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Total Synthesis of Natural (+)-FR900482. 3. Completion of the Synthesis

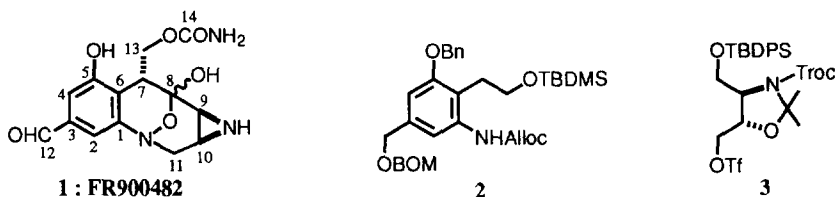
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Abstract: The title synthesis was accomplished by featuring (i) coupling of the aromatic fragment **2** with the optically active aliphatic fragment **3** to install the requisite carbon unit (**2+3**→**4**); (ii) intramolecular aldol reaction of the highly functionalized dialdehyde **10** to produce the desired eight-membered ring system **11** (**10**→**11**); (iii) epimerization of the C-7 position of hydroxy ketone **14** to obtain the correct stereochemistry (**14**→**15**); (iv) internal hemiacetal formation of hydroxylamino ketone **23** in situ generated from ketone **22** to construct the requisite tetracyclic ring system **24** (**23**→**24**) as key steps. Copyright © 1996 Elsevier Science Ltd

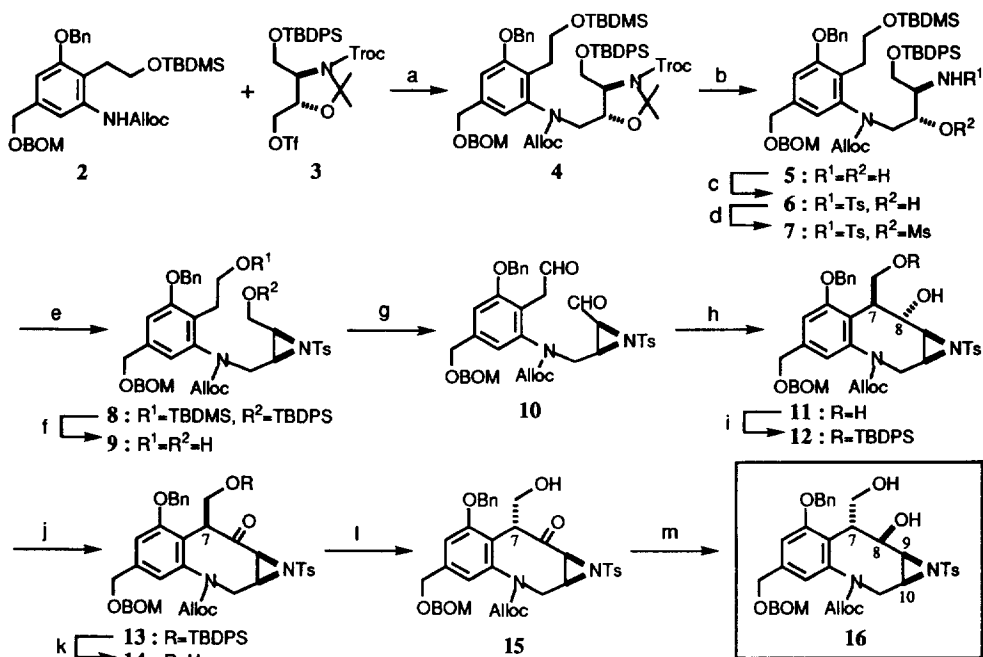
(+)-FR900482 (**1**) isolated from *Streptomyces sandaensis* No.6897, has been the subject of recent synthetic endeavors due to its unique structure and significant antitumor activity.¹ As detailed in the preceding paper,² we have succeeded in developing facile and efficient synthetic routes to the aromatic and the optically active aliphatic fragments **2** and **3** required for the total synthesis of (+)-**1** (**Figure 1**). We describe here the first enantioselective total synthesis of natural (+)-**1** in a convergent manner utilizing **2** and **3** as the key fragments. Our synthetic strategy involves the following four key steps : (i) coupling reaction of **2** with **3** to install the requisite carbon unit (**2+3**→**4**) (**Scheme 1**); (ii) intramolecular aldol reaction of the highly functionalized dialdehyde **10** to produce the desired eight-membered ring system **11** representing the core skeleton of **1** (**10**→**11**) (**Scheme 1**); (iii) epimerization at the C-7 position of hydroxy ketone **14** to obtain the correct stereochemistry (**14**→**15**) (**Scheme 1**); (iv) internal hemiacetal formation of hydroxylamino ketone **23** to construct the requisite tetracyclic ring system **24** (**23**→**24**) (**Scheme 2**).

