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Further Model Studies Related to Fredericamycin A: Analogues in which Ring C is Expanded to Six Atoms, and an Examination of the Diastereoselectivity of Radical Spirocyclization

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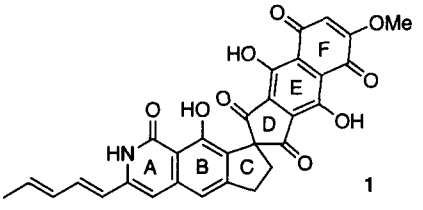
Abstract. The fredericamycin A analogues **5** and **23** were synthesized. A key step is the process of radical spirocyclization, and the diastereoselectivity of this reaction was studied with model compounds. *In vitro* tests showed that **23** was active against certain cell lines of colon and prostate cancer, while compound **5** was essentially inactive. Copyright © 1996 Elsevier Science Ltd

Introduction

The antitumor agent fredericamycin A (**1**) has an unusual structure, of which the spirodiketone unit is a conspicuous feature. Since this unit is unprecedented among antitumor agents it was worthwhile to examine its influence on biological activity. Against this background, we decided to prepare an analogue of **1** in which ring C is expanded to six atoms. Examination of Dreiding models shows that such an analogue has greater conformational mobility than **1** about the spiro center, and that the angle between the two flat plates making up the molecule — rings ABC and DEF — is also changed. These alterations may influence binding with the cellular target and/or change the electronic interaction between the rings.



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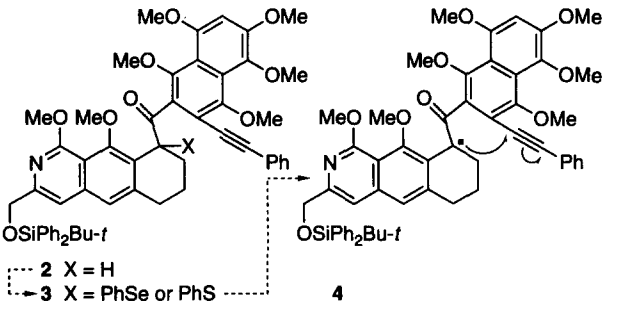
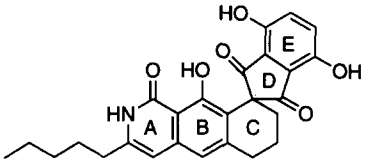
We had initially assumed that the route developed[1] for synthesis of fredericamycin A itself could simply be extrapolated to prepare the analogue, but this turned out not to be the case: in particular, advanced intermediates with a six-membered C-ring were very susceptible to aromatization of that ring and, with compounds such as **2** (Scheme 1), as well as related substances, we were unable to introduce a PhSe- or PhS-group that was needed for generation of a carbon radical (Scheme 1; **2**→**3**→**4**). However, after a rather large number of exploratory experiments we were able to develop a route in which a PhS-group is introduced *before* attachment of the EF ring system, and the aromatization is avoided.

Scheme 1



Preparation of Analogue 5

To gain some respite from the many unexpected difficulties that we met, we first prepared the simpler model **5**, which lacks ring F, and in which the pentadienyl side chain has been saturated. Side-chain modification in this way reduces the biological activity of fredericamycin A itself by about a factor of 10,[2] but has the big advantage of avoiding the possibly difficult[1] task of controlling double bond geometry.

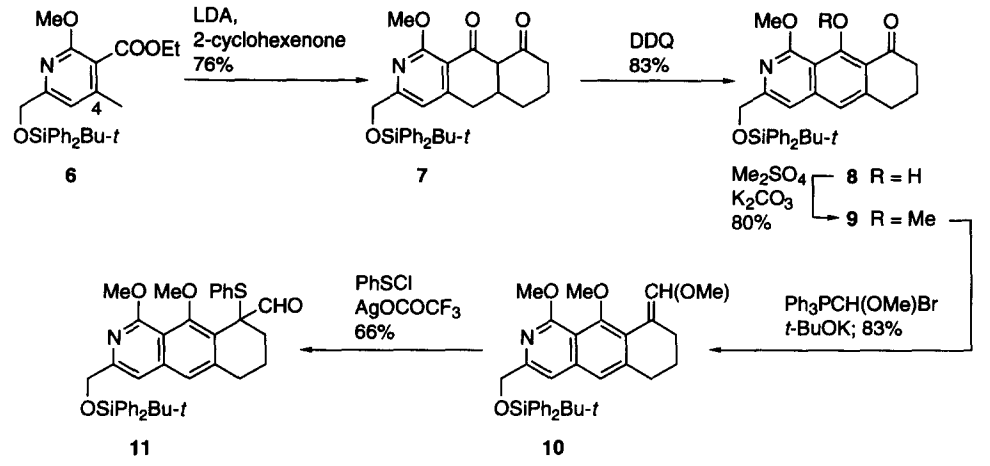


5

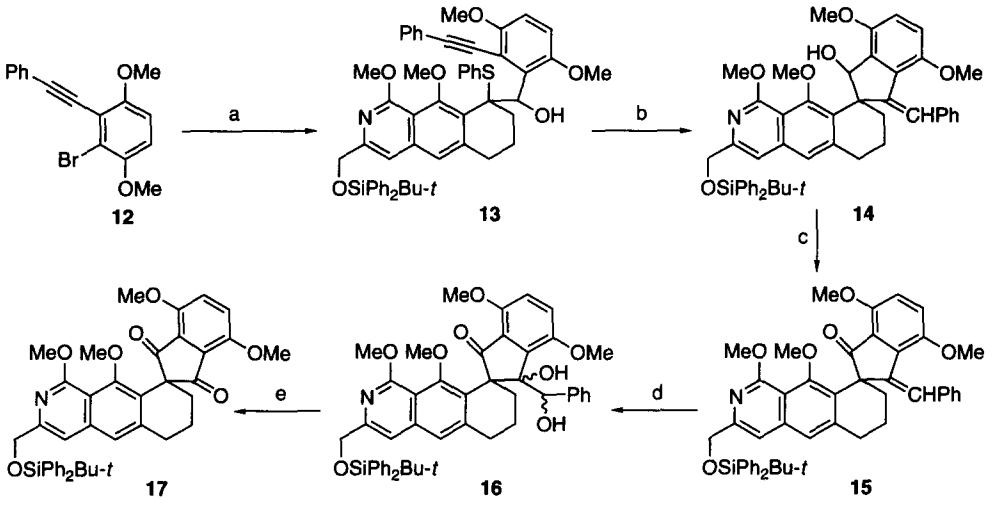
The first key intermediate needed — the phenylthio aldehyde **11** — was prepared as summarized in Scheme 2. Deprotonation at the C(4) methyl of the substituted pyridine **6**[1] (LDA, -78 °C), gave a carbanion that underwent smooth conjugate addition to 2-cyclohexenone, and the resulting intermediate cyclized directly to **7** when the basic reaction mixture was allowed to warm to room temperature. Partial dehydrogenation of **7** with DDQ required close monitoring, but gave the desired naphthol **8** in good yield (83%), and the compound could be methylated easily (**8**→**9**) under classical conditions (Me_2SO_4, K_2CO_3; 80%). Further elaboration of **9** to **11** was immensely troublesome, and a good many routes were tried before we found that **11** was best made by Wittig olefination (**9**→**10**; 83%), followed by titration with PhSCl in the presence of $AgOCOCF_3$. The choice of solvent appears to be critical, and a 1:19 mixture of CH_2Cl_2 and Et_2O is best (66% yield). The corresponding phenylseleno aldehyde was also made (by a different route and without full characterization), but seemed too unstable to be useful.

The known bromo acetylene **12**[3] (Scheme 3) was next converted into a carbanion by halogen/metal exchange (*n*-BuLi, THF-Et_2O), and then condensation with **11** proceeded without incident (**12**→**13**; 81%). Treatment of the product with an excess of Ph_3SnH in refluxing benzene, and in the presence of AIBN, effected efficient radical cyclization (**13**→**14**; 87%), giving the product as a mixture of diastereomers.

Scheme 2



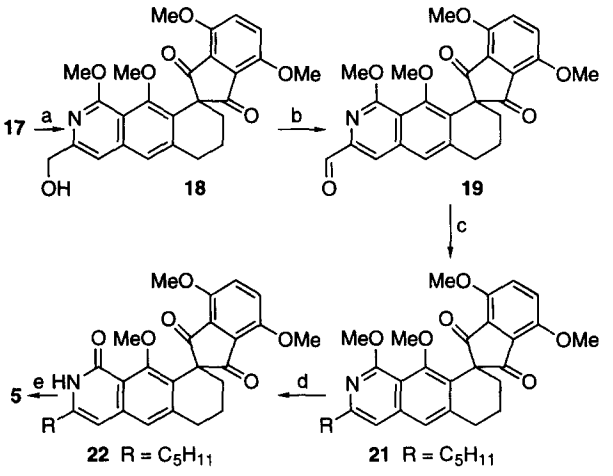
Scheme 3



[a]BuLi, THF-Et_2O, -78 °C; compound **11**; 81%. [b]Ph_3SnH, AIBN, PhH, reflux; 87%. [c]Ph_3BiCO_3, PhMe, pyridine, 80 °C; 85%. [d]OsO_4, pyridine. [e]$Pb(OAc)_4$; 62% from **15**.

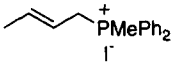
The exocyclic double bond in the derived ketones **15** appears to be especially hindered, and many experiments were required in order to identify suitable conditions for cleaving the bond — primarily, in the initial dihydroxylation, use of a more concentrated solution (0.33 M) of OsO_4 than is usual, and allowance of sufficient time for the (slow) osmate reduction. With the double bond cleaved, however, we were ready to

Scheme 4



[a]TBAF; 80%. [b]MnO_2; 89%. [c]Compound **20**, *t*-BuOK; Pd/C, H_2; 86% from **19**. [d]Me_3SiCl, NaI; 74%. [e]BBr_3; 63%.

attach the ring A side chain. To this end, the silicon protecting group was removed (Scheme 4, **17**→**18**) and the resulting alcohol was oxidized to an aldehyde (**18**→**19**), both steps being efficient under standard conditions (TBAF; 80%; MnO_2, 89%). Aldehyde **19** is poorly soluble in Et_2O, THF, or dioxane, and Wittig reaction in any of these solvents was very inefficient. However, use of CH_2Cl_2 — an unusual medium for Wittig olefination — as a cosolvent, and the ylide generated (in THF) from **20**,[4] by the action of *t*-BuOK, was thoroughly successful, the reaction being over within 1 minute, and giving a quantitative yield of dienes, not separable by chromatography. Hydrogenation of the diene mixture afforded **21** in 86% overall yield from **19**.



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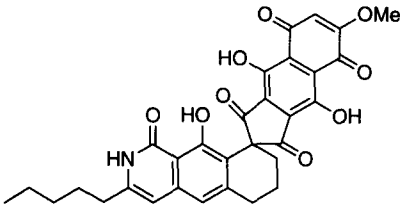
Finally, as was the case in our synthesis of fredericamycin A, the deprotection — at least under the conditions[5] we use — had to be done in two steps: Treatment with Me_3SiCl/NaI liberated the pyridone system (**21**→**22**; 74%), and the remaining *O*-methyl groups were then removed (63%) with BBr_3 to complete the preparation of the fredericamycin analogue **5**.

Preparation of Analogue 23

We now sought to extend the approach of Schemes 3 and 4 to the more sophisticated fredericamycin analogue **23**.

The known[6] bromo naphthalene **24** was converted by halogen/metal exchange into the corresponding carbanion, and condensed with phenylthio aldehyde **11**. Alcohol **25** was obtained as a single stereoisomer.

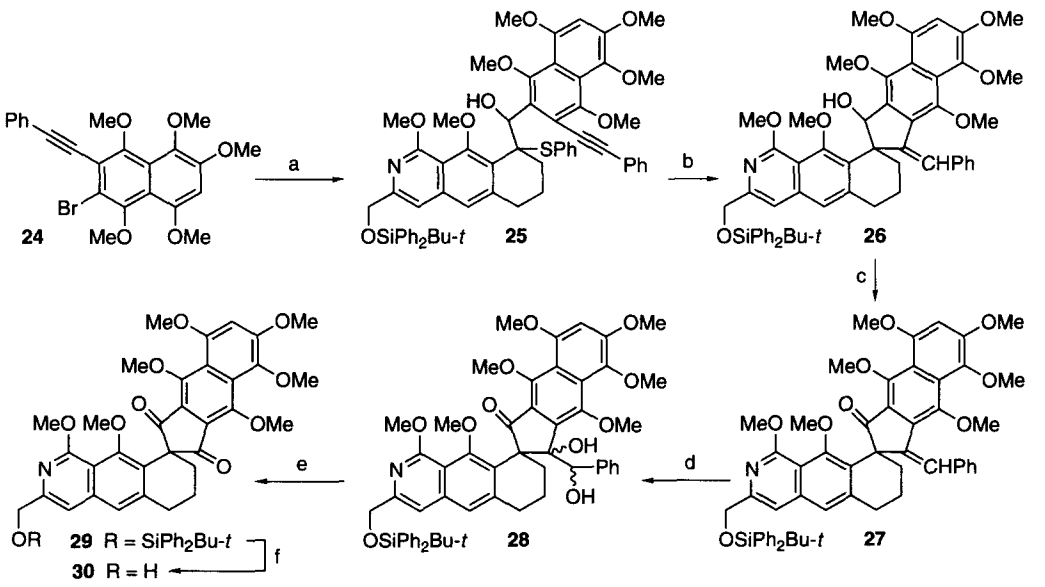
Initially, our attempts to carry out the radical cyclization **25**→**26** were unpromising, but we were obliged to persevere, and we eventually found that use of a large excess of Et_3B (40 mole per mole **25**) and Ph_3SnH (11 mole per mole **25**), in the presence of air, gave the desired product (as a mixture of diastereoisomers) in almost



23

80% yield. Oxidation, best done with Ph_3BiCO_3,[7] was very efficient (88%), and brought us to the stage where we had to cleave the exocyclic double bond. Many different methods were tried, but we were forced to

Scheme 5



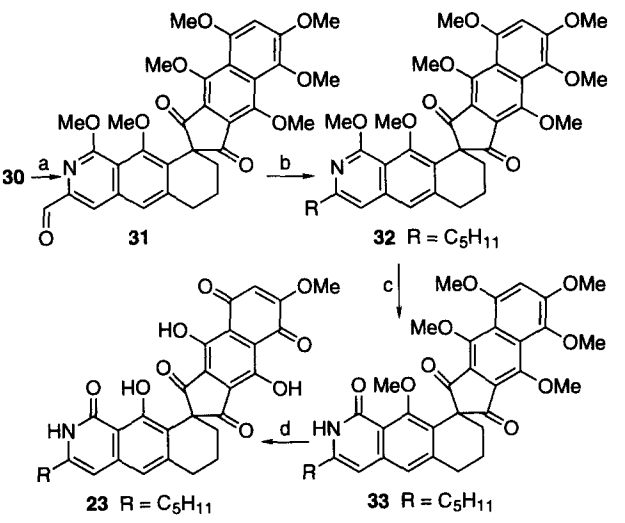
[a]BuLi, THF-Et_2O, -78 °C; compound **11**; 75%. [b]Ph_3SnH, Et_3B, air; 79%. [c]Ph_3BiCO_3, PhMe, pyridine, 80 °C; 88%. [d]OsO_4, pyridine; 20%. [e]$Pb(OAc)_4$; 50-60%. [f]TBAF; 74%.

accept a poor yield (20%) in the dihydroxylation — done by using OsO_4 — and 50-60% in the cleavage of the resulting diols. Fortunately, though, enough of **29** was made to complete the synthesis, without the need to go back and bring up further supplies.

Building the side chain on **29** was straightforward, by the methods we had used for the simpler model

5. Desilylation (Scheme 5, **29**→**30**; TBAF; 74%), oxidation (Scheme 6, **30**→**31**; MnO_2; 65%), Wittig reaction and, finally, hydrogenation (75% from **31**) brought us to the now familiar task of selective demethylation. This process (**32**→**33**→**23**) worked well, but only after we had recognized that **33** is unstable and must be used promptly. With fresh material, the desired fredericamycin analogue **23** was easily obtained.

Scheme 6



[a]MnO_2; 65%. [b]Compound **20**; *t*-BuOK; Pd/C, H_2; 75% from **31**.
[c]Me_3SiCl, NaI; 83%. [d]BBr_3; THF-water, air; 62%.

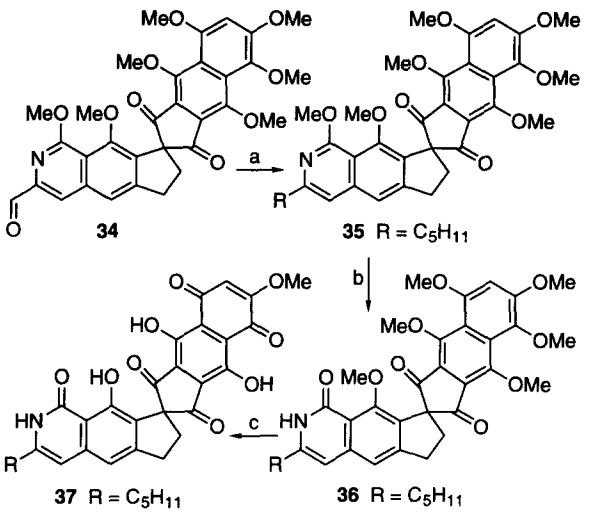
Preparation of 1",2",3",4"-Tetrahydrofredericamycin A (37)[2a]

For comparison in biological tests, we also prepared 1",2",3",4"-tetrahydrofredericamycin A (**37**). Our route starts with aldehyde **34**, an intermediate in our synthesis[1] of fredericamycin A. The route follows the — by now — straightforward steps summarized in Scheme 7, and proceeded without incident.

