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Total Synthesis of Natural (+)-FR900482. 1. Synthetic and End-Game Strategies

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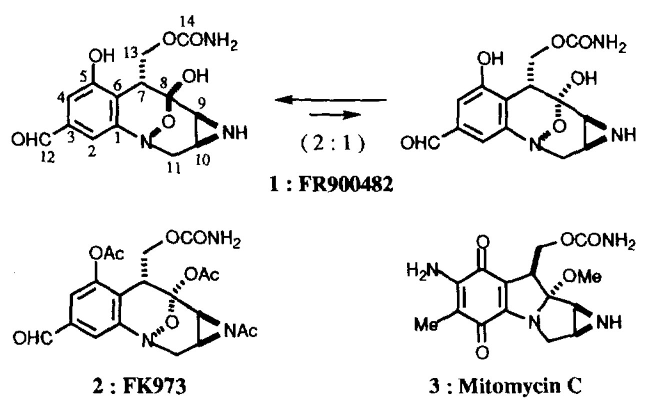
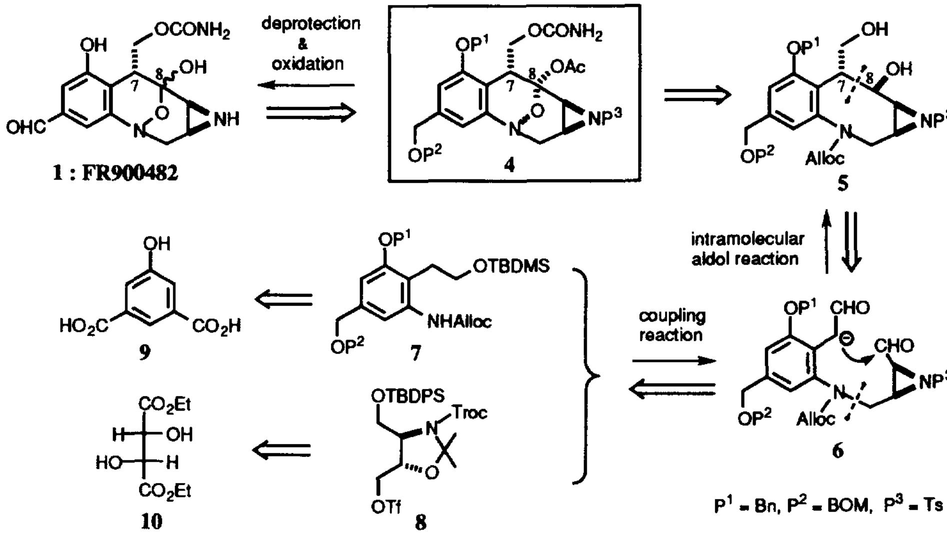
Abstract: *A synthetic strategy for natural (+)-FR900482 (1) was developed by featuring a convergent and enantioselective sequence which commences with 5-hydroxyisophthalic acid and L-diethyl tartrate. The proposed key intermediate 4 was synthesized starting from FK973, the triacetyl derivative of 1, and successful reconversion of 4 into 1 was also achieved. These preliminary studies definitely demonstrated that 4 is suitable as a potential relay compound toward 1 and that the crucial final sequence of reactions (4→1) involving delicate deprotection and oxidation steps can be realized.* Copyright © 1996 Elsevier Science Ltd

(+)-FR900482 (**1**) isolated from the culture broth of *Streptomyces sandaensis* No.6897 at Fujisawa Pharmaceutical Co. in 1987,[1] exhibits exceptionally potent antitumor activity against various types of mammalian solid tumors.[2] The structure of **1** including stereochemistries was revealed by spectroscopic analyses, X-ray diffraction of FK973[3] (**2**), the semisynthetic triacetyl derivative of **1**, and chemical correlation (**Figure 1**).[4] This unusual natural product exists as a 2:1 mixture of two tautomers due to its unique hydroxylamine hemiacetal functionality. Similarly to mitomycin C (MMC) (**3**), **1** possesses an aziridine ring and a carbamoyloxymethyl group, but lacks a quinoid nucleus. Its remarkable antitumor activity as well as its unique structural features make **1** an exceptionally intriguing and timely target for total synthesis. A number of synthetic studies on **1** have been reported,[5] and two total syntheses of racemic **1** were accomplished by Fukuyama *et al.*[6] in 1992 and by Schkeryantz *et al.*[7] in 1995. However, none of the total syntheses of optically active **1** has been reported to date. We embarked on the project directed at the total synthesis of **1** and its congeners in enantiomerically pure forms with an aim to explore the structure-activity relationships. In this

