Organic LETTERS

Letter

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Radical Approach to the Chiral Quaternary Center in Asperaculin A: Synthesis of 9-Deoxyasperaculin A

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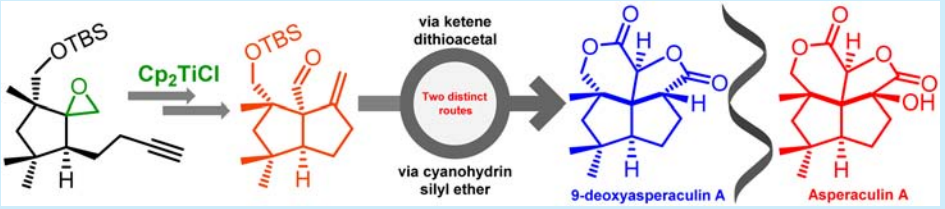
Supporting Information



ABSTRACT: Diastereoselective approaches toward the synthesis of a marine-derived sesquiterpenoid fungal metabolite, asperaculin A, are delineated, combining step economy and simplicity. Two distinct lactonization sequences from a common intermediate led to the first synthesis of 9-deoxyasperaculin A, a novel dioxa[5.5.5.6]fenestrane, in 14 steps (16% overall yield) and 16 steps (18% overall yield), respectively. [2,3]-Wittig−Still rearrangement and Ti(III)-mediated epoxide opening−cyclization were employed as some of the key steps for the stereoselective generation of the vicinal all-carbon quaternary centers of the target molecule.

Terpenoids belong to a major class of organic compounds produced by varieties of natural sources with wide-ranging biological activity profiles extensively chronicled in many traditional, folk, as well as modern medicines.[1] A large repertoire of biologically active and structurally diverse terpenoids have been isolated from myriad marine organisms.[2] The marine-derived fungus *Aspergillus aculeatus* is a rich source of various natural products of medicinal importance.[3] A sesquiterpenoid lactone, asperaculin A (**1**, Figure 1), was isolated from the mycelial extract of *A. aculeatus* (CRI 323-04) in 2011.[3]

The structure of asperaculin A was elucidated with the aid of high-field NMR experiments which revealed a novel dioxa[5.5.5.6]fenestrane framework[4] decorated with six stereogenic centers, including two vicinal all-carbon quaternary centers and the C_9-heteroquaternary center. Structurally, asperaculin A (**1**) is related to penifulvin A (**2**, Figure 1),[5] which contains a dilactone fenestrane, which differs in its transposition of the δ-lactone ring and the presence of an extra hydroxyl group at C_9 in asperaculin A. Asperaculin A did not exhibit any cytotoxic activity at 50 μg/mL concentration against HepG2, MOLT-3, A549, and HuCCA-1 cancer cell lines.

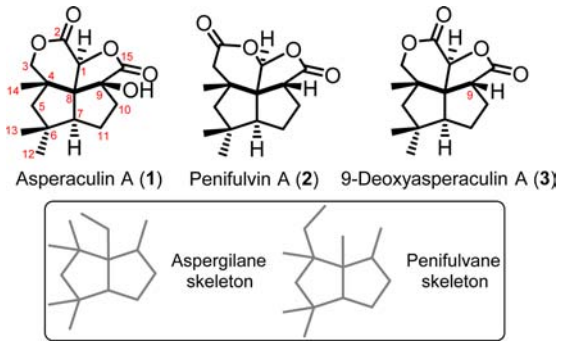


Figure 1. Structures of asperaculin A (**1**), penifulvin A (**2**), and 9-deoxyasperaculin A (**3**) with their novel skeletons.

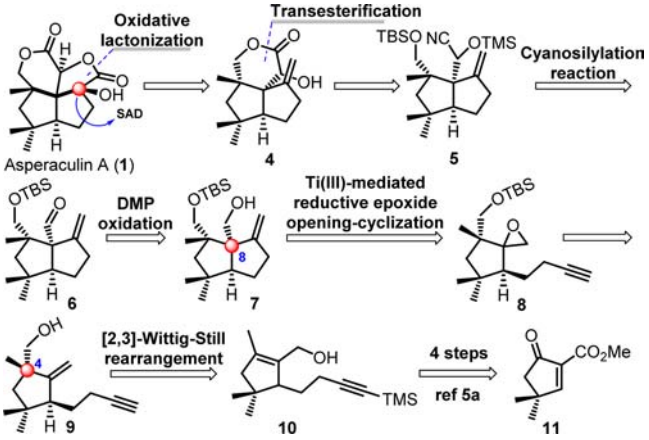
Since its isolation, no total synthesis of this molecule has been reported to date. Mehta et al. devised a strategy to construct its fenestrane framework that utilized an iterative Pauson−Khand reaction starting from a glycerol-derived solketal.[6] After successful completion of the total synthesis of penifulvin A,[5a] we next undertook the challenge to synthesize asperaculin A (**1**) and disclose, herein, the first total synthesis of its deoxy congener, (±)-9-deoxyasperaculin A (**3**).

