

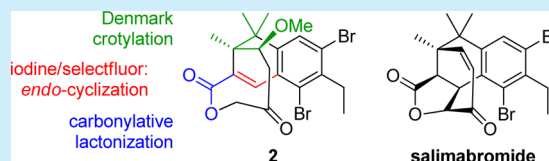
Concise Synthesis of the Tricyclic Core of Salimabromide

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S Supporting Information

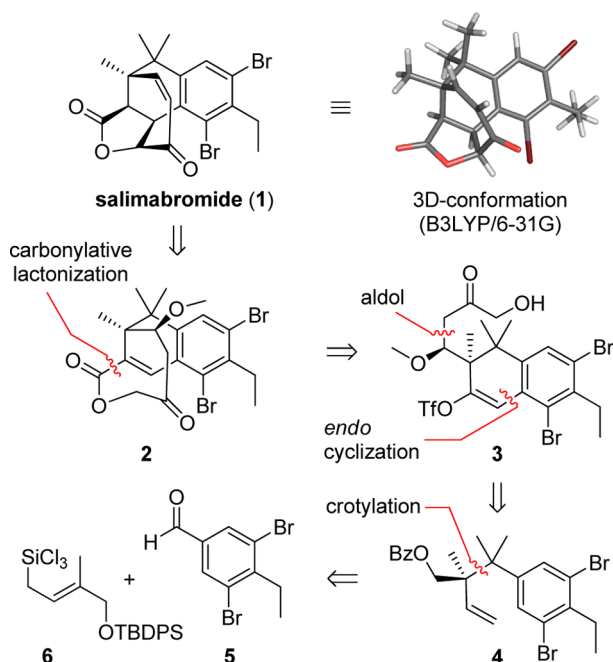
ABSTRACT: A concise synthesis of the tricyclic core **2** of the structurally unique marine myxobacterial natural product salimabromide has been developed. Compound **2** contains the tetraline subunit including the two quaternary centers and the eight-membered ring of salimabromide. Major features for its synthesis include a Lewis base catalyzed Denmark-crotylation for stereoselective construction of the highly hindered quaternary stereocenter, an innovative iodine/selectfluor induced *endo*-carbocyclization, and a unique chemoselective carbonylative lactonization of the eight-membered ring.



The group of G. König has reported the isolation and structural assignment of salimabromide from the marine myxobacterium *Enhygromyxa salina* in 2013.¹ It presents one of the first secondary metabolites isolated from a marine myxobacterium.² Salimabromide has a structurally novel tetracyclic carbon skeleton with no apparent resemblance to any known natural products. In detail, the unique architecture comprises a dibrominated benzene ring, a butyrolactone residue, and a cyclohexane ring that is bridged by a seven-/eight-membered cyclic moiety (Scheme 1). It contains four stereogenic centers including a sterically highly congested quaternary center. Salimabromide could only be isolated in

minute amounts (0.5 mg) and revealed antibiotic activity toward *Arthrobacter crystallopoietes*. Further biological evaluation was hampered by the scarce natural supply.¹ Inspired by the unique structure together with its highly limited natural availability, we initiated a program directed toward a first total synthesis of salimabromide. Such an approach is also of key importance for unambiguous proof of the unusual constitution and relative and absolute configuration. Herein, we report a concise synthesis of the tricyclic core **2** of salimabromide by an innovative strategy involving a Lewis base catalyzed Denmark-crotylation for stereoselective construction of the highly hindered quaternary stereocenter, an effective iodine/selectfluor induced *endo*-carbocyclization for construction of the tetraline ring, and a unique carbonylative lactonization that proceeds with excellent chemoselectivities.

Scheme 1. Retrosynthetic Analysis of the Tricyclic Core (2) of Salimabromide (1)



