VIP Natural Product Synthesis

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First Stereoselective Total Synthesis of FD-594 Aglycon**

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In memory of Katsumi Kakinuma

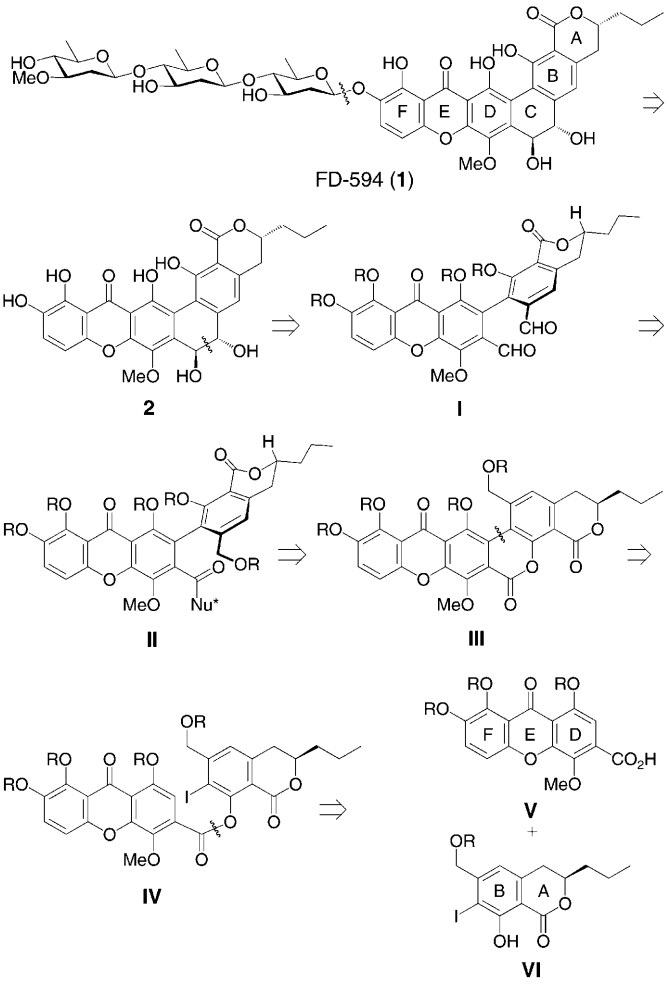
FD-594 (**1**) is an antitumor antibiotic isolated from *Streptomyces sp*. TA-0256.[1] The unique structure characterized by the densely functionalized, curved hexacyclic core having a trisaccharide unit was elucidated by Kakinuma and coworkers, wherein an interesting stereochemical behavior, solvent-dependent atropisomerism, was identified to possibly have biological relevance.[2] Intrigued by the significant bioactivities as well as the challenging structural motifs, we embarked on the synthetic study. Herein, we report the first total synthesis of the FD-594 aglycon (**2**).

Scheme 1 outlines our retrosynthetic analysis based on the chirality-transfer strategy;[3] the chiral centers in diol **2** could be derived from the pinacol cyclization of axially chiral biaryl dialdehyde **I**,[4] which could be related to biaryl lactone **III**, given that the axial chirality was established at the stage of biaryl **II** by the Bringmann-type asymmetric cleavage with a chiral nucleophile (Nu*; **III**→**II**).[3,5] Furthermore, disconnection of lactone **III**, derived by using a Pd-catalyzed cyclization,[6] suggested ester **IV** as the precursor, which could then be dissected into xanthone **V** and iodophenol **VI**.

Scheme 2 shows the synthesis of the AB-ring fragment **9**, which began with a three-step conversion of vanillin (**3**) into bromide **4**.[7] Halogen–lithium exchange of **4** (*n*BuLi, −78 °C) and subsequent reaction with (*R*)-propyloxirane (**10**)[8] at −78 °C in the presence of $BF_3{\cdot}OEt_2$ afforded alcohol **5**.[9] The selective removal of the MOM group in **5** was achieved by heating the mixture in 1,3-propanediol (140 °C, 7 min),[10] and then carbonylation via triflate **6**, prepared by the careful monotriflation, cleanly afforded lactone **7** in excellent yield. Demethylation of **7** and subsequent hydrolysis of the dioxane acetal and reduction of the resulting aldehyde gave alcohol **8**. Regioselective iodination of **8** and protection of the primary alcohol as a TIPS ether gave the AB-ring fragment **9**.

