Synthesis of (±)-Calicheamicinone by Two Methods

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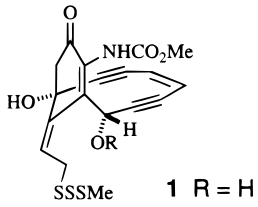
Abstract: Ketene acetal **25** was converted into silyl enol ether **20**, which underwent a Diels−Alder reaction with methyl (*E*)-3-nitropropenoate to afford ketone **27**. This was converted by two routes into (±)-calicheamicinone (**1**). In the first, modification of the nitro, ester, and allyl substituents gave ketone **38**, which reacted stereoselectively with cerium trimethylsilylacetylide to place the acetylene unit syn to the nitrogen function (**38** → **39**). Further elaboration took the route as far as aldehyde **42**. A slightly different series of reactions served to convert ketone **27** into tricyclic ketone **43**. This also reacted with cerium trimethylsilylacetylide, but in the opposite stereochemical sense to **38**, so as to place the acetylene unit anti to the nitrogen function (**43** → **50**). Further elaboration took this second route as far as lactone **44**. Both **42** and **44** serve as advanced intermediates for the synthesis of (±)-calicheamicinone. The monoacetylenic aldehyde **42** reacted stereoselectively with cerium trimethylsilylacetylide to give the bis(acetylene) **53** as the major product. This was elaborated into lactone **60**, which was desaturated (**60** → **68**) and methoxycarbonylated on nitrogen. The acetylenic silyl groups were then removed, so as to generate syn bis(acetylene) **72**, and the terminal acetylenic hydrogens were replaced by iodine. The resulting diiodide **81** formed the cyclic enediyne **82** on reaction with (*Z*)-1,2-bis(trimethylstannyl)ethene in the presence of $(Ph_3P)_4Pd$, and the enediyne was converted into (±)-calicheamicinone. *syn*-Bis(acetylene) **72** was also synthesized from the other advanced intermediate (lactone **44**), using, as a key step, free radical bromination of the derived unsaturated lactone **77**. The resulting bromo lactones **78** were converted into an aldehyde ester **79**, and this reacted stereoselectively with cerium trimethylsilylacetylide to give **80**, convertible by the action of TBAF into **72**.

Introduction

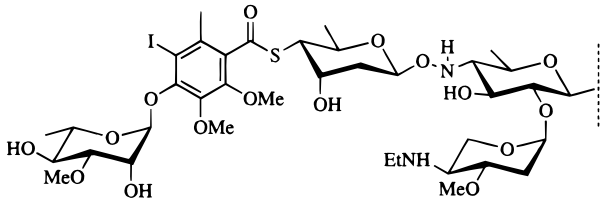
In this paper, we describe full details[1] of two related methods for the synthesis of (±)-calicheamicinone (**1**),[2] the aglycon (in racemic form) of the antitumor antibiotic calicheamicin γ_1^I (**2**).[3−5]

Compounds **1** and **2** have attracted an exceptional degree of interest, not only because they represent very difficult synthetic targets but also because they pose fascinating and important biochemical questions concerning the mode of action of enediyne antitumor agents.[6]



1 R = H

2 R =



The chemistry and biological properties of calicheamicin γ_1^I have been reviewed extensively,[6] the essential details being that calicheamicin γ_1^I has extremely potent anticancer activity[7,8] and that the mode of action involves binding in the minor groove

(1) Preliminary communication: Clive, D. L. J.; Bo, Y.; Tao, Y.; Daigneault, S.; Wu, Y.-J.; Meignan, G. *J. Am. Chem. Soc*. **1996**, *118*, 4904.

(2) (a) Synthesis of (±)-calicheamicinone: Haseltine, J. N.; Paz Cabal, M.; Mantlo, N. B.; Iwasawa, N.; Yamashita, D. S.; Coleman, R. S.; Danishefsky, S. J.; Schulte, G. K. *J. Am. Chem. Soc*. **1991**, *113*, 3850. (b) Synthesis of (−)-calicheamicinone: Smith, A. L.; Pitsinos, E. N.; Hwang, C.-K.; Mizuno, Y.; Saimoto, H.; Scarlato, G. R.; Suzuki, T.; Nicolaou, K. C. *J. Am. Chem. Soc*. **1993**, *115*, 7612. (c) Aiyer, J.; Hitchcock, S. A.; Denhart, D.; Liu, K. K.-C.; Danishefsky, S. J.; Crothers, D. M. *Angew. Chem., Int. Ed. Engl*. **1994**, *33*, 855.

(3) Nonsystematic numbering is used in this manuscript, except for chemical names in the Experimental Section.

(4) (a) Structure determination: Lee, M. D.; Dunne, T. S.; Chang, C. C.; Siegel, M. M.; Morton, G. O.; Ellestad, G. A.; McGahren, W. J.; Borders, D. B. *J. Am. Chem. Soc*. **1992**, *114*, 985. (b) For a related compound (namenamicin) reported recently that also shows powerful antitumor and antimicrobial activity, see: McDonald, L. A.; Capson, T. L.; Krishnamurthy, G.; Ding, W.-D.; Ellestad, G. A.; Bernan, V. S.; Maiese, W. M.; Lassota, P.; Discafani, C.; Kramer, R. A.; Ireland, C. M. *J. Am. Chem. Soc*. **1996**, *118*, 10898.

(5) The corresponding disulfide has also been isolated: (a) Ellestad, G. A.; Hamann, P. R.; Zein, N.; Morton, G. O.; Siegel, M. M.; Pastel, M.; Borders, D. B.; McGahren, W. J. *Tetrahedron Lett*. **1989**, *30*, 3033. (b) McGahren, W. J.; Ding, W.-D.; Ellestad, G. A. In *Enediyne Antibiotics as Antitumor Agents*; Borders, D. B., Doyle, T. W., Eds.; Dekker: New York, 1995; p 75.

(6) Reviews on the chemistry and biology of enediyne anticancer antibiotics and model systems: (a) Lee, M. D.; Ellestad, G. A.; Borders, D. B. *Acc. Chem. Res*. **1991**, *24*, 235. (b) Nicolaou, K. C.; Dai, W.-M. *Angew. Chem., Int. Ed. Engl*. **1991**, *30*, 1387. (c) Nicolaou, K. C.; Smith, A. L. *Acc. Chem. Res*. **1992**, *25*, 497. (d) Nicolaou, K. C.; Smith, A. L.; Yue, E. W. *Proc. Natl. Acad. Sci. U.S.A*. **1993**, *90*, 5881. (e) Murphy, J. A.; Griffiths, J. *Nat. Prod. Rep*. **1993**, *10*, 551. (f) Weymouth-Wilson, A. C. *Nat. Prod. Rep*. **1997**, *14*, 99.

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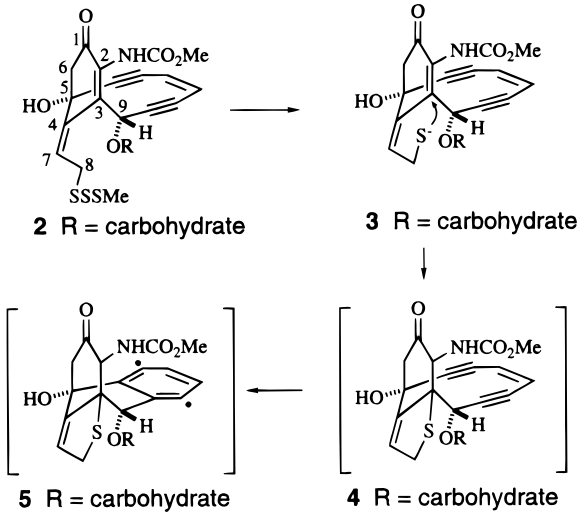
Scheme 1



of DNA[9] followed by activation of the enediyne portion so as to afford a highly reactive biradical. This, in turn, initiates cleavage of both DNA strands. The recognition process[6a,e,10]—certain sequences are preferentially cleaved—is effected largely[10a−d] by the aryl carbohydrate segment. Activation (Scheme 1) involves cleavage of the trisulfide (**2** → **3**) followed by intramolecular Michael addition (**3** → **4**).[11] Once that addition has taken place and C(3) (nonsystematic numbering) becomes sp^3 hybridized, Bergman cyclization[11,12] occurs, and the resulting biradical **5** abstracts hydrogen[6a,e,10e−g] from both strands of the DNA sugar backbone, leading to DNA cleavage. Each of these steps has been scrutinized carefully, and a detailed picture has emerged. Many of the mechanistic features are shared by other enediyne antitumor agents, and the mode of activation (though not the sequence selectivity[13] or propensity to cause *double* strand cleavage[14]) of the closely related esperamicins[15] is likely to be similar.

As a synthetic target, calicheamicin γ_1^I represents an especially large number of complex problems that are inherent not only in the construction of the sensitive enediyne segment and the unusual tetrasaccharide but also in the linking of both of these substructures, or portions of them, in a way that preserves their integrity during the remaining steps of the synthesis. We have dealt with the first of these tasks—the synthesis of the aglycon.

During the course of our work, two syntheses[2] of calicheamicinone, and of calicheamicin γ_1^I itself,[16] were completed by the research teams led by Danishefsky and by Nicolaou, but the routes to the enediyne section in each of these remarkable syntheses were so very different from the one we were exploring that it was appropriate to continue our studies.

Results and Discussion

Development of the Synthetic Plan. Although no synthesis of calicheamicinone had been reported when we began,[17] a number of papers had appeared that dealt with the most conspicuous features of the molecule: the allylic trisulfide and the cyclic enediyne. Published model studies[18] on the enediyne emphasized the difficulties in constructing such a unit and prompted us to take appropriate precautions in the form of unusually extensive backup plans.

The properties of allylic trisulfides[19] had received little attention, but we were greatly helped by the pioneering studies of Magnus and his collaborators on the synthesis and thermal

(7) (a) Against murine tumors the optimum dose is 0.5−1.5 mg/kg Thomas, J. P.; Carvagal, S. G.; Lindsay, H. L.; Citarella, R. V.; Wallace, R. E.; Lee, M. D.; Durr, F. E. *Program and Abstracts*, 26th Interscience Conference on Antimicrobial Agents and Chemotherapy, New Orleans, LA, Sept 1986; American Society for Microbiology: Washington, DC.; 1986; Abstr. 229 (quoted in Lee, M. D.; Dunne, T. S.; Siegel, M. M.; Chang, C. C.; Morton, G. O.; Borders, D. B. *J. Am. Chem. Soc*. **1987**, *109*, 3464). (b) Measurement of cytotoxic activity against numerous cancer cell lines gave IC_{50} values in the nanomolar range: Nicolaou, K. C.; Li, T.; Nakada, M.; Hummel, C. W.; Hiatt, A.; Wrasidlo, W. *Angew. Chem., Int. Ed. Engl*. **1994**, *33*, 183.

(8) For measurements of its antimicrobial activity, see ref 4b.

(9) NMR studies of the binding: (a) Walker, S.; Murnick, J.; Kahne, D. *J. Am. Chem. Soc*. **1993**, *115*, 7954. (b) Walker, S. L.; Andreotti, A. H.; Kahne, D. E. *Tetrahedron* **1994**, *50*, 1351. (c) Cf. Paloma, L. G.; Smith, J. A.; Chazin, W. J.; Nicolaou, K. C. *J. Am. Chem. Soc*. **1994**, *116*, 3697. (d) Zein, N.; McGahren, W. J.; Morton, G. O.; Ashcroft, J.; Ellestad, G. A. *J. Am. Chem. Soc*. **1989**, *111*, 6888.

(10) (a) Drak, J.; Iwasawa, N.; Danishefsky, S.; Crothers, D. M. *Proc. Natl. Acad. Sci. U.S.A.* **1991**, *88*, 7464. (b) Nicolaou, K. C.; Tsay, S.-C.; Suzuki, T.; Joyce, G. F. *J. Am. Chem. Soc*. **1992**, *114*, 7555. (c) Li, T.; Zeng, Z.; Estevez, V. A.; Baldenius, K. U.; Nicolaou, K. C.; Joyce, G. F. *J. Am. Chem. Soc*. **1994**, *116*, 3709. (d) Ikemoto, N.; Kumar, R. A.; Ling, T.-T.; Ellestad, G. A.; Danishefsky, S. J.; Patel, D. J. *Proc. Natl. Acad. Sci. U.S.A.* **1995**, *92*, 10506. (e) Zein, N.; Sinha, A. M.; McGahren, W. J.; Ellestad, G. A. *Science* **1988**, *240*, 1198. (f) Cf. De Voss, J. J.; Townsend, C. A.; Ding, W.-D.; Morton, G. O.; Ellestad, G. A.; Zein, N.; Tabor, A. B.; Schreiber, S. L. *J. Am. Chem. Soc*. **1990**, *112*, 9669. (g) Hangeland, J. J.; De Voss, J. J.; Heath, J. A.; Townsend, C. A.; Ding, W.-d.; Ashcroft, J. S.; Ellestad, G. A. *J. Am. Chem. Soc*. **1992**, *114*, 9200. See Supporting Information for additional references.

(11) (a) Lee, M. D.; Dunne, T. S.; Chang, C. C.; Ellestad, G. A.; Siegel, M. M.; Morton, G. O.; McGahren, W. J.; Borders, D. B. *J. Am. Chem. Soc*. **1987**, *109*, 3466. (b) For studies of the Bergman mechanism in model compounds, see: Magnus, P.; Carter, P. A. *J. Am. Chem. Soc*. **1988**, *110*, 1626. (c) Stability of model enediynes: Nicolaou, K. C.; Zuccarello, G.; Ogawa, Y.; Schweiger, E. J.; Kumazawa, T. *J. Am. Chem. Soc*. **1988**, *110*, 4866. (d) Magnus, P.; Lewis, R. T.; Huffman, J. C. *J. Am. Chem. Soc*. **1988**, *110*, 6921. (e) In vitro NMR studies of the activation mechanism: De Voss, J. J.; Hangeland, J. J.; Townsend, C. A. *J. Am. Chem. Soc*. **1990**, *112*, 4554. (f) Chatterjee, M.; Cramer, K. D.; Townsend, C. A. *J. Am. Chem. Soc*. **1993**, *115*, 3374. (g) Cf. Myers, A. G.; Cohen, S. B.; Kwon, B. M. *J. Am. Chem. Soc*. **1994**, *116*, 1255. (h) Chatterjee, M.; Smith, P. J.; Townsend, C. A. *J. Am. Chem. Soc*. **1996**, *118*, 1938. (i) Theoretical treatment of trisulfide cleavage: Mulhearn, D. C.; Bachrach, S. M. *J. Am. Chem. Soc*. **1996**, *118*, 9415.

(12) Bergman, R. G. *Acc. Chem. Res*. **1973**, *6*, 25. See the Supporting Information for additional references.

(13) (a) Sugiura, Y.; Takahashi, Y.; Uesawa, Y.; Kuwahara, J. *Nucleic Acids Symp. Ser*. **1988**, *20*, 63. (b) Long, B. H.; Golik, J.; Forenza, S.; Ward, B.; Rehfuss, R.; Dabrowaik, J. C.; Catino, J. J.; Musial, S. T.; Brookshire, K. W.; Doyle, T. W. *Proc. Natl. Acad. Sci. U.S.A.* **1989**, *86*, 2. (c) Sugiura, Y.; Uesawa, Y.; Takahashi, Y.; Kuwahara, J.; Golik, J.; Doyle, T. W. *Proc. Natl. Acad. Sci. U.S.A.* **1989**, *86*, 7672. (d) Christner, D. F.; Frank, B. L.; Kozarich, J. W.; Stubbe, J.; Golik, J.; Doyle, T. W.; Rosenberg, I. E.; Krishnan, B. *J. Am. Chem. Soc*. **1992**, *114*, 8763. (e) Esperamicin−DNA NMR studies: Ikemoto, N.; Kumar, R. A.; Dedon, P. C.; Danishefsky, S. J.; Patel, D. J. *J. Am. Chem. Soc*. **1994**, *116*, 9387. (f) Langley, D. R.; Golik, J.; Krishnan, B.; Doyle, T. W.; Beveridge, D. L. *J. Am. Chem. Soc*. **1994**, *116*, 15.

(14) Esperamicin A_1 causes single strand cleavage (see ref 13b−d).

(15) Golik, J.; Dubay, G.; Groenewold, G.; Kawaguchi, H.; Konishi, M.; Krishnan, B.; Ohkuma, H.; Saitoh, K.; Doyle, T. W. *J. Am. Chem. Soc*. **1987**, *109*, 3462.

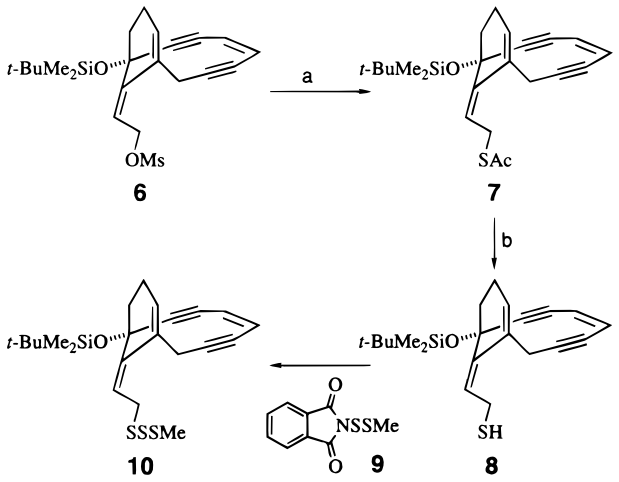
(16) (a) Nicolaou, K. C.; Hummel, C. W.; Nakada, M.; Shibayama, K.; Pitsinos, E. N.; Saimoto, H.; Mizuno, Y.; Baldenius, K.-U.; Smith, A. L. *J. Am. Chem. Soc*. **1993**, *115*, 7625. (b) Hitchcock, S. A.; Chu-Moyer, M. Y.; Boyer, S. H.; Olson, S. H.; Danishefsky, S. J. *J. Am. Chem. Soc*. **1995**, *117*, 5750.

(17) Taken in part from the Ph.D. Thesis (April 1991) of S.D.

(18) Reviews: (a) Lhermitte, H.; Grierson, D. S. *Contemp. Org. Synth*. **1996**, *3*, 41. (b) Review: Lhermitte, H.; Grierson, D. S. *Contemp. Org. Synth*. **1996**, *3*, 93. See the Supporting Information for additional references.

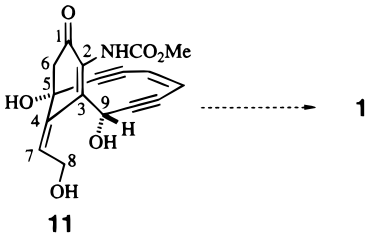
(19) Reviews on polysulfides: (a) Harpp, D. N. *Perspectives in the Organic Chemistry of Sulfur*; Zwanenburg, B., Klunder, A. J. H., Eds.; Studies in Organic Chemistry 28; Elsevier: Amsterdam, 1987. (b) Kutney, G. W.; Turnbull, K. *Chem. Rev*. **1982**, *82*, 333. Diallyl trisulfide: (c) Ariga, T.; Oshiba, S.; Tamada, T. *Lancet* **1981**, *1*, 150. Synthetic methods for trisulfides: (d) Harpp, D. N.; Ash, D. K. *Int. J. Sulfur Chem. Part A* **1971**, *1*, 57. (e) Cf. Sullivan, A. B.; Boustany, K. *Int. J. Sulfur Chem. Part A* **1971**, *1*, 207. (f) Cf. Harpp, D. N.; Ash, D. K. *Int. J. Sulfur Chem. Part A* **1971**, *1*, 211. (g) Mott, A. W.; Barany, G. *Synthesis* **1984**, 657. (h) Derbesy, G.; Harpp, D. N. *Tetrahedron Lett*. **1994**, *35*, 5381.

