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Studies toward the Total Synthesis of the Marine Macrolide Salarin C

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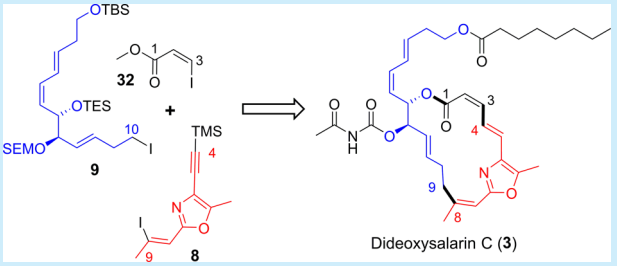
Supporting Information

ABSTRACT: A convergent strategy for the synthesis of dideoxysalarin C (**3**) as a potential intermediate for the total synthesis of the marine macrolide salarin C (**1**) is described. The macrolactone core of **3** was assembled by Suzuki coupling between alkyl iodide **9** and vinyl iodide **8** and Shiina macrolactonization as key transformations. All macrocyclic intermediates were found to be of low stability.



Salarin C (**1**) (Figure 1) is a marine macrolide of mixed polyketide/nonribosomal peptide synthase origin that was isolated in 2008 by Kashman and co-workers from the sponge *Fascaplysinopsis* sp., collected in waters off the coast of Madagascar.[1] It is the most potent member of a small family of structurally related, sponge-derived nitrogenous macrolides (salarins A−J and tausalarin C), which exhibit different degrees of antiproliferative activity.[1−4]

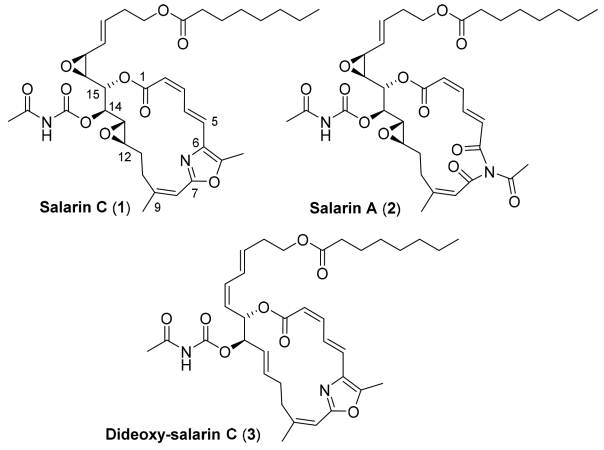


Figure 1. Molecular structures of salarin C (**1**), salarin A (**2**), and dideoxysalarin C (**3**).

Salarin C (**1**) has been reported to inhibit the growth of the human leukemia cell lines UT-7 and K562 with approximate IC_{50} values of 1 and 0.1 μM, respectively; the growth of the murine pro B cell line Ba/F3 was completely inhibited by 0.1 μM salarin C (**1**).[1b] The compound has also been found to induce apoptosis in K562 cells.[4]

Structurally, salarin C (**1**) features an 18-membered macrolactone core structure with an embedded oxazole moiety and two appended side chains of different sizes at C14 and C15. The compound incorporates an unusual bis-epoxide motif, with one of the epoxide moieties being adjacent to a double bond. In chloroform solution, salarin C (**1**) is slowly converted into salarin A (**2**) (ca. 50% conversion within 3 days), and it has been suggested that this transformation involves the reaction of **1** with singlet oxygen in a Wasserman-type rearrangement.[1a]

In spite of its intriguing structural properties and its appealing biological activity, no total synthesis of salarin C (**1**) has been reported so far. In fact, apart from the preparation of a series of semisynthetic derivatives of salarin C (**1**) and A (**2**),[5] only a single publication on synthetic work in relation to any salarin can be found in the literature at this point. Thus, Schäckermann and Lindel have recently described the synthesis of the C1−C12 segment of salarin C (**1**) (i.e., **4**, Figure 2), and they showed that treatment of this compound with singlet oxygen in methanol leads to oxazole ring opening and formation of the corresponding *N*-triacylamine.[6]

This transformation reflects the conversion of salarin C (**1**) into salarin A (**2**) as previously observed by Kashman and co-workers[1a] (vide supra).

