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Total Synthesis of Natural (+)-FR900482. 2. Efficient Syntheses of the Aromatic and the Optically Active Aliphatic Fragments

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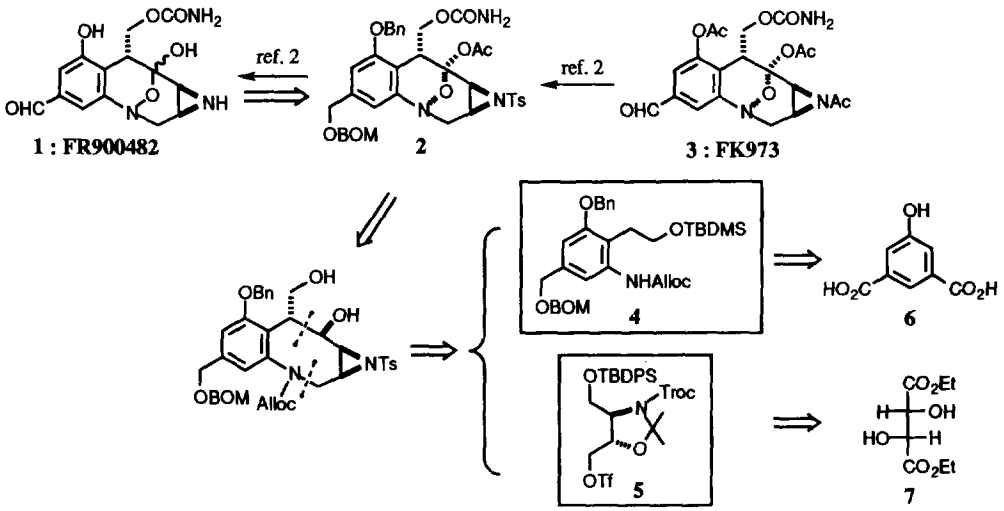
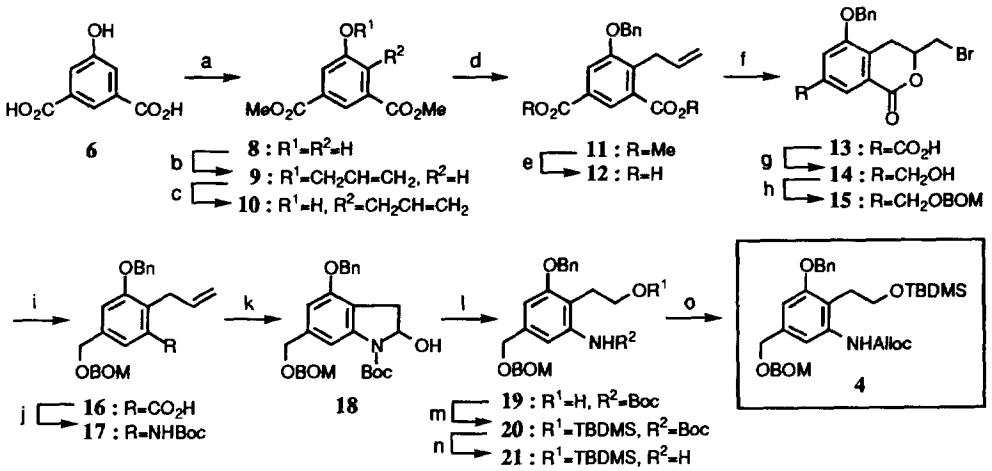
Abstract: *The synthesis of the aromatic fragment 4 was achieved starting from commercially available 5-hydroxyisophthalic acid (6) by utilizing Claisen rearrangement of 9, bromolactonization of 12, and modified Curtius rearrangement of 16 as key steps. Furthermore, the optically active aliphatic fragment 5 was synthesized in an optically pure form starting with L-diethyl tartrate (7) by featuring epoxide formation of 26, nucleophilic epoxide opening of 27 with an azide anion, reduction of the azide function in 33 to an amine, and formation of the N-protected 1,3-oxazolidine 35.* Copyright © 1996 Elsevier Science Ltd

