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Exploring a Ring-Closing Metathesis Approach to the Archazolid Macrocycle

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Abstract

The synthesis of a new “eastern domain” of a proposed dihydroarchazolid analogue is described along with initial results from attempted macrocyclization by RCM. This work has revealed a competing backbiting process that may be preventable by alcohol functionalization and installation of a metathesis relay.

Keywords

Total synthesis; Natural products; Olefin metathesis; Relay ring-closing metathesis

The archazolids are a family of structurally related natural products that display powerful growth inhibitory activity against a number of human cancer cell lines based on selective inhibition of the vacuolar-type ATPase (V-ATPase).¹ Over the past two decades, the importance of the V-ATPase to a range of critical cellular functions has become increasingly appreciated and this work has revealed important aspects of these proteins to various pathological processes.² For instance, recent studies involving the archazolids demonstrated the role of the V-ATPase in cancer metastasis.³ The archazolids were shown to effectively inhibit the migration of cancer cells and this activity was recently linked to impaired cellular secretion of mature proteases that degrade the extracellular matrix and allow the spread of cancer.⁴

The archazolid structure is characterized by a densely functionalized 24-membered lactone along with a pendant thiazole/carbamate side-chain (Figure 1). Glycosylation of either the C₇- or C₁₅-hydroxyls significantly reduces cell growth inhibitory activity (archazolids C and E respectively), implying that these two groups form important interactions with the V-ATPase. Interestingly, these same two groups are connected by a *Z,Z,E*-conjugated triene unique to the archazolid scaffold. Archazolids B (**1**) and F (**2**) differ only in the location of a double bond within the C₂-C₄ region (^{2,3} = archazolid B; ^{3,4} = archazolid F). Yet these compounds exhibit similar inhibitory potency, suggesting that a certain amount of structural flexibility is tolerated within this region. Taken to the extreme, we envisioned removal of

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Supporting Information Spectral data for compounds **9**, **10**, **12**, **13**, **17**, **18–26** is available online at <http://www.thieme-connect.com/ejournals/toc/synthesis>.

this isomeric double bond altogether and generation of a dihydroarchazolid B analogue **3** (Figure 2).⁵ This slight variant would be expected to retain V-ATPase inhibitory activity while simplifying the synthesis and improving stability by removal of the “skipped” C-C 6 π -systems found in each of the archazolids.⁶ Previously we had described a synthesis of both a “western” (**4**)⁷ and suitable eastern domain⁸ of the archazolids aimed at macrocycle formation by ring-closing metathesis (RCM). In order to adapt this strategy toward the proposed dihydroarchazolid B analogue, we would need to prepare a new eastern fragment **5** and saw this opportunity to improve upon our original synthesis.

Our first generation eastern fragment synthesis began with the preparation of ester **6** in 14% yield from 4-hydroxy-2-butanone by a non-selective Wittig reaction according to reference 9 (Scheme 1). Only after lactonization of the *cis*-isomer could the desired *trans*-ester **6** be separated. For this new dihydro-eastern fragment we envisioned a more selective approach toward construction of the C₅-C₆ *trans*-trisubstituted double bond utilizing a zirconium-mediated carboalumination reaction.¹⁰ In the event, treatment of alkyne **7**¹¹ with trimethylaluminum in the presence of zirconocene dichloride and water¹² followed by trapping with aldehyde **8**¹³ led directly to alcohol **9** exclusively as the *trans*-isomer and as a 6:1 separable mixture of diastereomers in favor of the desired Cram-chelate product (Scheme 1).¹⁴ Straightforward protecting group manipulations produced alcohol **10**. This was then oxidized allowing for a Still-Gennari modified Horner-Wadsworth-Emmons reaction¹⁵ with phosphonate **11**¹⁶ to generate E,*Z*-ester **12** as a single stereoisomer by ¹H NMR analysis.

At this stage we found it best to install the terminal carboxylic acid found in **5**. Treatment of **12** with the Jones reagent resulted in deprotection of the primary TBS-group with concomitant oxidation giving acid **13** in 90% yield (Scheme 2). The ester in **13** could then be selectively reduced using LiAlH₄ affording the corresponding alcohol which was taken crude into the oxidation to produce aldehyde **14**. As in our first-generation synthesis, we turned to the tandem allylzirconation/Peterson elimination sequence of Huang and Pi¹⁷ to generate a *Z,Z*-terminal triene and complete our synthesis of the eastern fragment acid **5**. It is worth noting that the *Z*-selectivity for this reaction was superior to that from our first-generation synthesis (**5** vs. **15**). We attribute this to the higher reaction temperatures required for the reaction from lactol **16**, presumably due to a requisite initial equilibration to the open chain aldehyde. Whereas triene installation from lactol **16** required room temperature, aldehyde **14** was completely consumed upon slowly warming from -78 to rt over roughly 15 h. Even with these prolonged reaction times (and consistent with what we had observed previously), the intermediate zirconium alkoxide did not undergo spontaneous Peterson elimination as originally described by Huang and Pi. Instead the reaction was quenched and the crude product treated with NaH in THF at 0 °C to affect a *syn*-Peterson elimination,¹⁸ giving triene **5** with 8:1 selectivity in favor of the desired *Z,Z*-isomer.

With acid **5** in hand we were then able to investigate its esterification with the previously synthesized western domain **4**⁷ in preparation for macrocyclization by RCM. Esterification using Yamaguchi conditions¹⁹ proceeded nicely to give **17** in 86% yield (Scheme 3). Late-stage esterification reactions in the total synthesis of archazolid A by the group of Menche

have utilized the reagent (benzotriazol-1-yloxy)tris(dimethylamino) phosphonium hexafluorophosphate (BOP) for this purpose.²⁰ BOP produces certainly a more mild reaction mixture but is non-ideal due to the formation of hexamethylphosphoramide (HMPA) as a toxic byproduct. The use of Yamaguchi esterification conditions with α,β -unsaturated acids can be problematic²¹ and may explain this group's choice of the BOP reagent. Trauner et al. turned to a ruthenium-mediated Kita esterification for their synthesis of archazolid B, noting that other basic esterification protocols resulted in isomerization of the C₂-C₃ alkene.²² By removal of the C₂-C₃ double bond in our dihydroarchazolid B analogue we eliminate these concerns allowing for the use of this robust and more benign esterification protocol.

Our RCM investigations of **17** centered on the use of Grubbs'-type ruthenium catalysts **Ru-X**, **Ru-Y**, and **Ru-Z** (Table 1).²³ Each catalyst was employed in reactions using either dichloromethane (DCM) or toluene (PhMe) as solvent and at a range of temperatures (room temperature (rt) to 110 °C). For those reactions conducted at rt and up to 50 °C, irrespective of the solvent or catalyst used, analysis of the reaction mixture by ¹H NMR and mass spectrometry (MS) revealed primarily starting material (SM). Increasing the temperature to 80 or 110 °C led to consumption of the starting material and formation of a complex mixture of products. The failure of these RCM reactions was blamed in part on the TBS-protecting group flanking one of the alkenes that is to be engaged for the reaction to be successful as allylic silyloxy substitution is known to diminish metathesis reactivity.²⁴

Unfortunately all conditions tried for removal of the C₁₅-OTBS (numbered according to the natural product) gave either only starting material or decomposition under more forcing conditions (e.g TBAF, HF, TASF). This can be explained in part by the somewhat sensitive nature of the terminal conjugated triene in **17**, particularly to acid. We therefore prepared a new western fragment bearing a more labile TES-protecting group at this position starting from advanced intermediate ketone **18**⁷ (Scheme 4). Gratifyingly, after esterification with **5**, the TES-group could be cleanly removed giving the free hydroxyl RCM substrate **20**.

Treatment of **20** with catalyst **Ru-Y** now led to complete consumption of starting material even at room temperature (Scheme 5). However, none of the desired macrocycle was detected for these as well as other reactions conducted at higher temperature or with catalysts **Ru-X** and **Ru-Z**. Careful examination of MS data along with the ¹H NMR spectrum from these crude reaction mixtures revealed a competing backbiting process and production of cyclopentene **21**.²⁵ Indeed treatment of **19** alone with catalyst **Ru-Y** at rt led to rapid formation of **21** by NMR analysis. Interestingly, TBS-protected **4** (*ref.* Scheme 4) was inert to these conditions.

We interpreted this lack of reactivity for **4** as the C₁₅-OTBS preventing catalyst engagement of the neighboring alkene altogether and/or cyclopentene formation being hindered by incorporation of a sterically demanding TBS-group. To examine these possibilities we prepared model compound **26** containing a metathesis relay²⁶ to direct catalyst movement adjacent to the allylic -OTBS (Scheme 6). This was accomplished by acyloxysulfone cross-metathesis (CM)²⁷ of **22** followed by a thiazolidinethione chiral auxiliary-driven aldol reaction²⁸ and elimination giving ester **23** in 69% yield for the three steps. Conversion to phosphonate **24** then allowed for HWE-coupling with cinnamyl aldehyde to give *trans*-

ketone **25**. Reduction of the ketone and methylation as previously described for fragment **4**⁷ then gave relay-containing compound **26** in 61% yield from **25**.

