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JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

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Enantio- and Diastereoselective Synthesis of *N*-Acetyl Dihydrotetrafibricin Methyl Ester

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Supporting Information

ABSTRACT: A highly diastereoselective synthesis of *N*-acetyl dihydrotetrafibricin methyl ester (**34**) is described. The synthesis features three enantioselective double allylboration reactions and an intramolecular hydrosilylation/Fleming−Tamao oxidation sequence to establish seven of the hydroxy-bearing stereocenters of **34**. Especially noteworthy is the fragment-assembly double allylboration reaction of **2** and **7** using reagent **3**, which provides the advanced intermediate **6** with >20:1 diastereoselectivity.

Tetrafibricin (**1**) (Figure 1) is a structurally unique natural product isolated from *Streptomyces neyagawaensis*[1] that

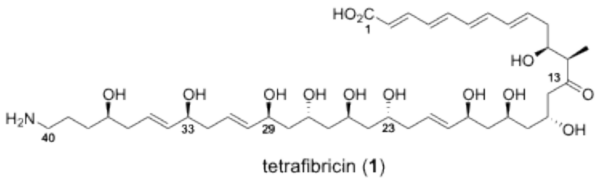
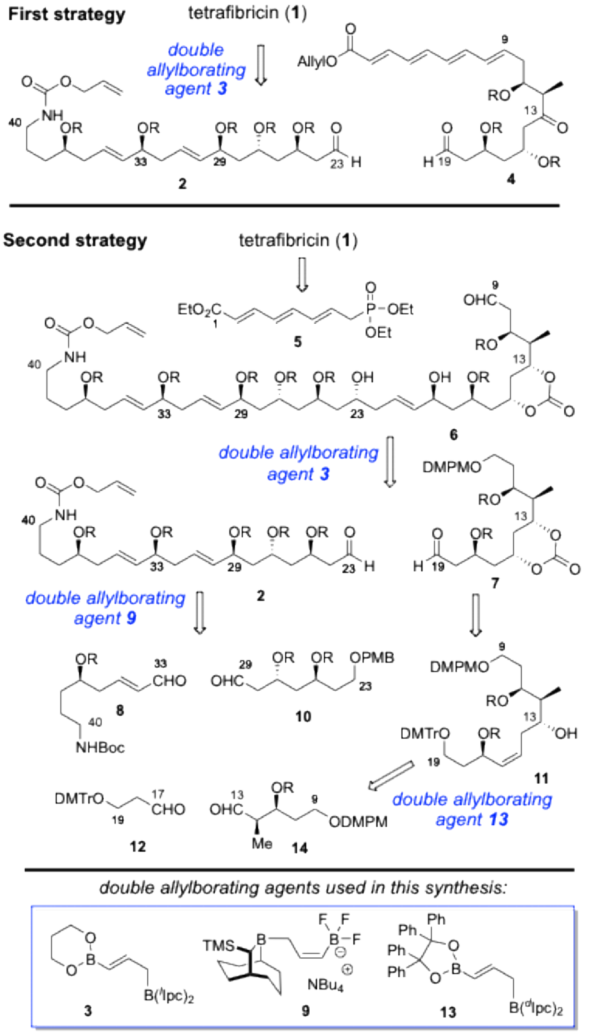


Figure 1. Structure of tetrafibricin (**1**).

displays potent antiaggregation properties against human platelets by blocking the glycoprotein (GP) IIb/IIIa receptor on the platelet surface, which is important for blood clotting.[2] The stereochemistry of tetrafibricin was assigned by Kishi on the basis of ^{1}H NMR database technology.[3] Studies directed toward the synthesis of tetrafibricin have been described by Cossy,[4] Curran,[5] Friestad,[6] Krische,[7] and our group.[8] However, a total synthesis of tetrafibricin, which is necessary to confirm Kishi's relative and absolute stereochemical assignment, has not been reported.

