

Total Synthesis of the Antitumor Antibiotic ($\pm$)-Fredericamycin A by a Linear Approach

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Abstract: A linear approach to the total synthesis of racemic fredericamycin A (**1**) through the oxidative intramolecular [4 + 2] cycloaddition of a (phenylthio)acetylene–cobalt complex is described, which is applicable for the asymmetric total synthesis of naturally occurring **1**. The highlight of this work is the aromatic Pummerer-type reaction with 1-ethoxyvinyl chloroacetate, which effects the introduction of the oxygen functional group to the internal B-ring of the highly functionalized, congested polyaromatic ABC-ring moiety.

Keywords: antitumor agents • cycloadditions • fredericamycin A • Pummerer-type reactions • total synthesis

Introduction

Asymmetric total synthesis of the antitumor antibiotic, fredericamycin A (**1**), has been a challenging subject during these two decades due to its unique structure as well as its potent antitumor properties (Figure 1).^[1] Structurally, **1** consists of two sets of *peri*-hydroxy tricyclic aromatic moieties

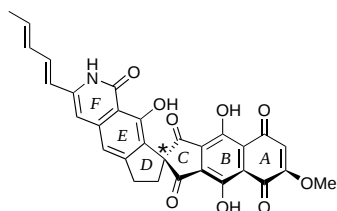
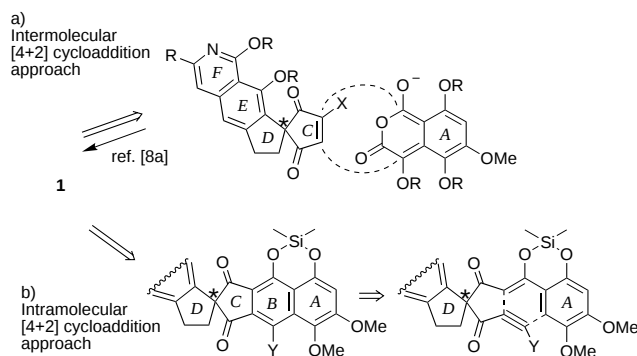


Figure 1. Fredericamycin A (**1**).

connected through a spiro quaternary carbon center, which is chiral due to the presence of a single methoxy group at the most distant position on the A-ring. Intensive efforts toward this goal include five total syntheses of racemic **1**^[2–6] and the first synthesis of optically pure **1** by separation of a fully protected racemic **1** using a chiral HPLC column;^[7] however, no one has succeeded so far in its asymmetric synthesis and

therefore also its absolute configuration remained unknown. The majority of the reported approaches feature the construction of the spiro C- or D-ring at their final stages, and the difficult distinction of the enantioface of the highly symmetrical ABC-ring has been the obstacle to their application to the asymmetric version.

We envisioned that one of the most promising way to the asymmetric synthesis of **1** would be the preparation of an intermediate with an optically pure quaternary carbon center with a definite stereochemistry and the completion of the total synthesis while retaining its chiral integrity. According to this strategy, two approaches, that is, a convergent approach via an intermolecular cycloaddition reaction (Scheme 1a) and a



Scheme 1. Retrosyntheses of optically active fredericamycin A (**1**).

linear approach via an intramolecular cycloaddition reaction (Scheme 1b), were planned. Only very recently, did we achieved an asymmetric total synthesis of **1** via a convergent

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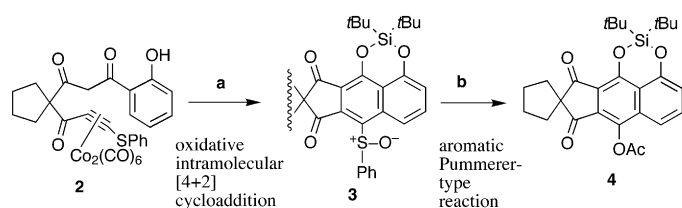
approach using a strong base induced intermolecular [4 + 2] cycloaddition reaction of homophthalic anhydrides.^[8, 9] The regiochemistry of the cycloaddition reaction was controlled by the phenylsulfinyl substituent (X = PhSO), and thereby the absolute stereochemistry of natural **1** could be determined for the first time.

On the other hand, the intramolecular cycloaddition approach generally benefits from the entropy, reactivity, and easy control of the regio- and stereochemistry compared with the intermolecular version.^[10] Particularly, this approach should be attractive for the asymmetric total synthesis of **1**, because the chiral integrity of the key intermediate would be easily retained. Herein, we would like to describe the total synthesis of racemic **1** via our intramolecular cycloaddition approach (Scheme 1b), which is believed to become an alternative asymmetric synthesis of **1**. The highlight of this work is the development of the aromatic Pummerer-type reaction with 1-ethoxyvinyl chloroacetate (**7b**).^[11–13] Use of this acylating reagent was inevitable for introduction of the oxygen functional group to the internal B-ring of the highly functionalized, congested polyaromatic ABCD-ring moiety.

Results and Discussion

Despite the above-mentioned advantages of the intramolecular cycloaddition approach, no one has succeeded in the preparation of the ABCD-ring with this approach. A few approaches have been reported;^[14, 15] however, the difficulty remains in the lack of an effective preparation method for the highly oxygen-substituted polycyclic aromatic structures.

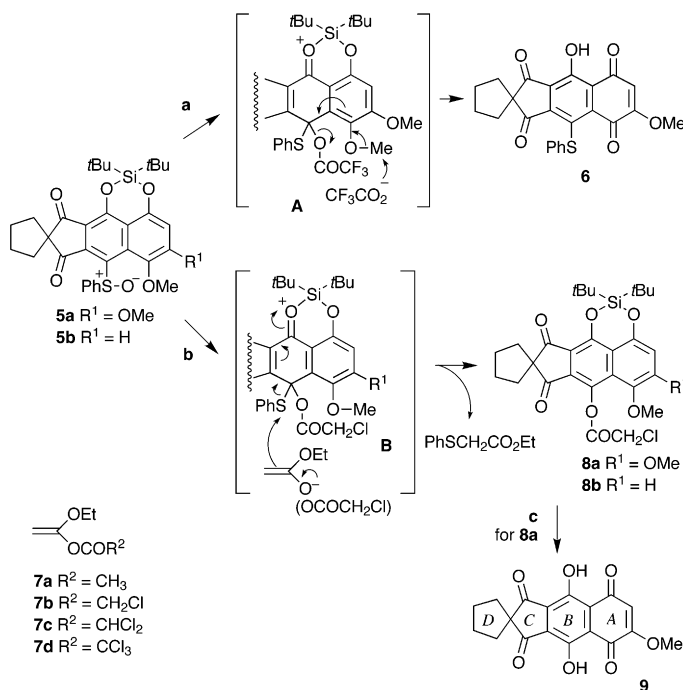
In order to circumvent this problem, very recently we have presented a basic concept involving the oxidative intramolecular [4 + 2] cycloaddition reaction of the (phenylthio)acetylene–cobalt complex **2** to give the cycloadduct **3** and the subsequent aromatic Pummerer-type reaction to substitute the sulfinyl group by the oxygen functional group (**3** → **4**) (Scheme 2).^[16]



Scheme 2. Synthesis of the ABCD-ring precursor compound **4**. a) 1. Me₂-SiCl₂, Et₃N, chloranil, 100 °C, 2. *t*Bu₃Si(OTf)₂, Et₃N, 3. *m*CPBA; b) 1. (CF₃CO)₂O, styrene, 2. Ac₂O, AcONa, pyridine.

However, a similar Pummerer-type reaction of the ABCD-ring precursor **5a** under the standard reaction conditions (trifluoroacetic anhydride/styrene) did not give the desired **4**-type product. Thus, the presence of the methoxy group at the *peri*-position of the sulfinyl group of **5** resulted in its cleavage to give the quinone sulfide **6** (71 % yield) as the single product. After intensive studies involving changing the acylating reagents, solvents, and additives, we finally found that the reaction of **5a** with 1-ethoxyvinyl chloroacetate (**7b**)

(5 equiv) and a catalytic amount (ca. 0.3 equiv) of *p*-TsOH in refluxing toluene^[13] exclusively provided **8a** (ca. 65 % yield). The use of **7b** gave the best yield of the oxygenated product **8** among the four different ethoxyvinyl esters **7a–d**. Note-worthy, a similar reaction using chloroacetic anhydride instead of **7b** proceeded tardily to give only **6** (ca. 80 % yield). Compound **8a** was subjected to successive deprotection with Bu₄NF, BBr₃, and 80 % aqueous trifluoroacetic acid to give the ABCD-ring **9** in 62 % overall yield from **5a** (Scheme 3). The efficiency of **7b** was also apparent from the similar reaction of **5b**, where **8b** was isolated in 72 % yield.

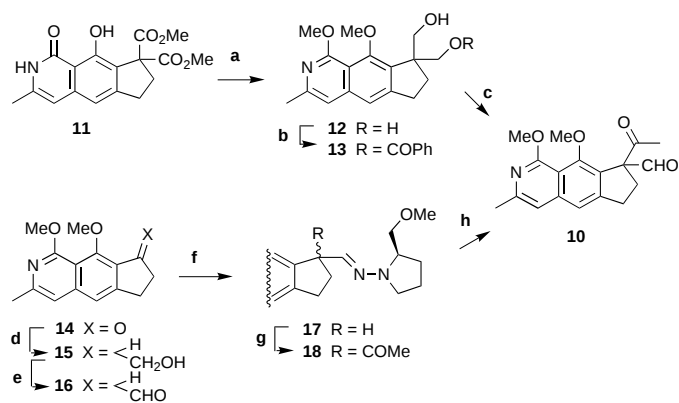


Scheme 3. Aromatic Pummerer-type reaction of **5**. a) (CF₃CO)₂O, styrene, CHCl₃, 0 °C, 71 %; b) **7b**, cat. *p*-TsOH, toluene, 110 °C, 72 % for **8b**; c) 1. Bu₄NF, THF/H₂O, room temperature, 2. BBr₃, CH₂Cl₂, –78 → –45 °C, 3. 80 % CF₃CO₂H, reflux, 62 % from **5a**.

These contradicting effects between the acid anhydrides and the ethoxyvinyl esters seem to be ascribed to the different nucleophilic nature of the counteranions in the intermediates (**A** and **B**), although we have not sufficiently clarified that yet. In the reaction with **7b**, the nucleophilic attack of the enolate anion or the excess **7b** took place at the sulfur atom of **B** to give **8** along with ethyl phenylthioacetate.

With an efficient method at hand, our attention focused next on the total synthesis of racemic **1**. The key intermediate (**10**) was obtained from either the known DEF-ring moiety **11**^[17] or **14**^[3] in 12 % and 51 % overall yield, respectively (Scheme 4). In the latter route, the acetylation of **17** gave a 1:1 mixture of two diastereomers **18**, which was hydrolyzed to (±)-**10**. Direct introduction of acetyl group to **16** or the use of the *N,N*-dimethylhydrazone instead of **17** gave low yields of **10**.

