Enantioselective Total Synthesis of a Potent Antitumor Antibiotic, Fredericamycin A

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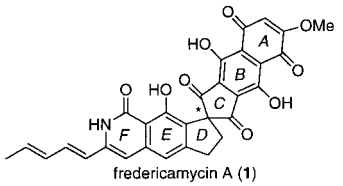
Abstract: The asymmetric total synthesis of both enantiomers of the potent antitumor antibiotic fredericamycin A (**1**) is detailed based on the protocol for the construction of its *peri*-hydroxy polyaromatic skeleton bearing the chirality at the spiro carbon via a strong base-induced cycloaddition of suitably substituted homophthalic anhydrides (AB-ring unit) with an optically active CDEF-ring unit. Particular attention has been given to the novel synthesis of the optically active spiro carbon center by a stereospecific rearrangement of optically active benzofuzed-*trans*-epoxy acylates leading to spirocyclopentane-1,1′-indane systems. This method is quite useful for the construction of an optically active spiro compound and was applied to the synthesis of the optically pure CDEF-ring unit of **1**. Cycloaddition of the optically pure CDEF-ring unit to AB-ring units prepared via benzyne afforded two natural and unnatural-type hexacyclic compounds, which were converted to natural and unnatural enantiomers of synthetic **1**, and the absolute configuration of natural **1** was determined as *S*.

Fredericamycin A (**1**), isolated from *Streptomyces griseus* in 1981, exhibits potent antitumor activity against several tumor models (in vivo) such as P388 leukemia, B16 melanoma, and CD8F mammary carcinoma, and does not show mutagenicity in the Ames test.[1,2] Recent studies revealed that **1** inhibits both topoisomerases I and II; however, little is known about the actual mechanism of its action. In addition to these promising biological profiles, its unique structure has attracted many synthetic organic chemists. Compound **1** consists of two sets of *peri*-hydroxy tricyclic aromatic moieties connected through a spiro quaternary carbon center, whose chirality is determined by the presence of a single methoxy group at the farthest position on the A-ring.



fredericamycin A (**1**)

Numerous synthetic studies of **1** have been achieved so far, which include six total syntheses: five in racemic form[3−7] and one in optically active form.[8] Although the last synthesis by Boger's group achieved the synthesis of the optically active **1**, it requires an optical resolution of the racemic compound using a chiral HPLC separation at the final stage of the synthesis. Therefore the absolute configuration of **1** still remains unknown. Most of the reported total syntheses and the related model studies involve the construction of the spiro CD-ring in their final stages, and the lack of an efficient method for the enantiodifferentiation of the highly symmetrical AB-plane has been the major obstacle in these asymmetric approaches (Scheme 1).

We then planned to synthesize the optically active **1** and determine the absolute configuration by a completely new approach, which is also useful to synthesize its analogues.[9] Scheme 2 shows our synthetic plan. Thus, the strong base-induced intermolecular [4+2]-cyclocondensation[10] of an optically active CDEF-ring unit and a suitably functionalized AB-

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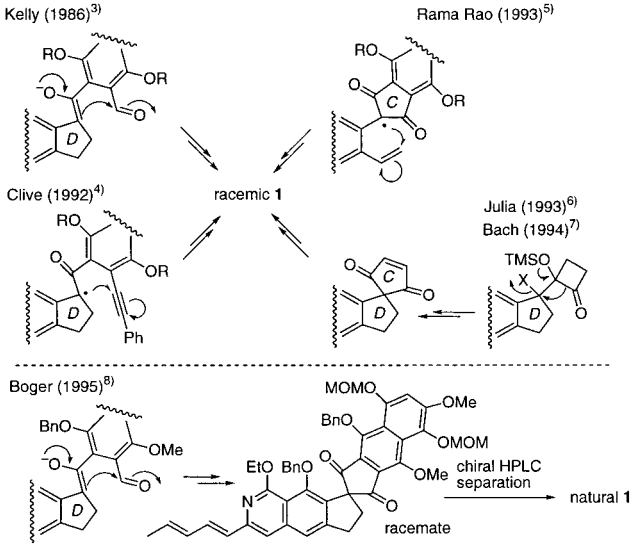
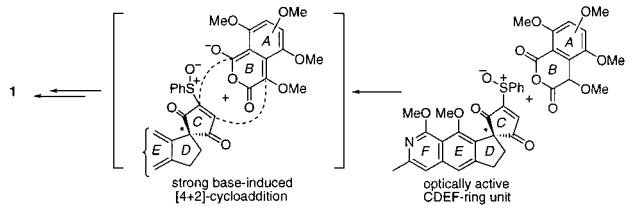
Scheme 1. Reported Total Synthesis of Fredericamycin A (**1**)



Scheme 2. Our Synthetic Plan for Optically Active Fredericamycin A (**1**)



ring unit would afford the optically active fredericamycin A. The success of this synthesis would supply a way to synthesize various analogues because various types of homophthalic anhydrides are available as the AB-ring unit. According to our synthetic plan, we recently communicated the first asymmetric total synthesis of **1**[11,12] and succeeded in determining its absolute configuration. In this paper, we describe the full details of our study on the synthesis of optically active **1**.

Synthesis of Optically Active CDEF-Ring Unit: Construction of Optically Active Spiro Centers. The determination of the absolute stereochemistry of the spiro center is usually difficult.[13] For the purpose of the synthesis of the optically active CDEF-ring unit, we first studied the construction of the chiral spiro center whose stereochemistry could be easily determined.

As a new approach to the chiral spiro compounds,[14,15] we planned to use the stereoselective rearrangement of the optically active cyclic 2,3-epoxy acylates for the following five reasons:[16,17] (i) acyloxy epoxides are easily constructed in optically active forms from the optically active allyl alcohols, (ii) many methodologies are available for the synthesis of optically active allyl alcohols, (iii) it is easy to determine the absolute configuration of the allyl alcohol systems, (iv) the absolute configurations of the spiro centers produced are readily determined if the rearrangement proceeds in a stereoselective manner, and (v) the acyloxy group would suppress the rearrangement of substituent on the carbon attached to the acyloxy group because of its electron-withdrawing nature, although most epoxy alcohol derivatives such as siloxy, alkoxy, and hydroxy groups tend to

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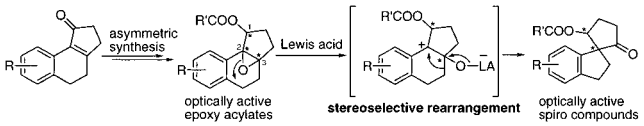
Scheme 3. Synthetic Plan for the Optically Active Spiro Compounds



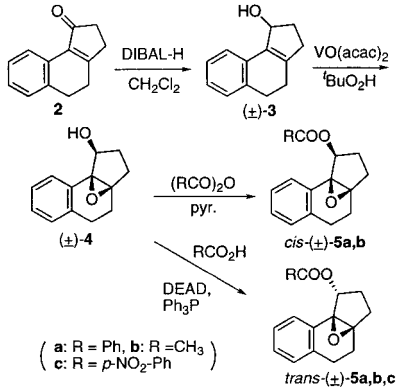
cause the rearrangement of a substituent next to the alcohol function.[18]

Our synthetic plan for the optically active spiro compounds is outlined in Scheme 3. Optically active epoxy acylates could be synthesized from enones by asymmetric reduction followed by stereoselective epoxidation and acylation. Although an acyloxy group is known as a neighboring participating group, if such participation could be suppressed, the desired rearrangement would proceed.[19] Although the electron-withdrawing nature of the acyloxy alkyl group makes the formation of the C2-carbocation unfavorable, the phenyl ring would effect more strongly the formation of the C2-carbocation intermediate,[20] which causes ring contraction leading to the spiro compounds. The optically active spiro compounds would then be constructed by stereoselective rearrangement from the optically active tricyclic epoxy acylates whose absolute configuration could be determined easily.[21]