Results from the relay-RCM (RRCM) reactions of **26** are summarized in Table 2. Several interesting observations were made during the course of these studies. First, the relay portion of **26** failed to trigger at room temperature, the reaction giving primarily starting material and trace relay intact dimer. Fürstner reported a similarly unreactive metathesis relay tether that was flanked by the large *bis*-spiroketal subunit of the spirastrellolide natural products.²⁹ There are however many examples of metathesis reactions for alkenes bearing allylic OTBS-groups and this type of five-membered ring closure within **26** would be expected to be facile.³⁰ Second, elevating the reaction temperature to 50 or 80 °C resulted not only in relay loss and subsequent formation of cyclopentene **27**, but also generation of **28**. Production of **28** can be explained by a post relay-loss CM with a second equivalent of substrate. All of these metathesis reactions were performed under high dilution (0.005 M). The observation of **28** from some reactions demonstrates that the ruthenium alkylidene intermediate following relay loss does indeed have an appreciable lifetime under certain conditions. Macrocyclization by RRCM through formation of the ^{13,14} alkene might therefore be possible.

In conclusion, we have developed an optimized synthesis of a suitable “eastern fragment” carboxylic acid **6** toward the preparation of a dihydroarchazolid B analogue. Highlights include a Cram-chelate controlled vinylalanane addition and installation of the Z,Z-terminal triene by a tandem allylzirconation/Peterson elimination. Our ability to perform a Yamaguchi esterification of **6** with a fully functionalized western domain supports an anticipated enhanced stability for our proposed analogue relative to the natural product. Initial RCM attempts failed, and this was blamed on the presence of a sterically large C₁₅-OTBS flanking one of the reacting alkenes. We therefore synthesized a substrate containing a free-hydroxyl at this position which led to the discovery of a competing backbiting process and formation of cyclopentene **21**. Cyclopentene formation could be slowed by incorporation of a TBS-protecting group on the C₁₅-hydroxyl that in combination with a relay tether may allow for a novel RRCM approach to the archazolid macrocycle.²²

Experimental Section

All reactions were carried out under N₂ in flame-dried glassware. The solvents used were dried by passing the solvent through a column of activated alumina under nitrogen immediately prior to use. All other reagents were purchased and used as received. All TLC analysis used 0.25 mm silica layer fluorescence UV254 plates. Flash chromatography: SilaCycle silica gel P60 (230–400 mesh). IR: Nicolet iS10 spectrometer, wavenumbers ($\bar{\nu}$) in cm⁻¹. NMR: Spectra were recorded on a Varian Mercury 300, or Inova 500 spectrometer in the solvents indicated; chemical shifts (δ) are given in ppm, coupling constants (*J*) in Hz. The solvent signals were used as references (CDCl₃: δ C = 77.0 ppm; residual CHCl₃ in CDCl₃: δ H = 7.26 ppm). MS(ESI): Waters LCT Premier mass spectrometer.

Alcohol **9**.

To a solution of zirconocene dichloride (0.88 g, 3.0 mmol) in DCM (100 mL) at –20 °C was added trimethylaluminum (2.0 M, 30.0 mL) and water (0.54 mL, 30 mmol) and the mixture

was warmed to rt for 10 min. The reaction was then cooled to 0 °C before adding alkyne **7**¹¹ (6.4 g, 30 mmol) and the mixture was stirred for 40 min. Aldehyde **8**¹² (5.0 g, 24 mmol) was then added and the reaction was stirred for 1 h before quenching carefully with ice-cold water (30 mL) and aq. HCl (1.0 M, 30 mL) and extracting with DCM (2 × 50 mL). The combined organic extracts were dried over MgSO₄, filtered, and concentrated *in vacuo*. Purification by flash column chromatography on silica (10:1 to 2:1 hexanes:ethyl acetate) afforded **9** (8.6 g, 85%) as a partially separable 6:1 mixture of diastereomers; *Spectral data for the major stereoisomer*: IR (ATR) 3320, 2932, 2861, 1640, 1439, 1058, 992, 907 cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ 7.25 (d, *J* = 8.5 Hz, 2H), 6.87 (d, *J* = 8.5 Hz, 2H), 5.15 (dd, *J* = 9.0, 1.0 Hz, 1H), 4.46 (s, 2H), 4.27 (dd, *J* = 7.0, 1.5 Hz, 1H), 3.80 (s, 3H), 3.60 (t, *J* = 5.5 Hz, 2H), 3.55 (dd, *J* = 9.5, 5.0 Hz, 1H), 3.45 (dd, *J* = 9.5, 8.0 Hz, 1H), 3.18 (d, *J* = 2.5 Hz, OH), 2.02 (t, *J* = 7.5 Hz, 2H), 1.88 (m, 1H), 1.65 (d, *J* = 1.5 Hz, 3H), 1.48 (m, 4H), 0.89 (s, 9H), 0.80 (d, *J* = 7.0 Hz, 3H), 0.04 (s, 6H). ¹³C NMR (125 MHz, CDCl₃): δ 158.9, 139.0, 131.0, 129.1, 127.1, 113.6, 72.6, 72.4, 63.0, 55.2, 39.4, 32.5, 26.0, 24.0, 18.3, 16.7, 13.0, -5.3. HRMS (TOF ES⁺): Calcd for C₂₅H₄₄O₄SiNa (M + Na)⁺: 425.2906. Found 425.2909.

Alcohol 10.

To a solution of **9** (7.5 g, 17.7 mmol) in DCM (90 mL) at 0 °C was added imidazole (3.02 g, 44.4 mmol) and TBSCl (3.5 g, 23.0 mmol) and the mixture was allowed to slowly warm to rt for 15 h. The reaction was quenched with water (50 mL) and extracted with DCM (2 × 30 mL). The combined organic extracts were dried over MgSO₄, filtered through a plug of silica, and concentrated *in vacuo*. The crude product was used directly without further purification; ¹H NMR (500 MHz, CDCl₃): δ 7.26 (d, *J* = 9.0 Hz, 2H), 6.87 (d, *J* = 9.0 Hz, 2H), 5.10 (dd, *J* = 9.0, 1.0 Hz, 1H), 4.40 (m, 2H), 4.31 (dd, *J* = 9.5, 7.0 Hz, 1H), 3.81 (s, 3H), 3.61 (t, *J* = 5.5 Hz, 2H), 3.46 (dd, *J* = 9.0, 5.5 Hz, 1H), 3.32 (dd, *J* = 9.0, 6.5 Hz, 1H), 1.99 (t, *J* = 7.5 Hz, 2H), 1.85 (m, 1H), 1.61 (d, *J* = 1.0 Hz, 3H), 1.52–1.42 (m, 4H), 0.90 (s, 9H), 0.85 (s, 9H), 0.84 (d, *J* = 7.0 Hz, 3H), 0.05 (s, 3H), 0.01 (s, 3H), 0.00 (s, 3H), -0.03 (s, 3H). ¹³C NMR (125 MHz, CDCl₃): δ 158.9, 136.0, 131.0, 129.1, 127.1, 113.63, 72.6, 72.4, 70.8, 63.0, 55.2, 40.8, 39.4, 32.5, 26.0, 25.7, 24.0, 18.3, 16.7, 13.0, -2.9, -4.1, -4.8, -5.3.

To a solution of the crude TBS-ether (1.1 g, 2.0 mmol) in DCM (20 mL) and pH = 7 buffer (20 mL) was added portionwise DDQ (1.1 g, 6.0 mmol) and the resulting mixture was stirred vigorously for 30 min. The layers were then separated and the organic phase was diluted with MTBE (20 mL) and washed with aq. NaOH (1.0 M, 20 mL). The organic phase was dried over MgSO₄, filtered and concentrated *in vacuo*. Purification by flash column chromatography on silica (10:1 to 4:1 hexanes:ethyl acetate) afforded **10** (0.82 g, 95%) as an oil; [α]_D²⁰ = -5.3 (*c* 1.0, CH₂Cl₂). IR (ATR) 3318, 2926, 2861, 1635, 1430, 1058, 992, 907 cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ 5.18 (dd, *J* = 9.5, 1.5 Hz, 1H), 4.27 (dd, *J* = 8.5, 1.5 Hz, 1H), 3.70 (m, 1H), 3.60 (t, *J* = 6.0 Hz, 2H), 3.58 (m, 1H), 3.12 (m, OH), 2.00 (t, *J* = 6.0 Hz, 2H), 1.66 (m, 1H), 1.60 (s, 3H), 1.52 – 1.42 (m, 4H), 0.88 (s, 9H), 0.87 (s, 9H), 0.84 (d, *J* = 7.0 Hz, 3H), 0.05 (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H), 0.01 (s, 3H). ¹³C NMR (125 MHz, CDCl₃): δ 136.4, 127.7, 75.8, 66.9, 62.9, 41.6, 39.3, 32.5, 25.9, 25.8, 23.9, 18.3, 18.0, 16.7, 13.8, -3.9, -5.1, -5.3. HRMS (TOF ES⁺): Calcd for C₂₃H₅₀O₃Si₂Na (M + Na)⁺: 453.3196. Found 453.3193.

