processes may proceed with retention of intrastrand, but must occur with breakage of interstrand stacking, such local structural fluctuations can result in local fluctuations of pairing strength within a duplex. To what extent such effects are significant in biological processes of the type mentioned above is an open, yet interesting, question. The definition of backbone inclination for helical duplexes and the application of this parameter for differentiating DNA and RNA duplex structures will be described in a forthcoming paper together with M. Egli (Northwestern University, Illinois, USA).

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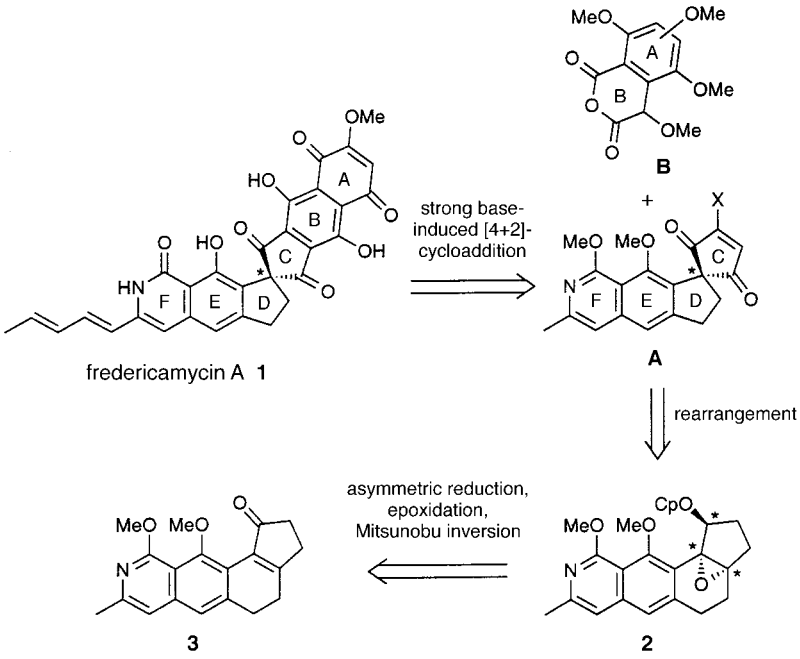
[10] Data of the homo-DNA duplexes No. 7, 9, and 10 were determined by S. Guntha (ETH, Zürich).

## Asymmetric Total Synthesis of Fredericamycin A**

Yasuyuki Kita,* Kazuhiro Higuchi, Yutaka Yoshida, Kiyosei Iio, Shinji Kitagaki, Shuji Akai, and Hiromichi Fujioka

Fredericamycin A (**1**), isolated from *Streptomyces griseus* in 1981, possesses potent antitumor activity against a variety of tumor models (in vivo) such as P388 leukemia, B16 melanoma, and CD8F mammary, and does not show mutagenicity in the Ames test.[1, 2] Its structure consists of two sets of *peri*-hydroxy tricyclic aromatic moieties connected through a spiro quaternary carbon center, which is made chiral by the presence of a single methoxy group at the farthest position on the A-ring. Its promising biological profile as well as its unprecedented unique structure has made **1** quite attractive as a lead compound for a novel type of chemotherapeutic drug for human cancers, and hence extensive attention is being focused on its total synthesis. In spite of the enormous efforts towards this goal, including the total syntheses of racemic **1** by five research groups[3–7] and a recently reported synthesis of optically pure **1** by HPLC separation of a racemic intermediate of **1** using a special chiral column,[8] no one has so far succeeded in the asymmetric total synthesis of **1**, and its absolute configuration still remains unknown. Most of the reported total syntheses and the related model studies involved the construction of the spiro CD-ring at their final stages, and the lack of sufficient methods for the enantiodifferentiation of the highly symmetrical AB-plane has been the major obstacle in these asymmetric approaches. We present here the first asymmetric total synthesis of **1** with definite absolute configuration of the spiro center, which elucidates the absolute configuration of natural **1** 17 years after its isolation.[9, 10]

