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# C(21)−C(40) of Tetrafibricin *via* Metal Catalysis: Beyond Stoichiometric Chiral Reagents, Auxiliaries, and Premetalated Nucleophiles

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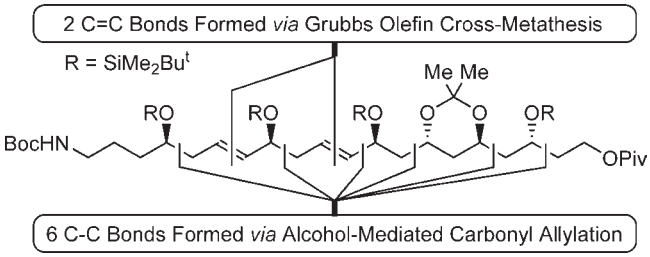
## ABSTRACT




**The C(21)−C(40) fragment of fibrinogen receptor inhibitor tetrafibricin was prepared in 12 steps from propane diol (longest linear sequence). In this approach, 6 C—C bonds are formed *via* asymmetric iridium catalyzed transfer hydrogenative carbonyl allylation and 2 C═C bonds are formed via Grubbs olefin cross-metathesis.**

In the course of exploring C−C bond forming hydrogenations beyond alkene hydroformylation, we have identified a broad new class of catalytic C−C couplings in which alcohol dehydrogenation triggers reductive generation of nucleophiles from π-unsaturated reactants.[1] Under transfer hydrogenation conditions employing isopropanol as a hydrogen source, the reductive coupling of π-unsaturated reactants to aldehydes and activated ketones is achieved. Of greater interest, primary alcohols can serve dually as hydrogen donors and aldehyde precursors, enabling carbonyl addition directly from the alcohol oxidation level.[2] Such C−C bond forming transfer hydrogenations merge oxidation and construction events, bypassing discrete oxidation and use of stoichiometric organometallic reagents. Accordingly, applications of this methodology in target oriented synthesis have begun to emerge.[3]

In this account, a concise synthesis of the C(21)−C(40) substructure of tetrafibricin is disclosed employing alcohol-mediated carbonyl allylations developed in our laboratory.[4] Tetrafibricin is a fibrinogen receptor inhibitor that

(1) For selected reviews on C−C bond forming hydrogenation and transfer hydrogenation, see: (a) Patman, R. L.; Bower, J. F.; Kim, I. S.; Krische, M. J. *Aldrichimica Acta* **2008**, *41*, 95. (b) Bower, J. F.; Kim, I. S.; Patman, R. L.; Krische, M. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 34. (c) Han, S. B.; Kim, I. S.; Krische, M. J. *Chem. Commun.* **2009**, 7278. (d) Bower, J. F.; Krische, M. J. *Top. Organomet. Chem.* **2011**, *43*, 107.

(2) In related "hydrogen auto-transfer" or "borrowing hydrogen" processes, alcohol dehydrogenation and nucleophile generation occur independently. Hence, conventional preactivated nucleophiles are required. Such processes deliver products of formal alcohol substitution rather than carbonyl addition. For selected reviews, see: (a) Guillena, G.; Ramón, D. J.; Yus, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 2358. (b) Hamid, M. H. S. A.; Slatford, P. A.; Williams, J. M. J. *Adv. Synth. Catal.* **2007**, *349*, 1555. (c) Nixon, T. D.; Whittlesey, M. K.; Williams, J. M. J. *Dalton Trans.* **2009**, 753. (d) Dobereiner, G. E.; Crabtree, R. H. *Chem. Rev.* **2010**, *110*, 681. (e) Guillena, G.; Ramón, D. J.; Yus, M. *Chem. Rev.* **2010**, *110*, 1611. (f) Related dehydrogenative couplings of amines also require pre-activated nucleophiles; see: Li, C.-J. *Acc. Chem. Res.* **2009**, *42*, 335.

(3) For applications in total synthesis, see: (a) Lu, Y.; Krische, M. J. *Org. Lett.* **2009**, *11*, 3108. (b) Harsh, P; O'Doherty, G. A. *Tetrahedron* **2009**, *65*, 5051. (c) Sawant, P.; Maier, M. E. *Tetrahedron* **2010**, *66*, 9738. (d) Han, S. B.; Hassan, A.; Kim, I.-S.; Krische, M. J. *J. Am. Chem. Soc.* **2010**, *132*, 15559.

