



Published in final edited form as:

Tetrahedron Lett. 2011 April 27; 52(17): 2254–2257. doi:10.1016/j.tetlet.2011.01.086.

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

Venugopal Gudipati and Dennis P. Curran*

Department of Chemistry, University of Pittsburgh, Pittsburgh, PA 15260 USA

Abstract

Efficient syntheses of suitably functionalized top and bottom fragments of tetrafibrin 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.

Keywords

tetrafibrin; natural product synthesis; fibrinogen; dithiane

1. Introduction

During the course of a screening program for fibrinogen receptor antagonists, Kamiyama and coworkers isolated tetrafibrin **1** from the culture broth of *streptomyces neyagawaensis* NR0577, and assigned its two-dimensional structure.¹ In 2003, Kishi elucidated the complete stereochemistry of tetrafibrin (Figure 1) by using NMR databases along with experiments in achiral and chiral solvents.² Tetrafibrin inhibits the binding of fibrinogen to its receptors with an IC₅₀ of 46 nM and inhibits 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 quasisomers of other fragments in a fluororous mixture synthesis (FMS) of four stereoisomers of the C21–C40 fragment of tetrafibrin.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 tetrafibrin. The recently published FMS fragment synthesis⁶ was patterned after the route described herein. The retrosynthetic analysis of tetrafibrin 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 allows the formation of C20–C21, C30–C31 and C34–C35 bonds from fragments **4** (C35–C40), **5**

curran@pitt.edu.

Dedicated to Professor Harry H. Wasserman in celebration of his 90th Birthday

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

(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

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-dithiane 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 to 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 reaction of the primary alcohol with di-*tert*-butyl-iminodicarboxylate in presence of DIAD, provided **4** in 74% yield.¹²

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)ethanol (*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 the 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 the three steps.

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.

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 presence of BF₃·OEt₂¹³ resulted in conversion of aldehyde to the 1,3-dithiane and simultaneous removal of the 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 conversion of the corresponding primary alcohol to iodide¹⁴ completed the synthesis of C14–C20 fragment **7**.

C9–C13 Fragment

The synthesis of dithiane **8** is illustrated in Scheme 4. Asymmetric aldol reaction of the freshly distilled acrolein with oxazolidinone **22**¹⁵ (78%) followed by protection of the derived secondary alcohol provided adduct **23** in 82% yield. Reduction of oxazolidinone **23** with LiBH₄ followed by oxidation of the resulting primary alcohol with Dess-Martin reagent afforded aldehyde **24** in 88% yield. Addition of propane-1,3-dithiol and MgBr₂·OEt₂ to aldehyde **24** in THF furnished dithiane **8** in 89% yield.

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 alcohol¹⁶ followed by HWE-olefination of the corresponding aldehyde with methyl-2-(diethoxyphosphoryl)-acetate provided triene **27** in 79% yield. Cleavage of the TBS ether, conversion of the resulting allylic alcohol to bromide, then treatment of the bromide with excess triethylphosphite¹⁷ in toluene to give the target phosphonate (*E,E,E*)-**9** in 94% yield.

Large Bottom Fragment C21–C40

With all six fragments (**4–9**) in hand, the assembly of the bottom C21–C40 carbon framework of tetrafibrin 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 the 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.

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 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 deprotonation of phosphonate **9** with LiHMDS to generate an orange-colored anion, which was then reacted with aldehyde **32** to furnish the conjugated methyl ester **33** ($J_{\text{H8-H9}} = 15.1$ 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 target aldehyde **3** was then carried out with SO₃-pyr in 85% yield.

With two half fragments (C1–20 and C21–C40) of tetrafibrin 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 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 tetrafibrin 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 tetrafibrin. The reaction to couple these halves failed, so other orders of fragment coupling need to be pursued to make tetrafibrin. 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 key spectra can be found in the thesis of Dr. V. Gudipati.¹⁸

Acknowledgments

We thank the National Institutes of Health, National Institute of General Medical Sciences, for funding this work.

