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Total synthesis of fomitellic acid B

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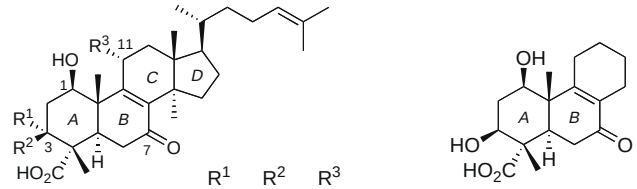
ABSTRACT

Herein, we describe the first total synthesis of fomitellic acid B (**2**), a potent inhibitor of DNA polymerases α and β. There are two key features in this synthesis: (i) the AB ring system, with all requisite chiral centers, is stereoselectively constructed by means of titanium(III)-mediated radical cascade cyclization of epoxypolyene; and (ii) an enone moiety in the B-ring is generated by isomerization of an olefin followed by allylic oxidation.

Fomitellic acids, originally isolated by Sakaguchi and co-workers[1] from the mycelium of a basidiomycete, *Fomitella fraxinea*, are potent inhibitors of calf DNA polymerase α, rat DNA polymerase β, and human DNA topoisomerases I and II (Fig. 1).[2] Structurally, fomitellic acids belong to the lanostane-type triterpenoids, which are characterized by a highly oxygenated steroidal AB ring moiety with five contiguous stereogenic centers. Among several efficient methodologies for constructing a *trans*-decaline ring system, we were particularly interested in a cascade cyclization of epoxypolyene, considering the presence of the hydroxy group at C3. Recently, we have achieved the stereoselective synthesis of the fully functionalized AB ring moiety (**5**) as a model study using a titanium(III)-mediated radical cascade cyclization of epoxypolyene.[3] In this Letter, we describe the first asymmetric total synthesis of fomitellic acid B (**2**).

Our retrosynthetic analysis is shown in Scheme 1. Fomitellic acid B (**2**) can be derived from the key tetracyclic intermediate **6** containing all requisite stereogenic centers. As a key step, we reasoned that the tetracyclic skeleton could be stereoselectively constructed by means of titanium(III)-mediated radical cascade cyclization[4] of epoxypolyene **7**. The cyclization precursor **7** was divided into two fragments, the vinyl iodide part **8** and the aldehyde part **10**. We planned to couple these two parts by 1,2-addition of the vinyl lithium species derived from **8** to the aldehyde **10**. We have already reported the enantioselective synthesis of the aldehyde **10** using stereoselective vinylogous Mukaiyama aldol reaction and Sharpless asymmetric epoxidation.[3] The vinyl iodide **8** can be stereoselectively prepared from the known dione **9**[5] derived from the (−)-Wieland–Miescher ketone.

Therefore, our initial task was the preparation of vinyl iodide **8**[6] as shown in Scheme 2. The synthesis commenced with the known dione **9**[5] which was available in two steps from the (−)-Wieland–Miescher ketone. Selective ketalization of the carbonyl function of the six-membered ring in dione **9**, followed by the Wittig reaction afforded the olefin **14**[5c,e] in 46% yield (80% br sm) for the two steps. After hydroboration–oxidation of **14**, the resultant alcohol was subjected to a Dess–Martin periodinane[7] oxidation to give the corresponding ketone as a diastereomeric mixture. Epimerization proceeded successfully by treatment of the mixture with a base to give the desired ketone **15** as a single diastereomer in 88% overall yield from **14**.[5c] The ketone **15** was converted to the olefin by the Wittig reaction. Stereoselective hydroboration of the olefin with 9–BBN,[8]



	R^1	R^2	R^3
Fomitellic Acid A (**1**) :	H	OH	OH
B (**2**) :	H	OH	H
C (**3**) :	H	OH	OMe
D (**4**) :	OH	H	H

AB Ring Moiety (**5**)

Figure 1. Structures of fomitellic acids.