Ester 12.

To a solution of oxalyl chloride (0.33 mL, 3.8 mmol) in DCM (20 mL) at -78°C was added DMSO (0.41 mL, 5.7 mmol) and the mixture was stirred for 15 min. Alcohol **10** (0.82 g, 1.9 mmol) was then added and the mixture was stirred for 20 min before adding triethylamine (1.33 mL, 9.5 mmol). The reaction was warmed to rt for 1 h before quenching with water (20 mL) and extracting with DCM (2×20 mL). The combined organic extracts were dried over MgSO_4 , filtered through a plug of silica and concentrated *in vacuo*. The crude aldehyde was used immediately without further purification.

To a solution of phosphonate **11**¹⁶ (0.67 g, 1.93 mmol) in THF (16 mL) at -78°C was added KHMDS (1.0 M, 3.8 mL) and the mixture was stirred for 30 min before adding the crude aldehyde (0.69 g, 1.61 mmol) and the mixture was allowed to slowly warm to rt for 15 h. The reaction was quenched with aq. NaHCO_3 (20 mL) and extracted with MTBE (2×20 mL). The combined organic extracts were dried over MgSO_4 , filtered, and concentrated *in vacuo*. Purification by flash column chromatography on silica (20:1 hexanes:ethyl acetate) afforded **12** (0.81 g, 98%) as an oil; $[\alpha]_{\text{D}}^{20} = -3.9$ (c 0.5, CH_2Cl_2). IR (ATR) 2890, 1703, 1359, 1236, 1166, 1058, 943 cm^{-1} . ^1H NMR (500 MHz, CDCl_3): δ 5.80 (dd, $J = 9.5, 1.0$ Hz, 1H), 5.07 (dd, $J = 8.0, 1.0$ Hz, 1H), 4.20–4.10 (m, 3H), 3.60 (t, $J = 6.0$ Hz, 2H), 3.18 (m, 1H), 1.97 (t, $J = 7.5$ Hz, 2H), 1.88 (d, $J = 1.5$ Hz, 3H), 1.58 (d, $J = 1.5$ Hz, 3H), 1.52–1.40 (m, 4H), 1.28 (t, $J = 7.5$ Hz, 3H), 0.93 (d, $J = 7.0$ Hz, 3H), 0.88 (s, 9H), 0.85 (s, 9H), 0.04 (s, 6H), 0.00 (s, 3H), -0.03 (s, 3H). ^{13}C NMR (125 MHz, CDCl_3): δ 168.2, 145.3, 135.8, 127.3, 126.7, 73.0, 63.0, 59.9, 40.7, 39.3, 32.4, 26.0, 25.8, 24.0, 20.9, 18.1, 16.6, 16.1, 14.3, -4.1 , -4.9 , -5.3 . HRMS (TOF ES⁺): Calcd for $\text{C}_{28}\text{H}_{56}\text{O}_4\text{Si}_2\text{Na}$ ($M + \text{Na}$): 535.3615. Found 535.3608.

Acid 13.

To a solution of **12** (0.3 g, 0.60 mmol) in acetone (10 mL) at 0°C was added the Jones reagent (0.5 mL) and the resulting red solution was stirred for 1 h. The reaction was quenched with *i*-PrOH (1.0 mL) and then washed with water (15 mL) and extracted with MTBE (2×15 mL). The combined organic extracts were dried over MgSO_4 , filtered, and concentrated *in vacuo*. Purification by flash column chromatography on silica (4:1 hexanes:ethyl acetate) afforded **13** (0.21 g, 90%) as an oil; $[\alpha]_{\text{D}}^{20} = -2.8$ (c 0.3, CH_2Cl_2). IR (ATR) 3360, 2922, 2852, 1659, 1632, 1461, 1377, 1045, 722 cm^{-1} . ^1H NMR (500 MHz, CDCl_3): δ 5.80 (dd, $J = 10.0, 1.5$ Hz, 1H), 5.10 (dd, $J = 8.5, 1.0$ Hz, 1H), 4.20–4.10 (m, 3H), 3.19 (m, 1H), 2.31 (t, $J = 7.0$ Hz, 2H), 2.02 (t, $J = 5.5$ Hz, 2H), 1.88 (d, $J = 1.0$ Hz, 3H), 1.74 (m, 2H), 1.60 (s, 3H), 1.28 (t, $J = 7.0$ Hz, 3H), 0.94 (d, $J = 7.0$ Hz, 3H), 0.85 (s, 9H), 0.01 (s, 3H), -0.03 (s, 3H). ^{13}C NMR (125 MHz, CDCl_3): δ 179.4, 168.3, 144.9, 134.3, 128.5, 126.9, 72.8, 60.0, 40.6, 38.8, 33.3, 25.8, 25.7, 22.6, 20.9, 18.1, 16.5, 16.2, 14.2, -4.2 , -4.9 . HRMS (TOF ES⁺): Calcd for $\text{C}_{22}\text{H}_{40}\text{O}_5\text{SiNa}$ ($M + \text{Na}$)⁺: 435.2543. Found 435.2553.

Eastern fragment 5.

To a solution of **13** (0.2 g, 0.50 mmol) in Et_2O (5 mL) at -78°C was added LiAlH_4 (57 mg, 1.5 mmol) and the mixture was slowly warmed to -40°C over 2 h (until completion by TLC). The reaction was quenched with aq. HCl (1.0 M, 15 mL) and extracted with EtOAc (2×15 mL). The combined organic extracts were dried over MgSO_4 , filtered through a plug of

silica and concentrated *in vacuo*. The crude alcohol was used immediately without further purification.

To a solution of the crude alcohol in DCM (5.0 mL) at 0 °C was added NaHCO₃ (0.21 g, 2.5 mmol) and Dess-Martin periodinane (0.32 g, 0.75 mmol) and the mixture was stirred for 1 h. The reaction was quenched with 1:1 aq. Na₂S₂O₃:NaHCO₃ (10 mL:10 mL) and stirred vigorously for 45 min. The layers were separated and the aqueous phase was extracted with DCM (15 mL). The combined organic extracts were dried over MgSO₄, filtered, and concentrated *in vacuo*. Purification by flash column chromatography on silica (10:1 to 4:1 hexanes:ethyl acetate) afforded the somewhat sensitive aldehyde **14** (0.14 g, 76% 2 steps) that was used immediately in the next reaction.

To a suspension of zirconocene hydrochloride (0.30 g, 1.16 mmol) in DCM (3.8 mL) at –78 °C was added 1-methyl-1-(trimethylsilyl)-allene (0.38 mL, 1.52 mmol) and the mixture was warmed to room temperature for 15 min (until a red homogeneous solution developed) and then cooled back to –78 °C. To the allylzirconocene thus obtained was added aldehyde **14** (0.14 g, 0.38 mmol) and the reaction was allowed to slowly warm to rt for 15 h. The reaction was quenched with aq. NaHCO₃ (15 mL) and extracted with DCM (2 × 15 mL). The combined organic extracts were dried over MgSO₄, filtered, and concentrated *in vacuo*. The crude product was triturated with hexanes and then redissolved in THF (3.8 mL) at 0 °C. NaH (0.11 g, 4.56 mmol) was added and the mixture was warmed to room temperature for 1 h before diluting with MTBE (15 mL) and washing with aq. NH₄Cl (15 mL). The layers were separated and the organic phase dried over MgSO₄, filtered, and concentrated *in vacuo*. Purification by flash column chromatography on silica (10:1 to 4:1 hexanes:ethyl acetate) afforded **5** (0.14 g, 91%) as an inseparable 8:1 (NMR) mixture of *Z:E* isomers; [α]_D²⁰ = –6.6 (*c* 0.5, CH₂Cl₂). IR (ATR) 2988, 2970, 1631, 1604, 1505, 1437, 1391, 1229, 1029, 896, 854, 826 cm^{–1}. ¹H NMR (500 MHz, CDCl₃): δ 6.68 (dd, *J* = 18.0, 11.0 Hz, 1H), 5.82 (s, 1H), 5.18 (dd, *J* = 17.5, 1.0 Hz, 1H), 5.11 (m, 1H), 5.09 (m, 1H), 5.04 (dd, *J* = 10.5, 1.5 Hz, 1H), 4.10 (dd, *J* = 9.0, 5.5 Hz, 1H), 2.40 – 2.30 (m, 3H), 2.01 (t, *J* = 7.5 Hz, 2H), 1.85 (s, 3H), 1.76 (s, 3H), 1.75 (m, 2H), 1.58 (s, 3H), 0.86 (d, *J* = 7.0 Hz, 3H), 0.85 (s, 9H), –0.01 (s, 3H), –0.03 (s, 3H). ¹³C NMR (125 MHz, CDCl₃): δ 178.9, 135.7, 133.8, 133.0, 132.1, 132.0, 130.4, 128.4, 113.4, 72.8, 40.4, 38.8, 33.2, 25.8, 24.5, 22.7, 19.4, 18.1, 16.5, 15.7, –4.4, –4.9. HRMS (TOF ES⁺): Calcd for C₂₄H₄₂O₃SiNa (M + Na)⁺: 429.2801. Found 429.2797.