References and Notes

1. (a) Kamiyama T, Umino T, Fujisaki N, Fujimori K, Satoh T, Yamashita Y, Ohshima S, Watanabe J, Yokose K. *J Antibiot.* 1993; 46:1039–1046. [PubMed: 8360097] (b) Kamiyama T, Iteazono Y, Umino T, Satoh T, Nakayama N, Yokose K. *J Antibiot.* 1993; 46:1047–1054. [PubMed: 8360098]
2. Kobayashi Y, Czechitzky W, Kishi Y. *Org Lett.* 2003; 5:93–96. [PubMed: 12509899]
3. (a) Satoh T, Yamashita Y, Kamiyama T, Watanabe J, Steiner B, Hadvary B, Arisawa M. *Thromb Res.* 1993; 72:389–396. [PubMed: 8303682] (b) Satoh T, Yamashita Y, Kamiyama T, Arisawa M. *Thromb Res.* 1993; 72:401–409. [PubMed: 8303683]
4. BouzBouz S, Cossy J. *Org Lett.* 2004; 6:3469–3472. [PubMed: 15387525]
5. Lira R, Roush WR. *Org Lett.* 2007; 9:533–536. [PubMed: 17249805]
6. a) Gudipati V, Bajpai R, Curran DP. *Collect Czech Chem Commun.* 2009; 74:774–783. (b) Zhang K, Gudipati V, Curran DP. *Synlett.* 2010:667–674. [PubMed: 20686632]
7. Friestad GK, Sreenilayam G. *Org Lett.* 2010; 12:5016–5019. [PubMed: 20939544]
8. Blakemore PR. *J Chem Soc, Perkin Trans.* 2002; 1:2563–2585.
9. Smith AB, Adams CM. *Acc Chem Res.* 2004; 37:365–377. [PubMed: 15196046]
10. Schaus SE, Brandes BD, Larrow JF, Tokunaga M, Hansen KB, Gould AE, Furrow ME, Jacobson EN. *J Am Chem Soc.* 2002; 124:1307–1315. [PubMed: 11841300]
11. Nicolaou KC, Fylaktakidou KC, Monenschein H, Li Y, Weyershausen B, Mitchell HJ, Wei H, Guntupalli P, Hepworth D, Sugita K. *J Am Chem Soc.* 2003; 125:15443–15454. [PubMed: 14664590]
12. Davidson MH, McDonald FE. *Org Lett.* 2004; 6:1601–1604. [PubMed: 15128246]
13. Hori N, Matsukura H, Matsuo G, Nakata T. *Tetrahedron.* 2002; 58:1853.
14. a) Garegg PJ, Samuelsson B. *J Chem Soc, Chem Commun.* 1979:978–980. b) Fuwa H, Okamura Y, Natsugari H. *Tetrahedron.* 2004; 60:5341–5438.
15. Funel JA, Pronet J. *J Org Chem.* 2004; 69:4555–4558. [PubMed: 15202921]
16. Yoshimura T, Yakushiji F, Kondo S, Wu X, Shindo M, Shishido K. *Org Lett.* 2006; 8:475–478. [PubMed: 16435863]
17. a) Mori Y, Asai M, Kawade J, Furukawa H. *Tetrahedron.* 1995; 51:5315–5321. b) Denmark S, Shinji F. *J Am Chem Soc.* 2005; 127:8971–8973. [PubMed: 15969572]
18. Gudipati, V. PhD Thesis. University of Pittsburgh; 2009. <http://etd.library.pitt.edu/ETD/available/etd-04212008-115104/>

