A Synthesis of the C_3–C_{15} Fragment of the Archazolids

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Abstract: Ring-closing metathesis and an allylation–elimination reaction sequence have been used to complete a synthesis of the conjugated triene subunit of the archazolids.

Key words: stereoselective synthesis, tandem reactions, allylations, eliminations, metathesis

Archazolid A and B, along with the glucopyranoside derivative archazolid C, represent a family of structurally related natural products isolated from the myxobacterium *Archangium gephyra* (Figure 1).[1] They display powerful growth-inhibitory activity against a number of murine and human cancer cell lines based on the selective inhibition of vacuolar-type ATPase.[2]

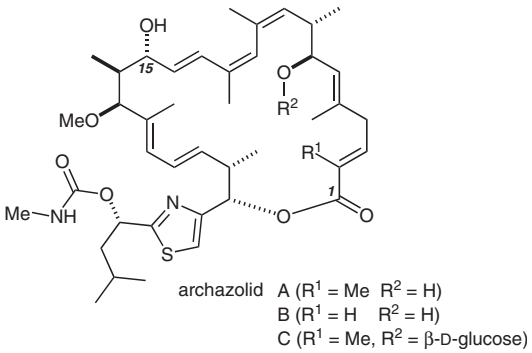

Figure 1 Myxobacterium natural products archazolid A–C

V-ATPases play a central role in several aspects of cellular function, including acidification of intracellular organelles and regulation of extracellular pH.[3] Their malfunction has been correlated with various diseases ranging from cancer[4] to renal acidosis[5] and osteoporosis.[6] As potent and selective inhibitors, the archazolids present an opportunity to study the development of these diseases and to design drugs for their therapy.

The 30-carbon linear polyketide backbone of the archazolids has been incorporated into a highly functionalized 24-membered macrolactone. Extensive NMR analysis of archazolid A led to the determination of relative stereochemistry.[7] This was later confirmed and the absolute stereochemistry assigned by total synthesis.[8] Embedded within the core is a synthetically challenging C_9–C_{14} *Z*,*Z*,*E*-conjugated triene unique to the archazolids.

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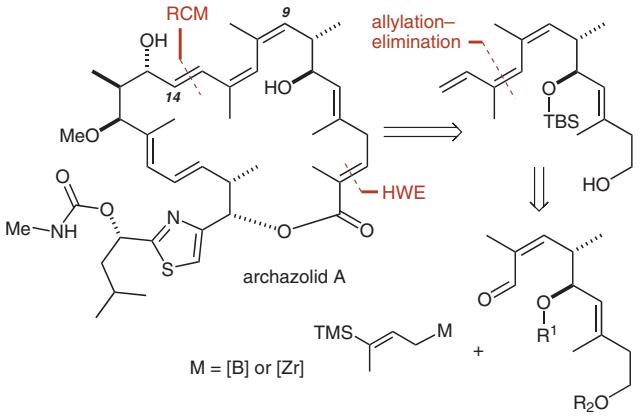
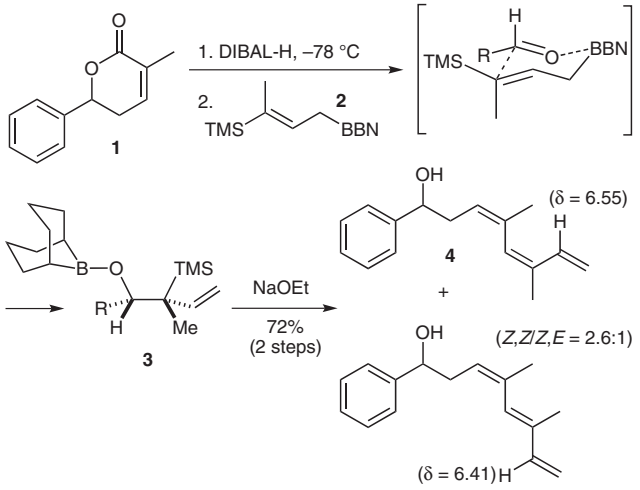
Negishi and Huang recently described an elegant solution to this subunit exploiting a regio- and stereoselective hydroboration of haloalkynes.[9] Our retrosynthetic analysis, including macrocycle formation by ring-closing metathesis (RCM) at C_{13}–C_{14} and olefination at C_2–C_3, requires the synthesis of a previously unknown *Z*,*Z*-terminal triene (Scheme 1). We questioned if two recently reported methods for the stereoselective construction of terminal 1,3-butadienes could be extended to substituted conjugated triene synthesis. Specifically, TMS-substituted allylboration[10] or allylziroconation[11] followed by *syn*-Peterson elimination[12] would provide rapid access to this motif.