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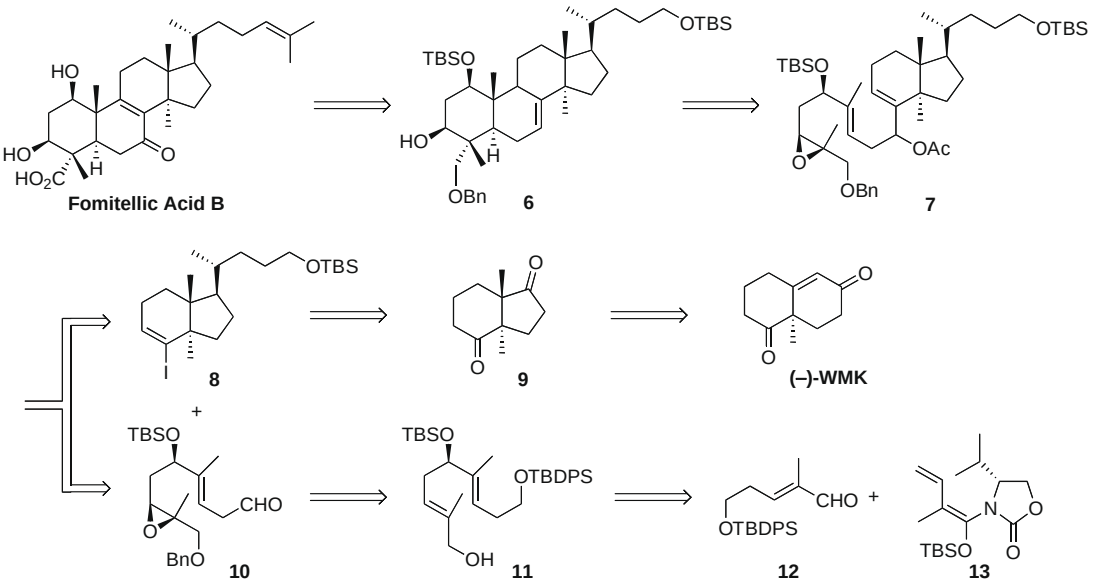
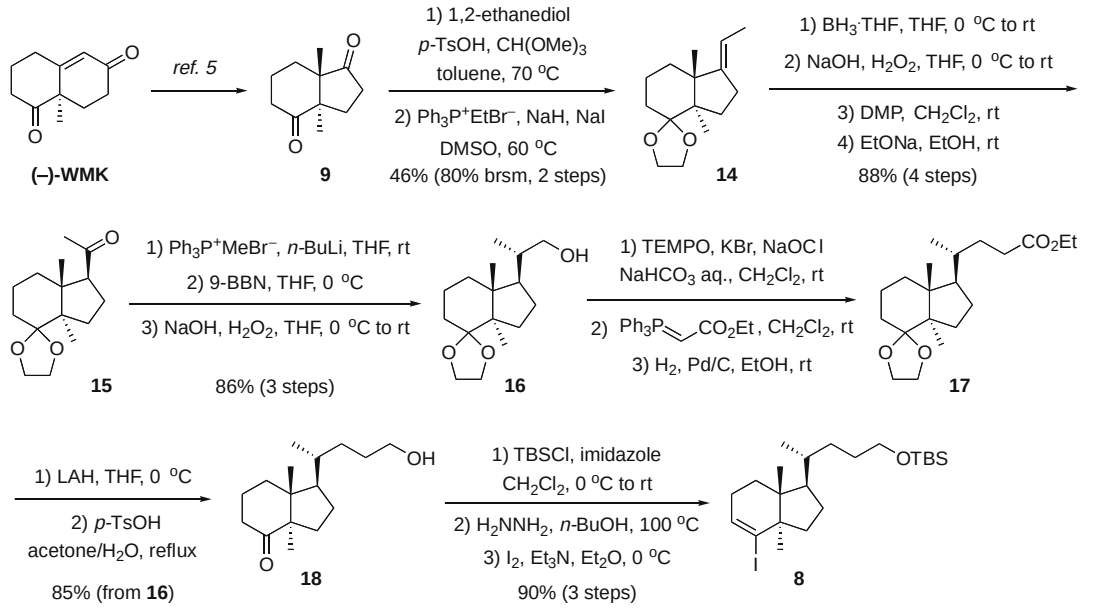


Scheme 1. Synthetic strategy for fomitellic acid B (**2**).

