4.04 (s, 3 H), 4.07 (s, 3 H), 4.13 (s, 3 H), 4.71 (d, J = 5.3 Hz, 1 H, signal collapses to a singlet in the presence of D_2O), 4.87 (q, J = 15.0 Hz, 2 H), 6.28 (d, J = 5.3 Hz, 1 H, exchanges in the presence of D_2O), 6.78 (s, 1 H), 7.01 (d, J = 7.1 Hz, 2 H), 7.10–7.22 (m, 3 H), 7.38–7.53 (m, 8 H), 7.75–7.82 (m, 4 H); ^{13}C NMR ($CDCl_3$, 100.614 MHz) δ 19.45 (t′), 26.98 (q′), 32.30 (t′), 41.91 (s′), 53.55 (q′), 56.61 (q′), 57.35 (q′), 62.64 (q′), 63.48 (q′), 63.76 (q′), 63.90 (q′), 66.35 (t′), 73.86 (s′), 76.13 (d′), 89.03 (s′), 97.29 (d′), 109.91 (d′), 111.55 (s′), 118.07 (s′), 118.57 (d′), 124.71 (s′), 127.21 (d′), 127.59 (d′), 127.79 (d′), 128.75 (s′), 129.74 (d′), 129.97 (s′), 133.59 (s′), 135.42 (s′), 135.62 (d′), 136.23 (s′), 140.06 (s′), 143.17 (s′), 148.84 (s′), 151.89 (s′), 152.51 (s′), 151.60 (s′), 153.01 (s′), 154.64 (s′), 157.01 (s′), 159.23 (s′), 198.20 (s′); mass (HRFAB) m/z calcd for $C_{55}H_{58}NO_{11}Si$ (M + 1) 936.3779, found 936.3734.

3′-[[[(1,1-Dimethylethyl)diphenylsilyl]oxy]methyl]-6′,7′-dihydro-1′,4,5,6,8,9,9′-heptamethoxyspiro[2*H*-benz[*f*]indene-2,8′-[8*H*]cyclopent[*g*]isoquinoline]-1,3-dione (31). Powdered anhydrous K_2CO_3 (46

mg, 0.336 mmol) and then, in one batch, $Pb(OAc)_4$ (75 mg, 0.168 mmol) were added to a stirred solution of diol **57** (157 mg, 0.168 mmol) in dry CH_2Cl_2 (10 mL). The mixture was stirred under argon for 30 min (TLC control, silica, 1:2 acetone−hexane), and a further portion of $Pb(OAc)_4$ (75 mg, 0.168 mmol) was added. After 10 min (TLC control, silica 1:2 acetone−hexane), the mixture was applied directly to a flash chromatography column made up with silica gel (1.5 × 15 cm) and acetone. Elution with acetone gave **31** (124 mg, 90%) as a pure (^{1}H NMR, 400 MHz) brownish yellow, glassy solid. The experiment can be done on a gram scale with a yield greater than 90%. An excess of $Pb(OAc)_4$ was needed because the reagent was not of high quality.

Compound **31**: FTIR (CH_2Cl_2, cast) 1735, 1703, 1626, 1596, 1572, 1358, 1340 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.16 (s, 9 H), 2.57 (t, J = 7.4 Hz, 2 H), 3.43 (dt, J = 3.6, 7.4 Hz, 2 H), 3.49 (s, 3 H), 3.90 (s, 3 H), 3.91 (s, 3 H), 4.05 (s, 3 H), 4.07 (s, 3 H), 4.08 (s, 3 H), 4.09 (s, 3 H), 4.81 (s, 2 H), 6.93 (s, 1 H), 7.33−7.46 (m, 7 H), 7.48 (s, 1 H), 7.74 (dd, J = 1.0, 8.0 Hz, 4 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 19.39 (s′), 26.92 (q′), 32.40 (t′), 36.28 (t′), 53.55 (q′), 56.59 (q′), 57.41 (q′), 62.26 (q′), 62.62 (q′), 63.10 (q′), 63.27 (q′), 66.29 (s′ or t′), 66.32 (t′ or s′), 99.87 (d′), 110.37 (d′), 112.00 (s′), 116.12 (d′), 121.18 (s′), 124.54 (s′), 127.73 (d′), 129.67 (d′), 131.10 (s′), 133.55 (s′), 135.07 (s′), 135.54 (d′), 139.40 (s′), 143.12 (s′), 150.24 (s′), 150.95 (s′), 151.23 (s′), 152.55 (s′), 153.67 (s′), 153.98 (s′), 156.89 (s′), 159.06 (s′), 199.23 (s′), 200.42 (s′); mass (HRFAB) m/z calcd for $C_{48}H_{50}NO_{10}Si$ (M + 1) 828.3203, found 828.3216.

