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

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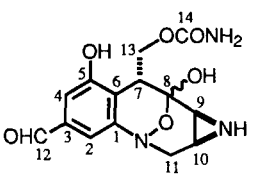
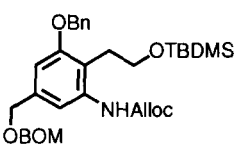
Abstract: *The title synthesis was accomplished by featuring (i) coupling of the aromatic fragment* **2** *with the optically active aliphatic fragment* **3** *to install the requisite carbon unit (* **2+3→4** *); (ii) intramolecular aldol reaction of the highly functionalized dialdehyde* **10** *to 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**).

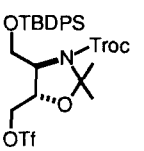
Figure 1. Structures of FR900482 (**1**) and the Aromatic and Aliphatic Fragments **2** and **3**



1 : FR900482



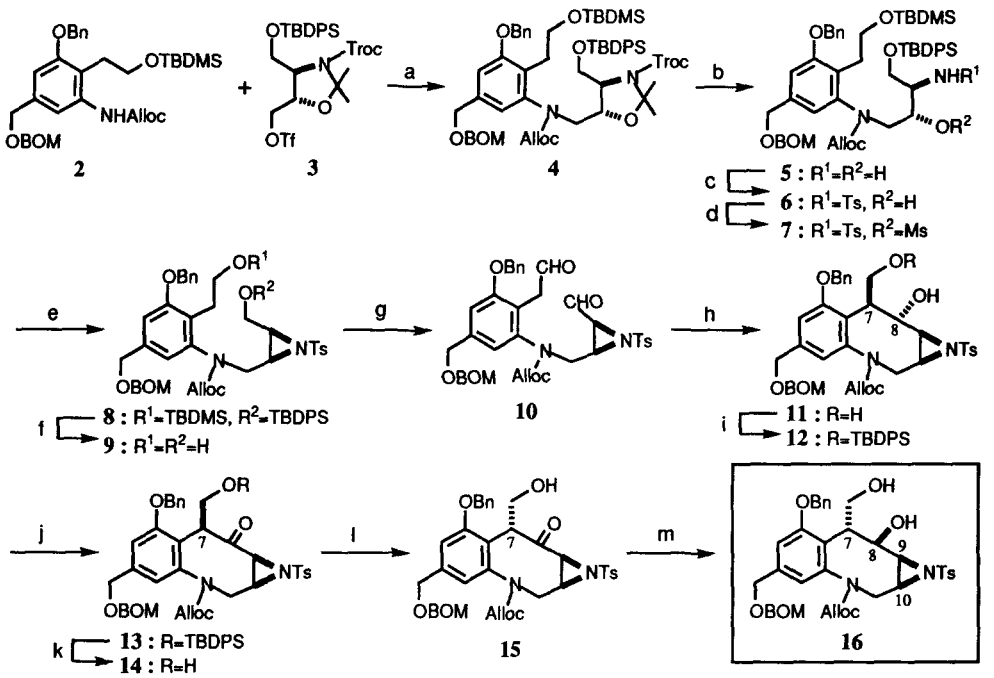
2



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° (*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 group[4] in the resulting amino alcohol **5**, provided *N*-protected amino alcohol **6** (77%, 2 steps), $[\alpha]_D^{20}$ +4.7°

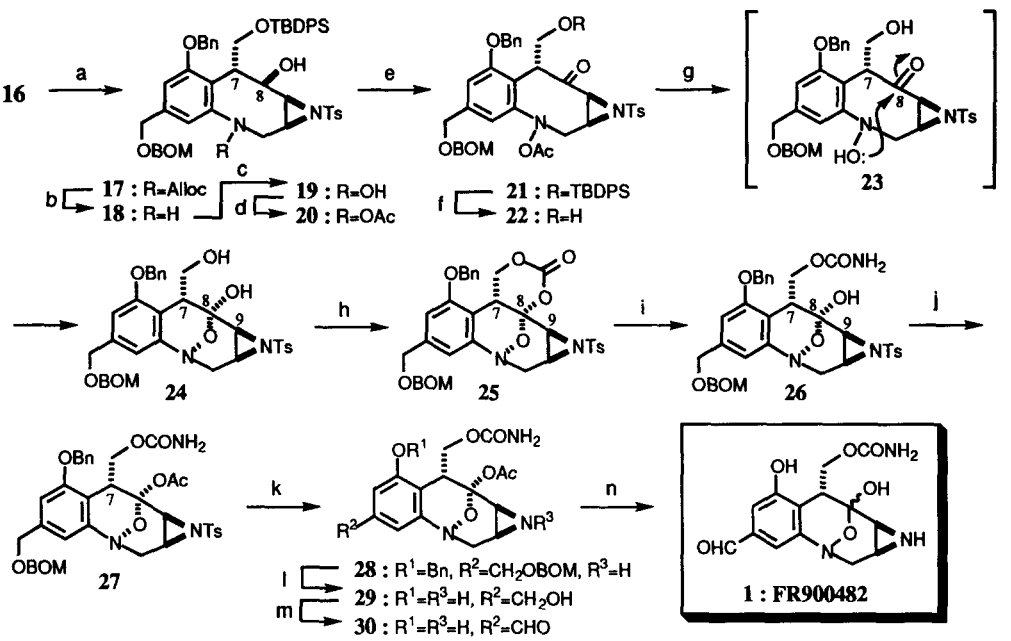
Scheme 1. Synthesis of the Eight-Membered Key Intermediate **16**