Diastereoselectivity of Radical Spirocyclization

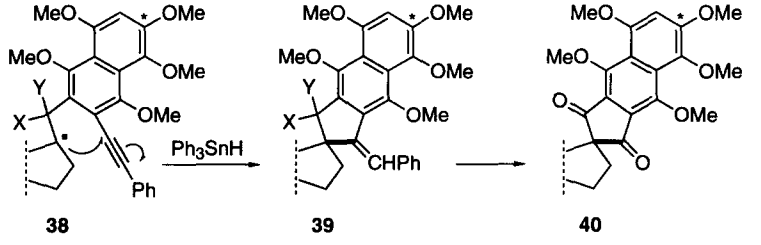
In the synthesis of **23**, and in our earlier synthesis of fredericamycin A,[1] the product of radical spirocyclization (see Scheme 8, **38**→**39**, X,Y = ketone carbonyl oxygen, or X = OH, Y = H) has the CHPh group *syn* to the methoxy group that is retained (see starred position in **38**-**40**); in the absence of this methoxy group the spiro center of **40** would not be stereogenic. In order to evaluate radical spirocyclization for use in the synthesis of optically pure materials we needed to establish the diastereoselectivity[8] in cyclizations of the type shown in Scheme 9, where Z is a removable group and CXY represents C=O or CH(OH).

Scheme 7

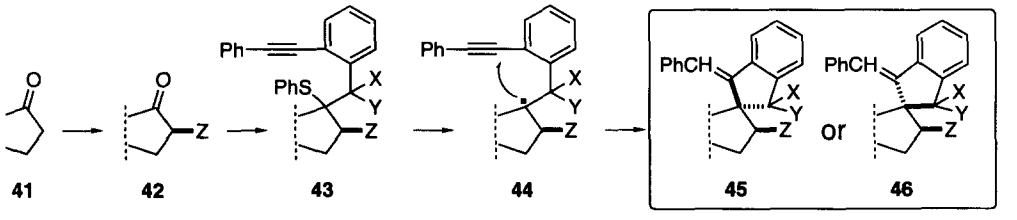


[a]Compound **20**; *t*-BuOK; Pd/C, H_2; 75% from **34**.
[b]Me_3SiCl, NaI; 84%. [d]BBr_3; THF-water, air; 50%.

Scheme 8

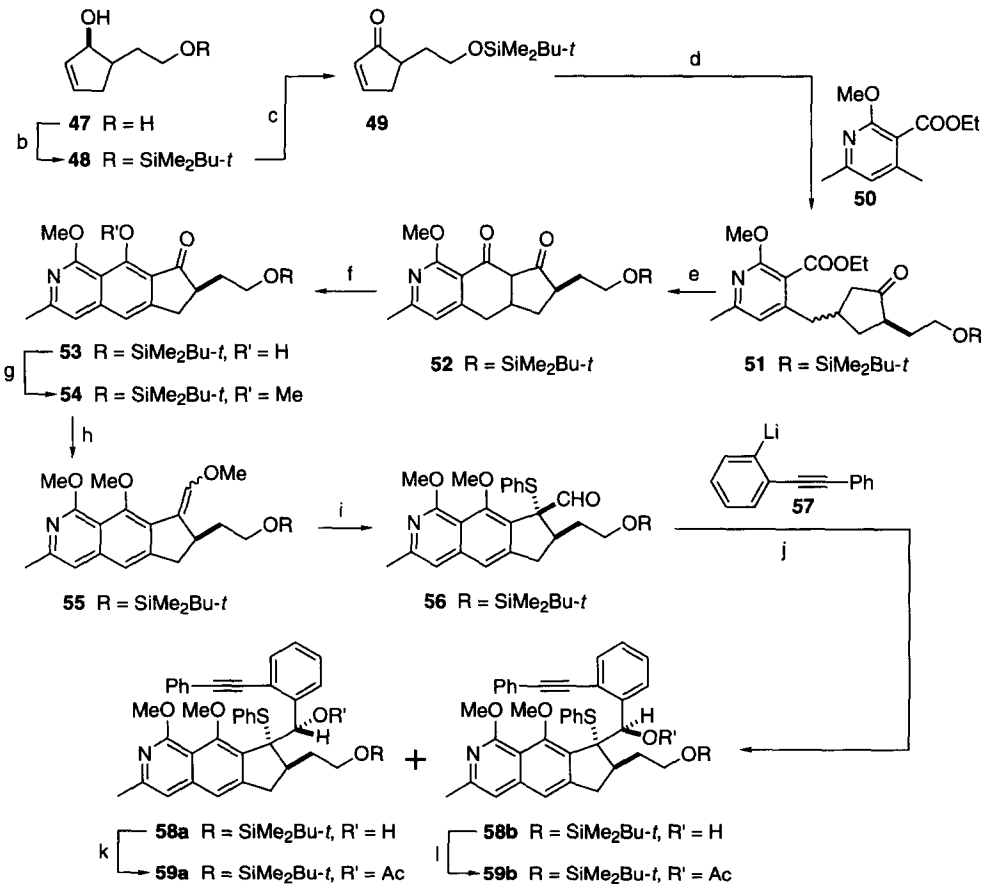


Scheme 9



Although there are a number of ways of implementing radical spirocyclization, we thought that, for the present purpose, the simplest might involve temporary asymmetric alkylation of a ketone (Scheme 9, **41**→**42**, Z = functionalized *and* removable alkyl group), followed by elaboration to the radical precursor (**42**→**43**), and generation of the radical (**43**→**44**). It was the fate of this radical — whether it reacts *syn* to the group Z (**44**→**45**) or *anti* to Z (**44**→**46**) — that would determine if the process could be used to make optically pure spiro compounds (after removal of Z) along the lines we planned. With these ideas in mind, we first prepared a (racemic) ketone corresponding to **42**. Our target (**54**),[9] and its method of synthesis, are shown in Scheme 10.

Scheme 10[a]

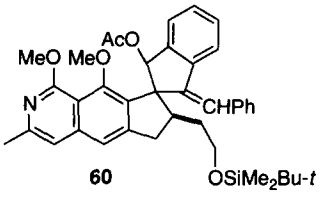


[a]All compounds are racemic. [b]*t*-BuMe$_2$SiCl, imidizadole; 62%. [c]MnO_2; 45%. [d]LDA added to **50**, then mixture added to **49**; 60%. [e]NaH, trace EtOH. [f]DDQ. [g]Ph_3P, DEAD, MeOH; 55% from **51**. [h]$Ph_3PCH_2(OMe)$, t-BuOK; 78%. [i]PhSCl; 30-35%. [j]Addition of **57**; 40% of **58a**, 33% of **58b**. [k]Ac_2O, pyridine; 83%. [l]Ac_2O, pyridine; 80%.

As in earlier model studies (see above), our efforts to introduce a PhS- or PhSe-group *after* attachment of the acetylene-bearing unit were unsuccessful, and so we introduced the homolyzable group (PhS) at an earlier stage (**54**→**55**→**56**). The yield in the last step (**55**→**56**) was poor (35-40%), but the isolated product was a single isomer with the relative stereochemistry as shown. In trying — unsuccessfully — to improve this yield, we noticed that both individual isomers of **55** give the same phenylthio aldehyde. Reaction with organolithium **57**, then afforded two diastereoisomeric (and racemic) alcohols (**58a**, 40%; **58b**, 33%), and the stereochemistry of the minor product was determined by X-ray analysis of the derived acetate (**59b**).

When alcohol **58a** was treated with Ph_3SnH, in the presence of Et_3B and air, we could isolate what we believe to be (low resolution MS and ^1H NMR spectra) the desired spiro compound, but the yield was at best 33%. The material was a 1:9 mixture of isomers, and oxidation (Ph_3BiCO_3, 50%) gave two ketones, as a 1:3 isomer mixture. These observations are consistent with radical closure in one stereochemical sense, and production of two geometrical isomers of the alkene, but the yields in both steps are not high enough to conclude that this is the only pathway, and we were unable to separate the two ketones.

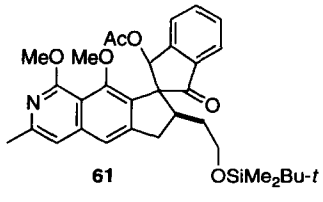
In the hope of improving the yields, we next examined compounds in which the hydroxyl had been protected and, to this end, the acetates **59a** and **59b** were prepared (Ac_2O, DMAP; 80% in each case). When **59a** was subjected to our usual conditions for radical cyclization we obtained (90%) the expected cyclization product **60**, as mixture of four isomers. Under similar conditions, we obtained from acetate **59b** a single cyclization product in 88% yield.



60

The mixture of four isomers was separated chromatographically into two fractions, each containing two isomers. One fraction gave a single ketone on cleavage of the exocyclic double bond by treatment with OsO_4/$NaIO_4$. Unfortunately, the yield (30%) is not high enough to let us conclude with certainty that the pair of isomers from the radical closure in the particular fraction used differ only with regard to double bond geometry. The other fraction gave no identifiable products on attempted double bond cleavage.

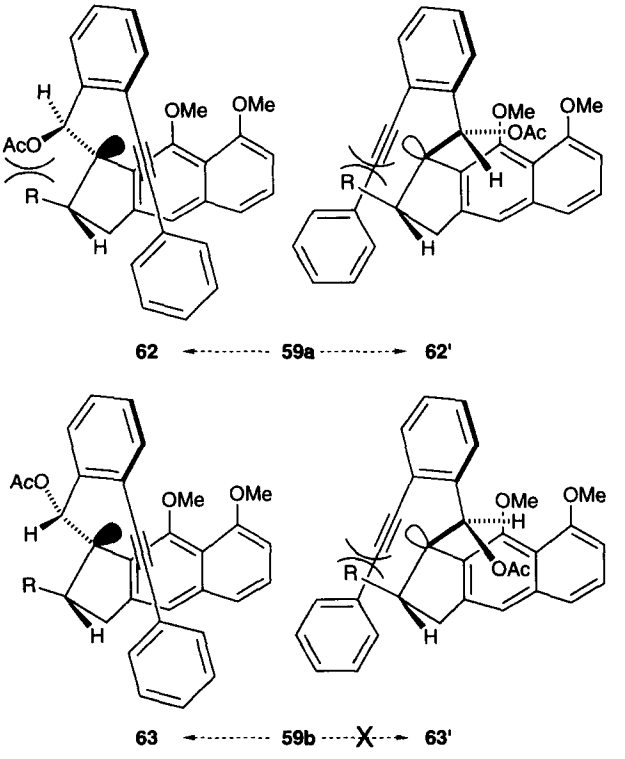
The single radical cyclization product from **59b** gave (30%) a single ketone (**61**) on treatment with OsO_4/$NaIO_4$, but NOE studies, undertaken to establish the relative stereochemistry, were inconclusive.



61

The fact that cyclization of **59a** gives a mixture of isomers, while cyclization of **59b** gives essentially a single isomer, is informative. Possible conformations for radical closure are shown in diagrams **62**, **62'**, **63**, and **63'**. Conformation **63** from **59b** must be more stable than **63'**; in the latter, significant non-bonded interactions between the alkyne and the side chain R are expected. By inspection of Dreiding models of conformations **62** and **62'**, derived from **59a**, one can identify non-bonded interactions between AcO and R in **62**, and between the alkyne and R in **62'**. Consequently, there is one clearly favored stereochemical path for closure of **59b**, while for **59a** no such distinction exists.

Scheme 11



Biological Evaluation

Fredericamycin A (**1**), the tetrahydro analogue **37**, and the two ring-C expanded analogues **5** and **23** were subjected to a number of *in vitro* tests for antitumor activity. Log_{10} of the molar concentration that causes 50% cell death, i.e. Log_{10} LC_{50}, for a number of cancers is shown in Table 1.[10] Compound **5** is essentially inactive, but **23** retains significant activity, but the changes we have made by expanding ring C do not dramatically influence biological activity.

Table 1

	1	37	5	23
	Log_{10} LC_{50}	Log_{10} LC_{50}	Log_{10} LC_{50}	Log_{10} LC_{50}
Ovarian cancer (OVCAR-3	-6.04	-5.13	> -4.00	> -4.73
Colon cancer (COLO-205)	--	-6.01	> -4.00	-5.94
Prostate cancer (PC-3)	-6.04	-5.19	> -4.00	-5.06

Conclusions

We had hoped that expansion of ring C would make a decisive change to the biological activity, so that the unusual spiro system, and the rigid way it holds the component parts of fredericamycin A, would be clearly linked to biological activity. This turned out not to be the case, but it may still be of interest to prepare and test *seco*-compounds, in which ring C has been cleaved.

Our synthetic work shows that cleavage of the exocyclic double bond can be a serious problem in the present type of radical spirocyclization, and that a different radical acceptor is needed that will lead to a more easily cleaved unit than =CHPh. It is also clear that the stereochemistry of radical spirocyclization is quite sensitive to steric effects.

Experimental

General Procedures. Unless stated to the contrary, the following conditions apply. Reactions were carried out under a slight static pressure of Ar that had been purified by passage through a column (3.5 x 42 cm) of R-311 catalyst[11] and then through a similar column of Drierite. Glassware was dried in an oven for at least 3 h before use (120 °C) and either cooled in a desiccator over Drierite, or assembled quickly, sealed with rubber septa, and allowed to cool under a slight static pressure of Ar. Reaction mixtures were stirred by Teflon-coated magnetic stirring bars.

Solvents for chromatography and extractions were distilled before use.

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

All the compounds purified by chromatography were pure as judged by TLC analysis.

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

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

Commercial thin layer chromatography (TLC) plates (silica gel, Merck 60F–254) were used. Spots were detected by spraying the plate with a solution of phosphomolybdic acid,[12] followed by charring on a hot plate, or by examination under UV light. Silica gel for flash chromatography was Merck type 60 (230-400 mesh).

Dry solvents were prepared under an inert atmosphere and transferred by syringe or cannula. Dry THF and Et_2O were distilled from Na and benzophenone ketyl. Dry PhH was distilled from sodium. Dry Et_3N,

CH_2Cl_2, MeOH, MeCN, and pyridine were distilled from CaH_2. Commercial (Aldrich) solutions of *n*–BuLi and MeLi were assumed to have the stated molarity.

FTIR spectra were obtained for casts made by depositing the compound from solution on a KBr plate.

The symbols s', d', t', and q' used for ^{13}C NMR signals indicate 0, 1, 2, or 3 attached hydrogens, respectively.

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

Microanalyses were performed by the Microanalytical Laboratory of this Department.

3-[[[(1,1-Dimethylethyl)diphenylsilyl]oxy]methyl]-5a,6,7,8-tetrahydro-10-hydroxy-1-methoxybenz[*g*]iso-quinolin-9(5*H*)-one (7). This experiment must be done on a small scale (a maximum of 10 g of starting pyridine). Use of more concentrated solutions than specified below results in diminished yields. *n*-BuLi (1.6 M in hexane, 16.2 mL, 25.9 mmol) was added to a stirred and cooled (-78 °C) solution of *i*-Pr_2NH (4.57 mL, 34.9 mmol) in THF (600 mL). The solution was stirred for 30 min at this temperature and a solution of ester **6**[1] (3.00 g, 6.47 mmol) in THF (16 mL) was added dropwise over 5 min. The deep orange solution was stirred for 5 min, and cyclohexenone (2.83 mL, 29.2 mmol) was then added over 30 sec. [The color of the pyridyllithium ranges from dark brown to dark green.] Stirring was continued for a further 5 min and the cold bath was removed. After 3 h, AcOH (8 mL, 140 mmol) was added and the solvents were evaporated. The residue was diluted with water (300 mL), extracted with CH_2Cl_2 (2 x 100 mL), and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (5 x 15 cm), using 1:5 EtOAc-hexane, gave diketone **7** (2.53 g, 76 %) as a pure (TLC, silica, 1:5 EtOAc-hexane), yellow foam: FTIR 1587, 1113 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.15 (s, 9 H), 1.28-1.43 (m, 1 H), 1.59-1.73 (m, 1 H), 1.92-2.00 (m, 1 H), 2.02-2.10 (m, 1 H), 2.41-2.49 (m, 2 H), 2.54-2.62 (m, 1 H), 2.66-2.76 (m, 1 H), 2.78-2.86 (m, 1 H), 3.96 (s, 3 H), 4.76 (dd, *J* = 14, 1.4 Hz, 2 H), 7.12 (s, 1 H), 7.37-7.48 (m, 6 H), 7.68-7.75 (m, 4 H), 8.28 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 19.4 (s'), 20.9 (t'), 26.9 (q'), 30.1 (t'), 31.2 (t'), 32.6 (d'), 37.2 (t'), 54.1 (q'), 66.4 (t'), 109.1 (s'), 112.5 (d'), 113.5 (s'), 127.8 (d'), 129.9 (d'), 133.1 (s'), 133.1 (s'), 135.5 (d'), 155.3 (s'), 161.9 (s'), 162.7 (s'), 182.3 (s'), 186.1 (s'); exact mass *m/z* calcd for $C_{27}H_{26}NO_4Si$ (M - C_4H_9) 456.1631, found 456.1625. Anal. Calcd for $C_{31}H_{35}NO_4Si$: C, 72.48; H, 6.87; N, 2.73. Found: C, 72.31; H, 6.90; N, 2.71.

If workup is done at -78 °C, the intermediate conjugate addition product can be isolated as a pure (^1H NMR, 300 MHz), clear oil: FTIR 2930, 1715, 1600, 1140 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.13 (s, 9 H), 1.38 (t, *J* = 6.6 Hz, 3 H), 1.40-1.78 (m, 2 H), 1.83-1.93 (m, 1 H), 1.98-2.17 (m, 3 H), 2.19-2.46 (m, 3 H), 2.64 (d, *J* = 6.0 Hz, 2 H), 3.86 (s, 3 H), 4.39 (t, *J* = 6.6 Hz, 2 H), 4.76 (s, 2 H), 7.05 (s, 1 H), 7.33-7.47 (m, 6 H), 7.67-7.76 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 14.3 (q'), 19.4 (s'), 25.0 (t'), 26.9 (q'), 30.9 (t'), 39.8 (d'), 39.9 (t'), 41.3 (t'), 47.9 (t'), 53.8 (q'), 61.4 (t'), 66.3 (t'), 113.7 (d'), 115.8 (s'), 127.8 (d'), 129.9 (d'), 133.2 (s'), 135.5 (d'), 149.0 (s'), 159.4 (s'), 160.3 (s'), 167.2 (s'), 210.6 (s'); exact mass *m/z* calcd for $C_{29}H_{32}NO_5Si$ (M - C_4H_9) 502.2050, found 502.2049.