Scheme 2[a]



[a] Key: (a) AcSNa; (b) $LiAlH_4$.

Scheme 3

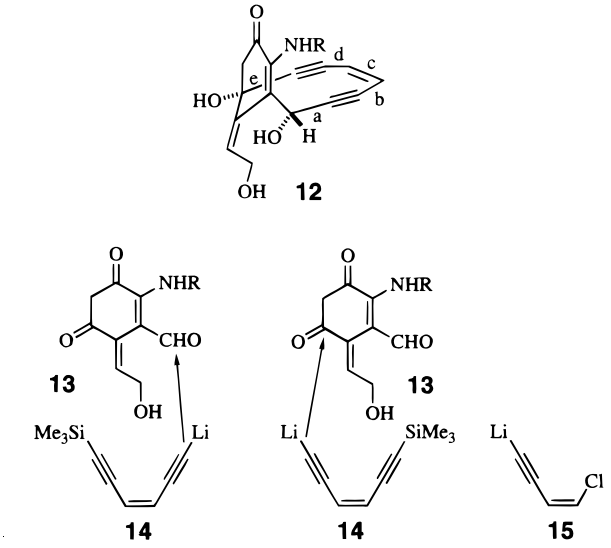


stability of such compounds. Particularly valuable guidance was provided by the transformations summarized in Scheme 2.[20] The mesylate **6** was subjected to nucleophilic displacement using AcSNa, and then hydride reduction afforded the free thiol **8**. This reacted with the phthalimido disulfide **9** to give the desired allylic trisulfide (**8** → **10**). A number of other allylic trisulfides were prepared, and their thermal stability was examined; some of them can survive heating (85−110 °C) in toluene, which suggested that calicheamicinone might best be synthesized by way of allylic alcohol **11** (Scheme 3), at least in approximate terms, since the need for protecting groups is totally ignored in Scheme 3. The most appropriate stage at which to elaborate the alcohol into the trisulfide would be decided once it became clear what protecting groups still had to be removed after the trisulfide was in place.

As far as the cyclic enediyne was concerned, the most obvious point, in view of the mode of action of calicheamicinone, was that the enediyne should not be assembled in a structure in which C(3) (see **11**) is sp^3 hybridized, as an otherwise premature Bergman rearrangement would be likely to occur. But apart from that, it was not very clear[21] what type of relevant structures could accommodate the enediyne,[11c] and so we decided to assemble it at a stage that seemed convenient on the basis of other considerations. We would then find out if the compounds were stable enough for further elaboration.

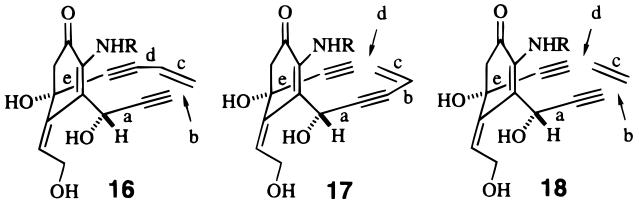
Our plan was to generate the enediyne late in the synthesis by building it onto a substructure that already had most of the remaining features present in the final target, and it seemed clear that this might be accomplished in a number of ways, depending

Scheme 4[a]



[a] Key: R = unspecified group.

Scheme 5[a]



[a] Key: R = unspecified group.

on the choice of a ring-closing step. For example, if bonds a or e (see **12**, Scheme 4) are made last to close the ring, then the enediyne could be introduced in one segment (e.g., as in **14**) by reaction at the aldehyde or ketone carbonyl of compounds synthetically equivalent to the hypothetical structure **13**. A prefabricated enediyne would not be essential as a smaller acetylide, such as **15**, might serve equally well, although, in that case, the product would have to be coupled with a two-carbon unit.

If bonds b or d are made last (Scheme 5, see structures **16** and **17**), then the two-carbon and four-carbon acetylenic components could be introduced individually, or introduced while they are joined together by a removable or modifiable tether. There was also the possibility of making bonds b and d sequentially in the same reaction (cf. **18**), and ultimately, this was the procedure we used.

Last of all, we considered ways of forming bond c as the ring-closing step, and we intended to rely for that purpose on some type of dicarbonyl coupling (Scheme 6) such as a McMurry reaction (path A), a pinacol coupling (path B), or a double extrusion[22] (path C). One particular advantage of forming the enediyne at a late stage, along the lines we had in mind, was that if one approach did not work then others would be available without the need for redesigning the whole route. This range of opportunities reassured us that what we suspected might be a very difficult part of the synthesis could be tackled in a number of ways.

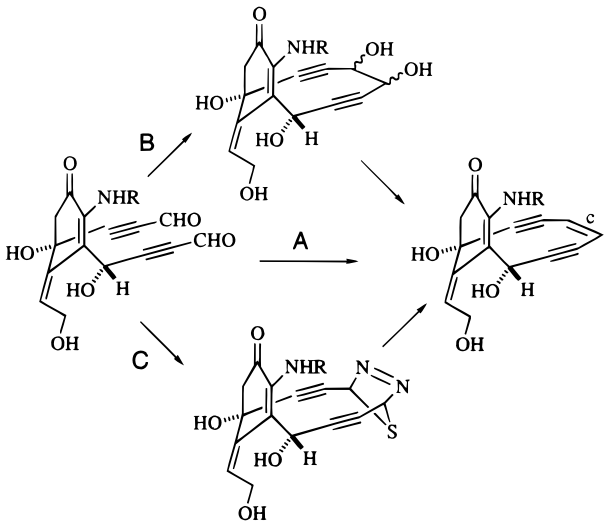
At this stage of the planning there remained the question of how to control the stereochemistry of the C(4)═C(7) double bond, and it seemed most sensible to form that bond within a

(20) Magnus, P.; Lewis, R. T.; Bennett, F. *J. Chem. Soc., Chem. Commun.* **1989**, 916, and references therein.

(21) For an early demonstration with a model compound of thermal sensitivity as a function of the state of hybridization of C(3) (present numbering system), see: (a) Magnus, P.; Lewis, R. T. *Tetrahedron Lett.* **1989**, *30*, 1905. (b) For a counter example, see ref 11d.

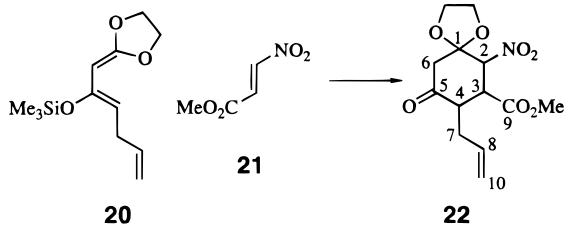
(22) Cf. Back, T. G.; Barton, D. H. R.; Britten-Kelly, M. R.; Guziec, F. S. *J. Chem. Soc., Perkin Trans 1* **1976**, 2079, and references therein.

Scheme 6[a]

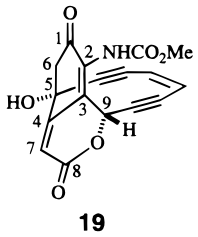


[a] Key: R = unspecified group.

Scheme 7



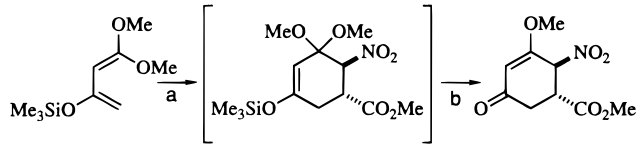
six-membered ring so that only the required geometry was possible. On the basis of this argument, therefore, the preliminary target **11** was changed to a compound of type **19** where, again, the need for protecting groups was ignored.



With the above considerations as background, it was clear that a highly functionalized six-membered ring with suitably disposed carbonyl groups for acetylide attachment and a chain to provide C(7) and C(8) of the target was required. We considered several possibilities that might correspond to the hypothetical structure **13**, and after a good deal of exploratory work,[23] we settled on a compound of structure **22** (see Scheme 7), as representing the essential features implied by **13**.

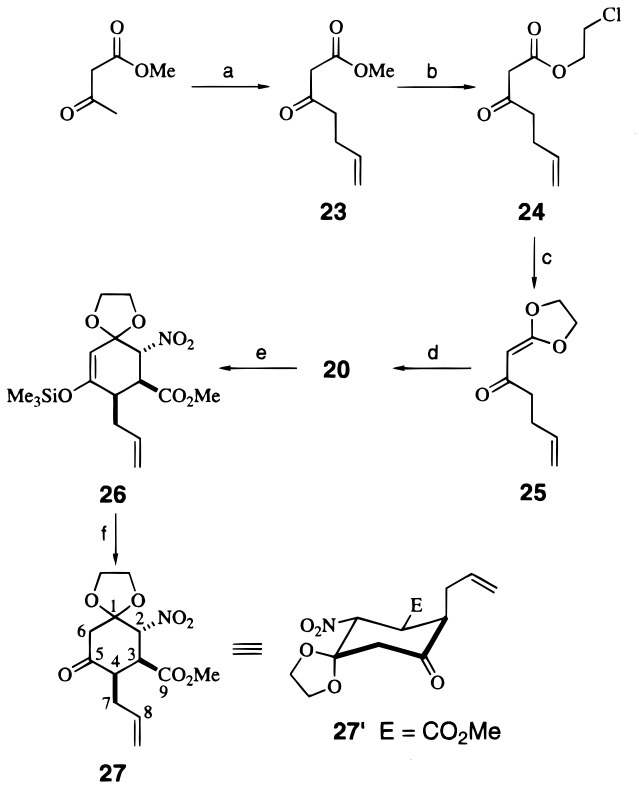
We felt that **22** should be accessible by a Diels−Alder reaction between the ketene acetal silyl enol ether **20** and methyl (*E*)-2-nitropropenoate[24,25] (**21**). The use of a *cyclic* acetal was based on the expectation that it would afford greater protection than an acyclic acetal against aromatization because expulsion of one of the acetal oxygens from **22** (in the presence of acid or base) would be more easily reversible than with, for example, a dimethyl acetal.

Scheme 8[a]



[a] Key: (a) methyl (*E*)-2-nitropropenoate; (b) H_3O^+, 82%.

Scheme 9[a]



[a] Key: (a) NaH, BuLi, THF; allyl bromide; 80%; (b) 2-chloroethanol, Ti(O-*i*-Pr)$_4$; 63%; (c) K_2CO_3, DMF; 80%; (d) $(Me_2PhSi)_2NLi$, Me_3SiCl, THF, −78 °C; (e) methyl (*E*)-2-nitropropenoate (**21**), THF; (f) aq NH_4Cl; 56% from **25**.

Scheme 7 summarizes this plan, which was quickly recognized as a worthwhile approach because it could build upon the background information available in the literature. A few cases had been reported in which **21** was used in Diels−Alder reactions, and one paper in particular[25a] was encouraging because it showed (see Scheme 8) that the regiochemistry is controlled by the nitro group, exactly in the sense we had hoped.

The use of ketene acetal silyl enol ether **20** also requires some comment. A few simpler compounds of this type had been described[26] before, and some guidance was available, therefore, for developing a route to our particular example.

Synthesis of the First Key Intermediate (27) by a Diels−Alder reaction. To put the ideas of Scheme 7 into practice, we first prepared the β-keto ester **23** (Scheme 9), which is a known substance,[27] easily made on a large scale by the allylation

(23) For exploratory studies involving radical cyclization, see the Supporting Information.

(24) (a) Shechter, H.; Conrad, F.; Daulton, A. L.; Kaplan, R. B. *J. Am. Chem. Soc*. **1952**, *74*, 3052. (b) Cf. McMurry, J. E.; Musser, J. H. *Org. Synth*. **1977**, *56*, 65. (c) Cf. McMurry, J. E.; Musser, J. H.; Fleming, I.; Fortunak, J.; Nübling, C. *Organic Syntheses*; Wiley & Sons: New York, 1988: Collect. Vol. VI, p 799.

(25) Cf. (a) Danishefsky, S.; Prisbylla, M. P.; Hiner, S. *J. Am. Chem. Soc*. **1978**, *100*, 2918. (b) Danishefsky, S. *Acc. Chem. Res*. **1981**, *14*, 400.

(26) Cf. (a) Banville, J.; Brassard, P. *J. Chem. Soc., Perkin Trans. 1* **1976**, 1852. (b) Broadhurst, M. D. *J. Org. Chem*. **1985**, *50*, 1117. (c) Eid, C. N., Jr.; Konopelski, J. P. *Tetrahedron* **1991**, *47*, 975. (d) Konopelski, J. P.; Kasar, R. A. *Tetrahedron Lett*. **1993**, *34*, 4587.

(27) Huckin, S. N.; Weiler, L. *J. Am. Chem. Soc.* **1974**, *96*, 1082.

of doubly deprotonated methyl acetoacetate. Next, ester exchange with 2-chloroethanol under standard conditions of titanium catalysis[28] gave the chloroethyl ester **24**, and this could be cyclized to acyl ketene acetal **25** by treatment[26b] with potassium carbonate. Surprisingly, attempts to effect cyclization with sodium hydride were unsuccessful.

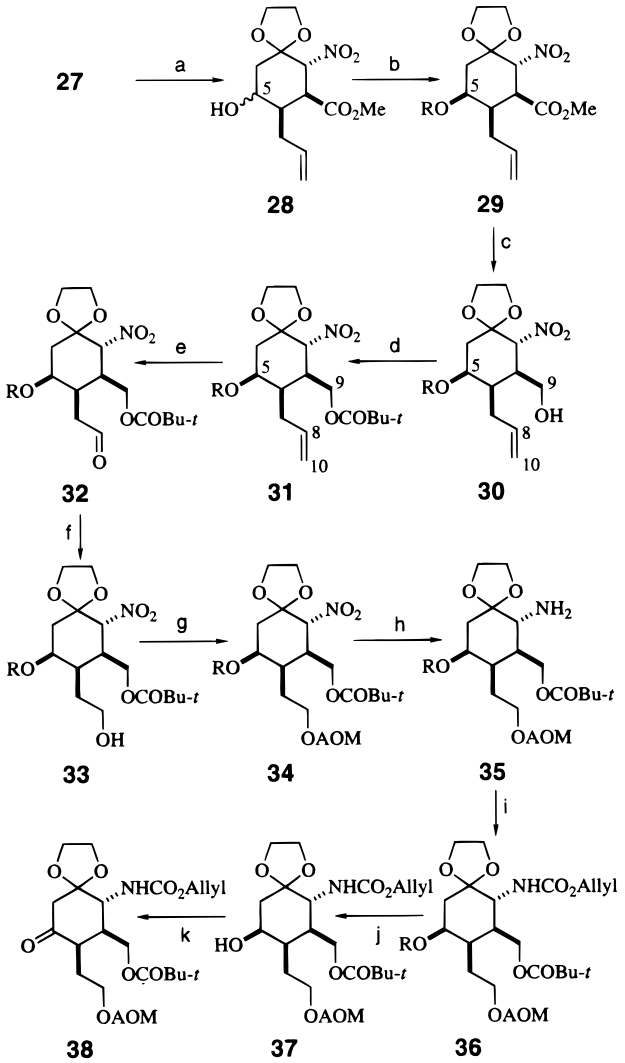
With the acyl ketene acetal in hand, the next task was to convert it into a silyl enol ether, preferably with *Z* geometry (as shown in structure **20**) because the *E* isomer would be less reactive in Diels−Alder cycloadditions. Deprotonation of **25** with LDA, followed by trapping with chlorotrimethylsilane, gave a 3:7 mixture of the *Z* and *E* isomers.[29] The use of lithium hexamethyldisilazide improved the ratio (3:2 in favor of the *Z* isomer) but, with an even more hindered base [$(Me_2PhSi)_2NLi$[31]], the desired *Z* enol ether **20** was formed in great preponderance, and perhaps exclusively. Compound **20** can be made on a large scale (ca. 40 g of starting material), but it is rather sensitive, and attempts to isolate it by distillation (ca. 0.001 mmHg) caused extensive decomposition. Fortunately, the compound can be used in situ because the hindered base that is present [$(Me_2PhSi)_2NH$] does not react with our dienophile. Addition of methyl (*E*)-2-nitropropenoate (**21**) to a solution of freshly generated silyl enol ether **20** (Scheme 9) gave the adduct **27**,[32] after mild acid hydrolysis, as a crystalline compound in 56% overall yield from the ketene acetal **25**.

Ketone **27** is a key intermediate in the synthesis of calicheamicinone. Its structure and stereochemistry could be deduced from the ^{1}H NMR spectrum, and the interpretation was confirmed by X-ray methods;[33] the shape of the molecule is as shown in structure **27′**. The ketone was the starting point for a very large number of exploratory experiments, and after a considerable effort, we learned how to take it forward to calicheamicinone by two routes.

The first tasks were to protect the C(5) carbonyl and to modify the ester. We decided to protect the ketone by reduction, and it was quickly found that this could be accomplished in high yield, but only at the expense of good stereoselectivity. Treatment with sodium borohydride gave a 2:1 mixture of C(5) epimeric alcohols, and these could be separated after silylation (Scheme 10, **27** → **28** → **29**). The yield of the 5β-silyl ether from ketone **27** is 65%, and the yield of the 5α-isomer is 33%. Scheme 10 shows only the 5β-isomer **29**, but both isomers were individually subjected to the same reactions. All yields shown in parentheses in Scheme 10 refer to the 5α series, but only the 5β compounds are drawn. In the text, only the yields for the 5β series are specified. Elaboration of each of the C(5) epimers eventually leads to the same compound so that *both* products from the initial ketone reduction are used in the synthesis. In principle, the C(5) epimers could be processed without separation.

Both of the silyl ethers are crystalline, but the 5α compound affords better crystals, and these were used for X-ray analysis.[33] The shape of the molecule is very much like the shape of the starting ketone (cf. **27′**), with the notable feature that the large silyloxy group at C(5) is axial.

Scheme 10[a]



[a] Key: Yields in parentheses refer to the 5-α series; R = *t*-$BuMe_2Si$; AOM = $CH_2OC_6H_4OMe$-*p*; (a) $NaBH_4$, MeOH; (b) *t*-$BuMe_2SiOTf$, 2,6-lutidine, CH_2Cl_2; 65% 5β, 33% 5α from **27**; (c) DIBAL-H, CH_2Cl_2; 99% (99%); (d) *t*-BuCOCl, DMAP, PhMe; 99% (99%); (e) OsO_4, $NaIO_4$, CCl_4, H_2O, *t*-BuOH; 73% (77%); (f) $NaBH_4$, MeOH; 96% (92%); (g) *p*-$MeOC_6H_4OCH_2Cl$, *i*-$PrNEt_2$, DMAP, PhMe; 91% (89%); (h) $NaBH_4$, $NiCl_2{\cdot}6H_2O$, MeOH, sonication; 95% (95%); (i) allyl chloroformate, pyridine, THF; 82% (82%); (j) Bu_4NF, THF, 95% (96%); (k) CrO_3, pyridine, CH_2Cl_2; 95% (90%).