Scheme 3 illustrates synthesis of the DEF-ring fragment **17**, starting from diester **11**.[11] Upon treatment with NCS (1 equiv) in AcOH, diester **11** was cleanly oxidized to the corresponding hydroquinone diester. One of the esters was reduced using $NaBH_4$ in wet THF, and then acetalization gave phenol **12**. The regioselective bromination of phenol **12** using pyridinium bromide perbromide ($PyHBr_3$) and a subsequent four-step conversion (methylation, acetal cleavage, oxidation, and benzylation) afforded aldehyde **13** in high overall yield. The F-ring fragment **18** was lithiated and reacted with aldehyde **13** to afford adduct **14** in high yield. Alcohol **14** was converted into the cyclization precursor **15** by IBX oxidation[12] and then the MOM group was removed.

At the stage of the key S_NAr cyclization by using Cs_2CO_3, the chemoselectivity was highly dependent on the solvent.[13] In MeOH, a 1:1 mixture of two cyclized products, **16** and **19**, was obtained in quantitative yield,[14] whereas the use of DMF



Scheme 1. Synthetic plan.

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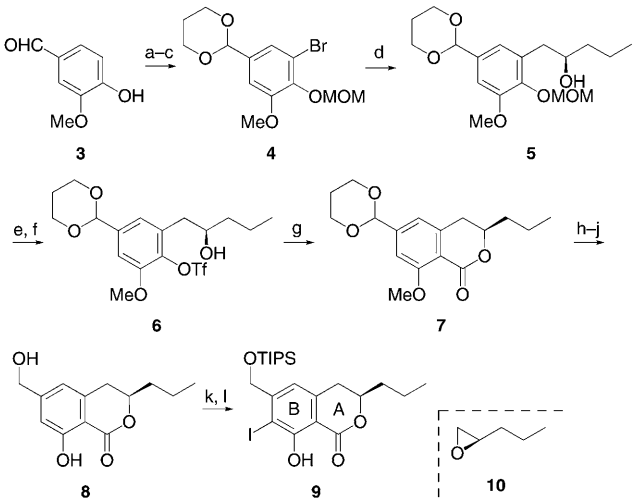
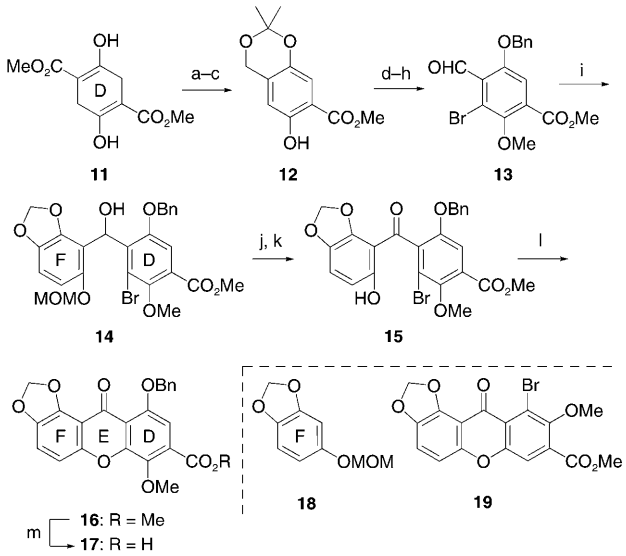