Scheme 1 Archazolid retrosynthesis

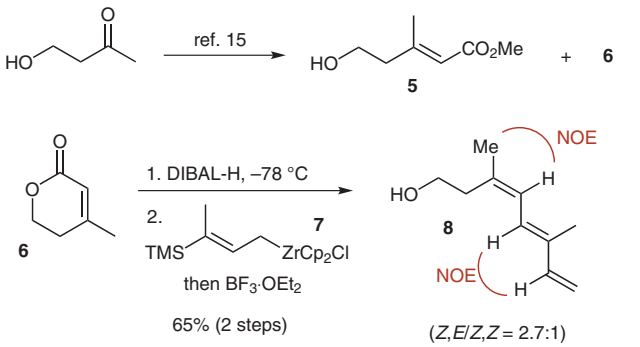
In order to test the allylation–elimination reaction sequence, an appropriately functionalized model lactone **1**[13] was partially reduced with DIBAL-H at –78 °C and subsequently treated with the in situ prepared[10] TMS-substituted allylborane reagent **2** (Scheme 2).

After several hours at room temperature the starting material was completely consumed, converted to presumably β-alkoxysilane **3** proceeding through a cyclic chair-like transition state. Base-induced elimination with NaOEt afforded a 2.6:1 (NMR) mixture of 2,3-substituted conjugated trienes. The use of different bases such as NaOH or NaH for the elimination step had no effect on the resulting stereochemical ratio suggesting that the observed isomeric mixture is determined during the formation of the intermediate β-alkoxysilane. The stereochemistry of the major product was tentatively assigned as the expected *Z*,*Z*-isomer **4** by chemical shift correlation. In particular, the terminal alkene methine ^{1}H NMR signal was diagnostic, appearing consistently downfield for the *Z*-isomer.[14]



Scheme 2

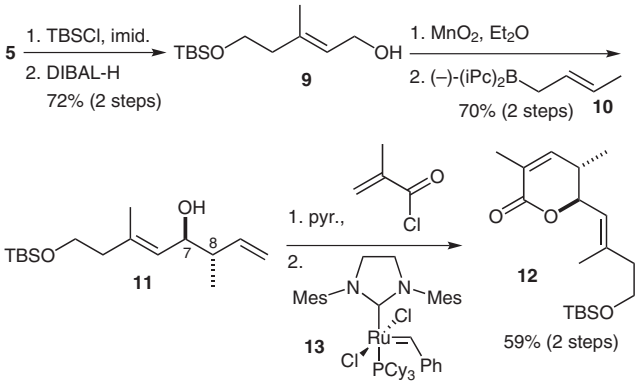
Encouraged by this result, an application to the archazolid-conjugated triene was next investigated. Our synthesis began with ester **5**, prepared as a separable mixture along with lactone **6** from 4-hydroxy-2-butanone (Scheme 3).[15]



Scheme 3

Lactone **6** was identified as a suitable substrate with which to investigate the tandem TMS-substituted allylzirconation–elimination. Partial reduction of **6** with DIBAL-H gave an intermediate lactol that was immediately treated with an in situ prepared[11] allylzirconocene **7**. In contrast to previously described substrates, the intermediate zirconium alkoxide did not spontaneously undergo a *syn*-Peterson-type elimination. This afforded an opportunity to control the stereochemistry of the newly formed trisubstituted alkene by choice of either basic or acidic workup conditions. For instance, addition of $BF_3{\cdot}OEt_2$ to the reaction mixture resulted in rapid *anti*-elimination giving triene **8** as a 2.7:1 (NMR) *Z,E*/*Z,Z* mixture of stereoisomers in 65% yield from **6**.[16]