The methyl ester was next reduced (Scheme 10, DIBAL-H, 99%), and the resulting primary alcohol was protected as its pivaloate (*t*-BuCOCl, DMAP, 99%, **29** → **30** → **31**). At this point, with the oxygen functions at C(5) and C(9) protected, it was necessary to remove C(10) and introduce oxygen at C(8).

Cleavage of the double bond under classical conditions[34] (Scheme 10), using osmium tetroxide and sodium periodate, gave an aldehyde (**31** → **32**, 73%), and that was reduced with sodium borohydride (96%) to the expected primary alcohol. Finally, the hydroxyl group was protected as its *p*-anisyloxymethyl ether[35] (**33** → **34**, 91%).

Having reached the stage of **34**, the nitro group now had to be reduced. While reduction of *aromatic* nitro compounds is

(28) Seebach, D.; Hungerbühler, E.; Naef, R.; Schnurrenberger, P.; Weidmann, B.; Züger, M. *Synthesis* **1982**, 138.

(29) The assignment was made by analogy with results for simple ketones (see ref 30).

(30) Cf. Masamune, S.; Ellingboe, J. W.; Choy, W. *J. Am. Chem. Soc*. **1982**, *104*, 5526.

(31) Made from the amine (Zhinkin, D. Ya.; Mal'nova, G. N.; Gorislavskaya, Zh. V. *J. Gen. Chem. USSR* **1968**, *38*, 2702) by treatment with BuLi (THF, 0 °C; 20 min).

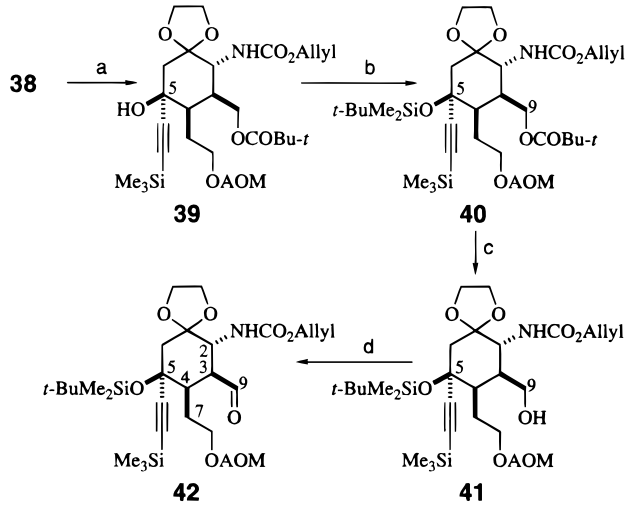
(32) Unlike a literature precedent (see ref 25a), the Diels−Alder reaction proceeds with good endo selectivity. Cf. (a) Node, M.; Nishide, K.; Imazato, H.; Kurosaki, R.; Inoue, T.; Ikariya, T. *J. Chem. Soc., Chem. Commun*. **1996**, 2559. (b) Stoodley, R. J.; Yuen, W.-H. *Chem. Commun*. **1997**, 1371.

(33) See the Supporting Information for X-ray data.

(34) Pappo, R.; Allen, D. S., Jr.; Lemieux, R. U.; Johnson, W. S. *J. Org. Chem*. **1956**, *21*, 478.

(35) Masaki, Y.; Iwata, I.; Mukai, I.; Oda, H.; Nagashima, H. *Chem. Lett*. **1989**, 659.

Scheme 11[a]



[a] Key: AOM = $CH_2OC_6H_4OMe$-*p*; (a) lithium trimethylsilylacetylide, $CeCl_3$, THF; 91%; (b) *t*-$BuMe_2SiOTf$, 2,6-lutidine; 97%; (c) DIBAL-H, CH_2Cl_2; 95%; (d) CrO_3, pyridine, CH_2Cl_2; 90%.

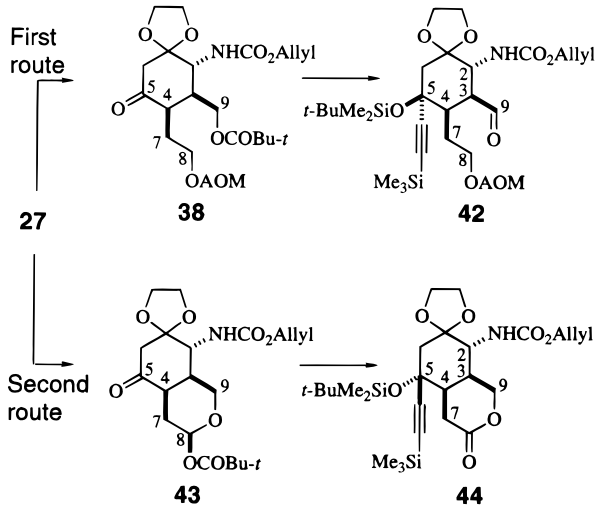
usually straightforward, the same process in the aliphatic series is often inefficient;[36] however, we found that the reagent generated by sonication of sodium borohydride and nickel(II) chloride hexahydrate[37] works very well and affords the corresponding amine in high (95%) yield. The latter was then protected as its allyl carbamate (**35** → **36**, 82%). To prepare for construction of the enediyne, the C(5) oxygen function was deprotected in the usual way with tetrabutylammonium fluoride (**36** → **37**, 95%), and finally, Collins oxidation of the resulting alcohol gave ketone **38** (95%). At this stage, both the 5α and 5*β* series converge to a single compound, and with the exception of the double bond cleavage **31** → **32** (73% for the 5α compound and 77% for the 5*β*), the yields are excellent throughout each of the two sequences.

Preparation of the First Monoacetylenic Advanced Intermediate (42). Treatment of ketone **38** with the lithium salt of trimethylsilylacetylide gave a complex mixture. However, when we changed to the cerium salt[38,39] (Scheme 11), not only was the yield high but the reaction was stereoselective, and in fact, the only product isolated (91%) was **39**, in which the acetylene group is syn to the nitrogen. The stereochemistry of **39** was inferred from the X-ray structure[33] of a more advanced intermediate (see **62**) derived by further elaboration of **39**. Acetylide addition is very straightforward, but initially it presented some difficulties; indeed, the optimized procedure for generating and for using the cerium reagent (see the Experimental Section) *must be followed exactly*. The cerium chloride is first dehydrated by heating at 130 °C under an oil pump vacuum for 3−12 h. The cooled material is then covered with THF and sonicated overnight[39d,e] to produce a white suspension. This is then diluted at a low temperature (−78 °C) with a THF solution of the lithium salt of trimethylsilylacetylene, and the mixture is kept for 40 min at −78 °C before use. Quite recently, the nature of cerium chloride has been subjected to various dehydration procedures as described in the literature,[40] and though it is clear that the material we use is not pure cerium trichloride, we have not gone back to repeat our experiments with what is now judged to be the pure anhydrous salt.

The tertiary alcohol resulting from the acetylide addition was protected by silylation (**39** → **40**, 97%), and the pivaloyl group was removed by the action of DIBAL-H (95%). The resulting alcohol **41** was then oxidized (90%) to aldehyde **42** by the Collins procedure. This aldehyde is a key advanced intermediate because it brought us directly to several critical points in the synthesis: the attachment of an acetylene at C(9) in a stereocontrolled manner and the introduction of a double bond at C(2)−C(3) and also at C(4)−C(7). In the latter case, the stereochemistry must be controlled.

The reactions leading to aldehyde **42** were selected after considerable exploratory work, and in fact, we encountered so many unexpected difficulties during our examination of potential routes from the Diels−Alder adduct to calicheamicinone that we took the precaution of synthesizing an alternative advanced intermediate (**44**, Scheme 12) that again brought us to the stage where attachment of an acetylene and introduction of two double bonds was required. The relationship between the two routes is summarized in Scheme 12. Both start with ketone **27**, derived by the Diels−Alder reaction, and the main structural difference is at the stage of the intermediate ketones **38** and **43**. In the former, C(7), C(8), and C(9) are part of acyclic units; in the latter, they are in a ring and the stereochemical outcome of the first acetylide addition is different as the acetylide now enters anti to the nitrogen (**43** → **44**).

Scheme 12[a]



[a] Key: AOM = $CH_2OC_6H_4OMe$-*p*.

Preparation of a Second Monoacetylenic Advanced Intermediate (44). The first three steps from the original Diels−Alder adduct **27** are the same as before (see Scheme 10, **27** → **28** → **29** → **30**). Once again, the two C(5) epimers were individually subjected to the same reactions (Scheme 13) until the sequences converge to a single compound. Only the 5*β* series is shown in Scheme 13; the yields in parentheses refer to the 5α series.

(36) (a) For a listing of many available methods, see: Larock, R. C. *Comprehensive Organic Transformations*; VCH publishers: New York, 1989; p 411. (b) Ganem, B.; Osby, J. O. *Chem. Rev.* **1986**, *86*, 763. (c) Kende, A. S.; Mendoza, J. S. *Tetrahedron Lett.* **1991**, *32*, 1699.

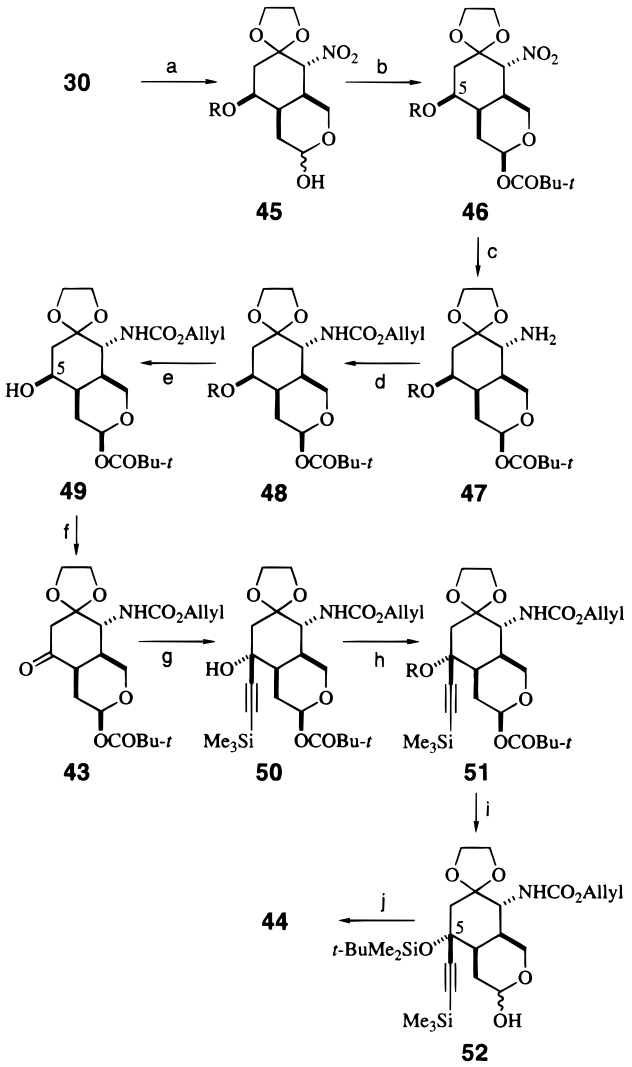
(37) (a) Osby, J. O.; Ganem, B. *Tetrahedron Lett.* **1985**, *26*, 6413. (b) Cf. Yoon, N. M.; Choi, J. *Synlett* **1993**, 135. Petrini, M.; Ballini, R.; Rosini, G. *Synthesis* **1987**, 713.

(38) Stoichiometry: $Me_3SiC{\equiv}CLi/CeCl_3$ = 1:1.

(39) Cf. (a) Imamoto, T.; Sugiura, Y.; Takiyama, N. *Tetrahedron Lett.* **1984**, *25*, 4233. (b) Suzuki, M.; Kimura, Y.; Terashima, S. *Chem. Lett.* **1984**, 1543. (c) Jung, P. M. J.; Burger, A.; Biellmann, J.-F. *Tetrahedron Lett.* **1995**, *36*, 1031. (d) Greeves, N.; Lyford, L. *Tetrahedron Lett.* **1992**, *33*, 4759. (e) Bailey, P. D.; Morgan, K. M.; Smith, D. I.; Vernon, J. M. *Tetrahedron Lett.* **1994**, *35*, 7115. (f) Review on organocerium reagents: Imamoto, T. In *Comprehensive Organic Synthesis*, Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. 1, p 231.

(40) (a) Dimitrov, V.; Kostova, K.; Genov, M. *Tetrahedron Lett.* **1996**, *37*, 6787. (b) Evans, W. J.; Feldman, J. D.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 4581.

Scheme 13[a]

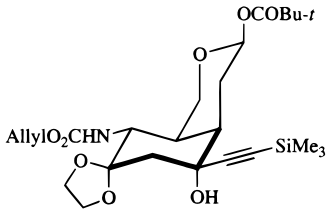


[a] Key: Yields in brackets refer to the 5α series; R = *t*-BuMe$_2$Si; (a) OsO_4, $NaIO_4$, CCl_4, H_2O, *t*-BuOH; 98% (98%); (b) *t*-BuCOCl, pyridine, CH_2Cl_2; 96% (96%); (c) $NaBH_4$, $NiCl_2 \cdot 6H_2O$, MeOH, sonication; 95% (91%); (d) allyl chloroformate, pyridine, THF; 94% (93%); (e) Bu_4NF, THF; 97% (95%); (f) PCC, 4 Å sieves CH_2Cl_2; 91% (92%); (g) lithium trimethylsilylacetylide, $CeCl_3$, THF; 91%; (h) *t*-BuMe$_2$SiOTf, 2,6-lutidine, CH_2Cl_2; 93%; (i) DIBAL-H, CH_2Cl_2; 96%; (j) CrO_3, pyridine, CH_2Cl_2; 97%.

In the earlier route, the C(9) hydroxyl of **30** was protected before cleavage of the double bond; this time the double bond was cleaved (OsO_4, $NaIO_4$, 98%) without hydroxyl protection, and the result, as expected, was a mixture of epimeric lactols (**30** → **45**). These were then protected using pivaloyl chloride. In this acylation, a single product is formed in high yield (96%) from a mixture of epimers, and so it is clear that equilibration occurs during the reaction and that one epimer reacts faster than the other, so as to afford a product (**46**) in which the bulky pivaloyl group is equatorial.

At this point, we were ready to reduce the nitro group to an amine, protect the amine, and regenerate the carbonyl at C(5). All of these tasks were achieved by the same reactions that had served us well in the first route. Nitro group reduction (**46** → **47**) with the sodium borohydride−nickel chloride combination again proceeded in excellent yield (95%), and the amine was protected under standard conditions with allyl chloroformate (94%). Then the silicon group was removed by the action of fluoride ion (**48** → **49**, 97%), and the liberated hydroxyl at C(5) was oxidized to a ketone (**49** → **43**, 91%). Once again the two series of 5α and 5β epimers converged to a single ketone, and for both series, identical reactions have been used, with very high yields (above 90%) throughout.

From ketone **43**, introduction of the acetylene was again accomplished with the cerium salt of trimethylsilylacetylene, and we obtained in high yield (91%) alcohol **50**, in which the acetylide had entered anti to the nitrogen—a different stereochemical relationship from the first route. Alcohol **50** is crystalline, and X-ray analysis[33] confirmed our structural assignment and established the conformation as shown in **50′**.



50'

The tertiary hydroxyl was protected by silylation (**50** → **51**, 93%), and the product was treated with DIBAL-H to afford a mixture of lactols (**51** → **52**, 96%). Finally, Collins oxidation gave lactone **44** (97%), bringing the work once more to the stage of an advanced intermediate where the next tasks were desaturation at C(2)−C(3) and C(4)−C(7) and the attachment of an acetylene at C(9).

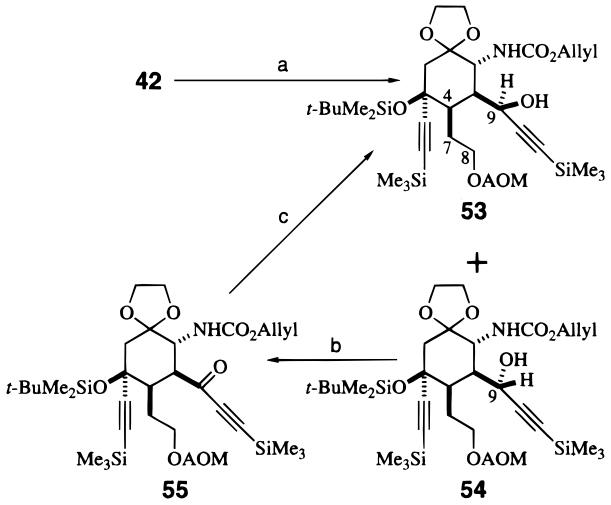
Introduction of a double bond at C(2)−C(3) involves no geometrical considerations because the bond will be generated within a six-membered ring for both **44** and the first advanced intermediate (**42**, see Scheme 12) and can have only the desired geometry. Formation of a double bond at C(4)−C(7), in the case of compound **44**, is likewise free of any geometrical problems, but introducing the C(4)−C(7) double bond in **42** is more difficult because there are no obvious constraints to control the stereochemistry. We decided, therefore, to delay operating on that part of the molecule until we had incorporated the C(7)−C(8) chain of **42** into a ring.

The remaining key step for both routes was the attachment of another acetylene unit at C(9) in the proper stereochemical sense. In the case of **42**, a suitable functional group (−CHO) was already present to react with an acetylide anion, but with **44** attachment of an acetylene required that C(9) be oxidized to the aldehyde level. In principle, for both **42** and **44**, there is also the choice of using direct bimolecular reaction with an acetylide or of first attaching the second acetylenic unit to the one that is already present. For bimolecular processes, the stereochemical outcome at C(9) is difficult to predict.

Elaboration of Advanced Intermediate 42: Attachment of the Second Acetylene Unit and Introduction of the C(4)−C(7) Double Bond. Treatment (Scheme 14) of aldehyde **42** with the cerium salt of trimethylsilylacetylene, generated exactly as in our earlier experiments, gave the desired alcohol **53** in 79% yield, together with the C(9) epimer **54** (16%). We tried to increase the stereoselectivity by running the reaction at an even lower temperature, but achieved little, if any, improvement. We also evaluated the corresponding ytterbium acetylide because there is reason[41] to expect that use of ytterbium organometallics may generally result in greater stereoselection, but in the present case the reaction was too slow. With the lithium salt of the acetylene, the yield was very poor. Fortunately, alcohol **54**

(41) Utimoto, K.; Nakamura, A.; Matsubara, S. *J. Am. Chem. Soc*. **1990**, *112*, 8189.

Scheme 14[a]



[a] Key: AOM = $CH_2OC_6H_4OMe$-*p*; (a) lithium trimethylsilylacetylide, $CeCl_3$, THF; 79% for **53**, 16% for **54**; (b) PCC; (c) $NaBH_4$, MeOH; 82% from **54**.

