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Asymmetric Total Synthesis of Fredericamycin A: An Intramolecular Cycloaddition Pathway

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Abstract: The asymmetric total synthesis of the potent antitumor antibiotic fredericamycin A ((*S*)-**1**) was achieved by the intramolecular [4+2] cycloaddition of the silylene-protected styrene derivative (*S*)-**7** followed by the aromatic Pummerer-type reaction of the sulfoxide (*S*)-**5**. Although we had already succeeded in the total synthesis of racemic **1** by the same approach, synthesis of its asymmetric version was more complicated than we had expected due to the difficulties involved in constructing the quaternary carbon center and the tendency of this center to undergo facile racemization. Racemization of this center during the installation of the acetylene moiety on the dione (*R*)-**8** was the most serious aspect. Systematic studies of its DE-ring analogue (*R*)-**25** revealed that racemization of the quaternary carbon center proceeded by a retro-aldol–aldol reaction of the initial adduct, (1*R*)-**39a**-Li, and that the degree of racemization was dependent on the reaction temperature. The racemization process could be completely depressed by keeping the reaction temperature at −78 °C. The construction of the stereogenic quaternary carbon center was achieved by the lipase-catalyzed desymmetrization of the prochiral 1,3-diol **9a** bearing the DEF-ring moiety. These studies enabled us to attain the asymmetric total synthesis of (*S*)-**1** while completely retaining the chiral integrity created by the enzymatic reactions.

Keywords: antitumor agents · asymmetric synthesis · enzymatic desymmetrization · intramolecular cycloaddition · Pummerer-type reaction · racemization

Introduction

Fredericamycin A (**1**) was isolated from a new strain of *Streptomyces griseus* at the Frederick Cancer Research Center in Frederick, MD, in 1981. It exhibits potent antitumor activity against several in vivo tumor models, such as P388 leukemia, B16 melanoma, and CD8F mammary, and does not show mutagenicity in the Ames test.[1,2] It has been suggested that the biological properties of **1** originate from its inhibition of RNA and protein syntheses, preferentially to DNA synthesis, and later studies have also demonstrated that **1** inhibits both topoisomerases I and II.[2d] Another important characteristic of **1** is its unique and complicated structure, which consists of two sets of *peri*-hydroxy tricyclic aromatic moieties connected through a stereogenic spiro quaternary carbon atom, which is made chiral by the presence of a single methoxy group at the farthest position on the A-ring. However, its absolute configuration could not be determined by either X-ray crystallography or spectroscopic studies (Figure 1).

Due to its prospective biological activities, the unusual spiro structure, and the difficulty in determining its absolute stereochemistry, numerous synthetic studies on the total syn-

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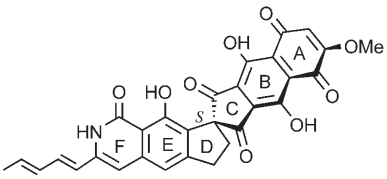


Figure 1. Structure of fredericamycin A (**1**).

thesis of **1** and its derivatives have been conducted. These studies have, thus far, resulted in five total syntheses of racemic **1**,[3–7] and the first synthesis of the optically pure natural **1**.[8,9] The last accomplishment by Boger's group in this area required the optical resolution of a fully protected racemic compound by using a chiral HPLC column at the final stage, and therefore the absolute configuration of **1** was not determined by this group. The majority of these total syntheses, and the related model studies, involved the construction of the spiro C- or D-ring during the final stage of the synthesis; however, the lack of sufficient methods that can distinguish between the enantiotopic faces of the highly symmetrical ABC-plane has been the most probable obstacle in the application of these methods to asymmetric synthesis. To date, no group besides our own (vide infra),[10–13] has succeeded in the asymmetric construction of the optically active spiro system of **1**, and even the methods that could be potentially applicable to the asymmetric synthesis of **1** are few.[9h,14]

Boger and his colleagues reported that the L1210 cytotoxic activities of **1** and its enantiomer were similar, and that a racemic ABCDE-ring analogue was less potent.[8a] However, the biological activities of both enantiomers of partial structures or analogues of **1** has not been evaluated.

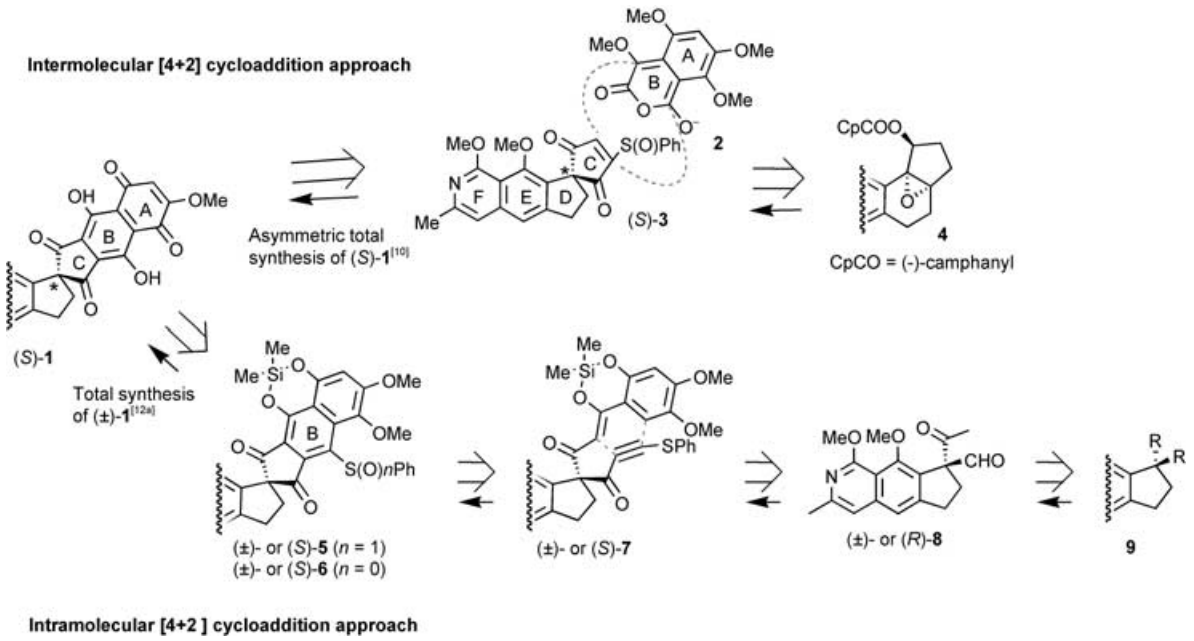
We have been investigating the asymmetric synthesis of **1** by two approaches as shown in Scheme 1, each of which features: 1) the preparation of a pivotal intermediate, early in the synthesis, containing the optically active quaternary carbon center with defined stereochemistry and 2) the completion of the total synthesis with retention of configuration. Another important subject in our studies was the development of effective protocols for the enantiodivergent synthesis of both enantiomers of **1** and its various analogues.

Recently, we achieved[10,11] the asymmetric total synthesis of natural **1**, by the regioselective intermolecular [4+2] cycloaddition[15,16] of the dienolate anion **2** (the AB-ring unit) to the optically pure CDEF-ring unit (*S*)-**3**, and thereby determined the absolute stereochemistry of the natural product as *S* for the first time. The stereogenic quaternary carbon center of (*S*)-**3** was created by the stereospecific rearrangement of the optically pure benzofuzed *trans*-epoxy acylate **4**.[17,18] A similar reaction of (*S*)-**3** with the regioisomer of **2**, which has a methoxy group at a different position on the A-ring, produced the enantiomer of natural **1**.

At the same time, we also completed the total synthesis of racemic **1** by the second route shown in Scheme 1.[12a] The key steps in this route include the intramolecular cycloaddition reaction[12b–e] of the silylene-protected styrene derivative (±)-**7** to construct the hexacyclic carbon framework found in (±)-**6**, and the aromatic Pummerer-type reaction[19] of the sulfoxide (±)-**5**, which acts to substitute the B-ring sulfinyl group with a hydroxyl group.

Provided we could prepare the pivotal dione intermediate (*R*)-**8** with a high optical purity, the latter route was believed to be the best route towards a asymmetric total synthesis of (*S*)-**1**. However, our challenge to make (*S*)-**1** presented a few significant problems; namely, the difficult construction of the quaternary carbon center of (*R*)-**8**, its facile racemization, and the difficulties involved in detecting this racemization.

After quite intensive studies, we have finally developed a useful method for the preparation of (*R*)-**8** by the lipase-catalyzed desymmetrization of a prochiral diol **9** (R = CH_2OH). We have also elucidated the racemization mechanism and discovered a means to prevent it. Thereby, the asymmetric

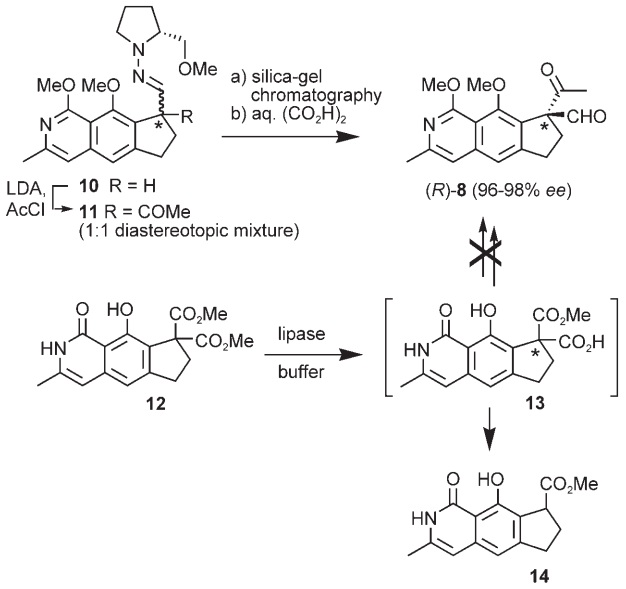


Scheme 1. Our two approaches for the asymmetric total syntheses of fredericamycin A (**1**).

total synthesis of natural **1** has been accomplished, and we describe here the full details of this synthesis.

Results and Discussion

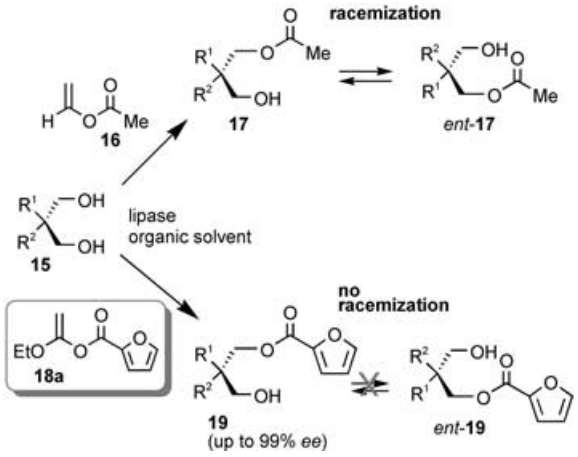
Preparation of the optically active dione intermediate (*R*)-8: To pursue the asymmetric total synthesis of **1** according to Scheme 1, the first objective of our group was to prepare the pivotal optically active dione (*R*)-**8**. Although we could obtain (*R*)-**8** with 96–98% *ee* by the separation of a 1:1 mixture of the two diastereomers of the RAMP-hydrazone **11** by column chromatography, prepared by the acetylation of the hydrazone **10**,[12a] the separation process was too laborious to produce a satisfactory amount of (*R*)-**8** (Scheme 2). Trials to improve the diastereoselectivity of the reaction of **10** to **11** were also fruitless.[20]



Scheme 2. Initial trials for the preparation of (*R*)-**8**.

