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Synthesis of C1–C20 and C21–C40 fragments of tetrafibricin

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ABSTRACT

Efficient syntheses of suitably functionalized top and bottom fragments of tetrafibricin are described. The bottom fragment is prepared by two consecutive Kocienski–Julia couplings, while the top fragment synthesis features a dithiane alkylation and a Horner–Wadsworth–Emmons reaction.

1. Introduction

During the course of a screening program for fibrinogen receptor antagonists, Kamiyama and co-workers isolated tetrafibricin **1** from the culture broth of *streptomyces neya–gawaensis NR0577* and assigned its two-dimensional structure.[1] In 2003, Kishi elucidated the complete stereochemistry of tetrafibricin (Fig. 1) by using NMR databases along with experiments in achiral and chiral solvents.[2] Tetrafibricin inhibits the binding of fibrinogen to its receptors with an IC_{50} of 46 nM and inhibits the aggregation of human platelets induced by ADP, collagen, and thrombin. Accordingly, it has potential therapeutic applications for thrombotic diseases, such as coronary occlusion and myocardial infarction.[3]

In synthetic progress to date, Cossy prepared C1–C13, C15–C26, and C27–C40 fragments,[4] while Roush made a C1–C19 fragment.[5] We have described routes to several fragments and have joined a single C21–C30 fragment with quasiisomers of other fragments in a fluorous mixture synthesis (FMS) of four stereoisomers of the C21–C40 fragment of tetrafibricin.[6] This work featured Kocienski–Julia reactions, which have also recently been exploited by Friestad to make a C24–C40 fragment.[7]

Here we describe convergent routes to single stereoisomers of the C1–C20 and C21–C40 fragments of tetrafibricin. The recently published FMS fragment synthesis[6] was patterned after the route described herein. The retrosynthetic analysis of tetrafibricin is outlined in Figure 2. Cleavage at the strategic C20–C21 alkene provides large bottom **2** and top **3** fragments.

A series of Kocienski–Julia reactions (**A**)[8] with appropriate aldehydes and sulfones allow the formation of C20–C21, C30–C31, and C34–C35 bonds from fragments **4** (C35–C40), **5** (C31–C34), and **6** (C21–C30). Disconnection at C13–C14 bond of **3** provides iodide **7** (C14–C20) and dithiane **8** (C9–C13), which will be coupled by alkylation (**B**).[9] Disconnection at C8–C9 provides fragment **9** (C1–C8) as a partner for Horner–Wadsworth–Emmons (HWE) olefination (**C**).

2. Results and discussion

2.1. C35–C40 fragment

The synthesis of C35–C40 sulfone **4** is shown in Scheme 1. Epoxide (*R*)-**10** is readily available in 96% ee by Jacobsen hydrolytic kinetic resolution of the corresponding racemate (prepared by silylation and epoxidation of pent-4-en-1-ol).[6b,10] Reaction of (*R*)-**10** with lithio-1,3-dithane followed by trapping with TBS-triflate afforded **11** in 83% yield. Hydrolysis of dithiane **11** gave an aldehyde (80% yield)[11] that was reduced with DiBAL-H to give alcohol **12** in 98% yield. This was converted into an alkylthiophenyltetrazole by a Mitsunobu reaction, and then the sulfide was oxidized to provide sulfone **13**. Selective cleavage of the primary silyl ether, followed by the reaction of the primary alcohol with di-*tert*-butyl-iminodicarboxylate in the presence of DIAD, provided **4** in 74% yield.[12]

2.2. C31–C34 fragment

The synthesis of C31–C34 aldehyde **5** commenced with the commercially available (*S*)-2-(2,2-dimethyl-1,3-dioxolan-4-yl)eth-

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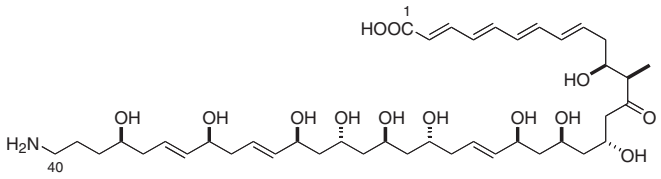


Figure 1. Structure of tetrafibricin **1**.