In this paper, we describe the synthesis of dideoxysalarin C (**3**) as a potential precursor for the synthesis of **1**. In addition, we considered **3** as an interesting synthetic target in its own

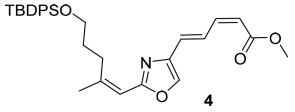


Figure 2. Structure of the C1−C12 segment of salarin C (**1**) prepared by Schäckermann and Lindel.[6]

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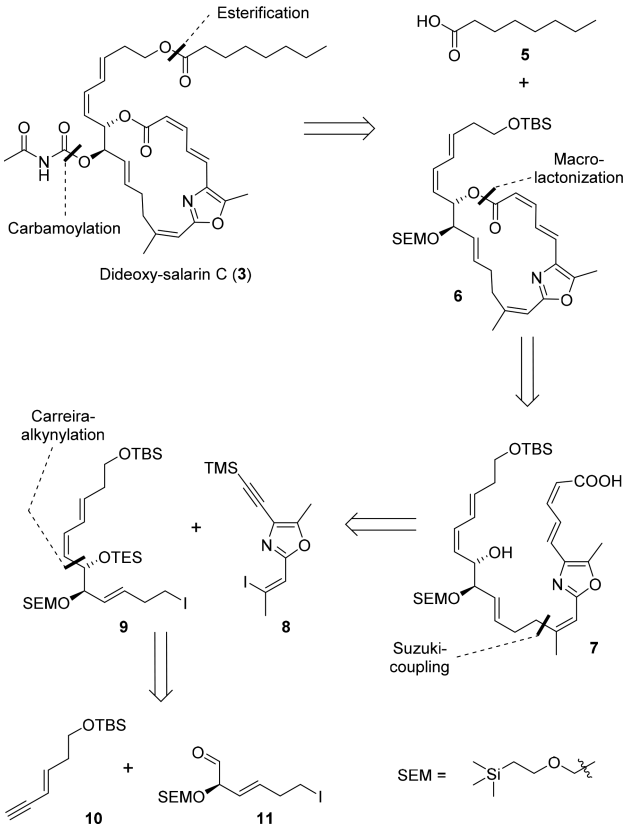
right, as it has been shown for other natural products that the replacement of an epoxide moiety by a C−C double bond of the corresponding geometry does not significantly impair biological activity; examples are epothilones A/B[7] or rhizoxin.[8] If so, dideoxysalarin C (**3**) would provide a structurally less complex starting point for SAR studies and optimization.

Our final retrosynthesis of **3** is depicted in Scheme 1. According to this strategy, macrocycle formation was to be

Scheme 1. Retrosynthesis of Dideoxysalarin (3)

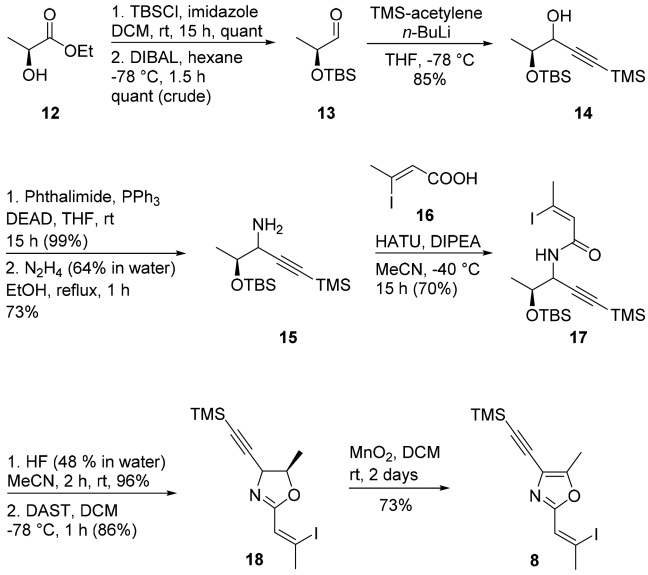


performed by macrolactonization of seco acid **7**; conversion of the cyclization product **6** into **3** would then involve deprotection/esterification of the primary hydroxy group, followed by deprotection of the secondary hydroxy group at C14 and final carbamoylation with acetylisocyanate.[9] Seco acid **7** was to be formed by Suzuki cross coupling between a boronate derived from alkyl iodide **9** and vinyl iodide **8**, followed by elaboration of the terminal triple bond into the $\alpha,\beta,\gamma,\delta$-unsaturated dienoate moiety. Alkyl iodide **9** was envisaged to be accessed from enyne **10** and aldehyde **11** in a stereoselective Carreira alkynylation reaction,[10] followed by reduction of the triple bond.

