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Modular Total Synthesis of Archazolid A and B

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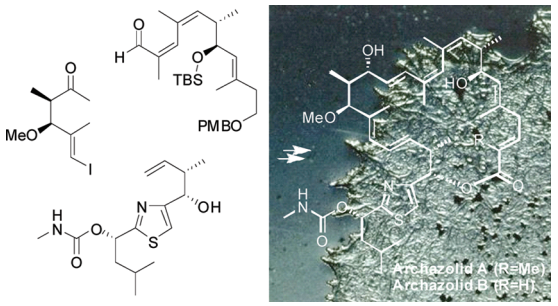

A modular total synthesis of the potent V-ATPase inhibitors archazolid A and B is reported. The convergent preparation was accomplished by late-stage diversification of joint intermediates. Key synthetic steps involve asymmetric boron-mediated aldol reactions, two consecutive Still−Gennari olefinations to set the characteristic (*Z*,*Z*)-diene system, a Brown crotyboration, and a diastereoselective aldol condensation of highly elaborate intermediates. For macrocyclization, both an HWE reaction and a Heck coupling were successfully employed to close the 24-membered macrolactone. During the synthetic campaign, a generally useful protocol for an *E*-selective Heck reaction of nonactivated alkenes and a method for the direct nucleophilic displacement of the Abiko−Masamune auxiliary with sterically hindered nucleophiles were developed. The expedient and flexible strategy will enable further SAR studies of the archazolids and more detailed evaluations of target-inhibitor interactions.

Introduction

Myxobacterial fermentation broths of *Archangium gephyra* and *Cystobacter violaceus* are the natural sources of the archazolids (Figure 1), structurally complex polyketide macrolactones, which were originally reported by the group of Höfle and Reichenbach.[1,2] They constitute highly potent antiproliferative agents which inhibit the growth of various cancer cell lines in subnanomolar concentrations.[1] On a molecular level, they constitute powerful and selective inhibitors of vacuolar type ATPases (V-ATPases),[3] heteromultimeric, proton translocating proteins that are localized in a multitude of eukaryotic membranes, where they energize many different transport processes.[4] As a malfunction of these enzymes is associated with various diseases such as cancer[5] and osteoporosis, the development and molecular understanding of novel inhibitors present important research goals.[4]

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(1) (a) Höfle, G.; Reichenbach, H.; Sasse, F.; Steinmetz, H. German Patent DE 41 42 951 C1, **1993**. (b) Sasse, F.; Steinmetz, H.; Höfle, G.; Reichenbach, H. *J. Antibiot*. **2003**, *56*, 520.

(2) For a recent review on polyketides from myxobacteria, see: Menche, D. *Nat. Prod. Rep*. **2008**, *25*, 905.

(3) Huss, M.; Sasse, F.; Kunze, B.; Jansen, R.; Steinmetz, H.; Ingenhorst, G.; Zeeck, A.; Wieczorek, H. *BMC Biochem*. **2005**, *6*, 13.

(4) For reviews, see: (a) Huss, M.; Wieczorek, H. *J. Exp. Biol*. **2001**, *204*, 2597. (b) Beyenbach, K. W.; Wieczorek, H. *J. Exp. Biol*. **2006**, *209*, 577. (c) Huss, M.; Wieczorek, H. *J. Exp. Biol*. **2009**, *212*, 341.

(5) Lebreton, S.; Jaunbergs, J.; Roth, M. G.; Ferguson, D. A.; De Brabander, J. K. *Bioorg. Med. Chem. Lett*. **2008**, *18*, 5879.

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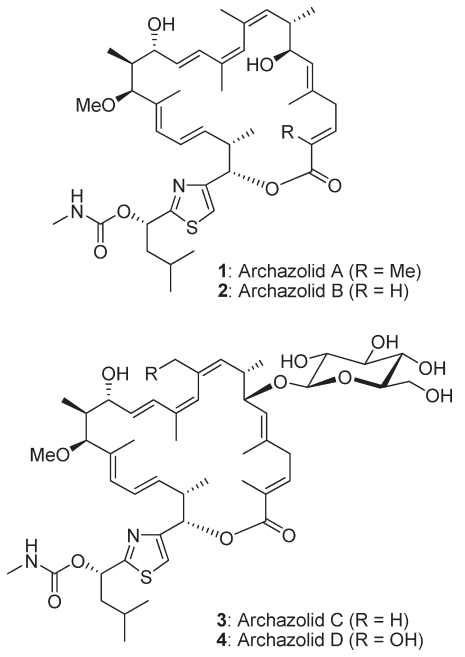
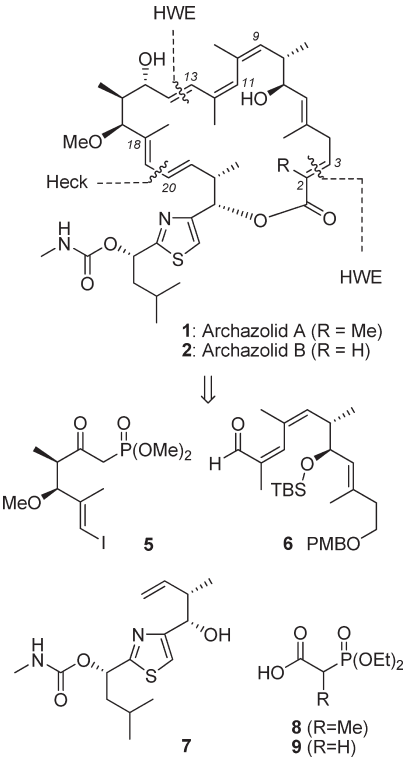


FIGURE 1. Natural archazolids: polyketide macrolactones of myxobacterial origin.

The unique three-dimensional architecture of the archazolids is characterized by a 24-membered polyunsaturated macrolactone ring together with a thiazole side chain terminating in a methyl carbamate. In total, they contain eight stereogenic centers. Archazolids A (**1**) and B (**2**), the most potent metabolites, differ only in the methylation pattern at C-2, while the glucosides **3**[6] and **4**[7] are less active by a factor of ~1000. Originally reported as planar structures, their absolute and relative stereochemistry has been determined in our group by a combination of *J*-based configurational analysis with molecular modeling and chemical derivatization.[8] Recently, this assignment was independently validated by an innovative method based on residual dipolar couplings.[9] SAR data suggest the hydroxyl at C-7 to be part of the pharmacophoric region. In contrast, removal of the carbamate leads only to slight loss of activity, suggesting that the full biological potential of the archazolids can be retained while simplifying the structural complexity.[10]

The important biological properties of these macrolide antibiotics together with their natural scarcity and unique and challenging structure render these metabolites attractive synthetic targets to support further biological evaluation but also to enable more elaborate structure−activity relationship (SAR) studies. Recently, the first total synthesis of archazolid A was accomplished in our group,[11] which also unambiguously confirmed our stereochemical assignment. Shortly thereafter,

SCHEME 1



an alternative route was reported to access archazolid B by the Trauner group.[12,13] Furthermore, an innovative synthetic approach to the characteristic trisubstituted *Z*-alkenes of the archazolids has been disclosed.[14] Herein, we report in full detail our synthetic strategies toward these potent macrolide antibiotics, which culminated in a joint total synthesis of archazolids A and B.

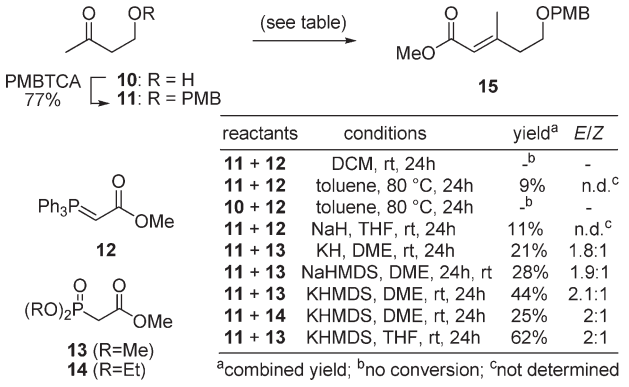
Results and Discussion

As shown in Scheme 1, our original retrosynthetic route was based on three main building blocks of similar complexity: a northwestern, an eastern, and a southern fragment (**5**, **6**, and **7**) in combination with phosphonates **8** and **9**. The delicate 9*Z*,11*Z*,13*E* triene was planned to originate from a Horner−Wadsworth−Emmons reaction (HWE reaction) between phosphonate **5** and dienone **6**, while a more challenging Heck reaction between **5** and **7** was envisioned to set the 18*E*,20*E*-diene. The 2,3-double bond, in turn, should be generated by another phosphonate coupling. In principle, all three reactions should be suitable for macrocyclization as an alternative for a more conventional Yamaguchi reaction for ring closure. Importantly, deliberate choice of phosphonates **8** or **9** should enable access to both archazolid A and B by late-stage diversification. Notably, this convergent and modular approach is flexible and should be readily amenable to analogue synthesis.

Synthesis of building block **6** was initiated by olefination of ketone **11**, readily available from commercial alcohol **10**

(6) Menche, D.; Hassfeld, J.; Steinmetz, H.; Huss, M.; Wieczorek, H.; Sasse, F. *Eur. J. Org. Chem.* **2007**, 1196.
(7) Menche, D.; Hassfeld, J.; Steinmetz, H; Huss, M.; Wieczorek, H.; Sasse, S. *J. Antibiot.* **2007**, *60*, 328.
(8) Hassfeld, J.; Farès, C.; Steinmetz, H.; Carlomagno, T.; Menche, D. *Org. Lett.* **2006**, *8*, 4751.
(9) Farès, C.; Hassfeld, J.; Menche, D.; Carlomagno, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 3722.
(10) Menche, D.; Hassfeld, J.; Sasse, F.; Huss, M.; Wieczorek, H. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1732.
(11) Menche, D.; Hassfeld, J.; Li, J.; Rudolph, S. *J. Am. Chem. Soc.* **2007**, *129*, 6100.
(12) Roethle, P. A.; Chen, I. T.; Trauner, D. *J. Am. Chem. Soc.* **2007**, *129*, 8960.
(13) For a review on archazolid syntheses, see: von Zezschwitz, P. *Nachr. Chem.* **2008**, *56*, 535.
(14) Huang, Z. H.; Negishi, E. *J. Am. Chem. Soc.* **2007**, *129*, 14788.