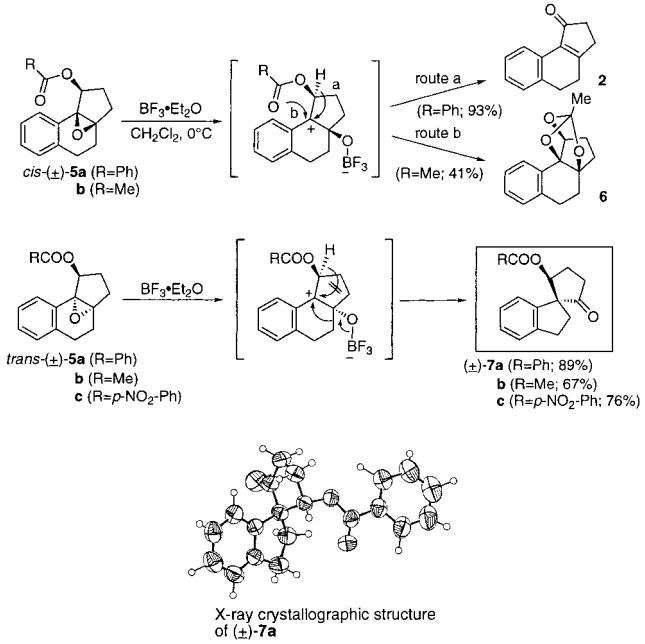
To examine the above concept, we initially investigated the reactions of racemic tricyclic *cis*- and *trans*-2,3-epoxy acylates (*cis*-(±)-**5** and *trans*-(±)-**5**). They were stereoselectively synthesized from the enone **2**.[22] Thus, reduction of **2** with DIBAL-H afforded the allyl alcohol (±)-**3**, which was epoxidized by the stereoselective Sharpless condition[23] to give the *cis*-2,3-epoxy alcohol (±)-**4** as a single isomer. Acylation of (±)-**4** gave the *cis*-2,3-epoxy acylates, *cis*-(±)-**5a**,**b**. Mitsunobu reaction[24] of (±)-**4** in the presence of benzoic acid or *p*-nitrobenzoic acid afforded the *trans*-2,3-epoxy acylates, *trans*-(±)-**5a**−**c** (Scheme 4).

Treatment of *cis*-(±)-**5** with 1 equiv of BF_3·Et_2O in CH_2Cl_2 at 0 °C[25] afforded undesired products: the enone **2** (93%) from

Scheme 4. Synthesis of Racemic Epoxy Acylates



Scheme 5. Reaction of Tricyclic Epoxy Acylates **5a**−**c**



X-ray crystallographic structure of (±)-**7a**

cis-(±)-**5a** and the orthoester **6** (41%) from *cis*-(±)-**5b**.[26] On the other hand, treatment of *trans*-(±)-**5a**−**c** with BF_3·Et_2O under similar conditions gave the desired spiro products (±)-**7a**−**c** in good yields, respectively (Scheme 5). The same tendency was observed in the reactions with other Lewis acids, such as $SnCl_4$ and $CF_3SO_3SiMe_3$. No spiro compound was obtained from *cis*-(±)-**5a**, whereas the *trans*-(±)-**5a** afforded (±)-**7a** in 89% yield with $SnCl_4$ and 29% yield with $CF_3SO_3SiMe_3$. The stereochemistry of (±)-**7a**, which was confirmed by X-ray analysis, showed that the benzene ring is laid anti to the acyloxy group as was expected by the stereoselective reaction sequence.[27] The explanation for these reactions is as follows. In tricyclic *cis*-epoxy acylates, a benzylic cation is formed first, and the hydride at the anti periplanar position shifts

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(23) Sharpless, K. B.; Michaelson, R. C. *J. Am. Chem. Soc.* **1973**, *95*, 6136−6137.

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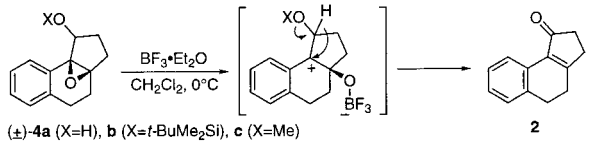
(26) Almost quantitative formation of **6** was observed by TLC analysis. Compound **6** was rather unstable and a fair amount of the enone **2** was formed during purification of **6** (SiO_2 column separation). In the case of *cis*-**5a**, the formation of the orthoester was not detected even by TLC examination.

(27) Crystallographic data for the structures reported in this paper have been deposited with the Cambridge Crystallogrpahic Data Center as supplementary publication no. CCDC-152839 [for (±)-**7a**], 152840 [(−)-**10**], 152841 [for (+)-**11**], 102892 [for (−)-**25**], 102893 [for (+)-**26**], and 102894 (for **34**).

in the case of *cis*-(±)-**5a** (R = Ph) because of the steric hindrance to the cation center and the hydride occupies the position suitable for rearrangement (route a). However in the case of *cis*-(±)-**5b** (R = Me), steric hindrance between the cation center and the methyl group does not give the same rearrangement and the formation of the orthoester **6** proceeds predominantly (route b). On the other hand, the hydride next to the acyloxy group does not occupy the position suitable for rearrangement in the cases of *trans*-epoxy acylates (*trans*-(±)-**5a**−**c**), and the formation of the five-membered ring by the neighboring participation of the acyloxy group is unfavorable because the resulting tetracyclic compound is not stable due to the *cis*, *trans*-five-, five-, six-membered-ring junctions.

The acyloxy group is essential for the present rearrangement reaction. Thus, the *cis*- and *trans*-epoxy alcohols (±)-**4a**, and the ethers (±)-**4b**,**c** with 1 equiv of BF_3·Et_2O afforded the enone **2** (Scheme 6). The different reactivity of the epoxy alcohol

Scheme 6. Rearrangement of Epoxy Alcohol **4a** and Ethers **4b**,**c**

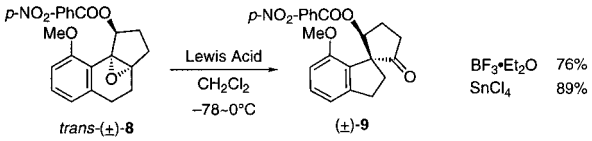


(±)-**4a** (X=H), **b** (X=*t*-BuMe$_2$Si), **c** (X=Me) **2**

derivatives is rationalized by the electronic nature of the alcohol moiety. The cleavage of the oxirane ring occurs at the benzylic position in all cases, and the electron-donating group X in (±)-**4a**−**c** (X = H, *t*-BuMe$_2$Si, Me) accelerates the hydride shift rather than the skeletal rearrangement. In contrast, the electron-withdrawing acyloxy groups would decrease the tendency of the hydride shift. In these cases, the relative stereochemistry of the hydride and the newly formed carbocation is very important. Only in the case where the hydride lays syn to the cleaving oxirane ring, the hydride shift is prevented and a skeletal rearrangement occurs.