Our strategy for the synthesis of tetrafibricin is outlined in Scheme 1. The synthesis was designed with the intention of applying the double allylboration methodology developed in our laboratory[8,9] to establish several of the 1,5-diol relationships in the natural product. We initially envisioned that **1** would be accessed by a late-stage fragment-assembly double allylboration reaction of aldehydes **4**[8a] and **2**[8c,d] with the first-generation reagent **3**.[9] As it turned out, several attempts[8b] at this coupling with these and related intermediates proceeded in low yield, which we ultimately traced to the instability of **4**. Curran's group reported similar issues in their attempts to effect a Kocienský−Julia olefination reaction with an analogue of **4**.[5c] These observation prompted us to reexamine our synthesis and to plan to install the polyene unit in the last stage by means of a

Scheme 1. Retrosynthetic Analysis of Tetrafibricin (R = TBS)



Horner−Wadsworth−Emmons reaction between known phosphonate **5**[8a] and the C(9)−C(40) aldehyde **6**. We envisaged that **6** could be obtained in a highly convergent way from an (*E*)-1,5-*anti* double allylboration reaction[9] of aldehydes **2** and **7** with 1,3-bifunctional allylborane **3**. The key aldehyde intermediate **2** would be accessed by applying an (*E*)-1,5-*syn*

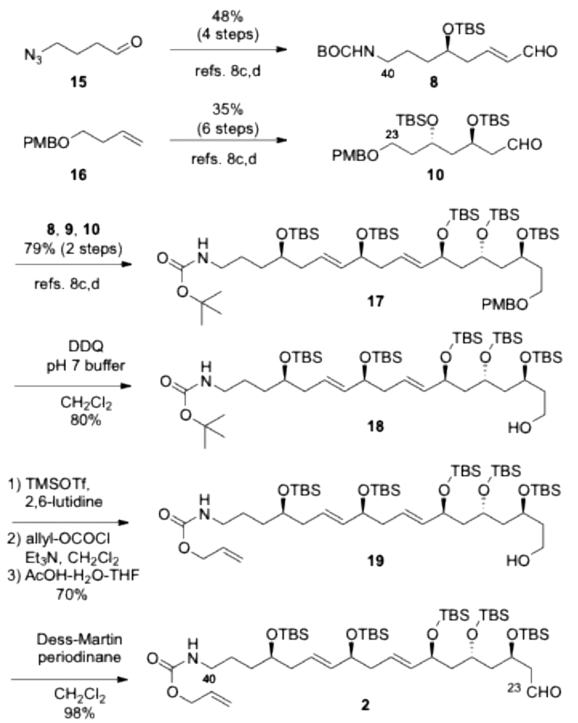
Received: February 21, 2013

   dx.doi.org/10.1021/ja401918r | J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

double allylboration reaction of aldehydes **8** and **10** and 1,3-bifunctional allylborane **9**.[8c,d] Aldehyde fragment **7** would be derived from (*Z*)-1,5-diol **11** by an intramolecular hydrosilylation/Tamao−Fleming oxidation sequence.[10,11] Finally, 1,5-diol **11** would be obtained from a third double allylboration reaction, in this case using 1,3-bifunctional allylborane **13**[9] to couple aldehydes **12** and **14**.

The synthesis of aldehyde **2** proceeded from the previously synthesized carbamate intermediate **17**[8c,d] (as briefly summarized at the beginning of Scheme 2). Deprotection of the *p*-