RCM substrate **17**.

To a solution of alcohol **4**⁷ (20 mg, 0.034 mmol) and acid **5** (16 mg, 0.040 mmol) in toluene (3.0 mL) at –78 °C was added triethylamine (0.06 mL, 0.41 mmol), DMAP (0.10 g, 0.85 mmol) and 2,4,6-trichlorobenzoylchloride (0.06 mL, 0.38 mmol) and the resulting mixture was allowed to slowly warm to rt for 15 h. The reaction was quenched with aq. NaHCO₃ (15 mL) and extracted with MTBE (2 × 15 mL). The combined organic extracts were dried over MgSO₄, filtered, and concentrated *in vacuo*. Purification by flash column chromatography on silica (4:1 to 2:1 hexanes:ethyl acetate) afforded **17** (29 mg, 86%) as an oil; [α]_D²⁰ = –5.2 (*c* 0.5, CH₂Cl₂). IR (ATR) 3062, 2983, 1736, 1614, 1415, 1274, 1267, 1129, 1078, 930 cm^{–1}. ¹H NMR (500 MHz, CDCl₃): δ 7.01 (s, 1H), 6.67 (dd, *J* = 17.5, 11.0 Hz, 1H), 6.24

(dd, $J = 15.0, 11.0$ Hz, 1H), 6.06 (dd, $J = 9.0, 5.0$ Hz, 1H), 5.86 (s, 1H), 5.84 (dd, $J = 6.5, 2.5$ Hz, 1H), 5.82 – 5.78 (m, 4H), 5.55 (dd, $J = 14.5, 8.5$ Hz, 1H), 5.17 (d, $J = 17.5$, 1H), 5.08 (d, $J = 9.5$ Hz, 1H), 5.03 (ddd, $J = 10.5, 3.5, 1.5$ Hz, 1H), 4.76 (d, $J = 4.5$ Hz, 1H), 4.62 (d, $J = 5.5$ Hz, 1H), 4.09 (m, 1H), 4.08 (dd, $J = 8.5, 5.5$ Hz, 1H), 3.32 (d, $J = 10$ Hz, 1H), 3.10 (s, 3H), 3.00 (dd, $J = 9.5, 7.0$ Hz, 1H), 2.82 (d, $J = 5.0$ Hz, 3H), 2.35 (m, 2H), 2.31 (t, $J = 8.0$ Hz, 2H), 1.96 (t, $J = 8.0$ Hz, 2H), 1.88 (m, 1H), 1.84 (s, 3H), 1.70 (m, 2H), 1.74 (s, 3H), 1.72 (m, 2H), 1.58 (s, 3H), 1.55 (d, $J = 1.5$ Hz, 3H), 0.97 (d, $J = 2.5$ Hz, 3H), 0.96 (d, $J = 3.0$ Hz, 3H), 0.95 (d, $J = 6.5$ Hz, 3H), 0.92 (s, 9H), 0.84 (s, 9H), 0.82 (d, $J = 7.0$ Hz, 3H), 0.60 (d, $J = 7.0$ Hz, 3H), 0.05 (s, 3H), 0.00 (s, 3H), -0.03 (s, 3H), -0.06 (s, 3H). ^{13}C NMR (125 MHz, CDCl_3): δ 172.8, 171.2, 155.9, 154.3, 141.5, 135.7, 134.5, 134.4, 134.0, 133.0, 132.1, 131.9, 130.4, 129.6, 128.2, 127.1, 116.0, 113.7, 113.4, 88.1, 75.1, 72.8, 72.1, 71.1, 55.5, 44.4, 41.6, 41.5, 40.4, 38.9, 33.8, 29.7, 27.6, 26.0, 25.9, 25.8, 24.6, 24.5, 23.0, 22.1, 19.4, 18.2, 18.1, 16.9, 16.5, 15.6, 10.5, 8.6, -3.9 , -4.3 , -4.9 , -5.2 . HRMS (TOF ES $^{+}$): Calcd for $\text{C}_{55}\text{H}_{94}\text{N}_2\text{O}_7\text{SSi}_2\text{Na}$ ($\text{M} + \text{Na}$) $^{+}$: 1005.6218. Found 1005.6210.

Alcohol 19.

To a solution of ketone **18**⁷ (0.30 g, 0.45 mmol) in THF (5 mL) at 0 °C was added HF-pyridine (70%, 185 μL) and the mixture was kept at 4 °C for 20h. The reaction was quenched with aq. NaHCO_3 (10 mL) and extracted with MTBE (2×10 mL). The combined organic extracts were dried over MgSO_4 , filtered, and concentrated *in vacuo*. Purification by flash column chromatography on silica (4:1 to 1:1 hexanes:ethyl acetate) afforded alcohol **18–2** (0.21 g, 82%) as an oil. IR (ATR) 3405, 2955, 2928, 2855, 2323, 1687, 1472, 1384, 1321, 1250, 1147, 1084, 1024, 920, 834, 775, 671. ^1H NMR (500 MHz, CDCl_3): δ 8.12 (s, 1H), 6.45 (ddd, $J = 17.2, 10.7, 2.3$ Hz, 1H), 5.95 – 5.75 (m, 3H), 5.16 (dd, $J = 17.1, 1.5$ Hz, 1H), 5.08 (m, 1H), 5.03 (dd, $J = 10.7, 5.0$ Hz, 1H), 4.61 (d, $J = 5.4$ Hz, 1H), 4.43 (m, 1H), 3.34 (d, $J = 9.9$ Hz, 1H), 3.09 (d, $J = 1.4$ Hz, 3H), 2.68 (bs, OH), 1.91 (m, 1H), 1.79 (t, $J = 6.4$ Hz, 2H), 1.58 (m, 1H), 1.35 (dd, $J = 2.8, 6.9$ Hz, 3H), 1.25 (s, 3H), 1.01 (m, 6H), 0.91 (s, 9H), 0.59 (d, $J = 6.9$ Hz, 3H), 0.04 (s, 3H), -0.01 (s, 3H). ^{13}C NMR (75 MHz, CDCl_3): δ 195.95, 175.69, 153.99, 141.72, 135.77, 132.67, 129.64, 127.68, 126.38, 113.99, 88.34, 71.42, 70.62, 55.86, 47.46, 47.43, 46.52, 41.94, 29.90, 26.28, 24.80, 23.44, 22.07, 18.45, 16.96, 8.85, -3.73 , -5.04 . HRMS (TOF ES $^{+}$): Calcd for $\text{C}_{29}\text{H}_{49}\text{NO}_4\text{SSiNa}^{+}$ ($\text{M} + \text{Na}$) $^{+}$: 558.3049. Found: 558.3052.

To a solution of **18–2** (0.21 g, 0.36 mmol) in DCM (7.3 mL) was added carbonyldiimidazole (240 mg, 1.46 mmol) portionwise over 1h. The solution was then cooled to 0 °C before adding methylamine (2.0 M, 1.1 mL) and mixture was allowed to warm to rt over 4 h. The reaction was quenched with aq. NaHCO_3 (15 mL) and extracted with DCM (2×10 mL). The combined organic extracts were dried over MgSO_4 , filtered, and concentrated *in vacuo*. Purification by flash column chromatography on silica (4:1 to 1:1 hexanes:ethyl acetate) afforded ketone **18–3** (212 mg, 91%) as an oil. IR (ATR) 3350, 2956, 2929, 1721, 1687, 1527, 1472, 1386, 1249, 1126, 1085, 919, 833, 774, 647. ^1H NMR (500 MHz, CDCl_3): δ 8.11 (d, $J = 2.4$ Hz, 1H), 6.46 (m, 1H), 6.08 (m, 1H), 5.95 – 5.75 (m, 3H), 5.16 (dd, $J = 17.2, 1.7$ Hz, 1H), 5.03 (dd, $J = 10.6, 1.7$ Hz, 1H), 4.78 (s, 1H), 4.61 (m, 1H), 4.47 (m, 1H), 3.34 (d, $J = 9.9$ Hz, 1H), 3.11 (m, 3H), 2.83 (d, $J = 4.7$ Hz, 3H), 1.89 (m, 2H), 1.76 (m, 1H), 1.59 (m, 4H), 1.35 (m, 3H), 0.99 (m, 6H), 0.91 (s, 9H), 0.58 (m, 3H), 0.04 (s, 3H), -0.01 (s, 3H).

