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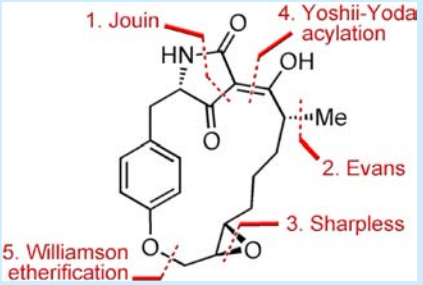
Synthesis of the Bioherbicidal Fungus Metabolite Macrocidin A

Robert G. Haase[†] and Rainer Schobert*[,†]

[†]Organic Chemistry Laboratory, University of Bayreuth, Universitätsstrasse 30, 95440 Bayreuth, Germany

Supporting Information

ABSTRACT: The second total synthesis of macrocidin A afforded the bioherbicidal fungal metabolite in 16 steps starting from doubly protected L-tyrosine. The 3-octanoyl side chain with the α-methyl group and an ω-bromo epoxide already in place was attached to the tetramic acid via a Yoshii–Yoda acylation, and the macrocycle was eventually closed in 55% yield by a Williamson etherification between the phenolate and the epoxy bromide.



Macrocidins A (**1**) and B (**2**) are macrocyclic 3-acyltetramic acids (Figure 1). While the related

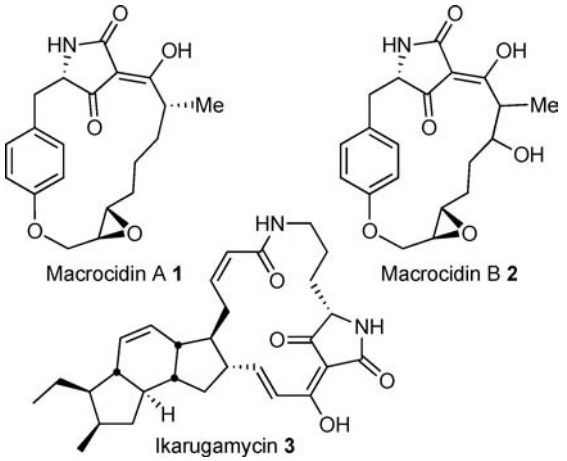


Figure 1. Structures of macrocidins A (**1**) and B (**2**) and ikarugamycin (**3**).

polycyclic tetramate macrolactams (PTMs),[1] such as ikarugamycin (**3**),[2] are antiprotozoal, antibacterial, or antifungal metabolites of bacteria featuring annulated carbocyclic ring systems, the macrocidins are herbicidal metabolites of the fungus *Phoma macrostoma* Montagne featuring a *para*-cyclophane. They were extracted in minute quantities in 2003 by a Dow AgroSciences group from field isolates of this pathogenic fungus dwelling on diseased Canada thistles.[3] Macrocidin A was found only lately to induce chlorosis, i.e., bleaching and withering of susceptible plants, preferentially broadleaf weeds, by a unique pleiotropic mode of action.[4] As a consequence of its metal chelating propensity, it interferes with vital enzymes and processes such as electron transfer and the light-harvesting complex in photosystem II and phytoene synthase and desaturase, resulting in reduced chlorophyll and carotenoid biosynthesis. This multimodal effect, which makes resistance development unlikely, combined with its species selectivity and biodegradability, renders macrocidin A an interesting new crop protection lead.

The only total synthesis of macrocidin A to date, which also confirmed its absolute configuration, was published by Pfaltz, Suzuki, and co-workers in 2009.[5] It employed a macrolactamization by intramolecular ketene trapping followed by a Dieckmann cyclization to partition off the pyrrolidine ring. Syntheses of structurally simplified derivatives of macrocidin A were reported by Ramana et al.[6] and our group.[7] Here we present a conceptually new total synthesis of **1** comprising easy-to-purify intermediates and lending itself to large-scale production of **1** or simplified derivatives in the course of lead optimization studies.

Scheme 1 delineates the retrosynthetic approach. Unlike the Pfaltz–Suzuki synthesis, ours is based on a late-stage ring-closing Williamson etherification between the phenolate and the epoxy bromide of fully functionalized 3-acyltetramic acid **4**. The latter was built up by a Yoshii–Yoda acylation of the known bisprotected tetramic acid **5**,[7] derived from protected tyrosine **6**, with carboxylic acid **7**. The three stereogenic centers of **7** were installed by Sharpless epoxidation and Evans methylation, offering the advantage of easy-to-purify diastereomers after each step. The oct-6-enoic acid backbone of allylic alcohol precursor **8** was obtained by Negishi coupling between ω-zincated pentanoyl reagent **9**, still attached to the Evans auxiliary used for introduction of the α-methyl residue, and vinyl iodide **10**.