Scheme 2. Synthesis of the AB-ring fragment **9**. Unless otherwise noted, the reactions were performed at ambient temperature. a) Br_2, MeOH, 1 h (94%). b) 1,3-propanediol, 1 mol% $Bu_4N^+Br_3^-$, $HC(OEt)_3$, 25 min. c) MOMCl, NaH, DMF, 15 min (2 steps, 94%). d) *n*BuLi (1.1 mol equiv), Et_2O, −78°C, 35 min. **10** (1.2 mol equiv), $BF_3{\cdot}OEt_2$ (1.3 mol equiv), −78°C, 80 min, then 26°C, 30 min (68%). e) 1,3-propanediol, 140°C, 7 min (91%). f) $PhNTf_2$ (1.2 mol equiv), K_2CO_3 (1.1 mol equiv), DMF, 15 h (82%). g) CO (1 atm), $Pd(OAc)_2$ (10 mol%), dppp (10 mol%), Et_3N (2 mol equiv), DMF, 100°C, 4 h (91%). h) BCl_3, CH_2Cl_2, 0°C, 15 min. i) 0.5 M H_2SO_4, 1,4-dioxane, 100°C, 5.5 h (2 steps, 99%). j) $NaBH_4$, THF/MeOH (10:1), −78°C, 1.5 h (99%). k) $BnMe_3N^+ICl_2^-$, $NaHCO_3$, CH_2Cl_2, MeOH, −10°C, 57 h (85%). l) TIPSCl, imidazole, DMF, 4 h (quant.). MOM = methoxymethyl, DMF = *N*,*N*-dimethylformamide, Tf = trifluoromethanesulfonyl, dppp = 1,3-bis(diphenylphosphino)propane, Bn = benzyl, TIPS = triisopropylsilyl.



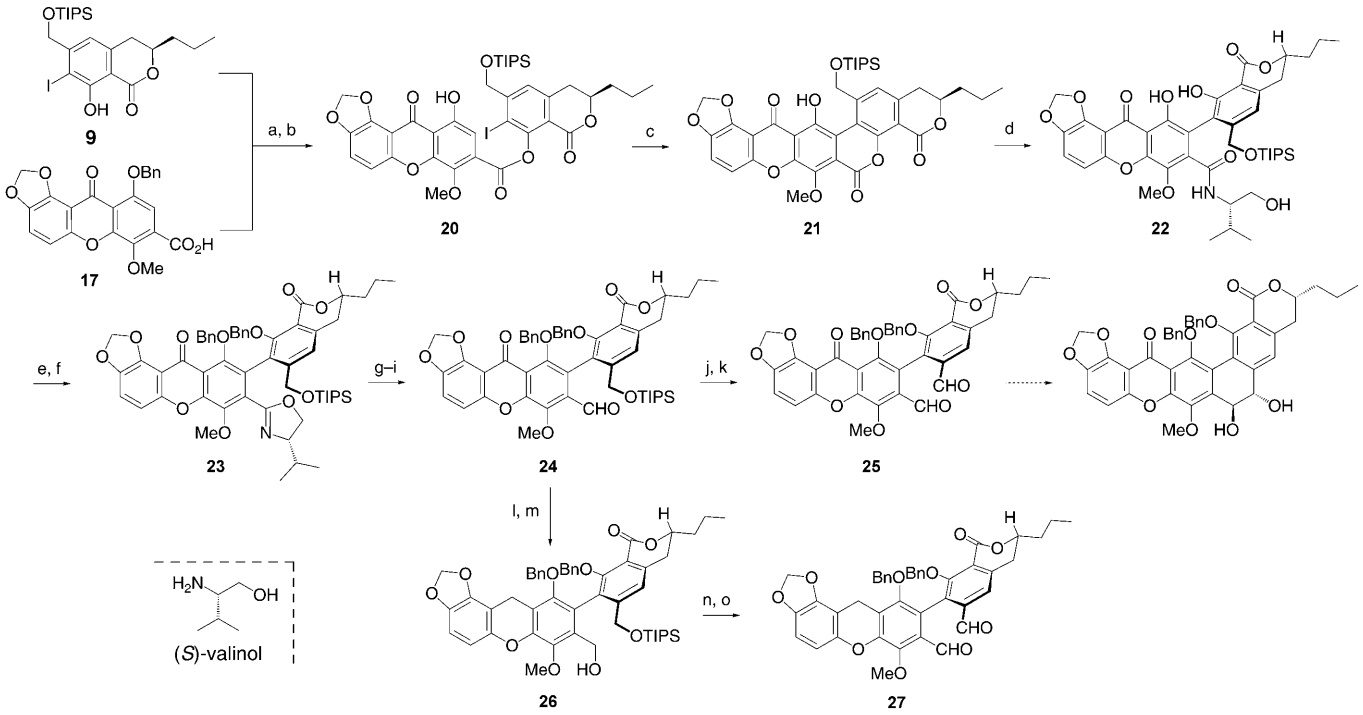
Scheme 3. Synthesis of the DEF-ring fragment **17**. Unless otherwise noted, reactions were performed at ambient temperature. a) NCS (1.0 mol equiv), AcOH, 80°C, 1 h (89%). b) $NaBH_4$, THF/H_2O (9:1), 1 h. c) 2,2-dimethoxypropane, TsOH, acetone, 1 h. d) $PyHBr_3$, pyridine, 1 h. e) $(MeO)_2SO_2$, K_2CO_3, DMF, 31 h. f) 10% H_2SO_4 aq., 1,4-dioxane, 50°C, 2.5 h. g) MnO_2, EtOAc, 30 min (6 steps, 66%). h) BnBr, K_2CO_3, DMF, 1.5 h (99%). i) **18** (1.1 mol equiv), *n*BuLi (1.1 mol equiv), toluene, 0°C, 1.5 h; **13**, THF, −78→−50°C, 30 min (85%). j) IBX, DMSO, 3 h (quant.). k) 0.7 M H_2SO_4 aq., 1,4-dioxane, 90°C, 1 h (97%). l) Cs_2CO_3, cyclohexane, reflux, 81 h (84%). m) LiOH, H_2O, 1,4-dioxane, 2 h (99%). NCS = *N*-chlorosuccinimide, Ts = *p*-toluenesulfonyl, IBX = *o*-iodoxybenzoic acid, DMSO = dimethyl sulfoxide.