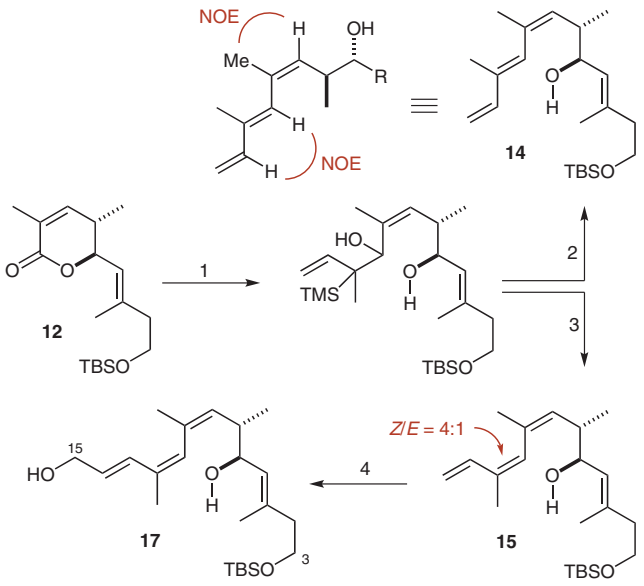
Continuation of the archazolid synthesis from **5** began with protection of the free hydroxyl as the TBS-ether and reduction of the ester with DIBAL-H giving allylic alcohol **9** in 72% yield over the two steps (Scheme 4). The C_7–C_8 *anti*-propionate was installed by oxidation followed by crotylation using Brown's method[17] giving compound **11** in 70% yield from **9**. Acylation with methacryloyl chloride then set the stage for formation of the C_9–C_{10} trisubstituted *cis*-alkene by RCM. After some optimization, it was found that lactone **12** could be obtained in 65% yield using 5 mol% Grubbs second-generation catalyst (**13**)[18] in a dilute (0.01 M) solution of refluxing (110 °C) toluene.



Scheme 4

Reduction of **12** with DIBAL-H at –78 °C proceeded cleanly to give an intermediate lactol that was immediately exposed to the allylation–elimination conditions (Scheme 5). The best yields and selectivities were obtained using an allylzirconation–elimination sequence. Consistent with our previous observations, the intermediate zirconium alkoxide did not eliminate under the reaction conditions. Attempts to purify this intermediate in order to ascertain its diastereomeric purity resulted in rapid *anti*-Peterson elimination giving tetraene **14**. Preferential formation of the desired *Z,Z*-conjugated triene was affected by treatment of the product mixture with NaOEt affording **15** as an inseparable 4:1 (NMR) mixture of stereoisomers. To test the reactivity of this compound toward metathesis, exposure of **15** to catalyst **13** in the presence of an excess of *cis*-1,4-bisacetylated butenediol **16** gave upon removal of the acetate diol **17**. The stereoisomers from the allylation–elimination sequence were separable at this point by flash chromatography marking a completion of a stereocontrolled synthesis of the C_3–C_{15} fragment of the archazolids.

In summary, a tandem lactol allylation–Peterson elimination reaction sequence has been used to stereoselectively prepare several substituted conjugated trienes. In contrast to previously described substrates, intermediate β-silyl zirconium alkoxides could be selectively converted to both *Z,E*- and *Z,Z*-terminal trienes by acid- or base-induced elimination, respectively. This method was successfully applied to a synthesis of the archazolid-conjugated triene subunit. The resulting tetraene underwent a highly chemoselective cross-metathesis thus completing a synthesis of the C_3–C_{15} archazolid fragment. Current efforts are directed toward improving the selectivity of the allylation process through the use of different organometallic reagents and a completion of the archazolid synthesis.



Scheme 5 *Reagents and conditions*: (1) (a) DIBAL-H, CH_2Cl_2, –78 °C; (b) **7**, CH_2Cl_2, r.t., (2) SiO_2, 42% (2 steps); (3) NaOEt, THF, r.t., 68% (2 steps); (4) (a) **16**, **13** (10 mol%), PhMe, 60 °C; (b) DIBAL-H, CH_2Cl_2, 0 °C, 60% (2 steps).

Allylboration–*syn*-Elimination Sequence for the Synthesis of Compound 4

To a solution of lactone **1** (50 mg, 0.27 mmol) in CH_2Cl_2 (2.7 mL) at –78 °C was added dropwise a solution of DIBAL-H (1.0 M hexanes, 0.27 mL), and the resulting mixture was stirred for 10 min. The reaction was quenched with aq Rochelle's salt (10 mL) and stirred with EtOAc (10 mL) for 30 min. The layers were separated and the organic phase dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting lactol was used without further purification.