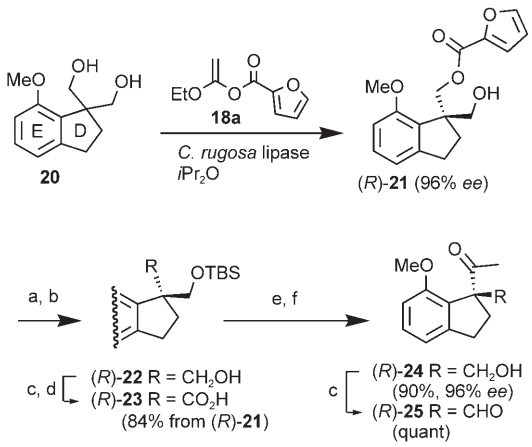
The hydrolase-catalyzed desymmetrization of the prochiral disubstituted malonates has been recognized as a powerful and environmentally conscious method for the production of optically active compounds with a stereogenic quaternary carbon center.[21,22] However, our studies on the desymmetrization of the diester **12**[12d] ended in the spontaneous decarboxylation of the monoester **13** to give only **14** (Scheme 2).

Therefore, our attention shifted to the lipase-catalyzed enantiotopic selective acylation of the prochiral 2,2-disubstituted propan-1,3-diol **9a** (R = CH_2OH) in organic solvents. Although the existing method using the most popular acyl donor, vinyl acetate **16**, has often suffered from the facile racemization of the products **17** by intramolecular acyl group migration,[23] we have recently developed a novel acyl donor, 1-ethoxyvinyl 2-furoate **18a**; this acyl donor provides products **19**, which have a greater degree of stability against racemization under various conditions (Scheme 3).[24] As a model study, we have applied this method to the diol **20**,



Scheme 3. Lipase-catalyzed desymmetrization of prochiral 1,3-diols **15**.

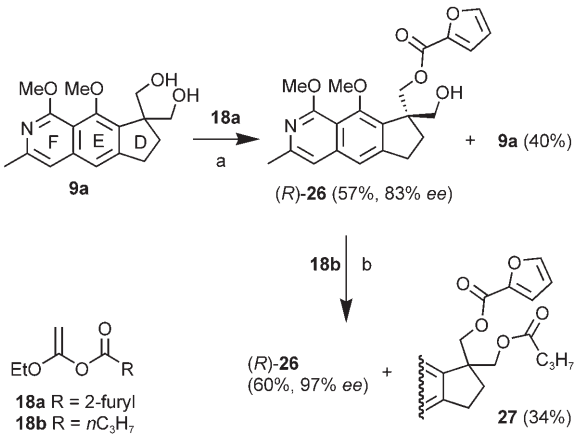
which contains the DE-ring moiety, to afford (*R*)-**21** with 96% *ee*.[24c] The conversion of (*R*)-**21** to the pivotal DE-ring dione intermediate (*R*)-**25** was achieved with a good overall yield (Scheme 4).[13]



Scheme 4. Preparation of (*R*)-**25** by the lipase-catalyzed desymmetrization of the prochical diol **20**. a) TBSCl, pyridine, DMF; b) K_2CO_3, MeOH; c) Dess–Martin periodinane, MeCN; d) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*BuOH/H_2O; e) $BF_3{\cdot}Et_2O$, CH_2Cl_2; f) MeLi, HMPA, THF.

With these promising results in hand, we intended to apply this desymmetrization protocol to the prochiral 1,3-diol **9a**,[25] followed by the conversion of the product to the pivotal dione intermediate (*S*)-**8**. However, the reaction conducted under similar conditions (*i*Pr_2O at 40 °C) was very sluggish due to the very poor solubility of **9a**, and provided the product with unsatisfactory enantioselectivity

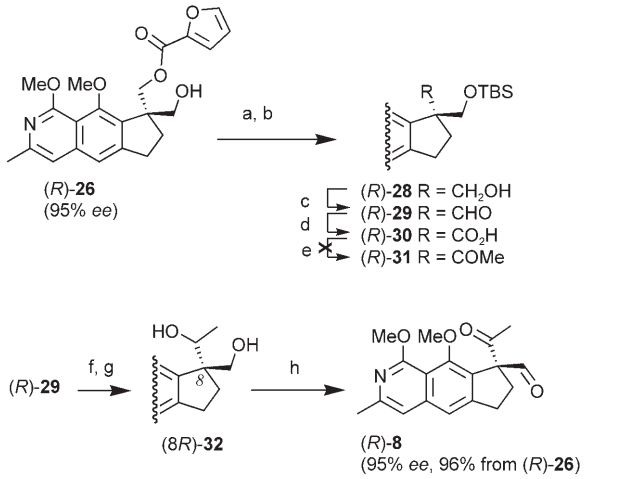
(43% *ee*).[26] The use of other less polar solvents, such as cyclohexane, heptane, toluene, and *t*BuOMe also resulted in slow reaction rates and moderate enantioselectivities (22–54% *ee*). Although polar solvents such as MeCN and THF were found to improve the solubility of **9a**, the enantioselectivities of these reactions were disappointing (up to 28% *ee*). We finally found that the use of a mixture of iPr_2O and MeCN produced better results. The enantioselectivity was affected by the ratio of these solvents, among which the use of a 10:1 mixture of iPr_2O and MeCN at 40°C for eight days provided the best optical purity of (*R*)-**26** (83% *ee*, 57% yield).[27] In this reaction, **9a** was recovered in 40% yield. The optical purity of (*R*)-**26** (83% *ee*) was further improved by its kinetic resolution with ethoxyvinyl butylate **18b** (Scheme 5) and *Pseudomonas aeruginosa* lipase



Scheme 5. Preparation of (*R*)-**26** by lipase-catalyzed reactions. a) **18a**, *Candida rugos*a lipase (Meito MY), iPr_2O/MeCN/H_2O (1000:100:1), 40°C; b) **18b**, *Pseudomonas aeruginosa* lipase (Toyobo-LIP), iPr_2O, 40°C.

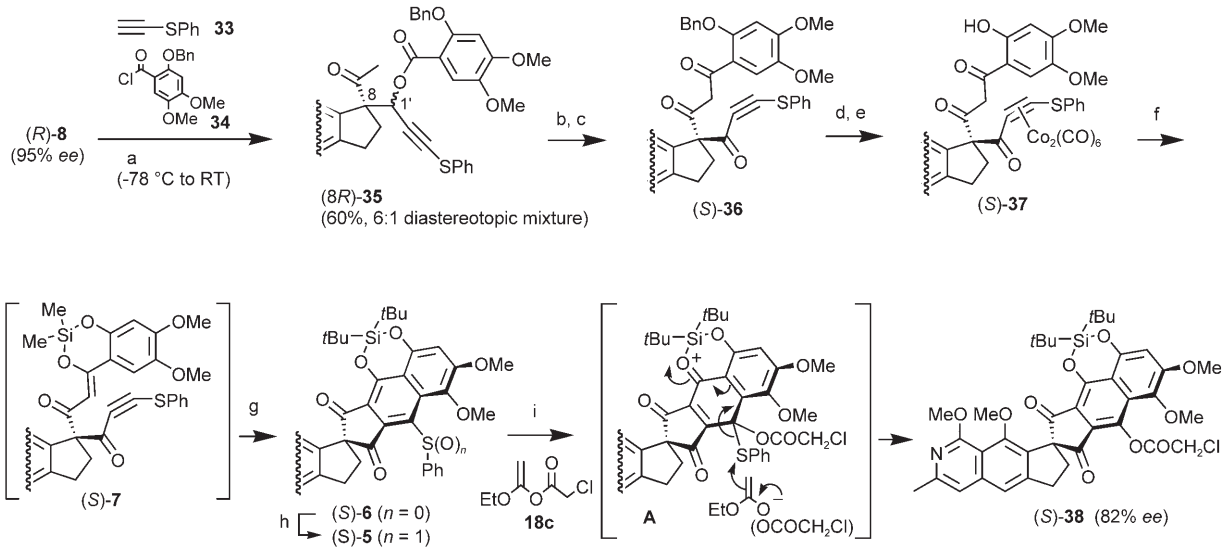
(Toyobo LIP). The latter reagent combination accelerated the enantioselective esterification of (*S*)-**26** to afford (*R*)-**26** (97% *ee*, 60% yield) and the diester **27** (34% yield). Quantitative recycling of **27** to **9a** by alkaline hydrolysis increased the yield of (*R*)-**26** (97% *ee*) to 86% (based on the consumed amount of **9a**), and the repeated experiment afforded a satisfactory amount of (*R*)-**26** with 95–97% *ee*. The absolute stereochemistry of **26** was tentatively assigned as *R* based on the structural similarity of **9a** to **20**; this was later confirmed (see, Figure 2 later and its explanation).

The derivatization of (*R*)-**26** (95% *ee*) to (*R*)-**8** (95% *ee*) was achieved in 96% overall yield with some modifications to the above-mentioned conversion of the DE-ring analogue (*R*)-**20**. These modifications were based on the following experimental results. Firstly, silylation of the hydroxyl group of (*R*)-**26** with organic bases, such as Et_3N and pyridine resulted in partial racemization of the product (about a 20% *ee* decrease) by intramolecular acyl-group migration, whereas the use of inorganic solid bases such as Na_2CO_3 completely suppressed the racemization. Secondly, as the conversion of the carboxylic acid (*R*)-**30** to the methyl ketone with MeLi did not proceed, we adopted an alternative method to produce (*R*)-**8**; this method involved the methylation of the aldehyde (*R*)-**29**, followed by the oxidation of the resultant diol (8*R*)-**32** (Scheme 6). The difference between the behavior of the DEF-ring compounds compared with the DE-ring analogues may be attributed to the significantly greater steric hindrance produced by the two methoxy groups on the E- and F-rings, relative to that produced by the single methoxy group of the DE-ring analogues.



Scheme 6. Preparation of (*R*)-**8** from (*R*)-**26**. a) TBSOTf, Na_2CO_3, THF; b) K_2CO_3, MeOH; c) Dess–Martin periodinane, MeCN; d) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*BuOH, H_2O; e) MeLi, THF/HMPA; f) MeLi, THF; g) Bu_4NF, THF; h) Swern oxidation.