^{13}C NMR (125 MHz, CDCl_3): δ 195.90, 171.48, 156.06, 154.24, 141.72, 135.71, 132.65, 129.76, 127.72, 126.22, 113.99, 88.35, 72.45, 71.37, 55.88, 46.44, 44.28, 41.91, 27.91, 26.19, 24.80, 23.15, 22.36, 18.46, 16.62, 10.86, 8.87, -3.72 , -5.04 . HRMS (TOF ES $^{+}$): Calcd for $\text{C}_{31}\text{H}_{52}\text{N}_2\text{O}_5\text{SSiNa}^{+}$ ($\text{M}+\text{Na}$) $^{+}$: 615.3264. Found: 615.3256.

To a solution of ketone **18–3** (42 mg, 0.07 mmol) in THF (1.5 mL) at 0 °C was added HF-pyridine (70%, 0.39 mL) and the mixture was kept at rt for 20h. The reaction was quenched with aq. NaHCO_3 (5 mL) and extracted with MTBE (2×10 mL). The combined organic extracts were dried over MgSO_4 , filtered, and concentrated *in vacuo*. Purification by flash column chromatography on silica (4:1 to 1:1 hexanes:ethyl acetate) afforded the intermediate secondary alcohol **19** (27 mg, 86%) as an oil. IR (ATR) 3350, 2959, 2929, 2871, 1715, 1687, 1532, 1472, 1368, 1252, 1125, 1082, 964, 920, 813, 750. ^1H NMR (500 MHz, CDCl_3): δ 8.11 (s, 1H), 6.44 (ddd, $J = 17.2, 10.7, 2.3$ Hz, 1H), 6.08 (dd, $J = 8.3, 2.7$ Hz, 1H), 5.94–5.79 (m, 3H), 5.29 (dd, $J = 17.2, 1.7$ Hz, 1H), 5.19 (d, $J = 10.6$ Hz, 1H), 4.79 (m, 1H), 4.47 (m, 1H), 4.19 (s, 1H), 3.41 (d, $J = 9.7$ Hz, 1H), 3.13 (d, $J = 8.7$ Hz, 3H), 2.10–2.01 (m, 2H), 1.96–1.83 (m, 4H), 1.77 (m, 1H), 1.65 (s, 3H), 1.35 (dd, $J = 6.9, 1.8$ Hz, 3H), 0.98 (m, 6H), 0.67 (dd, $J = 12.2, 7.2$ Hz, 3H). ^{13}C NMR (125 MHz, CDCl_3): δ 195.86, 171.59, 156.11, 154.38, 138.42, 134.36, 133.61, 129.61, 127.58, 126.28, 115.39, 90.82, 75.72, 56.01, 46.50, 44.38, 40.07, 29.93, 27.92, 24.84, 23.19, 22.36, 16.76, 13.12, 11.28. HRMS (TOF ES $^{+}$): Calcd for $\text{C}_{25}\text{H}_{38}\text{N}_2\text{O}_5\text{SNa}^{+}$ ($\text{M}+\text{Na}$) $^{+}$: 501.2399. Found: 501.2388.

Hydroxy-RCM substrate 20.

To a solution of alcohol **19** (27 mg, 0.057 mmol) in DCM (1.0 mL) at -78 °C was added 2,6-lutidine (10 μL , 0.086 mmol) and TES-OTf (15 μL , 0.068 mmol) and the resulting mixture was stirred for 2.5 h. The reaction was quenched with aq. NaHCO_3 (5 mL) and extracted with DCM (2×2 mL). The combined organic extracts were dried over MgSO_4 , filtered, and concentrated *in vacuo*. Purification by flash column chromatography on silica (4:1 to 1:1 hexanes:ethyl acetate) afforded ketone **19–2** (27 mg, 81%) as an oil. IR (ATR) 3350, 3955, 2929, 2872, 1716, 1688, 1525, 1471, 1418, 1369, 1244, 1126, 1084, 1008, 963, 919, 828, 730. ^1H NMR (300 MHz, CDCl_3): δ 8.10 (s, 1H), 6.46 (m, 1H), 6.28 (t, $J = 5.6$ Hz, 1H), 5.94–5.76 (m, 3H), 5.17 (d, $J = 17.2$ Hz, 1H), 5.03 (dd, $J = 10.4, 1.2$ Hz, 1H), 4.78 (d, $J = 4.1$ Hz, 1H), 4.64 (d, $J = 5.7$ Hz, 1H), 4.46 (dd, $J = 6.9, 6.9$ Hz, 1H), 3.35 (d, $J = 10$ Hz, 1H), 3.12 (d, $J = 5.4$ Hz, 3H), 2.83 (d, $J = 4.8$ Hz, 3H), 1.89 (m, 2H), 1.77 (m, 1H), 1.60 (m, 1H), 1.59 (s, 3H), 1.35 (dd, $J = 6.8, 2.2$ Hz, 3H), 0.96 (m, 15H), 0.58 (m, 9H). ^{13}C NMR (75 MHz, CDCl_3): δ 195.90, 171.48, 171.16, 156.07, 154.27, 141.87, 135.73, 132.83, 129.77, 127.74, 126.20, 113.81, 88.39, 72.46, 71.78, 55.85, 46.46, 44.30, 41.97, 27.90, 24.82, 23.15, 22.37, 16.63, 10.88, 8.91, 7.19, 5.27. HRMS (TOF ES $^{+}$): Calcd for $\text{C}_{31}\text{H}_{52}\text{N}_2\text{O}_5\text{SSiNa}^{+}$ ($\text{M}+\text{Na}$) $^{+}$: 615.3264. Found: 615.3259.

To a solution of ketone **19–2** (27 mg, 0.046 mmol) in THF (0.5 mL) at -78 °C was added L-Selectride (1.0 M, 70 μL) and the mixture was stirred for 30 min. The reaction was quenched with aq. NH_4Cl (15 mL) and extracted with MTBE (2×15 mL). The combined organic extracts were dried over MgSO_4 , filtered, and concentrated *in vacuo*. Purification by flash column chromatography on silica (4:1 to 1:1 hexanes:ethyl acetate) afforded **19–3** (28 mg, 98%) as a 10:1 (NMR) mixture of stereoisomers. *Spectral data for the major stereoisomer.*

IR (ATR) 3212, 3996, 2875, 1713, 1455, 1242, 1196, 1127, 1085, 1005, 964, 739. ^1H NMR (500 MHz, CDCl_3): δ 7.07 (s, 1H), 6.34 (m, 1H), 6.04 (m, 1H), 5.86 (m, 3H), 5.61 (q, J = 7.8 Hz, 1H), 5.18 (dt, J = 1.5, 10.4 Hz, 1H), 4.75 (bs, 1H), 4.65 (m, 1H), 4.61 (m, 1H), 3.36 (d, J = 9.8 Hz, 1H), 3.14 (d, J = 2.9 Hz, 3H), 2.81 (d, J = 4.7 Hz, 3H), 2.44 (bs, 1H), 1.96–1.40 (m, 5H), 1.59 (s, 3H), 1.00–0.90 (m, 18H), 0.70–0.50 (m, 9H). ^{13}C NMR (125 MHz, CDCl_3): δ 171.33, 156.20, 141.89, 134.90, 129.67, 129.66, 127.87, 114.64, 113.84, 88.41, 71.73, 55.85, 49.67, 44.72, 44.01, 41.93, 29.91, 27.84, 27.19, 24.81, 23.24, 22.22, 16.83, 14.34, 10.87, 8.93, 7.21, 5.27. HRMS (TOF ES $^+$): Calcd for $\text{C}_{31}\text{H}_{54}\text{N}_2\text{O}_5\text{SSiNa}^+$ ($\text{M}+\text{Na}$) $^+$: 617.3420. Found: 617.3426.

