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Access to an *anti*,*syn*-1,5,7-Triol via Configuration-Encoded 1,5-Polyol Synthesis: The C15–C25 Fragment of Tetrafibricin

Ryan M. Friedrich, Gregory K. Friestad*[a]

Abstract: A configuration-encoded strategy provides unambiguous stereocontrol in an efficient synthesis of 1,5-polyols. To access the *anti*,*syn*-1,5,7-triol moiety in the C15–C25 fragment of tetrafibricin, a fibrinogen receptor antagonist, a strategy is introduced which sequences the 1,5-polyol synthesis with selective desilylation and diastereoselective intramolecular conjugate addition. For tetrafibricin, assembly of the C15–C25 *anti*-1,5-diol in five steps is followed by the conjugate addition to introduce a *syn*-1,3-diol, completing the *anti*,*syn*-1,5,7-triol and providing the functionality and stereochemistry required for tetrafibricin synthesis.

Introduction

Tetrafibricin (Figure 1), isolated from *Streptomyces neyagawaensis* NR0577 in 1993, is a potent nonpeptidic fibrinogen receptor antagonist (IC_{50} = 46 nM) that inhibits platelet aggregation by blocking GPIIb/IIIa receptors, making it a potential drug candidate for arterial thrombotic diseases.[1] Since its stereochemical structure elucidation in 2003 using an NMR database approach,[2] strategies toward the synthesis of tetrafibricin have generated considerable interest; the laboratories of Cossy,[3] Curran,[4] and Krische[5] each reported preparations of various fragments of the natural product. Studies from the Roush group[6] led to a synthesis of *N*-acetyl dihydrotetrafibricin methyl ester.[6a]

We previously reported an efficient route to a C27–C40 fragment of tetrafibricin[7] which addressed the problem of stereocontrolled 1,5-polyol synthesis.[8] Although many methods have been devised for the synthesis and stereochemical assignment of 1,3-diol motifs,[9] few are applicable to the more distant 1,5 stereochemical relationships.[8] We introduced a strategy to rapidly assemble any of the relative configurations of chiral 1,5-polyols with unambiguous stereocontrol (Figure 2a). The alcohol configurations are encoded within enantiopure α-silyloxy-γ-sulfononitrile building blocks which may be coupled iteratively via Julia–Kocienski olefinations; the nitrile serves as a masked aldehyde, revealed by hydride reduction.[7] In contrast to other approaches to 1,5-diol synthesis, this iterative coupling sequence employs commercial reagents commonly on hand in most synthetic chemistry labs (KHMDS and DIBAL-H) making it practical to adopt. The configuration-encoded strategy avoids the difficulties of both control and assignment of 1,5-stereochemical relationships at each coupling event, contributing to the efficiency of our route to the C27–C40 fragment of tetrafibricin (**A**, Figure 2a).[7]

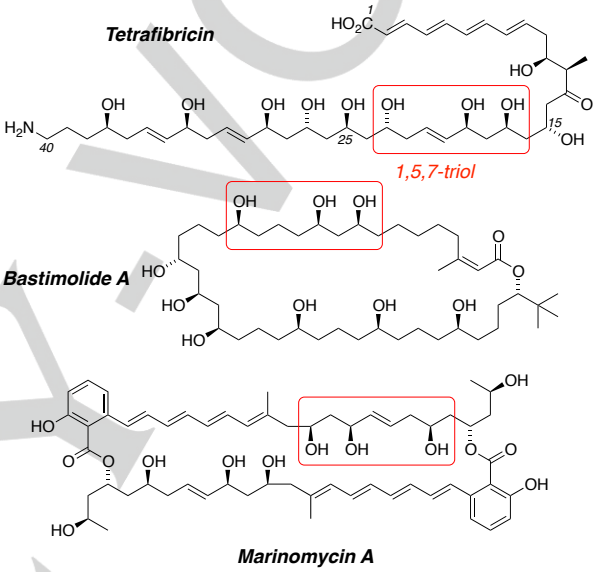

Figure 1. Biologically active natural product structures with chiral 1,5,7-triol motifs.

With the 1,5-polyol stereochemical obstacle surmounted, we sought to expand this strategy in order to address 1,5,7-triol systems that appear in tetrafibricin and in a variety of other bioactive natural products (Figure 1) such as bastimolide A (antimalarial)[10a] and marinomycin A (antitumor, antimicrobial).[10b] We noted that two iterations of our polyol synthesis approach furnishes a 1,5,9-triol complemented by two alkene functionalities, and hypothesized that the alkenes might be engaged for the subsequent delivery of additional hydroxyl equivalents, expanding the repertoire of polyols accessible by our configuration-encoded approach. The feasibility of this would require selectively addressing a new oxygen substituent to a defined location, as implied in structures **B** and **C** (Figure 2b). The Evans tactic of benzylidene acetal construction, exploiting a free hydroxyl group to direct intramolecular conjugate addition to an unsaturated ester,[11] appeared well-suited for this purpose. Here we present a successful test of this hypothesis en route to the *anti*,*syn*-1,5,7-triol which appears in the C15–C25 fragment of tetrafibricin.

