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Stereoselective Synthesis of the C(1)–C(19) Fragment of Tetrafibricin

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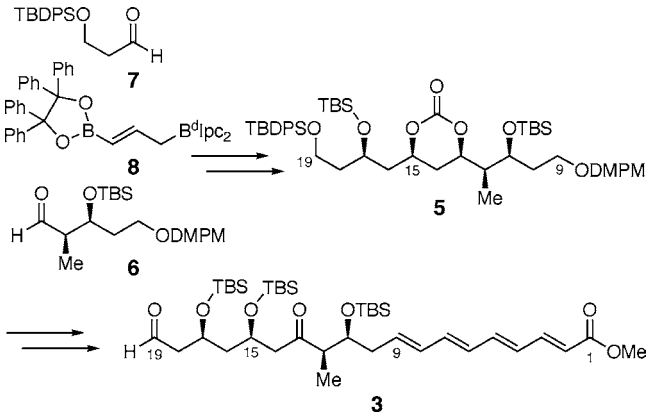
ABSTRACT



A stereoselective synthesis of the C(1)–C(19) fragment of tetrafibricin has been accomplished via a highly diastereoselective double allylboration reaction of 6–8 and an iodonium ion promoted urethane cyclization for the installation of the C(15) alkoxy function in 3.

Tetrafibricin is a polyoxygenated fibrinogen receptor inhibitor that was isolated in 1993 from the culture broth of *Streptomyces neyagawaensis* NR0577.[1] Fibrinogen binding to the glycoprotein GPIIb/IIIa complex on the platelet surface plays a crucial role in platelet aggregation.[2] The ability of tetrafibricin to block fibrinogen from binding to its glycoprotein receptor makes it a viable target for the potential therapeutic intervention of arterial thrombotic diseases such as coronary occlusion.[3,4] Kishi and co-workers recently assigned the stereochemistry of tetrafibricin (**1**) through the use of an NMR database method, supplemented by data obtained from NMR measurements in chiral solvents.[5] The interesting biological properties and challenging structure, which includes 11 stereocenters of which 10 are secondary hydroxyls arrayed as 1,3- and 1,5-diols, render tetrafibricin an excellent target for synthetic study. Development of an efficient, convergent synthesis of tetrafibricin (**1**) will facilitate structure−activity relationship studies designed to probe its biological properties. To our knowledge, only Cossy has disclosed efforts toward the total synthesis of tetrafibricin.[6] We report herein our initial synthetic studies on **1**, culminating in an efficient synthesis of the C(1)−C(19) fragment **3** via application of the double allylboration methodology developed in our laboratory.[7]

Our retrosynthetic analysis of tetrafibricin is outlined in Figure 1. We envisaged that tetrafibricin can be assembled from a late-stage double allylboration sequence involving the coupling of the functionalized aldehydes **2** and **3** with bifunctional allylborane **4**.[7] It is expected that this reaction will provide the C(19)−C(23) *anti*-1,5-diol unit of **1** with an embedded *trans*-olefin in a single step. Aldehyde **3** would be assembled in turn from cyclic carbonate **5** through a