To a solution of acid **5** (20 mg, 0.049 mmol) and alcohol **19-3** (16 mg, 0.027 mmol) in toluene (2.7 mL) at -78°C was added Et_3N (45 μL , 0.32 mmol), DMAP (82 mg, 0.68 mmol) and 2,4,6-trichlorobenzoylchloride (48 μL , 0.31 mmol) and the mixture was warmed to rt for 15 h. The reaction was quenched with aq. NaHCO_3 (5 mL) and extracted with EtOAc (2×3 mL). The combined organic extracts were dried over MgSO_4 , filtered, and concentrated *in vacuo*. Purification by flash column chromatography on silica (4:1 to 1:2 hexanes:ethyl acetate) afforded ester **19-4** (16 mg, 60%) as an oil. ^1H NMR (500 MHz, CDCl_3): δ 7.06 (s, 1H), 6.67 (dd, J = 11, 17.6 Hz, 1H), 6.23 (m, 1H), 6.05 (m, 1H), 5.90–5.78 (m, 4H), 5.55 (dd, J = 14.8, 8.6 Hz, 1H), 5.17 (dd, J = 6.5, 17.3 Hz, 1H), 5.10–5.00 (m, 4H), 4.75 (bs, 1H), 4.65 (d, J = 5.4 Hz, 1H), 4.20–4.10 (m, 2H), 3.34 (dd, J = 2.9, 10.2 Hz, 1H), 3.13 (d, J = 12.2 Hz, 3H), 3.01 (m, 1H), 2.82 (d, J = 4.6 Hz, 3H), 2.31 (m, 2H), 2.01–1.51 (m, 9H), 1.84 (d, J = 1.1 Hz, 3H), 1.74 (s, 3H), 1.55 (s, 6H), 1.25 (s, 6H), 0.99–0.81 (m, 27H), 0.59 (m, 6H), -0.03 (s, 3H), -0.06 (s, 3H). ^{13}C NMR (75 MHz, CDCl_3): δ 173.05, 171.53, 156.27, 156.26, 154.55, 142.02, 136.03, 134.81, 134.34, 133.38, 132.41, 132.34, 130.72, 129.83, 128.59, 127.28, 113.95, 113.76, 88.54, 73.14, 71.90, 71.88, 55.93, 55.82, 44.81, 42.07, 41.82, 40.75, 39.27, 34.18, 30.04, 27.99, 26.17, 24.97, 24.86, 23.35, 22.46, 19.70, 18.49, 17.21, 17.18, 15.96, 10.90, 9.03, 7.33, 5.41, -3.98 , -4.55 .

To a solution of **19-4** (15 mg, 0.0153 mmol) in THF (2 mL) at 0°C was added HF-pyridine (70%, 50 μL) and the mixture was kept at 4°C for 20 h. The reaction was quenched with aq. NaHCO_3 (5 mL) and extracted with EtOAc (2×5 mL). The combined organic extracts were dried over MgSO_4 , filtered, and concentrated *in vacuo*. Purification by flash column chromatography on silica (4:1 to 1:1 hexanes:ethyl acetate) afforded the intermediate secondary alcohol **20** (8.7 mg, 65%) as an oil. ^1H NMR (300 MHz, CDCl_3): δ 7.05 (s, 1H), 6.67 (dd, J = 10.7, 17.2 Hz, 1H), 6.22 (m, 1H), 6.05 (m, 1H), 5.97–5.77 (m, 4H), 5.59 (dd, J = 5.8, 1.9 Hz, 1H), 5.54 (d, J = 8.4 Hz, 1H), 5.35–4.99 (m, 5H), 4.76 (bs, 1H), 4.19 (bs, 1H), 3.95 (m, 2H), 3.39 (d, J = 9.9 Hz, 1H), 3.12 (d, J = 6.4 Hz, 3H), 3.02 (m, 1H), 2.81 (d, J = 4.8 Hz, 3H), 2.29 (m, 2H), 2.09–1.51 (m, 21H), 1.24 (s, 3H), 0.99–0.79 (m, 18H), 0.67 (t, J = 7.6 Hz, 3H), -0.03 (s, 3H), -0.06 (s, 3H).

Cyclopentene 21.

To a solution of **19** (50 mg, 0.10 mmol) in degassed DCM (10 mL) was added catalyst **Ru-Y** (4 mg, 0.005 mmol) and the resulting mixture was stirred at rt for 8 h. The reaction was concentrated *in vacuo* and the crude residue purified by flash column chromatography on silica gel (1:1 to 1:2 hexanes:ethyl acetate to 100% ethyl acetate) affording cyclopentene **21**

(12 mg, 90%) as an oil. IR (ATR) 3360, 2925, 1653, 1558, 1456, 1375, 1192, 1090, 1019, 968, 897. ^1H NMR (500 MHz, CDCl_3): δ 5.57 (s, 1H), 4.41 (d, $J = 1.6$ Hz, 1H), 4.17 (d, $J = 6.1$ Hz, 1H), 3.38 (s, 3H), 2.16 (m, 1H), 1.78 (s, 3H), 1.59 (s, 1H), 1.06 (d, $J = 7.2$ Hz, 3H). ^{13}C NMR (125 MHz, CDCl_3): δ 144.79, 130.81, 88.51, 82.72, 58.81, 46.93, 14.98, 12.28. HRMS (TOF CI+) Calcd for $\text{C}_8\text{H}_{13}\text{O}_2^-(\text{M}-\text{H})^-$: 141.0916. Found: 141.0916.

Acyloxysulfone 22.

To a solution of methyl phenyl sulfone (3.75 g, 24 mmol) in THF (100 mL) at -78°C was added lithium bis(trimethylsilyl)amide (1.0 M, 24 mL) and the mixture was warmed to 0°C for 10 min before cooling back to -78°C and adding 5-hexenal (1.96 g, 20 mmol). The reaction was allowed to warm to rt and stirred for 5 h before cooling to -78°C and adding acetyl chloride (1.43 mL, 20 mmol) and the mixture was allowed to slowly warm to rt for 15 h. The reaction was quenched with aq. NH_4Cl (100 mL) and extracted with MTBE (2×50 mL). The combined organic extracts were dried over MgSO_4 , filtered, and concentrated *in vacuo*. Purification by flash column chromatography on silica (4:1 hexanes:ethyl acetate) afforded **22** (5.4 g, 97%) as an oil; IR (ATR) 2928, 1739, 1640, 1585, 1447, 1305, 1232, 1146, 1085, 1025, 916, 744, 688, 537. ^1H NMR (500 MHz, CDCl_3): δ 7.90 (dd, $J = 1.2, 8.4$ Hz, 2H), 7.68 (dd, $J = 6.7, 1.3$ Hz, 1H), 7.58 (m, 2H), 5.72 (m, 1H), 5.25 (m, 1H), 4.99 (d, $J = 17.0$ Hz, 1H), 4.96 (d, $J = 10.2$ Hz, 1H), 3.46 (dd, $J = 14.8, 8.1$ Hz, 1H), 3.26 (dd, $J = 14.8, 3.4$ Hz, 1H), 2.02 (m, 2H), 1.79 (s, 3H), 1.65 (m, 2H), 1.36 (m, 2H). ^{13}C NMR (125 MHz, CDCl_3): δ 170.09, 137.94, 134.05, 129.53, 128.43, 115.49, 68.12, 59.45, 33.76, 33.29, 24.14, 20.94. HRMS (TOF ES+) Calcd for $\text{C}_{15}\text{H}_{20}\text{O}_4\text{SNa}^+ (\text{M}+\text{Na})^+$: 319.0980. Found: 319.0971.

Ester 23.

To a solution of **22** (500 mg, 1.79 mmol) and crotonaldehyde (1.50 mL, 17.9 mmol) in degassed toluene (18 mL) was added catalyst **Ru-Y** (38 mg, 0.045 mmol) and the resulting mixture was warmed to 60°C for 6 h before cooling to rt and concentrating *in vacuo*. Purification by flash column chromatography on silica gel (1:1 hexanes:ethyl acetate) afforded aldehyde **22-2** (548 mg, 94%) that was used immediately in the next reaction; ^1H NMR (300 MHz, CDCl_3): δ 9.47 (d, $J = 7.8$ Hz, 1H), 7.89 (d, $J = 7.8$ Hz, 2H), 7.65 (m, 1H), 7.57 (m, 2H), 6.76 (dt, $J = 15.6, 6.6$ Hz, 1H), 6.06 (dd, $J = 15.6, 7.8$ Hz, 1H), 5.25 (m, 1H), 3.45 (dd, $J = 7.7, 14.8$ Hz, 1H), 3.25 (dd, $J = 3.9, 14.8$ Hz, 1H), 2.31 (m, 2H), 1.79 (s, 3H), 1.69 (m, 2H), 1.49 (m, 2H). ^{13}C NMR (75 MHz, CDCl_3): δ 193.82, 169.88, 157.04, 139.36, 133.95, 133.37, 129.37, 128.11, 67.53, 59.11, 33.55, 31.92, 23.05, 20.67, -1.61 .

To a solution of the *N*-acylthiazolidinethione (404 mg, 1.52 mmol) in DCM (6.5 mL) at 0°C was added titanium tetrachloride (1.0 M, 1.6 mL) and the resulting mixture was stirred for 5 min before adding triethylamine (0.21 mL, 1.52 mmol). The mixture was stirred for 10 min before cooling to -78°C and adding *N*-methylpyrrolidine (0.15 mL, 1.52 mmol). The mixture was stirred for 20 min and then aldehyde **22-2** (0.54 g, 1.67 mmol) was added as a solution in DCM (3 mL). The mixture was stirred for 1 h and then warmed to 0°C for 1 h before quenching with aq. half-saturated NH_4Cl (20 mL) and extracting with DCM (2×15 mL). The combined organic extracts were dried over MgSO_4 , filtered, and concentrated *in vacuo*. The crude product was used without further purification.

