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Total Synthesis of Archazolid A

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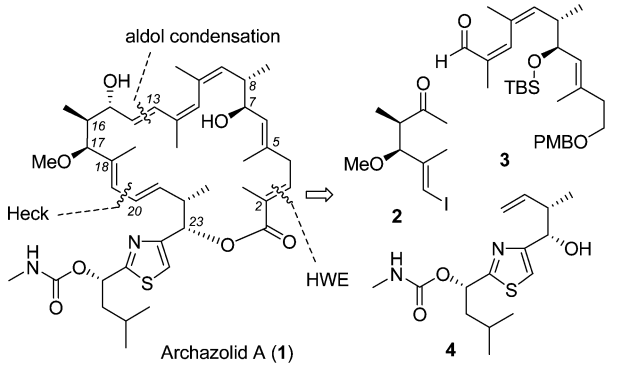
The archazolids are structurally unique macrolides first isolated by Höfle et al. from the myxobacterium *Archangium gephyra*.[1] They display powerful growth-inhibitory activity against a number of murine and human cancer cell lines at subnanomolar concentrations,[1] based on selective inhibition of vacuolar-type ATPases, in vitro[2] and in vivo.[1] These multimeric proton translocating enzymes present important targets from the perspective of medicinal chemistry as their malfunction is associated with various diseases such as cancer, osteoporosis, and renal acidosis.[3] The archazolids bind selectively to the membrane-bound V_o subunit c in a reversible, noncovalent fashion,[2] which adds to the attractiveness for further development. Their unique structures comprise a polyunsaturated 24-membered macrolactone with 8 stereogenic centers and a pendant thiazole side chain at C23. Recently, we proposed a full stereochemical assignment, as indicated in **1** for archazolid A, the most potent archazolid, (Scheme 1), by the use of extensive high-field NMR experiments in combination with molecular modeling and chemical derivatization.[4] Herein, we disclose the first total synthesis of archazolid A (**1**) and establish unequivocally its relative and absolute configuration.

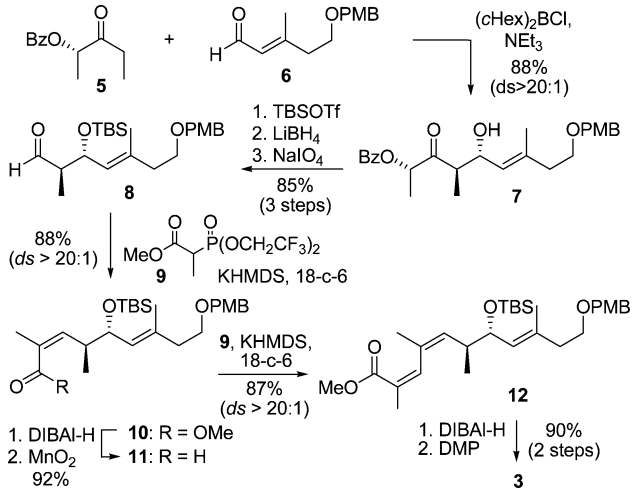
As outlined retrosynthetically in Scheme 1, our synthetic approach relies on assembly of three main building blocks of similar complexity, that is, **2**, **3**, and **4**. The 13*E*-alkene moiety was planned to arise from an aldol condensation between methyl ketone **2** and aldehyde **3**, while a Heck cross-coupling of **2** with alkene **4** was envisioned to deliver the 18*E*,20*E*-diene. In principle, this methodology could be employed to close the macrocycle as an alternative to a Horner−Wadsworth−Emmons macrocyclization or a more conventional Yamaguchi reaction for ring closure, thus offering considerable flexibility in the synthesis. Notably, the modular synthetic approach employed is flexible, highly convergent, and stereocontrolled, and thus offers the potential to provide useful quantities of archazolid A as well as a range of structural derivatives for SAR-studies.[5]