This rearrangement was successfully applied to the methoxy-substituted *trans*-epoxy acylate (*trans*-(±)-**8**), and its generality was proven (Scheme 7). With the successful conversion of the

Scheme 7. Rearrangement of Methoxy-Substituted Epoxy Acylates **8**

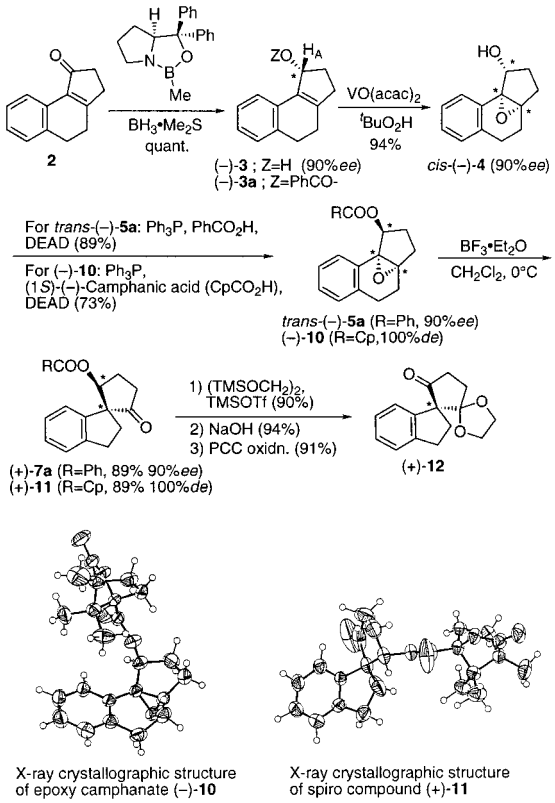


trans-(±)-**8** (±)-**9**

trans-epoxy acylates to the chiral spiro compounds in hand, we next examined in the optically active system (Scheme 8). Asymmetric reduction of **2** by Corey's method[28] afforded (−)-**3** whose optical purity (90% ee) was determined by the ^{1}H NMR analysis of its benzoate (−)-**3a** using the chiral shift reagent, Eu(hfc)$_3$. Epoxidation of (−)-**3** by the stereoselective Sharpless epoxidation afforded *cis*-(−)-**4** as a sole product. The Mitsunobu reaction of *cis*-(−)-**4** gave *trans*-(−)-**5a** (90% ee) in 89% yield. Treatment of *trans*-(−)-**5a** with BF_3·Et_2O afforded (+)-**7a** in 89% yield with retention of optical purity (90% ee). This means that the rearrangement occurs stereospecifically. Although the asymmetric reduction of **2** did not proceed with sufficient

(28) (a) Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen, C.-P.; Singh, V. K. *J. Am. Chem. Soc.* **1987**, *109*, 7925−7926. Review: Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986−2012. (b) The signal H_A of (−)-**3a** is most affected by the shift reagent. (Baseline separation at 11.5 and 11.9 ppm.)

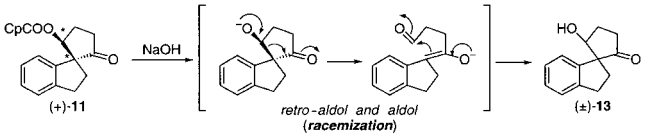
Scheme 8. Rearrangement of Optically Active Epoxy Acylates (−)-**5a** and (−)-**10**



X-ray crystallographic structure of epoxy camphanate (−)-**10**

X-ray crystallographic structure of spiro compound (+)-**11**

Scheme 9. Direct Hydrolysis of β-Acyloxy Ketone (+)-**11**



(+)-**11** (±)-**13**

stereoselectivity, the optically pure (−)-**10** could be obtained after one recrystallization of crude (−)-**10** from CH_2Cl_2−hexane. The treatment of optically pure (−)-**10** with BF_3·Et_2O gave the optically pure (100% de) spiro compound (+)-**11** in 89% yield. The absolute stereochemistries of *trans*-(−)-**5a** and (+)-**7a** were deduced from the reaction mechanisms and finally confirmed by the X-ray analysis of the camphanoate (−)-**10** and the spiro compound (+)-**11**.[27] The discrimination of the two carbonyl groups of (+)-**11** was next studied. Conversion of (+)-**11** to the optically pure chiral spiro-1,3-dione derivative (+)-**12** was achieved in a three-step sequence in 77% overall yield. First we protected the ketone as an acetal. Without protection of the keto group of (+)-**11** as an acetal, retro-aldol and aldol reaction occurred during hydrolysis, which resulted in the racemization of the spiro center (Scheme 9). Acetalization of (+)-**11** by Noyori's method followed by hydrolysis of the acylate yielded the acetal alcohol, which was subjected to PCC oxidation to give the keto acetal (+)-**12**.

As mentioned above, we have developed a new stereoselective synthesis of the chiral, nonracemic spiro[cyclopentane-1,1′-indan]-2,5-dione system found in **1**. We then applied this methodology to the synthesis of the CDEF-ring unit of **1**.

The tetracyclic hydroxy ketone **18** was prepared from the tricyclic keto aldehyde **17** synthesized in two ways. First, we prepared **17** by a modification of Clive's procedure.[29] Thus,

(29) Clive, D. L. J.; Sedgeworth, J. *J. Heterocycl. Chem.* **1987**, *24*, 509−511.

Scheme 10. Synthesis of Tetracyclic α-Hydroxy Ketone **18**

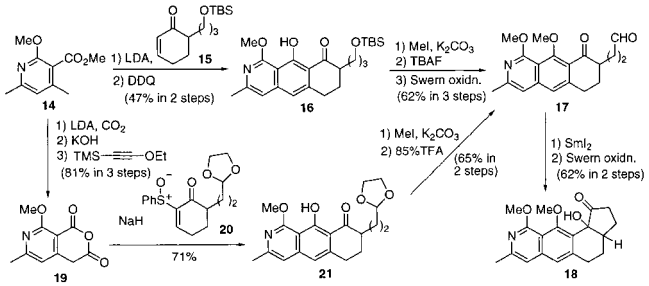
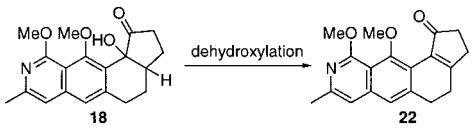
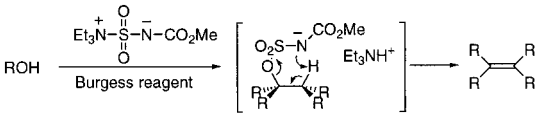


Table 1. Dehydroxylation of Tetracyclic α-Hydroxy Ketone **18**



entry	reaction conditions	yield of **22**
1	PPTS, CH_2Cl_2, reflux	trace
2	*p*-TsOH, CH_2Cl_2, reflux	trace
3	(1) MsCl, Et_3N, CH_2Cl_2; (2) DBU	trace
4	$SOCl_2$, pyridine, −10 °C	43%
5	HCO_2H, H_2SO_4, 60 °C	51%
6	NaOH, CS_2, MeI, toluene, r.t. ∼ reflux	no reaction
7	NaOH, CS_2, MeI, Et_2O-$CHCl_3$, r.t. ∼ reflux	no reaction
8	NaOH, CS_2, MeI, Et_2O, r.t. ∼ reflux	no reaction
9	Burgess reagent, C_6H_6, 50 °C ∼ reflux	no reaction
10	**Burgess reagent, THF, reflux**	**quantitative**

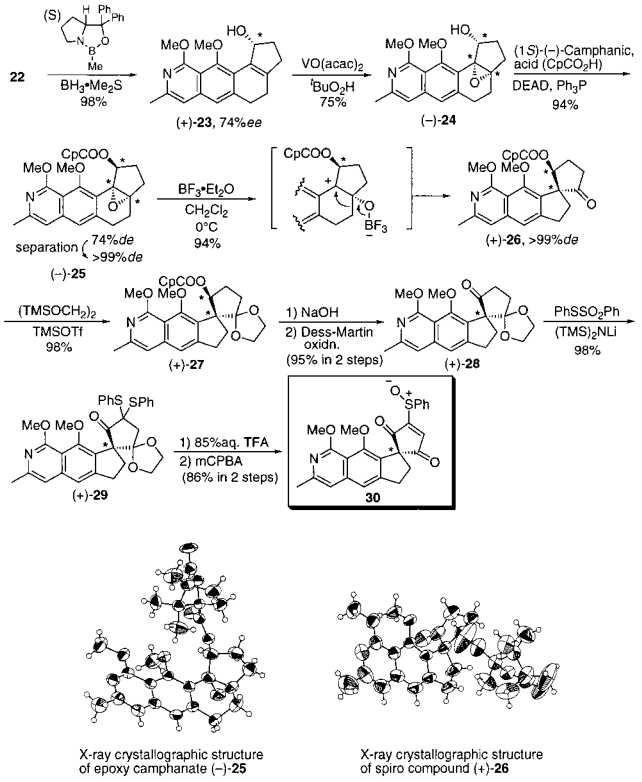
Scheme 11. *cis*-Elimination by Burgess Reagent



the reaction between methyl 2-methoxy-4,6-dimethylpyridine-3-carboxylate **14** treated with LDA and α′-substituted cyclohexenone **15** proceeded to the 1,4-addition and Claisen-type condensation to give the coupling product, whose E-ring was aromatized by DDQ. Methylation of the phenolic hydroxy function, desilylation, and then Swern oxidation[30] gave **17** in 29% overall yield. Intramolecular pinacol coupling of **17** with SmI_2 gave the diol,[31] which was oxidized by Swern's method to give the hydroxy ketone **18** in 62% yield from **17**. The same aldehyde **17** was alternatively prepared by the strong base-induced cycloaddition of homophthalic anhydride **19** with α-sulfinylenone **20** in 37% overall yield[32] (Scheme 10).