Our synthetic strategy, outlined in Scheme 1, is based on the strong base-induced intermolecular [4+2] cycloaddition of a suitably functionalized homophthalic anhydride (**B**) to an optically pure dienophile (**A**) corresponding to the CDEF-moiety, in which the regiochemistry during the cycloaddition is known to be controlled by the substituent X on the dienophile.[11, 12] We envisaged that the cycloaddition of **A** having unambiguous absolute configuration would afford **1** with the retention of the chiral integrity. Since the absolute stereochemistry of **1** is unknown, any synthetic strategy to be developed should be planned in such a way that it allows the synthesis of both enantiomers readily. The dienophile **A** could be prepared from the optically pure *trans*-epoxy camphanate **2** through the stereospecific rearrangement which we have disclosed recently.[13] As per our previous study, **2** in turn could be prepared from the enone **3** by an asymmetric reduction of




Scheme 1. Retrosynthesis of fredericamycin A (**1**).

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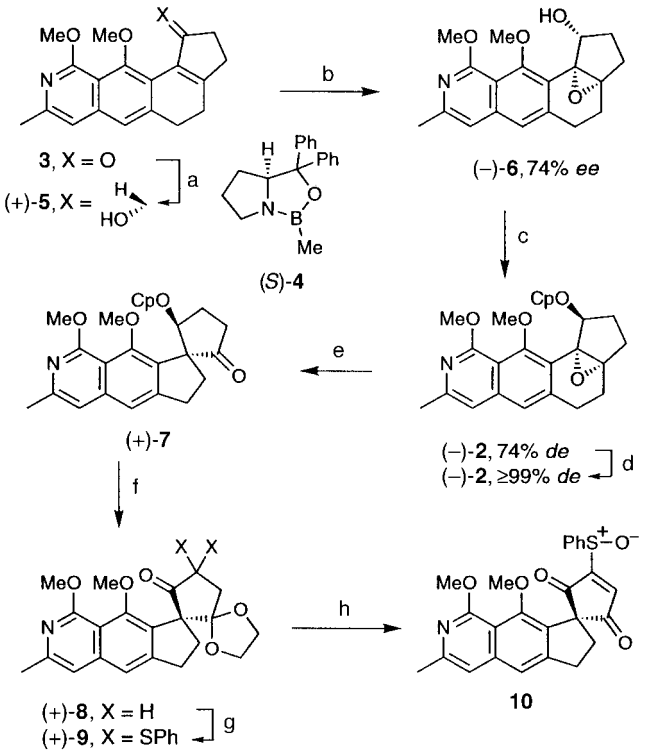
the keto group followed by the epoxidation of the olefin and Mitsunobu inversion of the hydroxy group.

On the basis of this retrosynthesis, we initially examined the transformation of **3**[14] to **2**. Asymmetric reduction of **3** using the chiral borane (*S*)-**4** and $BH_3 \cdot Me_2S$ as developed by Corey et al.[15] gave a quantitative yield of the (*R*)-alcohol (+)-**5** with 74% *ee* (Scheme 2).[16] Sharpless epoxidation of (+)-**5** afforded stereoselectively the *cis*-epoxy alcohol (−)-**6** (81%, 74% *ee*), which was treated with (−)-camphanic acid (>98% *ee*)

