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Tetrafibricin: Synthesis of the C1–C13, C15–C25, and C27–C40 Fragments

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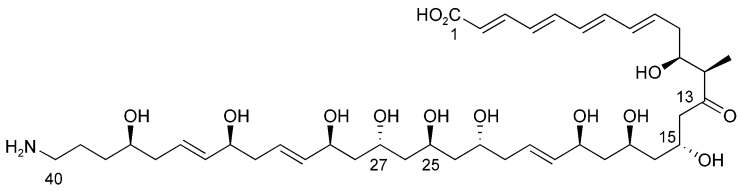
ABSTRACT



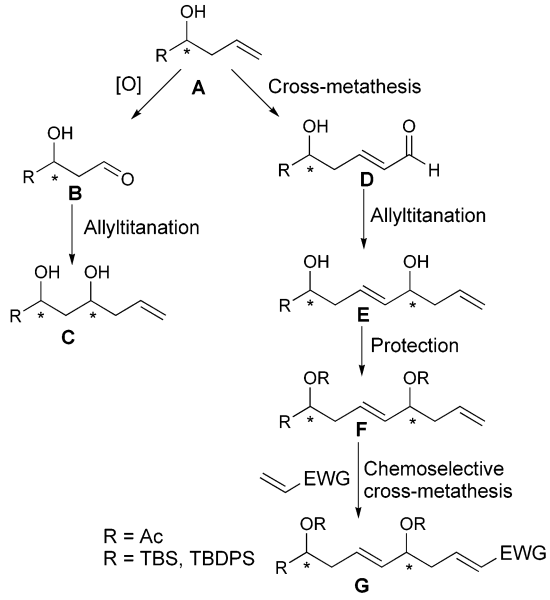
Tetrafibricin

A sequence of chemoselective cross-metathesis reactions and enantioselective allyltitanations of aldehydes has been used to prepare the C1–C13, C15–C26, and C27–C40 fragments of tetrafibricin.

The 1,2-, 1,3-, and 1,5-diol units, as well as polyene units, are present in a great number of natural products possessing interesting biological properties. Among these, tetrafibricin, a polyoxygenated polyene, was isolated in 1993 from *Streptomyces neyagawaensis* NR0577,[1] and its structure was fully established in 2003.[2] Tetrafibricin exhibits potent inhibition on platelet aggregation through the blockage of the GPIIb/IIIa receptor on the platelet surface.[3,4] Compared to other fibrinogen receptor antagonists, tetrafibricin is unique, as its structure lacks any peptidic sequence.[5] Tetrafibricin bears an extended chain of polyalcohols, in particular, 1,3-diols and hexa-1,5-dien-3-ols, as well as a functionalized tetraene. Recently, we have shown that optically active 1,3-*syn*- and 1,3-*anti*-diols of type **C** can be obtained from optically active homoallylic alcohols of type **A** via non-protected β-hydroxy-aldehydes of type **B** by utilizing an enantioselective allyltitanation.[6]

Furthermore, from homoallylic alcohol of type **A**, we were able to obtain the optically active hexa-1,5-dien-3-ols of type **E** with good stereo-, diastereo-, and enantioselectivity via α,β-unsaturated aldehydes of type **D** using a cross-metathesis

