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Total Synthesis of Archazolid F

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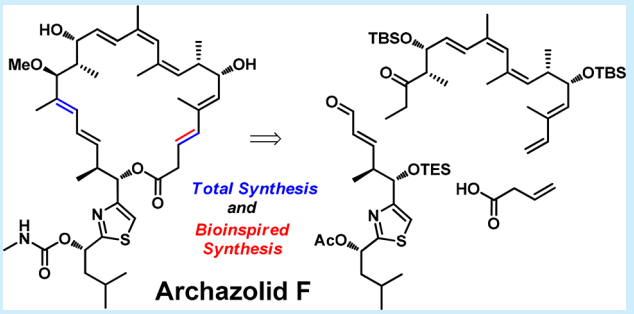
Supporting Information

ABSTRACT: A partial bioinspired as well as the total synthesis of archazolid F, a highly potent V-ATPase inhibitory, antiproliferative polyketide macrolide, is described. Key features of the synthetic routes include a highly stereoselective aldol condensation of two elaborate fragments and macrocyclizations either by a Shiina macrolactonization or by a challenging RCM reaction of an octaene substrate. The syntheses unequivocally confirm the full architecture of this very scarce archazolid.



The myxobacterial polyketide macrolides archazolids A (**1**) and B (**2**, Figure 1) demonstrate extremely potent antiproliferative activities based on selective inhibition of functional subunit c vacuolar-type ATPases (V-ATPases).[1,2] On a molecular level, this selective noncovalent interaction is increasingly well understood by cross-linking, mutagenesis, and EPR studies in combination with limited SAR data and a modeling study.[2,3] More recently, archazolid V-ATPase inhibition has emerged as a novel strategy in anticancer therapy.[4] The archazolids abrogate tumor metastasis,[5a] lead to impaired cathepsin B activation,[5b] modulate anoikis resistance,[5c] overcome trastuzumab resistance of breast cancers,[5d] augment cancer therapy by blocking iron metabolism,[5e] and sensitize tumors in the context of the MDM2 antagonist nutlin-3a.[5f] However, their further advancement is severely hampered by their low natural supply, rendering total synthesis of high importance to resolve the supply issue and enable further SAR exploration. Thus far, one total synthesis of archazolid A[6a] and two syntheses of archazolid B[6b,c] as well as several fragment syntheses of 2,3-dihydroarchazolid B[6d,e] have been reported.[6f] In all previous total syntheses of archazolids, the ring closure of the macrocycle was critical. In the total synthesis of archazolid A (**1**) in our group, the macrocyle was closed by a somewhat unreliable HWE reaction along the C2−C3 bond.[6a] In alternative strategies for total syntheses of archazolid B (**2**), a very innovative but only moderately yielding relay-RCM reaction along the C20−C21 was accomplished by the Trauner group,[6b] while an alternative Heck macrocyclization along the C19−C20 bond gave a mixture of isomers in our approach.[6c] Despite these impressive advances, the development of an alternative strategy remains an important research goal, particularly with respect to a more efficient macrocyclization and direct applicability to useful analogue synthesis.