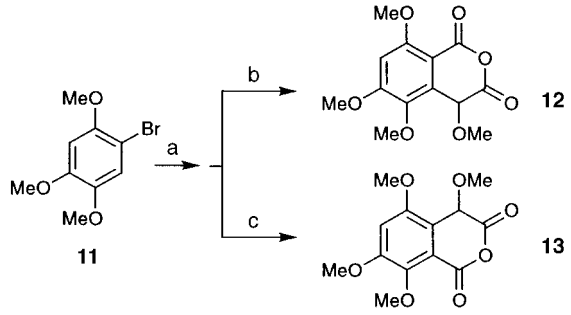



Scheme 2. Synthesis of the dienophile **10**. a) (*S*)-**4**, $BH_3 \cdot Me_2S$, THF, 0 °C, 98%; b) $[VO(acac)_2]$, $tBuO_2H$, $C_6H_6$, 0 °C → room temperature, 81%; c) CpOH, $Ph_3P$, diethyl azodicarboxylate, toluene, 0 °C → room temperature; d) $SiO_2$ column chromatography, 59% from (−)-**6**; e) $BF_3 \cdot Et_2O$, $CH_2Cl_2$, 0 °C, 94%; f) 1. $(CH_2OTMS)_2$, TMSOTf, $CH_2Cl_2$, 0 °C → room temperature, 93%, 2. 10% NaOH, MeOH, room temperature, 97%, 3. Dess–Martin periodinane, $CH_2Cl_2$, room temperature, 98%; g) $PhSSO_2Ph$, $LiN(TMS)_2$, THF, −78 °C → room temperature, 98%; h) 1. 85% aqueous $CF_3CO_2H$, 50 °C, 92%, 2. *m*-CPBA, $CH_2Cl_2$, −40 °C → room temperature, 93%. acac = acetylacetonate, Cp = (−)-camphanyl, *m*-CPBA = *m*-chloroperoxybenzoic acid, Tf = trifluoromethanesulfonyl, TMS = trimethylsilyl.

under Mitsunobu reaction conditions to give a diastereomeric mixture (74% *de*) of the *trans*-epoxy camphanate [(−)-**2**], from which optically pure (−)-**2** (≥99% *de*, ≥99% *ee*) was obtained by $SiO_2$-column chromatography.[16] The absolute configuration of (−)-**2** was determined by X-ray crystallographic analysis.[17]

The rearrangement reaction of (−)-**2** (≥99% *de*, ≥99% *ee*) using $BF_3 \cdot Et_2O$ proceeded at 0 °C with a perfect stereoselectivity to give a 94% yield of the spiro compound (+)-**7** (≥99% *ee*).[16] Based on our previous results,[13] the configuration of (+)-**7** was envisaged as depicted in Scheme 2 and finally ascertained by its X-ray crystallographic analysis.[17] Next, (+)-**7** was transformed to the dienophile **10** while keeping the chiral integrity by taking into consideration the following two points: 1) To prevent the easy racemization of the spiro keto camphanate (+)-**7** under alkaline conditions (NaOH/MeOH) by retro aldol reaction, acetalization was carried out prior to the alkaline hydrolysis of (+)-**7**. 2) According to our recent study,[18] a sulfinyl group was introduced as a powerful directing and activating substituent on the dienophile. Thus, $\alpha,\alpha$-disulfenylation of (+)-**8**, elimination of PhSH by treatment with an acid, and oxidation of sulfide gave **10** as a diastereomeric mixture (ca. 1:1).

The regioisomeric diene parts **12** and **13** were prepared from **11**[19] with some modifications of the reported method[12g] (Scheme 3). Reaction of **11** with dimethyl malonate (2.0 equiv), *n*BuLi (3.0 equiv), and tetramethylpiperidine (1.5 equiv) afforded a regioisomeric mixture (3:2) of the




Scheme 3. Synthesis of the diene precursors **12** and **13**. a) Dimethyl malonate, *n*BuLi, 2,2,6,6-tetramethylpiperidine, THF, −78 °C, 3:2 mixture of regioisomers, 58% in total; b) 1. $LiN(TMS)_2$, NBS, THF, −78 °C, 54%, 2. AgOTf, 2,6-lutidine, MeOH, $CH_2Cl_2$, 0 °C, 87%, 3. KOH, EtOH/$H_2O$, reflux, then 10% HCl, 98%, 4. trimethylsilyl(ethoxy)acetylene, $CH_2Cl_2$, room temperature, 80%; c) 1. $LiN(TMS)_2$, NBS, THF, −78 °C, 2. NaOMe, MeOH/$CH_2Cl_2$, −78 °C → room temperature, 60% over 2 steps, 3. KOH, EtOH/$H_2O$, reflux, then $CF_3CO_2H$, 71%, 4. trimethylsilyl(ethoxy)acetylene, $CH_2Cl_2$, room temperature, 91%. NBS = *N*-bromosuccinimide.