6′,7′-Dihydro-3′-(hydroxymethyl)-1′,4,5,6,8,9,9′-heptamethoxyspiro-[2*H*-benz[*f*]indene-2,8′-[8*H*]cyclopent[*g*]isoquinoline]-1,3-dione (58). Bu_4NF (850 μL, 1.0 M solution in THF, 0.850 mmol) was added under argon to a stirred solution of spirodiketone **31** (630 mg, 760 mmol) in dry THF (24 mL). The solution darkened immediately. Stirring at room temperature was continued for 1 h (TLC control, silica, 3:1 EtOAc−hexane), and the mixture was then quenched with saturated aqueous NH_4Cl (*ca.* 40 mL). The mixture was extracted with EtOAc (3 × 40 mL), and the combined extracts were washed with brine (1 × 50 mL) and dried (Na_2SO_4). Evaporation of the solvent and flash chromatography of the residue over silica gel (2 × 30 cm), using 2:1 EtOAc−hexane, gave **58** (360 mg, 80%) as a pure (^{1}H NMR, 200 MHz) yellow foam. [The alcohol appears to be sensitive to silica, and the combined fractions from the chromatography should be carefully filtered to remove traces of silica before evaporation.] The material could be crystallized from MeOH to afford yellow crystals (208 mg): mp 150−152 °C; FTIR: (CH_2Cl_2, cast) 3500, 1729, 1701, 1625, 1595, 1572, 1358, 1344 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.57 (t, J = 7.4 Hz, 2 H), 3.08 (t, J = 5.1 Hz, 1 H, exchanges in the presence of D_2O), 3.41 (dt, J = 3.6, 7.4 Hz, 2 H), 3.49 (s, 3 H), 3.91 (s, 3 H), 4.03 (s, 3 H), 4.05 (s, 3 H), 4.06 (s, 3 H), 4.07 (s, 3 H), 4.08 (s, 3 H), 4.70 (d, J = 5.1 Hz, 2 H, signal collapses to a singlet in the presence of D_2O), 6.93 (s, 1 H), 7.09 (s, 1 H), 7.40 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100.614 MHz) δ 32.35 (t′), 36.18 (t′), 53.58 (q′), 56.52 (q′), 57.27 (q′), 62.20 (q′), 62.61 (q′), 63.05 (q′), 63.22 (q′), 64.36 (t′), 66.23 (s′), 99.65 (d′), 110.66 (d′), 112.07 (s′), 117.88 (d′), 121.02 (s′), 124.34 (s′), 127.54 (s′), 131.02 (s′), 135.32 (s′), 139.22 (s′), 142.86 (s′), 149.69 (s′), 150.57 (s′), 150.93 (s′), 152.44 (s′), 153.71 (s′), 154.00 (s′), 156.86 (s′), 159.42 (s′), 199.13 (s′), 200.33 (s′); exact mass m/z calcd for $C_{32}H_{31}NO_{10}$ 589.1938, found 589.1949.