Racemization of the quaternary carbon center and the solution to this problem: Next, we examined the conversion of (*R*)-**8** (95% *ee*) to the hexacyclic compound (*S*)-**38** by a series of transformations similar to the racemate synthesis (Scheme 7).[12a] Thus, (*R*)-**8**, the alkyne **33**, the acyl chloride **34**, and $LiN(TMS)_2$ were mixed in THF at −78°C, and the mixture was warmed to room temperature to give a 6:1 mixture of two diastereomers (8*R*)-**35**. This mixture was then treated with $LiN(TMS)_2$ (3 equiv) in THF to induce the acyl-group migration to the methyl ketone terminus, and the subsequent Moffatt oxidation of the alcohol afforded a single product, the trione (*S*)-**36**, which was converted to the cobalt complex (*S*)-**37**. The treatment of (*S*)-**37** with Me_2SiCl_2, Et_3N, and chloranil in refluxing toluene was one of the key steps in the direct construction of the hexacyclic skeleton (*S*)-**6**; the procedure involved the intramolecular [4+2] cycloaddition of the silylene derivative (*S*)-**7**, followed by oxidative aromatization.[12b–e] The application of our aromatic Pummerer-type reaction[19] to the sulfoxide (*S*)-**5** using 1-ethoxyvinyl chloroacetate **18c** replaced the B-ring sulfinyl group with the acyloxy group via the *O,S*-acetal intermediate **A**. However, the optical purity of the desired product (*S*)-**38** was reduced to 82% *ee* (determined by chiral HPLC analysis). We found it difficult to ascertain at which step in the synthesis racemization of the quaternary carbon center

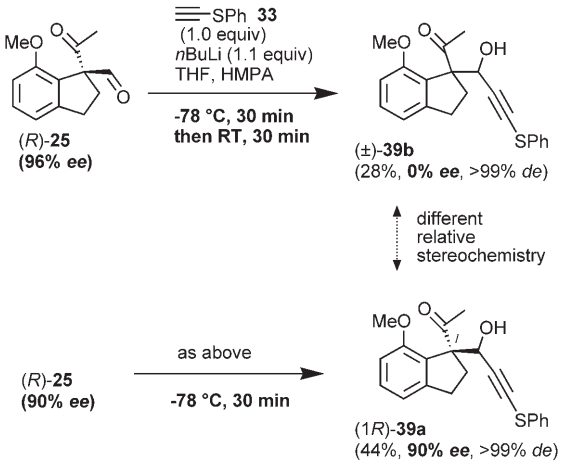


Scheme 7. First trials to convert (*R*)-**8** to (*S*)-**38**. a) **33** (1.0 equiv), **34** (4 equiv), LiN(TMS)$_2$ (2.0 equiv), THF; b) LiN(TMS)$_2$, (3 equiv), THF; c) Dess–Martin periodinane, MeCN; d) [$Co_2(CO)_8$], CH_2Cl_2; e) BCl_3, CH_2Cl_2; f) Me_2SiCl_2, Et_3N, chloranil, toluene; g) ($tBu)_2Si(OTf)_2$, Et_3N, DMF; h) *m*CPBA, CH_2Cl_2; i) **18c**, cat. *p*TsOH, toluene.

was occurring for the following two reasons. Firstly, we could not find an accurate method to determine the optical purity of the synthetic intermediates between (*R*)-**8** and (*S*)-**38**. Secondly, any racemization of the intermediate compounds was hard to detect as most of the intermediates only contain a single stereogenic carbon center.

A similar racemization process also occurred during our concurrent study towards the asymmetric synthesis of the ABCDE-ring analogue of **1** from the dione (*R*)-**25**.[13] Thus, the treatment of (*R*)-**25** (96% *ee*) with lithium phenylthioacetylide at −78 °C, followed by the warming of the resulting reaction mixture to room temperature, produced the adduct **39b** (28% yield) as the only identifiable product (Scheme 8). In this case, the optical purity of **39b** could be determined by HPLC analysis by using a chiral column. To our surprise, this compound had been produced with 0% *ee*. On the other hand, when we carried out the same reaction of (*R*)-**25** (90% *ee*) at −78 °C, followed by quenching at the same temperature after 30 min, the product (1*R*)-**39a**, expected to be a diastereomer of **39b**, was isolated without any loss of chiral integrity. Having been intrigued by these results, we investigated the effect of temperature on the degree of racemization and ratio of these two products in an attempt to clarify the racemization mechanism.

Thus, (*R*)-**25** (90% *ee*) was treated with lithium phenylthioacetylide at −78 °C for 30 min to ensure complete consumption of (*R*)-**25**; then the reaction mixture was warmed to the temperature indicated in Table 1 and stirred for a further 30 min before being quenched with an aqueous solution of NH_4Cl. The results of these experiments (Table 1) provided us with useful information about the relation of the quenching temperature to both the optical purity and the diastereoselectivity of the products: In the range from −60 to −20 °C, partial racemization and/or isomerization took place to give a mixture of (1*R*)-**39a**[28] and (1*R*)-**39b**[28] (entries 2–6). However, at higher temperatures, the ratio of **39a** to **39b** decreased with the decreasing optical purity of both **39a** and **39b**, and at 0 °C or above only **39b** was obtained as a racemate (entries 7 and 8). In addition, the treatment of **39a** (90% *ee*) with pyridine (1.2 equiv) in THF at room temperature overnight produced racemic **39b** as a single product [Eq. (1)].



Scheme 8. Model studies examining the installation of an ethynyl group on (*R*)-**25.**

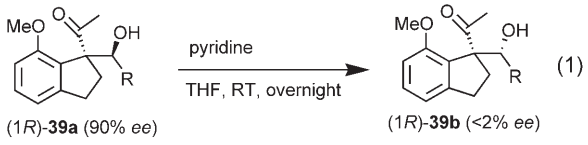
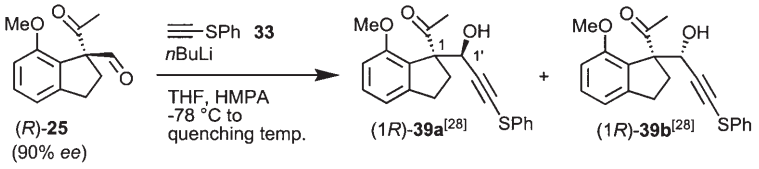


Table 1. The effect of temperature on the reaction of (*R*)-**25** with lithium phenylthioacetylide.

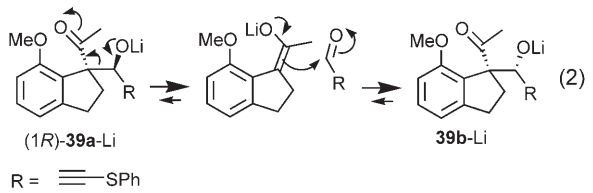


(*R*)-**25** (90% *ee*) (1*R*)-**39a**[28] (1*R*)-**39b**[28]

Entry	Quenching Temp. [°C][a]	(1*R*)-**39a** and (1*R*)-**39b** Ratio of **39a**/**39b**[b]	*ee* [%] of **39a**[c]	*ee* [%] of **39b**[c]	Total yield [%][b]
1	−78	>99/<1[d]	90	–	43
2	−60	≥96/≤4	90	–	44
3	−50	91/9	90	64	46
4	−40	83/17	90	51	46
5	−30	51/49	84	40	45
6	−20	14/86	37	29	42
7	0	<1/>99[d]	–	2	31
8	20	<1/>99[d]	–	0	32

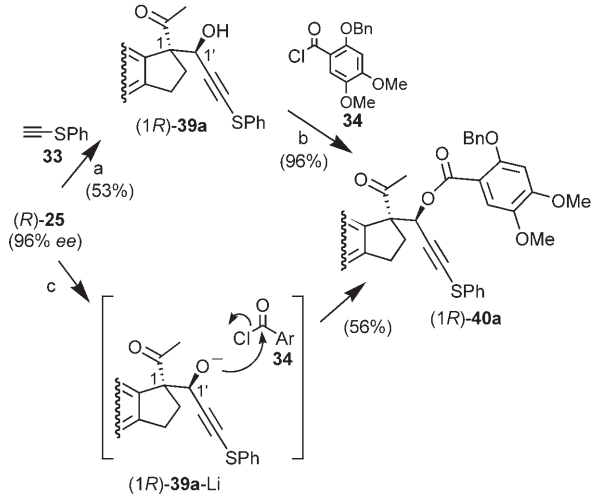
[a] After a mixture of (*R*)-**25** (90% *ee*), **33** (1.0 equiv), and *n*BuLi (1.1 equiv) was stirred at −78°C for 30 min, the reaction mixture was warmed to the given temperature, stirred for 30 min, and then quenched. [b] Based on the isolated yield of **39a**,**b** after silica-gel chromatography. [c] Determined by HPLC using a Daicel Chiralcel OJ column. [d] Formation of the isomer was not detected by ^{1}H NMR spectroscopy or by HPLC.

These results provided a plausible racemization mechanism [Eq. (2)]. According to this mechanism, **39a** was initially formed under kinetic control, and upon warming of the reaction mixture this compound gradually underwent isomerization to the thermodynamically more stable compound **39b**, with racemization occurring by the retro-aldol–aldol process.[29] Therefore, it was concluded that the reaction below −60°C inevitably produced the product with complete retention of absolute configuration.



In our previous communication, the ester (1*R*)-**40a** was obtained by the acylation of (1*R*)-**39a** (96% *ee*) with the A-ring acid chloride **34**.[13] Later we disclosed that by mixing (*R*)-**25** (96% *ee*), **33** (1 equiv), **34** (4 equiv), and LiN(TMS)$_2$ (2 equiv) together in THF/HMPA (HMPA = hexamethylphosphoramide), two reactions consecutively proceeded, even at −78°C, to directly produce (1*R*)-**40a** (56% yield) as a single diastereomer with perfect retention of absolute configuration (Scheme 9).[30]

The asymmetric total synthesis of natural 1: Based on the promising results obtained during the synthesis of the DE-ring analogues, we restarted our studies towards the asymmetric total synthesis of natural **1** (Scheme 10). Thus, (*R*)-**8** (95% *ee*) was treated with **33** (1.0 equiv), **34** (4 equiv), and LiN(TMS)$_2$ (2.0 equiv) in THF at −78°C for 1–1.5 h. Quenching the reaction mixture at the same temperature with an aqueous solution of NH_4Cl provided a separable mixture of (8*R*)-**35a**[28] and its diastereomer (8*R*)-**35b**.[28] This reaction was found to be reproducible, producing **35a** and **35b** in a ratio of 19–21:1. (8*R*)-**35a** and (8*R*)-**35b** were isolated in yields of 41–57% and 2–3%, respectively. Although we could not find any effective method to determine their optical purity, the major product (8*R*)-**35a** was expected to have maintained its chiral integrity, whereas the minor product (8*R*)-**35b** might have undergone some degree of racemization. Therefore, only (8*R*)-**35a**