The synthesis of oxazole **8** is summarized in Scheme 2 and departed from L-ethyl lactate (**12**), which was converted into aldehyde **13** by TBS protection and subsequent reduction of the ester group with DIBAL;[11] addition of lithiated TMS-acetylene to the crude aldehyde then provided propargylic alcohol **14** in 85% overall yield from **12**.[11]

Alcohol **14** was further elaborated into the corresponding amine **15** via a two-step Mitsunobu/Gabriel sequence (72%)[12] followed by HATU-mediated[13] amide bond formation with (*Z*)-3-iodobut-2-enoic acid (**16**) at −40 °C to furnish amide **17** in 70% yield. Notably, carrying out the coupling reaction at

Scheme 2. Synthesis of Oxazole Building Block 8



rt gave **17** in significantly lower yield. The TBS ether in **17** was then selectively cleaved with aq HF/CH_3CN, and the resulting hydroxy amide was treated with DAST to provide oxazoline **18** in excellent yield (83% for the two-step sequence from **17**).[14] Finally, oxidation of **18** with MnO_2[15] cleanly furnished the desired oxazole in excellent overall yield (26%) for the nine-step sequence from L-ethyl lactate. Initial attempts to oxidize **18** with $BrCCl_3$ and DBU[14] were unsuccessful, as these conditions led to elimination of HI and alkyne formation.

As depicted in Scheme 3, the synthesis of iodide **9** commenced with the elaboration of *S*-glycidol (**19**) into allylic alcohol **20** by TBS protection and subsequent one-carbon homologation with dimethylsulfonium methylide.[16] Olefin **20** was then submitted to cross-metathesis with PMB-protected 3-butenol (**21**) in the presence of a Hoveyda−Grubbs second-generation catalyst;[17] the reaction produced a mixture of the desired *E* olefin and homocoupling products together with unreacted starting material that was not separated but directly reacted with SEMCl to furnish SEM ether **22** in 43% overall yield from **20** after purification by flash chromatography. Treatment of **22** with buffered TBAF led to selective cleavage of the primary TBS ether, and the ensuing free alcohol was oxidized to the corresponding aldehyde **23** with Dess−Martin periodinane (DMP);[18] in the best case, **23** was obtained in 97% yield (73% for the two-step sequence from **22**), but yields for this oxidation varied significantly, mostly due to decomposition of the product aldehyde **23**.[19] Other methods investigated for the oxidation of deprotected **22** (Parikh−Doering oxidation,[20] TEMPO,[21] PDC[22]) did not offer any advantages and uniformly gave lower yields than DMP.

In one of the key steps of the synthesis, aldehyde **23** was then to be joined with terminal enyne **24** in a stereoselective Carreira alkynylation[10] to produce intermediate **25**, which comprises more than half of the heavy atom framework of the macrolactone core of dideoxysalarin C (**3**).

As depicted in Scheme 4, the terminal enyne **24** was prepared in a four-step sequence from but-3-yn-1-ol (**27**), which was first converted into vinyl iodide **28** by radical hydrostannylation with Bu_3SnH/AIBN and subsequent tin−iodine exchange, according to the methodology developed by de Meijere and co-workers.[23]