To a solution of the crude aldol product in DCM:MeOH (10:1, 15 mL) at 0 °C was added imidazole (1.53 g, 22.5 mmol) and the resulting mixture was allowed to slowly warm to rt for 15 h. The reaction was quenched with aq. half-saturated NH₄Cl (30 mL) and extracted with DCM (2 × 15 mL). The combined organic extracts were dried over MgSO₄, filtered, and concentrated *in vacuo*. Purification by flash column chromatography on silica (1:2 hexanes:ethyl acetate to 100% ethyl acetate) afforded the ethyl ester (297 mg, 93%) as a 1:1 (NMR) mixture of diastereomers; *Spectral data for the mixture of stereoisomers*: ¹H NMR (300 MHz, CDCl₃): δ 7.89 (m, 4H), 7.65 (m, 2H), 7.56 (m, 4H), 5.61 (m, 2H), 5.42 (dd, *J* = 1.1, 6.3 Hz, 2H), 5.23 (m, 2H), 4.27 (m, 2H), 3.64 (s, 6H), 3.44 (dd, *J* = 7.9, 10.2 Hz, 2H), 3.26 (dd, *J* = 7.9, 3.6 Hz, 2H), 2.68 (bs, OH (2)), 2.55 (m, 2H), 1.97 (m, 4H), 1.74 (d, *J* = 1.2 Hz, 6H), 1.56 (m, 4H), 1.29 (m, 4H), 1.11 (d, *J* = 7.0 Hz, 3H), 1.10 (d, *J* = 6.8 Hz, 3H). ¹³C NMR (75 MHz, CDCl₃): δ 175.58, 169.85, 139.41, 133.84, 133.68, 131.99, 130.27, 130.23, 129.30, 128.12, 127.29, 73.04, 73.02, 67.78, 67.76, 59.13, 59.07, 51.72, 45.01, 44.99, 44.43, 33.42, 33.36, 31.49, 31.43, 26.94, 24.07, 24.05, 20.66, 11.64, 11.62. HRMS (TOF ES+) Calcd for C₂₀H₂₈O₇SNa⁺ (M+Na)⁺: 435.1454. Found: 435.1449.

To a mixture of sodium mercury amalgam (1.9 g, 4.14 mmol) and NaH₂PO₄ (685 mg, 4.82 mmol) was added MeOH (9 mL) and the substrate (247 mg, 0.60 mmol) as a solution in THF (3 mL). The resulting mixture was stirred for 30 min before filtering through cotton into aqueous brine (20 mL) and extracting with MTBE (2 × 10 mL). The combined organic extracts were dried over MgSO₄, filtered, and concentrated *in vacuo*. Purification by flash column chromatography on silica (1:1 hexanes:ethyl acetate) afforded **23** (87 mg, 72 %) that could be used directly without further purification; ¹H NMR (300 MHz, CDCl₃): δ 5.77 (ddd, *J* = 17.0, 10.1, 6.7 Hz, 1H), 5.66 (m, 1H), 4.43 (ddt, *J* = 15.4, 6.6, 1.3 Hz, 1H), 4.94 (m, 2H), 4.29 (dd, *J* = 5.6, 5.6 Hz, 1H), 3.67 (s, 3H), 2.58 (m, 1H), 2.01 (m, 4H), 1.45 (m, 2H), 1.15 (dd, *J* = 7.5, 0.8 Hz, 3H). ¹³C NMR (75 MHz, CDCl₃): δ 175.68, 138.52, 133.17, 129.41, 144.06, 73.24, 51.71, 45.06, 33.09, 31.58, 28.28, 11.61.

Phosphonate 24 To a solution of **23** (87 mg, 0.41 mmol) in DCM (4.1 mL) at 0 °C was added imidazole (70 mg, 1.03 mmol) and TBSCl (80 mg, 0.53 mmol) and the resulting mixture was allowed to slowly warm for 15 h. The reaction was quenched with MeOH (0.1 mL) and stirred for 30 min before diluting with DCM (15 mL) and washing with water (15 mL). The aqueous phase was re-extracted with DCM (15 mL) and the combined organic extracts were dried over MgSO₄, and filtered through a plug of silica. Concentration under high vacuum (1 × 10⁻³ torr) gave the TBS-ether (129 mg, 96%) that could be used without further purification; ¹H NMR (300 MHz, CDCl₃): δ 5.79 (ddd, *J* = 17.1, 10.1, 6.3 Hz, 1H), 5.57 (dt, *J* = 15.4, 6.7 Hz, 1H), 5.41 (ddt, *J* = 15.4, 6.8, 1.0 Hz, 1H), 4.98 (m, 2H), 4.31 (t, *J* = 6.3 Hz, 1H), 3.63 (s, 3H), 2.49 (dt, *J* = 13.0, 6.9 Hz, 1H), 2.03 (m, 4H), 1.44 (m, 2H), 1.14 (d, *J* = 6.9 Hz, 3H), 0.86 (s, 9H), 0.01 (d, *J* = 0.8 Hz, 3H), -0.01 (d, *J* = 1.0, 3H). ¹³C NMR (75 MHz, CDCl₃): δ 174.96, 138.61, 131.85, 131.54, 114.57, 74.93, 51.35, 47.14, 33.16, 31.47, 28.41, 25.74, 18.07, 11.89, -2.96, -4.05, -5.05.

To a solution of diethyl ethylphosphonate (0.14 mL, 0.84 mmol) in THF (2 mL) at -78 °C was added *n*-butyl lithium (1.6 M, 0.48 mL, 0.78 mmol) and the resulting light-yellow solution was stirred for 30 min before adding TBS-23 (110 mg, 0.34 mmol) as a solution in THF (2 mL). The reaction was stirred for 30 min before quenching with half saturated aq.

NH₄Cl (15 mL) and extracting with MTBE (2 × 15 mL). The combined organic extracts were dried over MgSO₄, filtered, and concentrated *in vacuo*. Purification by flash column chromatography on silica (1:1 hexanes:ethyl acetate) afforded phosphonate **24** (121 mg, 78%) as a 1:1 mixture of diastereomers; *Spectral data for the mixture of stereoisomers*: IR (ATR) 3064, 2903, 1735, 1640, 1350, 1194, 1067, 910, 730 cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ 5.75 (ddd, *J* = 17.0, 6.6, 1.2 Hz, 2H), 5.46 (m, 2H), 5.25 (dtd, *J* = 15.4, 7.8, 1.3 Hz, 2H), 4.96 (dd, *J* = 17.0, 2.0 Hz, 2H), 4.91 (dd, *J* = 10.2, 1.0 Hz, 2H), 4.12–3.98 (m, 10H), 3.58 (q, *J* = 6.9 Hz, 1H), 3.54 (q, *J* = 6.9 Hz, 1H), 3.27 (m, 2H), 1.99 (m, 8H), 1.45–1.35 (m 4H), 1.28 (m, 12H), 1.26 (d, *J* = 7.0 Hz, 3H), 1.20 (d, *J* = 7.0 Hz, 3H), 0.98 (dd, *J* = 6.7, 1.2 Hz, 6H), 0.85 (s, 18H), 0.03 (s, 6H), –0.03 (s, 6H). ¹³C NMR (125 MHz, CDCl₃): δ 208.69, 138.63, 132.85, 132.15, 131.67, 130.18, 114.80, 74.64, 62.58, 53.77, 52.89, 49.01, 48.02, 46.29, 45.25, 33.37, 31.63, 29.35, 25.95, 24.06, 18.24, 16.56, 13.94, 13.31, 11.66, 11.61, 10.47, 10.42, –3.79, –3.98, –4.66, –4.78. HRMS (TOF ES+) Calcd for C₂₃H₄₅O₅PSiNa⁺ (M+Na)⁺: 483.2672. Found: 483.2665.

Ketone 25.