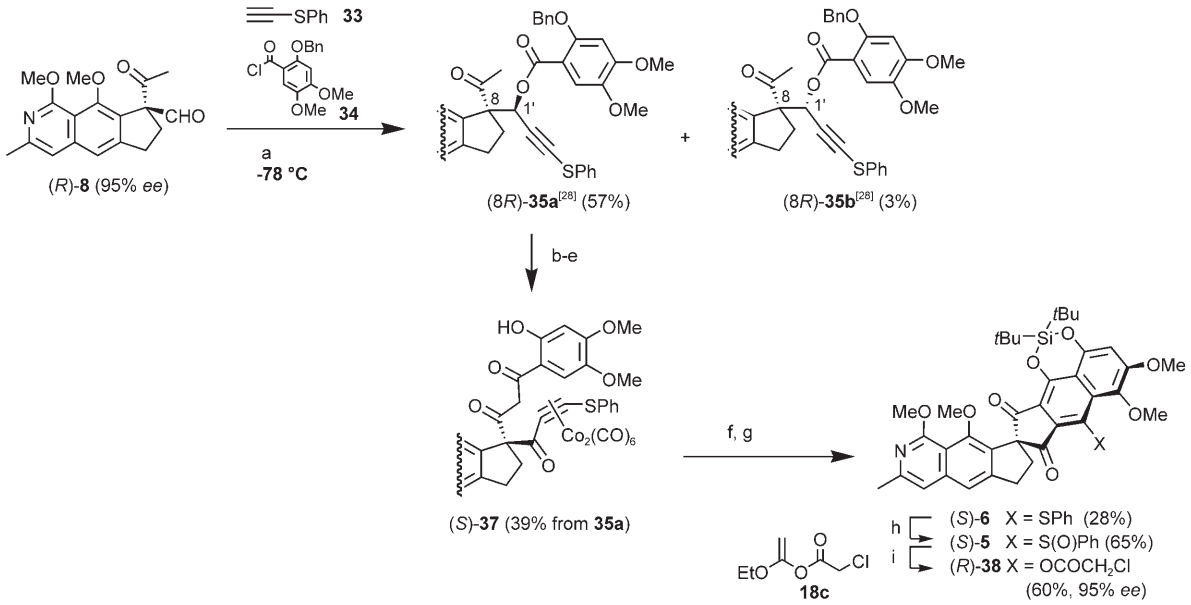


Scheme 9. One-pot preparation of (1*R*)-**40a** from (*R*)-**25**. a) **33** (1.0 equiv), *n*BuLi (1.1 equiv), HMPA/THF, −78°C; b) **34**, DMAP, CH_2Cl_2; c) **33** (1.0 equiv), **34** (4 equiv), LiN(TMS)$_2$ (2.0 equiv), THF, −78°C.

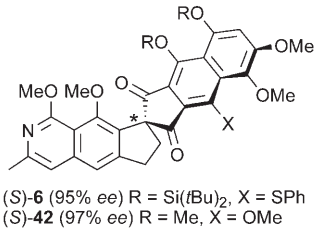
was subjected to the subsequent transformation to give the hexacyclic product (*R*)-**38**. The optical purity of (*R*)-**38** was determined to be 95% *ee*, and therefore, this proved that the chiral integrity of the intermediate compounds had been completely retained throughout the transformation steps.

The absolute stereochemistry of (*S*)-**6** was confirmed by the similarity of its CD spectrum to that of a known related compound (*S*)-**42**[10a] (Figure 2).

The final transformation of (*R*)-**38** to natural fredericamycin A (**1**) was achieved without any difficulty (Scheme 11). Thus, the demethylation of the F-ring of (*R*)-**38**, followed by oxidation afforded the aldehyde (*R*)-**44** in 91% yield. The Wittig reaction of (*R*)-**44** gave (*R*)-**45** as a ≥10:1 mixture of the *E,E*- and *E,Z*-side chain isomers; compound (*R*)-**45** was



Scheme 10. Improved conversion of (*R*)-**8** to (*R*)-**38**. a) **33** (1.0 equiv), **34** (4 equiv), $LiN(TMS)_2$ (2.0 equiv), THF, −78 °C; b) $LiN(TMS)_2$, (3 equiv), THF; c) Dess–Martin periodinane, MeCN; d) $[Co_2(CO)_8]$, CH_2Cl_2; e) BCl_3, CH_2Cl_2; f) Me_2SiCl_2, Et_3N, chloranil, toluene, 100 °C; g) $(tBu)_2Si(OTf)_2$, Et_3N, DMF; h) *m*CPBA, CH_2Cl_2; i) **18c**, cat. *p*TsOH, toluene.



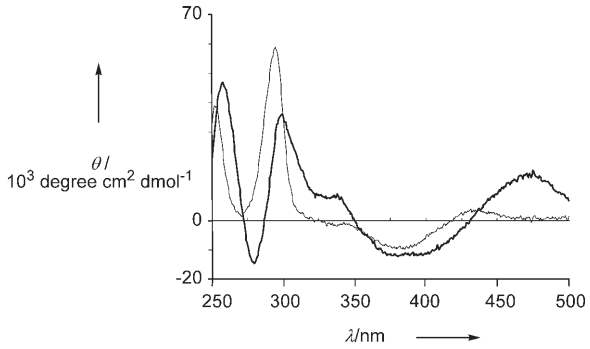
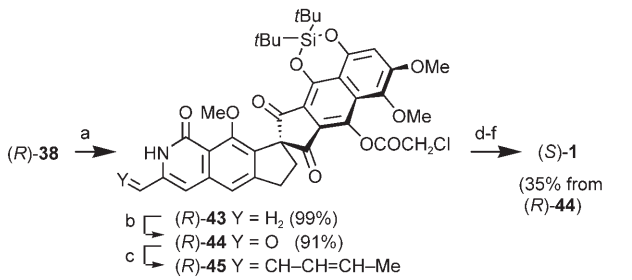


Figure 2. CD spectrum of (*S*)-**6** (thin line) and (*S*)-**42** (thick line) in *i*PrOH.

subjected to deprotection with BBr_3 followed by autoxidation to afford a mixture of (*S*)-**1** and its *E,Z*-isomers. Separation of the minor impurity by HPLC (Jasco Megapak SIL NH2–10, 1×25 cm, $CHCl_3$/hexane/acetic acid 800:200:1, flow rate 5 mL min^{-1})[10a] afforded pure (*S*)-**1** (35% yield from (*R*)-**44**). This product was identical in all respects (^{1}H NMR, IR, UV, and CD spectroscopy, m.p., HRMS, HPLC, and TLC) with the authentic natural fredericamycin A as well as the synthetic sample obtained by our intermolecular cyclization route.[10a]



Scheme 11. Completion of the asymmetric total synthesis of (*S*)-**1**. a) $(tBu)_2Si(OTf)_2$, Et_3N, MeI, DMF; b) SeO_2, dioxane; c) $(MeCH{=}CHCH_2)Ph_3P^+Br^-$, *n*BuLi, THF; d) BBr_3, CH_2Cl_2; e) air, THF/H_2O; f) HPLC separation.

Conclusion

We have demonstrated herein the synthetic utility of our intramolecular cycloaddition pathway as a method for the asymmetric total synthesis of natural **1**. This follows our previous report on the enantiodivergent synthesis of both enantiomers of the ABCDE-ring analogue by a similar intramolecular cycloaddition pathway.[13] This protocol features the following advantages: 1) the enantiodivergent preparation of either enantiomer can be achieved with perfect retention configuration and 2) this methodology is applicable to various analogues by changing the A-ring moiety[12a,e] or the DE(F)-ring diols, and provides an effective alternative to our intermolecular cycloaddition pathway.[10] It is worth noting that among the large number of synthetic studies towards the asymmetric total synthesis of natural **1** as well as its analogues,[9] successful examples have been limited to only our two routes (Scheme 1).

During this and our previous studies,[13,29] we have disclosed the latent risk of racemization of the stereogenic quaternary carbon center of the compounds, such as **39,** bearing an α,α-disubstituted β-hydroxycarbonyl moiety. The racemization took place under basic conditions by the retro-aldol–aldol process; however, these issues were solved by the choice of the proper reaction conditions. In the reported syntheses of racemic **1**[3,8] and its partial structures,[31] the base-initiated aldol reactions have often been employed to construct the spiro CD-ring system. Special caution will be a requisite for the application of these reactions to the asymmetric synthesis.

Experimental Section

General aspects: Melting points (m.p.) are not corrected. ^{1}H NMR spectra were measured at 270–500 MHz with either Me_4Si or $CHCl_3$ (δ = 7.26 ppm) as an internal standard. ^{13}C NMR spectra were measured at 67.8–150 MHz with $CDCl_3$ (δ = 77.0 ppm) as an internal standard. IR spectra were recorded by diffuse reflectance measurement of samples dispersed in KBr powder. Chiral HPLC analyses were carried out using Daicel CHIRALCEL OD (250 mm × 4.6 mm), CHIRALCEL OJ (250 mm × 4.6 mm), and CHIRALPAK AD (250 mm × 4.6 mm) columns with a hexane/*i*PrOH mixture as the eluent. Flash column chromatography was carried out using silica gel BW-300 (200–400 mesh, Fuji Silysia Chemicals (Japan)). Pressure glass reactors (Taiatsu Techno (Japan)) were used for the intramolecular [4+2] cycloaddition reactions. Starting materials: **18a**,[24c] **18b**,[24e] **18c**,[32] **33**,[33] **34**,[12a] and crotyltriphenylphosphonium bromide[34] were prepared according to the reported methods. The preparation of **9a** and the conversion of (*R*)-**25**–(1*R*)-**40a** are described in the Supporting Information. *Candida rugosa* lipase and *Pseudomonas aeruginosa* lipase were gifts from Meito Sangyo (Japan) and Toyobo (Japan), respectively, and were dried (1 mmHg, RT, overnight) prior to use. All other materials were commercially available. Yields refer to the isolated material with ≥95% purity as determined by ^{1}H NMR spectroscopic analysis, unless otherwise noted.

Lipase-catalyzed desymmetrization of 9a: A mixture of **9a** (0.30 g, 0.99 mmol), *Candida rugosa* lipase (Meito MY, 0.60 g), and **18a** (0.54 g, 2.97 mmol) was stirred in a mixture of *i*Pr$_2$O (20 mL), MeCN (2.0 mL), and H$_2$O (0.020 mL) at 40 °C for eight days. After this time, the reaction mixture was filtered through a Celite pad. Water (20 mL) was added to the resulting filtrate, which was stirred vigorously for a further 2 h. The product was then extracted with EtOAc, and the combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. Purification of the residue by flash column chromatography (hexanes/EtOAc, 2:1→1:2) afforded both (*R*)-**26** (0.22 g, 57% yield) and **9a** (0.120 g, 40% yield). The optical purity of (*R*)-**26** was determined to be 83% *ee* by chiral HPLC analysis (Daicel CHIRALCEL OD-H, hexanes/*i*PrOH 98:2, flow rate 1.0 mL min^{-1}, 38 °C). Retention time: 43.7 min for (*S*)-**26** and 46.9 min for (*R*)-**26**.

Kinetic resolution of (*R*)-26 (83% *ee*): A mixture of (*R*)-**26** (83% *ee*, 0.22 g, 0.56 mmol), *Pseudomonas aeruginosa* lipase (Toyobo LIP, 0.45 g), and **18b** (0.54 g, 3.4 mmol) was stirred in *i*Pr$_2$O (23 mL) at 40 °C for 6 h. After this time, the reaction mixture was filtered through a Celite pad, and water (20 mL) was added to the resulting filtrate, which was stirred vigorously for a further 2 h. The product was then extracted with EtOAc, and the combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. Purification of the residue by flash column chromatography (hexanes/EtOAc 2:1) afforded both (*R*)-**26** (97% *ee*, 134 mg, 60% yield) and **27** (96 mg, 34% yield) as colorless oils.