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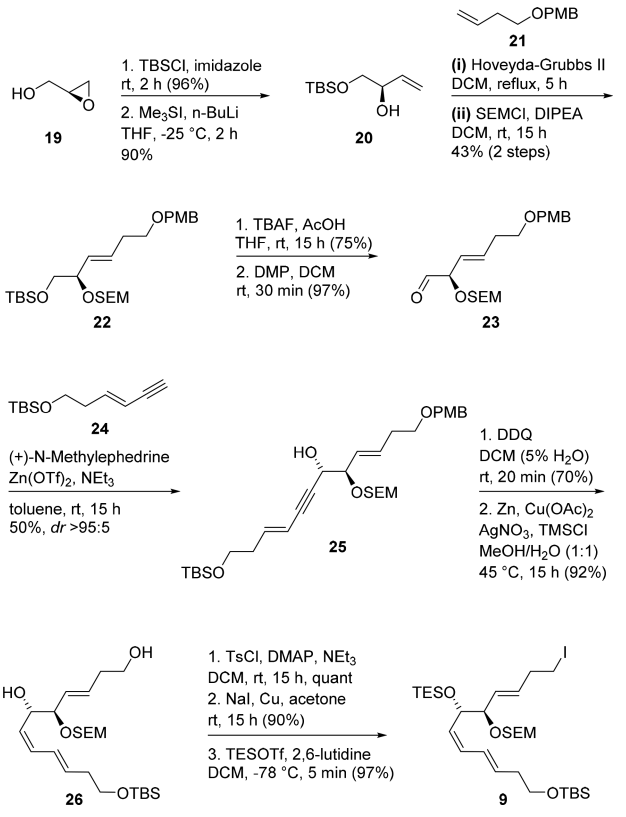
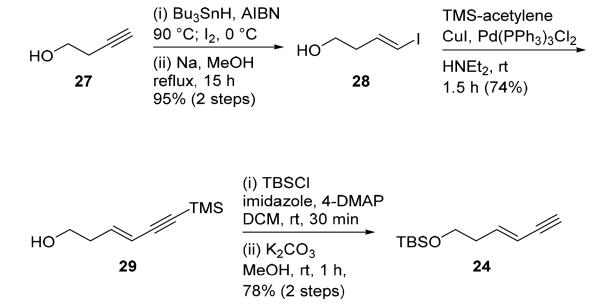
Scheme 3. Synthesis of Iodide 9