The formation of enone from **18** by dehydration was first studied under acidic conditions (Table 1, entries 1−5). Treatment of **18** with H_2SO_4/HCO_2H gave the enone **22** in 51% yield (entry 5). This result was reported in the preliminary communication.[11] The yield of dehydration was not satisfactory, therefore we next examined the *cis*-elimination reaction. The Chugaev reaction,[33] a typical *cis*-elimination reaction, was first examined for **18**, but it failed to form the requisite thioester. This is due to the steric hindrance of the tertiary hydroxy group (entries 6−8). However, the reaction of **18** with the Burgess reagent[34] in refluxing THF proceeded smoothly to give the enone **22** quantitatively (entry 10), whereas the reaction in refluxing benzene did not work at all and the starting material was recovered (Scheme 11).

Scheme 12. Synthesis of Tetracyclic Vinyl Sulfoxide **30**



X-ray crystallographic structure of epoxy camphanate (−)-**25**

X-ray crystallographic structure of spiro compound (+)-**26**

Corey's asymmetric reduction of **22** using the chiral borane reagent and BH_3·Me_2S gave a quantitative yield of the (*R*)-alcohol (+)-**23** with 74% ee. The asymmetric reduction with the chiral borane, prepared in situ, and BH_3·Me_2S was also examined.[35] However, no improvement in ee could be achieved (47% ee). Sharpless epoxidation of (+)-**23** (74% ee) afforded stereoselectively the *cis*-epoxy alcohol (−)-**24** (81%, 74% ee), which was treated with (−)-camphanic acid (>98% ee) under Mitsunobu conditions to give the mixture of diastereomers (74% de) of the *trans*-epoxy camphanate (−)-**25**. This mixture of diastereomers was separated by SiO_2-column chromatography to give the optically pure (−)-**25** (≥99% de). The absolute stereochemistry of (−)-**25** was determined by X-ray crystallographic analysis.[27] The rearrangement reaction of (−)-**25** (≥99% de) with BF_3·Et_2O proceeded at 0 °C to give the optically pure spiro compound (+)-**26** (≥99% de in 94% yield). The rearrangement reaction of (−)-**25** (74% de) with BF_3·Et_2O gave a 94% yield of the spiro compound (+)-**26** (≥74% de), which was used as the standard sample for HPLC analysis, and the rearrangement reaction of this compound was found to proceed with perfect stereoselectivity. Based on our model study described above, the stereochemistry of (+)-**26** was envisaged as depicted in Scheme 12 and finally ascertained by its X-ray crystallographic analysis.[27] The transformation of (+)-**26** to the vinyl sulfoxide **30** was achieved retaining the chiral integrity by taking into consideration the following two points. The first

(30) Omura, K.; Sharma, A. K.; Swern, D. *J. Org. Chem.* **1976**, *41*, 957−962.

(31) (a) Chiara, J. L.; Cabri, W.; Hanessian, S. *Tetrahedron Lett.* **1991**, *32*, 1125−1128. (b) Uenishi, J.; Masuda, S.; Wakabayashi, S. *Tetrahedron Lett.* **1991**, *32*, 5097−5100.

(32) (a) Kita, Y.; Iio, K.; Okajima, A.; Takeda, Y.; Kawaguchi, K.; Whelan, B. A.; Akai, S. *Synlett* **1998**, 292−294. (b) Iio, K.; Ramesh, N. G.; Okajima, A.; Higuchi, K.; Fujioka, H.; Akai, S.; Kita, Y. *J. Org. Chem.* **2000**, *65*, 89−95.

(33) (a) Depuy, C. H.; King, R. W. *Chem. Rev.* **1960**, *60*, 431−457. (b) Nace, H. R. *Org. React.* **1962**, *12*, 57−100.

(34) Burgess, E. M.; Penton, H. R., Jr.; Taylor, E. A. *J. Org. Chem.* **1973**, *38*, 26−31.

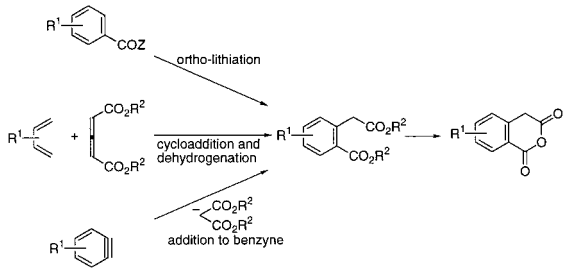
(35) Masui, M.; Shioiri, T. *Synlett* **1997**, 273−274.

point is the acetalization of (+)-**26** prior to the alkaline hydrolysis to prevent the easy racemization of the spiro center by retro-aldol and aldol reaction. In fact, without acetalization of (+)-**26**, easy racemization of the spiro center occurred in this compound. The second point is the introduction of a sulfinyl group. Based on our recent study,[32] a sulfinyl group was estimated as a powerful directing and activating substituent on the dienophile. Treatment of the keto acetal (+)-**28** with lithium bis(trimethylsilyl)amide and $PhSSO_2Ph$ afforded the α,α-diphenylsulfenyl compound (+)-**29**. Acid treatment of (+)-**29** caused deacetalization and elimination of PhSH to give the diketovinyl sulfide, which was then oxidized with mCPBA, and the optically active CDEF-ring unit **30** was obtained as a diastereo mixture at sulfur centers (approximately 1:1) (Scheme 12).

Synthesis of the AB-Ring Unit. Because the absolute stereochemistry of **1** was unknown, two regioisomers of the AB-ring units, suitably functionalized homophthalic anhydride derivatives, were necessary, which allows the synthesis of both enantiomers (*S*)- and (*R*)-**1**, respectively.

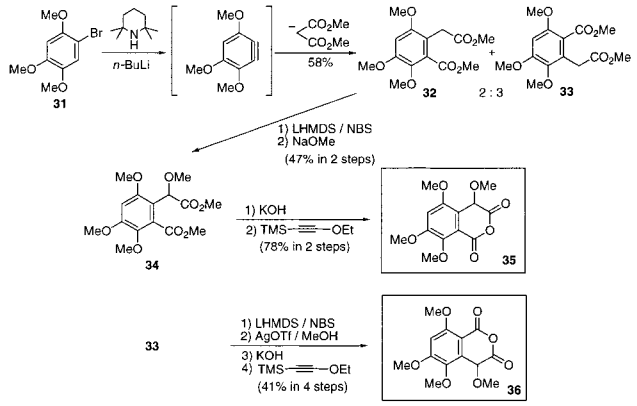
Homophthalic anhydride derivatives are generally obtained from the corresponding homophthalic acid derivatives, which are prepared by several methodologies such as (1) ortho-lithiation of benzoic acid derivatives,[36a] (2) cycloaddition reaction of allenyl esters to dienes,[36b] and (3) addition of malonate anion to benzynes[36c] (Scheme 13).