The side-chain precursor **8** was prepared starting from 5-bromovaleric acid (**11**), which was converted to a mixed anhydride and attached to the Evans auxiliary (*R*)-benzyl-2-oxazolidinone to give imide **12** in 88% yield (Scheme 2). Its deprotonation with NaHMDS at −78 °C and quenching of the

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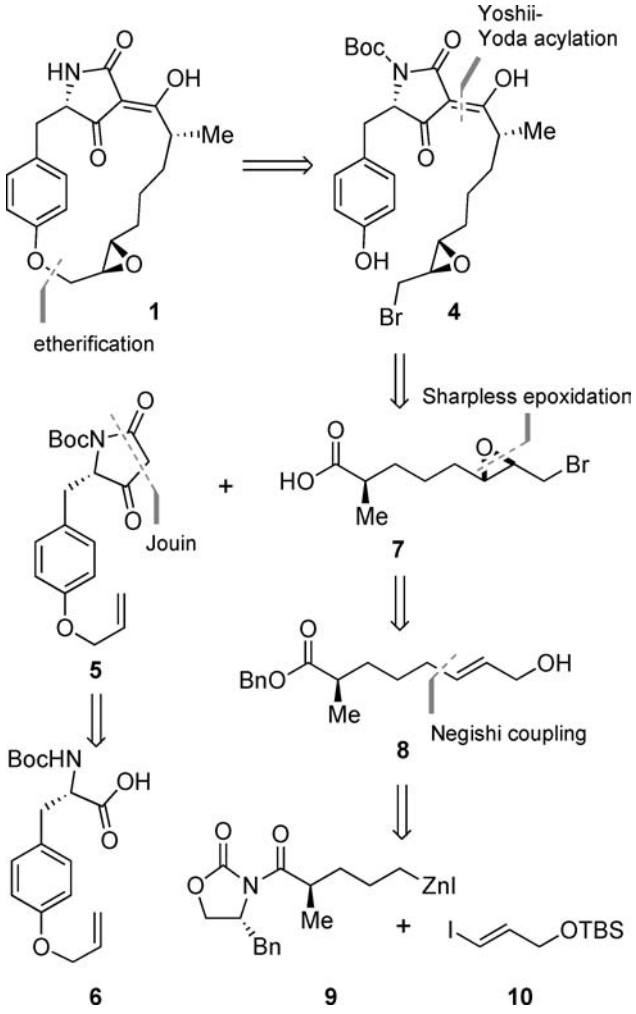
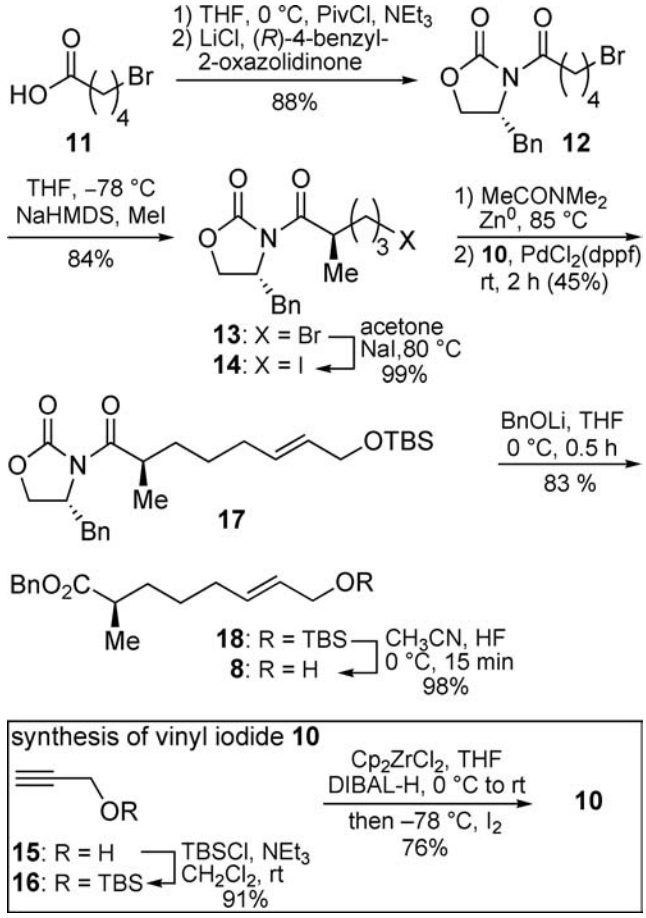
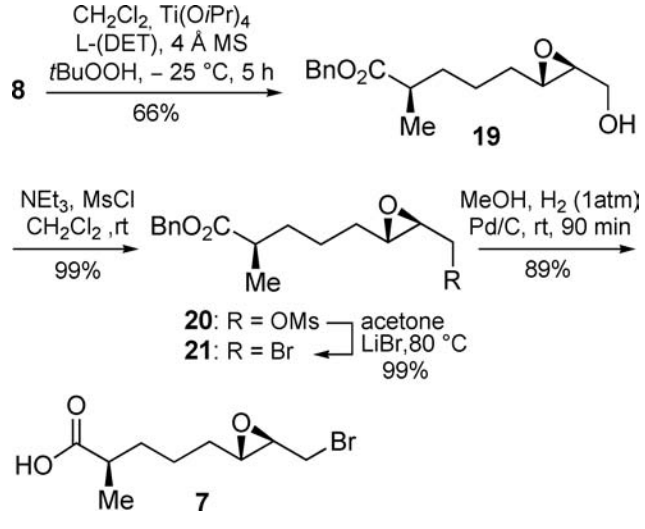
Scheme 1. Retrosynthesis of Macrocidin A



