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Synthesis of the Core Structure of Salicylihalamide A by Intramolecular Suzuki Reaction

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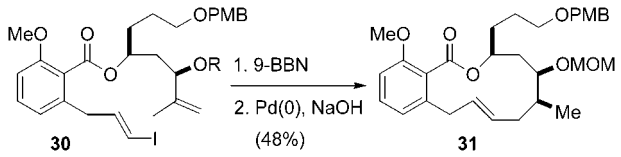
ABSTRACT



An intramolecular Suzuki coupling was used to establish the core structure of the benzolactone enamide salicylihalamide A. This strategy combines a diastereoselective hydroboration with a subsequent cross-coupling.

Molecules that selectively interact with a cellular protein, RNA, or DNA are important biological tools, particularly in the context of chemical genetics.[1] In addition, such compounds are indispensable for the treatment of human dysfunctions and diseases. While the number of natural products might be insufficient for targeting each gene product, they still help to find new targets and provide new structural leads. Fascinating examples in this regard are the benzolactone enamides, natural products that turned out to be selective inhibitors of mammalian vacuolar (H^+)-ATPase.[2] This mode of action, resulting in high cytoxicity with a GI_{50} in the low nanomolar range, was discovered by comparing the activity profile against the profile database of the NCI. Prominent members from the benzolactone enamides include the salicylihalamides,[3] isolated from the sponge *Haliclona* sp., and the apicularens,[4] produced by myxobacteria (Figure 1). Further members of this class include the lobatamides,[5]

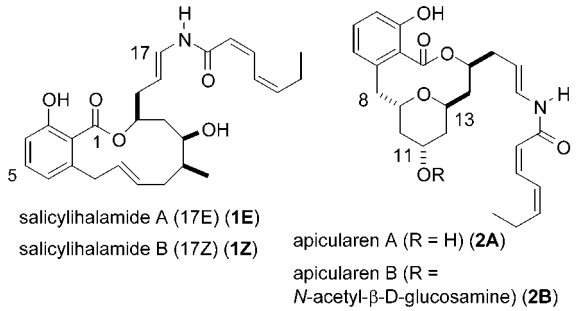


Figure 1. Two representative benzolactone enamides.

the oximidines,[6] YM-75518,[7] and the fungal metabolites CJ-12,950[8] and CJ-13,357. Structurally, these compounds have in common a salicylic acid substructure, a macrolactone, and an enamide side chain. The enamide side chain, which seems

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to be important for conferring biological activity, is also found in some other natural products, including the chondriamides, zampanolide, and the proteasome inhibitors TMC-95.[9]

From a synthetic point of view the benzolactone enamides represent challenging targets. In the meantime, total syntheses of apicularen A[10] and salicylihalamide[11] were reported. In addition, synthetic approaches to the core structure of these natural products[12,13] and studies aimed at the enamide side chains[14] have been published. The macrolactone portion of salicylihalamide is unique in that it features a double bond in an allylic position to the aromatic ring. A classical macrolactonization approach is difficult as a result of steric hindrance of the carboxylic group and participation of the double bond. However, if the double bond is of a styrene type, the macrolactonization works in acceptable yields.[15] So far all successful approaches to salicylihalamide are based on an intramolecular ring-closing metathesis reaction. We asked ourselves how one would synthesize this molecule if the ring-closing metathesis were not known. According to the retrosynthetic analysis (Figure 2) we opted for formation