Our strategy toward the synthesis of asperaculin A (**1**) would involve a crucial [Cp_2TiCl]-mediated reductive epoxide cleavage and radical cyclization[5a,b,7] to install the C_8-quaternary stereogenic center at the heart of the fenestrane scaffold. Retrosynthetically, we envisioned asperaculin A (**1**) arising from the advanced intermediate **4** through Sharpless asymmetric dihydroxylation (SAD)[8] followed by an oxidative lactonization of the resulting diol (Scheme 1). The latter was planned to be derived from the cyanohydrin **5** via acid hydrolysis. Cyanohydrin **5** would be obtained from aldehyde **6**, which in turn, would be accessed from the epoxide **8** through a Ti(III)-mediated reductive epoxide-opening−cyclization protocol followed by oxidation of the resulting primary alcohol **7**. Construction of epoxide **8** would

Received: December 26, 2016
Published: January 20, 2017

DOI: 10.1021/acs.orglett.6b03854
Org. Lett. 2017, 19, 682−685

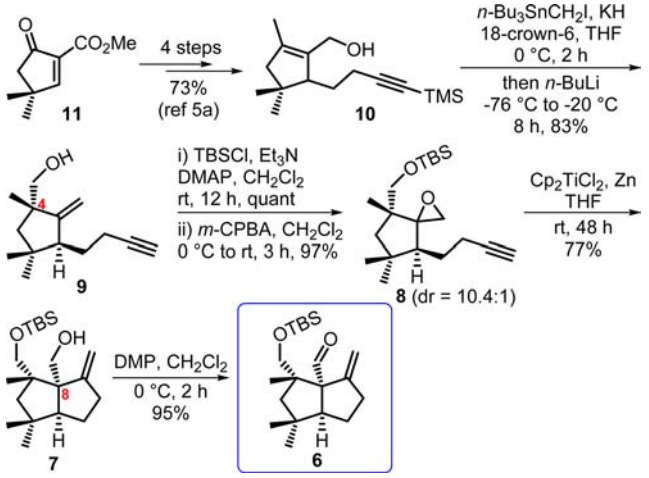
Scheme 1. First-Generation Retrosynthetic Strategy for the Synthesis of Asperaculin A (1)



require one hydroxyl protection with subsequent epoxidation of the properly functionalized homoallylic alcohol **9**. It was planned to assemble **9** from the allylic alcohol **10** via a [2,3]-Wittig–Still rearrangement.[9] The latter would be accessed from a known substrate **11**[5a] using an already established protocol.

The synthesis of the bicyclic aldehyde **6**, shown in Scheme 2, commenced from the allylic alcohol **10**, which was readily