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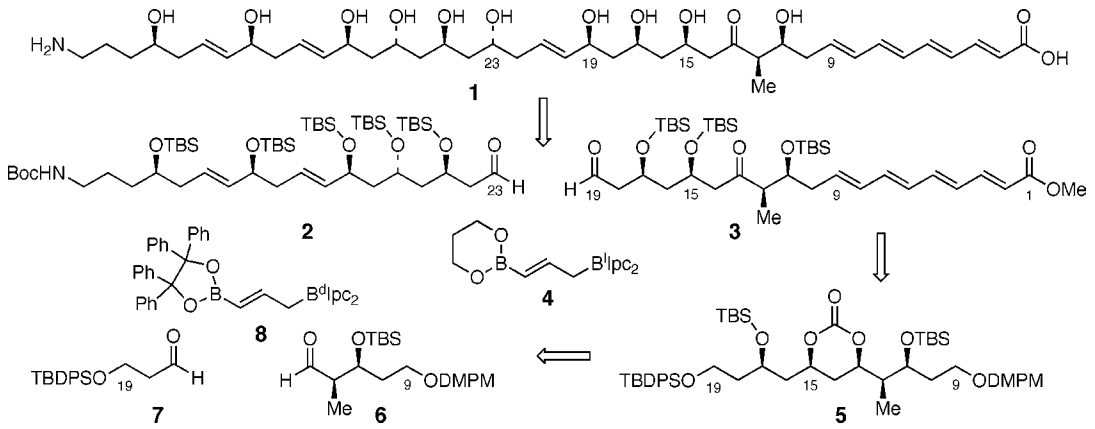
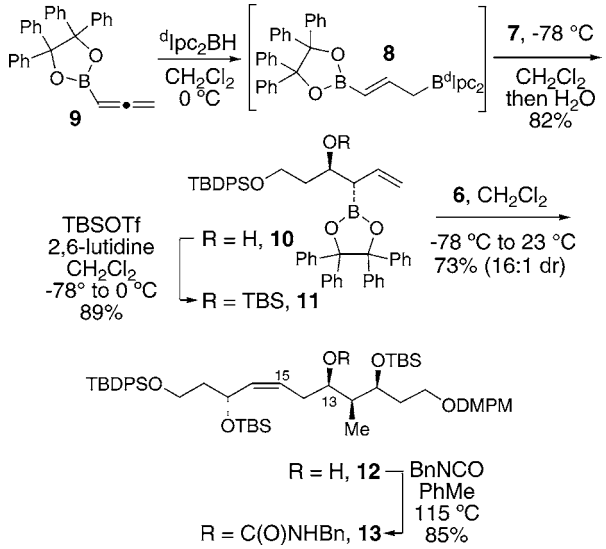


Figure 1. Tetrafibricin retrosynthetic analysis.

Horner−Wadsworth−Emmons olefination sequence, followed by oxidation of the C(13) and C(19) alcohols. Further analysis of carbonate **5** suggests it can be accessed via a three-component coupling of aldehydes **6**[8] and **7**[9] with bifunctional allylborane **8**, followed by installation of C(15)−OH.

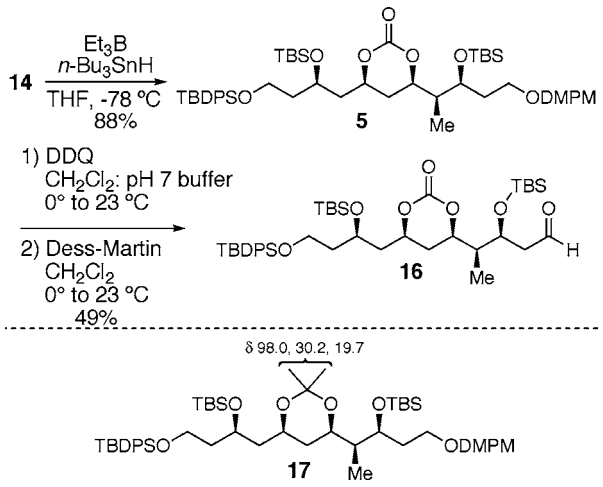
The synthesis of the C(1)−C(19) fragment **3** commenced with the construction of benzyl carbamate **13** (Scheme 1).

Scheme 1. Synthesis of Benzyl Carbamate **13**



Intially, we pursued the synthesis of alcohol **12** via a one-pot double allylboration sequence followed by selective protection of the C(17) allylic alcohol.[10] However, we were only able to achieve ca. 2:1 selectivity in protecting the allylic alcohol of the diol corresponding to **12**. Therefore, it proved advantageous to synthesize **12** via an interrupted, three-pot double allylboration sequence to differentiate the secondary C(17) and C(13) alcohols.[11] Thus, treatment of aldehyde **7**[9] with the in situ generated bifunctional (*E*)-allylborane **8**[7] [derived from the hydroboration of allene **9**[7] with (^{d}Ipc)$_2$BH],[12] followed by quenching with water, afforded *β*-hydroxy allylboronate **10** in 82% isolated yield.[13] The resultant allylic alcohol was protected by treatment with TBSOTf and 2,6-lutidine to afford allylboronate **11** in 89% yield. Treatment of **11** with 1.1 equiv of aldehyde **6**[8] at 23 °C for 96 h proceeded in a matched fashion and provided homoallyl alcohol **12** in 73% yield as a 16:1 mixture of