Scheme 13. Preparation of Homophthalic Anhydrides



Among them, we chose the method with the benzyne intermediate (ref 36c) because this method is quite simple and would afford two regioisomers in one operation. The regioisomeric diene parts **35** and **36** were prepared from **31** with some modifications of the reported method (Scheme 14).[36c] Reaction of **31**[37] with dimethyl malonate (2.0 equiv), *n*-BuLi (3.0 equiv), and tetramethylpiperidine (1.5 equiv) afforded a regioisomeric mixture (2:3) of the homophthalates **32** and **33** through a nonregioselective addition of the lithiomalonate to the benzyne intermediate. Each regioisomer was readily separated by SiO_2 column chromatography to give the pure **32** and **33**, which were subjected to sequential bromination and methanolysis to give the respective dimethyl esters. Alkaline hydrolysis of these dimethyl esters followed by dehydration of the resulting dicarboxylic acid with trimethylsilyl(ethoxy)acetylene[38] afforded

Scheme 14. Synthesis of Homophthalic Anhydrides **35** and **36**



the corresponding anhydrides **35** and **36**, respectively. In the case of **34**, a careful workup with trifluoroacetic acid instead of aqueous HCl was necessary since the dicarboxylic acid formed after alkaline hydrolysis was found to be somewhat unstable in the acidic condition. The regiochemistry of the products was deduced by the nuclear Overhauser effect (NOE) experiment with the benzyl ether derivatives of **33**[39] and finally confirmed by X-ray crystallographic analysis of **34**.[27]

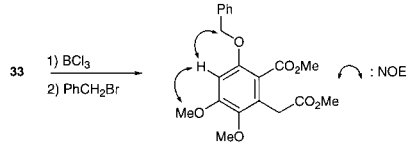
Intermolecular [4+2]-Cyclocondensation[10] and Total Synthesis of Optically Active Fredericamycin A (1) and *ent*-1. The three-step sequences, (1) treatment of **35** with 1.15 equiv of NaH, (2) [4+2]-cyclocondensation with **30**, and (3) methylation of hydroxyl group, afforded the hexacyclic product (*S*)-**38** (76%, 97% ee). Its enantiomer (*R*)-**38** (71%, 94% ee) was obtained by using **36** in place of **35** in the above reaction (Scheme 15). CD spectra of these products showed symmetrical curves (Figure 1) and among them the CD spectra of the (*S*)-isomer closely resembled that of the fully protected **1** reported by Boger's group.[8a] We then first studied the conversion of (*S*)-**38**. Selective demethylation of the methyl ether on the F-ring of (*S*)-**38** by NaBr and *p*-TsOH[3b] gave the α-pyridone compound, which was oxidized with SeO_2 to give (*S*)-**39**.[40] The Wittig reaction[3] of (*S*)-**39** with *trans*-2-butenyl triphenylphosphonium bromide gave a 5 to 1 mixture of (*E*,*E*)- and (*E*,*Z*)-side chain isomers in 46% yield. An attempt for assembling the mixture of side chain isomers to one isomer, (*E*,*E*)-form, by isomerization of olefins with Br_2, TMSI,[4b] or I_2[3b] did not work at all and the starting mixture was recovered. Deprotection of the mixture with BBr_3 (12.5 equiv) and subsequent autoxidation afforded a 5 to 1 mixture of **1** and its (*E*,*Z*)-side chain isomer in a total yield of 74%. The pure **1** was obtained in 40% yield after purification by HPLC column (Jasco Megapak SIL NH2-10, 1 × 25 cm, 800:200:1 $CHCl_3$−*n*-hexane−acetic acid, 5.0 mL/min flow rate). Transformation of (*R*)-**38** to *ent*-**1** was done in the same manner. CD spectra of natural and unnatural enantiomers of synthetic **1** showed symmetrical curves (Figure 2).

(36) (a) For example see: Cushman, M.; Dekow, F. W. *Tetrahedron* **1978**, *34*, 1435−1439. De Silva, S. O.; Ahmad, I.; Snieckus, V. *Can. J. Chem.* **1979**, *57*, 1598−1605. Tamura, Y.; Sasho, M.; Akai, S.; Wada, A.; Kita, Y. *Tetrahedron* **1984**, *40*, 4539−4548. (b) For example, see: Tamura, Y.; Fukata, F.; Tsugoshi, T.; Sasho, M.; Nakajima, Y.; Kita, Y. *Chem. Pharm. Bull.* **1984**, *32*, 3259−3262. Roush, W. R.; Murphy, M. *J. Org. Chem.* **1992**, *57*, 6622−6629. Langer, P.; Kracke, B. *Tetrahedron Lett.* **2000**, *41*, 4545−4547 and references therein. (c) Shair, M. D.; Yoon, T. Y.; Mosny, K. K.; Chou, T. C.; Danishefsky, S. J. *J. Am. Chem. Soc*. **1996**, *118*, 9509−9525.

(37) Blatchly, J. M.; McOmie, J. F. W.; Searle, J. B. *J. Chem. Soc. (C)* **1969**, 1350−1353.

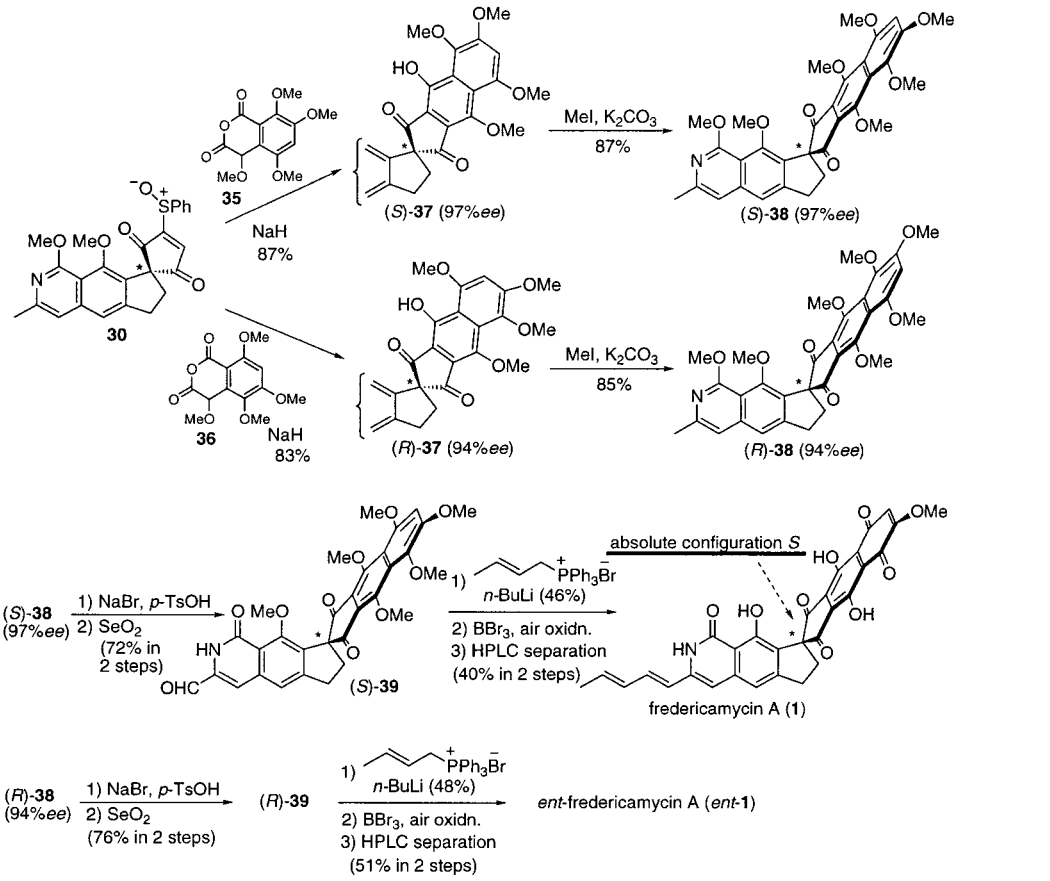
(38) Kita, Y.; Akai, S.; Ajimura, N.; Yoshigi, M.; Tsugoshi, T.; Yasuda, H.; Tamura, Y. *J. Org. Chem.* **1986**, *51*, 4150−4158.