Scheme 1



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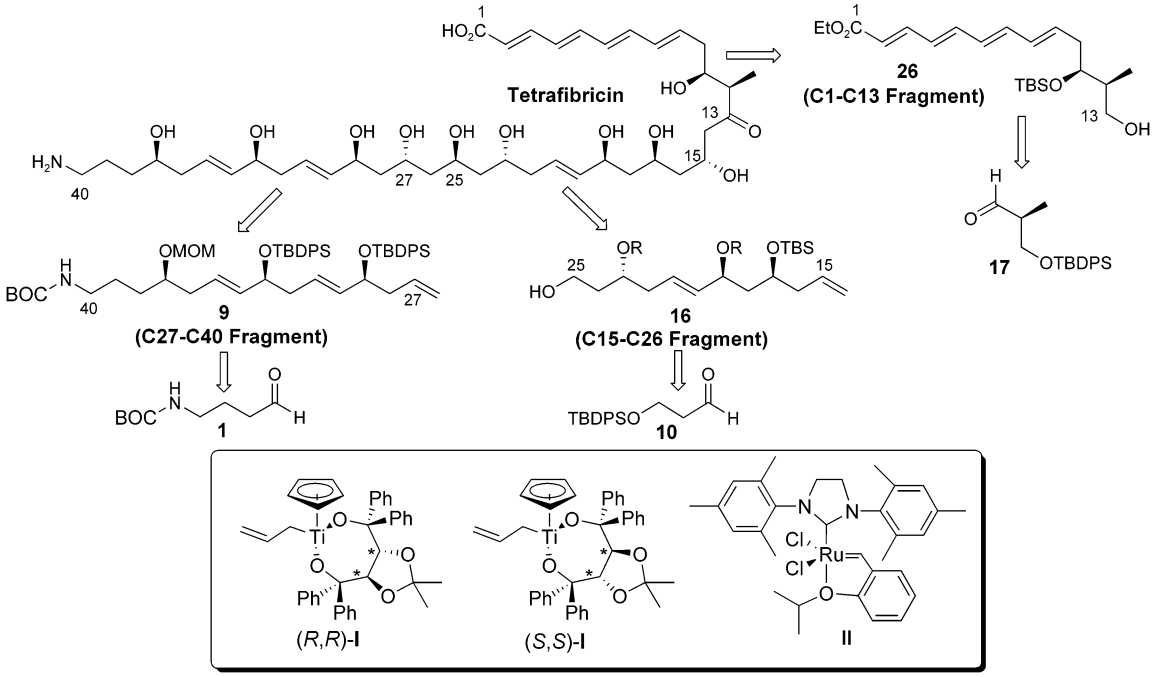
Scheme 2



reaction (CM) followed by an enantioselective allyltitanation. We have also demonstrated that electronic and/or chelating effects[7] (R = Ac) as well as steric effects[8] (R = Si*t*-BuPh$_2$, Si*t*-BuMe$_2$) induced chemoselective CM reactions when protected 1,5-diols of type **F** were treated with an activated olefin in the presence of catalyst **II** (Scheme 1).

The enantioselective allyltitanation and chemoselective CM reactions were envisaged to enable the construction of the C27−C40 and C15−C25 fragments of tetrafibricin from the protected amino aldehyde **1** and the hydroxy aldehyde **10**, respectively. Furthermore, as tetraenes can be obtained by dehydration of 1,5-diols via their corresponding acetates under basic conditions, the same allyltitanation/cross-metathesis sequence was considered for preparation of the C1−C13 fragment of tetrafibricin from aldehyde **17**, which can be prepared from (*S*)-methyl hydroxyl propionate[9] (Scheme 2). The control of all the stereogenic centers in the C1−C13, C15−C25, and C27−C40 fragments could be achieved by treatment of aldehydes with the highly face-selective allyltitanium complexes (*R*,*R*)-**I** and (*S*,*S*)-**I**.[10] The synthesis of the C27−C40 fragment was accomplished by action of the allyltitanium complex (*R*,*R*)-**I** on the *N*-Boc amino-aldehyde **1** to control the stereogenic centers at C29, C33, and C37 and by using cross-metathesis reactions to control the (*E*)-double bonds at C30−C31 and C34−35 (Scheme 3). When *N*-Boc amino aldehyde **1** was treated with the allyltitanium complex (*R*,*R*)-**I** (ether, −78 °C), the homoallylic alcohol **2** was isolated in 83% yield with an ee greater than 95%. In the aim of introducing the C34−C35 double bond, compound **2** was treated with acrolein (3 equiv) in the presence of Hoveyda's catalyst **II**[11] (5 mol %, CH_2Cl_2, 25 °C, 4 h) and the unsaturated hydroxy aldehyde **3** was produced in 81% yield with an *E*/*Z* ratio greater than 20/1. After protection of the hydroxy group in **3** as a methoxymethyl ether (MOMCl, *i*-Pr$_2$NEt, CH_2Cl_2, 25 °C, 91% yield) the resulting protected unsaturated hydroxy aldehyde **4** was treated with the allyltitanium (*R*,*R*)-**I** to introduce the hydroxyl group at C33, and compound **5** was produced in 86% yield (dr = 95/5). As the CM has to be chemoselective to introduce the C30−C31 (*E*)-double bond, the hydroxy group at C33 was protected by a sterically hindered protecting group. Thus, **5** was transformed into the *tert*-butyldiphenylsilyl ether **6** (imidazole, CH_2Cl_2, 25 °C, 1 h, 88% yield), which was then treated with acrolein (3 equiv) in the presence of **II** (5 mol %, CH_2Cl_2, 25 °C, 24 h), and the corresponding unsaturated aldehyde **7** was obtained in 53% yield. The third stereogenic center present in the C27−C40 fragment of tetrafibricin was introduced by addition of the (*R*,*R*)-**I** complex to aldehyde **7** (ether, −78 °C). The unsaturated triol **8** was isolated in 85% yield, and the resulting hydroxy group at C16 was protected as a *tert*-butyldiphenylsilyl ether (TBDPSCl, imidazole, CH_2Cl_2, 25 °C, 2 h) to lead to **9** in 89% yield. This compound corresponds to the C27−C40 fragment of tetrafibricin.

