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Asymmetric Total Synthesis of FD-594

Tao Xie[a], Chaoying Zheng[a], Kuanwei Chen[a], Haibing He[b], Shuanhu Gao*[a,b]

Abstract: A highly convergent approach was developed to achieve the first asymmetric and scalable total synthesis of FD-594, a complex polycyclic xanthone natural product from *Streptomyces sp.* TA-0256, in (LLS) 20 steps. The *trans*-9,10-dihydrophenanthrene-9,10-diol fragment (B-C-D ring) was generated through a new strategy involving an asymmetric dihydroxylation, followed by Cu-mediated oxidative cyclization. Late-stage stereoselective glycosylation assembled the angular hexacyclic framework with a β-linked 2,6-dideoxy trisaccharide fragment.

FD-594 (**1**), a complex polycyclic xanthone-type natural product,[1] was isolated from *Streptomyces sp.* TA-0256 by Kakinuma and co-workers in 1998 (Figure 1). [2] It was reported that FD-594 inhibits growth of P388 and HeLa tumor cells with an IC_{50} of 0.25 and 0.10 μg/mL.[2] It also exhibits moderate activity against some Gram-positive bacteria, such as *staphylococcus aureus* 209P-J (IC_{50}=0.10 μg/mL). FD-594 contains a challenging structure featured by a highly oxygenated angular hexacyclic framework that includes an isochromanone moiety (A-B ring), a *trans*-9,10-dihydrophenanthrene-9,10-diol fragment (B-C-D ring), a xanthone scaffold (D-E-F ring) and a β-linked trisaccharide unit comprising D-oleandrose and D-olivose. The biogenetically related polycyclic xanthone MS0901809 (**2**), discovered in the same Streptomyces species as FD-594, differs from it only in the way in which the E and F rings are connected.[3] FD-594 differs from other polycyclic xanthones such as kigamicin A (**3**) [4] and kibdelone C (**4**) [5] primarily in oxidation state and functional groups on the C and F rings. The intriguing structures and biological activities of polycyclic xanthones have led many groups to develop syntheses,[1] including Kelly, [6] Porco, [7] Ready, [8] and Martin. [9] A breakthrough toward the synthesis of FD-594 came in 2009 when Suzuki and coworkers prepared the corresponding aglycone. [10] They used a creative strategy to shift chirality from axial to central in order to build the B-C-D ring of *trans*-9,10-dihydrophenanthrene-9,10-diol (Scheme 1A). [11] The same group also used this strategy in their total syntheses of TAN-1085, [12] PD-116740[13] and pradimicinone. [14] Recently, Bennett and coworkers reported the stereoselective formation of the β-linked trisaccharide unit through a reagent-controlled strategy in which the dideoxy-sugar donors are activated using *p*-toluenesulfonyl chloride. [15]

We aimed to achieve the first total synthesis of FD-594 (**1**) as part of our on-going interest in the total synthesis of bioactive polycyclic natural products and their medicinal chemistry.[16] In previous work, we constructed tetrahydroxanthones using photo-induced C–O bond formation,[17] and synthesized dimeric xanthone ascherxanthone A [18] as well as polycyclic xanthone kibdelone C (**4**).[19] Herein, we report a new strategy of asymmetric dihydroxylation followed by oxidative cyclization to form the *trans*-9,10-dihydrophenanthrene-9,10-diol core (Scheme 1B, **I**→**II**). We propose that **II** may serve as an advanced intermediate to prepare both FD-594 and biogenetically related kigamicins, when followed by selective dehydroxylation of the C-6 hydroxyl group.