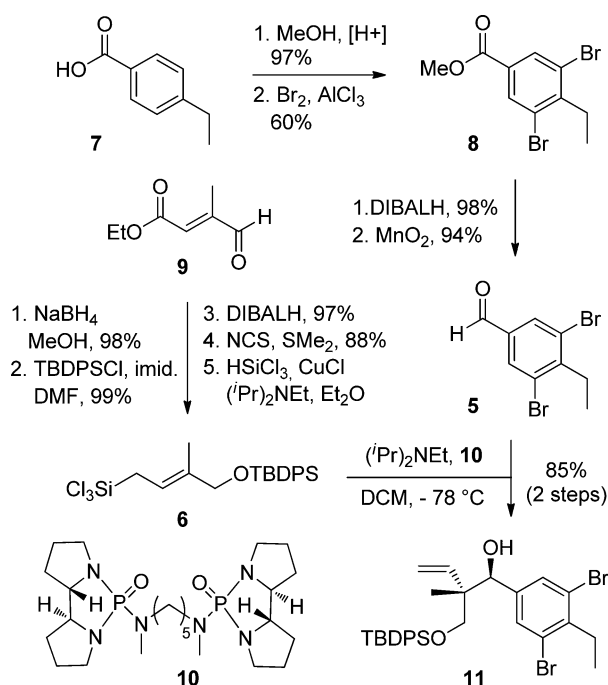
As shown in Scheme 1 our synthetic approach to the tricyclic core **2** relied on an adventurous carbonylative lactonization of triflate **3** to form the eight-membered lactone ring of **2**. Construction of the tetraline core of **3** in turn was envisioned to arise from **4** by an electrophilic cyclization reaction of the aromatic ring to the appending terminal alkene. It was anticipated that the two neighboring quaternary centers of the alkene may favor an unusual *endo*-cyclization for steric reasons. Finally, a suitable asymmetric crotylation by coupling of allylsilane **6** with aldehyde **5** was scheduled to set the chiral quaternary center in a stereoselective fashion.

As starting material to build up the aromatic core **11** of salimabromide, 4-ethylbenzoic acid (**7**) was chosen (Scheme 2). The acid was first transformed to the corresponding methyl ester by using sulfuric acid in methanol, followed by introduction of the bromides *ortho* to the ethyl-residue by treatment with bromine and aluminum trichloride.³ The desired compound could be readily purified by simple washings of the resulting solid. DIBAL reduction of ester **8** then gave the corresponding benzylic alcohol, which was subsequently

Received: April 27, 2015

Published: May 28, 2015

Scheme 2. Stereoselective Construction of the Quaternary Chiral Center

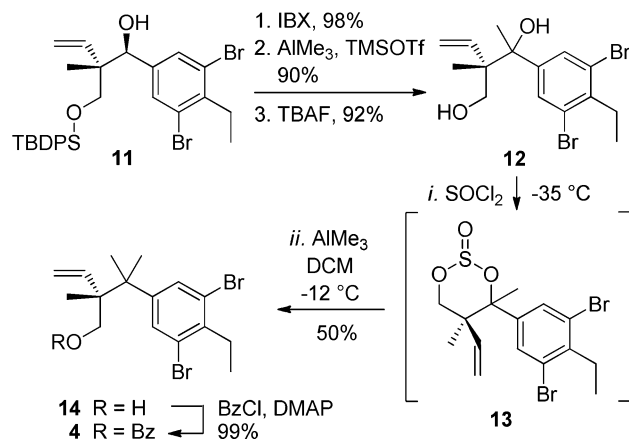


oxidized by means of activated manganese dioxide. Notably, scale up of this sequence was facile, as none of these steps needed purification by column chromatography and no expensive chemicals were used. Therefore, large amounts of aldehyde 5 could easily be prepared.

The required trichlorosilane 6 in turn was synthesized in five steps starting from commercially available aldehyde 9. First, the aldehyde was reduced using sodium borohydride followed by protection of the resulting alcohol with TBDPSCI.⁴ Next, the ester function was reduced by use of DIBALH, ensued by transformation of the allylic alcohol to the corresponding allyl chloride by utilizing the Corey–Kim protocol. The resulting allyl chloride was then converted to the desired silane 6 by usage of trichlorosilane and catalytic amounts of copper chloride.⁵ Due to the reactive nature of 6 the allylsilane was directly used in the crotylation reaction with 5. After optimization of the original procedure developed by Denmark,⁵ this coupling proceeded in high yield (85%) and enantioselectivity (95% *ee*) in the presence of the chiral bispyrrolidine-based bisphosphoramidate 10.⁶

