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Enantiodivergent Synthesis of Either Enantiomer of ABCDE-Ring Analogue of Antitumor Antibiotic Fredericamycin A via Intramolecular [4 + 2] Cycloaddition Approach

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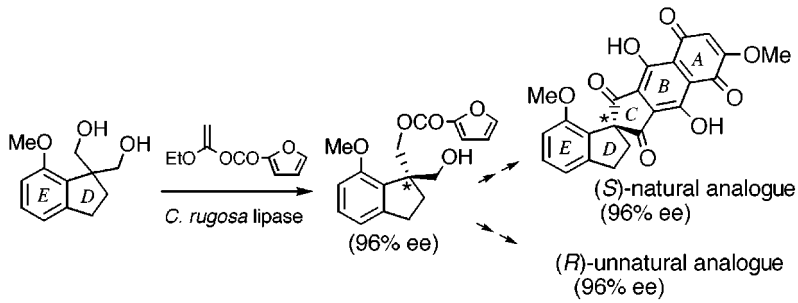
ABSTRACT



An intramolecular enantiodivergent synthesis of both enantiomers of the ABCDE-ring analogue 22 of fredericamycin A is reported. Key steps involve an intramolecular [4 + 2] cycloaddition of 17 and an aromatic Pummerer-type reaction of 19. A lipase-catalyzed enantioselective desymmetrization of prochiral diol 2 using 1-ethoxyvinyl 2-furoate 3 led to the pivotal intermediate (*R*)-4.

Due to potent antitumor activity against a variety of in vivo tumor models and negative mutagenicity in the Ames test, an antibiotic, fredericamycin A (**1**), has drawn much attention as a leading compound for developing novel types of chemotherapeutic drugs for human cancers.[1] **1** consists of two *peri*-hydroxy tricyclic aromatic moieties, connected through a chiral, spiro, quaternary carbon center, and its chirality arises from the presence of a single methoxy group at the farthest position of the A-ring. Intensive efforts have been made toward asymmetric total synthesis of **1**, including the total syntheses of racemic **1** by five research groups[2−6] and the HPLC separation of a racemic intermediate of **1** using a chiral column.[7] Until recently, no one had succeeded in

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(1) Isolation and structure elucidation: (a) Pandey, R. C.; Toussaint, M. W.; Stroshane, R. M.; Kalita, C. C.; Aszalos, A. A.; Garretson, A. L.; Wei, T. T.; Byrne, K. M.; Geoghegan, R. F., Jr.; White, R. J. *J. Antibiot.* **1981**, *34*, 1389. (b) Misra, R.; Pandy, R. C.; Silverton, J. V. *J. Am. Chem. Soc.* **1982**, *104*, 4478. Studies on biological activity: (c) Latham, M. D.; King, C. K.; Gorycki, P.; Macdonald, T. L.; Ross, W. E. *Cancer Chemother. Pharmacol.* **1989**, *24*, 167. (d) Dalal, N. S.; Shi, X. *Biochemistry* **1989**, *28*, 748.

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

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(6) Wendt, J. A.; Gauvreau, P. J.; Bach, R. D. *J. Am. Chem. Soc.* **1994**, *116*, 9921.

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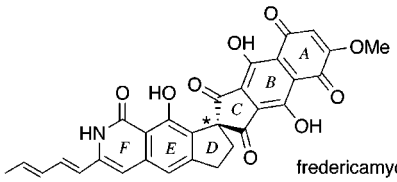
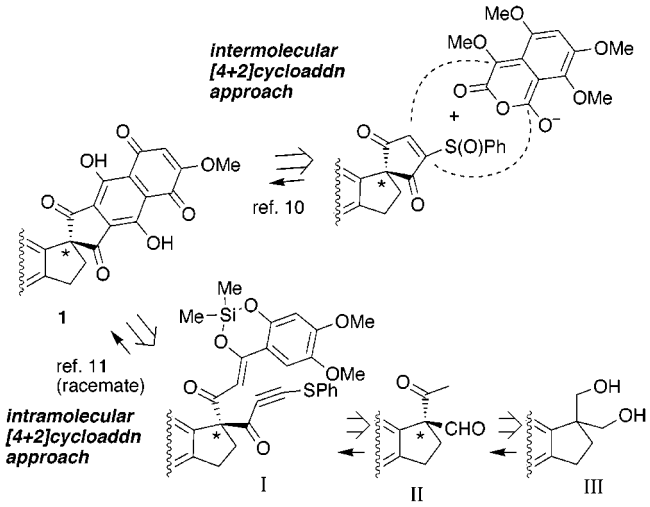
the asymmetric total synthesis of either **1** or its analogue[8] because of the lack of an efficient distinction of the enantio face of the highly symmetrical AB-plane.[9]