In order to introduce the (phenylthio)ethynyl group and the A-ring acyl group into **10**, this compound was first treated with lithium (phenylthio)acetylide (1.1–1.3 equiv) in THF at



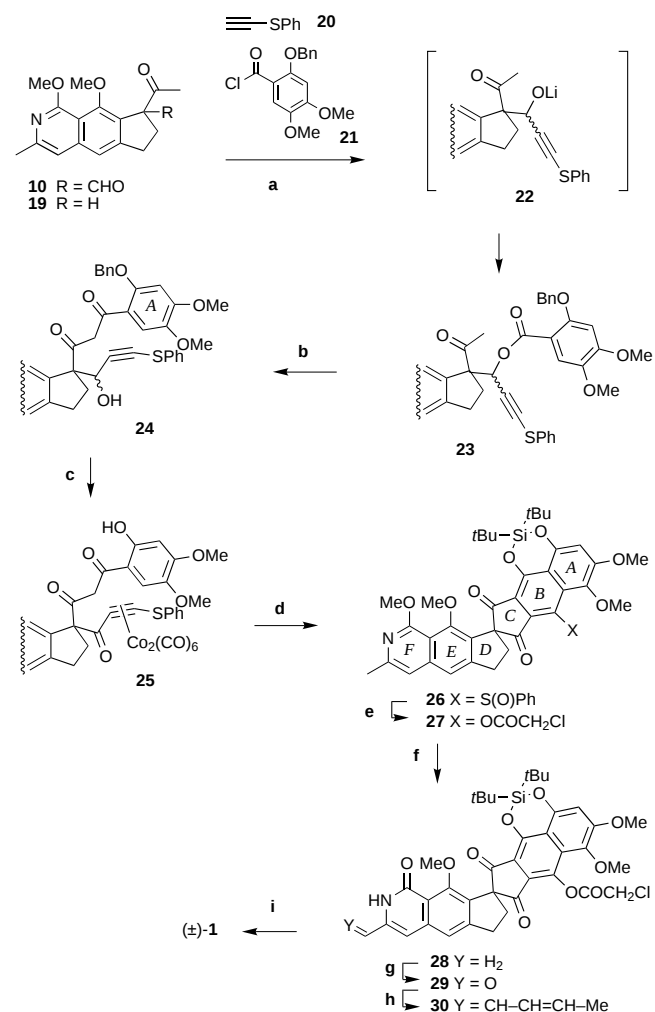
Scheme 4. Synthesis of the key intermediate **10**. a) 1. MeI, Ag₂O, dioxane, 2. LiAlH₄, THF, 35% for two steps; b) BzCl, pyridine, CH₂Cl₂, 45%; c) 1. Dess–Martin periodinane, MeCN, 2. MeMgBr, THF, then MeLi, 93% for two steps, 3. DMSO, (COCl)₂, Et₃N, CH₂Cl₂, 80%; d) 1. (Me)₃Ph₃P⁺Br[−], *t*BuOK, THF, 83%. 2. BH₃·THF, THF then H₂O₂, 2N NaOH, 92%; e) Dess–Martin periodinane, CH₂Cl₂; f) (*R*)-1-amino-2-(methoxymethyl)-pyrrolidine, CH₂Cl₂, 87% for two steps; g) LDA, AcCl, THF, 77%; h) aqueous (CO₂H)₂, Et₂O, 99%.

−78 °C for a selective addition to the formyl group; however, a retro-aldol reaction of the primary adduct **22** took place while warming the reaction mixture and the chromatography (silica gel) of the crude product; this results in the formation of ketone **19** as the major product. Quenching **22** with the A-ring acid chloride **21** (2–3 equiv) at −78 or −100 °C provided the ester **23** in poor yields. However, addition of 2 equiv LiN(TMS)₂ to a solution of **10** (1 equiv), **20** (1 equiv), and **21** (2 equiv) in THF at −78 °C followed by gradual warming the reaction mixture to room temperature caused the sequential lithium acetylide formation, addition of the lithium acetylide to the formyl group of **10**, and the esterification of **22** with **21** to afford **23** (69% yield) as a 17:1 mixture of two diastereomers.

We then tried to induce the migration of the A-ring aroyl group to the methyl ketone terminus under basic conditions. Thus, the 17:1 diastereomeric mixture of **23** was dissolved in toluene and treated with LiN(TMS)₂ (3 equiv) at room temperature. After consumption of the major isomer (for 2–3 h), HMPA (3 equiv) was added, and the stirring was continued at room temperature for another 30 min to consume the minor isomer to provide **24** (70% yield) as a 17:1 mixture of two diastereomers. This mixture was subjected to Dess–Martin oxidation, followed by formation of the cobalt complex and debenzoylation to provide **25**.

Similarly to the preparation of **3**,^[16] the cycloaddition of **25** in the presence of Me₂SiCl₂ (4 equiv), Et₃N (8 equiv), and chloranil (4 equiv) proceeded in toluene at 100 °C to give the hexacyclic sulfoxide **26** (47% overall yield from **25**) after protection of the *peri*-diol moiety by the silylene group and the oxidation of the sulfenyl group. The aromatic Pummerer-type reaction of **26** with **7b** and a catalytic amount of *p*-TsOH in refluxing toluene afforded **27** in 77% yield. Demethylation of the F-ring of **27** with Me₃SiI,^[3, 5, 8a] gave the expected pyridone **28** in 40% yield due to the cleavage of relatively labile protective groups such as bis(*tert*-butyl)silylene and chloroacetyl groups. However, the employment of *t*Bu₂Si(OTf)₂, Et₃N, and MeI was found to be effective for the

demethylation to give **28** quantitatively. Oxidation of the methyl group of the F-ring by SeO₂ gave the formyl group (→ **29**), which was in turn subjected to the usual Wittig reaction to give **30** (28% yield, a 5:1 mixture of *E,E*- and *Z,E*-isomers) with recovery of a 67% yield of **29**. Treatment of **30** with BBr₃ removed all protecting groups simultaneously, and the subsequent auto-oxidation and separation of the minor impurity of the diene isomer by HPLC (Jasco Megapak SIL NH2-10, 1 × 25 cm, CHCl₃/hexane/acetic acid 800:200:1, 5 mL min^{−1} flow rate)^[8a] afforded (±)-**1** (52% yield). The synthetic compound was identical with an authentic sample of natural fredericamycin A (¹H NMR, UV, TLC, HPLC) (Scheme 5).



Scheme 5. Synthesis of racemic fredericamycin A (**1**). a) **20**, **21**, LiN(TMS)₂, THF, 69%; b) LiN(TMS)₂, toluene then HMPA, 70%; c) 1. Dess–Martin periodinane, CH₂Cl₂, 2. Co₂(CO)₈, CH₂Cl₂, 84% for two steps, 3. BCl₃, CH₂Cl₂, 37%; d) 1. Me₂SiCl₂, Et₃N, chloranil, toluene, 2. *t*Bu₂Si(OTf)₂, Et₃N, DMF, 3. *m*CPBA, CH₂Cl₂, 47% for three steps; e) **7b**, cat. *p*-TsOH, toluene, 77%; f) *t*Bu₂Si(OTf)₂, Et₃N, MeI, DMF, quant.; g) SeO₂, dioxane, 78%; h) (MeCH=CHCH₂)Ph₃P⁺Br[−], *n*BuLi, THF, 28% (85% based on consumed **29**); i) 1. BBr₃, CH₂Cl₂, 2. THF/H₂O, air, 3. HPLC separation, 52% for three steps.

Conclusion

A new, linear synthesis of the highly oxygen-substituted polyaromatic, fredericamycin A (**1**) was elucidated by the

combination of the oxidative intramolecular [4 + 2] cycloaddition of the suitably functionalized (phenylthio)acetylene–Co₂(CO)₈ complex **25** and the aromatic Pummerer-type reaction of the sulfoxide **26** with 1-ethoxyvinyl chloroacetate (**7b**). Application of this protocol to the optically pure intermediate **10** would lead to the total synthesis of natural **1** and its derivatives and is now in progress in our laboratory.

Experimental Section

General techniques: Melting and boiling points are uncorrected. IR-absorption spectra were recorded as a solution in an organic solvent or by diffuse reflectance measurement of samples dispersed in KBr powder. ¹H- and ¹³C-NMR spectra were measured in CDCl₃ with SiMe₄ or CHCl₃ as internal standards. High-resolution mass spectra (HRMS) were recorded at 70 eV with a direct inlet system. Silica gel BW-300, Fuji Silysia Chemical, Japan, particle size 38–75 μm, was used for flash column chromatography and silica gel 60 F₂₅₄ glass plates, E. Merck, for preparative TLC. Anhydrous solvents were prepared by the standard methods. Glass reactors used for the intramolecular [4 + 2] cycloadditions were purchased from Taiatsu Scientific Glass, Japan.

Compounds **7a**,^[11] **7b**,^[12c] **11**,^[17] **14**,^[3] **20**,^[18] **31**,^[15] and crotyltriphenylphosphonium bromide^[19] were prepared as previously reported.

1-Ethoxyvinyl dichloroacetate (7c): Under a nitrogen atmosphere, a solution of dichloroacetic acid (1.32 mL, 16 mmol) in anhydrous THF (12 mL) was slowly added to an ice-cooled solution of ethoxyacetylene (2.0 mL, 24 mmol) and [RuCl₂(*p*-cymene)]₂ (30 mg, 0.048 mmol) in anhydrous THF (10 mL) over a period of 15 min. After being stirred at 0 °C for 2 h, the reaction mixture was concentrated in vacuo at room temperature, and the residue was purified by distillation to give **7c** (1.94 g, 61%) as a yellow oil. B.p. 90–91 °C/19 Torr; IR (THF): ν = 1794, 1678 cm^{−1}; ¹H NMR (270 MHz, CDCl₃): δ = 1.36 (t, 3 H, *J* = 7.0 Hz), 3.86 (d, 1 H, *J* = 4.0 Hz), 3.92 (q, 2 H, *J* = 7.0 Hz), 3.98 (d, 1 H, *J* = 4.0 Hz), 6.01 (s, 1 H); HRMS: anal. calcd for C₆H₈Cl₂O₃: 197.9850; found 197.9865.

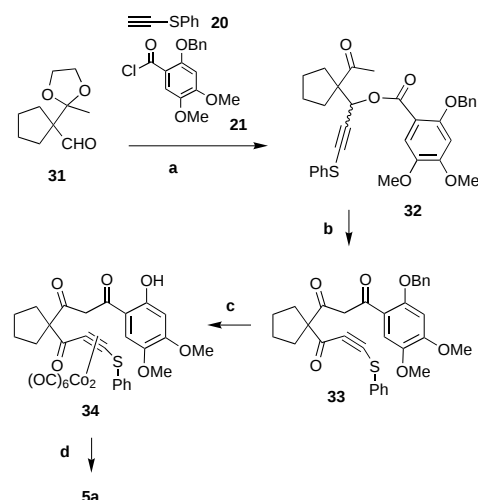
1-Ethoxyvinyl trichloroacetate (7d): Similar to the preparation of **7c**, **7d** (1.36 g, 73%) was prepared from trichloroacetic acid (1.31 g, 8.0 mmol) to yield a yellow oil. B.p. 85–86 °C/17 Torr; IR (THF): ν = 1796, 1676 cm^{−1}; ¹H NMR (300 MHz, CDCl₃): δ = 1.38 (t, 3 H, *J* = 7.0 Hz), 3.90 (d, 1 H, *J* = 4.5 Hz), 3.96 (q, 2 H, *J* = 7.0 Hz), 4.04 (d, 1 H, *J* = 4.5 Hz); elemental analysis calcd for C₆H₇Cl₃O₃: C 30.87, H 3.02; found C 31.05, H 3.05.

2-Benzyloxy-4,5-dimethoxybenzoyl chloride (21): NaClO₂ (4.9 g, 54 mmol) was added to a mixture of 2-benzyloxy-4,5-dimethoxybenzaldehyde (11.3 g, 42 mmol), NaH₂PO₄ (12.5 g, 104 mmol), 2-methyl-2-butene (22 mL, 0.21 mol), *t*BuOH (700 mL), and water (100 mL). The reaction mixture was stirred at room temperature overnight and concentrated in vacuo to one-fourth of its volume. The residue was poured into a mixture of water and CH₂Cl₂. The organic layer was separated and extracted with 10% NaOH (2 ×). The aqueous layer was acidified with 10% HCl to pH 2–3 and extracted with CH₂Cl₂ (5 ×). The combined organic layer was dried (Na₂SO₄) and concentrated in vacuo. Recrystallization of the residual solid from ClCH₂CH₂Cl gave 2-benzyloxy-4,5-dimethoxybenzoic acid (9.8 g, 61%) as colorless crystals. M.p. 72–74 °C (ClCH₂CH₂Cl); IR (KBr): ν = 3400–2400, 1732, 1682, 1609, 1576 cm^{−1}; ¹H NMR (270 MHz, CDCl₃): δ = 3.90 (s, 3H), 3.91 (s, 3H), 5.28 (s, 2H), 6.61 (s, 1H), 7.42–7.44 (m, 5H), 7.63 (s, 1H), 10.76 (brs, 1H); ¹³C NMR (68 MHz, CDCl₃): δ = 56.28, 56.31, 73.2, 97.8, 109.5, 114.1, 127.9, 129.1, 129.2, 134.2, 144.1, 152.6, 153.9, 165.0; elemental analysis calcd for C₁₆H₁₆O₅: C 66.66, H 5.59; found C 66.63, H 5.60.

