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Scalable and efficient synthesis of the mycolactone core

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ABSTRACT

A highly efficient, scalable, and stereoselective synthesis of the mycolactone core is reported. The synthesis consists of 14 longest linear steps, with 19% overall yield.

1. Introduction

Buruli ulcer is a devastating, but neglected disease of the skin and soft tissue caused by *Mycobacterium ulcerans*, the third most common mycobacterial pathogen of humans after *Mycobacterium tuberculosis* and *Mycobacterium leprae*.[1] The disease is characterized by the formation of necrotic lesions that are usually painless and can extend to over 15% of a patient's skin surface if left untreated. In 1999, Small and co-workers isolated two equilibrating toxins, mycolactone A and B, from West African strains of *M. ulcerans* and later demonstrated with animal tests that these toxins are responsible for the observed pathology of the disease.[2] The gross structures of mycolactone A and B were elucidated primarily through 2-D NMR experiments,[3] and their stereochemistry was subsequently predicted via the NMR database approach and confirmed by total synthesis.[4] In addition, several other groups have described syntheses of the mycolactone core or unsaturated fatty acid side chain.[5] Because mycolactone A and B exist as an equilibrium mixture of geometric isomers, they are referred to as mycolactone A/B in this paper.

Since the structure of mycolactone A/B was reported, five more structurally distinct mycolactones have been described from different strains of *M. ulcerans*, and close relatives from fish and frogs (Fig. 1). All of the mycolactones described to date are composed of a common and conserved 12-membered macrolactone core and a highly unsaturated fatty acid side chain that differs amongst the members of this class of natural products. Mycolactone C, which lacks a C12′ hydroxyl group, was identified as the major toxin in Australian strains of *M. ulcerans* in 2003.[6] Later, in 2005, a toxin bearing methyl substitution at the C2′ position, mycolactone D, was proposed as the major metabolite in Chinese strains of *M. ulcerans*.[7] Mycobacteriosis was then discovered in African clawed frogs (*Xenopus laevis and Xenopus tropicalis*), leading to the isolation of the tetraene-containing mycolactone E from *Mycobacterium liflandii*.[8]

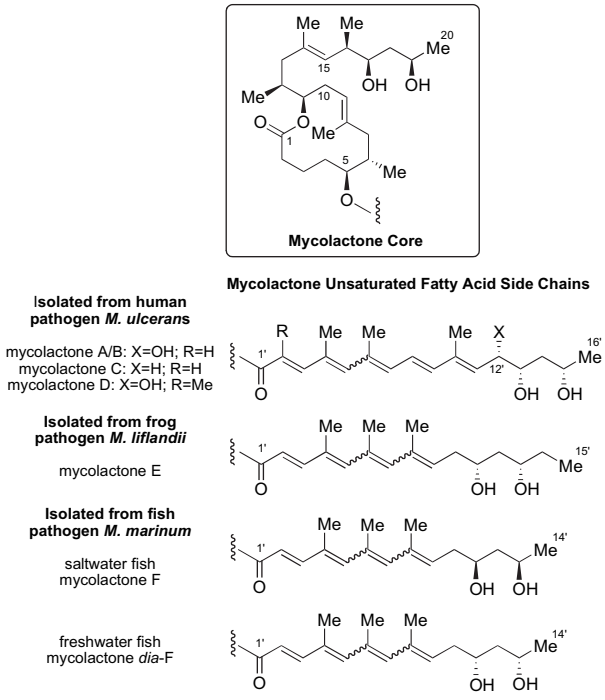

Figure 1. Structures of the mycolactones.

Most recently, mycolactone F has been isolated from mycobacterial pathogens infecting *saltwater* fish,[9] and mycolactone *dia*-F has been isolated from pathogens of *freshwater* fish.[10]

While much has been learned about Buruli ulcer throughout the last decade, many questions still remain unanswered. For example, many researchers have wondered whether it would be feasible to

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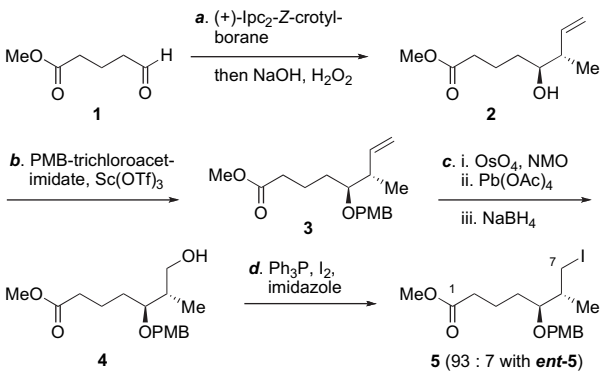
develop a diagnostic method for the early detection of Buruli ulcer that relies on recognition of mycolactone toxins in human skin.[1a] Other highly important research areas are centered on the study of the trafficking and cellular actions of mycolactones,[11] as well as the identification of the cellular target of these toxins. In order for research into these, and other, fields of study to be practically conducted, we feel it is necessary to have reliable and scalable methods for the production of mycolactones of high purity.[1e] This is particularly important considering that the mycolactones isolated from laboratory-scale cultivation of these slow-growing mycobacteria are often scant in quantity (typically microgram) and difficult to isolate cleanly given that mycolactones of varying side chain structures are often present in the crude lipid extracts from the cultured mycobacteria.[1e]

2. Results and discussion

Based on the knowledge accumulated through our first- and second-generation total syntheses,[4] we recognized the need for improvements in two areas. First, we wished to develop shorter, more efficient, and easily scalable syntheses of the fragments used to assemble the mycolactone core. Second, we wished to prepare the mycolactone core with a high level of stereochemical homogeneity, i.e., no contamination of minor stereoisomers.

2.1. Synthesis of the C1–C7 fragment

We began our synthesis of the mycolactone core by turning our attention to the C1–C7 fragment (Scheme 1). Starting from known aldehyde **1**,[12] the C5 and C6 stereocenters were installed using Brown crotylboration[13] in 86% ee as determined by (*R*)- and (*S*)-Mosher's ester analysis. Given that we wished to prepare the mycolactone core in optically pure form, it was important to be mindful of the minor enantiomer present in **2**, as downstream products resulting from this contaminant would need to be removed at some later stage in the synthesis. Notably, we mentioned in our previous synthesis that a significant amount of the δ-lactone was often formed during the Brown crotylboration to convert **1**–**2**[4d]; however, in this work we found that shortened reaction times during the oxidative workup step allowed us to avoid this byproduct altogether.

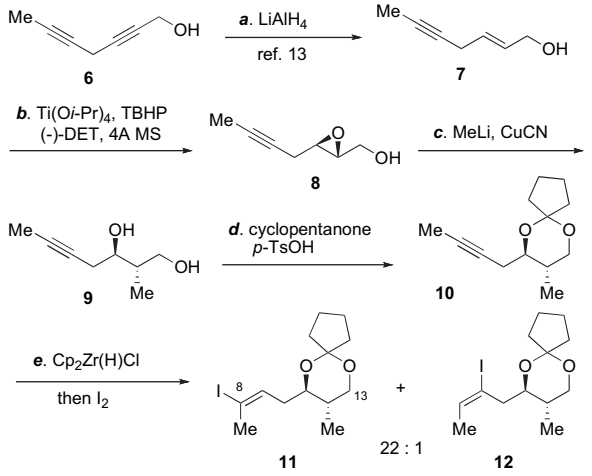


Scheme 1. Reagents and conditions: (a) *Z*-2-Butene, *t*-BuOK, *n*-BuLi, (+)-$(Ipc)_2$BOMe, $BF_3{\cdot}OEt_2$, THF, −78 °C; then NaOH, H_2O_2, 1 h, 78%, 86% ee; (b) PMB-trichloroacetimidate, $Sc(OTf)_3$, PhMe, 0 °C, 81%; (c) (i) OsO_4, NMO, 3:1 acetone-H_2O; (ii) $Pb(OAc)_4$, PhH, rt; (iii) $NaBH_4$, MeOH, 0 °C, 71% for three steps; (d) Ph_3P, imidazole, I_2, CH_2Cl_2, rt, 92%. PMB=*para*-methoxybenzyl, THF=tetrahydrofuran, Tf=trifluoromethane-sulfonate, NMO=*N*-methylmorpholine *N*-oxide, Ac=acetyl.

To continue with the synthesis, we wished to convert alcohol **2** to the corresponding *p*-methoxybenzyl (PMB) ether. Under the majority of conditions examined, however, mixtures of the desired product **3** and the *δ*-lactone were observed. Fortunately, on treatment of **2** with *p*-methoxybenzyl trichloroacetimidate in the presence of a catalytic amount of scandium(III) triflate, we were able to obtain **3** in 81% yield without observing a significant quantity of the *δ*-lactone. Using standard conditions (OsO_4/NMO followed by $Pb(OAc)_4$), alkene **3** was oxidatively cleaved to furnish the aldehyde, which was reduced to alcohol **4** with $NaBH_4$ in good overall yield (71% for three steps). Lastly, **4** was converted to the corresponding alkyl iodide **5**, providing the desired C1–C7 fragment as a 93:7 mixture with its corresponding enantiomer, ***ent*-5**.

2.2. Synthesis of the C8–C13 fragment

Next we focused on a new synthesis of the C8–C13 segment (Scheme 2). Subjection of readily available allylic alcohol **7**, prepared from **6** by the protocol of Jamison,[14] to Sharpless asymmetric epoxidation[15] provided the expected epoxide **8**. The optical purity of **8** thus obtained was found to be 80% ee.[16] Fortunately, we were able to crystallize and recrystallize **8** from acetone/hexanes (10:1) or toluene/hexanes (1:1) to obtain the optically pure **8** (>99% ee) in 70% yield.