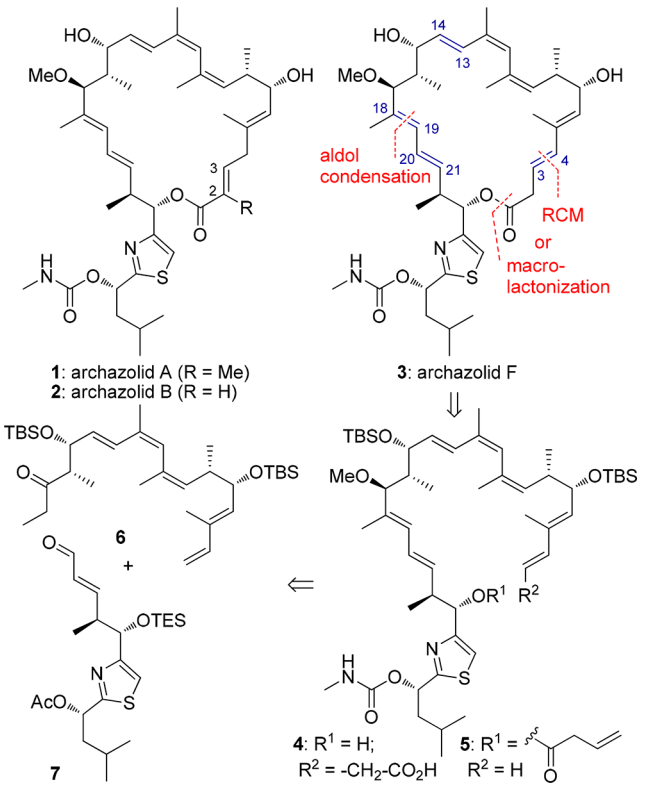


Figure 1. Archazolids, an emerging class of potent V-ATPase inhibitory anticancer drugs: retrosynthesis of archazolid F.

More recently, archazolid F (**3**), has been discovered as an extremely scarce but more potent natural derivative that bears a 3,4- instead of the 2,3-olefin substructure present in archazolid B (Figure 1).[7]

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Herein, we report the first total synthesis of archazolid F (**3**) that unequivocally confirms the full 3D architecture of this most potent and least abundant archazolid based on a novel, improved strategy that will be directly applicable for useful analog synthesis.

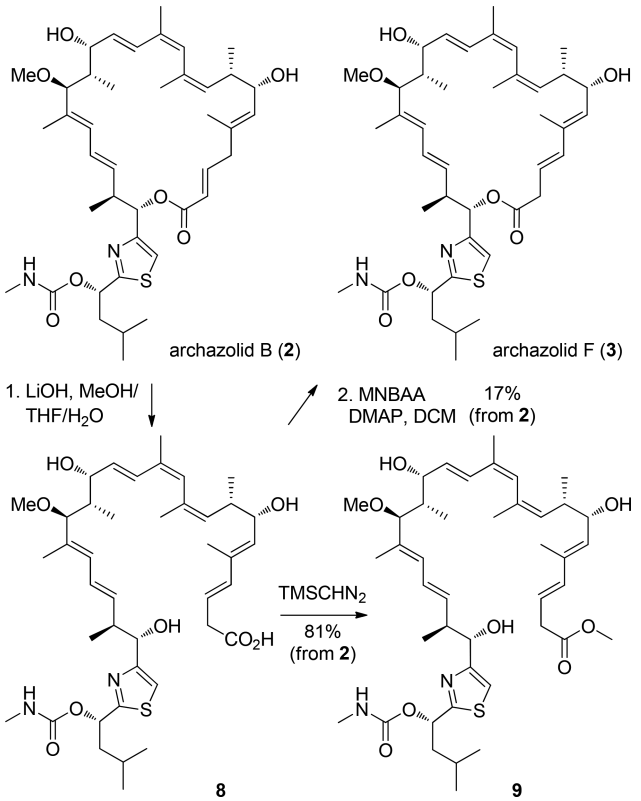
On the basis of existing SAR data available so far in combination with the in silico model for the target−inhibitor interactions,[3a−c] it was rationalized that the C4−C18 part would be critical for target interaction, while more flexibility was suggested for the southern region. Consequently, our synthetic strategy was based on a separate formation of this northern pharmacophore **6** and its connection to the southern building block **7** (Figure 1). For fragment union, an adventurous stereoselective propionate aldol condensation was envisioned that would also enable a direct modulation of the hydroxylation and oxidation pattern in the northwestern region.[3a] Given the existing limitations of the reported archazolid macrocyclization, two alternative strategies were planned, either by a more conventional macrolactonization involving a compound of type **4** or a more challenging RCM reaction of an octane substrate (**5**).