(*R*)-8-(2-Furoyloxy)methyl-8-hydroxymethyl-1,9-dimethoxy-3-methyl-6,7-dihydro-8*H*-cyclopenta[*g*]isoquinoline ((*R*)-26): $[\alpha]_D^{25} = -152$ (c = 0.50 in $CHCl_3$) for 97% *ee*; IR (KBr): $\tilde{\nu}$ = 3600–3200, 1720, 1628, 1612, 1566 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.06–2.18 (m, 1H), 2.21–2.30 (m, 1H), 2.50 (s, 3H), 2.94–3.18 (m, 3H), 3.94 (s, 3H), 3.98–4.00 (m, 1H), 4.14 (s, 3H), 4.61 (d, J = 11.0 Hz, 1H), 4.74 (d, J = 11.0 Hz, 1H), 6.49 (dd, J = 1.5, 3.5 Hz, 1H), 6.96 (s, 1H), 7.10 (dd, J = 0.5, 3.5 Hz, 1H), 7.26 (s, 1H), 7.57 ppm (dd, J = 0.5, 1.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.7, 30.2, 32.3, 53.7, 55.2, 63.9, 67.1, 67.4, 111.1, 111.8, 112.7, 117.6, 118.0, 133.2, 142.8, 144.4, 146.4, 148.9, 149.7, 154.3, 158.7, 158.8 ppm; HRMS (FAB): m/z: calcd for $C_{22}H_{23}NO_6$: 398.1604 $[M+H]^+$; found: 398.1598.

8-Butyryloxymethyl-8-(2-furoyloxy)methyl-1,9-dimethoxy-3-methyl-6,7-dihydro-8*H*-cyclopenta[*g*]isoquinoline (27): IR (KBr): $\tilde{\nu}$ = 1732, 1628, 1612, 1566 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.80 (t, J = 7.5 Hz, 3H), 1.50 (q, J = 7.5 Hz, 2H), 2.13–2.21 (m, 2H), 2.16 (t, J = 7.5 Hz, 2H), 2.42 (s, 3H), 2.98–3.03 (m, 2H), 3.81 (s, 3H), 4.06 (s, 3H), 4.41 (d, J = 11.0 Hz, 1H), 4.54 (d, J = 11.0 Hz, 1H), 4.57 (d, J = 11.0 Hz, 1H), 4.73 (d, J = 11.0 Hz, 1H), 6.38 (dd, J = 1.5, 3.5 Hz, 1H), 6.88 (s, 1H), 6.97 (d, J = 3.5 Hz, 1H), 7.17 (s, 1H), 7.47 ppm (br s, 1H); ^{13}C NMR (68 MHz, $CDCl_3$): δ = 13.7, 18.4, 23.7, 30.5, 32.6, 36.2, 53.0, 53.7, 63.5, 67.4, 68.0, 111.2, 111.7, 112.7, 117.0, 117.9, 132.0, 142.7, 144.3, 146.3, 148.6, 149.2, 154.7, 158.4, 158.8, 173.4 ppm; HRMS (FAB): m/z: calcd for $C_{26}H_{30}NO_7$: 468.2022 $[M+H]^+$; found: 468.2003.

Hydrolysis of 27: A mixture of **27** (96 mg), KOH (2 N, 0.13 mL), MeOH (1.3 mL), and CH_2Cl_2 (0.80 mL) was stirred at 0 °C for 5 h. After this time, the reaction mixture was quenched with saturated aqueous NH_4Cl, and the product extracted with EtOAc. The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. Purification of the residue by flash column chromatography (hexanes/EtOAc 1:1→EtOAc) provided **9a** (61 mg, 98% yield).

(*R*)-8-(*tert*-Butyldimethylsilyloxy)methyl-8-hydroxymethyl-1,9-dimethoxy-3-methyl-6,7-dihydro-8*H*-cyclopenta[*g*]isoquinoline ((*R*)-28): Under a nitrogen atmosphere, Na_2CO_3 (130 mg, 1.25 mmol) and TBSOTf (*tert*-butyldimethylsilyl triflate, 0.30 mL, 1.25 mmol) were added to a solution of (*R*)-**26** (95% *ee*, 100 mg, 0.25 mmol) in anhydrous THF (13 mL), and the reaction mixture was stirred for 20 min. After this time, iced water was added, and the product was extracted with diethyl ether. The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was roughly purified by filtration through a short pad of silica gel (hexanes/EtOAc 3:1) to give (*R*)-8-(*tert*-butyldimethylsilyloxy)methyl-8-(2-furoyloxy)methyl-1,9-dimethoxy-3-methyl-6,7-dihydro-8*H*-cyclopenta[*g*]isoquinoline as a colorless oil. Although this product contained a small amount of TBSOH (*tert*-butyldimethylsilyl alcohol), it was used for the following reaction without further purification. A sample of the pure material was obtained by preparative TLC (hexanes/EtOAc 3:1). IR (KBr): $\tilde{\nu}$ = 1730, 1628, 1612, 1566 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = −0.03 (s, 3H), 0.03 (s, 3H), 0.84 (s, 9H), 2.18–2.27 (m, 1H), 2.31–2.41 (m, 1H), 2.49 (s, 3H), 3.02–3.07 (m, 2H), 3.74 (d, J = 9.5 Hz, 1H), 3.87 (s, 3H), 4.13 (s, 3H), 4.17 (d, J = 9.5 Hz, 1H), 4.72 (d, J = 11.0 Hz, 1H), 4.82 (d, J = 11.0 Hz, 1H), 6.40–6.41 (m, 1H), 6.93 (d, J = 3.0 Hz, 1H), 6.94 (s, 1H), 7.22 (s, 1H), 7.51 ppm (d, J = 1.0 Hz, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$): δ = −5.6, −5.5, 18.2, 23.6, 25.8, 30.7, 32.2, 53.7, 55.3, 63.3, 66.7, 69.0, 111.3, 111.6, 112.8, 116.9, 117.6, 133.4, 142.6, 144.6, 146.2, 148.3, 150.2, 154.5, 158.8, 158.9 ppm; HRMS (FAB): m/z: calcd for $C_{28}H_{38}NO_6Si$: 512.2468 $[M+H]^+$; found: 512.2471.

Potassium carbonate (70 mg, 0.50 mmol) was added to a solution of the above crude product in MeOH (13 mL), and the reaction mixture was stirred at RT for 3 h. After this time, the reaction mixture was concentrated in vacuo, and then purified by flash column chromatography (hexanes/EtOAc, 5:1) to afford (*R*)-**28** (105 mg, quant from (*R*)-**26**) as a colorless oil. $[\alpha]_D^{30} = +45.6$ (c = 0.88 in $CHCl_3$); IR (KBr): $\tilde{\nu}$ = 3600–3200, 1628, 1612, 1564 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$): δ = 0.02 (s, 3H), 0.06 (s, 3H), 0.87 (s, 9H), 2.16–2.33 (m, 2H), 2.45 (s, 3H), 2.95–3.00 (m, 2H), 3.43 (br s, 1H), 3.67 (d, J = 9.5 Hz, 1H), 3.76–3.85 (m, 1H), 3.84 (s, 3H), 4.10 (s, 3H), 4.21 (d, J = 10.5 Hz, 1H), 4.26 (d, J = 9.5 Hz, 1H), 6.87 (s, 1H), 7.16 ppm (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = −5.7, −5.6, 18.0, 23.5, 25.7, 30.1, 31.4, 53.5, 56.5, 63.6, 68.1, 68.3, 110.9, 112.5, 117.1, 133.9, 142.4, 148.2, 149.7, 153.8, 158.4 ppm; HRMS (FAB): m/z: calcd for $C_{23}H_{36}NO_4Si$: 418.2413 $[M+H]^+$; found: 418.2422.

(*R*)-8-(*tert*-Butyldimethylsilyloxy)methyl-8-formyl-1,9-dimethoxy-3-methyl-6,7-dihydro-8*H*-cyclopenta[*g*]isoquinoline ((*R*)-29): Under a ni-

trogen atmosphere, Dess–Martin periodinane (0.40 g, 0.96 mmol) was added to an ice-cooled solution of (*R*)-**28** (195 mg, 0.47 mmol) in MeCN (10 mL), and the mixture was stirred at RT for 4 h. After this time, saturated aqueous $Na_2S_2O_3$ was added at 0 °C, and the product was extracted with EtOAc. The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. Purification of the residue by flash column chromatography (hexanes/EtOAc 5:1) produced (*R*)-**29** (192 mg, 99 % yield) as a colorless oil. $[\alpha]_D^{30} = -22.2$ ($c = 1.1$ in $CHCl_3$); IR (KBr): $\nu = 1726$, 1628, 1612, 1568 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$): $\delta = -0.02$ (s, 3H), 0.04 (s, 3H), 0.83 (s, 9H), 2.23–2.31 (m, 1H), 2.48 (s, 3H), 2.48–2.59 (m, 1H), 3.04–3.13 (m, 2H), 3.75 (d, $J = 10.0$ Hz, 1H), 3.80 (s, 3H), 4.12 (s, 3H), 4.52 (d, $J = 10.0$ Hz, 1H), 6.93 (s, 1H), 7.21 (s, 1H), 10.00 ppm (s, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$): $\delta = -5.5$, −5.4, 18.2, 23.7, 25.8, 30.0, 31.0, 53.7, 63.5, 64.7, 65.0, 110.9, 112.7, 117.2, 132.5, 142.9, 148.8, 149.4, 153.5, 158.6, 202.2 ppm; HRMS (FAB): *m/z*: calcd for $C_{23}H_{34}NO_4Si$: 416.2257 $[M+H]^+$; found: 416.2273.