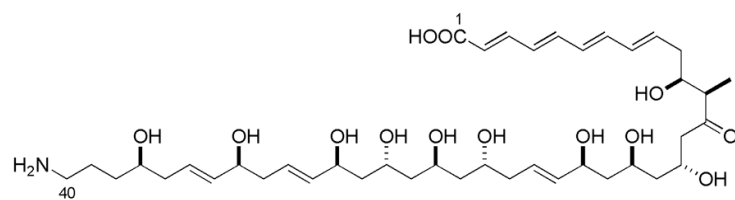


Figure 1.
Structure of tetrafibricin 1

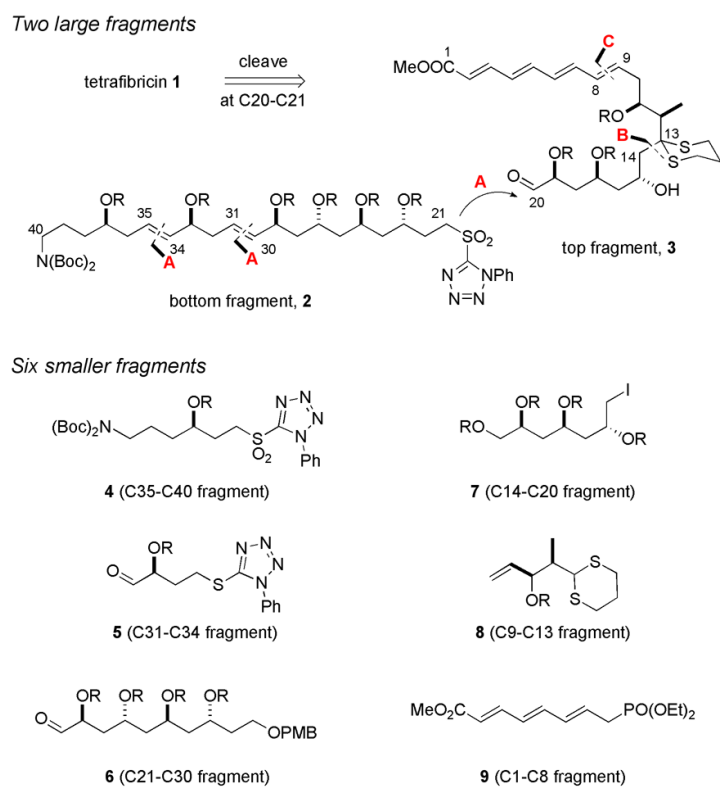
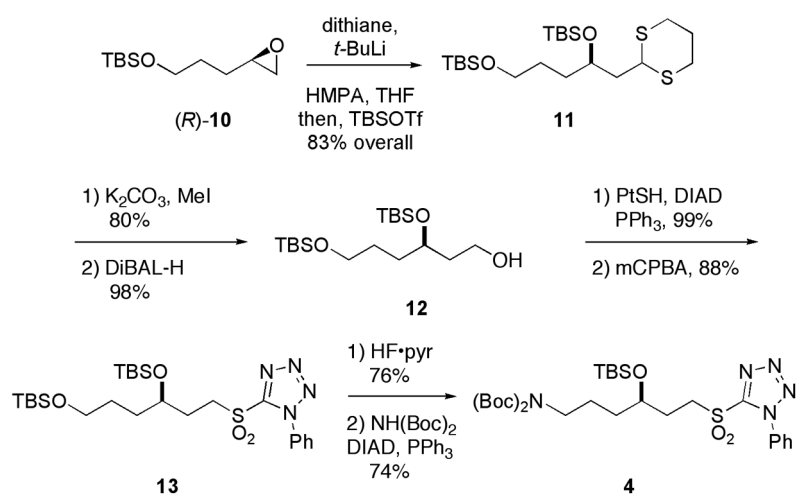
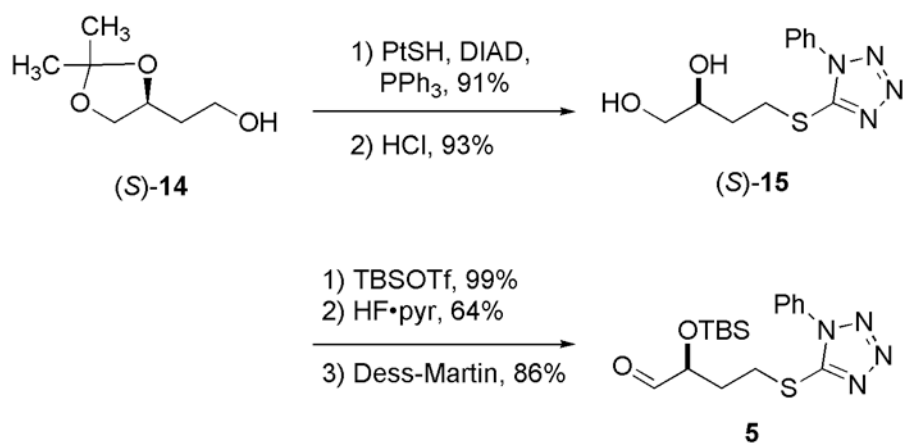