In order to evaluate the first macrocyclization strategy, we turned our attention to a bioinspired partial synthesis of archazolid F. In contrast to common polyketide biosynthesis, the olefins in the northern and eastern part of the archazolids are not situated between the acetate building blocks but within these units,[1a] suggesting an isomerization during biosynthesis. This is further corroborated by the co-occurrence of isomers B (**2**) and F (**3**), which may suggest that an isomerization may occur during the biosynthesis of archazolid F. Inspired by this observation, in combination with a related double-bond shift previously observed in our group,[8] we turned our attention to a direct conversion of archazolid B to F. Consequently, as shown in Scheme 1, we first opened archazolid B (**2**) to ring-opened seco-acid **8**. Gratifyingly, a complete double-bond migration was observed by use of LiOH (Scheme 1), thus confirming our bioinspired design. After some experimentation, the desired macrolactonization could also be accomplished under Shiina conditions, giving archazolid F in a direct process and without a need to protect the two additional hydroxyl groups. However, the obtained yields remained low (17%). In contrast, a direct esterification to **9** with $TMSCHN_2$ (81%) proceeded in good yields.

Therefore, we turned our attention to an apparently more challenging RCM approach.[9] As shown in Scheme 2, synthesis of the required northern fragment **6** was based on reliable aldol methodology and olefination reactions, previously established for related systems in our group.[6a,c]

An initial Wittig reaction of commercial aldehyde **10** gave diene **11**,[10] and the corresponding highly volatile aldehyde **12**, obtained by DIBALH reduction of the ester and allylic oxidation (MnO_2), was elongated by a boron mediated *anti*-aldol reaction with lactate derived ethyl ketone to give the aldol product **13** with excellent selectivity following a procedure originally reported by Paterson.[6a,c,11] After protection as a TBS ether (**14**) and removal of the chiral auxiliary involving $LiBH_4$ reduction and periodate cleavage, the derived aldehyde **15** was homologated by a Still−Gennari olefination with **16** to give ester **17** in high yield and selectivity (90%, dr > 20:1). In an analogous fashion, aldehyde **18**, readily obtained by DIBALH reduction and allylic oxidation, was homologated with **16** installing the (*Z*,*Z*)-diene **19**, likewise in excellent yield and selectivity (98%, dr > 20:1). Finally, an HWE reaction of

Scheme 1. Synthesis of Archazolid F by a Shiina Macrolactonization of a Protective Group Free Precursor (8)



derived aldehyde **19** (96%, two steps) set the required (*Z*,*Z*,*E*)-triene moiety with high stereocontrol and again with excellent degrees of conversion. The corresponding aldehyde **20** was then homologated by an Ipc-boron aldol reaction[11] giving *syn*-aldol product **21** in a reliable fashion which was protected as a TBS ether to give the desired northern fragment (**6**). This route proved reliable, rapid, and well scalable, enabling a multigram access in 27% overall yield.

In contrast to previous routes,[6] a shorter and more concise entry into the southern fragment **7** was realized. As shown in Scheme 3, this was based on a Grignard addition of commercial thiazole **22** to isovaleraldehyde.[12] After conversion of the resulting alcohol **23** into the dicarbonyl derivative **24**, a selective Brown crotylation[6a−c] of the aldehyde functionality set the required two vicinal stereogenic centers. After protection of the derived hydroxyl group, ketone **25** was reduced stereoselectively with the CBS reagent, and the resulting alcohol was protected as an acetate (**26**). Finally, an efficient cross-metathesis with acrolein completed the synthesis of southern building block **7**.

While only a few stereoselective propionate aldol condensations have been reported in complex target synthesis,[13a−e] this limited precedence with less elaborate substrates suggested that a base-mediated elimination may lead preferentially to the required *E*-isomer, independent of the initial relative configuration.[13] As shown in Scheme 4 judicious choice of the base for the initial coupling were critical for useful degrees of conversion. Finally, good yields were obtained with uncommon Ph_2NLi,[14] while more conventional bases (LiHMDS or LDA) led to side reactions or lower conversion on a representative test system. Inspired by a