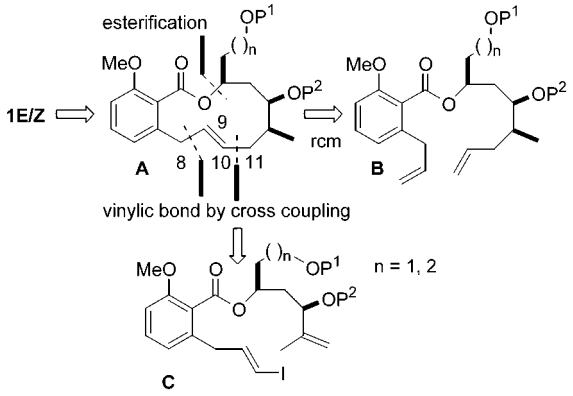
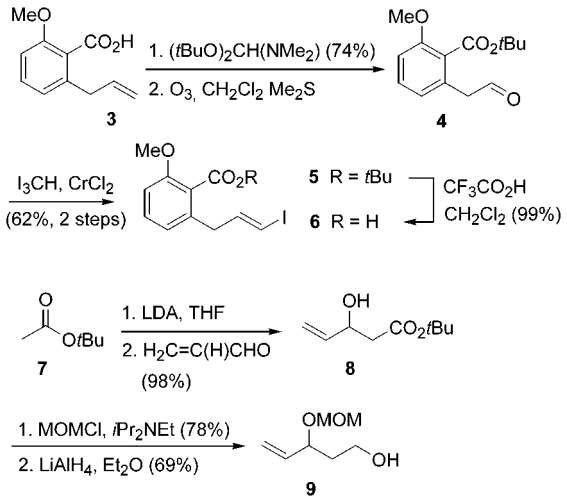


Figure 2. Retrosynthetic analysis for salicylihalamide A based on a Suzuki coupling to form the C10−C11 bond.

of a vinylic C−C bond, either in an inter- or intramolecular fashion. The ester bond would be formed by a Mitsunobu reaction. The creation of the C8−C9 bond has been described in the literature but suffers from moderate yield.[11f] Another alternative would be the formation of the C10−C11 bond by a cross-coupling reaction. In this paper we show that indeed a sequence of a diastereoselective hydroboration followed by Suzuki coupling[16,17] allows for the formation of the salicylihalamide core structure.

Initial studies focused on the Suzuki coupling on a model system. First, the benzoic acid **6** with a iodopropenyl side chain was prepared from the known acid **3**.[11e] Esterification of **3** with dimethylformamide-di-*tert*-butyl acetal[18] (Scheme 1) followed by ozonolysis gave the aldehyde **4**. A subsequent

Scheme 1. Synthesis of Acid **6** and Propenol **9**



Takai reaction[19] of **4** gave the vinyl iodide **5** (E/Z = 4:1). The acid **6** was obtained by treatment of the ester **5** with trifluoroacetic acid. It was important to employ the *tert*-butyl ester **5** because a basic hydrolysis of the ester group (on the corresponding methyl ester) is not survived by the vinyl iodide. The pentenol derivative **9** was prepared in racemic

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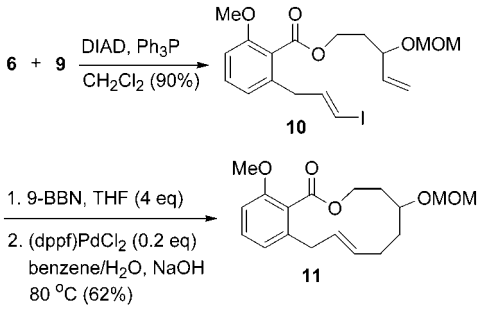
form by an aldol reaction of *tert*-butyl acetate with acrolein to give the hydroxy ester **8**. This was followed by MOM protection of the secondary hydroxyl group and reduction of the ester function to produce alcohol **9**.

With the substrates **6** and **9** in hand, the intramolecular Suzuki reaction was investigated. Thus, by esterification of the acid **6** with the alcohol **9** under Mitsunobu conditions, the cyclization substrate **10** was prepared (Scheme 2).

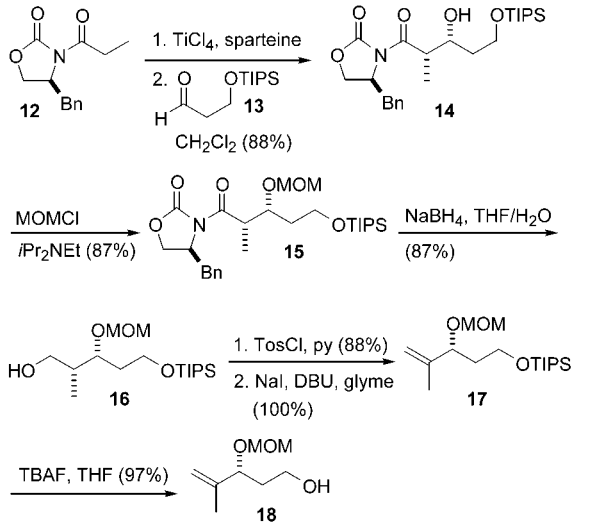
Scheme 2. Synthesis of Macrolactone **11** by Intramolecular Suzuki Coupling