SCHEME 2



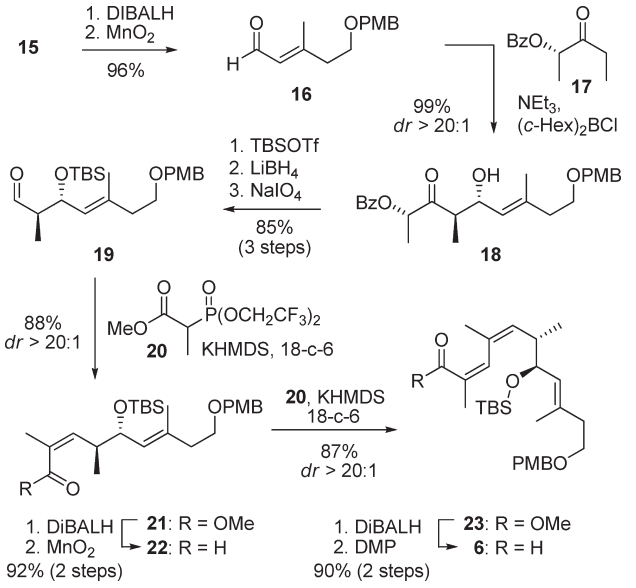
reactants	conditions	yield[a]	*E*/*Z*
11 + **12**	DCM, rt, 24h	-[b]	-
11 + **12**	toluene, 80 °C, 24h	9%	n.d.[c]
10 + **12**	toluene, 80 °C, 24h	-[b]	-
11 + **12**	NaH, THF, rt, 24h	11%	n.d.[c]
11 + **13**	KH, DME, rt, 24h	21%	1.8:1
11 + **13**	NaHMDS, DME, 24h, rt	28%	1.9:1
11 + **13**	KHMDS, DME, rt, 24h	44%	2.1:1
11 + **14**	KHMDS, DME, rt, 24h	25%	2:1
11 + **13**	KHMDS, THF, rt, 24h	62%	2:1

[a]combined yield; [b]no conversion; [c]not determined

(Scheme 2). Initial attempts using conventional Wittig ylide **12**, however, soon revealed this reagent to be too unreactive for the desired C2-homologation. Even at elevated temperatures and extended reaction times, only small degrees of conversion could be observed, regardless of the presence of a hydroxyl-protective group. In contrast, use of Horner−Wadsworth−Emmons reagent **13** was more efficient. Evaluation of reaction parameters (see the table in Scheme 2) revealed the methyl reagent to be more effective as compared to the ethyl analogue **14** and use of potassium as counterion to be superior to the use of sodium. Optimal conditions involved a slight excess of KHMDS and phosphonate **13** (1.25 equiv each). Running the reaction in THF at room temperature overnight resulted in the formation of desired enoate **15** with preparatively useful yields (62%), albeit only moderate *E*/*Z* selectivity (2:1). Nevertheless, this route was selected to prepare multigram quantities of **15** due to the robustness, low cost of starting materials, and good scalability of the process.

The undesired *Z*-isomer could be readily removed by chromatography after reduction to the corresponding allylic alcohol (Scheme 3). Subsequent allylic oxidation (MnO_2) gave diastereomerically pure enal **16** in essentially quantitative yield. Our successful strategy for converting **16** to building block **6** was based on a boron-mediated Paterson[15] *anti*-aldol reaction with lactate-derived ketone **17** to give the desired aldol product **18** with excellent selectivity and yield (99%, dr > 20:1). After conversion of **18** in three steps to aldehyde **19** (TBSOTf, $LiBH_4$, and $NaIO_4$, 85% yield), two consecutive Still−Gennari olefinations[16] using phosphonate **20** with aldehyde **19** and subsequently with enal **22**, derived from ester **21**, proceeded with excellent selectivity to give the desired (*Z*,*Z*)-dienone **23** in high yield and *Z*-selectivity of the newly generated double bonds (88%/87%, dr > 20:1). This route proved to be superior in terms of overall chemical yield, scalability, and cost to a likewise tested alternative sequence of first introducing the required *anti*-propionate by a Brown crotylation of aldehyde **16**, esterification of the derived secondary alcohol with methacrylic acid, and ring-closing metathesis reaction of the derived ester (not shown).[17] Overall, several grams of building block **23** could be readily

SCHEME 3

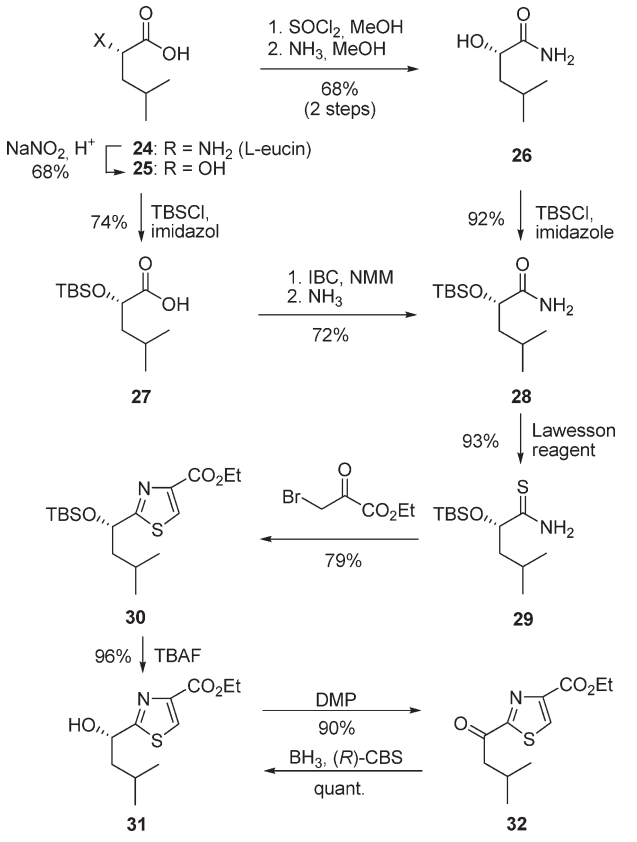


obtained from **15** in 10 steps and 56% overall yield. Reduction and allylic oxidation proceeded smoothly to give **6** in a straightforward fashion.

For the synthesis of side-chain fragment **7**, natural L-leucine (**24**) was chosen as a cheap starting material, already containing the characteristic aliphatic isopentyl residue of the archazolids with the desired configuration. Following a known procedure,[18] nucleophilic substitution of the derived diazo acid ($NaNO_2/H_2SO_4$) gave the corresponding α-hydroxy acid **25** with overall retention of configuration (68%). The corresponding amide **26** was best prepared by first activation with thionyl chloride, conversion to the respective methyl ester, and subsequent treatment with ammonia in methanol (68%). TBS protection of hydroxy amide **26** as silyl ether **28** proceeded smoothly under conventional conditions in high yields (92%). Alternatively, amide **28** may also be obtained from **25** by a shorter route involving protecting the hydroxyl as TBS ether, IBC activation of the derived acid as the mixed anhydride, and in situ substitution with NH_3. However, this sequence proved less scalable, proceeded with slightly lower yields, and consequently, was not further pursued. Subsequently, amide **28** was treated with the Lawesson reagent[19] to give thioamide **29** in high yields (93%), which was then condensed with ethyl bromopyruvate to form thiazole **30**. At the stage of the derived free alcohol **31**, however, Mosher ester analysis revealed variable degrees of isomerization, which presumably occurs during thiazole formation, in agreement with previous findings.[20,21] Loss of stereochemical purity at an earlier stage of the synthesis can be excluded as the optical properties of **28** prepared by the two routes discussed above were identical. At this stage, the enantiomeric purity of **31** could be readily

(15) For a review on asymmetric boron-mediated aldol reactions, see: Cowden, C. J.; Paterson, I. *Org. React.* **1997**, *51*, 1.
(16) Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405.
(17) For a similar sequence, see: Cossy, J.; Bauer, D.; Bellosta, V. *Tetrahedron* **2002**, *58*, 5909.
(18) (a) Barrow, R. A.; Hemscheidt, T.; Liang, J.; Paik, S.; Moore, R. E; Tius, M. A. *J. Am. Chem. Soc.* **1995**, *117*, 2479. (b) Bitan, G.; Gilon, C. *Tetrahedron* **1995**, *51*, 10513.
(19) Thomsen, I.; Clausen, K.; Scheibye, S.; Lawesson, S.-O. *Organic Syntheses*; Wiley: New York, 1990; Vol. 7, p 372.
(20) Riedrich, M.; Harkal, S.; Arndt, H.-D. *Angew. Chem., Int. Ed.* **2007**, *46*, 2701.
(21) Schmidt, U.; Gleich, P.; Griesser, H.; Utz, R. *Synthesis* **1986**, *12*, 992.