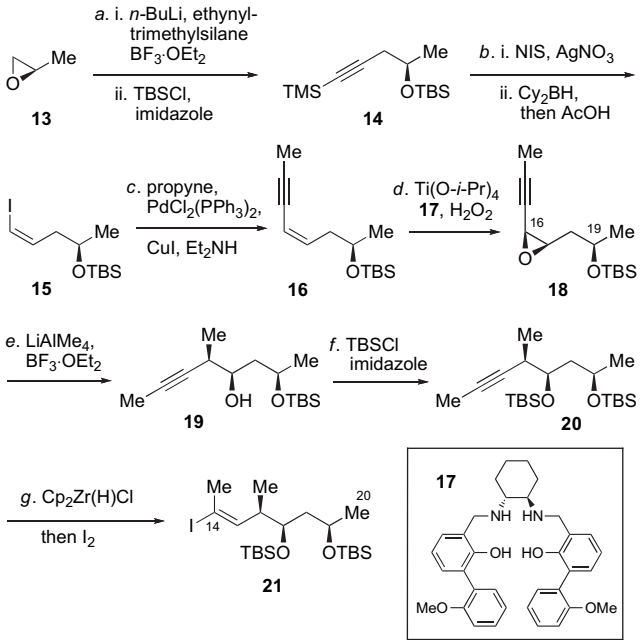
Scheme 2. Reagents and conditions: (a) $LiAlH_4$, Et_2O, rt, 98%; (b) Ti(O-*i*-Pr)$_4$, TBHP, (−)-DET, 4 Å MS, CH_2Cl_2, −25 °C, 70%; then recrystallization from 10:1 hexanes/acetone, −24 °C (c) MeLi, CuCN, THF, −20 °C, 79%; (d) *p*-TsOH, cyclopentanone, rt, 89%; (e) $Cp_2Zr(H)Cl$, THF, 50 °C, then I_2, THF, 0 °C, 68%. TBHP=*tert*-butyl hydroperoxide, DET=diethyl tartrate, MS=molecular sieves, *p*-TsOH=*para*-toluenesulfonic acid.

As in examples previously reported,[17] optically pure **8** was treated with the higher-order cuprate prepared from CuCN and MeLi to furnish 1,3-diol **9** exclusively. Upon treatment with *p*-TsOH and cyclopentanone, **9** was uneventfully converted to cyclopentylidene acetal **10**.

The last step required for the synthesis of the C8–C13 fragment was the conversion of alkyne **10** to vinyl iodide **11**. We examined several protocols for this transformation, all of which relied on the use of the Schwartz hydrozirconation reagent, $[Cp_2Zr(H)Cl]$.[18] First, we attempted hydrozirconation using $Cp_2Zr(H)Cl$ prepared in situ from DIBAL-H and Cp_2ZrCl_2,[19] but found that this reagent gave poor regioselectivity (1:1.3 **11**/**12** at room temperature and 6:1 **11**/**12** at 50 °C) as well as multiple byproducts. We eventually found that the Schwartz reagent, prepared from Red-Al and Cp_2ZrCl_2 following the reported protocol,[18c] gave improved regioselectivity as well as attenuated levels of byproduct formation. After optimization of temperature, reagent equivalents, and reaction duration, we were consistently able to obtain close to 70% yield of **11** as a 22:1 mixture with **12**. It is noteworthy that **8** was obtained in optically pure form and therefore **11** was free from any enantiomeric contaminants.

2.3. Synthesis of the C14–C20 fragment

Having completed syntheses of the C1–C7 and C8–C13 fragments, we set out to prepare the remaining C14–C20 segment required for the synthesis of the mycolactone core (Scheme 3). The synthesis commenced with (*R*)-propylene oxide **13** (Alfa Aesar, >99% optical purity), which was opened with the lithium anion of ethynyltrimethylsilane. The resultant secondary alcohol was protected as a TBS ether to furnish **14**. Upon treatment with NIS and $AgNO_3$, **14** was converted to the alkynyl iodide, which underwent subsequent hydroboration with Cy_2BH to provide **15** after quenching with acetic acid. The overall yield for these four steps was 95%.



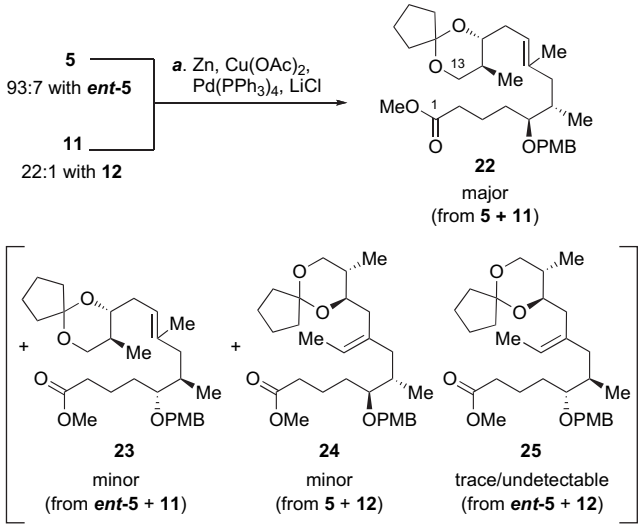
Scheme 3. Reagents and conditions: (a) (i) *n*-BuLi, ethynyltrimethyl-silane, $BF_3{\cdot}OEt_2$, Et_2O, −78 °C; (ii) TBSCl, imidazole, DMF, rt; (b) (i) NIS, $AgNO_3$, DMF, rt; (ii) Cy_2BH, THF, 0 °C, then AcOH, 95% for four steps; (c) propyne, $PdCl_2(PPh_3)_2$, CuI, Et_2NH, rt, 96%; (d) Ti(O-*i*-Pr)$_4$, **17**, 4,4′-thiobis(6-*t*-butyl-*m*-cresol), H_2O_2, phosphate buffer, CH_2Cl_2, 40 °C, 91%, ≥50:1 dr; (e) $LiAlMe_4$, $BF_3{\cdot}OEt_2$, CH_2Cl_2, −78 °C, 87%; (f) TBSCl, imidazole, DMF, rt, 99%; (g) $Cp_2Zr(H)Cl$, THF, 50 °C, then I_2, THF, 0 °C, 68%. TBS=*tert*-butyldimethylsilyl, DMF=*N*,*N*-dimethylformamide, NIS=*N*-iodosuccinimide, Cy=cyclohexyl.

To continue the synthesis of the C14–C20 fragment, vinyl iodide **15** was coupled with propyne under Sonogashira conditions[20] to produce enyne **16**. At this stage we wished to oxidize the *cis*-olefin in **16** in a stereoselective manner. We hoped that an enantioselective epoxidation could override the pre-existing stereocenter at C19, thereby allowing us to introduce the C–O bond at C16 stereoselectively. A literature search revealed ample precedent for enyne epoxidation,[21] and we felt that ligand **17** recently reported by Katsuki and co-workers could meet our need.[21b] Indeed, on treatment with Ti(O-*i*-Pr)$_4$ and H_2O_2 in the presence of **17**, *cis*-olefin **16** was smoothly converted to propargylic epoxide **18** in excellent yield with outstanding selectivity (≥50:1 dr, as estimated by ^{1}H NMR). Satisfied with this result, we proceeded forward with the synthesis of the C14–C20 fragment.

Upon treatment with $LiAlMe_4$, a highly regio- and stereospecific opening of the propargylic epoxide **18** was observed to furnish homopropargylic alcohol **19**.[22] To complete the synthesis, alcohol **19** was protected as the TBS ether **20**, and subsequent hydrozirconation–iodination under the same conditions optimized for the conversion of **10**→**11** provided vinyl iodide **21**, this time with complete regioselectivity.

2.4. Assembly of the mycolactone core

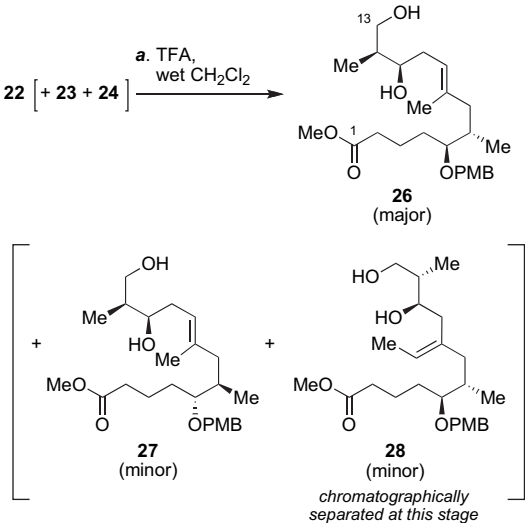
With scalable and efficient routes established for the requisite fragments, we turned our attention to their assembly to construct the mycolactone core. The first two fragments coupled were **5** and **11**, and this was accomplished using a Negishi coupling (Scheme 4).[23] Notably, we chose to prepare the alkylzinc iodide species via zinc insertion using an active Zn–Cu couple[24] rather than by transmetallation from Li to Zn due to the electrophilic ester present in **5**. In the event, the coupling proceeded smoothly in the presence of eight equivalents of LiCl in *N*-methylpyrrolidinone (freshly distilled) to furnish **22** in excellent yield (95%). Notably, we were able to detect minor diastereoisomers in the ^{1}H NMR of **22**. These minor products resulted from coupling of alkyl iodide **5**, which was obtained as a 93:7 mixture of enantiomers (Scheme 1), with vinyl iodide **11**, which was synthesized in enantiomerically pure form but contained a small amount of regioisomer **12** (Scheme 2). We were unable to estimate the exact ratio of the components in the mixture by ^{1}H NMR, as the signals overlapped significantly. However, if we assume the rates of formation of the various products are similar, statistically **22**, **23**, **24**, and **25** should be present in a ratio of 89:6.7:4:0.3. In accordance with this, it was possible to detect **22**, **23**, and **24** by ^{1}H NMR, although we were unable to observe **25** as it was present in such low quantity.



Scheme 4. Reagents and conditions: (a) Zn, $Cu(OAc)_2$, $Pd(PPh_3)_4$, LiCl, NMP, 55 °C, 95% (for mixture of **23**, **24**, and **25**). NMP=*N*-methyl-2-pyrrolidinone.