3-[[[(1,1-Dimethylethyl)diphenylsilyl]oxy]methyl]-7,8-dihydro-10-hydroxy-1-methoxybenz[*g*]isoquinolin-9(6*H*)-one (8). DDQ (1.24 g, 5.46 mmol) was added portionwise over 30 min to a stirred solution of ketone **7** (2.53 g, 4.93 mmol) in CH_2Cl_2 (50 mL) at room temperature. Stirring was continued for an additional 10 min and the mixture was then filtered. Evaporation of the solvent and flash chromatography of the residue over silica gel (5 x 15 cm), using 1:5 EtOAc-hexane, gave **8** (2.10 g, 83%) as a pure (^{1}H NMR, 400 MHz), light yellow solid: mp 168.0-169.2 °C; FTIR 1627, 1565, 1119 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.16 (s, 9 H), 2.07-2.17 (m, 2 H), 2.75 (t, *J* = 6.4 Hz, 2 H), 3.03 (t, *J* = 5.6 Hz, 2 H), 4.05 (s, 3 H), 4.82 (s, 2 H), 6.96 (s, 1 H), 7.35 (s, 1 H), 7.36-7.47 (m, 6 H), 7.73-7.77 (m, 4 H), 9.97 (s, 1 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 19.3 (s'), 22.5 (t'), 26.9 (q'), 30.2 (t'), 38.6 (t'), 53.9 (q'), 66.3 (t'), 107.9 (s'), 109.3 (d'), 112.8 (s'), 115.3 (d'), 127.8 (d'), 129.8 (d'), 133.2 (s'), 135.5 (d'), 144.2 (s'), 145.3 (s'), 156.8 (s'), 162.1 (s'), 165.8 (s'), 204.2 (s'); exact mass *m/z* calcd for $C_{27}H_{24}NO_4Si$ (M - C_4H_9) 454.1744, found 454.1475. Anal. Calcd for $C_{31}H_{33}NO_4Si$: C, 72.77; H, 6.50; N, 2.74. Found: C, 72.87; H, 6.75; N, 2.73.

This reaction can also be done in benzene, but it is then slower, and it is more difficult to isolate the product because the material for flash chromatography is too thick to be easily loaded onto the column.

3-[[[(1,1-Dimethylethyl)diphenylsilyl]oxy]methyl]-7,8-dihydro-1,10-dimethoxybenz[*g*]isoquinolin-9(6*H*)-one (9). K_2CO_3 (2.46 g, 17.8 mmol) and Me_2SO_4 (1.68 mL, 17.8 mmol) were added to a solution of naphthol **8** (1.82 g, 3.56 mmol) in acetone (40 mL), and the suspension was refluxed for 12 h. Aqueous NH_4OH (10%, 20 mL) was added and the mixture was extracted with Et_2O (2 x 100 mL), washed with brine (30 mL), and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (4 x 15 cm), using 1:3 EtOAc-hexane, gave **9** as a pure (TLC, silica, 1:3 EtOAc-hexane), yellow foam (1.50 g, 80%): FTIR 1620, 1350, 1115 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.16 (s, 9 H), 2.00-2.20 (m, 2 H), 2.65 (t, *J* = 6.6 Hz, 2 H), 3.03 (t, *J* = 5.8 Hz, 2 H), 3.96 (s, 3 H), 4.02 (s, 3 H), 4.82 (s, 2 H), 7.27-7.50 (m, 8 H), 7.62-7.83 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 19.4 (s'), 22.6 (t'), 26.9 (q'), 31.1 (t'), 41.1 (t'), 54.0 (q'), 63.3 (q'), 66.3 (t'), 109.1 (d'), 113.2 (s'), 121.1 (d'), 124.4 (s'), 127.8 (d'), 129.8 (d'), 133.4 (s'), 135.5 (d'), 143.5 (s'), 145.9 (s'), 154.5 (s'), 161.0 (s'), 161.2 (s'), 196.6 (s'); exact mass *m/z* calcd for $C_{28}H_{26}NO_4Si$ (M - C_4H_9) 468.1631, found 468.1635. Anal. Calcd for $C_{32}H_{35}NO_4Si$: C,73.11; H, 6.71; N, 2.66. Found: C, 72.85; H, 6.64; N, 2.63.

3-[[[(1,1-Dimethylethyl)diphenylsilyl]oxy]methyl]-6,7,8,9-tetrahydro-1,10-dimethoxy-9-[(methoxy)-methylene]benz[*g*]isoquinoline (10). *t*-BuOK (4.5 g, 40.1 mmol) was added to a solution of (methoxymethyl)triphenylphosphonium chloride (15.6 g, 45.5 mmol) in THF (240 mL), and the mixture was stirred at room temperature for 30 min. Ketone **9** (6.0 g, 11.4 mmol) in THF (100 mL) was added dropwise by cannula over 10 min, and stirring was continued for 1 h after the addition. Water (120 mL) was added, and the mixture was extracted with Et_2O (2 x 300 mL). The combined organic extracts were washed with brine and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (10 x 15 cm), using 1:10 EtOAc-hexane, gave enol ether **10** (5.2 g, 83%) as a pure (^{1}H NMR, 400 MHz), light yellow solid. The material was a single isomer of undetermined geometry: mp 154.8-155.8 °C; FTIR (neat) 2920, 1550, 1100 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.16 (s, 9 H), 1.76-1.83 (m, 2 H),

2.57-2.62 (m, 2 H), 2.76-2.81 (m, 2 H), 3.73 (s, 3 H), 3.74 (s, 3 H), 4.05 (s, 3 H), 4.81 (s, 2 H), 7.27 (s, 1 H), 7.34-7.49 (m, 8 H), 7.79-7.74 (m, 4 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 19.4 (s'), 22.3 (t'), 23.7 (t'), 26.9 (q'), 31.9 (t'), 53.9 (q'), 60.0 (q'), 60.4 (q'), 66.4 (t'), 109.6 (d'), 109.7 (s'), 112.7 (s'), 121.2 (d'), 126.7 (s'), 127.7 (d'), 129.7 (d'), 133.6 (s'), 135.6 (d'), 138.7 (s'), 143.6 (s'), 149.3 (d'), 150.4 (s'), 153.4 (s'), 159.2 (s'); exact mass *m/z* calcd for $C_{34}H_{39}NO_4Si$ 553.2648, found 553.2648. Anal. Calcd for $C_{34}H_{39}NO_4Si$: C, 73.74; H, 7.10; N, 2.53. Found: C, 73.77; H, 7.10: N, 2.57.

3-[[[(1,1-Dimethylethyl)diphenylsilyl]oxy]methyl]-6,7,8,9-tetrahydro-1,10-dimethoxy-9-(phenylthio)-benz[*g*]isoquinoline-9-carboxaldehyde (11). Enol ether **10** (577 mg, 1.04 mmol) was dissolved in CH_2Cl_2 (3 mL) at room temperature. Et_2O (58 mL) was added and the solution was cooled to -78 °C and stirred. After 5 min, CF_3COOAg (300 mg, 1.36 mmol) was added, and then PhSCl[13] (0.155 mL, 1.18 mmol) in Et_2O (29 mL) was added dropwise by cannula over 15 min. Stirring was continued at -78 °C for 30 min after the addition. The cold bath was removed and, after 20 min, the solvent was evaporated. Flash chromatography of the residue over grade I neutral aluminum oxide (4 x 15 cm), using 1:13 EtOAc-hexane, gave aldehyde **11** (449 mg, 66%) as a pure (^{1}H NMR, 400 MHz), yellow foam: FTIR 2950, 1715, 1623, 1560 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.17 (s, 9 H), 1.76-1.88 (m, 2 H), 2.01-2.10 (m, 1 H), 2.33-2.45 (m, 1 H), 2.89-3.01 (m, 1 H), 3.08-3.16 (m, 1 H), 3.96 (s, 3 H), 4.03 (s, 3 H), 4.82 (s, 2 H), 7.28-7.46 (m, 11 H), 7.60-7.65 (m, 2 H), 7.73-7.78 (m, 4 H), 10.17 (s, 1 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 17.8 (s'), 19.4 (t'), 27.0 (q'), 29.0 (t'), 29.5 (t'), 53.8 (q'), 62.7 (s'), 64.3 (q'), 66.3 (t'), 109.3 (d'), 111.4 (s'), 122.9 (d'), 127.1 (s'), 127.8 (d'), 128.9 (d'), 129.1 (d'), 129.8 (d'), 131.8 (s'), 133.5 (s'), 135.6 (d'), 136.8 (d'), 140.9 (s'), 141.3 (s'), 152.2 (s'), 155.5 (s'), 158.9 (s'), 199.0 (d'); exact mass *m/z* calcd for $C_{35}H_{32}NO_4SSi$ (M - C_4H_9) 590.1821, found 590.1824. Anal. Calcd for $C_{39}H_{41}NO_4SSi$: C, 72.30; H, 6.38; N, 2.16. Found: C, 71.97; H, 6.27; N, 2.17.

3-[[[(1,1-Dimethylethyl)diphenylsilyl]oxy]methyl]-6,7,8,9-tetrahydro-1,10-dimethoxy-9-(phenylthio)-α-[3,6-dimethoxy-2-(phenylethynyl)phenyl]benz[*g*]isoquinoline-9-methanol (13). *n*-BuLi (1.6 M in hexane, 2.0 mL, 3.20 mmol) was added dropwise over 1 min to a stirred and cooled (-78 °C) solution of bromide **12** (0.923 g, 2.91 mmol) in Et_2O (22 mL). The mixture was stirred for an additional 30 min, and aldehyde **11** (1.72 g, 2.65 mmol) in a mixture of THF (7.7 mL) and Et_2O (7.7 mL) was then added by cannula over 5 min. Stirring was continued for 10 min after the addition. The cold bath was removed and, after *ca.* 20 min, saturated aqueous NH_4Cl (20 mL) was added. The mixture was extracted with Et_2O (2 x 100 mL), and the combined organic extracts were washed with brine (30 mL) and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (4 x 15 cm), using 1:3.5 EtOAc-hexane, gave alcohol **13** (1.90 g, 81%) as a pure (^{1}H NMR, 400 MHz), light yellow foam: FTIR 3500, 1620, 1556, 1475, 1105 cm^{-1}; ^{1}H NMR (CD_2Cl_2, 400 MHz) δ 1.18 (s, 9 H), 1.57-1.67 (m, 1 H), 1.75-1.84 (m, 1 H), 2.01-2.10 (m, 1 H), 2.32-2.41 (m, 1 H), 2.64-2.79 (m, 2 H), 3.50 (br s, 3 H), 3.86 (s, 3 H), 3.99 (s, 3 H), 4.10 (s, 3 H), 4.44 (d, J = 8.8 Hz, 1 H), 4.78 (d, J = 16 Hz, 1 H), 4.84 (d, J = 16 Hz, 1 H), 6.34 (d, J = 8.8 Hz, 1 H), 6.68 (d, J = 8.8 Hz, 1 H), 6.76 (d, J = 8.8 Hz, 1 H), 7.12-7.19 (m, 3 H), 7.22-7.49 (m, 15 H), 7.76-7.84 (m, 4 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 19.4 (s'), 20.3 (t'), 27.0

(q'), 32.0 (t'), 53.4 (q'), 55.1 (q'), 56.7 (q'), 62.9 (s'), 64.3 (q'), 66.3 (t'), 85.2 (s'), 109.1 (d'), 110.5 (d'), 111.5 (d'), 111.8 (s'), 121.1 (d'), 123.5 (s'), 127.8 (d'), 127.9 (d'), 128.0 (d'), 128.1 (d'), 128.3 (d'), 129.7 (d'), 131.0 (d'), 131.4 (d'), 133.2 (s'), 133.6 (s'), 135.1 (s'), 135.6 (d'), 136.5 (d'), 140.1 (s'), 142.1 (s'), 150.8 (s'), 151.7 (s'), 154.9 (s'), 159.1 (s') (some of the signals overlap); mass (HRFAB) *m/z* calcd for $C_{55}H_{56}NO_6SSi$ (M + H) 886.3597, found 886.3575. Anal. Calcd for $C_{55}H_{55}NO_6SSi$: C, 74.54; H, 6.26; N, 1.58. Found: C, 74.51; H, 6.30; N, 1.59.

3'-[[[(1,1-Dimethylethyl)diphenylsilyl]oxy]methyl]-3-(phenylmethylene)-1,3,6',7',8',9'-hexahydro-1',4,7,10'-tetramethoxyspiro[2*H*-indene-2,9'-benz[*g*]isoquinolin]-1-ol (14). AIBN (10 mg, 0.061 mmol) was added to a stirred solution of alcohol **13** (1.10 g, 1.24 mmol) in PhH (23 mL). The mixture was lowered into an oil bath set at 80 °C. As soon as the solution began to reflux, solid Ph_3SnH (0.77 g, 2.19 mmol) was added in one portion. Refluxing was continued for 6 h and the mixture was then cooled to room temperature. Evaporation of the solvent and flash chromatography of the residue over silica gel (3 x 15 cm), using 1:4 EtOAc-hexane, gave alcohol **14** (0.84 g, 87%) as a 10:1 mixture of isomers (^1H NMR, 400 MHz): FTIR 3570, 1620, 1550, 1495 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.19 (s, 9 H), 1.65-1.73 (m, 1 H), 1.76-1.84 (m, 1 H), 1.86-1.97 (m, 1 H), 2.08-2.20 (m, 1 H), 2.36-2.47 (m, 1 H), 2.71-2.82 (m, 1 H), 3.13 (s, 1 H), 3.70 (s, 3 H), 3.85 (s, 3 H), 3.92 (s, 3 H), 3.96 (s, 3 H), 4.83 (s, 2 H), 5.69 (s, 1 H), 6.61 (s, 1 H), 6.63 (s, 1 H), 6.77 (d, *J* = 8 Hz, 1 H), 6.86 (d, *J* = 8 Hz, 1 H), 6.90-7.03 (m, 3 H), 7.13 (s, 1 H), 7.34-7.47 (m, 7 H), 7.73-7.84 (m, 5 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 19.5 (s'), 20.3 (t'), 27.0 (q'), 32.0 (t'), 53.4 (q'), 55.2 (q'), 56.7 (q'), 62.9 (t'), 64.3 (q'), 66.4 (t'), 85.2 (s'), 109.1 (d'), 110.5 (d'), 111.5 (d'), 111.8 (s'), 121.1 (d'), 123.5 (s'), 127.9 (d'), 128.1 (d'), 128.1 (d'), 128.3 (d'), 129.7 (d'), 131.0 (s'), 131.4 (d'), 133.2 (s'), 133.6 (s'), 135.1 (s'), 135.6 (d'), 136.5 (d'), 140.1 (s'), 142.1 (s'), 150.7 (s'), 151.8 (s'), 154.9 (s'), 159.1 (s'), 159.3 (s') (some of the signals overlap); mass (HRFAB) *m/z* calcd for $C_{49}H_{52}NO_6Si$ (M + H) 778.3564, found 778.3535. Anal. Calcd for $C_{49}H_{51}NO_6Si$: C, 75.64; H, 6.61; N, 1.80. Found: C, 75.63; H, 6.64; N, 1.86.

3'-[[[(1,1-Dimethylethyl)diphenylsilyl]oxy]methyl]-6',7',8',9'-tetrahydro-1',4,7,10'-tetramethoxy-3-(phenylmethylene)spiro[2*H*-indene-2,9'-benz[*g*]isoquinolin]-1(3*H*)-one (15). Ph_3BiCO_3[7] (1.58 g, 3.16 mmol) was added to a stirred solution of alcohols **14** (708 mg, 0.91 mmol) in a mixture of PhMe (26 mL) and pyridine (1.7 mL). The mixture was heated at 80 °C for 4.5 h, and then filtered through a pad of silica gel (3 x 5 cm), using EtOAc (200 mL). The filtrate was washed with hydrochloric acid (10%, 1 x 25 mL) and brine (1 x 25 mL), and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (3 x 15 cm), using 1:3 EtOAc-hexane, gave ketones **15** (604 mg, 85%) as a pure (TLC, silica, 2:3 EtOAc-hexane), yellow foam: FTIR 1700, 1624, 1598, 1586, 1472, 1459 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) (major isomer only) δ 1.17 (s, 9 H), 1.59-1.70 (m, 1 H), 1.96-2.25 (m, 4 H), 2.72-2.81 (m, 2 H), 3.48 (s, 3 H), 3.93 (s, 3 H), 3.94 (s, 3 H), 3.98 (s, 3 H), 4.48 (dd, *J* = 15, 4.5 Hz, 2 H), 6.61 (d, *J* = 6 Hz, 2 H), 6.83-6.93 (m, 3 H), 7.10 (s, 1 H), 7.17 (d, *J* = 8.4 Hz, 1 H), 7.34 (s, 1 H), 7.36-7.49 (m, 6 H), 7.72-7.83 (m, 4 H), 8.03 (s, 1 H); ^{13}C NMR ($CDCl_3$, 75.5 Hz) δ 19.1 (t'), 19.4 (s'), 27.0 (q'), 30.7 (t'), 34.5 (t'), 53.5 (q'), 54.4 (s'), 55.7 (q'), 56.0 (q'), 62.1 (q'), 66.4 (t'), 109.5 (d'), 110.8

(d'), 111.4 (s'), 117.5 (d'), 121.6 (d'), 122.2 (s'), 125.9 (d'), 127.4 (d'), 127.7 (d'), 128.3 (d'), 128.6 (d'), 129.7 (d'), 131.3 (s'), 133.5 (s'), 133.7 (s'), 135.6 (d'), 137.4 (s'), 138.0 (s'), 140.1 (s'), 143.7 (s'), 146.3 (s'), 150.4 (s'), 150.9 (s'), 152.4 (s'), 155.5 (s'), 158.8 (s'), 205.1 (s'); mass (HRFAB) *m/z* calcd for $C_{49}H_{50}NO_6Si$ (M + H) 776.3407, found 776.3381. Anal. Calcd for $C_{49}H_{49}NO_6Si$: C, 75.84; H, 6.36; N, 1.80. Found: C, 75.87; H, 6.26; N, 1.81.