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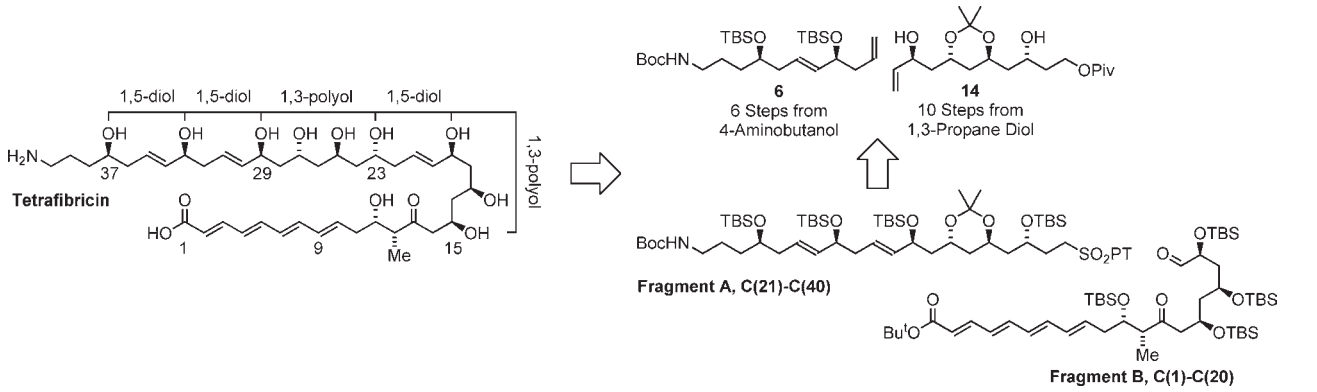
**Scheme 1.** Retrosynthetic Analysis of the Fibrinogen Receptor Inhibitor Tetrafibricin

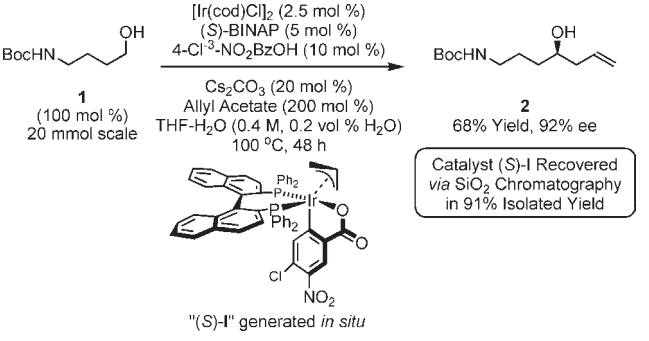



embodies a unique array of functionality, including alternating 1,3-diol and 1,5-ene-diol substructures, a tetraenoic acid moiety, and a primary amine.[5] Although biosynthetically related to oxo-polyene macrolide antibiotics such as lienomycin,[6] tetrafibricin lacks a macrocyclic structure and is inactive against *Bacillus subtilis* and *Escherichia coli*. Additionally, the structure of tetrafibricin deviates from all other naturally occurring fibrinogen receptor antagonists. Tetrafibricin is of interest as a tool to study fibrinogen binding as well as platelet aggregation and as a potential therapeutic agent for treatment of arterial thrombotic disease.[7] The total synthesis of tetrafibricin remains an unrequited challenge, which, if met, would enable further investigations into its biological properties. Toward this end Cossy,[8] Roush,[9] Curran,[10] and Friestad[11] report syntheses of various tetrafibricin fragments.

We envisioned a convergent approach to tetrafibricin involving the union of fragment **A** C(21)−C(40) and fragment **B** C(1)−C(20) *via* Julia−Kocienski olefination. As demonstrated in this account, the C(21)−C(40) fragment **A** can itself be prepared through cross-metathesis of homoallylic ether **6** and allylic alcohol **14** (Scheme 1).

Synthesis of the C(31)−C(40) fragment **6** begins with the enantioselective iridium catalyzed allylation of commercial *N*-Boc-4-aminobutan-1-ol **1** to provide the homoallylic alcohol **2**. For reactions performed on a large scale (20 mmol), the cyclometalated iridium *C*,*O*-benzoate catalyst modified by (*S*)-BINAP, designated (*S*)-**I**, was generated in situ. The desired homoallylic alcohol **2** was produced in 68% isolated yield and 92% enantiomeric excess. Notably, (*S*)-**I** exhibits excellent chromatographic stability and can be recovered from the reaction in 91% yield. Recovered (*S*)-**I** may be recycled in a second round of allylation to provide homoallylic alcohol **2** in comparable yield and with equally high levels of enantioselectivity. The ability to recycle the catalyst, along with the ability to bypass discrete alcohol oxidation, enhances the cost-effectiveness of this allylation methodology (Scheme 2).