(39) Benzyl ether derivative of **33** was obtained by BCl_3 hydrolysis of **33** followed by benzylation. NOE was observed between the methylene of benzyl ether and the aromatic proton.



(40) Kita, Y.; Ueno, H.; Kitagaki, S.; Kobayashi, K.; Iio, K.; Akai, S. *J. Chem. Soc., Chem. Commun.* **1994**, 701−702.

Scheme 15. Enantioselective Total Synthesis of Fredericamycin A (**1**) and *ent*-**1**



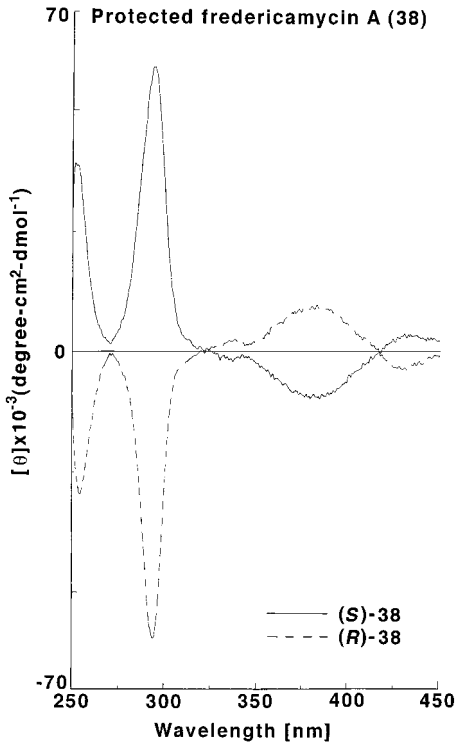


Figure 1. CD spectra of **38** in *i*-PrOH.

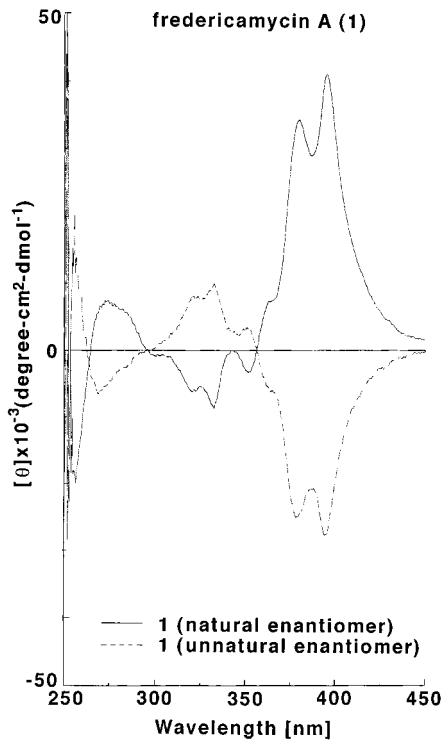


Figure 2. CD spectra of **1** in DMF−MeOH−Et_3N.

The synthetic compound was identical in all respects {^{1}H NMR, IR, UV, MS, TLC, HPLC, and CD} with the authentic material provided by the SS Pharmaceutical Co., Ltd., Japan.

CD Spectra and HPLC Charts of Intermolecular Coupled Products and Optically Active Fredericamycin A: Determination of the Absolute Configuration. CD Spectra of intermolecular coupled products, optically active natural and unnatural enantiomers of synthetic **1**, are shown in Figures 1 and 2. Figure 1 shows the CD spectra of the permethylates (*R*)- and (*S*)-**38**, obtained by methylation of the coupled products,

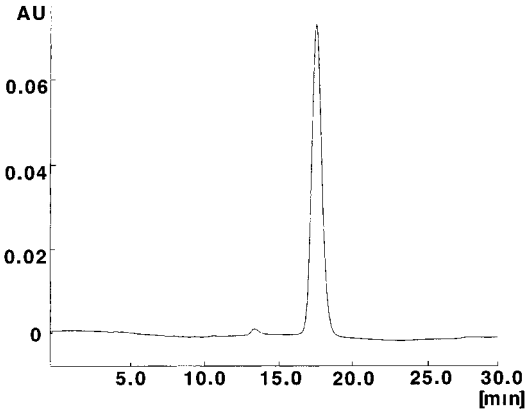


Figure 3. HPLC chart of (*S*)-**38**.

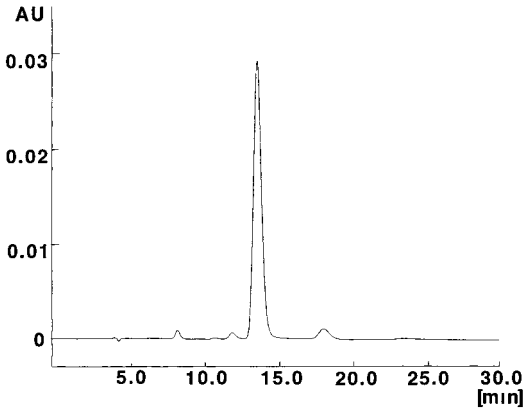


Figure 4. HPLC chart of (*R*)-**38**.

showing symmetrical curves, among which that of (*S*)-**38** showed a similar CD pattern as that of Boger's fully protected natural enantiomer of **1**.[8a] Figure 2 shows the CD spectra of optically active synthetic **1** (97% ee) and its enantiomer (94% ee). The curve of the synthetic **1** from the AB-ring part **35** is identical with that of natural **1**. Thus, the absolute configuration of natural **1** was ascertained to be *S*. Figures 3 and 4 show HPLC analyses of the permethylates (*R*)- and (*S*)-**38**, from which their ee values could be deduced.

Conclusion

We have developed a new method for the construction of chiral spiro centers, the chiral spiro[cyclopentane-1,1′-indan]-2,5-dione system, through a stereospecific rearrangement of the *trans*-2,3-epoxy acylates using Lewis acid. This method was successfully applied to construct the chiral spiro center of **1** and utilized in the asymmetric total synthesis of **1** and *ent*-**1** in combination with strong-base-induced [4+2]-cyclocondensation. This is the first asymmetric total synthesis of **1** and *ent*-**1**, which establishes the absolute configuration of the single chiral center of **1**.

Experimental Section

Rearrangement Product ((+)-26). BF_3·Et_2O (68 μL, 0.54 mmol) was added dropwise to a solution of (−)-**25** (0.14 g, 0.27 mmol) in CH_2Cl_2 (7.0 mL) at 0 °C under Ar atmosphere. The resulting mixture was stirred for 1.5 h at the same temperature. The reaction mixture was cooled in an ice−water bath, diluted with CH_2Cl_2, mixed with saturated aqueous $NaHCO_3$, and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by SiO_2 column chromatography with hexane−AcOEt (3/1 to 2/1) as an eluent to give (+)-**26** (0.13 g, 94%, >99% de by HPLC (CHIRALPAK AD, flow rate 1.0 mL/min, Hex/^{i}PrOH 92/8)) as a colorless crystal: mp 163 °C (hexane/AcOEt); $[\alpha]^{20}_D$ +9.7 (*c* 1.20, $CHCl_3$); IR (KBr) 1794, 1740, 1736 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.94 (6H, s), 1.09 (3H, s), 1.58−1.68 (2H, m), 1.81−2.04 (3H, m), 2.17−2.79 (5H, m), 2.47 (3H, s), 3.02−3.25 (2H, m), 3.73 (3H, s), 4.11 (3H, s), 5.70 (1H, dd, J = 5.5, 8.0 Hz), 6.94 (1H, s), 7.21 (1H, s); ^{13}C NMR (68 MHz, $CDCl_3$) δ 9.7, 16.5, 16.8, 23.7, 27.2, 28.8, 30.4, 32.2, 32.5, 36.7, 53.6, 54.3, 54.8, 62.3, 63.4, 81.4, 90.8, 111.1, 112.9, 116.9, 135.6, 143.1, 148.8, 149.2, 152.5, 158.8, 166.7, 178.2, 217.4; HRMS calcd for $C_{29}H_{33}NO_7$ (M^+) 507.2257, found 507.2260. Anal. Calcd for $C_{29}H_{33}NO_7$: C, 68.62; H, 6.55; N, 2.76. Found: C, 68.59; H, 6.55; N, 2.77.