The synthesis of the C15−C25 fragment of tetrafibricin, which possesses three stereogenic centers and an (*E*)-double bond, was thought possible from the protected aldehyde **10** by using the (*R*,*R*)-**I** complex to control the stereogenic

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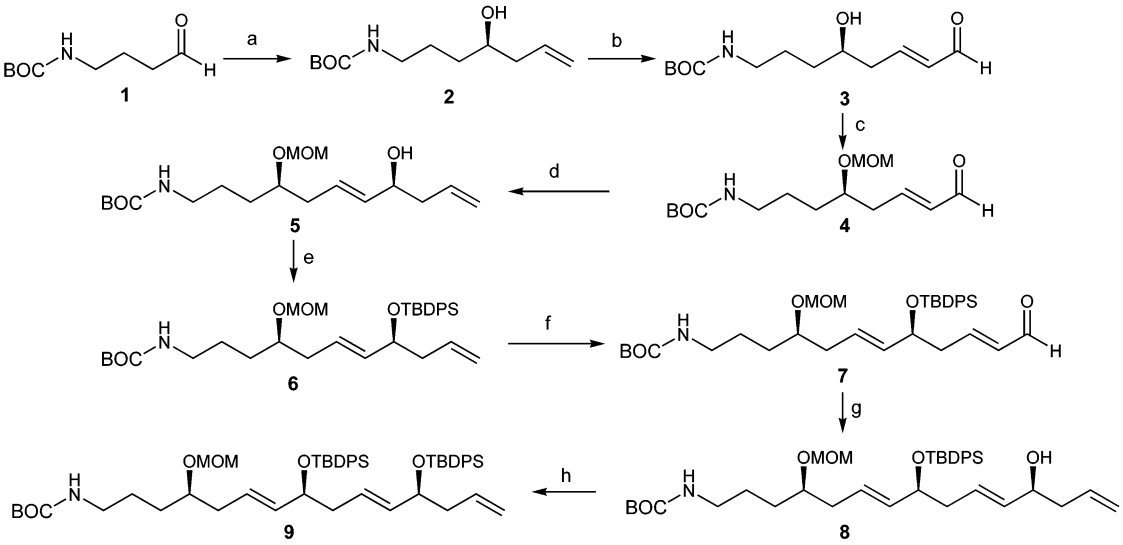
Scheme 3[a]



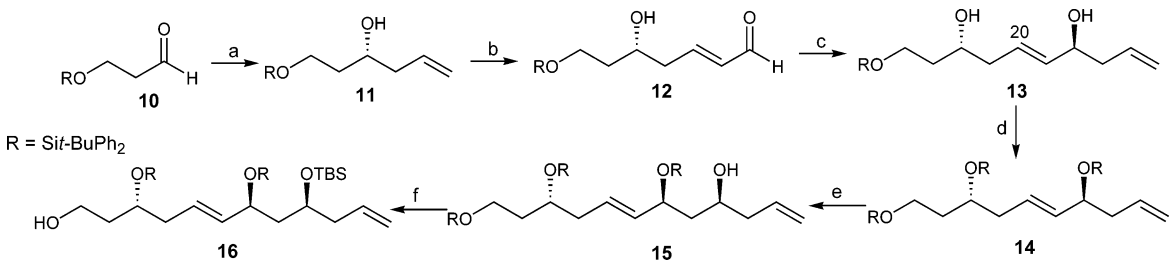
[a] Reagents and conditions: (a) (*R*,*R*)-**I**, ether, −78 °C, 83%; (b) acrolein (3 equiv), 5 mol % **II**, CH_2Cl_2, 25 °C, 81%; (c) MOMCl, *i*-Pr_2NEt, CH_2Cl_2, 25 °C, 91%; (d) (*R*,*R*)-**I**, ether, −78 °C, 86%; (e) TBDPSCl, imidazole, CH_2Cl_2, 25 °C, 88%; (f) Acrolein (3 equiv), 5 mol % **II**, CH_2Cl_2, 25 °C, 24 h, 53%; (g) (*R*,*R*)-**I**, ether, −78 °C, 85%; (h) TBDPSCl, imidazole, CH_2Cl_2, 25 °C, 89%.