Scheme 2. Synthesis of the Side-Chain Precursor 8



Scheme 3. Sharpless Epoxidation and Completion of the Side-Chain Precursor 7



resulting enolate with iodomethane gave a separable 10:1 mixture of two product diastereomers. The major isomer **13** was subjected to Finkelstein halogen exchange to afford iodide **14**. This was converted in situ to organozinc compound **9** according to a protocol by Huo[8] and then treated with vinyl iodide **10** and $PdCl_2$(dppf) to give the coupling product **17**. Syntheses and reactions of organozinc compounds bearing Evans auxiliaries were hitherto unknown, to the best of our knowledge.

Vinyl iodide **10** was made in 76% yield from **16**, a TBS-protected derivative of propargyl alcohol (**15**), using Negishi's hydrozirconation protocol with DIBAL-H and zirconocene dichloride.[9] Imide **17** was then cleaved to give benzyl ester **18** in 83% yield. Near-quantitative removal of the silyl protecting group with hydrofluoric acid left allylic alcohol **8**, which underwent diastereoselective Sharpless epoxidation to furnish epoxy alcohol **19** as a single stereoisomer (Scheme 3).

Alcohol **19** was converted quantitatively to mesylate **20**, which in turn was treated with lithium bromide in acetone to afford the desired epoxy bromide **21**, also in 99% yield. Hydrogenolytic cleavage of the benzyl ester liberated carboxylic acid **7** in 89% yield without compromising the epoxide. Overall, the fully functionalized side-chain precursor **7** was synthesized in only 10 steps and in 14% yield.

Next, *N*-Boc-(5*S*)-5-(4-(allyloxy)benzyl)-pyrrolidine-2,4-dione (**5**) was prepared in 98% yield as described earlier[7] by reacting Boc-Tyr(Allyl)-OH (**6**) with Meldrum's acid according to a general protocol by Jouin et al.[10] (Scheme 4). Tetramic acid **5** was then acylated with carboxylic acid **7** employing Yoda's modified version[11] of the older Yoshii protocol.[12] In a two-step process, compounds **5** and **7** were first reacted with DMAP and EDC·HCl to give 4-*O*-acyltetramate **22**. Its Fries-type acyl rearrangement, mediated by NEt_3, afforded 3-acyltetramic acid **23**. The addition of $CaCl_2$ was necessary to

