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Asymmetric Alcohol C−H Allylation and *syn*-Crotylation: C9−C20 of Tetrafibricin

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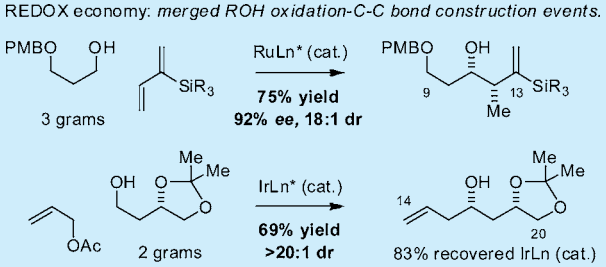
Supporting Information

ABSTRACT: The C9−C20 segment of the fibrinogen receptor inhibitor tetrafibricin was prepared in 10 steps (longest linear sequence). Ruthenium catalyzed enantioselective *syn*-crotylation is used to construct C9−C13. Iridium catalyzed asymmetric alcohol C−H allylation of a commercial malic acid derived alcohol is used to construct C14−C20. Recovery and recycling of the iridium catalyst is described.



Tetrafibricin[1] is a potent fibrinogen receptor inhibitor isolated from *Streptomyces neyagawaensis* NR0577 that functions by blocking GPIIb/IIIa receptors on the platelet surface, thus inhibiting platelet aggregation.[2,3] While biosynthetically related to the oxo-polyene macrolide antibiotic lienomycin,[4] tetrafibricin is acyclic and inactive against *Bacillus subtilis* and *Escherichia coli*. Further, the structure of tetrafibricin, which includes alternating 1,3-diol and 1,5-enediol motifs, represents a significant departure from all known fibrinogen receptor antagonists. Tetrafibricin has garnered interest with regard to the study of fibrinogen binding, platelet aggregation, and as a treatment for arterial thrombosis,[3,5] which in turn has evoked interest in its preparation *via* total synthesis. Despite efforts reported from the laboratories of Cossy,[6] Curran,[7] Friestad,[8] Roush,[9] and the present author,[10] including syntheses of a protected derivative of the natural product by Curran[7d] and of *N*-acetyl dihydrotetrafibricin methyl ester by Roush,[9c] the total synthesis of tetrafibricin remains an unmet challenge.

Using catalytic C−C bond-forming processes that occur through the addition, transfer, or removal of hydrogen,[11] total syntheses of 6-deoxyerythronolide B,[12a] bryostatin 7,[12b] trienomycins A and F,[12c] cyanolide A,[12d] and roxaticin[12e] were completed in our laboratory. Due to the redox economy[13] of the methods underlying their construction, the aforementioned syntheses represent the most concise routes to any member of their respective natural product families.[11d] Inspired by the unanswered synthetic challenges posed by tetrafibricin, a 12 step route to the C21−C40 segment was devised using iridium catalyzed alcohol C−H allylation developed in our laboratory.[10,14] Here, we report a 10 step synthesis of the C9−C20 substructure of tetrafibricin featuring enantioselective methods for ruthenium catalyzed alcohol C−H *syn*-crotylation[15] and iridium catalyzed alcohol C−H allylation.[14]

The C9−C20 substructure of tetrafibricin was envisioned to arise through the reductive coupling of bromide **6** to epoxide **13** (Scheme 1). Synthesis of bromide **6** was readily accomplished through ruthenium catalyzed hydrohydroxyalkylation of 2-silyl-butadiene **2** with the monoprotected 1,3-propane diol **1**. A modification of our previously reported conditions,[15a] which involves use of the catalyst generated from $RuHCl(CO)(PPh_3)_3$ and (*R*)-DM-SEGPHOS in the presence of substoichiometric sodium sulfate, provided the desired product of diene hydrohydroxyalkylation **3** in 75% yield with excellent control of *syn*-diastereo- and enantioselectivity (92% ee, 18:1 dr). Adduct **3** was converted to the *p*-methoxy benzylidene acetal in 87% yield upon DDQ oxidation.[16] Finally, exposure of the alkenyl silane to pyridinium bromide perbromide gave the crude dibromide **5**, which was treated with sodium methoxide to furnish the alkenyl bromide **6** (Scheme 2).[17]