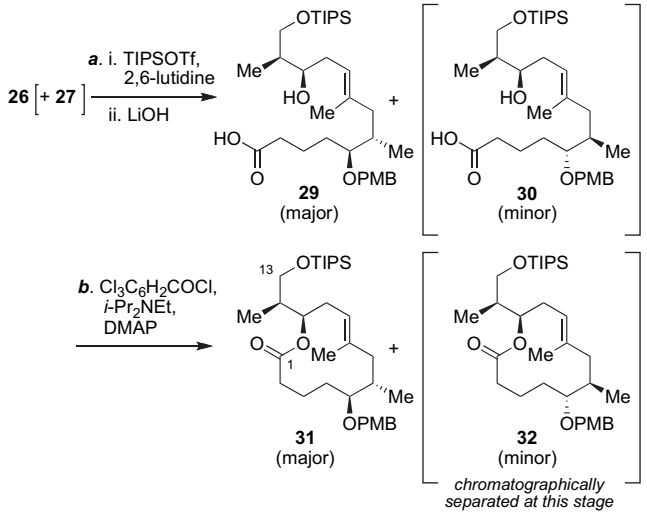
At this point, we began to search for a point at which the minor contaminants could be removed (Scheme 5). Fortunately, once the cyclopentylidene acetal had been cleaved under acidic conditions to form **26**, we were readily able to chromatographically separate 1,3-diol **28**, derived from **24**. However, at this stage, it was not practical to separate the minor diastereoisomer **27** resulting from **23**. Despite this, we carried on with the synthesis with the hope that the remaining diastereoisomeric contaminant could be removed at a later stage.

Accordingly, we proceeded to convert **26** to *seco*-acid **29** in a two-step sequence consisting of primary alcohol protection and saponification of the methyl ester (Scheme 6). In our previous study,[4d] selective protection of the primary alcohol was cleanly achieved under standard conditions (TIPSCl, imidazole, DMF). In this study, however, we observed mixtures of the primary- and secondary-protected alcohols in varying ratios. The reason for the discrepancy in these studies is not clear at this time. Nevertheless, we were eventually able to selectively protect the primary position using triisopropylsilyl triflate and 2,6-lutidine at −78 °C. After



Scheme 5. Regents and conditions: (a) 1:4:16 TFA/H_2O/CH_2Cl_2, 91%. (for mixture of **27** and **28**). TFA=trifluoroacetic acid.

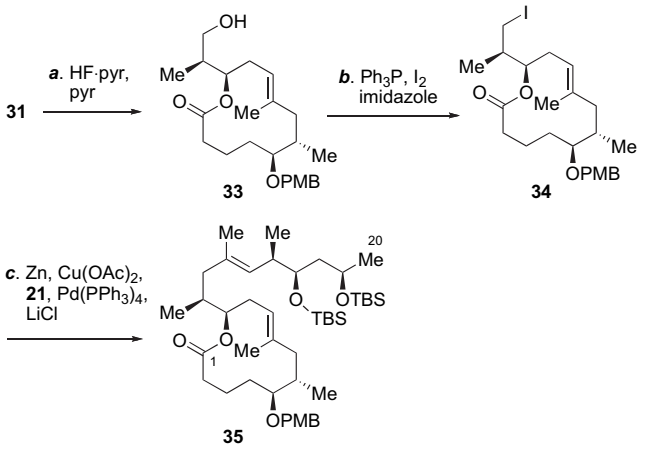
hydrolysis of the methyl ester to form **29**, the stage was set for macrolactonization. On exposure to standard Yamaguchi conditions,[25] *seco*-acid **29** was converted to macrolactone **31**. To our delight, the remaining minor diastereoisomeric lactone, **32**, was readily removed chromatographically at this stage to afford **31** in optically pure form (>99% ee).



Scheme 6. Reagents and conditions: (a) (i) TIPSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C; (ii) LiOH, 1:1:4H_2O/MeOH/THF, 88% for two steps (as mixture of **29** and **30**); (b) $Cl_3C_6H_2COCl$, *i*-Pr_2NEt, benzene, then DMAP, benzene, 74% (for single compound, **31**). TIPS=triisopropylsilyl, DMAP=4-(dimethylamino)pyridine.

To complete the synthesis of the mycolactone core, the triisopropyl ether of **31** was cleaved,[26] and the resultant primary alcohol, **33**, was converted to alkyl iodide **34** (Scheme 7). Under the same Negishi coupling conditions optimized for the case of **5**+**11**→**22**, alkyl iodide **34** was coupled with **21** (1.5 equiv) to provide **35** in 88% yield.

To summarize, the synthesis of the mycolactone core described herein proceeds in 14 linear steps and 19% overall yield. This synthesis features scalable and efficient methods for the preparation of the C1–C7, C8–C13, and C14–C20 fragments, and has allowed for the preparation of 6.0 grams of protected mycolactone core **35** with relative ease. Furthermore, we anticipate that it should be straightforward to prepare even larger quantities of this material should the need arise. Importantly, by synthesizing the C8–C13 fragment in optically pure form and removing the minor contaminants chromatographically, we can be confident that the material produced through this sequence is >99% optically pure.



Scheme 7. Reagents and conditions: (a) HF·pyr, pyr, CH_3CN, 0 °C, 92%; (b) Ph_3P, I_2, imidazole, CH_2Cl_2, rt, 99%; (c) Zn, $Cu(OAc)_2$, **20**, $Pd(PPh_3)_4$, LiCl, NMP, 60 °C, 88%. pyr=pyridine.

3. Conclusion

A third synthesis of the mycolactone core has been described. While our first and second syntheses allowed us to unambiguously confirm the relative and absolute stereochemistry of the mycolactones and optimize protecting group strategy, respectively, the synthetic efforts described herein have resulted in a scalable and efficient route to the mycolactone core, which has allowed for the preparation of multi-gram quantities in high purity. We feel that this material will be useful for research efforts aimed at addressing some of the many unsolved questions still surrounding Buruli ulcer.

4. Experimental

4.1. General procedures and methods

NMR spectra were recorded on Varian Inova 500 MHz or 600 MHz spectrometers. Chemical shifts are reported in parts per million (ppm). For ^{1}H NMR spectra ($CDCl_3$ or C_6D_6), the residual solvent peak was used as the internal reference (7.26 ppm in $CDCl_3$; 7.15 ppm in C_6D_6). For ^{13}C NMR spectra, the central solvent peak was used as the internal reference (77.0 ppm in $CDCl_3$; 128.0 ppm in C_6D_6). Mass spectrometry was performed on an Agilent 6210 Time-of-Flight mass spectrometer with an electrospray ionization source. Analytical thin layer chromatography (TLC) was performed with E. Merck pre-coated TLC plates, silica gel 60F-254, layer thickness 0.25 mm. Flash chromatography separations were performed on E. Merck Kieselgel 60 (230–400) mesh silica gel. Reagents and solvents are of commercial grade and were used as supplied. All reactions were conducted under an inert atmosphere. Reaction vessels were flame-dried or oven-dried and allowed to cool to rt under inert atmosphere.

4.2. Synthesis outlined in Scheme 1

4.2.1. Preparation of ***2****.* To a solution of potassium *tert*-butoxide (13.45 g, 120 mmol) in THF (60 mL) at −78 °C was added condensed *cis*-2-butene (42 mL, 461 mmol) followed by *n*-BuLi in hexanes (1.6 M in hexanes, 75 mL, 120 mmol) dropwise. The resultant bright yellow suspension was stirred for 10 min at −78 °C, 20 min at −50 °C, and 10 min at −78 °C. A solution of (+)-Ipc_2-BOMe (43.80 g, 151 mmol) in Et_2O (100 mL) was added dropwise via

cannula. The colorless solution was stirred at −78 °C for 40 min, and then $BF_3{\cdot}OEt_2$ (19.2 mL, 151 mmol) was added dropwise. Aldehyde **1**[11] (12.0 g, 92.2 mmol) was then added dropwise as a solution in THF (90 mL). The resultant mixture was stirred a further 3 h at −78 °C before being quenched with 3 M aqueous NaOH (73.2 mL) and diluted with EtOAc (500 mL). 30% H_2O_2 (35.4 mL) was added carefully, the cold bath was removed, and the resultant mixture was stirred for 1 h. The layers were separated, and the aqueous extracted with EtOAc (3×200 mL). The combined organics were washed with saturated aqueous NaCl, dried ($MgSO_4$), and concentrated in vacuo. The crude residue was purified by flash column chromatography in a solvent gradient (SiO_2, 5%→10%→30% EtOAc/hexanes) to provide **2** (13.38 g, 78% yield, 86% ee as determined by conversion to the corresponding (*R*)- and (*S*)-Mosher's esters) as a colorless oil. $[\alpha]_D^{27}$ −25.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.04 (3H, d, *J*=7.0 Hz), 1.36–1.45 (1H, m), 1.51–1.60 (2H, m), 1.64–1.75 (1H, m), 1.80–1.90 (1H, m), 2.25–2.33 (1H, m), 2.37 (2H, t, *J*=7.5 Hz), 3.47–3.54 (1H, m), 3.69 (3H, s), 5.07–5.13 (2H, m), 5.75–5.83 (1H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.16, 21.41, 33.32, 33.83, 43.51, 51.50, 74.23, 115.40, 140.77, 174.17; HRMS (ESI) exact mass calculated for $[M+Na]^+$ ($C_{10}H_{18}O_3Na$) requires *m*/*z* 209.1148, found 209.1141.

4.2.2. Preparation of ***3****.* Alcohol **2** (0.90 g, 4.83 mmol) and PMB-trichloroacetimidate (2.44 g, 9.66 mmol) were dissolved in PhMe (48 mL) and cooled to 0 °C. Scandium(III) trifluoromethanesulfonate (0.12 g, 0.24 mmol) was added portionwise over 2 min. Stirring at 0 °C was continued for a further 15 min. The reaction was diluted with hexanes and filtered over Celite. The filtrate was concentrated in vacuo, and the crude residue was purified by flash column chromatography (SiO_2, 7.5% EtOAc/hexanes) to provide **3** (1.20 g, 81% yield) as a colorless oil: $[\alpha]_D^{27}$ −25.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.05 (3H, d, *J*=7.0 Hz), 1.43–1.59 (2H, m), 1.60–1.72 (1H, m), 1.75–1.86 (1H, m), 2.24–2.36 (2H, m), 2.51 (1H, apparent sextet, *J*=6.5 Hz), 3.23–3.29 (1H, m), 3.68 (3H, s), 3.81 (3H, s), 4.48 (2H, AB quartet, *J*=11.5 Hz, 33.0 Hz), 5.01–5.09 (2H, m), 5.80–5.89 (1H, m), 6.86–6.92 (2H, m), 7.26–7.31 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.63, 21.00, 30.40, 34.04, 40.60, 51.42, 55.25, 71.36, 82.11, 113.71, 114.45, 129.35, 130.89, 140.75, 159.09, 174.06; HRMS (ESI) exact mass calculated for $[M+Na]^+$ ($C_{18}H_{26}O_4Na$) requires *m*/*z* 329.1723, found 329.1730.