3'-[[[(1,1-Dimethylethyl)diphenylsilyl]oxy]methyl]-6',7',8',9'-tetrahydro-1',4,7,10'-tetramethoxyspiro[2*H*-indene-2,9'-benz[*g*]isoquinoline]-1,3-dione (17). OsO_4 (460 mg, 1.81 mmol) was added to a stirred solution of ketones **15** (185 mg, 0.24 mmol) in pyridine (5.46 mL) under Ar. Stirring was continued for 4 h at room temperature and aqueous $NaHSO_3$ (10%, 10 mL) was then added. After 15 min, more aqueous $NaHSO_3$ (10%, 50 mL) was added and the mixture was immediately extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with 10% hydrochloric acid (2 x 10 mL) and brine (1 x 20 mL), dried ($MgSO_4$), and evaporated. The resulting crude diols **16** were dissolved in CH_2Cl_2 (12 mL). The solution was stirred, and K_2CO_3 (98 mg, 0.709 mmol) and $Pb(OAc)_4$ (159 mg, 0.341 mmol) were added. After 30 min the solvent was evaporated, and flash chromatography of the residue over silica gel (2 x 15 cm), using 2:1 EtOAc-hexane, gave diketone **17** (104 mg, 62%) as a pure (TLC, silica, 2:3 EtOAc-hexene), yellow foam: FTIR 1739, 1707, 1624, 1579 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.16 (s, 9 H), 1.98-2.13 (m, 4 H), 2.95-3.12 (m, 2 H), 3.38 (s, 3 H), 3.88 (s, 3 H), 3.98 (s, 6 H), 4.79 (s, 2 H), 7.29 (s, 2 H), 7.35-7.49 (m, 8 H), 7.70-7.80 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 18.7 (t'), 19.4 (s'), 27.0 (q'), 30.2 (t'), 32.8 (t'), 53.4 (q'), 56.5 (q'), 57.4 (s'), 62.4 (q'), 66.3 (t'), 109.5 (d'), 111.1 (s'), 119.6 (d'), 122.4 (d'), 125.7 (s'), 127.7 (s'), 127.8 (d'), 129.7 (d'), 133.6 (s'), 135.6 (d'), 140.7 (s'), 143.0 (s'), 151.1 (s'), 151.3 (s'), 155.1 (s'), 158.7 (s'), 201.3 (s'); mass (HRFAB) *m/z* calcd for $C_{42}H_{44}NO_7Si$ (M + H) 702.2887, found 702.2865. Anal. Calcd for $C_{42}H_{43}NO_7Si$: C, 71.87; H, 6.18; N, 1.99. Found: C, 71.88; H, 6.19; N, 2.03.

6',7',8',9'-Tetrahydro-3'-(hydroxymethyl)-1',4,7,10'-tetramethoxyspiro[2*H*-indene-2,9'-benz[*g*]isoquinoline]-1,3-dione (18). TBAF (1 M in THF, 0.23 mL, 0.23 mmol) was added to a stirred solution of diketone **17** (144 mg, 0.21 mmol) in THF (6.5 mL). After 40 min, the mixture was evaporated, and flash chromatography of the residue over silica gel (2 x 15 cm), using 3:1 EtOAc-hexane, gave alcohol **18** (76 mg, 80 %) as a pure (^1H NMR, 400 MHz), yellow solid: mp 250-255 °C; FTIR 3500, 1737, 1700, 1624, 1578, 1557, 1492, 1275 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.98-2.10 (m, 4 H), 2.97-3.05 (2 H), 3.38 (s, 3 H), 3.97 (s, 6 H), 4.00 (s, 3 H), 4.66 (s, 2 H), 7.02 (s, 1 H), 7.28 (s, 1 H), 7.29 (s, 2 H) (OH proton was not observed); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 18.6 (t'), 30.2 (t'), 32.7 (t'), 53.6 (q'), 56.5 (q'), 57.4 (s'), 62.4 (q'), 64.3 (t'), 110.0 (d'), 111.3 (s'), 119.7 (d'), 122.1 (d'), 126.2 (s'), 127.5 (s'), 140.5 (s'), 143.6 (s'), 149.2 (s'), 151.3 (s'), 155.1 (s'), 159.2 (s'), 201.2 (s'); exact mass *m/z* calcd for $C_{26}H_{25}NO_7$ 463.1631, found 463.1636.

1,3,6',7',8',9'-Hexahydro-1',4,7,10'-tetramethoxy-1,3-dioxospiro[2*H*-indene-2,9'-benz-[*g*]isoquinoline]-3'-carboxaldehyde (19). MnO_2 (100 mg, 1.15 mmol) was added in three portions at 15 minute-intervals to a stirred solution of alcohol **18** (26.5 mg, 0.57 mmol) in a mixture of CH_2Cl_2 (3 mL)

and Et_2O (9 mL). After 30 min, the suspension was filtered through a pad of silica gel (2 x 3 cm), using acetone. Evaporation of the solvent and flash chromatography of the residue over silica gel (1 x 15 cm), using 2:1 EtOAc-hexene, gave aldehyde **19** (23.5 mg, 89%) as a pure (TLC, silica, 2:1 EtOAc-hexene), light yellow solid: mp 281-286 °C; FTIR 2941, 1738, 1704, 1610, 1578, 1555, 1492, 1275 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 1.98-2.18 (m, 4 H), 3.05-3.10 (m, 2 H), 3.48 (s, 3 H), 3.99 (s, 6 H), 4.13 (s, 3 H), 7.36 (s, 2 H), 7.58 (s, 1 H), 7.83 (s, 1 H), 9.98 (s, 1 H); ^{13}C NMR (CD_2Cl_2, 75.5 MHz) δ 18.9 (t'), 30.5 (t'), 32.7 (t'), 54.3 (q'), 56.7 (q'), 58.2 (s'), 63.1 (q'), 114.3 (d'), 118.0 (d'), 120.4 (d'), 124.7 (s'), 127.7 (s'), 130.7 (s'), 139.3 (s'), 144.6 (s'), 145.0 (s'), 151.7 (s'), 155.4 (s'), 160.3 (s'), 192.7 (d'), 200.7 (s'); exact mass *m/z* calcd for $C_{26}H_{23}NO_7$ 461.1474, found 461.1471.

6',7',8',9'-Tetrahydro-1',4,7,10'-tetramethoxy-3'-pentylspiro[2*H*-indene-2,9'-benz[*g*]isoquinoline]-1,3-dione (21). *t*-BuOK (140 mg, 1.19 mmol) was added to a stirred and cooled (0 °C) solution of (*E*)-2-butenylmethyldiphenylphosphonium iodide[4a] (475 mg, 1.25 mmol) in THF (5.3 mL). After 30 min, a portion (3.4 mL) of the resulting orange-red suspension was added to a stirred solution of aldehyde **19** (134 mg, 0.29 mmol) in CH_2Cl_2 (6.3 mL) at room temperature. After 15 min, the mixture was evaporated, and flash chromatography of the residue over silica gel (2 x 15 cm), using 2:1 EtOAc-hexane, gave a mixture of three diene isomers (^1H NMR, 200 MHz), which was used immediately in the next step.

Pd/C (10%, 30 mg) was added to a stirred solution of the dienes in EtOAc (16 mL) under Ar. Stirring was then continued for 12 h under H_2 (balloon) at room temperature. The suspension was filtered through a pad of silica gel (3 x 2 cm), using EtOAc. Evaporation of the solvent and flash chromatography of the residue over silica gel (2 x 15 cm), using 2:1 EtOAc-hexane, gave **21** (126 mg, 86%) as a pure (^1H NMR, 400 MHz), yellow solid: mp 181.5-182.3 °C; FTIR 1739, 1706, 1622, 1578, 1492, 1240 cm^{-1}; ^1H NMR (400 MHz, CD_2Cl_2) δ 0.92 (t, *J* = 7 Hz, 3 H), 1.30-1.40 (m, 4 H), 1.73-1.82 (m, 2 H), 1.94-2.04 (m, 4 H), 2.70 (t, *J* = 8 Hz, 2 H), 2.97-3.03 (m, 2 H), 3.32 (s, 3 H), 3.98 (s, 6 H), 3.99 (s, 3 H), 6.94 (s, 1 H), 7.28 (s, 1 H), 7.33 (s, 2 H); ^{13}C NMR (CD_2Cl_2, 75.5 MHz) δ 14.2 (q'), 19.1 (t'), 23.0 (t'), 29.0 (t'), 30.5 (t'), 31.9 (t'), 32.9 (t'), 37.7 (t'), 53.5 (q'), 56.7 (q'), 57.8 (s'), 62.6 (q'), 110.7 (s'), 111.7 (d'), 120.3 (d'), 121.7 (d'), 125.9 (s'), 127.8 (s'), 141.1 (s'), 143.3 (s'), 151.7 (s'), 153.4 (s'), 155.0 (s'), 158.9 (s'), 201.4 (s'); exact mass *m/z* calcd for $C_{30}H_{33}NO_6$ 503.2308, found 503.2307. Anal. Calcd for $C_{30}H_{33}NO_6$: C, 71.55; H, 6.61; N, 2.78. Found: C, 71.41; H, 6.54; N, 2.82.

6',7',8',9'-Tetrahydro-4,7,10'-trimethoxy-3'-pentylspiro[2*H*-indene-2,9'-benz[*g*]isoquinoline]-1,1',3-(2'*H*)-trione (22). Me_3SiCl (0.11 mL, 0.87 mmol) and NaI (22 mg, 0.15 mmol) were added to a stirred solution of **21** (56 mg, 0.11 mmol) in a mixture of CH_2Cl_2 (9 mL) and MeCN (9 mL). Stirring under Ar was continued for 1 h at room temperature. Evaporation of the solvent and flash chromatography of the residue over silica gel (1 x 15 cm), using EtOAc, gave **22** (40 mg, 74%) as a pure (^1H NMR, 400 MHz), yellow foam: FTIR 2931, 1739, 1706, 1641, 1604, 1578, 1492, 1459, 1275 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 0.81-0.87 (m, 3 H), 1.23-1.34 (m, 4 H), 1.61-1.69 (m, 2 H), 1.93-2.02 (m, 4 H), 2.47 (t, *J* = 8 Hz, 2 H), 2.92-2.08 (m, 2 H), 3.42 (s, 3 H), 3.97 (s, 6 H), 6.18 (s, 1 H), 7.08 (s, 1 H), 7.33 (s, 2 H), 9.82 (br s, 1 H); ^{13}C NMR (CD_2Cl_2, 75.5 MHz) δ 14.1 (q'), 19.0 (t'), 22.7 (t'), 28.0 (t'),

30.5 (t'), 31.4 (t'), 32.7 (t'), 33.3 (t'), 56.8 (q'), 57.5 (s'), 62.2 (q'), 103.5 (d'), 115.5 (s'), 120.2 (d'), 121.9 (d'), 126.2 (s'), 127.9 (s'), 141.0 (s'), 142.6 (s'), 146.2 (s'), 151.7 (s'), 158.6 (s'), 162.1 (s'), 201.4 (s'); exact mass *m/z* calcd for $C_{29}H_{31}NO_6$ 489.2151, found 489.2143.

6',7',8',9'-Tetrahydro-4,7,10'-trihydroxy-3'-pentylspiro[2*H*-indene-2,9'-benz[*g*]isoquinoline]-1,1',3-(2'*H*)-trione (5). BBr_3 (1 M in CH_2Cl_2, 0.44 mL, 0.44 mmol) was added in one portion to a stirred and cooled (-78 °C) solution of **22** (21.5 mg, 0.044 mmol) in CH_2Cl_2 (3 mL). Stirring was continued at -78 °C for 2 h. The cold bath was removed and, after 2 h, water (3 mL) was added. The mixture was extracted with 200:1 $CHCl_3$-AcOH (2 x 25 mL) and the combined organic extracts were washed with brine and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (1 x 15 cm), using 1:35:64 AcOH-EtOAc-hexane, gave **5** (12.3 mg, 63%) as a pure (^1H NMR, 400 MHz), yellow solid: mp 285.5-288.0 °C; FTIR 3417, 2930, 1684, 1661, 1640, 1625, 1160 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 0.86 (t, *J* = 7 Hz, 3 H), 1.23-1.36 (m, 4 H), 1.55-1.68 (m, 2 H), 1.97-2.28 (m, 4 H), 2.47 (t, *J* = 8 Hz, 2 H), 2.95 (t, *J* = 7 Hz, 2 H), 6.26 (s, 1 H), 6.82 (s, 1 H), 7.21 (s, 2 H), 7.99 (s, 2 H), 8.87 (s, 1 H) (the OH signal was not observed); ^{13}C NMR (C_2D_6SO, 100.6 MHz) δ 13.8 (q'), 18.4 (t'), 21.8 (t'), 27.6 (t'), 29.7 (t'), 30.5 (t'), 31.8 (t'), 32.1 (t'), 56.2 (s'), 103.9 (d'), 107.4 (s'), 114.8 (d'), 116.6 (s'), 123.4 (s'), 126.0 (d'), 137.4 (s'), 142.2 (s'), 146.9 (s'), 148.3 (s'), 158.0 (s'), 166.7 (s'), 201.4 (s'); exact mass *m/z* calcd for $C_{26}H_{25}NO_6$ 447.1682, found 447.1673.

3-[[[(1,1-Dimethylethyl)diphenylsilyl]oxy]methyl]-6,7,8,9-tetrahydro-1,10-dimethoxy-9-(phenylthio)-α-[1,4,5,6,8-pentamethoxy-3-(phenylethynyl)-2-naphthalenyl]benz[*g*]isoquinoline-9-methanol (25). *n*-BuLi (1.6 M in hexane, 2.35 mL, 3.76 mmol) was added dropwise over 1 min to a stirred and cooled (-78 °C) solution of bromide **24** (1.41 g, 3.08 mmol) in a mixture of THF (20 mL) and Et_2O (20 mL). After 10 min, aldehyde **11** (2.05 g, 3.16 mmol), in a mixture of THF (5 mL) and Et_2O (15 mL), was added over 5 min. Stirring was continued for 15 min. The cold bath was then removed and, after 5 min, saturated aqueous NH_4Cl (20 mL) was added. The mixture was extracted with Et_2O (2 x 100 mL) and the combined organic extracts were washed with brine (30 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (4 x 15 cm), using 1:3 EtOAc-hexane, gave alcohol **25** (2.38 g, 75%) as a pure (^1H NMR, 400 MHz), light yellow foam: FTIR 3525, 2999, 1621, 1572, 1491, 1262 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.16 (s, 9 H), 1.52 (br s, 1 H), 1.85 (br s, 1 H), 2.18-2.28 (m, 1 H), 2.40-2.51 (m, 1 H), 2.57 (br s, 1 H), 2.65-2.74 (m, 1 H), 2.99 (br s, 3 H), 3.65 (s, 3 H), 3.83 (s, 3 H), 3.93 (s, 3 H), 3.98 (s, 3 H), 4.06 (s, 3 H), 4.11 (s, 3 H), 4.82 (s, 2 H), 6.69 (s, 2 H), 6.97 (s, 1 H), 7.12-7.23 (m, 3 H), 7.27-7.47 (m, 12 H), 7.59-7.70 (m, 2 H), 7.72-7.83 (m, 4 H) (the OH signal was not observed); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 19.4 (s'), 19.5 (t'), 20.1 (t'), 26.5 (q'), 32.2 (t'), 53.3 (q'), 56.5 (q'), 59.7 (q'), 62.0 (q'), 62.0 (q'), 64.0 (s'), 64.2 (q'), 66.4 (t'), 108.9 (d'), 112.0 (s'), 117.5 (s'), 120.4 (d'), 123.3 (s'), 125.4 (s'), 127.8 (d'), 128.1 (d'), 128.4 (d'), 128.4 (d'), 129.7 (d'), 129.7 (d'), 131.3 (d'), 133.6 (s'), 133.7 (s'), 134.9 (s'), 135.1 (d'), 135.6 (d'), 137.4 (d'), 137.8 (s'), 140.1 (s'), 150.5 (s'), 150.7 (s'), 153.4 (s'), 159.3 (s') (several of the signals overlap); mass (HRFAB) *m/z* calcd for $C_{62}H_{64}NO_9SSi$ (M + H) 1026.4071, found 1026.4007. Anal. Calcd for $C_{62}H_{63}NO_9SSi$: C 72.56, H 6.19, N 1.36. Found: C

72.66, H 6.31, N 1.38.

3'-[[[(1,1-Dimethylethyl)diphenylsilyl]oxy]methyl]-1,3,6',7',8',9'-hexahydro-1',4,5,6,8,9,10'-heptamethoxy-3-(phenylmethylene)spiro[2*H*-benz[f]indene-2,9'-benz[*g*]-isoquinolin]-1-ol (26). Et_3B (1 M in hexane, 118 mL, 118 mmol) was added to a stirred solution of Ph_3SnH (7.9 mL, 30.92 mmol) and alcohol **25** (3.00 g, 2.92 mmol) in PhH (75 mL) in an open flask, stirring was continued for 30 min. Evaporation of the solvent and flash chromatography of the residue over silica gel (5 x 15 cm), using 1:2 EtOAc-hexane, gave alcohols **26** (2.12 g, 79%) as a pure (^1H NMR, 400 MHz), yellow foam: FTIR 3220, 2920, 1340 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.18 (s, 9 H), 1.67-1.75 (m, 1 H), 1.80-2.06 (m, 2 H), 2.20-2.35 (m, 2 H), 2.80 (d, *J* = 17.8 Hz, 1 H), 3.51 (s, 1 H), 3.68 (s, 3 H), 3.84 (s, 3 H), 3.85 (s, 3 H), 3.86 (s, 3 H), 3.93 (s, 3 H), 4.01 (s, 3 H), 4.02 (s, 3 H), 4.80 (s, 2 H), 5.72 (s, 1 H), 6.73 (d, *J* = 7.2 Hz, 2 H), 6.79 (s, 1 H), 6.89-7.03 (m, 3 H), 7.15 (s, 1 H), 7.32 (s, 1 H), 7.35-7.50 (m, 6 H), 7.76-7.83 (m, 4 H), 8.03 (s, 1 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 19.7 (s'), 22.2 (t'), 27.1 (q'), 31.4 (t'), 32.9 (t'), 52.6 (s'), 53.5 (q'), 57.1 (q'), 57.4 (q'), 60.9 (q'), 62.1, (q'), 62.2 (q'), 62.4 (q'), 66.9 (t'), 84.4 (d'), 97.9 (d'), 109.9 (d'), 112.2 (s'), 117.9 (s'), 121.7 (d'), 125.9 (d'), 126.2 (d'), 127.6 (d'), 128.1 (d'), 129.4 (d'), 130.1 (d'), 131.2 (s'), 134.1 (s'), 134.2 (s'), 136.0 (d'), 138.2 (s'), 140.1 (s'), 140.3 (s'), 142.9 (s'), 143.6 (s'), 148.5 (s'), 149.5 (s'), 150.6 (s'), 152.6 (s'), 153.4 (s'), 156.7 (s'), 159.3 (s') (some of the peaks overlap); mass (HRFAB) *m/z* calcd for $C_{56}H_{59}NO_9Si$ 917.3959, found 917.3861. Anal. Calcd for $C_{56}H_{59}NO_9Si$: C 73.26, H 6.48, N 1.53. Found: C 73.12, H 6.63, N 1.57.