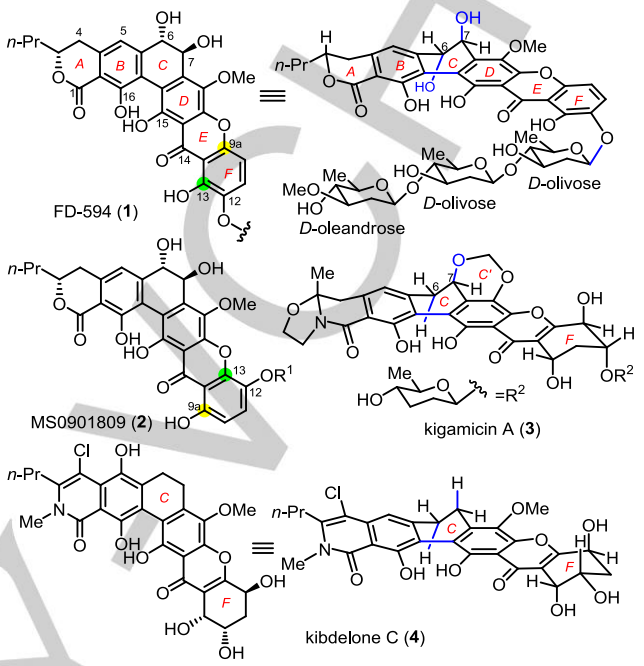
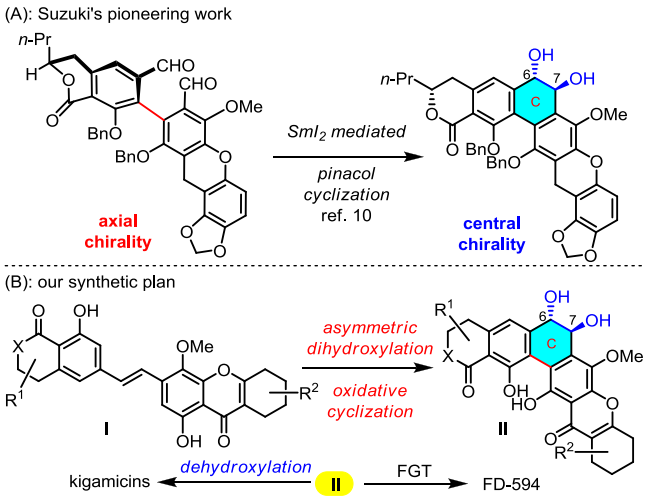


Figure 1. Polycyclic xanthone natural products.



Scheme 1. Synthetic plan.