**Scheme 2.** Enantioselective Allylation of *N*-Boc-4-aminobutan-1-ol **1** with Recovery of the Iridium Catalyst




Exposure of homoallylic alcohol **2** to acrolein in the presence of the second generation Grubbs catalyst provides the product of cross-metathesis **3** in 83% yield. The δ-hydroxy enal **3** was converted to the *tert*-butyldimethylsilyl ether **4** in 52% yield, which was subjected to iridium catalyzed carbonyl allylation to furnish the homoallyllic alcohol **5** in 83% yield as a 30:1 mixture of diastereomers, as determined by chiral stationary phase HPLC analysis. Here, the cyclometalated iridium *C*,*O*-benzoate catalyst modified by (*S*)-Cl,MeO-BIPHEP, designated (*S*)-**II**, was generated in situ and no attempt at catalyst recovery was

(5) For isolation and stereochemical assignment, see: (a) Kamiyama, T.; Umino, T.; Fujisaki, N.; Satoh, T.; Yamashita, Y.; Ohshima, S.; Watanabe, J.; Yokose, K. *J. Antibiot*. **1993**, *46*, 1039. (b) Kamiyama, T.; Itezono, Y.; Umino, T.; Satoh, T.; Nakayama, N.; Yokose, K. *J. Antibiot*. **1993**, *46*, 1047. (c) Kobayashi, Y.; Czechtizky, W.; Kishi, Y. *Org. Lett*. **2003**, *5*, 93.

(6) Pawlak, J.; Nakanishi, K.; Iwashita, T.; Borowski, E. *J. Org. Chem*. **1987**, *52*, 2896.

(7) (a) Satoh, T.; Yamashita, Y.; Kamiyama, T.; Arisawa, M. *Thromb. Res*. **1993**, *72*, 401. (b) Satoh, T.; Yamashita, Y.; Kamiyama, T.; Arisawa, M. *Thromb. Res*. **1993**, *72*, 401. (c) Satoh, T.δ; Kouns, W. C.; Yamashita, Y.; Kamiyama, T.; Steiner, B. *Biochem. J*. **1994**, *301*, 785. (d) Satoh, T.; Kouns, W. C.; Yamashita, Y.; Kamiyama, T.; Steiner, B. *Biochem. Biophys. Res. Commun*. **1994**, *204*, 325.

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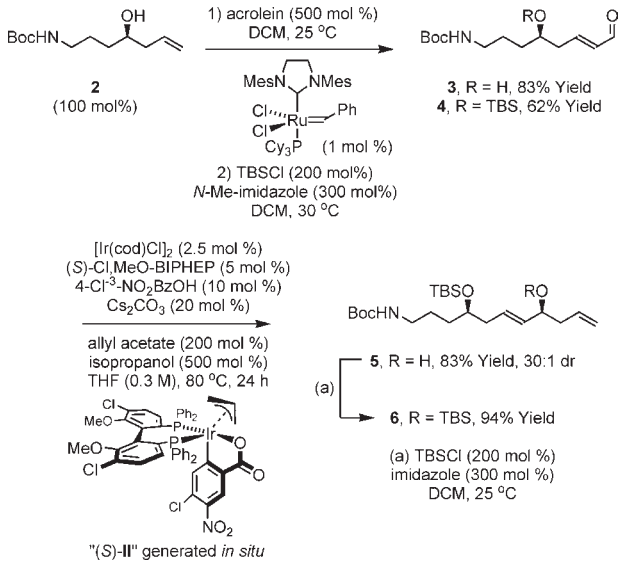
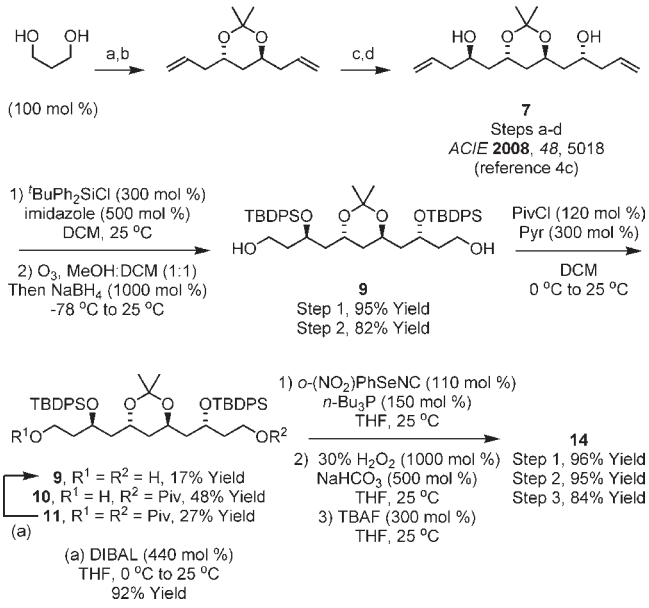
(11) Friestad, G. K.; Sreenilayam, G. *Org. Lett*. **2010**, *12*, 5016.