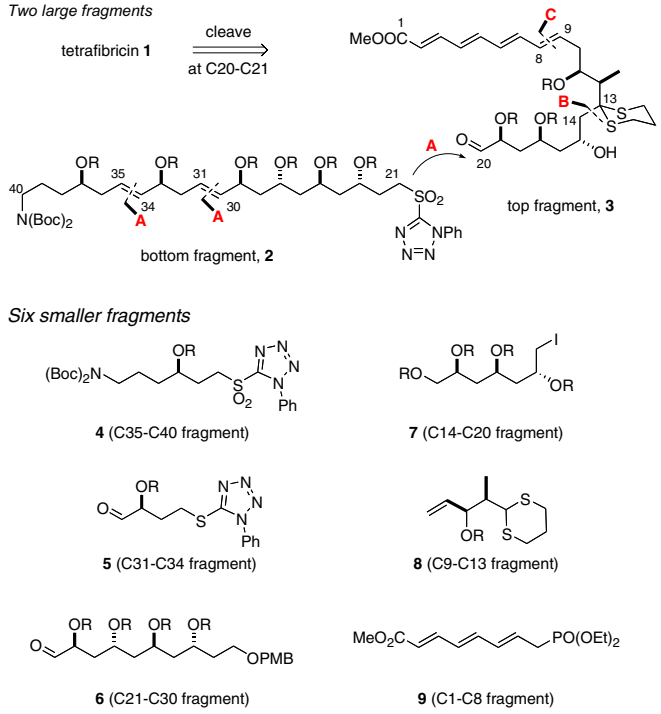
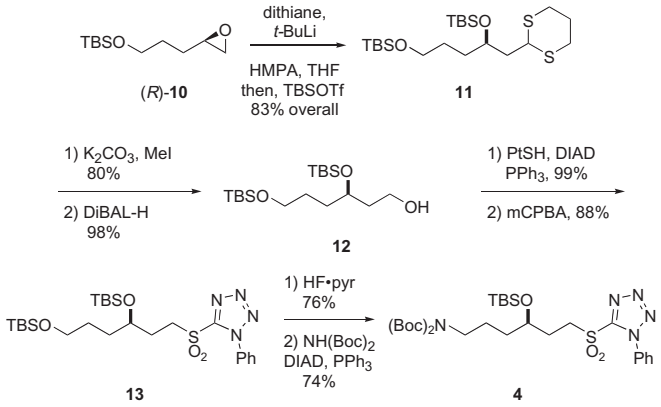
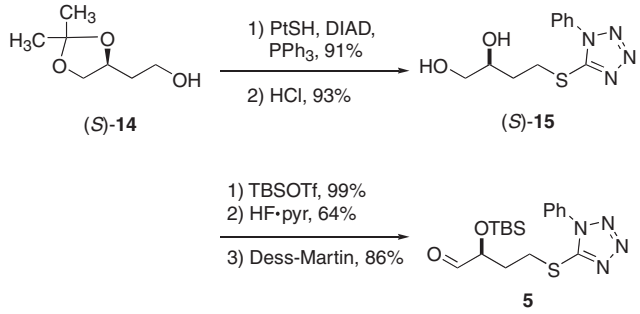


Figure 2. Retrosynthetic analysis with six main fragments **4**–**9**. **A** = Kocienski–Julia rxn; **B** = Dithiane alkylation; **C** = HWE rxn; R = TBS (*tert*-butyldimethysilyl).



Scheme 1. Synthesis of sulfone **4** (C35–C40). PtSH = 1-phenyl,5-thiotetrazole, DIAD = diisopropylazodicarboxylate.

anol (*S*)-**14** as shown in Scheme 2. Alcohol (*S*)-**14** was subjected to a Mitsunobu reaction to incorporate phenylthiotetrazole, then the acetal was cleaved to give diol **15**. Bis-silylation of diol **15**, followed by selective cleavage of the primary silyl-ether and oxidation of the corresponding primary alcohol with the Dess–Martin reagent furnished aldehyde **5** in 54% yield over three steps.



