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Synthesis of the Fully Functionalized Core Structure of the Antibiotic Abyssomicin C

Jean-Philippe Rath, Stephan Kinast, and Martin E. Maier*

Institut für Organische Chemie, Universität Tübingen, Auf der Morgenstelle 18, D-72076 Tübingen, Germany

martin.e.maier@uni-tuebingen.de

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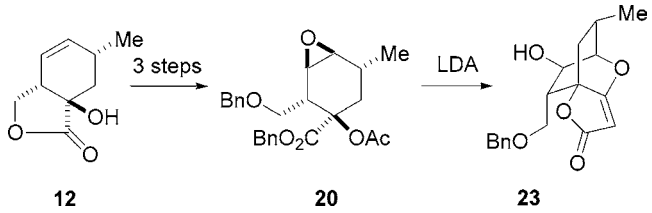
ABSTRACT



The fully functionalized core structure 23 of abyssomicin C (6) containing an oxabicyclooctane ring and a tetronate was prepared via a Diels–Alder approach. After hydroxylation of lactone 10 to the α-hydroxylactone 12, lactone opening led to the hydroxy ester 16. A directed epoxidation furnished the desired *syn*-epoxide 20. Acetylation of the tertiary hydroxyl group, followed by intramolecular Claisen condensation, gave directly the core structure 23.

A large number of natural products are polyketides, and their relative ease of formation is exploited frequently by bacteria in the production of antibiotics. One type of polyketide known as the spiro tetronates[1] contains an oxaspirobicyclic unit in which a tetronate is attached in a spiro manner to a cyclohexene ring. In addition, the cyclohexene is bridged to the tetronate to give a macrocyclic ring. Some typical structures are depicted in Figure 1[2] and include okilactomycin (**1**),[3] tetronothiodin (**2**),[4] kijanolide (**3**),[5] tetronolide (**4**),[6] and A88696F (**5**).[7] Recently, the Süssmuth group described the absyssomicins, which are spiro tetronates with a new level of structural complexity.[8,9] In these antibiotics, the spiro tetronic acid bridges the cyclohexane ring yielding a tricyclic structure with an oxabicyclo[2.2.2]octane ring. Three abyssomicins have so far been isolated, with abyssomicin C (**6**) being the most active one, inhibiting *Staphylococous aureus* at 4 μg mL^{-1}. Significantly, the abyssomicins showed activity in a screen for the inhibition of the *p*-aminobenzoate (*p*ABA) biosynthesis.

The fascinating and challenging structures of the abyssomicins immediately caught our attention and led us to initiate a program aimed at the total synthesis of abyssomicin C. In a previous model study, we were able to show that the tricyclic core structure can be fashioned from a spiro tetronic acid via a transannular Mitsunobu lactonization.[10] The

(1) For reviews, see: (a) Yoshii, E.; Takeda, K. *Recent Prog. Chem. Synth. Antibiot. Relat. Microb. Prod.* **1993**, 67−98. (b) Tejedor, D.; Garcia-Tellado, F. *Org. Prep. Proc. Intl.* **2004**, *36*, 35−59.

(2) For recent fundamental work, see: Roush, W. R.; Sciotti, R. J. *J. Am. Chem. Soc.* **1998**, *120*, 7411−7419 and references therein.

(3) Imai, H.; Kaniwa, H.; Tokunaga, T.; Fujita, S.; Furuya, T.; Matsumoto, H.; Shimizu, M. *J. Antibiotics* **1987**, *40*, 1483−1489.

(4) Ohtsuka, T.; Nakayama, N.; Itezono, Y.; Shimma, N.; Kuwahara, T.; Yokose, K.; Seto, H. *J. Antibiot.* **1993**, *46*, 18−24.

(5) Mallams, A. K.; Puar, M. S.; Rossman, R. R.; McPhail, A. T.; Macfarlane, R. D.; Stephens, R. L. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1497−1534.