To a solution of 1-methyl-1-(trimethylsilyl)allene (0.134 mL, 0.80 mmol) in THF (1.6 mL) at r.t. was added a 9-BBN solution (1.0 M THF, 0.80 mL), and the resulting mixture was stirred for 2 h. To the allylborane thus obtained at 0 °C was added the crude lactol as a solution in THF (1.6 mL), and the reaction was allowed to slowly warm to r.t. overnight. The reaction was cooled to 0 °C and NaOEt (216 mg, 3.24 mmol) was added, and the mixture was stirred for 1 h before diluting with Et_2O (15 mL) and washing with aq NH_4Cl (15 mL). The layers were separated and the organic phase dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash column chromatography on silica (10:1 to 4:1 hexanes–EtOAc) afforded triene **4** (44 mg, 72%) as an inseparable 2.6:1 (NMR) mixture of *Z*/*E* isomers.

IR (ATR): 3320, 2937, 1496, 1453, 1029, 917, 742 cm^{-1}.

Characteristic signals for the major stereoisomer: ^1H NMR (500 MHz, $CDCl_3$): δ = 7.35–7.31 (m, 5 H), 6.54 (ddd, *J* = 17.6, 10.6, 0.7 Hz, 1 H), 5.74 (s, 1 H), 5.36 (m, 1 H), 5.22 (ddd, *J* = 17.6, 1.5, 0.8 Hz, 1 H), 5.08 (dt, *J* = 10.6, 1.8 Hz, 1 H), 4.69 (dd, *J* = 7.7, 5.1 Hz, 1 H), 2.45–2.32 (m, 2 H), 1.86 (d, *J* = 1.5 Hz, 3 H), 1.78 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 144.2, 135.8, 135.4, 129.5, 128.4, 128.3, 127.4, 125.9, 123.7, 114.3, 74.1, 39.0, 24.4, 19.3. HRMS (CI^+): *m*/*z* calcd for $C_{16}H_{20}OH^+$ $[M + H]^+$: 229.1592; found: 229.1571.

Allylzirconation–*anti*-Elimination Sequence for the Synthesis of Compound 8

To a solution of lactone **6** (50 mg, 0.46 mmol) in CH_2Cl_2 (4.6 mL) at –78 °C was added dropwise a solution of DIBAL-H (1.0 M hexanes, 0.53 mL), and the resulting mixture was stirred for 10 min. The reaction was quenched with aq Rochelle's salt (15 mL) and stirred with EtOAc (15 mL) for 30 min. The layers were separated and the organic phase dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting lactol was used without further purification.

To a suspension of zirconocence hydrochloride (0.47 g, 1.84 mmol) in CH_2Cl_2 (6.9 mL) at –78 °C was added 1-methyl-1-(trimethylsilyl)allene (0.46 ml, 2.76 mmol), and the mixture was warmed to r.t. for 15 min (until a red homogeneous solution developed). To the allylzirconocene thus obtained was added the crude lactol as a solution in CH_2Cl_2 (2.3 mL), and the reaction was stirred for 15 h. The reaction was cooled to 0 °C and $BF_3{\cdot}OEt_2$ (0.17 mL, 1.38 mmol) was added, and the mixture was stirred for 1 h before diluting with CH_2Cl_2 (15 mL) and quenching with aq $NaHCO_3$ (15 mL). The layers were separated and the organic phase dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash column chromatography on silica (4:1 hexanes–EtOAc) afforded triene **8** (46 mg, 65%) as an inseparable 2.7:1 (NMR) mixture of *E*/*Z* isomers.

IR (ATR): 3360, 2922, 2852, 1659, 1632, 1461, 1377, 1045, 722 cm^{-1}.