(8*R*)-8-(1-Hydroxyethyl)-8-hydroxymethyl-1,9-dimethoxy-3-methyl-6,7-dihydro-8*H*-cyclopenta[*g*]isoquinoline ((8*R*)-32): Under a nitrogen atmosphere, MeLi (1.0 M in Et_2O, 1.0 mL, 1.0 mmol) was added to a solution of (*R*)-**29** (0.22 g, 0.52 mmol) in anhydrous THF (15 mL) at −78 °C, and the reaction mixture was stirred at −78 °C for 1.5 h. After this time, saturated aqueous NH_4Cl was added at −78 °C, and the reaction mixture was warmed to RT with vigorous stirring. The product was then extracted with EtOAc, and the combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. Purification of the residue by flash column chromatography (hexanes/EtOAc 4:1) produced (8*R*)-8-(*tert*-butyldimethylsilyloxy)methyl-8-(1-hydroxyethyl)-1,9-dimethoxy-3-methyl-6,7-dihydro-8*H*-cyclopenta[*g*]isoquinoline (0.22 g, 96 % yield) as a colorless oil and as a 1:1 mixture of two diastereomers. $[\alpha]_D^{30} = +62.6$ ($c = 1.0$ in $CHCl_3$); IR (KBr): $\tilde{\nu} = 3600$–3200, 1626, 1612, 1562 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$): $\delta = -0.04$ (s, 3/2H), 0.03 (s, 3/2H), 0.06 (s, 3/2H), 0.10 (s, 3/2H), 0.80 (s, 9/2H), 0.90 (s, 9/2H), 0.93 (d, $J = 6.5$ Hz, 3/2H), 1.10 (d, $J = 6.5$ Hz, 3/2H), 2.03–2.22 (m, 2H), 2.46 (s, 3H), 2.93–3.05 (m, 2H), 3.28 (br d, $J = 6.5$ Hz, 1/2H), 3.66 (d, $J = 9.5$ Hz, 1/2H), 3.82–3.88 (m, 1/2H), 3.85 (s, 3/2H), 3.89 (s, 3/2H), 4.10 (s, 3/2H), 4.11 (s, 3/2H), 4.07–4.15 (m, 1H), 4.49–4.52 (m, 1H), 4.79 (q, $J = 6.5$ Hz, 1/2H), 6.90 (s, 1H), 7.18 ppm (s, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$): $\delta = -5.7$, −5.6, −5.5, 18.0, 18.1, 18.7, 19.2, 23.6, 25.7, 26.8, 30.7, 30.9, 31.4, 53.5, 53.6, 58.9, 61.2, 63.3, 63.4, 67.4, 70.8, 71.0, 73.3, 110.8, 111.0, 112.5, 117.0, 117.1, 133.7, 134.3, 142.2, 142.3, 148.0, 148.2, 149.3, 150.8, 153.3, 153.8, 158.49, 158.50 ppm; HRMS (FAB): *m/z*: calcd for $C_{24}H_{38}NO_4Si$: 432.2570 $[M+H]^+$; found: 432.2569.

Under a nitrogen atmosphere, Bu_4NF (1.0 M in THF, 1.3 mL, 1.3 mmol) was added to a solution of the above product (0.22 g, 0.50 mmol) in anhydrous THF (15 mL) at −78 °C, and the reaction mixture was stirred at −78 °C for 10 min. After this time, the reaction mixture was gradually warmed to RT. Water was then added and the product was extracted with EtOAc. The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. Purification of the residue by flash column chromatography (hexanes/EtOAc 1:1) produced (8*R*)-**32** (160 mg, quant) as colorless oil and as a 1:1 mixture of two diastereomers. $[\alpha]_D^{24} = +18.8$ ($c = 1.0$ in $CHCl_3$); IR (KBr): $\tilde{\nu} = 3700$–3100, 1626, 1562 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$): $\delta = 1.02$ (d, $J = 6.5$ Hz, 3/2H), 1.14 (d, $J = 6.5$ Hz, 3/2H), 1.91–2.04 (m, 1H), 2.12–2.22 (m, 1/2H), 2.32–2.43 (m, 1/2H), 2.49 (s, 3H), 2.99–3.06 (m, 2H), 3.73 (d, $J = 11.0$ Hz, 1/2H), 3.80 (d, $J = 11.0$ Hz, 1/2H), 3.89 (s, 3/2H), 3.95 (s, 3/2H), 4.05 (d, $J = 11.0$ Hz, 1/2H), 4.14 (s, 3H), 4.14–4.23 (m, 1/2H), 4.17 (d, $J = 11.0$ Hz, 1/2H), 4.70 (q, $J = 6.5$ Hz, 1/2H), 6.94 (s, 1H), 7.22 (s, 1/2H), 7.24 ppm (s, 1/2H); ^{13}C NMR (67.8 MHz, $CDCl_3$): $\delta = 18.5$, 18.8, 23.6, 27.6, 29.7, 30.3, 31.1, 36.6, 53.69, 53.72, 59.2, 60.7, 63.66, 63.70, 66.9, 69.6, 70.8, 71.8, 110.7, 110.8, 112.49, 112.51, 117.4, 117.5, 132.9, 135.2, 142.3, 142.4, 148.3, 148.5, 149.4, 150.3, 153.48, 153.5, 158.42, 158.44 ppm; HRMS (FAB): *m/z*: calcd for $C_{18}H_{24}NO_4$: 318.1705 $[M+H]^+$; found: 318.1689.

(*R*)-8-Acetyl-8-formyl-1,9-dimethoxy-3-methyl-6,7-dihydro-8*H*-cyclopenta[*g*]isoquinoline ((*R*)-8): Under a nitrogen atmosphere, DMSO (0.94 mL, 11.8 mmol) was added to a solution of oxalyl chloride (0.56 mL, 5.9 mmol) in anhydrous CH_2Cl_2 (3.0 mL), and the reaction mixture was stirred at −78 °C for 1 h. After this time, a solution of (*R*)-**32** (160 mg, 0.49 mmol) in anhydrous CH_2Cl_2 (3.0 mL) was added at −78 °C, and the reaction mixture was stirred for 2 h. Finally, Et_3N (2.8 mL, 17.6 mmol) was added at −78 °C, and the reaction mixture was warmed to RT and stirred for a further 45 min. The reaction mixture was then quenched with saturated aqueous NH_4Cl, and the product was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. Purification of the residue by flash column chromatography (hexanes/EtOAc 4:1) produced (*R*)-**8** (152 mg, quant) as a colorless oil. The optical purity of this product was determined to be 95 % *ee* by chiral HPLC analysis (Daicel CHIRALPAK AD-H, hexanes/*i*PrOH 99:1, flow rate 0.8 mL min^{-1}, 25 °C). Retention time: 15.3 min for (*R*)-**8** and 21.8 min for (*S*)-**8**. $[\alpha]_D^{26} = +303$ ($c = 1.0$ in $CHCl_3$); IR (KBr): $\tilde{\nu} = 1726$, 1701, 1628, 1570 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 2.20$ (s, 3H), 2.33 (ddd, $J = 5.0$, 8.5, 13.0 Hz, 1H), 2.50 (s, 3H), 2.75 (ddd, $J = 6.0$, 7.0, 13.0 Hz, 1H), 3.06–3.19 (m, 2H), 3.85 (s, 3H), 4.13 (s, 3H), 6.96 (s, 1H), 7.28 (s, 1H), 10.04 ppm (s, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$): $\delta = 23.7$, 26.7, 30.9, 31.6, 53.7, 63.7, 74.2, 111.0, 112.7, 117.5, 130.1, 143.4, 148.3, 149.5, 154.0, 158.7, 197.1, 206.7 ppm; HRMS (FAB): *m/z*: calcd for $C_{18}H_{20}NO_4$: 314.1392 $[M+H]^+$; found: 314.1397.

(8*R*)-1-(8-Acetyl-1,9-dimethoxy-3-methyl-6,7-dihydro-8*H*-cyclopenta[*g*]-isoquinolin-8-yl)-3-phenylthio-2-propynyl-2-benzyloxy-4,5-dimethoxybenzoate ((8*R*)-35a) and its diastereomer ((8*R*)-35b): Under a nitrogen atmosphere, lithium bis(trimethylsilyl)amide (1.0 M in THF, 0.60 mL, 0.60 mmol) was added at −78 °C to a solution of (*R*)-**8** (95 mg, 0.30 mmol), **33** (1.0 M in THF, 0.30 mL, 0.30 mmol), and **34** (prepared in situ from 2-benzyloxy-4,5-dimethoxybenzoic acid (0.34 g, 1.2 mmol)) in anhydrous THF (3.0 mL). The reaction mixture was stirred at −78 °C for 1.5 h, and then quenched by the addition of saturated aqueous NH_4Cl. This solution was warmed to RT with vigorous stirring, and the product was extracted with EtOAc. The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. Purification of the residue by flash column chromatography (hexanes/EtOAc 3:1→benzene/diethyl ether 9:1) produced both (8*R*)-**35a** (124 mg, 57 % yield) and (8*R*)-**35b** (6 mg, 3 % yield) as pale yellow gums.

(8*R*)-**35a** (less polar): $[\alpha]_D^{25} = +173$ ($c = 1.0$ in $CHCl_3$); IR (KBr): $\tilde{\nu} = 2183$, 1727, 1711, 1626, 1611, 1566 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$): $\delta = 2.19$ (s, 3H), 2.45 (s, 3H), 2.57 (ddd, $J = 7.0$, 9.0, 14.0 Hz, 1H), 2.85 (ddd, $J = 5.0$, 9.0, 14.0 Hz, 1H,), 3.15 (ddd, $J = 5.0$, 9.0, 14.5 Hz, 1H), 3.34 (ddd, $J = 7.0$, 9.0, 14.5 Hz, 1H), 3.56 (s, 3H), 3.73 (s, 3H), 3.83 (s, 3H), 4.06 (s, 3H), 4.91 (d, $J = 12.5$ Hz, 1H), 4.97 (d, $J = 12.5$ Hz, 1H), 6.35 (s, 1H), 6.71 (s, 1H), 6.78 (s, 1H), 6.85 (s, 1H), 7.14–7.19 (m, 2H), 7.23–7.35 (m, 7H), 7.40–7.45 ppm (m, 2H); ^{13}C NMR (67.8 MHz, $CDCl_3$): $\delta = 23.7$, 26.4, 31.9, 32.2, 53.7, 55.9, 56.0, 63.3, 67.9, 68.2, 72.1, 73.0, 77.2, 96.2, 100.1, 111.0, 111.3, 112.4, 113.3, 116.8, 126.1, 126.3, 127.0, 127.6, 128.3, 129.1, 131.5, 132.4, 136.6, 142.5, 143.1, 149.1, 149.6, 153.0, 154.4, 154.5, 159.0, 163.5, 205.5 ppm; HRMS (FAB): *m/z*: calcd for $C_{42}H_{40}NO_8S$: 718.2474 $[M+H]^+$; found: 718.2444.