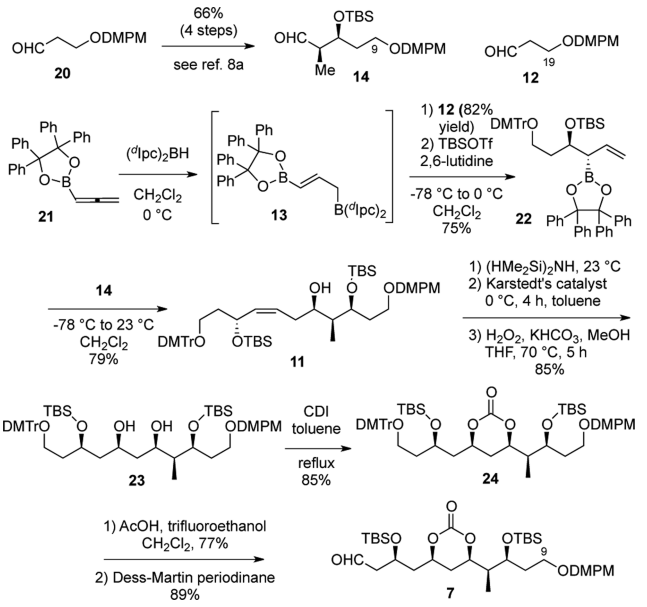
Scheme 2. Synthesis of C(23)−C(40) Aldehyde 2



methoxybenzyl (PMB) ether was accomplished by using 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ), which provided **18** in 80% yield. The *tert*-butyl carbamate (Boc) unit was replaced by an allyl carbamate (Alloc) group to facilitate the deprotection chemistry at the end of the synthesis. Thus, treatment of **18** with trimethylsilyl triflate (TMSOTf) and 2,6-lutidine in CH_2Cl_2 resulted in protection of the primary alcohol as a TMS ether and cleavage of the Boc group. The primary amine was then protected by treatment with allyl chloroformate, and the TMS ether was removed in acidic media to give **19** in 70% yield over three steps. Finally oxidation of the primary alcohol with Dess−Martin periodinane[12] gave the targeted C(23)−C(40) aldehyde **2** in 98% yield (Scheme 2).

The synthesis of the C(9)−C(19) aldehyde fragment **7** is presented in Scheme 3. Treatment of aldehyde **12** with bifunctional (*E*)-allylborane **13**, which was generated in situ via hydroboration of allene **21** with bis(*d*-isopinocampheyl)borane [(^{d}Ipc)$_2$BH],[9] afforded a *β*-hydroxyallylboronate intermediate, which was isolated and then protected by treatment with TBSOTf, thereby providing allylboronate **22** in 62% yield over two steps. Treatment of **22** with the partner aldehyde **14**[8a] provided homoallylic alcohol **11** in 79% yield with 15:1 d.r. The latter intermediate was treated with 1,1,3,3-tetramethyldisilazane, and the crude alkoxysilane was subjected to a hydrosilylation/Fleming−Tamao oxidation sequence[10,11] using plat-