3'-[[[(1,1-Dimethylethyl)diphenylsilyl]oxy]methyl]-6',7',8',9'-tetrahydro-1',4,5,6,8,9,10'-heptamethoxy-3-(phenylmethylene)spiro[2*H*-benz[*f*]indene-2,9'-benz[*g*]-isoquinolin]-1(3*H*)-one (27). Ph_3BiCO_3[7] (3.2 g, 6.40 mmol) was added to a stirred solution of alcohols **26** (1.60 g, 1.74 mmol) in a mixture of PhMe (43 mL) and pyridine (2.8 mL). The mixture was heated at 90 °C for 3 h, and then filtered through a pad of silica gel (3 x 5 cm), using EtOAc (500 mL). Evaporation of the solvent and flash chromatography of the residue over silica gel (4 x 15 cm), using 2:3 EtOAc-hexane, gave ketones **27** (1.4 g, 88%) as a pure (TLC, silica, 2:3 EtOAc-hexene), yellow foam: FTIR 2931, 1572, 1345 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.17 (s, 9 H), 1.65-1.78 (m, 1 H), 1.98-2.14 (m, 3 H), 2.23-2.39 (m, 1 H), 2.92 (d, *J* = 15.6 Hz, 1 H), 3.47 (s, 3 H), 3.89 (s, 3 H), 3.90 (s, 3 H), 3.93 (s, 3 H), 3.98 (s, 3 H), 4.02 (s, 3 H), 4.05 (s, 3 H), 4.76 (d, *J* = 15.6 Hz, 1 H), 4.76 (d, *J* = 15.6 Hz, 1 H), 4.83 (d, *J* = 15.6 Hz, 1 H), 6.68 (d, *J* = 9 Hz, 2 H), 6.77 (s, 1 H), 6.80-6.98 (m, 3 H), 7.06 (s, 1 H), 7.29 (s, 1 H), 7.35-7.48 (m, 6 H), 7.72-7.81 (m, 4 H), 8.18 (s, 1 H); ^{13}C NMR (CD_2Cl_2, 75.5 MHz) δ 19.7 (t'), 27.1 (q'), 31.0 (t'), 35.2 (t'), 53.4 (q'), 55.7 (s'), 57.0 (q'), 57.4 (q'), 60.9 (q'), 62.2 (q'), 62.4 (q'), 62.0 (q'), 66.9 (t'), 97.7 (d'), 109.9 (d'), 111.7 (s'), 118.3 (s'), 121.2 (s'), 121.6 (d'), 126.3 (d'), 127.7 (d'), 127.8 (d'), 128.1 (d'), 128.8 (d'), 130.1 (d'), 131.1 (s'), 134.0 (s'), 134.1 (s'), 134.4 (s'), 136.0 (d'), 138.0 (s'), 140.4 (s'), 144.1 (s'), 146.2 (s'), 148.4 (s'), 150.8 (s'), 153.4 (s'), 154.8 (s'), 155.6 (s'), 156.9 (s'), 159.2 (s'), 204.3 (s') (some of the signals overlap); mass (HRFAB) *m/z* calcd for $C_{56}H_{58}NO_9Si$ (M + H) 916.3881, found 916.3870. Anal. Calcd for $C_{56}H_{57}NO_9Si$: C 73.42, H 6.27, N 1.53. Found: C 73.36, H 6.23, N 1.57.

3'-[[[(1,1-Dimethylethyl)diphenylsilyl]oxy]methyl]-6',7',8',9'-tetrahydro-1',4,5,6,8,9,10'-heptamethoxy-spiro[2*H*-benz[*f*]indene-2,9'-benz[*g*]isoquinoline]-1,3-dione (29). OsO_4 (1.0 g, 3.93 mmol) and $MeSO_2NH_2$ (0.30 g, 3.15 mmol) were added to a stirred solution of ketone **27** (440 mg, 0.48 mmol) in pyridine (8.1 mL) under Ar. Stirring was continued for 9 h at room temperature. Pyridine (10 mL) and 10% aqueous $NaHSO_3$ (20 mL) were added and stirring was continued for 30 min. More 10% aqueous $NaHSO_3$ (200 mL) was added and the mixture was immediately extracted with EtOAc (3 x 200 mL). The combined organic extracts were washed with 10% hydrochloric acid (2 x 50 mL), and brine (1 x 50 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (2 x 15 cm), using 2:3 EtOAc-hexane, gave diols **28**, which were dissolved in CH_2Cl_2 (3.7 mL). The solution was stirred and K_2CO_3 (17 mg, 0.123 mmol) and $Pb(OAc)_4$ (55.1 mg, 0.124 mmol) were added. Stirring was continued for 30 min, and the suspension was then evaporated. Flash chromatography of the residue over silica gel (2 x 15 cm), using 2:3 EtOAc-hexane, gave diketone **29** (40.6 mg, 10%) as a pure (^1H NMR, 400 MHz), yellow foam: FTIR 2933, 1732, 1705, 1624, 1596, 1359, 1344 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 1.15 (s, 9 H), 1.97-2.13 (m, 4 H), 3.06-3.13 (m, 2 H), 3.19 (s, 3 H), 3.90 (s, 3 H), 3.92 (s, 3 H), 4.01 (s, 3 H), 4.02 (s, 3 H), 4.08 (s, 6 H), 4.82 (s, 2 H), 6.94 (s, 1 H), 7.38-7.50 (m, 8 H), 7.73-7.82 (m, 4 H); ^{13}C NMR (CD_2Cl_2, 75.5 MHz) δ 19.1 (t'), 19.6 (s'), 27.1 (q'), 30.5 (t'), 33.1 (t'), 53.7 (q'), 56.9 (q'), 57.6 (q'), 59.5 (s'), 62.1 (q'), 62.7 (q'), 63.1 (q'), 63.3 (q'), 66.0 (s'), 66.8 (t'), 100.1 (d'), 109.9 (d'), 111.4 (s'), 121.3 (s'), 122.4 (d'), 123.5 (s'), 126.6 (s'), 127.0 (s'), 128.1 (d'), 130.1 (d'), 131.4 (s'), 134.0 (s'), 135.9 (d'), 139.8 (s'), 141.0 (s'), 143.6 (s'), 151.5 (s'), 154.1 (s'), 154.4 (s'), 155.0 (s'), 157.1 (s'), 159.1 (s') (some of the signals overlap); mass (HRFAB) *m/z* calcd for $C_{49}H_{52}NO_{10}Si$ (M + H) 842.3360, found 842.3342.

6',7',8',9'-Tetrahydro-3'-(hydroxymethyl)-1',4,5,6,8,9,10'-heptamethoxyspiro[2*H*-benz-[*f*]indene-2,9'-benz[*g*]isoquinoline]-1,3-dione (30). TBAF (1 M in THF, 75 μL, 0.075 mmol) was added to a stirred solution of diketone **29** (56 mg, 0.067 mmol) in THF (2.1 mL). After 40 min, the mixture was evaporated. Flash chromatography of the residue over silica gel (2 x 15 cm), using 2:1 EtOAc-hexane, gave alcohol **30** (29.5 mg, 74 %) as a pure (^1H NMR, 400 MHz), yellow foam: FTIR 3500, 1732, 1702, 1651, 1624, 1596, 1557, 1340 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 1.97-2.10 (m, 4 H), 2.95 (t, J = 6 Hz, 1 H), 3.02-3.08 (m, 2 H), 2.79 (s, 3 H), 3.89 (s, 3 H), 3.99 (s, 3 H), 4.02 (s, 6 H), 4.06 (s, 6 H), 4.63 (d, J = 6 Hz, 2 H), 6.94 (s, 1 H), 7.09 (s, 1 H), 7.36 (s, 1 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 19.0 (t'), 30.5 (t'), 33.1 (t'), 53.9 (q'), 56.9 (q'), 57.6 (q'), 59.5 (s'), 62.1 (q'), 62.8 (q'), 63.1 (q'), 63.3 (q'), 64.8 (t'), 100.1 (d'), 110.1 (d'), 111.6 (s'), 121.3 (s'), 122.2 (d'), 123.4 (s'), 126.5 (s'), 127.4 (s'), 131.4 (s'), 139.8 (s'), 140.9 (s'), 144.1 (s'), 150.4 (s'), 151.6 (s'), 154.1 (s'), 154.4 (s'), 155.1 (s'), 157.1 (s'), 159.6 (s'), 200.4 (s'), 201.2 (s'); exact mass *m/z* calcd for $C_{33}H_{33}NO_{10}$ 603.2104, found 603.2105.

1,3,6',7',8',9'-Hexahydro-1',4,5,6,8,9,10'-heptamethoxy-1,3-dioxospiro[2*H*-benz[*f*]-indene-2,9'-benz[*g*]isoquinoline]-3'-carboxaldehyde (31). MnO_2 (80 mg, 0.92 mmol) was added in three equal portions at 15 minute-intervals to a stirred solution of alcohol **30** (28.0 mg, 0.046 mmol) in Et_2O (10 mL). After an additional 30 min, the suspension was filtered through a pad of silica gel (2 x 3 cm), using

EtOAc (50 mL). Evaporation of the solvent and flash chromatography of the residue over silica gel (1 x 15 cm), using 2:1 EtOAc-hexane, gave aldehyde **31** (18.2 mg, 65%) as a pure (^{1}H NMR, 400 MHz), light yellow foam: FTIR 2932, 1732, 1703, 1594, 1556, 1360, 1340, 1030 cm^{-1}; ^{1}H NMR (CD_2Cl_2, 400 MHz) δ 1.99-2.14 (m, 4 H), 3.07-3.15 (m, 2 H), 3.43 (s, 3 H), 3.90 (s, 3 H), 3.99 (s, 3 H), 4.02 (s, 3 H), 4.05 (s, 6 H), 4.10 (s, 3 H), 6.93 (s, 1 H), 7.61 (s, 1 H), 7.83 (s, 1 H), 9.99 (s, 1 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 18.9 (t'), 30.5 (t'), 33.0 (t'), 54.2 (q'), 56.9 (q'), 57.6 (q'), 59.8 (s'), 62.2 (q'), 63.1 (q'), 63.4 (q'), 100.1 (d'), 114.4 (s'), 118.2 (d'), 121.3 (s'), 123.2 (s'), 124.6 (d'), 126.5 (s'), 131.3 (s'), 131.5 (s'), 139.3 (s'), 139.8 (s'), 144.6 (s'), 145.1 (s'), 151.7 (s'), 154.3 (s'), 154.6 (s'), 155.2 (s'), 157.1 (s'), 160.4 (s'), 192.7 (d'), 199.9 (s'), 200.8 (s') (two of the methyl signals overlap); exact mass *m/z* calcd for $C_{33}H_{31}NO_{10}$ 601.1948, found 601.1945.

6',7',8',9'-Tetrahydro-1',4,5,6,8,9,10'-heptamethoxy-3'-pentylspiro[2*H*-benz[*f*]-indene-2,9'-benz[*g*]isoquinoline]-1,3-dione (32). *t*-BuOK (14 mg, 0.125 mmol) was added to a stirred suspension of (*E*)-2-butenylmethyldiphenylphosphonium iodide[4a] (47 mg, 0.123 mmol) in THF (0.5 mL), and the mixture was stirred at room temperature for 20 min. A portion of the resulting orange-red suspension (0.4 mL) was then added to a stirred solution of aldehyde **31** (13 mg, 0.022 mmol) in THF (1 mL). After 5 min, the mixture was evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 3:2 EtOAc-hexane, gave a mixture of three diene isomers, which was used immediately in the next step.

Pd/C (10%, 3 mg) was added to a stirred solution of the dienes in EtOAc (1 mL) under Ar. Stirring was continued under H_2 (balloon) overnight at room temperature. The suspension was filtered through a pad of silica gel (3 x 2 cm), using EtOAc. Evaporation of the solvent and flash chromatography of the residue over silica gel (1 x 15 cm), using 3:2 EtOAc-hexane, gave **32** (10.4 mg, 75%) as a pure (^{1}H NMR, 400 MHz), yellow foam: FTIR 2933, 2854, 1734, 1703, 1600, 1350, 1340, 1050 cm^{-1}; ^{1}H NMR (400 MHz, CD_2Cl_2) δ 0.91 (t, *J* = 7.8 Hz, 3 H), 1.30-1.41 (m, 4 H), 1.74-1.81 (m, 2 H), 1.95-2.09 (m, 4 H), 2.71 (t, *J* = 7.8 Hz, 2 H), 2.98-3.05 (m, 2 H), 3.39 (s, 3 H), 3.87 (s, 3 H), 3.98 (s, 3 H), 3.99 (s, 3 H), 4.02 (s, 3 H), 4.05 (s, 6 H), 6.95 (s, 2 H), 7.33 (s, 1 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 14.2 (q'), 19.1 (t'), 23.0 (t'), 29.0 (t'), 30.5 (t'), 31.9 (t'), 33.1 (t'), 37.7 (t'), 56.9 (q'), 57.6 (q'), 59.4 (s'), 62.1 (q'), 62.6 (q'), 63.1 (q'), 63.3 (q'), 100.1 (d'), 110.7 (s'), 111.8 (d'), 121.3 (s'), 121.7 (d'), 123.5 (s'), 126.4 (s'), 126.6 (s'), 131.4 (s'), 139.7 (s'), 141.1 (s'), 143.2 (s'), 151.5 (s'), 153.3 (s'), 154.1 (s'), 154.3 (s'), 154.8 (s'), 157.0 (s'), 158.9 (s'), 200.5 (s'), 201.4 (s') (two methyl signals overlap); exact mass *m/z* calcd for $C_{37}H_{41}NO_9$ 643.2781, found 643.2770.

6',7',8',9'-Tetrahydro-4,5,6,8,9,10'-hexamethoxy-3'-pentylspiro[2*H*-benz[*f*]indene-2,9'-benz[*g*]isoquinoline]-1,1',3(2*H*)-trione (33). Me_3SiCl (12 μL, 0.095 mmol) and NaI (4.0 mg, 0.027 mmol) were added to a stirred solution of **32** (7.0 mg, 0.011 mmol) in a mixture of dry CH_2Cl_2 (1 mL) and dry MeCN (1 mL). Stirring under Ar was continued for 1 h at room temperature. Evaporation of the solvent and flash chromatography of the residue over silica gel (1 x 15 cm), using EtOAc, gave **33** (5.7 mg, 83%) as pure (^{1}H NMR, 400 MHz), yellow foam: FTIR 2931, 1734, 1703, 1642, 1601, 1595, 1540, 1360 cm^{-1}; ^{1}H NMR (400 MHz, CD_2Cl_2) δ 0.85 (t, *J* = 7.6 Hz, 3 H), 1.24-1.35 (m, 4 H), 1.55-1.70 (m, 2 H), 1.93-2.06

(m, 4 H), 2.45 (t, J = 8.4 Hz, 2 H), 2.92-2.99 (m, 2 H), 3.46 (s, 3 H), 3.88 (s, 3 H), 3.98 (s, 3 H), 4.01 (s, 3 H), 4.05 (s, 6 H), 6.16 (s, 1 H), 6.94 (s, 1 H), 7.09 (s, 1 H), 8.75 (br s, 1 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 14.0 (q'), 18.9 (t'), 22.7 (t'), 28.0 (t'), 30.5 (t'), 31.4 (t'), 32.9 (t'), 33.3 (t'), 56.9 (q'), 57.5 (q'), 59.2 (s'), 62.1 (q'), 62.3 (q'), 63.1 (q'), 63.3 (q'), 100.1 (d'), 103.5 (d'), 115.6 (s'), 121.3 (s'), 121.8 (d'), 123.6 (s'), 126.6 (s'), 126.8 (s'), 131.4 (s'), 139.8 (s'), 141.0 (s'), 142.5 (s'), 146.2 (s'), 151.5 (s'), 154.0 (s'), 154.3 (s'), 157.0 (s'), 158.4 (s'), 162.1 (s'), 200.4 (s'), 201.3 (s'); exact mass m/z calcd for $C_{36}H_{39}NO_9$ 629.2625, found 629.2602.

6',7',8',9'-Tetrahydro-4,9,10'-trihydroxy-6-methoxy-3'-pentylspiro[2*H*-benz[*f*]-indene-2,9'-benz[g]isoquinoline]-1,1',3,5,8(2'H)-pentone (23). The precursor (**33**) must be freshly purified by flash chromatography before the reaction, otherwise the product will be very difficult to purify.