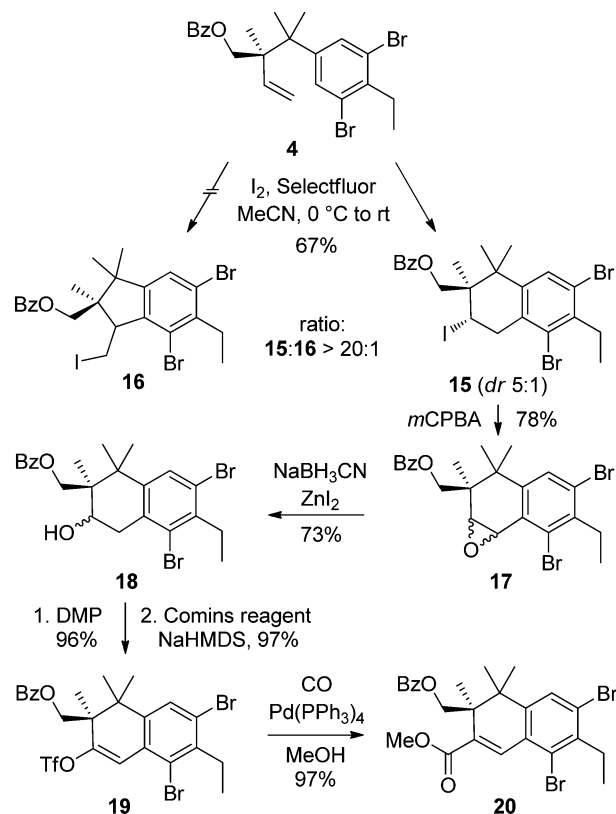
As shown in Scheme 3, installation of the two methyl groups in benzylic position was initiated by oxidation of the benzylic alcohol 11 to the corresponding ketone by treatment with IBX in DMSO (Scheme 3). After initial attempts to introduce both geminal methyl groups in one step using the Reetz protocol or other one-step procedures⁷ failed, we turned our attention to a stepwise procedure. Accordingly, the first methyl group was installed using trimethylaluminum and TMS-triflate. For introduction of the second methyl group considerable experimentation was required. Finally, this transformation could be realized by first forming a six-membered sulphite ring (13) of the neighboring hydroxyls of 12 with thionyl chloride. Notably, only small amounts of the corresponding benzylic chloride were formed during this transformation. The resulting cyclic intermediate 13 was then directly converted to the desired compound 14 by treatment with trimethylalumi-

Scheme 3. Completion of the Synthesis of Building Block 5



num.⁸ Finally, protection of the terminal alcohol as the benzoate proceeded in a straightforward manner to give the desired building block 4.

With 4 in hand, efforts could be directed toward formation of the tetralin ring 15 (Scheme 4). Gratifyingly, cyclohexane

Scheme 4. Synthesis of the Tetralin Core 5 by an *endo*-Selective Iodocyclization

formation could be effected smoothly by treatment of 4 with iodine and selectfluor in acetonitrile. Importantly, this iodocyclization proceeded with excellent *endo*-regioselectivity and no traces of the *exo*-product 16 were observed. Also, preparatively useful diastereoselectivities were observed (5:1), which can be further increased by applying the same procedure to the unprotected analog of 4 that does not bear a benzoate group (*dr* > 20:1, not shown).⁹ Notably, to the best of our

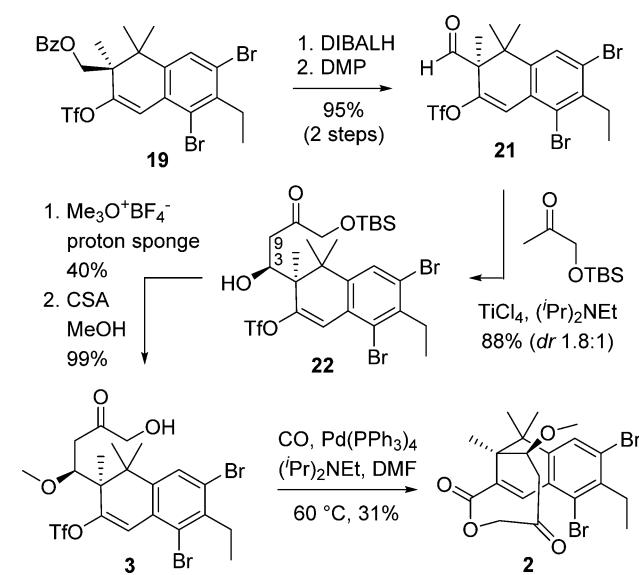
knowledge, this is the first example of an iodotetralin synthesis by using iodine.¹⁰ The iodine in molecule **15** then had to be replaced by a hydroxyl group for further functionalization. Since compound **15** was very prone to elimination, this could not be achieved in one step. Finally, an oxidative elimination of the iodo group by means of *m*CPBA was followed by *in situ* epoxidation through excess peroxybenzoic acid.¹¹ The resulting epoxide **17** was then opened in a regioselective fashion at the benzylic position by using sodium cyanoborohydride and zinc chloride to yield the homobenzylic alcohol **18** in a 1:2.3 mixture of diastereomers.¹² Further elaboration by oxidation with DMP and treatment with the Comins reagent and NaHMDS gave the enol triflate **19**.¹³ As a prelude for the envisioned carbonylative lactonization (*vide infra*), a chemoselective methoxycarbonylation of **19** was then evaluated. This proceeded in excellent yields using $\text{Pd}(\text{PPh}_3)_4$ ^{14a,b} as the catalyst. Alternatively, $\text{PdCl}_2(\text{PPh}_3)_4$ ^{14c} and $\text{Pd}(\text{tBu})_2$ were also active but resulted in lower yields. All investigated bisphosphane ligands gave unsatisfactory results. No conversion of the aryl bromides was observed, which further corroborated our synthetic design.¹⁵