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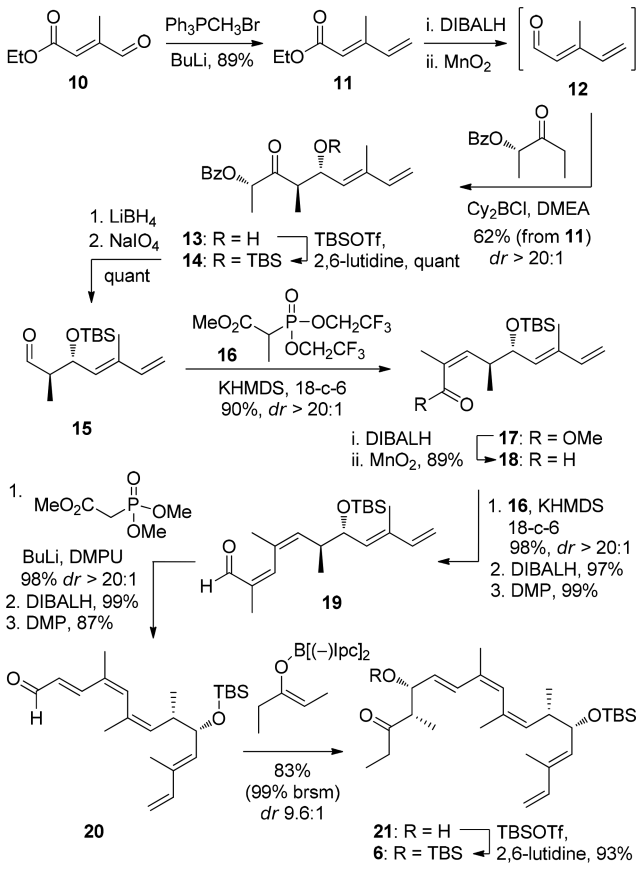
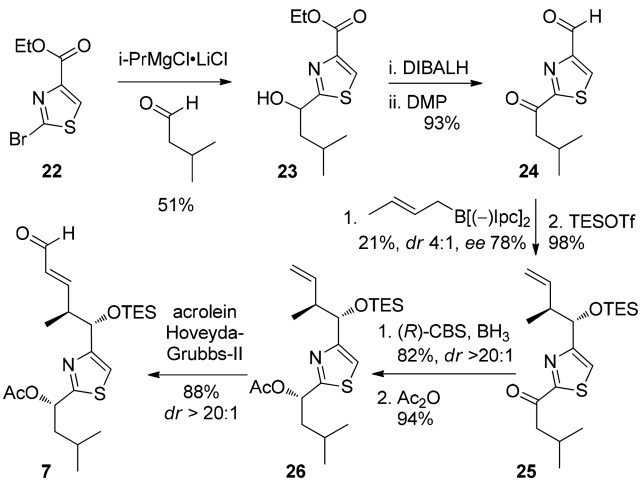
Scheme 2. Synthesis of Northern Fragment 6