Scheme 2. Synthesis of the Bicyclic Aldehyde 6

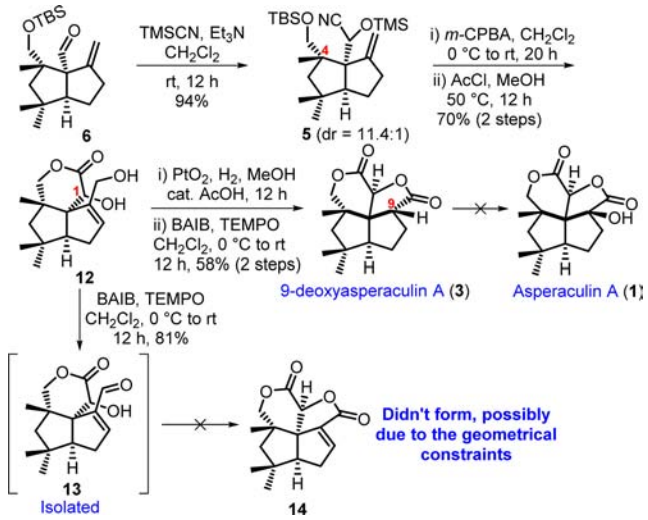


prepared from **11** in a four-step sequence following our previously reported procedure.[5a] Next, the major goal was to synthesize the homoallylic alcohol **9** via a [2,3]-Wittig–Still rearrangement[9] (Scheme 2). We used the KH/18-crown-6 combination to alkylate the allyl alcohol **10** with *n*-Bu_3SnCH_2I, and this was followed by the rearrangement with *n*-butyllithium in one pot.[9b] During the course of the reaction, the TMS group was also deprotected,[9a] ultimately leading to the formation of **9** in 83% of overall yield. The relative stereochemistry in **9** was anticipated due to the steric restrictions offered by the alkynyl chain at C_7 (asperaculin A numbering) during the rearrangement.

Having successfully constructed the C_4-quaternary center, we turned our attention toward installation of the adjacent C_8-quaternary center (asperaculin A numbering) present in the target molecule **1**. For that, the protection of the primary hydroxyl group in **9** by TBS followed by epoxidation with *m*-CPBA led to **8** (10.4:1 dr by ^{1}H NMR, see the Supporting Information), which set the stage for implementation of our crucial epoxide-opening–cyclization step. Reductive epoxide cleavage mediated by [Cp_2TiCl] (generated in situ from Cp_2TiCl_2 and activated Zn dust) followed by 5-*exo*-*dig* cyclization onto the pendant alkyne moiety successfully gave rise to the bicyclic framework with a *cis* ring junction in **7** (Scheme 2) in 77% yield.[5a] NOE experiments were used to establish the relative stereochemistries of the substituents on the bicyclic backbone of **7** (see the Supporting Information). Next, oxidation of the primary hydroxyl group with DMP (Dess–Martin periodinane) afforded the target aldehyde **6** in 95% yield.

After successful installation of the two vicinal all-carbon quaternary centers present in asperaculin A (**1**) in a highly stereoselective manner, our next task was to install the secondary hydroxyl group at the C_1-carbon in **4**. A variety of reagent combinations such as TMSCN–ZnI_2, TMSCN–NMO, TMSCN–DMSO, and catalytic cyanosilylation with phosphonium salt were used, but none was effective. Finally, the cyanosilylation reaction with TMSCN–Et_3N[10] was found to provide the best method for converting **6** to the cyanohydrin silyl ether **5** in 94% yield (Scheme 3, 11.4:1 dr by ^{1}H NMR; see the Supporting Information).

Scheme 3. First-Generation Approach to Asperaculin A (1) and Completion of the Synthesis of 9-Deoxyasperaculin A (3)



To construct the δ-lactone ring in one step from **5**, we investigated various conditions for the hydrolysis of the cyanide group as well as deprotection of the silyl ethers. However, we were unable to realize our goal due to unwanted acid-mediated isomerization of the double bond present in **5** under the reaction conditions. That forced us to divert from our proposed route and functionalize the double bond first as an epoxide. The epoxidized product was then subjected to hydrolysis using AcCl–MeOH at 50 °C and led to a transesterification reaction with the TBS-deprotected primary alcohol at C_3 to provide the required δ-lactone with concomitant hydrolysis of the epoxide ring to give an allylic alcohol moiety furnishing **12** with an overall yield of 70% (Scheme 3). The stereostructure of **12** was confirmed on the basis of the NOE experiments (see the Supporting Information).

Next, we focused our attention on formation of the γ-lactone ring prior to installing the C_9-hydroxyl group. It was anticipated

DOI: 10.1021/acs.orglett.6b03854
Org. Lett. 2017, 19, 682–685

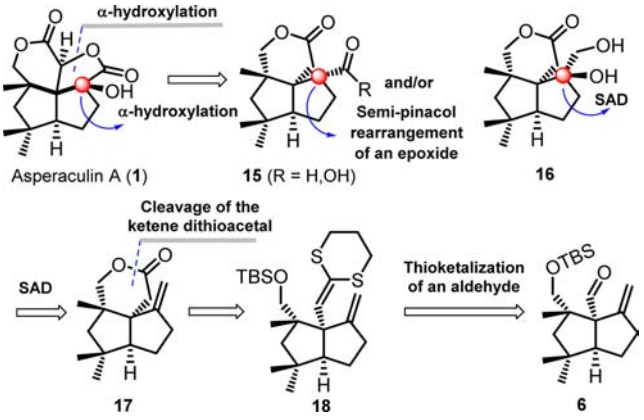
that the α,β-unsaturated γ-lactone **14** would provide a facile access to the desired C_9-hydroxyl group present in asperaculin A. Unfortunately, the synthesis of **14** proved to be very difficult. Attempted oxidative lactonization of **12** by $PhI(OAc)_2$–TEMPO[11] provided only the unsaturated aldehyde **13** with no trace of **14**, which might be due to the geometrical constraints preventing the functional groups coming close for the desired cyclization (Scheme 3). Use of other reagents like MnO_2, PCC, TPAP-NMO, and DMP gave only mixtures of overoxidized products. DDQ also provided **13**, but it took longer to complete the reaction. Further oxidation of the aldehyde **13** to its corresponding acid derivative also did not help us access the cyclized product **14**.