We have planned two different asymmetric approaches for **1** through an optically pure quaternary carbon intermediate with a definite stereochemistry at an early stage and the completion of the total synthesis while retaining its chiral integrity (Scheme 1). Accordingly, we have quite recently

Scheme 1

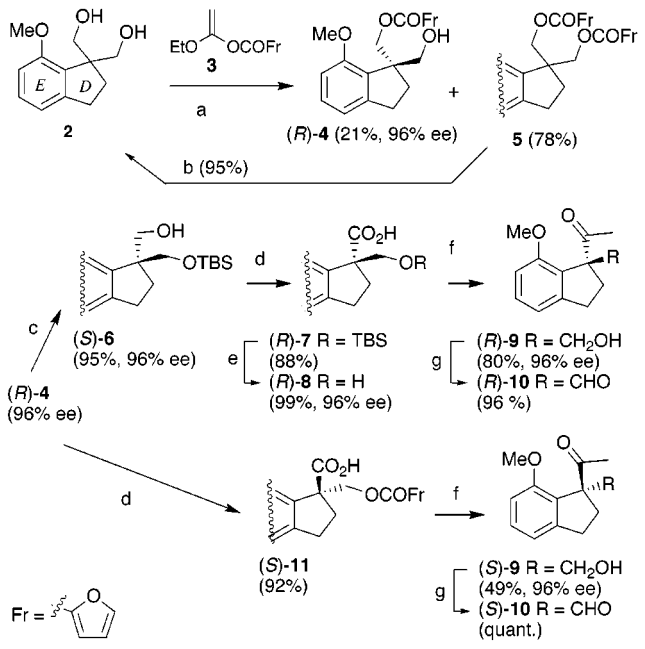


succeeded in the asymmetric total synthesis of natural **1** by the intermolecular cycloaddition approach, and the absolute stereochemistry of the natural product was determined for the first time.[10] Simultaneously, we have also achieved an intramolecular total synthesis of racemic **1**,[10c,11] which is believed to be useful for the asymmetric synthesis of optically active **1**. In this Letter we report an application of this intramolecular cycloaddition approach involving the intermediates **I**−**III** to the asymmetric synthesis of the optically active ABCDE-ring analogue **22**. Either enantiomer (*R*)- or (*S*)-**22** was obtained from a single key intermediate, (*R*)-**4**, with perfect retention of its chiral integrity.

Preparation of both enantiomers of the optically active keto aldehyde, (*R*)- and (*S*)-**10**, corresponding to **II**, was the first objective in this study. Creation of the chiral quaternary carbon center was performed by the lipase-catalyzed desymmetrization of prochiral diol **2** using 1-ethoxyvinyl 2-furoate **3**.[12] The desired (*R*)-**4** (21% yield, 96% ee) was obtained along with the diester **5** (78% yield), and **5** was recycled to **2** almost quantitatively. Silylation of (*R*)-**4** followed by saponification afforded the monosilyl ether (*S*)-**6** (95% yield, 96% ee). Stepwise oxidation of (*S*)-**6** by the Dess−Martin periodinane and then by $NaClO_2$ afforded the carboxylic acid (*R*)-**7** (88% yield), which was treated with $BF_3{\cdot}Et_2O$ to give (*R*)-**8** (99% yield, 96% ee).[13] Reaction of (*R*)-**8** with MeLi at 0 °C followed by quenching with aqueous NH_4Cl solution at −78 °C gave the keto-carbinol (*R*)-**9** (80% yield, 96% ee).[13] The Dess−Martin oxidation of (*R*)-**9** afforded (*R*)-**10** (96% yield). A similar two-step oxidation of (*R*)-**4** gave the carboxylic acid (*S*)-**11** (92% yield), which was then converted to (*S*)-**10** (49% yield, two steps) (Scheme 2).