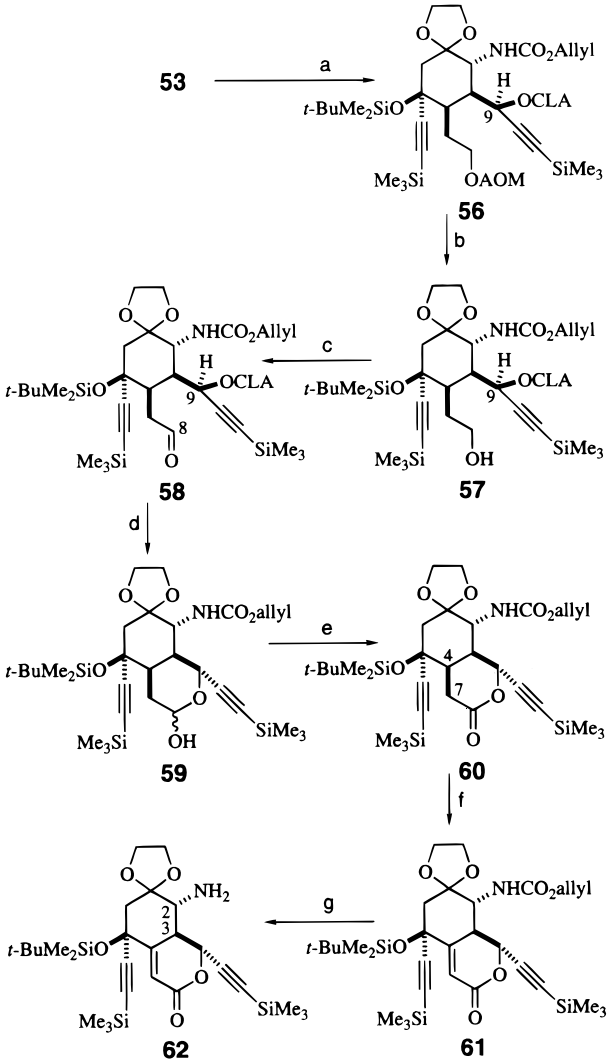
could be oxidized easily (PCC, ca. 93%) to the corresponding ketone (**55**), and then reduction with sodium borohydride gave (ca 96%) an 11.6:1 mixture of C(9) epimeric alcohols in favor of the desired isomer **53**. The components of the mixture are easily separated, so that the conversion of **42** into **53** is efficient, but requires a recycling step.

The next tasks were to incorporate C(7), C(8), and C(9) into a ring and then to form the C(4)−C(7) double bond. For this purpose, temporary protection of the C(9) hydroxyl as a chloroacetate proved ideal. Acylation with chloroacetic anhydride (Scheme 15) gave the expected chloroacetate (**53** → **56**, 99%), and then exposure to ceric ammonium nitrate served to remove[35] the *p*-anisyloxymethyl group and release the parent alcohol (**56** → **57**, 89%). Collins oxidation converted the alcohol into the corresponding aldehyde (**57** → **58**, 91%) and set the stage for generating the desired ring structure.

When chloroacetate **58** was treated with aqueous ammonia,[42] the C(9) hydroxyl was released, and it immediately closed onto the C(8) aldehyde to afford a mixture of lactols which, in turn, were oxidized efficiently by the Collins reagent (**58** → **59** → **60**, 92% overall). The double bond at C(4)−C(7) was then introduced by phenylselenenylation[43] followed by oxidation with dimethyldioxirane[44] (**60** → **61**, 67%). The intermediate phenyl selenide is rather unstable, and we have no spectroscopic evidence for its stereochemistry, but assume that the phenylseleno group is syn to the C(4) hydrogen, so as to accommodate the standard syn mechanism of selenoxide fragmentation.

The nitrogen-protecting group was next removed in order to prepare for desaturating the system at C(2)−C(3). While the use of tetrakis(triphenylphosphine)palladium(0) is well established for the deprotection of allyl esters, the choice of an added nucleophile in the present case was important, and dimedone[45] proved best (**61** → **62**, 80%). Amine **62** is a crystalline substance; X-ray analysis[33] confirmed the desired structure and showed that the two acetylene pendants are axial to their respective rings.

Scheme 15[a]



[a] Key: AOM = $CH_2OC_6H_4OMe$-*p*, CLA = $ClCH_2C(O)$; (a) $(ClCH_2CO)_2O$, pyridine; 99%; (b) $(NH_4)_2Ce(NO_3)_6$, pyridine, MeOH, H_2O; 89%; (c) CrO_3, pyridine, CH_2Cl_2; 91%; (d) NH_4OH; (e) CrO_3, pyridine, CH_2Cl_2; 92% from **58**; (f) LDA, THF, PhSeBr; dimethyldioxirane; 67%; (g) $(Ph_3P)_4Pd$, dimedone, THF; 80%.

Further Elaboration of Advanced Intermediate 42: Introduction of the C(2)−C(3) Double Bond. With amine **62** in hand, we came to what was initially a very troublesome job: introducing the C(2)−C(3) double bond. We had planned to do that by forming a double bond between C(2) and the nitrogen: i.e., we would make an imine and then allow the double bond to move into conjugation. An appropriate method for converting a primary amine into an imine[46] seemed to be the classical procedure of N-chlorination followed by base treatment, and we applied this method to a number of compounds, such as **63**−**66**,[47] as well as to some others that were all made during our exploratory studies. In these early experiments, we obtained either complex mixtures or substances that we suspected (but did not prove) to be aziridines. All of the test compounds contained the basic six-membered ring (carbons 1−6 of our target), but differed in the nature of the appendages at C(3), C(4), and C(5). Eventually, we gained the impression that the presence of a C(4)−C(7) double bond and incorporation of C(8)

(42) Cf. Reese, C. B.; Stewart, J. C. M.; van Boom, J. H.; de Leeuw, H. P. M.; Nagel, J.; de Rooy, J. F. M. *J. Chem. Soc., Perkin Trans. 1* **1975**, 934.

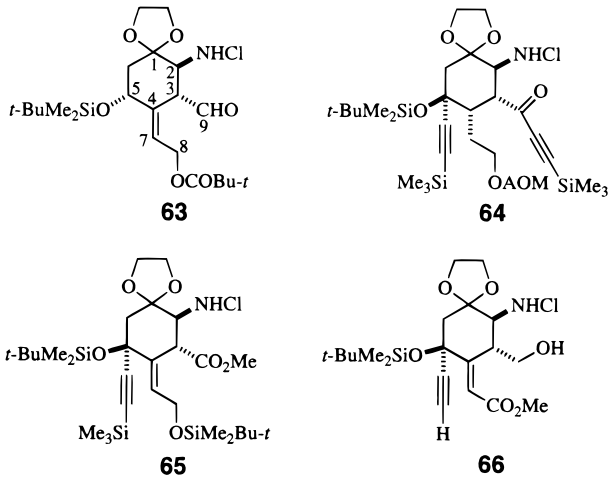
(43) Some selenenylation probably also occurs on nitrogen.

(44) Preparation and estimation: Adam, W.; Chan, Y.-Y.; Cremer, D.; Gauss, J.; Scheutzow, D.; Schindler, M. *J. Org. Chem.* **1987**, *52*, 2800.

(45) Kunz, H.; Unverzagt, C. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 436.

(46) Cf. Dayagi, S.; Degani, Y. In *The Chemistry of the Carbon−Nitrogen Double Bond*; Patai, S., Ed.; Interscience: New York, 1970; p 61. See Supporting Information for additional references.

(47) These compounds were used without full characterization.



and C(9) into a ring are features that would permit desaturation at C(2)−C(3) by the N-chlorination method. Careful examination of our exploratory work then allowed us to select the most felicitous combination of steps that yielded such a structure, and this analysis led us to the route shown in Scheme 15 and described above.

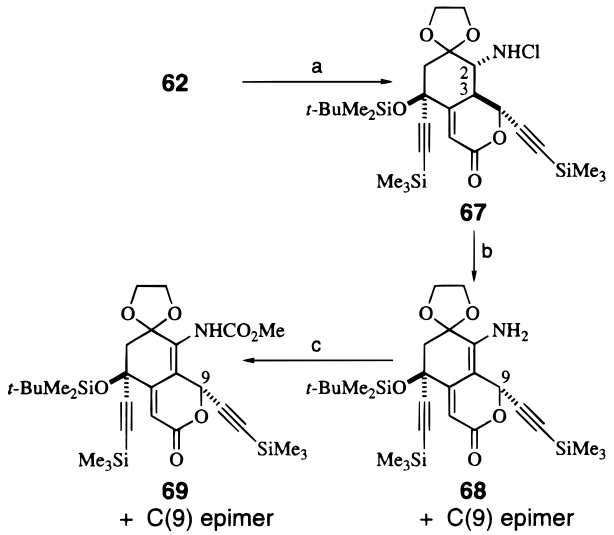
Exposure of amine **62** to freshly prepared *tert*-butyl hypochlorite[48] gave the *N*-chloro compound **67** (Scheme 16), which was immediately treated at room temperature with a 5-fold excess of DABCO or DBU. Those operations gave the fully conjugated enamine as an 8:1 mixture of C(9) epimers (**67** → **68**, 78% from **62**). We suspect (on the basis of a single experiment) that the use of a larger amount of DABCO gives an improved ratio, but it turned out that the epimerization is not so important, as the stereochemistry can be corrected easily (see below). The enamine is unstable and must be used without delay. It was, therefore, converted directly into the corresponding isocyanate by treatment with triphosgene, and the isocyanate was quenched with methanol.[2a,b,49] That experiment gave the methyl carbamate **69** in almost 80% yield from the parent amine **62**, again as an 8:1 mixture of C(9) epimers. Neither of the last two epimer mixtures were chromatographically separable, but separation and stereochemical correction were easily achieved at the next stage. We assume that the epimerization, which can take place with both **68** and the derived carbamate (**69**) in the presence of an acid or a base, occurs by the mechanism summarized in Scheme 17.

Having reached carbamate **69**, we had next to remove the acetylenic silyl groups in order to attempt formation of the enediyne ring. The desilylation was done with tetrabutylammonium fluoride (Scheme 18) under standard conditions, but during the course of the reaction there was further epimerization at C(9) (**69** → **71** and **72**), attributable to the basic nature of the reagent. Starting from **69** (as an 8:1 mixture in favor of the syn isomer shown), it was possible to isolate the desired syn bis-acetylene **72** in 46% and the anti bis-acetylene **71** in 39% yield. However, when the anti compound is treated with tetrabutylammonium acetate, it is converted quantitatively into a 6:4 mixture of the two epimers, with the desired one predominating. The syn and anti bis-acetylenes are easily separated, and so, after one recycling, the yield for conversion of **69** into **72** is 69%.

(48) (a) Mintz, M. J.; Walling, C. *Organic Syntheses*; Wiley & Sons: New York, 1973, Collect. Vol. V, p 184. (b) **Hazard warning**: *Organic Syntheses*; Wiley & Sons: New York, 1973, Collect. Vol. V, p 183.

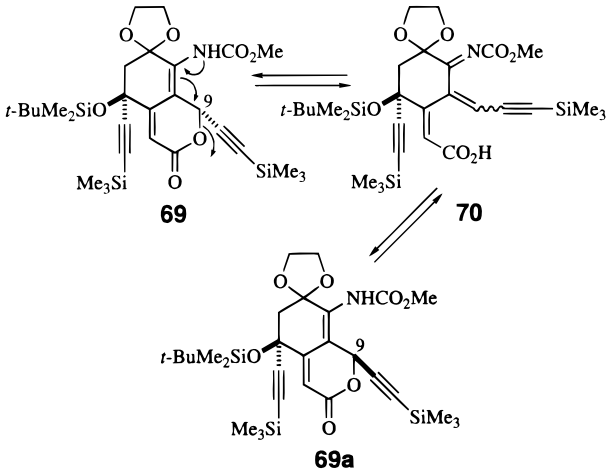
(49) Cf. Eckert, H.; Forster, B. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 894.

Scheme 16[a]

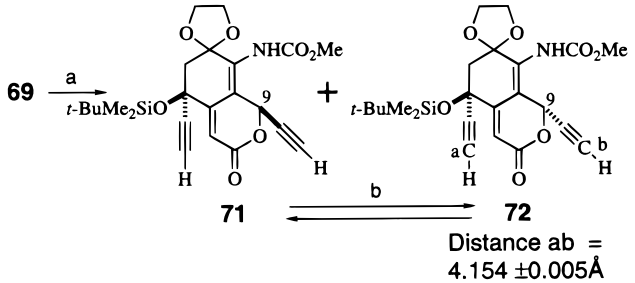


[a] Key: (a) *t*-BuOCl, Et_2O−THF; (b) DABCO, PhMe; (c) $Cl_3COCOOCCl_3$, pyridine, CH_2Cl_2; MeOH; 78% from **62**.

Scheme 17



Scheme 18[a]



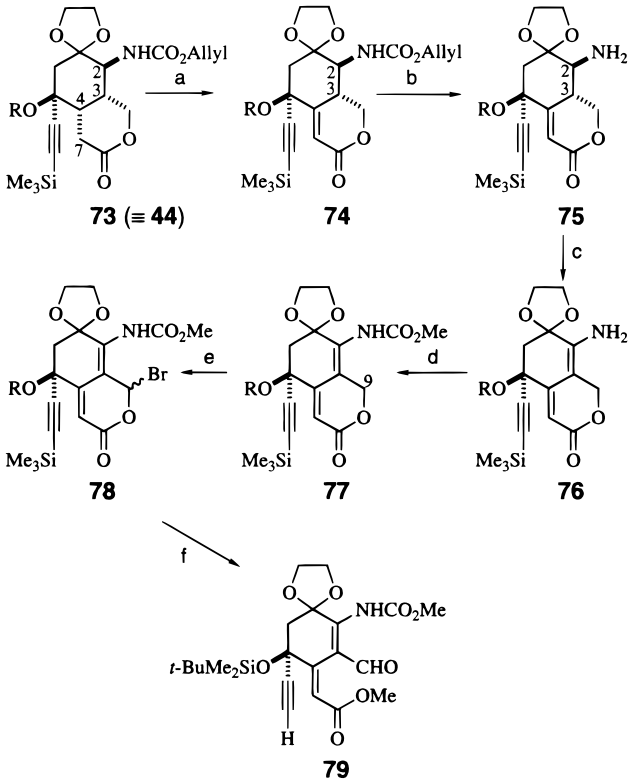
[a] Key: (a) Bu_4NF, THF; 46% for **72**, 39% for **71**; 69% for **72** after one recycling; (b) Bu_4NOAc; 100%, **71**:**72** = 4:6.

An X-ray structure determination[33] showed that the distance between the terminal acetylenic carbons of **72** is 4.154 ± 0.005 Å.

With a small supply of **72** in hand, the stage was set for construction of both the enediyne ring and the trisulfide, followed by removal of residual protecting groups. At about this time, however, we completed a different route to the syn bis-acetylene, and it was material from this new source that was actually taken on to calicheamicinone.

Elaboration of Advanced Intermediate 44: Introduction of the C(4)−C(7) Double Bond, Attachment of the Second

Scheme 19[a]



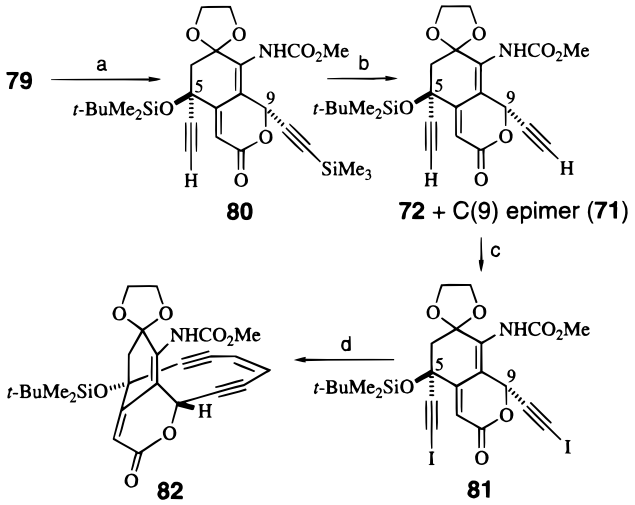
[a] Key: R = *t*-BuMe$_2$Si. (a) LDA, THF, PhSeBr; dimethyldioxirane, CH_2Cl_2, acetone; 85% + 5% **73**; (b) $(Ph_3P)_4Pd$, dimedone, THF; 93%; (c) *t*-BuOCl, Et_2O-THF; DBU, PhMe; 81%; (d) $Cl_3COCOOCCl_3$, pyridine, CH_2Cl_2; MeOH; 91%; (e) NBS, $(PhCO)_2O_2$, light, CCl_4; (f) $AgNO_3$, THF, H_2O, pyridine; CH_2N_2; 77% from **77**.

Acetylene Unit, and Completion of the Synthesis. As indicated earlier, we developed an alternative route that proceeds by way of the advanced intermediate **44**. In both routes, we deal with racemic compounds, but represent each of them by a single enantiomer. It is permissible, therefore, to depict compound **44** by the enantiomeric form **73** (see Scheme 19), so that elaboration to the syn bis-acetylene **72** (see Schemes 19 and 20) is more conveniently described; at the stage of the syn bis-acetylene, both approaches via **42** and **73** converge to a single compound from which (±)-calicheamicinone is easily reached.

Compound **73** was desaturated at C(4)−C(7) by the method that had served us well in the first route. Phenylselenenylation under standard conditions gave an unstable selenide, and as before, we assumed that the phenylseleno group was on the same face as the C(4) hydrogen. Oxidation with dimethyldioxirane then afforded the selenoxide, and that, in turn, collapsed to generate the required double bond [**73** → **74**, 85%, uncorrected for recovered **73** (5%)]. Removal of the allyloxycarbonyl group (**74** → **75**) by the action of tetrakis(triphenylphosphine)-palladium(0) in the presence of dimedone again liberated the amino group in high yield (93%), and that group was chlorinated with *tert*-butyl hypochlorite. Prompt exposure to a hindered base—in this case DBU—gave an imine which immediately isomerized to the unstable conjugated enamine (**75** → **76**, 81%). For making the derived methyl carbamate, we again used triphosgene and quenched the resulting isocyanate with methanol (**76** → **77**, 91%).

To introduce an acetylene at C(9), it was necessary to oxidize that carbon, and the oxidation was accomplished by taking advantage of the fact that the C(9) hydrogens are allylic. When

Scheme 20[a]



[a] Key: R = *t*-BuMe$_2$Si. (a) Lithium trimethylsilylacetylide, $CeCl_3$, THF; 91%; (b) Bu_4NF, THF; 46% for **72**, 42% for the C(9) epimer (**71**), 71% for **72**, after one recycling of syn bis(acetylene); (c) NIS, $AgNO_3$, acetone; 89%; (d) (*Z*)-1,2-bis(trimethylstannyl)ethene, $(Ph_3P)_4Pd$, DMF; 72%.

we treated **77** with *N*-bromosuccinimide under standard free radical conditions we obtained a mixture of bromides in good yield (**77** → **78**). These could be hydrolyzed with aqueous silver nitrate to an aldehyde acid,[50] which is easily trapped in the form of its methyl ester **79** by reaction with diazomethane. During the hydrolysis, the acetylenic trimethylsilyl group is lost, and that was very convenient, as we would have had to remove it anyway. The overall yield for the steps from **77** to **79** was 77%.