Preliminary studies on the methyl ester analogue of **5** had shown that the vinyl iodide gives high yields in intermolecular Suzuki coupling reactions using the conditions of Trost [(dppf)$PdCl_2$ (5 mol %), Ph_3As (5 mol %), Cs_2CO_3 (1.3 equiv), THF, 23 °C, 4 h].[20] In contrast, the Suzuki cyclization of **10** required some experimentation. First, hydroboration of **10** turned out to be relatively slow, requiring stirring overnight with up to 5 equiv of 9-BBN. The progress of the hydroboration reaction could be followed by ^1H NMR spectroscopy. While the "Trost" conditions did not give the cyclization product, the original Suzuki conditions[21] brought about the desired cyclization. This was achieved by adding the intermediate borane via syringe pump to a heated mixture (80 °C) of benzene, 3 N NaOH, and the palladium catalyst. Because of the high dilution, a larger amount of the catalyst (dppf)$PdCl_2$ (20 mol %) was used. The steric hindrance at the ester group probably retards cleavage of the lactone. This way, a 62% yield of the macrocycle **11** was obtained.

The next phase of the project focused on a substrate with a 1,1-disubstituted double bond and the issue of the diastereoselective hydroboration prior to the cyclization. Accordingly, the alkene part **18** lacking the side chain was prepared in optically pure form as illustrated in Scheme 3. An Evans aldol reaction[22,23] of the chiral propionate **12** with aldehyde **13**[24] using $TiCl_4$ (1.05 equiv) in the presence of sparteine[25] (2.5 equiv) gave a high yield of the *syn*-aldol product **14**.

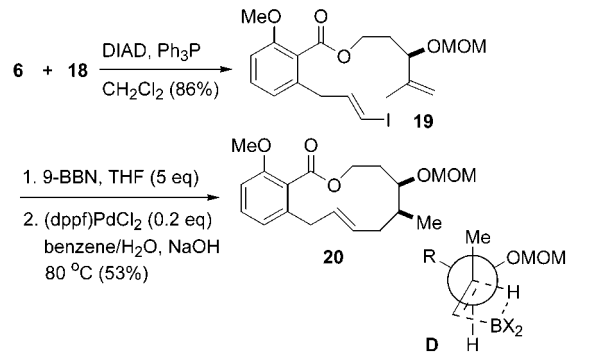
Scheme 3. Synthesis of Alkene **18** via Evans Aldol−Reduction−Elimination Sequence



After protecting the secondary alcohol of **14** as MOM ether, a reductive removal of the chiral auxiliary with $NaBH_4$ in a THF/H_2O mixture[26] provided the primary alcohol **16**. Next, the corresponding tosylate was prepared. The elimination to give the alkene **17** could be smoothly accomplished by heating the tosylate in glyme in the presence of NaI (2.5 equiv) and DBU (5.0 equiv). Treatment of **17** with tetrabutylammonium fluoride (TBAF) furnished the alcohol **18**.

Esterification of the acid **6** with the alcohol **18** under Mitsunobu conditions[27,28] generated the cyclization substrate **19** (Scheme 4). For the intramolecular Suzuki reaction the same conditions as before were employed. After workup, a 53% yield of the macrolactone **20** was obtained. The stereochemistry of the hydroboration[29] was assumed to follow the Houk model.[30,31]