Scheme 3. Synthesis of C(9)−C(19) Aldehyde 7



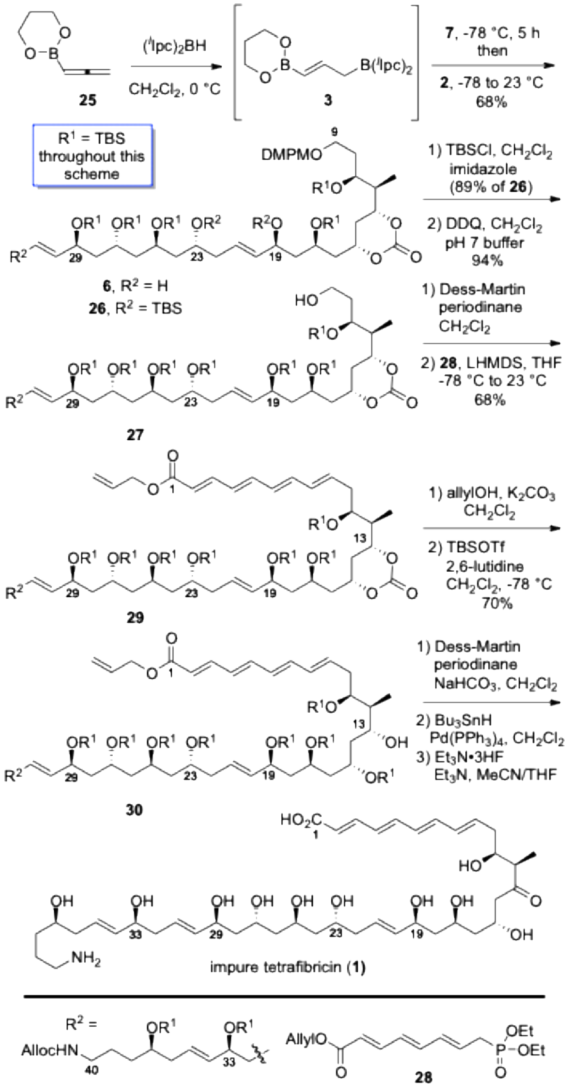
inum(0)-1,3-divinyl-1,1,3,3-tetramethyldisiloxane (Karstedt's catalyst)[13] for the hydrosilylation step. This two-pot sequence afforded alcohol **23** in 85% yield. Treatment of diol **23** with carbonyldiimidazole (CDI) afforded cyclic carbonate **24** in 85% yield. Finally, cleavage of the dimethoxytrityl (DMTr) ether under acidic conditions[14] followed by oxidation of the primary alcohol with Dess−Martin periodinane[12] furnished aldehyde **7** in 69% yield. The absolute configuration of the C(13) hydroxyl group of **11** was assigned by using the Mosher ester method.[15] The absolute and relative configurations of the C(17) hydroxyl group were deduced by analogy to the previously reported C(19) TBDPS ether.[8a,b] The 1,3-*syn* stereochemistry of diol **23** was assigned by using Rychnovsky's acetonide analysis.[16]

Sequential treatment of 1,3-bifunctional allylborane **3**, which was generated in situ from hydroboration of allenylboronate **25** with (^{l}Ipc)$_2$BH,[9a] with aldehydes **7** (0.54 equiv) and **2** (1.0 equiv) provided C(9)−C(40) fragment **6** in 68% yield with exceptional diastereoselectivity (>20:1) and *E*/*Z* ratio (>20:1) (Scheme 4). Protection of the 1,5-diol unit using TBSCl and imidazole followed by oxidative cleavage[17] of the 3,4-dimethoxybenzyl ether gave primary alcohol **27** in 83% yield over two steps. Oxidation of the primary alcohol using Dess−Martin periodinane[12] followed by Horner−Wadsworth−Emmons olefination of the resulting aldehyde with phosphonate **28** yielded C(1)−C(40) fragment **29** in 68% yield over the two steps. Cleavage of the cyclic carbonate (allyl alcohol, K_2CO_3) followed by selective monoprotection of the C(15) alcohol using TBSOTf gave secondary alcohol **30** in 70% yield. Finally, Dess−Martin oxidation of **30**, removal of both the allyl ester and Alloc groups,[18] and global cleavage of the TBS ethers provided a small sample of impure material that we tentatively identified as tetrafibricin (**1**) on the basis of LC−MS and ^{1}H NMR data.