(+)-FR900482 (**1**), a natural secondary metabolite produced by *Streptomyces sandaensis* No.6897, displays prominent antitumor activity against various types of mammalian solid tumors.[1] In the preceding paper, we have succeeded in synthesizing the key relay compound **2** starting with FK973 (**3**), the semisynthetic triacetyl derivative of **1**, and in developing an efficient synthetic route to **1** from **2** through which our total synthesis can proceed (**Scheme 1**).[2] Based on the informations accumulated in these preliminary studies, we next undertook the execution of the projected synthesis. Herein, we report facile and efficient syntheses of the aromatic fragment **4** and the optically active aliphatic fragment **5**, both of which are required for

Scheme 1. Synthetic Plan for FR900482 (**1**)



Scheme 2. Synthesis of the Aromatic Fragment **4**

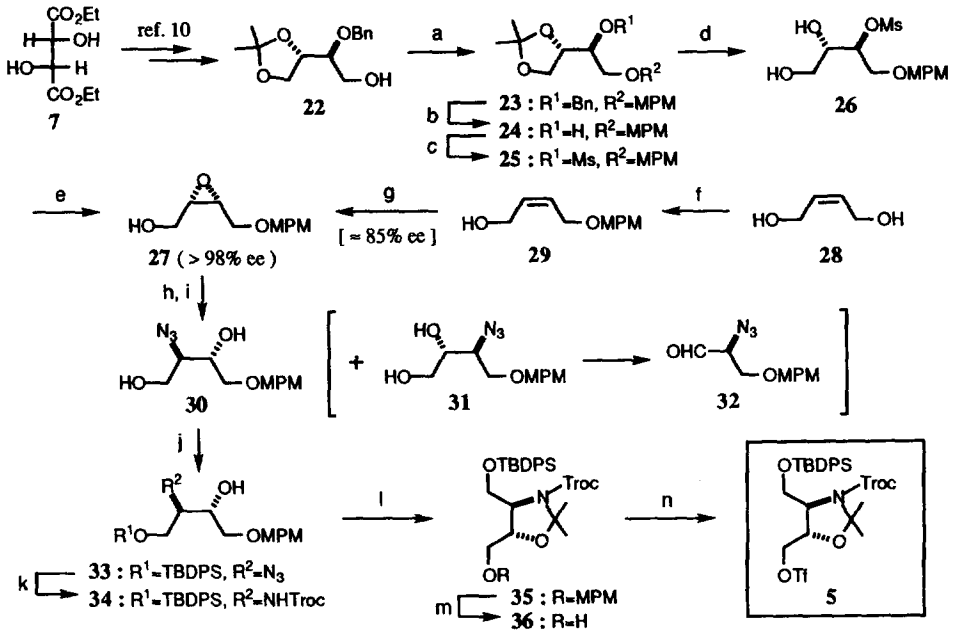


a) $SOCl_2$, MeOH, reflux, 100% b) allylbromide, K_2CO_3, acetone, reflux, 98% c) *N,N*-diethylaniline, reflux, 88% d) BnBr, K_2CO_3, acetone, reflux, 99% e) 2M NaOH, THF, reflux, 95% f) Br_2, aq $NaHCO_3$, $CHCl_3$, 0°C, 72% g) $ClCO_2{}^iPr$, Et_3N, THF ; $NaBH_4$-H_2O, 81% h) BOMCl, $^iPr_2EtN$, CH_2Cl_2, rt, 85% i) Zn, NH_4Cl, EtOH-H_2O, 81% j) DPPA, Et_3N, ^tBuOH, rt→reflux, 76% k) OsO_4, $NaIO_4$, dioxane-H_2O, rt, 73% l) $NaBH_4$, EtOH, rt, 100% m) TBDMSCl, Et_3N, DMAP, CH_2Cl_2, rt, 97% n) TBDMSOTf, Py, CH_2Cl_2, rt ; TBAF, 92% o) AllocCl, aq $NaHCO_3$, CH_2Cl_2, rt, 98%

the enantioselective total synthesis of natural (+)-**1**, starting with commercially available 5-hydroxyisophthalic acid (**6**) and L-diethyl tartrate (**7**), respectively.

