Using a Readily Accessible Chiral Building Block for the Synthesis of Polyketides

Studies towards the Synthesis of Tetrafibricin and Bastimolide B

Authors: Fabia Mittendorf, Ibrahim-Ethem Celik, and Stefan F. Kirsch

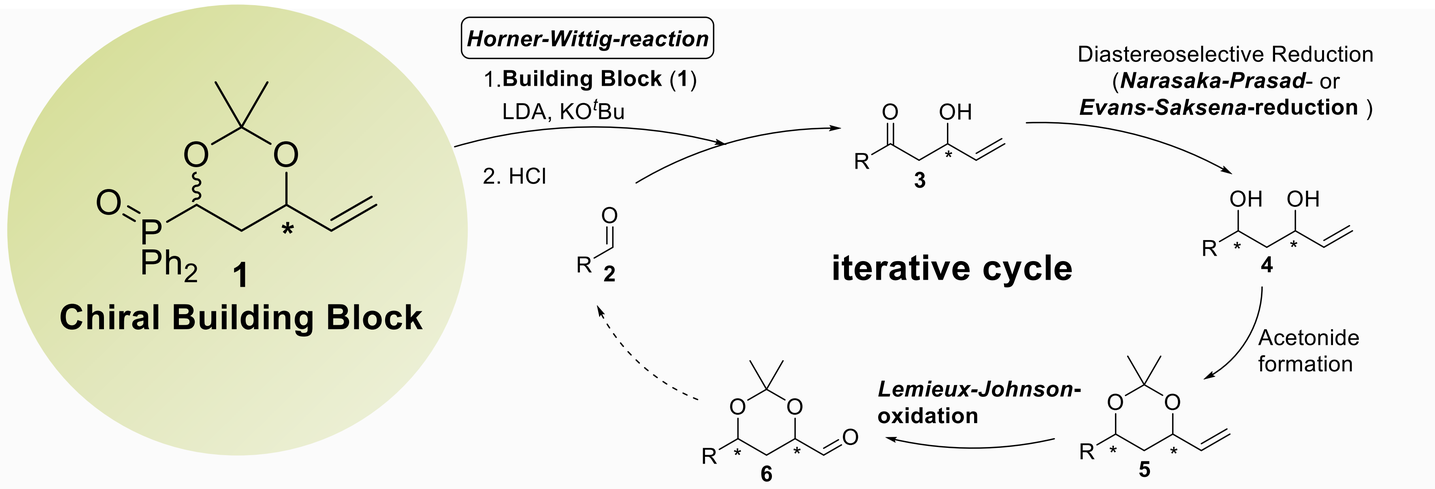
SF KIRSCH GROUP

BERGISCHE UNIVERSITÄT WUPPERTAL

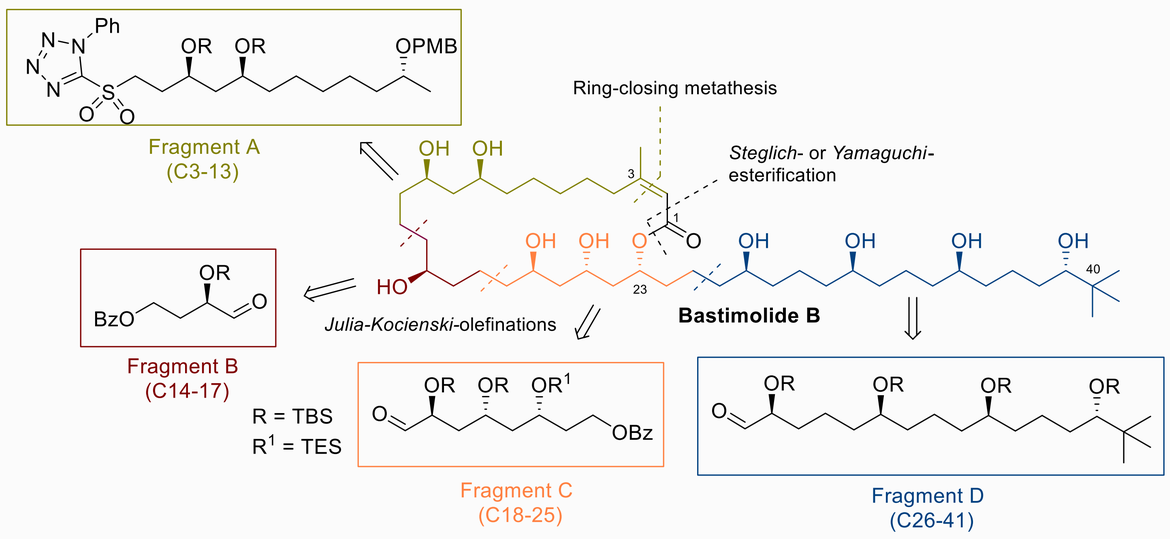
E-mail: sfkirsch@uni-wuppertal.de

Summary

In 2016, our group developed an iterative strategy for the stereoselective synthesis of 1,3-polyols, many of which occur in a wide range of bioactive natural products of polyketidic origin.[1,2] Employing the chiral diphenylphosphane oxide building block **1**, two stereogenic centers are easily installed through a *Horner-Wittig* reaction and a subsequent diastereoselective *syn*- or *anti*-reduction of the β-hydroxy ketone intermediates. This method was successfully employed a.o. for the synthesis of Harzialactone A and (+)-Cryptocaryol A.