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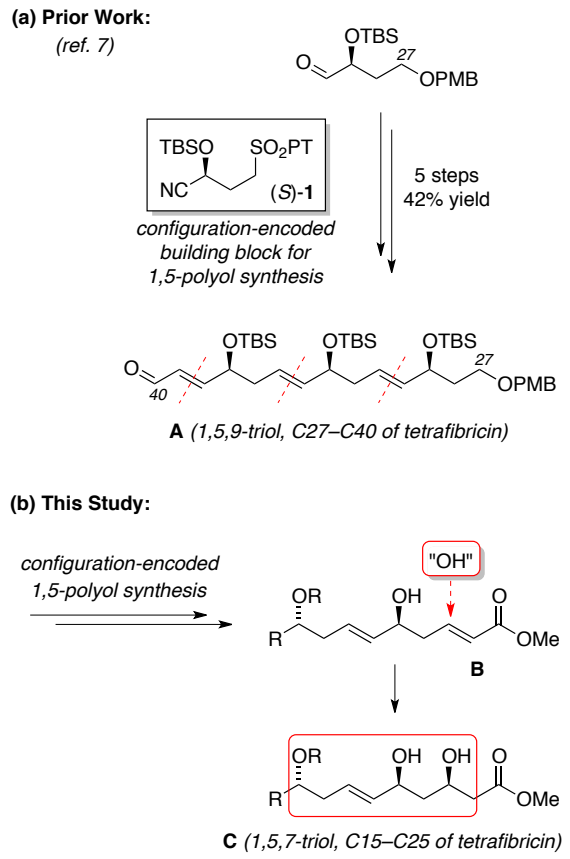
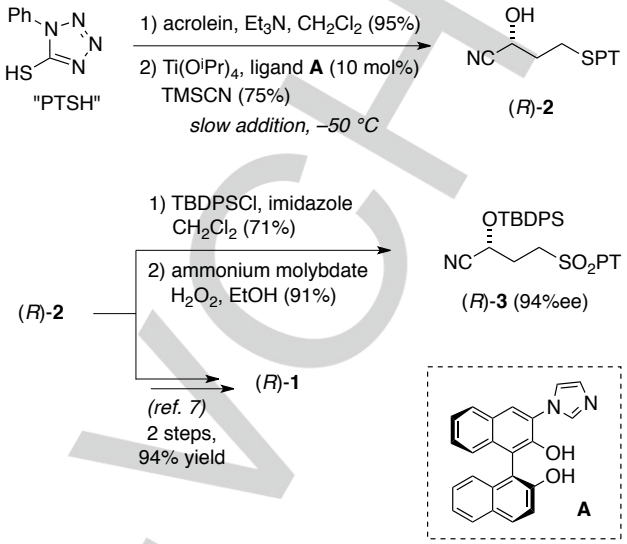


Figure 2. a) Application of configuration-encoded 1,5-polyol synthesis to the C27–C40 fragment of tetrafibricin; b) New strategy to access 1,5,7-triols and application to the C15–C25 fragment of tetrafibricin.