As shown in Scheme 2, our synthesis of the C3−C11 subunit **3** utilizes a boron-mediated Paterson aldol reaction[6] of lactate derived ethyl-ketone **5** with readily available aldehyde **6** to give anti-aldol **7** with very high levels of diastereoselectivity and yield. After TBS protection, aldehyde **8** was then generated by reduction and periodate cleavage (85% from **7**) and subsequently submitted to a Still−Gennari modification of the HWE olefination with phosphonate **9**.[7] By employing KHMDS as the base in combination with 18-crown-6, *Z*-enone **10** was obtained in 88% yield as the only detectable isomer. After conversion of **10** into enal **11** by DIBAl-H reduction and allylic oxidation (MnO_2), the required 11*E*-alkene was installed by another Still−Gennari olefination, proceeding again with very high stereoselectivity (ds >20:1) and yield (87%). The synthesis of **3** was completed in two steps involving ester reduction

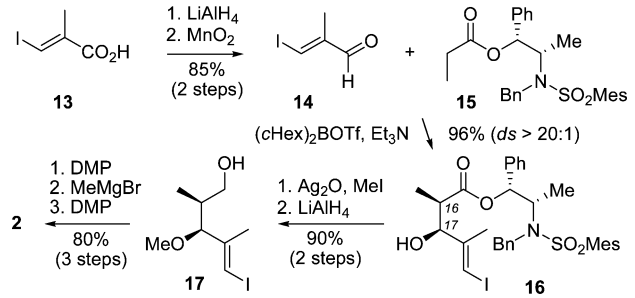
Scheme 1. Retrosynthetic Analysis of Archazolid A



Scheme 2. Synthesis of the C3−C13 Subunit **3**



Scheme 3. Preparation of the C14−C19 Subunit **2**



(DIBAL-H) and oxidation of the resulting primary alcohol with Dess−Martin periodinane.

As shown in Scheme 3, construction of the C14−C19 subunit **2**, starts with the *E*-vinyliodide **13**, which was conveniently prepared by a known method.[8] After conversion to aldehyde **14** (85% yield), the pivotal anti aldol coupling to install the centers at C16 and C17 proceeded with excellent diastereoselectivity and yield (ds >

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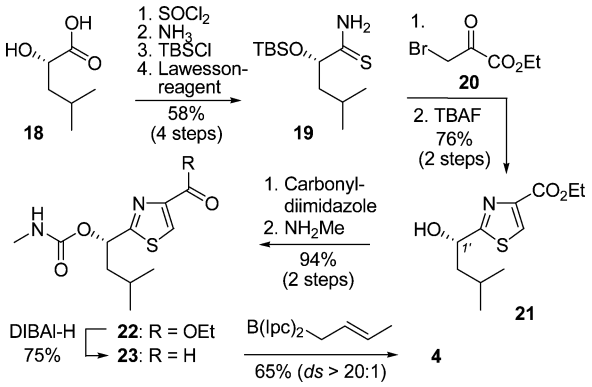
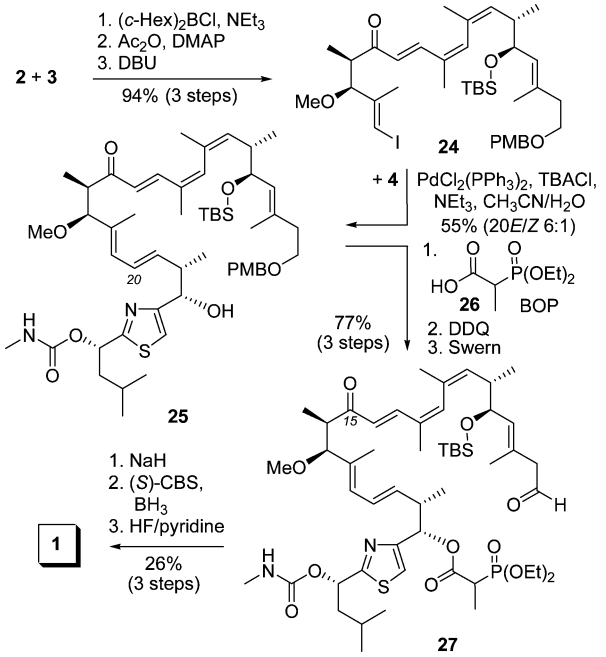
Scheme 4. Assembly of the C20−C1″ Subunit **4**