Scheme 2. Synthesis of Aldehyde **16**



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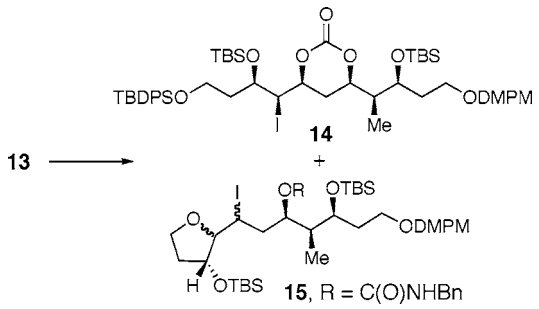
(13) The absolute stereochemistry of C(17)−OH of **10** was assigned by Mosher ester analysis of an analogue of **13**; see Supporting Information for details.

diastereomers.[14] The homoallyl alcohol was then treated with benzyl isocyanate in toluene at 115 °C to provide key benzyl carbamate **13** in 85% yield.

Attention was next focused on the diastereoselective installation of the C(15)-β alkoxy group of fragment **3** via an iodonium ion promoted urethane cyclization. Initial attempts to effect this cyclization by treatment of **13** with iodine monochloride in CH_2Cl_2 at −78 °C[15] afforded a mixture of the desired iodo carbonate **14** along with an inseparable furan side product **15** (Table 1, entry 1). This

Table 1. Installation of the C(15) Oxygen by an Iodonium Ion Promoted Urethane Cyclization



entry	conditions	**13**/**14**/**15**[a]	yield of **14** (%)
1	ICl/CH_2Cl_2, −78 °C	0:80:20	
2	ICl-Pyr/CH_2Cl_2, −78 to 23 °C	50:20:0	17
3	NIS/$CHCl_3$, 0−23 °C	0:100:0	70

[a] Ratio determined by ^{1}H NMR analysis.

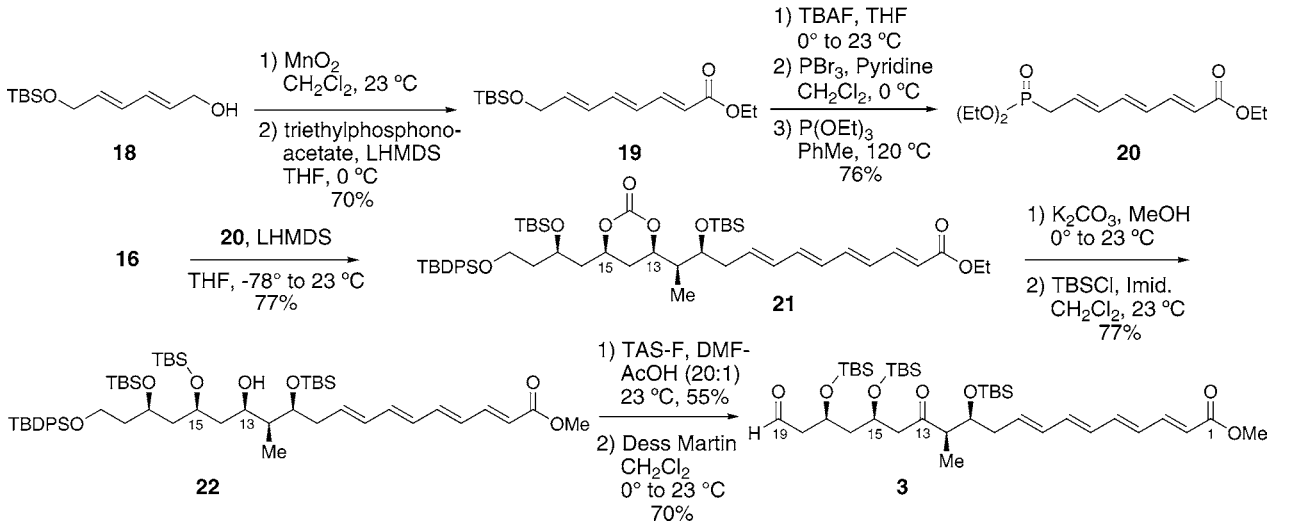
side product arises from a 5-*exo*-type cyclization with concomitant deprotection of the TBDPS ether. We anticipated that use of a pyridine−ICl complex would slow the rate of the competing furan formation by moderating the reactivity of the iodonium ion. Accordingly, treatment of carbamate **13** with a preformed pyridine−ICl complex in CH_2Cl_2 at −78 °C and warming to 23 °C provided a small amount of the targeted iodo carbonate **14** (17%, entry 2); however, more importantly, formation of the furan side product was completely suppressed. This observation prompted an investigation of NIS as the iodine source due to its stability and ease of handling. Gratifyingly, treatment of benzyl carbamate **13** in $CHCl_3$ at 23 °C with NIS (added portionwise) effected a clean cyclization which provided carbonate **14** as the sole product in 70% yield and >20:1 diastereoselectivity as judged by ^{1}H NMR analysis.[16]