Scheme 2. Synthesis of aldehyde **5** (C31–C34).

2.3. C21–C30 fragment

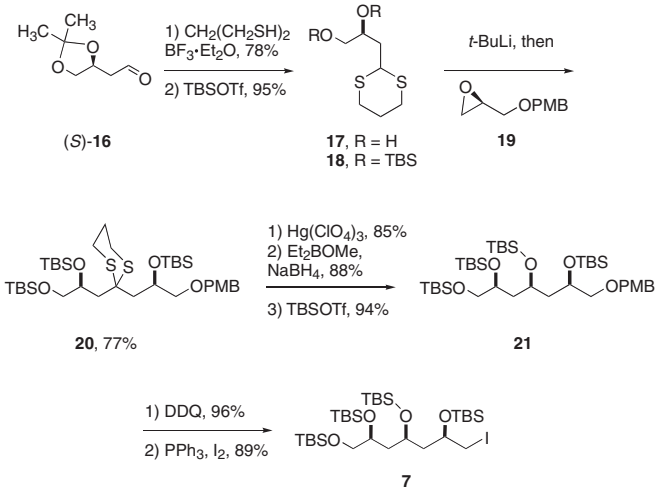
Aldehyde **6** was prepared from (*S*)-2,2-dimethyl-4-((*S*)-oxiran-2-ylmethyl)-1,3-dioxolane as previously described.[6] The published route to **6** takes nine steps and gives 18% yield overall.

2.4. C14–C20 fragment

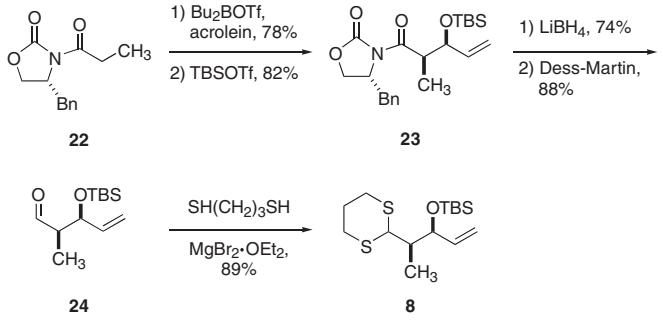
The synthesis of the C14–C20 fragment is shown in Scheme 3. The reaction of aldehyde **16** with propane-1,3-dithiol in the presence of $BF_3{\cdot}OEt_2$[13] resulted in the conversion of aldehyde to 1,3-dithiane and the simultaneous removal of acetal. Diol **17** was isolated in 78% yield. Silylation of the diol (TBSOTf and 2,6-lutidine) proceeded smoothly to give bis-silyl ether **18** in 95% yield. Deprotonation of **18** with *t*-BuLi and reaction of the derived dithiane anion with epoxide **19** provided **20** in 77% yield. Dithiane hydrolysis (85%) followed by directed reduction provided a 1,3-diol bis-silyl ether that was further protected with TBSOTf to provide tetrakis-silyl ether **21** in 70% yield over three steps. Cleavage of the PMB-ether with DDQ followed by the conversion of the corresponding primary alcohol to iodide[14] completed the synthesis of C14–C20 fragment **7**.

2.5. C9–C13 fragment

The synthesis of dithiane **8** is illustrated in Scheme 4. An asymmetric aldol reaction of the freshly distilled acrolein with oxazolidinone **22**[15] (78%) followed by the protection of the derived secondary alcohol provided adduct **23** in 82% yield. Reduction of oxazolidinone **23** with $LiBH_4$ followed by the oxidation of the



Scheme 3. Synthesis of aldehyde **7** (C14–C20).



Scheme 4. Synthesis of dithiane **8** (C9–C13).

resulting primary alcohol with Dess–Martin reagent afforded aldehyde **24** in 88% yield. An addition of propane-1,3-dithiol and $MgBr_2{\cdot}OEt_2$ to aldehyde **24** in THF furnished dithiane **8** in 89% yield.