We initially pursued the synthesis of **4** starting from **6** as shown in **Scheme 2**. Thus, **6** was converted to allyl ether **9** (98%, 2 steps) , mp 71-72°C [lit.[3] mp 71-72°C], by way of dimethyl ester **8**, mp 169-171°C, [lit.[3] mp 162-163°C, lit.[4,5] mp 162-163.5°C], according to the reported methods[3-5] with several improvements of the reaction conditions. Claisen rearrangement of **9** cleanly took place to afford the phenol **10** (88%), mp 119-120°C, possessing an allyl group on the aromatic ring. After protection of the hydroxy group in **10**, alkaline hydrolysis of the two ester groups in the resulting benzyl ether **11**, mp 96-97°C, furnished dicarboxylic acid **12** (94%, 2 steps), mp 260-262°C. In order to differentiate the two carboxyl groups in **12**, it was converted to the corresponding bromolactone **13** (72%), mp 211-212°C. The remaining carboxyl group in **13** was then reduced by way of the mixed anhydride, giving rise to the benzyl alcohol **14** (81%), mp 189-190°C. Further protection of the hydroxy group in **14** as its benzyloxymethyl (BOM)[6] ether followed by reductive cleavage of the bromolactone moiety in the resulting BOM ether **15**, mp 75-76°C, liberated carboxylic acid **16** (69%, 2 steps), mp 61-63°C. For converting the carboxyl group to an amino functionality, modified Curtius rearrangement of **16** was next attempted by employing the protocol reported by Shioiri *et al.*[7] Thus, treatment of **16** with diphenylphosphoryl azide (DPPA) in the presence of triethylamine in refluxing *tert*-butyl alcohol, afforded the *N-tert*-butoxycarbonyl (Boc) aniline **17** (76%), mp 68-69°C. Oxidative cleavage of the terminal olefin in **17** by employing the Lemieux-Johnson's procedure,[8] resulted in the formation of aminal **18** in 73% yield. Finally, **18** was converted to **4** (87%, 4 steps) by sequential reduction with sodium borohydride, silylation of the resulting alcohol **19**, and exchange of the Boc protecting group of **20** with an allyloxycarbonyl (Alloc)[9] group.

Scheme 3. Synthesis of the Optically Active Aliphatic Fragment **5**



a) NaH, MPMCl, DMF, rt, 97% b) H_2, Raney Ni, EtOH, rt, 93% c) MsCl, Et_3N, CH_2Cl_2,0°C, 100% d) conc HCl, MeOH, rt, 97% e) K_2CO_3, MeOH, rt, 88% f) NaH, MPMCl, DMF, rt, 74% g) L-(+)-DET, $Ti(O^iPr)_4$, TBHP, CH_2Cl_2, -30°C, 59% h) NaN_3, NH_4Cl, EtOH, reflux, 92% i) $NaIO_4$, THF-H_2O, rt, 55% j) TBDPSCl, Et_3N, DMAP,CH_2Cl_2, rt, 91% k) PPh_3, THF-H_2O, rt ; TrocCl, aq $NaHCO_3$, rt, 98% l) TsOH, $Me_2C(OMe)_2$, acetone, rt, 97% m) DDQ, CH_2Cl_2-H_2O, rt, 98% n) Tf_2O, Et_3N, CH_2Cl_2, -78°C, 94%