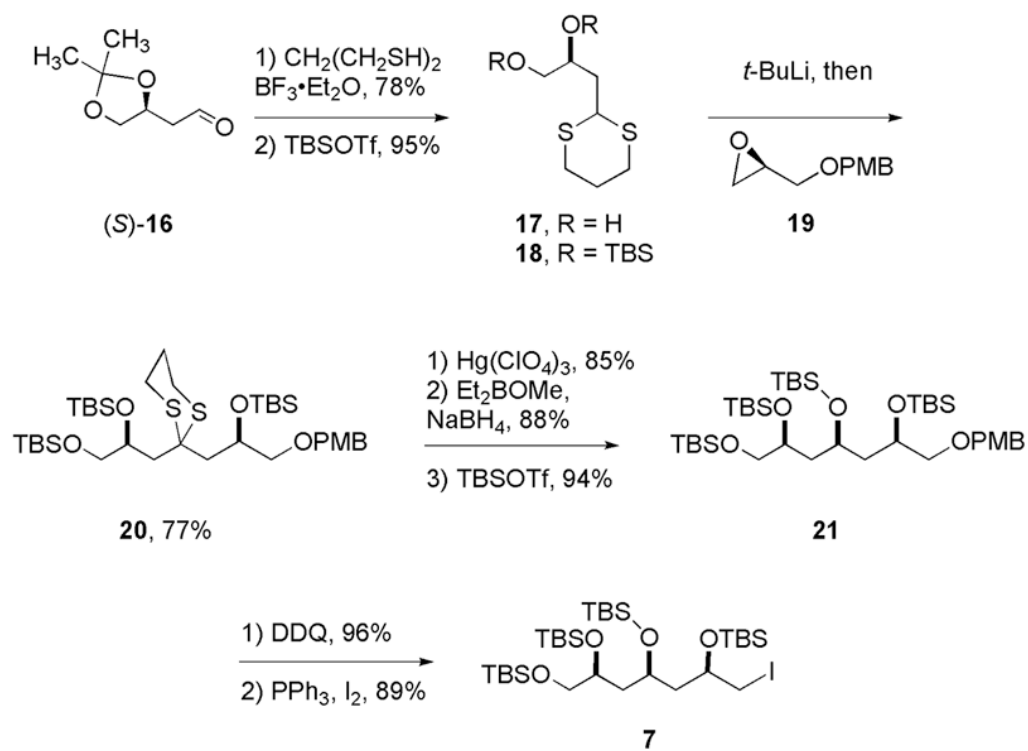
Figure 2. Retrosynthetic analysis with six main fragments **4–9**. **A** = Kocienski-Julia rxn; **B** = Dithiane alkylation; **C** = HWE rxn; R = TBS (*tert*-butyldimethylsilyl).

**Scheme 1.**

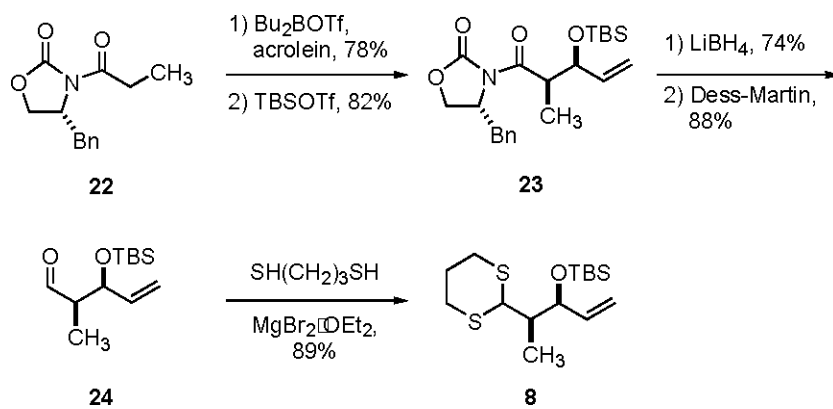
Synthesis of sulfone **4** (C35–C40). PtSH = 1-phenyl,5-thiotetrazole, DIAD = diisopropylazodicarboxylate.



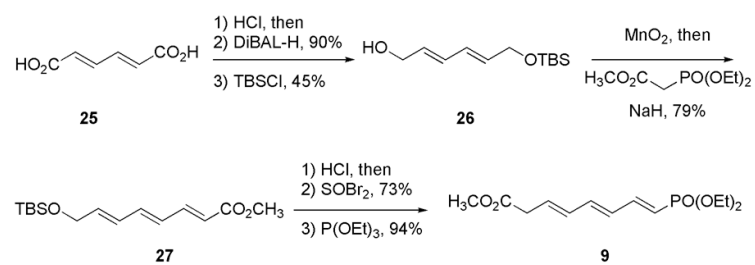
Scheme 2.
Synthesis of aldehyde **5** (C31–C34).



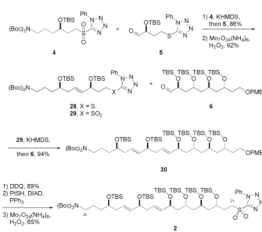
Scheme 3.
 Synthesis of aldehyde **7** (C14–C20).



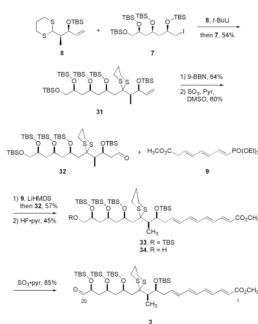
Scheme 4.
Synthesis of dithiane **8** (C9–C13).



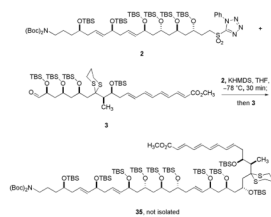
Scheme 5.
Synthesis of phosphonate **9** (C1–C8)



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



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



Scheme 8.
Attempted coupling reactions