Synthetic studies on the mycolactone core†

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Two approaches are presented for the synthesis of the macrolide core of the mycolactone polyketides. The first intertwines ring closing metathesis (RCM) within a two-step Julia olefination protocol, while the second intercepts the optimized routes of Kishi, thereby providing formal access to the mycolactones.

Introduction

In 1999, Small identified mycolactones A (**1a**) and B (**1b**) as an inseparable mixture of isomers that acts as the etiological agent of *Mycobacterium ulcerans*.[1] Since this discovery, studies conducted in animal models indicate that mycolactones **1a** and **1b** are capable of producing the lesion formation associated with Buruli ulcer.[2] This evidence, along with detailed biosynthetic studies[3] and the isolation of congeners **1c–1f** from fish and amphibians, has led to significant understanding of this family of polyketides.[4] To date, the known mycolactones, **1a–1f**, contain the common core macrolide **2**,[5] and differ within their polyunsaturated side chain (Fig. 1).

Since their initial characterization, a series of biological studies have provided an early understanding of the role mycolactone polyketides play in Buruli ulcer.[6] However, the story is far from complete. Recently, it was shown that **1a/1b** induces apoptosis and necrosis within cells involved in inflammation.[7] Such effects are associated with a lack of wound healing and the eventual formation of large symptomatic ulcerations.[8] These studies are further complicated by the fact that there is a clear difference between the *in vivo* and *in vitro* activity of **1a/1b**.[9] Given these requirements, larger quantities (≥100 mg) of the natural products and their associated probes are required to develop an understanding as to the targets and the pathways modulated by the mycolactones. Unfortunately, culturing efforts have been limited to the production of milligrams of material,[10] and therefore a viable synthetic entry to developing an understanding of the mode of action of these polyketides.

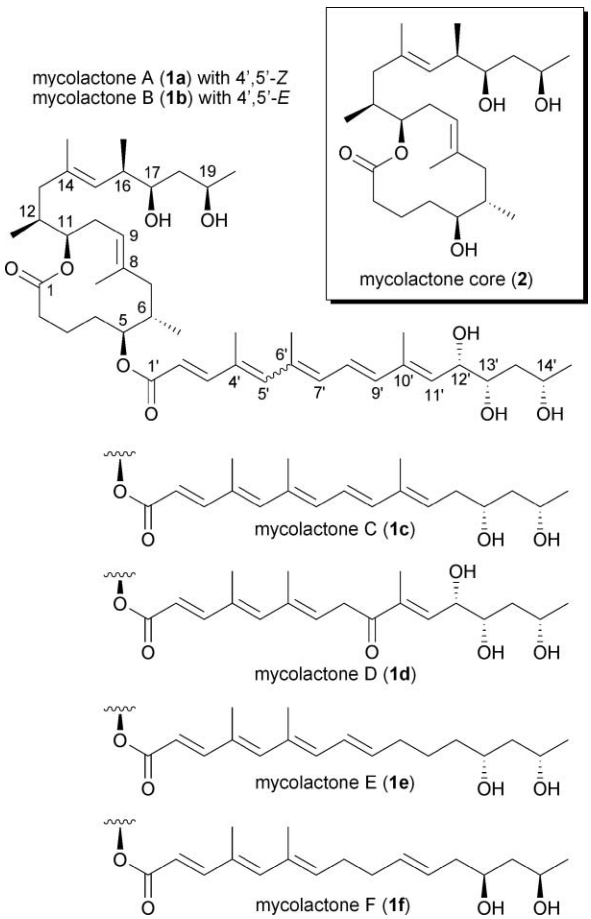

Fig. 1 Mycolactones A–F (**1a–f**) and the mycolactone core (**2**). While modifications appear within the polyunstaturated side chain, each of the mycolactones isolated to date bears a common core unit **2**.

Results and Discussion

Strategy

Our efforts have focused on synthesis of core **2**, as the routes of Kishi, Negishi, and Minnaard provide access to the polyunsaturated acid side chain.[11] The goal of our studies was to complement these syntheses by providing an effective access to the core **2**. Our approach focused on the use of olefin metathesis to install the C8–C9 tri-substituted olefin providing access to macrolides such as **3** and **5** (Fig. 2). In 2006, we demonstrated this in the synthesis of **3** (Fig. 2).[12]

Unfortunately, the planned route for converting **3** into **2** resulted in a dead end, as the attempts to install the C14–C15 olefin *via* a Wittig or Julia–Kocienski olefination with **4a** or **4b**, respectively, resulted in recovery starting material or decomposition (route A, Fig. 2). Closely following this report, Altmann further confirmed