centers and by using a chemoselective CM to control the (*E*)-double bond. Aldehyde **10** was transformed to the homoallylic alcohol **11** by using the allyltitanium complex (*S*,*S*)-**I** (ether, −78 °C, 85% yield, ee = 95%), the stereogenic center of which corresponds to the C23 stereogenic center in tetrafibricin. To introduce the C20−C21 (*E*)-double bond, the homoallylic **11** was treated with acrolein (3 equiv) in the presence of the ruthenium complex **II** (5 mol %) in CH_2Cl_2 at 25 °C to afford the aldehyde **12** in 87% yield. As the C17 and C19 stereogenic centers have a 1,3-relationship, they can be introduced by using an allyltitanation/oxidation/allyltitanation sequence. Thus, the unsaturated aldehyde **12** was treated with the (*R*,*R*)-**I** (ether, −78 °C) resulting in the homoallylic alcohol **13** in 84% yield. The choice of a hindered protecting group for the hydroxy group is of significant importance, as it will protect the disubstituted double bond at C20−C21 during the oxidation of the terminal olefin.[12] Thus, the homoallylic alcohol **13** was subjected to TBDPSCl (imidazole, CH_2Cl_2, 25 °C) and transformed into the silyl ether **14** in 77% yield. Compound **14** was then selectively oxidized to the corresponding aldehyde (OsO_4, NMO then $NaIO_4$, THF/H_2O) which was not purified but directly subjected to the allyltitanation [(*R*,*R*)-**I**, −78 °C, ether] to produce the homoallylic alcohol **15** with an overall yield of 75%. After protection of the secondary alcohol (TBSOTf, 2,6-lutidine) and selective deprotection of the primary alcohol, the C15−C25 fragment of tetrafibricin, compound **16**, was obtained in 59% yield (Scheme 4).

The C1−C13 fragment of tetrafibricin contains the tetraene unit and stereogenic centers at C11 and C12. It should be obtained by dehydration of an unsaturated diacetate ester of type **G** (EWG = CO_2Et) which can be generated from compound of type **F** using a chemoselective cross-metathesis reaction (Scheme 1).

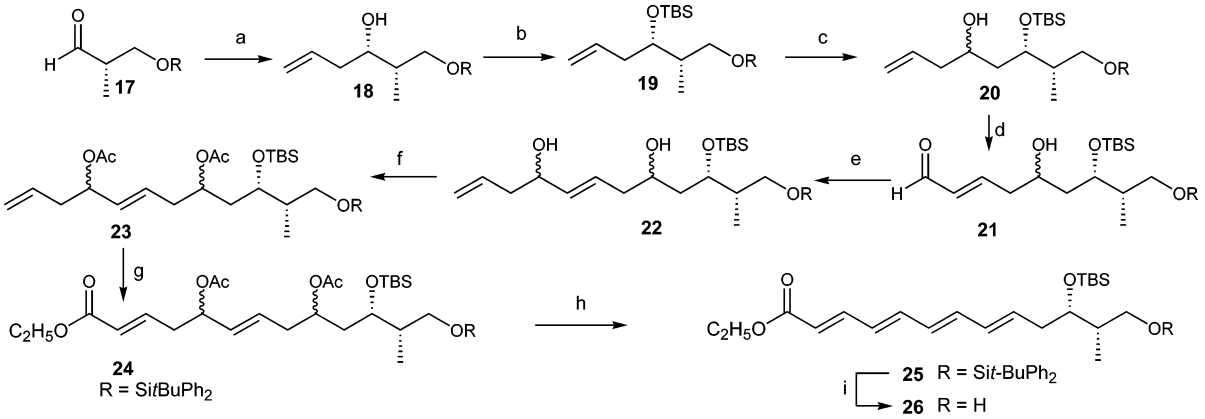
The synthesis of the C1−C13 fragment originated with aldehyde **17**, the stereogenic center of which corresponds to the C12 center present in tetrafibricin. Aldehyde **17** was subjected to the (*R*,*R*)-**I** titanium complex (ether, −78 °C)