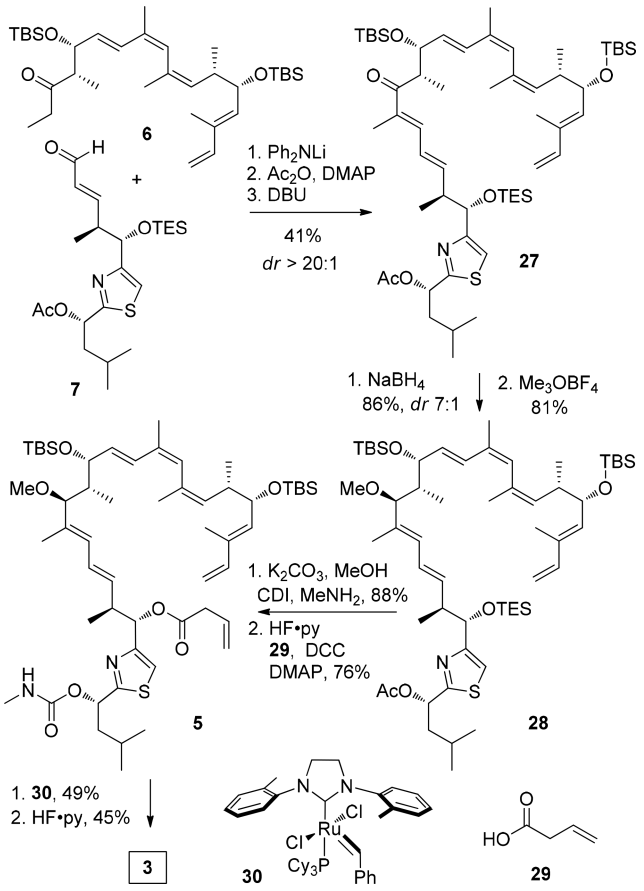


Scheme 3. Concise Synthesis of the Southern Fragment 7



methyl ketone aldol condensation,[6a] an acetate derivative was then submitted to the elimination. Gratifyingly, after careful balancing of the terminal protective group, this conversion proceeded with excellent stereoselectivity to give the desired (*E*)-isomer exclusively, independent of the initial configuration, in a stereoconvergent manner. Following this procedure, desired enone **27** was obtained with complete diastereoselectivity. This enone was then reduced stereoselectively with $NaBH_4$ (dr 7:1),[6b] and methylation of the alcohol set the required C15−C17 region **28** in good yields. After acetate saponification and carbamate installment, the butenoic acid **29** was attached after TES cleavage to access key intermediate **5**

Scheme 4. Completion of the Total Synthesis of Archazolid F



for the pivotal RCM reaction. Notably, this polyene containing eight olefinic double bonds presents a highly challenging substrate for this key RCM reaction,[6b,9,15] due to molecular reversibility of the process enabling several competitive side reactions including ring contraction[15a,b,e] or formation of undesired isomers.[15b] After considerable experimentation with suitable test systems, it was found that the cyclization could indeed be realized with very unusual catalyst **30**[16] to give the macrocyclic core in useful yields (49%) that compare favorably to the results of reported procedures.[6] Lower degrees of selectivity and conversion were obtained with all other catalysts studied (i.e., Grubbs II, nitro-Grela catalyst). Finally, completion of the total synthesis of archazolid F was achieved by global deprotection using HF/pyr. The analytical data of synthetic archazolid F, obtained either by semi- or total synthesis, were identical and in agreement with the data of an authentic sample,[7,17] thus confirming its full architecture.

In summary, we have reported a bioinspired partial synthesis and the total synthesis of archazolid F (**3**). These syntheses unequivocally confirm the full architecture of this most potent and least abundant archazolid. The partial synthesis pursued a bioinspired approach. It involved a remarkable double-bond isomerization, which should be further analyzed and may be effectively utilized in other ventures. The total synthesis, in turn, was inspired by a pharmacophore analysis and relies on two main fragments, a northern and a southern building block. Key features include a scalable synthesis of the northern region involving reliable olefination and aldol methodology and an improved preparation of the southern fragment as well as the

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connection of these elaborate fragments by an adventurous highly stereoselective propionate aldol condensation. Finally, macrocyclization was accomplished by an RCM reaction of a challenging octaene precursor. Best results were obtained with a very uncommon and underutilized catalyst (**30**), which may find further applications in complex target synthesis. These results demonstrate that RCM approaches may be effectively used also for cyclizations of very elaborate polyenes. In addition, the reported protocol for stereoselective propionate aldol condensation may find further applications for connection of complex fragments. This synthesis enhances the supply of archazolid F for further biological evaluation. Finally, the novel synthetic strategy will be directly applicable for useful and simplified analogues by enabling a facile replacement of the biologically presumably less important southern fragment with retention of the northern, synthetically easily available pharmacophore.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03715.

Detailed experimental procedures, characterization, and copies of ^{1}H and ^{13}C NMR spectra of new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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(17) In some cases, the ^{13}C NMR assignment had to be corrected (see the SI). A full spectral data set in two different solvents is provided.

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