Scheme 4. Intramolecular Suzuki Coupling to Give Macrolactone **20**



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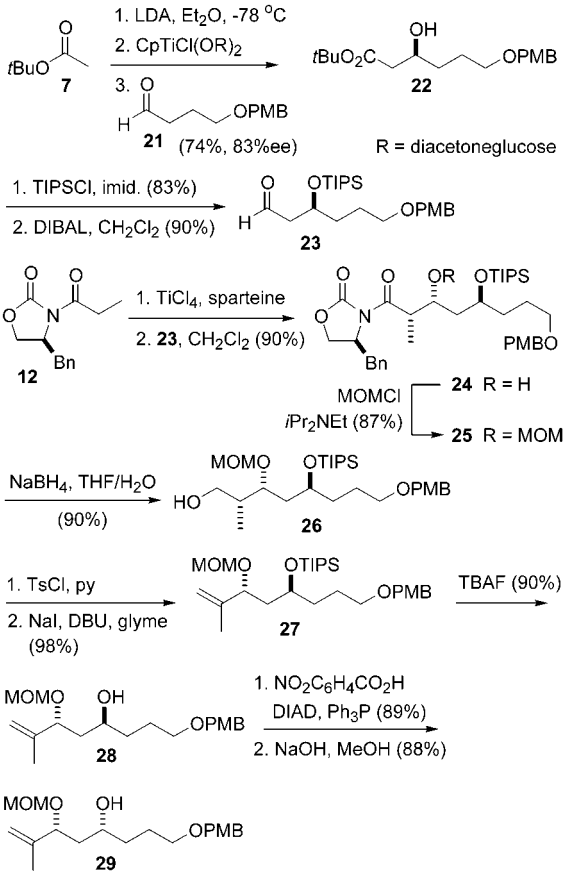
The Suzuki cyclization was also extended to a system containing a side chain at C-15. By applying a Duthaler aldol reaction[32] between the aldehyde **21**[33] and *tert*-butyl acetate, the 3-hydroxy ester **22** was prepared in 83% ee (Scheme 5).

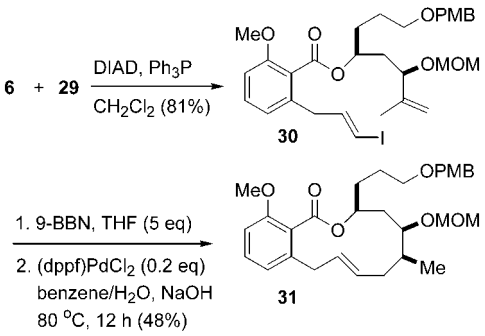
Scheme 5. Synthesis of Alcohol **29**



Protection of the secondary hydroxy group with triisopropylsilyl chloride followed by DIBAL reduction furnished the aldehyde **23**. Again, an Evans aldol reaction was used to extend the carbon chain, yielding compound **24**. After reductive removal of the chiral auxiliary, tosylation of the primary alcohol and elimination in the presence of NaI provided the 1,1-disubstituted alkene **27** in excellent yield. Since di-*O*-isopropylidene-D-glucofuranose was employed in the Duthaler aldol reaction, the stereochemistry at C-15 (salicylihalamide numbering) had to be inverted. This was accomplished on the alcohol **28** by a Mitsunobu reaction[34] using *p*-nitrobenzoic acid. Basic hydrolysis provided the *syn*-configured diol derivative **29**.

Next, the acid **6** was esterified with the alcohol **29** under Mitsunobu conditions, providing the cyclization substrate **30** in 81% yield (Scheme 6). The macrocyclization was performed as described before. This gave a 48% yield of the macrolactone **31**. The ^{1}H NMR spectrum of **31** shows 2 methyl doubletts (δ = 0.91 major, 1.02 minor) that are due to the major product and the *cis*-double bond isomer. From this, it can be followed that the hydroboration is highly diastereoselective. Separation of the isomers by preparative HPLC gave pure **31**.

Scheme 6. Intramolecular Suzuki Coupling to Give Salicylihalamide Core Structure **31**



In summary, we developed a synthesis of the core system of salicylihalamide A by employing an intramolecular Suzuki coupling as a key step. This exemplifies a novel strategic retrosynthetic cut for reaching the macrocyclic ring. The Suzuki cyclization is preceded by a diastereoselective hydroboration. In essence, the aldol−elimination−hydroboration sequence inverts the stereochemistry at C-12. Our efforts concentrate now on the synthesis of isomerically pure vinyl iodide **6** and streamlining the route to the alkenol **29** in order to complete the total synthesis of salicylihalamide A.

Acknowledgment. Financial support by the Deutsche Forschungsgemeinschaft (grant Ma 1012/10-1) and the Fonds der Chemischen Industrie is gratefully acknowledged.

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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