[1-3] We established an improved synthesis of **1** involving 6 steps starting from *D*-Deoxyribose and here we describe our studies towards the first total syntheses of the biologically active polyketides Bastimolide B and Tetrafibricin. Using the diphenylphosphane oxide **1**, we were able to synthesize and connect all fragments to obtain the full carbon skeleton of both polyketides.

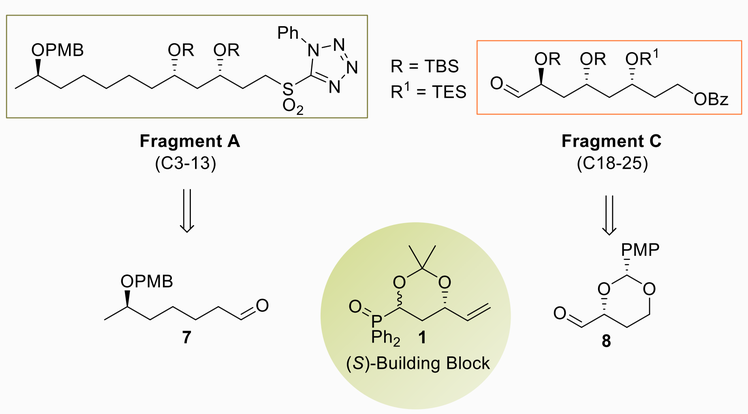


Bastimolide B

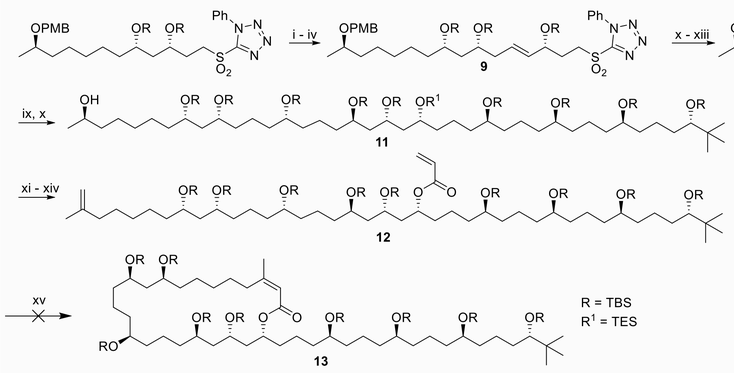


Bastimolide B was isolated from the cyanobacterium *Okeania hirsuta* by the group of *Gerwick* et al. in 2018. It shows potent antimalarial activity against the chloroquine-sensitive *Plasmodium falciparum* strain HB3.[4] Retrosynthetically it can be divided into four main fragments, whereas two of the fragments contain 1,3-diol motifs.