We next addressed on the synthesis of **5** as shown in **Scheme 3**. Thus, protection of the hydroxy group in 2-*O*-benzyl-3,4-*O*-isopropylidene-L-threitol (**22**), $[\alpha]_D^{22}$ -21.1° (*c* 1.21, $CHCl_3$) [lit.[10] $[\alpha]_D^{22}$ -16.8°, lit.[11] $[\alpha]_D$ -14.1°], prepared from commercially available L-diethyl tartrate (**7**) according to the procedure reported by Ohno *et al.*,[10] provided *p*-methoxyphenylmethyl (MPM) ether **23** (97%), $[\alpha]_D^{20}$ -3.9° (*c* 1.50, $CHCl_3$). Chemoselective removal of the benzyl group in **23** was achieved by catalytic hydrogenolysis over Raney nickel,[12] affording the corresponding secondary alcohol **24** (93%), $[\alpha]_D^{20}$ +5.7° (*c* 1.30, $CHCl_3$). This was further converted to 2,3-epoxy alcohol **27** (85%, 3 steps), mp 36-37°C, $[\alpha]_D^{20}$ -27.4° (*c* 0.78, $CHCl_3$), by a three-step sequence of reactions involving mesylation of the secondary hydroxy group, acidic hydrolysis of the acetonide moiety in mesylate **25**, and epoxide-ring formation of diol **26**. The optical purity of **27** was estimated to be more than 98% ee by comparison of the 400MHz ^{1}H-NMR spectra of (*R*)- and (*S*)-MTPA esters[13] derived from **27**. On the other hand, **27** could be produced more directly by employing the Sharpless asymmetric epoxidation[14] of the allyl alcohol **29**[15] prepared from commercially available *cis*-2-butene-1,4-diol (**28**). Unfortunately, the optical purity of **27** prepared by the asymmetric epoxidation was found to be approximately 85% ee.[16] Therefore, the sequence starting from **7** was selected to prepare **27** in an optically pure form. To forward the synthetic scheme, nucleophilic epoxide opening of **27** with an azide anion[15,17] was next attempted. Thus, treatment of **27** with sodium azide in the presence of ammonium chloride resulted in the formation of a mixture of regioisomers **30** and **31** (92%) in a ratio of *ca.* 3 : 2. Upon exposure of this mixture to sodium periodate, the desired azide alcohol **30**, $[\alpha]_D^{20}$ -31.6° (*c* 1.16, $CHCl_3$), could be readily isolated by

column chromatography on silica gel (55% from **27**). Selective protection of the primary hydroxy group in **30** afforded *tert*-butyldiphenysilyl (TBDPS) ether **33** (91%), $[\alpha]_D^{20}$ -20.1° (*c* 1.14, $CHCl_3$). Further reduction of the azide moiety in **33** with triphenylphosphine followed by selective protection of the amino group in the resulting amino alcohol furnished the *N*-2,2,2-trichloroethoxycarbonyl (Troc)[18] amino alcohol **34** (98%), $[\alpha]_D^{20}$ -14.5° (*c* 1.04, $CHCl_3$). Finally, **34** was successfully converted to **5**[19] (81%, 3 steps) by sequential acetonide formation, deprotection[12] of the MPM group in the *N*-protected 1,3-oxazolidine **35**, $[\alpha]_D^{20}$ -16.9° (*c* 1.14, $CHCl_3$), and triflation of alcohol **36**, $[\alpha]_D^{20}$ -22.4° (*c* 1.11, $CHCl_3$).

As described above, we have succeeded in preparing the aromatic fragment **4** and the optically active aliphatic fragment **5** from commercially available 5-hydroxyisophthalic acid (**6**) and L-diethyl tartrate (**7**), respectively. By utilizing **4** and **5** as the key fragments, the first enantioselective total synthesis of natural (+)-**1** was accomplished in a convergent manner. This is the subject of the following paper.[20]

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19. After purification by column chromatography on silica gel, **5** was immediately used for the next coupling reaction[20] due to its instability.
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