The next task was to introduce the second acetylenic unit (Scheme 20). Fortunately, the potential problem of stereochemical control did not arise, because treatment of aldehyde **79** with the cerium salt of trimethylsilylacetylene gave in high yield (91%) the desired lactone **80**, which forms by stereoselective acetylide addition to the aldehyde and lactonization of the resulting alkoxide. Removal of the acetylenic trimethylsilyl group with tetrabutylammonium fluoride afforded the syn bis-acetylene **72** in 46% yield and almost as much (42%) of the anti isomer **71** (see Scheme 20). Treatment of that material with tetrabutylammonium acetate gave more of the desired syn compound; with one such recycling, the yield of **72** is 71%.

The acetylenic hydrogens were next replaced by iodine (Scheme 20, **72** → **81**, 89%), using *N*-iodosuccinimide with a catalytic amount of silver nitrate,[51] and we were ready to close the enediyne ring by means of a double Stille coupling.[52] Such couplings had been used[53] on a few occasions to generate large rings, and one example was actually reported[54] in the case of an enediyne (dynemicin) shortly before our own experiment.[55] A DMF solution of freshly distilled (*Z*)-1,2-bis(trimethylstan-

(50) The compound exists as two hydroxy lactones, epimeric at C(9).

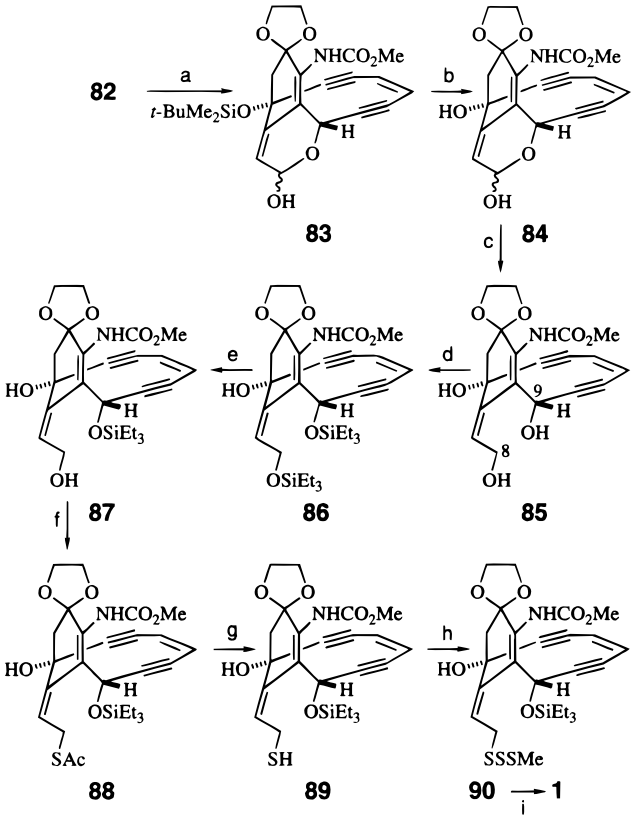
(51) (a) Hofmeister, H.; Annen, K.; Laurent, H.; Wiechert, R. *Angew. Chem., Int. Ed. Engl*. **1984**, *23*, 727. (b) For a listing of other methods, see: Brunel, Y.; Rousseau, G. *Tetrahedron Lett*. **1995**, *36*, 2619. (c) Bis-iodide **81** can be made directly from **69** (see Scheme 16), but desilylation in a separate step (**69** → **72** → **81**) is more efficient overall: Cf. Nishikawa, T.; Shibuya, S.; Hosokawa, S.; Isobe, M. *Synlett* **1994**, 485.

(52) Farina, V.; Krishnamurthy, V. *Org. React. (N.Y.)* **1997**, *50*, 1.

(53) E.g. (a) Pattenden, G.; Thom, S. M. *Synlett* **1993**, 215. (b) Nicolaou, K. C.; Chakraborty, T. K.; Piscopio, A. D.; Minowa, N.; Bertinato, P. *J. Am. Chem. Soc.* **1993**, *115*, 4419. (c) Barrett, A. G. M.; Boys, M. L.; Boehm, T. L. *J. Chem. Soc., Chem. Commun*. **1994**, 1881.

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

Scheme 21[a]



[a] Key: (a) DIBAL-H, CH_2Cl_2; 98%; (b) Bu_4NF, THF; 94%; (c) $NaBH_4$, MeOH; 76%; (d) Et_3SiOTf, 2,6-lutidine; 95%; (e) AcOH, THF, H_2O; 94%; (f) *i*-$PrO_2CN{=}NCO_2Pr$-*i*, Ph_3P, AcSH; 94%; (g) DIBAL-H, CH_2Cl_2; (h) *N*-(Methyldithio)phthalimide (**9**), CH_2Cl_2; 88% from **88**; (i) $TsOH{\cdot}H_2O$, THF, H_2O; 84%.

nyl)ethene[56] was added slowly to a warm solution of the bis-iodide **81** and a catalytic amount of tetrakis(triphenylphosphine)-palladium(0) in the same solvent. A few hours after the addition, it was possible to isolate the cyclic enediyne **82** as a white solid in 72% yield[52,57] (Scheme 20).

By the time we had reached this point, publications from the laboratories of Danishefsky[2a] and Nicolaou[2b] reported how compounds very similar to **82**—only the status of the tertiary hydroxyl was different—could be converted into calicheamicinone, and we used a method similar to theirs.[2a,b,20]

We first reduced the lactone to a mixture of lactols, using DIBAL-H (Scheme 21, **82** → **83**, 98%), and then removed the silicon group (**83** → **84**) in the usual way (Bu_4NF, 94%). The timing of these simple operations is critical. The silicon group has to be removed before making the trisulfide, because the trisulfide is not stable to tetrabutylammonium fluoride, at least under conditions needed for deprotection of a *tert*-butyldimethylsilyloxy ether. And the DIBAL-H reduction must be done before desilylation, because if the silicon is removed first, the product is not soluble enough in dichloromethane, which is the solvent we use for the reduction.

Further reduction (**84** → **85**, 76%) with sodium borohydride gave a triol, and the secondary hydroxyl was protected by a two-step procedure. Treatment with triethylsilyl triflate served to place a silicon group on both the C(8) and C(9) oxygens (**85** → **86**, 95%), and when the doubly silylated material was stored for a short time in a mixture of acetic acid, THF, and water at 0 °C, the primary allylic alcohol was released (**86** → **87**, 94%), but the other silicon unit was not disturbed.

The primary hydroxyl was next replaced by a thioacetyl group (**87** → **88**, 94%)[2a] by using typical Mitsunobu conditions, and the free thiol was then liberated by the action of DIBAL-H (**88** → **89**).

The next step, elaboration to the trisulfide, required that freshly chromatographed thiol be used, and as soon as that was established, we found that treatment with a large excess—about 8-fold—of freshly crystallized *N*-(methyldithio)phthalimide[2a,19d-f] then gave the desired trisulfide[58] **90** in nearly 90% yield from the thioacetate (**88**).

Finally, mild acid hydrolysis served to disengage the remaining two protecting groups and release racemic calicheamicinone as a white foam (**90** → **1**, 84%).

Conclusion

The two syntheses illustrate the remarkable level of stereoselectivity that can be obtained with alkynyl cerium reagents and also show the usefulness of a set of oxygen protecting groups, especially the *p*-anisyloxymethyl group.

In **42** and **44**, the stereochemical relationship between the acetylene unit at C(5) and the nitrogen at C(2) is different, but the only stereogenic center that is preserved after elaboration to (±)-calicheamicinone is C(5); consequently, *both* compounds give the same *racemic* end product. The stereochemical relationship between the two routes confers on the present work the very unusual characteristic that, with corresponding optically pure compounds, *either* enantiomer of calicheamicinone can be reached *irrespective* of the absolute configuration of the initial Diels—Alder adduct.[59] In a potential synthesis of (−)-calicheamicinone (of natural stereochemistry, as actually depicted in diagram **1**), intermediates corresponding to the Diels—Alder adduct **27** with a (2*R*) absolute configuration would have to be processed by the methods based on **42**, while the route via **44** would be used for the (2*S*) isomer. We also note the curious fact that a calicheamicinone of unnatural stereochemistry is probably[60] more efficient at producing double strand cuts in DNA than material of natural stereochemistry.

Experimental Section

General Procedures. The same general procedures as used previously[61] were followed. DMF was stirred overnight with crushed CaH_2 and then distilled under a water pump vacuum with protection from moisture.

The symbols s′, d′, t′, and q′ used for ^{13}C NMR signals indicate zero, one, two, or three attached hydrogens, respectively. In cases where the number of signals is less than expected, we assumed that this was due to coincident chemical shifts.

(55) Recent examples of the use of Stille coupling for construction of large rings: (a) Boden, C.; Pattenden, G. *Synlett* **1994**, 181. (b) Smith, A. B., III.; Condon, S. M.; McCauley, J. A.; Leazer, J. L., Jr.; Leahy, J. W.; Maleczka, R. E., Jr. *J. Am. Chem. Soc.* **1995**, *117*, 5407. (c) Boyce, R. J.; Pattenden, G. *Tetrahedron Lett.* **1996**, *37*, 3501. (d) Critcher, D. J.; Pattenden, G. *Tetrahedron Lett.* **1996**, *37*, 9107. (e) Paterson, I.; Man, J. *Tetrahedron Lett.* **1997**, *38*, 695.

(56) Mitchell, T. N.; Amamria, A.; Killing, H.; Rutschow, D. *J. Organomet. Chem.* **1986**, *304*, 257.

(57) We have not examined the effect of additives or ligands (see the Supporting Information for references) other than triphenylphosphine.

(58) ^1H NMR chemical shifts for MeS_xMe ($x = 2-4$) are characteristic: MeSSMe (δ 2.41), MeSSSMe (δ 2.56), MeSSSSMe (δ 2.64) (Douglas, I. B.; Douglas, M. L. *Sulfur Rep.* **1995**, *17*, 129.) See also ref 5a. Our product had δ 2.54 ($CDCl_3$).

(59) Cf. Clive, D. L. J.; Selvakumar, N. *J. Chem. Soc., Chem. Commun.* **1996**, 2543.

(60) Such a difference has been found using an analogue of **1** (in which the group SSSMe is replaced by SAc): See ref 2c.

(61) Clive, D. L. J.; Wickens, P. L.; Sgarbi, P. W. M. *J. Org. Chem.* **1996**, *61*, 7426.

Compound numbers followed by "α" refer to the stereochemistry at C(5), the substituent being below the plane of the paper. The α-series is the minor isomer series arising from hydride reduction of the C(5) carbonyl in **27**, and the experimental procedures, which are identical to those for the 5*β* series, are given in the Supporting Information.

Procedures for the Advanced Intermediate (30) Common to Both Routes. 2-Chloroethyl 3-Oxo-6-heptenoate (24). 2-Chloroethanol (750 mL, 11.19 mol) was added to methyl 3-oxo-6-heptenoate (**23**) (53 g., 0.34 mol), and Ti(OPr-*i*)$_4$ (5 mL, 16.9 mmol) was added to the resulting solution. The flask was closed with a $CaSO_4$ guard tube, and the mixture was stirred at 55 °C for 16 h and then at 75 °C for 24 h. The solvent was then distilled off under reduced pressure (ca. 50 °C, water pump vacuum), and the residue was filtered through a pad (5.5 × 20 cm) of silica gel using 3:7 EtOAc−hexane. Evaporation of the solvents and distillation of the yellowish residue under vacuum (0.02 mmHg) gave a colorless liquid, which contained (^{1}H NMR, 200 MHz) ca. 15% of the starting ester. Fractional distillation gave first the starting material (bp 40−50 °C, 0.02 mmHg) and then **24** as a pure (^{1}H NMR, 200 MHz) colorless liquid (43.8 g, 63%).

The 2-chloroethanol was recycled. We suspect that the yield could have been raised if, at the end of ca. 12 h, some of the MeOH was distilled off, fresh batches of 2-chloroethanol and Ti(OPr-*i*)$_4$ were added, and the reaction was allowed to continue.

1-(1,3-Dioxolan-2-ylidene)-5-hexen-2-one (25). A solution of **24** (20.4 g, 0.1 mol) in dry DMF (40 mL) was added to a magnetically stirred suspension of K_2CO_3 (Aldrich item no. 34,782-5, -325 mesh, 98%, dried overnight at 80 °C under oil pump vacuum, 16.58 g, 0.12 mol) in dry DMF (80 mL, Argon atmosphere). Stirring was continued for 9 h, and the suspension was then allowed to settle. The supernatant liquid was transferred by cannula to another flask (protection from moisture, Ar atmosphere). Dry Et_2O (20 mL) was added to the solid residue, and the mixture was stirred for 2 min and again allowed to settle. The supernatant Et_2O layer was transferred to the other flask as before. (We did not repeat the Et_2O rinse, but in future experiments would do so.) The Et_2O−DMF solution was evaporated by connection, via a bent adaptor with stopcock, to a large trap cooled in liquid nitrogen and connected to an oil pump. The evaporation was done first (briefly) at room temperature (for removal of the Et_2O) and then at 50 °C (oil bath). **From this point on, do not expose the compound to air, only to argon.** [Some of us who have done this experiment used a rotary evaporator (with provision for protection from moisture), but felt that the compound obtained was then less pure.] Kugelrohr distillation of the residue (diffusion pump, 0.001 mmHg, oven temperature 116−125 °C) gave **25** (13.44 g, 80%) as a pure (^{1}H NMR, 200 MHz) colorless liquid, which solidified in a freezer but melted again at room temperature. The compound can be kept in a refrigerator for several weeks. Brief exposure to air is not harmful after the distillation.

Note: During the distillation, the pressure must be at least 0.001 mmHg in order to obtain a white distillate.

[[1-(1,3-Dioxolan-2-ylidenemethyl)-1,4-pentadienyl]oxy]trimethylsilane (20) and Methyl (6α,7*β*,8a*β*)-6-Nitro-9-oxo-8-(2-propenyl)-1,4-dioxaspiro[4.5]decane-7-carboxylate (27). (a) 1,1,3,3-Tetramethyl-1,3-disilazane [(Me$_2$PhSi)$_2$NH]. NH_3 was passed for 6 h directly from an ammonia tank (via a Dreschel safety bottle) into a mechanically stirred solution of commercial $Me_2PhSiCl$ (200 g, 1.17 mol) in dry PhH (1200 mL). During this time, NH_4Cl precipitated. The mixture was filtered, and the solid was washed with bench benzene (300 mL). Evaporation of the solvent and distillation of the residue (oil pump, 0.5 mmHg) gave 1,1,3,3-tetramethyl-1,3-disilazane (150.5 g, 90%).

(b) [[1-(1,3-Dioxolan-2-ylidenemethyl)-1,4-pentadienyl]oxy]trimethylsilane (20) and Methyl (6α,7*β*,8a*β*)-6-Nitro-9-oxo-8-(2-propenyl)-1,4-dioxaspiro[4.5]decane-7-carboxylate (27). *n*-BuLi (2.5 M, 32.8 mL, 82 mmol) was added over ca. 10 min to a stirred and cooled (ice bath) solution of (Me$_2$PhSi)$_2$NH (24.4 g, 86 mmol) in dry THF (300 mL) (Ar atmosphere). Stirring was continued for a further 15 min, and then the ice bath was replaced by a dry ice−acetone bath. A solution of **20** (12.76 g, 76 mmol) in THF (50 mL) was added by cannula over 1 h (stirring). The mixture was stirred for a further 10 min and then quenched by rapid addition (over ca. 1 min) of Me_3SiCl (fresh Aldrich material, used as received, 12 mL, 95 mmol). The cold bath was removed, and the solution was allowed to attain room temperature (ca. 20 min) and then was stirred for a further 10 min. The solution was then cooled in an ice bath, and methyl (*E*)-3-nitropropenoate (11.94 g, 91.1 mmol) in dry THF (12 mL plus 3 mL as a rinse) was added by cannula over 5 min. The ice bath was removed, and the mixture was stirred for 1.5 h. At this point, it was quenched by addition of saturated aqueous NH_4Cl (500 mL). The resulting mixture was stirred for 2 h and then extracted with EtOAc (3 × 300 mL). The combined organic extracts were washed with brine (1 × 200 mL) and dried ($NaSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (10 × 40 cm), using 1:4 EtOAc−hexane, followed by crystallization from EtOAc−hexane gave pure (^{1}H NMR, 300 MHz) **27** (12.73, 56% overall from ketene acetal **25**) as large colorless crystals. The crystallization was done by covering the solid with EtOAc and warming the mixture (ca. 50 °C); more solvent was added until the solid just dissolved. The solution was then allowed to cool to room temperature; finally, the solution was kept overnight in a refrigerator. The compound can also be crystallized from 1:4 EtOAc−hexane by dissolving the solid in EtOAc and then adding hexane until turbidity is observed. The solution is then left at room temperature.

An X-ray structure was determined on **27** crystallized from 1:4 EtOAc−hexane.[33]

Methyl (6α,7*β*,8*β*,9α)- and (6α,7*β*,8*β*,9*β*)-9-Hydroxy-6-nitro-8-(2-propenyl)-1,4-dioxaspiro[4.5]decane-7-carboxylate (28). $NaBH_4$ (1.39 g, 36.75 mmol) was added in one portion to a stirred and cooled (0 °C) solution of **27** (10.00 g, 33.41 mmol) in MeOH (200 mL), and the mixture was stirred at 0 °C for 10 min. Water (400 mL) was added, and the aqueous solution was extracted with EtOAc (4 × 200 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (5.5 × 20 cm), using 1:1 EtOAc−hexane, gave a 2:1 mixture of **28** and the C(5) epimer **28**α as a white solid (10.02 g, 99%).

Methyl (6α,7*β*,8*β*,9*β*)-9-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-6-nitro-8-(2-propenyl)-1,4-dioxaspiro[4.5]decane-7-carboxylate (29) and Methyl (6α,7*β*,8*β*,9α)-9-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-6-nitro-8-(2-propenyl)-1,4-dioxaspiro[4.5]decane-7-carboxylate (29α). *t*-BuMe$_2$SiOSO$_2$CF$_3$ (11.4 mL, 49.7 mmol) was added over ca. 10 min (syringe pump) to a stirred solution of **28** and **28**α (10.00 g, 33.19 mmol) and 2,6-lutidine (7.7 mL, 66.11 mmol) in CH_2Cl_2 (300 mL). Stirring was continued for 2 h at room temperature, and water (400 mL) was then added. The mixture was extracted with EtOAc (3 × 150 mL), and the combined organic extracts were washed with brine (300 mL), dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel (5.5 × 38 cm), using 1:20 EtOAc−hexane, gave **29** (8.97 g, 65%) and the C(5) epimer **29**α (4.50 g, 32%). Both compounds are solids.

An X-ray structure was determined on **29**α crystallized from EtOAc−hexane.[33]

(6α,7*β*,8*β*,9*β*)-9-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-6-nitro-8-(2-propenyl)-1,4-dioxaspiro[4.5]decane-7-methanol (30). DIBAL-H (1.0 M in CH_2Cl_2, 39.0 mL, 39.0 mmol) was added over ca. 10 min (syringe pump) to a stirred and cooled (−78 °C) solution of **29** (6.50 g, 15.64 mmol) in dry CH_2Cl_2 (200 mL). Stirring at −78 °C was continued for 40 min, and then Na_2SO_4·10H_2O (100 g) and Celite (20 g) were added sequentially at −78 °C. The cold bath was removed, and the mixture was stirred for 1 h. The mixture was then filtered through a pad of Celite (5 × 1 cm) with EtOAc. Evaporation of the filtrate and flash chromatography of the residue over silica gel (4.5 × 17 cm), using 1:3 EtOAc−hexane, gave **30** (6.00 g, 99%) as a colorless oil.