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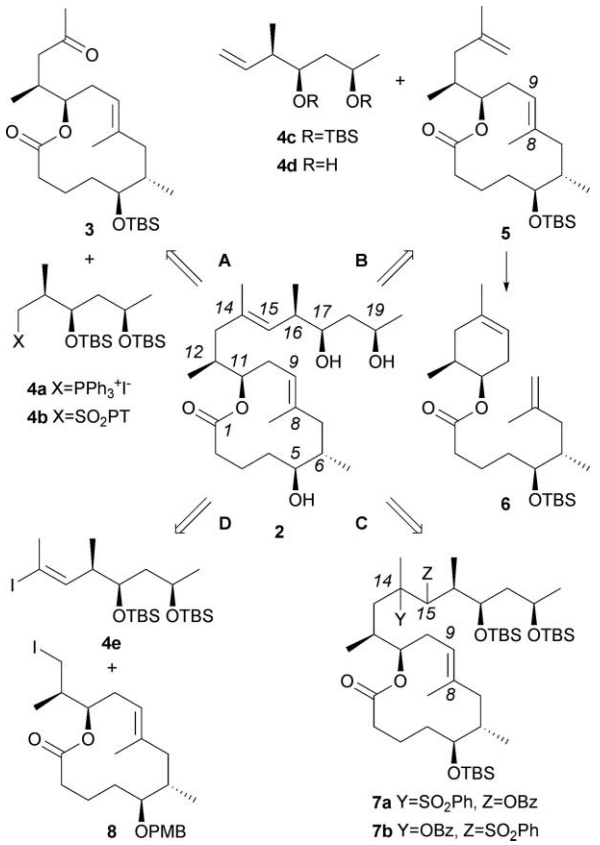
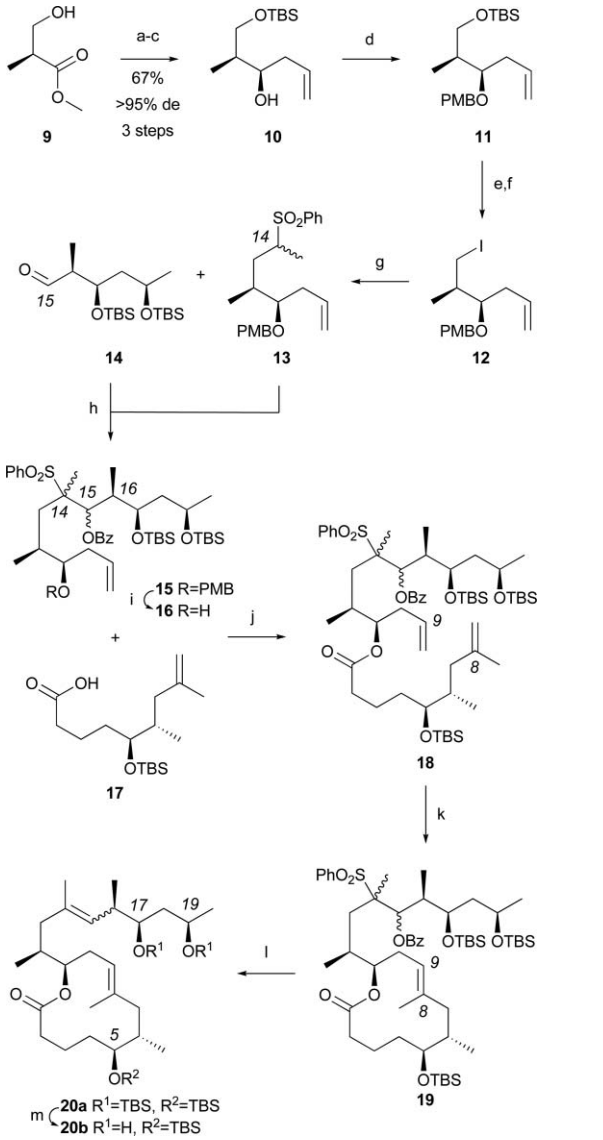


Fig. 2 Retrosynthetic analyses of the mycolactone core **2**. Four approaches are presented as given by routes A–D. PT = phenyltetrazol.

the potential of RCM for the formation of the 12 membered lactone found in the mycolactones – although their substrate similarly lacked the northern chain and the critical tri-substituted olefin linker.[13]

We then examined the use of cross-metathesis (route B, Fig. 2), as an alterative to the Wittig and Julia type olefination reactions for installation of the northern chain. Alkene **5** (Fig. 2) was prepared from ketone **3** in 82% yield by Wittig olefination with $Ph_3P{=}CH_2$ in THF and screened for its cross-metathesis with **4c**[11c] and **4d**[11f] Unfortunately, complex mixtures of products were obtained including formation of cyclohexene ester **6** (Fig. 2). Conversion to the desired core **2** could not be encouraged even under high concentrations of the northern chain component **4c** or **4d**, or variance of the solvent, temperature, or catalyst.

First-generation approach: application of an intercepted Julia–Lythgoe olefination to direct ring-closing metathesis. Next, we sought a method for masking the C14–C15 olefin. The Julia–Lythgoe olefination[14] provided an excellent solution for this task as the two step process could be interupted and the intermediate adduct intercepted. The resulting product, a β-acyloxysulfone (route C, Fig. 2), would effectively serve as a protecting group for the C14–C15 olefin during formation of the C8–C9 double bond by RCM, and prevent the undesired scrambling to **6**. Of the options (Fig. 2), placmement of the sulfone at C14 in **7a** provided the most logical entry due to the more stable alkoxide intermediate generated from an aldehyde (*i.e.*, **14**) *versus* a ketone. Our focus turned to components **13** and **14** (Scheme 1).



Scheme 1 First-generation approach. (a) TBSCl, imidazole, DMF, 0 to 23 °C, 97%; (b) DIBAL-H, CH_2Cl_2, −78 °C, 90%; (c) allyltri-n-butylstannane, $SnCl_4$, THF, −78 °C, 80%, >95% de; (d) *p*-methoxybenzyltrichloroacetimidate, $BF_3{\cdot}Et_2O$, cyclohexane, CH_2Cl_2, 0 °C, 73% (23% recovered **10**); (e) TBAF, THF, 93%; (f) I_2, PPh_3, imidazole, toluene, 0 °C, 98%; (g) $PhSO_2Et$, HMPA, *n*-BuLi, THF, −78 °C to rt, 95%; (h) *n*-BuLi in hexanes to **13** in THF, −78 °C, then warm to −20 °C, then **14** in THF, −78 °C, warm to −20 °C, add BzCl, −78 °C to rt, 57%; (i) DDQ, wet CH_2Cl_2, rt, 2 h, 95%; (j) **16**, **17**, DCC, DMAP, CSA, CH_2Cl_2, 8 h, 96%; (k) Grubbs II generation catalyst, CH_2Cl_2, reflux, 2 d, 94%; (l) Na/Hg, MeOH, −20 °C, 90% (2 : 1 *E*/*Z*); (m) TASF, DMF, 42% of *E*-isomer and 19% of *Z*-isomer.

