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C(21)-C(40) of Tetra fibrin via Metal Catalysis: Beyond Stoichiometric Chiral Reagents, Auxiliaries and Premetallated Nucleophiles

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Abstract

The C(21)-C(40) fragment of fibrinogen receptor inhibitor tetra fibrin 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 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 tetra fibrin is disclosed employing alcohol-mediated carbonyl allylations developed in our laboratory.⁴ Tetra fibrin is a fibrinogen receptor inhibitor that 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 tetra fibrin lacks a macrocyclic structure and is inactive against *Bacillus subtilis* and *Escherichia coli*. Additionally, the structure of tetra fibrin deviates from all other naturally occurring fibrinogen receptor antagonists. Tetra fibrin is of interest as a tool to study fibrinogen binding, platelet aggregation and as a potential therapeutic

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

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 Curran¹⁰ and Friestad¹¹ 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 large scale (20 mmol), the cyclometallated 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).

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 a second round of iridium catalyzed carbonyl allylation to furnish the homoallylic alcohol **5** in 83% yield as a 30:1 mixture of diastereomers, as determined by chiral stationary phase HPLC analysis. Here, the cyclometallated iridium *C*,*O*-benzoate catalyst modified by (*S*)-ClMeO-BIPHEP, designated (*S*)-**II**, was generated in situ and no attempt at catalyst recovery was made. Finally, homoallylic 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 dehydration¹² 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 HoveydaGrubbs catalyst delivered the product of cross-metathesis **15** in 58% yield with complete (*E*)-selectivity, as determined by ¹H NMR. The free hydroxyl moieties of compound **15** were converted to the corresponding *tert*-butyldimethylsilyl 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 premetallated 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 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References

1. For selected reviews on C-C bond forming hydrogenation and transfer hydrogenation, see: (a) Patman RL, Bower JF, Kim IS, Krische MJ. *Aldrichim. Acta*. 2008; 41:95. (b) Bower JF, Kim IS, Patman RL, Krische MJ. *Angew. Chem. Int. Ed.* 2009; 48:34. (c) Han SB, Kim IS, Krische MJ. *Chem. Commun.* 2009:7278. (d) Bower JF, Krische MJ. *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 pre-activated nucleophiles are required. Such processes deliver products of formal alcohol substitution rather than carbonyl addition. For selected reviews, see: (a) Guillena G, Ramón DJ, Yus M. *Angew. Chem. Int. Ed.* 2007; 46:2358. (b) Hamid MHSA, Slatford PA, Williams MJ. *Adv. Synth. Catal.* 2007; 349:1555. (c) Nixon TD, Whittlesey MK, Williams MJ. *Dalton Trans.* 2009:753. [PubMed: 19156265] (d) Dobereiner GE, Crabtree RH. *Chem. Rev.* 2010; 110:681. [PubMed: 19938813] (e) Guillena G, Ramón DJ, Yus M. *Chem. Rev.* 2010; 110:1611. [PubMed: 19928825] (f) Li C-J. *Acc. Chem. Res.* 2009; 42:335. [PubMed: 19220064]
3. For applications in total synthesis, see: (a) Lu Y, Krische MJ. *Org. Lett.* 2009; 11:3108. [PubMed: 19586066] (b) Harsh P, O'Doherty GA. *Tetrahedron.* 2009; 65:5051. [PubMed: 20161297] (c) Sawant P, Maier ME. *Tetrahedron.* 2010; 66:9738. (d) Han SB, Hassan A, Kim I-S, Krische MJ. *J. Am. Chem. Soc.* 2010; 132:15559. [PubMed: 20961111]
4. (a) Kim IS, Ngai M-Y, Krische MJ. *J. Am. Chem. Soc.* 2008; 130:6340. [PubMed: 18444616] (b) Kim IS, Ngai M-Y, Krische MJ. *J. Am. Chem. Soc.* 2008; 130:14891. [PubMed: 18841896] (c) Lu Y, Kim IS, Hassan A, Del Valle DJ, Krische MJ. *Angew. Chem., Int. Ed.* 2009; 48:5018. (d) Hassan A, Lu Y, Krische MJ. *Org. Lett.* 2009; 11:3112. [PubMed: 19586067]
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. [PubMed: 8360097] (b) Kamiyama T, Itezono Y, Umino T, Satoh T, Nakayama N, Yokose K. *J. Antibiot.* 1993; 46:1047. [PubMed: 8360098] (c) Kobayashi Y, Czechtizky W, Kishi Y. *Org. Lett.* 2003; 5:93. [PubMed: 12509899]
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. [PubMed: 8303683] (b) Satoh T, Yamashita Y, Kamiyama T, Arisawa M. *Thromb. Res.* 1993; 72:401. [PubMed: 8303683] (c) Satoh T, Kouns WC, Yamashita Y, Kamiyama T, Steiner B. *Biochem. J.* 1994; 301:785. [PubMed: 7519850] (d) Satoh T, Kouns WC, Yamashita Y, Kamiyama T, Steiner B. *Biochem. Biophys. Res. Commun.* 1994; 204:325. [PubMed: 7524499]
8. BouzBouz S, Cossy J. *Org. Lett.* 2004; 6:3469. [PubMed: 15387525]
9. (a) Lira R, Roush WR. *Org. Lett.* 2007; 9:533. [PubMed: 17249805] (b) Kister J, Nuhant P, Lira R, Sörg A, Roush WR. *Org. Lett.* 2011 doi: 10.1021/ol2003836.

10. (a) Gudipati V, Bajpai R, Curran DP. Collect. Czech. Chem. 2009; 74:774.(b) Zhang K, Gudipati V, Curran DP. Synlett. 2010:667. [PubMed: 20686632] (c) Gudipati V, Curran DP. Tetrahedron Lett. 2011; 52:2254.
11. Friestad GK, Sreenilayam G. Org. Lett. 2010; 12:5016. [PubMed: 20939544]
12. Grieco PA, Gilman S, Nishizawa M. J. Org. Chem. 1976; 41:1485.
13. (a) BouzBouz S, Simmons R, Cossy J. Org. Lett. 2004; 6:3465. [PubMed: 15387524] (b) Nyavanandi VK, Nadipalli P, Nanduri S, Naidu A, Iqbal J. Tetrahedron Lett. 2007; 48:6905. and reference 3d.
14. As described in reference 10c, the C(21)-C(40) fragment of tetrafabricin was produced in 14 linear steps and 34 total steps from a commercial chiral building block derived from malic acid. Also, As described in reference 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 JB. J. Am. Chem. Soc. 1975; 97:5784.

Scheme 1.
Retrosynthetic analysis of the fibrinogen receptor inhibitor tetrafribrin.

Scheme 2.
Enantioselective allylation of *N*-Boc-4-aminobutan-1-ol **1** with recovery of the iridium catalyst.

Scheme 3. Conversion of homoallylic alcohol **2** to 1,5-enediol **6**.

Scheme 4.
Conversion of 1,3-propanediol to 1,3-polyol **14**.

Scheme 5.

Cross-metathesis to form the C(21)-C(40) fragment of tetrafibricin.