Procedures for route via 44 (≡73). (3α,4aα,5*β*,8α,8aα)- and (3α,-4a*β*,5α,8*β*,8a*β*)-5-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]hexahydro-8-nitrospiro[1*H*-2-benzopyran-7(3*H*),2′-[1,3]dioxolan]-3-ol (45). OsO_4 (2.5% w/w in *t*-BuOH, 4.0 mL, 0.319 mmol) was added to a stirred solution of **30** (2.13 g, 5.5 mmol) in 2:2:1 CCl_4−water−*t*-BuOH (75 mL) (the starting material was dissolved in CCl_4-*t*-BuOH, and the water was added last). The mixture was stirred for 15 min, and $NaIO_4$ (2.93 g, 13.75 mmol) was added in one portion. After 3 h, the resulting suspension was diluted with water (20 mL) and extracted with Et_2O (400 mL). The organic extract was washed with water (20 mL), 10% aqueous $NaHSO_3$ (20 mL), and water (20 mL), dried ($MgSO_4$), and

evaporated. Flash chromatography of the residue over silica gel (6 × 18 cm), using 1:3 to 3:7 EtOAc−hexane, gave **45** (2.10 g, 98%) as a white solid consisting of a 3:1 mixture [^{1}H NMR (400 MHz)] of anomeric lactols.

(3α,4a*β*,5α,8*β*,8a*β*)-5-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-hexahydro-8-nitrospiro[1*H*-2-benzopyran-7(3*H*),2′-[1,3]dioxolan]-3-yl 2,2-Dimethylpropanoate (46). *t*-BuCOCl (6.68 mL, 55.66 mmol) was injected over ca. 20 min into a stirred solution of lactols **45** (4.33 g, 11.12 mmol) and dry pyridine (9.10 mL, 111.3 mmol) in dry CH_2Cl_2 (100 mL). Stirring was continued at room temperature for 30 h, and then saturated aqueous $NaHCO_3$ (100 mL) was added. The organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 100 mL). All the organic phases were combined and dried (Na_2SO_4). Evaporation of the solvent and flash chromatography of the residue over silica gel (4 × 30 cm), using 3:17 EtOAc−hexane, gave **46** (5.06 g, 96%) as a pure (^{1}H NMR, 400 MHz) solid.

(3α,4a*β*,5α,8*β*,8a*β*)-8-Amino-5-[[(1,1-dimethylethyl)dimethylsilyl]-oxy]hexahydrospiro[1*H*-2-benzopyran-7(3*H*),2′-[1,3]dioxolan]-3-yl 2,2-Dimethylpropanoate (47). Bench MeOH (100 mL) was added to a flask containing $NiCl_2·6H_2O$ (1.24 g, 5.23 mmol), and the mixture was sonicated open to the air for 30 min (Branson, model B-12, 80 W). Then $NaBH_4$ (594 mg, 15.71 mmol) was added in one portion, and sonication was continued for 30 min. A solution of **46** (4.95 g, 10.45 mmol) in bench MeOH (100 mL plus 20 mL as a rinse) was added over 30 min from a dropping funnel (continued sonication, no protection from air). After the addition, more $NaBH_4$ (2.77 g, 73.27 mmol) was added in portions over 30 min (continued sonication). Sonication was continued for 15 min after the end of the addition, and the solvent was then evaporated at room temperature. The residue was immediately filtered through a column (4 × 25 cm) of flash chromatography silica gel, using 9:1 CH_2Cl_2−MeOH. Evaporation of the filtrate and flash chromatography of the residue over silica gel (4 × 30 cm), using 9:1 CH_2Cl_2−MeOH, gave **47** (4.41 g, 95%) as a pure (^{1}H NMR, 400 MHz) solid, which must be used the same day it is made.

(3α,4a*β*,5α,8*β*,8a*β*)-5-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-hexahydro-8-[[(2-propenyloxy)carbonyl]amino]spiro[1*H*-2-benzopyran-7(3*H*),2′-[1,3]dioxolan]-3-yl 2,2-Dimethylpropanoate (48). Allyl chloroformate (Aldrich material, used directly, 1.48 mL, 13.92 mmol) was injected dropwise over ca. 15 min into a stirred and cooled (ice bath) solution of **47** (4.11 g, 9.26 mmol) and dry pyridine (1.51 mL, 18.56 mmol) in dry THF (100 mL). After the addition, the cold bath was removed, and stirring was continued for 1 h. EtOAc (200 mL) was added, and the mixture was washed successively with 1:1 brine−water (50 mL), and brine (50 mL). The organic phase was dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (4 × 26 cm), using 3:7 EtOAc−hexane, gave pure (^{1}H NMR, 400 MHz) **48** (4.59 g, 94%) as a foam.

(3α,4a*β*,5α,8*β*,8a*β*)-Hexahydro-5-hydroxy-8-[[(2-propenyloxy)-carbonyl]amino]spiro[1*H*-2-benzopyran-7(3*H*),2′-[1,3]dioxolan]-3-yl 2,2-Dimethylpropanoate (49). Bu_4NF (1.0 M in THF, 10.2 mL, 10.2 mmol) was added dropwise from a syringe over 10 min to a stirred solution of **48** (4.49 g, 8.51 mmol) in THF (100 mL). The mixture was stirred for 5 h, and the solvent was then evaporated. EtOAc (300 mL) was added, and the solution was washed with 1:1 brine−water (50 mL) and brine (50 mL). The organic extract was dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (4 × 20 cm), using 4:1 EtOAc−hexane, gave **49** (3.42 g, 97%) as a pure (^{1}H NMR, 400 MHz) white solid.

(3α,4a*β*,8*β*,8a*β*)-Hexahydro-5-oxo-8-[[(2-propenyloxy)carbonyl]-amino]spiro[1*H*-2-benzopyran-7(3*H*),2′-[1,3]dioxolan]-3-yl 2,2-Dimethylpropanoate (43) from 49. A mixture of PCC (10.4 g, 48.23 mmol) and powdered 4 Å molecular sieves (2.0 g) was tipped into a stirred solution of **49** (3.32 g, 8.03 mmol) in dry CH_2Cl_2 (100 mL), and stirring was continued for 2 h. The mixture was then filtered through a column of flash chromatography silica gel (4 × 22 cm), using 1:1 EtOAc−hexane, to afford **43** (3.01 g, 91%) as a pure (^{1}H NMR, 400 MHz) solid. The filtration must be done quickly to avoid epimerization α to the ketone carbonyl.

(3α,4a*β*,5*β*,8*β*,8a*β*)-Hexahydro-5-hydroxy-8-[[(2-propenyloxy)-carbonyl]amino]-5-[(trimethylsilyl)ethynyl]spiro[1*H*-2-benzopyran-7(3*H*),2′-[1,3]dioxolan]-3-yl 2,2-Dimethylpropanoate (50). The $CeCl_3·7H_2O$ used in this experiment was washed with THF and air-dried to give white material.

Hydrated cerium chloride ($CeCl_3·7H_2O$, 11.70 g, 31.35 mmol) contained in a round-bottomed flask closed by a bent adaptor with a tap was dried for 3 h (oil bath at 130 °C, 0.05 mmHg) with magnetic stirring and then was cooled to room temperature (protection from moisture).

THF (50 mL) was added with vigorous stirring to the resulting anhydrous[40] $CeCl_3$, and the suspension was sonicated (Branson, model B-12, 80 W) overnight to obtain a fine suspension free of any lumps, which was then cooled to −78 °C. Freshly made lithium (trimethylsilyl)acetylide in THF [prepared by addition of *n*-BuLi (1.6 M in hexane, 16.3 mL, 26.0 mmol) to (trimethylsilyl)acetylene (Aldrich, 4.08 mL, 28.60 mmol) in THF (50 mL) at −78 °C, followed by stirring for 15 min at this temperature] was added to the above suspension by cannula over ca. 10 min. After the addition, stirring was continued at −78 °C for 30 min. During this procedure, the suspension remained white.

The above organocerium reagent in THF was added by cannula over ca. 15 min to a stirred and cooled (−78 °C) solution of **43** (1.07 g, 2.60 mmol) in THF (30 mL). Stirring was continued for 30 min, and the reaction was quenched by addition of saturated aqueous NH_4Cl (50 mL) at −78 °C. The cold bath was removed, and the mixture was stirred for 30 min. The mixture was extracted with EtOAc (3 × 100 mL), and the combined organic extracts were washed with brine (50 mL) and dried (Na_2SO_4). (If an emulsion forms, more water is added; should the emulsion not crack, the mixture is then filtered through a pad of Celite.) Evaporation of the solvent and flash chromatography of the residue over silica gel (4 × 10 cm), using 3:2 EtOAc−hexane, gave **50** (1.21 g, 91%) as a white solid. An X-ray structure was determined on **50** crystallized from EtOH.[33]

(3α,4a*β*,5*β*,8*β*,8a*β*)-5-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-hexahydro-8-[[(2-propenyloxy)carbonyl]amino]-5-[(trimethylsilyl)-ethynyl]spiro[1*H*-2-benzopyran-7(3*H*),2′-[1,3]dioxolan]-3-yl 2,2-Dimethylpropanoate (51). *t*-$BuMe_2SiOTf$ (1.35 mL, 5.60 mmol) was added at a fast, dropwise rate from a syringe to a stirred and cooled (ice bath) solution of **50** (2.58 g, 5.06 mmol) and 2,6-lutidine (1.33 mL, 11.20 mmol) in dry CH_2Cl_2 (15 mL). Stirring was continued for 30 min (ice bath) (TLC control; silica, 1:4 EtOAc−hexane), and then MeOH (2 mL) was added, followed by Et_2O (300 mL). The mixture was washed with 10% aqueous $CuSO_4$ (2 × 30 mL) and then with brine (50 mL). The organic extract was dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (4 × 16 cm), using 3:17 EtOAc−hexane, gave **51** (2.94 g, 93%) as a pure (^{1}H NMR, 400 MHz), white solid.

2-Propenyl (3α,4a*β*,5*β*,8*β*,8a*β*)- and (3α,4aα,5α,8α,8aα)-[5-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]hexahydro-3-hydroxy-5-[(trimethylsilyl)ethynyl]spiro[1*H*-2-benzopyran-7(3*H*),2′-[1,3]dioxolan]-8-yl]carbamate (52). DIBAL-H (1.0 M solution in CH_2Cl_2, 13.4 mL, 13.4 mmol) was added dropwise by syringe over ca. 15 min to a stirred and cooled (−78 °C) solution of **51** (2.78 g, 4.46 mmol) in CH_2Cl_2 (100 mL). Stirring at −78 °C was continued for 30 min, and then MeOH (2 mL) was added, followed successively by Na_2SO_4 (2 g), Celite (5 g), and water (2 mL). The cold bath was removed, and stirring was continued for 30 min. The mixture was then filtered through a sintered disk, and the solid was washed with EtOAc. Evaporation of the filtrate and flash chromatography of the residue over silica gel (4 × 15 cm), using 2:3 EtOAc−hexane, gave **52** (2.31 g, 96%) as a pure (TLC, silica, 1:1 EtOAc−hexane), white solid.

2-Propenyl (4aα,5α,8α,8aα)-[5-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]hexahydro-3-oxo-5-[(trimethylsilyl)ethynyl]spiro[1*H*-2-benzopyran-7(3*H*),2′-[1,3]dioxolan]-8-yl]carbamate (44). Note that **44** ≡ **73**. CrO_3 (6.53 g, 65.3 mmol) was added in portions over ca. 5 min to a stirred solution of pyridine (10.5 mL, 130.6 mmol) in dry CH_2Cl_2 (50 mL) at room temperature. Stirring was continued for 10 min, and the resulting Collins reagent was poured (over ca. 1 min) into a stirred solution of **52** (2.20 g, 4.08 mmol) in dry CH_2Cl_2 (50 mL). Stirring was continued for 20 min, and the mixture was then filtered through a column (4 × 18 cm) of flash silica gel, using a 2:3 mixture of EtOAc−hexane. Evaporation of the solvent gave **44** (2.12 g, 97%) as a pure (^{1}H NMR, 400 MHz), white solid.

2-Propenyl (5α,8α,8aα)-[5-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-5,6,8,8a-tetrahydro-3-oxo-5-[(trimethylsilyl)ethynyl]spiro[1*H*-2-benzopyran-7(3*H*),2′-[1,3]dioxolan]-8-yl]carbamate (74). (a) 2-Propenyl (4α,4aα,5α,8α,8aα)-[5-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]hexahydro-3-oxo-4-(phenylseleno)-5-[(trimethylsilyl)ethynyl]spiro[1*H*-2-benzopyran-7(3*H*),2′-[1,3]dioxolan]-8-yl]carbamate. *n*-BuLi (1.6 M in hexane, 2.44 mL, 3.91 mmol) was added dropwise over ca. 10 min to a stirred and cooled (ice bath) solution of *i*-Pr_2NH (0.69 mL, 4.69 mmol) in THF (25 mL). Stirring was continued for 15 min, and the solution was then cooled to −78 °C. The resulting solution of LDA was added over ca. 1 min by cannula to a stirred and cooled (−78 °C) solution of **73** (≡ **44**) (700 mg, 1.30 mmol) in THF (25 mL), and stirring was continued for 40 min.

During this time, PhSeBr was prepared by adding bromine (234 μL, 4.55 mmol) dropwise to a stirred solution of PhSeSePh (1.63 g, 5.20 mmol) in THF (10 mL) at room temperature. The mixture was stirred for 10 min, cooled to −78 °C, and then added over ca. 20 s by cannula to the main reaction mixture. Stirring was continued for 15 min, saturated aqueous NH_4Cl (50 mL) was added, and the mixture was extracted with EtOAc (2 × 100 mL). The combined organic extracts were washed with brine (50 mL), dried (Na_2SO_4), and evaporated *at room temperature*. Flash chromatography of the residue over silica gel (2 × 30 cm), using first 1:10 and then 3:7 EtOAc−hexane, gave the crude phenyl selenide, which was used directly in the next step without purification or characterization. The compound is not stable, and should be used the same day.

Our impression from the integration of ^{1}H NMR spectra run on the crude product is that C,N-diselenated material (almost 50% of the total) is present, but the crude material is still suitable for the next step.

(b) Selenoxide Fragmentation. Ice-cold dimethyldioxirane[44] (0.07 M in acetone, 28.0 mL, 1.96 mmol) was added over ca. 10 min from a syringe to a stirred and cooled (−45 °C) solution of the above crude selenide in CH_2Cl_2 (30 mL). Stirring at −45 °C was continued for 30 min (TLC control, silica, 3:7 EtOAc−hexane), by which time the initially yellow solution had become almost colorless, and no starting material was detected by TLC. The solution was evaporated at room temperature, and flash chromatography of the residue over silica gel (2 × 30 cm), using 1:3 EtOAc−hexane, gave **74** (592 mg, 85% over two steps) as a pure (^{1}H NMR, 400 MHz) white solid. Some starting material (36 mg, 5%) was also recovered. The yield of product, corrected for recovered starting material, was 89%.

(5α,8α,8aα)-8-Amino-5-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-5,6,8,8a-tetrahydro-5-[(trimethylsilyl)ethynyl]spiro[1*H*-2-benzopyran-7(3*H*),2′-[1,3]dioxolan]-3-one (75). $(Ph_3P)_4Pd$ (173 mg, 0.150 mmol) was tipped into a stirred solution of **74** (800 mg, 1.49 mmol) and dimedone (1.26 g, 8.97 mmol) in dry THF (25 mL) (Ar atmosphere, protection from light by aluminum foil). Stirring in the dark at room temperature was continued for 3 h, and the mixture was then evaporated. The residue was dissolved in CH_2Cl_2 (50 mL), and the solution was washed with saturated aqueous Na_2CO_3 (30 mL). The aqueous phase was extracted with CH_2Cl_2 (2 × 30 mL), and the combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2 × 25 cm), using 3:2 EtOAc−hexane, gave **75** (628 mg, 93%) as a pure (^{1}H NMR, 400 MHz), faintly yellow solid.

8-Amino-5-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-5,6-dihydro-5-[(trimethylsilyl)ethynyl]spiro[1*H*-2-benzopyran-7(3*H*),2′-[1,3]-dioxolan]-3-one (76). (a) (5α,8α,8aα)-8-Chloramino-5-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-5,6,8,8a-tetrahydro-5-[(trimethylsilyl)ethynyl]spiro[1*H*-2-benzopyran-7(3*H*),2′-[1,3]dioxolan]-3-one. Freshly prepared *t*-BuOCl[48] (156 mg, 1.44 mmol) in dry Et_2O (18 mL) was added by syringe pump over 1 h to a stirred and cooled (−45 °C) solution of **75** (590 mg, 1.31 mmol) in a mixture of THF (10 mL) and Et_2O (20 mL). Stirring at −45 °C was continued for 15 min after the end of the addition, and the mixture was then evaporated at room temperature to afford the crude *N*-chloro compound. The material appeared to be homogeneous by TLC (silica, 1:1 EtOAc−hexane), but was used directly in the next step without characterization.

(b) Elimination of HCl. DBU (1.55 mL, 10.40 mmol) was added over 3 min to a stirred solution of the above crude *N*-chloro compound (all the material from the previous experiment) in PhMe (15 mL) at room temperature. Stirring was continued for 45 min. Next, Et_2O (50 mL) and then 10% aqueous $CuSO_4$ (30 mL) were added. The mixture was shaken vigorously, and the aqueous phase was extracted with Et_2O (2 × 50 mL). The combined organic extracts were washed with brine (30 mL), dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel (2 × 22 cm), using 1:1 EtOAc−hexane, gave **76** (476 mg, 81% over the two steps) as a pure (^{1}H NMR, 400 MHz), yellowish foam. Some starting amine (**75**) (36 mg, 6%) was also recovered. The material (**76**) should be stored in a refrigerator and used within 2 days.

Methyl [5-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-5,6-dihydro-3-oxo-5-[(trimethylsilyl)ethynyl]spiro[1*H*-2-benzopyran-7(3*H*),2′-[1,3]-dioxolan]-8-yl]carbamate (77). Dry pyridine (1.29 mL, 15.57 mmol) was injected into a stirred and cooled (0 °C) solution of **76** (466 mg, 1.04 mmol) in dry CH_2Cl_2 (50 mL). Then, triphosgene (927 mg, 3.11 mmol) was tipped into the mixture. The cold bath was removed, and stirring was continued for 50 min. The mixture was recooled to 0 °C. Pyridine (1.29 mL, 15.57 mmol) and dry MeOH (12.8 mL) were injected, and stirring at 0 °C was continued for 1 h. At this stage, brine (30 mL) was added, and the organic phase was separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2 × 20 cm), using 3:7 EtOAc−hexane, gave **77** (479 mg, 91%) as a pure (^{1}H NMR, 400 MHz) white solid.