Scheme 5. Completion of the Synthesis



20:1, 96%) by use of Masamune's chiral ephedrine-derived ethyl ketone.[9] After methylation of the 17-OH of **16** with Ag_2O/MeI, removal of the ephedrine auxiliary was best performed reductively ($LiAlH_4$) to give **17**, which was converted to fragment **2** by DMP-oxidation, addition of MeMgBr and DMP-oxidation in 80% yield over three steps.

Our preparation of the C11−C1″ subunit **4**, as shown in Scheme 4, starts with readily available α-hydroxyacid **18**,[10] which was converted to thioamide **19** in four-steps and 58% yield, by amide formation, treatment with TBSCl and the Lawesson reagent. After cyclization with **20** and liberation of the 1′-hydroxyl with TBAF (76%), the carbamate was introduced in two steps on thiazol **21**[11] by the use of carbonyldiimidazole and trapping of the activated carbamate with methylamine. After DIBAl-H reduction of ester **22** to aldehyde **23**, the desired alcohol **4** was prepared with excellent diastereoselectivity and useful yield (65%) through Brown's asymmetric crotylation protocol.[12]

In a rationale to install the presumably[4] labile (2,5)-enoate unit of archazolid A (Scheme 1) in succeeding reactions, our strategy for fragment union relied on first combining **2** and **3** (Scheme 5). This was accomplished by employing a boron-mediated aldol reaction followed by a two-step elimination to give **24** in 94% yield. Subsequent Heck reaction of **24** with **4** under more conventional conditions, however, gave **25** with only poor *E*/*Z*-diastereoselectivity (∼1.5:1). Gratifyingly, after evaluating different catalysts, additives, and solvents, preparatively useful selectivity (6:1) was obtained, by performing the reaction at 80 °C in the presence of TBACl and H_2O. Notably, this conversion constitutes one of the first examples of controlling the *E*-to *Z*-ratio in a Heck coupling on such an elaborate substrate.[13] After attachment of phosphonate **26** by use of BOP, oxidative removal of the PMB group, and Swern oxidation, the resulting keto-phosphonate **27** was successfully cyclized by employing NaH as base. For the required reduction of the C15-ketone, best results in terms of diastereoselectivity and yield were obtained by use of oxazaborolidine-assisted borane reduction (ds >20:1, 73%).[14] Finally, deprotection with HF/pyridine in THF gave archazolid A (**1**) in 80% yield. The spectroscopic data (^{1}H NMR, ^{13}C NMR) and specific rotation of our synthetic material were in agreement with those published for an authentic sample of archazolid A,[1] thus allowing confident assignment of the relative and absolute configuration of archazolid A and validating our earlier proposal.[4]

In conclusion, this expedient first total synthesis of archazolid A proceeds in 20 steps and 4% overall yield (longest linear sequence) and establishes unequivocally the relative and absolute configuration. Notable features include highly enantio- and diastereoselective anti aldol reactions, an aldol condensation for construction of the delicate (*Z*,*Z*,*E*)-triene-system, an advantageous *E*-selective Heck-coupling on a highly elaborate substrate and a subsequent HWE macrocyclization. Importantly, this modular, convergent synthesis should be amenable to designed analogues of this novel V-ATPase inhibitor, thus enabling extensive exploration of its biological potential.

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Supporting Information Available: Experimental procedures, characterization data, and ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) On large scale, minor amounts of epimerization at C1′ occurred during cyclization. This can be readily remedied by an oxidation−reduction sequence (90%) (see Supporting Information).

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(13) Depending on the conditions also some isomerization along the labile (9*Z*,11*Z*,13*E*) triene system, that is, the 11*Z*-double bond, may occur. This minor diastereomer can be removed after macrocyclization. Notably, after cyclization the triene system is more stable toward isomerization.

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