SCHEME 4

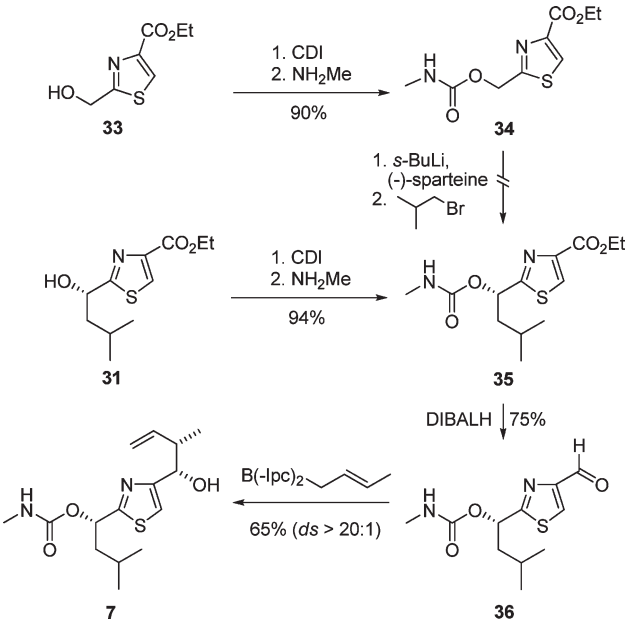


remedied by a two-step procedure, involving first Dess–Martin oxidation[22] and stereoselective reduction (er > 20:1) of the derived ketone **32** using the CBS method (Scheme 4).[23]

As shown in Scheme 5, enantiopure alcohol **31** was homologated to carbamate **35** by CDI-treatment and trapping the intermediate imidazole carboxylate with methylamine. At this stage, also an alternative strategy as compared to the multistep approach discussed so far (Scheme 4) was evaluated. Relying on a method of Hoppe,[24] this involved use of chiral amines for stereoselective deprotonation of **34**, readily available from **33** using our previously established sequence. Thiazole **33** was readily available by condensation of hydroxyacetonitrile, hydrogen sulfide, and ethyl bromopyuvate (see the Supporting Information). Accordingly, carbamate **34** was first deprotonated at −40 °C with *s*-BuLi in the presence of (−)-sparteine, and subsequently, the reaction mixture was treated with isobutyl bromide. However, only complex product mixtures were obtained, with no formation of trace amounts of desired **35**, even after modification of reaction parameters. Presumably, the carbamate was not sufficiently sterically hindered to overcome direct carbonyl addition of BuLi. Accordingly, this concept was not further pursued. For completing the synthesis of building block **36**, ester **35** was first directly reduced to aldehyde **36** with DIBALH at low temperatures in CH_2Cl_2, which proceeded with consistently good yields (75%) also on large scale-up, depending on the use of K–Na tartrate solution during workup. Subsequent asymmetric crotylation using

(22) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.
(23) Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986.
(24) Hoppe, D.; Hintze, F.; Tebben, P. *Angew. Chem., Int. Ed.* **1990**, *29*, 1422.

SCHEME 5

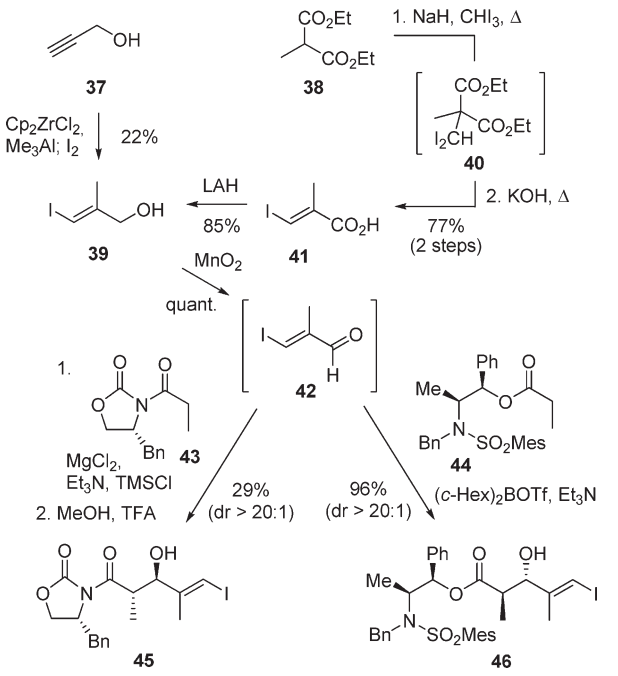


Brown's methodology[25] gave the desired building block **7** in high stereoselectivity (dr > 20:1) and preparatively useful yields (65%). Overall, the route toward **7** was readily adaptable for a large-scale approach, and several grams of the fragment could be obtained.

As shown in Scheme 6, our synthesis of the northwestern fragment **5** was based on known vinylic iodide **39**. A reported route from propargylic alcohol **37** by zirconation–methylation–iodination,[26] however, gave only low yields in our hands (22%). Also a carbocupration–iodination sequence involving $MeMgBr/CuBr\cdot SMe_2$ and I_2 (not shown) failed to give the desired product.[27] In contrast, a much more practical synthesis was based on diethyl 2-methylmalonate (**38**), following a procedure by Baker and Castro.[28] In the course of this study, the original two-step reaction sequence was optimized. This involved first treatment of **38** with iodoform and sodium hydride in Et_2O at reflux to give intermediate **40**, which was, however, not isolated but directly converted into acid **41** under basic conditions. This optimized procedure resulted in higher yields and was readily amenable to production of multigram quantities of acid **41** (40 g). Reduction to alcohol **39** ($LiAlH_4$) and subsequent allylic oxidation (MnO_2) to aldehyde **42** proceeded smoothly. For the required *anti*-propionate homologation, an Abiko–Masamune aldol reaction[29] with norephedrin-derived ethyl ester **44** to give **46** proved the method of choice in terms chemical yield and stereoselectivity (96%, dr > 20:1), as compared to a likewise tested alternative of using Evans methodology[30] (**43** to **45**).

(25) Brown, H. C.; Bhat, K. S.; Randad, R. S. *J. Org. Chem.* **1989**, *54*, 1570.
(26) White, J. D.; Blakemore, P. R.; Green, N. J.; Hauser, E. B.; Holoboski, M. A.; Keown, L. E.; Nylund Kolz, C. S.; Phillips, B. W. *J. Org. Chem.* **2002**, *67*, 7750.
(27) For an example, see: Layton, M. E.; Morales, C. A.; Shair, M. D. *J. Am. Chem. Soc.* **2002**, *124*, 773.
(28) Baker, R.; Castro, J. L. *J. Chem. Soc., Perkin Trans. 1* **1990**, 47–65.
(29) Inoue, T.; Liu, J.-F.; Buske, D. C.; Abiko, A. *J. Org. Chem.* **2002**, *67*, 5250.
(30) Evans, D. A.; Tedrow, J. S.; Shaw, J. T.; Downey, C. W. *J. Am. Chem. Soc.* **2002**, *124*, 392.

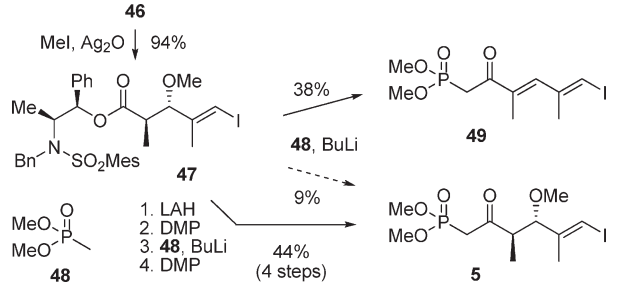
SCHEME 6



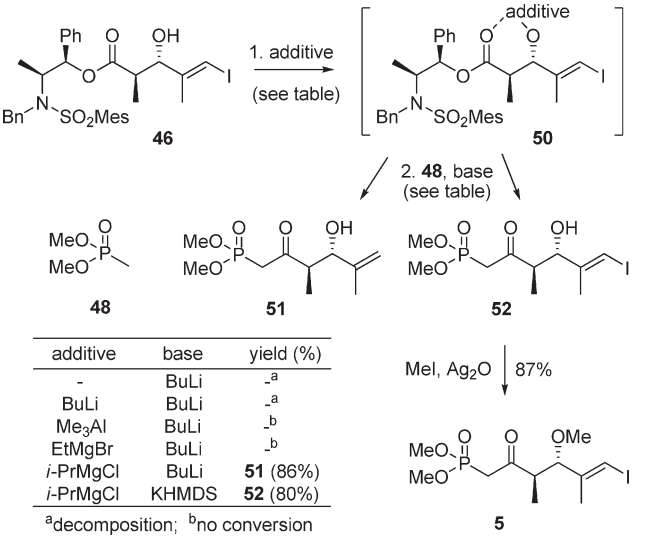
A major drawback of this Abiko−Masamune aldol route was, however, the subsequent difficulties to cleave the norephedrin-derived auxiliary of **47** with nucleophiles other than hydride. Apparently this presents a general limitation of the method, which so far may only be circumvented by resorting to a derived auxiliary.[31] As shown in Scheme 7, direct treatment with metalated phosphonate **48** resulted in extensive decomposition, giving eliminated derivative **49** as the main product (38%), and only traces of the desired phosphonate **5** (9%) were found. Therefore, at this stage we had to resort to a four-step sequence, relying on first removing the auxiliary reductively with $LiAlH_4$, Dess−Martin oxidation of the resulting primary alcohol, addition of lithiated phosphonate **48** to the resulting aldehyde, followed by another Dess−Martin oxidation, affording the desired phosphonate **5** in acceptable yields (44%) over four steps.

To improve this result, efforts were directed to enable a direct displacement of the Abiko−Masamune auxiliary. As shown in Scheme 8, our concept to promote such a direct substitution was based on ester activation by suitable additives. As schematically shown in **50**, they are expected to chelate the characteristic hydroxy ester, leading to an activation of the ester moiety and thereby promoting nucleophilic attack. According to this concept, a variety of Lewis acids were evaluated in the substitution of **46** with metalated **48** using mild reaction conditions (−78 to −20 °C, THF). Best results were obtained with *i*-PrMgCl among those screened. Furthermore, it was found that the choice of base (KHMDS) was critical in order to avoid hydrodehalogenation to **51**. Under optimized conditions, the desired phosphonate could be obtained in high yields (80%) in a straightforward fashion. Notably, the chiral auxiliary may be recovered after the reaction by chromatography, which adds to the efficiency of

SCHEME 7



SCHEME 8



additive	base	yield (%)
-	BuLi	-[a]
BuLi	BuLi	-[a]
Me_3Al	BuLi	-[b]
EtMgBr	BuLi	-[b]
i-PrMgCl	BuLi	**51** (86%)
i-PrMgCl	KHMDS	**52** (80%)

[a]decomposition; [b]no conversion

this process. Methylation of phosphonate **52** to give building block **5** proceeded smoothly. Notably, this direct procedure was superior as compared to the stepwise displacement discussed above (Scheme 7), in terms of steps and overall yields.