Methyl *trans*- and *cis*-[1-Bromo-5-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-5,6-dihydro-3-oxo-5-[(trimethylsilyl)ethynyl]spiro[1*H*-2-benzopyran-7(3*H*),2′-[1,3]dioxolan]-8-yl]carbamate (78). Lactone **77** (200 mg, 0.39 mmol) and $(PhCO)_2O_2$ (two small grains; less than 1 mg) were covered with dry CCl_4 (20 mL), and the mixture was refluxed under Ar and illuminated by a 100 W tungsten filament bulb held close to the flask. The lamp, flask, and oil bath were surrounded by aluminum foil. The condenser was removed momentarily, and a small portion of NBS was added. Addition of NBS was repeated at intervals of 10−15 min after each batch had reacted (disappearance of the reagent from the bottom of the flask—which could be detected clearly) until all the NBS (176 mg, 0.99 mmol) had been added. The addition took ca. 1 h. Refluxing and irradiation was continued for a further 15 min after the end of the last addition. At this point, the last batch of NBS had reacted, and none was left at the bottom of the flask. The mixture was cooled and filtered through a pad (2 × 3 cm) of Celite, using CCl_4 (ca. 10−15 mL). Evaporation of the filtrate at room temperature gave crude **78**, which was used directly without characterization: The ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) shows disappearance of the C(9)-H_2 signal and new signals at δ 8.05, 7.25, and 6.5.

We suspect, from the stoichiometry of reagents used (2.5 equiv of NBS), that the nitrogen of the carbamate has been brominated, but we have no spectral data to confirm this point. When we used 1.2 equiv of NBS, the overall yield, after conversion to **79**, was the same, and presumably, the nitrogen has not been brominated.

Methyl (8*E*)-[9-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-9-ethynyl-7-formyl-6-[(methoxycarbonyl)amino]-1,4-dioxaspiro[4.5]dec-6-en-8-ylidene]acetate (79). (a) Methyl *trans*- and *cis*-[5-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-5-ethynyl-5,6-dihydro-1-hydroxy-3-oxospiro[1*H*-2-benzopyran-7(3*H*),2′-[1,3]dioxolan]-8-yl]carbamate. The crude product from the above experiment was dissolved in dry THF (15 mL), and dry pyridine (0.16 mL, 1.97 mmol) was injected. A solution of $AgNO_3$ (201 mg, 1.18 mmol) in water (2 mL) was then added dropwise with stirring over ca. 1.5 min. The flask was then immediately wrapped with aluminum foil, and stirring was continued for 3 h. Brine (30 mL) was added, and stirring was continued for 15 min. The mixture was then filtered through a pad (2 × 3 cm) of Celite, which was washed with CH_2Cl_2. The organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 15 mL). The combined organic phases were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1 × 20 cm), using 1:1 EtOAc−hexane, gave the desired hydroxy lactone (147 mg, ca. 83%) as a slightly impure (^{1}H NMR, 400 MHz) oil, which was suitable for the next step.

(b) Methyl (8*E*)-[9-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-9-ethynyl-7-formyl-6-[(methoxycarbonyl)amino]-1,4-dioxaspiro[4.5]dec-6-en-8-ylidene]acetate (79). Ethereal CH_2N_2 (made by the procedure supplied with the Aldrich Diazald kit, 1.1 mL) was added to a stirred and cooled (0 °C) solution of the above hydroxy lactone (127 mg, ca. 0.282 mmol) in shelf Et_2O (5 mL). After the addition, a faint yellow color persisted. Stirring was continued for 1 h. Evaporation of the yellowish solution, and flash chromatography of the residue over silica gel (1 × 15 cm), using 2:3 EtOAc−hexane, gave the crude product. Rechromatography, under the same conditions, gave **79** (121 mg, ca. 93%, or 77% over three steps) as a pure (^{1}H NMR, 400 MHz) white solid.

Methyl *trans*-[5-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-5-ethynyl-5,6-dihydro-3-oxo-1-[(trimethylsilyl)ethynyl]spiro[1*H*-2-benzopyran-7(3*H*),2′-[1,3]dioxolan]-8-yl]carbamate (80). The $CeCl_3\cdot 7H_2O$ used in this experiment was washed with THF and air-dried to give a white material.

Hydrated cerium chloride ($CeCl_3\cdot 7H_2O$, 1.12 g, 3.01 mmol) contained in a round-bottomed flask closed with a bent adaptor with a tap was dried for 3 h (oil bath at 130 °C, 0.05 mmHg) with magnetic stirring and then cooled to room temperature (protection from moisture).

THF (6 mL) was added with vigorous stirring to the resulting anhydrous $CeCl_3$, and the suspension was sonicated (Branson, model B-12, 80 W) overnight to obtain a fine suspension free of any lumps, which was then cooled to −78 °C. Freshly made lithium (trimethylsilyl)acetylide in THF [prepared by addition of *n*-BuLi (1.6 M in hexane, 1.45 mL, 2.32 mmol) to (trimethylsilyl)acetylene (Aldrich, 0.35 mL, 2.55 mmol) in THF (6 mL) at −78 °C, followed by stirring for 15 min at this temperature] was added to the above suspension by cannula over ca. 3 min. After the addition, stirring was continued at −78 °C for 45 min. During this procedure, the suspension remained white.

The above organocerium reagent in THF was added by cannula over ca. 3 min to a stirred and cooled (−78 °C) solution of **79** (108 mg, 0.232 mmol) in THF (5 mL). Stirring was continued for 30 min, and the reaction was quenched by the addition of saturated aqueous NH_4Cl (6 mL) at −78 °C. The cold bath was removed, and the mixture was stirred for 10 min. The mixture was extracted with EtOAc (3 × 10 mL), and the combined organic extracts were washed with brine (5 mL) and dried (Na_2SO_4). Evaporation of the solvent and flash chromatography of the residue over silica gel (1 × 15 cm), using 3:7 EtOAc−hexane, gave **80** (112 mg, 91%) as a pure (^{1}H NMR, 400 MHz), white solid.

Methyl *trans*-[5-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-1,5-diethynyl-5,6-dihydro-3-oxospiro[1*H*-2-benzopyran-7(3*H*),2′-[1,3]dioxolan]-8-yl]carbamate (72) and Methyl *cis*-[5-[[(1,1-Dimethylethyl)-dimethylsilyl]oxy]-1,5-diethynyl-5,6-dihydro-3-oxospiro[1*H*-2-benzopyran-7(3*H*),2′-[1,3]dioxolan]-8-yl]carbamate (71). Bu_4NF (1.0 M in THF, 62 μL, 0.062 mmol[62]) was added to a stirred and cooled (0 °C) solution of **80** (66 mg, 0.124 mmol[62]) in THF (3 mL), and stirring was continued at 0 °C for 30 min. A 1:1 water−brine mixture (2 mL) was added, and the mixture was extracted with EtOAc (3 × 5 mL). The combined organic extracts were washed with brine (3 mL), dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel (1 × 10 cm), using 2:3 EtOAc−hexane, gave the less polar isomer **71** (24 mg, 42%) and the more polar isomer **72** (26 mg, 46%), identical to the corresponding compounds obtained from a mixture of **69** and its anti isomer.

Methyl *trans*-[5-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-1,5-diethynyl-5,6-dihydro-3-oxospiro[1*H*-2-benzopyran-7(3*H*),2′-[1,3]dioxolan]-8-yl]carbamate (72) from 71. Bu_4NOAc (7.5 mg, 0.022 mmol) was added to a solution of **71** (20 mg, 0.044 mmol) in THF (2 mL), and the mixture was stirred at room temperature for 5 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (0.6 × 8 cm), using 2:3 EtOAc−hexane, gave **72** (12 mg, 60%) and recovered **71** (8 mg, 40%).

Methyl *trans*-[5-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-5,6-dihydro-1,5-bis(iodoethynyl)-3-oxospiro[1*H*-2-benzopyran-7(3*H*),2′-[1,3]dioxolan]-8-yl]carbamate (81). NIS (88 mg, 0.393 mmol) and $AgNO_3$ (1.5 mg, 0.0088 mmol) were added to a stirred solution of **72** (82 mg, 0.179) in acetone (3 mL) contained in a flask protected from light by being wrapped in aluminum foil. Stirring at room temperature was continued for 5 h. The mixture was poured into ice water (5 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (5 mL), dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel (1 × 12 cm), using 7:13 EtOAc−hexane, gave **81** (113 mg, 89%) as a pure (^{1}H NMR, 400 MHz), white solid.

Methyl (1′*R,5′*S**,11′*Z*)-[5′[[(1,1-Dimethylethyl)dimethylsilyl]-oxy]-5′,6′-dihydro-3′-oxospiro[1,3-dioxolane-2,7′(3′*H*)-[1,5][3]hexene-[1,5]diyno[1*H*-2]benzopyran]-8′-yl]carbamate (82).** Freshly distilled (*Z*)-1,2-bis(trimethylstannyl)ethene[56] (54.7 mg, 0.155 mmol) in dry DMF (10 mL) was added by syringe pump over 30 min to a stirred and warmed (60 °C) solution of **81** (110 mg, 0.155 mmol) and $(Ph_3P)_4$-Pd (from a freshly opened ampule, 17.9 mg, 0.0155 mmol) in DMF (20 mL). Stirring at 60 °C was continued, and the reaction was monitored by TLC (silica, 1:1 EtOAc−hexane). (First a polar spot appears and then a less polar spot of similar R_f to that of the starting material. This is the desired product.) After 3 h, the reaction was complete, and the solvent was then evaporated under oil pump vacuum at 40 °C. Flash chromatography of the residue over silica gel (1 × 15 cm), using 2:3 EtOAc−hexane, gave **82** (54 mg, 72%) as a pure (^{1}H NMR, 400 MHz), white solid.

Methyl (1′*R,3′*R**,5′*S**,11′*Z*)- and (1′*R**,3′*S**,5′*S**,11′*Z*)-[5′-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-5′,6′-dihydro-3′-hydroxyspiro[1,3-dioxolane-2,7′(3′*H*)-[1,5][3]hexene[1,5]diyno[1*H*-2]benzopyran]-8′-yl]carbamate (83).** DIBAL-H (1.0 M in CH_2Cl_2, 0.25 mL, 0.25 mmol) was added dropwise to a stirred and cooled (−78 °C) solution of **82** (40 mg, 0.0828 mmol) in CH_2Cl_2 (3 mL). Stirring was continued at −78 °C for 30 min. MeOH (0.2 mL) was added, followed by Na_2SO_4 (0.5 g), Celite (2 g), and water (4 drops). The cold bath was removed, and stirring was continued for 30 min. The mixture was filtered through a sintered disk, and the insoluble material was washed with EtOAc. The combined filtrates were evaporated, and flash chromatography over silica gel (1 × 8 cm), using 2:3 EtOAc−hexane, gave **83** (39.2 mg, 98%) as a pure (^{1}H NMR, 400 MHz), white solid that was a mixture of anomers.

Methyl (1′*R,3′*R**,5′*S**,11′*Z*)- and (1′*R**,3′*S**,5′*S**,11′*Z*)-(5′,6′-Dihydro-3′,5′-dihydroxyspiro[1,3-dioxolane-2,7′(3′*H*)-[1,5][3]hexene-[1,5]diyno[1*H*-2]benzopyran]-8′-yl)carbamate (84).** Bu_4NF (1.0 M in THF, 0.089 mL, 0.089 mmol) was added to a stirred and cooled (0 °C) solution of **83** (39 mg, 0.080 mmol) in THF (2 mL). Stirring was continued at 0 °C for 30 min, and saturated aqueous NH_4Cl (5 mL) was added. The mixture was extracted with EtOAc (3 × 10 mL), and the combined organic extracts were washed with brine (5 mL), dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel (1 × 8 cm), using 4:1 EtOAc−hexane, gave **84** (28.2 mg, 94%) as a pure (^{1}H NMR, 400 MHz), colorless glass that was a mixture of epimers.

Methyl (1*R,4*Z*,8*S**,13*E*)-[1,8-Dihydroxy-13-(2-hydroxyethylidene)-spiro[bicyclo[7.3.1]trideca-4,9-diene-2,6-diyne-11,2′-[1,3]dioxolan]-10-yl]carbamate (85).** $NaBH_4$ (57.5 mg, 1.52 mmol) was added to a stirred and cooled (0 °C) solution of **84** (28.2 mg, 0.076 mmol) in bench MeOH (1.5 mL). Stirring was continued for 2 h, and then AcOH (0.6 mL) was added dropwise at 0 °C. Stirring was continued for 5 min, and the solution was evaporated. THF (1 mL), MeOH (2 mL), and water (4 drops) were added sequentially, and the mixture was stirred for 20 min and then evaporated. THF (3 mL), MeOH (3 drops) and water (3 drops), were again added sequentially. The mixture was stirred for 20 min and then filtered through a pad (0.6 × 2 cm) of Celite, which was washed well with THF. Evaporation of the filtrate and flash chromatography of the residue over silica gel (1 × 8 cm), using first 4:1 EtOAc−hexane and then 1:19 MeOH−EtOAc, gave **85** (21.5 mg, 76%) as a pure (^{1}H NMR, 400 MHz), white glass.

Methyl (1*R,4*Z*,8*S**,13*E*)-[1-Hydroxy-8-[(triethylsilyl)oxy]-13-[2-[(triethylsilyl)oxy]ethylidene]spiro[bicyclo[7.3.1]trideca-4,9-diene-2,6-diyne-11,2′-[1,3]dioxolan]-10-yl]carbamate (86).** Dry 2,6-lutidine (30.1 μL, 0.254 mmol) and then Et_3SiOTf (30.3 μL, 0.127 mmol) were added dropwise to a stirred and cooled (0 °C) solution of **85** (21.5 mg, 0.0576 mmol) in dry CH_2Cl_2 (2 mL). Stirring at 0 °C was continued

(62) A deficiency of Bu_4NF is used: Cf. Nishikawa, T.; Ino, A.; Isobe, M. *Tetrahedron* **1994**, *50*, 1449.

for 20 min, and then 10% aqueous $CuSO_4$ (3 mL) was added. The mixture was extracted with Et_2O (2 × 20 mL). The combined organic extracts were washed with brine (5 mL), dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel (1 × 8 cm), using 1:3 EtOAc−hexane, gave **86** (32.9 mg, 95%) as a pure (^{1}H NMR, 400 MHz) oil.

Methyl (1*R,4*Z*,8*S**,13*E*)-[1-Hydroxy-13-(2-hydroxyethylidene)-8-[(triethylsilyl)oxy]spiro[bicyclo[7.3.1]trideca-4,9-diene-2,6-diyne-11,2′-[1,3]dioxolan]-10-yl]carbamate (87).** A 3:6:1 mixture (0.6 mL) of AcOH, THF, and water was added to **86** (32.9 mg, 0.0547 mmol) contained in a flask immersed in an ice bath at 0 °C, and the resulting solution was stirred for 30 min. Saturated aqueous $NaHCO_3$ (5 mL) was added, the mixture was extracted with CH_2Cl_2 (3 × 5 mL), and the combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1 × 8 cm), using 4:1 EtOAc−hexane, gave **87** (25 mg, 94%) as a pure (^{1}H NMR, 400 MHz) oil.

(1*R,4*Z*,8*S**,13*E*)-*S*-[2-[1-Hydroxy-10-[(methoxycarbonyl)amino]-8-[(triethylsilyl)oxy]spiro[bicyclo[7.3.1]trideca-4,9-diene-2,6-diyne-11,2′-[1,3]dioxolan]-13-ylidene]ethyl] Ethanethioate (88).** Diisopropyl azodicarboxylate (40.6 μL, 0.205 mmol) was added to a stirred and cooled (0 °C) solution of Ph_3P (70.0 mg, 0.267 mmol) in THF (1 mL). Stirring was continued for 30 min, and then AcSH (15 μL, 0.205 mmol) followed immediately by a solution of **87** (12.5 mg, 0.0256 mmol) in THF (0.4 mL plus 0.2 mL as a rinse) were added dropwise. Stirring at 0 °C was continued for 30 min. Saturated aqueous $NaHCO_3$ (4 mL) was added, and the mixture was extracted with EtOAc (3 × 5 mL). The combined organic extracts were washed with brine (5 mL), dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel (0.6 × 8 cm), using 7:13 EtOAc−hexane, gave **88** (13.1 mg, 94%) as a pure (^{1}H NMR, 400 MHz) white solid.

Methyl (1*R,4*Z*,8*S**,13*E*)-[1-hydroxy-13-(2-mercaptoethylidene)-8-[(triethylsilyl)oxy]spiro[bicyclo[7.3.1]trideca-4,9-diene-2,6-diyne-11,2′-[1,3]dioxolan]-10-yl]carbamate (89).** DIBAL-H (1.0 M in CH_2Cl_2, 0.097 mL, 0.097 mmol) was added dropwise to a stirred and cooled (−78 °C) solution of **88** (6.60 mg, 0.0121 mmol) in CH_2Cl_2 (2 mL). Stirring was continued for 30 min, and then MeOH (0.03 mL), Na_2SO_4 (0.5 g), Celite (1 g), and water (3 drops) were added. The cold bath was removed, and the mixture was stirred for 30 min and then filtered through a sintered disk. The insoluble material was washed with EtOAc. Evaporation of the combined filtrates and flash chromatography of the residue over silica gel (0.6 × 6 cm), using 3:7 EtOAc−hexane, gave crude **89**, suitable for the next stage. No spectroscopic data were obtained. Chromatography is necessary to ensure a pure product in the next step, which was carried out *immediately*.

Methyl (1*R,4*Z*,8*S**,13*E*)-[1-Hydroxy-13-[2-(methylthio)ethylidene]-8-[(triethylsilyl)oxy]spiro[bicyclo[7.3.1]trideca-4,9-diene-2,6-diyne-11,2′-[1,3]dioxolan]-10-yl]carbamate (90).** In this experiment, it is important to use freshly chromatographed thiol and a large (ca. 8-fold) excess of *N*-(methyldithio)phthalimide.

The chromatographed crude thiol from the last experiment was dissolved in dry CH_2Cl_2 (0.5 mL), and the solution was cooled to 0 °C. *N*-(Methyldithio)phthalimide[2a] (recrystallized[63] from CH_2Cl_2−EtOH, 21.8 mg, 0.0968 mmol) was tipped in, and stirring was continued for 2 h. Hexane (1 mL) was added, and the mixture was applied directly to a flash chromatography column (0.6 × 8 cm) packed with silica gel, a little 3:7 EtOAc−hexane being used as a rinse. The column was developed with 3:7 EtOAc−hexane to obtain pure (^{1}H NMR, 400 MHz) **90** (6.2 mg, 88% over two steps) as an oil.

Methyl (1*R,4*Z*,8*S**,13*E*)-(±)-[1,8-Dihydroxy-13-[2-(methylthio)-ethylidene]-11-oxobicyclo[7.3.1]trideca-4,9-diene-2,6-diyne-10-yl]-carbamate (1) [(±)-calicheamicinone)].** $TsOH·H_2O$ (4.1 mg, 0.0213 mmol) was added to a stirred solution of **90** (6.2 mg, 0.0107 mmol) in a mixture of THF (0.6 mL) and water (1 drop), and stirring was continued at room temperature for 15 h. Hexane (1 mL) was added, and the mixture was applied directly to a flash chromatography column (0.6 × 8 cm) packed with silica gel, a little 1:1 Et_2O−hexane being used as a rinse. The column was developed with 1:1 Et_2O−hexane to obtain pure (^{1}H NMR, 400 MHz) (±)-calicheamicinone (**1**) (3.8 mg, 84%) as a white foam.