The preparation of sulfone **13** began from allyl alcohol **10**, which was prepared from commercially-available Roche's ester (**9**) using the methods of Keck (Scheme 1).[15] Compound **10** was protected as PMB ether **11** using 4-methoxybenzyl 2,2,2-trichloroacetimidate.[16] The TBS either in **11** was removed by treatment with TBAF in THF, and the resulting alcohol was converted to iodide **12** by treatment with a mixture of I_2, PPh_3, and imidazole in toluene. Component **13** was completed by alkylating the monolithium anion of ethylphenylsulfone with iodide **12**. The

second component aldehyde **14**, was prepared by ozonolysis of olefin **4c**.[11b,11c]

The first step of Julia–Lythgoe reaction provided adduct **15** as ~12 : 6 : 1 : 0.5 mixture of diastereomers[17] in good yield after trapping of the incipient alkoxysulfone *in situ* with benzoylchloride. Higher yields were obtained by benzoylation *versus* acylation with AcCl or Ac_2O.

Continuing with the mixture of adducts **15**, the PMB ether was removed by oxidation with DDQ, and the resulting alcohol **16** was coupled with acid **17**[12] using a Keck-modified Steglich esterification.[18] Ester **18** was subjected to RCM with Grubbs II generation catalyst.[19] With the olefin protected as a benzoyloxysulfone, the RCM reaction occurred in high yield to deliver macrolide **19**. Once the C8–C9 olefin was installed, the C14–C15 olefin was generated. Reductive elimination of the benzyloxy and sulfone groups in **20a** with sodium-mercury amalgam in MeOH afforded a 2 : 1 mixture of *E*- and *Z*-isomers **20a**.[20]

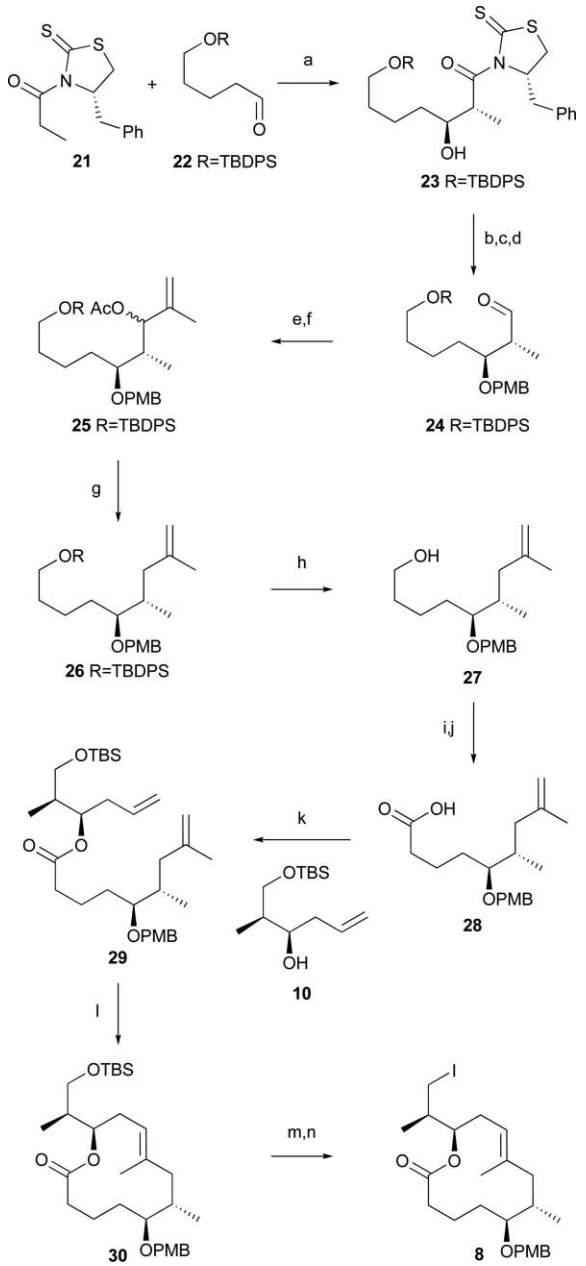
We then turned to evaluate the influence of stereochemistry in **19** on the reduction to **20a**. The isomers of **19** were separated using flash chromatography and subjected individually to the reduction conditions. Unfortunately, the same 2 : 1 *E*/*Z* ratio was obtained, regardless of the choice of isomer.[21]

To add additional concern, the removal of TBS protection in **20a** provided complications. First, both of the TBS groups in the northern chain (at C17 and C19) were removed by treatment with tris-(dimethylamino)sulfonium-difluorotrimethylsilicate (TASF)[22] affording a single *E*-isomer **20b** in 42% yield (along with 19% of the *Z*-isomer) after chromatographic purification. Unfortunately, the TBS ether at C5 proved challening to remove, as decomposition occured under a number of conditions for silyl-deprotection (over 20 screened). Ultimately, we failed to identify an effective method to remove the TBS ether at C5, as only small amounts of **2** could be obtained using this strategy.

Second-generation approach: reorganizing to an optimized component assembly. A solution to this problem was identified in parallel with that recently published by Kishi[11b] in their elegant synthesis of the core precursor, iodide **8** (route D, Fig. 2). The complementary use of TBS protection at C17 and C19 with PMB protection at C5 provided a logical solution to the sluggish deprotection at C5, as well as allowing the orthagonal installation of the polyunstaturated side chain. Kishi also demonstrated that core **8** served as an effective intermediate for installation the C11–C19 northern chain by developing a high-yielding and scalable Negishi coupling with TBS protected vinyliodide **4e** (route D, Fig. 2).[11b,11c] Our studies therefore shifted to the synthesis of macrolide **8**.

A 14-step synthesis of **8** was developed, beginning with the propionylated Crimmins thiazolidinethione auxilary **21** (Scheme 2).[23] Condesation of **21** with aldehyde **22**[24] afforded adduct **23** in excellent yield. The auxiliary was released and recycled by treatment with *N*,*O*-dimethylhydroxylamine.[25] After PMB protection, reduction of the resulting Weinreb amide[25] with DIBAL-H afforded aldehyde **24**.