A mixture of the above acid (2.0 g, 6.9 mmol) and SOCl₂ (15 mL) was heated under reflux for 8 h. After cooling under a nitrogen atmosphere, the reaction mixture was concentrated in vacuo. Anhydrous toluene (5 mL) was added, and the mixture was concentrated in vacuo and dried under vacuum (0.1 Torr) at room temperature for 2 h to give **21** as a yellow solid. IR (CH₂Cl₂): ν = 1763, 1611, 1572, 1514 cm^{−1}; ¹H NMR (270 MHz, CDCl₃): δ = 3.89 (s, 6H), 5.18 (s, 2H), 6.51 (s, 1H), 7.28–7.49 (m, 5H), 7.62 (s, 1H); ¹³C NMR (68 MHz, CDCl₃): δ = 56.3, 56.4, 71.4, 98.3, 112.9, 116.6, 126.8,

127.9, 128.5, 135.8, 142.5, 155.7, 155.9, 162.0. This compound was used for the preparation of **23** and **32** without prior purification.

Sulfoxide (**5a**) was synthesized as shown in Scheme 6.



Scheme 6. Synthesis of the sulfoxide **5a**. a) 1. **20**, *n*BuLi, THF/HMPA, 81%, 2. *p*TsOH, acetone, 98%, 3. **21**, 4-(dimethylamino)pyridine, CH₂Cl₂, quant.; b) 1. LiN(TMS)₂, THF, 88%, 2. DMSO, DCC, pyridinium trifluoroacetate, benzene, 64%; c) 1. Co₂(CO)₈, CH₂Cl₂, 82%, 2. BCl₃, CH₂Cl₂, 73%; d) 1. Me₂SiCl₂, Et₃N, chloranil, toluene, 2. *t*Bu₂Si(OTf)₂, Et₃N, DMF, 57%, 3. *m*CPBA, CH₂Cl₂, 78%.

4,4-Tetramethylene-5-oxo-1-phenylthio-1-hexyn-3-yl 2-benzyloxy-4,5-dimethoxy benzoate (32): Under a nitrogen atmosphere, *n*BuLi (1.6 M solution in hexane, 36 mL, 59 mmol) and anhydrous HMPA (10 mL, 59 mmol) were added to a solution of **20** (7.9 g, 59 mmol) in anhydrous THF (70 mL) at −50 °C. The reaction mixture was stirred at −50 °C for 30 min, to which was added a solution of **31** (9.8 g, 54 mmol) in anhydrous THF (70 mL). The reaction mixture was stirred at −50 °C for 40 min, and the cooling bath was removed. The reaction mixture was warmed to room temperature and then poured into saturated aqueous NH₄Cl. The aqueous layer was extracted with EtOAc and the combined organic layer was washed with brine, dried (Na₂SO₄), and concentrated in vacuo. The residue was purified by flash column chromatography (hexane/EtOAc 5:1 → 3:1) to give 5,5-ethylenedioxy-3-hydroxy-4,4-tetramethylene-1-phenylthio-1-hexyne (13.7 g, 81%) as a pale yellow oil. IR (KBr): ν = 3700–3000, 1705, 1584 cm^{−1}; ¹H NMR (270 MHz, CDCl₃): δ = 1.36 (s, 3H), 1.66–1.78 (m, 8H), 4.00–4.10 (m, 4H), 4.19 (d, 1H, *J* = 2.0 Hz), 4.87 (d, 1H, *J* = 2.0 Hz), 7.20–7.45 (m, 5H); HRMS: anal. calcd for C₁₈H₂₂O₃S: 318.1290; found 318.1288.

A mixture of the above product (13.7 g, 43 mmol) and *p*-toluenesulfonic acid · H₂O (0.82 g, 4.3 mmol) in acetone (360 mL) was stirred at room temperature for 1 h. The reaction mixture was concentrated in vacuo to a half of its volume and poured into saturated aqueous NaHCO₃. The aqueous layer was extracted with EtOAc (3 ×), and the combined organic layer was washed with brine, dried (Na₂SO₄), and concentrated in vacuo. The residue was purified by flash column chromatography (hexane/EtOAc 3:1 → 1:1) to give 3-hydroxy-4,4-tetramethylene-1-phenylthio-1-hexyn-5-one (11.6 g, 98%) as a pale yellow oil. IR (KBr): ν = 3700–3000, 2181, 1703, 1582 cm^{−1}; ¹H NMR (200 MHz, CDCl₃): δ = 1.65–2.13 (m, 8H), 2.23 (s, 3H), 3.28 (d, 1H, *J* = 7.0 Hz), 4.68 (d, 1H, *J* = 7.0 Hz), 7.20–7.43 (m, 5H); elemental analysis calcd for C₁₆H₁₈O₂S: C 70.04, H 6.61, S 11.68; found C 69.76, H 6.60, S 11.57.

Under a nitrogen atmosphere, a solution of the above product (1.27 g, 4.6 mmol) and 4-(dimethylamino)pyridine (2.8 g, 23 mmol) in anhydrous CH₂Cl₂ (50 mL) was stirred at 0 °C for 30 min, to which was added a solution of the crude acid chloride (**21**) [prepared from the corresponding carboxylic acid (2.0 g, 6.9 mmol)] in anhydrous CH₂Cl₂ (40 mL). The reaction mixture was stirred at room temperature for 2 h and poured into saturated aqueous NH₄Cl. The organic layer was separated, and the aqueous layer was extracted with CH₂Cl₂. The combined organic layer was

washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography (hexane/EtOAc 6:1) to give **32** (2.6 g, quant.) as a brown oil. IR (KBr): $\tilde{\nu}$ = 1725, 1709, 1613, 1582 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3): δ = 1.58–1.70 (m, 4H), 1.86–1.97 (m, 3H), 2.18–2.24 (m, 1H), 2.24 (s, 3H), 3.82 (s, 3H), 3.86 (s, 3H), 5.15 (s, 2H), 6.16 (s, 1H), 6.49 (s, 1H), 7.21 (dd, 1H, J = 8.0, 6.5 Hz), 7.27–7.47 (m, 10H); elemental analysis calcd for $\text{C}_{32}\text{H}_{32}\text{O}_6\text{S}$: C 70.57, H 5.92, S 5.89; found C 70.39, H 6.02, S 5.84.

1-(2-Benzyloxy-4,5-dimethoxyphenyl)-4,4-tetramethylene-7-phenylthio-6-heptyne-1,3,5-trione (33): Under a nitrogen atmosphere, $\text{LiN}(\text{TMS})_2$ (1.0 M solution in THF, 11.3 mL, 11.3 mmol) was added to a solution of **32** (2.1 g, 3.8 mmol) in anhydrous THF (35 mL) at -78°C . The reaction mixture was stirred at -78°C for 30 min, and the cooling bath was removed. The reaction mixture was warmed to room temperature and poured into saturated aqueous NH_4Cl . The aqueous layer was extracted with EtOAc ($2 \times$), and the combined organic layer was washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography (hexane/EtOAc 4:1) to give 1-(2-benzyloxy-4,5-dimethoxyphenyl)-5-hydroxy-4,4-tetramethylene-7-phenylthio-6-heptyne-1,3-dione (1.82 g, 88%) as pale yellow crystals. M.p. $102-103^\circ\text{C}$ (hexane/ Et_2O); IR (KBr): $\tilde{\nu}$ = 3600–3200, 1615, 1518 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3): δ = 1.26–1.99 (m, 8H), 3.65 (d, 1H, J = 8.5 Hz), 3.92 (s, 3H), 3.94 (s, 3H), 4.43 (d, 1H, J = 8.5 Hz), 5.02 (d, 1H, J = 10.0 Hz), 5.05 (d, 1H, J = 10.0 Hz), 6.59 (s, 1H), 6.72 (s, 1H), 7.13 (t, 1H, J = 7.5 Hz), 7.22–7.41 (m, 9H), 7.58 (s, 1H), 16.63 (s, 1H); elemental analysis calcd for $\text{C}_{32}\text{H}_{32}\text{O}_6\text{S}$: C 70.57, H 5.92, S 5.89; found C 70.51, H 5.96, S 5.80.

Under a nitrogen atmosphere, a solution of the above product (27 mg, 49 μmol) in anhydrous benzene (2.0 mL) was cooled to 0°C , and DMSO (42 μL , 0.59 mmol), dicyclohexylcarbodiimide (DCC) (61 mg, 0.30 mmol), and pyridinium trifluoroacetate (9.4 mg, 50 μmol) were added successively. The reaction mixture was stirred at room temperature for 1 h and poured into water. The organic layer was extracted with Et_2O ($2 \times$), and the combined organic layer was washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography (hexane/EtOAc 4:1) to give **33** (17.1 mg, 64%) as yellow crystals. M.p. $148-149^\circ\text{C}$ (hexane/ Et_2O); IR (KBr): $\tilde{\nu}$ = 2116, 1615, 1518 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3): δ = 1.53–1.56 (m, 4H), 1.94–1.97 (m, 2H), 2.16–2.19 (m, 2H), 3.89 (s, 3H), 3.91 (s, 3H), 5.08 (s, 2H), 6.57 (s, 1H), 6.67 (s, 1H), 7.25–7.41 (m, 10H), 7.52 (s, 1H), 16.23 (s, 1H); elemental analysis calcd for $\text{C}_{32}\text{H}_{30}\text{O}_6\text{S}$: C 70.83, H 5.57, S 5.91; found C 70.76, H 5.53, S 5.92.

[1-(2-Hydroxy-4,5-dimethoxyphenyl)-4,4-tetramethylene-7-phenylthio-6-heptyne-1,3,5-trione]hexacarbonyldicobalt (34): Under a nitrogen atmosphere, $\text{Co}_2(\text{CO})_8$ (180 mg, 0.52 mmol) was added to an ice-cooled solution of **33** (140 mg, 0.26 mmol) in anhydrous CH_2Cl_2 (5 mL), and the flask was covered with aluminum foil. The reaction mixture was stirred at 0°C for 30 min and then at room temperature for another 30 min. Silica gel for flash column chromatography (2 g) was added to the reaction mixture and the whole mixture was concentrated in vacuo. The crude product absorbed on the silica gel was purified by flash column chromatography (hexane/EtOAc 2:1) to give [1-(2-benzyloxy-4,5-dimethoxyphenyl)-4,4-tetramethylene-7-phenylthio-6-heptyne-1,3,5-trione]hexacarbonyldicobalt (174 mg, 82%) as a dark-brown gum. IR (KBr): $\tilde{\nu}$ = 2099, 2062, 2037, 1576 cm^{-1} ; ^1H NMR (270 MHz, CDCl_3): δ = 1.56–1.61 (m, 4H), 2.01–2.07 (m, 2H), 2.26–2.31 (m, 2H), 4.10 (s, 3H), 4.13 (s, 3H), 5.11 (s, 2H), 6.56 (s, 1H), 6.78 (s, 1H), 7.38–7.55 (m, 11H), 16.29 (s, 1H).

Under a nitrogen atmosphere, BCl_3 (1.0 M solution in CH_2Cl_2 , 0.30 mL, 0.30 mmol) was added to an ice-cooled solution of the above product (125 mg, 0.15 mmol) in CH_2Cl_2 (4 mL). The reaction mixture was stirred at 0°C for 5 min and then at room temperature for 10 min and poured into ice-water. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 . The combined organic layer was washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography (hexane/EtOAc 3:1) to give **34** (81 mg, 73%) as a dark-brown gum. IR (KBr): $\tilde{\nu}$ = 2099, 2066, 2041, 1667, 1632, 1574 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3): δ = 1.77–1.85 (m, 4H), 2.19–2.29 (m, 2H), 2.50–2.59 (m, 2H), 3.82 (s, 3H), 3.90 (s, 3H), 6.20 (s, 1H), 6.43 (s, 1H), 6.98 (s, 1H), 7.38–7.58 (m, 5H), 12.08 (s, 1H), 15.60 (s, 1H).