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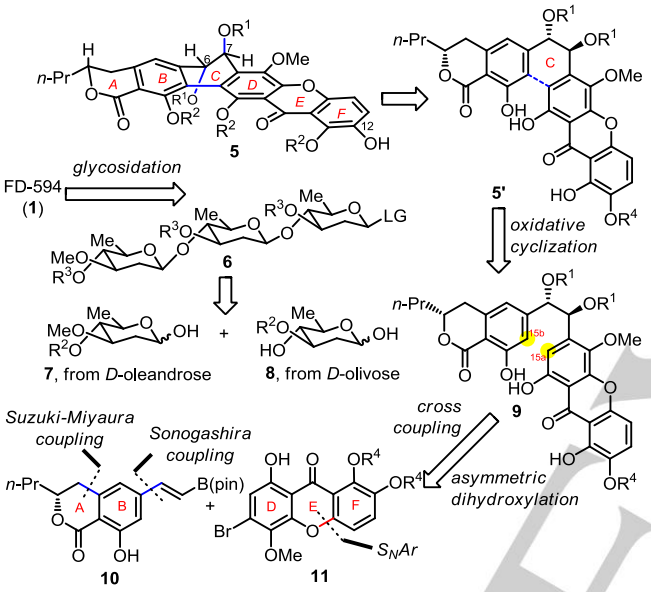
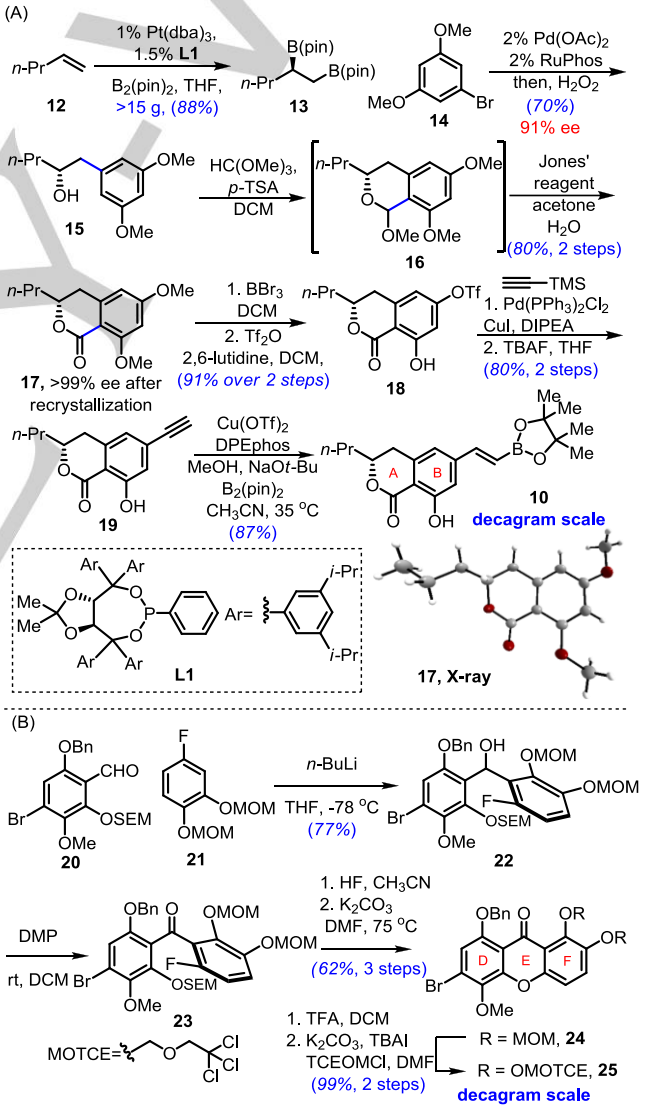
We envisioned the overall synthetic efficiency to synthesizing FD-594 lies on a right ring forming sequence and stereo-controlled bond forming transformations. A highly convergent approach was proposed (Scheme 2), in which late-stage glycosylation would couple the angular hexacyclic framework **5** with the trisaccharide scaffold **6**, formed through selective β-linking of the 2-deoxy-sugars **7** and **8**. The hexacyclic core structure **5** would be generated through an asymmetric dihydroxylation of the product formed through Suzuki–Miyaura coupling of fragments **10** (isochromanone A-B ring) and **11** (xanthone D-E-F ring). The dihydroxylation product would then undergo oxidative cyclization to furnish the *trans*-9,10-dihydrophenanthrene-9,10-diol fragment (B-C-D ring).



Scheme 2. Retrosynthetic analysis of FD-594.

Our synthesis started from the scalable preparation of two fragments **10** and **11** for the cross-coupling reaction (Scheme 3). We constructed the chiral isochromanone A-B ring through Pt-catalyzed enantioselective diboration followed by Pd-catalyzed cross-coupling, recently developed by Morken and coworkers [20] (Scheme 3A). Treating pentene **12** with $Pt(dba)_3$ in the presence of chiral phosphonite ligand **L1** and bis(pinacolato)diboron gave the desired pinacol boronate **13** in 88% yield on a >15-g scale, [20] and this boronate was selectively cross-coupled with 1-bromo-3,5-dimethoxybenzene **14** using $Pd(OAc)_2$ and RuPhos. The resulting product was oxidized to produce alcohol **15** in 70% yield with enantioselective excess (ee) of 91%. The isochromanone ring was installed through acid-mediated cyclization with trimethoxymethane and Jones oxidation reagent. The structure and absolute configuration of **17** was confirmed by X-ray diffraction analysis. Simple recrystallization of **17** increased ee to >99%. Removal of methyl groups and selective activation of the phenol group generated triflate **18** in good yield over two steps. Pd-catalyzed Sonogashira coupling of **18** with ethynyltrimethylsilane followed by desilylation afforded the terminal alkyne **19**, which underwent Cu-catalyzed vinyl boration in the presence of DPEphos to stereospecifically generate **10** in 87% yield on a decagram scale.