Deiodination of **14** by treatment with Et_3B and *n*-Bu_3SnH generated desired intermediate **5** in 88% yield.[17] To verify the C(13)−C(15) *syn* stereochemistry, intermediate **5** was converted to acetonide analogue **17** via a two-step sequence.[18] ^{13}C NMR analysis of the acetonide according to the Rychnovsky method[18] confirmed the presence of a *syn*-1,3-diol relationship (see Supporting Information for details). Deprotection of the primary DMPM group of **5** with DDQ followed by Dess−Martin oxidation[19] yielded sensitive aldehyde **16**, the substrate for the subsequent Horner−Wadsworth−Emmons olefination with phosphonate **20**.

Horner−Wadsworth−Emmons reagent **20** was synthesized starting with the MnO_2 oxidation of the known alcohol **18**[20] (Scheme 3). Subjection of the derived aldehyde to a Horner−Wadsworth−Emmons[21] olefination with triethyl phosphonoacetate afforded intermediate **19** in 70% yield. Deprotection of **19** by treatment with TBAF, followed by conversion of the allylic alcohol to the corresponding allylic bromide by treatment with PBr_3 and pyridine, and then treatment of the allylic bromide with $P(OEt)_3$ in refluxing toluene yielded the phosphonate coupling partner **20** in 76% yield over three steps.[22] Gratifyingly, treatment of **20** with LHMDS followed by addition of a solution of aldehyde **16** at −78 °C with warming to 0 °C provided intermediate **21** in 77% yield.[23]

Tetraenoate **21** contains all the carbon atoms of the C(1)−C(19) fragment **3** of tetrafibricin; all that remained to

Scheme 3. Completion of the Synthesis of the C(1)−C(19) Fragment **3** of Tetrafibricin



access keto-aldehyde **3** was to adjust the oxidation state of the C(13) and C(19) alcohols. This was achieved by cleavage of the cyclic carbonate in **21**, followed by a selective silylation of the less-hindered C(15)−OH, which provided **22** with 10:1 regioselectivity. The crucial and selective deprotection of the C(19) TBDPS ether was accomplished in 55% yield by using TAS-F in a DMF−AcOH solvent mixture.[24] Finally, oxidation of the C(13)−C(19) diol with the Dess−Martin reagent[19] provided the fully elaborated C(1)−C(19) fragment **3** of tetrafibricin.

In summary, we have accomplished an efficient and highly diastereoselective synthesis of **3** corresponding to the C(1)−C(19) fragment of tetrafibricin. This synthesis proceeds in 13 steps from aldehyde **7**. The highlights of this synthesis include the highly diastereoselective interrupted double allylboration sequence used to prepare intermediate **12**, the diastereoselective iodonium ion promoted urethane cyclization of **13** for the installation of the *syn*-C(15) alkoxy group in **14**, and a Horner−Wadsworth−Emmons olefination of **16** for introduction of the tetraenoate moiety. Further progress toward the completion of the total synthesis of tetrafibricin will be reported in due course.

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Supporting Information Available: Experimental procedures and tabulated 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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