Figure 1. Structures of FR900482 (**1**) and the Aromatic and Aliphatic Fragments **2** and **3**



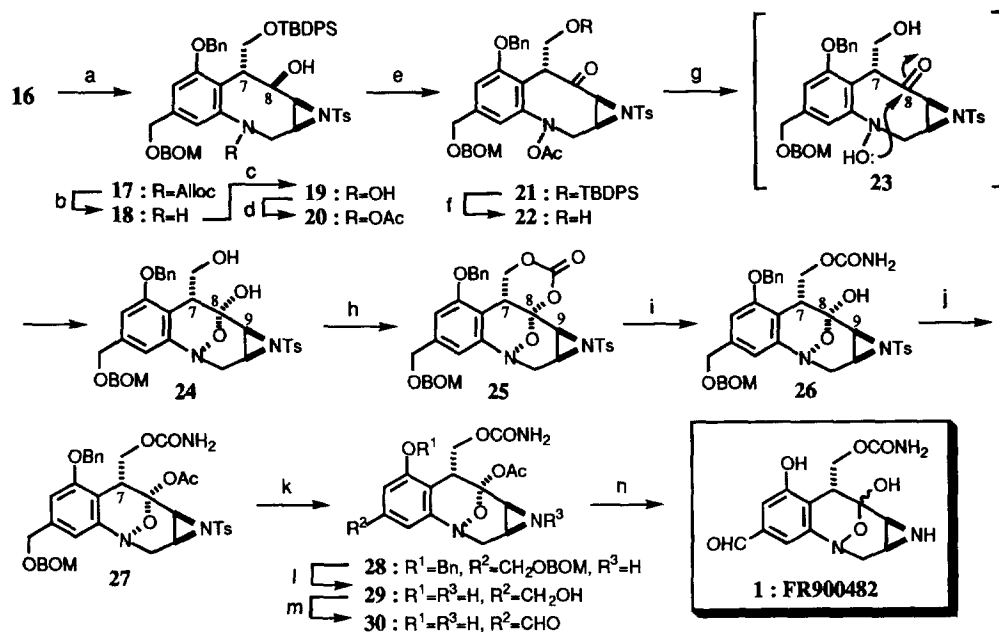
First, we undertook the synthesis of the eight-membered key intermediate **16** possessing the requisite core skeleton and functional groups with the correct absolute stereochemistries at the C-7, C-9, and C-10 positions as shown in **Scheme 1**. Thus, the critical coupling reaction of **2** with **3** proceeded cleanly to give the desired adduct **4**, $[\alpha]_D^{20} -0.2^\circ$ (c 1.15, CHCl_3), in a quantitative yield. Simultaneous removal of the 2,2,2-trichloroethoxycarbonyl (Troc)³ and the acetonide groups in **4** followed by chemoselective tosylation of the amino group⁴ in the resulting amino alcohol **5**, provided *N*-protected amino alcohol **6** (77%, 2 steps), $[\alpha]_D^{20} +4.7^\circ$

Scheme 1. Synthesis of the Eight-Membered Key Intermediate 16



(*c* 1.07, CHCl₃). This was elaborated to *N*-protected aziridine **8** (86%, 2 steps), [α]_D²⁰ -8.7° (*c* 1.20, CHCl₃), by mesylation of the secondary hydroxy group in **6** and subsequent treatment of the resulting mesylate **7** with sodium hydride in the presence of imidazole in refluxing THF.⁵ Both of the two silyl protecting groups in **8** were cleanly removed by treatment with hydrogen fluoride-pyridine complex⁶ in pyridine, providing diol **9** (99%), [α]_D²⁰ -9.6° (*c* 0.94, CHCl₃). Subsequent Dess-Martin oxidation⁷ of the two primary hydroxy groups in **9** furnished the key cyclization precursor **10** (98%), [α]_D²⁰ -4.0° (*c* 1.09, CHCl₃). The crucial intramolecular aldol reaction was best carried out by treating a solution of **10** in THF (0.01 M) with LiN(TMS)₂ (1.0 equiv) at -78°C followed by warming to -5°C. After reduction with sodium borohydride, the requisite cyclization product **11**, [α]_D²⁰ +96.5° (*c* 1.07, CHCl₃), was obtained as a sole product in 42% yield along with a recovery of **9** (33%).⁸ The stereostructure of **11** wherein the configuration at the C-7 position is incorrect, was unambiguously established as depicted by X-ray diffraction analysis of its bis(*p*-bromobenzoate) derivative.⁹ Consequently, it appeared evident that the C-7 stereochemistry in **11** should be inverted. After considerable experiments, the inversion of the C-7 stereochemistry could be realized by base-catalyzed epimerization¹⁰ of hydroxy ketone **14**, [α]_D²⁰ +5.6° (*c* 1.07, CHCl₃), derived from **11** via a three-step sequence involving selective silylation of the primary hydroxy group, Dess-Martin oxidation of the resulting silyl ether **12**, and desilylation of ketone **13** with hydrogen fluoride-pyridine complex.⁶ Thus, **14** was treated with 1,8-diazabicyclo[5,4,0]-undec-7-ene (DBU) in THF at ambient temperature for 2 h,¹¹ leading to an equilibrium mixture of **14** and **15** in