2.6. C1–C8 fragment

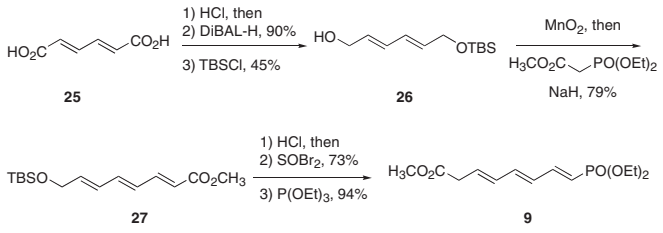
The synthesis of phosphonate **9** is shown in Scheme 5. Alcohol **26** was readily prepared from (*E*,*E*)-muconic acid **25** in a three-step sequence consisting of esterification, reduction, and finally TBS-protection (40% yield overall). Oxidation of the alcohol[16] followed by HWE-olefination of the corresponding aldehyde with methyl-2-(diethoxyphosphoryl)-acetate provided triene **27** in 79% yield. Cleavage of TBS-ether, conversion of the resulting allylic alcohol to bromide, then treatment of bromide with excess triethylphosphite[17] in toluene gave the target phosphonate (*E*,*E*,*E*)-**9** in 94% yield.

2.7. Large bottom fragment C21–C40

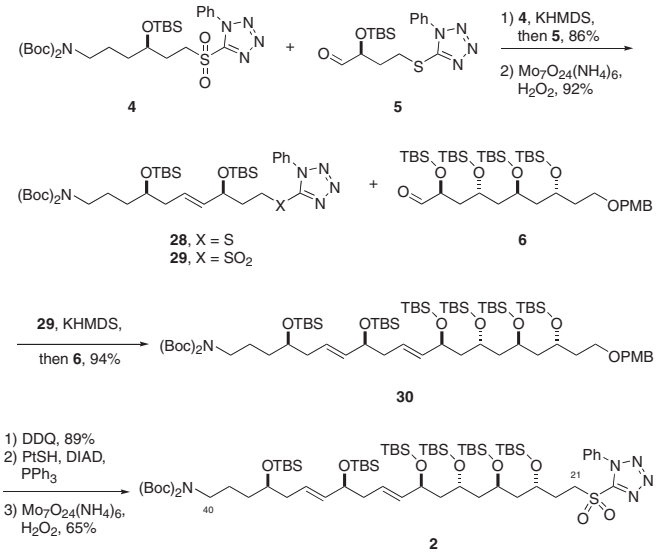
With all six fragments (**4**–**9**) in hand, the assembly of the bottom C21–C40 carbon framework of tetrafibricin was accomplished as shown in Scheme 6. Kocienski–Julia olefination of sulfone **4** with aldehyde **5** provided alkene **28** as the *E*-isomer in 86% yield. Oxidation of sulfide to sulfone **29**, followed by another Kocienski–Julia olefination this time with aldehyde **6** provided **30** as the *E*,*E*-isomer in 94% yield. Cleavage of the PMB-ether, then conversion of alcohol to the alkylthiophenyltetrazole, followed by oxidation of sulfide provided **2** in 58% yield over three steps.