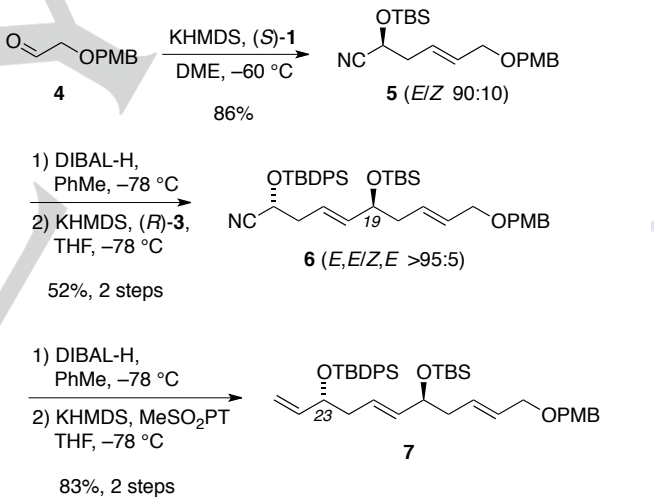
Results and Discussion

In the plan for the 1,5,7-triol synthesis, two configuration-encoded building blocks with differentiated hydroxyl groups were required. After 1,5-polyol assembly, this would permit selective deprotection and hydroxyl-directed benzylidene acetal construction upon an unsaturated ester (see structure **B**, Figure 2b). We opted for selective desilylation, exploiting the differential reactivity of *tert*-butyldimethylsilyl (TBS) and *tert*-butyldiphenylsilyl (TBDPS) groups. Preparation of the TBS building block **1** (Figure 2a) followed our earlier route (Scheme 1) from commercially available acrolein and 1-phenyl-1*H*-tetrazol-5-thiol. This provided multigram quantities of enantiopure α-silyloxy-γ-sulfononitriles (*R*)-**1** and (*S*)-**1** in 87% and 89% yields respectively over 4 steps (>99% ee after recrystallization).[7]

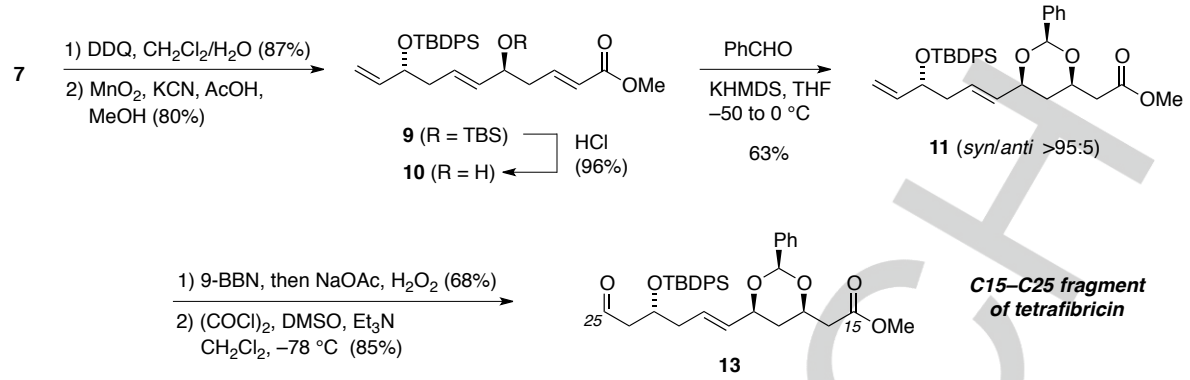
For the building block with the hydroxyl group differentiated from that in **1**, we returned to cyanohydrin (*R*)-**2** (Scheme 1), prepared via catalytic asymmetric cyanohydrin construction en route to (*R*)-**1**. Silylation of cyanohydrin (*R*)-**2** with TBDPSCl, followed by molybdate-catalyzed oxidation of the sulfide to sulfone, smoothly furnished (*R*)-**3** as a waxy solid (94% ee, HPLC). The enantiomeric excess of (*R*)-**3** was generated during cyanohydrin construction without any enrichment through crystallization, and the 94% ee represents an improvement versus the prior report.[12]



Scheme 1. Synthesis of α-Silyloxy-γ-Sulfononitrile Building Blocks



Scheme 2. Application of Iterative 1,5-Polyol Methodology to Carbon Skeleton of C15–C25 Fragment of Tetrafibricin



Scheme 3. Diastereoselective Conjugate Addition to Access the *anti*,*syn*-1,5,7-Triol of the C15–C25 Fragment of Tetrafibricin

With the enantiopure α-silyloxy-γ-sulfononitrile building blocks (*S*)-**1** and (*R*)-**3** in hand, we turned to assembly of the carbon skeleton of the C15–C25 fragment of tetrafibricin via configuration-encoded 1,5-polyol synthesis (Scheme 2). Julia–Kocienski coupling of protected glycolaldehyde **4**[13] with (*S*)-**1** afforded olefin **5** in 86% yield (*E*/*Z* 90:10 after purification).[14,15] Nitrile reduction with DIBAL-H would reveal the aldehyde needed for the next iteration. Unexpectedly,[16] the hydrolysis of the crude imine intermediate in this step was very sensitive to acid-catalyzed racemization, readily observable after the next coupling event.[17] After extensive exploration, a dilute (0.1 mM) aqueous tartaric acid workup corrected this problem. Prompt Julia–Kocienski coupling of the crude aldehyde with building block (*R*)-**3** gave *anti*-1,5-diol **6** in 52% yield over 2 steps with excellent stereocontrol (*E*,*E*/*Z*,*E* >95:5, 19*S*/19*R* 97:3).[18] The DIBAL-H reduction of nitrile **6** behaved normally during workup, with no detected epimerization, and methylenation of the resulting α-silyloxy aldehyde with 5-(methylsulfonyl)-1-phenyl-1*H*-tetrazole ($MeSO_2PT$)[19] under Julia–Kocienski conditions furnished 1,5,9-triol **7** with an 83% yield over 2 steps (23*R*/23*S* >95:5).[20]

