ORGANIC LETTERS

2004
Vol. 6, No. 20
3469−3472

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

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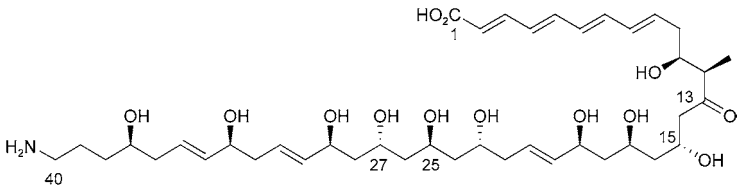
Received June 16, 2004

ABSTRACT



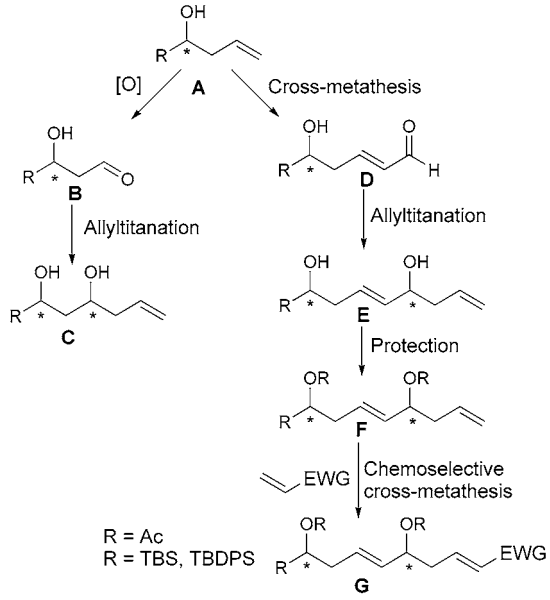
Tetrafibricin

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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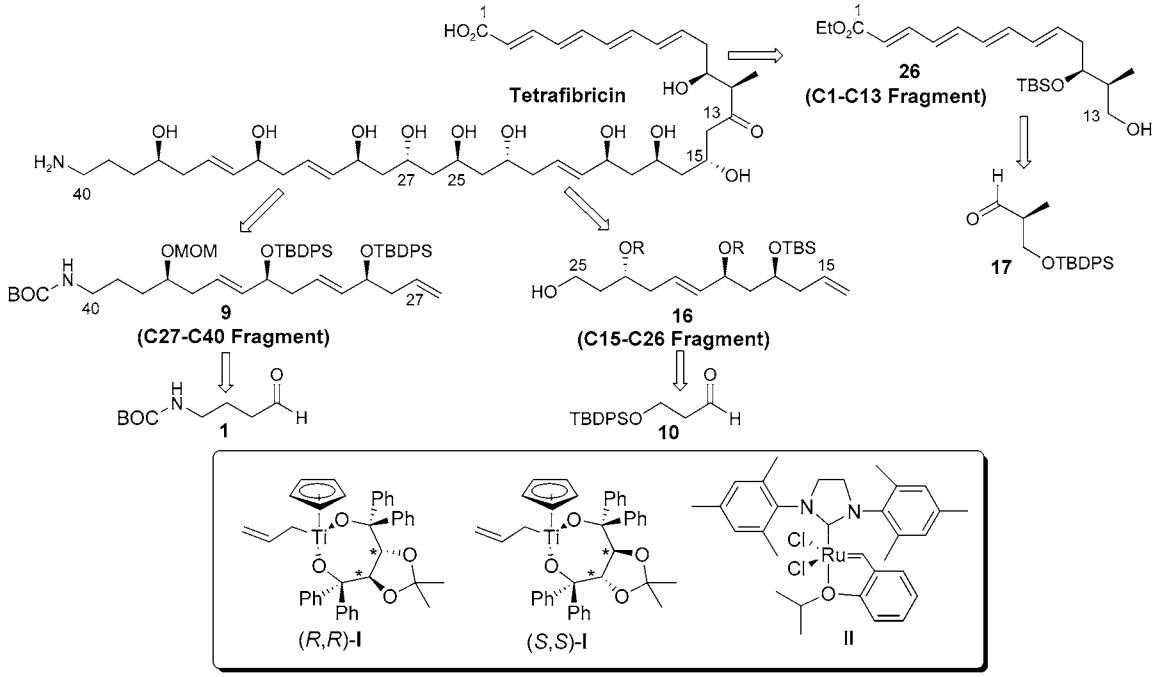
10.1021/ol048862i CCC: $27.50
Published on Web 09/10/2004