Scheme 4. Synthesis of Enyne 24

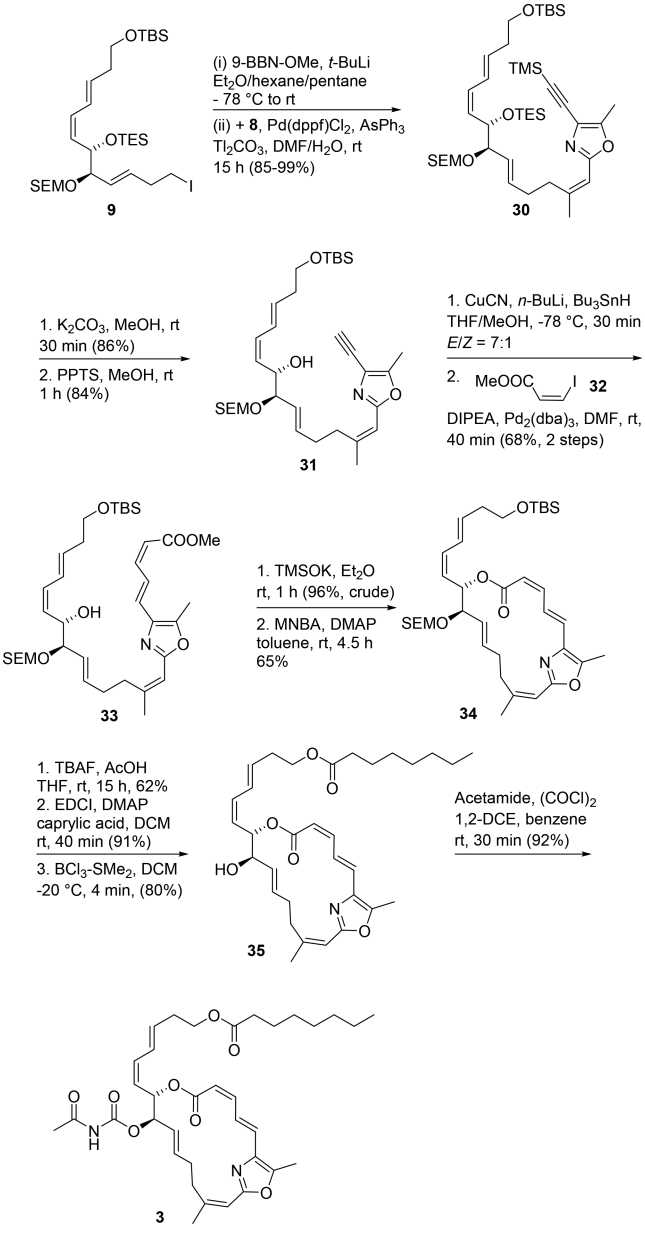


The reaction yielded a mixture of double bond isomers that was isomerized to the pure *E* isomer by treatment with sodium in refluxing methanol. Vinyl iodide **28** was then submitted to Sonogashira coupling with TMS-acetylene[24] to produce the free enynol **29** in 74% yield; subsequent TBS protection followed by cleavage of the TMS group from the terminal triple bond with K_2CO_3 in methanol then gave the desired enyne **24**.

The Carreira alkynylation[10] of aldehyde **23** with enyne **24** gave the desired propargylic alcohol **25** in moderate isolated yields of up to 50% but with excellent stereochemical purity (dr > 95:5) (Scheme 3). The reaction proved to be scale-dependent, and yields declined significantly below 50% on scales larger than 1.5 g of **23**. Gratifyingly, the subsequent PMB cleavage and *syn*-selective reduction of the triple bond with a mixture of Zn(Cu/Ag), water, and methanol in the presence of TMSCl[25] proceeded smoothly to furnish the free trienediol **26** in 64% overall yield (from **25**). Care had to be taken in the reduction step for the TMSCl to be of high quality and free of traces of HCl in order to avoid loss of the TBS-group. The conversion of diol **26** into the primary tosylate followed by S_N2 displacement with iodide and protection of the secondary hydroxy group as a TES ether then gave the desired iodide building block **9** in excellent overall yield (87% for the three-step sequence from free trienediol **26**). The total yield for the synthesis of **9** from *S*-glycidol (11 steps) was 8%.

Initial experiments on the Suzuki coupling between vinyl iodide **8** and the ate complex derived from iodide **9** via iodine−lithium exchange and reaction with 9-methoxy-BBN at −78 °C (Scheme 5) were conducted with Cs_2CO_3 as the base

Scheme 5. Building Block Assembly and Endgame for the Synthesis of 3



and gave the desired coupling product **30** in 66% yield. While, in principle, this outcome appeared acceptable, further investigation of the reaction conditions revealed that the use of Tl_2CO_3[26] instead of Cs_2CO_3 led to improved yields of 85−99%. Interestingly, TlOEt, which has been successfully employed as a base for Suzuki cross-couplings in other