(2*S*)-3′-Methyl-1′,4,5,6,8,9,9′-heptamethoxy-6′,7′-dihydrospiro-[2*H*-benz[*f*]indene-2,8′-8′*H*-cyclopent[*g*]isoquinoline]-1,3-dione ((*S*)-38). (a) [4+2]-Cyclocondensation: NaH (16 mg, 60% in mineral oil, 0.39 mmol) was added to a solution of **35** (94 mg, 0.33 mmol) in THF (4.0 mL) at 0 °C under Ar atmosphere, and the resulting mixture was stirred for 1 h at room temperature. A solution of **30** (79 mg, 0.18 mmol, 97% ee) in THF (5.0 mL) was added dropwise to the mixture cooled to 0 °C, and the reaction mixture was stirred for 7 h at room temperature. Saturated aqueous NH_4Cl was added to the reaction mixture cooled in an ice−water bath, and the resulting solution was extracted with AcOEt and CH_2Cl_2. Each organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo, respectively. The combined residue was purified by SiO_2 column chromatography with CH_2Cl_2−MeOH (50/1) as an eluent to give (*S*)-**37** (86 mg, 87%, 97% ee by HPLC (CHIRALPAK AD, flow rate 0.9 mL/min, Hex/^{i}PrOH 70/30)) as a yellow solid: mp 102 °C; $[\alpha]^{19}_D$ +50.2 (*c* 1.07, $CHCl_3$); IR (KBr) >3000, 1727, 1703 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.39 (3H, s), 2.47 (2H, t, J = 7.5 Hz), 3.32 (2H, t, J = 7.5 Hz), 3.45 (3H, s), 3.93 (9H, s), 3.95 (3H, s), 3.98 (3H, s), 6.82 (1H, s), 6.88 (1H, s), 7.24 (1H, s), 11.00 (1H, brs); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.7, 32.4, 35.9, 53.5, 56.7, 57.4, 62.5, 62.6, 62.9, 66.1, 100.4, 111.0, 113.0, 117.2, 118.2, 120.7, 123.6, 125.1, 134.2, 139.8, 143.2, 148.7, 149.5, 150.0, 151.2, 151.9, 152.5, 156.9, 158.9, 199.5, 202.8; HRMS calcd for $C_{31}H_{29}NO_9$ (M^+) 559.1842, found 559.1833.

(b) Methylation: K_2CO_3 (0.14 g, 1.0 mmol) and MeI (0.12 mL, 2.0 mmol) were added to a solution of the above product (56 mg, 0.10 mmol) in DMF (6.0 mL) at 0 °C under N_2 atmosphere, and the resulting mixture was stirred for 1 h at room temperature. Saturated aqueous NH_4Cl was added to the reaction mixture cooled in an ice−water bath, and the resulting solution was extracted with Et_2O. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by SiO_2 column chromatography with hexane−AcOEt (1/2) as an eluent to give (*S*)-**38** (49 mg, 87%, 97% ee by HPLC (CHIRALPAK AD, flow rate 1.0 mL/min, Hex/^{i}PrOH 70/30)) as a yellow solid: mp 98 °C; $[\alpha]^{19}_D$ +15.9 (*c* 0.76, $CHCl_3$); CD (*c* 1.1 × 10^{-5}, ^{i}PrOH) $[\theta]^{20}_{max}$ (nm) +5.9 × 10^4 (295), −0.98 × 10^4 (380); IR (KBr) 1732, 1703 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.38 (3H, s), 2.47 (2H, t, J = 7.5 Hz), 3.33 (2H, t, J = 7.5 Hz), 3.41 (3H, s), 3.82 (3H, s), 3.92 (3H, s), 3.96 (3H, s), 3.99 (9H, s), 6.84 (1H, s), 6.87 (1H, s), 7.24 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.7, 32.3, 36.2, 53.4, 56.5, 57.3, 62.2, 62.5, 63.0, 63.2, 66.2, 99.7, 111.1, 112.9, 117.1, 121.1, 124.4, 127.6, 131.0, 134.5, 139.2, 143.2, 148.6, 150.0, 150.8, 152.4, 153.6, 153.9, 156.8, 158.9, 199.2, 200.4; HRMS calcd for $C_{32}H_{31}NO_9$ (M^+) 573.1998, found 573.1982.

(2*S*)-3′-Formyl-4,5,6,8,9,9′-hexamethoxy-6′,7′-dihydrospiro[2*H*-benz[*f*]indene-2,8′-8′*H*-cyclopent[*g*]isoquinoline]-1,1′,(2′*H*),3-trione ((*S*)-39). (a) Demethylation: NaBr (0.41 g, 4.0 mmol) and *p*-TsOH·H_2O (0.16 g, 0.83 mmol) were added to a solution of (*S*)-**38** (19 mg, 33 μmol) in MeOH (15 mL) at room temperature, and the resulting solution was refluxed for 1.5 h at 80 °C. The reaction mixture was poured into saturated aqueous $NaHCO_3$. The mixture was extracted with AcOEt. The organic layer was washed with H_2O and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by SiO_2 column chromatography with CH_2Cl_2−AcOEt−MeOH (100/50/6) as an eluent to give the demethylated compound (18 mg, 95%, 97% ee by HPLC (CHIRALPAK AD, flow rate 1.0 mL/min, Hex/^{i}PrOH 67/33)) as a yellow solid: mp 157 °C; $[\alpha]^{20}_D$ +24.7 (*c* 0.94, $CHCl_3$); IR (KBr) 1732, 1703, 1661, 1651, 1620 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.19 (3H, s), 2.51 (2H, t, J = 7.5 Hz), 3.32 (2H, t, J = 7.5 Hz), 3.57 (3H, s), 3.87 (3H, s), 4.01 (3H, s), 4.02 (3H, s), 4.03 (3H, s),

4.04 (3H, s), 6.14 (1H, s), 6.89 (1H, s), 7.09 (1H, s,), 10.71 (1H, brs); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.8, 32.7, 35.8, 56.5, 57.4, 62.1, 62.2, 63.1, 63.3, 66.1, 99.6, 104.8, 116.0, 117.4, 121.1, 124.5, 127.7, 131.0, 134.8, 137.6, 139.2, 143.1, 150.8, 152.9, 153.6, 153.9, 156.1, 156.8, 162.5, 199.3, 200.5; HRMS calcd for $C_{31}H_{29}NO_9$ (M^+) 559.1842, found 559.1846.

(b) SeO_2 oxidation: SeO_2 (16 mg, 0.13 mmol) was added to a solution of the above product (41 mg, 74 μmol) in 1,4-dioxane (7.0 mL) at room temperature, and the resulting solution was refluxed for 1.5 h at 110 °C. The mixture was filtered through a Celite pad. The filtrate was concentrated in vacuo. The residue was purified by SiO_2 column chromatography with CH_2Cl_2-MeOH (50/3) and CH_2Cl_2-AcOEt−MeOH (50/25/2) as an eluent to give (*S*)-**39** (32 mg, 76%, 97% ee by HPLC (CHIRALPAK AD, flow rate 1.0 mL/min, Hex/^{i}PrOH 70/30)) as a yellow solid: mp 258 °C; $[\alpha]^{20}_D$ +30.3 (*c* 1.32, $CHCl_3$); IR (KBr) 1732, 1701−1653 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.60 (2H, t, J = 7.5 Hz), 3.42 (2H, t, J = 7.5 Hz), 3.61 (3H, s), 3.89 (3H, s), 4.04 (6H, s), 4.05 (3H, s), 4.07 (3H, s), 6.92 (1H, s), 7.05 (1H, s), 7.43 (1H, s), 8.76 (1H, brs), 9.52 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 32.7, 35.7, 56.6, 57.3, 62.3, 62.7, 63.2, 63.4, 66.6, 99.7, 118.2, 120.6, 120.7, 121.0, 124.3, 127.5, 131.0, 134.8, 139.3, 139.5, 140.4, 151.1, 153.8, 154.1, 154.2, 156.9, 157.0, 159.2, 183.8, 198.5, 199.7; HRMS calcd for $C_{31}H_{27}NO_{10}$ (M^+) 573.1634, found 573.1637.