To prepare the key intermediate (*S*)-**16**, the installation of the acetylene and the A-ring moieties to (*R*)-**10** without loss of its chiral integrity was troublesome. When the reaction

Scheme 2[a]



[a] (a) **3**, *Candida rugosa* lipase (Meito MY), iPr_2O, 30 °C; (b) K_2CO_3, MeOH; (c) 1. TBSCl, pyridine, DMF; 2. K_2CO_3, MeOH; (d) 1. Dess−Martin periodinane, MeCN, 2. $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH, H_2O; (e) $BF_3{\cdot}Et_2O$, CH_2Cl_2; (f) MeLi, HMPA, THF; (g) Dess−Martin periodinane, MeCN.

(7) Boger, D. L.; Hüter, O.; Mbiya, K.; Zhang, M. *J. Am. Chem. Soc.* **1995**, *117*, 11839.

(8) Studies in this field are well summarized in ref 7. For recent synthetic studies on the racemates, see: Baskaran, S.; Nagy, E.; Braun, M. *Liebigs Ann./Recl.* **1997**, 311. Clive, D. L. J.; Kong, X.; Paul, C. C. *Tetrahedron* **1996**, *52*, 6085. Evans, P. A.; Brandt, T. A. *Tetrahedron Lett.* **1996**, *37*, 1367. Perumal, P. T.; Venugopal, M.; Velusamy, T. P. *Indian J. Chem., Sect. B* **1996**, *35B*, 242.

(9) Quite a few methods applicable to asymmetric synthesis of **1** have been developed, see: (a) Toyota, M.; Terashima, S. *Terahedron Lett.* **1989**, *30*, 829. (b) Trypke, W.; Steigel, A.; Braun, M. *Synlett* **1992**, 827.

(10) (a) Kita, Y.; Higuchi, K.; Yoshida, Y.; Iio, K.; Kitagaki, S.; Akai, S.; Fujioka, H. *Angew. Chem., Int. Ed.* **1999**, *38*, 683. (b) Kita, Y.; Higuchi, K.; Yoshida, Y.; Iio, K.; Kitagaki, S.; Ueda, K.; Akai, S.; Fujioka, H. *J. Am. Chem. Soc.* **2001**, *123*, 3214. (c) For a review, see: Kita, Y.; Akai, S.; Fujioka, H. *J. Synth. Org. Chem. Jpn.* **1998**, *56*, 963.

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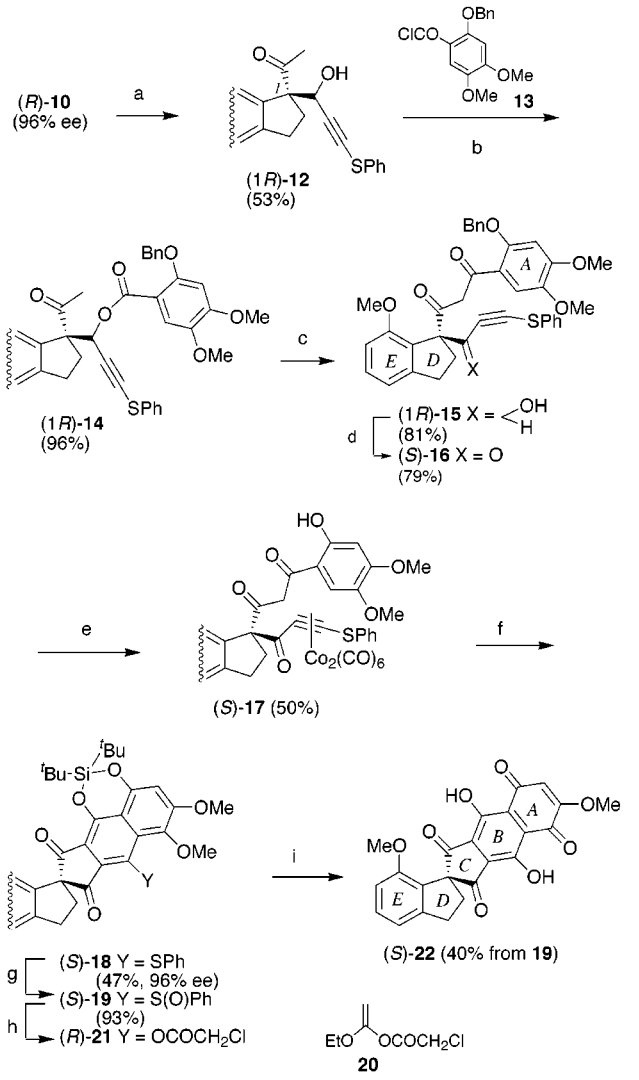
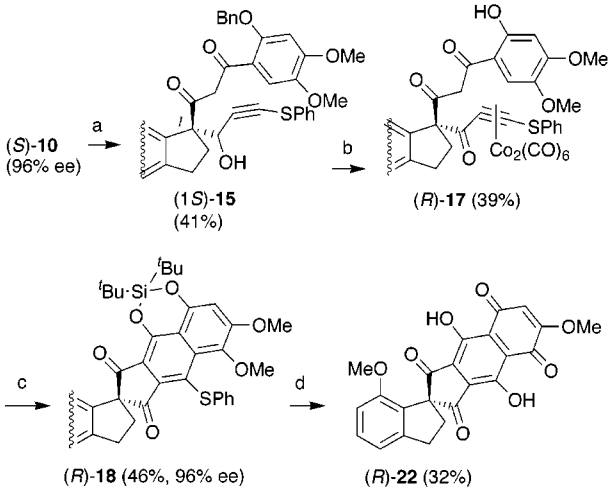
Scheme 3[a]