Attempts were also made to install first the C_9-hydroxyl group on **12** by utilizing Sharpless asymmetric dihydroxylation (SAD), oxymercuration–reduction, and Mukaiyama hydration. Unfortunately, all of these attempts resulted only in failures. Then a straightforward transformation was attempted involving hydrogenation of the double bond with PtO_2–H_2, which freed the molecule from geometric constraints leading to a successful oxidative lactonization in the following step with $PhI(OAc)_2$–TEMPO[11] to furnish 9-deoxyasperaculin A (**3**) having the elusive dioxa[5.5.5.6]fenestrane framework of the target (Scheme 3). Its formation in the desired stereochemistry was confirmed by NOE experiments (see the Supporting Information).

Next, we examined a variety of reagents and conditions such as the Davis reagent,[12] MoOPH,[13] Rubottom oxidation,[14] LDA–O_2–$P(OMe)_3$,[15] and asymmetric dihydroxylation of enol ether[16] to introduce the C_9 hydroxyl group in **3** but were unable to find any trace of asperaculin A (**1**).

Failure in the installation of the C_9-hydroxyl group prompted us to devise an alternative route to the target. The first-generation strategy, however, provided a facile workbench from where to develop our second-generation approach (Scheme 4). It was

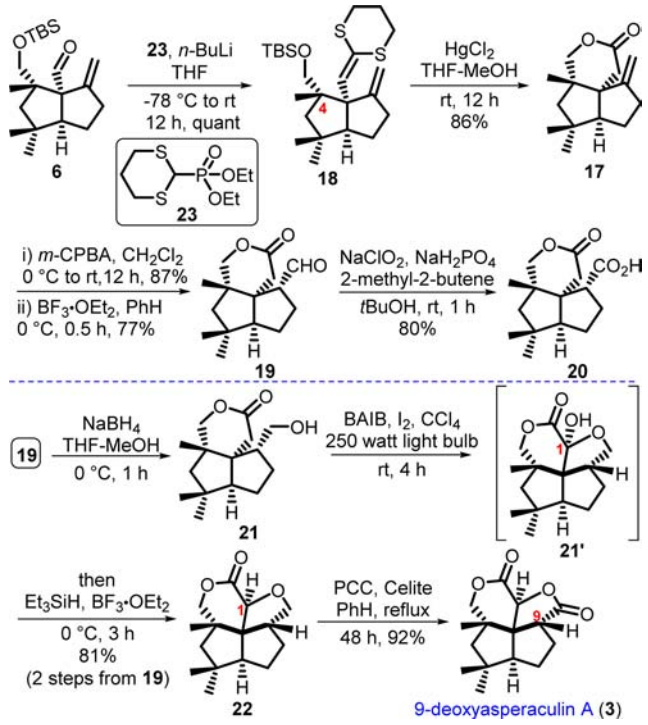
Scheme 4. Second-Generation Retrosynthetic Strategy of Asperaculin A (1)



assumed that the intermediates **15** and/or **16** derived from the tricyclic lactone **17** could lead to **1** through any late-stage α-hydroxylation, simultaneously at C_1 and C_9 (asperaculin A numbering). The δ-lactone ring in **17** was planned to be assembled through a cleavage of the ketene dithioacetal **18** which, in turn, could be traced back to the same aldehyde **6** (Scheme 2).

The starting point of the second-generation approach, depicted in Scheme 5, was the preparation of the tricyclic

Scheme 5. Second-Generation Approach to Asperaculin A (1) and Completion of the Synthesis of 9-Deoxyasperaculin A (3)



lactone **17** from an already synthesized aldehyde **6**. Aldehyde **6** was transformed into the ketene dithioacetal **18** using 1,3-dithiane-2-diethyl phosphonate (**23**) in quantitative yield.[17] Next, cleavage of the ketene dithioacetal in the presence of $HgCl_2$ in MeOH[17] led to an in situ formation of the methyl ester which underwent a facile lactonization with the TBS-deprotected C_3 primary alcohol, furnishing the desired δ-lactone **17** in 86% yield. The structure of **17** was confirmed by 2D-NMR and NOE studies (see the Supporting Information).