Natural Enantiomer of Synthetic Fredericamycin A ((*S*)-1). *trans*-2-Butenylphosphonium bromide (0.25 g, 0.63 mmol) was stirred for 1 h at room temperature under Ar atmosphere to become a powder. THF (10 mL) was added to the powder, and the resulting mixture was cooled to −78 °C. ^{n}BuLi (0.41 mL, 1.5 M in hexane, 0.63 mmol) was added dropwise to the mixture, and the solution was stirred for 40 min at room temperature to form the ylide.

The obtained ylide (0.49 mL, 63 mM in THF, 31 μmol), cooled to −78 °C, was added dropwise to a solution of (*S*)-**39** (15 mg, 26 μmol) in THF (2.0 mL) at −78 °C under Ar atmosphere. The resulting mixture was allowed to stand at room temperature and stirred for 6 h. MeOH (1.0 mL) and saturated aqueous NH_4Cl were added to the reaction mixture successively, and the resulting solution was extracted with CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo, respectively. The combined residue was purified by SiO_2 column chromatography with CH_2Cl_2-MeOH (50/3) and benzene−*n*-hexane−EtOH (5/10/2−9/10/2) as eluents to give the yellow solid (7.1 mg, 46%, *E*−*E*:*E*−*Z* = 5:1): mp 172 °C; IR (KBr) 1734, 1707, 1638 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.71 (2.5H, major, d, J = 7.0 Hz), 1.81 (0.5H, minor, dd, J = 1.5, 7.0 Hz), 2.54 (2H, t, J = 7.5 Hz), 3.35 (2H, t, J = 7.5 Hz), 3.60 (3H, s), 3.90 (3H, s), 4.04 (6H, s), 4.05 (3H, s), 4.07 (3H, s), 5.66−5.72 (0.17H, minor, m), 5.88 (0.83H, major, dq, J = 7.0, 15.0 Hz), 6.08 (1H, d, J = 16.0 Hz), 6.15 (1H, dd, J = 10.5, 15.0 Hz), 6.31 (0.83H, major, s), 6.35 (0.17H, minor, s), 6.67 (0.83H, major, dd, J = 10.5, 16.0 Hz), 6.88−7.00 (0.17H, minor, m), 6.91 (1H, s), 7.17 (0.83H, major, s), 7.19 (0.17H, minor, s), 8.93 (0.17H, minor, brs), 9.07 (0.83H, major, brs); HRMS (FAB) calcd for $C_{35}H_{34}NO_9$ (M^+ + H) 612.2233, found 612.2240.

BBr_3 (0.10 mL, 1.0 M in CH_2Cl_2, 0.10 mmol) was added to a solution of the above solid (4.9 mg, 8.0 μmol) in CH_2Cl_2 (2.0 mL) at −78 °C under Ar atmosphere. The resulting mixture was stirred for 1 h at the same temperature. The reaction mixture was treated with H_2O (2.0 mL) and concentrated in vacuo at room temperature. THF (45 mL) and H_2O (15 mL) were added to the residue, and the resulting solution was stirred for 24 h at room temperature. The mixture was extracted with AcOEt. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by SiO_2 column chromatography with $CHCl_3-$MeOH−acetone−AcOH (93/3/3/1) and HPLC (Jasco Megapak SIL NH2-10, 1 × 25 cm, flow rate 5.0 mL/min, $CHCl_3-$*n*-hexane−AcOH 800/200/1) to give reddish solid, natural enantiomer of synthetic fredericamycin A (1.7 mg, 40%). The spectral data (^{1}H NMR, mp, IR, UV, CD, HRMS, HPLC, TLC) of the obtained natural enantiomer of synthetic fredericamycin A agreed with those of the natural one provided by the SS Pharmaceutical Co., Ltd., Japan.

(2*R*)-3′-Methyl-1′,4,5,6,8,9,9′-heptamethoxy-6′,7′-dihydrospiro-[2*H*-benz[*f*]indene-2,8′-8′*H*-cyclopent[*g*]isoquinoline]-1,3-dione ((*R*)-38). (a) [4+2]-Cyclocondensation: Similarly to the preparation of (*S*)-**38**, a solution of **36** (19 mg, 66 μmol) in THF (0.60 mL) was added dropwise to a suspension of NaH (3.2 mg, 60% in mineral oil, 79 μmol) in THF (0.30 mL) at 0 °C under Ar atmosphere, and the resulting mixture was stirred for 1.5 h at room temperature. A solution of **30** (20 mg, 44 μmol) in THF (0.60 mL) was added dropwise to the mixture cooled to 0 °C, and the reaction mixture was stirred for 1.5 h at room temperature. Similar workup and purification gave (*R*)-**37** (20 mg, 83%, 94% ee by HPLC (CHIRALPAK AD, flow rate 0.9 mL/min, Hex/^{i}PrOH 70/30)) as a yellow solid: mp 118 °C; $[\alpha]^{20}_D$ +18.0 (*c* 1.11, $CHCl_3$); IR (KBr) >3000, 1728, 1701 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.47 (3H, s), 2.53 (2H, t, J = 7.5 Hz), 3.38 (2H, t, J = 7.5 Hz), 3.52 (3H, s), 3.89 (3H, s), 4.01 (3H, s), 4.03 (3H, s), 4.08 (3H, s), 4.11 (3H, s), 6.88 (1H, s), 6.96 (1H, s), 7.32 (1H, s), 10.92 (1H, brs); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.7, 32.4, 35.9, 53.5, 56.6, 57.1, 62.3, 62.6, 63.2, 66.0, 97.9, 111.1, 113.0, 115.0, 115.8, 117.3, 126.4, 131.3, 134.0, 139.9, 143.3, 146.9, 148.8, 150.0, 152.6, 154.2, 154.3, 157.1, 158.9, 200.4, 202.5; HRMS calcd for $C_{31}H_{30}NO_9$ (M^+ + H) 560.1921, found 560.1934.

(b) Methylation: Similarly to the preparation of (*S*)-**38**, K_2CO_3 (7.4 mg, 54 μmol) and MeI (10 μL, 0.16 mmol) were added to a solution of the above product (6.0 mg, 11 μmol) in DMF (3.0 mL) at 0 °C in N_2 atmosphere, and the resultimg mixture was stirred for 2 h at room temperature. Similar workup and the purification gave (*R*)-**38** (5.2 mg, 85%, 94% ee by HPLC (CHIRALPAK AD, flow rate 1.0 mL/min, Hex/^{i}PrOH 70/30)) as a yellow solid. The spectroscopic data (mp, IR, ^{1}H NMR, ^{13}C NMR, HRMS) of (*R*)-**38** showed good agreement with those of (*S*)-**38**. $[\alpha]^{20}_D$ −15.1 (*c* 0.86, $CHCl_3$); CD (*c* 1.30 × 10^{-5}, ^{i}PrOH) $[\theta]^{20}_{max}$ (nm) −6.0 × 10^4 (295), +0.98 × 10^4 (383).

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Supporting Information Available: Experimental procedures for the synthesis of model systems and NMR spectra of all compounds lacking elemental analysis (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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