Scheme 4[a]



[a] Reagents and conditions: (a) (*S*,*S*)-**I**, ether, −78 °C, 85%. (b) Acrolein (3 equiv), 5 mol % **II**, CH_2Cl_2, 25 °C, 87%. (c) (*R*,*R*)-**I**, ether, −78 °C, 84%. (d) TBDPSCl, imidazole, CH_2Cl_2, 25 °C, 77%. (e) (i) OsO_4, NMO, $NaIO_4$, acetone/H_2O, 25 °C; (ii) 24 h, (*R*,*R*)-**I**, ether, −78 °C, 75% for the two steps. (f) (i) TBSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C; (ii) NH_4F, MeOH, 60 °C, 59% for the two steps.

Scheme 5[a]



[a] Reagents and conditions: (a) (*R*,*R*)-**I**, ether, −78 °C, 87%. (b) TBSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C, 90%. (c) (i) O_3, CH_2Cl_2, −78 °C, Me_2S, 25 °C; (ii) allylMgCl, THF, −40 °C, 70% for the two steps. (d) Acrolein (3 equiv), 5 mol % **II**, CH_2Cl_2, 25 °C, 82%. (e) $AllylSnBu_3$, CH_2Cl_2, −78 °C, 76%. (f) Ac_2O, pyridine, DMAP, 25 °C, 86%. (g) Ethyl acrylate (3 equiv), 5 mol % **II**, CH_2Cl_2, 25 °C, 78%. (h) DBU, THF, 25 °C, 36 h, 79%. (i) NH_4F, MeOH, 60 °C, 70%.

and transformed into the homoallylic alcohol **18** in 87% yield (de = 95%). After protection of the hydroxy group as a *tert*-butyldimethylsilyl ether (TBSOTf, 2,6-luditine, CH_2Cl_2, −78 °C, yield = 90%), the resulting compound **19** was ozonolyzed (O_3, CH_2Cl_2, −78 °C, Me_2S) to produce the corresponding aldehyde, which was directly treated with allylmagnesium chloride (THF, −40 °C) to produce two inseparable homoallylic alcohols **20** (dr = 1/1) with an overall yield of 70% from **19**. A CM reaction between the mixture of homoallylic alcohols **20** and acrolein in the presence of catalyst **II** (5 mol %, CH_2Cl_2, 25 °C) afforded aldehyde **21** in 82% yield, which was allylated with tri-*n*-butylstannane in the presence of $BF_3{\cdot}OEt_2$ (CH_2Cl_2, −78 °C).[13] The tetraol **22** was isolated in 76% yield as a mixture of stereoisomers. To complete the synthesis of the C1−C13 fragment from **22**, a chemoselective CM reaction as well as a deoxygenation were necessary. As allylic acetates can be eliminated under basic conditions[14] to produce dienes and as we have shown previously that a chemoselective CM can take place with hexa-1,5-dien-3-acetates, compound **23** was transformed into the corresponding diacetate **24** (Ac_2O, pyridine, DMAP, 25 °C) in 86% yield. The introduction of an unsaturated ester group, precursor of the carboxylic functionality at C1, was achieved by treatment of **24** with ethyl acrylate under the CM conditions [ethyl acrylate (3 equiv), **II** (5 mol %), CH_2Cl_2, 25 °C, 16 h]. The unsaturated ester **24** was isolated in 78% yield. After treatment of **25** with DBU in THF at 25 °C for 36 h, the desired tetraene **26** was obtained in 79% yield with good stereoselectivity (*E*/*Z* = 10/1). A selective cleavage of the primary silyl ether in compound **25** by using NH_4F in refluxing methanol gave compound **26** in 70%. This compound corresponds to the C1−C13 fragment of tetrafibricin.

The extreme versatility of the cross-metathesis reaction/allylmetallation of aldehydes has allowed the synthesis of the C1−C13, C15−C25, and C27−C40 fragments of tetrafibricin via the formation of hexa-1,5-dien-3-ols. The synthesis of homoallylic 1,5-diols could represent a biomimetic method of obtaining polyenes. The complete synthesis of tetrafibricin will be reported in due course.

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Supporting Information Available: ^1H NMR and ^{13}C NMR spectrum for compounds **3**, **5**, **7**, **9**, **12**, **15**, **16**, and **24**−**26**. This material is available free of charge via the Internet at http://pubs.acs.org.

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