Key-Fragments A&C:

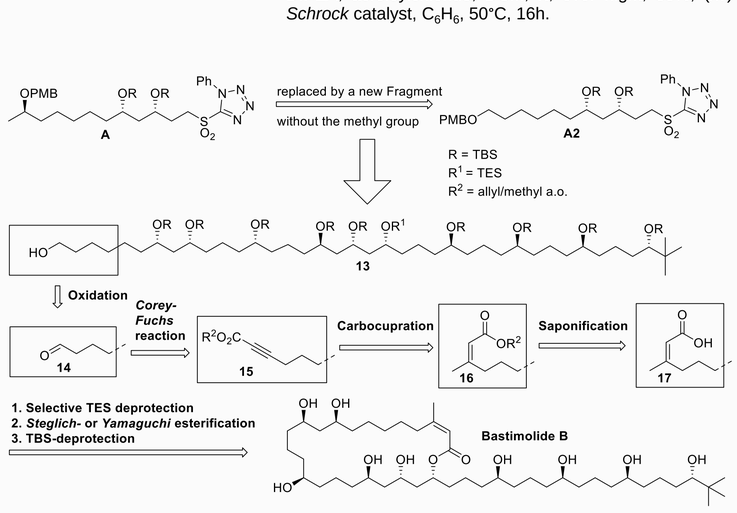


Ring closing metathesis as key step for the cyclization: Fragments **A** to **D** were connected by *Julia-Kocienski*-olefination steps. The following hydrogenation led to the saturated aliphatic chain **11**. The metathesis precursor **12** was obtained via oxidation and methylenation of the sec. alcohol followed by a selective TES-deprotection at C-23 and subsequent acrylate formation. However, the metathesis using the *Schrock* catalyst was unsuccessful.

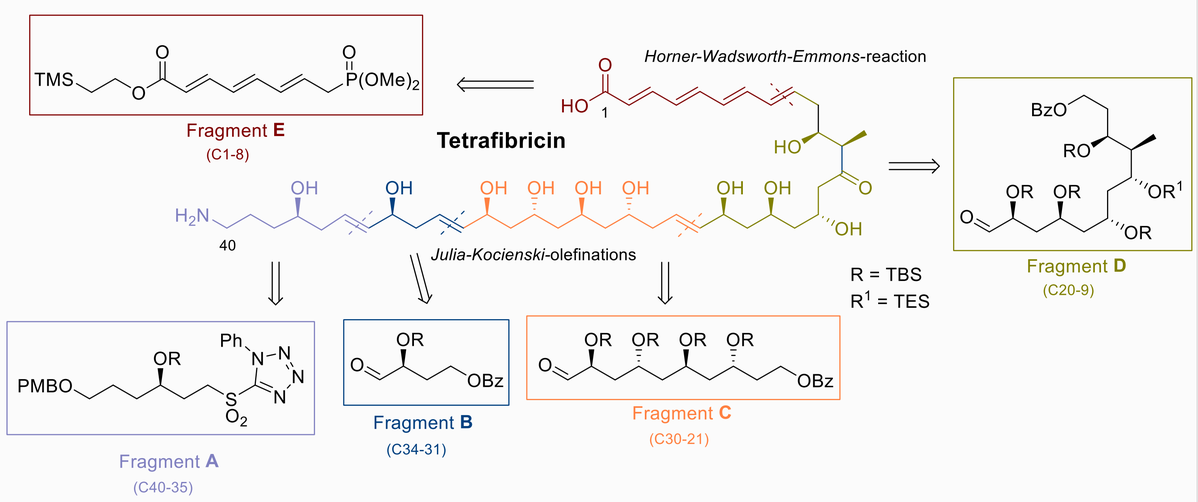


Reaction conditions: (i) KHMDS, **Fragment B**, DME, -78°C, 3h, 81%; (ii) DIBAL-H, DCM, -78°C, 1h, 92%; (iii) 1-Phenyl-1*H*-tetrazol-5-thiol, PPh_3, DIAD, THF, 0°C, 3h, 98%; (iv) $(NH_4)_6Mo_7O_{24}.4H_20$, H_2O_2, EtOH, rt, over night, 92%; (v) KHMDS, **Fragment C**, DME, -78°C, 3h, 85%; (vi) DIBAL-H, DCM, -78°C, 1h, 86%; (vii) 1-Phenyl-1*H*-tetrazol-5-thiol, PPh_3, DIAD, THF, 0°C, 3h, 93%; (viii) $(NH_4)_6Mo_7O_{24}.4H_20$, H_2O_2, EtOH, rt, over night, 50%; (ix) KHDMS, **Fragment D**, DME, -78°C, 3h, 74%; (x) H_2 (500 psi), $Pd(OH)_2$/C, EtOAc rt, 24h, H_2 (500 psi), Pd/C, cyclohexane, rt, 48h, 82%; (xi) IBX, DMSO, THF, rt, over night, 87%; (xii) Ph_3PMeBr, NaHMDS, THF, -78°C, 1h, 85%; (xiii) $NaIO_4$, THF, H_2O, rt, over night, 91%; (xiv) DIPEA, acroloylchloride, DCM, rt, over night, 83%; (xv) *Schrock* catalyst, C_6H_6, 50°C, 16h.