Using established methods,[12] alkene **26** was prepared by the addition of propenylmagensium bromide to **24** with *in situ* acylation of the resulting alkoxide to set up the regioselective hydrogenolysis of allylic acetate **25** under Tsuji conditions.[26] While each of the processes to **25** were readily run at 100 mmol scale, the



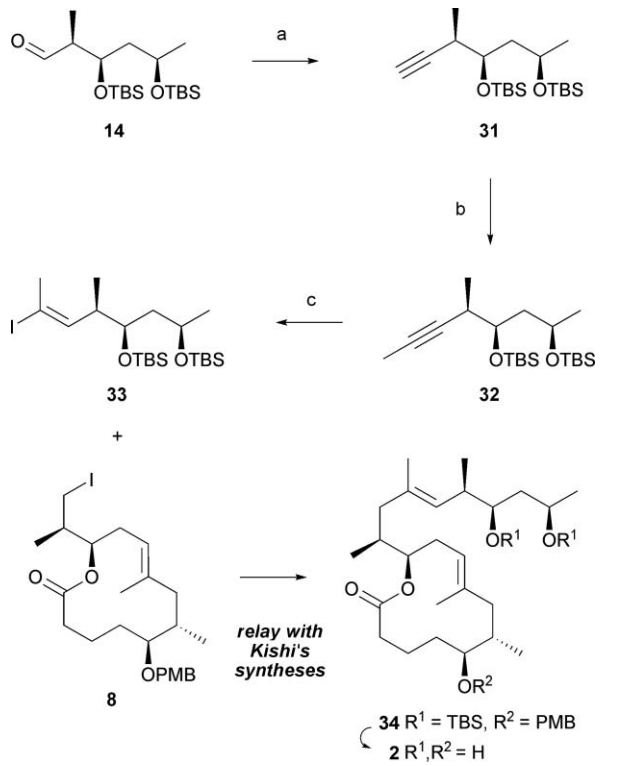
Scheme 2 Second-generation synthesis delivering core unit **8**. (a) $TiCl_4$, *i*-Pr_2NEt, CH_2Cl_2, −78 °C, 96%; b) *N*,*O*-dimethylhydroxyamine hydrochloride, imidazole, CH_2Cl_2, 95%; (c) *p*-methoxybenzylbromide, NaH, DMF, 89%, (d) DIBAL-H, toluene, −78 °C, 99%; (e) 2-propenylmagnesium bromide, THF, −78 °C to rt, 92%; (f) Ac_2O, DMAP, pyridine, 89%; (g) HCO_2NH_4, $Pd(PPh_3)_4$, PBu_3, dioxane, reflux, 88%; (h) TBAF, THF, rt, 90%; (i) $(ClCO)_2$, Et_3N, DMSO; (j) $NaClO_2$, NaH_2PO_4, *t*-BuOH, 2-methyl-2-butene, 97% over 2 steps; (k) DCC, DMAP, pyridine, CH_2Cl_2, 8 h, 87%; (l) Grubbs II generation catalyst, CH_2Cl_2, reflux, 2 d, 78%; (m) TBAF, THF, 85%; (n) I_2, PPh_3, imidazole, toluene, 0 °C, 98%.

Tsuji reduction proved to be difficult to scale, requiring multiple runs at the 5 mmol scale. The remaining steps including removal of the TBDPS protecting group and oxidation of the resulting carbinol **27** to acid **28** were scalable. Using this method, we were able to scale this approach to deliver 30 mmol of **28**.

With PMB protected acid **28** in hand, we applied our RCM strategy[12] to assemble the core unit **8**. This process began by

coupling **28** with alcohol **10**[27] using the Keck-modified Steglich esterification conditions[18] to afford **29**. The resulting ester **29** was subjected to RCM with Grubbs II generation catalyst[19] to afford a single olefin isomer **30**. Removal of the TBS protection and iodination completed the synthesis of **8**. Spectroscopic data from **8** was identical to that reported by Kishi.[11b,11c] This route provides a stereoselective entry to **8** that operates at gram scales without the need for tedious chromatographic removal of stereoisomers.

The synthesis of **8** also enables a direct relay with the routes developed in the Kishi laboratory[11b,11c] utilizing vinyliodide **33**, therein completing the formal synthesis of **2**. As shown in Scheme 3, aldehyde **14**[11b,11c] was converted to alkyne **31** using the Bestmann protocol.[28] Methylation of **31** to **32**, followed by reduction with Schwartz's reagent[29] provided the vinyl iodide **33** in 3 steps and 70% yield from **14**. Each step in this process could be conducted at a 50 mmol scale, providing viable access to the northern chain. Using Kishi's optimized approach,[11b,11c] orthagonally protected core **34** is obtained by a Negishi coupling of **33** and **8**, and the synthesis of **2** is completed by sequential removal of the TBS and PMB protecting groups.



Scheme 3 Synthesis of the mycolactone core **2**. (a) dimethyl-1-diazo-2-oxopropylphosphonate, K_2CO_3, MeOH, rt., 87%; (b) *n*-BuLi, MeI, THF, −78 °C to rt, 99%; (c) Cp_2ZrHCl, THF, 65 °C, 3 h to −25 °C, add I_2, 82%; the optimized conversion of **8** to **2** *via* **34** was reported by Kishi.[11b,11c]

Conclusions

In summary, we describe two approaches that apply RCM in the synthesis of the mycolactone core **2**. The first approach involved a RCM reaction in between the two steps of a Julia–Lythgoe olefination in order to efficiently form both trisubstituted double bonds without complication from side reactions. The olefin within the 12-membered ring was formed with exclusively *E*-geometry and the alkene in the northern chain was obtained as a 2 : 1 mixture of *E*- and *Z*-isomers, respectively. Our second route rapidly and efficiently delivered core **8**, which can be converted to **34** and **2** using the methods of Kishi.[11b,11c]

Our second generation synthesis was convergent and incorporated the preparation of four components: (a) alcohol **10** (Scheme 1) prepared in 3 steps from Roche's ester;[27] (b) propionylated Crimmins auxilary **21** (Scheme 2) prepared in 2 steps from D-phenylalanine;[23] (c) aldehyde **22** (Scheme 2) prepared in 2 steps from 1,5-pentanediol;[24] and (d) vinyl iodide **33** (Scheme 3) prepared in 7 steps from ethyl (*R*)-3-hydroxybutyrate.[11bc] The assembly of these components requires 15 steps to achieve orthogonally protected core **34** with an overall yield of 24%. This outcome compares favorably with the total syntheses developed by the Kishi laboratory and provides an alternative for developing mycolactone probes, a key next step in understanding the progression of Buruli ulcer.