4.2.3. Preparation of ***4****.* To a solution of **3** (9.00 g, 29.4 mmol) in 3:1 acetone/H_2O (488 mL) was added 4-methylmorpholine *N*-oxide·H_2O (7.94 g, 58.8 mmol) and OsO_4 (0.1 M in H_2O, 5.9 mL, 0.59 mmol). The resultant solution was stirred at rt for 14 h. Saturated aqueous $Na_2S_2O_3$ (300 mL) and EtOAc (300 mL) were added, and the mixture was stirred for 1 h. The phases were separated, and the aqueous extracted with EtOAc (3×200 mL). The combined organic phase was washed with H_2O and brine, dried (Na_2SO_4), and concentrated in vacuo to yield an inconsequential 3:1 mixture of diol diastereoisomers, which was carried on to the following step without further purification.

To a solution of the diol from the above step in benzene (185 mL) was added $Pb(OAc)_4$ (20.6 g, 46.4 mmol). The resultant mixture was stirred at rt for 20 min. Saturated aqueous $NaHCO_3$ was added until the aqueous phase reached pH 7.0, and the mixture was extracted with EtOAc (3×200 mL). The combined organic phase was washed with brine, dried ($MgSO_4$), and concentrated in vacuo to provide the crude aldehyde, which was used in the following step without further purification.

The crude aldehyde from the preceding step was dissolved in MeOH (300 mL) and cooled to 0 °C. $NaBH_4$ (2.22 g, 58.8 mmol) was added portionwise over 5 min, and the solution was stirred at 0 °C for 1 h. Saturated aqueous NH_4Cl was added to quench the reaction, and the mixture was extracted with EtOAc (3×200 mL). The combined organic phase was washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The crude residue was purified by flash column chromatography (SiO_2, 25% EtOAc/hexanes) to provide alcohol **4** (6.51 g, 71% over three steps) as a colorless oil: $[\alpha]_D^{23}$ +0.8 (*c* 1.77, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.87 (3H, d, *J*=7.0 Hz), 1.45–1.56 (1H, m), 1.56–1.67 (2H, m), 1.71–1.82 (1H, m), 2.05–2.14 (1H, m), 2.25–2.37 (2H, m), 3.47–3.52 (1H, m), 3.54 (1H, dd, *J*=5.0, 11.0 Hz), 3.665 (1H, apparent dd, *J*=8.0, 11.0 Hz), 3.67 (3H, s), 3.80 (3H, s), 4.49 (2H, AB quartet, *J*=11.0, 26.5 Hz), 6.85–6.90 (2H, m), 7.24–7.28 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.9, 159.2, 130.3, 129.5 (2C), 113.8 (2C), 81.4, 71.4, 65.8, 55.2, 51.5, 36.7, 33.9, 29.3, 21.6, 11.9 LRMS (ES) calculated for $[M+H]^+$ ($C_{17}H_{27}O_5$) requires *m*/*z* 311, found 311.

4.2.4. Preparation of ***5****.* To a solution of alcohol **4** (0.217 g, 0.699 mmol) in CH_2Cl_2 (8 mL) was added imidazole (0.143 g, 2.10 mmol), PPh_3 (0.385 g, 1.47 mmol), and iodine (0.373 g, 1.47 mmol). The resultant brown reaction mixture was stirred at rt for 1 h. The reaction was diluted with EtOAc and poured into saturated aqueous $Na_2S_2O_3$. The aqueous layer was separated and extracted with EtOAc (3×20 mL). The combined organics were washed with saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated in vacuo. The crude material was purified by flash column chromatography (SiO_2, 10% EtOAc/hexanes) to provide alkyl iodide **5** (0.269 mg, 92% yield) as a colorless oil: $[\alpha]_D^{26}$ +18.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.04 (3H, d, *J*=6.5 Hz), 1.45–1.54 (1H, m), 1.54–1.78 (3H, m), 1.89–1.98 (1H, m), 2.27–2.39 (2H, m), 3.09 (1H, dd, *J*=7.6, 9.6 Hz), 3.37 (1H, dd, *J*=6.0, 9.6 Hz), 3.42–3.48 (1H, m), 3.68 (3H, s), 3.82 (3H, s), 4.48 (2H, AB quartet, *J*=11.5, 21.0 Hz), 6.87–6.92 (2H, m), 7.25–7.29 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.17, 15.40, 20.90, 29.96, 33.74, 38.88, 51.34, 55.09, 71.70, 80.57, 113.62, 129.15, 130.53, 159.02, 173.60; HRMS (ESI) exact mass calculated for $[M+Na]^+$ ($C_{17}H_{25}IO_4Na$) requires *m*/*z* 443.0690, found 443.0659.

4.3. Synthesis outlined in Scheme 2

4.3.1. Preparation of ***7****.* To a 0 °C solution of $LiAlH_4$ (1 M in Et_2O from Aldrich, 179 mL, 179 mmol) was added diynol **6**[13] (19.34 g, 179 mmol) in Et_2O (200 mL) dropwise. The resultant mixture was heated to a gentle reflux and stirred for 9 h. The reaction was diluted with Et_2O (310 mL) and treated, in sequence, with H_2O (6.5 mL), 2 N NaOH (6.5 mL) and H_2O (6.5 mL). After stirring for a further 15 min, the mixture was filtered through Celite, dried ($MgSO_4$), and concentrated in vacuo to provide pure **7** (19.37 g, 98% yield) as a colorless oil whose ^{1}H NMR was identical to that published previously.[14]

4.3.2. Preparation of ***8****.* To a suspension of activated 4 Å molecular sieves (30.0 g, powdered) in anhydrous CH_2Cl_2 (430 mL) at −10 °C were added (−)-diethyl D-tartrate (3.21 mL, 18.8 mmol) and titanium tetraisopropoxide (4.40 mL, 15.0 mmol). The resultant mixture was cooled to −25 °C and treated with *tert*-butyl hydroperoxide (78.6 mL, 5.5 M solution in decane, 432 mmol). After 20 min, a solution of alcohol **7**[14] (20.7 g, 188 mmol) in anhydrous CH_2Cl_2 (110 mL) was added dropwise via cannula over 30 min. The resultant mixture was stirred 4 h at −25 °C, then warmed to rt over 2 h. After 30 min at rt, H_2O (52 mL) and 4 M aqueous NaOH (26 mL) were added. The resultant mixture was stirred for 30 min, and the cloudy suspension was filtered through Celite. After diluting with CH_2Cl_2 (300 mL), the organic phase was washed with 10% Na_2SO_3. The layers were separated, and the aqueous phase extracted with CH_2Cl_2 (2×300 mL). The combined organic phase was washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The crude residue was purified by flash column chromatography (SiO_2, 15% acetone/hexanes) to afford **8** (19.8 g,

83%) as white solid. It was determined by conversion of **9** (for preparation of **9**, see the following step) to the corresponding (*R*)- and (*S*)-Mosher esters that the Sharpless asymmetric epoxidation had proceeded in 80% ee. Optically pure **8** (16.5 g, 70%, >99% ee) was obtained by recrystallization from hexanes/acetone (10/1) or toluene/hexanes (1/1) in a −20 °C freezer: R_f 0.35 (hexanes/acetone, 4/1); $[\alpha]_D^{20}$ +18.7 (*c* 0.4, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.75 (1H, dd, *J*=5.4, 7.8 Hz), 1.83 (3H, t, *J*=1.8 Hz), 2.48–2.65 (2H, m), 3.14–3.20 (2H, m), 3.67–3.75 (1H, m), 3.95–4.05 (1H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 3.44, 21.63, 53.50, 57.80, 61.16, 73.08, 78.15; HRMS (ESI) exact mass calculated for $[M+Na]^+$ ($C_7H_{10}O_2Na$) requires *m*/*z* 149.0573, found 149.0576.

4.3.3. Preparation of ***9****.* To a suspension of CuCN (34.6 g, 387 mmol) in anhydrous THF (560 mL) was added MeLi (1.6 M in ether, 524 mL, 838 mmol) dropwise at −20 °C under argon. The mixture was stirred until it became clear, then epoxide **8** (16.2 g, 129 mmol) was added as a solution in anhydrous Et_2O (250 mL) via cannula over 30 min. The resultant mixture was stirred at −20 °C overnight, then warmed to 0 °C. The reaction was diluted with Et_2O (500 mL) and saturated aqueous NH_4Cl (115 mL) and stirred vigorously for 10 min. The precipitate was removed by filtration through Celite, then the organic layer was separated, washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was dissolved in acetone (40 mL) and H_2O (50 mL), and was treated with $NaIO_4$ (6.10 g, 28.5 mmol). After 2 h, the mixture was quenched by the addition of Na_2SO_3 (7.2 g, 57.0 mmol), diluted with Et_2O, and filtered through Celite. The organic phase was separated, washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography in a solvent gradient (SiO_2, 33% EtOAc/hexanes→50% EtOAc/hexanes) to give pure diol **9** (19.4 g, 79%): R_f 0.25 (50% EtOAc/hexanes); $[\alpha]_D^{20}$ +17.6 (*c* 0.4, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.92 (3H, d, J=7.2 Hz), 1.85 (3H, t, *J*=3.0 Hz), 1.85–1.93 (1H, m), 2.36–2.40 (1H, m), 2.50–2.54 (1H, m), 2.77–3.83 (2H, m), 3.63–3.67 (1H, m), 3.68–3.72 (1H, m), 3.73–3.78 (1H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 3.39, 13.54, 25.81, 38.94, 67.00, 74.84, 75.06, 78.31; HRMS (ESI) exact mass calculated for $[M+Na]^+$ ($C_8H_{14}O_2Na$) requires *m*/*z* 165.0886, found 165.0884.