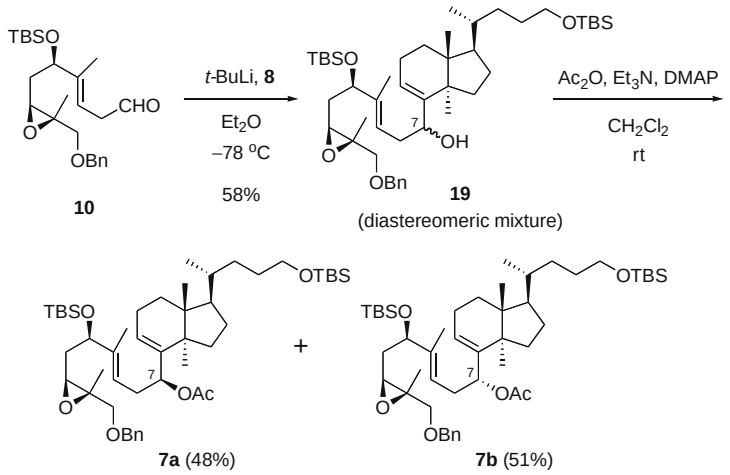


Scheme 2. Preparation of vinyl iodide **8**.

followed by the oxidative workup provided the desired alcohol **16** as a single diastereomer in 86% yield for the three steps. Oxidation of the primary alcohol with TEMPO, two-carbon elongation by the Wittig reaction, and hydrogenation of the resulting unsaturated olefin afforded ethyl ester **17**. Reduction of the ethyl ester with $LiAlH_4$, followed by an acid-catalyzed hydrolysis of the ketal gave ketoalcohol **18** in 85% overall yield from **16**. After protection of the hydroxyl group in **18** as the TBS ether, the ketone was transformed into the vinyl iodide **8** according to Barton's procedure[9] in 90% yield for the three steps.

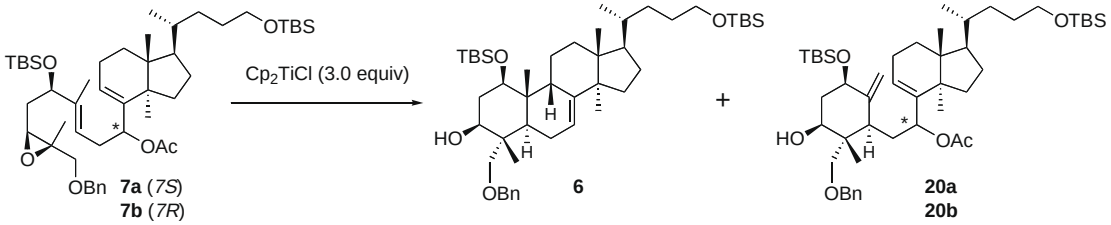
Next, the coupling of vinyl iodide **8** and epoxyaldehyde **10** was examined (Scheme 3). Iodine–lithium exchange of vinyl iodide **8** with *t*-BuLi in Et_2O at −78 °C, followed by the addition of epoxyaldehyde **10,** gave a 1:1 diastereomeric mixture of alcohol **19** in 58% yield. Subsequent acetylation of the secondary alcohol provided epoxypolyenes **7a** and **7b** in 48% and 51% yield, respectively (separable by silica gel column chromatography). Stereochemistry at the C7 position was determined using modified Mosher's method.[10,11]

With epoxypolyene in hand, we then examined a titanium(III)-mediated radical cascade cyclization (Table 1). Thus, epoxypolyene **7a** was treated with 3 equiv of Cp_2TiCl,[12] prepared from Cp_2TiCl_2 and Zn, in THF at 60 °C to afford the desired tetracyclic product **6** as a single diastereomer in 30% yield, along with the monocyclization product **20a**[13] in 33% yield (entry 1). However, a remarkable increase in yield was observed by carrying out the reaction at 100 °C in toluene–THF (2:1) (entry 3). By contrast, epimer **7b** did not undergo cascade cyclization to give the monocyclization product **20b** (entry 4). Nevertheless, in the model study, both epimers underwent a cascade cyclization.[3] These differences will be discussed later by considering the corresponding transition states. Therefore, **7b** was converted into **7a** in 60% yield for the four steps (i.e., deacetylation, oxidation, Luche reduction, and acetylation).[11]



Scheme 3. Preparation of epoxypolyenes **7a** and **7b**.