4,5-[Di(*tert*-butyl)silylenedioxy]-7,8-dimethoxy-2,2-tetramethylene-9-phenylsulfanyl-2,3-dihydrobenz[*f*]indene-1,3-dione (5a): Under a nitrogen

atmosphere, **34** (16 mg, 19 μmol) and anhydrous toluene (2.0 mL) were placed in a glass reactor, and Et_3N (22 μL , 0.16 mmol), Me_2SiCl_2 (10 μL , 77 μmol), and chloranil (19 mg, 77 μmol) were added successively. The reactor was sealed and heated at 100°C for 12 h. After cooling, the reaction mixture was transferred to a round-bottomed flask and concentrated in vacuo. Under a nitrogen atmosphere, the residue was dissolved in anhydrous DMF (1.0 mL), and Et_3N (0.10 mL, 0.72 mmol), and $t\text{Bu}_2\text{Si}(\text{OTf})_2$ (0.12 mL, 0.34 mmol) were added. The reaction mixture was stirred at room temperature overnight and cooled to 0°C . Saturated aqueous NaHCO_3 and Et_2O were added, and the organic layer was separated. The aqueous layer was extracted with Et_2O ($5 \times$), and the combined organic layer was washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified twice by flash column chromatography with different eluents (hexane/ CH_2Cl_2 3:1 $\rightarrow$ 1:1 and hexane/EtOAc 10:1) to give 4,5-[di(*tert*-butyl)silylenedioxy]-7,8-dimethoxy-2,2-tetramethylene-9-phenylthio-2,3-dihydrobenz[*f*]indene-1,3-dione (6.5 mg, 57%) as a yellow oil. IR (KBr): $\tilde{\nu}$ = 1730, 1701, 1603, 1574 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3): δ = 1.17 (s, 18H), 1.52–1.77 (m, 8H), 3.95 (s, 3H), 4.00 (s, 3H), 6.93 (s, 1H), 7.15–7.17 (m, 5H); HRMS: anal. calcd for $\text{C}_{33}\text{H}_{38}\text{O}_6\text{Si}$: 590.2158; found 590.2152.

Under a nitrogen atmosphere, *m*CPBA (80% purity, 43 mg, 0.20 mmol) was added to a solution of the above product (118 mg, 0.20 mmol) in anhydrous CH_2Cl_2 (5 mL) at -78°C , and the reaction mixture was stirred at -40°C for 30 min. Saturated aqueous $\text{Na}_2\text{S}_2\text{O}_3$ was added, and the mixture was vigorously stirred at room temperature for 10 min. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 . The combined organic layer was washed with saturated aqueous NaHCO_3 , dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography (hexane/EtOAc 10:1 $\rightarrow$ 1:1) to give **5a** (94 mg, 78%) as a yellow oil. IR (KBr): $\tilde{\nu}$ = 1744, 1711, 1605, 1568 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3): δ = 1.16 (s, 9H), 1.17 (s, 9H), 1.86–2.05 (m, 8H), 3.74 (s, 3H), 4.02 (s, 3H), 6.94 (s, 1H), 7.39–7.45 (m, 3H), 7.79 (d, 2H, J = 7.0 Hz); HRMS: anal. calcd for $\text{C}_{33}\text{H}_{38}\text{O}_7\text{Si}$: 606.2107; found 606.2107.

4,5-[Di(*tert*-butyl)silylenedioxy]-8-methoxy-2,2-tetramethylene-9-phenylsulfanyl-2,3-dihydrobenz[*f*]indene-1,3-dione (5b): Compound **5b** was prepared similar to the reported method^[9d] to yield a yellow oil. IR (KBr): $\tilde{\nu}$ = 1742, 1713, 1605, 1586 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3): δ = 1.15 (s, 9H), 1.16 (s, 9H), 1.87–2.10 (m, 8H), 3.68 (s, 3H), 7.05 (d, 1H, J = 8.5 Hz), 7.09 (d, 1H, J = 8.5 Hz), 7.42–7.50 (m, 3H), 7.72–7.74 (m, 2H); HRMS: anal. calcd for $\text{C}_{33}\text{H}_{38}\text{O}_6\text{Si}$: 576.2002; found 576.1996.

4-Hydroxy-7-methoxy-2,2-tetramethylene-9-phenylthio-2,3-dihydrobenz[*f*]indene-1,3,5,8-tetrone (6): Under a nitrogen atmosphere, trifluoroacetic anhydride (32 μL , 0.23 mmol) was added to an ice-cooled solution of **5a** (14.0 mg, 23 μmol) and styrene (7.9 μL , 69 μmol) in CHCl_3 (1.5 mL). The reaction mixture was stirred at 0°C for 30 min and concentrated in vacuo. The residue was purified by preparative TLC (hexane/EtOAc 1:1) to give **6** (7.1 mg, 71%) as dark-blue crystals. M.p. $244-246^\circ\text{C}$ (hexane/EtOAc); IR (KBr): $\tilde{\nu}$ = 1748, 1715, 1669, 1621, 1607 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3): δ = 1.43–1.76 (m, 8H), 4.00 (s, 3H), 6.24 (s, 1H), 7.05–7.18 (m, 5H), 13.74 (s, 1H); HRMS: anal. calcd for $\text{C}_{24}\text{H}_{18}\text{O}_6\text{S}$: 434.0824; found 434.0820.

9-Chloroacetoxy-4,5-[di(*tert*-butyl)silylenedioxy]-7,8-dimethoxy-2,2-tetramethylene-2,3-dihydrobenz[*f*]indene-1,3-dione (8a): Under a nitrogen atmosphere, **7b** (29 μL , 0.17 mmol) and anhydrous *p*-toluenesulfonic acid (1.5 mg, 8.7 μmol) were added to a solution of **5a** (21 mg, 35 μmol) in anhydrous toluene (2.0 mL). The flask was set in an oil bath, pre-heated at 110°C , and stirred for 3.5 h. After cooling, Et_3N (one drop) was added, and the reaction mixture was concentrated in vacuo to give crude **8a**. Due to partial decomposition of **8a** during flash column chromatography, the crude product was used for the following step without prior purification. Analytically pure **8a** was obtained by flash column chromatography twice with different eluents (hexane/EtOAc 5:1 then hexane/benzene 3:1 $\rightarrow$ 1:1) as a yellow oil. IR (KBr): $\tilde{\nu}$ = 1790, 1732, 1707, 1605, 1582 cm^{-1} ; ^1H NMR (270 MHz, CDCl_3): δ = 1.15 (s, 18H), 1.93–2.05 (m, 8H), 3.86 (s, 3H), 4.00 (s, 3H), 4.52 (s, 2H), 6.92 (s, 1H); HRMS: anal. calcd for $\text{C}_{29}\text{H}_{35}\text{ClO}_8\text{Si}$: 574.1790; found 574.1790.

9-Chloroacetoxy-4,5-[di(*tert*-butyl)silylenedioxy]-8-methoxy-2,2-tetramethylene-2,3-dihydrobenz[*f*]indene-1,3-dione (8b): Similar to the preparation of **8a**, **5b** (28 mg, 49 μmol) was heated with **7b** (40 μL , 0.24 mmol) at 110°C for 4.5 h. The product was purified by flash column chromatography twice with different eluents (hexane/EtOAc 5:1 then benzene) to give **8b**

(19 mg, 72 %) as a yellow oil. IR (KBr): ν = 1788, 1732, 1709, 1607 cm^{-1} ; ^1H NMR (CDCl_3): δ = 1.14 (s, 18 H), 1.93–1.96 (m, 8 H), 3.91 (s, 3 H), 4.51 (s, 2 H), 6.98 (d, 1 H, J = 8.5 Hz), 7.06 (d, 1 H, J = 8.5 Hz); HRMS: anal. calcd for $\text{C}_{28}\text{H}_{35}\text{ClO}_5\text{Si}$: 544.1684; found 544.1697.

4,9-Dihydroxy-7-methoxy-2,2-tetramethylene-2,3-dihydrobenz[*f*]indene-1,3,5,8-tetrone (9): A solution of the crude **8a** obtained above in THF (2 mL) and water (0.4 mL) was cooled to 0 °C, to which was added Bu_4NF (1.0 M solution in THF, 10 μL , 10 μmol). The reaction mixture was stirred at room temperature for 40 min and poured into brine. The aqueous layer was extracted with CH_2Cl_2 , and the combined organic layer was washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was dried under vacuum (0.1 Torr) at room temperature for 2 h and dissolved in anhydrous CH_2Cl_2 (2 mL). Under a nitrogen atmosphere, BBr_3 (1.0 M solution in CH_2Cl_2 , 0.17 mL, 0.17 mmol) was added to this solution at –78 °C, and the reaction mixture was gradually warmed, with stirring, to –45 °C over a period of 3.5 h and then poured into ice-water. The aqueous layer was extracted with CH_2Cl_2 (2 $\times$), and the combined organic layer was washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was heated in CF_3COOH (3.0 mL) and water (0.75 mL) under reflux for 3 h, cooled, and concentrated in vacuo. The residue was purified by flash column chromatography ($\text{CH}_2\text{Cl}_2 \rightarrow \text{CH}_2\text{Cl}_2/\text{EtOAc}/\text{AcOH}$ 400:200:1) to give **9** (7.3 mg, 62 % from **5a**, as dark red crystals. M.p. 248–250 °C (lit.^[20] m.p. 247–249 °C); IR (CH_2Cl_2): ν = 1750, 1715, 1692, 1611, 1563 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3): δ = 1.96–2.17 (m, 8 H), 3.99 (s, 3 H), 6.28 (s, 1 H), 12.50 (brs, 1 H), 13.15 (s, 1 H); HRMS: anal. calcd for $\text{C}_{18}\text{H}_{14}\text{O}_7$: 342.0740; found 342.0756.

Preparation of **10** from **11**:

8,8-Bis(hydroxymethyl)-1,9-dimethoxy-3-methyl-6,7-dihydro-8H-cyclopent[*g*]isoquinoline (12): Under a nitrogen atmosphere, a mixture of **11** (5.0 mg, 15 μmol), Ag_2O (27 mg, 0.12 mmol), MeI (0.20 mL, 3.2 mmol) in anhydrous dioxane (1.0 mL) was stirred at 65 °C for 3 h. The reaction mixture was filtered through a Celite pad, and the filtrate was concentrated in vacuo. The residue was purified by preparative TLC (hexane/EtOAc 1:1) to give dimethyl 1,9-dimethoxy-3-methyl-6,7-dihydro-8H-cyclopent[*g*]isoquinoline-8,8-dicarboxylate (3.1 mg) as a colorless oil. IR (KBr): ν = 1732, 1630, 1570 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3): δ = 2.48 (s, 3 H), 2.83 (t, 2 H, J = 7.0 Hz), 3.03 (t, 2 H, J = 7.0 Hz), 3.79 (s, 6 H), 3.87 (s, 3 H), 4.11 (s, 3 H), 6.94 (s, 1 H), 7.22 (s, 1 H); HRMS: anal. calcd for $\text{C}_{19}\text{H}_{21}\text{NO}_6$: 359.1369; found 359.1369.