slightly improved the selectivity (**16**/**19** = 3:1). Additional screening showed that cyclohexane was the solvent of choice, giving the desired xanthone **16** in high selectively (**16**/**19** = 23:1), which was easily isolated by re-precipitation ($CHCl_3$/petroleum ether = 1:3). The saponification of methyl ester **16** gave the DEF-fragment **17**.

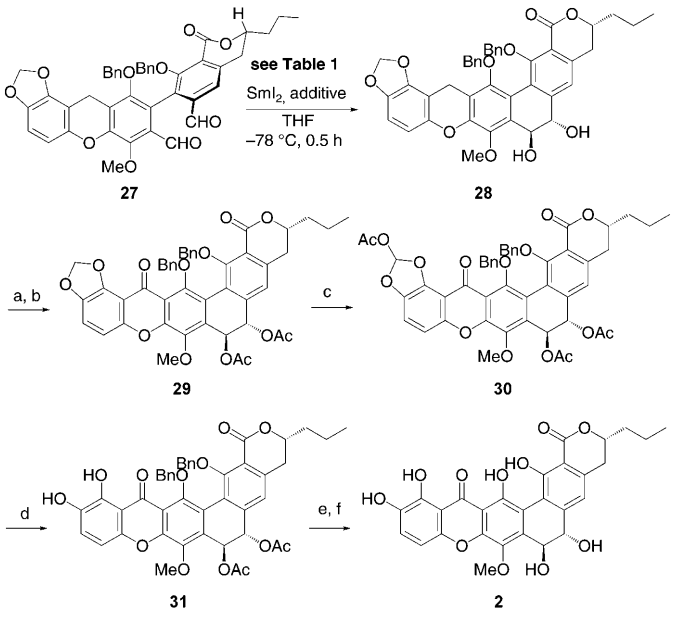
Two fragments, **9** and **17**, were combined via the acid chloride, giving the corresponding ester quantitatively (Scheme 4). After the removal of the benzyl group to give **20**, the palladium-catalyzed cyclization gave hexacycle **21** in high yield.[15] For inducing the axial chirality, biaryl lactone **21** was subjected to the asymmetric ring-opening using (*S*)-valinol as a chiral nucleophile.[5] The stereoselectivity proved to be highly dependent on the solvent, and THF gave the best result, affording diastereomeric amides **22** and **22'** in a 93% combined yield with excellent selectivity (14:1);[16] the diastereomers were easily separated by using silica gel column chromatography (*n*-hexane/EtOAc = 2:1). After separation, the major isomer (**22**) was converted into dialdehyde **25**: treatment of **22** with PPh_3 and I_2 afforded a mixture of the corresponding iodide and oxazoline, which, without separation, was treated with BnBr and Cs_2CO_3 in DMF, wherein the two phenols were benzylated and the cyclization to the oxazoline was complete, giving oxazoline **23**. The next stage was the selective conversion of the oxazoline into the corresponding aldehyde without altering the xanthone and the lactone moieties. This conversion was achieved by N-methylation and subsequent treatment with $NaBH(OMe)_3$. The resulting *N*,*O*-acetal was hydrolyzed with acid to give aldehyde **24**.[17] The desilylation of **24** and oxidation of the resulting alcohol gave dialdehyde **25** in high yield, ready for the key pinacol cyclization.[18]