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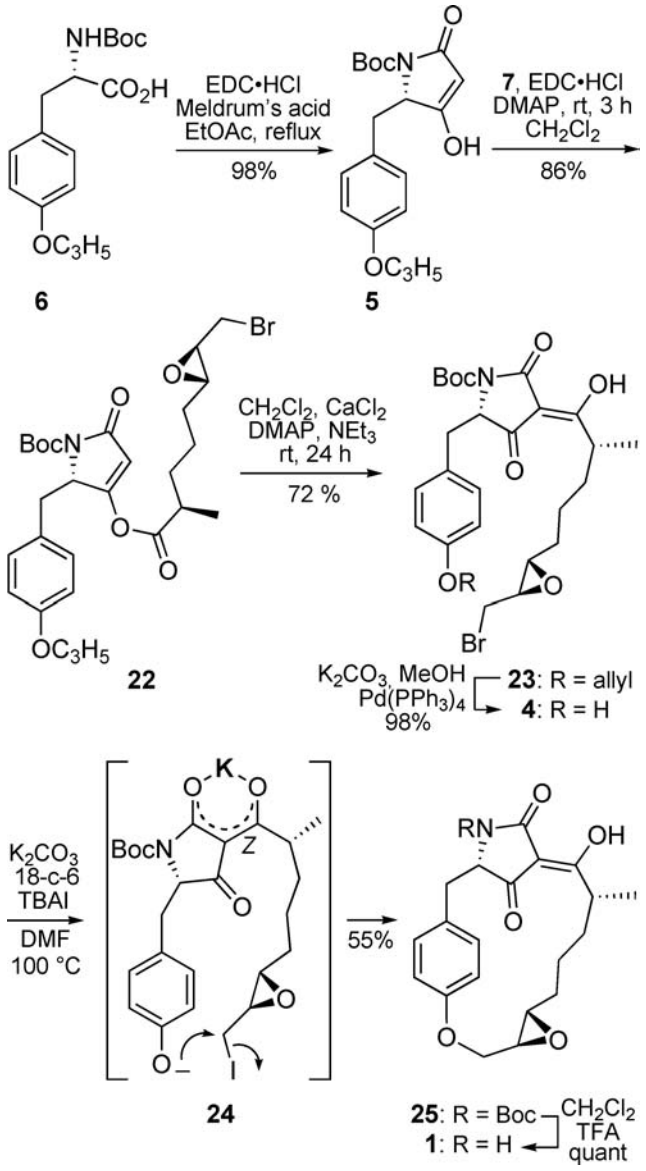
Scheme 4. 3-Acylation and Ring-Closing Etherification



prevent racemization of the α-stereogenic center in the acyl residue, possibly by chelate complex formation. Compound **23** was deallylated in methanol with $Pd(PPh_3)_4$ as a catalyst and in the presence of potassium carbonate to give phenol **4**.[13] This was submitted to a ring-closing Williamson etherification. Since this reaction does not normally proceed well for the alkylation of phenols with alkyl bromides, we had to apply special conditions. Phenol **4** was dissolved in DMF and heated for 24 h together with an excess of potassium carbonate, 0.5 equiv of crown ether 18-c-6, and trace amounts of tetrabutylammonium iodide (TBAI) to afford a 55% yield of the *N*-Boc protected macrocidin A **25**. We assume that cyclization takes place only when a relatively nucleophilic phenolate anion can attack a nearby iodide, generated in situ by TBAI. The crown ether would sequester part of the potassium, keeping the phenolate anion "naked", and the rest of the potassium should be chelated by the exocyclic and amide oxygens of the 3-acyltetramic acid with the usual *Z* configuration,[14,15] thus forcing the side chain to point toward the phenolate as shown in structure **24**. It is also worth noting that the ring-closing etherification step leading to macrocidin A does not require palladium catalysis, as we had previously assumed[7] for the cyclization of structurally simplified derivatives.

Removal of the *tert*-butyloxycarbonyl group of **25** with trifluoroacetic acid eventually gave macrocidin A (**1**) in quantitative yield with a specific optical rotation of $[\alpha]_D^{25}$ +40 (*c* 0.35, CH_3OH). The natural isolate[3] was reported to have $[\alpha]_D^{25}$ +45 (*c* 0.35, CH_3OH), and the synthetic sample obtained by Pfaltz, Suzuki, and co-workers[5] showed $[\alpha]_D^{27}$ +42 (*c* 0.18, CH_3OH).

In summary, we developed the second total synthesis of macrocidin A, which afforded the product in ca. 4% yield over 16 steps. Its chiral intermediates are all easy-to-purify diastereomers, and it is flexible enough to give access to analogues with widely varied structures. The Williamson etherification, which is rarely used as a macrocyclization method, worked well here, probably because the chelation of potassium by the added crown ether and the 3-acyltetramic acid itself enhanced the nucleophilicity of the phenolate and also oriented the chain ends of the acyclic precursor in a favorable way. Work is in progress now to identify a simplified herbicidal lead structure.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03240.

Experimental details of chemical syntheses, characterizations, and NMR spectra of new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: Rainer.Schobert@uni-bayreuth.de. Fax: +49 (0)921 552671. Phone: +49 (0)921 552679.

ORCID

Rainer Schobert: 0000-0002-8413-4342

Notes

The authors declare no competing financial interest.

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