Outlook: Fragment **A** will be replaced by Fragment **A2** without bearing a methyl group. The carbon scaffold **13** is built up the same way as described above. Conversion of the terminal alcohol to the propargylic ester **15** should be accomplished via oxidation, *Corey-Fuchs* reaction and acylation. *Michael*-addition of dimethylcuprate and esterhydrolysis should give rise to the (*Z*)-acrylate **16**. Bastimolide B should be obtained via selective TES-deprotection, intramolecular *Yamaguchi* esterification and global TBS-deprotection.

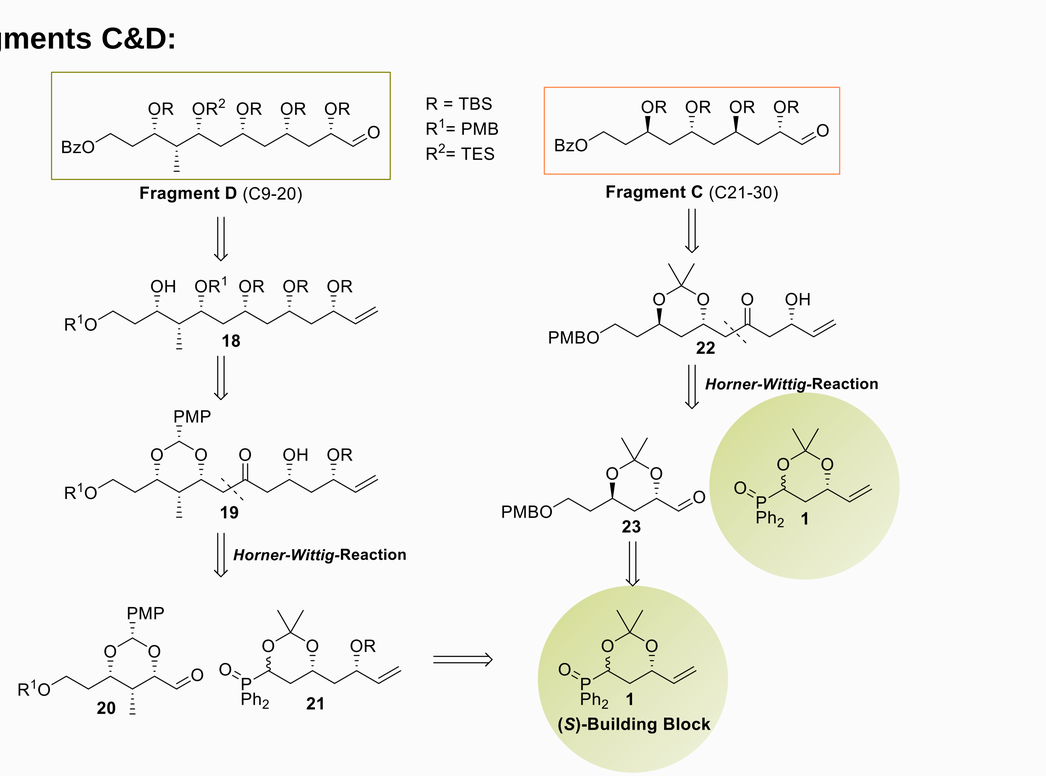


Tetrafibricin

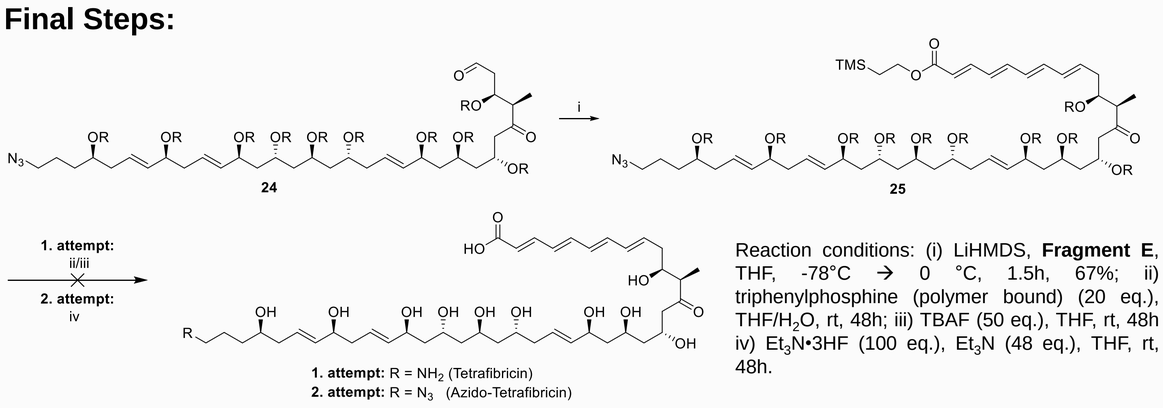


Tetrafibricin was isolated 1993 from the bacterial strain *Streptomyces neyagawaensis* NR0577 in Japan and is reported to have antithrombotic activity. It acts as a competitive inhibitor of the fibrinogen receptor and inhibits blood platelet aggregation.[5] The polyketidic C40 framework of Tetrafibricin contains several 1,3-diol motifs, a tetraene as well as a ketone moiety. Our retrosynthetic approach started with the division of Tetrafibricin into the five fragments **A** to **E**. Fragments **A** to **D** should be connected via *Julia-Kocienski*-olefination reactions, while fragment **E** should be connected via an *HWE-reaction*.

Key-Fragments C&D:



Final Steps:



Reaction conditions: (i) LiHMDS, **Fragment E**, THF, -78°C → 0 °C, 1.5h, 67%; ii) triphenylphosphine (polymer bound) (20 eq.), THF/H_2O, rt, 48h; iii) TBAF (50 eq.), THF, rt, 48h iv) Et_3N•3HF (100 eq.), Et_3N (48 eq.), THF, rt, 48h.