We then attempted stereoselective dihydroxylation of the double bond present in **17** using Sharpless asymmetric dihydroxylation (SAD), OsO_4–NMO, OsO_4–Py, OsO_4–DMAP, and K_2OsO_4–NMO, but none of them were found to be effective. To overcome the problem, compounds **19** and **20** were synthesized from **17** via epoxidation of the exocyclic double bond and $BF_3{\cdot}OEt_2$-mediated semipinacol rearrangement (to get the required aldehyde **19**)[5a] followed by oxidation to acid derivative **20**[5a] (Scheme 5). Unfortunately, simultaneous α-hydroxylation of the C_1 and C_9 centers in **19** and **20**, as per our second-generation retrosynthetic strategy (Scheme 4), using Davis reagent,[12] MoOPH,[13] Rubottom oxidation,[14] and LDA–O_2–$P(OMe)_3$,[15] failed to provide the desired product. Copper acetate promoted oxidation and Fe(PDP)-catalyzed carboxylic acid directed $C(sp^3)$–H oxidation[18] of **20** also failed.

Overall, fixation of the C_9-hydroxyl group proved to be much more challenging than anticipated, which prompted us to explore the synthetic feasibility of this second-generation approach toward the synthesis of 9-deoxyasperaculin A (**3**). Due to the difficulties associated with the carboxylic acid directed C–H oxidation, it was decided to begin with its alcohol precursor **21**. 9-Deoxyasperaculin A (**3**) was envisaged as being accessible from the alcohol **21** via a one-pot $C_1(sp^3)$–H oxidation–cycloetherification step followed by the oxidation of the resulting cyclic ether **22**. To realize the plan, aldehyde **19** was first selectively reduced to the alcohol **21**. The crude alcohol was next

DOI: 10.1021/acs.orglett.6b03854
Org. Lett. 2017, 19, 682–685

treated with $PhI(OAc)_2$ and I_2 under irradiation[19] to promote 1,5-hydrogen atom abstraction by the alkoxy radical, which unexpectedly afforded an overoxidized product **21′** that was deoxygenated[20] at C_1 (asperaculin A numbering) in the same pot leading to the formation of the desired tetracyclic ether derivative **22** with an overall yield of 81% (Scheme 5).

The structure of **22** was confirmed by 2D-NMR and NOE studies (see the Supporting Information). Use of RuO_4 (generated in situ) and CrO_3–Py failed to provide the desired γ-lactone, but PCC adsorbed on Celite[21] furnished the desired 9-deoxyasperaculin A (**3**) in 92% yield. The spectroscopic data of 9-deoxyasperaculin A (**3**) obtained from this approach were in full accord with the previous one.

In conclusion, we have completed the first total synthesis of 9-deoxyasperaculin A (**3**) in racemic form through two divergent strategies from a suitably functionalized common aldehyde intermediate **6** in 14 steps (16% overall yield) and 16 steps (18% overall yield), respectively. The two vicinal all-carbon quaternary centers were assembled in a highly regio- and stereoselective manner employing a Ti(III)-mediated reductive epoxide opening–cyclization protocol and [2,3]-Wittig–Still rearrangement, respectively. Our synthetic schemes also relied on the utilization of a cyanohydrin silyl ether (first approach) and ketene dithioacetal (second approach) to install the δ-lactone ring. Also highlighted is the power of a late-stage $C(sp^3)$–H oxidation followed by an oxidation of the cyclic ether (second approach) and an oxidative lactonization protocol (first approach) to install the γ-lactone moiety present in the target molecule. Further investigations on the substrate scope to complete the total synthesis of asperaculin A (**1**) are correctly underway and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03854.

Experimental procedures and characterization data for new compounds described herein (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We gratefully acknowledge financial support by SERB, New Delhi, for a JC Bose Fellowship (T.K.C., SERB No. SR/S2/JCB-30/2007) and CSIR, New Delhi, for a research fellowship for D.D. We are also thankful to SAIF, CSIR-CDRI, and the Department of Organic Chemistry, IISc, for providing the spectroscopic and analytical data.

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DOI: 10.1021/acs.orglett.6b03854
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