BBr_3 (0.53 M in CH_2Cl_2, 0.12 mL, 0.063 mmol) was added in one portion to a stirred and cooled (-78 °C) solution of **33** (4.0 mg, 0.0064 mmol) in dry CH_2Cl_2 (0.66 mL) under Ar. The solution became red-purple immediately. Stirring was continued for 1 h, and the dry-ice cold bath was changed to an ice bath. After 10 min, water (0.5 mL) was added and the red color faded to yellow. The solvent was evaporated at room temperature and the resulting aqueous mixture was diluted with 3:1 THF-water (20 mL). The mixture was stirred for 50 h open to the air (and without protection from light), the progress of the reaction being followed by UV measurements (growth of a peak at 510 nm). EtOAc (10 mL) was added and the mixture was washed with brine and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (1 x 15 cm), using 1:0.5:20 acetone:AcOH:CH_2Cl_2, gave **23** (2.2 mg, 62%) as a pure (^{1}H NMR, 400 MHz), red solid: mp 350 °C dec; FTIR 2925, 2854, 1745, 1698, 1650, 1605, 1110 cm^{-1}; ^{1}H NMR (400 MHz, CD_2Cl_2) δ 0.88 (t, J = 7.1 Hz, 3 H), 1.25-1.38 (m, 4 H), 1.58-1.69 (m, 2 H), 1.96-2.09 (m, 4 H), 2.50 (t, J = 8.8 Hz, 2 H), 2.95 (t, J = 6.2 Hz, 2 H), 3.98 (s, 3 H), 6.27 (s, 1 H), 6.36 (s, 1 H), 6.83 (s, 1 H), 8.50 (br s, 1 H), 12.53 (s, 1 H), 12.75 (s, 1 H), 13.19 (s, 1 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 14.1, 19.1, 22.7, 28.1, 30.5, 31.4, 32.1, 33.4, 57.3, 57.7, 106.3, 108.1, 111.4, 116.5, 116.8, 118.6, 118.7, 133.9, 135.6, 139.1, 142.1, 148.2, 153.0, 153.9, 157.9, 161.8, 177.6, 183.9, 189.4, 200.2, 200.2; mass (HRFAB) m/z calcd for $C_{31}H_{28}NO_9$ (M + H) 558.1764, found 558.1771. Irradiation of the methoxy signal at δ 3.98 in the ^{1}H NMR spectrum caused a nuclear Overhauser enhancement of 7% in the vinyl hydrogen signal at δ 6.36.

6',7'-Dihydro-1',4,5,6,8,9,9'-heptamethoxy-3'-pentylspiro[2*H*-benz[*f*]indene-2,8'-[8*H*]-cyclopent[*g*]-isoquinoline]-1,3-dione (35). *t*-BuOK (28 mg, 0.248 mmol) was added to a stirred suspension of (*E*)-2-butenylmethyldiphenylphosphonium iodide[4a] (94 mg, 0.246 mmol) in THF (1 mL), and the mixture was stirred at room temperature for 20 min. A portion of the resulting orange-red suspension (0.8 mL) was added to a stirred solution of aldehyde **34** (20 mg, 0.034 mmol) in THF (1.5 mL) at room temperature. After 5 min, the mixture was evaporated at room temperature. Flash chromatography of the residue over silica gel (1 x 15 cm), using 3:2 EtOAc-hexane, gave a mixture of three alkene isomers, which was used immediately in the next step.

Pd/C (10%, 5 mg) was added to a stirred solution of the alkenes in EtOAc (1 mL) under Ar. Stirring

was continued under H_2 (balloon) overnight at room temperature. The suspension was filtered through a pad of silica gel (3 x 2 cm), using EtOAc. Evaporation of the solvent and flash chromatography of the residue over silica gel (1 x 15 cm), using 3:2 EtOAc-hexane, gave **35** (16 mg, 75%) as a pure (^{1}H NMR, 400 MHz), yellow foam: FTIR 2960, 2850, 1732, 1702, 1630, 1350, 1340, 1020 cm^{-1}; ^{1}H NMR (400 MHz, CD_2Cl_2) δ 0.92 (t, J = 7.0 Hz, 3 H), 1.30-1.41 (m, 4 H), 1.72-1.82 (m, 2 H), 2.51 (t, J = 7.0 Hz, 2 H), 2.71 (t, J = 7.4 Hz, 2 H), 3.34-3.39 (m, 2 H), 3.40 (s, 3 H), 3.88 (s, 3 H), 3.99 (s, 3 H), 4.01 (s, 3 H), 4.02 (s, 3 H), 4.03 (s, 3 H), 4.05 (s, 3 H), 7.95 (s, 1 H), 7.00 (s, 1 H), 7.39 (s, 1 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 14.2 (q'), 23.0 (t'), 29.1 (t'), 31.9 (t'), 32.8 (t'), 36.4 (t'), 37.7 (t'), 56.9 (q'), 57.5 (q'), 62.2 (q'), 62.8 (q'), 63.1 (q'), 63.3 (q'), 66.7 (s'), 100.1 (d'), 111.6 (s'), 112.6 (d'), 117.5 (s'), 121.4 (d'), 124.8 (s'), 127.9 (s'), 131.5 (s'), 135.2 (s'), 139.7 (s'), 143.5 (s'), 150.5 (s'), 151.3 (s'), 152.7 (s'), 153.5 (s'), 154.3 (s'), 154.3 (s'), 157.2 (s'), 159.4 (s'), 199.6 (s'), 200.6 (s') (two methyl signals overlap); exact mass *m/z* calcd for $C_{36}H_{39}NO_9$ 629.2625, found 629.2919.

6',7'-Dihydro-4,5,6,8,9,9'-hexamethoxy-3-pentylspiro[2*H*-benz[f]indene-2,8'-[8*H*]cyclopent[g]isoquinoline]-1,1',3(2'*H*)-trione (36). Me_3SiCl (25 μL, 0.20 mmol) and NaI (4.8 mg, 0.032 mmol) were added to a stirred solution of **35** (16 mg, 0.025 mmol) in a mixture of CH_2Cl_2 (2 mL) and MeCN (2 mL). Stirring under Ar was continued for 1 h at room temperature. Evaporation of the solvent and flash chromatography of the residue over silica gel (1 x 15 cm), using EtOAc, gave **36** (13.1 mg, 84%) as a pure (^{1}H NMR, 400 MHz), yellow foam: FTIR 2930, 1732, 1702, 1640, 1617, 1360 cm^{-1}; ^{1}H NMR (400 MHz, CD_2Cl_2) δ 0.78-0.82 (m, 3 H), 1.20-1.33 (m, 4 H), 1.58-1.70 (m, 2 H), 2.41-2.53 (m, 4 H), 3.28-3.37 (m, 2 H), 3.47 (s, 3 H), 3.88 (s, 3 H), 3.99 (s, 3 H), 4.01 (s, 3 H), 4.04 (s, 6 H), 6.22 (s, 1 H), 6.95 (s, 1 H), 7.18 (s, 1 H), 10.35 (br s, 1 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 14.0 (q'), 22.7 (t'), 28.0 (t'), 31.4 (t'), 33.0 (t'), 33.2 (t'), 36.1 (t'), 56.9 (q'), 57.5 (q'), 62.1 (q'), 62.4 (q'), 63.1 (q'), 63.3 (q'), 66.6 (s'), 100.1 (d'), 104.1 (d'), 116.6 (s'), 117.7 (d'), 121.3 (s'), 124.8 (s'), 127.9 (s'), 131.4 (s'), 135.4 (s'), 139.7 (s'), 142.6 (s'), 143.5 (s'), 151.3 (s'), 153.3 (s'), 154.2 (s'), 154.3 (s'), 156.3 (s'), 157.2 (s'), 162.5 (s'), 199.6 (s'), 200.7 (s'); exact mass *m/z* calcd for $C_{35}H_{37}NO_9$ 615.2468, found 615.2448.

6',7'-Dihydro-4,9,9'-trihydroxy-6-methoxy-3'-pentylspiro[2*H*-benz[f]indene-2,8'-[8*H*]-cyclopent-[*g*]isoquinoline]-1,1',3,5,8(2'*H*)-pentone (37). BBr_3 (0.53 M in CH_2Cl_2, 0.41 mL, 0.22 mmol) was added in one portion to a stirred and cooled (-78 °C) solution of **36** (13.5 mg, 0.022 mmol) in dry CH_2Cl_2.(2.0 mL) under Ar. The solution became red-purple immediately. Stirring was continued for 1 h and the dry-ice cold bath was changed to an ice bath. After 10 min, water (0.5 mL) was added. The red color faded to yellow. The solvent was evaporated at room temperature and the resulting aqueous mixture was diluted with 3:1 THF-water (80 mL). The mixture was stirred for 48 h open to the air (and without protection from light), the progress of the reaction being followed by UV measurements (growth of a peak at 510 nm). Most of the THF was evaporated at room temperature under water pump vacuum. Water (5 mL) was added and the mixture was extracted with EtOAc (2 x 10 mL). The combined organic extracts were washed with brine (10 mL), dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 1:0.5:20 acetone-AcOH-CH_2Cl_2, gave **37**[2a] (6.0 mg, 50%) as a pure (^{1}H NMR, 400 MHz), red

solid: mp 350 °C dec.; FTIR 2948, 2929, 1747, 1716, 1650, 1610 cm^{-1}; ^1H NMR (400 MHz, CD_2Cl_2) δ 0.92 (t, *J* = 7.2 Hz, 3 H), 1.35-1.39 (m, 4 H), 1.58-1.70 (m, 2 H), 2.43-2.58 (m, 4 H), 3.32 (t, *J* = 6.6 Hz, 2 H), 3.99 (s, 3 H), 6.30 (s, 1 H), 6.36 (s, 1 H), 6.93 (s, 1 H), 8.30 (br s, 1 H), 12.44 (s, 1 H), 12.47 (s, 1 H), 13.20 (s, 1 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 14.0, 22.7, 28.1, 30.1, 31.5, 33.3, 35.3, 57.7, 65.1, 106.9, 111.5, 112.3, 118.7, 124.1, 135.7, 137.4, 141.8, 142.2, 152.8, 155.4, 156.2, 161.9, 168.0, 184.0, 189.6, 199.2, 199.3 (several signals overlap); mass (HRFAB) *m/z* calcd for $C_{30}H_{26}NO_9$ (M + H) 544.1607, found 544.1609.

5-[2-[[Dimethyl(1,1-dimethylethyl)silyl]oxy]ethyl]-2-cyclopenten-1-ol (48). A solution of imidazole (21.27 g, 312.5 mmol) in dry CH_2Cl_2 (125 mL) was added to a cold (0 °C) and stirred solution of **47**[14] (16.0 g, 125 mmol) in dry CH_2Cl_2 (220 mL). After 5 min, *t*-$BuMe_2SiCl$ (18.84 g, 125 mmol) in dry CH_2Cl_2 (80 mL plus 25mL as a rinse) was injected over 5 min, and the resulting solution was stirred for 10 min. Saturated aqueous NH_4Cl (125 mL) was added and the mixture was extracted with CH_2Cl_2 (3 x 100 mL). The organic extract was washed with brine (1 x 350 mL), and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue in two batches, each over silica gel (5 x 23 cm), using 1:19 EtOAc-hexane, gave **48** (18.7 g, 62%) as a pure (^1H NMR, 200 MHz), clear oil: FTIR 3404 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.09 (s, 6 H), 0.90 (s, 9 H), 1.55-1.75 (m, 1 H), 1.8-2.25 (m, 3 H), 2.25-2.5 (m, 1 H), 3.2 (br s, 1 H), 3.65 (dt, *J* = 10, 3.2 Hz, 1 H), 3.75-3.90 (m, 1 H), 4.6-4.71 (m, 1 H), 5.8-5.93 (m, 1 H), 5.93-6.5 (m, 1 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ -5.6 (q'), 18.2 (s'), 25.8 (q'), 31.6 (t'), 37.6 (t'), 42.0 (d'), 63.4 (t'), 75.9 (d'), 132.7 (d'), 134.7 (d'); exact mass *m/z* calcd for $C_{13}H_{26}O_2Si$ 242.17021, found 242.17040. Anal. Calcd for $C_{13}H_{26}O_2Si$: C, 64.41; H, 10.81. Found: C, 64.35; H, 10.94.

5-[2-[[Dimethyl(1,1-dimethylethyl)silyl]oxy]ethyl]-2-cyclopenten-1-one (49). Activated manganese(IV) oxide (Aldrich no. 21,764-6, 39.30 g, 452.2 mmol) and anhydrous NaOAc (2.78 g, 33.92 mmol) were added to a stirred solution of **48** (5.47 g, 22.61 mmol) in dry $CHCl_3$ (225 mL). After 24, 48, and 72 h, additional dry $CHCl_3$ (25 mL), activated manganese(IV) oxide (39 g, 448.6 mmol) and anhydrous NaOAc (2.78 g, 33.92 mmol) were added. After the last addition of reagents, stirring was continued for 12 h. The mixture was filtered through a pad of Celite (4 x 10 cm), and the pad was washed well with CH_2Cl_2 (*ca.* 1000 mL). Evaporation of the combined filtrates and flash chromatography of the residue over silica gel (5 x 23 cm), using 1:19 EtOAc-hexane, gave pure (^1H NMR, 400 MHz) **49** (2.43 g, 45%) as a thick, clear oil: FTIR 1717 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.05 (s, 6 H), 0.88 (s, 9 H), 1.58 (m, 1 H), 1.80 (m, 1 H), 2.05 (dd, *J* = 19, 2.5 Hz, 1 H), 2.55 (dd, *J* = 18.5, 6.2 Hz, 1 H), 3.12 (m, 1 H), 3.72 (m, 2 H), 6.14 (dd, *J* = 6.0, 2.0 Hz, 1 H), 7.67 (dd, *J* = 5.8, 2.4 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ -3.6 (q'), 18.3 (s'), 25.9 (q'), 34.2 (t'), 36.1 (t'), 42.4 (d'), 61.5 (t'), 133.7 (d'), 163.4 (d'), 212.4 (s'); exact mass *m/z* calcd for $C_9H_{15}O_2Si$ (M - C_4H_9) 183.08414, found 183.08392.

Ethyl [[4-[2-[[Dimethyl(1,1-dimethylethyl)silyl]oxy]ethyl]-3-oxocyclopentyl]methyl]-6-methyl-2-methoxy-3-pyridinecarboxylate (51). LDA was prepared by dropwise addition of *n*-BuLi (1.6 M in hexanes, 6.36 mL, 10.17 mmol) to a stirred and cooled (0 °C) solution of *i*-Pr_2NH (1.43 mL, 10.34

mmol) in THF (30 mL). The solution was stirred for 10 min at 0 °C, cooled to -78 °C, and then added dropwise over 5 min by cannula to a stirred and cooled (-78 °C) solution of pyridine ester **50**[15] (1.7 g, 8.13 mmol) in THF (82 mL). Stirring was continued for 30 min at -78 °C and then a precooled (-78 °C) solution of freshly prepared cyclopentenone **49** (2.54 g, 10.58 mmol) in THF (55 mL plus 5 mL as a rinse) was added dropwise by cannula. Stirring at -78 °C was continued for 1 h, after which the cold bath was removed and saturated aqueous NH_4Cl (100 mL) was added immediately. Stirring was continued until the mixture had attained *ca.* 0 °C, and it was then promptly extracted with Et_2O (3 x 100 mL). The organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (4 x 20 cm), using 1:19 EtOAc-hexane (the mixture containing 1%$^v/_v$ Et_3N), gave pure (^1H NMR, 300 MHz) **51** (2.19 g, 60%) as a mixture of two diastereomers. The material is a thick clear oil: FTIR 1735 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.03 (br s, 6 H), 0.85 (br s, 9 H), 1.35 (br t, *J* = 7 Hz, 3 H), 1.4-1.55 (m, 1 H), 1.7-2.1 (m, 4 H), 2.2-2.75 (m, 8 H), 3.55-3.75 (m, 2 H), 3.94 (s, 3 H), 4.30-4.45 (m, 2 H), 6.55 (br s, 1 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) (signals corresponding to the same isomer are identified by an asterisk) δ -5.4 (q'), 14.2 (q'), 18.2 (s'), 24.1 (q'), 25.9 (q'), 32.5 (t')*, 33.4 (t'), 34.5 (t'), 34.6 (d'), 35.8 (d')*, 36.5 (t')*, 38.0 (t'), 38.5 (t')*, 43.7 (d'), 44.1 (t'), 44.5 (t')*, 47.5 (d')*, 53.7 (q'), 60.8 (t'), 61.1 (t')*, 61.3 (t')*, 61.3 (t'), 114.3 (s')*, 114.5 (s'), 116.6 (d')*, 116.6 (d'), 149.3 (s'), 157.1 (s')*, 157.1 (s'), 160.4 (s'), 167.2 (s'), 167.3 (s')*, 218.8 (s')*, 220.1 (s'); exact mass *m/z* calcd for $C_{20}H_{30}NO_5Si$ (M - C_4H_9) 392.18933, found 392.18966. Anal. Calcd for $C_{24}H_{39}O_5NSi$: C, 64.11; H, 8.74; N, 3.11. Found: C, 64.22; H, 9.07; N, 3.13.

7-[2-[[Dimethyl(1,1-dimethylethyl)silyl]oxy]ethyl]-6,7-dihydro-1,9-dimethoxy-3-methyl-8*H*-cyclopent[g]isoquinolin-8-one (54). A solution of ketones **51** (2.5146 g, 5.59 mmol) in dry THF (40mL plus 2mL as a rinse) was added to a cooled (0 °C) and stirred suspension of NaH (80% dispersion in oil, 503 mg, 16.77 mmol of NaH) in dry THF (40 mL). Absolute EtOH (0.49 mL) was then injected. Stirring at 0 °C was continued for 80 min, and then saturated aqueous NH_4Cl (50 mL) was added dropwise. The ice bath was removed after the addition, and the solution was acidified to pH 4-5 with 5%$^v/_v$ hydrochloric acid. The mixture was extracted with Et_2O (2 x 100 mL) and the organic extracts were washed with brine, and dried ($MgSO_4$). Evaporation of the solvent gave the crude diketone **52** as a yellow oil that crystallized on standing. The crude material was dried under oil pump vacuum for 30 min, and then used directly in the next step.