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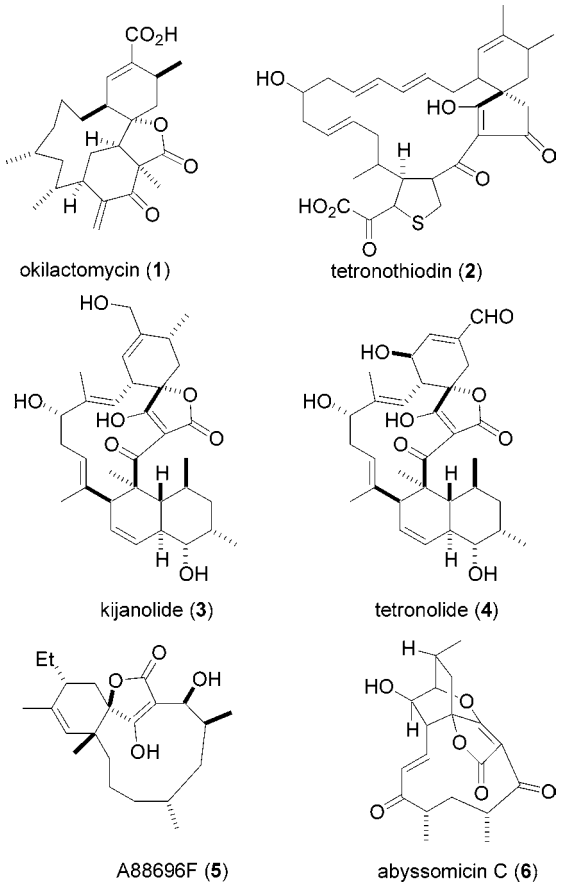


Figure 1. Representative structures of spiro tetronic acid derivatives.

structural similarity of A88696F and abyssomicin C allowed us to put forward a biosynthesis hypothesis featuring a late-stage transannular epoxide opening of the cyclohexane epoxide by the tetronic acid. We asked ourselves whether this strategy might work in a laboratory setting. In this paper we describe the realization of this strategy and show that the macrocyclic ring is not required to achieve regioselective epoxide opening.

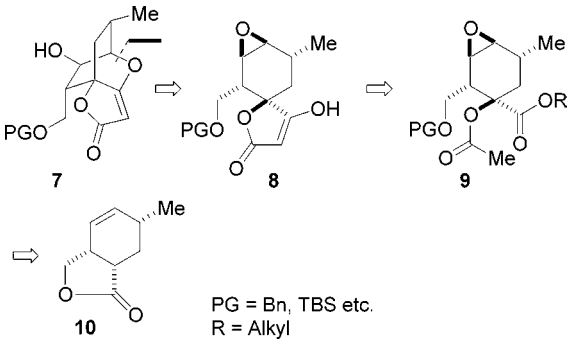
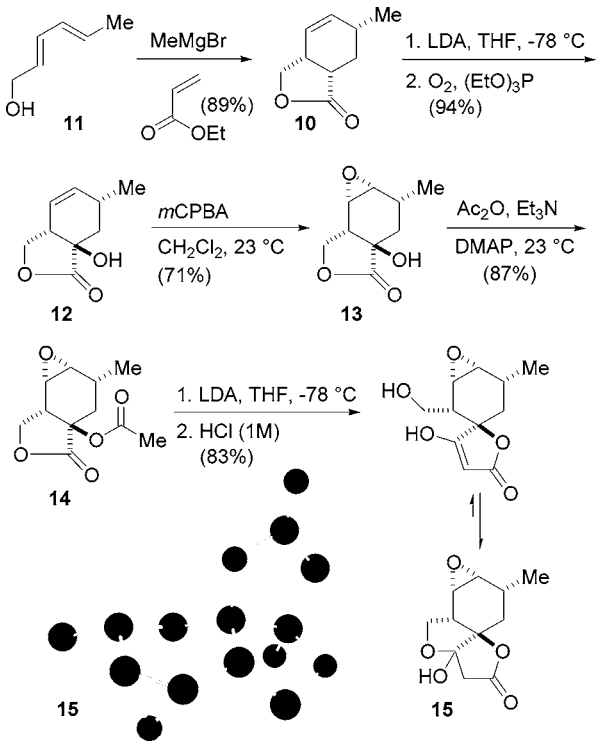


Figure 2. Retrosynthesis of the core structure **7**.

A brief retrosynthetic analysis of the tricyclic core is shown in Figure 2. Thus, **7** would originate from the epoxide **8**. This compound itself can be traced back to the acetate **9**. The acetate **9**, in turn, should originate from the cyclohexene **10**. Some precedence for such a plan up to a spiro tetronate exists in the work of Yoshii[11] and Page.[12] Nevertheless, issues such as incorporation of all functional groups and controlling the diastereoselective epoxidation had to be addressed.