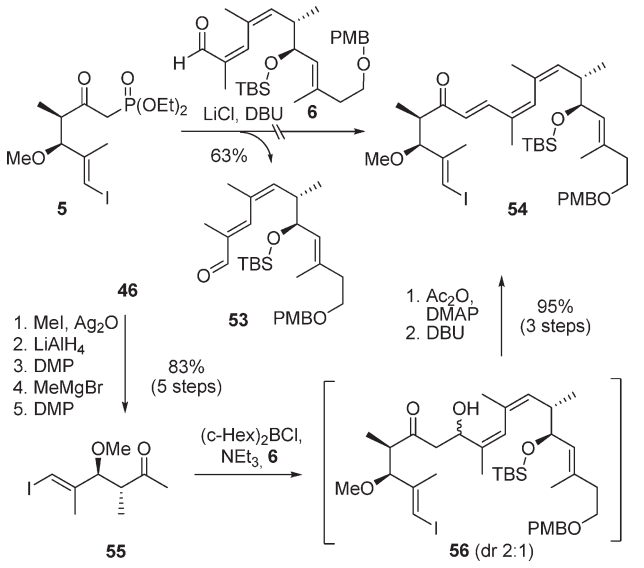
With efficient approaches to the three building blocks established, our strategy for fragment union was initiated by attempted HWE reactions of phosphonate **5** with aldehyde **6** (Scheme 9). However, to our disappointment, this coupling proved extremely challenging, leading to extensive decomposition. Even under very mild conditions according to the Masamune−Roush protocol (LiCl, DBU, CH_3CN, rt),[32] no conversion to the desired trienone **54** was observed and mainly isomerization of aldehyde **6** to **53** was found.

Accordingly, the original strategy had to be revised, and an alternative approach was pursued. This involved union of the two northern fragments by an aldol condensation. Accordingly, Abiko−Masamune aldol product **46** was transformed to the required methyl ketone **55**. Initially, a five-step procedure was used involving methylation of Abiko−Masamune aldol product **46**, reductive cleavage of the chiral auxiliary ($LiAlH_4$), DMP oxidation of the derived alcohol, addition of MeMgBr, and DMP oxidation (83%, five steps). For subsequent coupling of methyl ketone **55** with aldehyde **6**, lithium- and boron-mediated aldol reactions

(31) (a) Fanjul, S.; Hulme, A. N.; White, J. W. *Org. Lett.* **2006**, *8*, 4219. (b) Fanjul, S.; Hulme, A. N. *J. Org. Chem.* **2008**, *73*, 9788.

(32) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183.

SCHEME 9

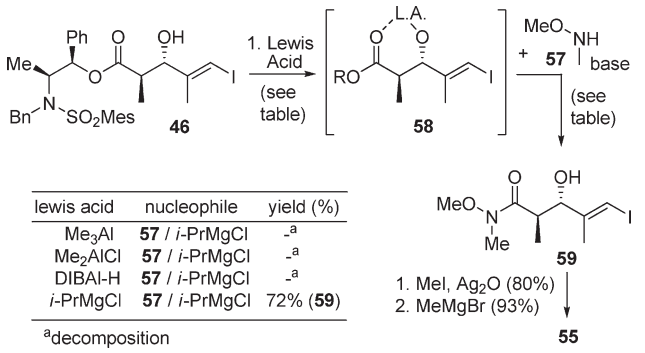


were evaluated, with the latter giving better results in terms of yield and scalability. Optimum conditions involved use of NEt_3 and $(c\text{-Hex})_2BCl$ giving aldol product **56** in high yields. For elimination, a two-step procedure proved optimal, which involved first acylating the free hydroxyl group with Ac_2O/DMAP and subsequent treatment of the acetate with DBU, enabling access to **54** in excellent 95% yield over three steps.

In order to shorten the synthetic sequence to methyl ketone **55**, also a more direct access from Masamune aldol product **46** was evaluated by direct displacement of the auxiliary with Weinreb amine **57**. Following our successful concept for Lewis acid activation as established above, an analogous approach was studied also for this purpose.[33] As shown in Scheme 10, this involved again Lewis acid activation to give intermediate **58** which was then treated with metalated Weinreb amine. As shown in the table in Scheme 10, best results were again obtained with *i*-PrMgCl, giving the desired product **59** with preparatively useful yields (72%). Subsequent methylation and substitution with MeMgBr of derived ether **59** proceeded smoothly to enable access to the desired methyl ketone **55** in a straightforward fashion (74%, two steps).

After successful construction of the northern carbon skeleton of the archazolids, efforts were then directed to stereoselective reducing the C-15 ketone to alcohol **60** with the desired *R*-configuration. Accordingly, a variety of reducing agents were evaluated for this purpose, as shown in Scheme 11. However, it soon became apparent that this transformation was hampered by a strong substrate bias toward the here-undesired (*S*)-isomer, presumably by coordinative effects of the 15-OMe group. Using achiral reducing agents (e.g., K-Selectride, LAH), this unnatural epimer was obtained with high selectivity (9 to 10:1), which could also not be overturned by addition of Lewis acids (e.g., LiI, $CeCl_3$).[34] Finally, selective access to the desired (*R*)-isomer

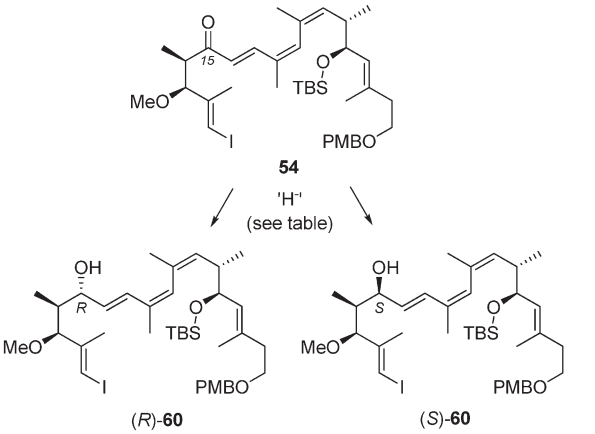
SCHEME 10



lewis acid	nucleophile	yield (%)
Me_3Al	**57** / *i*-PrMgCl	-[a]
Me_2AlCl	**57** / *i*-PrMgCl	-[a]
DIBAl-H	**57** / *i*-PrMgCl	-[a]
i-PrMgCl	**57** / *i*-PrMgCl	72% (**59**)

[a]decomposition

SCHEME 11



'H-'	yield (%)	*R*/*S*-**60**
K-selectride	65%	1:10
LAH, LiI	72%	1:9
LAH	79%	1:9
LAH, (*M*)-binaphthol	-[a]	

[a]no conversion

'H-'	yield (%)	*R*/*S*-**60**
$CeCl_3$, $NaBH_4$	-[b]	
(-)-DIPCl	-[b]	
(*R*)-CBS, BH_3	3-12%	1:15
(*S*)-CBS, BH_3	3-9%	7:1 ⇐

[b]decomposition

with good stereoselectivity (dr = 7:1) was accomplished by using the CBS method.[23] At this stage, yields remained however only low (3−9%), mainly due to isomerization or decomposition of the labile triene substrate. Therefore, at this stage the synthetic campaign was pursued with ketone **54** and the prospect of reducing the ketone at a later step of the synthesis (vide infra).

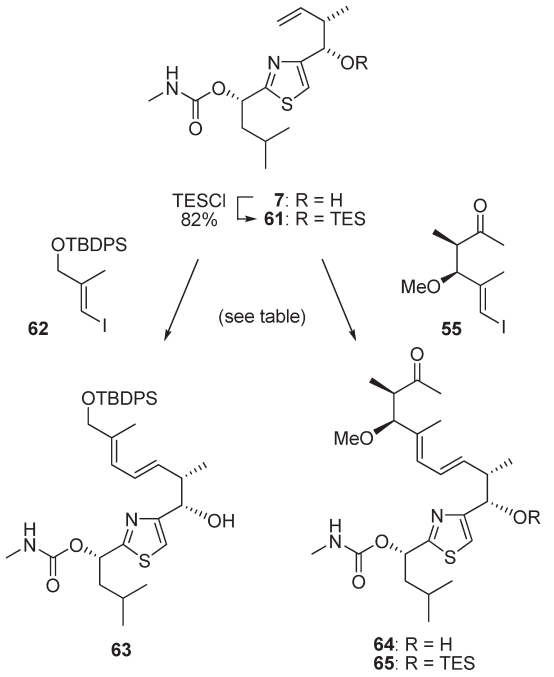
As a prelude to forge the northern and southern ring fragment of the archazolids by means of a Heck reaction, first model studies were carried out with the southern fragments **7** and **61** and simplified building blocks for the northern part, i.e., **55** and **62**, in order to evaluate substituent effects and establish suitable reaction conditions. For this purpose, part of the material of homoallylic alcohol **7** was transformed into TES ether **61**. As shown in the table in Scheme 12, a free hydroxyl group on the iodide coupling partner was beneficial in all cases (entries 2/3, 5/6, and 8/9). This may be explicable by additional coordinative effects, in agreement with previous results.[35] However, to our surprise,

(33) Direct replacement of Abiko−Masamune aldol product **47** with the Weinreb amid resulted in only low yields of the product, giving mainly elimination.

(34) Gemal, A. L.; Luche, J.-L. *J. Am. Chem. Soc.* **1981**, *103*, 5434.

(35) For an example of the beneficial effect of a free hydroxyl, see, e.g.: Hosoya, T.; Takashiro, E.; Matsumoto, T.; Suzuki, K. *J. Am. Chem. Soc.* **1994**, *116*, 1004.