Experimental Section

General Experimental Information

Unless otherwise noted, all reagents and chemical compounds were purchased from commercial sources (Alfa Aesar, GFS Chemicals, Strem Chemicals, Sigma-Aldrich and TCI) and used without further purification. High purity anhydrous solvents (tetrahydrofuran, dichloromethane, *N*,*N*-dimethylformamide, diethyl ether, and toluene) were obtained by passing through a solvent column composed of dry activated A-1 alumina. Triethylamine (Et_3N) and *N*,*N*-diisopropylethylamine (i-Pr_2NEt) were distilled from ninhydrin, dried (Na_2SO_4), and then freshly distilled from sodium. MeOH was distilled from magnesium. Dioxane was distilled from sodium-benzophenone ketyl. All air or moisture sensitive reactions were performed under a positive pressure of dry Ar in oven-dried glassware sealed with a septum. Reactions were magnetically stirred with a Teflon-coated stir bar. Flash chromatography was performed on Silica Gel 60, 230–400 mesh (EM Sciences). TLC analyses were conducted on 250 μm Silica Gel 60 F254 glass plates (EM Sciences). Visualization was achieved with UV light and/or an appropriate stain (I_2 on SiO_2, $KMnO_4$, bromocresol green, dinitrophenylhydrazine, ninhydrin, and ceric ammonium molybdate). Yields and characterization data correspond to isolated, homogeneous materials. Unless otherwise noted all solvent mixtures are given in v : v ratios. NMR spectra were recorded on a Varian Mercury Plus 400 MHz, Varian Unity 500 MHz, Jeol ECA 500 MHz, Bruker DMX 500 MHz or Varian VX 500 MHz (equipped with XSens cold probe) spectrometer. COSY, NOESY, TOCSY, HMBC and HSQC spectra were collected on a Bruker DMX 500 with 5 mm ^{1}H (^{13}C/^{15}N) triple-resonance indirect XYZ gradient probe. FID files were processed using MestRe-C software version 6.0.2 (MestreLab Research) and were printed from MestraNova. Chemical shifts for ^{1}H-NMR and ^{13}C-NMR analyses were reported using the signal from residual $CHCl_3$ (7.26 ppm, ^{1}H-NMR) or the $CDCl_3$ signal (77.16 ppm, ^{13}C-NMR). Mass spectra were collected by Dr Yongxuan Su (UC San Diego). Electrospray (ESI) and atmospheric pressure chemical ionization (APCI) analysis was

performed using a Finnigan LCQDECA mass spectrometer, and fast atom bombardment (FAB) analysis was carried out using a ThermoFinnigan MAT900XL mass spectrometer. Spectral data and procedures are provided for all new compounds and copies of select spectra have been provided within the ESI. Procedures for the preparation of select key intermediates have been provided in the following discussion.

Coupling of components 13 and 14 affords the intercepted Julia adducts 15

A solution of sulfone **13** (30.0 mg, 0.075 mmol) in anhydrous THF (2 mL) at −78 °C was treated with *n*-BuLi in hexanes (1.4 M, 64 μL, 0.05 mmol). After stirring for 30 min, a solution of aldehyde **14** (19 mg, 0.05 mmol) in THF (2 mL) was added drop wise and the yellow solution was stirred at −78 °C for 1 h. Benzoyl chloride (14.0 μL, 0.118 mmol) was added at −78 °C. The cooling bath was removed and the reaction mixture was stirred for 1 h as it warmed to rt. The reaction was quenched by addition of 1 : 1 MeOH/Et_3N (0.5 mL). The mixture was diluted with Et_2O (30 mL) and washed with H_2O (10 mL). The combined organic layers were washed sequentially with 10% HCl (10 mL), 5% $NaHCO_3$ (10 mL) and brine (10 mL) and then treated to flash chromatography (20 : 1 hexanes/EtOAc) to afford 37.4 mg (57%) of adducts **15** as a colorless oil that contained a 12 : 6 : 1 : 1 (w : w : w : w) mixture of diastereomers: IR (neat) ν 2955, 2929, 2856, 1721, 1514, 1302, 1249, 1070, 835; ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm 8.02–7.86 (m, 6H), 7.62–7.10 (m, 12H), 7.21–7.16 (m, 3H), 6.84 (m, 4H). 5.92–5.66 (m, 4H), 5.12–5.01 (m, 2H), 4.92 (m, 2H), 4.56–4.30 (m, 4H), 3.96–3.88 (m, 2H), 3.81 (m, 6H), 3.52 (m, 1H), 3.28 (m, 1H), 3.14 (m, 1H), 2.82 (m, 1H), 2.58 (m, 1H), 2.30–2.18 (m, 4H), 1.84 (m, 1H), 1.70 (m, 2H), 1.50 (m, 3H), 1.14 (m, 6H), 1.04 (m, 4H), 0.88–0.78 (m, 30H), 0.10–0.08 (m, 18H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ ppm 164.9, 159.2, 159.1, 138.6, 138.3, 136.3, 136.4, 136.1, 135.4, 133.7, 133.6, 133.4, 133.1, 131.4, 131.2, 131.1, 131.0, 130.7, 130.6, 130.0, 129.8, 129.5, 129.4, 128.9, 128.8, 128.5116.8, 116.3, 113.8, 113.7, 83.2, 82.8, 82.6, 75.6, 73.7, 73.2, 71.4, 71.2, 70.9, 70.6, 70.5, 69.9, 66.2, 66.1, 65.6, 55.4, 44.6, 43.9, 43.9, 40.7, 39.6, 37.9, 37.3, 36.6, 34.8, 34.5, 33.9, 33.8, 31.7, 30.7, 30.326.3, 26.2, 26.1, 26.0, 25.4, 24.0, 23.8, 22.8, 20.0, 18.2, 18.2, 18.0, 17.4, 17.2, 16.1, 14.3, 12.1, 11.8, 9.6, −3.6 (3), −4.0 (4), −4.52; MS (FAB) m/z 903.15 ([M+Na]$^+$, 100%); HRMS (FAB) m/z calcd. for $C_{49}H_{79}O_8SSi_2$ (M)$^+$ 880.4799, found 880.4794.