The synthesis started from 2,4-hexadienol[13] (**11**), which was subjected to an intramolecular Diels−Alder reaction with ethyl acrylate in the presence of a Lewis acid template (Scheme 1). This reaction, described by Ward and Abaee,[14]

Scheme 1. Formation of the Hemiacetal **15**



could be run on a multigram scale but required chromatography to remove polymeric byproducts. In the next step, the lactone **10** was hydroxylated by oxygenation of the derived enolate according to the Corey method.[11,15] Due to the bowl shape of **10**, hydroxylation from the convex face was assumed.[11,12] The same was expected for the epoxidation of the double bond with *m*CPBA. Surprisingly, however, epoxidation of **12** led mainly to epoxide **13** (cis/trans = 1:9). Continuing with the synthesis, the tertiary hydroxyl function was acetylated and the resulting acetate subjected to an intramolecular Claisen condensation[11] to give the tetronic acid **15**. The missing alkene hydrogen and other data

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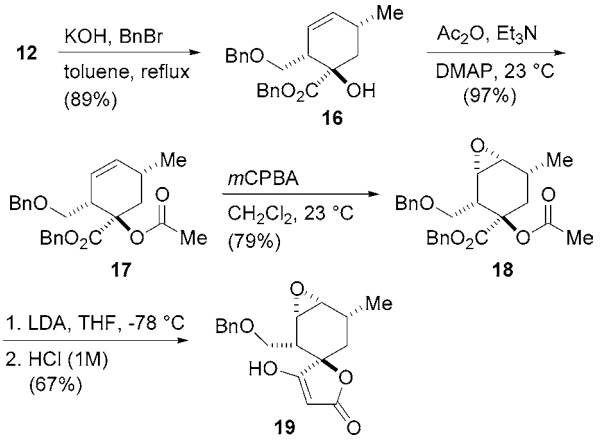
indicated that **15** actually is the hemiacetal. We were surprised to see that similar compounds in the literature are depicted as the open tautomer.[11,12] The structure of **15** could be additionally supported by X-ray analysis, which showed the hemiacetal and the relative stereochemistry.

To prevent formation of the hemiacetal, the lactone **12** was opened under basic conditions, and the carboxylate and primary hydroxyl functions were trapped as *O*-benzyl derivatives (Scheme 2). Acetylation and epoxidation provided

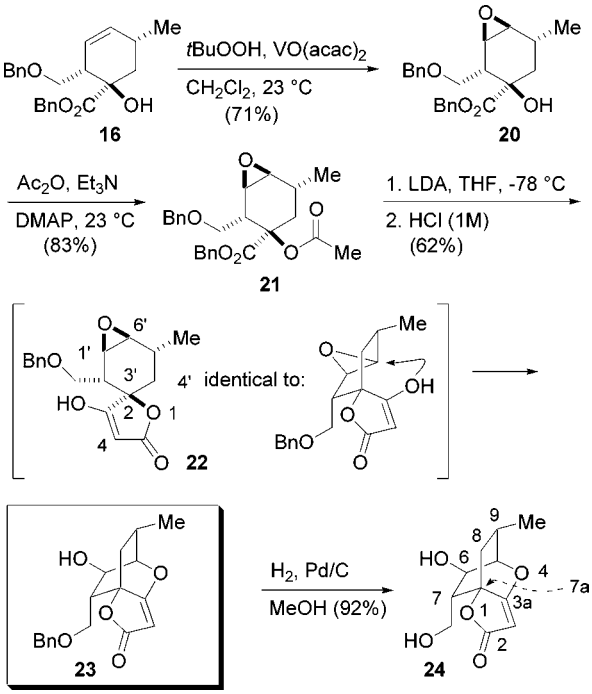
Scheme 2. Synthesis of the Spiro Tetronic Acid **19**



epoxide **18**. Again, intramolecular Claisen condensation proceeded smoothly to give the tetronic acid **19**. The tetronic acid **19** is a rather polar compound. Characteristic is the alkene H of the tetronic acid at $\delta = 4.81$ ppm. We thought that epoxidation of the alkene **17** had occurred syn to the acetate. However, the tetronic acid **19** was rather stable in the presence of Lewis acids (BF_3 Et_2O, CH_2Cl_2; Ti(O*i*Pr)$_4$, CH_2Cl_2). Therefore, the stereochemistry was assigned as shown with the epoxide anti to the acetate.