Ba(OH)₂•8H₂O (83 mg, 0.26 mmol) was dried at 130 °C for 3 hours under vacuum prior to cooling to rt and the adding phosphonate **24** (121 mg, 0.26 mmol) as a solution in THF (1.6 mL). The resulting mixture was stirred for 1.25 h and then cinnamic aldehyde (100 μL, 0.79 mmol) was added as a solution in 40:1 THF:H₂O (1.32 mL). The reaction was stirred for 12 h before quenching with aq. NaHCO₃ (15 mL) and extracting with MTBE (2 × 15 mL). The combined organic extracts were washed with 1M HCl (15 mL), dried over MgSO₄, filtered, and concentrated *in vacuo*. Purification by flash column chromatography on silica (20:1 hexanes:ethyl acetate) afforded ketone **25** (100 mg, 87%) as an oil; [*α*]_D²⁰ = –2.8 (*c* 1.0, CH₂Cl₂). IR (ATR) 3064, 2903, 1735, 1640, 1350, 1194, 1067, 910, 730 cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ 7.49 (d, *J* = 7.3 Hz, 2H), 7.37 (t, *J* = 7.2 Hz, 2H), 7.31 (t, *J* = 7.2 Hz, 1H), 7.22–7.11 (m, 2H), 6.91 (d, *J* = 14.8 Hz, 1H), 5.75 (ddd, *J* = 16.9, 10.0, 6.6 Hz, 1H), 5.49 (dt, *J* = 15.4, 6.9 Hz, 1H), 5.34 (dtd, *J* = 15.4, 8.5, 1.1 Hz, 1H), 4.95 (dd, *J* = 17.0, 1.2 Hz, 1H), 4.90 (dd, *J* = 10.1, 1.2 Hz, 1H), 4.19 (dd, *J* = 7.7, 7.7 Hz, 1H), 3.43 (m, 1H), 2.05–1.90 (m, 4H), 1.97 (s, 3H), 1.39 (m, 2H), 1.16 (d, *J* = 6.8 Hz, 3H), 0.89 (s, 9H), 0.06 (s, 3H), 0.02 (s, 3H). ¹³C NMR (75 MHz, CDCl₃): δ 204.36, 139.45, 138.66, 138.31, 136.73, 136.53, 131.94, 131.67, 128.85, 128.81, 127.11, 124.69, 114.46, 76.38, 46.64, 33.10, 31.47, 28.33, 25.88, 18.19, 15.12, 12.04, –3.98, –4.76. HRMS (TOF ES+) Calcd for C₂₈H₄₂O₂SiNa⁺ (M+Na)⁺: 461.2852. Found: 461.2860.

Relay metathesis substrate 26.

To a solution of ketone **25** (50 mg, 0.11 mmol) in MeOH (1.5 mL) at 0 °C was added NaBH₄ (17 mg, 0.46 mmol) and the resulting mixture was stirred for 1 h. The reaction was quenched with aq. NaHCO₃ (15 mL) and extracted with MTBE (2 × 15 mL). The combined organic extracts were dried over MgSO₄, filtered, and concentrated *in vacuo*. The crude **hydroxy-26** was obtained as a 10:1 (NMR) mixture of diastereomers and was used without further purification; *Spectral data for the major stereoisomer*. ¹H NMR (300 MHz, CDCl₃): δ 7.41 (d, *J* = 7.7 Hz, 2H), 7.30 (t, *J* = 7.2 Hz, 2H), 7.19 (m, 1H), 7.02 (dd, *J* = 15.5, 10.9 Hz, 1H), 6.51 (d, *J* = 15.5 Hz, 1H), 6.14 (d, *J* = 11 Hz, 1H), 5.82 (m, 1H), 5.61 (m, 2H), 5.08 (dd, *J* = 17.0, 1.2 Hz, 1H), 4.98 (dd, *J* = 10.1, 1.2 Hz, 1H), 4.31 (m, 1H), 4.01 (d, *J* = 9.4 Hz,

1H), 2.09 (m, 4H), 1.92 (m, 1H), 1.85 (s, 3H), 1.50 (m, 2H), 0.92 (s, 9H), 0.67 (d, $J = 7.1$ Hz, 3H), 0.10 (s, 3H), 0.06 (s, 3H). ^{13}C NMR (75 MHz, CDCl_3): δ 139.57, 138.61, 137.76, 132.93, 131.95, 129.08, 128.55, 127.47, 127.23, 126.24, 124.96, 114.67, 80.70, 78.00, 41.37, 33.24, 31.67, 28.48, 25.79, 18.05, 13.10, 11.75, -0.0097 , -4.18 , -5.11 .

To a solution of the crude alcohol in THF (2 mL) at -78°C was added lithium bis-(trimethylsilyl)amide (1.0 M, 0.13 mL) and the solution was stirred for 30 min before adding methyl iodide (0.02 mL, 0.33 mmol). The reaction was allowed to slowly warm to rt for 15 h before quenching with aq. NaHCO_3 (15 mL) and extracting with MTBE (2×15 mL). The combined organic extracts were dried over MgSO_4 , filtered, and concentrated *in vacuo*. Purification by flash column chromatography on silica (20:1 hexanes:ethyl acetate) afforded **26** (34 mg, 68% 2-steps) as an oil; $[\alpha]_D^{20} = +36.0$ (c 1.0, CH_2Cl_2). IR (ATR) 2958, 2930, 2859, 1447, 1371, 1308, 1221, 1143, 1085, 1024, 755, 699 cm^{-1} . ^1H NMR (300 MHz, CDCl_3): δ 7.42 (d, $J = 7.5$ Hz, 2H), 7.32 (t, $J = 7.4$ Hz, 2H), 7.21 (t, $J = 7$ Hz, 1H), 7.04 (dd, $J = 15.5, 10.9$ Hz, 1H), 6.56 (d, $J = 15.5$ Hz, 1H), 6.12 (d, $J = 11.2$ Hz, 1H), 5.81 (m, 1H), 5.53 (m, 2H), 5.08 (dd, $J = 17.0, 1.2$ Hz, 1H), 4.98 (dd, $J = 10.1, 1.2$ Hz, 1H), 4.60 (d, $J = 6.2$ Hz, 1H), 3.45 (d, $J = 9.9$ Hz, 1H), 3.17 (s, 3H), 2.20–2.00 (m, 4H), 1.73 (s, 3H), 1.62 (m, 1H), 1.47 (m, 2H), 0.94 (s, 9H), 0.66 (d, $J = 6.9$ Hz, 3H), 0.07 (s, 3H), 0.02 (s, 3H). ^{13}C NMR (75 MHz, CDCl_3): δ 138.81, 137.64, 137.36, 133.25, 132.09, 130.02, 128.59, 127.36, 127.25, 126.26, 124.53, 114.45, 88.39, 71.07, 55.75, 42.37, 33.28, 31.67, 28.59, 26.02, 18.25, 11.00, 8.81, 0.49, -3.72 , -5.11 . HRMS (TOF ES+) Calcd for $\text{C}_{29}\text{H}_{46}\text{O}_2\text{SiNa}^+$ ($\text{M} + \text{Na}$) $^+$: 477.3165. Found: 477.3150.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Natural products archazolid B and F

Figure 2.
Dihydroarchazolid B retrosynthesis.

Scheme 1.

Original and second-generation synthesis of a C_5 - C_6 *trans*- trisubstituted alkene-containing fragment.

Scheme 2.

Eastern fragment synthesis toward a dihydroarchazolid B analogue.

Scheme 3.
Yamaguchi esterification in preparation for RCM.

Scheme 4.

Preparaion of a C15-free hydroxyl RCM substrate **20**.

Scheme 5.

Yamaguchi esterification in preparation for RCM.

Scheme 6.
Synthesis of relay RCM (RRCM) substrate **26**.

Table 1.

Results from RCM of 17^{a)}

<p style="text-align: center;">17, P = TBS</p> <p><i>conditions</i> ----- see Table 1</p>				
<i>catalysts:</i>
<p style="text-align: center;">Ru-X Ru-Y Ru-Z</p>				
Catalyst	Solvent	Temp	Time	result
Ru-X	DCM	rt	24 h	SM
Ru-X	DCM	45 °C	24 h	mostly SM ^{b)}
Ru-X	PhMe	50 °C	24 h	mostly SM ^{b)}
Ru-Y	DCM	rt	24 h	SM
Ru-Y	PhMe	50 °C	24 h	mostly SM ^{b)}
Ru-Y	PhMe	80 °C	24 h	complex mix
Ru-Y	PhMe	110 °C	24 h	complex mix
Ru-Z	DCM	rt	24 h	SM
Ru-Z	PhMe	50 °C	24 h	mostly SM ^{b)}
Ru-Z	PhMe	80 °C	24 h	complex mix
Ru-Z	PhMe	110 °C	24 h	complex mix

^{a)} Reactions from room temperature (rt) to 50 °C were performed using 10 mol% catalyst (added in two 5% batches, with the second at roughly half of the time indicated). Those performed at 80 and 110 °C used a single lot of 5% catalyst added once the reaction mixture had reached the desired temperature. All reactions were performed in degassed solvent (0.005 M) under a steady stream of N₂

^{b)} No RCM product was detected by MS.

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Table 2.

RRCM results from **26**^{a)}

Solvent	Temp	Time	Result (27:28) ^{b)}
PhMe	rt	17 h	Mostly 26
DCM	45 °C	15 h	27 and 28 (1:1)
PhMe	50 °C	12 h	27 and 28 (1:1)
PhMe	80 °C	8h	27 and 28 (4:1)
PhMe	110°C	6h	Mostly 27

^{a)} Reactions were performed using 5 mol% catalyst in degassed solvent (0.005 M) under a steady stream of N₂.

^{b)} Results were determined by ¹H NMR and MS. Ratios given are approximate values from integration of the ¹H NMR spectrum.