The xanthone fragment (D-E-F ring) was efficiently prepared from two highly substituted benzene rings **20** and **21** (see details in Supporting Information). Site-selective lithiation of **21** followed by intermolecular addition of **20** and Dess-Martin oxidation gave diaromatic ketone **23** (Scheme 2B). HF promoted deprotection of the SEM group followed by C-O bond formation via an S_NAr procedure under the basic condition gave **24** bearing the xanthone framework in 62% yield over three steps on a large scale. Replacing the methoxymethyl ether with the methoxy-2,2,2-trichloroethyl (MOTCE) ether on F ring afforded substrate **25** in high yield over 2 steps, which facilitates the selective deprotection step required in the following glycosylation.



Scheme 3. Preparation of fragments **10** and **25**.

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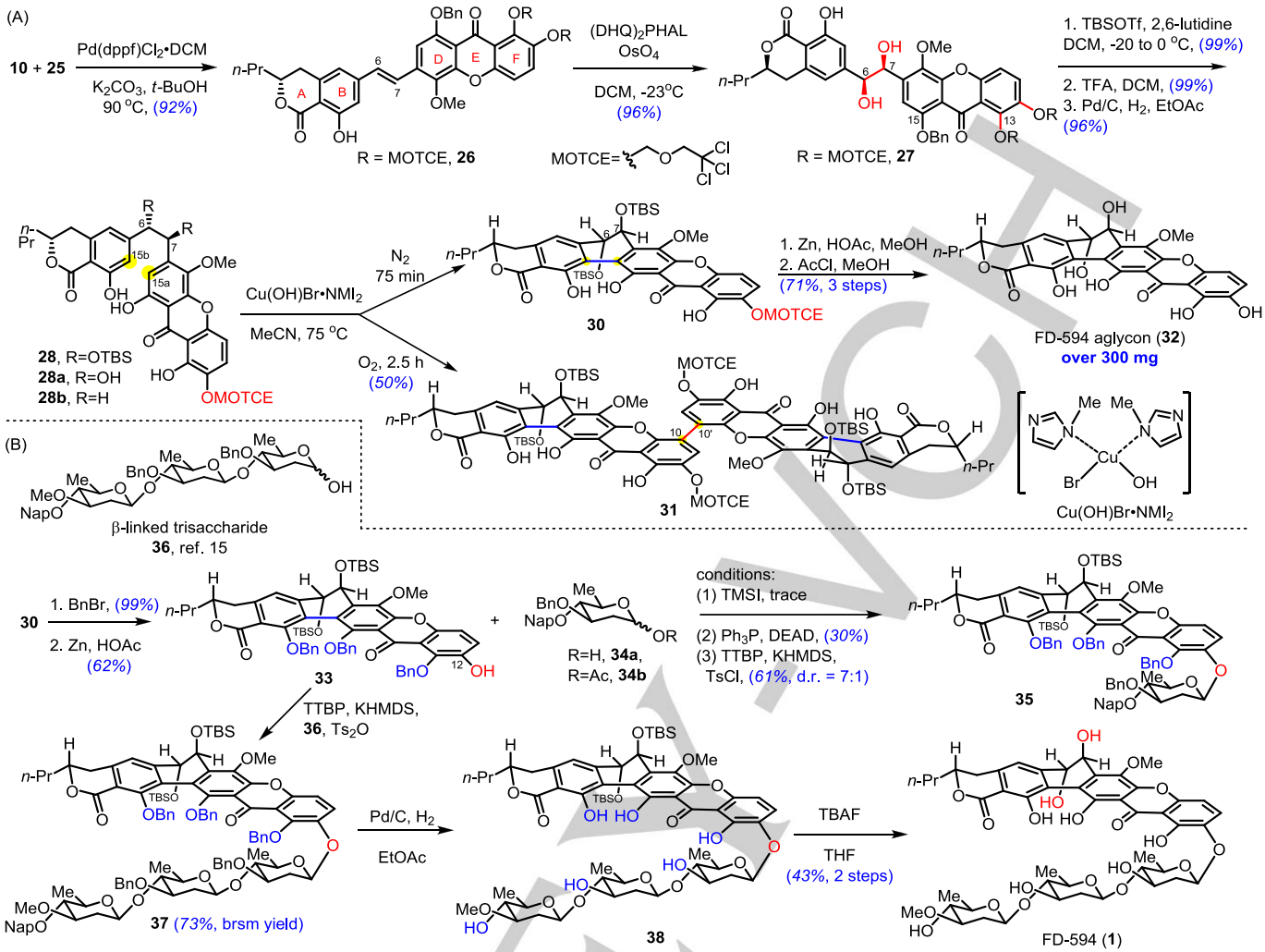

Scheme 4. Total synthesis of FD-594 aglycon and FD-594.