homophthalates, through a non-regioselective addition of the lithiomalonate to the aryne intermediate. Each regioisomer was readily separated and subjected to sequencial bromination, methanolysis, alkaline hydrolysis of the diester, and dehydration of the dicarboxylic acid by using trimethylsilyl(ethoxy)acetylene[20] to afford the corresponding anhydrides **12** and **13**. The regiochemistry of the products was determined by a nuclear Overhauser effect (NOE) experiment and further confirmed by X-ray crystallographic analysis.[17]

With both components for the [4+2] cycloaddition in hand, we then examined the intermolecular cycloaddition. Treatment of **12** with NaH (1.15 equiv) generated the anion, to which was added **10** at 0 °C. The reaction mixture was then stirred at room temperature for 7 h, and subsequent treatment with MeI in the presence of $K_2CO_3$ provided the hexacyclic compound (*R*)-**14** (71%, 90% *ee*). A similar reaction of **13** with **10** afforded the enantiomer (*S*)-**14** (76%, 97% *ee*) (Scheme 4).[16] Circular dichroism (CD) spectra of both enantiomers of **14** presented a couple of symmetrical curves (Figure 1), among which the CD of the (*S*)-isomer closely resembled that of the fully protected fredericamycin A reported by Boger et al.[8a] Hence, the following sequence of reactions to obtain **1** was performed on (*S*)-**14**. The F-ring was

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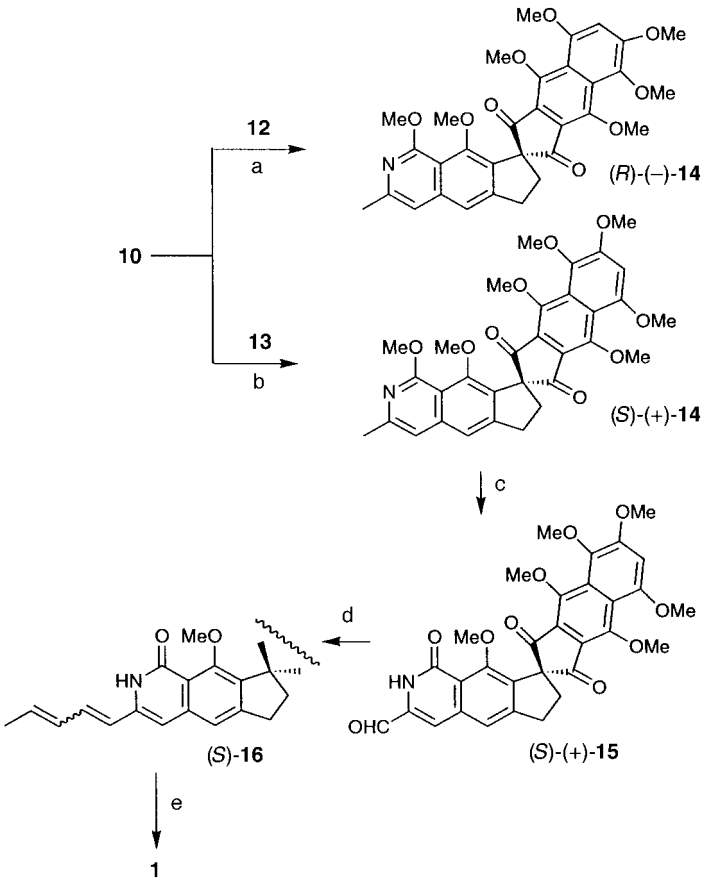