DDQ (1.12 g, 4.93 mmol) was added in small portions over 5 min to a stirred solution of crude **52** in dry PhH at room temperature. Stirring was continued for 1 h, and the mixture was then filtered through a pad of Celite (2 x 6 cm) that was covered with a layer of flash chromatography silica gel (1 cm thick). The pad was washed with PhH (150 mL). Evaporation of the filtrate gave the crude naphthol **53** as a yellow-brown oil. The material was dried under oil pump vacuum for 30 min and then used directly in the next step.

Diethyl azodicarboxylate (2.40 mL, 15.24 mmol) was added dropwise to a cooled (-78 °C) and stirred solution of Ph_3P (4.30 g, 16.4 mmol) in dry THF (100 mL). Stirring at -78 °C was continued for 30 min, during which time a thick precipitate formed. Dry MeOH (19.68 mL, 485.8 mmol) was then added dropwise over 10 min, and stirring was continued at -78 °C until all precipitates had dissolved (*ca.* 20 min). As soon as a clear solution was obtained, a room temperature solution of crude naphthol **53** in dry THF (40 mL plus 2 mL

as a rinse) was added by cannula over *ca.* 20 min. After the addition, stirring was continued for 12 h, the cold bath being left in place and allowed to attain room temperature. Without any workup, the solvent was evaporated, and flash chromatography of the residue over silica gel (5 x 23 cm), using 1:99 acetone-hexane (the mixture containing 1%$^{v}/_{v}$ Et_3N), gave the desired ketone **54** (1.2719 g, 55% over three steps) as a pure (^1H NMR, 300 MHz), white solid: mp 92-94 °C; FTIR 1710, 1617, 1349 cm^{-1}; ^1H NMR (acetone-d_6, 300 MHz) δ 0.055 (s, 3 H), 0.065 (s, 3 H), 0.87 (s, 9 H), 1.64 (m, 1 H), 2.17 (m, 1 H), 2.44 (s, 3 H), 2.83 (m, 1 H), 2.96 (ddd, *J* = 17, 5.3, 1.0 Hz, 1 H), 3.42 (ddd, *J* = 17, 8.5, 1.0 Hz, 1 H), 3.85 (m, 2 H), 4.0 (s, 3 H), 4.05 (s, 3 H), 7.07 (s, 1 H), 7.43 (s, 1 H); ^{13}C NMR (acetone-d_6, 75.5 MHz) δ -5.2 (q'), -5.2 (q'), 18.8 (s'), 24.1 (q'), 26.3 (q'), 32.9 (t'), 35.1 (t'), 46.1 (d'), 54.0 (q'), 61.9 (t'), 63.0 (q'), 111.5 (s'), 113.1 (d'), 118.5 (d'), 125.5 (s'), 146.5 (s'), 152.5 (s'), 154.2 (s'), 158.9 (s'), 162.6 (s'), 204.9 (s'); exact mass *m/z* calcd for $C_{23}H_{33}NO_4Si$ 415.21790, found 415.21662. Anal. Calcd for $C_{23}H_{33}NO_4Si$: C, 66.47; H, 8; N, 3.37. Found: C, 66.27; H, 8.16; N, 3.33.

7-[2-[[Dimethyl(1,1-dimethylethyl)silyl]oxy]ethyl]-7,8-dihydro-1,9-dimethoxy-8-(methoxy)methylene-3-methyl-6*H*-cyclopent[g]isoquinoline (55). Dry dioxane (42 mL) was added to a mixture of (methoxymethyl)triphenylphosphonium chloride (4.09 g, 11.9 mmol) and *t*-BuOK (1.33 g, 11.9 mmol). The resulting deep orange solution was stirred at room temperature for 5 min, sonicated for 15 min [Branson, model B-12, 80 W], and stirred again for an additional 10 min. A solution of **54** (760 mg, 1.83 mmol) in dry dioxane (25 mL plus 10 mL as a rinse) was then added by syringe, over 5 min. The mixture was stirred for 1.5 h. Water (50 mL) was added and the resulting mixture was extracted with Et_2O (2 x 75 mL). The organic extract was washed with brine (1 x 100 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the dark red residue over silica gel (3 x 23 cm), using 1:99 acetone-hexane (the mixture containing 1% v/v Et_3N), gave the faster eluting enol ether (426 mg, 53%) and the slower eluting enol ether (204 mg, 25%). The faster eluting enol ether **55** had: FTIR 1656 cm^{-1}; ^1H NMR (C_6D_6, 300 MHz) δ 0.04 (s, 3 H), 0.06 (s, 3 H), 1.0 (s, 9 H), 1.6-1.8 (m, 1 H), 2.15-2.30 (m, 1 H), 2.50 (s, 3 H), 2.74 (ddd, *J* = 17, 2.3, 1.0 Hz, 1 H), 3.05 (ddd, *J* = 17, 8.5, 1.45 Hz, 1 H), 3.26 (s, 3 H), 3.45-3.6 (m, 1 H), 3.71 (s, 3 H), 3.71-3.80 (m, 2 H), 4.03 (s, 3 H), 6.80 (s, 1 H), 7.02 (s, 1 H), 7.41 (d, *J* = 2 Hz, 1 H); ^{13}C NMR (C_6D_6, 75.5 MHz) δ -5.2 (q'), -5.1 (q'), 18.5 (s'), 23.9 (q'), 26.2 (q'), 37.1 (t'), 37.1 (d'), 38.5 (t'), 53.4 (q'), 59.5 (q'), 59.8 (q'), 62.0 (t'), 112.8 (s'), 113.2 (d), 117.9 (d'), 124.1 (s'), 130.9 (s'), 141.6 (s'), 145.8 (d'), 148.1 (s'), 149.0 (s'), 152.4 (s'), 159.9 (s'); exact mass *m/z* calcd for $C_{25}H_{37}NO_4Si$ 443.24918, found 443.25062. The slower eluting enol ether **55**: FTIR 1664.96 cm^{-1}; ^1H NMR (C_6D_6, 300 MHz) δ 0.075 (s, 3 H), 0.085 (s, 3 H), 1.0 (s, 9 H), 1.55-1.65 (m, 2 H), 2.40-2.55 (m, 4 H), 2.96-3.07 (m, 2 H), 3.30 (s, 3 H), 3.53-3.65 (m, 1 H), 3.65-3.75 (m, 1 H), 3.85 (s, 3 H), 4.06 (s, 3 H), 6.06 (s, 1 H), 6.81 (s, 1 H), 7.04 (s, 1 H); ^{13}C NMR (C_6D_6, 75.5 MHz) δ -5.2 (q'), 18.5 (s'), 24.0 (q'), 26.2 (q'), 37.8 (t'), 38.7 (t'), 40.5 (d'), 53.5 (q'), 59.9 (q'), 60.6 (q'), 61.1 (t'), 112.9 (d'), 113.1 (s'), 116.9 (d'), 119.5 (s'), 128.7 (s'), 142.4 (d'), 142.5 (s'), 148.7 (s'), 149.3 (s'), 155.0 (s'), 160.8 (s'); exact mass *m/z* calcd for $C_{25}H_{37}NO_4Si$ 443.24918, found 443.24923.

(7R*,8R*)-7-[2-[[Dimethyl(1,1-dimethylethyl)silyl]oxy]ethyl]-7,8-dihydro-1,9-dimethoxy-3-methyl-8-phenylthio-6*H*-cyclopent[g]isoquinoline-8-carboxaldehyde (56). A solution of PhSCl[13] (325 mg, 2.25 mmol) in dry Et_2O (8 mL) was added dropwise over 10-15 min to a stirred and cooled (-78 °C) solution of the **55** (two geometric isomers) (769 mg, 1.73 mmol) in dry Et_2O (15 mL). Stirring was continued for 3.5 h, after which the cooling bath was removed and the mixture was allowed to reach room temperature (*ca.* 30 min). Direct evaporation of the solvent, without workup, and flash chromatography of the residue over silica gel (3 x 20 cm), using 1:39 EtOAc-hexane, gave pure (^{1}H NMR, 300 MHz) aldehyde **56** (256.7 mg, 30%) as a thick, yellow oil: FTIR (film) 1724 cm^{-1}; ^{1}H NMR (acetone-d_6, 300 MHz) δ 0.0 (s, 6 H), 0.84 (s, 9 H), 1.38 (m, 1 H), 1.8 (m, 1 H), 2.46 (s, 3 H), 2.85-3.0 (m, 2 H), 3.18 (ddd, *J* = 17, 8, 1.2 Hz, 1 H), 3.63 (m, 2 H), 3.93 (s, 3 H), 4.09 (s, 3 H), 7.08 (s, 1 H), 7.20-7.40 (m, 4 H), 7.45-7.60 (m, 2 H), 10.05 (s, 1 H); ^{13}C NMR (acetone-d_6, 75.5 MHz) δ -5.3 (q'), -5.3 (q'), 18.7 (s'), 23.8 (q'), 26.3 (q'), 33.5 (t'), 36.6 (t'), 46.3 (d'), 53.8 (q'), 61.7 (t'), 63.8 (q'), 74.6 (s'), 112.2 (s'), 113.5 (d'), 118.7 (d'), 129.7 (d'), 130.0 (d'), 132.0 (s'), 132.5 (s'), 137.4 (d'), 144.5 (s'), 148.9 (s'), 150.3 (s'), 155.9 (s'), 160.1 (s'), 196.3 (d'); mass (HRFAB) *m/z* calcd for $C_{30}H_{40}NO_4SSi$ (M + H) 538.2447, found 538.2445.

When the experiment was done on a smaller scale (300 mg of starting material) the yield was 45%.

In other experiments, it was found that the two geometric isomers of the enol ether **55**, when separately reacted with PhSCl, each gave the same aldehyde product (**56**) in 32% and 35% yields.

(7R*,8R*,αS*)- and (7R*,8R*,αR*)-7-[2-[[Dimethyl(1,1-dimethylethyl)silyl]oxy]-ethyl]-7,8-dihydro-1,9-dimethoxy-α-[2-(phenylethynyl)benzenyl]-8-phenylthio-6*H*-cyclopent[g]-isoquinoline-8-methanol (58a) and (58b). *n*-BuLi (1.6 M in hexanes, 1.5 mL, 2.39 mmol) was added to a stirred and cooled (-78 °C) solution of 2-bromo-1-(phenylethynyl)benzene (617 mg, 2.39 mmol) in dry THF (5 mL). The resulting golden brown solution was stirred for 10 min at -78 °C and then a cold (0 °C) solution of aldehyde **56** (256.7 mg, 0.477 mmol) in dry THF (10 mL plus 2 mL as a rinse) was injected. Stirring at -78 °C was continued for 0.5 h, after which the cold bath was removed. Saturated aqueous NH_4Cl (10 mL) was added and the mixture was stirred and allowed to reach room temperature. The mixture was extracted with Et_2O (2 x 30 mL), and the organic extract was washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 23 cm), using 1:28 EtOAc-hexane, gave two diastereomeric alcohols in a 6:5 ratio, the faster eluting isomer (**58b**) being obtained in 33% overall yield, and the slower eluting isomer (**58a**) in 40% overall yield. For the faster eluting isomer (**58b**) had: FTIR 3427 cm^{-1}; ^{1}H NMR (C_6D_6, 300 MHz) δ -0.05 (s, 3 H), -0.03 (s, 3 H), 0.9 (s, 9 H), 1.6-1.8 (m, 1 H), 2.07-2.23 (m, 1 H), 2.46 (s, 3 H), 2.70-2.83 (m, 1 H), 3.12 (dd, *J* = 15.5, 6 Hz, 1 H), 3.24-3.38 (m, 2 H), 3.46 (dd, *J* = 15.5, 7 Hz, 1 H), 3.7 (s, 3 H), 3.85 (s, 3 H), 4.54 (d, *J* = 2.5 Hz, 1 H), 6.22 (d, *J* = 3 Hz, 1 H), 6.6-7.1 (m, 9 H), 7.18-7.45 (m, 5 H), 7.55 (dd, *J* = 7.8, 1 Hz, 1 H), 8.6 (d, *J* = 8 Hz, 1 H); ^{13}C NMR (acetone-d_6, 75.5 MHz) δ -5.2 (q'), 18.7 (s'), 23.8 (q'), 26.3 (q'), 32.6 (t'), 38.7 (t'), 47.4 (d'), 53.6 (q'), 63.1 (t'), 63.5 (q'), 72.2 (s'), 76.3 (d'), 90.1 (s'), 94.5 (s'), 112.2 (s'), 113.3 (d'), 117.6 (d'), 123.7 (s'), 124.5 (s'), 128.1 (d'), 128.8 (d'), 129.2 (d'), 129.3 (d'), 129.4 (d'), 131.0 (d'), 132.1 (d'), 132.3 (d'), 134.9 (s'), 135.0 (d'), 135.8 (s'), 143.7 (s'), 144.5 (s'), 149.5 (s'), 149.8 (s'), 156.1 (s'), 160.2 (s'); mass (HR FAB) *m/z* calcd for $C_{44}H_{50}NO_4SSi$ (M + H) 716.3230, found 716.3221.

The slower eluting isomer (**58a**) had: mp 171-172 °C; FTIR 3470, 2575 cm^{-1}; ^{1}H NMR (C_6D_6, 300

MHz) δ 0.07 (s, 6 H), 1.0 (s, 9 H), 1.93 (ddd, *J* = 15.5, 11.65, 1.25 Hz, 1 H), 2.05-2.25 (m, 2 H), 2.51 (s, 3 H), 2.95 (dd, *J* = 15.5, 8 Hz, 1 H), 3.30-3.55 (m, 3 H), 4.04 (s, 3 H), 4.16 (s, 3 H), 6.05 (d, *J* = 4.8, 1 H), 6.46 (d, *J* = 4.8, 1 H), 6.5-6.6 (m, 1 H), 6.73-6.85 (m, 2 H), 6.90 (s, 1 H), 6.95-7.09 (m, 4 H), 7.10-7.20 (m, 3 H), 7.40-7.50 (m, 1 H), 7.50-7.60 (m, 2 H), 7.75-7.90 (m, 2 H); ^{13}C NMR (acetone-d_6, 75.5 MHz) δ -5.2 (q'), 18.9 (s'), 23.8 (q'), 26.4 (q'), 33.7 (t'), 38.6 (t'), 49.6 (d'), 53.9 (q'), 63.4 (t'), 65.0 (q'), 73.0 (s'), 74.8 (d'), 88.8 (s'), 94.6 (s'), 112.4 (s'), 113.5 (d'), 118.0 (d'), 124.1 (s'), 124.2 (s'), 128.5 (d'), 128.7 (d'), 128.9 (d'), 129.4 (d'), 129.5 (d'), 129.7 (d'), 129.8 (d'), 132.4 (d'), 133.1 (d'), 133.4 (s'), 134.7 (s'), 137.0 (d'), 144.1 (s'), 144.2 (s'), 148.9 (s'), 150.2 (s'), 156.0 (s'), 160.0 (s'); mass (HRFAB) *m/z* calcd for $C_{44}H_{51}NO_4SSi$ (M + H) 716.3230, found 716.3198.

(7R*,8R*,αS*)- and (7R*,8R*,αR*)-7-[2-[[Dimethyl(1,1-dimethylethyl)silyl]oxy]-ethyl]-7,8-dihydro-1,9-dimethoxy-α-[2-(phenylethynyl)benzenyl]-8-phenylthio-6*H*-cyclopent[g]-isoquinoline-8-methanol acetate (59a) and (59b). Ac_2O (0.3 mL, 3.18 mmol) and DMAP (9.8 mg, 0.08 mmol) were added to a stirred solution of the slower eluting alcohol **58a** (110 mg, 0.154 mmol) in dry pyridine (7 mL) at room temperature. The resulting solution was stirred for 6 h, then poured into brine (25 mL) and extracted with Et_2O (3 x 25 mL). The organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 20 cm), using 1:19 acetone-hexane, gave **59a** (96.7 mg, 83%) as a white solid: mp 141-143 °C; FTIR 1740 cm^{-1}; ^{1}H NMR (acetone-d_6, 300 MHz) δ -0.05 (s, 6 H), 0.82 (s, 9 H), 1.35-1.60 (m, 2 H), 2.10 (s, 3 H), 2.34-2.48 (m, 4 H), 2.90-3.17 (m, 2 H), 3.20-3.45 (m, 2 H), 3.68 (s, 3 H), 4.0 (s, 3 H), 6.90 (s, 1 H), 6.93 (s, 1 H), 7.0 (s, 1 H), 7.10-7.35 (m, 6 H), 7.40 (s, 6 H), 7.74-7.83 (m, 2 H); ^{13}C NMR (acetone-d_6, 75.5 MHz) δ -5.2 (q'), 18.7 (s'), 21.4 (q'), 23.7 (q'), 26.3 (q'), 34.0 (t'), 38.9 (t'), 50.1 (d'), 53.5 (q'), 63.1 (t'), 63.7 (q'), 69.2 (s'), 74.8 (d'), 88.1 (s'), 93.8 (s'), 112.3 (s'), 113.2 (d'), 116.6 (d'), 124.2 (s'), 124.4 (s'), 128.4 (d'), 128.7 (d'), 129.2 (d'), 129.4 (d'), 129.6 (d'), 130.1 (d'), 132.1 (d'), 132.2 (d'), 134.0 (s'), 134.1 (s'), 138.1 (d'), 140.8 (s'), 143.9 (s'), 147.9 (s'), 149.6 (s'), 157.2 (s'), 160.1 (s'), 169.8 (s') (several of the signals coincide); mass (HRFAB) *m/z* calcd for $C_{46}H_{52}NO_5SSi$ (M + H) 758.3335, found 758.3335.