Selected Procedures for Route via 42. (6α,7*β*,8*β*,9*β*)-[6-Amino-9-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-8-[2-[(4-methoxyphenoxy)-methoxy]ethyl]-1,4-dioxaspiro[4.5]dec-7-yl]methyl 2,2-Dimethyl-propanoate (35). $NiCl_2·6H_2O$ (1.12 g, 4.71 mmol) in commercial MeOH (200 mL) was sonicated (Branson, model B-12, 80 W) to complete dissolution (ca. 2 min). $NaBH_4$ (535.0 mg, 14.14 mmol) was then added in one portion, and the mixture was sonicated for ca. 10 min to give a fine black suspension. A solution of **34** (5.25 g, 8.58 mmol) in MeOH (50 mL plus 2 × 10 mL as a rinse) was added over ca. 30 min, and more $NaBH_4$ (4.87 g, 128.7 mmol) was then added portionwise over 30 min (continuous sonication). Sonication was continued for a further 30 min after the addition of $NaBH_4$. Most of the solvent was then evaporated. The mixture was diluted with $CHCl_3$ (60 mL) and filtered through a column of silica gel (4.5 × 20 cm) by gravity, using 5:1 $CHCl_3$−MeOH, to give a crude material (all black Ni_2B was left on the column). This was purified by flash chromatography over silica gel (4.5 × 25 cm), using 10:1 $CHCl_3$−MeOH, to give **35** (4.75 g, 95%) as a colorless oil.

(6α,7*β*,8*β*)-[8-[2-[(4-Methoxyphenoxy)methoxy]ethyl]-9-oxo-6-[[(2-propenyloxy)carbonyl]amino]-1,4-dioxaspiro[4.5]dec-7-yl]methyl 2,2-Dimethylpropanoate (38) from 37. CrO_3 (10.00 g, 100.0 mmol) was added at room temperature in three portions to a vigorously stirred solution of dry pyridine (16.2 mL, 200.0 mmol) in CH_2Cl_2 (130 mL), and the mixture was stirred for 10 min. The resulting freshly made Collins reagent was then poured slowly into to a stirred solution of **37** (3.57 g, 6.47 mmol) in CH_2Cl_2 (250 mL). Stirring was continued for 10 min, and the mixture was then filtered through a pad (4.5 × 4.0 cm) of silica gel, using EtOAc. The filtration and subsequent chromatography must be done quickly to avoid epimerization α to the ketone carbonyl. Evaporation of the solvent and flash chromatography of the residue over silica gel (3.5 × 18 cm), using 3:2 EtOAc−hexane, gave **38** (3.39 g, 95%).

(6α,7*β*,8*β*,9*β*)-[9-Hydroxy-8-[2-[(4-methoxyphenoxy)methoxy]-ethyl]-6-[[(2-propenyloxy)carbonyl]amino]-9-[(trimethylsilyl)ethynyl]-1,4-dioxaspiro[4.5]dec-7-yl]methyl 2,2-Dimethylpropanoate (39). The following is the maximum scale for this reaction (at least with our Branson sonicator (model B-12, 80 W). If more powerful sonication is used, it is possible that the reaction could be scaled up, but we have not tried this.

Hydrated cerium chloride ($CeCl_3·7H_2O$, 10.7309 g) contained in a round-bottomed flask closed with a bent adaptor with a tap was dried overnight (oil bath at 130 °C, 0.05 mmHg) with vigorous magnetic stirring and then cooled to room temperature (protection from moisture) to obtain anhydrous[40] $CeCl_3$ (7.1850 g).

THF (25 mL) was added with vigorous stirring to the resulting anhydrous $CeCl_3$ (7.1850 g, 29.15 mmol), and the suspension was sonicated (Branson, model B-12, 80 W) for 4 h to obtain a fine suspension free of any lumps, which was then cooled to −42 °C. Freshly made lithium (trimethylsilyl)acetylide in THF [prepared by addition of *n*-BuLi (1.6 M in hexane, 13.0 mL, 20.8 mmol) to (trimethylsilyl)acetylene (Aldrich, 3.3 mL, 23.00 mmol) in THF (14 mL) at −78 °C, followed by stirring for 5 min at this temperature] was added to the above suspension by cannula (over ca. 5 min). After the addition, the suspension partially dissolved. Stirring was continued at −42 °C for 40 min. (*If the suspension is yellowish and the color does not fade after stirring for 40 min, do not use the reagent, because the yield in the reaction will be low*.)

The above organocerium reagent in THF was added by cannula (over ca. 5 min) to a stirred and cooled (−78 °C) solution of **38** (1.19 g, 2.17 mmol) in THF (35 mL). Stirring was continued for 10 min, and the reaction was quenched by addition of saturated aqueous NH_4Cl (20 mL) at −78 °C. The cold bath was removed, and the mixture was allowed to attain room temperature (over ca. 45 min). The mixture was diluted with saturated aqueous NH_4Cl (40 mL) and extracted with EtOAc (3 × 60 mL). The combined organic extracts were washed with brine (100 mL) and dried (Na_2SO_4). Evaporation of the solvent and flash chromatography of the residue over silica gel (2.0 × 22 cm), using 3:2 and then 3:1 EtOAc−hexane, gave **39** (1.28 g, 91%) as a colorless oil.

(63) Pure reagent can be used even after storage at room temperature for 1 year.

2-Propenyl (6α,7β,8β,9β)-[9-[[(1,1-Dimethylethyl)dimethylsilyl]-oxy]-7-formyl-8-[2-[(4-methoxyphenoxy)methoxy]ethyl]-9-[(trimethylsilyl)ethynyl]-1,4-dioxaspiro[4.5]dec-6-yl]carbamate (42). CrO_3 (10.00 g, 100.0 mmol) was added at room temperature in three portions to a vigorously stirred solution of dry pyridine (16.2 mL, 200.0 mmol) in dry CH_2Cl_2 (150 mL), and the mixture was stirred for 10 min. The resulting freshly made Collins reagent was then poured slowly into a stirred solution of **41** (4.47 g, 6.59 mmol) in CH_2Cl_2 (150 mL). Stirring was continued for 10 min, and the mixture was then filtered through a pad (4.5 × 3.5 cm) of silica gel, using EtOAc. Evaporation of the solvent and flash chromatography of the residue over silica gel (4.5 × 20 cm), using 3:1 EtOAc−hexane, gave **42** (4.04 g, 90%) as a colorless oil.

2-Propenyl [6α,7β(*R),8β,9β]- and [6α,7β(*S**),8β,9β]-[9-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-7-[1-hydroxy-3-(trimethylsilyl)-2-propynyl]-8-[2-[(4-methoxyphenoxy)methoxy]ethyl]-9-[(trimethylsilyl)-ethynyl]-1,4-dioxaspiro[4.5]dec-6-yl]carbamate (53) and (54).** Hydrated cerium chloride ($CeCl_3 \cdot 7H_2O$, 10.7002 g) contained in a round-bottomed flask closed with a bent adaptor with a tap was dried overnight (oil bath at 130 °C, 0.05 mmHg) with vigorous magnetic stirring and then cooled to room temperature (protection from moisture) to obtain $CeCl_3$ (7.0849 g).

THF (25 mL) was added by syringe to the resulting anhydrous $CeCl_3$ (7.0849 g, 28.74 mmol) with vigorous stirring, and stirring was continued for 30 min. The suspension was then sonicated (Branson, model B-12, 80 W) for 4 h to obtain a fine suspension, which was then cooled to −42 °C. (We suspect that a more powerful sonicator would have been better.) Freshly made, cold (−78 °C) lithium (trimethylsilyl)acetylide in THF [prepared by addition of *n*-BuLi (1.6 M in hexane, 13.0 mL, 20.8 mmol) to (trimethylsilyl)acetylene (3.3 mL, 23.00 mmol) in THF (15 mL) at −78 °C, followed by stirring for 5 min at this temperature] was added to the above suspension by cannula (over ca. 2 min). After the addition, the yellowish suspension partially dissolved (sometimes the color was nearly white; this color indicates that the reagent is of good quality). Stirring was continued at −42 °C (dry ice−MeCN) for 40 min, by which time the color had almost faded. (*If the suspension is yellowish and the color does not fade after stirring for 40 min, the reagent should not be used, because the yield in the reaction will be low*.) Then the mixture was cooled in an acetone/dry ice bath.

The above organocerium reagent in THF was added by cannula (over ca. 3 min) to a stirred and cooled (MeOH/liquid N_2, bath temperature −90 °C) solution of **42** (1.29 g, 1.91 mmol) in THF (30 mL). Stirring was continued for 10 min, and the reaction was quenched by addition of saturated aqueous NH_4Cl (20 mL) at −90 °C. The cold bath was removed, and the mixture was stirred for ca. 30 min, during which time it attained room temperature. The mixture was diluted with saturated aqueous NH_4Cl (50 mL) and extracted with EtOAc (3 × 60 mL). The combined organic extracts were washed with brine (100 mL) and dried (Na_2SO_4). After evaporation of the solvent, the ^1H NMR spectrum of the residue showed that the crude material was a mixture of two isomers in a ratio of 5:1 (desired compound to undesired compound). Flash chromatography of the material over silica gel (3.5 × 30 cm), using 1:15 and then 1:5 EtOAc−hexane, gave **53** (1.168 g, 79%) as a colorless oil and its C(9) epimer **54** (233 mg, 16%) as a colorless oil.

2-Propenyl [6α,7β,8β,9β]-[9-[[(1,1-Dimethylethyl)dimethylsilyl]-oxy]-7-[1-oxo-3-(trimethylsilyl)-2-propynyl]-8-[2-[(4-methoxyphenoxy)-methoxy]ethyl]-9-[(trimethylsilyl)ethynyl]-1,4-dioxaspiro[4.5]dec-6-yl]carbamate (55). PCC (147 mg, 0.682 mmol) and powdered 4 Å molecular sieves (50 mg) were added to a stirred solution of **54** (88 mg, 0.114 mmol) in dry CH_2Cl_2 (10 mL). Stirring was continued overnight, and the mixture was then applied directly to a column (1 × 15 cm) of silica gel. The column was developed with 1:4 EtOAc−hexane to give **55** (82 mg, 93%) as a pure (^1H NMR, 400 MHz) oil.

2-Propenyl [6α,7β(*R),8β,9β]-[9-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-7-[1-hydroxy-3-(trimethylsilyl)-2-propynyl]-8-[2-[(4-methoxyphenoxy)methoxy]ethyl]-9-[(trimethylsilyl)ethynyl]-1,4-dioxaspiro-[4.5]dec-6-yl]carbamate (53) by reduction of 55.** $NaBH_4$ (20 mg, 0.531 mmol) was added to a stirred and cooled (0 °C) solution of **55** (82 mg, 0.106 mmol) in MeOH (2 mL). After 30 min, saturated aqueous NH_4Cl (5 mL) was added, and the mixture was extracted with EtOAc (3 × 20 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1 × 15 cm), using 1:4 EtOAc−hexane, gave **53** (72 mg, 88%) and the C(9) epimer **54** (6.2 mg, 7.5%).

2-Propenyl (1α,3α,4aα,5β,8α,8aα)- and (1α,3β,4aα,5β,8α,8aα)-[5-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]hexahydro-3-hydroxy-5-[(trimethylsilyl)ethynyl]spiro[1*H*-2-benzopyran-7(3*H*),2′-[1,3]dioxolan]-8-yl]carbamate (59). Aqueous ammonia (28−30% w/w, 6.0 mL) was added to a stirred and cooled (0 °C) solution of **58** (1.92 g, 2.69 mmol) in commercial MeOH (150 mL). Stirring was continued at 0 °C for 1 h. Water (300 mL) was then added and the mixture was extracted with EtOAc (3 × 150 mL). The combined organic extracts were washed with brine (300 mL), dried ($MgSO_4$), and evaporated, and the crude material (**59**) was used directly for the next step.

2-Propenyl (1α,4α,4aα,5β,8α,8aα)-[5-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]hexahydro-3-oxo-4-(phenylseleno)-1,5-bis-[(trimethylsilyl)ethynyl]spiro[1*H*-2-benzopyran-7(3*H*),2′-[1,3]dioxolan]-8-yl]carbamate and 2-Propenyl (1α,5β,8α,8aα)-[5-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-5,6,8,8a-tetrahydro-3-oxo-1,5-bis[(trimethylsilyl)ethynyl]spiro[1*H*-2-benzopyran-7(3*H*),2′-[1,3]dioxolan]-8-yl]carbamate (61). (a) Selenation. *n*-BuLi (1.6 M in hexane, 5.3 mL, 8.48 mmol) was added to a stirred and cooled (0 °C) solution of *i*-Pr_2NH (1.25 mL, 9.54 mmol) in THF (10.0 mL), and the solution was stirred at 0 °C for 10 min.

A portion of the above freshly made LDA solution (14.0 mL, ca. 7.0 mmol) was added to a stirred and cooled (−78 °C) solution of **60** (1.47 g, 2.32 mmol) by syringe at a fast dropwise rate, and the reaction mixture was stirred for 40 min at −78 °C.

During this period, a freshly made solution of PhSeBr in THF was prepared by the following procedure: Br_2 (300 μL, 5.82 mmol) was added to a stirred solution of PhSeSePh (2.05 g, 6.57 mmol) in THF (15 mL) at room temperature, and the mixture was stirred for 5 min.

A portion of the above solution of PhSeBr (ca. 0.77 M, 13.6 mL, 10.44 mmol) was added by syringe at a fast dropwise rate (ca. 2−3 min) to the enolate solution at −78 °C, and stirring was continued for a further 10 min. The reaction was quenched by addition of saturated aqueous NH_4Cl (40 mL) at −78 °C. The cold bath was removed, and the mixture was stirred for 40 min. Another portion of saturated aqueous NH_4Cl (100 mL) was added, and the mixture was extracted with EtOAc (3 × 60 mL). The combined organic extracts were washed with brine (1 × 100 mL) and dried (Na_2SO_4). Evaporation of the solvent and flash chromatography of residue over silica gel (3.5 × 24 cm), using first 1:10 EtOAc−hexane to remove selenium species and then 1:2 EtOAc−hexane, gave the crude *C*-selenide, which was used without characterization.

(b) Selenoxide Fragmentation. Dimethyldioxirane (prepared and estimated as described in the literature[44]) (ca. 0.05 M in acetone, 56 mL, ca. 2.8 mmol) was added over ca. 5 min by syringe to a stirred and cooled (−42 °C) solution of the above crude selenide (ca. 2.32 mmol) in CH_2Cl_2 (150 mL), and stirring was continued for a further 30 min at −42 °C. Evaporation of the solvent and flash chromatography of residue over silica gel (2.5 × 24 cm), using first 1:5 EtOAc−hexane and then 1:4 EtOAc−hexane, gave **61** (0.98 g, 67% over the two steps) as a white solid.

***trans*- and *cis*-8-Amino-5-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-5,6-dihydro-1,5-bis[(trimethylsilyl)ethynyl]spiro[1*H*-2-benzopyran-7(3*H*),2′-[1,3]dioxolan]-3-one (68) and Its C(9)[3] Epimer.** A solution of *t*-BuOCl[48] (48.9 mg, 0.450 mmol) in dry Et_2O (4.5 mL) was added over 10 min (syringe pump) to a stirred and cooled (−42 °C, MeCN-dry ice) solution of **62** (149.4 mg, 0.273 mmol) in 1:2 THF−Et_2O (9 mL), with both syringe and cold bath wrapped in aluminum foil to protect the contents from light. The mixture was stirred at −42 °C for a further 10 min after the end of the addition, and the solvent was then evaporated (rotary evaporator, room temperature) to give the crude monochloride **67** [which was not weighed, but which contains one major component (TLC, silica, 1:1 hexane−EtOAc)]. The material was used directly, without characterization.

The crude monochloride was dissolved in dry PhMe (10 mL), and DABCO (purified by sublimation under oil pump vacuum, 153 mg, 1.365 mmol) was added at room temperature with stirring. Stirring

was continued for 2 h at room temperature. Then, saturated aqueous NH_4Cl (20 mL) was added, and the mixture was extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with brine (30 mL), dried (Na_2SO_4), and evaporated to afford **68** as a glassy solid (140 mg), which was an ca. 8:1 mixture of syn and anti isomers. This crude material [**68** and its C(9) epimer] was not characterized. Compound **68** is easily epimerized at C(9), and so the material must be used immediately in the next step without further purification by flash chromatography. If the ^1H and ^{13}C NMR spectra are measured, dissolve only the spectral sample, and not the whole supply, in the NMR solvent.

In this experiment, use of DBU or DBN gave a mixture of isomers. Use of 1−3 equiv DABCO also gave mixtures because the reaction took a long time (more than 4 h). A bigger excess (5-fold) of DABCO gives an improved isomer ratio (better than 8:1). Acid also appears to cause isomerization since, when a sample of the 8:1 syn/anti isomer mixture was kept in $CDCl_3$ for 36 h, we obtained a 1:1 mixture of the isomers. When we dissolved the 8:1 syn/anti isomer mixture in CD_2Cl_2, we observed rapid (<15 min) isomerization. We did not test any other batches of CD_2Cl_2, but we think that the isolated enamine should not be exposed for more than a few seconds to dichloromethane. We suggest that, in the future, the NMR spectrum should be run in $CDCl_3$ (that has been passed through a column of basic alumina) or in some none acidic solvent, such as benzene-d_6. We do not know if pyridine-d_5 would also be suitable.

Methyl *trans*-[5-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-1,5-diethynyl-5,6-dihydro-3-oxospiro[1*H*-2-benzopyran-7(3*H*),2′-[1,3]dioxolan]-8-yl]carbamate (72) and Methyl *cis*-[5-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-1,5-diethynyl-5,6-dihydro-3-oxospiro[1*H*-2-benzopyran-7(3*H*),2′-[1,3]dioxolan]-8-yl]carbamate (71) by desilylation of 69 and Its C(9)[3] Epimer. The starting material for this experiment was made by the above procedure, the only difference being that DBU was used as the base. We did not establish which stereoisomer (syn or anti) was the major component.

Bu_4NF (1.0 M in THF, 0.56 mL, 0.56 mmol) was added dropwise over ca. 1 min to a stirred and cooled (ice bath) solution of **69** [2:1 mixture of C(9) stereoisomers, 160 mg, 0.265 mmol] in THF (10 mL). The mixture immediately turned yellow. Stirring was continued for 1 h (ice bath), and then water (30 mL) was added. (We suspect, from TLC monitoring, that the reaction is over in less than 5 min, and we later found that the mixture should be worked up as soon as the reaction is over.) The mixture was extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with brine (30 mL), dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel (1 × 15 cm), using first 1:2 EtOAc−hexane to separate the minor isomer **71** (47.5 mg, 39%) and then 2:3 EtOAc−hexane to separate the major (syn) isomer **72** (56.5 mg, 46%).

An X-ray structure was determined on **72** crystallized from EtOAc−hexane.[33]

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Supporting Information Available: X-ray data for **27**, the 5α epimer of **29**, and **50**, **62**, and **72**; a description of exploratory studies, involving radical cyclization; experimental procedures and characterization data not given in the main text; and preparation of dimethyldioxirane (160 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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