1,3,6′,7′-Tetrahydro-1′,4,5,6,8,9,9′-heptamethoxy-1,3-dioxospiro-[2*H*-benz[*f*]indene-2,8′-[8*H*]cyclopent[*g*]isoquinoline]-3′-carboxaldehyde (59). MnO_2 (Aldrich, manganese(IV) oxide "activated", 3.60 g, 41.38 mmol) was added in one portion to a stirred solution of alcohol **58** (800 mg, 1.363 mmol) in bench Et_2O (300 mL). The suspension was stirred for 1 h at room temperature (TLC control, silica, 2:1 EtOAc−hexane). The mixture was filtered through a pad of silica gel (4 × 3 cm), and the pad was washed with EtOAc. The combined filtrates were evaporated at room temperature. Flash chromatography of the residue over silica gel (4 × 20 cm), using 1:1 EtOAc−hexane, gave **59** as a homogeneous (^{1}H NMR, 400 MHz), yellow foam (620 mg, 77%) that decomposes slightly on examination by TLC (silica, 2:1 EtOAc−hexane, the plate developed in two orthogonal directions). (The solution from the flash chromatography should be filtered to remove traces of silica gel, before evaporation.) A portion of the product, obtained in a different experiment but done in the same way, was crystallized from 10:1 MeOH−$CHCl_3$ (by dissolution in $CHCl_3$ followed by dilution with MeOH) to afford material that contained traces (^{1}H NMR, 400 MHz) of MeOH, removed by keeping the sample overnight under diffusion pump vacuum. Compound **59**: mp 182−184 °C; FTIR (CH_2Cl_2 cast) 1718, 1701, 1590, 1566, 1357, 1344 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.60 (t, J = 7.4 Hz, 2 H), 3.46 (ddt, J = 1.1, 3.5, 7.4 Hz, 2 H), 3.51 (s, 3 H), 3.91 (s, 3 H), 4.06 (s, 3 H), 4.07 (s, 3 H), 4.08 (s, 3 H), 4.09 (s, 3 H), 4.12 (s, 3 H), 6.94 (s, 1 H), 7.63 (br s, 1 H), 7.87 (s, 1 H), 10.02 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100.614 MHz) δ 32.35 (t′), 36.09 (t′), 53.90 (q′), 56.56 (q′), 57.29 (q′), 62.15 (q′), 62.84 (q′), 63.02 (q′), 63.20 (q′), 66.55 (s′), 99.93 (d′), 115.31 (s′), 117.96 (d′), 120.09 (s′), 121.07 (s′), 124.22 (s′), 127.41 (s′), 131.05 (s′), 139.19 (s′), 139.40 (s′), 141.31 (s′), 144.01 (s′), 151.07 (s′), 151.53 (s′), 152.71 (s′), 153.84 (s′), 154.16 (s′), 156.89 (s′), 160.25 (s′), 192.56 (d′), 198.48 (s′), 199.69 (s′); exact mass m/z calcd for $C_{32}H_{29}NO_{10}$ 587.1792, found 587.1786.

(*E*)-2-Butenylmethyldiphenylphosphonium Iodide (60).[30a] (a) BuLi (89 mL, 1.6 M in hexanes, 142.4 mmol) was added to a stirred and cooled (−78 °C) solution of commercial crotyl alcohol [*Z*:*E* = 95:5 (^{1}H NMR, 400 MHz)] (10.8 mL, 130 mmol) in dry Et_2O (100 mL). After 5 min, a white solid had precipitated and, at this stage, $(EtO)_2P(O)Cl$ (20.4 mL, 141.2 mmol) was added at a fast dropwise rate. The solid dissolved, the cold bath was removed, and stirring was continued overnight. At this stage another solid had precipitated. The mixture was washed with water (2 × 100 mL), and the organic phase was dried (Na_2SO_4) and evaporated. Distillation of the residue under water pump vacuum gave 2-butenyl diethyl phosphate (bp 117−120 °C) as a mixture [94:6 (^{1}H NMR, 200 MHz)] of isomers.