Scheme 4. Synthesis of fredericamycin A (**1**). a) 1. NaH, THF, 0 °C, 83 %, 2. MeI, $K_2CO_3$, DMF, room temperature, 85 %; b) same as a, 76 % over 2 steps; c) 1. TMSI, $CH_2Cl_2$, room temperature, 74 %, 2. $SeO_2$, 1,4-dioxane, reflux, 76 %; d) 2-butenyl(triphenyl)phosphonium bromide, *n*BuLi, THF, −78 °C →room temperature, 46 %; e) 1. $BBr_3$, $CH_2Cl_2$, −78 °C, 2. air, THF/$H_2O$, room temperature, 3. HPLC separation (see the text), 40 % from (*S*)-**16**.

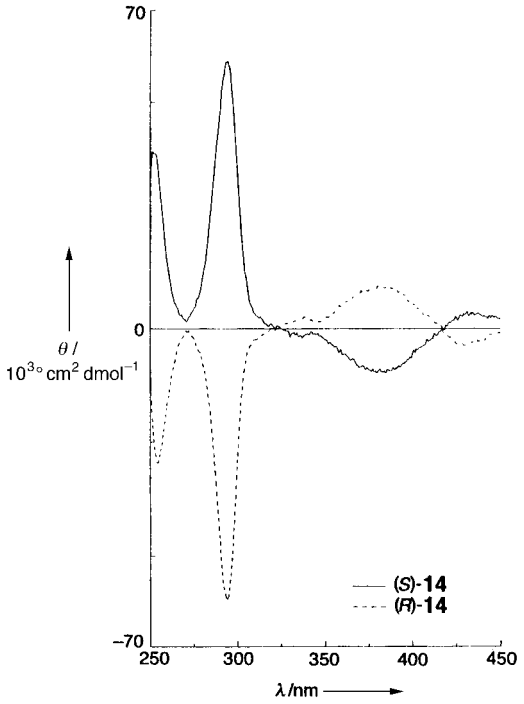


Figure 1. CD spectra of **14** in *i*PrOH.

selectively demethylated with trimethylsilyl iodide (TMSI)[4b] and the resulting compound was oxidized with $SeO_2$ to give the aldehyde (*S*)-**15**.[21] The pentadienyl side chain was introduced by using a standard Wittig reaction[3] to give a 5:1 mixture of (*E*,*E*)- and (*E*,*Z*)-(*S*)-**16** in 46 % yield. Deprotection of this mixture with $BBr_3$ (12.5 equiv) and subsequent autooxidation afforded a 5:1 mixture of the desired (*E*,*E*)-isomer (**1**) and its (*E*,*Z*)-isomer in a total yield of 74 % yield, from which the pure (*E*,*E*)-isomer **1** was separated by using HPLC column (Jasco Megapak SIL NH2-10, 1 × 25 cm, 800:200:1 $CHCl_3$/*n*-hexane/acetic acid, 5 mL min$^{-1}$ flow rate).[22] The spectral features of synthetic **1** ($^1$H NMR, IR, UV, CD, and HPLC) were completely identical with those of the isolated natural **1**. Thus, the absolute configuration of natural **1** was ascertained to be *S*.

In summary, the asymmetric total synthesis of fredericamycin A (**1**) has been accomplished for the first time and thereby the absolute configuration of its single chiral center established. This success also highlights the efficacy of our protocols; that is, 1) stereospecific rearrangement of the epoxy acylate and 2) the regiocontrolled intermolecular [4+2] cycloaddition of homophthalic anhydrides to dienophiles, for the construction of unique structures such as fredericamycin A (**1**), for which the reported methods are not effective.