2.8. Large top fragment C1–C20

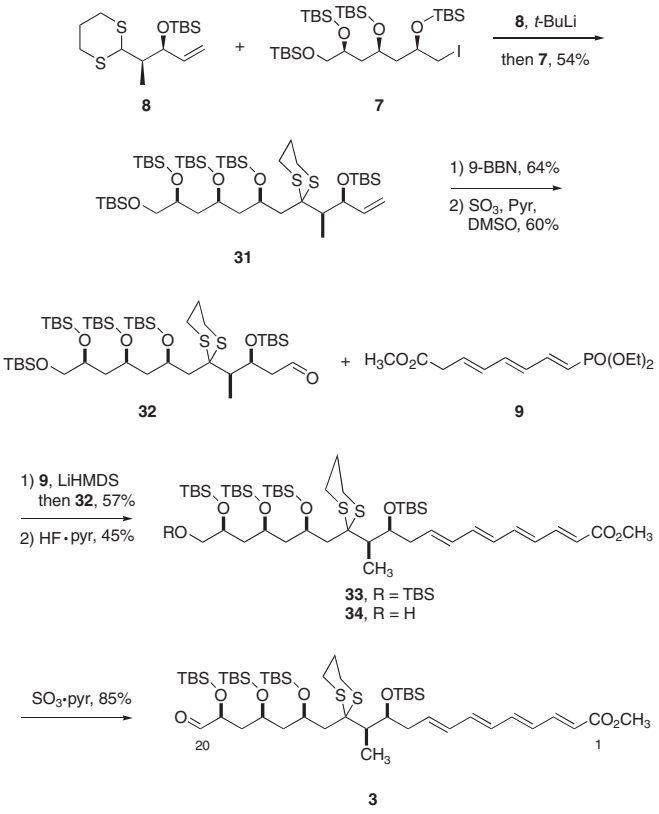
Synthesis of the C1–C20 fragment is shown in Scheme 7. Deprotonation of dithiane **8** with *t*-BuLi followed by the addition of iodide **7** provided **31** in 54% yield. Hydroboration–oxidation of alkene **31** followed by oxidation of the corresponding alcohol provided aldehyde **32** in 38% yield for two steps. The formation of C8–C9 (*E*)-alkene was then carried out by the deprotonation of



Scheme 5. Synthesis of phosphonate **9** (C1–C8).



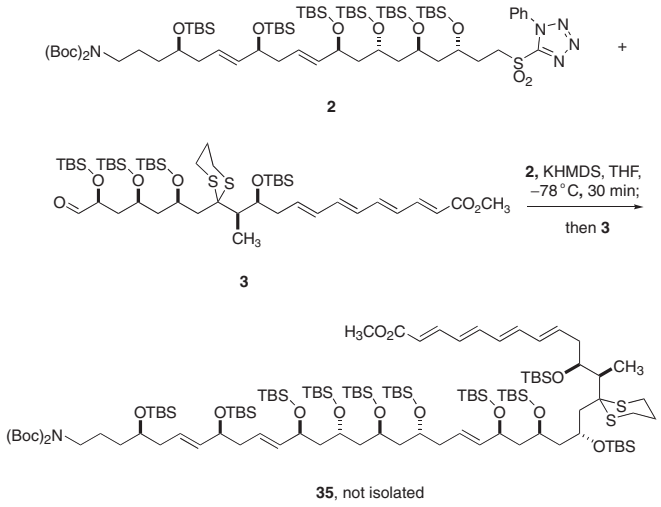
Scheme 6. Synthesis of the large bottom fragment C21–C40.



Scheme 7. Synthesis of the large top fragment **3** C1–C20.

phosphonate **9** with LiHMDS to generate an orange-colored anion, which was then reacted with aldehyde **32** to furnish the conjugated methyl ester **33** ($J_{H8\text{-}H9}$ = 15.1 Hz) in 57% yield. The primary TBS-ether of **33** was cleaved with HF·pyr to provide the primary alcohol **34** in 45% yield. Oxidation of alcohol **34** to the target aldehyde **3** was then carried out with $SO_3{\cdot}$pyr in 85% yield.

With two half fragments (C1–20 and C21–C40) of tetrafibricin in hand, Kocienski–Julia olefination of sulfone **2** with aldehyde **3** was attempted on several different scales (up to ~10 mg) and with different conditions (Scheme 8).[18] Unfortunately, product **35** could



Scheme 8. Attempted coupling reactions.

not be isolated from any experiment. Neither sulfone **2** nor aldehyde **3** was recovered in substantial quantities.

3. Conclusions

Efficient, scalable, and stereoselective syntheses of six main fragments (**4**–**9**) of tetrafibricin have been achieved. These fragments can potentially be assembled to make the natural product in several different ways. Here a highly convergent route was explored to couple three fragments each to make two large halves (C1–20 and C21–C40) of tetrafibricin. The reaction to couple these halves failed, so other orders of fragment coupling need to be pursued to make tetrafibricin. The availability of these fragments and the successful coupling reactions described herein will facilitate that work.

4. Experimental

Complete experimental details and compound characterization data along with copies of the key spectra can be found in the thesis of Dr. V. Gudipati.[18]

Acknowledgments

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