Characteristic signals for the major stereoisomer: ^1H NMR (500 MHz, $CDCl_3$): δ = 6.44 (dd, *J* = 17.1, 10.7 Hz, 1 H), 6.33 (d, *J* = 11.7 Hz, 1 H), 6.28 (d, *J* = 11.7 Hz, 1 H), 5.19 (d, *J* = 17.1 Hz, 1 H), 5.01 (d, *J* = 10.8 Hz, 1 H), 3.76–3.70 (m, 2 H), 2.51 (t, *J* = 6.8 Hz, 2 H), 1.89 (s, 3 H), 1.85 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 141.6, 126.8, 124.6, 111.9, 60.9, 35.6, 35.3, 24.6, 24.4, 11.8. HRMS (ESI^+): *m*/*z* calcd for $C_{10}H_{16}ONa$ $[M + Na]^+$: 174.1021; found: 174.1032.

Allylzirconation–*syn*-Elimination Sequence for the Synthesis of Compound 15

To a solution of lactone **12** (56 mg, 0.17 mmol) in CH_2Cl_2 (1.7 mL) at –78 °C was added dropwise a solution of DIBAL-H (1.0 M hexanes, 0.204 mL), and the resulting mixture was stirred for 10 min. The reaction was quenched with aq Rochelle's salt (15 mL) and stirred with EtOAc (15 mL) for 30 min. The layers were separated and the organic phase was dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting lactol was used without further purification.

To a suspension of zirconocence hydrochloride (0.177 g, 0.69 mmol) in CH_2Cl_2 (1.7 mL) at –78 °C was added 1-methyl-1-(trimethylsilyl)allene (0.17 mL, 1.03 mmol), and the mixture was warmed to r.t. for 15 min (until a red homogeneous solution developed). To the allylzirconocene thus obtained was added the crude lactol as a solution in CH_2Cl_2 (0.86 mL), and the reaction was stirred for 15 h. The reaction was quenched with aq $NaHCO_3$ (15 mL) and extracted with CH_2Cl_2 (2 × 15 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was redissolved in THF (1.7 mL) at 0 °C, NaOEt was added (0.14 g, 2.04 mmol), and the mixture was warmed to r.t. for 1 h before diluting with MTBE (15 mL) and washing with aq NH_4Cl (15 mL). The layers were separated and the organic phase dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash column chromatography on silica (4:1 hexanes–EtOAc) afforded tetraene **15** (42 mg, 68%) as an inseparable 4.0:1 (NMR) mixture of *Z*/*E* isomers.

$[\alpha]_D^{20}$ –6.6 (*c* 0.5, CH_2Cl_2). IR (ATR): 2988, 2970, 1631, 1604, 1505, 1437, 1391, 1229, 1029, 896, 854, 826 cm^{-1}.

Characteristic signals for the major stereoisomer: ^1H NMR (500 MHz, $CDCl_3$): δ = 6.63 (ddd, *J* = 11.6, 10.7, 0.6 Hz, 1 H), 5.85 (s, 1 H), 5.21 (ddd, *J* = 17.6, 1.4, 0.8 Hz, 1 H), 5.20–5.15 (m, 2 H), 5.08 (dt, *J* = 10.7, 1.4 Hz, 1 H), 4.02 (t, *J* = 8.8 Hz, 1 H), 3.68 (t, *J* = 7.2 Hz, 2 H), 2.33 (m, 1 H), 2.27–2.18 (m, 2 H), 1.87 (d, *J* = 1.4 Hz, 3 H), 1.82 (s, 3 H), 1.69 (d, *J* = 1.4 Hz, 3 H), 0.88 (s, 9 H), 0.86 (d,

J = 6.9 Hz, 3 H), 0.04 (s, 6 H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 136.9, 135.2, 135.1, 133.9, 130.9, 129.5, 127.4, 114.2, 72.2, 62.1, 43.0, 10.5, 25.9, 24.7, 19.4, 18.3, 17.3, 16.1, –5.3. HRMS (CI^+): m/z calcd for $C_{22}H_{40}O_2Si$: 364.2798; found: 364.2827.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(14) The stereochemistry was later confirmed by NMR analysis. See Supporting Information for details.
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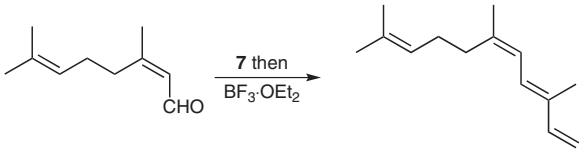
(16) A similar conjugated triene product was obtained with comparable yield and selectivity from an acyclic substrate (Scheme 6); see Supporting Information for details.



Scheme 6

(17) Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 5919.
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