Under a nitrogen atmosphere, LiAlH_4 (3.0 mg, 90 μmol) was added to an ice-cooled solution of the above product (3.1 mg) in THF (1.0 mL). The reaction mixture was stirred at 0 °C for 20 min and poured into a saturated aqueous solution of Rochelle salt. The product was extracted with EtOAc (3 $\times$). The combined organic layer was washed with brine, dried (MgSO_4), and concentrated in vacuo. Purification of the residue by preparative TLC (hexane/EtOAc 1:2) to give **12** (1.6 mg, 35 % from **11**) as colorless crystals. M.p. 139–140 °C (hexane/EtOAc); IR (KBr): ν = 3600–3100, 1628, 1612, 1565 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3): δ = 2.09 (t, 2 H, J = 7.0 Hz), 2.49 (s, 3 H), 2.86–2.96 (m, 2 H), 3.01 (t, 2 H, J = 7.0 Hz), 3.71–3.80 (m, 2 H), 3.93 (s, 3 H), 3.99–4.13 (m, 2 H), 4.14 (s, 3 H), 6.94 (s, 1 H), 7.26 (s, 1 H); ^{13}C NMR (75 MHz, CDCl_3): δ = 23.7, 29.8, 31.5, 53.4, 56.4, 64.1, 66.5, 110.8, 112.7, 117.8, 134.7, 142.6, 148.8, 149.7, 153.7, 158.6; elemental analysis calcd for $\text{C}_{17}\text{H}_{21}\text{NO}_4$: C 67.31, H 6.98, N 4.62; found C 67.13, H 6.84, N 4.57.

[8-(Hydroxymethyl)-1,9-dimethoxy-3-methyl-6,7-dihydro-8H-cyclopent[*g*]isoquinolin-8-yl]methyl benzoate (13): Under a nitrogen atmosphere, benzoyl chloride (10 μL , 86 μmol) was added to an ice-cooled solution of **12** (23 mg, 77 μmol) and pyridine (10 μL , 0.12 mmol) in anhydrous CH_2Cl_2 (4.0 mL). The reaction mixture was stirred at room temperature for 3 d and poured into an aqueous NaHCO_3 solution. The product was extracted with EtOAc (2 $\times$), and the combined organic layer was dried (Na_2SO_4) and concentrated in vacuo. Purification of the residue by preparative TLC (hexane/EtOAc 1:1) to give **13** (14 mg, 45 %) as a colorless oil. IR (KBr): ν = 3600–3100, 1723, 1717, 1628, 1615, 1565 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3): δ = 2.07–2.33 (m, 2 H), 2.50 (s, 3 H), 2.94 (brs, 1 H), 3.03–3.15 (m, 2 H), 3.94 (s, 3 H), 3.97–4.11 (m, 2 H), 4.14 (s, 3 H), 4.62 (d, 1 H, J = 11.0 Hz), 4.79 (d, 1 H, J = 11.0 Hz), 6.96 (s, 1 H), 7.27 (s, 1 H), 7.41 (dd, 2 H, J = 8.0, 7.5 Hz), 7.55 (t, 1 H, J = 7.5 Hz), 7.96 (d, 2 H, J = 8.0 Hz); HRMS: anal. calcd for $\text{C}_{24}\text{H}_{25}\text{NO}_5$: 407.1732; found 407.1733.

8-Acetyl-8-formyl-1,9-dimethoxy-3-methyl-6,7-dihydro-8H-cyclopent[*g*]isoquinoline (10): Under a nitrogen atmosphere, Dess–Martin periodinane

(62 mg, 0.15 mmol) was added to an ice-cooled solution of **13** (49 mg, 0.12 mmol) in acetonitrile (2.0 mL). The reaction mixture was stirred at room temperature for 5 h and poured into a saturated aqueous $\text{Na}_2\text{S}_2\text{O}_3$ solution. The product was extracted with EtOAc (2 $\times$), and the combined organic layer was washed with a saturated aqueous NaHCO_3 , dried (Na_2SO_4), and concentrated in vacuo to give (8-formyl-1,9-dimethoxy-3-methyl-6,7-dihydro-8H-cyclopent[*g*]isoquinolin-8-yl)methyl benzoate as a colorless oil. This product was used for the next reaction without further purification. IR (KBr): ν = 1727, 1628, 1568 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3): δ = 2.23–2.32 (m, 1 H), 2.51 (s, 3 H), 2.60–2.71 (m, 1 H), 3.10–3.27 (m, 2 H), 3.89 (s, 3 H), 4.14 (s, 3 H), 4.67 (d, 1 H, J = 11.5 Hz), 5.15 (d, 1 H, J = 11.5 Hz), 6.98 (s, 1 H), 7.30 (s, 1 H), 7.41 (t, 2 H, J = 8.0 Hz), 7.55 (t, 1 H, J = 8.0 Hz), 7.93 (d, 2 H, J = 8.0 Hz), 9.92 (s, 1 H).

Under a nitrogen atmosphere, a solution of the above crude product in THF (3.0 mL) was cooled to –78 °C, and MeMgBr (0.83 M solution in THF, 0.50 mL, 0.42 mmol) was added. The reaction mixture was stirred at –78 °C for 1.5 h, and MeLi (1.1 M solution in hexane, 0.38 mL, 0.42 mmol) was added. The reaction mixture was stirred at –78 °C for 10 min, warmed to 0 °C, and stirred at 0 °C for 30 min. The reaction mixture was poured into a saturated aqueous NH_4Cl and extracted with EtOAc. The organic layer was dried (Na_2SO_4) and concentrated in vacuo. Purification of the residue by flash column chromatography (hexane/EtOAc 3:1) gave 8-(1-hydroxyethyl)-8-hydroxymethyl-1,9-dimethoxy-3-methyl-6,7-dihydro-8H-cyclopent[*g*]isoquinoline (a 17:3 mixture of two diastereomers, 36 mg, 93 % from **13**) as a colorless oil. IR (KBr): ν = 3700–3100, 1628, 1615, 1565, 1559 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3): δ = 1.02 (d, 9/20 H, J = 6.5 Hz), 1.14 (d, 51/20 H, J = 6.5 Hz), 1.93–2.21 (m, 2 H), 2.25–2.42 (m, 3/20 H), 2.49 (s, 3 H), 2.59 (dd, 17/20 H, J = 8.5, 5.0 Hz), 2.83–2.87 (m, 3/20 H), 3.02 (dd, 2 H, J = 8.5, 7.5 Hz), 3.19 (d, 17/20 H, J = 8.5 Hz), 3.73 (dd, 17/20 H, J = 11.0, 8.5 Hz), 3.90 (s, 9/20 H), 3.95 (s, 51/20 H), 4.02–4.22 (m, 43/20 H), 4.13 (s, 3 H), 6.94 (s, 1 H), 7.24 (s, 1 H); HRMS: anal. calcd for $\text{C}_{18}\text{H}_{23}\text{NO}_4$: 317.1627; found 317.1620.

Under a nitrogen atmosphere, a mixture of oxalyl chloride (29 μL , 0.33 mmol) and DMSO (47 μL , 0.66 mmol) in anhydrous CH_2Cl_2 (2.0 mL) was stirred at –78 °C for 10 min, to which was added a solution of the above product (26 mg, 82 μmol) in anhydrous CH_2Cl_2 (1.5 mL). The reaction mixture was stirred at –78 °C for 1 h, and Et_3N (0.14 mL, 0.98 mmol) was added. The reaction mixture was stirred at –78 °C for 1 h, gradually warmed to room temperature, and stirred at room temperature for 30 min. The reaction mixture was poured into saturated aqueous NH_4Cl and extracted with CH_2Cl_2 . The combined organic layer was washed with brine, dried (Na_2SO_4), and concentrated in vacuo. Purification of the residue by flash column chromatography (hexane/EtOAc 3:1) gave **10** (21 mg, 80 %) as a pale yellow oil. IR (KBr): ν = 1728, 1705, 1628, 1611 cm^{-1} ; ^1H NMR (CDCl_3): δ = 2.21 (s, 3 H), 2.33 (ddd, 1 H, J = 13.0, 8.5, 5.0 Hz), 2.50 (s, 3 H), 2.75 (ddd, 1 H, J = 13.0, 7.0, 6.0 Hz), 3.06–3.19 (m, 2 H), 3.85 (s, 3 H), 4.13 (s, 3 H), 6.97 (s, 1 H), 7.28 (s, 1 H), 10.04 (s, 1 H); ^{13}C NMR (68 MHz, CDCl_3): δ = 23.5, 26.5, 30.7, 31.3, 53.4, 63.5, 74.0, 110.8, 112.5, 117.3, 129.9, 143.2, 148.2, 149.2, 153.8, 158.5, 196.8, 206.4; HRMS (FAB): anal. calcd for $\text{C}_{18}\text{H}_{20}\text{NO}_4$: 314.1393 [$M + \text{H}$] $^+$; found 314.1396.

Preparation of **10** from **14**:

8-Hydroxymethyl-1,9-dimethoxy-3-methyl-6,7-dihydro-8H-cyclopent[*g*]isoquinoline (15): Under a nitrogen atmosphere, $t\text{BuOK}$ (6.1 g, 53 mmol) was added to a suspension of methyltriphenylphosphonium bromide (18.9 g, 53 mmol) in anhydrous THF (130 mL) at room temperature, and the reaction mixture was stirred at room temperature for 1 h. A solution of **14** (6.8 g, 26 mmol) in anhydrous THF (85 mL) was added, and the reaction mixture was stirred at room temperature for 2 h. Water (100 mL) was added, and the mixture was concentrated in vacuo to a half of its volume. The product was extracted with CH_2Cl_2 (3 $\times$), and the combined organic layer was washed with brine, dried (Na_2SO_4), and concentrated in vacuo. Purification of the residue by flash column chromatography (hexane/EtOAc 20:1) gave 1,9-dimethoxy-3-methyl-8-methylene-6,7-dihydro-8H-cyclopent[*g*]isoquinoline (5.6 g, 83 %) as a colorless solid. M.p. 90–90.5 °C (hexane/EtOAc); IR (KBr): ν = 1614, 1565 cm^{-1} ; ^1H NMR (CDCl_3): δ = 2.48 (s, 3 H), 2.83–2.85 (m, 2 H), 3.01–3.04 (m, 2 H), 3.87 (s, 3 H), 4.14 (s, 3 H), 5.30 (s, 1 H), 6.07 (s, 1 H), 6.91 (s, 1 H), 7.22 (s, 1 H); ^{13}C NMR (75 MHz, CDCl_3): δ = 23.8, 29.9, 32.7, 53.7, 60.5, 109.0, 119.9, 112.7, 117.3, 130.6, 142.2, 147.4, 148.8, 151.2, 154.4, 159.9; $\text{C}_{16}\text{H}_{17}\text{NO}_2$: anal. calcd for C 75.27, H 6.71, N 5.49; found C 74.99, H 6.85, N 5.21.

Under a nitrogen atmosphere, $\text{BH}_3 \cdot \text{THF}$ complex (1.0 M solution in THF, 50 mL, 50 mmol) was added to a solution of the above product (12.5 g, 49 mmol) in anhydrous THF (200 mL) over a period of 5 min. The reaction mixture was stirred at room temperature for 30 min and cooled to 0 °C. 2 N NaOH (100 mL) was added dropwise over a period of 20 min, and then 30 % aqueous H_2O_2 (40 mL) was added over a period of 5 min. The reaction mixture was vigorously stirred at room temperature for 30 min and extracted with EtOAc (3 ×). The combined organic layer was washed with saturated aqueous $\text{Na}_2\text{S}_2\text{O}_3$ twice, dried (MgSO_4), and concentrated in vacuo. Recrystallization of the residual solid from hexane/EtOAc 1:1 gave **15** (7.0 g). The mother liquor was concentrated in vacuo, and the residue was recrystallized from the same solvent system to give **15** (4.0 g). The mother liquor was concentrated in vacuo, and purified by flash column chromatography (hexane/EtOAc 2:1) to yield another batch of colorless crystals (1.27 g) (total 92 % yield). M.p. 111–111.5 °C (hexane/EtOAc); IR (KBr): $\tilde{\nu}$ = 3467, 1634, 1568 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3): δ = 1.96–2.04 (m, 1H), 2.25–2.33 (m, 1H), 2.48 (s, 3H), 2.85 (brs, 1H), 2.92–2.98 (m, 1H), 3.03–3.11 (m, 1H), 3.65–3.70 (m, 1H), 3.83 (brd, 2H, J = 6.5 Hz), 3.90 (s, 3H), 4.13 (s, 3H), 6.93 (s, 1H), 7.24 (s, 1H); ^{13}C NMR (126 MHz, CDCl_3): δ = 23.7, 28.8, 31.4, 46.1, 53.6, 62.1, 66.1, 111.2, 112.7, 117.4, 134.9, 142.2, 148.4, 149.6, 153.2, 159.1; $\text{C}_{16}\text{H}_{19}\text{NO}_3$; elemental analysis calcd for C 70.31, H 7.01, N 5.12; found C 70.37, H 6.98, N 5.13.