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**Keywords:** asymmetric synthesis · antitumor agents · cycloadditions · natural products · rearrangements · total synthesis

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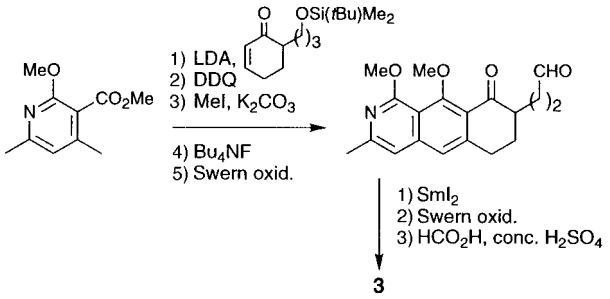
[14] The enone **3** was obtained from methyl 2-methoxy-4,6-dimethylpyridine-3-carboxylate as per Scheme 5. The details will be presented in the forthcoming full paper.




Scheme 5. Synthesis of **3**.

[15] E. J. Corey, R. K. Bakshi, S. Shibata, C.-P. Chen, V. K. Singh, *J. Am. Chem. Soc.* **1987**, *109*, 7925 – 7926.

[16] Optical purities of the intermediates (**5**, **6**, and **9**) were determined by HPLC using Daicel CHIRALCEL OD (*n*-hexane-*i*PrOH), and those of **2**, **7**, **8**, (*R*)- and (*S*)-**14**, and (*S*)-**15** by Daicel CHIRALPAK AD (*n*-hexane-*i*PrOH).

[17] Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC-102892 (for (−)-**2**), CCDC-102893 (for (+)-**7**), and CCDC-102894 {for methyl 2-methoxy-2-[3,4,6-trimethoxy-2-(methoxycarbonyl)phenyl]acetate, a precursor of **13**}. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

[18] We have recently elucidated that the dienophiles having sulfinyl group [X = S(O)Ph] are much more reactive for the anionic [4 + 2] cycloaddition to homophthalic anhydrides than the well known halogen-substituted ones.[11c]

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[22] Extensive research towards complete isomerization of the (*E*,*Z*)-**16** to its (*E*,*E*)-isomer by using a catalytic amount of $I_2$ in the dark under various conditions (in $CDCl_3$, $CHCl_3$, or $CH_2Cl_2$ at room temperature for two days to two weeks) as well as direct demethylation – isomerization by the combined use of $I_2$ and $BBr_3$ did not lead to the complete isomerization and, in some cases, caused gradual decomposition. Since **16** is sensitive to visible light leading to decomposition and diene-isomerization, the subsequent steps after chain elongation, that is, demethylation, autooxidation, and HPLC separation, were done immediately. The purified sample (**1**) readily isomerizes in organic solvents containing strong acids such as $CF_3COOH$.

## Regioselective Lactonization of $\alpha$-(2 → 8)-Trisialic Acid**

Mou-Chi Cheng, Chun-Hung Lin,* Kay-Hooi Khoo, and Shih-Hsiung Wu*

The polymer of $\alpha$-(2,8)-linked *N*-acetylneuraminic acids (poly(2,8-NeuAc)) is mainly distributed in mammalian cells and bacteria, and associated with many different biological functions.[1] It has been reported that $\delta$-lactonization, the condensation of the carboxyl group at C-2 of one residue with the hydroxyl group at C-9 of an adjacent residue, is observed in $\alpha$-2,8-linked polysialic acids at low pH.[2] Likewise, in gangliosides (glycosphingolipids containing one to three sialic acid moieties), $\delta$-lactone is also formed under acidic conditions.[3] The $\delta$-lactones of gangliosides have been suggested to be the true immunogens in the preparation of anti-ganglioside antibodies.[4] Since polysialic acid is a sugar polymer with highly negative charges, lactonization, which reduces the number of carboxylate groups, would influence the charge density. As a consequence, it was proposed that lactone formation may represent an on/off signal of a physiological function.[5]

Here we report the regioselective lactonization of the $\alpha$-2,8-linked trisialic acid. There are two lactonized sites in the sialic acid trimer, one at the reducing end and the other at the

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