a) NaH, THF, -78°C→rt, 100% b) Zn, AcOH, THF-H_2O, rt c) TsCl, Et_3N, DMF, 0°C→rt, 77% (2 steps) d) MsCl, Et_3N, CH_2Cl_2, 0°C→rt, 94% e) NaH, imidazole, THF, reflux, 92% f) $(HF)_n$·Py, Py, 0°C, 99% g) Dess-Martin periodinane, CH_2Cl_2, rt, 98% h) $LiN(TMS)_2$, THF, -78→-5°C ; $NaBH_4$-H_2O, -5→0°C, 42% i) TBDPSCl, Et_3N, DMAP, CH_2Cl_2, rt, 79% j) Dess-Martin periodinane, CH_2Cl_2, rt, 93% k) $(HF)_n$·Py, Py, 0°C→rt, 93% l) DBU, THF, rt ; separation (64% for **15**, 31% for **14**) m) $NaBH_4$, THF-H_2O, 0°C→rt, 87%

(*c* 1.07, $CHCl_3$). This was elaborated to *N*-protected aziridine **8** (86%, 2 steps), $[\alpha]_D^{20}$ -8.7° (*c* 1.20, $CHCl_3$), 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 complex[6] in pyridine, providing diol **9** (99%), $[\alpha]_D^{20}$ -9.6° (*c* 0.94, $CHCl_3$). Subsequent Dess-Martin oxidation[7] of the two primary hydroxy groups in **9** furnished the key cyclization precursor **10** (98%), $[\alpha]_D^{20}$ -4.0° (*c* 1.09, $CHCl_3$). 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**, $[\alpha]_D^{20}$ +96.5° (*c* 1.07, $CHCl_3$), 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 epimerization[10] of hydroxy ketone **14**, $[\alpha]_D^{20}$ +5.6° (*c* 1.07, $CHCl_3$), 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) TBDPSCl, Et_3N, DMAP, CH_2Cl_2, rt, 71% b) $Pd(PPh_3)_4$, PPh_3, THF, rt, 83% c) MCPBA, CH_2Cl_2, -5°C, 67% d) Ac_2O, $NaHCO_3$, rt, 69% e) Dess-Martin periodinane, CH_2Cl_2, rt, 88% f) $(HF)_n$•Py, Py, 0°C→rt, 88% g) K_2CO_3, MeOH, 0°C→rt, 89% h) $Cl_3COCOCl$, Py, 0°C→rt, 81% i) NH_3, THF, 0°C→rt, 94% j) Ac_2O, Py, DMAP, rt, 87% k) sodium naphthalenide, DME, -70°C, 84% l) H_2, 10%Pd-C, EtOAc, rt, 81% m) $(COCl)_2$, DMSO, CH_2Cl_2, -78°C ; Et_3N, 88% n) NH_3, MeOH, rt, 73%

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%), $[\alpha]_D^{20}$ -17.6° (*c* 0.91, $CHCl_3$), 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 afforded **16** (87%), $[\alpha]_D^{20}$ -36.4° (*c* 0.89, $CHCl_3$), 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), $[\alpha]_D^{20}$ +12.1° (*c* 1.06, $CHCl_3$), 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 oxidation[7] of **20** followed by desilylation of the resulting ketone **21** furnished alcohol **22** (77%, 2 steps), $[\alpha]_D^{20}$ +32.4° (*c* 1.04, $CHCl_3$). 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] $[\alpha]_D^{20}$ +30.4° (*c* 0.97, $CHCl_3$), was subjected to ammonolysis,[14] giving rise to urethane **26**[16] (76%, 2 steps), $[\alpha]_D^{20}$

-14.9° (*c* 1.03, $CHCl_3$). 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], $[\alpha]_D^{20}$ +66.8° (*c* 0.78, $CHCl_3$) [lit.[17] $[\alpha]_D^{20}$ +68.1° (*c* 0.76, $CHCl_3$)], whose spectroscopic properties (IR, ^{1}H-NMR, MS) were identical with those of the authentic sample[17] 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)], $[\alpha]_D^{23}$ +7.9° (*c* 0.97, H_2O) [lit.[18] $[\alpha]_D^{23}$ +8.0° (*c* 1.00, H_2O)], 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, ^{1}H-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.

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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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11. Prolonged reaction times caused dehydration of both **14** and **15** to produce the same exocyclic enone.
12. When silyl ether **13** was employed as the substrate for the epimerization, none of the emiperized 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.
13. See the reference 9 in the preceding paper.
14. Fukuyama, T., Xu, L., Goto, S., *J. Am. Chem. Soc.*, **1992**, *114*, 383-385.
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16. The stereochemistry at the C-8 position of this compound was determined by a clear NOE between the signals due to C7-H and C9-H observed in the 400MHz ^{1}H-NMR spectrum. A related assignment of the C-8 stereochemistries has been reported for the structure determination of **1**, see, Uchida, I., Takase, S., Kayakiri, H., Kiyoto, S., Hashimoto, M., Tada, T., Koda, S., Morimoto, Y., *J. Am. Chem. Soc.*, **1987**, *40*, 4108-4109.
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19. This compound was further converted to the triacetyl derivative, which was identical with an authentic sample of FK973.

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