Figure 1. Structures of FR900482 (**1**), FK973 (**2**), and Mitomycin C (**3**)



Scheme 1. Retrosynthetic Analysis of FR900482 (1)

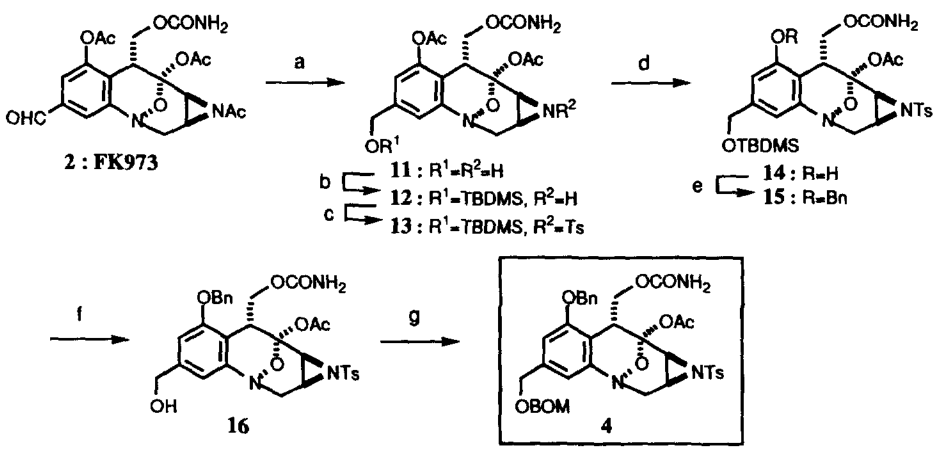


series of communications, we wish to report culmination of our efforts leading to the first enantioselective total synthesis of natural (+)-**1**.[8] This paper concerns with an efficient synthesis of the proposed key intermediate **4** starting with **2**[9] (**Scheme 2**) and a successful reconversion of **4** into **1** (**Scheme 3**), establishing the synthetic and end-game strategies for (+)-**1**.

Scheme 1 shows the retrosynthetic analysis of **1** by which the synthetic strategy is devised. The most crucial step in this scheme is envisioned to be the intramolecular aldol reaction of the highly functionalized dialdehyde **6** to construct the eight-membered ring system **5** representing the core skeleton of **1** (**6**→**5**). The cyclization product **5** would be converted into **1** by sequential functional group manipulations and deprotections or *vice versa* through the advanced key intermediate **4**. The cyclization precursor **6** can, in turn, be elaborated by coupling of the aromatic fragment **7** and the optically active aliphatic fragment **8** accessible from 5-hydroxyisophthalic acid (**9**) and L-diethyl tartrate (**10**), respectively. Considering the chemical instability of **1**, benzyl (Bn), benzyloxymethyl (BOM), and *p*-toluenesulfonyl (Ts) groups might be selected for promising protective groups P^1, P^2, and P^3, respectively, because they are expected to be removed under almost neutral conditions that the delicate core skeleton and functionalities involved in **1** could survive. Prior to execution of the designed synthetic scheme, we elected to examine feasibility of **4** as an advanced key intermediate for **1**.

At first, the synthesis of the proposed key intermediate **4** starting from FK973[9] (**2**) was investigated as shown in **Scheme 2**. Thus, treatment of **2** with sodium borohydride effected simultaneous reduction of the formyl group and removal of the acetyl group in the aziridine moiety to give alcohol **11** (100%), mp 129-131°C, $[\alpha]_D^{20}$ +108° (*c* 0.91, $CHCl_3$). Protection of the hydroxy group in **11** as its *tert*-butyldimethylsilyl (TBDMS) ether (91%) and subsequent tosylation of the imino group in the resulting silyl ether **12**, mp 208-209°C, $[\alpha]_D^{20}$ +85.3° (*c* 1.11, $CHCl_3$), provided the *N*-Ts-aziridine **13** (91%), $[\alpha]_D^{20}$ +73.9° (*c* 1.13, $CHCl_3$). This was further converted to benzyl ether **15** (50%, 2 steps), mp 185-186°C, $[\alpha]_D^{20}$ +68.0° (*c* 1.02, $CHCl_3$), by selective cleavage of the aryl acetate followed by benzylation of the resulting phenol **14**, $[\alpha]_D^{20}$ +75.5° (*c* 1.13, $CHCl_3$). Finally, exchange of the silyl protecting group in **15** with a BOM group furnished **4** (70%, 2 steps),