To steer epoxidation syn to the hydroxyl function, the alcohol **16** was subjected to a directed epoxidation using *t*-BuOOH in the presence of VO(acac)$_2$ (Scheme 3).[16] These conditions gave rise to the *cis*-epoxide **20** in reasonable yield. Conversion to the acetate **21** was accomplished under standard conditions (Ac_2O, Et_3N). Subsequent addition of the acetate to an LDA solution (THF, −78 °C) led to the tetronic acid **22**. This compound can be isolated as a solid by silica gel chromatography, but in solution it is rather unstable and reacts to give a new compound. Careful spectral analysis showed that in fact a regioselective transannular epoxide opening had taken place leading directly to the fully functionalized core structure **23** of abyssomicin C. Most supportive in this regard was the H,H−COSY spectrum of **23**. Thus, proton 6-H shows a cross-peak to 7-H and at the

Scheme 3. Synthesis of the Isomeric Epoxide **21** and Its Cyclization to **23**



same time to the hydroxyl H.[17] This would only be possible if the opening had taken place as shown. In the final step, the benzyl ether of **23** was cleaved by palladium-catalyzed hydrogenolysis, yielding the primary alcohol **24**.

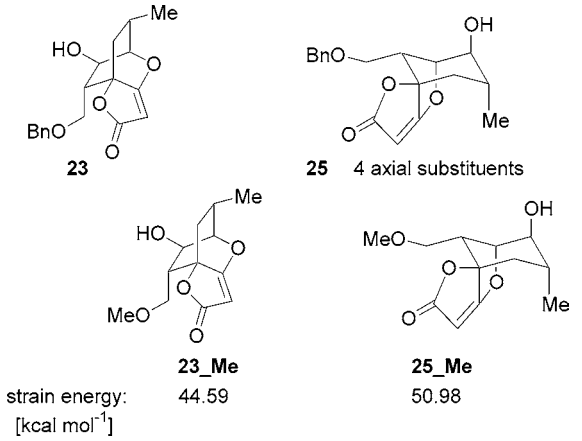


Figure 3. Rationalization of the regiochemistry of the transannular epoxide opening.

While opening of 3,4-epoxycyclohexane carboxylic acids usually takes place at the 3-position,[18] some hydroxymethyl compounds are known to open at the 4-position.[19] In the present case, we believe that opening to the 3-position

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(16) (a) Sharpless, K. B.; Verhoeven, T. R. *Aldrichimica Acta* **1979**, *12*, 63−74. (b) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307−1370.

(17) Core structure is a 6,7-dihydro-2*H*,5*H*-5,7a-ethanofuro[3,2-*b*]pyran-2-one.

(1′-position in compound **22**) would induce high strain in the two five-membered rings. Furthermore, the axially oriented Me group would suffer from 1,3-diaxial interactions. This assumption is supported by force-field calculations (Chem3D) that indicate a substantially higher strain energy ($\Delta SE = 6.39$ kcal mol^{-1}) for the methyl derivative **25_Me** over the isomer **23_Me**.

To summarize, we developed a concise route to the oxabicyclooctane ring system of abyssomicin C. Key steps include hydroxylation of lactone **10**, opening to the benzylester **16**, followed by a directed epoxidation resulting in epoxide **20**. Intramolecular Claisen condensation of the derived acetate **21** led via the tetronic acid **22** to a regioselective transannular epoxide opening to the tricyclic tetronate **23**. This result clearly supports our original biosynthesis hypothesis. Due to steric constraints, this cyclization might not need enzymatic catalysis. In the course of these studies we also discovered surprising diastereoselective epoxidations and the facile formation of hemiacetals such as **15**. Further studies will now focus on an enantioselective variant to **23** and closing of the macrocyclic ring. The hydroxymethyl group and the nucleophilic nature of the tetronate should allow for the synthesis of many abyssomicin analogues, either with or without a macrocyclic bridge.

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Supporting Information Available: Experimental procedures and characterization for all new compounds reported and copies of NMR spectra for important intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.

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