Table 1
Titanium(III)-mediated radical cascade cyclization



Entry	Substrate	Solvent	Temperature (°C)	Yield (%)	
				6	**20a** or **20b**
1	**7a**	THF	60	30	33
2	**7a**	Toluene–THF = 2:1	60	43	26
3	**7a**	Toluene–THF = 2:1	100	58	3
4	**7b**	THF	60	ND	34

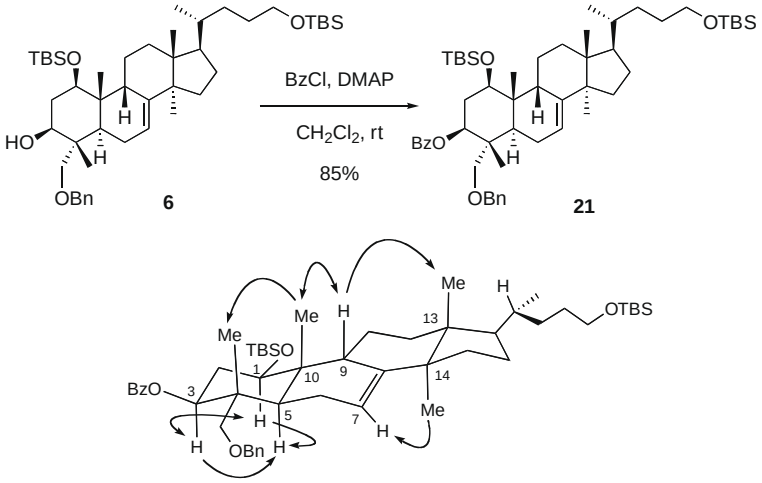


Figure 2. Key NOEs observed in **21**.

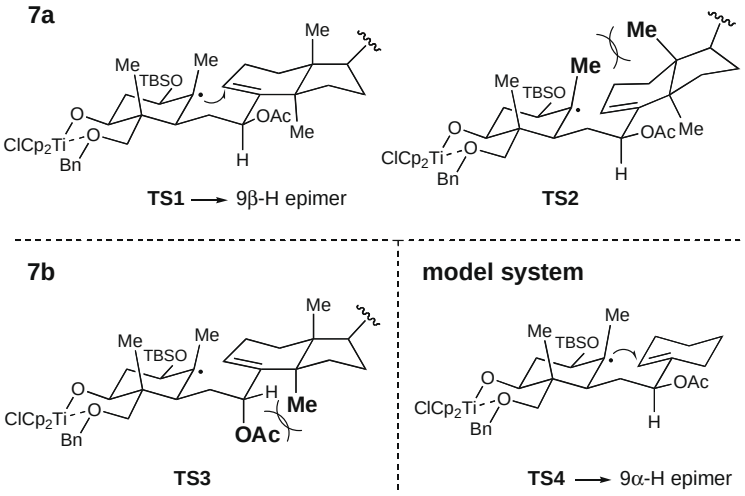
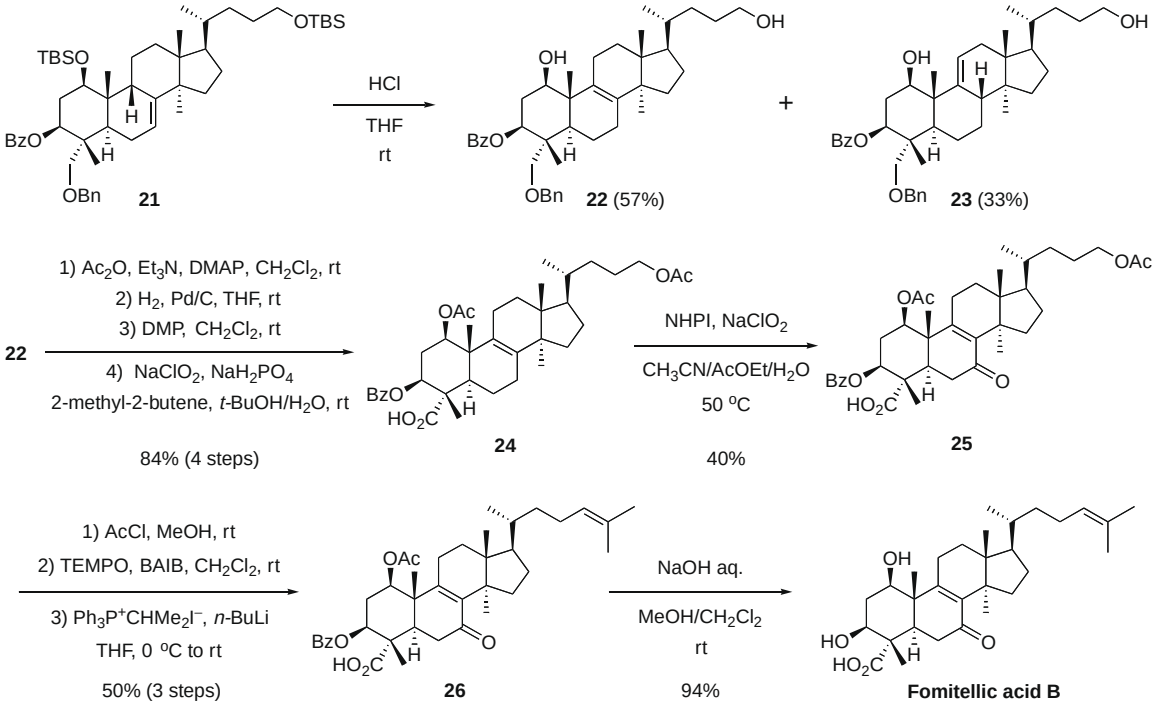