Coupling of alcohol 16 to acid 17 to afford esters 18

DMAP (4.0 mg), CSA (7.2 mg, 0.031 mmol) and DCC (11.4 mg, 0.053 mmol) were added sequentially to a solution of the alcohol **16** (25.0 mg, 0.033 mmol) and acid **17** (11.4 mg, 0.036 mmol) in CH_2Cl_2 (2 mL) at 0 °C. The resulting mixture was stirred at rt. After 8 h, the starting material was no longer detectable by TLC (4 : 1 hexanes/EtOAc). The reaction was diluted with hexanes (20 mL) and EtOAc (40 mL). The mixture was filtered and washed with 5% aqueous citric acid (10 mL), satd. $NaHCO_3$ (10 mL) and brine (10 mL), dried (Na_2SO_4) and concentrated by rotary evaporation. Purification by flash chromatography (2 : 1 hexanes/EtOAc) yielded 33.0 mg (96%) of ester **18** as a white solid: IR (neat) ν 2893, 1236, 1084, 917, 825; ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm 8.04–7.36 (m, 10H), 5.78–5.48 (m, 2H), 5.08–4.94 (m, 2H), 4.80 (m, 1H), 4.76–4.62 (m, 2H), 4.16–4.06 (m, 1H), 3.96–3.78 (m, 2H), 3.50 (m, 1.5H), 3.16 (m, 0.5H), 2.84–2.64 (m, 1H), 2.46–2.10 (m, 6H), 2.01 (m, 2H), 1.78–1.70 (m, 2H), 1.68–1.57 (m, 6H), 1.54–1.44 (m, 3H), 1.44–1.26 (m, 4H), 1.18–1.04 (m, 4H), 1.02–0.94 (m, 3H), 0.90–0.72 (m, 21H), 0.01 (12H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ ppm 173.5, 173.1, 172.9, 165.3, 164.8, 144.9, 144.8, 138.4, 138.2, 136.5, 134.4, 134.2, 133.7, 133.6, 133.5, 133.1, 133.1, 131.2, 131.0, 130.7, 130.5, 130.4, 130.1, 130.0, 129.9, 128.9, 128.8, 128.6, 128.5, 128.5, 128.4, 117.2, 117.6, 111.5, 111.5, 77.3, 76.9, 76.0, 75.6, 74.8, 74.8, 73.2, 73.2, 72.2, 71.3, 71.2, 69.9, 66.1, 66.0, 65.6, 55.9, 45.0, 44.0, 43.9 40.7, 40.7, 40.5, 39.8, 37.5, 35.9, 35.7, 35.6, 35.6, 35.2, 35.0, 34.8, 34.7, 34.5, 32.8, 32.7, 32.6, 32.4, 32.1, 31.9, 31.8, 26.9, 26.2, 26.0, 25.5, 24.8, 24.2, 23.8, 22.4, 21.8, 21.720.0, 18.9, 18.8, 18.2, 18.2, 18.0, 17.8, 17.4, 14.2, 14.1, 14.1, 12.1, 11.36, 8.9, −3.6, −3.8 (4), −4.0, −4.1, −4.2, −4.3, −4.4, −4.5; MS (ESI) m/z 1079.46 ([M+Na]$^+$,100%). HRMS (FAB) m/z calcd. for $C_{58}H_{100}O_9S_1Si_3$ (M)$^+$ 1056.6636, found 1056.6637.