4.3.4. Preparation of ***10****.* To a solution of diol **9** (18.7 g, 131 mmol) in cyclopentanone (200 mL) was added *p*-TsOH (monohydrate, 2.50 g, 13.1 mmol). The mixture was stirred 12 h at rt, then treated with Et_3N (3.64 mL, 26.3 mmol). The mixture was concentrated in vacuo, and the residue purified by flash column chromatography (SiO_2, 10% EtOAc/hexanes→50% EtOAc/hexanes) to provide **10** (22.3 g, 89% based on consumed diol) along with recovered diol **9** (1.63 g, 5%): R_f 0.40 (10% EtOAc/hexanes); $[\alpha]_D^{20}$ −4.1 (*c* 0.3, $CHCl_3$); ^{1}H NMR (500 MHz, C_6D_6) δ 0.42 (3H, d, *J*=6.5 Hz), 1.54 (3H, t, *J*=2.5 Hz), 1.50–1.63 (4H, m), 1.69–1.82 (2H, m), 1.85–1.95 (1H, m), 2.04–2.13 (2H, m), 2.28–2.43 (2H, m), 3.17 (1H, t, *J*=11 Hz), 3.24–3.30 (1H, m), 3.58 (1H, dd, *J*=11.5, 5.0 Hz); ^{13}C NMR (125 MHz, C_6D_6) δ 3.51, 12.30, 22.84, 24.23, 24.66, 30.85, 33.69, 40.43, 67.21, 75.89, 76.95, 110.41, 127.69; HRMS (ESI) exact mass calculated for $[M+Na]^+$ ($C_{13}H_{20}O_2Na$) requires *m*/*z* 231.1356, found 231.1357.

4.3.5. Preparation of ***11****.* Schwartz reagent (~70% pure homemade reagent,[18c] 13.5 g, 36.6 mmol) was transferred to a round bottom flask under inert atmosphere, then treated with a solution of alkyne **10** (5.08 g, 24.4 mmol) in THF (150 mL). The resultant suspension was heated to 50 °C and stirred for 30 min. The reaction was cooled to rt, then to 0 °C. A solution of iodine (9.28 g, 36.6 mmol) in THF (122 mL) was added dropwise to the 0 °C suspension until a brown color just persisted. At this point the addition of iodine/THF was ceased, and the remaining iodine/THF solution was discarded. The reaction was quenched after 5 min by dilution with 1:1 saturated aqueous $NaHCO_3$/saturated aqueous $Na_2S_2O_3$ (200 mL) and EtOAc (100 mL). The biphasic mixture was stirred vigorously for 10 min, then the layers were separated and the aqueous extracted with EtOAc (3×100 mL). The combined organics were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The crude residue was purified by flash column chromatography (SiO_2, 1% EtOAc/hexanes) to provide vinyl iodide **11** as an inseparable 22:1 mixture with the undesired regioisomer **12** as a clear oil (5.57 g, 68% yield). Spectroscopic data for the major regioisomer: $[\alpha]_D^{26}$ +10.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, C_6D_6) δ 0.28 (3H, d, *J*=6.7 Hz), 1.42–1.56 (5H, m), 1.56–1.64 (1H, m), 1.66–1.73 (1H, m), 1.85–1.96 (3H, m), 1.96–2.03 (1H, m), 2.12 (3H, d, *J*=1.5 Hz), 3.05 (1H, ddd, *J*=3.5, 8.0, 11.0 Hz), 3.09 (1H, apparent t, *J*=11.5 Hz), 3.51 (1H, dd, *J*=5.0, 11.5 Hz), 6.33 (1H, dt, *J*=1.7, 7.2 Hz); ^{13}C NMR (125 MHz, C_6D_6) δ 137.51, 110.21, 94.84, 76.00, 67.21, 40.33, 34.14, 33.70, 30.72, 27.72, 24.55, 22.73, 12.28; HRMS (ESI) exact mass calculated for $[M+Na]^+$ ($C_{13}H_{21}IO_2Na$) requires *m*/*z* 359.0478, found 359.0470.

4.4. Synthesis outlined in Scheme 3

4.4.1. Preparation of ***14****.* A solution of *n*-BuLi (91.5 mL of a 1.87 M solution in hexanes, 171 mmol) was added dropwise to a solution of ethynyltrimethylsilane (32.0 mL, 214 mmol) in Et_2O (950 mL) at −78 °C. Once addition was complete, the reaction mixture was warmed to 0 °C for 40 min, then recooled to −78 °C. (*R*)-2-Methyloxirane **13** (Alfa Aesar, >99% optical purity, 10.0 mL, 143 mmol) was added via syringe, and the resultant solution was stirred for 10 min. A solution of $BF_3\cdot OEt_2$ (freshly distilled, 21.5 mL, 171 mmol) in Et_2O (21.5 mL) was added dropwise over 3 min. The mixture was stirred at −78 °C for 1 h, then quenched with saturated aqueous $NaHCO_3$ (100 mL). The layers were separated, and aqueous was extracted with Et_2O (3×100 mL). The combined organic phase was dried ($MgSO_4$), and the solvent was removed by distillation through a Vigreux column (10 cm height, 55 °C oil bath) until 200 mL of solution remained. The crude residue, whose ^{1}H and ^{13}C NMR spectral data were consistent with those reported,[27] was used for the next step without purification.

To a solution of crude alcohol (143 mmol) and imidazole (19.4 g, 285 mmol) in DMF (150 mL) was added TBSCl (30.1 g, 200 mmol). The resultant solution was stirred at rt for 48 h. The mixture was diluted with Et_2O (1.5 L) and washed with brine (2×250 mL), H_2O (2×250 mL), and brine (250 mL). The organic phase was dried ($MgSO_4$), and gently concentrated in vacuo until 100 mL of solution remained. The crude residue of **14**, whose ^{1}H and ^{13}C NMR spectral data were consistent with those reported,[28] was used for the next step without purification.

4.4.2. Preparation of ***15****.* To a solution of crude alkyne **14** (143 mmol) and NIS (43.3 g, 192 mmol) in DMF (475 mL) was added $AgNO_3$ (3.63 g, 21.4 mmol). The resultant mixture was stirred for 5 h at rt. The mixture was quenched with brine (150 mL), filtered over Celite, and diluted with hexanes/Et_2O (1:1, 2 L). The separated organic phase was washed with brine (2×1 L) and H_2O (3×1 L), dried ($MgSO_4$), and gently concentrated in vacuo until 100 mL of solution remained. The crude residue was unstable and used for the next step immediately without purification.

THF (715 mL) was bubbled with Ar for 15 min at 0 °C, then cyclohexene (37.5 mL, 371 mmol) was added. To the resultant solution was cautiously added $BH_3\cdot S(CH_3)_2$ (17.6 mL, 185 mmol) dropwise over 20 min. The reaction was stirred for 2 h at 0 °C and 1 h at rt with constant bubbling of Ar through the solution. The resultant Cy_2BH solution was cooled to 0 °C, and the crude alkynyl iodide from the preceding step was added dropwise over 10 min. The reaction was stirred 3 h at rt, then quenched by addition of AcOH (32.6 mL, 570 mmol) at 0 °C over 5 min. After stirring at rt for 30 min, the reaction was allowed to stand at 5 °C for 12 h. The mixture was gently concentrated in vacuo to 200 mL, then K_2CO_3

(95 g in 300 mL water) was added to neutralize the mixture. Following dilution with hexanes (1.5 L), the organics were washed with saturated aqueous $NaHCO_3$ (3×400 mL) and brine (400 mL), dried ($MgSO_4$), and concentrated in vacuo. The crude residue was purified by flash chromatography (SiO_2, 100% hexanes→5% CH_2Cl_2/hexanes) to provide vinyl iodide **15** (44.1 g, 95% over four steps) as a colorless oil, whose ^1H and ^{13}C NMR spectral data were consistent with those reported.[29]

*4.4.3. Preparation of **16**.* Propyne was bubbled (via a balloon) through a solution of vinyl iodide **15** (44.1 mL, 135 mmol) in Et_2NH (0.9 L) for 10 min at 0 °C. $PdCl_2(PPh_3)_2$ (4.12 g, 5.4 mmol) and CuI (2.06 g, 10.8 mmol) were added. Propyne was continually bubbled into the resultant solution as the reaction stirred for 3 h at rt. The mixture was diluted with pentane (4 L) and washed with saturated aqueous NH_4Cl (3×2 L), H_2O (2×2 L) and brine (2 L). The organic phase was dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by flash chromatography (SiO_2, 100% pentane→5% Et_2O/pentane) to afford enyne **16** (30.5 g, 96%) as a colorless oil; $[\alpha]_D^{25}$ +4.9 (*c* 1.51, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$) δ 0.04 (3H, s), 0.04 (3H, s), 0.87 (9H, s), 1.13 (3H, d, *J*=6.0 Hz), 1.95 (3H, d, *J*=2.4 Hz), 2.46–2.35 (2H, m), 3.87 (1H, dq, *J*=6.0, 6.0 Hz), 5.49–5.44 (1H, m), 5.85 (1H, dt, *J*=10.2, 7.5 Hz); ^{13}C NMR (125 MHz) δ −4.78, −4.61, 4.36, 18.15, 23.49, 25.86, 40.11, 68.22, 76.61, 89.83, 110.89, 138.74; HRMS (ESI) exact mass calculated for $[M+H]^+$ ($C_{14}H_{27}OSi$) requires *m*/*z* 239.1831, found 239.1826.