Using the same procedure, the faster eluting diastereomeric alcohol **58b** (108.3 mg, 0.151 mmol) gave **59b** (91 mg, 80%) as a white solid: mp 177-179 °C, FTIR 1747 cm^{-1}; ^{1}H NMR (C_6D_6, 300 MHz) δ -0.01 (s, 3 H), 0.01 (s, 3 H), 0.93 (s, 9 H), 1.5 (s, 3 H), 1.8-2.0 (m, 1 H), 2.33-2.50 (m, 4 H), 3.05-3.23 (m, 3 H), 3.25-3.50 (m, 2 H), 3.68 (s, 3 H), 3.92 (s, 3 H), 6.73-6.85 (m, 4 H), 6.92-7.12 (m, 6 H), 7.35 (s, 1 H), 7.35-7.47 (m, 2 H), 7.50 (d, *J* = 7.5, 2 H), 7.55 (dd, *J* = 7.5, 1 Hz, 2 H), 7.73 (br d, *J* = 7.5 Hz, 2 H); ^{13}C NMR (acetone-d_6, 75.5 MHz) δ -5.1 (q'), 18.8 (s'), 21.3 (q'), 23.8 (q'), 26.4 (q'), 32.7 (t'), 39.3 (t'), 47.4 (d'), 53.7 (q'), 63.1 (q'), 63.2 (t'), 68.8 (s'), 78.0 (d'), 90.3 (s'), 94.8 (s'), 112.5 (s'), 113.4 (d'), 117.0 (d'), 124.5 (s'), 124.9 (s'), 128.5 (d'), 128.6 (d'), 129.2 (d'), 129.4 (d'), 129.7 (d'), 130.6 (d'), 132.3 (d'), 132.5 (d'), 133.7 (s'), 135.0 (d'), 140.5 (s'), 144.1 (s'), 149.1 (s'), 149.6 (s'), 157.2 (s'), 160.4 (s'), 169.1 (s') (several of the peaks must coincide); mass (HRFAB) *m/z* calcd for $C_{46}H_{52}NO_5SSi$ (M + H) 758.3335, found 758.3298.

The assigned structure was confirmed by X-ray analysis.

Cyclization of 59a. Et_3B (1 M in hexanes, 0.10 mL, 0.10 mmol) was added to a cold (0 °C) and stirred solution of **59a** (71.0 mg, 0.094 mmol) and Ph_3SnH (650 mg, 1.85 mmol) in 4:1 benzene-hexane (10 mL; ordinary distilled hexane was used). Air (1.0 mL) was then bubbled into the solution over 30 sec. The mixture was stirred at 0 °C for 25 min (or until the solution turned cloudy). Evaporation of the solvent and flash chromatography of the residue over silica gel (2 x 20 cm), using 1:19 EtOAc-hexane, gave the faster eluting fraction (33 mg, 0.051 mmol) and the slower eluting fraction (17 mg, 0.026 mmol) as thick colorless oils. Each fraction contained two diastereomers (^1H NMR, 300 MHz) corresponding in structure to **60**. The faster eluting (R_f 0.47, silica, 1:4 EtOAc-hexane, two developments) fraction had: FTIR 1741 cm^{-1}; ^1H NMR (acetone-d_6, 300 MHz) (signals corresponding to the same isomer are identified by an asterisk, and proton counts are given only for the major isomer) δ -0.84 (s)*, -0.86 (s)*, -0.91 (s, 3 H), -0.94 (s, 3 H), 0.7 (s)*, 0.80 (s, 9 H), 1.1-1.3 (m), 1.75-1.90 (m), 2.06 (s, 3 H), 2.5 (s, 3 H), 2.7-3.0 (m), 3.15-3.30 (m), 3.45-3.65 (m), 3.55 (s)*, 3.85 (s, 3 H), 3.93 (s)*, 3.98 (s, 3 H), 6.49 (s, 1 H), 6.76 (s, 1 H), 6.80-6.86 (m)*, 7.05 (s, 1 H), 7.08-7.60 (m); ^{13}C NMR (acetone-d_6, 75.5 MHz) δ -5.2 (q'), -5.1 (q'), 18.8 (s'), 21.0 (q'), 23.7 (q'), 26.2 (q')*, 26.3 (q'), 33.5 (t'), 33.8 (t')*, 38.3 (t'), 38.5 (t')*, 47.6 (d'), 53.5 (q'), 54.3 (q'), 62.1 (q')*, 62.8 (q')*, 62.8 (t'), 67.8 (s'), 83.7 (d'), 85.7 (d')*, 112.7 (s'), 113.5 (d'), 117.2 (d'), 117.6 (d')*, 120.7 (d')*, 122.0 (d')*, 124.1 (d'), 124.1 (d'), 124.2 (d'), 127.1 (d')*, 128.0 (d'), 128.4 (d')*, 128.5 (d'), 129.3 (d'), 129.3 (d'), 129.7 (d'), 130.2 (d')*, 130.8 (d'), 138.5 (s'), 138.6 (s'), 139.4 (s'), 143.8 (s'), 144.2 (s'), 147.8 (s'), 149.1 (s'), 149.8 (s'), 154.6 (s'), 159.9 (s'), 170.8 (s'); mass (HRFAB) *m/z* calcd for $C_{40}H_{48}NO_5Si$ 650.3302, found 650.3297.

The slower eluting (R_f 0.40, silica, 1:4 EtOAc-hexane, two developments) fraction had: FTIR 1736, 1716 cm^{-1}; ^1H NMR (acetone-d_6, 300 MHz) (signals corresponding to the same isomer are identified by an asterisk, and proton counts are given only for the major isomer) δ -0.07 (s, 3 H), -0.05 (s, 3 H), -0.02 (s)*, 0.02 (s)*, 0.82 (s, 9 H), 0.83 (s)*, 1.20-1.35 (m), 1.47 (ddd, *J* = 16, 10.5, 1.5 Hz, 1 H), 1.58 (s, 3 H), 1.60-1.8 (m), 1.67 (s)*, 2.53 (s)*, 2.55 (s, 3 H), 2.90 (br dd, *J* = 16, 9 Hz, 1 H), 3.0-3.23 (m), 3.41 (s)*, 3.43 (s, 3 H), 3.45-3.6 (m, 2 H), 3.65-3.8 (m)*, 3.98 (s)*, 3.99 (s, 3 H), 6.24 (s)*, 6.26 (s, 1 H), 6.35 (s)*, 6.45 (br d, *J* = 7.5 Hz, 2 H), 6.95 (br t, *J* = 7.5 Hz), 7.0-7.2 (m), 7.25-7.50 (m), 7.8 (br d, *J* = 7.5 Hz, 1 H); ^{13}C NMR (acetone-d_6, 75.5 MHz) (signals corresponding to the same isomer are identified by an asterisk) δ -5.2 (q'), 17.5 (q')*, 18.7 (s'), 20.6 (q'), 20.7 (q')*, 23.8 (q'), 26.3 (q'), 35.2 (t'), 35.5 (t)*, 38.2 (t')*, 38.6 (t'), 47.4 (d')*, 47.6 (d'), 53.6 (q'), 61.4 (q'), 61.9 (q')*, 62.4 (t)*, 62.6 (t'), 66.2 (s'), 82.9 (d')*, 86.5 (d'), 111.7 (s'), 113.5 (d'), 117.1 (d')*, 117.4 (d'), 120.8 (d'), 123.4 (d'), 124.5 (d')*, 125.6 (d'), 126.4 (d')*, 127.3 (d'), 128.1 (d')*, 128.5 (d'), 128.9 (d')*, 129.2 (d')*, 129.4 (d'), 129.5 (d')*, 129.6 (d'), 130.0 (d'), 138.7 (s'), 138.9 (s'), 142.9 (s'), 143.1 (s'), 143.5 (s'), 147.2 (s'), 148.8 (s'), 150.5 (s'), 156.3 (s'), 160.1 (s'), 171.0 (s'); mass (HRFAB) *m/z* calcd for $C_{40}H_{48}NO_5Si$ (M + H) 650.3302, found 650.3306.

Cyclization of 59b. Et_3B (1 M in hexanes, 0.20 mL, 0.20 mmol) was added to a cold (0 °C) and stirred solution of **59b** (30 mg, 0.04 mmol) and Ph_3SnH (313 mg, 0.89 mmol) in 2:1 benzene-hexane (4.5 mL; ordinary distilled hexane was used). Air (1.0 mL) was then bubble through the solution over 30 sec. The mixture was stirred at 0 °C for 25 min. Evaporation of the solvent and flash chromatography of the residue over silica gel (1.5 x 18 cm), using 1:19 EtOAc-hexane, gave the cyclization product **60** as a single isomer (23

mg, 88%): R_f 0.22 (silica, 1:9 EtOAc-hexane, two developments); FTIR 1740 cm^{-1}; ^1H NMR (C_6D_6, 300 MHz) δ 0.00 (s, 6 H), 0.93 (s, 9 H), 1.67 (s, 3 H), 1.7-1.83 (ddd, *J* = 15, 10, 1 Hz, 1 H), 1.7-2.0 (m, 2 H), 2.48 (s, 3 H), 2.76-3.0 (m, 2 H), 3.4-3.65 (m, 5 H), 3.85 (s, 3 H), 6.52 (br d, *J* = 7 Hz, 2 H), 6.7-6.9 (m, 5 H), 7.23 (s, 1 H), 7.4-7.5 (m, 1 H), 7.45-7.52 (m, 1 H), 7.55 (s, 1 H), signals corresponding to 2 aromatic H overlap with the benzene solvent peak; ^1H NMR (acetone-d_6, 300 MHz) (signals for aromatic portion only) δ 6.45 (br d, *J* = 7 Hz, 2 H), 6.8-7.06 (m, 5 H), 7.10 (s, 1 H), 7.35-7.5 (m, 4 H), 7.8 (br d, *J* = 7 Hz, 1 H); ^{13}C NMR (acetone-d_6, 75.5 MHz) δ 5.1 (q'), 18.9 (s'), 21.2 (q'), 23.8 (q'), 26.4 (q'), 35.4 (t'), 38.4 (t'), 41.9 (d'), 53.6 (q'), 62.1 (q'), 63.2 (t'), 64.4 (s'), 83.4 (d'), 112.3 (s'), 113.4 (d'), 117.8 (d'), 120.8 (d'), 123.4 (d'), 125.8 (d'), 127.1 (d'), 128.3 (d'), 129.4 (d'), 129.6 (d'), 129.7 (d'), 129.9 (d'), 138.4 (s'), 141.9 (s'), 142.8 (s'), 143.4 (s'), 143.8 (s'), 147.3 (s'), 148.9 (s'), 149.7 (s'), 154.5 (s'), 160.0 (s'), 170.8 (s'); mass (HRFAB) *m/z* calcd for $C_{40}H_{48}NO_5Si$ (M + H) 650.3302, found 650.3279.

Double Bond Cleavage of Cyclization Product from 59b. OsO_4 (25 mg, 0.10 mmol) was added in one portion to a stirred solution of the single cyclization product from **59b** (16 mg, 0.024 mmol) in dry pyridine (1 mL). The mixture was stirred under Ar at room temperature for 12 h. Then a suspension of $NaIO_4$ (21 mg, 0.098 mmol) in 10:1 THF-H_2O (1 mL) was added and stirring was continued for 12 h. The mixture was diluted with EtOAc (15 mL), and washed successively with brine (10 mL) and saturated aqueous $NaHSO_3$ (2 x 25 mL), and then dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (1 x 18 cm), using 2:23 acetone-hexane, gave **61** (4 mg, 30% yield) as a clear, sticky foam: FTIR 1742, 1712 cm^{-1}; ^1H NMR (acetone-d_6, 500 MHz) δ 0.00 (s, 6 H), 0.84 (s, 9 H), 1.45-1.6 (m, 1 H), 1.6-1.7 (m, 1 H), 2.13 (s, 3 H), 2.39 (s, 3 H), 2.8-2.95 (m, 1 H), 3.11 (ddd, *J* = 16, 11, 1.5 Hz, 1 H), 3.2 (s, 3 H), 3.27 (br dd, *J* = 16, 8 Hz, 1 H), 3.6-3.75 (m, 2 H), 3.95 (s, 3 H), 7.02 (s, 1 H), 7.27 (s, 1 H), 7.34 (s, 1 H), 7.64 (br t, *J* = 7.5 Hz, 1 H), 7.75-7.8 (m, 2 H), 7.86 (dt, *J* = 7.5, 1 Hz, 1 H); ^{13}C NMR (acetone-d_6, 500 MHz) δ -5.2 (q'), -5.2 (q'), 18.9 (s'), 21.0 (q'), 23.7 (q'), 29.0 (q'), 34.8 (t'), 37.9 (t'), 44.0 (d'), 53.6 (q'), 62.6 (q'), 62.8 (t'), 67.4 (s'), 76.4 (d'), 111.9 (s'), 113.4 (d'), 117.5 (d'), 122.3 (s'), 123.9 (d'), 127.3 (d'), 130.8 (d'), 136.7 (d'), 137.2 (s'), 140.7 (s'), 143.7 (s'), 149.5 (s'), 149.6 (s'), 153.3 (s'), 154.2 (s'), 159.8 (s'), 171.0 (s'); exact mass *m/z* calcd for $C_{33}H_{41}NO_6Si$ 575.27032, found 575.26893.

Double bond Cleavage of the Faster Eluting Cyclization Material from 59a. The above procedure was followed, using the faster eluting material from the cyclization of **59a** (17 mg, 0.026 mmol), OsO_4 (28 mg, 0.11 mmol), dry pyridine (1 mL), $NaIO_4$ (23 mg, 0.11 mmol), and 10:1 THF-water (1 mL). A single ketone of general structure **61** (4.5 mg, 30%) was obtained as a clear sticky foam: FTIR 1742, 1721 cm^{-1}; ^1H NMR (acetone-d_6, 400 MHz) δ -0.05 (s, 3 H), -0.036 (s, 3 H), 0.84 (s, 9 H), 1.3-1.45 (m, 2 H), 2.15 (s, 3 H), 2.43 (s, 3 H), 2.9-3.1 (m, 2 H), 3.25-3.35 (m, 1 H), 3.45-3.6 (m, 2 H), 3.61 (s, 3 H), 4.0 (s, 3 H), 6.67 (s, 1 H), 7.06 (s, 1 H), 7.34 (s, 1 H), 7.6-7.7 (m, 2 H), 7.8-7.9 (m, 2 H); ^{13}C NMR (acetone-d_6, 500 MHz) δ -5.3 (q'), -5.2 (q'), 18.7 (s'), 21.0 (q'), 23.7 (q'), 26.3 (q'), 33.8 (t'), 39.2 (t'), 49.8 (d'), 53.5 (q'), 62.4 (q'), 62.7 (t'), 67.5 (s'), 80.7 (d'), 112.3 (s'), 113.6 (d'), 117.4 (d'), 123.8 (d'), 125.8 (d'), 127.5 (s'), 130.5 (d'), 136.3 (d'), 137.6 (s'), 138.0 (s'), 143.9 (s'), 149.2 (s'), 149.4 (s'), 151.4 (s'), 153.2

(s'), 159.7 (s'), 170.9 (s'); exact mass *m/z* calcd for $C_{29}H_{32}NO_6Si$ (M - C_4H_9) 518.19989, found 518.19722.

No identifiable products were isolated from a similar experiment using the slower eluting fraction from the cyclization of **59a**.

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References & footnotes

1 Clive, D. L. J.; Tao, Y.; Khodabocus, A.; Wu, Y.-J.; Angoh, A. G.; Bennett, S. M.; Boddy, C. N.; Bordeleau, L.; Kellner, D.; Kleiner, G.; Middleton, D. S.; Nichols, C. J.; Richardson, S. R.; Vernon, P. G. *J. Amer. Chem. Soc.* **1994**, *116*, 11275.

2 *Cf.* (a) German Pat. Appl. DE 3430365 A1, 17 Aug. 1984 (*Chem. Abstr.* **1985**, *103*, 104798c). (b) See also biological test data reported in this paper.

3 Clive, D. L. J.; Angoh, A. G.; Bennett, S. M. *J. Org. Chem.* **1987**, *52*, 1339.

4 (a) *Cf.* Vedejs, E; Ahmad, S. *Tetrahedron Lett.* **1988**, *29*, 2291 and references therein. Huang, W.; Xiao, W.; Wang, J. *Youji Huaxue* **1986**, 376. [*Chem. Abstr.* **1987**, *106*, 138113c.] (b) Related reagents with the same substitution pattern on phosphorus show poor stereoselectivity with benzaldehyde. This reagent gives *E,E*-dienes with aliphatic aldehydes; in the one case we had examined (reference 1) it gave an isomer mixture with an aromatic aldehyde. Had it given a single product in the present case, we may have retained the double bonds (see later).

5 *Cf.* (a) Saint-Jalmes, L.; Lila, C.; Xu, J. Z.; Moreau, L.; Pfeiffer, B.; Eck, G.; Pelsez, L.; Rolando, C.; Julia, M. *Bull Chem. Soc. France* **1993**, *130*, 447. (b) Rama Rao, A. V.; Singh, A. K.; Venkateswara Rao, B.; Malla Reddy, K. *Tetrahedron Lett.* **1993**, *34*, 2665.

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

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

8 *Cf.* Srikrishna, A.; Reddy, T. J.; Nagaraju, S.; Sattigeri, J. A. *Tetrahedron Lett.* **1994**, *35*, 7841. Srikrishna, A.; Nagaraju, S.; Venkateswarlu, S. *Tetrahedron Lett.* **1994**, *35*, 429. Srikrishna, A.; Nagaraju, S.; Sharma, G. V. R. *J. Chem. Soc., Chem. Commun.* **1993**, 285. Srikrishna, A.; Viswajanani, R.; Sattigeri, J. A. *J. Chem. Soc., Chem. Commun.* **1995**, 469. Back, T. G; Gladstone, P. L. *Synlett* **1993**, 699.

9 In principle, the (silyloxy)ethyl substituent could be removed, after radical spirocyclization, by the sequence: $RCH_2CH_2OSiMe_2Bu\text{-}t \rightarrow RCH_2CH_2OH \rightarrow RCH{=}CH_2 \rightarrow RCHO \rightarrow RH$. The last step (RCHO → RH) might, perhaps, be done by decarbonylation or by oxidation and radical

decarboxylation.

10 The tests were run at the NCI (Bethesda).

11 Supplied by Chemical Dynamics Corp., South Plainfield, NJ.

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

13 Fieser, M.; Fieser, L. F. *Reagents for Organic Synthesis*; Wiley: New York, 1975; Vol. 5, p 522.

14 Clive, D. L. J.; Daigneault, S. *J. Org. Chem.* **1991**, *56*, 3801.

15 Clive, D. L. J.; Sedgeworth, J. *J. Heterocycl. Chem.* **1987**, *24*, 509.

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