Synthesis of the C14−C20 epoxide **13** began with the asymmetric iridium catalyzed alcohol C−H allylation[14] of the commercially available chiral alcohol **7** derived from (*S*)-malic acid. Using the cyclometalated iridium catalyst "(*S*)-**I**" generated *in situ* from $[Ir(cod)Cl]_2$, 4-chloro-3-nitrobenzoic acid, allyl acetate, and (*S*)-BINAP, the desired homoallylic alcohol **8** was obtained in 69% isolated yield as a single diastereomer as determined by ^1H NMR of the crude reaction product. As previously noted,[18] cyclometalated iridium catalysts of this type are remarkably stable to conventional silica gel flash chromatography. Given evidence that the carbonyl addition is turnover limiting,[14b] the chromatographically stable π-allyl complex "(*S*)-**I**" is a potential catalyst resting state. In accord with this interpretation, "(*S*)-**I**" can be recovered from the reaction mixture and recycled to provide homoallylic alcohol **8** in 53% yield with equally high levels of diastereoselectivity. No further erosion in yield or selectivity was observed upon further iterations of recovery and recycling. Catalyst recovery and recycling, along with the ability to bypass discrete alcohol-to-

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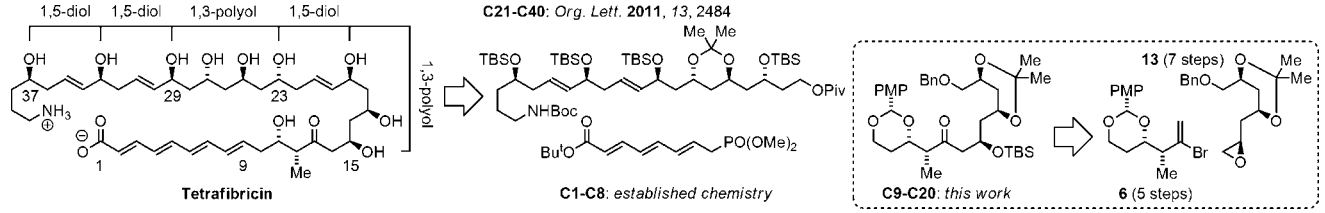
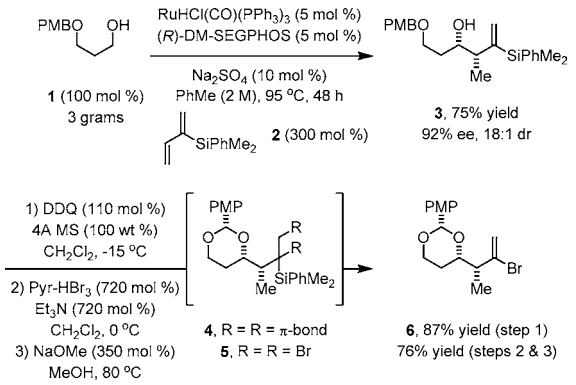
Scheme 1. Retrosynthetic Analysis of the Fibrinogen Receptor Inhibitor Tetrafibricin



Scheme 2. Synthesis of Alkenyl Bromide 6 *via* Ruthenium Catalyzed Hydrohydroxyalkylation of Diene 2[a]

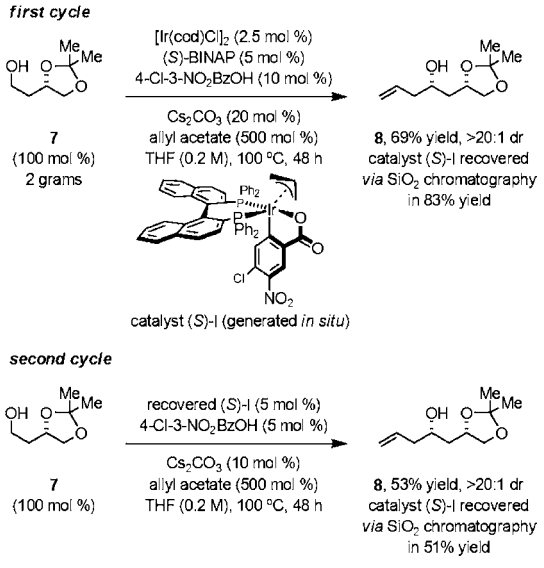


[a]Yields are of material isolated by silica gel chromatography. (*R*)-DM-SEGPHOS: (*R*)-(+)-5,5-bis(diphenylphosphino)-4,4-bi-1,3-benzodioxole. See Supporting Information for further details.

aldehyde redox reactions, renders our asymmetric allylation protocol more cost-effective (Scheme 3).