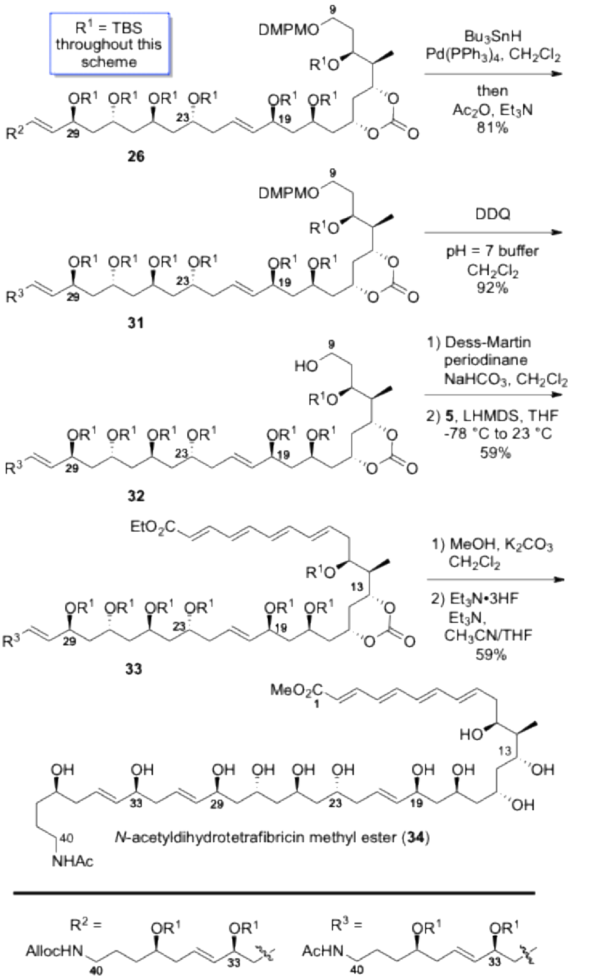
The ^{1}H NMR data that we obtained for the impure sample of synthetic **1** were consistent with the data for the natural product published in the isolation paper,[1a] but all attempts to purify the sample led to decomposition. Tetrafibricin is reported to be highly unstable in the isolation paper,[1] and comments about its instability also appear in Kishi's structure elucidation report.[3] Therefore, our attention shifted to the

dx.doi.org/10.1021/ja401918r | J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

Scheme 4. Attempted Synthesis of 1 (R^1 = TBS)



Scheme 5. Synthesis of *N*-Acetyldihydrotetrafibricin Methyl Ester (34)



synthesis of the more stable *N*-acetyl dihydrotetrafibricin methyl ester (**34**),[1b] which served as the focus of Kishi's stereochemistry assignment because of the instability of the natural product.[3]

The synthesis of **34** proceeded from C(9)−C(40) fragment **26** as follows (Scheme 5). Replacement of the *N*-Alloc group by an *N*-acetyl group was accomplished in a one-pot operation (81% yield) by treatment of **26** with Bu_3SnH and $Pd(PPh_3)_4$ followed by addition of acetic anhydride and Et_3N.[18] The 3,4-dimethoxybenzyl (DMPM) ether unit of **31** was cleaved by treatment with DDQ[17] to give primary alcohol **32** in 92% yield. Oxidation of **32** using Dess−Martin periodinane[12] followed by Horner−Wadsworth−Emmons olefination of the aldehyde with phosphonate **5**[9] provided the advanced C(1)−C(40) intermediate **33** in 59% yield over two steps. Finally, cleavage of the carbonate unit (MeOH, K_2CO_3), with concomitant transesterification of the ester, followed by deprotection of the nine TBS ethers with excess $Et_3N{\cdot}3HF$ provided **34** in 59% yield over the final two steps. The ^1H and ^{13}C NMR data obtained for **34** were in complete agreement with published data and with NMR spectra of a mixture of **34** and the C(13) epimer provided by Prof. Kishi.

In conclusion, attempts to complete the total synthesis of tetrafibricin (**1**) were compromised by the instability of the natural product, which prompted us to synthesize the more stable analogue *N*-acetyl dihydrotetrafibricin methyl ester (**34**). The longest linear sequence in the synthesis is 21 steps from 4-azidobutanal (**15**), and the synthesis proceeds with an overall yield of 2%. This work validates Kishi's stereochemical assignment of **1** and illustrates the utility of the double allylboration reaction technology developed in our group for use in the highly stereocontrolled and convergent synthesis of stereochemically complex natural products.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

dx.doi.org/10.1021/ja401918r | J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

■ ACKNOWLEDGMENTS

We thank the National Institutes of Health (GM038436) for support of this research; Dr. Ricardo Lira, who performed exploratory studies on the coupling of **2** and **4**; Professor Yoshito Kishi, who provided copies of the ^{1}H and ^{13}C NMR spectra of a 2:1 mixture of **34** and its C(13) epimer for comparison; and Professor Glenn Micalizio for helpful suggestions and comments.

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