Figure 3. Possible transition states for the formation of the B-ring.



Scheme 4. Synthesis of fomitellic acid B (**2**).

NOE experiments of the corresponding benzoate **21** revealed that the cyclization product **6** had the desired stereochemistry at all requisite stereogenic centers (Fig. 2). Moreover, cyclization using **7a** resulted in the formation of the 9β-H epimer through a trans-fused chair/boat-like transition state **TS1** (Fig. 3). This result suggested that steric repulsion between C10 and C13 methyl groups preclude a trans-fused chair/chair-like transition state **TS2**. By contrast, the model system involves stereoselective production of the 9α-H epimer via a thermodynamically more favorable trans-fused chair/chair-like transition state **TS4**. Furthermore, the fact that the cyclization of **7b** terminated at the monocyclization stage can also be understood by considering a steric repulsion between the C7 acetoxy group and the C14 methyl group (Fig. 3, **TS3**).

We were thus able to obtain the tetracyclic compound **6** with C7–C8 double bond. However, the same approach for the synthesis of **5** was unsuccessful due to the conformational change arising from 9β-H and the presence of the methyl groups at C13 and C14. Therefore, we had to develop a different approach for the construction of the enone moiety in the B-ring. To this end, the first total synthesis of fomitellic acid B (**2**) was accomplished by isomerization of the olefin and allylic oxidation as shown in Scheme 4. Deprotection of the two TBS groups and isomerization of the olefin were performed in one step by treatment of the benzoate ester **21** with concentrated HCl to give the diol **22** in 57% yield, along with its regioisomer **23** in 33% yield. After acetylation of both the hydroxy groups in diol **22**, the benzyl group was deprotected by hydrogenolysis, and the resultant primary alcohol was oxidized to carboxylic acid **24** by a conventional two-step procedure in 84% overall yield from **22**. Allylic oxidation at the C7 position was found to occur, following the treatment of **24** with $NaClO_2$ and *N*-hydroxyphthalimide (NHPI) at 50 °C to give enone **25**, albeit in low yield.[14] After selective cleavage of the primary acetyl group

by the treatment with AcCl in MeOH,[15] the resultant alcohol was oxidized with TEMPO to give the aldehyde in 80% yield for the two steps. The aldehyde was then subjected to the Wittig reaction with *n*-BuLi and isopropyltriphenylphosphonium iodide in THF to afford **26** in 63% yield. Finally, hydrolysis of the acyl-protecting groups in **26** with NaOH completed the synthesis of fomitellic acid B (**2**). The spectroscopic data (^{1}H, ^{13}C NMR and IR spectra, HRMS, and optical rotation) for the synthetic material were identical with those of natural fomitellic acid B.[16]

In summary, the first asymmetric total synthesis of fomitellic acid B (**2**) was accomplished. The essential features of the present synthesis are twofold; (i) stereoselective construction of the tetracyclic skeleton by a titanium(III)-mediated radical cascade cyclization of epoxypolyene, and (ii) generation of the enone moiety in the B-ring via isomerization of the olefin followed by allylic oxidation. The synthesis of other fomitellic acids and the related structure–activity relationship study are currently underway.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tetlet.2009.09.088.

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