*4.4.4. Preparation of **18**.* To a solution of ligand **17**[21b] (5.02 g, 9.38 mmol) in CH_2Cl_2 (200 mL) was added Ti(O-*i*-Pr)$_4$ (2.54 mL, 8.53 mmol). The reaction was stirred for 1 h at rt. Enyne **16** (20.0 g, 85.3 mmol), 4,4′-thiobis(6-*tert*-butyl-*m*-cresol) (Sumitomo Chemical, 2.0 g, 5.58 mmol), H_2O_2 (30% solution in H_2O, 20 mL, 176 mmol), and phosphate buffer (pH 7.4, 67 mM, 10 mL) were added. The resultant reaction mixture was stirred at 40 °C for 4 h, then H_2O_2 (30% solution in H_2O, 20 mL, 196 mmol) was added (repeated twice more, stirring 4 h between each H_2O_2 addition). The reaction was stirred at 40 °C for another 18 h until all of the enyne was converted to the epoxide. Solid NH_4Cl (30 g) was added, and the resultant mixture was diluted with hexanes (2 L) and filtered over Celite. The filtrate was washed with saturated NH_4Cl solution (3×400 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash chromatography in a solvent gradient (SiO_2, 3% CH_2Cl_2/hexanes→10% CH_2Cl_2/hexanes→10% Et_2O/hexanes) to afford epoxide **18** (19.8 g, 91%, ≥50:1 dr as determined by ^1H NMR) as a colorless oil; $[\alpha]_D^{25}$ −11.9 (*c* 1.80, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$) δ 0.04 (3H, s), 0.05 (3H, s), 0.87 (9H, s), 1.22 (3H, d, *J*=6.0 Hz), 1.75 (1H, dt, *J*=14.1, 6.0 Hz), 1.84 (3H, d, *J*=1.8 Hz), 1.86 (1H, dt, *J*=14.1, 6.0 Hz), 3.12 (1H, dt, *J*=6.0, 1.8 Hz), 3.38–3.35 (1H, m), 4.05 (1H, dq, *J*=6.0, 6.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.89, −4.53, 3.65, 18.04, 23.85, 25.79, 38.92, 44.85, 55.26, 66.37, 74.25, 82.13; HRMS (ESI) exact mass calculated for $[M+Na]^+$ ($C_{14}H_{26}O_2SiNa$) requires *m*/*z* 277.1600, found 277.1592.

*4.4.5. Preparation of **19**.* To a solution of epoxide **18** (19.8 mL, 78.0 mmol) in CH_2Cl_2 (780 mL) at −78 °C was added $AlMe_3$ (2 M solution in PhMe, Aldrich, 78.0 mL, 156 mmol) dropwise. After stirring for 10 min, MeLi (1.6 M solution in Et_2O, Aldrich, 98 mL, 156 mmol) was added dropwise. The reaction was stirred a further 20 min, then treated with a solution of $BF_3{\cdot}OEt_2$ (freshly distilled, 19.8 mL, 156 mmol) in Et_2O (19.8 mL). After 1 h at −78 °C, the reaction mixture was carefully quenched by dropwise addition of MeOH (100 mL) over 30 min while still stirring at −78 °C. The resultant mixture was warmed to rt, saturated aqueous NH_4Cl (100 mL) was added, and stirring was continued for 30 min. The mixture was then treated with saturated aqueous sodium potassium tartrate (150 mL) and stirred for 2 h. The phases were separated, and aqueous extracted with Et_2O (3×250 mL). The combined organic phase was dried ($MgSO_4$), concentrated in vacuo, and purified by flash chromatography (SiO_2, 33% CH_2Cl_2/hexanes→50% CH_2Cl_2/hexanes→10% Et_2O/hexanes) to afford alcohol **19** (18.3 g, 87%) as a colorless oil; $[\alpha]_D^{25}$ −8.5 (*c* 1.13, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$) δ 0.09 (3H, s), 0.10 (3H, s), 0.88 (9H, s), 1.14 (3H, d, *J*=4.8 Hz), 1.19 (3H, d, *J*=6.0 Hz), 1.55 (1H, dt, *J*=14.4, 9.6 Hz), 1.78 (3H, d, *J*=1.8 Hz), 1.83 (1H, ddd, *J*=14.4, 3.6, 1.8 Hz), 2.47–2.40 (1H, m), 3.57–3.53 (1H, m), 3.58 (1H, d, *J*=1.8 Hz), 4.11–4.06 (1H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.79, −3.93, 3.57, 17.07, 17.88, 24.53, 25.82, 33.05, 42.75, 70.13, 74.68, 77.36, 81.00; HRMS (ESI) exact mass calculated for $[M+Na]^+$ ($C_{15}H_{30}O_2SiNa$) requires *m*/*z* 293.1913, found 293.1907.

*4.4.6. Preparation of **20**.* TBSCl (14.3 g, 94.9 mmol) was added to a solution of alcohol **19** (18.3 g, 67.8 mmol) and imidazole (13.8 g, 203 mmol) in DMF (225 mL), and the reaction was stirred at rt for 48 h. The mixture was diluted with Et_2O/hexanes (1:1, 1.4 L). The organic layer was washed with brine (2×500 mL), H_2O (2×500 mL), and brine (500 mL), dried ($MgSO_4$), and concentrated. The residue was purified by flash chromatography (SiO_2, 100% hexanes→9% CH_2Cl_2/hexanes) to afford alkyne **20** (25.9 g, 99%) as a colorless oil: $[\alpha]_D^{23}$ +10.8 (*c* 1.28, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 0.057 (3H, s), 0.061 (3H, s), 0.07 (3H, s), 0.08 (3H, s), 0.90 (18H, overlapped two singlets), 1.07 (3H, *J*=6.0 Hz), 1.14 (3H, d, *J*=6.0 Hz), 1.54 (1H, ddd, *J*=6.0, 6.0, 13.5 Hz), 1.77 (3H, d, *J*=2.5 Hz), 1.82 (1H, ddd, *J*=6.0, 6.0, 13.5 Hz), 2.46–2.54 (1H, m), 3.68 (1H, apparent q, *J*=6.0 Hz), 3.98 (1H, apparent sextet, *J*=6.0 Hz); HRMS (ESI) exact mass calculated for $[M+H]^+$ ($C_{21}H_{44}O_2Si_2$) requires *m*/*z* 385.2958, found 385.2954.

*4.4.7. Preparation of **21**.* Schwartz reagent (~70% pure homemade reagent,[18c] 1.44 g, 3.90 mmol) was transferred to a round bottom flask under inert atmosphere, then treated with a solution of alkyne **20** (1.00 g, 2.60 mmol) in THF (4.3 mL). The resultant suspension was heated to 50 °C and stirred for 1 h. The reaction was cooled to rt, then to 0 °C. A solution of iodine (0.99 g, 3.90 mmol) in THF (4.3 mL) was added dropwise to the 0 °C suspension until a brown color just persisted. At this point the addition of iodine/THF was ceased, and the remaining iodine/THF solution was discarded. The reaction was quenched by dilution with 1:1 saturated aqueous $NaHCO_3$/saturated aqueous $Na_2S_2O_3$ (10 mL) and EtOAc (10 mL). The biphasic mixture was stirred vigorously for 10 min, then the layers were separated. The aqueous phase was extracted with EtOAc (3×10 mL). The combined organics were washed with brine, dried ($MgSO_4$), filtered, and concentrated. The crude residue was purified by flash column chromatography (SiO_2, 1% EtOAc/hexanes) to provide vinyl iodide **21** as a clear oil (0.88 g, 60% yield): $[\alpha]_D^{27}$ +10.9 (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz) δ 0.05–0.09 (12H, m), 0.90 (9H, s), 0.91 (9H, s), 0.93 (3H, d, *J*=6.5 Hz), 1.15 (3H, d, *J*=6.3 Hz), 1.54–1.67 (2H, m), 2.40 (3H, d, *J*=1.5 Hz), 2.49–2.58 (1H, m), 3.65–3.70 (1H, m), 3.89 (1H, apparent sextet, *J*=6.0 Hz), 6.15 (1H, dd, *J*=1.5, 10.3 Hz); ^{13}C NMR (125 MHz) δ −4.66, −4.55, −4.18, 14.10, 18.06, 24.06, 25.86, 25.91, 25.96, 27.89, 40.32. 44.90, 65.85, 71.87, 93.09, 145.04; HRMS (ESI) exact mass calculated for $[M+Na]^+$ ($C_{21}H_{45}IO_2Si_2Na$) requires *m*/*z* 535.1895, found 535.1889.

4.5. Synthesis outlined in Scheme 4

*4.5.1. Preparation of **22**.* To prepare active Zn–Cu couple, $Cu(OAc)_2$ (87.3 mg, 0.437 mmol) was suspended in glacial AcOH (20 mL). To this was added Zn dust (1.43 g, 21.9 mmol), and the resultant suspension was heated to reflux for one minute or until all of the copper had deposited onto the zinc (disappearance of blue color in the supernatant). Stirring was stopped, and the reddish-gray silt

was allowed to settle. The AcOH was removed by pipette, then another portion of AcOH (20 mL) was added and the suspension was heated to reflux for one minute. The AcOH was removed again by pipette, and this process was repeated once more. Finally, the Zn–Cu couple was rinsed with Et_2O (3×20 mL), with each rinse being removed by pipette. The resultant active couple was dried under vacuum for 30 min.