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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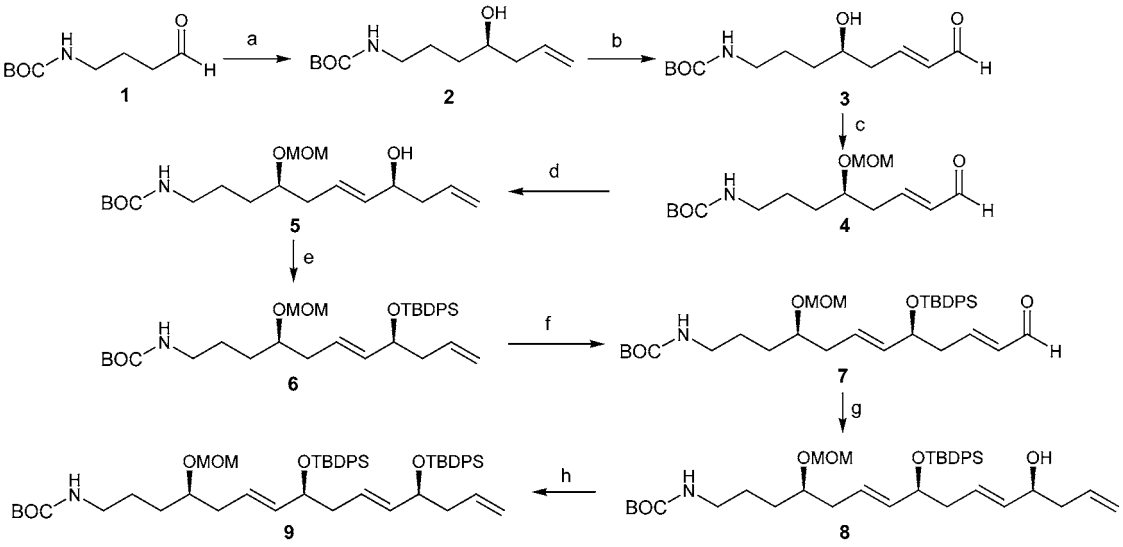
Scheme 3[a]



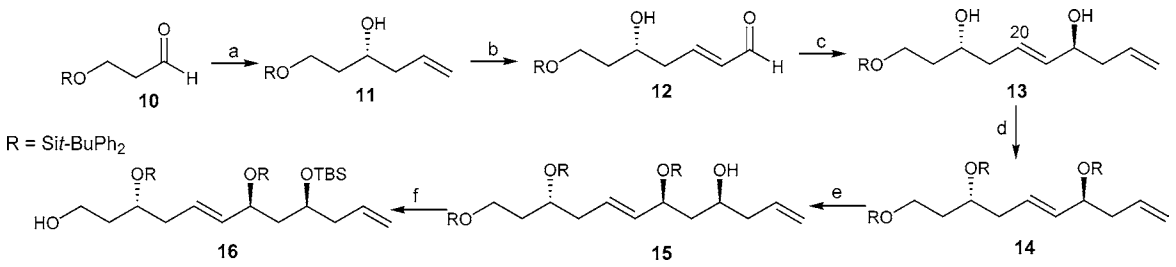
[a] Reagents and conditions: (a) (*R*,*R*)-**I**, ether, −78 °C, 83%; (b) acrolein (3 equiv), 5 mol % **II**, CH_2Cl_2, 25 °C, 81%; (c) MOMCl, *i*-Pr_2NEt, CH_2Cl_2, 25 °C, 91%; (d) (*R*,*R*)-**I**, ether, −78 °C, 86%; (e) TBDPSCl, imidazole, CH_2Cl_2, 25 °C, 88%; (f) Acrolein (3 equiv), 5 mol % **II**,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

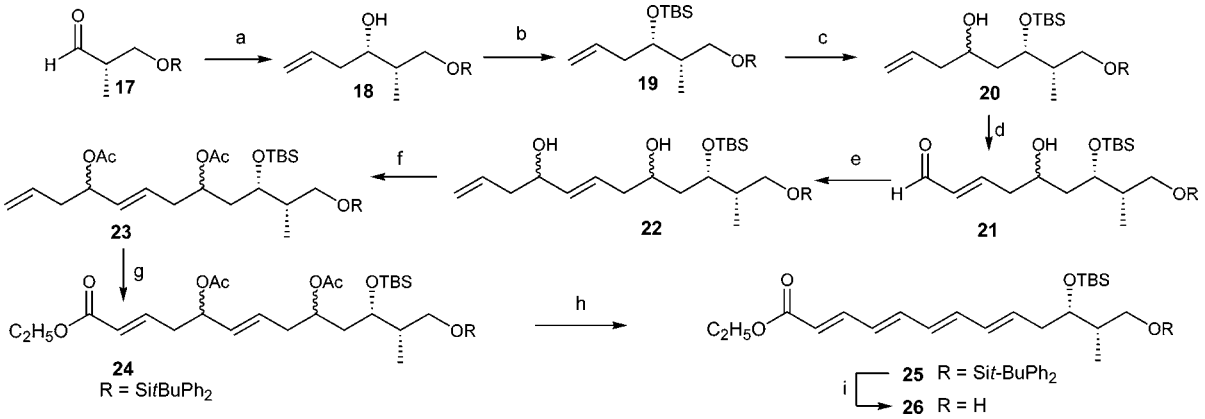
The synthesis of the C1−C13 fragment originated with aldehyde **17**, the stereogenic center of which corresponds to the C12 center present in tetrafibricin. Aldehyde **17** was subjected to the (*R*,*R*)-**I** titanium complex (ether, −78 °C)

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.

Acknowledgment. We thank Dr. R. A. Fisher (Materia, Inc.) and Prof. A. H. Hoveyda for generous gifts of catalyst **II**.

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.

OL048862I

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