8-Formyl-1,9-dimethoxy-3-methyl-6,7-dihydro-8H-cyclopent[*g*]isoquinoline (16): Under a nitrogen atmosphere, Dess–Martin periodinane (4.8 g, 10.7 mmol) was added to an ice-cooled solution of **15** (2.9 g, 10.7 mmol) in CH_2Cl_2 (120 mL). The reaction mixture was stirred at room temperature for 30 min. Dess–Martin periodinane (1.0 g, 2.3 mmol) was added, and the whole mixture was stirred at room temperature for 20 min and poured into saturated aqueous $\text{Na}_2\text{S}_2\text{O}_3$. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 . The combined organic layer was washed with aqueous saturated NaHCO_3 , dried (Na_2SO_4), and concentrated in vacuo to give **16** (2.8 g). This product was used for the following reaction without prior purification. Analytically pure sample was obtained by recrystallization from hexane/EtOAc. M.p. 103–104 °C; IR (KBr): $\tilde{\nu}$ = 1725, 1634, 1568 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3): δ = 2.25–2.47 (m, 2H), 2.50 (s, 3H), 3.05–3.13 (m, 2H), 3.85 (s, 3H), 4.14 (s, 3H), 4.15–4.21 (m, 1H), 6.96 (s, 1H), 7.29 (s, 1H), 9.75 (d, 1H, J = 3.0 Hz); ^{13}C NMR (75 MHz, CDCl_3): δ = 23.8, 26.1, 32.2, 53.7, 55.4, 61.9, 111.2, 112.8, 117.4, 130.2, 142.8, 148.9, 149.0, 153.7, 159.2, 199.6; HRMS (FAB): anal. calcd for $\text{C}_{16}\text{H}_{18}\text{NO}_3$: 272.1287 [$M + \text{H}$] $^+$; found 272.1295.

Hydrazone (17): Under a nitrogen atmosphere, a solution of the above crude **16** (2.8 g) and (*R*)-1-amino-2-(methoxymethyl)pyrrolidine (1.8 mL, 13 mmol) in CH_2Cl_2 (180 mL) was stirred at room temperature for 2 h. The reaction mixture was concentrated in vacuo, and the residue was immediately purified by flash column chromatography (hexane/EtOAc 5:1 → 4:1) to give **17** (a 1:1 mixture of two diastereomers, 3.6 g, 87 %) as a yellow oil. Due to instability of this product, it was used for the following reaction immediately. IR (KBr): $\tilde{\nu}$ = 1630, 1615 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3): δ = 1.77–1.97 (m, 4H), 2.22–2.35 (m, 2H), 2.48 (s, 3H), 2.74–2.80 (m, 1H), 2.93–2.96 (m, 1H), 3.05–3.10 (m, 1H), 3.30–3.34 (m, 1H), 3.38 (s, 3H), 3.34–3.46 (m, 2H), 3.61–3.64 (m, 1H), 3.81 (s, 3/2H), 3.82 (s, 3/2H), 4.110 (s, 3/2H), 4.112 (s, 3/2H), 4.18–4.22 (m, 1H), 6.75 (d, 1/2H, J = 6.5 Hz), 6.79 (d, 1/2H, J = 6.5 Hz), 6.92 (s, 1H), 7.23 (s, 1H); HRMS: anal. calcd for $\text{C}_{22}\text{H}_{29}\text{N}_3\text{O}_3$: 383.2209; found 383.2209.

Hydrazone (18): Under a nitrogen atmosphere, *n*BuLi (1.5 M solution in hexane, 7.3 mL, 11.2 mmol) was added to (*i*Pr) $_2$ NH (1.57 mL, 11.2 mmol) at 0 °C, and the mixture was stirred at 0 °C for 20 min. Anhydrous THF (30 mL) was added, and the resulting clear solution was cooled to –78 °C. A solution of **17** (3.6 g, 9.3 mmol) in anhydrous THF (60 mL) was added to this solution, and the reaction mixture was stirred at –78 °C for 1 h. Acetyl chloride (0.66 mL, 9.3 mmol) was added, and the reaction mixture was stirred at –78 °C for 1.5 h. Saturated aqueous NH_4Cl was added, and the product was extracted with CH_2Cl_2 (3 ×). The combined organic layer was washed with brine, dried (Na_2SO_4), and concentrated in vacuo. Purification of the residue by flash column chromatography (hexane/EtOAc 4:1) gave **18** (a 1:1 mixture of two diastereomers, 3.1 g, 77 %) as a pale yellow oil. IR (KBr): $\tilde{\nu}$ = 1709, 1568 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3): δ = 1.74–1.91 (m, 4H), 2.232 (s, 3/2H), 2.234 (s, 3/2H), 2.24–2.42 (m, 3/2H), 2.45 (s, 3H), 2.66–2.69 (m, 1/2H), 2.76–2.88 (m, 2H), 3.04–3.14 (m, 2H), 3.28 (s, 3/2H), 3.30 (s, 3/2H), 3.30–3.38 (m, 2H), 3.47–3.50 (m, 1H), 3.78 (s, 3/2H), 3.79 (s, 3/2H), 4.12 (s, 3H), 6.945 (s, 1/2H), 6.952 (s, 1/2H), 7.01 (s, 1/2H),

7.07 (s, 1/2H), 7.235 (s, 1/2H), 7.240 (s, 1/2H); HRMS (FAB): anal. calcd for $\text{C}_{24}\text{H}_{32}\text{N}_3\text{O}_4$: 426.2393 [$M + \text{H}$] $^+$; found 426.2392.

8-Acetyl-8-formyl-1,9-dimethoxy-3-methyl-6,7-dihydro-8H-cyclopent[*g*]isoquinoline (10): A mixture of **18** (1.41 g, 3.4 mmol), Et_2O (60 mL), and saturated aqueous oxalic acid (60 mL) was vigorously stirred at room temperature for 1 h. The organic layer was separated, and the aqueous layer was extracted with Et_2O (7 ×). The combined organic layer was successively washed with saturated aqueous NH_4Cl (3 ×) and brine, dried (Na_2SO_4), and concentrated in vacuo. Purification of the residue by flash column chromatography (hexane/EtOAc 4:1) gave **10** (1.05 g, 99 %) as a pale yellow oil. This product was identical with that obtained from **11**.

8-Acetyl-8-[1-(2-benzyloxy-4,5-dimethoxybenzoyloxy)-3-phenylthio-2-propyn-1-yl]-1,9-dimethoxy-3-methyl-6,7-dihydro-8H-cyclopent[*g*]isoquinoline (23): Under a nitrogen atmosphere, $\text{LiN}(\text{TMS})_2$ (1.0 M solution in THF, 2.7 mL, 2.7 mmol) was added to a solution of **10** (0.40 g, 1.3 mmol), **20** (0.17 g, 1.3 mmol), **21** [in situ prepared from 2-benzyloxy-4,5-dimethoxybenzoic acid (0.90 g, 3.1 mmol)] in THF (25 mL) at –78 °C. The reaction mixture was stirred at –78 °C for 2 h, gradually warmed to –20 °C over a period of 30 min, and poured into saturated aqueous NH_4Cl . The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 . The combined organic layer was washed with brine, dried (Na_2SO_4), and concentrated in vacuo. Purification of the residue by flash column chromatography (hexane/EtOAc 2:1) gave **23** (0.63 g, 69 %) as a separable mixture of two diastereomers in a ratio of 17:1.

Major diastereomer (less polar isomer); a pale yellow gum. IR (KBr): $\tilde{\nu}$ = 1727, 1715, 1628, 1613 cm^{-1} ; ^1H NMR (270 MHz, CDCl_3): δ = 2.19 (s, 3H), 2.45 (s, 3H), 2.58 (ddd, 1H, J = 14.0, 9.0, 7.0 Hz), 2.85 (ddd, 1H, J = 14.0, 9.5, 5.0 Hz), 3.15 (ddd, 1H, J = 14.5, 9.0, 5.0 Hz), 3.32 (ddd, 1H, J = 14.5, 9.5, 7.0 Hz), 3.56 (s, 3H), 3.73 (s, 3H), 3.83 (s, 3H), 4.05 (s, 3H), 4.91 (ABq, 1H, J = 12.5 Hz), 4.97 (ABq, 1H, J = 12.5 Hz), 6.35 (s, 1H), 6.71 (s, 1H), 6.78 (s, 1H), 6.85 (s, 1H), 7.13–7.21 (m, 2H), 7.23–7.35 (m, 7H), 7.40–7.46 (m, 2H); ^{13}C NMR (75 MHz, CDCl_3): δ = 23.7, 26.3, 31.8, 32.2, 53.6, 55.9, 56.0, 63.2, 67.9, 68.2, 72.2, 73.0, 96.3, 100.2, 111.1, 111.3, 112.5, 113.4, 117.0, 126.2, 126.4, 127.1, 127.8, 128.5, 129.2, 131.6, 132.5, 136.8, 142.7, 143.2, 149.3, 149.7, 153.2, 154.5, 154.7, 159.1, 163.7, 205.8; HRMS (FAB): anal. calcd for $\text{C}_{42}\text{H}_{40}\text{NO}_8$: 718.2475 [$M + \text{H}$] $^+$; found 718.2500.

Minor diastereomer (more polar isomer); a pale yellow gum; IR (KBr): $\tilde{\nu}$ = 1723, 1713, 1626, 1611 cm^{-1} ; ^1H NMR (270 MHz, CDCl_3): δ = 2.08 (s, 3H), 2.28 (ddd, 1H, J = 14.5, 8.5, 7.0 Hz), 2.49 (s, 3H), 2.65 (ddd, 1H, J = 14.5, 9.0, 8.0 Hz), 3.03–3.14 (m, 2H), 3.84 (s, 3H), 3.88 (s, 3H), 3.96 (s, 3H), 4.11 (s, 3H), 5.12 (ABq, 1H, J = 12.0 Hz), 5.13 (ABq, 1H, J = 12.0 Hz), 6.51 (s, 1H), 6.83–6.89 (m, 2H), 6.95 (s, 1H), 6.96–7.13 (m, 4H), 7.20–7.39 (m, 4H), 7.42–7.39 (m, 2H), 7.50 (s, 1H); ^{13}C NMR (68 MHz, CDCl_3): δ = 23.7, 26.0, 30.9, 32.0, 53.7, 56.0, 56.3, 63.5, 67.0, 68.2, 72.2, 73.6, 95.3, 99.7, 111.0, 111.4, 112.7, 114.8, 117.3, 126.1, 126.4, 127.9, 128.0, 128.6, 128.9, 131.7, 132.1, 136.8, 143.0, 143.4, 149.4, 149.5, 153.6, 154.7, 155.0, 159.2, 164.8, 204.9; elemental analysis calcd for $\text{C}_{42}\text{H}_{39}\text{NO}_8$: C 70.28, H 5.48, N 1.95, S 4.47; found C 70.07, H 5.52, N 1.91, S 4.40.