Alkyl iodide **5** (1.84 g, 4.37 mmol) dissolved in anhydrous 15:1 PhH/DMF (17.5 mL) was cannulated into to the active Zn–Cu couple, and the resultant suspension was heated at 55 °C for 1 h. Meanwhile, LiCl (1.11 g, 26.2 mmol, dried over flame/vacuum) and $Pd(PPh_3)_4$ (361 mg, 0.312 mmol) were combined and purged with argon. Freshly distilled anhydrous NMP (12.5 mL) was added, followed by the vinyl iodide **11** (1.05 g, 3.12 mmol) in NMP (4.1 mL, plus a little more to aid in transfer). Then the colorless alkylzinc iodide solution was added via cannula (the excess settled Zn was left behind in the original flask as much as possible). The reaction mixture was degassed with one freeze-pump-thaw cycle, and the mixture was heated to 55 °C for 35 min. The reaction was cooled to rt, diluted with EtOAc, and poured into saturated aqueous $NaHCO_3$. The layers were separated, and the aqueous extracted with EtOAc (3×50 mL). The combined organics were washed with H_2O (3×100 mL) and brine (100 mL), dried (Na_2SO_4) and concentrated in vacuo. The crude residue was purified by flash column chromatography in a solvent gradient (SiO_2, 5%→10% EtOAc/hexanes) to provide **22** (1.50 g, 95%) as a colorless oil, which contained small amounts of the diastereomeric products **23** and **24**. Spectral data is reported only for the major product, **22**: $[\alpha]_D^{26}$ +5.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.75 (3H, d, *J*=6.8 Hz), 0.83 (3H, d, *J*=6.8 Hz), 1.44–1.55 (2H, m), 1.55–1.70 (5H, m), 1.70–1.87 (6H, m), 1.87–1.96 (2H, m), 2.08–2.18 (1H, m), 2.24 (1H, dd, *J*=4.6, 12.9 Hz), 2.28–2.39 (3H, m), 3.26 (1H, ddd, *J*=3.5, 3.5, 7.0 Hz), 3.33–3.39 (1H, m), 3.40 (1H, t, *J*=11.0 Hz), 3.68 (3H, s), 3.73 (1H, dd, *J*=4.5, 11.0 Hz), 3.81 (3H, s), 4.46 (2H, AB quartet, *J*=11.0, 25.5 Hz), 5.27 (1H, dd, *J*=6.0, 7.0 Hz), 6.86–6.91 (2H, m), 7.25–7.31 (2H, m); ^{13}C NMR (125 MHz) δ 12.60, 14.46, 15.99, 21.47, 22.47, 24.24, 30.01, 30.53, 31.52, 33.29, 33.83, 34.02, 40.13, 42.67, 51.34, 55.13, 67.41, 71.34, 77.16, 81.89, 110.04, 113.60, 122.14, 129.09, 131.13, 134.89, 158.93, 173.93; HRMS (ESI) *m*/*z* exact mass calculated for $[M+H]^+$ ($C_{30}H_{47}O_6$) requires *m*/*z* 503.3372, found 503.3372.

4.6. Synthesis outlined in Scheme 5

*4.6.1. Preparation of **26**.* A mixture of CH_2Cl_2 (663 mL), H_2O (166 mL), and TFA (41 mL) was shaken vigorously in a separatory funnel. The lower organic layer was drained into a round bottom flask containing **22** (6.29 g, 12.5 mmol). The resultant solution was stirred at rt for 3.5 h. The reaction solution was cautiously and slowly poured into ice-cold saturated aqueous $NaHCO_3$. The layers were separated, and the aqueous extracted with EtOAc (3×250 mL). The combined organics were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The crude residue was purified by flash column chromatography in a solvent gradient (SiO_2, 25%→50% EtOAc/hexanes) to provide 1,3-diol **26** (4.97 g, 91%, contaminated with ~6% of **27**) as a white waxy solid. During this chromatographic separation, it was possible to remove minor contaminant **28**. Data for **26**: $[\alpha]_D^{27}$ +1.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.82 (3H, d, *J*=6.8 Hz), 0.89 (3H, d, *J*=7.2 Hz), 1.40–1.80 (8H, m), 1.63 (3H, s), 1.84 (1H, dd, *J*=9.0, 13.2 Hz), 2.16–2.34 (5H, m), 3.19–3.26 (1H, m), 3.50 (1H, dt, *J*=4.0, 8.0 Hz), 3.63 (1H, dd, *J*=7.6, 10.8 Hz), 3.67 (3H, s), 3.70 (1H, dd, *J*=3.2, 10.8 Hz), 3.80 (3H, s), 4.43 (2H, AB quartet, *J*=11.4, 23.4 Hz), 5.13 (1H, apparent t, *J*=7.2 Hz), 6.84–6.90 (2H, m), 7.22–7.29 (2H, m); ^{13}C NMR (125 MHz) δ 13.82, 15.39, 16.08, 21.51, 29.41, 32.86, 33.91, 34.20, 39.62, 42.89, 51.39, 55.17, 67.66, 71.35, 77.05, 82.26, 113.63, 121.35, 129.36, 130.77, 138.05, 159.03, 174.00; HRMS (ESI) exact mass calculated for $[M+H]^+$ ($C_{25}H_{41}O_6$) requires *m*/*z* 437.2903, found 437.2879.

4.7. Synthesis outlined in Scheme 6

*4.7.1. Preparation of **29**.* To a stirred −78 °C solution of diol **26** (9.70 g, 22.2 mmol) in CH_2Cl_2 (222 mL) was added 2,6-lutidine (6.20 mL, 53.3 mmol), followed by TIPSOTf (6.57 mL, 24.4 mL) dropwise. The resultant solution was stirred at −78 °C for 20 min, then poured into saturated aqueous NH_4Cl. The layers were separated, and the aqueous phase extracted with EtOAc (3×200 mL). The combined organics were washed with 1 M HCl, saturated aqueous $NaHCO_3$, and brine, then dried ($MgSO_4$) and concentrated in vacuo. The crude residue was carried on to the following step without further purification.

To the crude ester from the preceding step dissolved in 4:1:1 THF/MeOH/H_2O (1.11 L) was added 1 M LiOH (193 mL). The resultant solution was stirred at rt for 1.5 h. The reaction was cautiously and slowly poured into 1 M HCl, then the mixture was extracted with EtOAc (4×500 mL). The combined organics were washed with H_2O (2×500 mL) and brine, dried (Na_2SO_4), and concentrated in vacuo. The crude residue was purified by flash column chromatography (SiO_2, 25%→50% methyl *t*-butyl ether/hexanes) to provide *seco*-acid **29** (14.85 g, 88% over two steps, contaminated with ~6% of **30**) as a colorless oil: $[\alpha]_D^{26}$ +1.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.85 (3H, d, *J*=6.5 Hz), 0.91 (3H, d, *J*=7.0 Hz), 1.05–1.18 (21H, m), 1.50–1.62 (3H, m), 1.62 (3H, s), 1.62–1.72 (1H, m), 1.72–1.82 (2H, m), 1.82 (1H, dd, *J*=8.5, 13.0 Hz), 1.88–1.98 (1H, m), 2.22–2.30 (3H, m), 2.35 (2H, t, *J*=7.3 Hz), 3.26–3.32 (1H, m), 3.63 (1H, apparent dt, *J*=5.0, 7.0 Hz), 3.71 (1H, dd, *J*=7.3, 9.8 Hz), 3.81 (3H, s), 3.91 (1H, dd, *J*=3.9, 9.8 Hz), 4.47 (2H, AB quartet, *J*=11.5, 18.0 Hz), 5.25 (1H, apparent t, *J*=6.5 Hz), 6.86–6.90 (2H, m), 7.26–7.31 (2H, m); ^{13}C NMR (125 MHz) δ 11.73, 13.73, 14.83, 16.17, 17.94, 21.32, 29.68, 29.97, 33.33, 33.75, 33.99, 39.27, 42.97, 55.25, 68.42, 71.42, 76.53, 81.80, 113.71, 122.37, 129.28, 131.15, 135.70, 159.03, 178.22; HRMS (ESI) exact mass calculated for $[M+H]^+$ ($C_{33}H_{59}O_6Si$) requires *m*/*z* 579.4075, found 579.4043.

*4.7.2. Preparation of **31**.* To a solution of *seco*-acid **29** (14.9 g, 25.7 mmol) in PhMe (260 mL) was added *i*-Pr_2NEt (26.8 mL, 153.9 mmol) and 2,4,6-trichlorobenzoyl chloride (12.1 mL, 77.0 mmol). The resultant solution was stirred for 1.5 h at rt. In a separate flask, DMAP (9.41 g, 77.0 mmol) was dissolved in PhMe (1.3 L). To this solution was added the anhydride solution dropwise via cannula over 4 h, and the resultant cloudy suspension was stirred a further 12 h at rt. The reaction mixture was poured into 1 M HCl, and the layers were separated. The aqueous phase was extracted with EtOAc (3×150 mL), and the combined organics were washed with saturated aqueous $NaHCO_3$, H_2O, and brine. After drying ($MgSO_4$), the organic phase was concentrated in vacuo. The crude residue was purified by flash column chromatography in a solvent gradient (SiO_2, 100% hexanes→2% EtOAc/hexanes) to provide macrolactone **31** (10.61 g, 74%) in pure form as a white waxy solid. During this chromatography, **32** (0.86 g, 6%) was removed. Data for the **31**: $[\alpha]_D^{27}$ −17.9 (*c* .84, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.99 (3H, d, *J*=6.8 Hz), 1.04 (3H, d, *J*=7.0 Hz). 1.04–1.14 (21H, m), 1.40–1.52 (1H, m), 1.57–1.67 (1H, m), 1.66 (3H, s), 1.67–1.84 (3H, m), 1.85–1.92 (2H, m), 1.92–2.00 (1H, apparent septet, *J*=6.5 Hz), 2.06–2.13 (1H, m), 2.07 (1H, dt, *J*=3.5, 12.0 Hz), 2.42–2.53 (2H, m), 3.10–3.16 (1H, m), 3.54 (1H, dd, *J*=7.0, 10.0 Hz), 3.68 (1H, dd, *J*=5.5, 10.0 Hz), 3.81 (3H, s), 4.42 (2H, AB quartet, *J*=11.5, 97.0 Hz), 4.98–5.04 (1H, br d, *J*=10.0 Hz), 5.08 (1H, ddd, *J*=3.4, 6.1, 12.0 Hz), 6.87–6.90 (2H, m), 7.25–7.30 (2H, m); ^{13}C NMR (125 MHz) δ 11.90, 12.80, 15.64, 17.66, 17.97, 19.28, 20.51, 28.99, 30.59, 32.63, 35.84, 40.42, 45.68, 55.17, 65.17, 70.82, 73.62, 83.10, 113.63, 121.91, 129.34, 131.07, 137.10, 159.01, 173.39; HRMS (ESI)

exact mass calculated for $[M+H]^+$ ($C_{33}H_{57}O_5Si$) requires *m*/*z* 561.3975, found 561.3985.