Following a successful connection of fragments **A** to **D** via *Julia-Kocienski*-olefinations the aldehyde **24** was obtained in 26 steps in the longest linear sequence. An *HWE*-reaction with fragment **E** furnished 20 mg of the complete carbon skeleton of Tetrafibricin. Attempts to conclude the synthesis of Tetrafibricin via *Staudinger*-reduction of the azide and global removal of all silyl protecting groups with TBAF failed so far due to degradation of the highly sensitive product and separation from tetrabutylammonium salts. Model reactions suggest to use TBAF in THF/pH7 phosphate buffer (100:1) and subsequent removal of remaining TBAF with Dowex/$CaCO_3$.[6,7]

[1] A. Bredenkamp, Z.-B. Zhu, S. F. Kirsch, *Eur. J. Org. Chem*. **2016**, 252; [2] A. Bredenkamp, M. Wegener, S. Hummel, A. P. Häring, S. F. Kirsch, *Chem. Commun*. **2016**, *52*, 1875; [3] F. Ballaschk, Y. Özkaya, S. F. Kirsch, *Eur. J. Org. Chem*. **2020**, 6078; [4] C.-L. Shao, X.-F. Mou, F. Cao, C. Spadafora, E. Glukhov, L. Gerwick, C.-Y. Wang, W. H. Gerwick, *J. Nat. Prod.* **2018**, *81*, 211; [5] T. Kamiyama, T. Umino, N. Fujisaki, K. Fujimori, T. Satoh, Y. Yamashita, S. Ohshima, J. Watanabe, K. Yokose, *J. Antibiot*. **1993**, *46*, 1039; [6] C. M. Taylor, S. K. Kutty, B. J. Edagwa, *Org. Lett.* **2019**, *21*, 2281. [7] A. M. DiLauro, W. Seo, S. T. Phillips, *J. Org. Chem*. **2011**, *76*, 7352.

Organic Chemistry, Bergische Universität Wuppertal, Gaußstr. 20, 42119 Wuppertal, Germany