However, we were disappointed by the poor results for this key step; SmI_2 in THF at 0°C gave the desired product only in low yield (ca. 20%) and poor stereoselectivity (*trans*/*cis* = 3:1). After many unproductive trials, we became convinced that the difficulties mainly originated from the presence of the xanthone moiety, and decided to convert the xanthone into the corresponding xanthene temporarily. Thus, xanthone **24** was reduced by a two-step process [L-Selectride and $NaBH_3(CN)$] to give xanthene **26**, and removal of the silyl group and subsequent oxidation of the resulting diol gave dialdehyde **27**.

Pleasingly, xanthene **27** behaved nicely in the pinacol cyclization (Scheme 5); upon treatment with SmI_2, the reaction proceeded far more smoothly than the case of xanthone **25**, albeit the *trans*/*cis* selectivity remained low (Table 1, entry 1). Additional screening revealed that additives could improve this situation.[19] Whereas the addition of tetraglyme did not affect the stereoselectivity (Table 1, entry 2), various crown ethers gave much improved stereoselectivities (Table 1, entries 3–6). Furthermore, pybox ligands were effective for improving the yield and the stereoselectivity (Table 1, entries 7 and 8).



Scheme 4. Pinacol cyclization precursors **25** and **27**. Unless otherwise noted, reactions performed at ambient temperature. a) **17**, $(COCl)_2$, DMF, CH_2Cl_2, 0.5 h; **9** (1.1 mol equiv), DMAP, pyridine, 1 h (quant.). b) BBr_3, CH_2Cl_2, −5 °C, 15 min (91 %). c) $[Pd_2(dba)_3]\cdot CHCl_3$ (15 mol %), *t*$BuCO_2Na$ (3 mol equiv), DMA, 60 °C, 40 min. d) (*S*)-valinol (3.2 mol equiv), THF, 26 °C, 20 min (2 steps, 93 %, 14:1 d.r.); separation by silica gel column chromatography (87 % yield for isolated **22**, 6.4 % yield for isolated **22′**) e) I_2, PPh_3, imidazole, CH_2Cl_2, 30 min. f) BnBr, Cs_2CO_3, DMF, 40 °C, 2 h (2 steps, 97 %). g) MeOTf, 2,6-di-*tert*-butylpyridine, CH_2Cl_2, 2 h. h) $NaBH(OMe)_3$, −78 → −20 °C, 30 min. i) sat. citric acid aq. soln., THF, 0.5 h (76 % from **23**). j) *n*Bu_4NF, THF, 0 °C, 0.5 h (92 %). k) Dess–Martin periodinane, CH_2Cl_2, 0.5 h (87 %). l) L-Selectride, THF, −78 → −25 °C, 20 min. m) $NaBH_3(CN)$, AcOH, CH_2Cl_2, 0.5 h (2 steps, 96 %). n) *n*Bu_4NF, THF, 15 min (94 %). o) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, 50 min; Et_3N, −78 °C, 1 h (90 %). DMAP = 4-*N*,*N*-dimethylaminopyridine, dba = dibenzylideneacetone, DMA = *N*,*N*-dimethylacetamide, L-Selectride = lithium tri-*sec*-butylborohydride.