SCHEME 12

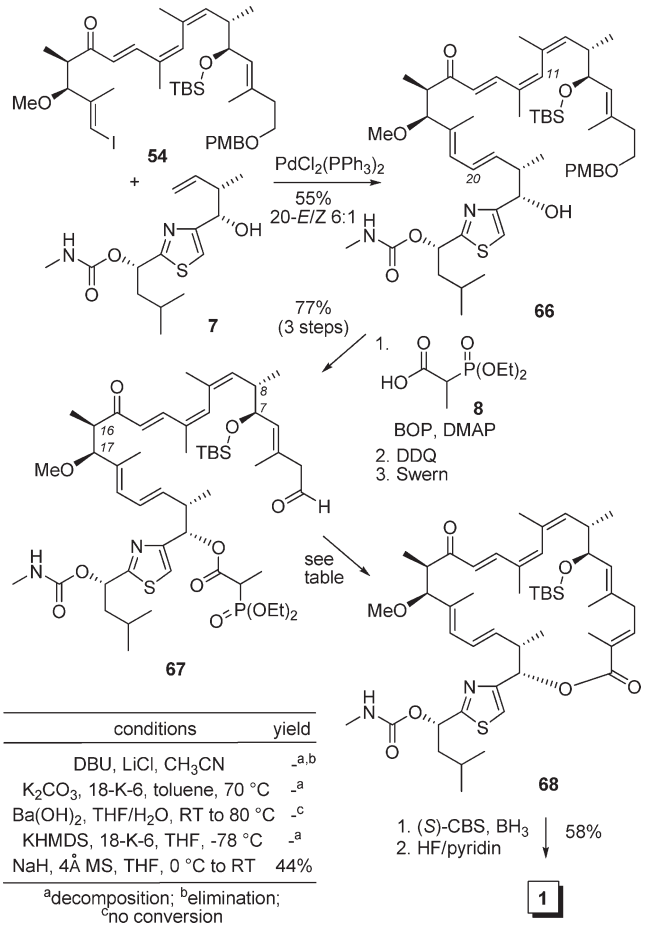


entry	substrates	conditions	*E*/*Z*	yield (%)
1	**7**+**62**	$Pd(OAc)_2/PPh_3$, NEt_3, DMF/H_2O, rt to 80 °C	1.2:1	33 (**63**)
2	**7**+**55**	$Pd(OAc)_2/PPh_3$, NEt_3, DMF/H_2O, rt to 80 °C	1.2:1	24 (**64**)
3	**61**+**55**	$Pd(OAc)_2/PPh_3$, NEt_3, DMF/H_2O, rt to 80 °C	1.5:1	12 (**65**)
4	**7**+**62**	$Pd(OAc)_2$, TBACl, $NaHCO_3$, DMF, rt	2:1	52 (**63**)
5	**7**+**55**	$Pd(OAc)_2$, TBACl, $NaHCO_3$, DMF, rt	2.5:1	29 (**64**)
6	**61**+**55**	$Pd(OAc)_2$, TBACl, $NaHCO_3$, DMF, rt	2:1	28 (**65**)
7	**7**+**62**	$PdCl_2[PPh_3]_2$, TBACl, NEt_3, $NaHCO_3$, DMF/CH_3CN/H_2O, 80 °C	6:1	61 (**63**)
8	**7**+**55**	$PdCl_2[PPh_3]_2$, TBACl, NEt_3, $NaHCO_3$, DMF/CH_3CN/H_2O, 80 °C	5:1	54 (**64**)
9	**61**+**55**	$PdCl_2[PPh_3]_2$, TBACl, NEt_3, $NaHCO_3$, DMF/CH_3CN/H_2O, 80 °C	6:1	39 (**65**)

essentially no *E*/*Z* selectivities were obtained by following either a conventional protocol [entries 1−3: $Pd(OAc)_2$, NEt_3, DMF/H_2O, rt to 80 °C][36] or Jeffrey conditions[37] [entries 4−6: $Pd(OAc)_2$, TBACl, $NaHCO_3$, DMF, rt]. After considerable experimentation, it was finally realized that this unfavorable result may be remedied by modification of reaction conditions (entries 7−9), giving diene **63** with preparatively acceptable yield (61%) and diastereoselectivity (6:1) (entry 7). Optimal conditions involved use of a more stable catalyst [$PdCl_2(PPh_3)_2$] and the presence of water as cosolvent (DMF/CH_3CN/H_2O = 5:5:1). Importantly, use of waters resulted in drastically reduced reaction times (several hours to a few minutes) and consistently good selectivities. These observations suggest that isomerization occurs after initial coupling by a hydropalladation−reductive elimination sequence. This assumption was further corroborated by minor degrees of isomerization observed also along the labile northern triene system.

With these optimized conditions in hand, union of the authentic coupling partners **54** and **7** proceeded smoothly, without the necessity of further adapting the protocol (Scheme 13).

SCHEME 13



conditions	yield
DBU, LiCl, CH_3CN	-[a,b]
K_2CO_3, 18-K-6, toluene, 70 °C	-[a]
$Ba(OH)_2$, THF/H_2O, RT to 80 °C	-[c]
KHMDS, 18-K-6, THF, -78 °C	-[a]
NaH, 4Å MS, THF, 0 °C to RT	44%

[a]decomposition; [b]elimination; [c]no conversion

Accordingly, the desired diene **66** was obtained in acceptable yields (55%) and selectivities (6:1).[38] The minor, here unwanted 20-*Z*-isomer was readily removed after the reaction by HPLC separation on normal phase. Subsequent esterification with phosphonate **8** (BOP, DMAP, 93%) and PMB-deprotection to the respective primary alcohol (DDQ) proceeded smoothly (94%). In contrast, oxidation to aldehyde **67** proved troublesome, leading to isomerization of the trienone system (TPAP oxidation) or elimination along the (7,8)- and/or (16,17)-bond (TEMPO oxidation) using a number of conditions. It was only after resorting to the Swern protocol that the desired transformation could be effected (88%).

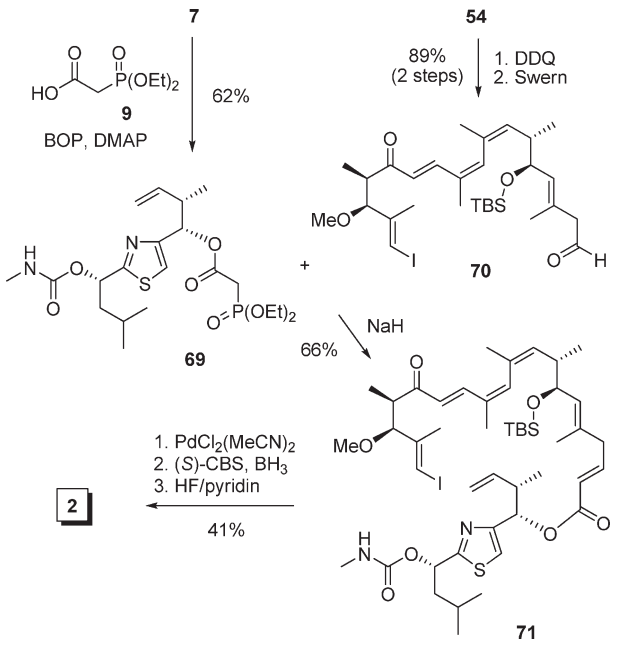
Overriding this distinct propensity for elimination along the (7,8)- and (16,17)-*anti*-configured bonds also constituted a major challenge in the subsequent macrocyclization of **67** to **68**. Even under very mild Masamune−Roush conditions (DBU, LiCl)[32] mainly elimination was observed. Decomposition products were also obtained with K_2CO_3 or KHMDS/18-C-6. Use of $Ba(OH)_2$ resulted in no conversion (reisolation of starting material). Finally, the desired cyclization to **68** could be effected by a serendipitously found combination of NaH as base and 4 Å molecular sieves, still present from drying the starting material. This resulted in ring closure with preparatively acceptable yields (44%), with

(36) (a) Heck, R. F. *J. Am. Chem. Soc.* **1974**, *96*, 1133. (b) Heck, R. F. *Org. React.* **1982**, *27*, 345.

(37) (a) Jeffrey, T. *Chem. Commun.* **1984**, 1287. (b) Jeffrey, T. *Tetrahedron Lett.* **1985**, *26*, 2267. (c) Jeffrey, T. *Synthesis* **1987**, 70.

(38) In addition, certain degrees of isomerization along the 11*Z*-double bond were observed. The unwanted 11*E* isomer was removed after cyclization to **68**.

SCHEME 14



regard to the lability and overall complexity of the substrate. Importantly, addition of molecular sieves was essential, in order to avoid elimination processes, which may be due to the slightly acidic nature of this additive. Completion of the total synthesis involved stereoselective reduction of the ketone on the basis of our previous results with (*S*)-oxazaborolidine-assisted borane, which proceeded again with high diastereoselectivity and this time also acceptable yields (73%), presumably by macrocyclic stabilization of the labile triene system by conformational restraints. Final deprotection of the secondary alcohol at C-7 with HF/pyridine completed the total synthesis of archazolid A in a straightforward fashion. The spectroscopic data and optical rotation were in agreement with those of the authentic natural products.[1]

For total synthesis of archazolid B (**2**), a modified endgame strategy was applied in order to demonstrate the modularity of our synthetic approach (Scheme 14). This involved first an intermolecular HWE coupling of phosphonate **69** with aldehyde **70**. Both starting materials were readily available from **7** and **54** by esterification with **9** and PMB deprotection/Swern oxidation, respectively. Again HWE coupling was efficiently carried out with NaH as base. Subsequently, a Heck macrocyclization of **71** was effected by a protocol of Ziegler.[39] Completion of the total synthesis of archazolid B proceeded uneventfully by stereoselective CBS reduction and HF deprotection, following our previously established protocols (41%, three steps). All data of synthetic archazolid B were identical with those of the authentic natural product.[1,8]

Conclusions

In conclusion, based on a modular synthetic strategy, an expedient and joint total synthesis of the potent antiproliferative polyketide macrolactone antibiotics archazolid A and B has been accomplised. Key steps for their syntheses involve an aldol condensation to construct the (*Z*,*Z*,*E*)-triene system, an *E*-selective Heck reaction for the (22,23)-diene moiety, and an HWE coupling. Two different methods, an HWE reaction and a Heck coupling, were successfully utilized to forge the macrocyclic core of these polyketides. Notably, the joint synthesis of archazolid A and B was enabled by late-stage diversification of joint late-stage intermediates, demonstrating an expedient and flexible endgame strategy. Furthermore, in the course of this campaign, efficient protocols for an *E*-selective Heck reaction of nonactivated alkenes, a direct nucleophilic displacement of the Abiko-Masamune auxiliary by Lewis acid activation, and a mild and highly reactive HWE protocol were developed. With the established robust and flexible synthetic approach to the archazolids in hand, efforts can now be directed for further SAR studies and more detailed target-inhibitor evaluations.