8-[3-(2-Benzyloxy-4,5-dimethoxyphenyl)-1,3-dioxoprop-1-yl]-8-(1-hydroxy-3-phenylthio-2-propyn-1-yl)-1,9-dimethoxy-3-methyl-6,7-dihydro-8H-cyclopent[*g*]isoquinoline (24): Under a nitrogen atmosphere, $\text{LiN}(\text{TMS})_2$ (1.0 M solution in THF, 3.3 mL, 3.3 mmol) was added to a solution of **23** (a 17:1 mixture of two diastereomers, 0.79 g, 1.1 mmol) in anhydrous toluene (20 mL). The reaction mixture was stirred at room temperature for 2.5 h, after which time the consumption of the major isomer was confirmed by silica gel TLC analysis ($\text{CHCl}_3/\text{MeOH}$ 100:1). Anhydrous HMPA (0.64 mL, 3.5 mmol) was added, and the reaction mixture was stirred at room temperature for 30 min, after which time, the consumption of the minor isomer was confirmed by TLC analysis, see above. The reaction mixture was poured into saturated aqueous NH_4Cl , and the product was extracted with CH_2Cl_2 (2 ×). The combined organic layer was washed with brine, dried (Na_2SO_4), and concentrated in vacuo. Purification of the residue by flash column chromatography (hexane/EtOAc 2:1) gave **24** (0.56 g, 70 %) as a separable mixture of two diastereomers in a ratio of 17:1.

Major isomer (less polar isomer); a yellow gum; IR (KBr): $\tilde{\nu}$ = 3600–3300, 1713, 1626, 1615 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3): δ = 2.34–2.42 (m, 2H), 2.49 (s, 3H), 2.87–3.04 (m, 2H), 3.80 (s, 3H), 3.86 (s, 3H), 3.88 (s, 3H), 4.04 (s, 3H), 4.87 (ABq, 1H, J = 11.5 Hz), 4.90 (ABq, 1H, J = 11.5 Hz), 5.02 (ABq, 1H, J = 9.5 Hz), 5.08 (ABq, 1H, J = 9.5 Hz), 6.41 (s,

1H), 6.66 (s, 1H), 6.77–6.86 (m, 3H), 6.80 (s, 1H), 6.93 (s, 1H), 6.89–7.02 (m, 1H), 7.18–7.24 (m, 3H), 7.32–7.39 (m, 3H), 7.49 (s, 1H), 16.29 (s, 1H); ¹³C NMR (75 MHz, CDCl₃): δ = 23.7, 30.6, 36.5, 53.6, 56.0, 56.3, 63.2, 67.8, 68.4, 71.3, 71.8, 98.3, 98.9, 99.6, 111.0, 111.9, 112.7, 114.9, 117.5, 125.6, 126.0, 127.5, 128.4, 128.7, 128.8, 132.1, 132.3, 136.1, 143.0, 143.4, 149.1, 150.1, 153.0, 153.8, 153.9, 159.1, 178.7, 198.6; HRMS (FAB): anal. calcd for C₄₂H₄₀NO₈S: 718.2474 [M + H]⁺; found 718.2474.

Minor isomer (more polar isomer); a yellow gum; IR (KBr): $\tilde{\nu}$ = 3600–3300, 1713, 1626, 1611 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ = 2.33 (ddd, 1H, *J* = 14.5, 9.0, 5.0 Hz), 2.45 (s, 3H), 2.83 (ddd, 1H, *J* = 16.5, 9.0, 6.0 Hz), 2.95 (ddd, 1H, *J* = 14.5, 9.0, 6.0 Hz), 3.09 (ddd, 1H, ddd, *J* = 16.5, 9.0, 5.0 Hz), 3.75 (s, 3H), 3.79 (s, 3H), 3.84 (s, 3H), 4.05 (s, 3H), 4.16 (d, 1H, *J* = 3.0 Hz), 4.76 (ABq, 1H, *J* = 12.0 Hz), 4.80 (ABq, 1H, *J* = 12.0 Hz), 5.96 (d, 1H, *J* = 3.0 Hz), 6.32 (s, 1H), 6.35 (s, 1H), 6.76–6.82 (m, 2H), 6.86–6.96 (m, 3H), 6.99–7.10 (m, 3H), 7.12 (s, 1H), 7.18–7.35 (m, 3H), 7.40 (s, 1H), 15.64 (s, 1H); ¹³C NMR (75 MHz, CDCl₃): δ = 23.7, 31.6, 32.6, 53.6, 55.9, 56.3, 62.7, 65.9, 66.5, 71.2, 71.6, 96.9, 98.5, 99.8, 111.4, 111.6, 112.8, 114.0, 117.0, 125.6, 125.9, 126.1, 127.3, 128.3, 128.8, 132.3, 134.5, 136.1, 143.1, 143.2, 148.9, 149.8, 152.8, 153.5, 154.3, 159.1, 175.1, 206.3; HRMS (FAB): anal. calcd for C₄₂H₄₀NO₈S: 718.2474 [M + H]⁺; found 718.2468.

[8-[3-(2-Hydroxy-4,5-dimethoxyphenyl)-1,3-dioxoprop-1-yl]-8-(1-oxo-3-phenylthio-2-propyn-1-yl)-1,9-dimethoxy-3-methyl-6,7-dihydro-8H-cyclopent[*g*]isoquinoline]hexacarbonyldicobalt (25): Dess–Martin periodinane (34 mg, 80 μmol) was added to a solution of **24** (a 17:1 mixture of two diastereomers, 38 mg, 53 μmol) in CH₂Cl₂ (2.0 mL). The reaction mixture was stirred at room temperature for 1 h and poured into saturated aqueous Na₂S₂O₃. The same workup as described for the preparation of **10** from **13** gave **8-[3-(2-benzyloxy-4,5-dimethoxyphenyl)-1,3-dioxoprop-1-yl]-8-(1-oxo-3-phenylthio-2-propyn-1-yl)-1,9-dimethoxy-3-methyl-6,7-dihydro-8H-cyclopent[*g*]isoquinoline** (34 mg) as a pale yellow gum. Due to its instability, the product was used without further purification. IR (KBr): $\tilde{\nu}$ = 2122, 1732, 1661, 1626, 1615 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ = 2.45 (s, 3H), 2.65–2.86 (m, 2H), 2.95–3.05 (m, 2H), 3.74 (s, 3H), 3.83 (s, 3H), 3.85 (s, 3H), 3.92 (s, 3H), 4.93 (ABq, 1H, *J* = 12.5 Hz), 5.04 (ABq, 1H, *J* = 12.5 Hz), 6.35 (s, 1H), 6.93 (s, 1H), 6.95 (s, 1H), 7.05–7.43 (m, 11H), 7.48 (s, 1H), 16.31 (s, 1H); ¹³C NMR (75 MHz, CDCl₃): δ = 23.7, 31.5, 37.9, 53.3, 55.8, 56.2, 60.4, 62.8, 71.0, 73.4, 98.4, 100.6, 101.4, 111.4, 111.7, 112.7, 114.8, 116.8, 126.5, 127.1, 127.4, 127.9, 128.6, 129.4, 129.9, 133.2, 136.3, 143.1, 143.3, 148.6, 149.1, 152.9, 153.8, 154.6, 159.1, 178.4, 183.7, 195.0; HRMS (FAB): anal. calcd for C₄₂H₃₈NO₈S: 716.2318 [M + H]⁺; found 716.2385.

Similarly to the preparation of **34**, the above product (34 mg) was stirred with Co₂(CO)₈ (37 mg, 0.12 mmol), and the product was purified by flash column chromatography (hexane/EtOAc 3:1) to give **8-[3-(2-benzyloxy-4,5-dimethoxyphenyl)-1,3-dioxoprop-1-yl]-8-(1-oxo-3-phenylthio-2-propyn-1-yl)-1,9-dimethoxy-3-methyl-6,7-dihydro-8H-cyclopent[*g*]isoquinoline** (KBr): $\tilde{\nu}$ = 2097, 2062, 2035, 1727, 1661, 1628, 1615 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ = 2.46 (s, 3H), 2.58–2.79 (m, 2H), 2.86–2.95 (m, 2H), 3.78 (s, 3H), 3.81 (s, 3H), 3.86 (s, 3H), 3.98 (s, 3H), 4.86 (ABq, 1H, *J* = 12.0 Hz), 4.92 (ABq, 1H, *J* = 12.0 Hz), 6.40 (s, 1H), 6.72 (s, 1H), 6.91 (s, 1H), 7.12–7.56 (m, 12H), 16.29 (s, 1H).

Under an argon atmosphere, BCl₃ (1.0 M in CH₂Cl₂, 0.010 mL, 10 μmol) was added to an ice-cooled solution of the above product (9.5 mg, 9.4 μmol) in anhydrous CH₂Cl₂ (3.0 mL). The reaction mixture was stirred at 0 °C for 1 h and poured into ice-water. The same workup as described for the preparation of **34** and the purification by preparative TLC (hexane/EtOAc 2:1) gave **25** (3.2 mg, 37%) as a 3:1 mixture of keto- and enol-forms as a dark green gum. IR (KBr): $\tilde{\nu}$ = 2099, 2064, 2039, 1717, 1628, 1615 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ = 2.49 (s, 3H), 2.76–2.98 (m, 2H), 3.03–3.25 (m, 2H), 3.62 (s, 3/4H), 3.78 (s, 9/4H), 3.86 (s, 3/4H), 3.89 (s, 3/4H), 3.90 (s, 9/4H), 3.95 (s, 9/4H), 4.04 (s, 9/4H), 4.05 (s, 3/4H), 4.27 (ABq, 3/4H, *J* = 16.0 Hz), 4.51 (ABq, 3/4H, *J* = 16.0 Hz), 6.27 (s, 1/4H), 6.40 (s, 3/4H), 6.71 (s, 1/4H), 6.96 (s, 3/4H), 6.97 (s, 1/4H), 7.26–7.48 (m, 25/4H), 7.57 (s, 3/4H), 12.02 (s, 1/4H), 12.39 (s, 1/4H), 15.60 (s, 3/4H).

8,9-[Di(*tert*-butyl)silylenedioxy]-1',5,6,9'-tetramethoxy-3'-methyl-4-phenylsulfanyl-6',7'-dihydrospiro[2H-benz[*f*]indene-2,8'-8H-cyclopent[*g*]isoquinoline]-1,3-dione (26): Under a nitrogen atmosphere, **25** (18 mg, 19 μmol) and anhydrous toluene (2.0 mL) were placed in a glass reactor, Et₃N (22 μL, 0.16 mmol) and Me₂SiCl₂ (10 μL, 78 μmol) were added. The reaction mixture was stirred at room temperature for 30 min, and chloranil

(19 mg, 77 μmol) was added. The reactor was sealed and heated at 100 °C for 10 h. After cooling, the reaction mixture was transferred to a round bottomed flask and concentrated in vacuo. The residue was dissolved in anhydrous DMF (1 mL), Et₃N (0.20 mL, 1.4 mmol) and *t*Bu₂Si(OTf)₂ (0.25 mL, 0.69 mmol) were added. The reaction mixture was stirred at room temperature overnight. Similar workup as described for the preparation of **5a** followed by purification by flash column chromatography (hexane → hexane/EtOAc 5:1) gave **8,9-[di(*tert*-butyl)silylenedioxy]-1',5,6,9'-tetramethoxy-3'-methyl-4-phenylthio-6',7'-dihydrospiro[2H-benz[*f*]indene-2,8'-8H-cyclopent[*g*]isoquinoline]-1,3-dione** (9.0 mg) as a yellow gum. This product was contaminated with small amounts of hardly separable impurities and used for the following reaction without further purification. IR (KBr): $\tilde{\nu}$ = 1736, 1703, 1630, 1603 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ = 1.11 (s, 9H), 1.12 (s, 9H), 1.93–2.02 (m, 1H), 2.31–2.38 (m, 1H), 2.45 (s, 3H), 3.07–3.16 (m, 1H), 3.18–3.25 (m, 1H), 3.43 (s, 3H), 3.94 (s, 3H), 4.00 (s, 3H), 4.02 (s, 3H), 6.90 (s, 1H), 6.93–6.98 (m, 1H), 6.95 (s, 1H), 7.09 (t, 2H, *J* = 7.5 Hz), 7.15 (d, 2H, *J* = 7.5 Hz), 7.20 (s, 1H); HRMS (FAB): anal. calcd for C₄₃H₄₆NO₈SSi: 764.2713 [M + H]⁺; found 764.2716.