[a] (a) LiC≡CSPh, HMPA−THF, −78 °C; (b) **13**, DMAP, CH_2Cl_2; (c) $LiN(TMS)_2$, THF; (d) Moffatt oxidation; (e) 1. $Co_2(CO)_8$, CH_2Cl_2; 2. BCl_3, CH_2Cl_2; (f) 1. Me_2SiCl_2, Et_3N, chloranil, toluene, 100 °C; 2. $(t\text{-Bu})_2Si(OTf)_2$, Et_3N, DMF; (g) *m*-CPBA, CH_2Cl_2; (h) **20**, catalytic *p*-TsOH, toluene; (i) 1. Bu_4NF, THF−H_2O; 2. BBr_3, CH_2Cl_2; 3. 80% aqueous CF_3CO_2H.

Scheme 4[a]



[a] (a) 1. LiC≡CSPh, HMPA−THF, −78 °C; 2. **13**, DMAP, CH_2Cl_2; 3. $LiN(TMS)_2$, THF; (b) 1. Moffatt oxidation; 2. $Co_2(CO)_8$, CH_2Cl_2; 3. BCl_3, CH_2Cl_2; (c) 1. Me_2SiCl_2, Et_3N, chloranil, toluene, 100 °C; 2. $(t\text{-Bu})_2Si(OTf)_2$, Et_3N, DMF; (d) 1. *m*-CPBA, CH_2Cl_2; 2. **20**, catalytic *p*-TsOH, toluene; 3. Bu_4NF, THF−H_2O; 4. BBr_3, CH_2Cl_2; 5. 80% aqueous CF_3CO_2H.

of (*R*)-**10** (96% ee) with lithium phenylthioacetylide was carried out at room temperature, unexpected racemization of the quaternary carbon center at the C-1 position was brought about.[14] This problem was overcome by running the reaction at −78 °C and quenching at the same temperature to give (1*R*)-**12** (53% yield, 96% ee) as a single diastereomer. Acylation of (1*R*)-**12** with **13** gave (1*R*)-**14** (96% yield), which was treated with $LiN(TMS)_2$ (3 equiv) in THF to induce the migration of the A-ring aroyl moiety to the methyl ketone terminus giving (1*R*)-**15** (81% yield). Moffatt oxidation of (1*R*)-**15** afforded the trione (*S*)-**16** (79% yield).