4.8. Synthesis outlined in Scheme 7

*4.8.1. Preparation of **33**.* To a stirred 0 °C solution of **31** (4.00 g, 7.13 mmol) in CH_3CN (300 mL) in a Teflon bottle was added pyridine (20.1 mL, 249.6 mmol). After 10 min, HF·pyridine (70%, 20.1 mL) was added. Stirring was continued at 0 °C for 72 h. Using extreme caution, the reaction was quenched slowly by repeatedly pipetting ~20 mL aliquots of the reaction mixture onto ice-cold saturated aqueous $NaHCO_3$. After all of the reaction mixture was transferred, the resultant biphasic mixture was stirred for 30 min, then the layers were separated. The aqueous phase was extracted with EtOAc (3×200 mL), and the combined organics were washed with 1 M HCl and brine, dried ($MgSO_4$), and concentrated in vacuo. The crude residue was purified by flash column chromatography (25% EtOAc/hexanes) to provide alcohol **33** (2.66 g, 92%) as a white solid: $[\alpha]_D^{25}$ −42.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.04 (3H, d, *J*=6.5 Hz), 1.06 (3H, d, *J*=7.0 Hz), 1.43–1.54 (1H, m), 1.55–1.65 (2H, m), 1.67 (3H, s), 1.67–1.77 (3H, m), 1.77–1.85 (1H, m), 1.85–1.96 (2H, m), 2.11 (1H, td, *J*=3.4, 12.5 Hz), 2.19 (1H, br d, *J*=12.5 Hz), 2.41 (1H, dt, *J*=11.0, 14.0 Hz), 2.54 (1H, dt, *J*=4.4, 12.7 Hz), 3.09–3.14 (1H, m), 3.45 (1H, dd, *J*=3.4, 11.7), 3.58 (1H, dd, *J*=3.9, 11.7), 3.81 (3H, s), 4.40 (2H, AB quartet, *J*=11.0, 98.5 Hz), 4.85 (1H, ddd, *J*=2.9, 8.8, 11.7 Hz), 4.99 (1H, br d, *J*=11.0 Hz), 6.85–6.90 (2H, m), 7.24–7.29 (2H, m); ^{13}C NMR (125 MHz) δ 13.70, 15.69, 19.00, 20.65, 28.84, 31.58, 32.44, 35.88, 40.20, 45.67, 55.23, 63.97, 70.76, 74.31, 83.16, 113.68, 121.71, 129.36, 130.95, 137.45, 159.06, 175.07; HRMS (ESI) exact mass calculated for $[M+H]^+$ ($C_{24}H_{37}O_5$) requires *m*/*z* 405.2641, found 405.2640.

*4.8.2. Preparation of **34**.* To a solution of alcohol **33** (1.67 g, 4.12 mmol) in CH_2Cl_2 (82 mL) was added imidazole (841 mg, 12.4 mmol), triphenylphosphine (2.27 g, 8.65 mmol), and iodine (2.20 g, 8.65 mmol). The resultant mixture was stirred at rt for 12 h. The reaction was quenched by dilution with 1:1 saturated aqueous $NaHCO_3$/saturated aqueous $Na_2S_2O_3$ and EtOAc. The layers were separated, and the aqueous phase was extracted with EtOAc (3×100 mL). The combined organics were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The crude residue was purified by flash column chromatography (SiO_2, 5% EtOAc/hexanes) to provide **34** (2.10 g, 99%) as a clear oil: $[\alpha]_D^{25}$ −8.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.04 (3H, d, *J*=7.0 Hz), 1.11 (3H, d, *J*=7.0 Hz), 1.37–1.49 (1H, m), 1.52–1.68 (1H, m), 1.65 (3H, s), 1.68–1.84 (3H, m), 1.84–1.96 (3H, m), 2.04–2.18 (2H, m), 2.37–2.47 (1H, m), 2.47–2.53 (1H, m), 3.01 (1H, td, *J*=1.0, 9.8 Hz), 3.10–3.14 (1H, m), 3.31 (1H, dd, *J*=3.9, 9.8 Hz), 3.82 (3H, s), 4.32 (1H, d, *J*=11.0 Hz), 4.52 (1H, d, *J*=11.0 Hz), 4.91–5.02 (2H, m), 6.86–6.91 (2H, m), 7.25–7.30 (2H, m); ^{13}C NMR (125 MHz) δ 10.55, 15.69, 17.16, 19.19, 20.67, 28.81, 31.21, 32.56, 35.79, 40.34, 45.58, 55.26, 70.81, 74.45, 83.12, 113.68, 120.89, 129.39, 131.00, 137.85, 159.05, 173.38; HRMS (ESI) exact mass calculated for $[M+Na]^+$ ($C_{24}H_{35}IO_4Na$) requires *m*/*z* 537.1472, found 537.1434.

*4.8.3. Preparation of **35**.* To prepare active Zn–Cu couple, $Cu(OAc)_2$ (39 mg, 0.194 mmol) was suspended in glacial AcOH (10 mL). To this was added Zn dust (636 mg, 9.72 mmol), and the resultant suspension was heated to reflux for one minute or until all of the copper had deposited onto the zinc (disappearance of blue color in the supernatant). Stirring was stopped, and the reddish-gray silt was allowed to settle. The AcOH was removed by pipette, then another portion of AcOH (10 mL) was added, and the suspension was heated to reflux for one minute. The AcOH was removed again by pipette, and this process was repeated once more. Finally, the Zn–Cu couple was rinsed with Et_2O (3×10 mL), with each rinse being removed by pipette. The resultant active couple was dried under vacuum for 30 min.

Alkyl iodide **34** (1.00 g, 1.95 mmol) dissolved in anhydrous 15:1 PhH/DMF (7.0 mL) was cannulated into to the active Zn–Cu couple, and the resultant suspension was heated at 50 °C for 1 h. Meanwhile, LiCl (494 mg, 11.7 mmol, dried over flame/vacuum) and $Pd(PPh_3)_4$ (337 mg, 0.292 mmol) were combined and purged with argon. Freshly distilled anhydrous NMP (8.0 mL) was added, followed by vinyl iodide **21** (1.5 g, 2.92 mmol) in NMP (3.7 mL, plus a little more to aid in transfer). Then the colorless alkylzinc iodide solution was added via cannula (the excess settled Zn was left behind in the original flask as much as possible). The reaction mixture was degassed with one freeze-pump-thaw cycle, and the mixture was heated to 60 °C for 17.5 h. The reaction was cooled to rt, diluted with EtOAc, and poured into saturated aqueous $NaHCO_3$. The layers were separated, and the aqueous extracted with EtOAc (3×50 mL). The combined organics were washed with H_2O (3×100 mL) and brine (100 mL), dried (Na_2SO_4) and concentrated in vacuo. The crude residue was purified by flash column chromatography in a solvent gradient (SiO_2, 1%→2%→3% EtOAc/hexanes) to provide **35** (1.318 g, 88%) as a colorless oil: $[\alpha]_D^{25}$ −8.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.02–0.07 (12H, m), 0.84 (3H, d, *J*=7.0 Hz), 0.88 (3H, d, *J*=6.5 Hz), 0.88 (9H, s), 0.90 (9H, s), 1.03 (3H, d, *J*=6.5 Hz), 1.14 (3H, d, *J*=6.5 Hz), 1.40–1.52 (1H, m), 1.52–1.83 (9H, m), 1.59 (3H, d, *J*=1.0 Hz), 1.66 (3H, s), 1.83–1.95 (2H, m), 2.02–2.08 (1H, m), 2.09 (1H, dd, *J*=3.5, 12.5 Hz), 2.14 (1H, dd, *J*=3.5, 13.5 Hz), 2.37–2.52 (3H, m), 3.10–3.15 (1H, m), 3.81 (3H, s), 3.90 (1H, apparent sextet, *J*=6.5 Hz), 4.31 (1H, d, *J*=11.0 Hz), 4.51 (1H, d, *J*=11.0 Hz), 4.84–4.91 (1H, m), 5.00 (1H, m), 5.12 (1H, d, *J*=9.5 Hz), 6.85–6.90 (2H, m), 7.25–7.30 (2H, m); ^{13}C NMR (125 MHz) δ −4.70, −4.39, −4.34, −4.05, 14.47, 15.66, 15.74, 16.01, 18.07, 18.10, 19.26, 20.61, 23.96, 25.89, 25.96, 28.97, 30.25, 32.61, 35.19, 35.67, 37.61, 43.03, 45.03, 45.74, 55.24, 66.00, 70.82, 73.14, 76.04, 83.21, 113.68, 121.89, 129.39, 130.46, 131.09, 131.60, 137.12, 159.05, 173.59; HRMS (ESI) exact mass calculated for $[M+H]^+$ ($C_{45}H_{81}O_6Si_2$) requires *m*/*z* 773.5572, found 773.5577.

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References and notes

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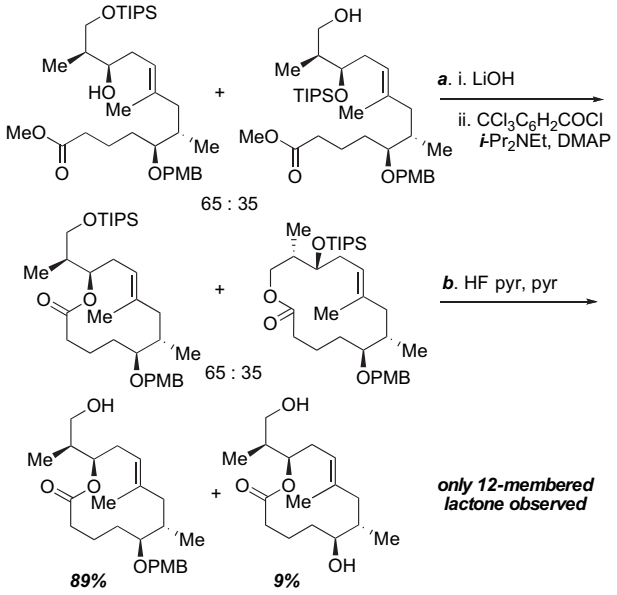
26. We also examined this transformation on a mixture of primary (14-membered) and secondary (12-membered) macrolactones. On exposure of a 65:35 mixture of TIPS-protected macrolactones to these deprotection conditions (HF·pyr, pyr, CH_3CN, 0 °C), we obtained solely the 12-membered deprotected macrolactone product.



Reagents and conditions: (i) 1 M LiOH, 4:1:1 THF/MeOH/H_2O, rt;$CCl_3C_6H_2COCl$, *i*-Pr_2NEt, DMAP, benzene, rt, 86%, two steps;HF·pyr, pyr, CH_3CN, 0 °C, 38 h, 89% (+9% loss of PMB product).

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