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cases,[27] delivered **30** only in 25% yield (still impure), although TLC had indicated rapid, complete conversion of starting material. Different methods were then investigated to induce the selective cleavage of the secondary TES ether without loss of the TBS group, including PPTS/MeOH, AcOH/THF/H_2O, and HF·pyridine. Of these, treatment of **30** with PPTS proved to be the most practical, since the reaction proceeded at a reasonable rate and with good selectivity. While AcOH/THF/H_2O was also selective, the reaction was slower and did not reach full conversion; HF·pyridine led to partial concomitant cleavage of the primary TBS ether. As the TMS group on the triple bond was unaffected by PPTS/MeOH, this group was removed prior to TES ether cleavage by treatment of **30** with K_2CO_3 in methanol. Subsequent TES ether cleavage then provided the free alcohol **31** in 72% overall yield (from **30**). The completion of the carbon framework of the salarin macrocycle involved two-carbon homologation of **31** into ester **33** by stannylcupration of the terminal triple bond[28] and subsequent Stille coupling with (*Z*)-methyl-2-iodoacrylate (**32**). Ester **33** was obtained in 68% overall yield from **31** with an *E*/*Z* ratio about the C4−C5 double bond of ca. 18/1. Ester saponification with TMSOK in Et_2O[29] provided the corresponding carboxylic acid (**7**), which proved to be unstable on silica gel and, therefore, was directly submitted to macrocyclication under Shiina conditions.[30] The macrocyclization gave a 65% yield of a ca. 9/1 mixture of the desired macrolactone **34** and a major impurity, which we assume to be the C2−C3 *E* isomer of **34**. Unfortunately, rigorous purification of this mixture was not possible due to partial decomposition during purification by flash chromatography. Stability problems were also encountered for all products downstream of **34**; as a consequence, these materials were all obtained as isomeric mixtures, and these are what the yields reported in Scheme 5 refer to. Partial deprotection of **34** with buffered TBAF followed by EDCI/DMAP-mediated esterification of the resulting primary alcohol with caprylic acid and subsequent removal of the SEM group with BCl_3·SMe_2 then furnished **35** as the precursor for the final carbamoylation reaction. Macrolactone **35** could be obtained in pure form after purification by RP-HPLC in 14% yield for the three-step sequence from **34**. Finally, reaction of **35** (non-HPLC purified) with in situ generated acetylisocyanate[9] installed the acetylcarbamate side chain in high yield. Pure **3** was obtained by RP-HPLC; however, due to the stability problems during the purification, only 0.2 mg of **3** was ultimately obtained from 1.6 mg of the original mixture of isomers.

Using the HPLC-purified macrolactones **35** and **3**, we have attempted to assess the stability of these compounds in pH7 phosphate buffer solution by means of RP-HPLC (see the Supporting Information). While the interpretation of these experiments is not entirely unambiguous, due to the formation of precipitates upon dilution of the respective DMSO stock solutions with phosphate buffer (100-fold dilution; nominal final concentration of 9 and 8 μM for **3** and **35**, respectively), the data strongly suggest that both compounds are unstable and at rt disappear with a half-life of less than 24 h. If such stability issues also exist for the natural product salarin C (**1**) how this would affect the interpretation of the biological data obtained for the compound remains to be determined.

In summary, we have elaborated a convergent strategy for the synthesis of dideoxysalarin C (**3**) that is based on alkyl iodide **9** and vinyl iodide **8** as key building blocks. Linking **8** and **9** by Suzuki coupling and macrocyclic ring closure by Shiina macrolactonization provided efficient access to the macrolactone core structure of **3**. All subsequent steps were hampered by the instability of intermediates, which also prevented their rigorous purification by conventional silica gel chromatography.[31] Independent of the question if **3** could, in fact, be converted into the natural product salarin C (**1**) in a selective fashion, our data may indicate that any practical approach toward the total synthesis of **1** should minimize the number of steps that have to be carried out after macrocycle formation.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03422.

Synthetic procedures, complete analytical data, and ^1H and ^{13}C NMR spectra for all new compounds. Description of the stability experiments with **35** and **3** and associated HPLC traces (PDF)

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Notes

The authors declare no competing financial interest.

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(19) Parameters such as the time of exposure to base upon workup, reaction time, and the contact time with silica gel during purification were carefully optimized for the reaction. The optimized procedure included a fixed reaction time of 30 min, filtration of the reaction mixture through Celite, and rapid purification on a short flash column (after solvent removal). Aldehyde **23** was then immediately used in the next step. On the basis of NMR analysis of decomposed batches of **23**, the double bond appeared to have migrated into conjugation with the carbonyl group, and this may have been associated with *E*/*Z* isomerization. However, the exact nature of the decomposition products has not been investigated. We have also prepared the TBS (instead of SEM)-protected variant of **22**, but oxidation of this alcohol delivered the corresponding aldehyde only in low yields, presumably due to TBS migration to the primary hydroxy group before oxidation.
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(31) Interestingly, Schäckermann and Lindel noted that their salarin C fragment **4** was stable in chloroform solution in the presence of air and light, in contrast to salarin C (**1**) itself (ref 6). They conclude that this "makes it likely that additional structural features of salarin C (**1**) contribute to its instability". This is in line with our observation that the pronounced instability of intermediates only surfaced after macrolactone formation.

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