Scheme 2. Synthesis of the Proposed Key Intermediate **4** from FK973 (**2**)

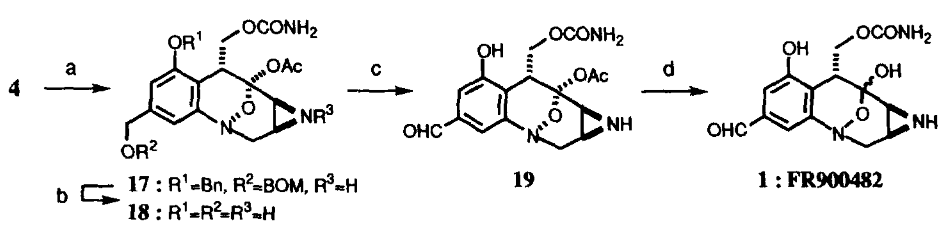


a) $NaBH_4$, $THF-H_2O$, 0°C, 100% b) TBDMSCl, imidazole, DMF, rt, 91% c) TsCl, Et_3N, MeCN, rt, 91% d) NH_3, THF, rt, 68% e) BnBr, $CsCO_3$, DMF, rt, 74% f) TBAF, THF, 0°C, 85% g) BOMCl, $^iPr_2EtN$, CH_2Cl_2-THF, rt, 82%

mp 130-132°C, $[\alpha]_D^{20}$ +68.1° (*c* 0.76, $CHCl_3$), *via* alcohol **16**, mp 211-213°C, $[\alpha]_D^{20}$ +85.4° (*c* 0.34, MeOH).

To confirm our planned synthetic strategy, the reconversion of **4** into (+)-FR900482 (**1**) was next attempted as shown in **Scheme 3**. Critical removal of the *N*-Ts protecting group in **4** turned out to be effected by employing sodium naphthalenide[10,11] in 1,2-dimethoxyethane (DME) at -70°C, giving rise to the deprotected aziridine **17** (81%), $[\alpha]_D^{20}$ +89.3° (*c* 0.62, $CHCl_3$). Hydrogenolysis of both the Bn and BOM protecting groups in **17** afforded alcohol **18** (87%), mp 130-132°C, $[\alpha]_D^{20}$ +81.3° (*c* 0.13, MeOH). Oxidation of the benzylic alcohol in **18** was best achieved by employing Swern oxidation, furnishing the corresponding aldehyde **19** (86%), mp 230°C (dec), $[\alpha]_D^{20}$ +129° (*c* 0.40, acetone). Final removal of the acetyl group in **19** was carried out by careful treatment with ammonia in methanol, producing **1** (79%), mp 174°C (dec) [lit.[1b] mp 175°C (dec)], $[\alpha]_D^{23}$ +7.8° (*c* 1.08, H_2O) [lit.[1b] $[\alpha]_D^{23}$ +8.0° (*c* 1.00, H_2O)], which was identical with an authentic natural sample of **1** in all spectroscopic properties (IR, ^1H-NMR, MS).

Scheme 3. Relay Conversion of **4** to FR900482 (**1**)



a) sodium naphthalenide, DME, -70°C, 81% b) H_2, 10%Pd-C, EtOAc, rt, 87% c) $(COCl)_2$, DMSO, CH_2Cl_2, -78°C; Et_3N, 86% d) NH_3, MeOH, rt, 79%

In summary, we have succeeded in synthesizing the key relay compound **4** starting with FK973 (**2**) and in developing an efficient synthetic route to (+)-FR900482 (**1**) from **4**. These preliminary studies definitely demonstrated that the proposed key intermediate **4** is suitable as a potential relay compound in our designed scheme for the total synthesis of natural (+)-**1** and that the crucial final sequence of reactions (**4**→**1**) (**Scheme 1**) can be realized. The successful first enantioselective total synthesis of natural (+)-**1** was accomplished employing these synthetic and end-game strategies. This is the subject of the two accompanying papers.[8]

Acknowledgments:

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