(b) A solution of Ph_2PLi [from Ph_2PCl (9 mL, 50 mmol) and Li (1.39 g, 200 mmol) in 50 mL of THF] was prepared.[40] This deep red solution is 1 M in the lithium salt. A portion of this solution (19.2 mL, 19.2 mmol) was added dropwise to a stirred and cooled (0 °C) solution of the above phosphate (4.0 g, 19.2 mmol) in THF (20 mL). The ice bath was removed and stirring was continued for 20 min. MeI (1.80 mL, 28.8 mmol) was then added at a fast dropwise rate. Stirring was continued for a further 40 min, by which stage a precipitate had formed. The solid was collected by filtration and dissolved in $CHCl_3$. Then Et_2O was added to precipitate phosphonium salt **60** (4.38 g, 59%) as a mixture [94:6 (^{1}H NMR, 400 MHz)] of isomers.

6′,7′-Dihydro-1′,4,5,6,8,9,9′-heptamethoxy-3′-(1,3-pentadienyl)-spiro[2*H*-benz[*f*]indene-2,8′-[8*H*]cyclopent[*g*]isoquinoline]-1,3-dione (61). The Wittig reaction was done a number of times, the reagent being generated from (a) crotyltriphenylphosphonium bromide[41] (*ca.* 5:1 mixture of isomers) and BuLi or (b) crotylmethyldiphenylphosphonium iodide **60** (*ca.* 15:1 mixture of isomers) and *t*-BuOK or $(Me_3Si)_2NK$ or BuLi. In each case, the product was obtained as an isomer mixture, usually two of the isomers making up about 90% of the material. The proportions of the isomers differed from run to run (of a particular procedure), and we suspect that the observed (^{1}H NMR, 400 MHz) ratio is sensitive to some or all of the following: the speed of workup, the extent of exposure to laboratory lighting, and the elapsed time between dissolution of the sample in $CDCl_3$ and measurement of the NMR spectrum. The following details represent our preferred procedure:

A solution of KHMDS (1.0 mL, 0.5 M solution in PhMe, 0.5 mmol) was added at a fast dropwise rate to a stirred and cooled (−78 °C) suspension of phosphonium iodide **60** (210 mg, 0,55 mmol) in THF (10 mL). Stirring was continued for 30 min after the addition, during which time the suspension took on a red-orange color. A portion (4.5 mL) of the resulting suspension was taken up into a syringe and added dropwise to a stirred and cooled (−78 °C) solution of aldehyde **59** (112 mg, 0.191 mmol) in THF (10 mL). Stirring was continued for 10 min after the addition, and the reaction was then quenched by addition of saturated aqueous NH_4Cl (25 mL) to the cold mixture. The mixture was extracted with EtOAc (2 × 35 mL), and the combined organic extracts were washed with brine (1 × 25 mL), dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel (2 × 15 cm) using first 1:2 EtOAc−hexane and then 1:1 EtOAc−

(40) Vedejs, E.; Fuchs, P. L. *J. Am. Chem. Soc.* **1973**, *95*, 822.
(41) Horner, L.; Hofer, W.; Ertel, I.; Kunz, H. *Chem. Ber.* **1983**, *116*, 2718.

hexane, gave pure (^{1}H NMR, 400 MHz; TLC, silica, 1:1 EtOAc–hexane) **61** as a yellow, glassy solid (113 mg, 88% after correction for the presence of EtOAc, as detected by ^{1}H NMR).

The compound should be used for the next step without delay, as it decomposes even when kept under oil pump vacuum with protection from light.