Experimental Section

Acid 41. A solution of diethyl methylmalonate (**38**, 33.2 g, 0.190 mol, 1 equiv) in Et_2O (60 mL) was added to NaH (55−65% in mineral oil, 9.21 g, 0.230 mol, 1.2 equiv) in Et_2O (120 mL) during 40 min under vigorous stirring, and the resulting mixture was refluxed for 3 h. After being cooled to rt, CHI_3 (75.0 g, 0.190 mol, 1 equiv) was added during 30 min, and the mixture was refluxed for 32 h. At 0 °C, 10% aqueous HCl (100 mL) was added and the mixture stirred for 20 min. The organic layer was separated, and the aqueous layer was extracted with Et_2O (3 × 30 mL). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The residue was dissolved in EtOH/H_2O (3:1, 520 mL), and KOH (28.1 g, 0.500 mol) was added. The mixture was refluxed for 24 h. After being cooled to rt, the mixture was concentrated in vacuo. The residue was redissolved in 10% aqueous K_2CO_3 (300 mL), and the precipitated CHI_3 was removed by filtration. The filtrate was washed with CH_2Cl_2 (2 × 50 mL), acidified with 12 M HCl (pH < 1, 130 mL) and extracted with CH_2Cl_2 (8 × 50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexanes/EtOAc = 10:1, 0.5% AcOH) to give the carboxylic acid **41** (31.1 g, 0.147 mol, 77%, over two steps) as a white solid: R_f = 0.25 (hexanes/EtOAc = 10:1, 0.5% AcOH); mp 58 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.05 (s, 3H), 8.03 (s, 1H), 12.08 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 19.8, 102.0, 139.0, 169.2; HRMS calculated for $C_4H_4IO_2$ $[M - H]^+$ 210.9256, found 210.9254. The spectroscopic data were identical to those previously reported.[25]

Direct Nucleophilic Substitution the Abiko−Masamune Auxiliary: Phosphonate 52. To a cooled solution (−78 °C) of dimethyl methylphosphonate (**48**, 156 mL, 2.93 mmol, 11.0 equiv) in THF (1 mL) was added KHMDS (0.5 M in toluene, 2.66 mL, 1.33 mmol, 10.0 equiv), and the resulting suspension was stirred at −20 °C for 2 h. To a cooled solution (−78 °C) of the ester **46** (92.1 mg, 0.136 mmol, 1.0 equiv) in THF (1 mL) was added *i*-PrMgCl (2.0 M in Et_2O, 204 μL, 0.409 mmol, 3.0 equiv). After 20 min, the above mixture was added via cannula. The reaction mixture was warmed to −20 °C for ca. 1.5 h and stirred at −20 °C for 5 h. Saturated aq NH_4Cl (6 mL) and H_2O (6 mL) were added, the organic layer was separated, and the aqueous layer thoroughly extracted with EtOAc (4 × 6 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. Silica gel chromatography (hexanes/EtOAc = 1:2) afforded the phosphonate **52** (40.9 mg, 0.109 μmol, 80%) as a colorless oil and the chiral Masamune alcohol auxiliary as white solid (50.6 mg, 0.120 mmol, 88%): R_f = 0.15

(39) Ziegler, F. E.; Chakraborty, U. R.; Weisenfeld, R. B. *Tetrahedron* **1981**, *37*, 4035.

(hexanes/EtOAc = 1:2); $[\alpha]^{20}_D = -34.9$ (c = 0.97, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.93 (d, J = 7.0 Hz, 3H), 1.82 (s, 3H), 3.06 (dq, J = 9.2, 7.0 Hz, 1H), 3.17 (dd, J = 18.7, 13.8 Hz, 1H), 3.25 (dd, J = 18.7, 13.8 Hz, 1H), 3.76 (s, 3H), 3.80 (s, 3H), 4.25 (d, J = 9.2 Hz, 1H), 6.30 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 13.7, 18.7, 41.2, 42.9, 50.2, 53.2, 53.3, 79.2, 80.9, 147.4, 205.4, 205.5; HRMS calculated for $C_{10}H_{18}IO_5PNa$ $[M+Na]^+$ 398.9834, found 398.9836.

Direct Nucleophilic Substitution the Abiko−Masamune Auxiliary: Weinreb Amide 59. To a solution of ester **46** (231 mg, 0.342 mmol, 1.0 equiv) in THF (1 mL) was added *i*-PrMgCl (~2 M in THF, 0.17 mL, 0.34 mmol, 1.0 equiv); after 10 min, a suspension of magnesium chloride methoxy(methyl)amide complex, which was prepared by addition of *i*-PrMgCl (~2 M in THF, 3.42 mL, 6.84 mmol, 20 equiv) to a suspension of N,O-dimethylhydroxylamine hydrochloride (334 mg, 3.42 mmol, 10 equiv) in THF (3 mL) at −20 °C, was added. The reaction mixture was stirred at −20 °C for 2 h and warmed to −10 °C (ca. 1 h). The reaction was quenched by addition of satd aq NH_4Cl (5 mL). The poduct was extracted into EtOAc (3 × 20 mL), and the combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. Flash chromatography (hexanes/EtOAc = 2:1 to 1:1) gave amide (77.0 mg, 0.246 mmol, 72%) as a white solid: R_f = 0.15 (hexanes/EtOAc = 2:1); $[\alpha]^{20}_D = -13.2$ (c = 1.94, $CHCl_3$); mp 82−83 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.09 (d, J = 7.1 Hz, 3H), 1.81 (d, J = 1.0 Hz, 3H), 3.15 (m, 1H), 3.17 (s, 3H), 3.58 (d, J = 6.1 Hz, 1H), 3.69 (s, 3H), 4.26 (t, J = 6.4 Hz, 1H), 6.30 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 15.1, 20.1, 32.2, 38.2, 61.8, 79.0, 80.1, 148.1, 176.3; HRMS calcd for $C_9H_{16}INO_3Na$ $[M+Na]^+$ 336.0073, found 336.0075.

***E*-Selective Heck Reaction of Nonactivated Alkenes: Diene 66.** To a solution of the vinyl iodide **54** (74.5 mg, 99.3 μmol, 1.0 equiv) and alkene **7** (46.0 mg, 147 μmol, 1.5 equiv) in DMF was added 100 mg of molecular sieves 5 Å under argon atmosphere. This mixture was stirred for 15 min at rt. Then $PdCl_2[PPh_3]_2$ (35.0 mg, 50 μmol, 0.5 equiv), $NaHCO_3$ (29.0 mg, 345 μmol, 3.5 equiv), and TBACl (13.8 mg, 50 μmol, 0.5 equiv) were added. After the mixture was warmed to 80 °C, NEt_3 (30 μL, 197 μmol, 2.0 equiv) was added, and the mixture was stirred at this temperature for further 10 min followed by an addition of a 5:1 mixture of CH_3CN and H_2O (2.4 mL). The solution was then allowed to cool to rt and was stirred for further 20 min before it was diluted by addition of Et_2O (5 mL), and the organic layer was separated. The aqueous layer was reextracted by Et_2O (3 × 15 mL), and the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure. Purification of the residue by column chromatography on silica gel (EtOAc/hexanes = 1:2), and subsuent purification by preparative HPLC (hexane/*i*PrOH = 95:5) gave the desired 20*E*-configurated compound **66** (43.6 mg, 46.0 μmol) as an unseparable mixture together with the 11*E*(20*E*)-isomer (6.1 mg, 6.5 μmol) in a ratio of 6:1 (11*Z*/11*E* = 6:1) as a yellow oil (combined yield 55%), as well as the 11*Z*,20*Z*-isomer (7.3 mg, 7.8 μmol, likewise ratio: 6:1), which was separated by HPLC purification (overall yield of all isomers: 61%). The desired product **66** was characterized as a mixture together with its 11*E* isomer (11*Z*:11*E* = 6:1): R_f = 0.37 (EtOAc/hexanes = 1:2); $[\alpha]^{20}_D = +11.6$ (c = 1.02, MeOH, dr (11*E*:*Z*) = 6:1); ^{1}H NMR (300 MHz, CD_3OD, data for major diastereomer) δ = −0.01 (s, 3H), 0.02 (s, 3H), 0.86 (d, J = 6.6 Hz, 3H), 0.89 (s, 9H), 0.94 (d, J = 6.6 Hz, 3H), 1.01 (d, J = 6.0 Hz, 3H), 1.02 (d, J = 6.0 Hz, 3H), 1.09 (d, J = 6.8 Hz, 3H), 1.66 (s, 3H), 1.68 (s, 3H), 1.84 (s, 3H), 1.98 (s, 3H), 2.30 (t, J = 6.9 Hz, 2H), 2.39 (m, 1H), 2.75 (s, 3H), 2.86 (m, 1H), 3.05 (s, 3H), 3.08 (m, 1H), 3.57 (t, J = 6.7 Hz, 2H), 3.67 (d, J = 9.8 Hz, 1H), 3.82 (s, 3H), 4.20 (dd, J = 9.0 Hz, J = 5.6 Hz, 1H), 4.46 (s, 2H), 4.71 (d, J = 5.5 Hz, 1H), 5.15 (d, J = 8.9 Hz, 1H), 5.28 (d, J = 10.2 Hz, 1H), 5.76 (dd, J = 15.1 Hz, J = 8.3 Hz, 1H), 6.03 (m, 2H), 6.25 (m, 1H), 6.31 (s, 1H), 6.38 (d, J = 15.6 Hz, 1H), 6.92 (d, J = 8.7 Hz, 2H), 7.29 (d, J = 8.7 Hz, 2H), 7.32 (s, 1H), 7.61 (d, J = 15.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, data for major 11*Z*,20*E*-diastereomer) δ = −4.8, −4.3, 10.9, 14.3, 15.7, 16.7, 17.3, 18.2, 20.0, 22.2, 23.1, 24.6, 24.7, 25.9, 27.7, 39.7, 40.7, 43.9, 44.5, 46.4, 55.3, 56.3, 69.1, 72.2, 72.6, 73.0, 74.5, 90.0, 113.8, 114.5, 126.7, 127.4, 129.0, 129.3, 130.2, 130.7, 137.7, 131.9, 132.6, 133.6, 134.8, 135.8, 138.9, 141.1, 156.0, 158.2, 159.2, 171.1, 203.4; HRMS calcd for $C_{53}H_{82}N_2O_8NaSiS$ 957.5459, found 957.5483.