For homologation by an aldol approach, the terminal benzoyl protecting group was first removed reductively by treatment with DIBALH since ester cleavage using aqueous conditions proved incompatible with the newly installed vinylic triflate. The free alcohol was then oxidized with DMP to the corresponding aldehyde. With this desired functional handle in position, the stage was set for performing an aldol reaction with TBS-protected hydroxyacetone. In the presence of titanium tetrachloride and Hünig's base this coupling gave the desired product **22** as a single regioisomer in a 1:1.8 mixture of the diastereomers.¹⁶ The necessary protection of the formed alcohol proved to be challenging, presumably due to high steric hindrance exerted by the neighboring quaternary center. Introduction of the methyl group could only be achieved for the major diastereomer in modest yields by Meerwein salt and proton sponge¹⁷ whereas the minor diastereomer did not react at all. Subsequent removal of the terminal TBS group proceeded smoothly with CSA in methanol and gave the desired substrate **3** for the crucial carbonylative lactonization to form the eight-membered ring of salimabromide.

As shown in Scheme 5, the pivotal carbonylative lactonization to form the eight-membered ring could indeed be successfully realized to give the desired tricyclic core **2** of salimabromide by treatment with CO in the presence of catalytic amounts of $\text{Pd}(\text{PPh}_3)_4$ (16 mol %) and Hünig's base (4.1 equiv) in DMF (60 °C). In accordance with our results for the methoxycarbonylation of **19** this was the only catalyst that provided acceptable conversion. Importantly, the reaction proceeded again in a completely chemoselective manner, with no activation of the aryl bromide to be observed. Finally, the structure of **2** was unambiguously confirmed by X-ray crystallography (see Supporting Information for details). Noteworthy, this presents to the best of our knowledge the first time an eight-membered lactone has been formed by this method.^{18,19}

It should be noted that the reported route is flexible and offers various late-stage options to finalize the first total synthesis of salimabromide. These include installment of different protective groups at the C-3-hydroxyl to effectuate an elimination across the C-3/C-9 bond or a suitable

Scheme 5. Carbonylative Methoxylation: Synthesis of the Tricyclic Core of Salimabromide



functionalization at the benzylic position by regioselective opening of epoxide **17**.

In summary, we have developed the first route to the tricyclic core **2** of the structurally unique tetracyclic metabolite Salimabromide. Notable features of our route include stereoselective generation of the chiral quaternary center by means of a Denmark crotylation, an innovative highly regioselective synthesis of the tetraline unit by means of an iodocyclization using iodine and selectfluor, and a challenging carbonylative macrocyclization of the eight-membered ring. Efforts are now focused on applying these tactics for realization of a first total synthesis of salimabromide. Furthermore, our studies are directed toward further evaluation of the general usefulness of the reagent combination iodine/selectfluor for related cyclizations and the further advancement of carbonylative lactonizations for medium and large ring systems.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures, characterization, and copies of ¹H and ¹³C NMR spectra of new compounds. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01231.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank Prof. G. König (University of Bonn) for fruitful cooperation on salimabromide, Andreas J. Schneider (University of Bonn) for HPLC-support, and Dr. G. Schnakenburg (University of Bonn) for X-ray structure analysis.

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