Formation of macrolide 19 *via* ring-closing metathesis

Grubbs second-generation catalyst (1.0 mg, 0.001 mmol) was added to a solution of diene **18** (24.3 mg, 0.023 mmol) in refluxing CH_2Cl_2 (1 mL). The solution was refluxed for 72 h until TLC indicated complete conversion. The solvent was removed by rotary evaporation. The residue was diluted with hexanes (10 mL) and filtered through a short pad of silica gel in order to remove the catalyst. The crude product was purified by flash chromatography (100 : 1 toluene–Et_2O) to provide 22.2 mg (64%) of macrolide **19** as a colorless oil. IR (neat) ν 2929, 2856, 1726, 1251, 1070, 836; ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm 8.04–7.22 (m, 20H), 5.70 (m, 0.6H), 5.48 (m, 0.4H), 5.41–4.84 (m, 2H), 4.82–4.64 (m, 1H), 4.16–4.04 (m, 2H), 3.96–3.78 (m, 3H), 3.52 (m, 0.5H), 3.39–3.28 (m, 2H), 3.20 (m, 0.5H), 2.87–2.75 (m, 1H), 2.58–2.10 (m, 6H), 2.05 (m, 2H), 1.78–1.80 (m, 8H), 1.68–1.32 (m, 30H), 1126 (m, 8H), 1.18–0.80 (m, 56H), 0.01 (m, 36H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ ppm 173.9, 173.6, 173.5, 165.4, 164.8, 138.4, 138.2, 137.7, 137.6, 136.6, 133.7, 133.6, 133.5, 133.0, 131.2, 131.0, 130.8, 130.4, 130.0 (2), 129.9, 128.9 (2), 128.6, 128.5, 128.5, 121.2, 121.1, 77.7, 77.5, 76.5, 76.3, 76.2, 75.9, 74.7, 74.4, 73.2, 73.2, 72.2, 71.3, 71.2, 70.1, 66.1, 66.0, 65.6, 60.5, 45.5, 45.3, 44.0, 43.9, 40.7, 39.7, 37.4, 36.3, 36.2, 36.1, 35.8, 35.3, 33.6, 33.5, 33.4, 33.3, 33.0 (2), 31.9, 30.9, 30.4, 30.1, 26.3, 26.2, 26.0, 24.3, 23.8, 23.8, 21.9, 20.1, 19.5, 18.6, 18.6, 18.3, 18.2, 18.1, 18.1, 18.0, 17.2, 15.8, 15.8, 15.6, 14.4, 12.1, 11.7, 8.7, −3.6, −3.7, −3.8, −3.9, −4.0, −4.1, −4.2, −4.3, −4.4, −4.5, −4.6; MS (ESI) m/z 1051.28 ([M+Na]$^+$, 100%); HRMS (FAB) m/z calcd. for $C_{56}H_{97}O_9S_1Si_3$ (M)$^+$ 1028.6776, found 1028.6775.

Revealing the masked C14–C15 olefin in macrolide 20a

To a stirred suspension of 6% (m/m) Na/Hg in 3 mL of MeOH at −20 °C was added lactone **19** (20.0 mg, 0.019 mmol). The resulting mixture was stirred at 0 °C until TLC indicated complete conversion of the substrate (~ 8 h). The reaction was quenched by the addition of satd. NH_4Cl (1 mL) and warmed to rt. The mixture was extracted with Et_2O (2 × 20 mL), and the combined organic layers washed sequentially with 5% $NaHCO_3$ (10 mL), H_2O (10 mL), and brine (10 mL), dried over Na_2SO_2, and concentrated

by rotary evaporation. Purification by flash chromatography (2 : 1 hexanes/EtOAc) yielded 13.0 mg (90%) of a 2 : 1 mixture **20a**, as a colorless oil: ^{1}H-NMR (500 MHz, $CDCl_3$) δ ppm 5.50 (d, J = 10.0 Hz, 0.3 H), 5.45 (d, J = 9.2 Hz, 0.7 H), 4.98 (m, 1H), 4.84 (m, 1H), 3.88 (m, 1H), 3.58 (m, 1H), 3.36 (m, 1H), 2.54–2.36 (m, 4H), 2.38 (m, 1H), 2.04–1.92 (m, 3H), 1.88–1.78 (m, 4H), 1.78–1.54 (m, 15H), 1.42 (m, 3H), 1.26 (m, 3H), 1.02 (m, 4H), 0.98–0.82 (m, 40H), 0.04 (m, 18H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ ppm 173.7, 137.6, 137.4, 131.8, 131.7, 131.4, 130.5, 121.6, 75.9, 75.5, 73.5, 73.3, 66.3, 66.1, 46.3, 45.5, 45.2, 43.2, 38.2, 37.8, 36.1, 35.4, 35.2, 33.5, 30.3, 29.9, 26.2, 26.1, 26.0 (2), 24.1, 24.0, 23.6, 21.9, 18.7, 18.3, 16.1, 15.9, 15.8 (2), 15.3, –3.8, –3.9, –4.1, –4.1, –4.2, –4.4, –4.5, –4.6; HRMS (FAB) m/z calcd. for $C_{43}H_{86}O_5Si_3$ $(M)^+$ 766.5774, found 766.5778.

Coupling of alcohol 10 to acid 28 to afford ester 29

Alcohol **10** (1.1 g, 4.8 mmol) and acid **28** (1.5 g, 4.8 mmol) were dissolved in CH_2Cl_2 (30 mL) and cooled to 0 °C. DMAP (0.7 g), and DCC (1.2 g), and pyridine (3 mL) were added sequentially to this solution. The reaction was for 8 h at which point the starting material had been consumed. The reaction was diluted with hexanes (100 mL), filtered, and concentrated. Purification by flash chromatography (20 : 1 hexanes/EtOAc) yielded 2.5 g (95%) of ester **29** as a colorless oil: ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm 7.26 (d, J = 8.5 Hz, 2H), 6.86 (d, J = 8.5 Hz, 2H), 5.73 (m, 1H), 5.06 (m, 1H), 5.01 (m, 1H), 4.86 (dt, J = 5.0, 7.5 Hz, 2H), 4.74 (s, 1H), 4.66 (s, 1H), 4.44 (dd, J = 11.6, 14.2 Hz, 2H), 3.79 (s, 3H), 3.67 (m, 1H), 3.60 (m, 1H), 3.26 (m, 1H), 3.19 (m, 1H), 2.24 (m, 3H), 1.81 (m, 4H), 1.68 (s, 3H), 1.54 (m, 2H), 1.29 (m, 3H), 0.90 (d, J = 7.0 Hz, 3H), 0.85 (s, 9H), 0.84 (d, J = 6.8 Hz, 3H), 0.04 (s, 6H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ ppm 173.4, 159.3, 144.7, 134.5, 131.4, 129.4, 117.6, 113.9, 111.8, 82.3, 76.9, 71.7, 61.3, 56.0, 55.5, 41.0, 35.8, 35.1, 35.0, 34.9, 33.4, 32.9, 30.3, 26.2, 25.7, 22.4, 22.0, 15.8, 14.9, –5.1, –5.1; HRMS (FAB) m/z calcd. for $C_{32}H_{54}O_5Si$ $(M)^+$ 546.4281 found 546.4283.