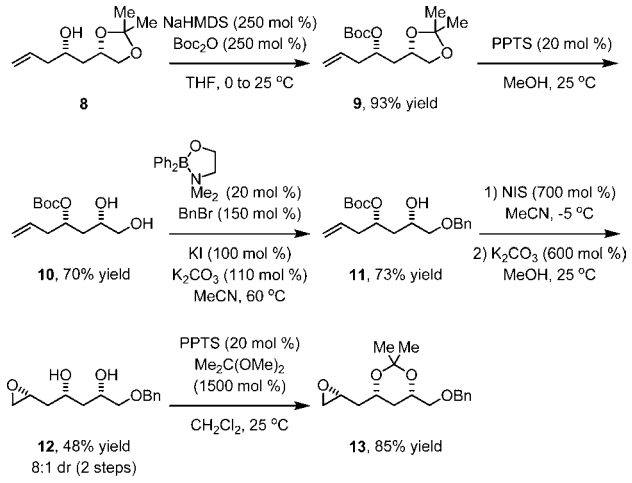
To complete the synthesis of epoxide **13**, homoallylic alcohol **8** was converted to the *tert*-butyl carbonate **9**, which was subjected to conditions for acid catalyzed methanolysis to furnish diol **10**. Primary benzyl protection of diol **10** using Taylor's diphenylborinic acid catalyst[19] was achieved with excellent levels of site-selectivity to provide *mono*-benzyl ether *mono*-Boc-carbonate **11**. Modified Bartlett halocyclization of the Boc-carbonate[20] followed by treatment of the crude mixture with K_2CO_3 in methanol delivered the epoxy diol **12** in 48% yield as an 8:1 mixture of diastereomers. Protection of the diol as the acetonide provides the requisite epoxide **13** (Scheme 4).

Scheme 3. Catalyst Recovery and Recycling in the Asymmetric Alcohol C−H Allylation of 7[a]



[a]Yields are of material isolated by silica gel chromatography. The third and higher cycles provided yields ranging between 50 and 60%. See Supporting Information for further details.

Scheme 4. Conversion of Homoallylic Alcohol 8 to Epoxide 13[a]



[a]Yields are of material isolated by silica gel chromatography. See Supporting Information for further details.

To form the C9−C20 substructure of tetrafibricin, the cuprate derived from alkenyl bromide **6** was reacted with epoxide **13**.[21,22] Initially, it was desired to use the commercially available lithium 2-thienyl(cyano)cuprate solution to form the higher order mixed organocuprate reagent,[21b,22b] so as to limit the stoichiometry of alkenyl bromide **6** used in the transformation. However, this method failed to deliver serviceable quantities of adduct **14**. In contrast, using cuprous iodide as the copper source with 2 equiv of alkenyl bromide, the product of epoxide opening was obtained in good yield, based on **13**.[21a,22a] Silyl protection of alcohol **14**, followed by ozonolysis of olefin **15**, delivered the C9−C20 fragment of tetrafibricin in 10 linear steps from the commercial malic acid derivative **7** and in 15 total steps (Scheme 5).

In summary, we report a synthetic route to the C9−C20 substructure of tetrafibricin using ruthenium catalyzed enantioselective *syn*-crotylation to construct C9−C13 and iridium catalyzed asymmetric alcohol C−H allylation to construct C14−C20. This synthetic exercise led to the observation that the cyclometalated iridium complex used in the C−H allylation of primary alcohols may be recovered and recycled. The ability to perform multiple rounds of catalyst recovery and recycling, along with the ability to engage alcohols directly as partners for catalytic C−C coupling in the absence of

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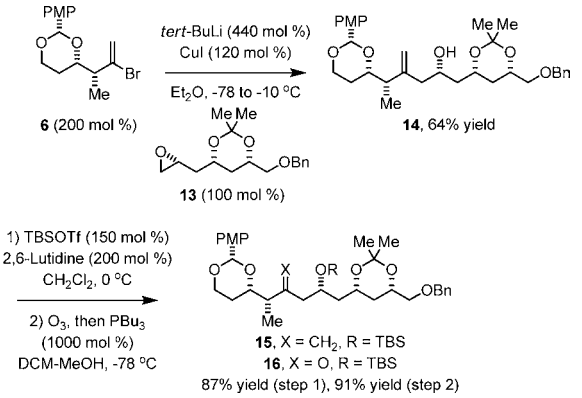
Scheme 5. Reductive Coupling of Alkenyl Bromide 6 and Epoxide 13 To Form the C9−C20 Substructure of Tetrafibricin[a]



[a]Yields are of material isolated by silica gel chromatography. See Supporting Information for further details.

discrete alcohol-to-aldehyde redox reactions, makes the present iridium catalyzed allylation protocol both cost-effective and step-economical. A more systematic study of catalyst recovery and recycling, including immobilization of the catalyst on a solid support, will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

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.

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Notes

The authors declare no competing financial interest.

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NOTE ADDED AFTER ASAP PUBLICATION

An updated version was reposted January 14, 2014 which includes reference 11d. On January 15, 2014 and error in Scheme 3 was corrected.

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