HWE Macrocyclization: Macrocycle 68. Aldehyde **67** (1.1 mg, 1.1 μmol, 1 equiv) was dissolved in absolute THF (1.5 mL) under argon and treated with molecular sieves 4 Å (20 mg). This solution was cooled to 0 °C before NaH (60% in mineral oil, 29 μg, 1.2 μmol, 1.1 equiv) was added. After the addition, the resulting suspension was stirred for 1 h at 0 °C and then warmed to ambient temperature and stirred for a further 4 h. Then the reaction was stopped by addition of 2 mL of pH 7 buffer and then diluted with Et_2O (10 mL). The organic layer was separated and the aqueous phase reextracted twice with Et_2O (10 mL). After the layers were combined, the organic layer was washed with brine, dried ($MgSO_4$), filtered, and separated from the solvent under reduced pressure. The residue was then purified by column chromatography (EtOAc/hexanes = 1:2) to obtain 0.41 mg (0.48 μmol) of the diastereomerically pure cyclization product **68** (44%): R_f = 0.61 (EtOAc/hexanes = 1:2); $[\alpha]^{20}_D = -12.5$ (c = 0.04, $CHCl_3$); ^{1}H NMR (600 MHz, CD_3OD) δ = 0.03 (s, 3H), 0.06 (s, 3H), 0.91 (s, 9H), 0.94 (d, J = 6.8 Hz, 3H), 0.95 (d, J = 6.8 Hz, 3H), 1.02 (d, J = 6.8 Hz, 3H), 1.03 (d, J = 6.8 Hz, 3H), 1.12 (d, J = 6.8 Hz, 3H), 1.72 (s, 3H), 1.75 (s, 3H), 1.79 (m, 2H), 1.85 (m, 2H), 1.83 (s, 3H), 1.91 (s, 3H), 1.94 (s, 3H), 2.40 (ddd-like, J = 17.0 Hz, J = 13.2 Hz, J = 6.4 Hz, 1H), 2.74 (s, 3H), 3.03 (d, J = 7.9 Hz, 2H), 3.05−3.10 (m, 1H), 3.15 (s, 3H), 3.17 (d, J = 6.8 Hz, 1H), 3.72 (d, J = 6.8 Hz, 1H), 4.21 (dd, J = 9.1 Hz, J = 6.0 Hz, 1H), 5.22 (m, 1H), 5.23 (m, 1H), 5.63 (dd, J = 15.1 Hz, J = 8.7 Hz, 1H), 5.90 (d, J = 11.0 Hz, 1H), 5.95 (d, J = 5.3 Hz, 1H), 6.04 (dd, J = 9.1 Hz, J = 4.5 Hz, 1H), 6.17 (dd, J = 15.1 Hz, J = 10.6 Hz, 1H), 6.22 (d, J = 16.2 Hz, 1H), 6.30 (s, 1H), 7.00 (t, J = 7.6 Hz), 7.15 (s, 1H), 7.55 (d, J = 16.2 Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ = −4.5, −4.1, 12.5, 14.0, 15.1, 15.9, 18.1, 18.3, 19.0, 19.4, 22.4, 23.3, 24.7, 25.8, 26.4, 27.5, 30.7, 39.2, 42.8, 43.1, 50.3, 57.2, 73.3, 74.0, 77.5, 88.5, 116.6, 127.9, 128.4, 128.5, 129.3, 129.5, 133.6, 133.9, 134.3, 135.0, 135.7, 139.9, 140.2, 142.2, 142.9, 149.2, 158.2, 168.2, 200.1; HRMS calcd for $C_{48}H_{74}N_2O_7NaSSi$ 873.4884, found 873.4880.

Archazolid A. A solution of compound **68** (1.50 mg, 1.76 μmol) in THF (0.3 mL) under argon atmosphere was cooled to 0 °C. Then 2 μL of a 1 M solution of 2-methyl (*S*)-2-methyl-CBS-oxazaborolidine in toluene (0.55 mg, 2.00 μmol, 1.1 equiv) and $BH_3 \cdot SMe_2$ (1.3 mg, 17.6 μmol, 10 equiv) was slowly added to this solution. After the mixture was stirred for 1 h at this temperature, the reaction was quenched carefully by addition of ethanol (0.5 mL) and warmed to rt. Additional H_2O (5 mL) and EtOAc (5 mL) were added, the organic layer was separated, and the aqueous phase was extracted with EtOAc (2 × 5 mL). The combined organic layer was dried with $MgSO_4$ and filtered, and the solvent was evaporated under reduced pressure. After purification by column chromatography on silica gel (EtOAc/hexanes = 1:4 to EtOAc/hexanes = 1:2), 1.1 mg (1.3 μmol, 73%) of the alcohol was obtained as a colorless oil: R_f = 0.44 (hexanes/EtOAc = 2:1); $[\alpha]^{20}_D = -74.3$ (c = 1.4 mg/mL, $CHCl_3$; ^{1}H NMR (CD_3OD, 600 MHz) δ = 0.03 (s, 3H), 0.06 (s, 3H), 0.78 (d, J = 7.3 Hz, 3H), 0.88 (d, J = 6.8 Hz, 3H), 0.91 (s, 9H), 1.01 (d, J = 6.80 Hz, 3H), 1.03 (d, J = 6.4 Hz, 3H), 1.12 (d, J = 6.8 Hz, 3H), 1.61 (d, J = 1.1 Hz, 3H) 1.72 (d, J = 1.1 Hz, 3H), 1.75 (ddq, J = 8.7 Hz, J = 4.2 Hz, J = 6.8 Hz, 1H), 1.78 (s, 3H), 1.80 (m, 2H), 1.84 (dd, J = 8.3 Hz, J = 4.9 Hz, 1H), 1.91 (s, 3H), 1.93 (d, J = 1.1 Hz, 3H), 2.30 (ddq, J = 9.8 Hz, J = 8.6 Hz, J = 6.8 Hz, 1H), 2.74 (s, 3H), 2.95 (dd, J = 15.1 Hz, J = 6.8 Hz, 1H), 3.00 (dd, J = 14.4 Hz, J = 9.1 Hz, 1H), 3.06 (ddq, J = 7.6 Hz, J = 4.5 Hz, J = 6.8 Hz, 1H), 3.13 (s, 3H), 3.29 (d, J = 8.7 Hz, 1H), 4.08 (dd, J = 8.9, J = 8.9 Hz, 1H), 4.20 (dd, J = 7.2 Hz, J = 4.2 Hz, 1H),

5.16 (dt, J = 10.1 Hz, J = 1.2 Hz, 1 H), 5.19 (d, J = 9.1 Hz, 1 H), 5.55 (dd, J = 15.1, J = 7.6 Hz, 1H), 5.80 (dd, J = 15.9 Hz, J = 7.9 Hz, 1H), 5.80 (s, 1H), 5.83 (d, J = 9.4 Hz, 1H), 5.96 (d, J = 4.5 Hz, 1H), 6.03 (dd, J = 9.1 Hz, J = 4.9 Hz, 1H), 6.06 (dd, J = 14.7 Hz, J = 10.6 Hz, 1H), 6.38 (d, J = 15.9 Hz, 1H), 6.87 (ddd, J = 8.3 Hz, J = 6.8 Hz, J = 1.5 Hz, 1H), 7.20 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = −4.71, −4.20, 11.4, 12.6, 13.8, 14.4, 16.6, 16.9, 17.7, 19.83, 22.2, 23.0, 24.4, 24.7, 25.9, 27.6, 39.8, 40.8, 41.1, 42.0, 44.4, 56.1, 72.1, 73. 8, 76.2, 76.3, 90.5, 115.1, 126.3, 128.6, 128.8, 129.3, 130.5, 130.6, 131.6, 132.3, 132.3, 133.0, 133.2, 134.6, 140.8, 141.1, 155.2, 156.0, 168.3, 174.3; HRMS calcd for $C_{48}H_{76}N_2O_7NaSSi$ 875.5040, found 875.5035.