FD-594 contains a unique trisaccharide fragment comprising the β-linked 2,6-dideoxy sugars D-oleandrose and D-olivose. Stereoselective glycosylation with 2,6-dideoxy sugars is challenging because the C-2 atom lacks a group that can participate in formation of the β-glycosidic bond. [21] We adopted the reagent-controlled strategy developed by Bennett and coworkers in which the dideoxy-sugar donors are activated using *p*-toluenesulfonyl chloride in the presence of 2,4,6-tri-tert-butylpyrimidine (TTBP). [15, 22] This generates a reactive α-glycosyl tosylate species that interacts with acceptors via an S_N2 process that shows excellent β-selectivity.[22, 23] Following the reliable glycosylation as described by Bennett and coworkers, [15, 22] we prepared the β-linked trisaccharide fragments on a gram scale (see details in Supporting Information).

With all of the coupling fragments in hand, we set about preparing the angular hexacyclic core framework (Scheme 4). The palladium-catalyzed Suzuki–Miyaura cross-coupling of fragments **10** and **25** produced the desired coupling product **26** in 92% yield. Sharpless asymmetric dihydroxylation of the C6-C7 olefin was attempted by treating **26** with osmium tetroxide (OsO_4) and chiral ligand $(DHQ)_2PHAL$ in dichloromethane.[24] This afforded **27** bearing the desired chiral diol at C-6 and C-7 in 96% yield as a single diastereomer. Asymmetric dihydroxylation of the coupling product between **10** and **24** were also investigated (see details in Supporting Information). The large TBS group was added to protect the diol as the corresponding silyl ether. Acidic condition and hydrogenation were used to selectively deprotect the phenols on C-13 and C-15, producing phenol **28** in 95% yield over 2 steps. Cu-mediated oxidative phenol coupling reactions are widely used to form aryl–aryl bonds,[25] which have proven to be a reliable methodology in the synthesis of TMC 66 by Tatsuta et al.,[25c] and kigamicins by Ready and Ma.[4d] To investigate the reactivity of oxidative cyclization, we also prepared **28a** and **28b** bearing free hydroxyl groups and saturated methylene on C-6 and C-7. We studied the reaction conditions including different Cu-oxidants and solvents (see Table S1 in Supporting Information). We found reaction of compound **28** with $Cu(OH)Br•NMI_2$ in acetonitrile at 75 °C under an N_2 atmosphere smoothly generated the cyclized hexacyclic core **30** in 90% crude yield after 75 min. This high yield depended on using acetonitrile as the solvent. Using DMF as solvent lead to a low conversion rate and $Cu(OH)Cl•NMI_2$ did not react efficiently under these conditions, even after prolonged incubation. The same reaction condition lead the decomposition of substrate **28a**. Alternatively, substrate **28b** underwent the oxidative cyclization in a low reaction rate, this result revealed that two

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bulky TBS protecting groups brought C-15a and C-15b closer together and thereby facilitated subsequent oxidative coupling. When we performed oxidative phenol coupling under an O_2 atmosphere, it was found the intermolecular coupling of cyclized product **30** occurred to form the 10,10'-*para*-dimer **31**, which could be achieved in 50% yield after prolonging the reaction time to 2.5 h. Global removal of protecting groups from **30**, by means of Zn/AcOH and acidic condition, gave the FD-594 aglycon **32**, whose analytical data were in good agreement with those reported by Suzuki.[2, 10] This convergent, 17-step strategy can generate over 300 mg of FD-594 aglycon from **14** with overall yield of 20%.