**Scheme 3.** Conversion of Homoallylic Alcohol **2** to 1,5-Enediol **6**




**Scheme 4.** Conversion of 1,3-Propanediol to 1,3-Polyol **14**

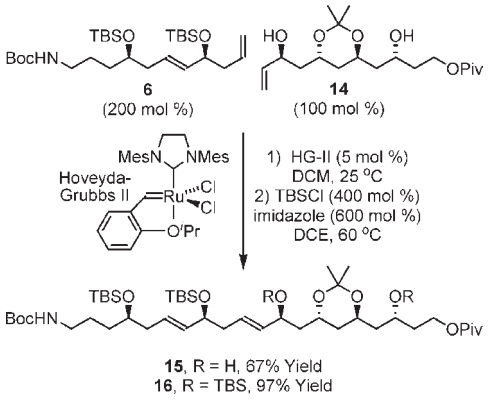



made. Finally, homoallyllic alcohol **5** was converted to the bis(*tert*-butyldimethylsilyl ether) **6** in 94% yield (Scheme 3).

With the C(31)−C(40) fragment **6** in hand, preparation of the C(21)−C(30) fragment **14** was undertaken. The synthesis of fragment **14** begins with the conversion of 1, 3-propanediol to 1,3-polyol **7**, which is performed *via* iterative two-directional carbonyl allylation from the diol oxidation level in accordance with our published procedure.[4c] Conversion of **7** to the bis(*tert*-butyldiphenylsilyl ether) **8** is followed by ozonolysis of the terminal olefins to provide the $C_2$-symmetric polyol **9** in good overall yield. Differentiation of the homotopic diol termini of **9** is accomplished through pivaloylation to form the *mono*-pivalic ester **10** as a component of a statistical mixture. However, the product of bis(pivaloylation) **11** could be recycled by treatment with DIBAL. Finally, Grieco's two-step method for primary alcohol dehydration[12] followed by removal of the *tert*-butyldiphenylsilyl ethers provides the C(21)−C(30) fragment **14** in ten steps from 1,3-propanediol (Scheme 4)

Guided by studies of the cross-metathesis of related polyketide fragments,[13] it was found that exposure of fragments **6** and **14** to the second generation Hoveyda−Grubbs catalyst delivered the product of cross-metathesis **15** in 58% yield with complete (*E*)-selectivity, as determined by $^1$H NMR. The free hydroxyl moieties of compound **15** were converted to the corresponding *tert*-butyldimethylsilyl

**Scheme 5.** Cross-Metathesis To Form the C(21)−C(40) Fragment of Tetrafibricin




ethers to give the fully protected C(21)−C(40) fragment of tetrafibricin **16** in 12 linear steps from propane diol and in only 17 total steps (Scheme 5).[14]

In summary, we report an approach to the C(21)−C(40) fragment of tetrafibricin that extends beyond classical strategies involving use of chiral auxiliaries, stoichiometric chiral reagents, and premetalated nucleophiles. Notably, all C−C bonds formed in the longest linear sequence are made via metal catalysis: 6 C−C bonds formed via transfer hydrogenative coupling and 2 C−C bonds formed via

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(13) (a) BouzBouz, S.; Simmons, R.; Cossy, J. *Org. Lett.* **2004**, *6*, 3465. (b) Nyavanandi, V. K.; Nadipalli, P.; Nanduri, S.; Naidu, A.; Iqbal, J. *Tetrahedron Lett.* **2007**, *48*, 6905 and ref 3d.

(14) As described in ref 10c the C(21)−C(40) fragment of tetrafibricin was produced in 14 linear steps and 34 total steps from a commercial chiral building block derived from malic acid. Also, as described in ref 9b, a synthesis of the C(23)−C(40) was recently disclosed.

(15) "The ideal synthesis creates a complex skeleton...in a sequence only of successive construction reactions involving no intermediary refunctionalizations, and leading directly to the structure of the target, not only its skeleton but also its correctly placed functionality." Hendrickson, J. B. *J. Am. Chem. Soc.* **1975**, *97*, 5784.

cross-metatheses. In keeping with longstanding ideals of synthetic efficiency,[15] this approach circumvents additional manipulations associated with the use of non-native directing groups to mediate bond construction and merges redox-construction events to further enhance step economy.

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**Supporting Information Available.** Spectral data for all new compounds ($^{1}$H NMR, $^{13}$C NMR, IR, HRMS). This material is available free of charge via the Internet at http://pubs.acs.org.