*m*CPBA (80% purity, 2.8 mg, 13 μmol) was added to a solution of the above product (9.0 mg) in CH₂Cl₂ (1.5 mL) at –70 °C. The reaction mixture was stirred at –70 °C for 1.5 h, and gradually warmed to –50 °C over a period of 30 min. Saturated aqueous Na₂S₂O₃ was added and purified further as described above for the preparation of **5a**; compound **26** (6.9 mg, 47% from **25**) was obtained as a separable 1:1 mixture of two diastereomers.

Less polar isomer; a pale yellow gum; IR (KBr): $\tilde{\nu}$ = 1740, 1709, 1629, 1605 cm⁻¹; ¹H NMR (270 MHz, CDCl₃): δ = 1.16 (s, 9H), 1.18 (s, 9H), 2.32–2.60 (m, 2H), 2.46 (s, 3H), 3.22–3.43 (m, 2H), 3.52 (brs, 3H), 3.54 (s, 3H), 4.00 (s, 3H), 4.01 (s, 3H), 6.93 (s, 1H), 6.96 (s, 1H), 7.26 (s, 1H), 7.34–7.44 (m, 3H), 7.74 (d, 2H, *J* = 7.5 Hz); ¹³C NMR (68 MHz, CDCl₃): δ = 21.1, 21.2, 23.7, 25.9, 26.0, 32.2, 35.9, 53.4, 56.3, 60.6, 62.8, 65.8, 103.9, 111.0, 112.9, 113.5, 117.0, 125.5, 128.3, 129.0, 134.0, 139.8, 143.2, 148.6, 149.8, 151.2, 152.7, 154.6, 155.5, 158.9, 197.6.

More polar isomer; a pale yellow gum; IR (KBr): $\tilde{\nu}$ = 1742, 1709, 1630, 1605 cm⁻¹; ¹H NMR (270 MHz, CDCl₃): δ = 1.15 (s, 9H), 1.17 (s, 9H), 2.43 (s, 3H), 2.50–2.67 (m, 2H), 3.10 (s, 3H), 3.25–3.40 (m, 2H), 3.81 (brs, 3H), 3.97 (s, 3H), 4.05 (s, 3H), 6.90 (s, 1H), 6.99 (s, 1H), 7.22 (s, 1H), 7.28 (t, 1H, *J* = 7.5 Hz), 7.36 (d, 2H, *J* = 7.5 Hz), 7.60 (d, 2H, *J* = 7.5 Hz); ¹³C NMR (68 MHz, CDCl₃): δ = 20.8, 21.4, 23.6, 26.0, 31.5, 32.3, 36.0, 53.3, 56.2, 61.1, 61.9, 65.7, 103.3, 110.8, 112.8, 116.6, 116.9, 125.9, 128.0, 128.1, 128.9, 133.8, 138.5, 142.9, 144.7, 148.2, 149.8, 150.9, 152.1, 154.1, 155.0, 158.5, 197.4; HRMS (FAB): anal. calcd for C₄₃H₄₆NO₉SSi: 780.2663 [M + H]⁺; found 780.2665.

4-Chloroacetoxy-8,9-[di(*tert*-butyl)silylenedioxy]-1',5,6,9'-tetramethoxy-3'-methyl-6',7'-dihydrospiro[2H-benz[*f*]indene-2,8'-8H-cyclopent[*g*]isoquinoline]-1,3-dione (27): Similarly to the preparation of **8a**, **26** (46 mg, 60 μmol) was heated with anhydrous *p*-toluenesulfonic acid (1.0 mg, 6 μmol) and **7b** (0.039 mL, 25 μmol) in anhydrous toluene (2.0 mL) at 120 °C for 20 min. Similar workup and the purification by flash column chromatography (hexane/EtOAc 5:1) gave **27** (35 mg, 77%) as a pale yellow gum. IR (KBr): $\tilde{\nu}$ = 1792, 1736, 1707, 1630, 1605 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ = 1.13 (s, 9H), 1.17 (s, 9H), 2.47 (s, 3H), 2.48–2.59 (m, 2H), 3.31–3.58 (m, 2H), 3.52 (brs, 3H), 3.75 (s, 3H), 4.02 (s, 3H), 4.03 (s, 3H), 4.46 (ABq, 1H, *J* = 15.5 Hz), 4.51 (ABq, 1H, *J* = 15.5 Hz), 6.96 (s, 2H), 7.31 (s, 1H); ¹³C NMR (68 MHz, CDCl₃): δ = 21.1, 21.2, 23.7, 26.0, 26.1, 31.6, 32.4, 40.7, 53.5, 56.5, 62.1, 62.5, 66.1, 104.3, 119.3, 111.0, 113.0, 115.0, 117.3, 127.0, 127.1, 127.5, 138.9, 143.3, 148.7, 148.8, 149.7, 149.9, 151.4, 154.8, 158.8, 165.9, 198.1, 205.8; HRMS (FAB): anal. calcd for C₃₉H₄₃ClNO₁₀Si: 748.2344 [M + H]⁺; found 748.2344.

4-Chloroacetoxy-8,9-[di(*tert*-butyl)silylenedioxy]-5,6,9'-trimethoxy-3'-methyl-6',7'-dihydrospiro[2H-benz[*f*]indene-2,8'-8H-cyclopent[*g*]isoquinoline]-1,1'(2'H),3-trione (28): Under a nitrogen atmosphere, Et₃N (51 μL, 0.37 mmol), *t*Bu₂Si(OTf)₂ (68 μL, 0.19 mmol), and MeI (12 μL, 57 μmol) were added successively to a solution of **27** (14 mg, 19 μmol) in anhydrous DMF (1.0 mL). The reaction mixture was stirred at room temperature for 4 h and poured into water. The product was extracted with EtOAc (2 ×), and the combined organic layer was washed with brine, dried (Na₂SO₄), and concentrated in vacuo. Purification of the residue by flash column chromatography (hexane/EtOAc 1:2) gave **28** (14 mg, quant.) as a pale

yellow gum. IR (KBr): ν = 1790, 1736, 1707, 1646, 1619, 1605 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ = 1.13 (s, 9H), 1.16 (s, 9H), 2.26 (s, 3H), 2.47–2.59 (m, 2H), 3.26–3.41 (m, 2H), 3.59 (brs, 3H), 3.89 (s, 3H), 4.01 (s, 3H), 4.46 (ABq, 1H, J = 15.0 Hz), 4.51 (ABq, 1H, J = 15.0 Hz), 6.17 (s, 1H), 6.94 (s, 1H), 7.10 (s, 1H), 9.28 (brs, 1H); HRMS (FAB): anal. calcd for C₃₈H₄₁ClNO₁₀Si: 734.2188 [M + H]⁺; found 734.2195.

4-Chloroacetoxy-8,9-[di(*tert*-butyl)silylenedioxy]-3'-formyl-5,6,9'-trimethoxy-6',7'-dihydrospiro[2H-benz[*f*]indene-2,8'-8'*H*-cyclopent[*g*]isoquinoline]-1,1'(2*H*),3-trione (29): Under a nitrogen atmosphere, a mixture of **28** (14 mg, 19 μ mol) and SeO₂ (8.3 mg, 75 μ mol) in anhydrous dioxane (1.0 mL) was stirred under reflux for 1 h. After cooling, the reaction mixture was filtered through a Celite pad, and the filtrate was concentrated in vacuo. Purification of the residue by flash column chromatography (hexane/EtOAc 1:1) gave **29** (11 mg, 78 %) as a pale yellow gum. IR (KBr): ν = 1788, 1734, 1707, 1682, 1607 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ = 1.13 (s, 9H), 1.17 (s, 9H), 2.53–2.65 (m, 2H), 3.34–3.47 (m, 2H), 3.62 (brs, 3H), 3.89 (s, 3H), 4.02 (s, 3H), 4.46 (ABq, 1H, J = 15.5 Hz), 4.51 (ABq, 1H, J = 15.5 Hz), 6.96 (s, 1H), 7.03 (s, 1H), 7.41 (s, 1H), 8.68 (brs, 1H), 9.53 (s, 1H); HRMS (FAB): anal. calcd for C₃₈H₃₉ClNO₁₁Si: 748.1981 [M + H]⁺; found 748.1962.

4-Chloroacetoxy-8,9-[di(*tert*-butyl)silylenedioxy]-5,6,9'-trimethoxy-3'-(1,3-pentadienyl)-6',7'-dihydrospiro[2H-benz[*f*]indene-2,8'-8'*H*-cyclopent[*g*]isoquinoline]-1,1'(2*H*),3-trione (30): Under a nitrogen atmosphere, *n*BuLi (1.5 M solution in hexane, 0.17 mL, 0.25 mmol) was added to an ice-cooled suspension of crotyltriphenylphosphonium bromide (0.10 g, 0.25 mmol) in anhydrous THF (4 mL), and the reaction mixture was stirred at 0 °C for 1 h. The supernatant (0.26 mL) of this mixture was added to a solution of **29** (9.4 mg, 13 μ mol) in anhydrous THF (1 mL) at –78 °C. The reaction mixture was stirred at –78 °C for 30 min, warmed to room temperature, stirred at room temperature for 2 h, and poured into a solution of saturated aqueous NH₄Cl solution. The organic layer was separated, and the aqueous layer was extracted with CH₂Cl₂. The combined organic layer was washed with brine, dried (Na₂SO₄), and concentrated in vacuo. Purification of the residue by preparative TLC (hexane/EtOAc 2:3) gave **30** (a 5:1 mixture of *E,E*- and *E,Z*-isomers, 2.8 mg, 28 %) and unreacted **29** (6.3 mg, 67 %). **30**: pale yellow gum; IR (KBr): ν = 1790, 1738, 1709, 1646, 1607 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ = 1.13 (s, 9H), 1.16 (s, 9H), 1.84 (d, 5/2H, J = 7.0 Hz), 1.86 (dd, 1/2H, J = 7.0, 1.5 Hz), 2.48–2.61 (m, 2H), 3.27–3.42 (m, 2H), 3.60 (brs, 5/2H), 3.61 (brs, 1/2H), 3.85 (s, 3H), 4.02 (s, 3H), 4.46 (ABq, 1H, J = 15.5 Hz), 4.51 (ABq, 1H, J = 15.5 Hz), 5.75 (dq, 1/6H, J = 10.5, 7.0 Hz), 5.93 (dq, 5/6H, J = 15.0, 7.0 Hz), 6.08 (d, 5/6H, J = 16.0 Hz), 6.13–6.22 (m, 1H), 6.18 (d, 1/6H, J = 16.0 Hz), 6.29 (s, 5/6H), 6.34 (s, 1/6H), 6.53 (dd, 5/6H, J = 16.0, 10.5 Hz), 6.87 (dd, 1/6H, J = 16.0, 10.5 Hz), 6.94 (s, 1H), 7.15 (s, 5/6H), 7.17 (s, 1/6H), 8.33 (brs, 5/6H), 8.46 (brs, 1/6H); HRMS (FAB): anal. calcd for C₄₂H₄₅ClNO₁₀Si: 786.2501 [M + H]⁺; found 786.2491.

(±)-Fredericamycin A (1): Under a nitrogen atmosphere, BBr₃ (1.0 M solution in CH₂Cl₂, 0.10 mL, 0.10 mmol) was added to a solution of **30** (2.4 mg, 3.0 μ mol) in anhydrous CH₂Cl₂ (1.0 mL) at –78 °C. The reaction mixture was stirred at –78 °C for 1 h and gradually warmed to room temperature over a period of 1 h. Water (1.0 mL) and THF (5.0 mL) were added, and the reaction mixture was stirred in the air at room temperature for 18 h. The product was extracted with CH₂Cl₂ twice, and the combined organic layer was successively washed with saturated aqueous NaHCO₃ and brine, dried (Na₂SO₄), and concentrated in vacuo. Purification of the residue by preparative TLC (CHCl₃/MeOH/AcOH 90:10:1) gave a mixture of **1** and its *E,Z*-isomer. Further purification of this mixture by HPLC (JASCO Megapac SIL NH2–10, CHCl₃/MeOH/AcOH 800:200:1) gave **1** (1.0 mg, 52 %) as a red solid. This product was identical (¹H NMR, UV, HPLC, TLC) with an authentic sample of natural fredericamycin A by direct comparison.

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