We then turned our attention to assembling the hexacyclic carbon skeleton and trisaccharide fragment. To do so, three free phenol groups were masked as benzyl ethers, and the phenolic MOTCE group on C-12 was selectively removed using zinc/acetic acid to give the glycosyl acceptor **33** as shown in Scheme 4B. We first selected 1-hydroxyl sugar **34a** and 1-O-acetate **34b** as model substrates to explore the reactivity and stereoselectivity of this glycosidation under three types of conventional reaction conditions. Treatment of glycosyl acetate **34b** with TMSI generated glycosyl iodide, which should interact with **33**,[21, 26] but this led to recovery of the starting material and only trace amounts of glycoside product. Mitsunobu glycosylation of **33** with 1-hydroxyl sugar **34a** in the presence of PPh_3 and DEAD produced glycoside product **35** in 30% yield, indicating poor reactivity of glycosyl donor and acceptor. We then attempted to activate the sugar donor using *p*-toluenesulfonyl chloride as described by Bennett's group. [15, 22] Compound **34a** was transformed into the corresponding α-glycosyl tosylate species, which reacted with acceptor **33** in the presence of KHMDS to afford the desired β-linked glycoside **35** as the major product in 61% yield (dr = 7:1). The same reaction conditions were used to couple trisaccharide **36** with **33**, furnishing the β-linked glycoside **37** in 55% yield and stereoselectivity of β:α=2.2:1. To improve the stereoselectivity, we optimized the reaction conditions of glycosylation by changing the sulfonylating agents, additives and base (see Table S2 in Supporting Information). We found that using *p*-trifluoromethanesulfonic anhydride (Tf_2O) as an activator gave the desired *β*-linked glycoside **37** as a single diastereomer in 48% yield (brsm yield: 73%). We reasoned that the hemiacetal of **36** was stereospecifically converted into an α-glycosyl tosylate, the reactive species in the glycosylation, under this condition, which matched with the results observed by Bennett. [22e] Palladium-catalyzed hydrogenation of **37** (8 Mpa H_2) afforded the desired **38** with five benzyl groups and naphthylmethyl group being cleaved. Finally, the two TBS groups on the C ring were removed using TBAF, providing FD-594 (**1**) in 43% yield over 2 steps. The ^1H and ^{13}C NMR spectra, high-resolution mass spectrum, and optical rotation of synthetic **1** were consistent with the corresponding data for the natural product. [2]

In conclusion, we have achieved the first asymmetric total synthesis of the complex polycyclic xanthone FD-594, isolated from *Streptomyces sp.* TA-0256, in LLS 20 steps using a convergent approach. The chiral isochromanone A-B ring is constructed using Pt-catalyzed enantioselective diboration followed by Pd-catalyzed cross-coupling. The *trans*-9,10-dihydrophenanthrene-9,10-diol fragment (B-C-D ring) is prepared by a new strategy involving an asymmetric dihydroxylation followed by Cu-mediated oxidative cyclization. Late-stage stereoselective glycosylation assembles the angular hexacyclic framework with a 2,6-dideoxy trisaccharide fragment. Generating the rings in this sequence ensures a scalable approach and maximal synthetic efficiency. We are currently exploring the medicinal chemistry of FD-594 and its analogues, and applying the synthetic strategy to the total synthesis of kigamicins, which will be reported in due course.

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Keywords: xanthone • FD-594 • oxidative cyclization • total synthesis • glycosylation

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Natural Product Synthesis

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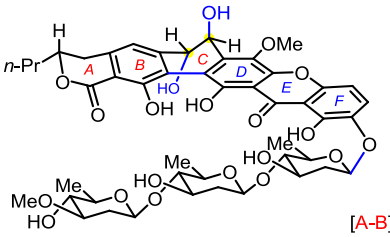
Asymmetric Total Synthesis of FD-594



FD-594 (a polycyclic xanthone)
1) convergent approach
2) scalable synthesis
3) asymmetric dihydroxylation
4) oxidative cyclization
5) late stage glycosylation

ring forming sequence:
[A-B]+[D-E-F]→C↔trisaccharide unit

The first asymmetric total synthesis of FD-594, a complex polycyclic xanthone from *Streptomyces sp. TA-0256,* was described herein.

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