Scheme 5. Final stages for the synthesis of **2**. Unless otherwise noted, reactions were performed at ambient temperature. a) Ac_2O, DMAP, pyridine, 20 min (98 %). b) DDQ, CH_2Cl_2, 1,4-dioxane, H_2O, 11 h (quant.). c) $Pb(OAc)_4$, benzene, reflux, 1 h (94 %). d) TsOH, MeOH, H_2O, 10 h (99 %). e) K_2CO_3, MeOH, 0.5 h (87 %). f) $Pd(OH)_2/C$, H_2 (1 atm), MeOH, 0.5 h (quant.). DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.

Table 1: Pinacol cyclization of xanthene dialdehyde **27**.[a]

Entry	Additive	*trans* [%]	*cis* [%]
1	none	53	15
2	tetraglyme	51[b]	16[b]
3	[12]crown-4	63	10
4	[15]crown-5	55	17
5	[18]crown-6	61	7
6	[24]crown-8	66	8
7	(*S*,*S*)-*i*Pr-pybox	72	10
8	(*R*,*R*)-*i*Pr-pybox	71	10

[a] Three molar equivalents of SmI_2 and six molar equivalents of the additive were used. [b] The yield was assessed after acetylation. (*S*,*S*)-*i*Pr-pybox = 2,6-bis[(4*S*)-(−)-isopropyl-2-oxazolin-2-yl]pyridine.

With diol **28** in hand, the final stages included two synthetic hurdles; 1) the regeneration of the xanthone and 2) the removal of the methylene protecting group for the catechol without touching the methyl and the benzyl groups. We were pleased to find that the first problem was solved by using DDQ. Thus, after masking the diol in **28** by acetylation, treatment with DDQ afforded xanthone **29** in quantitative yield.

As for the second issue, the methylene acetal in **29** was oxidatively removed by treatment of **29** with $Pb(OAc)_4$ allowing the clean formation of acetoxy acetal **30**, which was smoothly hydrolyzed in acidic methanol to provide the

desired catechol **31**. Finally, the removal of the two acetyl groups in **31** and the subsequent catalytic hydrogenolysis of the two benzyl groups furnished the FD-594 aglycon (**2**) as a yellow powder, which was identical with the authentic sample by direct comparison; the rotation was $[\alpha]_D^{26} = +5.4 \times 10^2$ ($c =$ 0.43, MeOH), and that of the authentic sample was $[\alpha]_D^{26} = +5.4 \times 10^2$ ($c = 0.35$, MeOH), and the melting point of the synthetic sample was 209–212 °C, compared to 207–210 °C for the authentic sample.[1b,20]

In conclusion, the first total synthesis of FD-594 aglycon (**2**) was achieved. Currently, we are studying the glycosylation, which is directed at the total synthesis of the natural product.

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[14] The product ratio (**16**/**19**) was assessed by ^{1}H NMR analaysis ($CDCl_3$, 300 MHz).

[15] We also attempted the cyclization before removal of the benzyl group. However, the reaction produced only many unidentified by-products.

[16] The same reaction with (*R*)-valinol gave two diastereomers in high selectivity (18:1). After separation, the major isomer of the (*R*)-valinol adducts was converted by the same synthetic sequence described in the text. The final product was the 6,7-bis(epimer) of **2**, implying that the stereochemical course of the lactone cleavage is mainly decided by the reagent control (by the chirality of the nucleophile), but not by the substrate control (by the chirality in lactone **21**). For a related paper, see S. Masamune, S. A. Ali, D. L. Snitman, D. S. Garvey, *Angew. Chem.* **1980**, *92*, 573–575; *Angew. Chem. Int. Ed. Engl.* **1980**, *19* 557–558. For the details see the Supporting Information.

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[20] All physical data (^{1}H and ^{13}C NMR , IR, elemental analysis, $[\alpha]_D$, and m.p.) of the synthetic material were to be consistent with an authentic sample of the natural product (see, Ref. [1b]), kindly provided by Prof. Dr. Tadashi Eguchi, Tokyo Institute of Technology.