Compounds **61**: FTIR (CH_2Cl_2 cast); 1732, 1702, 1620, 1595, 1572, 1359, 1344 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.85 (d, J = 6.6 Hz, 2.52 H, major isomer) and 1.90 (dd, J = 1.5, 7.1 Hz, 0.48 H, minor isomer, 16% of total) (both signals together correspond to 3 H), 2.55 (t, J = 7.4 Hz, 2 H), 3.39 (dt, J = 3.0, 7.4 Hz, 2 H), 3.49 (s, 2.52 H, major isomer), 3.50 (s, 0.48 H, minor isomer), 3.91 (s, 3 H), 4.05 (s, 3 H), 4.06 (s, 6 H), 4.07 (s, 3 H), 4.08 (s, 3 H), 5.60–5.74 (m, 0.16 H, minor isomer), 5.94 (dq, J = 15.0, 6.6 Hz, 0.84 H, major isomer), 6.29 (dd, J = 15.0, 12.0 Hz, 1 H), 6.45 (d, J = 15.0 Hz, 0.84 H, major isomer), 6.54 (d, J = 15.0 Hz, 0.16 H, minor isomer), 6.93 (s, 1 H), 6.98 (s, 0.84 H, major isomer), 7.33 (dd, J = 15.0, 12.0, 0.84 H, major isomer), 7.35 (br s, 0.84 H, major isomer), 7.37 (br s, 0.16 H, minor isomer), 7.69 (dd, J = 15.0, 12.0 Hz, 0.16 H, minor isomer); ^{13}C NMR ($CDCl_3$, 100.614 MHz, (only signals for major isomer could be identified) δ 18.52 (q′), 32.38 (t′), 36.24 (t′), 53.40 (q′), 56.59 (q′), 57.41 (q′), 62.28 (q′), 62.65 (q′), 63.12 (q′), 63.29 (q′), 66.34 (s′), 99.79 (d′), 112.21 (s′), 113.68 (d′), 118.01 (d′), 121.17 (s′), 124.50 (s′), 127.70 (s′), 128.98 (d′), 131.10 (s′), 131.69 (d′), 131.82 (d′), 132.15 (d′), 135.28 (s′), 139.35 (s′), 143.13 (s′), 146.59 (s′), 150.32 (s′), 150.94 (s′), 152.73 (s′), 153.68 (s′), 154.00 (s′), 156.90 (s′), 158.95 (s′), 199.21 (s′), 200.42 (s′); exact mass m/z calcd for $C_{36}H_{35}NO_9$ 625.2313, found 625.2310.

***(E,E)*-6′,7′-Dihydro-4,5,6,8,9,9′-hexamethoxy-3-(1,3′-pentadienyl)-spiro[2*H*-benz[*f*]indene-2,8′-[8*H*]cyclopent[*g*]isoquinoline]-1,1′,3-(2′*H*)-trione (62).** Me_3SiCl (75 μL, 0.59 mmol) and NaI (20 mg, 0.133 mmol) were added to a stirred solution of **61** (45.6 mg, 0.073 mmol) in dry CH_2Cl_2 (6 mL) and dry MeCN (6 mL). Stirring under argon was continued at room temperature for 75 min (TLC control, silica, 3:1 EtOAc–hexane). [The reaction actually appeared to be over after 1 h.] The mixture was evaporated under water pump vacuum at room temperature, and flash chromatography of the residue over silica gel (1 × 15 cm), using 1:1 EtOAc–hexane (to remove iodine) and then 2:1 EtOAc–hexane, gave a brownish yellow material which was rechromatographed over silica gel (1 × 10 cm), using 1:1 EtOAc–hexane (to remove more iodine) and then 3:1 EtOAc–hexane. Appropriate fractions were evaporated under water pump vacuum without protection from laboratory lighting to afford **62** (34.2 mg) as a yellow solid, which was washed with 1:10 EtOAc–Et_2O to yield isomerically pure (^{1}H NMR, 400 MHz, DMF-d_7) **62** (27.0 mg, 61%). Although stable in the solid state, the compound undergoes slow isomerization in commercial $CDCl_3$ in the dark. In DMF-d_7, no detectable isomerization [^{1}H NMR, 400 MHz] occurs in the dark (48 h) but does occur (12 h) in the light (the isomer ratio is then 22:78). Compound **62**: FTIR (CH_2Cl_2, cast) 1736, 1704, 1641, 1615, 1598, 1358, 1346 cm^{-1}; ^{1}H NMR (DMF-d_7, 400 MHz) δ 1.82 (d, J = 6.8 Hz, 3 H), 2.52 (t, J = 7.5 Hz, 2 H), 3.31 (br t, J = 7.5 Hz, 2 H), 3.46 (s, 3 H), 3.86 (s, 3 H), 4.00 (s, 3 H), 4.02 (s, 3 H), 4.15 (s, 3 H), 4.16 (s, 3 H), 5.97 (dq, J = 15.0, 6.8 Hz, 1 H), 6.29 (dd, J = 10.3, 15.0 Hz, 1 H), 6.31 (d, J = 15.8 Hz, 1 H), 6.60 (s, 1 H), 7.29 (dd, J = 10.3, 15.8 Hz, 1 H), 7.33 (s, 2 H), 10.84 (br s, 1 H); ^{13}C NMR ($CDCl_3$, 100.614 MHz) δ 18.36 (q′), 32.72 (t′), 35.88 (t′), 56.63 (q′), 57.46 (q′), 62.32 (q′), 63.20 (q′), 63.37 (q′), 66.32 (s′), 99.87 (d′), 106.82 (d′), 116.94 (s′), 118.24 (d′), 121.22 (s′), 121.97 (d′), 124.57 (s′), 127.71 (s′), 130.87 (d′), 131.03 (d′), 131.11 (s′), 133.89 (d′), 135.78 (s′), 137.00 (s′), 139.42 (s′), 142.63 (s′), 150.98 (s′), 153.22 (s′), 153.68 (s′), 154.01 (s′), 156.53 (s′), 156.92 (s′), 161.53 (s′), 199.24 (s′), 200.51 (s′); exact mass m/z calcd for $C_{35}H_{33}NO_9$ 611.2155, found 611.2164.