Next, with the C15–C25 carbon framework and *anti*-1,5-diol stereochemistry established, attention turned to delivering the remaining hydroxyl equivalent to complete the targeted *anti*-*syn*-1,5,7-triol moiety (Scheme 3). Oxidative hydrolysis of PMB ether **7** and oxidation of the resulting allylic alcohol (**8**) under Corey's conditions provided methyl ester **9** (80% yield).[21] Selective desilylation of the TBS ether with HCl (**10**, 96% yield) then set the stage for the Evans tactic of benzylidene acetal construction via intramolecular conjugate addition. Using a portionwise addition of benzaldehyde and KHMDS with warming between additions, construction of acetal **11** proceeded in 63% yield with excellent diastereoselectivity at the *syn*-1,3-diol moiety (*syn*/*anti* >95:5) and 15% recovery of unreacted alcohol **10**.[22] The *syn*-1,3 configuration was confirmed by two large vicinal coupling constants observed for the axial proton at C18 ($J_{geminal}$ = 13.1 Hz, $J_{vicinal}$ = 11.3, 11.3 Hz), consistent with precedent for similar compounds.[23]

Lastly, having the *anti*,*syn*-1,5,7-triol stereochemistry secured, adjustment of C25 functionality of the terminal olefin **11** would facilitate future fragment coupling studies. Selective hydroboration (9-BBN, then H_2O_2 and NaOAc) furnished a primary alcohol (**12**) in 68% yield with 7% recovery of unreacted olefin. Finally, Swern oxidation (85% yield) gave aldehyde **13**, having terminal functionality suitable for fragment coupling efforts. This C15–C25 fragment is endowed with all the stereochemical features needed for synthesis of tetrafibricin.

Conclusions

A new strategy to access *anti*,*syn*-1,5,7-triols has been designed and executed in the context of tetrafibricin, a fibrinogen receptor antagonist. Iterative configuration-encoded synthesis of chiral 1,5-polyols was merged with diastereoselective intramolecular conjugate addition, providing the *anti*,*syn*-1,5,7-triol subunit of tetrafibricin with excellent stereocontrol. Fragment coupling studies and further efforts toward the total synthesis of tetrafibricin will be reported in due course.

Acknowledgements

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Keywords: natural products • asymmetric synthesis • olefination • alcohols

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[12] a) Asymmetric cyanation to form (*R*)-**2** in the prior report (ref. 7) was of slightly lower selectivity (83–86%ee). The improvement noted herein may be attributed to better temperature control via slow addition, and to differences in the amount of HCN present in the TMSCN reagent. For precedent, see F. Yang, S. Wei, P. Xi, L. Yang, J. Lan, J. You, C. A. Chen, H. M. Gau, *Chem. Eur. J.* **2008**, *14*, 2223; b) Enantiomerically pure (*R*)-**3** was obtained by recrystallization of (*R*)-**1**, desilylation under acidic conditions (TsOH, MeOH), and silylation with TBDPSCl and imidazole (see Supporting Information).

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[18] Isomer ratios were measured by ^{1}H NMR integrations. No minor (*Z*,*E*)- or (*Z*,*Z*)-isomers were observed in ^{1}H and ^{13}C NMR spectra.

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[22] a) See ref. 11; b) When KO*t*-Bu used as the base instead of KHMDS, the product formed in 17% yield with 58% recovered starting material; c) No evidence of *anti*-1,3 diastereomer was observed in ^{1}H and ^{13}C NMR spectra.

[23] a) Peak assignments confirmed by ^{1}H–^{1}H COSY NMR; b) See ref. 11.

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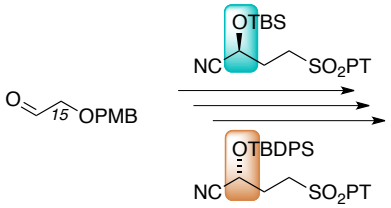

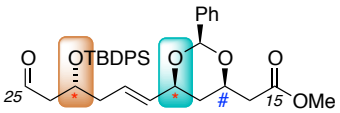

C15–C25 fragment of tetrafibricin

* *via configuration-encoded 1,5-polyol synthesis*

\# *via intramolecular conjugate addition*

Polyol Stereocontrol

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