The alcohol as prepared above (4.0 mg, 4.7 μmol) was dissolved in THF (0.2 mL). The resulting solution was cooled to 0 °C, and then pyridine (0.6 mL, 7.5 mmol) and HF (0.4 mL (70% in pyridine, 15.4 mmol) were added. The resulting mixture was warmed to rt, stirred at this temperature for 4 h, and quenched by addition of pH7 buffer (10 mL) afterward. The mixture was diluted with CH_2Cl_2 (5 mL), the organic layer was separated, and the aqueous phase was extracted twice with CH_2Cl_2 (2 × 5 mL). The combined organic layer was washed with saturated, aqueous $NaHCO_3$ solution (10 mL) and brine (10 mL), dried ($MgSO_4$), and filtered, and the solvent was removed in vacuo. The crude product was purified by HPLC (Nucleosil 100-7 C18, 250/21; CH_3CN/H_2O = 70:30 to CH_3CN/H_2O = 85:15) to give 2.8 mg (3.8 μmol, 80%) of archazolid A (**1**) as a colorless amorphous solid: R_f = 0.25 (hexanes/EtOAc = 2:1); $[\alpha]^{20}_D$ = −47.3 (c = 1.2 mg/mL, MeOH) [lit.[4] $[\alpha]^{22}_D$ = −64.0 (c = 12.8 mg/mL, MeOH)]; ^{1}H NMR (CD_3OD, 600 MHz) δ = 0.74 (d, J = 7.0 Hz, 3H), 0.84 (d, J = 7.0 Hz, 3H), 1.01 (d, J = 6.0 Hz, 3H), 1.02 (d, J = 6.0 Hz, 3H), 1.15 (d, J = 7.0 Hz, 3H), 1.64 (d, J = 1.2 Hz, 3H), 1.73 (d, J = 1.2 Hz, 3H), 1.77 (m, 1H), 1.80 (ddq, J = 9.0 Hz, J = 3.0 Hz, J = 7.0 Hz, 1H), 1.80 (s, 3H), 1.91 (d, J = 1.2 Hz, 3H), 1.92 (m, 2H), 1.93 (d, J = 1.2 Hz, 3H), 2.30 (ddq, J = 9.8, J = 9.5 Hz, J = 7.0 Hz, 1H), 2.75 (s, 3H), 2.91 (dd, J = 15.0 Hz, J = 7.5 Hz, 1H), 3.03 (dd, J = 15.0 Hz, J = 7.5 Hz, 1H), 3.10 (ddq, J = 7.5 Hz, J = 4.0 Hz, J = 7.0 Hz, 1H), 3.16 (s, 3H), 3.40 (d, J = 9.0 Hz, 1H), 4.03 (dd, J = 9.4 Hz, J = 9.3 Hz, 1H), 4.31 (dd, J = 6.4 Hz, J = 3.2 Hz, 1H), 5.21 (dd, J = 9.5 Hz, J = 1.2 Hz, 1H), 5.27 (d, J = 9.6 Hz, 1H), 5.63 (dd, J = 15.2 Hz, J = 7.0 Hz, 1H), 5.79 (dd, J = 15.5 Hz, J = 6.0 Hz, 1H), 5.81 (s, 1H), 5.87 (dd, J = 10.9 Hz, J = 1.2 Hz, 1H), 5.97 (d, J = 4.1 Hz, 1H), 6.04 (dd, J = 9.1 Hz, J = 4.5 Hz, 1H), 6.17 (dd, J = 15.5 Hz, J = 10.9 Hz, 1H), 6.56 (dd, J = 15.5 Hz, J = 0.9 Hz, 1H), 6.82 (ddd, J = 7.9 Hz, J = 7.5 Hz, J = 1.3 Hz, 1H), 7.21 (s, 1H); ^{13}C NMR (CD_3OD, 100 MHz) δ = 12.6, 12.6, 13.0, 16.8, 17.6, 17.7, 19.9, 22.4, 23.4, 24.7, 25.8, 27.5, 40.6, 41.8, 42.0, 44.5, 46.0, 56.2, 73.3, 73.6, 75.5, 77.6, 89.8, 116.7, 127.6, 129.3, 129.7, 130.8, 130.4, 130.7, 134.8, 132.7, 133.6, 133.6, 135.1, 135.7, 136.9, 142.1, 156.1, 158.2, 168.3, 173.9; HRMS calcd for $C_{42}H_{62}N_2O_7S$ 738.4277, found 738.4274. All data were identical to those previously reported for archazolid A from *A. gephyra*.[1,8]

Archazolid B. A solution of $PdCl_2(MeCN)_2$ (1.50 mg, 5.78 μmol) in MeCN (0.5 mL) was treated with iodide **71** (3.50 mg, 3.63 μmol) in MeCN (0.5 mL), NEt_3 (5 μL, 35.5 μmol), and formic acid (0.1 mL of a premixed solution of 4 μL formic acid in 1 mL MeCN, corresponds to 0.4 mL formic acid, 10.9 μmol) and stirred at rt for 2 h. Filtration through a pad of Celite, evaporation of the solvent in vacuo, and purification by HPLC (Nucleosil 100-7 C18, 250/21; hexane/MTBE = 15:1 to 6:3 gradient elution) gave the corresponding Heck product (1.80 mg, 2.20 μmol, 60%), which was directly used in the next step due to its base sensitivity. A solution of this Heck product (1.80 mg, 2.20 μmol) in THF (0.3 mL) under argon atmosphere was treated at 0 °C with 3 μL of a 1 M solution of 2-methyl (*S*)-2-methyl-CBS-oxazaborolidine in toluene (0.83 mg, 3.00 μmol) and $BH_3 \cdot SMe_2$ (2.0 mg, 27.0 μmol). After the mixture was stirred for 1 h at this temperature, ethanol (1 mL) was added carefully, the reaction mixture was warmed to rt, H_2O (5 mL) and EtOAc (5 mL) were added, the organic layer was separated, and the aqueous phase was extracted with EtOAc (2 × 5 mL). The combined organic layer was dried with $MgSO_4$ and filtered, and the solvent was evaporated under reduced pressure. A solution of the crude product in THF (0.2 mL) was treated at 0 °C with pyridine (0.6 mL, 7.5 mmol) and HF (0.4 mL, 70% in pyridine, 15.4 mmol), and the resulting mixture was stirred at rt for 4. After addition of pH 7 buffer (10 mL) and dilution with CH_2Cl_2 (5 mL), the organic layer was separated and the aqueous phase extracted twice with CH_2Cl_2 (2 × 5 mL). The combined organic layer was washed with saturated, aqueous $NaHCO_3$ solution (10 mL) and brine (10 mL), dried ($MgSO_4$), and filtered, and the solvent was removed in vacuo. The crude product was purified by HPLC (Nucleosil 100-7 C18, 250/21; CH_3CN/H_2O = 70:30 to CH_3CN/H_2O = 85:15) to give 1.0 mg (1.49 μmol, 41%, three steps) of archazolid B (**2**) as a colorless oil: R_f = 0.22 (hexanes/EtOAc = 2:1); $[\alpha]^{22}_D$ = −63.8 (c = 64, MeOH) [lit.[12] $[\alpha]^{25}_D$ = −61.9 (c = 0.52, MeOH)]; ^{1}H NMR (CD_3OD, 600 MHz) δ = 0.72 (d, J = 7.1 Hz, 3H), 0.81 (d, J = 6.6 Hz, 3H), 1.01 (d, J = 6.6 Hz, 3H), 1.02 (d, J = 6.1 Hz, 3H), 1.11 (d, J = 6.8 Hz, 3H), 1.67 (d, J = 1.2 Hz, 3H), 1.74 (d, J = 1.0 Hz, 3H), 1.78 (m, 1H), 1.79 (m, 1H), 1.79 (s, 3H), 1.92 (m, 2H), 1.93 (d, J = 1.1 Hz, 3H), 2.30 (ddq, J = 9.5, J = 9.5 Hz, J = 7.0 Hz, 1H), 2.75 (s, 3H), 2.91 (dd, J = 14.7 Hz, J = 6.6 Hz, 1H), 2.96 (dd, J = 14.7 Hz, J = 8.6 Hz, 1H), 3.09 (ddq, J = 6.6 Hz, J = 4.6 Hz, J = 6.8 Hz, 1H), 3.19 (s, 3H), 3.47 (d, J = 9.2 Hz, 1H), 4.03 (dd, J = 9.2 Hz, J = 9.2 Hz, 1H), 4.38 (dd, J = 5.6 Hz, J = 3.2 Hz, 1H), 5.18 (dd, J = 9.2 Hz, J = 1.0 Hz, 1H), 5.28 (d, J = 9.7 Hz, 1H), 5.75 (dd, J = 15.3 Hz, J = 6.6 Hz, 1H), 5.77 (dd, J = 16.2 Hz, J = 5.6 Hz, 1H), 5.79 (s, 1H), 5.90 (d, J = 10.2 Hz, 1H), 5.90 (d, J = 4.1 Hz, 1H), 5.92 (d, J = 15.7 Hz, 1H), 6.03 (dd, J = 8.9 Hz, J = 4.8 Hz, 1H), 6.28 (ddd, J = 15.3 Hz, J = 10.7 Hz, J = 1.0 Hz, 1H), 6.60 (d, J = 15.8 Hz, 1H), 6.94 (ddd, J = 15.5 Hz, J = 8.4 Hz, J = 6.4 Hz, 1H), 7.31 (s, 1H); ^{13}C NMR (CD_3OD, 100 MHz) δ = 11.6, 11.9, 16.2, 16.3, 17.1, 19.2, 21.6, 22.7, 24.1, 25.1, 26.8, 40.5, 40.7, 43.2, 43.3, 45.3, 55.7, 72.6, 73.0, 74.0, 76.5, 89.3, 116.7, 122.6, 126.5, 128.6, 129.3, 130.0, 130.0, 132.2, 132.6, 132.7, 133.8, 134.7, 134.8, 135.5, 148.3, 154.9, 157.5, 165.9, 173.5; HRMS calcd for $C_{41}H_{60}N_2O_7S$ 724.4121, found 724.4119. All data were identical to those previously reported for archazolid B from *A. gephyra*.[1,8]

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Supporting Information Available: Full experimental details and copies of the ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.