Formation of macrolide 30 *via* ring-closing metathesis

Grubbs second-generation catalyst (36 mg, 0.04 mmol) was dissolved in CH_2Cl_2 (50 mL) under an Ar atmosphere. The flask was fitted with a condenser and heated at reflux. A solution of diene **29** (2.3 g, 4.2 mmol) in CH_2Cl_2 (200 mL) was added *via* syringe. After 24 h, TLC analysis indicated the starting material had been consumed. The reaction mixture was flushed through a plug of silica gel with CH_2Cl_2 and concentrated to give a colorless oil. Purification by flash chromatography (20 : 1 hexanes/EtOAc) yielded 1.3 g (60%) of macrolide **30** as colorless oil: ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm 7.24 (d, J = 8.4 Hz, 2H), 6.84 (d, J = 8.5 Hz, 2H), 4.96 (d, J = 10.0 Hz, 1H), 4.91 (ddd, J = 2.9, 5.6, 11.6 Hz, 1H), 4.46 (d, J = 11.0 Hz, 1H), 4.28 (d, J = 11.0 Hz, 1H), 3.78 (s, 3H), 3.64 (m, 2H), 3.10 (m, 1H), 2.38 (m, 2H), 2.04 (m, 2H), 1.89–1.57 (m, 5H), 1.62 (s, 3H), 1.40 (m, 1H), 1.28 (m, 2H), 1.00 (d, J = 6.5 Hz, 3H), 0.92 (d, J = 6.8 Hz, 3H), 0.87 (s, 9H), 0.03 (s, 6H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ ppm 173.9, 159.3, 137.4, 131.3, 129.6, 122.1, 113.9, 83.4, 76.2, 71.1, 61.5, 55.5, 46.0, 36.2, 35.7, 34.4, 32.9, 30.6, 29.2, 26.2, 20.8, 19.5, 18.9, 15.7, –5.0, –5.1; HRMS (FAB) m/z calcd. for $C_{30}H_{50}O_5Si$ $(M)^+$ 518.3801, found 518.3802.

Completion of the macrolide intermediate 8

A two step procedure was used to complete the synthesis of intermediate **8**. A solution of lactone **30** (1.2 g, 2.3 mmol) was dissolved in dry THF (20 mL) under Ar and cooled to 0 °C. A solution of TBAF (3.4 mL, 3.5 mmol, 1 M in THF) was added drop wise. The cooling bath was removed and the reaction mixture stirred for 1 h at rt and then diluted with EtOAc (50 mL). The mixture was washed with satd. aqueous $NaHCO_3$ (20 mL), H_2O (20 mL), and brine (30 mL) and then dried over magnesium sulfate. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated by rotary evaporation. The crude product was purified by flash chromatography to obtain 864 mg (93%) of (6*S*,7*S*,12*R*,*E*)-12-((*S*)-1-hydroxypropan-2-yl)-6-((4-methoxybenzyl)oxy)-7,9-dimethyloxacyclododec-9-en-2-one as an oil: ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm 7.26 (d, J = 3.2 Hz, 2H), 6.87 (dd, J = 8.4, 3.2 Hz, 2H), 4.98 (m, 2H), 4.50 (d, J = 10.8 Hz, 1 H), 4.32 (d, J = 10.8 Hz, 1H), 3.79 (s, 3H), 3.74 (m, 1H), 3.63 (m, 1H), 3.10 (m, 1H), 2.49 (m, 2H), 2.06 (m, 2H), 1.88 (m, 2H), 1.79 (m, 2H), 1.27 (m, 2H), 1.64 (s, 3H), 1.58 (m, 1H), 1.44 (m, 1H), 1.37 (m, 3H), 0.95 (m, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ ppm 174.1, 159.3, 137.6,131.3, 129.6, 121.9, 113.9, 83.3, 76.1, 71.1, 60.9, 55.5, 45.9, 36.2, 35.5, 34.4, 32.9, 30.6, 29.2, 20.8, 19.5, 15.9, 15.6; HRMS (FAB) m/z calcd. for $C_{24}H_{36}O_5$ $(M)^+$ 404.2762, found 404.2763.

Imidazole (390 mg, 5.8 mmol), triphenylphosphine (750 mg, 2.9 mmol), and iodine (722 g, 2.9 mmol) were added sequentially to a solution of the preceeding alcohol (774 mg, 1.92 mmol) in toluene (25 mL) at 0 °C. The heterogeneous yellow mixture was stirred at rt for 1 h. The reaction was quenched by diluting with satd. $Na_2S_2O_3$ (25 mL) and the layers were separated. The aqueous layer was further extracted with Et_2O (3 × 25 mL) and the combined organic layers were washed with satd. $Na_2S_2O_3$, H_2O, and brine, dried (Na_2SO_4), and the solvent was removed by rotary evaporation. The crude product was purified by flash chromatography (4 : 1 hexanes/EtOAc) to provide 968 mg (98%) of **8** as a colorless oil: ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm 7.29 (m, 2H), 6.89 (m, 2H), 4.96 (m, 2H), 4.52 (d, J = 11.0 Hz, 1H), 4.33 (d, J = 11.0 Hz, 1H), 3.82 (s, 3H), 3.33 (m, 1H), 3.34 (dd, J = 3.8, 10.0 Hz, 1H), 3.13 (m, 1H), 2.49 (m, 1H), 2.46 (m, 1H), 2.07 (m, 2H), 1.88–1.32 (m, 8H), 1.64 (s, 3H), 1.05 (d, J = 6.9 Hz, 3H), 0.95 (d, J = 7.1 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ ppm 173.9, 159.3, 137.8, 131.3, 129.6, 121.6, 113.9, 83.3, 75.4, 71.1, 55.5, 45.9, 38.7, 36.6, 36.2, 32.9, 31.1, 29.2, 20.8, 19.5, 16.0, 14.9, 4.5; HRMS (FAB) m/z calcd. for $C_{24}H_{35}IO_4$ $(M)^+$ 514.2676, found 514.2679.

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