(±)-Fredericamycin A (1). BBr_3 (150 μL, 1.75 M in CH_2Cl_2, 0.263 mmol) was added in one portion to a stirred and cooled (−78 °C) solution of **62** (10.8 mg, 0.0177 mmol) in dry CH_2Cl_2 (3.5 mL) under argon. The solution became deep red immediately. Stirring was continued for 1 h and the mixture was then quenched by addition of water (2 mL). The red color faded to yellow. The solvent was evaporated at room temperature, and the resulting aqueous mixture was diluted with 3:1 THF–water (60 mL). The mixture was stirred for 72 h open to air (and without protection from light), progress of the reaction being followed by UV measurements. Most of the THF was evaporated at room temperature under water pump vacuum. Water (20 mL) was added to the residue, and the mixture was extracted with 98:2 $CHCl_3$–AcOH (2 × 30 mL). The organic extract was dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1 × 15 cm), using 87:3:3 $CHCl_3$–MeOH–AcOH, and crystallization from 1:1:trace $CHCl_3$–MeOH–AcOH gave (±)-fredericamycin A as dark red crystals (6.1 mg, 64%) identical [^{1}H NMR (400 MHz), ^{13}C NMR (100.6 MHz), FABMS, TLC (silica gel, 87:3:3 $CHCl_3$–MeOH–AcOH), TLC (RP-18, 70:30:1 MeOH–water–AcOH)] with an authentic sample. [The crystallization was done as follows. Appropriate fractions from the flash chromatography were combined and evaporated almost to dryness. The material was dissolved in a small volume of 1:1:trace CH_2Cl_2–MeOH–AcOH to give a solution which was left on the bench to evaporate under a small current of argon. Dark red crystals were deposited and collected.]

Acknowledgment. We thank the Natural Sciences and Engineering Research Council of Canada for financial support. An NSERC Postdoctoral Fellowship (Y.J.W.), an Alberta Heritage Foundation for Medical Research Graduate Fellowship (S.M.B.), an FCAR (Quebec) Postdoctoral Fellowship (L.B.), an NSERC Summer Undergraduate Award (G.K.), and AHFMR Summer Undergraduate Awards (C.J.N. and S.R.R.) are gratefully acknowledged. We thank H. W. Manning (U. of A.) and Professor E. Vedejs for advice; M. Cantin, D. Lucyk,[2] N. Khazanovich,[2] F. Sartorelli,[2] and Dr. C. Lowe for assistance; and Dr. S. Forenza (Bristol-Myers Squibb) and Dr. M. Suffness (NIH) for samples of natural **1** and its potassium salt, respectively.

Supplementary Material Available: Text describing experimental procedures for the preparations of **8–11**, **13**, **14**, **16–18**, **21**, **22**, and **48** (21 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.