(8*R*)-**35b** (more polar): The IR, ^1H NMR, and ^{13}C NMR spectroscopic data of this product compared well with the data for racemic **35b**.[12a]

(*S*)-{1-[1,9-Dimethoxy-3-methyl-8-(3-phenylthio-2-propioloyl)-6,7-dihydro-8*H*-cyclopenta[*g*]isoquinolin-8-yl]-3-(2-hydroxy-4,5-dimethoxyphenyl)-1,3-propanedione}hexacarbonyldicobalt ((*S*)-37): Under a nitrogen atmosphere, lithium bis(trimethylsilyl)amide (1.0 M in THF, 0.51 mL, 0.51 mmol) was added to a solution of (8*R*)-**35a** (123 mg, 0.17 mmol) in anhydrous toluene (3.2 mL) at −40 °C, and the reaction mixture was stirred for 4 h. After this time, the reaction mixture was quenched by the addition of saturated aqueous NH_4Cl at −40 °C, and the product was extracted with EtOAc. The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. Purification of the residue by flash column chromatography (hexanes/EtOAc 2:1) produced (*R*)-3-(2-benzyloxy-4,5-dimethoxy)phenyl-1-[8-(1-hydroxy-3-phenylthio-2-propynyl)-1,9-dimethoxy-3-methyl-6,7-dihydro-8*H*-cyclopenta[*g*]isoquinolin-8-yl]-1,3-propanedione (123 mg, quant) as a pale yellow gum. $[\alpha]_D^{27} = -125$ ($c = 1.0$ in $CHCl_3$); IR (KBr): $\tilde{\nu} = 3500$–3300 (br), 2190–2170, 1611, 1566 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$): $\delta = 2.34$–2.45, (m, 2H), 2.49 (s, 3H), 2.85–3.05 (m, 2H), 3.79 (s, 3H), 3.85 (s, 3H), 3.89 (s, 3H), 4.04 (s, 3H), 4.87 (d, $J = 11.5$ Hz, 1H), 4.90 (d, $J = 11.5$ Hz, 1H), 5.02 (d, $J = 9.5$ Hz, 1H), 5.10 (d, $J = 9.5$ Hz, 1H), 6.41 (s, 1H), 6.66 (s, 1H), 6.78–6.85

(m, 2H), 6.80 (s, 1H), 6.82 (s, 1H), 6.92–7.01 (m, 1H), 6.93 (s, 1H), 7.18–7.24 (m, 3H), 7.30–7.36 (m, 3H), 7.49 (s, 1H), 16.32 ppm (s, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 23.7, 30.7, 36.5, 53.6, 56.0, 56.2, 63.1, 67.7, 68.3, 71.2, 71.7, 77.2, 98.1, 98.7, 99.5, 111.8, 111.7, 112.5, 114.7, 117.3, 125.3, 125.8, 127.2, 128.1, 128.47, 128.53, 131.9, 132.1, 135.9, 142.7, 143.0, 148.8, 149.8, 152.7, 153.5, 153.6, 158.7, 178.3, 198.2 ppm; HRMS (FAB): *m/z*: calcd for $C_{42}H_{40}NO_8S$: 718.2474 $[M+H]^+$; found: 718.2444.

Dess–Martin periodinane (31 mg, 0.074 mmol) was added to an ice-cooled solution of the above product (35 mg, 0.049 mmol) in MeCN (2.8 mL), and the reaction mixture was stirred for 2 h. After this time, additional Dess–Martin periodinane (10 mg, 0.025 mmol) was added, and the reaction mixture was stirred at RT for a further 1 h. The reaction mixture was then quenched by the addition of saturated aqueous $Na_2S_2O_3$ at 0 °C, and the product was extracted with EtOAc. The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated in vacuo to afford (*S*)-3-(2-benzyloxy-4,5-dimethoxyphenyl)-1-[1,9-dimethoxy-3-methyl-8-(3-phenylthio-2-propioloyl)-7,8-dihydro-6*H*-cyclopenta[*g*]isoquinolin-8-yl]-1,3-propanedione ((*S*)-**36**). Due to its instability, this product was used for the following reaction without further purification.

Under an argon atmosphere, octacarbonyldicobalt (21 mg, 0.054 mmol) was added to the above crude product in anhydrous CH_2Cl_2 (1.4 mL). The reaction mixture was stirred at RT for 10 min and then concentrated in vacuo. Purification of the crude residue was achieved by flash column chromatography (hexanes/EtOAc 2:1) to afford (*S*)-{3-(2-benzyloxy-4,5-dimethoxyphenyl)-1-[1,9-dimethoxy-3-methyl-8-(3-phenylthio-2-propioloyl)-6,7-dihydro-8*H*-cyclopenta[*g*]isoquinolin-8-yl]-1,3-propanedione}hexacarbonyldicobalt (37 mg). Although this product was not pure, it was used for the following reaction without further purification due to its instability.

Under an argon atmosphere, BCl_3 (0.10 M in CH_2Cl_2, 0.10 mL, 0.010 mmol) was added drop wise to an ice-cooled solution of the above product (13 mg) in CH_2Cl_2 (4.0 mL), and the reaction mixture was stirred at 0 °C for 5 min. BCl_3 (0.10 M in CH_2Cl_2, 0.20 mL, 0.020 mmol) was then added, and the reaction mixture was stirred at 0 °C for another 25 min. After this time, the reaction mixture was poured into a mixture of ice and water. The product was extracted with CH_2Cl_2, and the combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. Purification of the residue by flash column chromatography (hexanes/EtOAc 3:1) produced (*S*)-**37** as a dark green gum and as a mixture of keto and enol forms (6.0 mg, 39% yield from (8*R*)-**35a**). IR (KBr): $\tilde{\nu}$ = 2099, 2064, 2039, 1717, 1628, 1615 cm^{-1}; HRMS (FAB): *m/z*: calcd for $C_{35}H_{32}NO_8S$: 626.1849 $[M+H-Co_2(CO)_6]^+$; found: 626.1837. ^{1}H and ^{13}C NMR spectra were complicated due to the presence of tautomers. ^{1}H NMR (300 MHz, $CDCl_3$) for the major isomer: δ = 2.42–2.55 (m, 1H), 2.49 (s, 3H), 3.06–3.20 (m, 3H), 3.79 (s, 3H), 3.90 (s, 3H), 3.95 (s, 3H), 4.04 (s, 3H), 4.27 (d, *J* = 15.5 Hz, 1H,), 4.51 (d, *J* = 15.5 Hz, 1H), 6.41 (s, 1H), 6.96 (s, 1H), 7.31 (s, 1H), 7.35–7.50 (m, 5H), 7.58 (s, 1H), 12.40 ppm (s, 1H).

Some typical ^{1}H NMR (300 MHz, $CDCl_3$) data for minor isomers: δ = 2.03 (s, 3H), 3.62 (s, 3H), 3.89 (s, 3H), 6.27 (s, 1H), 6.72 (s, 1H), 12.03 (s, 1H), 15.61 ppm (s, 1H).

(*S*)-8,9-[Di(*tert*-butyl)silylenedioxy]-1′,5,6,9′-tetramethoxy-3′-methyl-4-phenylthio-6′,7′-dihydrospiro[2*H*-benz[*f*]indene-2,8′-[8′*H*]cyclopent[*g*]isoquinoline]-1,3-dione ((*S*)-6): Under a nitrogen atmosphere, Et_3N (0.017 mL, 0.12 mmol) and Me_2SiCl_2 (0.074 mL, 0.058 mmol) were added successively to a solution of (*S*)-**37** (14 mg, 0.015 mmol) in anhydrous toluene (2.0 mL). A pressure glass reactor was used, and the reaction mixture was stirred at RT for 30 min, after which time chloranil (15 mg, 0.062 mmol) was added. The reactor was then sealed and heated at 100 °C for 6 h. After cooling, the reaction mixture was concentrated in vacuo and the resulting residue dissolved in anhydrous DMF (1.2 mL). Et_3N (0.077 mL, 0.54 mmol) and $(t\mathrm{Bu})_2Si(OTf)_2$ (0.040 mL, 0.11 mmol) were then added, and the reaction mixture was stirred at RT for 5 h. After this time, iced water and saturated aqueous $NaHCO_3$ solution were added to the reaction mixture and the product was extracted with diethyl ether. The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. Purification of the residue by flash column chromatography ($CH_2Cl_2 \rightarrow CH_2Cl_2$/EtOAc 100:1) afforded (*S*)-**6** (3.3 mg, 28% yield) as a yellow gum. $[\alpha]_D^{20}$ = +14.9 (*c* = 1.2 in $CHCl_3$); CD (*c* = 1.3 × 10^{-5} mol L^{-1} in *i*PrOH) $[\theta]_{max}^{20}$ = +4.7 × 10^4 (258), −1.5 × 10^4 (280), +3.6 × 10^4 (300), −1.2 × 10^4 (381), +1.7 × 10^4 cm^2 dmol^{-1} (475 nm); IR (KBr): $\tilde{\nu}$ = 1730, 1703, 1630, 1603, 1571 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.15 (s, 9H), 1.19 (s, 9H), 1.93–2.03 (m, 1H), 2.32–2.38 (m, 1H), 2.45 (s, 3H), 3.08–3.16 (m, 1H), 3.19–3.27 (m, 1H), 3.44 (s, 3H), 3.94 (s, 3H), 4.00 (s, 3H), 4.01 (s, 3H), 6.90 (s, 1H), 6.93–6.97 (m, 1H), 6.95 (s, 1H), 7.09 (t, *J* = 7.5 Hz, 2H), 7.16 (d, *J* = 7.5 Hz, 2H), 7.20 ppm (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.2, 23.7, 26.1, 26.2, 32.2, 35.8, 53.3, 56.4, 61.6, 62.3, 66.1, 103.9, 111.1, 113.0, 113.8, 116.9, 120.5, 125.3, 128.5, 128.7, 134.3, 134.6, 140.9, 141.0, 143.1, 148.4, 150.0, 150.9, 151.1, 152.5, 155.3, 159.0, 198.3, 198.8 ppm; HRMS (FAB): *m/z*: calcd for $C_{43}H_{46}NO_8SSi$: 764.2714 $[M+H]^+$; found: 764.2715.

(*S*)-8,9-[Di(*tert*-butyl)silylenedioxy]-1′,5,6,9′-tetramethoxy-3′-methyl-4-phenylsulfinyl-6′,7′-dihydrospiro[2*H*-benz[*f*]indene-2,8′-[8′*H*]cyclopent[*g*]isoquinoline]-1,3-dione ((*S*)-5): *m*CPBA (*meta*-chloroperoxybenzoic acid, 80% purity, 1.7 mg, 0.0080 mmol) was added to a solution of (*S*)-**6** (5.0 mg, 0.0065 mmol) in CH_2Cl_2 (1.7 mL) at −78 °C, and the reaction mixture was stirred for 1 h at −60 °C. After this time, saturated aqueous $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$ were added at 0 °C, and the product was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. Purification of the residue by flash column chromatography (hexanes/EtOAc 1:1) afforded (*S*)-**5** (3.3 mg, 65% yield) as a yellow gum. This product was found to consist of two diastereomers in ratio of approximately 3:2. IR (KBr): $\tilde{\nu}$ = 1740, 1709, 1630, 1605, 1568 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.15, 1.16, 1.17, 1.18 (4s, 18H), 2.43, 2.46 (2s, 3H), 2.35–2.65 (m, 2H), 3.10 (s, 9/5H), 3.25–3.40 (m, 2H), 3.54 (brs, 12/5H), 3.80 (s, 9/5H), 3.96, 4.00, 4.01, 4.05 (4s, 6H), 6.90, 6.93, 6.96, 6.98 (4s, 2H), 7.22–7.44 (m, 4H), 7.74 (d, *J* = 7.0 Hz, 4/5H), 7.86 ppm (d, *J* = 7.5 Hz, 6/5H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.0, 21.1, 21.3, 21.4, 23.65, 23.70, 26.07, 26.12, 26.17, 32.27, 32.35, 35.95, 36.04, 53.33, 53.38, 56.34, 56.37, 60.8, 61.1, 62.0, 62.8, 65.9, 66.0, 103.6, 104.1, 111.0, 111.2, 112.9, 113.0, 113.2, 116.8, 117.0, 125.6, 126.2, 128.2, 128.3, 129.0, 129.1, 134.0, 134.1, 143.2, 143.3, 145.2, 145.7, 148.5, 148.7, 149.9, 150.2, 151.16, 151.2, 152.8, 154.3, 155.3, 155.5, 158.8, 159.0, 197.6, 197.7 ppm; HRMS (FAB): *m/z*: calcd for $C_{43}H_{46}NO_9SiS$: 780.2662 $[M+H]^+$; found: 780.2667.