Scheme 2. Completion of the Total Synthesis of Natural (+)-FR900482 (1)



a ratio of *ca.* 1 : 2.¹² Fortunately, this mixture could be readily separated by column chromatography on silica gel to give the desired product **15** (64%), [α]_D²⁰ -17.6° (*c* 0.91, CHCl₃), possessing the correct configuration at the C-7 position, along with the starting material **14** (31% recovery). Finally, **15** was reduced with sodium borohydride to afford **16** (87%), [α]_D²⁰ -36.4° (*c* 0.89, CHCl₃), as a single diastereomer, whose stereostructure was rigorously confirmed by single crystal X-ray analysis of the corresponding bis(*p*-bromobenzoate) derivative.⁹

With the key intermediate **16** in hand, our next efforts were devoted to completion of the total synthesis of natural (+)-**1**. Towards this end, **16** was converted to acetate **20** (27%, 4 steps), [α]_D²⁰ +12.1° (*c* 1.06, CHCl₃), as shown in Scheme 2 via a sequence of the reactions involving selective silylation of the primary hydroxy group in **16**, palladium (0)-catalyzed cleavage of the *N*-allyloxycarbonyl (Alloc)¹³ group in silyl ether **17**, oxidation of the liberated amine **18** with *m*-chloroperbenzoic acid (MCPBA),¹⁴ and chemoselective acetylation of hydroxylamine **19**. Dess-Martin oxidation⁷ of **20** followed by desilylation of the resulting ketone **21** furnished alcohol **22** (77%, 2 steps), [α]_D²⁰ +32.4° (*c* 1.04, CHCl₃). One of the critical steps in our synthetic scheme was anticipated to be the internal hemiacetalization^{14,15} of hydroxylamine **23** *in situ* generated by removal of the acetyl group of **22** to provide the requisite tetracyclic compound **24**. In the event, removal of the acetyl group in **22** by treatment with potassium carbonate in methanol cleanly produced **23**, which spontaneously underwent the internal hemiacetalization to give **24**¹⁶ (89%) as a sole product. This was allowed to react with phosgene dimer (trichloromethyl chloroformate), and the resulting cyclic carbonate **25**,¹⁶ [α]_D²⁰ +30.4° (*c* 0.97, CHCl₃), was subjected to ammonolysis,¹⁴ giving rise to urethane **26**¹⁶ (76%, 2 steps), [α]_D²⁰

-14.9° (*c* 1.03, CHCl₃). Further acetylation of the hydroxy group in **26** afforded the key relay compound **27** (87%), mp 129-131°C [lit.¹⁷ mp 130-132°C], [α]_D²⁰ +66.8° (*c* 0.78, CHCl₃) [lit.¹⁷ [α]_D²⁰ +68.1° (*c* 0.76, CHCl₃)], whose spectroscopic properties (IR, ¹H-NMR, MS) were identical with those of the authentic sample¹⁷ prepared from FK973, the triacetyl derivative of **1**. Finally, **27** was converted to (+)-FR900482 (**1**), mp 174°C (dec) [lit.¹⁸ mp 175°C (dec)], [α]_D²³ +7.9° (*c* 0.97, H₂O) [lit.¹⁸ [α]_D²³ +8.0° (*c* 1.00, H₂O)], in the same manner as described in the preceding paper.¹⁷ The synthesized **1**¹⁹ was identical with a natural sample of **1** in all spectroscopic properties (IR, ¹H-NMR, MS).

In summary, we have succeeded in completing the first enantioselective total synthesis of natural (+)-FR900482 (**1**) in a convergent manner starting from 5-hydroxyisophthalic acid and L-diethyl tartrate. Since the explored synthetic scheme appears to be highly general and flexible to produce various structural types of the congeners of **1** in enantiomerically pure forms, these studies may open an opportunity for developing novel anticancer agents related to **1**. By employing the synthetic strategy explored in these studies, the enantioselective total syntheses of unnatural *ent*-**1**, 7-*epi*-FR900482, and *ent*-7-*epi*-FR900482 are presently being pursued in our laboratories.

Acknowledgments:

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References and Notes:

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8. Detailed discussions on the mechanism of the intramolecular aldol reaction will be presented in a full account.
9. To be published in a separate paper.
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12. When silyl ether **13** was employed as the substrate for the epimerization, none of the epimerized product was isolated, but the same enone as obtained from both **14** and **15** was produced by elimination of the siloxy moiety (see, ref. 11) in an almost quantitative yield.
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19. This compound was further converted to the triacetyl derivative, which was identical with an authentic sample of FK973.