The following manipulation of (*S*)-**16** was performed similarly to the total synthesis of the racemate[11] without any problem. Thus, treatment of (*S*)-**16** with $Co_2(CO)_8$ followed by debenzylation provided the cobalt complex (*S*)-**17** (50% yield), which was subjected to intramolecular [4 + 2] cycloaddition under the standard reaction conditions to afford the pentacyclic product (*S*)-**18** (47% yield). The optical purity of (*S*)-**18** was determined to be 96% ee by chiral HPLC analysis, and the perfect retention of the chiral integrity of (*R*)-**4** was confirmed. Oxidation of (*S*)-**18** to (*S*)-**19** followed by aromatic Pummerer-type reaction using 1-ethoxyvinyl chloroacetate **20** in refluxing toluene[15] introduced a hydroxyl group to the B-ring. The crude product (*R*)-**21** was subjected to stepwise deprotection to afford the optically active ABCDE-ring analogue (*S*)-**22** having the same absolute stereochemistry as natural **1** (Scheme 3).[16]

The same transformation was applied to (*S*)-**10** (96% ee) to provide the unnatural enantiomer (*R*)-**22** [96% ee based on the optical purity of (*R*)-**18**] (Scheme 4).[16] A symmetrical pair in the CD spectra of (*S*)- and (*R*)-**22** was obtained

(12) Akai, S.; Naka, T.; Fujita, T.; Takebe Y.; Kita, Y. *Chem. Commun.* **2000**, 1461.

(13) Special care was needed for the desilylation of (*R*)-**7** and the reaction of (*R*)-**8** with MeLi, because a partial racemization of them was often observed under basic conditions. For instance, the reaction of (*R*)-**8** with MeLi at 0 °C followed by quenching at the same temperature gave (*R*)-**9** in ≤92% ee.

(14) The racemization may arise from a retro-aldol-aldol process of the intermediate *β*-oxidoketone corresponding to **12**. A similar reaction was observed during a study of the asymmetric total synthesis of **1**.[10] A detailed investigation about this racemization is now in progress and will be discussed in the near future.

(15) (a) Kita, Y.; Takeda, Y.; Matsugi, M.; Iio, K.; Gotanda, K.; Murata K.; Akai, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1529. See also, (b) Kita, Y.; Takeda, Y.; Iio, K.; Yokogawa, K.; Takahashi, K.; Akai, S. *Tetrahedron Lett.* **1996**, *37*, 7545. (c) Akai, S.; Takeda, Y.; Iio, K.; Takahashi, K.; Fukuda, N.; Kita, Y. *J. Org. Chem.* **1997**, *62*, 5526.

(16) Due to the poor solubility of **22** in various organic solvents and its deep color, determination of its optical purity was difficult. All new compounds were fully characterized by spectroscopic means and combustion analysis.

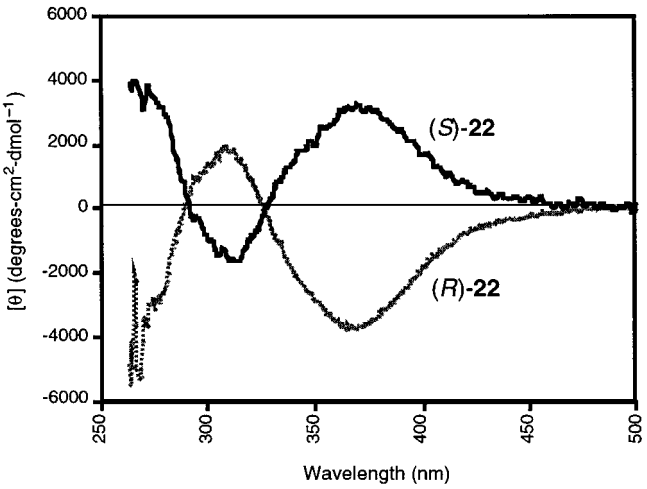


Figure 1. CD spectra of (*S*)- and (*R*)-**22**.

(Figure 1). The spectroscopic data (IR, ^{1}H NMR, ^{13}C NMR, HRMS) of (*S*)- and (*R*)-**22** showed good agreement with its structure.[17]

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Supporting Information Available: ^{1}H and ^{13}C NMR data of (*S*)-**22** and racemic **23**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) The similarity of the ^{1}H and ^{13}C NMR data of (*S*)-**22** with those of racemic **23** [Boger, D. L.; Jacobson, I. C. *J. Org. Chem.* **1991**, *56*, 2115] also supports its structure (In detail, see: Supporting Information).