(*R*)-4-Chloroacetoxy-8,9-[di(*tert*-butyl)silylenedioxy]-1′,5,6,9′-tetramethoxy-3′-methyl-6′,7′-dihydrospiro[2*H*-benz[*f*]indene-2,8′-[8′*H*]cyclopent[*g*]-isoquinoline]-1,3-dione ((*R*)-38): Under a nitrogen atmosphere, a solution of **18c** (2.0 μL, 0.12 mmol) in anhydrous toluene (0.05 mL) and a solution of anhydrous *p*TsOH (*para*-toluenesulfonic acid, 0.03 mg, 0.0002 mmol) in anhydrous toluene (0.05 mL) were added, in this order, to (*S*)-**5** (1.2 mg, 0.0015 mmol). The reaction flask was then set in an oil bath, which had been pre-heated to 110 °C, and stirred for 20 min. After cooling, saturated aqueous $NaHCO_3$ solution was added to the reaction mixture, and the product was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. Purification of the residue by preparative TLC (hexanes/EtOAc 4:1) afforded (*R*)-**38** (1.0 mg, 60% yield) as a yellow gum. The optical purity of (*R*)-**38** was determined to be 95% *ee* by chiral HPLC analysis (Daicel CHIRALCEL OD (hexanes/*i*PrOH 95:5, flow rate 1.0 mL min^{-1}, 20 °C). Retention time: 8.6 min for (*S*)-**38** and 9.9 min for (*R*)-**38**. $[\alpha]_D^{20}$ = −23.5 (*c* = 0.91 in $CHCl_3$); IR (KBr): $\tilde{\nu}$ = 1736, 1707, 1605, 1572 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.12 (s, 9H), 1.17 (s, 9H), 2.47 (s, 3H), 2.47–2.60 (m, 2H), 3.36–3.44 (m, 2H), 3.51 (brs, 3H), 3.89 (s, 3H), 4.01 (s, 3H), 4.02 (s, 3H), 4.46 (d, *J* = 15.5 Hz, 1H), 4.51 (d, *J* = 15.5 Hz, 1H), 6.95 (s, 2H), 7.30 ppm (s, 1H); HRMS (FAB): *m/z*: calcd for $C_{39}H_{43}{}^{35}ClNO_{10}Si$: 748.2344 $[M+H]^+$; found: 748.2319.

(*R*)-4-Chloroacetoxy-8,9-[di(*tert*-butyl)silylenedioxy]-5,6,9′-trimethoxy-3′-methyl-6′,7′-dihydrospiro[2*H*-benz[*f*]indene-2,8′-8′*H*-cyclopent[*g*]isoquinoline]-1,1′(2′*H*),3-trione ((*R*)-43): Under a nitrogen atmosphere, Et_3N (17 μL, 0.12 mmol), $(t\mathrm{Bu})_2Si(OTf)_2$ (22 μL, 0.060 mmol), and MeI (4 μL, 0.060 mmol) were added, in this order, to a solution of (*R*)-**38** (4.4 mg, 5.9 μmol) in anhydrous DMF (0.3 mL). The reaction mixture was then stirred at RT for 28 h. After this time, water was added, and the product was extracted with EtOAc. The combined organic layers were washed

with brine, dried (Na_2SO_4), and concentrated in vacuo. Purification of the residue by flash column chromatography (hexanes/EtOAc 1:1) afforded (*R*)-**43** (4.3 mg, 99% yield) as a yellow gum. $[\alpha]_D^{23} = -27.5$ ($c = 0.86$ in $CHCl_3$); IR (KBr): $\tilde{\nu} = 1790, 1736, 1707, 1643, 1605, 1580\ cm^{-1}$; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.12$ (s, 9H), 1.16 (s, 9H), 2.24 (s, 3H), 2.45–2.59 (m, 2H), 3.27–3.43 (m, 2H), 3.58 (br s, 3H), 3.89 (s, 3H), 4.02 (s, 3H), 4.45 (d, $J = 15.5$ Hz 1H), 4.52 (d, $J = 15.5$ Hz, 1H), 6.18 (s, 1H), 6.94 (s, 1H), 7.12 (s, 1H), 9.12 ppm (br s, 1H); HRMS (FAB): *m/z*: calcd for $C_{38}H_{41}{}^{35}ClNO_{10}Si$: 734.2188 $[M+H]^+$; found: 734.2186.

(*R*)-4-Chloroacetoxy-8,9-[di(*tert*-butyl)silylenedioxy]-3′-formyl-5,6,9′-trimethoxy-6′,7′-dihydrospiro[2*H*-benz[*f*]indene-2,8′-8′*H*-cyclopent[*g*]isoquinoline]-1,1′(2′*H*),3-trione ((*R*)-44): Under a nitrogen atmosphere, a mixture of (*R*)-**43** (4.3 mg, 5.9 μmol) and SeO_2 (2.6 mg, 23 μmol) in anhydrous dioxane (0.4 mL) was stirred under reflux for 1 h. After cooling, the reaction mixture was concentrated in vacuo. Purification of the residue by flash column chromatography (hexanes/EtOAc 1:1) afforded (*R*)-**44** (4.0 mg, 91% yield) as a yellow gum. $[\alpha]_D^{24} = -19.1$ ($c = 0.80$ in $CHCl_3$); IR (KBr): $\tilde{\nu} = 1788, 1734, 1707, 1659, 1605, 1580\ cm^{-1}$; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.12$ (s, 9H), 1.17 (s, 9H), 2.52–2.67 (m, 2H), 3.34–3.48 (m, 2H), 3.62 (br s, 3H), 3.89 (s, 3H), 4.02 (s, 3H), 4.46 (d, $J =$ 15.5 Hz, 1H), 4.51 (d, $J = 15.5$ Hz, 1H,), 6.96 (s, 1H), 7.04 (s, 1H), 7.42 (s, 1H), 8.70 (br s, 1H), 9.53 ppm (s, 1H); HRMS (FAB): *m/z:* calcd for $C_{38}H_{39}{}^{35}ClNO_{11}Si$: 748.1981 $[M+H]^+$; found: 748.1976.

(*S*)-Fredericamycin A (1): Under a nitrogen atmosphere, *n*BuLi (1.6 M solution in hexane, 0.051 mL, 0.082 mmol) was added to an ice-cooled suspension of crotyltriphenylphosphonium bromide (43 mg, 0.11 mmol) in anhydrous THF (2.4 mL), and the reaction mixture was stirred at 0 °C for 15 min. This mixture was then added to a solution of (*R*)-**44** (4.0 mg, 5.3 μmol) in anhydrous THF (0.5 mL) at −78 °C. The reaction mixture was stirred at −78 °C for 30 min, warmed to RT, and then stirred for 1 h. After this time, saturated aqueous NH_4Cl was added, and the product was extracted with EtOAc. The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated in vacuo to afford a mixture of (*R*)-**45** and a few partially deprotected products.

Under a nitrogen atmosphere, the above crude mixture was dissolved in anhydrous CH_2Cl_2 (1.0 mL), and the solution was cooled to −78 °C. BBr_3 (1.0 M solution in CH_2Cl_2, 0.10 mL, 0.10 mmol) was added, and the reaction mixture was stirred at −78 °C for 4 h. The reaction mixture was then warmed to RT and stirred overnight. After this time, water was added to the reaction mixture, and the product was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. THF (5 mL) and water (1 mL) were added to the resulting residue, and the reaction mixture was stirred, open to the air, at RT for 24 h. After this time, the product was extracted with CH_2Cl_2, and the combined organic layers were washed successively with brine, dried (Na_2SO_4), and concentrated in vacuo. Purification of the residue by preparative TLC ($CHCl_3$/MeOH/AcOH 90:10:1) afforded a mixture of **1** and its *E,Z* isomer. Further purification of this mixture by HPLC (JASCO Megapac SIL NH2–10, $CHCl_3$/MeOH/AcOH 800:200:1) afforded **1** (1.0 mg, 35% from (*R*)-**44**) as a red solid. This product was found to be identical (m.p., ^1H NMR, IR, UV, and CD spectroscopy, HPLC, TLC) with an authentic sample of natural fredericamycin A. HRMS (FAB): *m/z*: calcd for $C_{30}H_{22}NO_9$: 540.1294 $[M+H]^+$; found: 540.1274.

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[25] For the preparation of **9a** see Supporting Information.

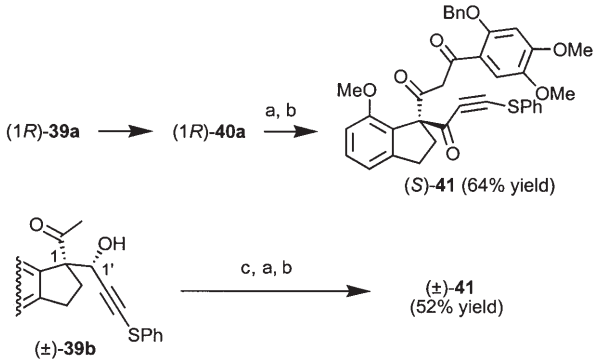
[26] Other *Candida* lipases (Amano AY, Meito OF, Roche Chirazyme L3, and Roche Chirazyme L5) also catalyzed the desymmetrization reaction but with similar or decreased enantioselectivities and chemical yields. The *Pseudomonas* lipases were not reactive.

[27] The optical purities of (*R*)-**36** for each ratio of iPr$_2$O to MeCN were as follows: 68% *ee* (5:1), 67% *ee* (1:1), 44% *ee* (1:5), and 28% *ee* (1:10).

[28] As we have not determined the absolute stereochemistry at the C1′ position, it has been tentatively assigned for convenience (see schemes).

[29] We have also observed a similar racemization of the stereogenic quaternary α-carbon center in the β-hydroxyketone see reference [10a]; in addition, a similar racemization of a β-hydroxynitrile has been reported see: T. Kimura, N. Yamamoto, Y. Suzuki, K. Kawano, Y. Norimine, K. Ito, S. Nagato, Y. Iimura, M. Yonaga, *J. Org. Chem.* **2002**, *67*, 6228–6231.

[30] The conversion of (1*R*)-**40a** to the trione (*S*)-**41** was carried out as reported see reference [13]. The same sequential treatment of (±)-**39b** produced (±)-**41** (52% overall yield), which provided us with additional evidence for the diastereomeric relationship between (1*R*)-**39a** and (±)-**39b** (Scheme 12).



Scheme 12. The conversion of (1*R*)-**39a** and (±)-**39b** to (*S*)-**41** and (±)-**41**, respectively a) LiN(TMS)$_2$, THF; b) Moffatt oxidation; c) **34**, DMAP, CH_2Cl_2.

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